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# Risk factors concerning complications following permanent pacemaker implantation for patients on antithrombotic therapy: a cohort study.



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**Title page**

**Title**

Risk factors concerning complications following permanent pacemaker implantation for patients on antithrombotic therapy: a cohort study.

**Authors**

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**Keywords:** Pacemaker, artificial; Perioperative Care; Anticoagulant drugs; Antithrombotic therapy; Postoperative Complications; Patient Safety.

**ABSTRACT**

**Objective**

The objective was to identify the complications and associated factors presented by patients after pacemaker implantation, according to a regimen of antithrombotic therapy or without it.

**Design**

An analytical observational study on a prospective cohort of 310 consecutive patients with a permanent pacemaker implanted, included from January 1 to December 31, 2014 from one single center.

**Results**

The follow-up was conducted on 310 patients for 6 months. 239 patients (77%) received antithrombotic therapy at the time of the pacemaker implantation. 20.8% of complications are presented in patients without anticoagulant therapy, 80.8% of them being minor ones.

In the case of patients with anticoagulant therapy, 30.3% of the complications are major ones. Factors associated with major complications were contusion (OR, 2; 95% CI, 1-3.8; p=0.049) and, minor complications, arm immobilization >24 hours (p= <0.001) and contusion (p=0.002).

**Conclusion**

This study found an increase in the overall risk and complications that can occur when implanting a permanent pacemaker in patients with antithrombotic therapy based on the time of immobilization and contusions after the implantation.

**Keywords:** Pacemaker, artificial; Perioperative Care; Anticoagulant drugs; Antithrombotic therapy; Postoperative Complications; Patient Safety.

**What is already known about this subject?**

- The perioperative management of oral anticoagulation/antiplatelet therapy is still controversial in pacemaker implantation and this leads to a very heterogeneous perioperative management of these patients.
- It would be necessary to propose an alternative therapy which avoids the combination of different kinds of antithrombotic treatments in order to undergo surgery without an interruption of anticoagulation therapy in patients with a high thrombotic risk.
- Although pacemaker implantations are considered to be minor surgery, this does not mean that they are exempt from complications that produce a negative impact on patients in terms of disability, delay their incorporation into daily activities, and generate a greater demand for care.

**What are the new findings?**

- There were more major complications (pneumothorax, lead dislodgement, and deaths) in patients on antithrombotic therapy, while minor complications (peripheral phlebitis, non-complicated hematomas and painful shoulder) were similar in both cohorts.
- There were more deaths because of more comorbidities and not because of oral anticoagulation.
- The main risk factors associated with complications are: the time of immobilization of the arm ipsilateral to the pacemaker implantation is higher than 24 hours and contusions after the implantation.

**How might these results change the focus of research or clinical practice?**

- Knowing these results allows us to have a complete view of the process, and it helps us identify strategies to make the preventive measures which are carried out in the many patients who undergo such a procedure more effective and safer.

## INTRODUCTION

According to the data, more than 1 million permanent pacemakers are implanted each year worldwide and the USA is the largest implanting country (around 23%).[1] A relevant percentage of patients who receive these devices require long-term anticoagulation therapy,[2] and this treatment varies from novel oral anticoagulants (NOACs) to antiplatelet or heparin. Although NOACs are increasingly used, their percentage continues being far from that of other kinds of anticoagulation therapy.[3]

The periprocedural management of anticoagulation presents a dilemma to physicians, in which many specialties are involved, and varies greatly between institutions in the way it is practiced, further complicating the issue.[4] The decision regarding interruption in anticoagulant or antiplatelet therapy is particularly important, as premature withdrawal has been linked to a higher risk of cardiovascular events.[4] The decision to continue or discontinue therapy prior to the procedure should be taken following an evaluation of the procedure's bleed risk , the thrombotic risk associated with anticoagulant interruption, and/or the bleed risk specific to the patient. In addition, the periprocedural management also depends on the type of anticoagulation therapy.[5]

Both anticoagulation and antiplatelet management strategies will be determined by the interaction between these risk factors, along with the specific features of the anticoagulant that the patient is taking.[4,6] Currently, guidelines and consensus documents [4,7-11] have been published about the perioperative management of antithrombotic therapy, and its application to clinical practice, whose ultimate aim, is to help standardize clinical practice.

Although the procedure is considered to be minor surgery, this does not mean that it is exempt from complications and technical failures in the short and long term. Previous evidence about the impact of prior antithrombotic therapy on complications due to pacemaker implants are not homogeneous[12-14] and tend to be more focused on major complications.

In this sense, implants require special consideration in patients with antithrombotic therapy, particularly for the subset of patients having a moderate-to-high risk (≥5% per year) of thromboembolic events,[2] and due to which perioperative management represents a challenge for the care needed by these patients.[15]

The objective of the current study was to identify the complications and associated factors presented by patients after pacemaker implantation, according to a regimen of antithrombotic therapy or without it.

## MATERIALS AND METHODS

### Study Design

Our observational analytical study was a prospective cohort in which patients with pacemakers implanted were divided into groups according to their exposure factor, anticoagulant/antiplatelet treatment present or absent before surgery. This was a consecutive sample from a single centre, taken from January 1st to December 31st of 2014. The patients were followed up for 6 months.

