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BRAZILIAN GUIDELINES ON ANTIPLATELET AND ANTICOAGULANT AGENTS IN CARDIOLOGY

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Brazilian Guidelines on Antiplatelet and Anticoagulant Agents in Cardiology

This guideline shall be referred as:

Serrano Jr CV, Fenelon G, Soeiro AM, Nicolau JC, Piegas LS, Montenegro ST, Lorga Filho AM, Azmus AD, Quadros AS, Avezum Junior A, Marques AC, Franci A, Manica ALL, Volschan A, De Paola AAV, Greco AIL, Ferreira ACN, Sousa ACS, Pesaro AEP, Simão AF, Lopes ASSA, Carvalho ACC, Timerman A, Ramos AIO, Alves BR, Caramelli B, Mendes BA, Polanczyk CA, Montenegro CEL, Barbosa CJDG, Melo CCL, Pinho C, Moreira DAR, Calderaro D, Gualandro DM, Armaganijan D, Machado Neto EA, Bocchi EA, Paiva EF, Stefanini E, D'Amico E, Evaristo EF, Silva EER, Fernandes F, Brito Junior FS, Bacal F, Ganem F, Gomes FLT, Mattos FR, Moraes Neto FR, Tarasoutchi F, Darrieux FCC, Feitosa GS, Morais GR, Correa Filho H, Castro I, Gonçalves Junior I, Atié J, Souza Neto JD, Ferreira JFM, Faria Neto JR, Annichino-Bizzacchi JM, Zimerman LI, Pires LJT, Baracioli LM, Silva LB, Mattos LAP, Lisboa LAF, Magalhães LPM, Lopes MACQ, Montera MW, Figueiredo MJO, Malachias MVB, Gaz MVB, Andrade MD, Bacellar MSC, Barbosa MR, Clausell NO, Dutra OP, Coelho OR, Yu PC, Lavítola PL, Lemos Neto PA, Andrade PB, Farsky PS, Franco RA, Kalil RAK, Lopes RD, Esporcatte R, Heinisch RH, Kalil Filho R, Giraldez RRCV, Alves RC, Leite REGS, Gagliardi RJ, Ramos RF, Accorsi TAD, Jardim TSV, Scudeler TL, Moisés VA, Portal VL

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Summary

Brazilian Guidelines on Antiplatelet and Anticoagulant Agents in Cardiology

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Marcus Vinicius Bolivas Malachias and Mário Sergio de Carvalho Bacellar

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Group 2 — Use of antiplatelet and anticoagulant agents in non-ST-segment elevation acute coronary syndrome (NSTEACS)

Coordinators: Oscar Pereira Dutra and Rogério Eduardo Gomes Sarmento Leite.

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Group 3 — Use of antiplatelet and anticoagulant agents in stroke and transient ischemic attack (TIA)

Coordinator: Carisi Anne Polanczyk.

Participants: Airton Massaro, Álvaro Avezum Júnior, Eberth Alves Machado Neto, Eli F. Evaristo, Fernando Ganem, Rubens José Gagliardi and Thiago Luís Scudeler

Group 4 — Use of antiplatelet and anticoagulant agents in atrial fibrillation (AF)

Coordinator: Guilherme Fenelon.

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Group 5 — Use of antiplatelet and anticoagulant agents in valvular disease

Coordinator: Flávio Tarasoutchi.

Participants: Antônio Sergio de Santis Andrade Lopes, Auristela Isabel de Oliveira Ramos, Frederico Penna Campos Abreu, Gilson Soares Feitosa, Lucas José Tachotti Pires, Paulo de Lara Lavítola, Tarso Augusto Duenhas Accorsi and Valdir Ambrósio Moisés

Group 6 — Use of antiplatelet and anticoagulant agents in venous thromboembolism (VTE)

Coordinator: André Volschan and Edson Stefanini.

Participants: Alexandre de Matos Soeiro, Edison Ferreira de Paiva, Fernando Luiz Torres Gomes, José Rocha Faria Neto, Joyce Maria Annichino-Bizzacchi and Thiago de Souza Veiga Jardim

Group 7 — Use of antiplatelet and anticoagulant agents in heart failure (HF)

Coordinator: Fernando Bacal.

Participants: Edimar Alcides Bocchi, João David de Souza Neto, Luis Beck da Silva, Marcelo W. Montera and Nadine Clausell

Group 8 — Use of antiplatelet and anticoagulant agents in the perioperative period of cardiac and noncardiac surgeries

Coordinator: Cláudio Pinho.

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Declaration of potential conflict of interest of authors / collaborators Brazilian Guidelines on Antiplatelet and Anticoagulant Agents in CardiologyIf the last three years the author / developer of the Guidelines:

Names Members of the Policy	Participated in clinical studies and / or experimental trials supported by pharmaceutical or equipment related to the guideline in question	Has spoken at events or activities sponsored by industry related to the guideline in question	It was (is) advisory board member or director of a pharmaceutical or equipment	Committees participated in completion of research sponsored by industry	Personal or institutional aid received from industry	Produced scientific papers in journals sponsored by industry	It shares the industry
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Roberto Esporcatte	No	Bayer, Pfizer	No	No	No	No	No
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1. Introduction

In the past 10 years, we have observed an exponential development of anticoagulant and antiplatelet agents for replacing heparin and vitamin K antagonists and/or aiding in the treatment of coronary artery disease. Scientific literature has increasingly shown new applications for these agents. Some of these are already approved for use by ANVISA in Brazil, such as dabigratan, rivaroxaban, apixaban, prasugrel, and ticagrelor. These new alternative drugs require recommendations on specific restrictions and risks that must be considered before administration to patients. During the development of new medications, the safety of patients is being increasingly valued and includes a greater use of bleeding risk scores.

Various multicenter randomized studies have been developed to validate the use of these drugs in acute coronary syndrome (ACS), venous thromboembolism (VTE), and pulmonary thromboembolism (PTE) and in the prevention of thrombotic events. Brazil has participated in some of the main trials and, the country's experience in the use and management of these drugs is increasing.

The Board of the Brazilian Heart Society (*Sociedade Brasileira de Cardiologia*, SBC) proposed to develop a guideline on recommendations regarding the use of anticoagulant and antiplatelet drugs owing to the importance of this fact in the field of cardiology in Brazil.

This guideline was prepared by an editorial board consisting of Brazilian cardiologists with recognized experience and qualifications in the area. The document is a compilation of many national and international findings and opinions of Brazilian specialists and aims to help physicians in making decisions regarding patients in various clinical situations. Didactically, antithrombotic drugs are classified as antiplatelet and anticoagulant agents.

SBC, the editors, and the group that collaborated in the preparation of this guideline hope that its dissemination will contribute to a better standardization of anticoagulant and antiplatelet drug management and will increase the effectiveness of their use and patient safety.

1.1. Methods and scientific evidence

The editorial board selected to write these recommendations consists of physicians with extensive experience in this area. These professionals are involved in the management and treatment of various clinical situations in which these drugs are widely used and work in major teaching and research centers in Latin America.

We selected relevant studies published up to 2012, according to the evidence pyramid, the organization into levels of recommendation (Classes I, IIa, IIb, and III; Table 1), and the impact of the evidence levels (A, B, and C; Table 2).

1.2. Presentation of the text

The guidelines in this document are presented in two manners. The first consists of a full text that includes the description of the pertaining to each agent, the recommendations, and the evidence levels shown in tables, together with the citations. This text is available on the website of *Arquivos Brasileiros de Cardiologia*.

The second consists of the executive summary, which contains only the tables with the recommendations and the evidence levels. The executive summary will be available in the publications of *Arquivos*.

Table 1 – Classification of the degrees of recommendations and class definition

Class of recommendation	Indications and definition
I	Consensus that the procedure/treatment is useful and effective
II	Conditions for which there is no consensus on the usefulness and efficacy of the procedure/treatment
IIa	The opinion favors the procedure/treatment indication
IIb	The opinion does not clearly favor the procedure/treatment indication
III	Consensus that the procedure/treatment is not useful, and in some cases, it can create risk

Table 2 – Levels of evidence

Level of evidence	Definition
A	Data obtained from high-quality randomized studies that follow the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) or meta-analyses of large randomized studies that follow the guidelines of CONSORT
B	Data obtained from a single high-quality randomized clinical trial that follows the guideline of CONSORT or various nonrandomized studies
C	Data obtained from studies that included series of cases and/or consensus data and/or opinions of specialists

2. Use of antiplatelet and anticoagulant agents in ST-segment elevation myocardial infarction (STEMI)

2.1. Introduction

ST-segment elevation myocardial infarction (STEMI) is the most severe form of unstable myocardial ischemia; its incidence varies between 29% and 47% of cases of acute coronary syndrome (ACS), and it is associated with high morbidity and mortality. Data from the Center for Disease Control and Prevention (CDC)[1] in the US show that in 2010, the main cause of mortality was cardiovascular disease and that acute myocardial infarction (AMI) accounted for approximately 5% of the overall mortality. In addition to the high impact on mortality in the general population, AMI has also an important economic impact because it involves a large number of hospitalizations. According to data from the Heart Diseases and Stroke Statistics[2], it is estimated that in 2006, the US spent 11.7 billion dollars on hospital expenses related to AMI.

In Brazil, according to data from DATASUS for 2003[3], cardiovascular diseases accounted for 11% of hospitalizations and approximately 19.5% of resources spent by SUS on hospitalizations in general. AMI accounted for 4.2% of all hospitalizations, which demonstrates the importance of this condition in terms of morbidity and hospital costs.

With regard to the treatment of this clinical entity, in addition to reperfusion therapies (pharmacological, thrombolytic, or percutaneous therapy via primary angioplasty), antiplatelet and anticoagulant therapy is essential to reduce mortality and recurrence of cardiovascular events[4].

This section aims to assess the use of antiplatelet and anticoagulant agents in the treatment of STEMI.

2.2. Antiplatelet therapy in STEMI

2.2.1. ASA

The use of acetylsalicylic acid (ASA, aspirin) in STEMI is based on solid evidence; its use is deemed to be essential. The Second International Study of Infarct Survival (ISIS-2)[5] assessed the use of ASA and streptokinase alone and in combination. The use of ASA alone led to a 23% reduction in all-cause mortality, and combined use of the drugs led to a 42% reduction in all-cause mortality. A 25 ± 7%, 21 ± 7%, and 21 ± 12% reductions in mortality were observed when used within 0–4 h, 5–12 h, and 13–24 h of the initial symptoms, respectively.

Subsequent meta-analyses reinforced the fundamental role of ASA in the reduction of mortality and cardiovascular events, when used at an early stage and in the long term. A study by the "Antiplatelet Trialists Collaboration"[6] group demonstrated a 29% reduction in the relative risk for the incidence of vascular events (nonfatal infarction, stroke, or vascular death). A more recent publication[7], which analyzed the same outcomes, revealed a reduction of 36 vascular events per 1,000 patients with previous myocardial infarction.

With regard to the ASA dose, the CURRENT-OASIS-7 study[8] evaluated the hypothesis of using a double maintenance dose of ASA in patients with ACS; 29% of them had STEMI and were undergoing primary percutaneous coronary intervention (PPCI). This study did not show any difference between the standard-dose regimen (75–100 mg/day) and the high-dose regimen (300–325 mg/day) in preventing cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or stroke) over 30 days (p = 0.61, 95% CI 0.86–1.09). Moreover, there was no difference in terms of the incidence of major bleeding (p = 0.90, 95% CI 0.84–1.17).

The use of ASA should be contraindicated in some exceptional situations, e.g., known hypersensitivity (hives, bronchospasm, or anaphylaxis), active peptic ulcers, blood dyscrasia, and severe hepatopathy.

Based on these findings, the use of ASA in patients with STEMI is essential in the prevention of mortality and cardiovascular events, both in the short and long term, and it should be indefinitely continued after the acute event (secondary prevention).

2.2.2. Clopidogrel

The use of clopidogrel, a thienopyridine derivative and inhibitor of adenosine diphosphate (ADP), in ACS began with the CURE study[9], which compared the use of ASA alone and in combination with clopidogrel in a situation of intermediate- or high-risk unstable angina as well as non-STEMI (NSTEMI). This study showed a 20% reduction in the relative risk for cardiovascular death, stroke, and nonfatal AMI.

In the context of STEMI, two important studies should be highlighted. The first study is the CLARITY-TIMI 28 study[10] that included 3,491 patients diagnosed with STEMI who were aged ≤ 75 years and were undergoing thrombolytic therapy (99.7% undergoing thrombolysis). These patients were assigned to ASA or ASA combined with clopidogrel groups; the study design envisaged the use of a 300 g loading dose of clopidogrel and a 75 mg maintenance dose/day. This study showed a 36% reduction in the combined outcome of death, nonfatal myocardial infarction, or revascularization of the target vessel; no difference was observed in terms of bleeding between the groups. In this study, the age limit for inclusion was 75 years and the mean time of clopidogrel use was 4 days.

The second study is the COMMIT study[11] that randomly assigned 45,852 patients with suspected STEMI in 1,250 centers in China to receive 162 mg of ASA/day or ASA (same dose) combined with 75 mg of clopidogrel/day, without the administration of a loading dose. This study included 26% of patients aged > 70 years (without a maximum age limit). In addition, 50% of patients were subjected to thrombolysis. In this study, a 9% reduction in the combined outcome (death, reinfarction, or stroke) was observed; no difference was observed in terms of bleeding. The mean time of clopidogrel use was 28 days. Clopidogrel was beneficial for patients who received thrombolytic therapy and those who did not undergo reperfusion. There was a 7% reduction in the overall mortality (RR 0.93, 95% CI 0.87–0.99).

In addition, the CURRENT-OASIS-7 study[7], which assessed 25,086 patients, tested two hypotheses: the use of a high-maintenance dose of ASA (described in section 2.2.1) and the use of a double loading dose of 600 mg of clopidogrel, followed by

a dose of 150 mg/day for 7 days and a dose of 75 mg/day thereafter, as opposed to the standard regimen (a loading dose of 300 mg, followed by 75 mg/day), in patients with ACS (29% of patients with STEMI). This study did not show any effect of the higher dose regimen on the prevention of cardiovascular events (cardiovascular deaths, nonfatal myocardial infarction, or stroke) over 30 days ($p = 0.30$). With regard to major bleeding, the group that received higher doses of clopidogrel exhibited a higher incidence of this event (2.5% × 2.0%, $p = 0.01$). Analysis of secondary outcomes revealed a significant decrease in the incidence of stent thrombosis (1.6% × 2.3%, $p = 0.001$) in the group subjected to PCI (17,263 patients). It should be noted that clopidogrel was never compared with a placebo in patients undergoing PPCI. The CURRENT-OASIS-7 study only compared the use of two doses of clopidogrel in patients with STEMI subjected to PPCI. A double dose of clopidogrel was also not assessed in patients who received thrombolytic therapy or those who were treated without reperfusion and should not be used in these patients.

A loading dose of 600 mg of clopidogrel is used in patients subjected to PPCI because it enables faster inhibition of the ADP receptor. This fact has been demonstrated in various observational studies[12,13].

Clopidogrel should be administered during 12 months after STEMI, particularly if the patient has undergone PPCI. This conclusion resulted from the extrapolation of studies on Non-ST-segment elevation ACS (NSTEACS), including the CURE study[8] described above.

Therefore, the use of clopidogrel is justified in the context of STEMI, with a loading dose of 300 mg, followed by 75 mg/day, from the acute phase up to 12 months after the event. It should be noted that the loading dose of 300 mg should not be administered to patients subjected to thrombolysis who are aged over 75 years. In patients undergoing PPCI, the loading dose should be 600 mg. A double dose of 150 mg/day should be restricted to patients at low risk for bleeding. In the case of surgical intervention, the administration of clopidogrel should be discontinued 5 days before the procedure.

2.2.3. Prasugrel

Prasugrel, an inhibitor of platelet aggregation induced by ADP via the irreversible blocking of the P2Y12 receptors, was developed to inhibit platelet aggregation more rapidly, more consistently, and to a greater extent than clopidogrel, thereby avoiding the well-known resistance to clopidogrel exhibited by a portion of the population.

The TRITON-TIMI 38 study[14], published in 2007, randomly assigned 13,608 patients with ACS, known as coronary anatomy, and planned PCI with clopidogrel or prasugrel, associated with standard therapy (including ASA). Within the sample, STEMI accounted for 26% of patients. In the general cohort, the group that used prasugrel exhibited a 19% reduction ($p < 0.001$) in the combined outcome of death from cardiovascular causes, nonfatal infarction, or stroke, particularly due to the reduction in cases of nonfatal infarction. With regard to bleeding, the prasugrel group exhibited a 32% increase ($p = 0.03$) in the risk for major bleeding (according to the TIMI score). Post hoc analyses identified three groups at higher risk for bleeding: age ≥ 75 years, weight < 60 kg, or previous stroke/transient ischemic attack (TIA).

Of the 3,534 patients with STEMI, 2,438 were subjected to PPCI and 1,096 were subjected to secondary PCI (patients referred to PCI approximately 38 h after AMI). The primary outcome of cardiovascular death, nonfatal AMI with stroke, was significantly less frequent in the prasugrel group than in the clopidogrel group (RC 0.79, 95% CI 0.65–0.97) over 15 months. A reduction in stent thrombosis from 2.8% to 1.6% was observed in the prasugrel group. There was no difference in the bleeding rate between the two groups[15].

Therefore, the use of prasugrel in STEMI is indicated for cases of PPCI, after knowing the coronary anatomy. Prasugrel should be administered at a loading dose of 60 mg and a maintenance dose of 10 mg/day for 12 months. A lower maintenance dose (5 mg) may be considered for individuals weighing less than 60 kg and aged older than 75 years; however, such a dose has not been prospectively tested in STEMI clinical studies. The drug is contraindicated in the following cases: in combination with thrombolytic therapy and in patients without reperfusion (not studied in this population), in patients aged ≥ 75 years or in patients with previous stroke/TIA. In case of surgical intervention, the administration of prasugrel should be discontinued 7 days before the procedure.

2.2.4. Ticagrelor

Ticagrelor, another ADP inhibitor antiplatelet agent, is a reversible inhibitor of the P2Y12 receptors of ADP. It does not depend on primary metabolism (it is therefore not a pro-drug) and inhibits aggregation more intensely, more rapidly, and more consistently than clopidogrel.

In ACS, the PLATO study[16] randomly assigned 18,624 patients to ticagrelor or clopidogrel, associated with the standard treatment (including ASA). In this study, clopidogrel or ticagrelor were administered during the initial treatment in the emergency room, without knowledge of the coronary anatomy. The prevalence of STEMI in the sample was approximately 38%. The group that used ticagrelor exhibited a 16% reduction in the incidence of the combined outcome of death from vascular causes, nonfatal infarction, or stroke ($p < 0.001$). Analysis of secondary outcomes revealed that in the ticagrelor group, there was a 21% ($p < 0.001$) reduction in mortality by vascular causes and a 22% ($p < 0.001$) reduction in all-cause mortality. With regard to the occurrence of major bleeding, ticagrelor was not significantly different from clopidogrel for the various criteria used (including the TIMI score). However, the ticagrelor group had a higher incidence of dyspnea, usually transient, which forced discontinuation in a higher number of individuals in this group. Moreover, this group exhibited a higher incidence of bradycardia, also usually transient and not leading to differences in clinical repercussions between the groups (pacemaker implant or symptoms).

Therefore, the use of ticagrelor is indicated for patients with ACS with or without ST-segment elevation, regardless of the knowledge of the coronary anatomy. Ticagrelor should be administered at a loading dose of 180 mg and a maintenance dose of 90 mg twice a day, and its use should be continued for 12 months. The drug combined with thrombolytic therapy is contraindicated as well as in patients

without reperfusion (not studied in this population). In case of surgical intervention, ticagrelor should be discontinued 5 days before the procedure.

2.2.5. Glycoprotein (GP) IIb/IIIa inhibitors

Studies with GP IIb/IIIa inhibitors, conducted prior to the current regimens of double antiplatelet therapy, revealed a significant reduction in the incidence of reinfarction, both in the context of PPCI and the use of thrombolytic agents. In the former situation, there was no increase in hemorrhage complications; however, there was a significant increase in bleeding in the context of thrombolysis[17].

With the routine use of clopidogrel and the advent of PCI with stent, doubts have arisen regarding the use of GP IIb/IIIa inhibitors in STEMI. Since then, physicians have been unsure about using them routinely or selectively and about the best administration route (intracoronary or intravenous).

The Relax-AMI study[18], which included 210 patients, compared the early use of abciximab and its use just before PCI in the hemodynamics laboratory, and the results revealed improved perfusion parameters and recovery of ventricular function over 30 days. The On-TIME 2 study[19], which randomly assigned 984 patients with STEMI to a prehospital high bolus dose of tirofiban or use during ICPP, showed a higher decrease in ST-segment elevation without a significant increase in major bleeding.

The FINESSE study randomly assigned patients to three groups: PPCI, PCI facilitated with abciximab, and PCI facilitated with a small dose of reteplase and abciximab. There was no reduction in the ischemic outcomes, and there was an increase in hemorrhagic events with the use of the GP IIb/IIIa inhibitor. After 12 months of follow-up, the subgroup with previous AMI exhibited reduced mortality with the use of reteplase and abciximab ($p = 0.093$). The BRAVE-3 study randomly assigned patients with STEMI to a 600 mg loading dose of clopidogrel for routine use of abciximab or placebo, and there was no reduction in the size of the infarction area with this strategy[20,21].

Therefore, the routine use of GP IIb/IIIa inhibitors in STEMI is not beneficial and may involve higher bleeding rates. The use of GP IIb/IIIa inhibitors alone during PPCI (high incidence of thrombi, no reflow, and other thrombotic complications) may be considered despite the absence of strong evidence. The best way to use tirofiban and abciximab together with the new antiplatelet drugs (prasugrel and clopidogrel) still remains unclear.

Another question is whether intracoronary administration of GP IIb/IIIa inhibitors is better than intravenous administration. Several small studies have evaluated this strategy; the majority evaluated abciximab and suggested that intracoronary administration leads to better perfusion after PCI, lesser need for new revascularization, and decreased early deaths[22].

The only large study on this subject is the AINDA study, which randomly assigned 2,065 patients with STEMI to intracoronary or intravenous (0.25 mg/kg) administration of abciximab and intravenous administration of a maintenance dose of 0.125 mg/kg/min for 12 h. There was no difference

Table 1 – Recommendations for the use of antiplatelet agents in STEMI

Recommendation class	Indications	Level of evidence	References
I	ASA (162–300 mg as a loading dose, with a maintenance dose of 81–100 mg/day), independent of reperfusion therapy	A	4
	Clopidogrel 300 mg, in addition to ASA, in patients who underwent thrombolytic therapy in the precedent 24 h and are undergoing an invasive strategy and PCI	A	9. 10
	Clopidogrel 600 mg, in addition to ASA, in patients who underwent thrombolytic therapy in the precedent 24 h and are undergoing an invasive strategy and PCI	C	10
I	Clopidogrel 600 mg, in addition to ASA, in patients who underwent PPCI	C	12
	Ticagrelor 180 mg loading dose, in addition to ASA, followed by 90 mg 12/12 h, in patients who underwent PPCI	B	13
	Prasugrel 60 mg loading dose, in addition to ASA, followed by 10 mg once daily, in patients who did not undergo clopidogrel treatment, had a known coronary anatomy, underwent PPCI, and had no known risk factors for bleeding (age ≥ 75 years, weighing less than 60 kg, previous stroke/TIA)	B	11
	Clopidogrel 75 mg/day in patients older than 75 years who did or did not undergo thrombolytic therapy	B	8
IIa	Clopidogrel 600 mg loading dose, followed by a maintenance dose of 150 mg/day for 1 week, in addition to ASA, in patients at low risk for bleeding who underwent PPCI	B	7
	GP IIb/IIIa inhibitor in patients receiving double antiplatelet therapy who underwent PPCI with a high thrombus load, slow/no reflow, and other thrombotic complications	C	-
IIb	Intracoronary abciximab during PPCI	B	21.22
III	Ticagrelor or prasugrel in patients who underwent thrombolytic therapy or no reperfusion	C	
	Loading dose of clopidogrel of 300 mg in elderly individuals (≥ 75 years) who underwent thrombolytic therapy	C	
	Routine use of GP IIb/IIIa inhibitors in patients receiving double antiplatelet therapy	B	

ASA: acetyl salicylic acid (aspirin); PPCI: primary percutaneous coronary intervention; TIA: transient ischemic attack; GP: glycoprotein.

in the primary outcome of death, AMI, and heart failure over 90 days, and there were no significant differences between the groups with regard to safety outcomes. However, analysis of secondary outcomes revealed that the group with intracoronary bolus exhibited a 43% reduction in the incidence of heart failure over 90 days. Based on these data, the intracoronary administration of GP IIb/IIIa inhibitors may be considered; however, the intravenous route remains the route of choice[23].

