

# Comparative Retrospective Study between Aspirin and Dabigatran in the Incidence of Thromboembolic Events in Hip and Knee Arthroplasty

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## ABSTRACT

**Objective:** To analyze the incidence of out-of-hospital thromboembolic events after a primary total knee or hip replacement in the first 90 postoperative days, using acetylsalicylic acid or dabigatran as thromboprophylaxis. As a secondary objective, to evaluate the cost of antiplatelet therapy compared to anticoagulants. **Materials and Methods:** A retrospective observational study was carried out in the postoperative period of primary total hip and knee replacement on the incidence of out-of-hospital thromboembolic events during the first 90 postoperative days in two groups of patients. Acetylsalicylic acid (325 mg per day) or dabigatran (150 to 220 mg per day) were used as thromboprophylaxis for 35 days. **Results:** The series consisted of 224 patients aged 68.5 years (38-95 years), 44.2% male. 51.3% corresponded to total hip replacement. 64.3% continued thromboprophylaxis with dabigatran and 35.7% with aspirin. The total incidence of thromboembolic events was 1.3%. In the patients who received dabigatran it was 1.4% and in those who received aspirin, 1.3% ( $p = 0.9$ ). The cost of thromboprophylaxis with aspirin 325 mg was US \$ 3.6 while with dabigatran it was US \$ 130 or \$ 175, according to its presentation, 75 and 110 mg. **Conclusion:** Aspirin as thromboprophylaxis after total hip or knee replacement in individuals at low risk of thromboembolic events has shown similar clinical outcomes as dabigatran, and a multimodal protocol based on the use of aspirin can be recommended. This improves patient adherence to antithrombotic therapy, due to the low cost of aspirin prophylaxis.

**Keywords:** Aspirin; acetylsalicylic acid; dabigatran; thromboprophylaxis; thromboembolic event; hip arthroplasty; knee arthroplasty.  
**Level of Evidence:** III

## Estudio retrospectivo comparativo entre aspirina y dabigatrán en la incidencia de efectos tromboembólicos en pacientes con artroplastia de cadera y rodilla

## RESUMEN

**Objetivo:** Analizar la incidencia de eventos tromboembólicos extrahospitalarios luego de un reemplazo total de rodilla o cadera primario en los primeros 90 días posoperatorios, utilizando como tromboprofilaxis ácido acetilsalicílico o dabigatrán. El objetivo secundario fue evaluar el costo de la terapia antiagregante y de la anticoagulante. **Materiales y Métodos:** Se realizó un estudio observacional retrospectivo en el posoperatorio de reemplazos totales de cadera y rodilla primarios sobre la incidencia de eventos tromboembólicos extrahospitalarios, durante los primeros 90 días posteriores a la cirugía, en dos grupos. Se administró ácido acetilsalicílico (325 mg/día) o dabigatrán (150-220 mg/día) por 35 días. **Resultados:** La serie incluyó a 224 pacientes (media de la edad 68.5 años), el 44,2% eran hombres. El 51,3% era un reemplazo total de cadera. El 64,3% continuó la tromboprofilaxis con dabigatrán y el 35,7%, con aspirina. La incidencia total de eventos tromboembólicos fue del 1,3%; 1,4% con dabigatrán y 1,3% con aspirina ( $p = 0,9$ ). El costo de la tromboprofilaxis fue de USD 3,6 con aspirina 325 mg y USD 130 o 175 con dabigatrán, según la presentación de 75 y 110 mg. **Conclusiones:** La aspirina como tromboprofilaxis tras un reemplazo total de cadera o rodilla en pacientes con bajo riesgo de sufrir eventos tromboembólicos ha logrado resultados clínicos similares a los del dabigatrán. Se puede recomendar un protocolo multimodal basado en el uso de aspirina. Este mejora el cumplimiento de la terapia antitrombótica por parte de los pacientes, debido al bajo costo de la profilaxis con aspirina.

**Palabras clave:** Aspirina; ácido acetilsalicílico; dabigatrán tromboprofilaxis; evento tromboembólico; artroplastia de cadera; artroplastia de rodilla.