### Participants

The sample was composed of patients with indications of permanent pacing hospitalized in any of the Medical-Surgical Units or in the Critical Care and Emergency Unit of the "Virgen del Rocío" University Hospital.

**Inclusion and exclusion criteria**

In order for a case to be included in the study, it had to meet three requirements: (a) be the first time of the implantation of a permanent pacemaker, (b) age over 18 years, (c) informed consent from the patient to participate. If patients had generator replacements, a device removal or an implantation of defibrillators or resynchronizers, they were excluded from the sample.

Finally, the inclusion criteria were met by 310 patients distributed into two groups: 71 in the group without antithrombotic therapy and 239 in the group with antithrombotic therapy. At the inclusion of each patient, the treatment regimen received regarding oral anticoagulation/anti-platelet agents was collected, this being hidden from the investigators.

**Implant procedure**

Implant procedural aspects were defined as elements related to the preparation of the patient (antibiotic prophylaxis); aspects related to the technique of the implant (difficulty of central venous access, use of imaging support); data concerning the perioperative care (surgical wound compression, arm immobilization); elements regarding patient follow-up; with respect to the work team, data related to the surgeon's experience (high>100 implants/year, medium <100 implants/year and low <50 implants/year).[16,17] Before leaving the operating room, all the patients underwent compression dressing, receiving local cold on the surgical wound, and immobilization of the arm ipsilateral to the pacemaker implant - the nurse informed each patient that this immobilization should last 24 hours.

**Definition of exposure**

According to the treatment systems followed by the patient before the implantation, in terms of anticoagulant and antithrombotic treatment, and in accordance with the protocol implemented in the hospital, the patients were distributed into two strata: 1) Patients not treated with antithrombotic therapy, considered in the analysis as "not exposed" (n=71; 23%); 2) Patients treated with anticoagulant and/or antiplatelet and/or heparin drugs, analyzed as the "exposed group" (n=239; 77%). At the same time, this latter group was subdivided into 4 subgroups: Patients only having oral anticoagulation (n=15; 6%) (acenocumarol, dabigatran, rivaroxaban, apixaban); having combined (n=103; 43%) oral anticoagulation/Antiplatelet treatment (aspirin or clopidogrel)/bridging heparin (low molecular weight heparin); having single or double antiplatelet therapy (n=76; 32%); and only having heparin (n=148; 62%). In this group, 3 patients received unfractionated heparin and 145 patients received low molecular weight heparin. The choice of type, dose and timing of antithrombotic and antiplatelet treatment was according to the discretion of the treating physician.

**Protocol for discontinuation of antithrombotic therapy**

The protocol varied according to the level of risk of thromboembolism. The doses of these medications were not assessed. At the time of the procedure no patients were therapeutically anticoagulated. Therefore, the specific protocols are explained below:

(1) Patients with a mechanical heart valve, atrial fibrillation, and a high risk of thromboembolism are given bridging heparin, while those with a low risk of thromboembolism stop anticoagulant therapy 3 days before the procedure, and resume 24 hours after surgery.
(2) In moderate- to high-risk patients who are receiving acetylsalicylic acid, this is continued around the time of surgery.
(3) For patients with a coronary stent, antiplatelet therapy is continued perioperatively.

**Definition of outcome**

Although surgical outcomes were reported as morbidity or mortality rates in the past, more recent studies have pointed out the appropriateness of considering them more broadly; that is, the complication rates.[2,18] The major and minor complications were defined based on previous reports of complications related to such devices.[19-21]

On the one hand, major complications were those that placed the patient at a significant risk, such as reoperation, readmissions for management or the death of the patient. On the other hand, minor complications were those associated with patient discomfort, treated on an outpatient basis or spontaneously resolved, our results being compared with some other studies.

The assessment of the hemorrhagic risk was calculated with the HAS-BLED scale[22] (low risk: score 0-1, medium risk: score 2, high risk: score 3 or more). The venous thrombotic risk was described according to the PRETEMED guide[23] (low risk: score 1-3, medium risk: score 4, high risk: score >4) since it is one of those most used in Spain.[24]

The data were prospectively collected in a registry designed for this purpose, including the basal measurements and the outcomes described.

**Cohort follow-up**

Follow-up was conducted on the patients in the study up to 6 months after the pacemaker implant. During the first 30 days, by telephone, with cut-off points at 7, 15 and 30 days. In the case of non-response, they were called again 48 hours later to avoid losses during the follow-up. A review of the clinical history was done after 6 months, exploring the presence of any episode related to the pacemaker implant documented as a complication. The patient outcomes were validated by a single researcher.

**Statistical Analyses**

Qualitative variables were expressed as frequencies and percentages, and quantitative variables as mean, median and mode. The correlation between the quantitative variables was calculated through Spearman's rho coefficient for the analysis of differences between groups, the Chi-square test was used for the qualitative variables, and the Student's-t for the quantitative variables.