2.3. Anticoagulant therapy in STEMI

2.3.1. Unfractionated heparin (UH)

The advantage of using UH in ACS was recognized even before using ASA and thrombolytic therapy[24]. Studies such as the GISSI-2[25] and ISIS-3 studies[26], wherein the use of UH during treatment with ASA and thrombolytic agents was assessed, revealed that it was not associated with a significant reduction in clinically relevant outcomes. However, in these studies, UH was subcutaneously administered 4–12 h after the administration of thrombolytic therapy.

The GUSTO-I study[27], published in 1993, evaluated the intravenous administration of UH using a 5,000 IU bolus, followed by initial continuous infusion of 1,000 or 1,200 IU/h, in patients weighing > 80 kg. The UH dose was adjusted to maintain an activated partial thromboplastin time (aPTT) between 60 and 85 s in patients with STEMI receiving ASA and subjected to various thrombolytic therapies. Among the 41,021 randomized patients, the group that was administered UH intravenously combined with thrombolytic therapy with r-TPA exhibited the lowest mortality (6.3%) over 30 days.

The ASSENT-3 study[28] assessed the efficacy and safety of tenecteplase in combination with enoxaparin, UH, or abciximab. In this study, a 60 IU/kg bolus of UH was intravenously administered (maximum 4.000 IU), followed by continuous infusion of 12 IU/kg/h (maximum 1.000 IU/h, initially), and adjusted to maintain aPTT between 50 and 70 s. The occurrence of death, reinfarction, or recurrent ischemia over 30 days was lower in the UH group than in the enoxaparin group; however, no difference in mortality was observed over 30 days. This UH administration regimen is associated with a lower incidence of hemorrhagic events (major bleeding and need for transfusions); however, it was not statistically different from enoxaparin.

2.3.2. Low-molecular-weight heparin (LMWH)

The above mentioned ASSENT-3 study[24] was one of the first large studies to compare LMWH and UH. Among 6,095 patients with STEMI or new left branch block (LBB) within 6 h of the onset of ischemic symptoms, the patients that received enoxaparin combined with thrombolytic therapy using tenecteplase exhibited a significant 26% reduction in the relative risk for death, reinfarction, or refractory ischemia over 30 days in comparison with those who received UH combined with tenecteplase, with the number of treated patients required to avoid an outcome (NNT) being 25.

However, the strongest data on efficacy and safety of enoxaparin in patients with STEMI were obtained from the ExTRACT TIMI 25 study[29-31], published in 2006. This was an international, multicenter, randomized, and double-blinded study that included 20,506 patients within 6 h of the onset of ischemic symptoms. ECG revealed ST-segment elevation in at least two contiguous leads or new LBB. Thrombolytic therapy was programmed. The patients were randomly assigned to UH for a minimum period of 48 h or enoxaparin for 8 days or until discharged. The enoxaparin regimen consisted of a 30 mg bolus intravenously administered 15 min before or up to 30 min after the onset of thrombolysis, followed by a subcutaneous injection of 1.0 mg/kg every 12 h (maximum 100 mg in the two first doses). Patients aged ≥ 75 years were not administered the bolus, and the dose of enoxaparin was adjusted to 0.75 mg/kg every 12 h (maximum 75 mg in the two first doses). In patients with an estimated creatinine clearance (CrCl) of < 30 ml/min, the dose was adjusted to 1.0 mg/kg every 24 h. A 60 IU/kg bolus of UH was intravenously administered (maximum 4,000 UI), followed by continuous infusion of 12 IU/kg/h (maximum 1.000 IU/h, initially). The results revealed a significant 17% reduction in the relative risk for death or nonfatal infarction over 30 days in the group assigned to enoxaparin, with NNT of 48. Safety analysis revealed that there was a significant 53% increase in the relative risk for major bleeding in the group that received enoxaparin; however, there was no significant increase in the occurrence of intracranial bleeding. In the prespecified evaluations of the clinical advantages of the drugs, wherein the occurrence of death, nonfatal AMI, stroke with severe sequelae, nonfatal major bleeding, or intracranial hemorrhage was analyzed, the results obtained for enoxaparin were better.

The use of enoxaparin in patients with STEMI subjected to PPCI was assessed in the ATOLL study, published in 2011. The study included 910 patients who were randomly assigned to receive 0.5 mg/kg of enoxaparin intravenously or 70–100 IU/kg of UH intravenously (in case of patients who did not receive GP IIb/IIIa inhibitors) and 50 –70 IU/kg of UH intravenously (in case of patients who received GP IIb/IIIa inhibitors). The UH dose was adjusted by TCA during the procedure. In this study, there was no significant difference in the outcome of death, infarction, failure to perform the procedure, or major bleeding over 30 days ($p = 0.063$)[32]. In Brazil, physicians prefer to use UH over enoxaparin after PPCI in the hemodynamics room.

A meta-analysis with six studies, published in 2007, compared enoxaparin with UH in 27,131 patients with STEMI. A significant 16% reduction in the clinical outcome of death, nonfatal infarction, or nonfatal major bleeding was observed in the patients treated with enoxaparin over 30 days[33].

2.3.4. Fondaparinux

Fondaparinux is an antithrombotic agent that indirectly inhibits the Xa factor via selective bonding to antithrombin, inhibiting thrombin generation. The administration of fondaparinux in patients with STEMI was assessed in only one large clinical study. The OASIS-6 study[34], published in 2006, included more than 12,000 patients assigned to receive fondaparinux for 8 days or until discharge or to receive UH or placebo according to the researcher's indication. The patients

were treated with thrombolytic therapy or PPCI or did not receive reperfusion therapy. In this study, compared with the group that received UH or the placebo, a slight reduction in the incidence of death or reinfarction was observed over 30 days in the group that received fondaparinux (2.5 mg, first intravenous dose, followed by a subcutaneous dose of 2.5 mg/day). This advantage was obvious in the patients who received thrombolytic therapy (RR 0.79, $p = 0.003$) and in those who did not receive reperfusion therapy (RR 0.80, $p = 0.03$). However, this advantage was not observed in the patients undergoing PPCI because there was an increase in the incidence of catheter-related thrombosis and complications during the procedure and fondaparinux should not be used in these patients. There was no significant difference between the groups with regard to the incidence of major bleeding over 9 days.

2.3.5. Bivalirudin

In the HORIZONS-AMI study[35,36], published in 2008, 3,602 patients with STEMI within 12 h before the onset of symptoms who were referred for ICPP were randomly assigned to bivalirudin or UH combined with GP IIb/IIIa inhibitors. In this study, a 24% reduction in the relative risk for the primary outcome of death, reinfarction, and need for revascularization of the target vessel due to ischemia or stroke was observed in the group treated with bivalirudin over 30 days. In addition, there was a 40% reduction in the occurrence of major bleeding. Analysis of the secondary outcomes revealed that there was a 38% reduction in the occurrence of deaths caused by cardiovascular events and a 36% reduction in all-cause mortality. Despite the clear advantage of the use of this drug in treating patients with STEMI who will be subjected to PPCI, bivalirudin is still not available in Brazil.

Table 2 – Recommendations for the use of anticoagulants in patients with STEMI who underwent thrombolytic therapy

Recommendation class	Indications	Level of evidence	References
I	Enoxaparin 30 mg IV in bolus followed by 1 mg/kg SC every 12 h for 8 days or until hospital discharge in patients younger than 75 years. The intravenous dose should not be administered in patients older than 75 years, and enoxaparin administration should be maintained at 0.75 mg/kg SC every 12 h. Use 1 mg/kg/day in patients with creatinine clearance ≤ 30 ml/min	A	24-27
	UH 60 U/kg IV (loading dose), to a maximum of 4,000 U, followed by continuous infusion at 12 U/kg/h, to a maximum of 1,000 U/h, initially. Maintain for a minimum period of 48 h, with infusion adjustment, so that aPTT is kept maintained between 1.5–2.0 times that of the control	C	23.24
IIa	Fondaparinux 2.5 mg IV followed by 2.5 mg SC once daily for 8 days or until hospital discharge	B	29

IV: intravenous; SC: subcutaneous; UH: unfractionated heparin; aPTT: activated partial thromboplastin time.

Table 3 – Recommendations for the use of anticoagulants in patients with STEMI who underwent primary percutaneous coronary intervention (PPCI)

Recommendation class	Indications	Level of evidence	References
I	UH adjusted to ACT during PPCI, in the presence or absence of an association with GP IIb/IIIa inhibitors	C	-
IIa	Intravenous enoxaparin 0.5 mg/kg (loading dose), in the presence or absence of an association with GP IIb/IIIa inhibitors in replacement of UH. Enoxaparin should be maintained at 1.0 mg/kg subcutaneously every 12 h after PPCI, according to the clinician's opinion	B	28
III	Fondaparinux should not be used in patients who underwent PPCI	B	29

UH: unfractionated heparin; ACT: activated clotting time; aPTT: activated partial thromboplastin time; GP: glycoprotein; PPCI: primary percutaneous coronary intervention.

2.4. References

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3. Use of antiplatelet and anticoagulant agents in non-ST-segment elevation acute coronary syndrome (NSTEACS)

3.1. Introduction

NSTEACS is the most common form of acute coronary disease. These include low-, intermediate-, and high-risk unstable angina and non-ST elevation myocardial infarction (NSTEMI), which are characterized by changes in myocardial necrosis markers such as troponin and the absence of ST-segment elevation on the electrocardiogram.

In a large North American register with more than 46,000 patients[1], the mean prevalence of NSTEACS between 1999 and 2008 was approximately 67% among patients hospitalized for ACS. A recent study conducted in developing countries revealed that this percentage was similar to that of patients with STEMI; there were clear regional differences in terms of treatments used[2,3]. Moreover, the North American register shows that during the period under analysis, the incidence of hospitalizations due to ACS decreased, mainly because of the persistent reduction in the occurrence of STEMI. On the other hand, the incidence of NSTEMI increased up to 2004 and began to decrease thereafter. This increase may be attributed to the improvement in myocardial necrosis detection techniques, particularly with the advent and dissemination of increasingly sensitive troponin tests. In addition, the register shows a reduction in mortality over 30 days, between 1999 and 2008, in patients hospitalized due to ACS. Interestingly, patients with NSTEMI exhibited an 18% (HR 0.82, 95% CI, 0.67–0.99) reduction in the relative risk for death; on the other hand, mortality in patients with STEMI did not change significantly during this period (HR 0.93, 95% CI 0.71-1.20) despite the increase in the number of patients undergoing revascularization. It has been suggested that the increasing use of cardioprotective medications prior to coronary events (statins, angiotensin-converting enzyme inhibitors, angiotensin II type I receptor blockers, and beta blockers) is responsible for the reduction in the incidence of death in this population. Moreover, the use of troponin (and consequently, the increased sensitivity of NSTEMI diagnosis) has led to the inclusion of patients experiencing a less severe course of the disease and with better prognosis.

Intrahospital mortality among patients with NSTEACS is lower than that among those with STEMI (3%–5% vs. 7%). However, 6-month mortality is similar (13% vs. 12%), and after 4 years, the risk for death in patients with NSTEACS is twofold higher than that in patients with STEMI. This difference in the medium- to long-term evolution may be explained by some differences between the patients' profiles because patients with NSTEACS are older and have more comorbidities, namely diabetes and renal impairment, in addition to higher incidence of previous arteries, which increase the likelihood of reinfarction[4].

Because NSTEACS includes patients with distinct forms of clinical presentation and evolution, it is essential to adequately stratify the patients' risk when making therapeutic decisions, both in terms of ischemic events and bleeding. The "occasional" stratification initially proposed by Braunwald[5] and the various previously published scores enable careful analysis of ischemic events. The most commonly used risk scores are probably the TIMI risk score[6] and the GRACE score[7-9], each with their qualities and limitations[10,11]. It should be noted that the same patient is often at low, intermediate, or high risk according to different methods; in this situation, the worst scenario should be taken into account when making a decision. With regard to bleeding, other scores have been proposed, such as the one that resulted from the CRUSADE study[12] and the one proposed by Mehran et al.[13]. Many guidelines on antiplatelet and anticoagulant therapy presented in this section are directly associated with the risk group in which the patient was included; this demonstrates the importance of this step in the evaluation of patients with NSTEACS.

3.2. Antiplatelet therapy in NSTEACS

There are two well-established indications for the use of double antiplatelet therapy in patients with coronary artery disease: coronary stent implant (to prevent stent thrombosis) and after ACS (to prevent the recurrence of ischemic events).

3.2.1. ASA

The importance of ASA in the treatment of NSTEACS is based on studies published since the 1980s. One of the first studies published by Cairns et al.[14] in 1985 assigned groups to ASA, sulfinpyrazone [a uricosuric agent with anti-inflammatory activity via cyclooxygenase (COX) blocking], both drugs, or no drugs, in the context of unstable angina. This study included 555 patients and found a significant 51% ($p = 0.008$) reduction in the combined outcome of death and nonfatal acute myocardial infarction (AMI) in individuals who received ASA.

Soon after this, in 1988, a study was published that compared the use of ASA, heparin, or both in the treatment of unstable angina in 479 patients[15]. A significant reduction in the incidence of nonfatal AMI was observed in the groups that received ASA, both when used alone (3% vs. 12% in the placebo group, $p = 0.01$) and in combination with heparin (3% vs. 1.6% in the placebo group, $p = 0.003$); a low incidence of mortality was observed in this study, and it was not possible to identify differences between the groups. In 1993, the same group published a study comparing the use of ASA and heparin in unstable angina, with the aim of preventing the occurrence of infarction[16]. This study included 484 patients; there were only nine cases of infarction in the group that received ASA (244 patients) and only two cases of infarction in the group that received heparin (240 patients); the results of this study favored the isolated use of heparin over ASA ($p = 0.035$).

With regard to the dosage, ASA should be initially administered at a loading dose of 150–300 mg[17-19], followed by a maintenance dose of 75–100 mg/day. The CURRENT OASIS-7 study[20] tested the hypothesis of using a double maintenance dose of ASA in patients with ACS (approximately 71% of patients with NSTEACS). This study did not show any difference between the standard maintenance dose (75–100 mg/day) and the high

dose (300–325 mg/day) in the prevention of cardiovascular events (mortality, nonfatal myocardial infarction, or stroke; $p = 0.61$, 95% CI 0.86–1.09); in addition, no difference was observed with regard to major bleeding ($p = 0.90$, 95% CI 0.84–1.17).

Furthermore, it should be noted that the use of nonsteroidal anti-inflammatory drugs (such as rofecoxib, celecoxib, ibuprofen, and diclofenac) is associated with increased risk for ischemic events (these compounds cause transient blocking of COX-1, thereby inhibiting the irreversible blocking by ASA). Therefore, their combination with ASA should be avoided[21].

Therefore, the use of ASA in the context of NSTEACS, at the previously mentioned doses, is well established and is fundamental in this context. ASA should not be administered to patients with known allergy to the compound (a rare condition; the estimated prevalence is less than 0.5% of the population) and in cases of active bleeding in the digestive tract, particularly those related to gastric ulcers (due to the direct irritant effect of the compound associated with the antiplatelet effect on the stomach).

3.2.2. Clopidogrel

Clopidogrel, a thienopyridine derivative, inhibits the P2Y12 receptor for ADP, and it consequently inhibits the platelet aggregation process, which is mediated by this path. Clopidogrel is a pro-drug and is dependent on its first passage through the liver (and two modifications in this organ) for the formation of the active metabolite via metabolism by cytochrome P450 enzymes.

This agent was first studied in the context of NSTEACS during the CURE study[22], in which the isolated use of ASA (75–325 mg/day) was compared with the combined use of ASA and clopidogrel (loading dose of 300 mg, followed by a daily maintenance dose of 75 mg), in the context of intermediate- or high-risk unstable angina and NSTEMI. This study included 12,562 patients and revealed a 20% (9.3% vs. 11.4%, $p < 0.001$, NNT 48) reduction in the relative risk for the combined outcome of cardiovascular death, stroke, and nonfatal acute myocardial reinfarction. This advantage was the result of the reduction in the incidence of reinfarction. With regard to safety outcomes, the group that received clopidogrel exhibited a 38% increase in the incidence of major bleeding (3.7% vs. 2.7%, $p = 0.001$, NND 100); however, there was no difference in the incidence of life-threatening bleeding (2.1% vs. 1.8%, $p = 0.13$). In this study, 43.7% of patients (5,491 patients) underwent cine coronary angiography, 16.5% (2,072 patients) underwent myocardial revascularization surgery, and 21.2% (2,658 patients) underwent PCI. Clopidogrel was used during 12 months, with a mean use time of 9 months.

Substudies of CURE revealed that adding clopidogrel to ASA remained advantageous regardless of the subsequent treatment received (clinical, percutaneous, or surgical). The PCI-CURE study[23] revealed a 30% reduction in the relative risk for the combined outcome of cardiovascular death, stroke, and nonfatal AMI (4.5% vs. 6.4%, $p = 0.03$, NNT 48); there was no significant difference between the groups in terms of major bleeding ($p = 0.64$). In the portion of the sample exclusively subjected to clinical treatment, the group that received clopidogrel exhibited a 20% reduction in the relative risk for the combined outcome of cardiovascular death, stroke, and nonfatal AMI (8.1% vs. 10%, 95% CI 0.69–0.92, NNT 53). In the group subjected to myocardial revascularization surgery, this advantage was less clear; the group that received clopidogrel exhibited a 11% reduction in the relative risk for the combined outcome of cardiovascular death, stroke, and nonfatal AMI (14.5% vs. 16.2%, 95% CI 0.71–1.11); however, this difference was not statistically significant[24].

Another peculiarity of this drug is how quickly it produces beneficial effects. Temporal analysis in the CURE study[25] demonstrated that the reduction in the combined outcome of cardiovascular death, stroke, nonfatal AMI, and refractory ischemia occurred within the first 24 h of the administration of clopidogrel combined with ASA, with a 34% decrease in the relative risk ($p < 0.01$); in addition, this effect lasted for at least 12 months when a stent was placed.

With regard to the dose regimen, the CURRENT OASIS-7 study[20] assessed 25,086 patients and tested two hypotheses the use of a double maintenance dose of ASA (results previously discussed in this document) and the use of a 600 mg loading dose of clopidogrel, followed by a dose of 150 mg/day for 7 days and 75 mg/day thereafter. This regimen was compared with the standard regimen (300 mg loading dose, followed by 75 mg/day) in patients with acute coronary disease (approximately 70% of patients with NSTEACS). This study did not show any difference between the high dose and the standard regimen in terms of preventing cardiovascular events (cardiovascular deaths, nonfatal myocardial infarction, or stroke) over 30 days ($p = 0.30$). With regard to major bleeding, the group that received higher doses of clopidogrel exhibited a higher incidence of major bleeding (2.5% vs. 2.0%, $p = 0.01$). Analysis of secondary outcomes revealed a significant reduction in the incidence of stent thrombosis (1.6% vs. 2.3%, $p = 0.001$) in the group subjected to PCI (17,263 patients). This subpopulation deserved a specific study[26], wherein a 14% reduction in the incidence of cardiovascular deaths, nonfatal myocardial infarction, or stroke was observed over 30 days ($p = 0.039$, NNT 167), in addition to a significant reduction in definite stent thrombosis (0.7% vs. 1.3%, $p = 0.0001$), owing to a higher incidence of major bleeding (1.6% vs. 1.1%, $p = 0.009$, NNH 200).

Another important point is the high intra- and interindividual variability in the response to this compound, which is not observed with the more modern antiplatelet drugs. These limitations can be explained by genetic variability, such as differences related to the process of liver metabolism by cytochrome P450 enzymes (polymorphisms related to CYP3A4 and mainly to CYP2C19)[27] and to the process of intestinal drug absorption, which is associated with the expression of P-glycoprotein (Pgp), a product of the ABCB1 gene, in intestinal epithelial cells[28]. The routine use of genetic tests is not indicated in clinical practice because they only partially explain the poor response to clopidogrel[29]; however, platelet aggregation tests have been increasingly used. The GRAVITAS study[30] assessed 2,214 patients with poor response to clopidogrel (as determined by VerifyNow®

12–24 h after elective angioplasty with pharmacological stents) who were randomly assigned to receive a high dose of the drug (loading dose of 600 mg and maintenance dose of 150 mg/day) or standard dose, without a loading dose and with a maintenance dose of 75 mg/day (both regimens administered for 6 months). At the end of the follow-up period, no difference was observed between the two groups in terms of events (2.3% vs. 2.3%, $p = 0.97$). On the other hand, another study[31] compared > 100 patients subjected to elective PCI and followed them for 1 year; the results revealed that at the end of the follow-up period, most tests significantly correlated with events; however, the predictive capacity was poor or moderate at best. Thus, the use of platelet aggregation tests to guide therapy still does not have a defined place in clinical practice, and its routine use in NSTEACS is not recommended, with the exception of cases of patients with acute coronary disease receiving appropriate treatment with ASA in combination with clopidogrel.

Furthermore, various drugs that interfere with liver metabolism mediated by cytochrome P450 enzymes affect the action of clopidogrel, such as ketoconazole (by inhibiting cytochrome P450 and reducing the action of clopidogrel) and rifampicin (by inducing cytochrome P450 and promoting the action of clopidogrel). The combined use of proton pump inhibitors (PPI) and clopidogrel, an important point in clinical practice, has not been completely clarified till date. Several *in vitro* studies have revealed a reduction in platelet inhibition induced by clopidogrel when used in combination with PPI, particularly omeprazole. Small clinical studies have suggested an increase in the incidence of ischemic events when this combination is used; however, only one randomized clinical study has tested this hypothesis: the COGENT study[32], which assessed 3,761 patients with indication for double antiplatelet therapy for at least 12 months (one group received clopidogrel and omeprazole and another group received clopidogrel and placebo). This study was prematurely terminated for funding reasons; however, no differences were observed in the incidence of ischemic events between the patients (4.9% in the omeprazole group × 5.7% in the placebo group, $p = 0.96$). In addition, the placebo group exhibited a higher incidence of bleeding in the digestive tract (2.9% vs. 1.1%, $p < 0.001$). Thus, the use of PPI (particularly omeprazole) in combination with clopidogrel should be restricted to groups at higher risk for gastrointestinal bleeding (history of hemorrhage in the digestive tract, peptic ulcer, infection by *Helicobacter pylori* in individuals aged ≥ 65 years, concomitant use of anticoagulant agents or steroids). On the other hand, H2 blockers (ranitidine, cimetidine) may be used as an alternative.

Therefore, the use of clopidogrel is indicated for individuals with NSTEACS at moderate and high risk for ischemic events; a loading dose of 300 mg and a daily maintenance dose of 75 mg should be administered. In patients at low risk for bleeding and undergoing PCI, a loading dose of 600 mg may be considered, followed by a maintenance dose of 150 mg in the first 7 days and a dose of 7–5 mg/day thereafter. The ideal time of clopidogrel use is 12 months, regardless of the subsequent treatment (clinical, percutaneous, or surgical). In case of surgical procedure, clopidogrel should be discontinued for at least 5 days before the procedure.

In patients with indication for triple antithrombotic therapy, the use of clopidogrel is recommended in addition to P2Y12 receptor blockers; the concomitant use of clopidogrel and anticoagulant agents has not yet been tested in these patients.

3.2.3. Prasugrel

Prasugrel, a new generation thienopyridine, was developed to inhibit platelet aggregation more effectively than clopidogrel, thereby minimizing its limitations. Its active metabolite is similar to the active metabolite derived from clopidogrel; however, their metabolism differs: prasugrel solely depends on one oxidation phase in the liver; the first phase occurs via plasma esterases. Consequently, the antiaggregation effect occurs faster and more consistently and is less affected by agents that act on cytochrome P450.

The TRITON-TIMI 38 study[33], published in 2007, randomly assigned 13,608 patients with ACS (who had not previously received clopidogrel and those with known coronary anatomy and planned PCI) to clopidogrel or prasugrel combined with the standard therapy (including ASA). NSTEACS accounted for 74% of the sample. In the general cohort, the group that used prasugrel exhibited a 19% (9.9% vs. 12.1%, $p < 0.001$) reduction in the combined outcome of cardiovascular death, nonfatal infarction, or stroke (primary efficacy outcome), mainly due to the reduction in cases of nonfatal infarction (7.3% vs. 9.5%, $p < 0.001$); there were no significant differences in terms of cardiovascular deaths and stroke; the results of using the AMI universal classification[34] revealed that the decrease in the incidence of reinfarction occurred in all five types of infarction[35]. With regard to bleeding, the prasugrel group exhibited a 32% increase in the risk for major bleeding according to the TIMI score, which is the main safety outcome (2.4% vs. 1.8%, $p = 0.03$). In addition, there was a significant increase in the incidence of life-threatening bleeding (1.4% vs. 0.9%, $p = 0.01$). When evaluating the benefit–harm relation, a clear benefit of 13% ($p = 0.004$) in favor of clopidogrel was observed. Post hoc analyses identified three groups at higher risk for bleeding: individuals aged ≥ 75 years, weighing less < 60 kg (in these two subgroups, there was no clear benefit), and with a history of stroke/TIA (in which the net benefit was significantly favorable to clopidogrel). Prespecified subanalyses revealed that prasugrel was more effective than clopidogrel in several subgroups and that there was a special benefit for diabetic patients, although a significant interaction between diabetes and the results obtained in the prasugrel and clopidogrel groups was not demonstrated[36].