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## INTRODUCTION

Although total hip and knee arthroplasties are common and safe procedures, patients who undergo these procedures are considered to be at high risk for thromboembolic complications, such as pulmonary embolism (PE) and deep vein thrombosis (DVT).<sup>1,2</sup> According to the literature, without prophylaxis, the postoperative incidence of these complications ranges between 15% and 30% for DVT, and between 1.7% and 7.8% for PE.<sup>1-3</sup> Thromboprophylaxis with anticoagulant drugs after these procedures has decreased the rate of thromboembolic events (TEEs) by 0.6-2%, according to different reports.<sup>3-5</sup>

To this end, there are multiple pharmacological treatments, including factor Xa inhibitors (rivaroxaban, apixaban), thrombin inhibitors such as dabigatran, low molecular weight heparin, and vitamin K antagonists (warfarin).<sup>6</sup> Likewise, the administration of antiplatelet drugs, such as acetylsalicylic acid (ASA) has largely increased in recent years due to the publication of clinical trials and meta-analyses that suggest that this agent has similar effectiveness rates as anticoagulants for the prevention of DVT and PE.<sup>1,3-5,7,8</sup>

In 2009, ASA was incorporated as a recommendation in antithrombotic prophylaxis for postoperative total hip replacement (THR) or knee replacement (TKR) by the guidelines of the *American Academy of Orthopedic Surgeons* (AAOS).<sup>9</sup> Later, in 2012, the *American College of Chest Physicians* (ACCP) guide listed this drug together with other thromboprophylactic agents (low molecular weight heparin, dabigatran, rivaroxaban, among others) with a grade 1B recommendation for its use as TEE prophylaxis.<sup>10</sup> Since then, the percentage of surgeons who decide to use it as the only drug for thromboprophylaxis has increased significantly, with similar rates of TEE as with the administration of anticoagulant drugs.<sup>4</sup>

On the other hand, ASA is presented as a drug with a high safety profile, easy to administer, well-tolerated, and accessible both due to its costs and its availability, with analgesic, anti-inflammatory and antiplatelet power, which plays a central role in the prevention of cardiovascular diseases.<sup>1,2,11,12</sup> This, associated with the favorable results as antithrombotic prophylaxis, makes it a safe and attractive alternative for the medical community. Likewise, numerous studies have demonstrated the cardioprotective effect of ASA, which would add a benefit to its use as an antithrombotic.<sup>12</sup>

In our Center, oral (dabigatran) or subcutaneous (enoxaparin) anticoagulant agents are usually prescribed at hospital discharge, for a minimum of 35 days.<sup>13</sup> We recently began to use ASA as a monodrug in the out-of-hospital prophylaxis of TEE during the postoperative period of joint replacement surgeries, after having observed lower compliance with the pharmacological treatment with the usual anticoagulant agents due to the higher costs they represent for patients and potential consequences that this entails.

The main objective of this study was to retrospectively analyze the incidence of out-of-hospital DVT and PE in two groups of patients: group I (ASA) and group II (dabigatran) after a primary TKR or THR, in the first 90 days after surgery. As secondary objectives, we sought to determine the rates of bleeding and reoperation complications associated with the use of these drugs and to analyze the cost of antiplatelet therapy (group I) and anticoagulant therapy (group II).

We hypothesize that the incidence of TEE in our Center is similar with ASA or with dabigatran in patients with a low risk of suffering a TEE, taking into account that the economic cost of prophylaxis with ASA is lower than that of dabigatran, which would improve patient compliance.

## MATERIALS AND METHODS

Between May 1, 2019, and April 20, 2020, a retrospective study was carried out to evaluate the incidence of out-of-hospital TEE during the first 90 days after a scheduled unilateral primary THR or TKR, which included operated patients, consecutively, who were divided into two groups. Those in group I were prescribed ASA 325 mg/day as thromboprophylaxis and those in group II, dabigatran 150-220 mg/day depending on age and creatinine clearance, until completing 35 days of prophylaxis for both THR and TKR.