The rates of cumulative incidence of complications were expressed with 95% confidence intervals (95% CI) and upper and lower limits, while measures of association were made through bivariate analysis with Relative Risk (RR) estimation. In order to calculate the effect of the study factor on the response variable adjusted by the rest of the independent variables, multivariate analysis with logistical regression was conducted for dichotomous variables.

A significance level of 5% ($p<0.05$) was considered for all the hypothesis verifications.

In order to avoid any selection bias, the subjects from both cohorts were selected from the same population group, ensuring they had the same likelihood of developing the event and identifying its outcome. Measurement bias was avoided by conducting the same prospective follow-up in all the patients.

Confusion variables were controlled through the multivariate analysis previously described in the statistical analysis.

The investigation complies with the principles outlined in the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the "Virgen del Rocío" University Hospital (2013PI/152).

## RESULTS

A total of 310 patients were included, followed-up for 6 months, without losses. The patients were distributed according to the exposure pattern into two cohorts. Of those, 239 (77%) had antithrombotic therapy and 71 (23%) did not.

In the no antithrombotic therapy cohort, the alteration of atrioventricular conduction was 62%, and the sinus node disease was 25%, while in the with antithrombotic therapy cohort both indications were similar (45.2% and 46.4%, respectively). In the case of patients on oral anticoagulation and bridging heparin, the antithrombotic therapy was resumed in less than one day in around 14% of the patients. The mean age was 76.9±9.7 years, with more males (56.1%) than females (43.9%) The clinical and biological characteristics are described in Table 1.

**Table 1.** Pre-implant clinical and biological values characteristics.

| | | **Total n=310 (%)** | **N-ATT n=71 (%)** | **W-ATT n=239 (%)** | **p** |
|---|---|---|---|---|---|
| Diagnosis for intervention | Sinus node disease | 129 (41.6%) | 18 (25.4%) | 111 (46.4%) | 0.006 |
| | AV conduction system disease | 152 (49%) | 44 (62%) | 108 (45.2%) | |
| | Syncope and others | 29 (9.4%) | 9 (12.7%) | 20 (8.4%) | |
| Sex | Male | 174 (56.1%) | 38 (53.5%) | 136 (56.9%) | NS |
| | Female | 136 (43.9%) | 33 (46.5%) | 103 (43.1%) | |
| Age (mean ±SD) | | 76.9 ±9.7 | 75.3 ±13 | 77.4 ±8.5 | NS |
| INR (mean ±SD) | | 1.10 ±0.2 | 1.04 ±0.1 | 1.12 ±0.2 | <0.001 |
| Cardiovascular risk factors | Hypertension | 237 (76.5%) | 46 (64.8%) | 191 (80%) | 0.008 |
| | Diabetes | 109 (35.2%) | 15 (21.5%) | 94 (39.3%) | 0.004 |
| | Dyslipemia | 134 (43.2%) | 23 (32.4%) | 111 (46.4%) | 0.035 |
| | Obesity (BMI>28) | 186 (60%) | 37 (52.1%) | 149 (62.3%) | NS |
| | Smoking | 28 (9%) | 9 (12.7%) | 19 (8%) | NS |
| Comorbidity | Atrial fibrillation | 114 (36.8%) | 8 (11.3%) | 106 (44.4%) | <0.001 |
| | Previous Stroke | 37 (11.9%) | 2 (2.8%) | 35 (14.6%) | 0.006 |
| | DVT | 8 (2.6%) | 0 | 8 (3.4%) | NS |

| | | | | | |
|---|---|---|---|---|---|
| | Pulmonary embolism | 4 (1.3%) | 0 | 4 (1.7%) | NS |
| | Valvular heart disease | 49 (15.8%) | 5 (7%) | 44 (18.4%) | 0.021 |
| | Ischemic heart disease | 34 (11%) | 2 (2.3%) | 32 (13.4%) | 0.012 |
| | Active respiratory disease | 25 (8.1%) | 2 (2.8%) | 23 (9.6%) | NS |
| | Renal insufficiency | 46 (14.8%) | 5 (7%) | 41 (17.2%) | 0.035 |
| | Immunodeficiency | 24 (7.7%) | 9 (12.7%) | 15 (6.3%) | NS |
| | Active cancer | 27 (8.7%) | 5 (7%) | 22 (9.2%) | NS |
| Charlson score | Absence of comorbidity | 202 (65.2%) | 59 (83.1%) | 143 (59.8%) | <0.001 |
| | Low and high comorbidity | 108 (34.8%) | 12 (16.9%) | 96 (40.2%) | |
| HAS-BLED score | Low | 96 (31%) | 48 (67.6%) | 48 (20.1%) | < 0.001 |
| | Medium | 153 (49.4%) | 22 (31%) | 131 (54.8%) | |
| | High | 61 (19.7%) | 1 (1.4%) | 60 (25.1%) | |
| Venous thrombotic risk. PRETEMED Guide | Low | 108 (34.8%) | 40 (56.3%) | 68 (28.5%) | <0.001 |
| | Medium | 60 (19.4%) | 16 (22.5%) | 44 (18.4%) | NS |
| | High | 142 (45.8%) | 15 (21.1%) | 127 (53.1%) | <0.001 |

AV: Auriculoventricular; BMI: Body Mass Index; DVT: Deep Venous Thrombosis; INR: International Normalized Ratio

Ratio; N-ATT: No Antithrombotic Therapy; n: number of patients; NS: Non-significant; SD: Standard Deviation; W-ATT: With Antithrombotic Therapy.