In conclusion, after determination of the coronary anatomy, the use of prasugrel in NSTEACS is indicated in cases of intermediate- and high-risk unstable angina and NSTEMI that have been referred for PCI. Prasugrel should be administered at a loading dose of 60 mg and at a maintenance dose of 10 mg/day, and its use should be continued for 12 months. A lower maintenance dose (5 mg) can be considered for individuals weighing less than 60 kg; however, such a dose has not been prospectively tested in clinical studies. The drug should be avoided in patients aged ≥ 75 years; if it is used, the recommended dose is 5 mg/day. The medication is contraindicated in the case of patients with a history of stroke/TIA. In case of surgical intervention, prasugrel should be discontinued for at least 7 days before the procedure.

3.2.4. Ticagrelor

Ticagrelor also inhibits the action of ADP via P2Y12 receptor blocking; however, unlike clopidogrel and prasugrel, it is not a thienopyridine; it is a cyclopentyl-triazolo-pyrimidine (CPTP). The characteristics of this chemical class are very different from those of thienopyridine drugs, e.g., the fact that it inhibits P2Y12 receptors in a reversible manner. Because this drug does not depend on primary metabolism (it is therefore not a pro-drug and its main effect is mediated by ticagrelor itself and, to a lesser extent, by an active metabolite), it inhibits platelet aggregation more rapidly, more consistently, and to a greater extent than clopidogrel. It has a relatively short half-life (approximately 12 h).

In particular, in acute coronary disease, ticagrelor was tested in the PLATO study[37], which randomly assigned 18,624 to ticagrelor or clopidogrel. The study design was very interesting because it included all types of acute coronary disease (with the exception of STEMI treated with a fibrinolytic drug), the possibility of using clopidogrel before patient randomization, or the possibility of using an additional dose of clopidogrel before PCI. In this study, clopidogrel or ticagrelor was administered during the initial treatment, without determining the coronary anatomy, and the patients were followed during the period of 1 year. In the sample, the prevalence of NSTEACS was approximately 60% (intermediate- and high-risk unstable angina, in addition to NSTEMI). During the intrahospital phase, 61% of individuals received percutaneous treatment, approximately 10% underwent myocardial revascularization surgery, and the remaining received only clinical treatment.

The use of ticagrelor resulted in a 16% reduction in the incidence of the primary efficacy outcome, death from vascular causes, nonfatal reinfarction, or stroke (9.8% vs. 11.7%, $p < 0.001$). Separate analysis of the components of the combined outcome revealed a significant reduction in the incidence of reinfarction (5.8% vs. 6.9%, $p = 0.005$) and cardiovascular deaths (4.0% vs. 5.1%, $p < 0.001$), and there were no significant differences with regard to the incidence of stroke. In addition, a significant 22% reduction in the incidence of all-cause mortality (4.5 vs. 5.9%, $p < 0.001$) was observed. With regard to safety outcomes, there were no significant differences in the incidence of major bleeding (according to different definitions) or need for transfusions in the overall population. Other secondary effects that exhibited a higher incidence in the ticagrelor group included dyspnea (13.8% vs. 7.8%, $p < 0.001$), usually transient and leading to discontinuation of the drug in 0.9% vs. 0.1% ($p < 0.001$); bradycardia was also usually transient did not differ between the groups in terms of clinical repercussions (pacemaker implant, syncope, or heart block). This was noted on Holter monitoring, which revealed a significant increase in the incidence of ventricular pauses of more than 3 s in the first 7 days of ticagrelor use (5.8% × 3.6%, $p = 0.01$) but was less significant after 30 days of drug use (2.1% vs. 1.7%, $p < 0.52$)[38]. Finally, a significant increase in creatinine (10% vs. 8%) and uric acid (14% vs. 7%) levels was observed; however, there were no significant differences between the groups 1 month after the end of the treatment.

The PLATO database resulted in the publication of several analyses of prespecified subgroups of patients, such as diabetic and nondiabetic[39], with or without renal impairment[40], with or without previous stroke[41], on or not on proton-pump blockers[42], referred for invasive or noninvasive treatment[43], and undergoing myocardial revascularization surgery[44]. In general, the results were very similar to those described in the original publication, in which the entire population was studied.

Therefore, the use of ticagrelor in NSTEACS is indicated in cases of moderate- or high-risk unstable angina and NSTEMI, regardless of the subsequent treatment strategy. Ticagrelor should be administered at a loading dose of 180 mg and a maintenance dose of 90 mg twice a day, and its use should be continued for 12 months. This medication can be administered in the emergency room, even without the determination of the coronary anatomy. In case of surgical intervention, ticagrelor should be discontinued 5 days before the procedure. Among other precautions (see package insert), the use of the drug should be avoided in patients with uremic nephrotic syndrome and care should be taken when administering to patients with bradycardia.

3.2.5. Glycoprotein (GP) IIb/IIIa inhibitors

The use of GP IIb/IIIa inhibitors is well established in patients with high ischemic risk (diabetic patients, patients with positive myocardial necrosis markers) subjected to PCI. This evidence mainly stems from studies in which the early invasive strategy and double oral antiplatelet treatment were not used[45-47]. However, a meta-analysis with more than 20,000 patients subjected to PCI revealed a 31% decrease in mortality at 30 days of follow-up, when the drug was used[48].

No studies have compared the use of double antiplatelet therapy with ASA and GP IIb/IIIa inhibitors with that of double oral antiplatelet therapy (ASA with clopidogrel, prasugrel or ticagrelor). Recent studies have assessed the use of triple antiplatelet therapy (double antiplatelet therapy and GP IIb/IIIa inhibitors), with the aim of determining when and in which patients this therapy should be used.

The EARLY ACS study[49] evaluated 9,492 patients with NSTEACS receiving double antiplatelet therapy (ASA and clopidogrel) and randomly assigned them to additional routine use of the GP IIb/IIIa inhibitor before PCI or its use in selected cases during PCI (presence of thrombi, diffuse disease, thrombotic complications). In this study, the GP IIb/IIIa inhibitor used was eptifibatide, a synthetic cyclic heptapeptide, not commercially available in Brazil. The results of EARLY ACS revealed that the routine use of the GP IIb/IIIa inhibitor did not significantly reduce the combined outcome of death, AMI, recurrent ischemia, and thrombotic complications in PCI (9.3% in the routine group vs. 10% in the selective group, RR 0.92, $p = 0.23$). On the other hand, routine triple antiplatelet therapy led to a significant increase in the outcome of major hemorrhage according to the TIMI criterion (2.6% vs. 1.8%, RR 1.42, $p = 0.015$).

The ACUITY study assessed the best moment to use GP IIb/IIIa inhibitors. It included 9,207 patients and a 2 × 2 factorial design: in addition to evaluating three antithrombotic regimens (heparin with the GP IIb/IIIa inhibitor, bivalirudin with the GP IIb/IIIa inhibitor, or only

bivalirudin), it randomly assigned patients from the GP IIb/IIIa inhibitors groups to routine use before PCI or use in selected cases during PCI. The routine use of triple antiplatelet therapy did not significantly reduce the primary combined outcome of death, AMI, and new revascularization over 30 days (7.1% vs. 7.9%, RR 1.12, $p = 0.13$). On the other hand, the use of GP IIb/IIIa inhibitors in selected cases resulted in a lower incidence of major hemorrhagic events (4.9% vs. 6.1%, RR 0.8, $p = 0.009$)[50].

Therefore, GP IIb/IIIa inhibitors should be used as a third antiplatelet agent in patients who are not at high risk for hemorrhage and who, on the other hand, are at high risk for clinical ischemia (positive necrosis markers, recurrent ischemia, ST-segment depression), only after confirmation by angiography (severe atheromatosis, presence of thrombi, and thrombotic complications of PCI).

It has been shown that when the drug is concomitantly used with the new oral antiplatelet drugs (prasugrel and ticagrelor), the benefits of the latter (see relevant chapter) occur regardless of using GP IIb/IIIa inhibitors, e.g., both the TRITON study and the PLATO study showed nonsignificant *p* values for the interaction with prasugrel (or ticagrelor) vs. the interaction with clopidogrel in patients also using or not using GP IIb/IIIa inhibitors[37,51].

The GP IIb/IIIa inhibitors that are commercially available in Brazil are abciximab and tirofiban. The meta-analysis published in 2010 revealed that in the studies wherein a higher loading dose of tirofiban (25 μg/kg) was used, this compound was equivalent to abciximab in terms of ischemic outcomes[52,53].

3.3. Anticoagulant therapy in NSTEACS

3.3.1. Fondaparinux

This is a synthetic pentasaccharide that selectively binds to antithrombin, indirectly causing the inhibition of factor Xa. It does not interact with many plasma components and therefore acts in a predictable manner with low individual variability. It has a half-life of 17 h and renal excretion [contraindicated in CrCl < 20 ml/min). It does not induce thrombocytopnea and does not need to be monitored.

Fondaparinux was initially evaluated in NSTEACS in the PENTUA study[54], which randomly assigned 1,138 patients to different doses of fondaparinux or enoxaparin. This phase II study concluded that the subcutaneous administration of 2.5 mg/day was safe and as effective as enoxaparin in preventing death, AMI, and recurrent ischemia.

The use of fondaparinux in the context of NSTEACS was assessed in the OASIS 5 study[55], which randomly assigned 20,078 patients to a fondaparinux group (2.5 mg subcutaneously once a day) or enoxaparin group (1 mg/kg every 12 h or every 24 h if CrCl < 30 ml/min). Fondaparinux was not inferior to enoxaparin with regard to the combined outcome of death and refractory ischemia over 9 days (RR 1.01, 95% CI 0.9–1.13, $p = 0.007$ for noninferiority), which was the main aim of the study. Moreover, the incidence of the main secondary outcome (death and infarction over 9 days) did not differ significantly between the groups. During the 30-day and

Table 1 – Recommendations for the use of antiplatelet therapy in acute coronary syndrome without ST-segment elevation

Class of recommendation	Indications	Level of evidence	References
I	ASA (162–300 mg as a loading dose, with a maintenance dose of 81–100 mg/day), for all patients, unless this is contraindicated, regardless of treatment strategy and for an undetermined period	A	14-20
	Clopidogrel (300 mg as a loading dose, with a maintenance dose of 75 mg/day, in addition to ASA, in patients with moderate- or high-risk unstable angina or NSTEMI, for 12 months	A	20;22-26;32
	Use of double antiplatelet therapy for 12 months after the acute event, unless this is contraindicated	A	22;33;37
	Ticagrelor (180 mg as a loading dose, followed by 90 mg twice daily), in addition to ASA, in patients with moderate- or high-risk unstable angina or NSTEMI, regardless of subsequent treatment strategy (clinical, surgical, or percutaneous) for 12 months	B	37-44
	Prasugrel 60 mg as a loading dose, followed by 10 mg/day, in addition to ASA, in patients with moderate- or high-risk unstable angina, in addition to NSTEMI, who underwent angioplasty and do not have risk factors for bleeding (age ≥ 75 years, weighing less than 60 kg, previous stroke/TIA)	B	33;35;36
	Addition of a GP IIb/IIIa inhibitor in patients at low hemorrhagic risk receiving double antiplatelet therapy who underwent high-risk PCI	A	45-53
IIa	Clopidogrel (600 mg as a loading dose, followed by 150 mg/day for 7 days and a subsequent dose of 75 mg/day), in addition to ASA, in patients who underwent PCI with high risk for ischemic events and low risk for bleeding	B	20
	Resume ticagrelor or clopidogrel treatment as soon as possible after myocardial revascularization surgery.	B	33;37;44
IIa	Tirofiban in addition to ASA in patients at high risk for ischemic events (positive troponin, recurrent ischemia) before catheterization	C	47;52;53
IIb	Use of tests of platelet aggregation or genetic tests (genotyping) in selected cases.	B	27-31
III	Combination of ASA with other NSAIDs	C	21
	Routine use of GP IIb/IIIa inhibitors in patients receiving double antiplatelet therapy before catheterization	A	50

ASA: acetyl salicylic acid (aspirin); PCI: percutaneous coronary intervention; TIA: transient ischemic attack; GP: glycoprotein; NSAI: nonsteroidal anti-inflammatory agents.

90-day follow-up, a significant reduction in mortality was observed (RR 0.83, $p = 0.02$ and RR 0.89, $p = 0.05$, respectively), mainly due to clinical treatment of patients, because there were no significant differences between the groups of patients subjected to PCI (RR 0.94 and 0.92 at 30 days and 180 days, respectively, p = NS).

The results of hemorrhagic outcomes were as follows: a significant reduction in major bleeding (2.2% vs. 4.1%, RR 0.52, $p < 0.001$) and a significant reduction in fatal bleeding in the population using fondaparinux owing to the significant increase in the incidence of catheter thrombosis (RR 3.59, $p = 0.001$). On the other hand, subanalysis of the OASIS 5 study[56] revealed that a reduction in major bleeding occurred in the group treated with fondaparinux, regardless of the use of GP IIb/IIIa inhibitors or thienopyridine drugs.

A possible explanation for this reduction in hemorrhagic events is that fondaparinux has a lower anticoagulation potential than enoxaparin. This conclusion stems from the fact that anti-Xa levels in individuals treated with fondaparinux are 50% lower than those in individuals treated with enoxaparin, which explains the increase in the incidence of catheter thrombosis in patients undergoing PCI, observed in the abovementioned OASIS 5 study[57]. Subananalysis including only the patients subjected to PCI (approximately 40% of the population in the OASIS 5 study) revealed that even in this subpopulation, the fondaparinux group had a significantly lower incidence of bleeding; however, there were no significant differences between the fondaparinux and enoxaparin groups in terms of the main outcome of the study (death, reinfarction, or stroke) or any of its components at 9, 30, or 180 days of follow-up[58].

The increase in the incidence of catheter thrombosis led to the modification of the protocol during the course of the OASIS 5 study, with the incorporation of a bolus of UH in the fondaparinux group. However, the ideal dose of a bolus of UH to be administered to the patients treated with fondaparinux during PCI was subsequently determined in the FUTURA OASIS 8 study. In this study, 2,026 patients initially treated with fondaparinux were randomly assigned to receive distinct doses of a bolus of UH during PCI. The patients would receive 50 IU/kg (regardless of the use of GP IIb/IIIa inhibitors) or 85 IU/kg (reduced to 60 IU/kg in the case of concomitant use with GP IIb/IIIa inhibitors). There was no significant difference between the groups in terms of the combined primary outcome of major bleeding, minor bleeding, or vascular complications. However, the net benefit in terms of major bleeding over 48 h and revascularization of the target vessel over 30 days was favorable in the group receiving a dose of 85 IU/kg (RR 1.51, $p = 0.05$). It should be noted that in this study, the incidence of catheter thrombosis while using the 85 IU/kg bolus was only 0.1%[59].

Therefore, the use of fondaparinux (2.5 mg subcutaneously once a day) has been proven to be a similarly effective alternative; however, its safety profile is better than that of enoxaparin in patients with NSTEACS, and the concomitant use of a bolus of UH in patients undergoing PCI is mandatory.

3.3.2. Unfractionated heparin (UH)

UH is a heterogeneous mixture of polysaccharide molecules (mean molecular weight between 15,000 and 18,000 Da). In general, only one-third of the molecules found in a solution of heparin have the necessary pentasaccharide sequence to bind to antithrombin and establish anticoagulant activity.

A study by Théroux et al.[15] compared the isolated use of ASA or UH with the combined use of the two drugs or the use of a placebo. This was a randomized and double-blind study with 479 patients with unstable angina who were evaluated for the occurrence of refractory angina, AMI, or death. Compared with the placebo group, the isolated use of ASA and UH led to a significant reduction in the occurrence of IAM, with UH showing better results. Moreover, there was a marked reduction in the occurrence of recurrent angina in the group treated with UH. In this study, the combined use of ASA and UH did not confer additional protection against the risk for ischemic events and was associated with a slight increase in the risk for bleeding.

The ATACS study[19,60], published in 1994, randomly assigned 214 patients with unstable angina or NSTEMI to UH in addition to ASA or no therapy. A significant reduction in the occurrence of ischemic events was observed at 14 days of follow-up in the patients who received the combination of ASA and UH (10.5% vs. 27%, $p = 0.004$); however, this difference was not statistically significant in the 12-week evaluation (19% vs. 28%, $p = 0.09$). In addition, there was a slight increase in the incidence of bleeding in the group that received UH.

Analysis of the most relevant clinical studies comparing the benefits of UH and ASA in patients with unstable angina and NSTEMI revealed a significant reduction in the risk for AMI or death in the patients who received combined therapy (ASA) and UH compared with that in the patients who received only ASA (RR 0.44, 95% CI 0.21–0.93)[61].

With the advent of LMWH, several studies were conducted to compare the efficacy of UH with that of the new drugs in reducing the risk for ischemic events, associated with better results in terms of bleeding risk-related safety. In a meta-analysis published in 2000, involving 17,157 patients with NSTEACS included in 12 clinical studies, there was no significant difference in the occurrence of death or AMI between therapy with LMWH or UH (RR 0.88, $p = 0.34$). On the other hand, both were highly effective in reducing the risk for AMI or death in comparison with the placebo or untreated controls (RR 0.53, $p = 0.0001$)[62].

3.3.3. Low-molecular-weight heparin (LMWH)

LMWH is a heterogeneous group of compounds derived from heparin, and its molecular weights vary between 2,000 and 10,000 Da. This group of compounds exhibits some very important advantages over UH[61]; these include convenient dosage and administration route (i.e., intermittent use and subcutaneous administration); no need to monitor the anticoagulant effect, with the exception of special situations (such as obesity and renal failure) wherein anti-Xa activity should be monitored whenever possible (therapeutic target

between 0.6 and 1.0 IU/ml)[63]; almost complete absorption via the subcutaneous route; lower binding to proteins; lower platelet activation; and, most importantly, a more predictable dose–effect relation.

Compared with the use of UH, there was a nonsignificant 12% reduction in the occurrence of death or AMI during the initial phase of LMWH use. On the other hand, the main representative of LMWH is enoxaparin, and it is the most used in clinical practice. Enoxaparin was compared with UH in the context of NSTEACS in several studies. The ESSENCE and TIMI 11B studies showed, for the first time, the superiority of LMWH over UH[64]. However, because these studies were conducted at a time when the invasive strategy was not used and certain antithrombotic agents (such as GP IIb/IIIa inhibitors) still did not exist, further studies on the subject were required, and the SYNERGY study was therefore conducted[65]. This study randomly assigned 10,027 high-risk NSTEACS patients, allocated to early invasive strategy, to receive enoxaparin or UH. The primary aim of the study was to analyze the combined outcome of all-cause death or myocardial infarction in the first 30 days after randomization. Of the total sample, 92% of the patients were underwent cine coronary angiography, 47% underwent percutaneous revascularization, and 19% underwent surgical revascularization, distributed equally between the enoxaparin or UH groups. With regard to the primary outcome, there was no difference between the LMWH and UH groups (14% vs. 14.5%, $p = 0.4$). A similar result was observed at 48 h and at 14 days ($p = 0.10$ and 0.38, respectively). With regard to safety outcomes, the enoxaparin group exhibited a higher incidence of major bleeding according to the TIMI score ($p = 0.008$); however, no significant difference was observed according to the GUSTO score ($p = 0.08$) or when the number of transfusions was used as parameter ($p = 0.15$). In the population subjected to PCI, the incidence of any unsuccessful PCI, threat of acute occlusion, acute occlusion, and emergency myocardial revascularization surgery was similar between the groups. This study showed very relevant results regarding the crossover of heparin during the treatment of these patients. Of the total population, approximately 6,000 patients used only one heparin during hospitalization, and in this population receiving a "consistent therapy," post hoc analysis revealed a significant reduction in the incidence of the primary outcome of death or AMI over 30 days of evolution with the use of LMWH (12.8% vs. 15.6%, RR 0.81, $p = 0.003$).

A meta-analysis that included approximately 22,000 patients with NSTEACS treated with enoxaparin or UH[66] revealed the following: a significant reduction in the combined outcome of death and myocardial infarction over 30 days in the enoxaparin group (RR 0.91, 95% CI 0.83–0.99) and nonsignificant differences in the incidence of major bleeding (RR 1.04, CI 0.83–1.30) or need for transfusions (RR 1.01, 95% CI 0.89–1.14); in the subpopulation without heparin therapy before randomization, the benefits of enoxaparin with regard to death or AMI were amplified when compared with UH (HR 0.81; 95% 95% CI 0.70–0.94).

The recommended dose of enoxaparin to be used is 1 mg/kg every 12 h; this dose should be adjusted to 1 mg/kg once a day in case of renal failure with CrCl < 30 ml/min and to 0.75 mg every 12 h in elderly patients aged > 75 years. If a percutaneous procedure (angioplasty) is performed within 8 h of the last dose of enoxaparin, there is no need for an additional dose of enoxaparin; if the angioplasty is performed more than 8 h after the last dose of enoxaparin, an additional dose of 0.3 mg/kg should be intravenously administered. The concomitant use of enoxaparin and UH during hospitalization should be avoided[67].

Therefore, LMWH should be used in patients with high- and intermediate-risk NSTEACS in addition to NSTEMI, at the described doses, until PCI or myocardial revascularization surgery is performed; in case of clinical treatment, it should be used for 8 days or until the patient is discharged; its use for a longer period than this is associated with increased risk for bleeding without significant reduction in ischemic events[68,69].

3.3.4. New anticoagulant agents

Phase III studies have analyzed two oral Xa factor inhibitors (apixaban and rivaroxaban) combined with double antiplatelet therapy in the context of acute coronary disease. The APRAISE-2 study randomly assigned 7,392 patients to apixaban (5 mg every 12 h) or placebo, 6 days (on average) after the onset of symptoms compatible with ACS. The study was prematurely terminated owing to a significant increase in major bleeding according to the TIMI criterion (HR 2.59, $p = 0.001$), without the observation of significant benefits in terms of ischemic events[70]. The dose of apixaban used was the same as that tested in the context of atrial fibrillation (AF), which would explain the excessive severe bleeding.

The use of rivaroxaban in a similar population (4.7 days on average after an acute ischemic event) was assessed in the ATLAS ACS 2 study[71], in which > 15,000 patients were randomly assigned to three groups: rivaroxaban 2.5 mg every 12 h, rivaroxaban 5 mg every 12 h, and placebo (both doses were much lower than those tested in the context of AF). The 2.5 mg dose resulted in better results, with a relative 16% reduction in the primary goal of the study, the combined outcome of cardiovascular death, AMI , and stroke ($p = 0.007$), at the end of a 2-year follow-up; moreover, there was a significant reduction in cardiovascular death (HR 0.66, $p = 0.005$) and all-cause death (HR 0.68, $p = 0.004$). With regard to safety, the rivaroxaban group exhibited a significant increase in the incidence of nonsurgery-related bleeding (HR 3.46, $p < 0.001$), as expected; however, there was no significant increase in the incidence of fatal bleeding ($p = 0.45$).

With regard to thrombin inhibitors, the concomitant use of dabigratan and double antiplatelet therapy was evaluated after ACS in the REDEEM study[72]. In this study, there was a marked increase in the incidence of bleeding at the different doses tested (50, 75, 110, and 150 mg).

Table 2 – Recommendations for the use of anticoagulants in patients with acute coronary syndrome without ST-segment elevation

Class of recommendation	Indications	Level of evidence	References
I	UH 60–70 U/kg IV (loading dose), to a maximum of 5,000 U, followed by continuous infusion at 12–15 U/kg/h, to an initial maximum of 1,000 U/h, for a minimum period of 48 h. aPTT should be maintained between 1.5–2.0 times that of the control.	A	19.60.62
	Enoxaparin 1 mg/kg SC 12/12 h (if age > 75 years, 0.75 mg/kg subcutaneously 12/12 h; if CrCl < 30 ml/min, 1 mg/kg subcutaneously once daily) for 8 days or until hospital discharge	A	61.63-69
	In patients receiving fondaparinux, administer UH 85 U/kg intravenously at the time of PCI; administer 60 U/kg in patients using GP IIb/IIIa inhibitors.	B	55;59
	In patients who will continue receiving clinical treatment, anticoagulation should be maintained for 8 days or until hospital discharge.	A	61.63-65.68.69
IIa	Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated.	C	65;68;69
IIb	Rivaroxaban 2.5 mg every 12 h, in addition to double antiplatelet therapy with ASA and clopidogrel	B	71
III	Heparin switch (UH and enoxaparin)	B	65

IV: intravenous; SC: subcutaneous; UH: unfractionated heparin; aPTT: activated partial thromboplastin time; GP: glycoprotein; PCI: percutaneous coronary intervention; CrCl: creatinine clearance.

