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HEMORRHAGIC EVENTS WITH USE OF RIVAROXABAN AND ASPIRIN IN VASCULAR DISEASES: A LITERATURE REVIEW

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Abstract: Cardiovascular disease is the leading cause of morbidity and mortality in adults worldwide. Antithrombotic agents consisting of antiplatelet agents and anticoagulants are drugs commonly prescribed in clinical practice for the secondary prevention of complications in cardiovascular disease. These drugs act on different pathways in the coagulation cascade, via COX-1, via P2Y12 and the thrombin pathway. Aspirin and clopidogrel act on the platelet pathway, warfarin and new oral anticoagulants such as rivaroxaban act on the thrombin pathway. The aim of this review was to analyze clinically significant bleeding episodes with the use of rivaroxaban, aspirin and clopidogrel, alone or in combination, in vascular pathologies. A search for papers was performed on the PubMed platform and VHL-regional and a total of 25 scientific articles were included after applying the inclusion and exclusion criteria. Through the analyzed studies, it was observed that the drug regimen that presented the most hemorrhagic outcome in relation to the number of patients and total number of events was the association of warfarin with aspirin and clopidogrel (69.3%). In conclusion, warfarin showed a higher risk of bleeding and its use requires control with INR. Aspirin is associated with increased intracranial bleeding, but it is highly effective in secondary prevention, inexpensive and widely used in association with anticoagulants. Rivaroxaban at a dose of 2.5 mg twice daily associated with aspirin 100 mg/day has shown a reduction in recurrent ischemic events and less amputation in patients with peripheral arterial disease, with a high number of major bleeding with few fatal hemorrhagic events. Patients at higher risk of bleeding were those with multivessel diseases (coronary, carotid and peripheral) and/or with a greater number of associated comorbidities (SAH, DM, dyslipidemia, sedentary lifestyle). Those who had genitourinary or gastrointestinal bleeding

were found to have previous neoplasms. The use of pantoprazole for the prevention of gastrointestinal bleeding was not significant among those who did not use it, but in patients with high risk of bleeding and associated comorbidities, its use is indicated, even with a higher risk of intestinal infections. In the studies, the use of rivaroxaban alone at a dose of 10 mg/day did not result in a lower risk of thrombotic events, but a significantly higher risk of bleeding. The use of double-way blockade is associated with lower thrombotic outcomes and mortality, but with a high number of major bleedings.
Keywords: Rivaroxaban, aspirin, bleeding events, bleeding, cardiovascular.

INTRODUCTION

Cardiovascular disease is the leading cause of adult morbidity and mortality in Western nations. In recent decades, numerous researches have been conducted in the field of secondary prevention, in order to reduce recurrent cardiovascular events (PARASCANDOLO, ELIOT; EISEN, ALON., 2020). Antithrombotic agents, which consist of antiplatelet and anticoagulant medications, are some of the most commonly prescribed medications. They are currently used by millions of people to prevent thrombotic complications in a wide variety of cardiovascular conditions (BARNES, GEOFFREY, 2020; BENJAMIN et al. 2019). There are currently three main pathways that amplify platelet activation, including the COX-1 pathway, the ADP-P2Y12 pathway and the thrombin pathway (GURBEL, PAUL et al., 2019).

Aspirin therapy has been used for decades to prevent and treat cardiovascular disease, including myocardial infarction and ischemic stroke (SHAH et al., 2019). According to Levine et al. (2011, 2016), aspirin is often combined with a P2Y12 receptor antagonist (clopidogrel, prasugrel, or ticagrelor) for dual antiplatelet therapy. Aspirin monotherapy or dual antiplatelet therapy can also be used to prevent major adverse events in patients with vascular diseases (GERHAND-HERMAN et al., 2017). Although the most feared bleeding complications is intracranial bleeding, this is a rare occurrence of aspirin monotherapy, the main complication being gastrointestinal bleeding (VADUGANATHAN, M et al., 2016; VARDI, M et al., 2015; BHATT, DL et al., 2010).