As a whole, the biological characteristics of the sample show a significant baseline situation of greater fragility in the with antithrombotic therapy group, due to a higher comorbidity. The characteristics of the procedure are shown in Table 2.

**Table 2.** Implant-Related Characteristics.

| | | **TOTAL n=310 (%)** | **N-ATT n=71 (%)** | **W-ATT n=239 (%)** | **p** |
|---|---|---|---|---|---|
| Electric scalpel | | 17 (5.5%) | 4 (5.6%) | 13 (5.4%) | NS |
| Incision previous to vein puncture | | 97 (31.3%) | 28 (39.4%) | 69 (28.9%) | NS |
| Subclavian vein access† | | 308 (100%) | 70 (98.6%) | 238 (99.6%) | NS |
| Arterial puncture | | 48 (15.5%) | 9 (12.7%) | 39 (16.3%) | NS |
| Temporary pacemaker | | 34 (11%) | 5 (7%) | 29 (12.1%) | NS |
| No. of attempts for vein access | < 3 | 229 (73.9%) | 54 (76.1%) | 175 (73.2%) | NS |
| | > 3 | 74 (23.9%) | 15 (21.1%) | 59 (24.7%) | |
| | Contralateral | 7 (2.3%) | 2 (2.8%) | 5 (2.1%) | |
| Type of device | Dual-chamber | 184 (59.4%) | 52 (73.2%) | 132 (55.2%) | 0.006 |
| | Single-chamber | 126 (40.7%) | 19 (26.8%) | 107 (44.8%) | |

| | | | | | |
|---|---|---|---|---|---|
| Generator placement | Subcutaneous | 299 (96.5%) | 68 (95.8%) | 231 (96.7%) | NS |
| | Submuscular | 11 (3.6%) | 3 (4.2%) | 8 (3.4%) | |
| Experience of the implanter | Low | 61 (19.7%) | 11 (15.5%) | 50 (20.9%) | NS |
| | Medium | 94 (30.3%) | 15 (21.1%) | 79 (33.1%) | 0.054 |
| | High | 155 (50%) | 45 (63.4%) | 110 (46%) | 0.010 |
| Location of the RV electrode | Apex | 186 (60%) | 42 (59.2%) | 144 (60.3%) | NS |
| | Exit tract | 124 (40%) | 29 (40.9%) | 95 (39.8%) | |
| Pocket dressing | | 186 (60%) | 46 (64.8%) | 140 (58.6%) | NS |
| Hemostatic agent applied | | 125 (40.3%) | 28 (39.4%) | 97 (40.6%) | NS |
| Average duration of the implantation procedure – minutes - (±SD) | | 37±15.5 | 37.7 ±15.2 | 36.8 ±15.5 | NS |
| Immobilisation | ≤ 24 hours | 238 (76.8%) | 54 (76.1%) | 184 (77%) | NS |
| | ≥ 24 hours | 72 (23.2%) | 17 (23.9%) | 55 (23%) | |

† Two patients are not computed in the venous access because this is considered anecdotal: for one of them, there is a cephalic vein access, and in the other a femoral vein access.

n: number of patients; N-ATT: No Antithrombotic Therapy; NS: Non-significant; W-ATT: With Antithrombotic Therapy; SD: Standard Deviation.

The central venous access was the subclavian vein, similar in both cohorts, without support by imaging and included 100% of the patients. More dual-chamber pacemakers were implanted in the no antithrombotic therapy group, 73.2% vs. 55.2%, than in the with antithrombotic therapy group. This could be associated with the diagnosis of this cohort, because we must not forget that a high percentage presented an alteration in their atrioventricular conduction. On the other hand, both pacemaker types were distributed similarly in the with antithrombotic therapy cohort. This could be linked with the presence of more atrial arrhythmias.

The no antithrombotic therapy cohort presented a higher proportion of interventions conducted by professionals with a high experience in implantation (63.4% vs. 46%, respectively).

During hospitalization, the presence of some aspects was recorded, such as: level of pain, bleeding, fever, contusions (skin bruises of less than 2 cm without palpable mass), tension at the site of incision. The most frequent sign in the antithrombotic therapy cohort was contusions, with an additional 18%.

**Types of complications according to the antithrombotic therapy regimen**

The most frequent major complications were lead dislodgement and pneumothorax, with a similar distribution in both cohorts (Table 3). All deaths occurred in the with antithrombotic therapy cohort.

Regarding minor complications: uncomplicated hematomas were more frequent in the with antithrombotic cohort (24.7% versus 15.5%), painful shoulder was more frequent in the with no antithrombotic cohort (28.2% versus 15.9%) and phlebitis was similar in the no antithrombotic therapy cohort and each one of the 4 subgroups of antithrombotic therapy. In the subgroups of bridging therapy with unfractionated heparin, only one patient showed an uncomplicated hematoma.