One of the surgeons on the team decided to prescribe ASA to all his patients who met the inclusion criteria and the rest of the surgeons continued with dabigatran as prophylactic medication for their patients.

The inclusion criteria were: age >18 years, primary hip or knee arthroplasty as a treatment for osteoarthritis, out-of-hospital prophylaxis with ASA or dabigatran up to 35 days postoperatively, and a minimum follow-up of 90 days.

Exclusion criteria were: arthroplasties as a treatment for fracture and revision arthroplasty, conditions that contraindicate the use of ASA or dabigatran, previous anticoagulation, history of neoplasia or DVT/PE, body mass index >35, bilateral and simultaneous arthroplasties, a thrombotic event during hospital stay (since during this period, patients receive prophylaxis with subcutaneous enoxaparin 0.4 cc/day), associated intraoperative fractures, hospital stay >6 days, new surgery not related to the study intervention that required readmission during follow-up, and loss of follow-up.

The patients were admitted the same day as the scheduled surgery and were evaluated daily together with the professionals of the Internal Medicine Service.

The antithrombotic prophylactic measures adopted were:

- Subcutaneous Enoxaparin 0.4 cc/day during hospitalization, changing to oral administration on the day of hospital discharge.
- Compression bandage on both lower limbs placed in the immediate postoperative period. Hospital discharge with daytime compression stockings.
- Early mobilization in the immediate postoperative period and walking at 12-24 h with a walker or Canadian crutches according to tolerance.

After hospital discharge, the patients continued oral antithrombotic prophylaxis, in two different schedules. In group I, ASA 325 mg was used in a single daily dose. In group II, dabigatran was prescribed in doses adjusted according to age (<75 years, 220 mg/day and >75 years, 150 mg/day) and creatinine clearance. Antithrombotic prophylactic treatment continued in this way at home until day 35 after surgery.

Serial clinical and radiographic controls were carried out 10 days, 3, 6, and 12 weeks after surgery, in order to evaluate the evolution and detect complications.

Complications that occurred during the first 90 days after the operation, including symptomatic TEE (DVT and PE), bleeding complications, surgical wound complications, acute prosthesis infection, and death were recorded.

Given the clinical suspicion of DVT, it was confirmed or ruled out by venous echo-Doppler at the time of consultation. If PE was suspected, a pulmonary computed tomography angiography was performed. In both situations, if the result was positive, the corresponding anticoagulant treatment was started. If DVT or PE were ruled out, the ongoing prophylactic treatment was continued.

Acute infection of the prosthesis was confirmed taking into account clinical and laboratory parameters, according to the recommendations of the *Musculoskeletal Infection Society*.

The cost of antithrombotic prophylactic treatment until completing 35 postoperative days for both groups was calculated in United States dollars (USD), according to the official quote of the Banco de la Nación Argentina, on April 15, 2020, at 66.75 Argentine pesos.

This study was approved by the Bioethics Committee of our Center.