Clopidogrel is the most widely prescribed oral antiplatelet inhibitor of the P2Y12 receptor, a prodrug that requires cytochrome P450 enzymes for biotransformation into its active metabolite (PEREIRA, NAVEEN L et al., 2020; PRICE, MATTHEW et al., 2012; ANGIOLILLO, DOMINICK et al., 2006). It blocks platelet aggregation via the P2Y12 receptor pathway, a mechanism that is synergistic with aspirin in platelet aggregation assays. The combination of the two drugs has been more effective than aspirin alone in reducing the risk of ischemic events in patients with acute coronary syndromes (JOHNSTON, CLAIBORNE S et al., 2018; BOWRY AD; BROOKHART MA; CHOUDHRY NK, 2008; WANG, YONGJUN et al., 2013) Clopidogrel is a thienopyridine that has clinical indication, as part of dual antiplatelet therapy with aspirin, for use in patients with acute coronary syndrome, and is also indicated for use as monotherapy in patients with peripheral arterial disease stable. Its efficacy is limited by its pharmacology, which is characterized by the variable transformation of the prodrug into the active metabolite, leading to inconsistent platelet inhibition and limited clinical efficacy in some patients (PATEL, MANESH R et al., 2015; YUSUF S et al., 2001; GURBEL, PAUL A et al., 2009).

Warfarin inhibits thrombin generation, its mechanism acts to reduce the functional

levels of vitamin K-dependent coagulation factors, therefore it affects all phases of thrombin generation equally. (COHEN, HANNAH et al., 2016; KUBITZA D et al., 2005; PERZBORN E et al., 2005). It is highly effective in anticoagulation, but in clinical practice it is challenged by its variable dose response, need for frequent monitoring and associated risk of bleeding (HYLEK, ELAINE M et al., 2014). It was identified as the drug most frequently implicated in medication-related adverse events that lead to emergency hospital admission (BUDNITE, DANIEL S et al., 2011).

Due to increased bleeding and the complicated management of vitamin K antagonists, new anticoagulants, non-vitamin K antagonists, direct oral anticoagulants, including dabigatran, apixaban, rivaroxaban and darexaban, which have more favorable pharmacokinetics and pharmacodynamics, have been developed, as well as greater safety (RUBBOLI, ANDREA et al., 2013; AGNELLI, GIANCARLO; BECATTINI, CECILIA, 2009; IMBERTI, DAVIDE; DALL ASTA, CHIARA; PIERFRANCESCHI, GIORGIO, MATTEO; 2009). During the last 10 years, four direct oral anticoagulants have become available to prevent embolic events: dabigatran, rivaroxaban, apixaban and edoxaban. In August 2011, dabigatran was the first direct oral anticoagulant approved in Brazil for stroke prevention, followed by rivaroxaban four months later (FERREIRA, MUNIZ, ROBERTO; PINHEIRO, DA CAPELA, ISIS; DA ROCHA, FLEURY, ROQUETTE, JOÃO, 2020). The combination of anticoagulant warfarin and aspirin reduces cardiovascular events, but at the same time significantly increases the risk of bleeding and the blood concentration of warfarin fluctuates a lot, which requires regular monitoring. Non-vitamin K antagonist oral anticoagulants, such as rivaroxaban, have certain advantages in the efficacy and safety of a variety of high-risk thrombotic diseases compared to warfarin and other vitamin K antagonists (YAN et al., 2021). According to Squizzato et al. (2009), with the new oral anticoagulants, no laboratory monitoring is needed, with a remarkable improvement in the management of long-term anticoagulant treatment and administration without monitoring results in better patient compliance.

More attention has been focused on the efficacy and safety of dual-path inhibition strategies that combine antiplatelet agents and direct oral anticoagulants to prevent cardiovascular events. Direct oral anticoagulants inhibit the activity of the thrombin pathway that amplifies platelet activation through inhibition of thrombin generation, targeting factor Xa (GURBEL, PAUL A; TANTRY, UDAYA S, 2010; CHEN, CAN et al., 2021). An intensification of antithrombotic therapy is naturally associated with an increased risk of bleeding (OHMAN, MAGNUS E et al., 2017).