**Table 3.** Type of complications according to treatment regimen with oral anticoagulation and anti-platelet agents.

| Type of complications(n) | No therapy group (n=71) | Sub-group on OAC only (n=15) | Sub-group on OAC+AA+BH (n=103) | Sub-group on single or double AA (n=76) | Sub-group on heparin (n=45) |
|---|---|---|---|---|---|
| **No. of major complications (n=70)** | **10 (14.1%; 7-24.4)** | **2 (13.3%; 1.7-40.5)** | **25 (24.3%; 16.4-33.7)** | **19 (25%; 15.8-36.3)** | **14 (31.1%; 18.2-46.7)** |
| Lead Dislodgement (n=26) | 6 (8.5%; 3.2-17.5) | 1 (6.7%; 0.2-32) | 8 (7.8%; 3.4-14.7) | 7 (9.2%; 3.8-18.1) | 4 (8.9%; 2.5-21.2) |
| Interface failure (n=2) | 1 (1.4%; 0-7.6) | 0 | 0 | 0 | 1 (2.2%; 0.1-11.8) |
| Pre-erosion of Pocket (n=1) | 0 | 0 | 0 | 1 (1.3%; 0-7.1) | 0 |
| Infection (n=5) | 0 | 0 | 1 (0.1%; 0-5.3) | 3 (4%; 0.8-11.1) | 1 (2.2%; 0.1-11.8) |
| Pneumothorax (n=12) | 3 (4.2%; 0.1-11.9) | 0 | 0 | 4 (5.3%; 1.5-12.9) | 5 (11.1%; 3.7-24.1) |
| Perforation (n=1) | 0 | 0 | 0 | 1 (1.3%; 0-7.1) | 0 |
| Tamponade (n=2) | 0 | 0 | 1 (1%; 0-5.3) | 1 (1.3%; 0-7.1) | 0 |
| Stroke (n=4) | 0 | 0 | 3 (2.9%; 0.6-8.3) | 1 (1.3%; 0-7.1) | 0 |
| Death (n=16) | 0 | 1 (6.7%; 0.2-32) | 11 (10.7%; 5.5-18.3) | 1 (1.3%; 0-7.1) | 3 (6.7%; 1.4-18.3) |
| Hematoma with clinical significance (n=1) | 0 | 0 | 1 (1%; 0-5.3) | 0 | 0 |
| **No. of minor complications (n=180)** | **42 (59.2%; 46.8-70.7)** | **2 (13.3%; 1.7-40.5)** | **58 (56.3%; 46.2-66.1)** | **49 (64.5%; 52.7-75.1)** | **29 (64.4%; 48.8-78.1)** |
| Uncomplicated Hematomas (n=70) | 11 (15.5%; 8-26) | 1 (6.7%; 0.2-32) | 25 (24.3%; 16.4-33.7) | 23 (30.3%; 20.3-41.9) | 10 (22.2%; 11.2-37.1) |
| Peripheral nerve injury (n=5) | 1 (1.4%; 0-7.6) | 0 | 1 (1%; 0-5.3) | 1 (1.3%; 0-7.1) | 2 (4.4%; 0.5-15.2) |
| Painful shoulder (n=58) | 20 (28.2%; 18.1-40.1) | 1 (6.7%; 0.2-32) | 19 (18.5%; 11,5-27.3) | 11 (14.5%; 7.5-24.4) | 7 (15.6%; 6.5-29.5) |
| Cellulitis (n=1) | 0 | 0 | 0 | 1 (1.3%; 0-7.1) | 0 |
| Phlebitis (n=40) | 9 (12.7%; 6-22.7) | 0 | 13 (12.6%; 6.9-20.6) | 10 (13.2%; 6.5-22.9) | 8 (17.8%; 8-32.1) |
| Local pain (n=6) | 1 (1.4%; 0-7.6) | 0 | 0 | 3 (4%; 0.8-11.1) | 2 (4.4%; 0.5-15.2) |
| **Total (n=250)** | **52 (73.2%; 61.4-83.1)** | **4 (26.7%; 7.8-55.1)** | **83 (80.6%; 71.6-87.7)** | **68 (89.5%; 80.3-95.4)** | **43 (95.6%; 84.9-99.5)** |

Data are expressed as percentages (%); 95% Confidence Interval for the % (Lower Limit-Upper Limit). AA: Anti-platelet Agents; BH: Bridging Heparin; n: number of patients; OAC: Oral Anticoagulation.

When evaluating the number of deaths (Table 4), no significant association was found between comorbidity or the inexperience of the operators and the presence of complications, and this leads us to suspect that this could be due to the higher comorbidity and frailty in the with antithrombotic therapy cohort.

The presence of painful shoulder was more frequent in the no antithrombotic therapy cohort, 28.2% vs. 17.2%; (95% CI: -0.01 to 0.2). p=0.040, respectively. In addition, based on the results from Table 4, this complication is associated with the fact that the patient´s arm was immobilized more than 24 hours.

Analyzing the types of complications per sub-group of antithrombotic treatment (Table 3), it is observed that the sub-group on oral anticoagulation is the only one with fewer complications, while combination therapy, in any of its forms, confirms the association of this therapy with a significant increase in minor complications, particularly hematomas, painful shoulder, and peripheral phlebitis.