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4. Use of antiplatelet and anticoagulant agents in stroke and transient ischemic attack (TIA)

4.1. Introduction

Stroke is the second main cause of morbidity and mortality in Brazil. Data from the DATASUS of 2010 revealed that stroke accounted for deaths in 99,732 patients (http://tabnet.datasus.gov.br/cgi/tabcgi.e.,xe?sim/cnv/obt10uf.def)[1]; the leading cause is ischemic heart disease. In addition, it is essential to recognize TIA because it is a strong predictor of stroke.

Furthermore, it should be noted that of the patients who survived the first event, many will have recurrent stroke. Therefore, the secondary prevention of new events is fundamental.

This section aims to evaluate the use of antiplatelet and anticoagulant drugs in the secondary prevention of noncardioembolic stroke (described in section 5, "Use of antiplatelet and anticoagulant agents in atrial fibrillation"), particularly cases of atherosclerotic origin.

4.2. Antiplatelet therapy in stroke

The main mechanisms involved in the pathophysiology of stroke are arterial thrombosis, particularly related to atherosclerotic disease, and cardioembolic events, which confirms that platelet aggregation plays an important role in the development of stroke. Thus, the use of medications that act by blocking platelet aggregation reduces the rate of vascular events (including new stroke, acute myocardial infarction, and death).

Most studies involving antiplatelet agents in the secondary prevention of stroke analyze combined cardiovascular events; this prevents an effective determination of the rate of stroke recurrence.

Next, we describe the existing evidence in favor of prescribing antiplatelet agents for the secondary prevention of stroke /TIA after the acute 48-h phase.

4.2.1. ASA

The use of ASA is the standard secondary prevention against stroke and TIA. A meta-analysis published in 1999[2] assessed the efficacy of ASA in the prevention of new cerebrovascular events. In total, 11 studies were included in the analysis (with a total of over 9,500 patients), wherein ASA was compared with a placebo with regard to the prevention of *de novo* stroke in patients who had already suffered a previous episode of ischemic stroke/TIA. The results of this meta-analysis revealed that there was an approximately 15% reduction in the occurrence of *de novo* cerebrovascular events with the use of ASA and the difference was statistically significant. An important aspect of this study was the observation that the reduction in risk did not depend on higher doses of ASA, which suggests that even lower doses are effective in secondary prevention. Another factor to be taken into account is that higher doses of ASA are associated with a higher number of hemorrhagic events, particularly in the gastrointestinal tract. Therefore, the use of ASA at low doses (e.g., 100 mg) seems to be effective in the secondary prevention of stroke/TIA, with less adverse effects.

4.2.2. ASA in combination with dipiridamol

The effectiveness of dipiridamol compared with that of ASA in the secondary prevention of ischemic stroke was evaluated in four major clinical trials. Among these, the ESPS-2 study[3] randomly assigned more than 6,000 patients who had ischemic stroke or TIA to ASA (25 mg twice a day), sustained-release dipiridamol (200 mg twice a day), ASA in addition to sustained-release dipiridamol (25/200 mg twice a day), or placebo. The primary outcomes assessed were stroke and death. The group that received the combined therapy exhibited a 23.1% and 24.7% reduction in the relative risk for ischemic stroke and TIA, respectively, compared with the groups that received ASA and dipiridamol alone, and the difference was statistically significant. However, the dose of ASA used in this study was low. With regard to adverse effects, the incidence of bleeding was higher in patients who used ASA, both in the ASA group and in the group receiving ASA and dipiridamol. The patients who used dipiridamol experienced more headaches and gastrointestinal symptoms, particularly diarrhea.

The ESPRIT study[4] randomly assigned more than 2,500 patients with stroke or TIA to ASA (the dose varied between 30 and 325 mg/day and the average dose was 75 mg/day) or ASA combined with sustained-release dipiridamol (the dose of dipiridamol was 200 mg twice a day). The primary outcome assessed was a combination of acute myocardial infarction (AMI), stroke, and death from cardiovascular causes or bleeding. These events occurred in 13% of patients under double therapy and in 16% of patients in the group under monotherapy. However, an intriguing fact observed in this study was that there was a higher occurrence of hemorrhagic events in the patients receiving only ASA than in those receiving double therapy. Therefore, ASA combined with sustained-release dipiridamol (200 mg twice a day) is an interesting option for secondary prevention in patients with ischemic stroke or TIA. However, this form of dipiridamol is still not available in Brazil.

In general, the studies showed that dipiridamol combined with ASA was as effective as ASA alone, although the patients less tolerated it.

4.2.4. Ticlopidine

The CATS study[5] involved more than 1,000 patients who had stroke; they were randomly assigned to ticlopidine (250 mg twice a day) or placebo to determine the reduction in *de novo* stroke, AMI, or death from vascular causes. Compared with the placebo group, the ticlopidine group (assessed by intention to treat) exhibited a 23.3% reduction in the relative risk for events, and the difference was statistically significant. The most common adverse effects related to the use of ticlopidine were neutropenia, skin rash, and diarrhea (all were reversible after drug discontinuation).

The TASS study[6] randomly assigned more than 3,000 patients who had stroke or TIA to ticlopidine (250 mg twice a day) or ASA (625 mg twice a day). The primary outcome assessed was *de novo* stroke or all-cause mortality. There was a 12% reduction

in the relative risk as a result of using ticlopidine. However, the incidence of side effects when ticlopidine was used (similar to the CATS study) was higher than when ASA was used.

The AAASPS study[7] selected almost 2,000 African-American patients who recently had a stroke. The patients were randomly assigned to ticlopidine (250 mg twice a day) or ASA (325 mg twice a day). The outcomes assessed were *de novo* stroke, AMI, or death from cardiovascular causes. The incidence of stroke and TIA in the ticlopidine group was 14.7% and 12.3% in the ASA group; however, the difference was not statistically significant. The side effects of using ticlopidine were similar to those observed in the previous studies.

Considering that the number of severe adverse events observed with the use of ticlopidine is higher than that observed with the use of a similar drug, clopidogrel, the use of ticlopidine has no longer been considered as an alternative to ASA.

4.2.5. Clopidogrel

No studies have compared clopidogrel with a placebo in the secondary prevention of stroke.

The CAPRIE study[8] involved more than 19,000 patients with manifest atherosclerotic disease (ischemic stroke, acute myocardial infarction [AMI], and symptomatic peripheral vascular disease). The patients were randomly assigned to ASA (325 mg/day) or clopidogrel (75 mg/day). The primary outcome was a combination of ischemic stroke, AMI, intracranial hemorrhage, leg amputation, and death. There was a relative 8.7% reduction in risk for events with the use of clopidogrel. If we only consider patients with ischemic stroke, there was a relative 7.3% reduction in the risk for events with the use of clopidogrel; however, the difference was not statistically significant. It should be noted that this study was not designed to assess events only in patients with previous ischemic stroke.

The PRoFESS study[9] randomly assigned more than 20,000 patients with a history of stroke to clopidogrel (75 mg/day) or ASA in addition to sustained-release dipiridamol (25/200 mg twice a day). The primary outcome assessed was recurrent stroke. The rate of primary events in the patients who received clopidogrel was 8.8%, whereas that in the patients who received ASA in combination with sustained-release dipiridamol was 9.0%. This was a noninferiority study; however, the treatment regimens were found to be equivalent. Moreover, the number of hemorrhagic events was higher in the patients who received ASA in combination with sustained-release dipiridamol than in those who received clopidogrel.

4.2.6. ASA plus clopidogrel

The MATCH study[10] selected more than 7,500 patients who were using clopidogrel and had stroke or TIA to receive ASA (75 mg/day) or a placebo. The primary outcome assessed was stroke, AMI, death from vascular causes, or rehospitalization for acute ischemia. There was a 9.5% reduction in the relative risk for events in the patients who received clopidogrel in addition to ASA; however, the difference was not statistically significant. The group that received the combined therapy exhibited more hemorrhagic events.

The CHARISMA study[11] randomly assigned more than 15,000 patients with manifest atherosclerotic disease or with multiple risk factors to ASA combined with placebo or ASA combined with clopidogrel for determining whether the association of antiplatelet agents was more effective in reducing AMI, stroke, or death from cardiovascular causes than the use of ASA alone. The results demonstrated a reduction in the risk for events with the use of the antiplatelet drug combination; however, the difference was not statistically significant. The combination of ASA with clopidogrel increased the rate of bleeding. In subgroup analysis that included only the patients with manifest atherosclerotic disease (excluding the patients who only exhibited risk factors for atherosclerotic disease), a statistically significant reduction in the primary outcome was observed. However, analysis that only included the poststroke patients did not reveal a statistically significant reduction in primary outcomes with the combination of ASA and clopidogrel.

The FASTER study[12] aimed to assess the potential benefits of adding clopidogrel to ASA in terms of reducing the primary outcome (stroke, TIA, AMI, or all-cause mortality). However, the recruitment of patients failed and the study was prematurely terminated. The results of this study suggest that the combination of ASA (a loading dose of 162 mg, followed by a maintenance dose of 81 mg/day) and clopidogrel (a loading dose of 300 mg, followed by a maintenance dose of 75 mg/day) was not effective in reducing events and increased the bleeding rate.

4.2.7. Cilostazol

A Chinese pilot study (CASISP)[13] randomly assigned 720 postischemic patients to ASA or cilostazol; the dose used in each group of patients was not indicated. The primary outcome assessed was the recurrence of ischemic and hemorrhagic stroke. A 38% reduction in the relative risk for events was observed in the group that received cilostazol, and the event curves began to diverge 6 months after the use of medication. However, there was no statistically significant difference. Headaches, tachycardia, palpitations, and dizziness were the most common side effects among the patients who used cilostazol.

In the Japanese CSPS-2 study[14] (a noninferiority study), more than 2,500 postischemic stroke patients were randomly assigned to ASA (81 mg/day) or cilostazol (100 mg twice a day). The primary outcomes assessed were similar to those assessed in the CASISP study. Cilostazol reduced the likelihood of primary events in 25% patients and was thus not lesser effective than ASA in preventing postischemic stroke events. Another advantage of using cilostazol was the lower incidence of hemorrhagic events. However, it should be noted that patients in the ASA group used more antidiabetic, antihypertensive, and lipid-lowering medications, which confirmed the higher severity of the disease in this group. The adverse effects of using cilostazol were similar to those observed in the CASISP study.

4.2.8. Glycoprotein (GP) IIb/IIIa inhibitors

Abciximab was tested in a phase II study in postacute ischemic stroke patients and was shown to be safe if administered within 24 h after the event[15].

On the other hand, the AbESTT-II study16, a multicenter phase III study with a higher number of patients, did not show abciximab to be safe or effective in patients with ischemic stroke. The study was prematurely terminated owing to the higher incidence of bleeding in the group that received abciximab.

4.3. Anticoagulant therapy in stroke

Arterial thromboembolism is an important mechanism in the pathophysiology of ischemic stroke. In general, multicenter studies have not demonstrated that anticoagulant agents are beneficial in the secondary prevention of noncardioembolic ischemic stroke.

Next, we describe these studies and address the use of heparin after acute stroke.

4.3.1. Warfarin

The SPIRIT study[17] randomly assigned more than 1,700 poststroke or TIA patients to ASA 300 mg/day or warfarin (target INR [international normalization ratio] between 3.0 and 4.5). The primary outcome assessed was a combination of death from cardiovascular causes, stroke, AMI, or major hemorrhagic complications. This study was prematurely terminated owing to the statistically higher incidence of events in the group that received warfarin (RR 2.3). The occurrence of events was most influenced by hemorrhagic complications, including those that led to death. Therefore, the use of warfarin to keep INR between 3.0 and 4.5 is not safe in patients with ischemic stroke or TIA.

The WARSS study[18] involved more than 2,200 postischemic stroke patients who were randomly assigned to ASA (325 mg/day) or warfarin (target INR between 1.4 and 2.8). The primary outcomes assessed were all-cause mortality and recurrent ischemic stroke. The group that received warfarin exhibited a 1.13-fold higher risk for primary events than the group that received ASA, without a statistically significant difference. The risk for major bleeding was 1.48-fold higher in the warfarin group, without a statistically significant difference.

The ESPRIT study[3] randomly assigned postischemic stroke or TIA patients to warfarin (target INR between 2.0 and 3.0) or ASA (doses varying between 30 and 325 mg/day). The primary outcome assessed was similar to that evaluated in the SPIRIT study. Furthermore, post hoc analysis was performed to compare the use of warfarin with the combination of ASA and sustained-release dipiridamol (200 mg twice a day); the same outcome was assessed in both the cases. The incidence of events was 19% in the warfarin group and 18% in the ASA group, without a statistically significant difference. Considering only ischemic events, there was a 27% reduction in the relative risk for events with the use of warfarin; however, the difference was not statistically significant. The risk for major bleeding was 2.56-fold higher in the group that received warfarin; the difference was statistically significant. It is important to note that in post hoc analysis, the risk for primary events was 1.31-fold higher in the warfarin group than in the group using the combination of ASA with sustained-release dipiridamol, although there was no statistically significant difference.

The chronic use of oral anticoagulant drugs is recommended in some specific clinical conditions, such as stroke due to cerebral artery dissection, acquired thrombophilia, and antiphospholipid antibody syndrome, according to indirect evidence from clinical trial subgroups, series of cases, and the opinion of specialists. It is not within the scope of this review to address these conditions.

4.3.2. Unfractionated heparin (UH)

The number of studies on the use of UH in the acute phase of stroke is small.

A single-center study[19] randomly assigned more than 400 patients in the first 3 h after lacunar ischemic stroke to endovenous UH (target aPTT between 2.0 and 2.5) or saline solution. The primary outcome assessed was the autonomy in daily activities 90 days after the acute event. The safety outcomes were death, symptomatic intracranial hemorrhage, and other major bleeding. After 90 days, the percentage of patients who received heparin with primary outcome was 38.9% and that of patients who received saline solution was 28.6%; the difference was statistically significant. However, symptomatic intracranial hemorrhage occurred in 6.2% of patients in the treatment group and

Table 1 – Recommendations for the use of antiplatelet agents for the secondary prevention of noncardioembolic ischemic stroke or transient ischemic attack

Recommendation class	Indications	Level of evidence	References
I	ASA (81–300 mg/day) for secondary prevention in patients with ischemic stroke or TIA	A	2
	Clopidogrel (75 mg/day) for secondary prevention in patients with ischemic stroke or TIA or as an alternative treatment in cases with ASA contraindications	B	8.9
IIa	Ticlopidine (250 mg twice daily) as secondary prevention in patients with ischemic stroke or TIA or as an alternative treatment in cases with ASA contraindications	B	5-7
IIb	Cilostazol (100 mg twice daily) as secondary prevention in patients with ischemic stroke or TIA	B	13.14
III	ASA plus clopidogrel as secondary prevention in patients with ischemic stroke or TIA	A	10.11.12
	GP IIb/IIIa Inhibitors as secondary prevention in patients with ischemic stroke or TIA	B	15.16

ASA: acetylsalicylic acid; TIA: transient ischemic attack; GP: glycoprotein.

1.4% of patients in the control group; the difference was also statistically significant.

A meta-analysis[20] assessed the use of anticoagulant drugs (including heparin and oral anticoagulant agents) in acute ischemic stroke. The results showed that the use of anticoagulant drugs did not reduce mortality or improve the patients' autonomy.

4.3.3. Low-molecular-weight heparin (LMWH)

A study conducted in Hong Kong[21] randomly assigned approximately 300 patients within 48 h after acute stroke to receive nadroparin at high doses (4,000 IU twice a day), nadroparin at low doses (4,000 IU once a day), or a placebo for 10 days. The primary outcome assessed was death or autonomy in daily activities. At 3 months of follow-up, no difference was observed between the groups. However, in 6-month analysis, the percentages of patients with the primary outcome were as follows: 45% in the group that received high-dose nadroparin, 52% in the group that received low-dose nadroparin, and 65% in the placebo group, without any increase in hemorrhagic transformation. It is important to note that this study included patients with cardioembolic stroke.

Another study[22] on nadroparin did not show any advantages of using this medication and demonstrated that higher doses are associated with higher bleeding rates.

It should be noted that the use of any antiplatelet or anticoagulant drug is contraindicated within 24 h after intravenous thrombolytic treatment of ischemic stroke with alteplase[23].

4.3.4. Anticoagulation following a hemorrhagic cerebral event

Deciding the best time to return to full anticoagulation therapy after a hemorrhagic cerebral event in previously anticoagulated patients is a great challenge. The evaluation of the risk for thrombotic events and new hemorrhagic events is important. Therefore, some factors must be taken into account in this assessment: the motive for which the patient is anticoagulated, age, presence of systemic arterial hypertension, level of anticoagulation, presence of small bleeding areas on magnetic resonance, dialysis, and presence of lobar hemorrhage.

A study[24] assessed more than 230 patients who presented acute cerebral hemorrhage and used anticoagulant drugs. Of these patients, 177 survived the first week. Only 33% of patients restarted anticoagulation therapy after the hemorrhagic event. Recurrence of hemorrhagic events occurred in eight patients who restarted anticoagulant therapy and in 10 patients who did not receive anticoagulant therapy. The risk for embolic events was higher in the group that was not anticoagulated. After a statistical model was applied, the authors determined that the ideal time to restart anticoagulation therapy was between 10 and 30 weeks after the event.

In another study[25], in which more than 700 patients were followed after intracranial hemorrhage, Hanger et al. observed that the risk for a new hemorrhagic event was 2.1% in the first year of follow-up and the risk for ischemic stroke was 1.3%.

Overall, it is important to note that if there is a need to start the patient on anticoagulant therapy, the administration of UH using a continuous infusion pump should be preferred because titration and reversal are easier with this medication[26].

Table 2 – Recommendations for the use of anticoagulants after noncardioembolic ischemic stroke or transient ischemic attack

Recommendation class	Indications	Level of evidence	References
IIb	Resume anticoagulation 10–30 weeks after hemorrhagic stroke.	B	24.25
III	Warfarin after noncardioembolic ischemic stroke or TIA	A	3.17.18
	Unfractionated heparin after noncardioembolic ischemic stroke or TIA	A	19.20
	LMWH after noncardioembolic ischemic stroke or TIA	B	22.23

TIA: transient ischemic attack; LMWH: low-molecular-weight heparin.

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5. Use of antiplatelet and anticoagulant agents in atrial fibrillation (AF)

5.1. Introduction

AF is the most common form of sustained arrhythmia in clinical practice. Its incidence and prevalence increase as the population ages, doubling every decade of life after 50 years of age. AF is associated with an increase in the risk for stroke, heart failure and overall mortality[1-6].

Stroke is the third cause of death in developed countries and the main cause of severe long-term incapacity; it has a negative impact on treatment costs. At least one in every five strokes is caused by AF[5,7-10]. In addition, stroke secondary to a thromboembolic event in a patient with AF is usually more severe and disabling than ischemic stroke[9,10]. Furthermore, it is important to highlight the increased risk for cognitive disorders in the population with AF. Small observational studies have shown that asymptomatic embolic events can contribute to cognitive deficit in patients with AF in the absence of clinically diagnosed stroke[11].

This document focuses on the update of antithrombotic therapy in AF in view of the main advances in risk stratification in the prevention of thromboembolic phenomena and the incorporation of new antithrombotic therapies, such as dabigatran, rivaroxaban, and apixaban.

5.2. Application of thromboembolic risk scores in patients with AF

The main AF treatment strategies include the improvement of symptoms (via rhythm or heart rate control) and prevention of thromboembolic phenomena. However, AF can be silent in the preclinical and clinical phases or after invasive interventions. In the presence of risk factors, the prevention of thromboembolic phenomena is considered most important for the treatment of AF, regardless of the adopted strategy (rhythm or heart rate control)[12,13]. In addition, the paroxysmal form of AF exhibits the same risk for stroke as the persistent and permanent forms.

The risk for thromboembolic phenomena can be determined using the $CHADS_2$ score[14-16] as well as the recent CHA_2DS_2–VASc score[17] (Chart 1 and Table 1). This new score resulted in a "real" separation between uncertain low risk and certain low risk. Moreover, several patients previously classified as being at intermediate risk according to the old score were now part of high-risk groups according to the new risk score, with a clinical impact (less thromboembolic events). New risk factors were incorporated in the score, such as female gender, presence of arterial vascular disease (such as coronary artery disease, peripheral vascular disease, or plaque in the aorta), and intermediate age (between 65 and 74 years). Age ≥ 75 years now correspond to a score of 2 points because of the high risk associated with this factor. Thus, the CHA_2DS_2–VASc score is a refinement of the $CHADS_2$ score, when the latter is 0 or 1. Because the CHA_2DS_2–VASc score automatically includes the risk factors of the old $CHADS_2$ score, it is simpler and more accurate to assess the risk thromboembolic phenomena in AF using the CHA_2DS_2–VASc score. CHA_2DS_2–VASc scores above 1 indicate anticoagulant therapy (Table 2).

The customary indications for anticoagulation, based on the CHA_2DS_2–VASc score, are shown in Tables 2 and 3.

5.3. Risk for hemorrhagic phenomena during oral anticoagulation therapy

Strong evidence indicates a beneficial action of chronic oral anticoagulation (COA) therapy in patients at risk. On the other hand, this therapy is associated with hemorrhagic complications[18-22], one of the most feared complications being intracranial hemorrhage, which is almost always related to levels of INR above the therapeutic range (INR > 3.5–4.0). Because the therapeutic range of INR is very narrow, several scores have been developed to assess the hemorrhagic risk; the HAS-BLED risk score [Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly (> 65 years), Drugs/Alcohol Concomitantly][23] is the most used in patients with AF. If the score is ≥ 3, COA

Chart 1 – CHA_2DS_2–VASc score. The criteria for vascular disease include: previous myocardial infarction, peripheral arterial disease, aortic plaque. Score ≥2 points represents an indication for chronic anticoagulation.

CHA_2DS_2–VASc		
Acronym	**Parameter**	**Score**
C	CHF	1
H	Hypertension	1
A_2	Age = age > 75 years	2
D	Diabetes	1
S_2	Stroke = previous stroke/TIA	2
V	Vascular disease	1
A	Age = age between 65–74 years	1
Sc	Gender category = female gender	1

Table 1 – CHA_2DS_2–VASc score and annual stroke risk according to the score

CHA_2DS_2–VASc score	Annual stroke* risk (%)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

**Derived from multivariate analysis assuming the absence of use of ASA*
ASA, acetyl salicylic acid (aspirin)

should be administered very carefully and all efforts should be made to control the risk factors, such as arterial hypertension and alcohol consumption.

5.4. Use of new anticoagulant agents in patients with AF

5.4.1. Results from large studies

Warfarin, at adjusted doses, is highly effective in the prevention of thromboembolic phenomena in AF by reducing this risk by 64% in adequately treated patients[24-26]. Despite this success, 50% of patients who are supposed to be treated are not indeed, owing to several reasons that include the need for frequent evaluation of the anticoagulation rate (periodical INR monitoring) and hemorrhagic risk[24,25]. On the other hand, patients treated with this medication are not always within the appropriate therapeutic range. This is because of the irregular use of the medication, the interaction between warfarin and foods (particularly "greens") and other medications such as antibiotics and anti-inflammatory drugs. The likelihood of anticoagulation being outside the therapeutic range is particularly noteworthy in the elderly, who usually take other drugs for the treatment of associated conditions. Furthermore, there is the possibility of resistance to the drug owing to individual genetic characteristics. Thus, although anticoagulant therapy is highly effective, it has some disadvantages and does not benefit the population that needs it the most.

In recent years, the discovery of thrombin or factor Xa inhibitor drugs has brought a new perspective on anticoagulant therapy[27]. These drugs do not require anticoagulation monitoring (INR) and have little interaction with medications and foods. Owing to these characteristics as well as their high efficacy and safety, these new drugs have the potential to increase adherence to treatment with COA as well as the number of treated patients. Three new generation anticoagulant drugs had a phase III clinical trial approval: dabigatran, rivaroxaban, and apixaban. Dabigatran is a direct thrombin competitive inhibitor and the remaining are factor Xa inhibitors.

Dabigatran was compared to warfarin in the prevention of systemic thromboembolism (STE) in a study involving approximately 18,000 patients with paroxysmal or permanent AF. Patients were aged ≥ 75 years; in the latter case, patients had more than one associated risk factor such as heart failure, diabetes, arterial hypertension, or a previous history of stroke. Patients were randomly assigned to warfarin at doses adjusted according to INR or fixed doses of dabigatran (110 mg and 150 mg twice a day). This was an open study, based on intention to treat analysis, with a maximum follow-up period of 3 years. The mean $CHADS_2$ risk score of the assessed population was 2.3, and the time in therapeutic range for patients who used warfarin was 64%. The RE-LY study used the criterion of noninferiority of the new anticoagulant agent relative to warfarin, i.e., the criterion that the efficacy and safety of the new agent are at least equal to those of warfarin[28,29].