Research is ongoing into optimal dosing frequency (once versus twice daily), potentially safer gastrointestinal delivery, and possibly more effective formulations in terms of platelet inhibition to try to reduce bleeding complications that are a risk with all antithrombotic therapies (BHATT, DEEPAK L; JR, OLLACK, CHARLES V; 2020).

The aim of the study was to analyze the different episodes of clinically significant bleeding, major, minor, intracranial or hospital-requiring bleeding, with the use of rivaroxaban, aspirin and PYD12 inhibitor, alone or in combination, in vascular pathologies.

METHOD

This is an integrative, qualitative, retrospective and cross-sectional literature review. The databases used were the National

Library of Medicine (PubMed) and the Virtual Health Library (regional VHL). The search was performed considering the descriptors in English, "rivaroxaban", "aspirin" and "cardiovascular", using the Boolean operator "AND". The study included articles published in the last 10 years, comprising the period, beginning of 2011 to August 2021, open access studies, such as randomized clinical trials, sub-studies of clinical trials, studies with bleeding outcomes that refer to vascular diseases and/ or cardiovascular. Articles outside the studied topic and studies that did not address hemorrhagic events in their context were excluded. Language filter was not used, in order to expand the searches.

RESULTS

The search resulted in a total of 535 jobs. 301 articles were found in the PubMed database and 234 articles in the regional VHL database. After applying the inclusion and exclusion criteria, 17 articles were selected in the PubMed database and 21 articles in the regional VHL database, and 13 articles were removed from the regional VHL database because they were duplicated between the platforms.

Of the 25 studies, 3 are related to peripheral arterial disease; 2 with peripheral arterial disease treated surgically, with lower limb revascularization; 4 are related to patients with two vascular pathologies, peripheral arterial disease and coronary artery disease; 1 study related to patients with two peripheral vascular pathologies, arterial disease in the lower limbs and carotid disease; 3 related to clinically treated coronary artery disease; 5 studies related to invasive and vascular surgical procedures;; 2 with atrial fibrillation under clinical treatment and 1 study referring to patients with diabetes mellitus with peripheral arterial disease and coronary artery disease.

As for the types of bleeding events covered in the studies, there are: major or severe bleeding, small or light bleeding, fatal bleeding, intracranial, in a critical organ, clinically non-relevant bleeding, drop in hemoglobin, bleeding and hospitalization, multiple bleeding, bleeding in the surgical site, in gastrointestinal tract, urinary and bleeding only.

As shown in table 1, the medications used in the studies were rivaroxaban, aspirin, clopidogrel, ticagrelor and warfarin.

Number of studies	Medications used
15	Rivaroxaban and aspirin
5	Rivaroxaban, aspirin and clopidogrel
1	Rivaroxaban, aspirin, clopidogrel and ticagrelor
2	Rivaroxaban, aspirin, clopidogrel and warfarin
2	Rivaroxaban and warfarin

Table 1. Number of studies and medications covered.

Source: author (2021).

Of the 25 studies, 9 used the association of a factor Xa inhibitory anticoagulant with platelet antiaggregation versus a platelet antiaggregant alone, 5 used the association of a factor Xa inhibitory anticoagulant with dual platelet antiaggregation versus dual antiaggregation, 5 studies used the association of anticoagulation with 1 study used the association of factor Xa inhibitor anticoagulant with antiaggregant versus anticoagulant factor Xa inhibitor associated with dual antiaggregation versus vitamin K inhibitor anticoagulant associated with dual antiplatelet therapy, 1 study used or factor Xa inhibitor anticoagulation alone compared to a platelet antiaggregant alone and 2 studies used a factor Xa inhibitor anticoagulant alone compared to a vitamin K inhibitory anticoagulant alone.