The bivariate analysis of the presence of complications, when compared by groups of antithrombotic therapy, shows that there is a 1.8 higher likelihood (25.1% versus 14.1%) in the risk of presenting major complications in the with antithrombotic therapy cohort vs. the no antithrombotic therapy cohort, p=0.05. Comparing between the sub-groups established, the patients treated only with heparin presented twice the risk of patients without antithrombotic therapy, p=0.027. Regarding minor complications, it seems that therapy with oral anticoagulation presents a protective effect vs. the no antithrombotic therapy group, p=0.001, and patients on single or double anti-platelet agents and anticoagulation combined with the other drugs presented a higher risk of complications than the group with only anticoagulation (RR, 4.8, 95% CI, 1.3-17.8; p=<0.001 and RR, 4.2, 95% CI, 1.2-15.5; p=0.0019), respectively.

**Risk factors associated with major and minor complications**

The multivariate analysis showed that heparin therapy tends to be a factor associated with complications, with a higher number of fatal outcomes, while contusions were linked to twice the risk of presenting major complications (OR, 2; 95% CI, 1-3.8; p=0.049), (Table 4).

The main factors connected with minor complications were the time of immobilization of the arm ipsilateral to the pacemaker implantation >24 hours (OR, 19.1; 95% CI, 7.4-49.4; p=<0.001) and contusions after the implantation (OR,2.1; 95% CI, 1.2-3.7; p=0.007). Therapy with oral anticoagulants tended to be associated with minor complications (OR, 0.2; 95% CI, 0 – 1.1; p=0.060), while age was a protective factor against the development of these complications (OR,1; 95% CI, 0.9-1; p=0.013).

Regarding the factors linked to painful shoulder, the immobilization >24 hours of the arm ipsilateral to the pacemaker implantation (OR, 472.5; 95% CI, 133.6-1671.3; p=<0.001) was strongly connected both in the bivariate and the multivariate, and the type of dual-chamber pacemaker, with almost 3 times the risk of having it (OR, 2.8; 95% CI, 1.5-5.5; p=0.002), (Table 4). The use of an anti-platelet agent as monotherapy or in combination (OR, 1.7; 95% CI, 0.9-3; p=0.081) tends to be a factor associated with the presence of a higher level of hematomas; while the dual-chamber pacemaker, the medium experience of the implanting professional, the duration of the implantation procedure, and contusions were factors significantly linked with a higher presence of hematomas.

In relation to factors connected with the infectious complications considered, none shows a statistically significant effect. However, this is not significant, due to the low number of infections that developed,

(Table 4). The multivariate analysis shows that the incidence of death is not related to the inexperience of the operators. A high index of comorbidity is the factor associated with exitus, that is: the greater the comorbidity, the greater the probability of dying (p = 0.002).

**Table 4.** Bivariate and multivariate analysis of the factors associated with major, minor complications and main complications