## Statistical analysis

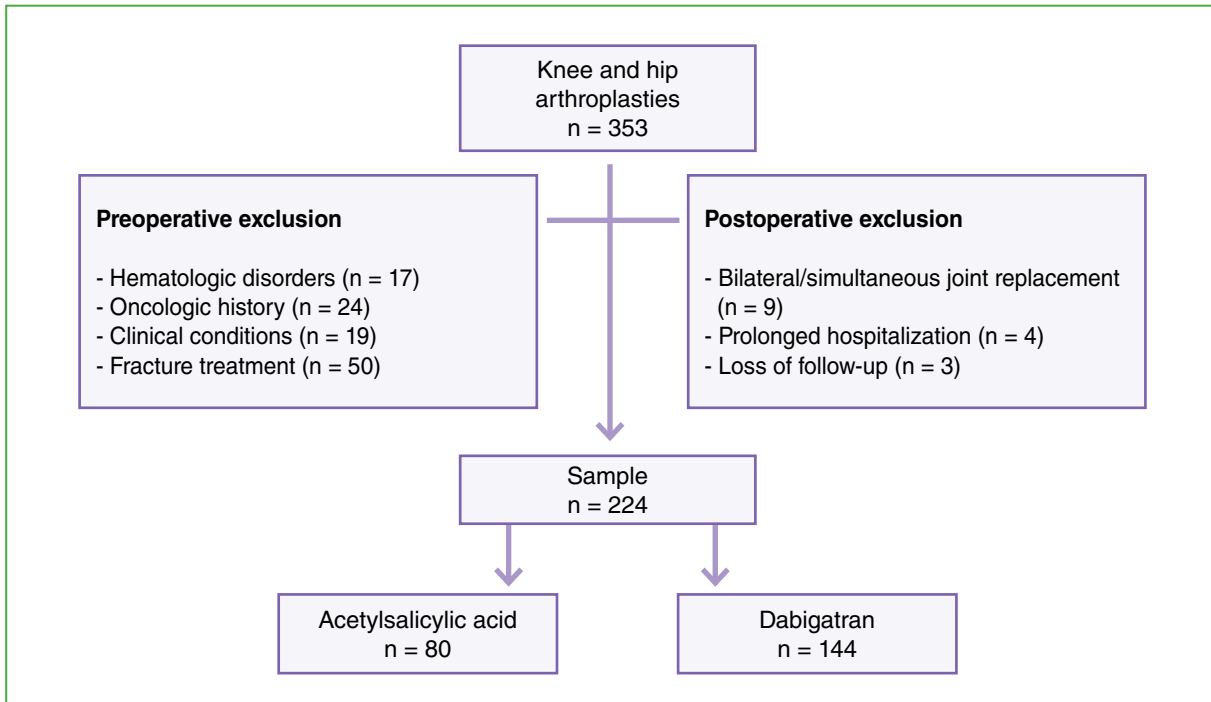
Continuous variables were described as average and standard deviation; and qualitative variables, as 95% confidence interval and percentage. The two analyzed groups were compared using a t-test for quantitative variables and Fisher's test for qualitative variables. A difference <0.05 was considered statistically significant. The Graph Pad Prism 8.0 program was used.

## FINDINGS

Between May 1, 2019, and April 20, 2020, 353 primary hip and knee arthroplasties were performed. 126 patients were excluded because they did not meet the inclusion criteria; some of them did not meet more than one criterion (Figure 1).

The series consisted of 224 patients, with an average age of 68.5 years (range 38-95). One hundred and twenty-five (55.8%) were women and 99 (44.2%) were men, with a body mass index of 28.1 (range 17-35). The procedures were 115 (51.3%) THR and 109 TKR (48.7%) and the average length of stay was 3.2 days (range 2-6).

After discharge, 80 patients continued oral thromboprophylaxis with ASA (35.7%) and 144 with dabigatran (64.3%) (Table 1). No statistically significant differences were observed in the demographic characteristics of both groups (Table 2).



**Figure 1.** Diagram of patient exclusion. Some patients had more than one exclusion criterion.

**Table 1.** Demographic characteristics of the series.

Sample: 224	
Age	68.5 (range 38-95)
Body mass index	28.1 (range 17-35)
Follow-up	3 months
Days of hospitalization	3.2 days (range 2-6)
Sex	Male: 99 (44.2%) Female: 125 (55.8%)
Surgical procedure	
Total hip replacement	115 (51.3%)
Total knee replacement	109 (48.7%)
Antithrombotic prophylaxis	
Acetylsalicylic acid	80 (35.7%)
Dabigatran	114 (64.3%)

**Table 2.** Demographic characteristics according to antithrombotic prophylaxis.

Sample: 224	Acetylsalicylic acid (n = 80)	Dabigatran (n = 144)	p
Age (years)	69.7 ± 8.8	67.8 ± 10.4	0.2
Sex	Male = 33 Female = 47	Male = 66 Female = 78	0.5
Body mass index	28 ± 3.9	28 ± 3.8	0.9
Days of hospitalization	3.2 ± 0.5	3.3 ± 0.6	0.7
Total knee / hip replacement	44 (55%) / 36 (45%)	66 (45%) / 78 (55%)	0.6

Overall, the out-of-hospital complication rate was 8% (n = 18); the total incidence of symptomatic TEE was 1.3%. Three patients suffered DVT confirmed by venous echo-Doppler, all of them men and >70 years.