Table 2 – Indications according to CHA_2DS_2–VASc score

Risk category	CHA_2DS_2–VASc	Recommended therapy
Absence of risk factors	0	No therapy or ASA 81–300 mg
1 nonmajor clinical risk factor	1	OAC or ASA 81–300 mg
1 major risk factor or ≥ 2 nonmajor clinically relevant risk factors	≥ 2	OAC

OAC: oral anticoagulation; ASA: acetyl salicylic acid (aspirin).

Table 3 – Recommendations for the use of antiplatelet and anticoagulant agents for atrial fibrillation

Class of recommendation	Indications	Level of evidence	References
I	The selection of antithrombotic therapy should be considered independently of the type of AF (paroxysmal, persistent, or permanent)	A	14.42
	It is recommended that the selection of antithrombotic therapy be based on the absolute risk of embolic events (CHA_2DS_2–VASc) and bleedings(HAS-BLED), relative risk, and benefits for each patient, particularly the elderly; in addition, oral anticoagulation therapy should be considered in most patients	A	8.14.17
	Warfarin (INR between 2.0 and 3.0) and ASA (81–300 mg/day) are also recommended in patients with a CHA_2DS_2–VASc score of 1	A C	14 14
	Anticoagulation therapy is recommended in patients with a CHA_2DS_2–VASc score ≥ 2. In cases in which vitamin K antagonists are selected, INR should be kept between 2.0 and 3.0	B	8.14.17
	In stable patients with AF who are scheduled to undergo electrical or chemical cardioversion, OAC is recommended for at least 3 weeks before and 4 weeks after cardioversion, with INR in the therapeutic range (2.0–3.0). Four weeks after cardioversion, OAC maintenance must be achieved according to the CHA_2DS_2–VASc risk score	B	14.43
	In patients with AF who have a mechanical valve prosthesis, the maintenance of warfarin is recommended, with INR of at least 2.5 (mitral and/or aortic prosthesis)	B	42.22
	OAC is indicated in patients with an atrial flutter under the same conditions as those described for AF	C	38-42
IIa	The combination of ASA 81-100 mg/day with clopidogrel 75 mg/day may be considered for the prevention of stroke in patients who refuse to receive anticoagulation therapy or when this therapy is contraindicated	B	42.44

OAC: oral anticoagulation; ASA: acetylsalicylic acid (aspirin); AF: atrial fibrillation; INR: international normalization ratio; HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (> 65 years), Drugs/alcohol concomitantly[23]

In the RE-LY study, the annual rate of stroke or systemic embolism was 1.71% for warfarin, 1.54% for the 110 mg dose of dabigatran (RR 0.90; 95% CI 0.74–1.10), and 1.11% for the 150 mg dose of dabigatran (RR 0.65; 95% CI 0.52–0.81). Hemorrhagic stroke rate was lower with the use of both doses of dabigatran [150 mg (0.10%) and 110 mg (0.12%)] than with the use of warfarin (0.38%) ($p < 0.001$ for both doses). Major bleeding rate was 3.57% with the use of warfarin, 2.8% with the use of 110 mg of dabigatran ($p = 0.003$), and 3.22% with the use of 150 mg of dabigatran ($p = 0.31$).

Regarding to side effects, there was a higher rate of dyspepsia in the group that received dabigatran and a slight increase in the risk for gastrointestinal bleeding at a dose of 150 mg. A higher numeric risk for myocardial infarction was observed in patients receiving dabigatran (0.82% and 0.81% for 110 mg and 150 mg, respectively) than in those receiving warfarin (0.64%/year; $p = 0.09$ and 0.12, respectively), but with no statistical significance.

These findings revealed that dabigatran was safe and effective in preventing TE in patients with AF. The 150 mg dose of dabigatran was superior to warfarin (with similar bleeding rate), while the 110 mg dose of dabigatran had a similar efficacy and lower bleeding rate.

The ROCKET-AF study[30] compared rivaroxaban with warfarin in the prevention of TE in 14,264 patients with nonvalvular AF and with risk factors for thromboembolism (mean $CHADS_2 = 3.47$). A 20 mg fixed dose of rivaroxaban once a day (dose of 15 mg for patients with renal clearance between 30 and 49 ml/min) was compared with warfarin in a double-blind manner using the criterion of noninferiority In a per protocol analysis, the annual rate of stroke was 1.7% for rivaroxaban and 2.2% for warfarin [the relative risk (RR) in the rivaroxaban group was 0.79; 95% CI 0.66–0.96, $p < 0.001$ for noninferiority]. Based on the intention to treat analysis, thromboembolic events occurred in 2.1% (per year) of patients who received rivaroxaban and in 2.4% of patients who received warfarin (RR 0.88, 95% CI 0.74–1.03, $p < 0.001$ for noninferiority; $p = 0.12$ for superiority). The rates of major and clinically nonmajor bleeding were similar in both groups (14.9% vs. 14.5%, RR 1.03, 95% CI 0.96–1.11, $p = 0.44$); however, the rates of hemorrhagic stroke were lower with rivaroxaban than with warfarin (0.5% vs. 0.7%, $p = 0.02$) and the same trend was observed in fatal bleeding rates (0.2% with rivaroxaban and 0.5% with warfarin, $p = 0003$).

Regarding to secondary prevention, a recent presentation confirmed the noninferiority of rivaroxaban relative to warfarin. In a prospective evaluation of 7,468 patients with a previous history of stroke/TIA (CHADS2 score of 3.93), the rate of stroke recurrence was 13% lower in the group that received rivaroxaban than in the group that received warfarin (2.26% in the rivaroxaban group and 2.60% in the warfarin group; RR 0.87, 95% CI 0.69–1.10)[31].

Apixaban was assessed in two large studies. The double-blind AVERROES study[32] compared apixaban (at a dose of 5 mg twice a day) with aspirin in 5,599 patients with AF and at risk for stroke, who, for some reason, could not use warfarin[32]. The study was prematurely stopped because there was a clear reduction in TE and stroke with the use of apixaban (1.6% for apixaban and 3.7% for aspirin, RR 0.45, 95% CI 0.32–0.62), with similar rates of major hemorrhage (1.4% for apixaban and 1.2% for aspirin, RR 1.13, 95% CI 0.74–1.75). Death rate was 3.5% in the apixaban group and 4.4% in the aspirin group (RR 0.79, 95% CI 0.62–1.02, $p < 0.07$).

The ARISTOTLE study[33,34] compared apixaban at a dose of 5 mg twice a day with warfarin (INR between 2 and 3) in a double-blind manner using the criterion of noninferiority in 18,201 patients with AF and with at least one additional risk factor for stroke. In a 1.8-year follow-up, the annual rate of primary events was 1.27% in the apixaban group and 1.60% in the warfarin group (RR with apixaban 0.79, 95% CI 0.66–0.95, $p < 0.001$ for noninferiority; $p < 0.01$ for superiority). Major bleeding rate was 2.13% in the apixaban group and 3.09% in the warfarin group (RR 0.69, 95% CI 0.60–0.80, $p < 0.001$). The annual rate of all-cause mortality was 3.52% for apixaban and 3.94% for warfarin (RR 0.89, 95% CI 0.80–0.99, $p = 0.047$). Hemorrhagic stroke rate was 0.24% in the apixaban group and 0.47% in the warfarin group (RR 0.51, 95% CI 0.35–0.75, $p < 0.001$). The annual rate of ischemic stroke or stroke of undetermined cause was 0.97% in the apixaban group and 1.05% in the warfarin group (RR 0.92, 95% CI 0.74–1.13, $p = 0.42$). Therefore, apixaban was superior to warfarin in reducing stroke and TE and exhibited a lower risk for hemorrhage and mortality[34].

5.5. Considerations on electrical cardioversion with the new oral anticoagulant agents

The use of new oral anticoagulant drugs for the prevention of thromboembolic phenomena in patients with AF leads us to an important topic regarding the strategy to be used in case these patients need to undergo electrical cardioversion. Data are still scarce in the literature; however, subgroup analysis resulting from the RE-LY study revealed that cardioversion could be performed without major risk for thromboembolic phenomena, provided the patients were on chronic dabigatran therapy[35]. Data on rivaroxaban and apixaban are still not available.

5.6. Recommendations on the use of the new oral anticoagulant agents

The results of the studies on the new oral anticoagulant drugs (NOACs) reinforce the new indications for their use (dabigatran, rivaroxaban, and apixaban) in patients with AF and risk factors for thromboembolic events. However, until the end of this paper, we will limit the recommendations to the drugs currently available in Brazil: dabigatran and rivaroxaban.

Pharmacovigilance is of utmost importance as the use of these new drugs in the "real world" increases. Till date, there is no specific antidote for dabigatran, whose half-life is short (between 12 and 17 h). In case of bleeding, treatment may vary from basic care (minor bleeding) to transfusion of blood derivatives, oral administration of activated charcoal, hemodialysis, and surgical intervention (major bleeding). In case of minor bleeding, interrupting the dose for 12–24 h or, if appropriate, reducing the subsequent dose (e.g., from 150 mg to 110 mg) may be sufficient. Although not a specific

antidote, the prothrombin complex can be used to reverse the anticoagulant activity of factor Xa inhibitors[36]. The recommendations on the use of dabigatran and rivaroxaban in AF are shown in Tables 4 and 5, respectively.

5.7. Use of heparin in patients with AF

UH is mainly used in the prevention of thromboembolic phenomena in patients subjected to electrical or chemical cardioversion of AF; however, it has lost prominence to LMWH. The type of heparin preferred for the maintenance of anticoagulation in patients with AF is LMWH, which is administered when the ideal adjustment of ACO has not been achieved or when its use must be temporarily interrupted because of diagnostic or therapeutic procedures that carry risk for hemorrhage. Although there are three types of LMWH (dalteparin, enoxaparin, and nadroparin), enoxaparin is the most used in clinical practice. The indications for the use of heparin in AF are shown in Tables 6 and 7[37].

Table 4 – Recommendations for therapy with dabigatran in atrial fibrillation

Class of recommendation	Indications	Level of evidence	References
I	Dabigatran is recommended as an alternative to warfarin in patients with nonvalvular AF in whom oral anticoagulation is indicated	A	27-29.39-42
	The preferential dose of dabigatran is 150 mg twice daily, particularly in patients with major risk for stroke and/or thromboembolic phenomenon, as long as they have low risk of bleeding	A	27-29.39-42
	This drug may be indicated as an alternative to vitamin K antagonist anticoagulation in case of patients who have difficulties in maintaining adequate INR or difficulties in controlling blood sampling or as per the patient's choice	C	42
IIa	Dabigatran is indicated for patients with nonvalvular atrial fibrillation and a CHA_2DS_2–VASc = 1	C	42
	In patients with major risk of bleeding (age ≥ 75 years; creatinine clearance between 30 and 50 ml/min; a previous history of gastrointestinal or intracranial bleeding; concomitant use of ASA, clopidogrel, amiodarone, or chronic or abusive use of NSAIDs; and BMI <18 kg/m^2), the preferential dose of dabigatran is 110 mg twice daily	C	27.35
	In stable patients with persistent AF who are scheduled to undergo electrical or chemical cardioversion, at least 3 weeks of continuous use of dabigatran (preferentially 150 mg/twice daily) is recommended, without a need for tests or monitoring. ETE is optional. During the 4 weeks of cardioversion, dabigatran should be administered and its continuation should be decided in accordance with the CHA_2DS_2–VASc risk score	C	35.39-42
III	Dabigatran was not tested adequately and should not be used in individuals with valvular prostheses or hemodynamically severe valvular disease or during pregnancy	B	27

AF: atrial fibrillation; ASA: acetyl salicylic acid (aspirin); NSAID: nonsteroidal anti-inflammatory drug; TEE: transesophageal echocardiogram; BMI: body mass index; INR: international normalization ratio.

Table 5 – Recommendations for therapy with rivaroxaban in atrial fibrillation

Class of recommendation	Indications	Level of evidence	References
I	Rivaroxaban is recommended as an alternative to warfarin in patients with nonvalvular AF and who have indication for oral anticoagulation	B	30,31,39-42
	The recommended dose of rivaroxaban is 20 mg once daily, provided that the bleeding risk is low	B	30,31,39-42
	This drug can be indicated as an alternative to the vitamin K antagonist in case of patients with difficulty in maintaining adequate INR or difficulties in controlling blood sampling or as per the patient's choice	C	42
IIa	Rivaroxaban is indicated for patients with nonvalvular atrial fibrillation and a CHA_2DS_2–VASc = 1	C	42
	In patients with creatinine clearance between 30 and 49 ml/min, the recommended dose of rivaroxaban is 15 mg once daily	C	30, 39-42
II	Rivaroxaban has not been adequately tested and should not be used in patients with prosthetic valves, in patients with hemodynamically severe valve disease, and during pregnancy	B	30
	In situations of CHADSVasc zero or up to 1 (if it is only by the female sex), the non-use of oral anticoagulation (such as rivaroxaban) may be considered	A	42

FAF: atrial fibrillation; INR: international normalization ratio.

5.8. Summary of the international guidelines

In addition to Diretrizes Brasileiras de Fibrilação Atrial[38], various international guidelines have been published regarding anticoagulation in AF, with a clear preference for the new anticoagulant drugs as anticoagulation agents in patients with nonvalvular AF[39-42]. However, other topics remain controversial, and consensus has not been reached with regard to recommendations such as which agent to use (and for how long) after AF ablation.

Table 6 – Recommendations for therapy with unfractionated heparin in atrial fibrillation

Class of recommendation	Indications	Level of evidence	References
I	Administration of UH should be considered during the first trimester and during the last month of pregnancy in patients with AF and risk factors for thromboembolism. The dose should be sufficient to prolong aPTT to a value 1.5–2 times the baseline control time, or it should be intermittently administered via the subcutaneous route at a dose of 10,000–20,000 U every 12 h, adjusted to prolong the mean interval (6 h after injection) of aPTT to a value 1.5 times the baseline control time	B	14
	In patients subjected to electrical cardioversion guided by transesophageal echocardiography and in the absence of thrombi, intravenous UH (bolus followed by continuous infusion) is recommended before cardioversion and should be maintained until full oral anticoagulation is reached	B	14
	In patients with AF who need emergency electrical cardioversion, intravenous UH (bolus followed by continuous infusion) is recommended	C	14

UGFH: unfractionated heparin; AF: atrial fibrillation; TEE: transesophageal echocardiogram.

Table 7 – Recommendations for therapy with low-molecular-weight heparin in atrial fibrillation

Class of recommendation	Indications	Level of evidence	References
I	In patients undergoing electrical cardioversion guided by transesophageal echocardiography and in the absence of thrombi, full dose of LMWH is recommended before cardioversion, and it should be maintained until full oral anticoagulation is reached	B	14,37
	In patients with AF who need emergency electrical cardioversion, full dose of LMWH is recommended	C	14,37
IIa	Despite the limited studies, subcutaneous administration of LMWH should be considered in the first and last trimesters of pregnancy in patients with AF and risk factors for thromboembolism	C	14,37

TEE: transesophageal echocardiogram; LMWH: low-molecular-weight heparin; AF: atrial fibrillation.

5.9. References

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6. Use of antiplatelet and anticoagulant agents in valvular disease

6.1. Introduction

It is well documented that valvular dysfunctions, regardless of the cardiac rhythm and mainly in the presence of atrial fibrillation (AF), put patients at increased risk for embolic events[1]. Systemic thrombolism (STE) has been shown to be one of the severe complications following the formation of a thrombus in the atrial chamber. Thromboembolic phenomena can significantly modify the natural history of valvular disease, and its prevention should be considered during disease follow-up[2].

In practice, two groups of antithrombotic agents are available:

- Oral anticoagulant drugs. This group includes phenprocumon (Marcoumar®), acenocoumarol (Sintrom®), phenindione (Dindevan®), crystalline sodium warfarin (Cumadin®), and sodium warfarin (Marevan®). Of the four compounds, sodium warfarin is the most used in clinical practice.
- Anticoagulant agents for parenteral use: heparin. This group includes UH (Liquemin®) and LMWH: dalteparin (Fragmin®), nadroparin (Fraxiparine®), and enoxaparin (Clexane®).

Treatment of valvular dysfunctions with oral anticoagulant agents is prolonged and oral administration is therefore preferred. The use of heparin (via endovenous or subcutaneous administration) is indicated for special treatment situations.

6.2. Oral anticoagulation with warfarin

Of the anticoagulant compounds that are administered orally, both forms of warfarin (sodium warfarin and crystalline sodium warfarin) are the most used because of their advantageous characteristics, namely good availability, predictable onset and duration of action[3,4].

Warfarin has been used in clinical practice for more than half a century. Despite this fact, it is still underused because of difficulties in controlling coagulation, drug interactions, and lack of compliance.

6.3. Parenteral anticoagulant agents

Of the injectable anticoagulant compounds, LMWH is the drug of choice because of its anticoagulation efficacy and practicality of use.

The isolated or combined use of both forms of anticoagulant drugs depends on their half-life. If the aim is to rapidly achieve antithrombotic protection, heparin is used concomitantly with oral warfarin[4].

Heparin, particularly LMWH, can be used after implanting a mechanical valvular prosthesis if the risk for bleeding is considered until oral anticoagulation is initiated and INR is within the appropriate range[5-15]. Moreover, it is useful in the transition between oral anticoagulation discontinuation and a surgical/intervention procedure ("heparin bridge") in patients with valvular disease and indication for permanent anticoagulation therapy[16-18], in pregnant women (from pregnancy diagnosis to week 12 of gestation), and in women with valvular disease and with indication for permanent anticoagulation therapy (from week 36 of gestation)[16,19,20].

6.4. Initial and maintenance doses of oral anticoagulant agents

The initial and maintenance doses should be guided by INR (international normalization ratio) values. The initial dose is 2.5 mg/day in patients aged > 65 years and 5 mg/day in the remaining patients. Laboratory monitoring of INR should be performed after 5 days. Following dose adjustment, the adequate dose is achieved when the values of three blood samples collected at 5-day intervals are within the desired range. It has been suggested that patients aged > 65 years are more sensitive to warfarin because of lower liver metabolism. Liver cells that form the sarcoplasmic reticulum of the P450 system, where warfarin is metabolized, secrete less enzyme[18]. Achievement of target values of INR throughout the treatment is difficult because of numerous external factors such as fluctuation of the vitamin K dose (the intake of this vitamin varies with frequently modified diets), use of multiple drugs with agonist or antagonist effects, and gastric mucosa edema resulting in lower drug absorption. It is recommended that the patient follows a balanced diet without great restrictions and anticipates blood collection for INR monitoring when there is a need to start a new medication. Once the correct dose is achieved, INR monitoring can be performed every 30 days[19].

The best moment for warfarin administration is open for debate. One study has reported that absorption is greater at the proximal level (stomach and duodenum) of the gastrointestinal tract[19], while another study has added that the absorption rate depends on the presence of food[20]. Based on reports, it is suggested that the drug should be taken in the morning, after fasting, to avoid the influence of gastric pH, which is modified by ingested foods. In clinical practice, no differences have been observed as a result of distinct times of drug intake.

6.5. Anticoagulation in valvular disease with native valve

Rheumatic mitral valve disease (RMVD) is more thrombogenic than aortic lesions, and it results in a fivefold increase in the incidence of embolic events. STE is not frequent among patients with aortic valve disease, particularly stenosis from calcification and sinus rhythm. Holley et al.[21] attribute the presence of microemboli, particularly renal microemboli, to aortic degeneration.

AF is the most common arrhythmia in mitral dysfunctions; it occurs in 26% of patients with mitral stenosis and in 16% of patients with mitral insufficiency. In aortic dysfunction, AF is also more common in stenotic lesions (5%). The presence of AF results in a 17.5-fold increase in TE[22].

Studies have failed to show that left atrial dilatation (55 mm) is associated with higher risk for STE *per se*. However, patients with left atrial diameter ≥ 55 mm and

associated risk factors such as advanced age, presence of intracavitary thrombus, or even spontaneous contrast are candidates for thromboembolism prevention[5].

Coulshed et al.[22] revealed that in mitral valve dysfunction (mitral stenosis and mitral insufficiency, even in sinus rhythm), the incidence of STE varies from 7.7% to 8%. In the presence of AF, this incidence is three- to fourfold higher (21.1% vs. 31.5%).

In patients who exhibit aortic calcification and sinus rhythm, without a previous history of thromboembolic events, anticoagulation is not recommended.

Oral anticoagulation is recommended in patients with aortic stenosis or insufficiency who develop AF[5,6].

Aspirin can be used as an alternative for STE prevention in patients in unfavorable economic conditions, at a dose of 200–300 mg/day[2].

6.6. Anticoagulation in patients with a mechanical prosthesis

It is generally agreed that a mechanical prosthesis exposes the patients to an increased risk for STE, regardless of the cardiac rhythm. This risk is estimated to be 12%/year for a prosthesis in the aortic position and 22% for a prosthesis in the mitral position, in the absence of oral anticoagulation therapy[7].

Patients with a mechanical prosthesis, regardless of their mitral/aortic position and cardiac rhythm, require antithrombotic prevention treatment. When they are implanted in the aortic position and the cardiac rhythm is sinusal, in the absence of other risk factors for STE, INR should be between 2.0 and 3.0[3]. Mechanical prostheses in the aortic position are less thrombogenic because this is a site of high flow and pressure where fibrin deposition is reduced. However, even with a prosthesis in the aortic position, if the patient has AF rhythm, it is recommended to maintain INR between 2.5 and 3.5. Because bleeding in elderly patients is a relatively common complication[8], it is recommended to keep INR between 2.0 and 2.5 and to monitor this parameter more frequently[9].

In patients with a mechanical prosthesis implanted in the mitral position, regardless of the cardiac rhythm, prophylactic care against thromboembolism should be greater and mean INR of 3.0 (2.5–3.5) is recommended.

In patients with a mechanical prosthesis, in the presence of any risk factor for STE, such as blood hypercoagulability, previous thromboembolism in the presence of adequate anticoagulation, or compromised ventricular function, it is recommended to add oral aspirin at a dose of 50–100 mg/day to the anticoagulation therapy. The exceptions are as follows: elderly patients aged ≥ 80 years or those with a tendency for gastrointestinal bleeding[10].

6.7. Anticoagulation in patients with a biological prosthesis

Bioprostheses are less thrombogenic. However, some authors believe that the risk for STE is higher in the first 3 months after implantating a prosthesis. Thrombogenicity may be associated with suture stitches and nonendothelized traumatized perivalvular tissues[11].

In patients with a biological prosthesis implanted in the mitral and aortic positions, even in sinus rhythm, the recommended oral anticoagulant agent for use in the first 3 months after surgery is class IIb (Table 3).

Regardless of the position of the bioprosthesis, in the presence of AF or hypercoagulability, oral anticoagulation should be prolonged and INR should be maintained at approximately 2.5.

The presence of an intracavitary thrombus found during the surgical procedure requires anticoagulation for a minimum period of 3 months after surgery. Even if the thrombus is removed during the procedure, INR should be kept at approximately 2.5 (2.0–3.0).

These recommendations are based on studies[13,14] in which the authors observed a high incidence of embolic events (6.9%) among patients who did not receive antithrombotic prevention treatment in the first 3 months after surgery.

Table 1 – Recommendations for the prevention of thromboembolism in valvular disease with native valve

Class of recommendation	Indications	Level of evidence	References
I	Oral anticoagulation in patients with valve disease and AF rhythm	B	5
	Oral anticoagulation in patients with valve disease and previous episode of TE, even in sinus rhythm	B	6
	Oral anticoagulation in the presence of thrombus in the left atrium	C	6
IIa	Antithrombotic prevention with aspirin in patients with valve disease and AF rhythm and contraindications for oral anticoagulant drugs	B	2
	Anticoagulation in patients with left atrium ≥ 55 mm in the presence of spontaneous contrast in sinus rhythm	C	6

AF: atrial fibrillation; TE: thromboembolism.

Table 2 – Recommendations for the prevention of thromboembolism in valvular disease with mechanical prosthesis

Class of recommendation	Indications	Level of evidence	References
I	Maintain INR between 2.0 and 3.0 in patients with an aortic mechanical prosthesis in sinus rhythm	B	16
	Maintain INR between 2.5 and 3.5 in patients with an aortic mechanical prosthesis in AF	B	16
	Combine ASA 81–100 mg/day with oral anticoagulation in patients with an aortic or mitral mechanical prosthesis and any risk factor for factor TE	B	10
	Maintain INR between 2.5 and 3.5 in patients with a mitral mechanical prosthesis, regardless of the cardiac rhythm	C	16

INR: international normalization ratio; AF: atrial fibrillation; TE: thromboembolism; ASA: acetyl salicylic acid (aspirin).

Table 3 – Recommendations for the prevention of thromboembolism in valve disease with biological prosthesis

Class of recommendation	Indications	Level of evidence	References
I	Oral anticoagulation in patients with a biological prosthesis in any position and AF rhythm	B	16
	Oral anticoagulation during the first 3 months after the implant of the biological prosthesis in the mitral position or in any position, if an intracavitary thrombus is found during surgery	C	16
IIb	Oral anticoagulation during the first 3 months after the implant of the biological prosthesis in the aortic and mitral position in patients in sinus rhythm	B	16
III	Antithrombotic prevention with long-term oral anticoagulant drugs in patients with a biological prosthesis in sinus rhythm, in the absence of other conditions that indicate anticoagulation	C	16

AF: atrial fibrillation.