Of the drug regimens used, rivaroxaban associated with aspirin had more bleeding than aspirin alone, the association of rivaroxaban

with aspirin and clopidogrel bled more than the association of aspirin with clopidogrel, rivaroxaban associated with aspirin had more bleeding compared to rivaroxaban and aspirin alone, in the scheme that used ticagrelor plus aspirin compared to rivaroxaban plus aspirin plus clopidogrel and aspirin plus clopidogrel, the number of bleedings were equal; rivaroxaban plus aspirin had more bleeding compared to the combination of warfarin plus aspirin plus clopidogrel; in the regimen that used warfarin plus aspirin with clopidogrel bled more compared to rivaroxaban plus asprine plus clopidogrel and rivaroxaban plus clopidogrel; in the rivaroxaban alone versus aspirin alone regimen there were no bleeds and in the rivaroxaban alone versus warfarin regimen had more bleeds with rivaroxaban alone.

The 25 studies totaled 221,221 patients studied, excluding the trial by Klim et al. (2020) with 75 patients, who did not have significant bleeding significance and the trial by Mahaffeey et al. (2014) with 14,264 patients, whose result was expressed as a patient-year ratio, leaving 206,957 patients studied in clinical trials.

Of these 206,957 patients, 81,304 used the rivaroxaban regimen combined with aspirin, 78,976 used only aspirin, 7,575 patients used rivaroxaban combined with aspiration with clopidogrel, 2,599 patients used aspirin combined with clopidogrel, 991 used warfarin associated with aspirin with clopidogrel associated on clopidogrel, 24,467 patients used rivaroxaban alone and 7,125 patients used warfarin itself.

Table 2 shows the result of the bleeding events that occurred according to the drug regimen used.

DISCUSSION

The study shows that the relationship: drug regimen used, number of patients and

Bleeding	RIV+ASP	ASP	RIV+ASP +CLO	ASP+ CLO	WAR+ ASP +CLO	RIV+ CLO	RIV	WAR
Major/Critical Body	1730	1080	188	80	20	72	378	-
Smaller/lighter/ Any/ Insignificant	3783	1955	982	376	532	552	1158	-
Fatal	20	13	2	1	-	-	-	-
Intracranial	149	136	36	23	-	13	53	-
Surgical site/ Hospitalization	431	148	103	-	120	93	23	-
Multiples	20	-	-	-	15	-	-	-
TGI	140	65	-	-	-	-	403	290
Urinary	3	21	-	-	-	-	30	-

Table 2. Type of hemorrhagic event according to the drug regimen used.

ASP: aspirin; CLO: clopidogrel; RIV: rivaroxaban; TGI: gastrointestinal tract; WAR: warfarin. Source: Author (2021).

total number of bleeding events, bleeding was greater in the association of warfarin + aspirin + clopidogrel (69.3%), followed by the regimen that used rivaroxaban + clopidogrel (40.4%). The two schemes that had more hemorrhagic events are present in the studies: Kerneis et al. (2019) who compared the use of rivaroxaban 15 mg/day + aspirin 100 mg/day with warfarin + aspirin + clopidogrel in patients with atrial fibrillation and stent. The sample had a low number of participants in the warfarin arm (294 patients) and therefore must be interpreted with caution. However, it shows that, in relation to the number of patients, the dual antiaggregation regimen associated with warfarin bled more (27.2%) than the dual antiaggregation regimen associated with rivaroxaban (18.4%). Following the regimen in the 1st month compared to the 6th month, there was a decrease in bleeding events in the sixth month with warfarin, but it remained higher than the regimen with rivaroxaban. Gibson et al. (2016) compared dual antiplatelet therapy (aspirin + clopidogrel) associated with warfarin, dual antiplatelet therapy associated with rivaroxaban with the regimen only with rivaroxaban associated with clopidogrel, in a patient with atrial fibrillation undergoing percutaneous coronary intervention. The warfarin regimen had more bleeding (48.6%) compared to the other regimens, 32% for rivaroxaban + clopidogrel and 33% for rivaroxaban + clopidogrel + aspirin. The samples of the 3 groups had a number of close participants with no significant difference between them. In the regimen that used rivaroxaban + clopidogrel, the dose of rivaroxaban was different, 3 times higher (15 mg/day) than that used in the other regimens (5 mg/day), even so the bleeding events were smaller compared to the regimen that used warfarin, and this one had more severe bleeding (20 events) compared to the other regimens (rivaroxaban + clopidogrel, 14 events; rivaroxaban + aspirin + clopidogrel, 12 events).