According to the type of procedure, the incidence of TEE was 1.7% for THR (2 cases) and 0.9% for TKR (1 case), without statistical significance (p 0.8).

If we analyze the groups separately, according to the thromboprophylactic treatment, the incidence of DVT was 1.3% for group I (1 case) and 1.4% for group II (2 cases).

The cases of DVT in patients treated with dabigatran occurred 16 and 30 days after surgery, that is, while the patient was still receiving antithrombotic prophylaxis. In the case treated with ASA, the TEE took place 60 days after the operation, after 35 days of thromboprophylaxis had ended. No statistically significant differences were observed in the incidence of TEE between both groups (p = 0.9).

Another seven patients presented with symptoms compatible with DVT that was later ruled out by venous echo-Doppler, so they continued the previous thromboprophylaxis scheme (4 with dabigatran and 3 with ASA).

Regarding infectious complications and mortality rate, if we compare both groups, the incidence of superficial infection of the surgical wound was 1.3% in the ASA group and 3.5% in the dabigatran group (p = 0.3) that was treated with oral antibiotics. Despite not being statistically significant, it was statistically higher in group II.

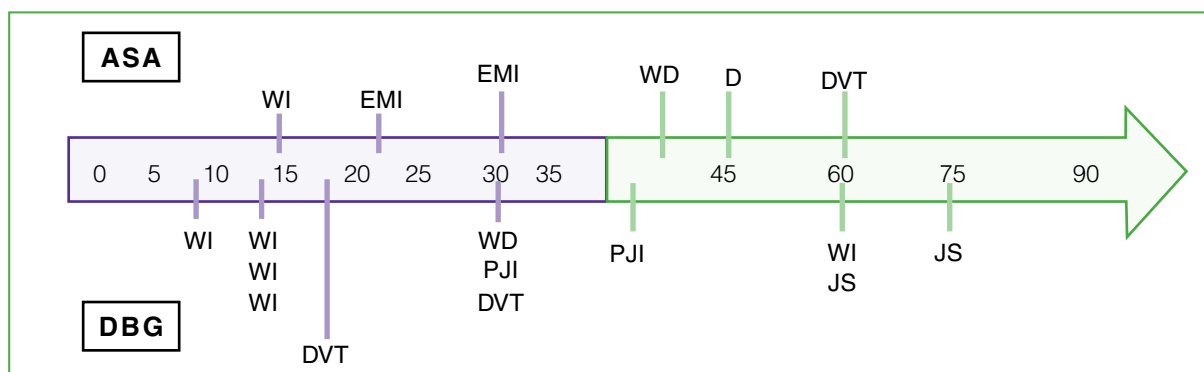
Two acute infections of the prosthesis (0.9%) treated with surgical debridement and with a good evolution were diagnosed in group II, and none in group I (p = 0.9), which was not statistically significant.

In group I, sudden death (0.4%) of an undetermined cause was recorded 45 days after surgery, once thromboprophylaxis with ASA was completed (p = 0.7).

No major bleeding complications were observed. There were no statistically significant differences in the incidence of the rest of the complications between both groups (Table 3 and Figure 2).

**Table 3.** Postoperative Complications According to Antithrombotic Prophylaxis

Sample: 224	Acetylsalicylic acid (n = 80)	Dabigatran (n = 144)	p
Thromboembolic event	1 (1.3%)	2 (1.4%)	0.9
Superficial infection	1 (1.3%)	5 (3.5%)	0.3
Prosthesis infection	0	2 (1.4%)	0.7
Wound dehiscence	1 (1.3%)	1 (0.7%)	0.7
Joint stiffness	0	2 (1.4%)	0.9
Injury to the extensor apparatus	1 (1.3%)	0	0.7
Death	1 (1.25%)	0	0.3
<b>Total events</b>	<b>6 (7.5%)</b>	<b>12 (8.3%)</b>	<b>0.9</b>



**Figure 2.** Chronological distribution of complications (in days)

ASA = acetylsalicylic acid, DBG = dabigatran, WI = wound infection, EMI = extensor mechanism injury, DVT = deep vein thrombosis, WD = wound dehiscence, PJI = prosthetic joint infection, JS = joint stiffness, D = death.