6.8. References

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7. Use of antiplatelet and anticoagulant agents in venous thromboembolism (VTE)

7.1. Introduction

VTE has a high impact on morbidity and mortality in the general population; however, it can be prevented in most cases. Thus, its treatment and prevention through the use of specific medication is very important. Until recently, the anticoagulant drugs used in clinical practice were fractioned heparin and UH, fondaparinux, and warfarin. However, these drugs exhibit limitations, such as its injectable use (heparin and fondaparinux) and a narrow therapeutic window associated with a strong interaction with various drugs and foods (warfarin). Therefore, new anticoagulant agents were developed to overcome these limitations and enable oral treatment with fixed doses, without the need for routine laboratory monitoring.

These drugs have been tested in randomized controlled studies that included a large number of patients. However, clinical studies do not represent the "real world" because patients at high risk for hemorrhage or with more clinical complications are usually excluded. Didactically, we will consider that VTE encompasses deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE).

Most studies comparing enoxaparin with the new anticoagulant drugs for primary prevention in case of knee and hip prostheses surgeries focus on the occurrence of asymptomatic DVT; however, cost/benefit analysis requires the assessment of the occurrence of symptomatic VTE and bleeding.

7.2. Assessment of the risk for VTE and prevention

The prevention of VTE is indicated for hospitalized medical patients who are aged > 40 years, have an expected duration of limited mobility of 3 days or more, have at least one risk factor for TEV, and are not at increased risk for bleeding; prophylactic therapy should be maintained at least until hospital discharge. All patients hospitalized in intensive care units are deemed at high risk for VTE.

Table 1 – Risk factors for thromboembolic phenomena in hospitalized patients (Padua risk score)

Risk factor	Points
Active cancer	3
Previous VTE	3
Reduced mobility	3
Thrombophilia	3
Recent trauma or surgery (less than 1 month)	2
Advanced age (> 70 years)	1
Heart or respiratory failure	1
Acute myocardial infarction or stroke	1
Acute infection and/or rheumatic disease	1
BMI ≥ 30 kg/m^2	1
Hormonal treatment	1

VTE: venous thromboembolism; BMI: body mass index.

Risk factors for VTE are as follows: previous VTE, advanced age (particularly > 55 years), surgery, major trauma or lower limb injury, immobility, lower limb paresis, varicose veins, cancer, cancer therapy (hormone therapy, chemotherapy, radiotherapy, angiogenesis inhibitors), myeloproliferative disorders, venous compression (hematoma, tumor, arterial abnormality), pregnancy and puerperium, estrogen therapy, estrogen receptor modulators, erythropoiesis-stimulating agents, acute disease, acute infectious disease, class III or IV congestive heart failure, AMI, acute respiratory disease, stroke, rheumatic disease, inflammatory bowel disease, nephrotic syndrome, renal failure, nocturnal paroxystic hemoglobinuria, obesity, central venous catheter, and inherited or acquired thrombophilia[1,2].

The indication for prevention using anticoagulant agents should take into account cost/benefit analysis of using these drugs with the potential risk for bleeding. In practice, it is difficult to determine when medical patients are at high or low risk for developing DVT on the basis of studies with very heterogeneous populations.

In an observational prospective study that included 1,180 patients hospitalized for medical treatment, 11 risk factors for DVT with different weights were established and scores were defined for risk for DVT on the basis of the total number of points considered for the presence of each one of these factors (see Table 1 for the Padua risk score)[3].

Patients were deemed to be at high risk when the score was ≥ 4 (39.7% of patients) and low risk when it was < 4 points (60.3%). After a 90-day follow-up, DVT occurred in 11% of high-risk patients and in 0.3% of low-risk patients. Despite the limitations of this study, the Padua risk score is a good means of determining risk for DVT in hospitalized patients. In surgical patients, preventive anticoagulation is recommended for patients deemed at moderate risk (patients undergoing gynecological, urological, or thoracic surgery or neurosurgery; patients undergoing small surgical procedures who exhibit an additional risk factor; patients aged between 40 and 60 years who will receive general anesthesia for more than 30 min without additional risk factors) or at high risk (patients aged > 60 years undergoing major surgical procedures; patients aged between 40 and 60 years with additional risk factors; patients undergoing hip or knee arthroplasty, pelvic or hip fracture surgery, colorectal surgery, major trauma, spinal cord surgery, or cancer surgery). Risk factors for the development of VTE in surgical patients also include the type and extent of the surgery or trauma as well as the duration of hospitalization. Prevention should be continued until hospital discharge. In some subgroups of patients, it may be advisable to maintain prevention for an extended period of time after discharge, e.g., patients undergoing major cancer surgery or having experienced a previous thromboembolic event (up to 28 days) and patients undergoing hip or knee prosthesis surgery or hip fracture surgery (up to 35 days)[4].

7.3. Risk for bleeding

Till date, there is no prospectively validated model for assessing the risk for bleeding in hospitalized medical patients.

A retrospective study including more than 15,000 patients presented the following risk factors for bleeding: active gastroduodenal ulcer, bleeding over the last 3 months, platelet count < 50,000/μl, older age, liver or kidney failure, prolonged stay in an intensive care unit, presence of a central venous catheter, rheumatic disease, cancer, and male gender[5].

7.4. Anticoagulant therapy in VTE

7.4.1. Unfractionated heparin (UH)

7.4.1.1. Prevention

The use of UH at low doses (5,000 IU subcutaneously every 8 or 12 h) for the prevention of thromboembolism in medical and surgical patients at risk is effective and safe and reduces the risk for VTE and fatal pulmonary embolism (in 60%–70% of patients)[6]. On the other hand, its use is associated with a slight increase in the incidence of wound hematoma and a nonstatistically significant increase in major bleeding (without an increase in fatal bleeding).

Patients hospitalized for stroke who exhibit reduced mobility should receive prophylactic treatment with low-dose anticoagulant drugs; however, these drugs should not be used during 24 h after the administration of thrombolytic drugs[9,10]. Patients hospitalized for hemorrhagic stroke should receive mechanical prophylactic treatment using pneumatic compression intermittent devices[11]. The use of heparin at low doses should be considered for high-risk patients, particularly bedridden patients, after bleeding cessation has been observed, on the second to fourth day following the onset of hemorrhagic stroke[12].

Platelet count should be performed every 2–3 days within 4–14 days or until the end of heparin treatment, whichever occurs first, in patients who are on prophylactic UH and on alternate days in patients who are on postoperative prophylactic UH because they represent the group at higher risk for thrombocytopenia induced by heparin. In patients who will start UH or LMWH therapy and who have received UH in the last 100 days, basal platelet count should be performed and repeated 24 h after the start of heparin therapy. Platelet count is not necessary in medical patients who are solely on UH catheter flush[13].

7.4.1.2. Treatment

UH is an effective drug in the treatment of DVT. It should be started as soon as the diagnosis is confirmed (or in case of high medical suspicion, until the diagnostic tests are performed) because pulmonary embolism occurs in approximately 50% of patients with symptomatic DVT in untreated lower limbs[14].

There are three forms of using UH in the initial treatment of DVT: intravenous administration with coagulation monitoring, subcutaneous administration with coagulation monitoring, and subcutaneous administration adjusted for weight without coagulation monitoring.

Intravenous administration with coagulation monitoring. Two administration regimens of intravenous UH are recommended for the treatment of DVT: a 5.000 IU bolus followed by continuous infusion of at least 30.000 IU in the first 24 h (1,250 IU/h) or a 80 IU kg bolus followed by 18 IU/kg/h (specific protocols are available to reach and maintain adequate aPTT levels, i.e., 1.5- to 2.5-fold the control value)[15]. Intravenous administration of heparin is difficult and can often result in inadequate treatment, with up to 60% of patients not reaching an adequate aPTT in the first 24 h[16]. The creation of specific protocols, such as the administration of weight-adjusted doses, aims to avoid incorrect dosing.

Subcutaneous administration with coagulation monitoring. A meta-analysis of eight clinical studies on the initial treatment of patients with DVT revealed that subcutaneous administration of UH twice a day is more effective (RR of extent or recurrence of thromboembolism: 0.62, 95% CI 0.39-0.98) and at least as safe (RR of major bleeding: 0.79, 95% CI 0.42–1.48) as continuous intravenous administration[17], which facilitates dosage and enables home treatment. The usual regimen in these studies included an initial intravenous bolus of approximately 5,000 IU and a subsequent subcutaneous dose of 17,500 IU twice a day in the first day, followed by adjustments to reach aPTT that is 1.5- to 2.5-fold the laboratory control value.

Subcutaneous administration of UH with aPTT adjustment was also as effective and safe as that of a fixed dose of LMWH in the initial treatment of patients with VTE, including patients with pulmonary embolism[18]. In this case, heparin therapy was initiated at a dose adjusted for weight (< 50 kg, 4,000 IU intravenously +

Table 2 – Recommendations for the use of unfractionated heparin for the prevention of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
I	Use of heparin at low doses (5,000 IU subcutaneously every 8 or 12 h) in hospitalized patients with at least one risk factor for VTE and without increased risk for bleeding	A	7,8
	Prophylactic anticoagulation in surgical patients at moderate or high risk	A	7,8
IIa	Platelet count every 2–3 days from day 4 to day 14 or until the end of the treatment with heparin in patients on prophylactic UH and patients on UH catheter flush during the postoperative period	C	8
	Platelet count every 2 days from day 4 to day 14 or until the end of the treatment with heparin in patients on prophylactic UH during the postoperative period	C	8,13

VTE: venous thromboembolism; UH: unfractionated heparin.

12,500 IU subcutaneously; 50–70 kg, 5,000 IU intravenously + 15,000 IU subcutaneously; > 70 kg, 6,000 IU intravenously + 17,500 IU subcutaneously) and the dose was adjusted according to the result of aPTT every 6 h.

Subcutaneous administration adjusted for weight without coagulation monitoring. The rates of recurrent VTE, major bleeding, and death after subcutaneous administration of UH at an initial dose of 333 IU/kg, followed by a fixed dose of 250 IU/kg twice a day, without coagulation monitoring were similar to those after the administration of LMWH[19].

The efficacy of treatment with UH depends on reaching a critical therapeutic level of heparin in the first 24 h (aPTT 1.5-fold higher than the control value or the upper limit of the normal variation of aPTT)[20]; the risk for thromboembolism recurrence in patients who do not attain this level is increased. The use of a dose adjusted to weight (initial bolus of 80 IU/kg, followed by a continuous infusion of 18 IU/kg/h) results in a higher number of patients (97% vs. 77%) reaching aPTT within the therapeutic range in the first 24 h and in a lower incidence of thromboembolism recurrence[15]. In the case of subcutaneous administration, the initial dose should be high to obtain an adequate response within the first 24 h[21].

At present, the simultaneous introduction of heparin and vitamin K antagonist, followed by heparin discontinuation after 5 days, is recommended, provided that INR is ≥ 2.0 for at least 24 h. In addition to the reduction in the risk for thrombocytopenia induced by heparin, two randomized clinical studies including patients with proximal DVT showed a similar efficacy in the use of intravenous UH for 5–7 days and 10–14 days[22,23]. Platelet counts should be regularly performed to monitor thrombocytopenia induced by heparin, which should be discontinued if there is a sharp or sustained platelet drop or a platelet count < 100,000.

7.4.2. Low-molecular-weight heparin (LMWH)

7.4.2.1. Prevention

The use of LMWH in the prevention of DVT is determined by the patient's risk for experiencing a medical event. Within this risk stratification, certain medical situations are differently assessed. In this context, patients are divided into three groups: nonsurgical patients, patients undergoing orthopedic surgeries, and patients undergoing nonorthopedic surgeries. In this section, we will focus on nonsurgical patients.

The use of heparin significantly reduces the incidence of VTE, with better efficacy obtained with LMWH, which can be administered once a day and exhibits a lower tendency for trombocytopenia[24].

Data from three systematic literature reviews were used to determine the indication for prophylaxis of thromboembolic phenomena in patients hospitalized for acute diseases. The results show that thromboprophylaxis is associated with a significant reduction in the risk for thromboembolic phenomena, particularly in patients deemed at higher risk for these events. Moreover, the risk for major bleeding was not significant[25,26].

Therefore, thromboprophylaxis with LMWH is recommended for high-risk individuals until mobility is recovered or until hospital discharge (whichever occurs first). In low-risk individuals, the incidence of events is very low and does not justify prophylaxis[27].

Interestingly, in the LIFENOX study[28] was a double-blind, placebo-controlled, randomized study that compared the effect of subcutaneous enoxaparin (40 mg/day) with that of a placebo (both administered for 10 ± 4 days in patients who wore elastic graduated compression stockings) as well as the rate of all-cause mortality among acute hospitalized patients. The results revealed that compared with the use of elastic graduated compression stockings alone, combined use of enoxaparin and elastic graduated compression stockings was not associated with a reduction in the rate of all-cause mortality.

Prevention of DVT in long-distance travel. Prophylaxis with LMWH or ASA has been discussed and often indicated in individuals who return from long-distance flights. Symptomatic VTE is rare in this specific group of patients.

High-risk patients are recommended to walk frequently, exercise, and massage the muscles. In addition, these patients should consider wearing below-the-knee elastic stockings with compression of 15–30 mmHg.

Table 3 – Recommendations for the use of unfractionated heparin for the treatment of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
I	Treatment of acute venous thrombosis (DVT) with intravenous or subcutaneous UH with aPTT monitoring (1.5–2.5 times the laboratory control value) or with a fixed subcutaneous dose	A	15
	Subcutaneous UH administration of 17,500 IU or 250 IU/kg twice daily, with dose adjustment to reach and maintain aPTT between 1.5 and 2.5 times the laboratory control value measured 6 h after administration	A	17
	Intravenous UH administration of a bolus of 80 IU/kg or 5,000 IU, followed by continuous infusion of 18 IU/kg/h, with dose adjustment to reach and maintain aPTT between 1.5 and 2.5 times the laboratory control value	C	15
	Simultaneous introduction of UH and oral anticoagulation with vitamin K antagonist	C	22
IIa	Treatment of patients with high clinical suspicion of DVT while awaiting diagnostic tests	C	14
	Discontinuation of UH after 5 days, provided INR is ≥ 2.0 for at least 24 h	C	22

DVT: deep vein thrombosis; UH: unfractionated heparin; INR: international normalization ratio.

Till date, no studies have been conducted using an adequate methodology to test the potential benefits of LMWH in this group of patients. In high-risk individuals, i.e., those with previous thromboembolism, known thrombophilia, body mass index above 40 kg/m^2 (third-degree obesity), active cancer, recent major surgery (less than 1 month), as well as those traveling for more than 6 h, the use of thromboprophylactic medications should be decided on a case-by-case basis, always taking into account that adverse events may outweigh any benefit[29].

The usual practice in this case is the use of 20–40 mg of enoxaparin (subcutaneously) 1 h before boarding a flight of more than 6 h, although this has not been scientifically demonstrated. Other drug options (also not tested under these conditions) include dabigatran (110 mg) or rivaroxaban (10 mg).

7.4.2.2. Treatment

The use of LMWH for initial anticoagulation after a diagnosis of DVT is associated with lower mortality, lower DVT recurrence, and a lower incidence of major bleeding. Moreover, there is a lower incidence of thrombocytopenia induced by heparin and its use is simple. Care should be taken when administering the drug to individuals with significantly impaired renal function (CrCl < 30 ml/min). The dose is adjusted according to the patient's age, with a predictable therapeutic effect. aPTT monitoring is unnecessary. LMWH exhibits better bioavailability than UH. The prolonged therapeutic activity of LMWH enables one or two daily administrations[30,31].

Therefore, combined use of LMWH and a vitamin K antagonist is recommended until INR monitoring reveals that the patient is adequately anticoagulated[32,33].

7.4.3. Warfarin

7.4.3.1. Prevention

In patients who underwent major orthopedic surgery and who do not accept or tolerate injections, warfarin can be used as an alternative to apixaban, dabigratan, or intermittent pneumatic compression devices for the prevention of DVT[34].

7.4.3.2. Treatment

In patients with acute DVT, warfarin must be started on the same day as that of the onset of the administration of LMWH or UH. Parenteral anticoagulation must be maintained for a minimum of 5 days or until INR of 2.0 is reached[35].

In patients with DVT treated with warfarin, the dose must be adjusted in view of reaching INR between 2.0 and 3.0 (target INR: 2.5)[36,37].

The anticoagulation period will depend on the existence of a thrombosis-predisposing factor, which may be transient such as surgery or definitive such as thrombophylic syndrome. A minimum period of 3 months is recommended, which can be extended in the presence of a causative factor. In patients with proximal lower-extremity DVT caused by surgery [38,39], proximal lower-extremity DVT caused by a transient risk factor not related to surgery, or an isolated episode of distal lower-extremity DVT caused by a transient risk factor or caused by surgery [40], the recommended period of anticoagulation with warfarin is also 3 months.

In patients with spontaneous DVT (without a known triggering factor) in the lower extremities, the minimum recommended period of anticoagulation with warfarin is 3 months. After this period, patients must be evaluated with regard to the risk/benefit of extending the anticoagulation treatment. In patients who present with a first episode

Table 4 – Recommendations for the use of low-molecular-weight heparin for the prevention of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
I	Enoxaparin can be used at a dose of 40 mg/day in patients at high risk for DVT	A	2,3,18,19
IIa	Enoxaparin can be used at a dose of 20–30 mg/day in patients at high risk for DVT, with creatinine clearance < 30 ml/min	C	2,3,18,19

DVT: deep vein thrombosis.

Table 5 – Recommendations for the use of low-molecular-weight heparin for the treatment of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
I	Enoxaparin can be used at a dose of 1 mg/kg every 12 h in patients with VTE	A	10,16,19
IIa	Enoxaparin should be used at a dose of 1 mg/kg once daily in patients with VTE, with creatinine clearance < 30 ml/min	C	10,16,19
	In patients with creatinine clearance < 30 ml/min, it is recommended to measure factor anti-Xa for therapeutic monitoring	C	10,16,19

VTE: venous thromboembolism.

of proximal lower-extremity DVT without a known risk factor, anticoagulation for a period greater than 3 months is recommended. Anticoagulation for 3 months is recommended for individuals who exhibit a first episode of proximal lower-extremity DVT without a known risk factor and with a high risk of bleeding. In patients who present with a first episode of proximal lower-extremity DVT without a known risk factor, regardless of the risk for bleeding, anticoagulation with warfarin for 3 months is recommended[41,42].

Another factor that should be considered with regard to anticoagulation time is the nature of the DVT episode: first episode or recurrent episode. Furthermore, the risk for bleeding should be evaluated.

In patients with a recurrent DVT episode without a known risk factor, the period of anticoagulation with warfarin should be extended beyond 3 months in individuals at low risk for bleeding[43,44].

In patients with a recurrent DVT episode without a known risk factor, it is suggested that the period of anticoagulation with warfarin should be extended beyond 3 months in individuals at moderate risk for bleeding. In patients with a recurrent DVT episode without a known risk factor, the period of anticoagulation with warfarin should be 3 months in individuals at high risk for bleeding[45,46].

In patients with active cancer, the period of anticoagulation with warfarin for lower-extremity DVT should be extended beyond 3 months in individuals not at high risk for bleeding. In patients with active cancer, the period of anticoagulation with warfarin for lower-extremity DVT should be 3 months in individuals at high risk for bleeding. Warfarin treatment for asymptomatic lower-extremity DVT should follow the same recommendations with regard to the INR therapeutic level and duration[47].

7.4.4. Fondaparinux

7.4.4.1. Prevention

The ARTEMIS double-blind, randomized, placebo-controlled study was designed to evaluate the efficacy and safety of the use of fondaparinux in the prevention of DVT in 849 patients aged ≥ 60 years who had been hospitalized for acute cardiac, respiratory, infectious, or inflammatory disease and who needed to be bedridden for at least 4 days and had moderate risk for DVT.

Subcutaneous administration of fondaparinux 2.5 mg/day (with an onset within the first 48 h after hospital admission and maintained for 6–14 days) significantly reduced the risk for DVT, from 10.5% in the placebo group to 5.6% (reduction in RR 47%, 95% CI 8–69). Major bleeding occurred in one patient in each group (0.2%)[48].

In the PEGASUS study, patients who underwent elective abdominal surgery were randomly assigned to receive fondaparinux 2.5 mg daily for 5–9 days, with treatment beginning 6 h after the surgery, or subcutaneously administered 2,500 U dalteparin 2 h before and 12 h after the preoperative dose, followed by 5,000 U daily for 5–9 days. Among the 2,048 patients, the rate of DVT was 4.6% in the fondaparinux group and 6.1% in the group that received dalteparin, which represented a 25% reduction in RR (95% CI −9–48). The goal of noninferiority of fondaparinux was reached, and the rate of major bleeding was similar (3.4% in the fondaparinux group vs. 2.4% in the dalteparin group)[49].

Based on the presence of a composite endpoint in bilateral ascending venography, phase III randomized studies revealed that compared with LMWH (enoxaparin), fondaparinux therapy, when started within 4–8 h postoperatively, exhibited a superior efficacy in the prevention of DVT in patients who underwent orthopedic surgery, such as total hip replacement, knee replacement, and hip fracture surgery, and objectively documented symptomatic events[50].

Table 6 – Recommendations for the use of warfarin for the prevention of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
IIa	Warfarin can be used as an alternative in the prevention of DVT in patients subjected to orthopedic surgery	A	35

DVT: deep vein thrombosis.

Table 7 – Recommendations for the use of warfarin for the treatment of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
I	Warfarin can be used for the treatment of VTE at an initial dose of 5 mg/day for a minimum period of 3 months, with target INR between 2.0 and 3.0, which can be prolonged in the presence of trombophilic syndrome or neoplasia.	A	38-40
	The use of subcutaneous or parenteral drugs should be discontinued after a minimum period of 5 days or when at least two INR measurements are ≥ 2.0, with an interval of 24 h	A	35
IIa	Doses of warfarin < 5 mg should be considered in elderly patients as well as in patients with malnutrition, liver disease, heart failure, or high risk for bleeding	C	38-40

VTE: venous thromboembolism.

A meta-analysis of four multicenter, double-blind, randomized studies on the prevention of DVT that compared fondaparinux with enoxaparin in patients who underwent major orthopedic surgery confirmed those findings in favor of fondaparinux[51].

Prolonged thromboprophylaxis was evaluated in a phase III study entitled PENTPHIRA-Plus, which evaluated patients who underwent hip fracture surgery. Prolongation of the duration of prophylaxis with subcutaneous administration of fondaparinux 2.5 mg once a day starting 1 to 4 weeks after the fracture considerably lowered the frequency of venographically confirmed DVT [from 35% to 1.4% ($p = 0.0001$)] as well as that of symptomatic DVT [from 2.7% to 0.3% ($p = 0.0021$)][52].

7.4.4.2. Treatment

Studies that evaluated treatments for DVT revealed that fondaparinux was as effective and safe as enoxaparin and UH in treating DVT and PTE.

The double-blind MATISSE study randomly assigned 2,205 patients with acute symptomatic DVT and weight < 50 kg, from 50 to 100 kg, and > 100 kg to receive an initial treatment with 5, 7.5, and 10 mg/day of fondaparinux, respectively, or with 1 mg/kg enoxaparin twice a day, for at least 5 days or until vitamin K inhibitors induced INR greater than 2.0. The main outcome, i.e., the recurrence of symptomatic DVT within 3 months, was 3.9% in the fondaparinux group and 4.1% in the enoxaparin group. The incidence of major bleeding during the initial period (1.1% and 1.2%, respectively) was also similar; the same was observed in case of the overall mortality (3.8% and 3.0%, respectively). It was concluded that the administration of fondaparinux once daily was at least as effective and safe as that of enoxaparin in the initial treatment of symptomatic DVT[53].

The CALISTO study, which was a randomized trial that included more than 3,000 patients with superficial vein thrombosis of the lower extremities, compared the administration of fondaparinux at a dose of 2.5 mg subcutaneously once daily for 45 days with the administration of a placebo. This study showed that the active treatment reduced the incidence of composite endpoints of symptomatic DVT, PTE, the spread of thrombosis into the sapheno-femoral junction, the recurrence of superficial vein thrombosis, and death (0.9% in the active treatment group vs. 5.9% in the placebo group), with an 85% reduction in RR in favor of fondaparinux ($p < 0.001$). No statistically significant difference was observed with regard to hemorrhagic complications between the two groups[54].

7.4.5. Dabigatran

7.4.5.1. Prevention

Four randomized, controlled, double-blind studies evaluated the efficacy and safety of dabigratan for the prophylaxis of VTE during knee or hip replacement surgery. The primary event was total VTE (including PTE and proximal and distal, symptomatic and asymptomatic DVT, as assessed by venography) and all-cause mortality.