The drug regimen that used aspirin + clopidogrel, which had 18.4% of bleeding events, and the rivaroxaban + aspirin + clopidogrel regimen, with 17.3% of events, were addressed in the studies: Hiatt et al. (2020) compared the use of rivaroxaban + aspirin with and without clopidogrel and aspirin + clopidogrel and aspirin alone in peripheral arterial disease, where rivaroxaban with clopidogrel at a dose of 2.5 mg twice a day and without clopidogrel at a dose of 15 mg/day. Rivaroxaban combined with dual antiaggregation (aspirin + clopidogrel) had more major bleeding (76; 4.58%) but less intracranial bleeding (3; 0.18%) compared to rivaroxaban + aspirin (13; 0.8%) and aspirin alone bleeding rate was 2.25% without clopidogrel, 2.24% with clopidogrel in use for less than 30 days and 3.74% with clopidogrel in use for more than 30 days. That is, the use of the association of clopidogrel in a short period of time is associated with a lower risk of bleeding. Yasuda et al. (2019) in their study of patients with atrial fibrillation undergoing percutaneous coronary intervention, the use of rivaroxaban + aspirin or clopidogrel had more bleeding (494; 44.6%) compared to rivaroxaban 15 mg/day (302; 27.2 %) and also more intracranial bleeding (13; 1.17%) compared to rivaroxaban (4; 0.36%). Rivaroxaban monotherapy had a lower bleeding outcome compared to combination therapy with antiplatelet, which also had more intracranial bleeding, 225% more than single therapy. Dangas et al. (2020) in their study with patients undergoing aortic valve replacement, used the regimen rivaroxaban 10 mg/day + aspirin + clopidogrel for 3 months compared to the regimen aspirin + clopidogrel, where there were more bleeding events in the regimen using anticoagulants (289; 55). 6%) compared to the antiplatelet

regimen (172; 27.5%). In a similar study with the same schemes, Backer et al. (2020), but with a smaller sample (N= 231), had more bleeding in the anticoagulant regimen (4; 3.47%), against (1; 0.86%) in the antiplatelet scheme. In both studies, the anticoagulation-based strategy had a greater number of bleeding events compared to an antiplatelet strategy alone. Klim et al. (2020) used 3 regimens for patients with acute coronary syndrome (ACS) undergoing percutaneous intervention. Ticagrelor 180 mg/day + aspirin 100 mg/day compared to rivaroxaban (5 mg/day) + aspirin + clopidogrel and aspirin + clopidogrel, bleeding events were equal between the groups that used ticagrelor (1; 4%) and rivaroxaban (1; 4%) and no events in the aspirin group. Study limited by the total number of randomized patients N=75. In the study by Gibson et al. (2018) where they used 2 regimens in the secondary prevention of patients with acute coronary syndrome, the rivaroxaban 5 mg/day + aspirin + clopidogrel regimen had more major bleeding events (66; 1.3%) compared to the aspirin + regimen clopidogrel (23; 0.4%) and in relation to intracranial bleeding was 0.69% and 0.48% respectively. In this study, data on major bleeds are limited due to the lack of long-term analysis and also patients who had minor bleeds were not included in the study, impairing further analysis of these patients as they may have had more severe later events. However, rivaroxaban at a dose of 5 mg/day (2.5 mg twice) is associated with a reduction in ischemic events and intracranial bleeding did not significantly increase compared to the aspirin + clopidogrel regimen.