Regarding the accessibility of the treatment, the cost of thromboprophylaxis with ASA (30 tablets with enteric coating 325 mg) for 31 days was USD 3.6 while, with dabigatran, it was USD 130 or 175, depending on its presentation, of 75 and 110 mg, respectively (BNA quotation on 4/15/2020 at 66.75 Argentine pesos).

## DISCUSSION

ASA was incorporated as a recommendation in antithrombotic prophylaxis for the postoperative period of THR and TKR by the guidelines of the *American Academy of Orthopedic Surgeons*<sup>9</sup> and later, by the guidelines of the *American College of Chest Physicians* for its use as TEE prophylaxis.<sup>10</sup> Since then, the percentage of surgeons who decide to use it as the sole drug for thromboprophylaxis has increased significantly.<sup>4</sup>

In 2018, the European guideline of the *National Institute of Health and Care Excellence* (NICE) incorporated ASA as a recommendation in antithrombotic prophylaxis after total knee arthroplasty and as extended prophylaxis in total hip arthroplasty.<sup>14,15</sup> However, there is no current consensus regarding the ideal dose and its time of use.<sup>1,7,10,16</sup>

In our study, we decided to administer 325 mg as a daily dose of ASA, because authors such as Parvizi et al.<sup>7</sup> and Feldstein et al.,<sup>16</sup> among others, found no significant differences in the prevention of PE with the administration of ASA at low doses (81 mg, twice/day) or high doses (325 mg, twice/day) for four weeks, or in the incidence of gastrointestinal events, infection of the prosthesis or death.<sup>3</sup> We prefer that dose to reduce the risk of bruising and bleeding from the wound. This decision is consistent with our findings, since we have not recorded bleeding complications or bruising with ASA at a dose of 325 mg per day.

In 2000, the results of a double-blind, randomized study, the Pulmonary Embolism Prevention (PEP) trial, were published<sup>11</sup>. In this study, the incidence of TEE was evaluated in more than 17,000 patients treated with ASA or placebo for hip fracture or elective knee or hip arthroplasty and it was concluded that ASA reduces the risk of PE and DVT by at least 30% in the first 35 days after the intervention.

In our study, the incidence of TEE was similar among patients who received ASA or dabigatran. The overall incidence of symptomatic TEE in general, during the first 90 postoperative days was 1.3%, and it was always DVT. The incidence of this complication in the group of patients treated with ASA and in those who received dabigatran was not statistically significant. The same was not verified between both procedures, THR and TKR, since the same agents are used as thromboprophylaxis for both procedures, as reported in different publications that evaluate them equally.<sup>3-5,8,16</sup>

It is worth noting that in our study, DVTs in the dabigatran group occurred at 16 and 30 days after surgery, that is, during the thromboprophylaxis period, while, in the ASA group, they occurred at 60 days, 25 days after the end of pharmacoprophylaxis.

In a multicenter study on the incidence of TEE, Bozic et al.<sup>17</sup> evaluated 93,840 patients undergoing TKR who received ASA, warfarin, or low molecular weight heparin, and the TEE rates were 2.3%; 4%, and 3.1%, respectively. On the other hand, in a prospective study of 11,459 patients undergoing TKR, THR or unicompartmental knee replacement, Ogonda et al.<sup>8</sup> verified the safety of ASA as a thromboprophylactic agent, since it did not increase the risk of death, PE, or DVT in low risk patients; the total incidence was 0.3% for DVT and 0.6% for PE in THR, 1.5% in TKR, and 1.2% in unicompartmental knee replacement.

In a systematic review of 39 articles, Vincent et al.<sup>3</sup> evaluated the results in relation to TEE of 69,551 patients undergoing THR and TKR who received ASA as antithrombotic pharmacoprophylaxis, and obtained a PE rate of 0.6% and DVT rate of 1.2%, data comparable to those obtained in our series.