The RE-NOVATE study included 3,494 patients who underwent hip replacement surgery and compared dabigratan at a dose of 150 or 220 mg once daily with enoxaparin at a dose of 40 mg/day, with a duration of 28-35 days. The frequency of the primary event after 220 mg of dabigratan, 150 mg of dabigratan, and enoxaparin was 6%, 8.6%, and 6.7%, respectively. These results revealed that dabigratan is not inferior to enoxaparin. In the same groups, the incidence of major bleeding was 2%, 1.3%, and 1.6%, respectively. Therefore, there was no difference between the groups[55].

The RE-NOVATE II study evaluated only a dose of 220 mg of dabigratan in 2,055 patients who underwent hip replacement surgery. In the dabigratan and enoxaparin groups, the primary event occurred with a frequency of 7.7% and 8.8%, respectively, and major bleeding occurred in 1.4% and 0.9%, respectively. Therefore, there was no difference between the groups with regard to both safety and efficacy[56].

Table 8 – Recommendations for the use of fondaparinux for the prevention of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
I	Fondaparinux can be used at a dose of 2.5 mg/day in patients at high risk for DVT	A	48,49

DVT: deep vein thrombosis.

Table 9 – Recommendations for the use of fondaparinux for the treatment of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
I	For the treatment of DVT, the recommended dose is 7.5 mg/day in patients weighing between 50 and 100 kg. In patients weighing less than 50 kg, the dose is 5 mg/day, and in patients weighing more than 100 kg, the dose is dose 10 mg/day	A	53,54
IIa	The use of fondaparinux for the treatment of DVT in patients with creatinine clearance < 30 ml/min is contraindicated	C	53,54

DVT: deep vein thrombosis.

Table 10 – Recommendations for the use of dabigatran for the prevention of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
IIa	Prevention of VTE in the postoperative period of hip and knee prosthesis surgery with a dose of 150 mg or 220 mg/day	A	60

VTE: venous thromboembolism.

The RE-MOBILIZE study included 2,615 patients and compared dabigratan 150 or 220 mg once daily with enoxaparin 30 mg twice daily for a period of 12–15 days in the context of knee replacement surgery. In the dabigratan 150 mg, dabigratan 220 mg, and enoxaparin 30 mg groups, the frequency of the primary event was 33.7%, 31.1%, and 25.3%, respectively. Major bleeding occurred in 0.6%, 0.6%, and 1.4% of cases, respectively. Therefore, these results revealed that despite having the same safety, the efficacy of debigratan was lower[57].

The RE-MODEL study included 2,076 patients who received debigratan 150 or 220 mg once daily or enoxaparin 40 mg once daily for 6–10 days. In the dabigratan 150 mg, dabigratan 220 mg, and enoxaparin 40 mg groups, the primary event occurred in 40.5%, 36.4%, and 37.7% of cases, respectively. The frequency of major bleeding was 1.3%, 1.5%, and 1.3%, respectively. Therefore, dabigratan was not inferior to enoxaparin, and it exhibited the same safety[58].

A meta-analysis that evaluated only 220 mg of dabigratan in the RE-MODEL, RE-NOVATE, and RE-MOBILIZE trials demonstrated a lack of inferiority and a similar hemorrhagic risk for dabigratan relative to enoxaparin[59].

Another meta-analysis that included the four studies revealed that the frequency of the occurrence of VTE or mortality associated with VTE was 3%, 3.8%, and 3.3% in the dabigatran 220 mg, dabigatran 150 mg, and enoxaparin groups, respectively. Major bleeding occurred in 1.4%, 1.1%, and 1.4% of cases, respectively. Therefore, dabigratan was as effective as enoxaparin and exhibited the same hemorrhagic risk[60].

No study has compared the presence thromboprophylaxis with dabigratan vs. absence of thromboprophylaxis in knee and hip replacement surgeries.

The NICE Guidance considers that dabigratan is safe and adequate for primary prophylaxis in knee and hip replacement surgery, with an adequate cost/effectiveness, while emphasizing on the lack of an antidote and the fact that a dose of 150 mg/day would be more adequate for patients with renal failure or elderly patients. Dabigratan may be considered as an alternative in situations in which enoxaparin is indicated[61].

The 9th ACCP Guideline, which uses the data obtained in the four studies described above, considered that dabigratan at a dose of 220 mg was similar to enoxaparin with regard to the occurrence of symptomatic VTE (PTE: RR 1.22, 95% CI, 0.52–2.85; DVT: RR 0.7, 95% CI 0.12–3.91) and major bleeding (RR 1.06, 95% CI 0.66–1.72). The absolute risk for bleeding and VTE was similar, with one event/1,000 patients. At a dose of 150 mg, dabigratan failed to demonstrate or exclude a beneficial VTE-preventive effect in comparison with enoxaparin (PTE: RR 0.31, 95% CI 0.04–2.48; symptomatic DVT: RR 1.52, 95% CI 0.45–5.05). Therefore, based on evidence with moderate quality, dabigratan may be considered to be similar to enoxaparin with regard to efficacy and safety; however, given the greater amount of experience with enoxaparin, this drug is indicated as the first choice[62].

For the prophylaxis of VTE in knee and hip replacement surgeries, a dose of 150 or 220 mg once daily for a period of 28–35 or 14 days is recommended. The administration of the drug should begin 1–4 h after the surgical procedure, with hemostasis established with half dose. The choice of dose is left to the discretion of the physician taking into consideration the age of the patient, CrCl, and the use of other drugs that interact with dabigratan.

7.4.5.2. Treatment

Studies conducted on patients with acute or chronic DVT were analyzed for comparing the noninferiority and safety of dabigratan and warfarin, considering the occurrence of symptomatic VTE.

The RE-COVER study was a phase III, double-blind, randomized, and controlled study on the treatment of acute VTE. After conventional treatment with enoxaparin for a minimum of 5 days, a total of 2,539 patients received 150 mg of dabigratan twice daily or warfarin at a dose adjusted for INR between 2.0 and 3.0 for 6 months. The results revealed that the recurrence of VTE (2.4% vs. 2.1%, RR 1.10, 95% CI 0.65–1.84) and major bleeding (1.6% vs. 1.9%, RR 0.83, 95% CI 0.46–1.49) was similar. During the study-inclusion period, 786 patients (31%) exhibited symptoms of TPE. The results showed no differences in the response to dabigratan with regard to the recurrence of VTE or bleeding in that subgroup of patients[63].

The RE-MEDY study compared the use of 150 mg of dabigratan twice daily with that of warfarin at a dose adjusted for INR between 2.0 and 3.0 for 6–36 months after a period of conventional treatment for VTE of 3–12 months. The study included 2,856 patients; the recurrence of VTE occurred in 1.8% and 1.3% of cases, respectively (RR 1.44, 95% CI 0.79–2.62), and the recurrence of major bleeding occurred in 0.9% and 1.8% of cases, respectively (RR 0.56, 95% CI 0.27–1.01). These results revealed that the efficacy of dabigratan is similar to that of warfarin, with the same hemorrhagic risk. An increased incidence of acute coronary events was observed. The results of this study have not been published till date.

Table 11 – Recommendations for the use of dabigatran for the treatment of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
IIa	Treatment of acute and chronic VTE with a dose of 150 mg twice daily	B	63

VTE: venous thromboembolism.

The RE-SONATE study was started in 2011 for evaluating the noninferiority of dabigratan and the placebo with regard to the recurrence of symptomatic VTE. After a conventional treatment period of 6–18 months, the patients will be included in the study for an additional treatment of 6 months.

The 9th ACCP, which was cited above, considers that the indication of dabigratan for the treatment of acute VTE is based on moderate-quality evidence because of serious imprecision regarding various occurrences and the lack of data on long-term safety. Because very few patients with cancer were included, the results cannot be extrapolated to that group of patients.

Some aspects that need to be evaluated when choosing an anticoagulant include the patient's tolerance to daily injections, history of heparin-induced thrombocytopenia, renal function, need for laboratory control, cost of treatment, and availability of an antidote to treat intoxication. Dabigratan can be very unpleasant for patients; however, no phase IV studies substantiate the safety of this drug in a better manner, particularly with regard to bleeding and hepatic complications.

In addition, there is a limitation in the use of this drug in patients with renal impairment as well as the lack of an antidote. In patients with CrCl between 30 and 50 ml/min or those older than 75 years, the dose can be reduced to 150 mg/day. Similarly, as mentioned in the RE-COVER study, the dose should be reduced to 150 mg/day in the presence of the concomitant administration of potent inhibitors of glycoprotein P, such as amiodarone or verapamil.

7.4.6. Rivaroxaban

7.4.6.1. Prevention

The most important studies that analyzed the efficacy and safety of rivaroxaban for the primary prophylaxis of VTE in knee and hip replacement surgeries are the RECORD 1–4 controlled, randomized, double-blind, phase III studies. The primary event was total VTE, including PTE, proximal and distal, symptomatic and asymptomatic DVT (as assessed by venography), and all-cause mortality.

In the RECORD 1 study, which included 4,541 patients who underwent hip replacement surgery, rivaroxaban was administered at a dose of 10 mg once daily, started on the day of surgery, and it was compared with enoxaparin 40 mg once daily, started 2 days before the surgery, for 35 days. Rivaroxaban was superior to enoxaparin with regard to the primary event (1.1% vs. 3.7%, RR 0.3, 95% CI 0.18–0.51, $p < 0.001$) and the occurrence of VTE (0.2% vs. 2.0%, RR 0.12, 95% CI 0.04–0.34, $p < 0.001$). Major bleeding was similar between the two groups (0.3% vs. 0.1%, RR 3.02, 95% CI 0.61–14.95, $p = 0.18$). These results revealed that rivaroxaban was more effective than enoxaparin, and it exhibited the same safety[64].

The RECORD 2 study compared 2,509 patients who received prophylaxis with rivaroxaban 10 mg once daily for 35 days or enoxaparin 40 mg once daily for 15 days. The primary event had a lower incidence in the rivaroxaban group than in the enoxaparin group (2.0% vs. 9.3%, RR 0.21, 95% CI 0.13–0.35, $p < 0.001$); the same was observed in case of VTE (0.6% vs. 5.1%, RR 0.12, 95% CI 0.04–0.34, $p < 0.001$). The incidence of major or clinically significant bleeding was similar in the two groups (0.1% vs. 0.1%, RR 1.0, 95% CI 0.06–15.98 and 9.9% vs. 8.21%; RR 1.20, 95% CI 0.93–1.54, respectively)[65]. Therefore, rivaroxaban was more effective and had the same safety as enoxaparin. However, it is important to stress that enoxaparin was used for 15 days only, whereas rivaroxaban was used for 35 days.

The RECORD 3 study ($n = 2,531$) compared patients who underwent knee replacement surgery and received 10 mg of rivaroxaban once daily or 40 mg of enoxaparin/day for 10–14 days. Rivaroxaban was superior to enoxaparin with regard to the prevention of the primary event (1.1% vs. 3.7%, RR 0.3, 95% CI 0.18–0.51, $p < 0.001$) and VTE (0.2% vs. 2.0%, RR 0.12, 95% CI 0.04–0.34). Major bleeding was similar in the two groups (0.3% vs. 0.1%, RR 3.02, 95% CI 0.61–14.95)[66]. Therefore, rivaroxaban was more effective and had the same safety as enoxaparin.

In the RECORD 4 study ($n = 3,148$), rivaroxaban was used at a dose of 10 mg once daily and was compared with enoxaparin 30 mg twice daily for knee replacement surgery. The primary event was less prevalent in the rivaroxaban group (6.9% vs. 10.1%, RR 0.69, 95% CI 0.51–0.92, $p < 0.001$); the same was observed in case of VTE (1.2% vs. 2.0%, RR 0.59, 95% CI 0.30–1.16). Bleeding was similar in the two groups (0.7% vs. 0.3%, RR 2.47, 95% CI 0.78–7.86)[67]. Therefore, these results confirmed those obtained in the RECORD 3 study.

The incidence of clinically significant bleeding was also low in all these studies: RECORD 1: 5.8% vs. 5.8%; RECORD 2: 6.5% vs. 5.5%; RECORD 3: 4.3% vs. 4.4%; and RECORD 4: 10.2% vs. 9.2%.

A meta-analysis of eight randomized clinical studies that included 15,586 patients who underwent knee or hip replacement surgery revealed that the use of rivaroxaban was associated with a lower incidence of VTE and all-cause mortality (9,244 patients, RR 0.56, 95% CI 0.39–0.80) and with a similar incidence of bleeding (major bleeding: 13,384

Table 12 – Recommendations for the use of rivaroxaban for the prevention of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
IIa	Prevention of VTE in the postoperative period of hip and knee prosthesis surgery at a dose of 10 mg/day	A	67,69

VTE: venous thromboembolism.

patients, RR 1.65, 95% CI 0.93–2.93; clinically significant bleeding: 13,384 patients, RR 1.21, 95% CI 0.98–1,50; total hemorrhagic events: 13,384 patients, RR 1.10, 95% CI 0.97–1.24)[68].

However, a limitation of the bleeding evaluation method used in those studies was that only bleeding that required reoperation was considered and bleeding at the surgical site was not and that the drop in hemoglobin was compared with the first postoperative day and not with the preoperative value.

Furthermore, approximately 30%–39% of patients included in the RECORD studies were excluded from analysis of the intention-to-treat because of inadequate evaluation of DVT. Moreover, the RECORD 4 study was completely excluded from the approval decision of FDA. Inadequate monitoring and loss of data compromised analyses and prevented the confirmation of the superiority of rivaroxaban over enoxaparin. In addition, the bleeding was considered to be similar.

The NICE Guidance considers that rivaroxaban is more effective than enoxaparin for the prevention of VTE; however, the risk for major bleeding is greater (when considering RR of the studies), and the drug can be considered in situations in which enoxaparin is indicated. With regard to the direct comparison between rivaroxaban and dabigatran, the former significantly reduced the risk of VTE, whereas the risk of bleeding favored dabigatran; therefore, these drugs were considered as being similar.

The 9th ACCP Guidelines included seven randomized clinical studies that included more than 10,000 patients to evaluate the indication of the use of rivaroxaban for the thromboprophylaxis of knee and hip replacement surgery. Rivaroxaban reduced symptomatic DVT by 50% (RR 0.41, 95% CI 0.20–0.83), with an increase in major bleeding or bleeding that required reoperation (major bleeding: RR 1.58, 95% CI 0.84–2.97; bleeding that required reoperation: RR 2.0, 95% CI 0.86–4.83; both: RR 1.73, 95% CI 0.94–3.17). The absolute risk for major bleeding was low; however, the criteria used for evaluating bleeding mentioned earlier were not adequate. It was estimated that the reduction of five symptomatic DVT among 1,000 patients would lead to nine major bleedings.

With regard to prolonged thromboprophylaxis in hip replacement surgery, which included more than 2,400 patients, rivaroxaban significantly reduced symptomatic VTE (symptomatic DVT: RR 0.18, 95% CI 0.04–0.82; PTE: RR 0.25, 95% CI 0.02–2.2). However, it is important to stress that enoxaparin was only used in the first 12 days. Analysis of bleeding also had the same limitations as those mentioned for the previous studies, and there was only one case of bleeding in the two groups. It is estimated that among 1,000 patients, 12 less DVTs will occur in the rivaroxaban group. However, given the uncertain results regarding bleeding, it remains unclear whether the beneficial effects will be overcome by the increase in the hemorrhagic risk.

Based on these studies (which are considered to provide moderate quality evidence), the increased hemorrhagic risk, and the lack of data on long-term safety, ACCP still recommends enoxaparin as the first choice for the thromboprophylaxis of knee and hip replacement surgery, even considering the inconvenience of subcutaneous injections.

The randomized, double-blind MAGELLAN study[69] evaluated rivaroxaban for the prevention of VTE in hospitalized medical patients. The study included 5,932 patients who were administered 10 mg of rivaroxaban/day for 35 days or 40 mg of enoxaparin/day for 10 days. Patients were also administered a placebo orally for 35 days or subcutaneously for 10 days. The risk factors were infectious disease, congestive heart failure, respiratory insufficiency, cancer, ischemic stroke, and inflammatory or rheumatologic disease. The results revealed that rivaroxaban reduced the incidence of VTE at 35 days (4.4% vs. 5.7%, RR 0.77, 95% CI 0.62–0.96, $p = 0.02$), albeit with a significant increase in bleeding (1.9% vs. 0.6%, RR 0.77, 95% CI 0.62–0.96, $p = 0.02$), which overcame the benefits of its use. The debate regarding this study includes the possibility that the heterogeneity of the patients and comparison with the placebo explain the findings and that subgroup analysis and long-term comparison with enoxaparin may be important because VTE is also common in hospitalized medical patients. The results of this study have not been published. For the prevention of VTE in knee and hip replacement surgeries, a dose of 10 mg once daily is recommended for a period of 35 and 14 days, respectively. The administration of the drug should be started 6–8 h after the surgical procedure, after hemostasis has been re-established.

7.4.6.2. Treatment

The efficacy and safety of rivaroxaban for the treatment of acute- and long-term VTE have been evaluated in more than 4,600 patients in two controlled, randomized, phase III clinical studies, EINSTEIN DVT[70] and EINSTEIN EXTENSION[71]. These two studies used the same primary (recurrent symptomatic VTE, defined as recurrent DVT or fatal or nonfatal PTE) and secondary (recurrent DVT, nonfatal PTE, and all-cause mortality) events for the evaluation of efficacy. In those studies, patients with moderate renal failure (CrCl 30–49 ml/min) were treated with the same dose as patients with CrCl greater than 50 ml/min.

One of A difference between the EINSTEIN DVT and RE-COVER studies was that rivaroxaban was started immediately after the diagnosis of VTE and not after the administration of enoxaparin.

Table 13 – Recommendations for the use of rivaroxaban for the treatment of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
IIa	Treatment of acute and chronic VTE at a dose of 15 mg twice a day in the first 21 days followed by 20 mg once a day for 3, 6, or 12 months or for a longer time at the physician's discretion	B	70,71

VTE: venous thromboembolism.

In the EINSTEIN study (n = 3,449), rivaroxaban was administered at a dose of 15 mg twice daily for 3 weeks, followed by 20 mg/day for 3, 6, or 12 months, and it was compared with enoxaparin for a minimum of 5 days and with warfarin at a dose adjusted for INR between 2.0 and 3.0. Only patients with proximal symptomatic DVT were included, and those with symptomatic PTE were excluded. The results revealed that the recurrence of VTE (2.1% vs. 3.0%, RR 0.70, 95% CI 0.46–1.07) and that of major bleeding (0.8% vs. 1.2%, RR 0.70, 95% CI 0.35–1.38, p = 0.21) were similar to those observed for enoxaparin and warfarin in the treatment of acute-stage VTE.

In the EINSTEIN EXTENSION study (n = 1,196), patients with proximal DVT who were previously treated with rivaroxaban or enoxaparin and warfarin for 6–12 months were administered rivaroxaban 20 mg/day or placebo for treatment over an additional 6–12 months. The results revealed that rivaroxaban was superior to the placebo with regard to the primary and secondary efficacy events (1.3% vs. 7.1%, RR 0.19, 95% CI 0.09–0.40, $p < 0.001$), with a nonsignificant increase in bleeding (0.7% vs. 0%, RR 7.89, 95% CI 0.42–148.99).

The 9th ACCP considers that the indication of rivaroxaban for the treatment of acute- and long-term DVT stems from moderate quality evidence resulting from serious imprecision regarding various events and the lack of data regarding long-term safety. Because very few patients with cancer were included, the results cannot be extrapolated to that group of patients.

Some aspects that need to be evaluated when choosing an anticoagulant include the patient's tolerance to daily injections, history of heparin-induced thrombocytopenia, renal function, need for laboratory control, cost of treatment, and availability of an antidote to treat intoxication. Rivaroxaban can be lesser unpleasant for patients; however, it was associated with greater bleeding in studies of primary thromboprophylaxis. At present, there are no phase IV studies to substantiate the safety of this drug in a better manner, particularly with regard to bleeding and hepatic complications. In addition, there is a limitation in the use of this drug in patients with renal impairment as well as the lack of an antidote. Although this has not been well established, there should be some precaution with regard to the administration of rivaroxaban to patients with CrCl between 15 and 30 ml/min, liver disease (Child–Pugh classes B and C), concomitant use of inhibitors/enhancers of CYP3A4 or glycoprotein P (amiodarone, verapamil, macrolides, rifampicin, phenytoin, carbamazepine, and phenobarbital), and use of nonsteroidal anti-inflammatory drugs and platelet inhibitors.

7.4.7. Apixaban

7.4.7.1. Prevention

The efficacy and safety of apixaban in the primary prevention of VTE in patients who underwent hip and knee prosthesis were assessed in three controlled, randomized, double-blind, phase III clinical studies, entitled ADVANCE 1-3. The primary event was total VTE (including PTE, proximal and distal DVT, symptomatic and asymptomatic, as assessed by venography) and all-cause mortality.

In the ADVANCE 1 study, 3,195 patients who underwent knee prosthesis received apixaban at a dose of 2.5 mg twice daily, starting on the day of the surgery, or anoxaparin at a dose of 30 mg twice daily, starting one day before the surgery, for 10–14 days. Apixaban was similar to enoxaparin with regard to the incidence of total VTE and death (9.9% vs. 8.8%, RR 1.02, 95% CI 0.78–1.32, p = 0.06). The incidence of major or clinically significant bleeding was lower in the apixaban group (2.9% vs. 4.3%, RR 0.67, 95% CI 0.47–0.97, p = 0.03)[72].

The ADVANCE 2 study[73] compared 3,057 patients who underwent knee arthroplasty and received 2.5 mg of apixaban twice daily or 40 mg of enoxaparin once daily for 10–14 days. The first dose of apixaban was administered between 12–24 h after the surgery, and enoxaparin was started between 9–15 h before the surgery. The incidence of the primary event was lower in the apixaban group (15.06% vs. 24.37%, RR 0.62, 95% CI 0.51–0.34, $p < 0.0001$), and major or clinically significant bleeding was similar in both the groups (4% vs. 5%, RR 0.74, 95% CI 0.52–1.05, p = 0.08).

The ADVANCE 3 study[74] (n = 5,407) compared the effect of 2.5 mg of apixaban twice daily with 40 mg of enoxaparin administered for 35 days in hip prosthesis surgery. Apixaban was superior to enoxaparin with regard to the primary event (1.4% vs. 3.9%, RR 0.36, 95% CI 0.22–0.54, $p < 0.001$). Major or clinically significant bleeding was similar in both the groups (4.8% vs. 5.0%, RR 0.96, 95% CI 0.76–1.21, p = 0.68).

One meta-analysis[75] included the three studies (n = 7,337) that compared the use of apixaban 2.5 mg twice daily with that of enoxaparin 40 mg/day or 30 mg twice daily for the prevention of VTE in knee prosthesis surgery. The risk for VTE when using apixaban and enoxaparin was 0.47 (95% CI 0.27–0.82, 0.6% vs. 1.2%) and 2.09 (95% CI 0.99–4.45, 0.6% vs. 0.3%), respectively. Death occurred in 0.2% of patients in the apixaban group and in 0.09% of patients in the enoxaparin group (OR 1.74, 95% CI 0.51–5.95). Apixaban was associated with a lower hemorrhagic risk (OR 0.55, 95% CI 0.32–0.96). These data demonstrated that in knee prosthesis surgery, apixaban is more effective and safe than enoxaparin.

Table 14 – Recommendations for the use of apixaban for the prevention of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
IIa	Prevention of VTE in the postoperative period of hip and knee prosthesis surgery with a dose of 2.5 mg twice daily	A	75,78

VTE: venous thromboembolism.

The NICE Guidance considered that apixaban was more effective than enoxaparin and exhibited lower hemorrhagic risk, although the difference was not statistically significant. However, it also points out that the observation period with regard to adverse events was short.

The 9th ACCP assessed four studies that included more than 12,000 patients using apixaban for prevention in case of knee or hip prosthesis surgery. Apixaban reduced the occurrence of symptomatic PVT by 59% (RR 0.41, 95% CI 0.18–0.95) and had little or no effect on the occurrence of major bleeding (RR 0.76, 95% CI 0.44–1.32) or bleeding that required reoperation (RR 0.82 95% CI 0.15–4.58) in comparison with enoxaparin. However, the criticism that was made in relation to the two studies with rivaroxaban is also applicable to the ADVANCE 2 and 3 studies because the drop in hemoglobin was compared with the hemoglobin value on the first postoperative day and not with the preoperative value, which may underestimate the rate of major bleeding. The results failed to show a beneficial or deleterious effect of apixaban with regard to nonfatal PTE (RR 1.09, 95% CI 0.31–3.88) and overall mortality (RR 1.87, 95% CI 0.61–5.74). The five deaths occurred in the apixaban group. The best estimations suggest that apixaban prevents seven symptomatic PVTs in 1,000 patients, without a significant increase in major bleeding (at least eight major bleedings or more less in five cases). However, the results failed to demonstrate a difference when all fatal and nonfatal VTEs were included. Therefore, based on moderate-quality evidence, the safety of apixaban was deemed to be similar to that of enoxaparin with regard to the occurrence of symptomatic VTE and hemorrhagic risk, which was infrequent. However, because of the lack of results on long-term safety in phase IV studies, there is still no indication for the preferential use of enoxaparin.