Two studies addressed the use of rivaroxaban alone and warfarin alone without combinations. Li et al. (2016) compared the use of rivaroxaban 10 mg/day for 14 days versus aspirin 100 mg/day for 3 months in patients with cardiac arrhythmia who received ablation treatment. There were no hemorrhagic events in both groups, a study limited by the number of randomized patients (N=176). In the study by Sherwood et al. (2015) where 14,236 patients were randomized and compared the use of rivaroxaban 10 mg/day (N=7111) and warfarin (N=7125) in the prevention of systemic embolism and stroke in patients with atrial fibrillation. Of the gastrointestinal bleeding outcomes, the one with the most high bleeding (hematemesis or melena) was the rivaroxaban group (190; 2.67%) compared to warfarin (138; 1.9%), as well as low or rectal bleeding, rivaroxaban (204; 2.86%) and warfarin (152; 2.13%). Gastrointestinal bleeding is a complication of oral anticoagulant therapy. Risk factors associated with bleeding were previous anemia, bleeding history, age, smoking, low glomerular filtration rate. Rivaroxaban increased rates of clinically relevant and unimportant digestive tract bleeding compared to warfarin. The rates of fatal bleedings or those requiring blood transfusions were low and similar between the two studied groups. The risk of intestinal bleeding in patients taking anticoagulants illustrates the need to minimize modifiable risk factors as well as the need for gastric protection with a proton pump inhibitor.

Kaplocitch et al. (2021) used in their study the association of rivaroxaban 5 mg/day with aspirin 100 mg/day compared to aspirin alone in peripheral arterial disease (PAD). The association of rivaroxaban + aspirin had a greater number of bleeding events (61; 4.32%) compared to aspirin alone (33; 2.42%). Fatal or critical organ bleeding increased numerically with combination therapy, with rivaroxaban + aspirin (15; 1.06%) and aspirin (7; 0.51%). The increased estimated risk of major bleeding was greatest in patients with PAD who had comorbidities. Bonaca et al. (2020) in a similar study, hemorrhagic events were higher in the group that used double-

route (62; 1.88%) compared to aspirin alone (44; 1.34%), but the group that used aspiration had more intracranial bleeding. (23; 0.70%) compared to the double route (19; 1.88%). The same occurred in the study by Paul et al. (2018) where the regimen using aspirin alone (8; 0.31%) had more intracranial bleeding compared to the dual-route rivaroxaban + aspirin regimen (4; 0.16%) in patients with peripheral arterial disease. Eikelboom et al. (2019) used the same therapeutic regimens in their study and followed the bleeding events for 3 years in patients with coronary artery disease or with peripheral arterial disease. Intracranial bleeding was similar in the 2 groups, rivaroxaban + aspirin (28; 0.30%) and aspirin (24; 0.26%). More severe bleeding events were in the double-route group (494; 5.39%) compared to the single-route with aspirin (286; 3.13%). It was observed that bleeding events were lower in the 3rd year in both groups, rivaroxaban + aspirin (32; 0.34%) and aspirin (30; 0.32%) compared to the 1st year with the dual route with more events (181; 1.97%), single route (78; 0.85%). Fox et al. (2019) in their study also used the same regimens in patients with CAD or PAD, randomizing patients with glomerular filtration rate (GFR) < 60 ml/m and with GFR > 60 ml/m. Patients with worse renal function (GFR < 60 ml/m) had more bleeding events, being rivaroxaban + aspirin (169; 8.22%) and aspirin (121; 5.72%) compared to those with better renal function with GFR > 60 ml/m, rivaroxaban + aspirin (419; 5.9%), aspirin (230; 3.28%). Fatal and intracranial bleeding were similar regardless of renal function, being in patients with GFR > 60 ml/m, rivaroxaban + aspirin (27; 0.38%), aspirin (23; 0.32%) and for those with GFR < 60 ml/m, rivaroxaban + aspirin (16; 0.77%), aspirin (11; 0.52%).