McHale et al.<sup>5</sup> retrospectively compared the incidence of TEE in two groups of patients, one treated with dabigatran 220 mg/day, for 28 days for THR and 10 days for TKR, versus another in which ASA 150 mg/day was administered during six weeks for both THR and TKR. They did not report TEEs in the group of patients with ASA, while the incidence of DVT was 2.2% and 1.6% for THR and TKR, respectively, in the group with dabigatran.

Regarding complications from infection, five of six cases of superficial wound infections and the two cases of acute infection of the prosthesis occurred in the dabigatran group. However, this difference was not statistically significant between the two groups. There is evidence that persistent drainage of the surgical wound is associated with a longer hospital stay and risk of infection of the prosthesis.<sup>1,7,18,19</sup>

Parvizi et al.<sup>18</sup> found a significant relationship between excess anticoagulants and wound complications in patients who subsequently had a prosthesis infection. On the other hand, in their prospective study, Aquilina et al.<sup>19</sup> reported that the average drainage time through the surgical wound after THR and TKR was 6.4 days for the group with dabigatran and 3.2 days for the group that received ASA, this was not verified in our study. Other studies associate commonly prescribed anticoagulant agents with higher rates of bleeding complications and persistent discharge from the surgical wound related to ASA,<sup>20,21</sup> as mentioned before.

In our series, a sudden death occurred six weeks after THR (a 72-year-old man). The risk of death after this procedure varies according to the time elapsed since the surgery; it is higher in the first 30 days and returns to the preoperative baseline risk after 90 days.<sup>22</sup> Strong evidence is available to suggest that advanced age and male sex predispose to premature death after THR.<sup>22,23</sup> Likewise, it is accepted that cardiovascular diseases, such as acute myocardial infarction or heart failure, are responsible for more than 50% of deaths, followed by cerebrovascular disease and PE.<sup>22,23</sup> Bayley et al.<sup>24</sup> reported that 11.7-17.1% of deaths within 90 days after a THR are due to PE. However, sometimes the true cause of death cannot be identified and numerous studies suggest that, in these cases, it could correspond to PE.<sup>1,7</sup> In our case, it was not possible to determine the reason for the death of this patient.

Our patients remained hospitalized for an average of 3.2 days, which implies that the administration of ASA or dabigatran lasted for an average of 31 days, until a total of 35 days of prophylaxis were completed.<sup>16</sup> It is important to highlight the multimodal approach to antithrombotic prophylaxis used, taking into account the administration of enoxaparin subcutaneously during hospitalization, oral pharmacoprophylaxis at discharge, early mobilization protocols, and the use of mechanical compression in the lower limbs.<sup>1</sup>

Regarding the cost of oral antithrombotic prophylaxis up to 35 days after surgery, it was USD 3.6 with ASA and USD 130 or 175 with dabigatran, depending on the presentation (75 and 110 mg, respectively). PE and DVT prophylaxis with ASA after a THR or TKR can be presented as an easy to obtain, inexpensive alternative and just as effective as dabigatran, allowing greater patient adherence to treatment.<sup>1,2,16,17,25</sup>

The weaknesses of this study are the small number of patients that make up the sample and that it was not double-blind. Some patients met more than one exclusion criterion. It is also worth mentioning that echo-Doppler studies were performed only in symptomatic patients, without considering subclinical DVT. Furthermore, the two groups were treated by different surgeons.

However, its strengths include that only three patients were excluded due to loss to follow-up (Figure 1). Furthermore, all were operated on using the same approach, the same types of implants, and the same anesthetic and rehabilitation protocol. This study is unprecedented in our country.

## CONCLUSIONS

The administration of ASA as thromboprophylaxis after THR or TKR to patients at low risk of TEE has achieved clinical outcomes similar to those of dabigatran. A multimodal protocol based on the use of ASA can be recommended. This protocol may improve patient compliance with antithrombotic therapy, due to the low cost of prophylaxis with ASA when compared to dabigatran.

There remains a need for a prospective, randomized and double-blind study to reinforce these findings.

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Conflict of interests: The authors declare they do not have any conflict of interests.

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