| **Major Complications** | **$OR_{raw}$ (95% CI)** | **p** | **$OR_{adjusted}$ (95% CI)** | **p** |
|---|---|---|---|---|
| OAC therapy only (yes) | 0.7 (0.2-3.3) | 0.670 | | |
| Anti-platelet Agents only or in combination (yes) | 0.9 (0.4-1.7) | 0.667 | | |
| OAC+AA+BH therapy (yes) | 1.1 (0.6-2.1) | 0.737 | | |
| BH therapy only (yes) | 1.7 (0.8-3.7) | 0.156 | 1.8 (0.8-3.9) | 0.157 |
| Contusion (yes) | 1.8 (0.9-3.5) | 0.076 | 2 (1-3.8) | 0.049 |
| **Minor Complications** | **$OR_{raw}$ (95% CI)** | **p** | **$OR_{adjusted}$ (95% CI)** | **p** |
| OAC therapy only (yes) | 0.2 (0-0.7) | **0.016** | 0.21 (0.04-1.07) | **0.060** |
| AA only or in combination (yes) | 1.4 (0.8-2.3) | 0.213 | 1.55 (0.86-2.80) | 0.142 |
| OAC+AA+BH therapy (yes) | 0.9 (0.6-1.4) | 0.600 | | |
| BH therapy only (yes) | 1.2 (0.7-2.3) | 0.516 | | |
| Age (years) | 1 (1-1) | **0.017** | 1 (0.9-1) | **0.013** |
| Immobilization (> 24 hours) | 19.1 (7.4-49.4) | **<0.001** | 21.9 (8.2-58.5) | **<0.001** |
| Contusion (yes) | 2.1 (1.2-3.7) | **0.007** | 2.7 (1.5-5) | **0.002** |
| **Main complications** | | | | |
| **Painful Shoulder** | **$OR_{raw}$ (95% CI)** | **p** | **$OR_{adjusted}$ (95% CI)** | **p** |
| Immobilization (> 24 hours) | 472.5 (133.6-1671.3) | **<0.001** | 462.6 (128-1672.5) | **<0.001** |
| Type of pacemaker (dual-chamber) | 2.8 (1.5-5.5) | **0.002** | 2.6 (0.7-9.7) | 0.166 |
| Experience of the implanter (low) | 0.7 (0.3-1.6) | 0.418 | | |
| Experience of the implanter (medium) | 0.7 (0.4-1.4) | 0.303 | | |
| **Hematomas** | **$OR_{raw}$ (95% CI)** | **p** | **$OR_{adjusted}$ (95% CI)** | **p** |
| AA only or in combination (yes) | 1.7 (0.9-3) | 0.081 | 1.1 (0.6-2.1) | 0.746 |
| OAC+AA+BH therapy (yes) | 1.1 (0.6-2) | 0.686 | | |
| BH therapy only (yes) | 1 (0.5-2.1) | 0.976 | | |
| Type of pacemaker (dual-chamber) | 2.4 (1.3-4.4) | **0.003** | 2.3 (1.2-4.5) | **0.018** |
| Experience of the implanter (low) | 1.1 (0.5-2.3) | 0.746 | 1.2 (0.6-3) | 0.432 |
| Experience of the implanter (medium) | 1.8 (1-3.2) | **0.061** | 2.4 (1.2-4.6) | **0.010** |
| Duration in minutes | 1 (1-1.1) | **<0.001** | 1 (1-1) | **0.009** |
| Contusion (yes) | 3.8 (2.1-6.7) | **<0.001** | 4.1 (2.2-7.7) | **<0.001** |
| **Infections** | **$OR_{raw}$ (95% CI)** | **p** | **$OR_{adjusted}$ (95% CI)** | **p** |
| Weight (Kilos) | 1 (0.9-1) | 0.180 | 0.9 (0.9-1) | 0.091 |
| Duration in minutes | 1 (1-1.1) | 0.313 | | |
| Experience of the implanter (low) | 5.2 (0.5-58.7) | 0.181 | 4.5 (0.4-52) | 0.225 |
| Experience of the implanter (medium) | 5.1 (0.5-49.5) | 0.162 | 6.1 (0.6-62.7) | 0.128 |
| **Exitus** | **$OR_{raw}$ (95% CI)** | **p** | **$OR_{adjusted}$ (95% CI)** | **p** |
| Age (years) | 1 (1-1.1) | 0.261 | | |
| Sex (Female) | 0.4 (0.1-1.3) | 0.129 | 0.5 (0.2-1.6) | 0.232 |
| Comorbidity (Low) | 3 (0.7-14) | 0.155 | 2.5 (0.5-11.5) | 0.254 |
| Comorbidity (High) | 9.5 (2.8-32.1) | **<0.001** | 6.8 (2-23.4) | **0.002** |
| Experience of the implanter (low) | 0.6 (0.1-3.3) | 0.591 | | |

| | | |
|---|---|---|
| Experience of the implanter (medium) | 1.6 (0.5-4.8) | 0.449 |

AA: Anti-platelet Agents; BH: Bridging Heparin; 95% CI: 95% Confidence Interval; OAC: Oral Anticoagulation; OR: Odds Ratio.

## DISCUSSION

Overall, in our study there were more major complications (pneumothorax, lead dislodgement, and deaths) in patients on antithrombotic therapy, while minor complications (peripheral phlebitis, non-complicated hematomas and painful shoulder) were similar in both cohorts.

The incidence of pneumothorax (3.9%) was above the <2% standard recommended by certain scientific societies such as the Spanish Society of Intensive and Critical Medicine and Coronary Units.[25] This increase in the rate in our series could be explained by the lack of use of safety measures ("blind" puncture of the subclavian vein), such as support by imaging, or the lack of use of alternative veins and techniques, such as cephalic or axillary vein dissection. The use of guided imaging, recommended by the current guidelines on venous access[26] would be a safe measure against exposing patients to a higher risk, thus ensuring their safety.

There is an increase in complications, particularly hematomas, when antithrombotic therapy is administered in combination. These results are confirmed by those found in similar studies,[27] stating that the administration of the therapy in combination will increase the risk up by to 8 times. This claim could be explained by the disorder caused by discontinuation/re-initiation and the combination of different drugs in the coagulation cascade, causing a new bleeding that is not controlled during the intraoperative stage. Nevertheless, if anticoagulation is not active, bleeding can be better controlled, allowing local hemostatic measures to be taken.

It would be advisable to provide recommendations about those strategies that are currently demonstrating higher safety, such as maintaining oral anticoagulation during pacemaker implantation in patients with a high thrombotic risk.[2,27] This new strategy would lead us to an optimization of measures and care for the prevention of hemorrhagic complications (a careful evaluation of the wound before discharge, and informing patients and their relatives about warning signs), without an increase in the risk of thrombosis.[28]

Comorbidity, quantified through the Charlson Index, was associated with an increase in the incidence of mortality at 6 months of follow-up. Different research studies[29-31] have confirmed that patient comorbidity is a decisive factor for mortality after the implantation of a pacemaker, and that there is a very weak association with the implantation of these devices. In our series, there is a 5% incidence of mortality at 6 months, similar to that reported in the bibliography consulted, with follow-ups from 6 months to 1 year.[29,31] The explanation for this connection is that the patients with a higher comorbidity and basal frailty were those on antithrombotic therapy, and all the deaths occurred within this group. This suggests the opportunity for using predictor scales based on comorbidity, which might help to make complex decisions, such as the limitation of therapeutic efforts, or certain interventions, such as the indication for pacemakers.[32]