Anand et al. (2018) compared 3 regimens in patients with peripheral arterial disease using rivaroxaban 5 mg/day + aspirin 100 mg/day compared to rivaroxaban alone and aspirin alone. Bleeding events were similar in patients with dual route (77; 3.08%) and rivaroxaban (79; 3.19%) compared to aspirin alone (48; 1.91%). The same author in another study, Anand et al. (2018) compared the same therapeutic regimens and adverse effects on the lower limbs of patients with peripheral arterial disease. Severe bleeding occurred in the lower limb and the aspirin regimen had the lowest number of events (42; 1.97%) compared to rivaroxaban + aspirin (68; 3.17%) and rivaroxaban (66; 3.1%). Fatal bleeding at the site of lower limb surgery (requiring approach) was also less in the aspirin group (18; 0.84%) compared to the other two regimens that were similar, rivaroxaban + aspirin (24; 1.12%) and rivaroxaban (23; 1.08%).

Bainey et al. (2020) used the regimen of rivaroxaban 5 mg/day + aspirin 100 mg/day and aspirin alone 100 mg/day, in patients with coronary artery disease undergoing percutaneous intervention. Major bleeding occurred in the rivaroxaban + aspirin group without statistical significance compared to patients with percutaneous intervention and those who did not undergo it, being rivaroxaban + aspirin in patients with subcutaneous intervention (165; 3.32%) and without intervention (98 ;2.98%). Intracranial bleeding had no statistical difference in both groups and regimens, with intervention rivaroxaban + aspirin (17; 1.7%), aspirin (13; 0.26%) and without intervention (9; 0.26%) and (10; 0.29%), respectively.

The study by Dangas et al. (2020) compared the dual-way regimen rivaroxaban 5 mg/day + aspirin 100 mg/day for 3 months, followed by aspirin monotherapy and the antiplatelet regimen with aspirin 100 mg/day + clopidogrel 75 mg/day followed by aspirin monotherapy in patients undergoing catheter aortic valve replacement. The rivaroxaban group had higher rates of major bleeding (289; 55.6%)

compared to the antiplatelet route (172; 27.5%), making dual route therapy a challenge in a patient undergoing valve replacement. Fatal bleeding was not statistically significant in either group.

Bhatt et al. (2020) compared in their study the dual pathway and antiplatelet aggregation schemes in patients with diabetes mellitus and without diabetes mellitus. The regimen of rivaroxaban 5 mg/day + aspirin 100 mg/day + clopidogrel 75 mg/day compared to aspirin + clopidogrel was used. There were numerically more bleedings in patients without DM in the two-way scheme (205; 1.8%) compared to those who had DM (126; 1.82%), but without statistical significance. The same was true for aspirin, patients without DM and with DM (129; 1.13%) and (75; 1.08%), respectively. In the study by Thomas et al. (2019) who compared bleeding in patients with coronary and peripheral artery disease with individual risk factors, such as hypertension, diabetes mellitus and smoking. Among the patients with DM, those who used dual route with rivaroxaban + aspirin (110; 1.2%) compared to aspirin alone (6; 0.30%) bled more. In patients with arterial hypertension, bleeding outcomes were higher in the rivaroxaban + aspirin regimen (288; 3.14%) compared to aspirin alone (170; 1.85%).

Branch et al. (2019) used 3 regimens in patients with coronary artery disease and peripheral artery disease in patients with heart failure (HF) and without heart failure. The regimens of rivaroxaban 5 mg/day + aspirin 100 mg/day, rivaroxaban 5 mg/day alone and aspirin 100 mg/day alone were used. A total of 5902 patients with HF were randomized, the bleeding events in these patients were greater in the double regimen (66; 3.36%), rivaroxaban (22; 1.12%) and aspirin (18; 0.9%). Intracranial bleeding was not statistically significant between the 3 groups, namely, rivaroxaban + aspirin (9; 03%), rivaroxaban (6; 0.3%) and aspirin (6; 0.3%). Lamy et al. (2019) in their study also used the same 3 schemes and followed up bleeding within a period of up to 30 days and after 30 days. There were more bleeding events in patients who used rivaroxaban 10 mg/day alone after 30 days (63; 13%), followed by the dual route rivaroxaban 5 mg/day + aspirin 100 mg/day (59; 11.7%) and aspirin alone (37; 7.99%). Bleeding that occurred up to 30 days was statistically similar in the 3 regimens used. In both studies the rivaroxaban + aspirin plus aspirin regimen had fewer bleeding events compared to rivaroxaban alone.

The COMPASS study performed by Eikelboom et al. (2019), a multicenter study with the participation of 33 countries and with 27,395 patients, compared the regimens of rivaroxaban 5 mg/day + aspirin 100 mg/day, rivaroxaban 10 mg/day alone and aspirin 100 mg/day alone in patients with disease coronary and peripheral arterial. The dual route rivaroxaban + aspirin group had better cardiovascular outcomes and more major bleeding events (494; 5.39%) compared to aspirin alone (286; 3.13%), there was no significant difference in intracranial or fatal bleeding between these groups, (28; 0.3%) and (24; 0.26%), respectively. It was observed in this study that bled more, patients who had a greater number of associated comorbidities, such as high blood pressure, diabetes mellitus, hypercholesterolemia, sedentary lifestyle, as well as bleeding, but patients who had multivessel, coronary, carotid and peripheral disease. Another interesting outcome was that in patients who had genitourinary and gastrointestinal bleeding, when investigating, they found that these patients had neoplasms, that is, the regimen with rivaroxaban + aspirin is not able to deteriorate the vascular endothelium and cause such bleeding, but rather to increase or trigger something that already had a bleeding situation, with this

the study itself suggests in clinical practice that patients who use this scheme and have genitourinary or gastrointestinal bleeding must be investigated for neoplasia. The use of pantoprazole to prevent gastrointestinal bleeding was also compared within the same study, but there was no difference between the groups that used pantoprazole and those that did not, and there was an increase in intestinal infections in the group that used pantoprazole. The study emphasizes that, in clinical practice, patients at higher risk of bleeding use pantoprazole. The study followed the bleeding events over a 3-year period and was found to have more bleeding events during the first year with the dual-path regimen (181; 1.97%) compared to aspirin (78; 0.85%) and interestingly, hemorrhagic events were smaller in the third year (32; 0.34%) and (30; 0.32%) respectively, this is perhaps due to the adaptation of the scheme used by the organism. The regimen that used rivaroxaban 10 mg/day alone had higher cardiovascular and hemorrhagic outcomes compared to the other two regimens used.

CONCLUSION

The use of oral anticoagulants and antiaggregants is highly prescribed in clinical practice in order to avoid cardiovascular outcomes, however, bleeding events inevitably occur secondary to their use and many of these factors. The association of two drugs acting on different pathways in the coagulation cascade, through thrombin and the platelet pathway, has greater thrombotic or embolic benefits, but with an increased risk of bleeding. It is important to emphasize that there are the same regimens with different doses for certain pathologies, such as for atrial fibrillation, rivaroxaban is used at a dose of 20 mg/day. Warfarin is a drug that has been shown to have a greater risk of hemorrhagic events and that its use requires greater laboratory control through the INR, making it a drug less and less used, except in some particularities. The use of aspirin has more intracranial bleeding, but it is low cost, easy to use and effective, being widely used even in association with anticoagulant. Rivaroxaban has been applied in several studies at different doses and associations. Its use at a dose of 2.5 mg twice a day associated with aspirin 100 mg once a day is indicated in clinical practice for secondary prevention in patients with coronary and peripheral artery disease at high risk of ischemic events. It demonstrated a 24% reduction in ischemic events (AMI, CVA) and in patients with peripheral arterial disease this new approach prevents amputation with a 70% reduction in cases. The regimen of rivaroxaban 2.5 mg twice daily associated with aspirin 100 mg/day is promising in reducing the recurrence of ischemic events and mortality, with a high number of major bleeding, but without as much fatal hemorrhagic event. Patients at higher risk of bleeding were those who had a greater number of associated comorbidities, in which the use of pantoprazole for gastric protection is necessary.

New multicenter and randomized studies with different schedules and dosages, or the use of a schedule with interspersed days, use of risk scores for bleeding, is needed. Finding a drug or scheme where there is a reduction in ischemic and embolic cardiovascular events and at the same time a lower risk of bleeding, the search for this binomial is ideal.

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