Contusions are associated with the overall presence of complications as well as larger hematomas. We have found no studies introducing this item of data in their analysis. In our series, the presence of

contusions could be explained by the link with antithrombotic therapy, the difficulty in central venous access, more tissue destroyed during the implantation of larger-sized pacemakers, the duration of the implantation procedure, and the medium and low experience of the professional conducting the implantation. When a contusion appears, its progression to a hematoma can be reduced by applying compression during an established period of time. Even though all patients received compression before leaving the operating room, this measure was not applied homogeneously to all of them, because patients were hospitalized in different ways. This could be due to the lack of knowledge of the nursing team in charge of this specific care recommendation, and its trust in the efficacy of this measure.

The experience of the person conducting the implantation, when medium and low, is a factor with clinical consequences, and it is associated with an increase in major complications, such as infection, similar to that reported in the bibliography reviewed.[33,34] This can be explained by a longer duration of the implantation procedure, lower skills in surgical techniques, and a longer time of prosthesis exposure, which increases the likelihood of contamination, and more hematomas due to more extensive handling of tissues. It would be interesting to develop training programs on the technical characteristics and procedures of current devices to reduce the rate of complications by improving the learning curve of younger professionals and the improvement of the whole team involved in the process. Special consideration must be given to those aspects that present additional associated costs, which might put at risk the safety of patient care, such as repeating procedures, with the risk of new complications and an increase in the hospital stay. However, the inexperience of operators was not associated with an increase in the incidence of mortality. This disagrees with the previous literature.[35-37] In this case, this disagreement is explained by most patients who died having had other diseases and a high cardiovascular risk as well as the percentage of cases operated by an inexperienced surgeon being lower in this group of patients.

The dual-chamber pacemaker was associated with the presence of hematomas, particularly in combination with antithrombotic therapy. These data concurred with previous studies,[16,38] where the size of the device was linked with the presence of hematomas and more cases of painful shoulder. This would be explained by more extensive destruction of tissue to create the generator pocket, and its larger size, which causes more pain and limits mobility, particularly in very thin patients. This criterion should be taken into account in order to select smaller devices.

Arm immobilization is a measure which has a confirmed efficacy: it prevents complications such as lead dislodgement, hematomas, and device dysfunction. But when it is prolonged, it is linked with the presence of painful shoulder. This complication is usually dismissed. However, it is disabling for the persons who experience it. Some studies[39,40] have reported higher rates of painful shoulder than ours. This is connected with the days of immobilization and the size of the devices.

Considering that there are not standardized discharge instructions, they should be made and the contents of these recommendations regarding arm immobilization ought to be personalized, based on the situation (unstable electrodes, tricuspid valve failure, or patients with cognitive impairment), in order to ensure the patients' safety and prevent other types of events. Therefore, for those patients who require a longer time of immobilization, a closer follow-up must be conducted, either by telephone or at outpatient units, developing a subsequent rehabilitation plan that will minimize the effects of this measure.

**Study limitations**

This is a single centre study, and its outcomes might not necessarily be generalizable regarding the number of complications, though not because of their causes. Due to the low number of patients assigned to some of the antithrombotic therapy sub-groups, this study lacks the power to examine certain associations, and this might explain the trend for certain links with more fatal outcomes, particularly in the multivariate analysis. Therefore, the results might not be conclusive. The level of experience of the Perioperative Nursing Team has not been included in the study, and so its impact on the final outcome is unknown. In addition, almost all the surgeries were carried out using subclavian vein access. If other pacemaker implantation techniques (such as axillary and/or brachial vein cut-downs) were used, the complication rates could be different.

Another limitation of the study is related to the reduced number of patients treated with NOACs but the study was carried out in 2014 when this treatment was not used as much as in recent years. Future research which includes more cases of NOACs will help to add more evidence to the literature about the complications in this setting.

In conclusion, in our study there were more major complications (pneumothorax, lead dislodgement, and deaths) in patients on antithrombotic therapy, while minor complications (peripheral phlebitis, non-complicated hematomas and painful shoulder) were similar in both cohorts. There were more deaths because of more comorbidities and not because of oral anticoagulation.

The main risk factors associated with complications are (1) the time of immobilization of the arm ipsilateral to the pacemaker implantation being higher than 24 hours and (2) contusions after the implantation. Therefore, oral anticoagulation and age were protective factors against the development of these complications. It seems necessary to propose an alternative therapy which avoids the combination of different kinds of antithrombotic treatments in order to undergo surgery without an interruption of anticoagulation therapy in patients with a high thrombotic risk.

Knowing procedure-related risk factors may identify patients with a particularly high risk of complications. This information should be taken into account in individual patient treatment, and when planning the implantation of more complex device types, in order to implement actions with a confirmed efficacy that would guarantee an improvement in patient safety.

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