The ADOPT study[76] assessed apixaban for the prevention of VTE in hospitalized patients with acute disease, congestive heart failure, respiratory failure or other acute condition, and at least one more risk factor for VTE. The study included 6,528 patients who used 2.5 mg of apixaban twice daily for 30 days or 40 mg of enoxaparin once daily for 6–14 days. The occurrence of VTE was similar in both the groups (2.71% vs. 3.06%, RR 0.87, 95% CI 0.62–1.23), with a higher bleeding rate in the apixaban group (2.7% vs. 2.1%, RR 1.28, 95% CI 0.93–1.76). Therefore, these results revealed that apixaban was not superior to enoxaparin with regard to the prevention of VTE in hospitalized medical patients and was associated with higher bleeding; its use is not indicated in this situation.

A dose of 2.5 mg twice daily for a period of 32–38 days and 10–14 days is recommended for the prevention of VTE in hip and knee prosthesis surgery, respectively. The medication should begin 12–24 h after the surgical procedure and after hemostasis has been achieved.

Some aspects that need to be evaluated when choosing an anticoagulant include the patient's tolerance to daily injections, history of thrombocytopenia induced by heparin, renal function, need for laboratory monitoring, cost of treatment, and availability of an antidote to treat intoxication. Apixaban can be lesser unpleasant for patients and its efficacy and safety are similar to or better than those of enoxaparin in the thromboprophylaxis of knee and hip prosthesis surgery. At present, there are no phase IV studies to substantiate the safety of this drug in a better manner, particularly with regard to bleeding and hepatic complications. Compared with dabigatran and rivaroxaban, there are lesser limitations in patients with renal impairment, and there is no antidote. Although this has not been well established, there should be some precaution with regard to the administration of apixaban to patients with CrCl between 15 and 30 ml/min, liver disease (Child–Pugh class A and B), concomitant use of inhibitors/inducers of CYP3A4 or glycoprotein P (amiodarone, verapamil, macrolides, rifampicin, phenytoin, carbamazepine, and phenobarbital), and use of nonsteroidal anti-inflammatory drugs and platelet inhibitors in patients with increased liver transaminase.

7.4.7.2. Treatment

There are no recommendations for the use of apixaban in the treatment of VTE. Studies are still ongoing.

7.5. Comparison between the new anticoagulant agents

Comparison between the use of apixaban, dabigatran, and rivaroxaban for the prevention of VTE in knee or hip prosthesis was indirectly performed through the various studies that compared these new drugs with enoxaparin. One of the criticisms to this type of comparison is that there may be differences in the design of the studies and the centers where they were developed may also have been different.

A review[77] that only included randomized studies comparing the safety and efficacy of apixaban with those of other anticoagulant drugs in the prevention of VTE in knee and hip prosthesis surgery revealed that VTE and death are more frequent with dabigatran than with apixaban in hip (OR 2.51, 95% CI 1.50–4.21) and knee (OR 1.72, 95% CI 1.22–2.42) surgery. Rivaroxaban was similar to apixaban in hip and knee surgery (OR 0.69, 95% CI 0.38–1.25 and OR 0.83, 95% CI 0.57–1.19, respectively). There was no difference with regard to major bleeding.

Another meta-analysis[78] that included 12 studies comparing rivaroxaban or apixaban with enoxaparin revealed that

apixaban was associated with a lower incidence of bleeding in knee prosthesis surgery (6,496 patients, RR 0.56, 95% CI 0.32–0.96) and that the number of major bleeding cases was similar (5,699 patients, RR 1.40, 95% CI 0.56–3.52). There was no difference in bleeding in hip prosthesis.

Maratea et al.[79] analyzed eight studies comparing the new anticoagulant agents in the prevention of VTE in knee and hip prosthesis surgery. Dabigatran at a dose of 150 mg/day was less effective than apixaban at a dose of 2.5 mg twice daily (RR 2.0, 95% CI 1.61–2.50) and rivaroxaban at a dose of 10 mg/day (RR 2.38, 95% CI 1.85–3.03). Dabigatran at a dose of 220 mg/day was also less effective than apixaban at a dose of 2.5 mg twice daily (RR 1.66, 95% CI 1.33–2.08) and rivaroxaban at a dose of 10 mg/day (RR 2.38, 95% CI 1.85–3.03). There was no difference in the efficacy of dabigatran at doses of 150 mg and 220 mg/day (RR 0.83, 95% CI 0.67–1.02). Rrivaroxabana at 10 mg/day was superior to apixaban at 2.5 mg twice daily (RR 0.70, 95% CI 0.53–0.90). Indirect comparison between rivaroxaban and dabigatran with regard to primary thromboprofilaxys in knee and hip prosthesis revealed that rivaroxaban was superior to dabigatran in the prevention of VTE (RR 0.50, 95% CI 0.37–0.68); however, the hemorrhagic risk was higher with rivaroxaban (RR 1.14, 95% CI 0.80–1.64).

Recently, a meta-analysis[80] revealed that compared with mechanical methods and warfarin, the use of powerful anticoagulant agents, including dabigatran and rivaroxaban, was associated with higher mortality. However, as noted by Eriksson et al.[81], this study had numerous flaws, from the inclusion of studies with distinct designs to the generalization of the results obtained for one anticoagulant to the entire group, different periods of prophylaxis, and lack of results corrected by interference factors.

7.6. Bivalirudin

We identified a single phase II open study[82], with 222 patients, which assessed the efficacy and safety of various doses of bivalirudin for the prevention of VTE in patients who underwent major hip and knee orthopedic surgery. Six different regimens were evaluated, varying from 0.3 mg/kg every 12 h to 1.0 mg/kg every 8 h, via subcutaneous administration. On discharge, patients were subjected to bilateral venography and the highest dose resulted in the lowest rates of total (17%) and proximal DVT (2%), which were significantly different from those observed at lower doses (overall incidences: 43% for total DVT and 20% for proximal DVT ($p = 0.01$ and $p = 0.023$, respectively). It is not possible to make recommendations regarding the use of bivalirudin for the treatment and prevention of DVT because of the lack of studies on the subject.

7.7. Antiplatelet therapy in VTE

Arterial and venous thromboses are considered to be distinct pathophysiological entities. Arterial thrombosis mainly involves platelets (white clot), and venous thrombosis is caused by the formation of fibrin and deposition of erythrocytes (red thrombus). However, some characteristics are common to arterial and venous events. In fact, platelets, fibrin, and erythrocytes are present in both arterial and venous thrombi, although in different proportions. Moreover, there is evidence that platelet activation occurs in venous thrombi and that the inhibition of P-selectin, a protein on the surface of activated platelets, can lead to the resolution of venous thrombosis[83]. These facts explain some effect of antiplatelet therapy on the prevention of venous events.

Although there is strong evidence regarding the beneficial effect of antiplatelet therapy on the secondary prevention of arterial events, these drugs have not been tested with regard to the treatment of DVT or PTE, and data related to the prevention of VTE are not very consistent. Some studies suggest that there is an approximately 25% reduction in the risk for VTE after surgical procedures; however, there is no indication that this is an ideal prophylactic method and there are no well-designed studies directly comparing this method with heparins or coumarin derivatives[84].

Two meta-analyses, one with general surgery patients published in 1988[6] and another with patients subjected to total hip arthroplasty published in 1994[85], did not demonstrate a beneficial effect of aspirin on the reduction of VTE. On the other hand, in a systematic review also published in 1994, which included data from 9,623 patients, 814 of which were medical patients and 8,809 were surgical patients, the authors concluded that antiplatelet drugs reduced the incidence of DVT by 39% and the incidence of PTE by 64% and that the effect was detected both in the groups of high-risk surgical and medical patients[86]. However, the validity of these conclusions has been widely questioned; most studies included in this systematic review were not blind and had been published in the 1970s and 1980s, and n was < 200. Moreover, a wide range of drugs were used, including ASA at various doses, dipiridamol, suloctidil, hydroxychloroquine, ticlopidine, and sulfinopyrazone, either isolated or in combination. The VTE detection method considerably varied, and in five studies, there was concomitant use of UH. Lastly, analysis of the various subgroups did not show any reduction in the risk for VTE in high-risk medical patients.

A large randomized prospective study [87] with 17,444 patients compared the effect of aspirin with that of a placebo with regard to the incidence of VTE after orthopedic surgery (13,356 hip fractures, 2,648 hip arthroplasties, and 1,440 knee arthroplasties). ASA at a dose of 160 mg or placebo was used for 35 days, and the aim was to assess morbidity and intrahospital mortality at 35 days. It should be noted that 18% of patients received UH, 26% received LMWH, and 30% wore elastic gradual compression stockings. A significant reduction in the incidence of total VTE was observed in the group that used ASA (HR 0.71, 95% CI 0.54–0.94), DVT (HR 0.71, 95% CI 0.52–0.97), and fatal PTE (HR 0.42, 95% CI 0.24–0.73). This reduction in risk was observed in patients who were not on heparin or UH but was not detected in those who also used LMWH. In patients subjected to hip or knee arthroplasty, the use of ASA did not reduce the incidence of DVT or PTE.

We only identified three small studies that performed a direct comparison between ASA and drugs normally used for preventing VTE. One of these studies compared the efficacy and safety of ASA with those of danaparoid in 251 patients subjected to hip fracture surgery. This was a randomized, blind study, and the dose of ASA used was 100 mg twice daily for 14 days. All the patients underwent labeled fibrinogen

scanning or pletismography, and suspected cases of DVT were confirmed by venography. The incidence of VTE was significantly lower in the danaparoid group [27.8% vs. 44.3% in the ASA group, RRR 37.3 (95% CI 3.7–59.7)], and the incidence of hemorrhages was 1.6% in the danaparoid group and 6.4% in the placebo group (p = NS)[88].

In another study, 312 patients subjected to hip or knee arthroplasty were randomly assigned to ASA (325 mg twice daily) or warfarin. The incidence of VTE was 33.1% in the aspirin group and 24.7% in the warfarin group (p = NS)[89]. In the last study on knee arthroplasty, Westrich et al.[90] randomly assigned 275 patients to 325 mg of ASA, which was started on the day of the surgery, or enoxaparin (30 mg twice daily), which was only started 48 h after the surgery. The drugs were maintained for 3 weeks and the dose of enoxaparin was reduced to 40 mg once daily after discharge. The incidence of VTE was 17.8% in the ASA group and 14.1% in the enoxaparin group (p = NS). In both studies, the small size of the sample and the lack of power of the study may explain why the differences observed between the ASA group and the control group were not statistically significant. In addition, the delayed administration of enoxaparin in Westrich's study may have contributed to the VTE events observed in this group.

Analysis of the data of two recent studies[91,92] suggests a beneficial effect of ASA (100 mg/day) in patients who discontinue oral anticoagulation after 3–6 months of DVT treatment. In these patients, a reduction of at least 30% was observed in the recurrence of VTE episodes and a 42% reduction was observed in the recurrence of other vascular events.

Table 15 – Recommendations for the use of antiplatelet agents for the prevention and/or treatment of venous thromboembolism

Class of recommendation	Indications	Level of evidence	References
IIb	ASA in the prevention of VTE in patients subjected to general surgery or major orthopedic surgery	C	89,91,92

ASA: acetyl salicylic acid (aspirin); VTE: venous thromboembolism.

7.8 References

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8. Use of antiplatelet and anticoagulant agents in heart failure (HF)

8.1. Introduction

Full anticoagulation in patients with HF has been the subject of various studies over recent years. Its wide use has been criticized, and it is only indicated for specific situations. New drugs have been recently developed; however, their function has not been definitely established in this context. As shown below, this guideline focuses on reporting the indications for antithrombosis, particularly in HF, taking into account the main studies that have been developed in the area.

8.2. Anticoagulation in patients with atrial fibrillation (AF)

Decreased left ventricular ejection fraction and nonrheumatic AF are independent predictors of stroke[1,2]. However, there are conflicting data with regard to the predictive value of history of HF because antithrombotic prevention is associated with increased risk for bleeding[3-5]. In addition, ASA can, in theory, interact with angiotensin-converting enzyme inhibitors and decrease their beneficial effect[4]. Recommendations for prophylaxis are based on the clinical effect by taking into account the risk for stroke and the risk for bleeding[5].

8.2.1. Application of thromboembolism risk scores in AF

Risk scores are applied to guide the use of drugs that reduce the incidence of thromboembolic phenomena. However, all scores that have been published only exhibit moderate ability to predict stroke in AF (statistic between 0.55 and 0.70)[6]. The most validated score is the $CHADS_2$ score for risk stratification (C, deterioration of heart failure; H, history of hypertension; A, age ≥ 75 years; D, diabetes; S, stroke or transient ischemic episode)[7]. Each risk factor has a weight of 1 point, with the exception of S, which has a weight of 2 points, and anticoagulation therapy with warfarin is recommended if the score is ≥ 2. Recently, the CHA_2DS_2VASc score, which includes new risk factors, has been used[8]. Age ≥ 75 years now weighs 2 points; moreover, V means previous AMI, peripheral vascular disease, or plaque in the aorta and weighs 1 point; A, age between 65 and 74 years adds a point; the female gender is represented by the letters Sc. Considering the previous version of the score, the absence of risk factor is considered to indicate low risk for AF and a score of 1 is considered to indicate intermediate risk. A score ≥ 2 indicates high risk. There are no specific prospective studies considering HF. (section 4, "Use of antiplatelet and anticoagulant agents in atrial fibrillation," also addresses the $CHADS_2$ and CHA_2DS_2VASc scores.)

The indication for medications should also be assessed taking into account the risk for the bleeding score HAS-BLED (H, arterial hypertension with systolic ≥ 160 mmHg weighing 1 point; A, impaired liver or renal function weighing 1 point each; S, stroke weighing 1 point; B, bleeding weighing 1 point; L, unstable INR weighing 1 point; E, elderly (> 75 years) weighing 1 point; D, drugs or alcohol weighing 1 point each)[9]. Three or more points indicate high annual risk for bleeding, and the use of medication for the prevention of thromboembolism needs to be weighed against the risk. To justify the use of medications that are not associated with the reduction of mortality, the number of avoided nonfatal strokes should be higher than 1/3 of the number of major extracranial bleeding episodes[6]. (section 4, "Use of antiplatelet and anticoagulant agents in atrial fibrillation," also addresses the HAS-BLED score.)

8.3. Anticoagulation therapy in patients with HF and sinus rhythm

The WATCH study assessed patients with heart failure and sinus rhythm who were using vitamin K antagonist (dose adjusted according to INR) over 23 months. The incidence of stroke was 0.7% with vitamin K antagonist, 2.1%, with the use of ASA 162 mg, and 2.5% with clopidogrel 75 mg ($p < 0.05$)[10]. The number of hospitalizations was higher in the ASA group (22.2%) than in the group receiving the vitamin K antagonist. There was no difference in mortality. However, there was no placebo group. The WASH study, with a limited number of patients with heart failure and sinus rhythm, did not show a beneficial effect of the vitamin K antagonist with regard to mortality: however, the incidence of stroke was lower in the vitamin K antagonist group than in the placebo and ASA groups. Hospitalization was more frequent in the ASA 300 mg group (58%) than in the vitamin K antagonist group (42%) and the group without prophylaxis (48%) ($p = 0.05$)[11]. The recently published WARCEF study[12] assessed 2,305 patients from 176 centers in 11 countries, with LVEF lower than 35%, with sinus rhythm. This double-blind study compared treatment with warfarin and target INR of 2–3.5 with treatment with aspirin at a dose of 325 mg/day. The mean follow-up of the study was 3.5 years. Compared with ASA,

Table 1 – Recommendations for the use of anticoagulant and antiplatelet agents in patients with heart failure and atrial fibrillation

Class of recommendation	Indications	Level of evidence	References
I	Oral anticoagulant drug vitamin K antagonist for patients with AF and HF with recent deterioration or reduction in FEVE to < 0.35 and $CHADS_2/CHA_2DS_2$–VASc score ≥ 2	A	5-8
	ASA or clopidogrel for patients with AF and HF at intermediate and/or high risk for thromboembolic events ($CHADS_2$ ≥ 1) and with contraindication for oral anticoagulant drugs due to bleeding	A	5-8
IIa	Oral anticoagulant drug vitamin K antagonist for patients with AF and with recent deterioration or reduction in LVEF to < 0.35 and $CHADS_2/CHA_2DS_2$–VASc score of 1, without additional risk factors	A	5-8

LVEF: left ventricular ejection fraction; ASA: acetyl salicylic acid (aspirin); AF: atrial fibrillation; HF: heart failure.

warfarin did not significantly reduce the rate of the primary outcome (7.47 events/100 person-years in the warfarin group and 7.93 in the aspirin group).

Therefore, at present, full anticoagulation is indicated for patients with heart failure and sinus rhythm, only as secondary prevention of thromboembolic events.

8.4. New anticoagulant agents for HF

New anticoagulant drugs have been recently proposed in the context of AF. The RE-LY, ROCKET AF, and ARISTOTLE clinical trials were recently published and compared warfarin with dabigatran, rivaroxaban, and apixaban with regard to the prevention of the primary outcome of stroke or systemic embolism. In the RE-LY trial, which tested dabigatran, a competitive thrombin inhibitor, of the 18,113 patients with AF, 5,793 had heart failure (32%)[13]. In the prespecified subgroup analysis of patients symptomatic for HF, dabigatran at the doses of 110 mg and 150 mg twice daily was not inferior or superior to warfarin in the prevention of the primary outcome, although at a dose of 150 mg, it reduced the primary outcome from 1.53% to 1.11% ($p < 0.001$ for superiority) in the overall group. There was no difference in mortality. Patients with CrCl < 30 ml/min should not receive dabigatran, and patients with some degree of renal impairment or low weight should receive a lower dose[14]. In the ROCKET study, rivaroxaban, a direct inhibitor of the activated factor X, was tested. It included 14,264 patients, 8,851 of which had heart failure (62%). Rivaroxaban was not inferior to warfarin in the overall group and in patients with heart failure with regard to the prevention of stroke or systemic embolism[15]. The ARISTOTLE study tested apixaban, an inhibitor of the activated factor X. It included 18,201 patients, 6,451 of which had heart failure[16]. In the overall group, compared with warfarin, apixaban reduced the primary outcome from 1.6% to 1.27% ($p = 0.01$ for superiority) and major bleeding from 3.09% to 2.13% ($p < 0.001$); however, there was a reduction in mortality from 3.95% to 3.52%, with $p = 0.047$, i.e., close to 0.05 despite the inclusion of a high number of patients. In the subgroup analysis of patients with HF, apixaban was not superior to warfarin. The disadvantages of using these new anticoagulant agents are the higher cost and the limitations in the treatment of bleeding episodes. The advantage is that there is no need to monitor INR, which is important in patients who do not adhere to an adequate control protocol. However, the main limitations are the lack of phase IV studies to assess safety in the "real world" and the lack of specific studies on HF. Moreover, there are no publications that include patients with heart failure caused by Chagas disease, which would be important because studies suggest that microembolism is more frequent in patients with this disease[17].

8.5. Anticoagulation in HF due to Chagas disease

Chagas disease remains a serious public health problem in Brazil, with approximately 5 million infected individuals. It is estimated that 30% of these patients will develop the symptomatic clinical form of the disease, chronic chagasic cardiopathy (CCC), which is the most severe stage of the disease. Its most common clinical manifestations are tachycardia, bradyarrhythmia, thromboembolic phenomena, and HF[18].

Table 2 – Recommendations on the use of anticoagulants and antiplatelet agents in patients with heart failure in sinus rhythm

Class of recommendation	Indications	Level of evidence	References
I	Oral vitamin K antagonist for intracavitary thrombus.	C	5,6
	ASA for ischemic cardiomyopathy with moderate or high risk of coronary event, with reduced risk of hospitalization for HF.	A	5,6
IIa	Anticoagulant in the first 6 months after anterior wall MI with systolic dysfunction without thrombus.	C	5,6
III	Antithrombotic drug for primary prevention in patients with HF not hospitalized or without immobilization, without additional risk factor*, without prior thromboembolic event, without intracavitary thrombus, and in sinus rhythm.	B	5,6

*ASA: acetyl salicylic acid (aspirin); MI: myocardial infarction; HF: heart failure. *Left ventricular ejection fraction < 0.35, hypertension, age > 75, diabetes and previous cerebral vascular accident.*

Table 3 – Recommendations for the use of new oral anticoagulant agents in patients with heart failure

Class of recommendation	Indications	Level of evidence	References
I	Oral anticoagulants other than vitamin K antagonist for patients who do not adhere to or are not available for INR monitoring for adjusting the antagonist dose or uncontrolled INR variability > 3 or < 2	C	5,6,13-16
IIa	Competitive inhibitor of thrombin or inhibitor of activated factor X as an alternative to the vitamin K antagonist in patients with indication for use of oral anticoagulant drugs with vitamin K antagonists.	C	5,6,13-16

INR: international normalization ratio.

Thromboembolic phenomena are common complications because of the presence of dyskinesia and ventricular aneurysm, cardiac chamber dilatation, venous stasis, and AF[19].

The presence of these factors favors the formation of intracavitary thrombi with subsequent systemic or pulmonary embolism. Chagas disease is the third cause of heart failure in Brazil[20]. The annual incidence of thromboembolic phenomena is 1%–2% in CCC, and they are associated with aneurysm of the left ventricular apex and mural thrombosis.

In view of the specificities of Chagas disease, the most recent update of the Brazilian guideline on chronic heart failure considers that the treatment of heart failure of chagasic origin is similar to that of other etiologies, the only difference being the level of evidence[5].

8.5.1. Application of thromboembolism risk scores in Chagas disease

The $CHADS_2$ score and more recently the CHA_2DS_2VASC score are used for risk stratification in the treatment to reduce thromboembolic phenomena in HF in the presence of AF. The recommendation made for the use of warfarin in other forms of heart failure is applicable.

A Brazilian study published in 2008[21] presented the development of a score (IPEC/FIOCRUZ — Instituto de Pesquisa Clínica Evandro Chagas/Fundação Osvaldo Cruz) for risk assessment and the prevention of stroke in Chagas disease, in particular. The presence of left ventricular systolic dysfunction contributed with 2 points, and apical aneurysm, ventricular repolarization alteration, and age > 48 years contributed 1 point each. Risk/benefit analysis revealed that warfarin is indicated for patients with 4–5 points (in this subgroup, the annual incidence of stroke was 4.4% and the annual incidence of major bleeding was 2%). In the subgroup with a score of 3 points, the rates of events and bleeding with anticoagulant agent are balanced, and both warfarin and ASA are indicated. In patients with 2 points, ASA or no prophylaxis is recommended because of the low incidence of stroke.

See Tables 4 and 5.

8.5.2. Anticoagulation with heparin in patients with Chagas disease

Anticoagulant drugs such as UH or LMWH can be used in this group of patients. Other antiplatelet and anticoagulant drugs have not been tested in the chagasic population; therefore, its use is not recommended. Recommendations follow the same line as those for patients with heart failure of other etiologies.

8.5.3. Use of new oral anticoagulant agents in patients with Chagas disease

Recent clinical trials such as the RE-LY, ROCKET AF, and the ARISTOTLE trials compared dabigatran, rivaroxaban, and apixaban with warfarin in the prevention of systemic thromboembolism. However, patients with Chagas disease were not included in this studies; therefore, there is no evidence in favor of its use in this group of patients[13,15,16].

Table 4 – Recommendations for the use of oral anticoagulant agents in heart failure caused by Chagas disease

Class of recommendation	Indications	Level of evidence	References
I	AF with systolic dysfunction or $CHADS_2$ score > 2	C	5,18
	Mural thrombosis	C	5,18
	Previous embolic stroke	C	5,18
IIb	Score IPEC/FIOCRUZ score ≥ 3	B	21
	Aneurysm of the apex of the left ventricle without thrombosis	C	5,18

AF: atrial fibrillation; IPEC/FIOCRUZ, Institute of Clinical Research Evandro Chagas/Oswaldo Cruz Foundation.

Table 5 – Recommendations for the use of antiplatelet agents in heart failure caused by Chagas disease

Class of recommendation	Indications	Level of evidence	References
IIa	Atrial fibrillation with $CHADS_2$ score of 1	C	5,18
IIb	IPEC/FIOCRUZ score ≥ 2	B	21

AF: atrial fibrillation; IPEC/FIOCRUZ, Institute of Clinical Research Evandro Chagas/Oswaldo Cruz Foundation.

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9. Use of antiplatelet and anticoagulant agents in the perioperative period of cardiac and noncardiac surgeries

9.1. Introduction

Certain cardiovascular diseases often present some thromboembolic complications. Consequently, their treatment includes the use of drugs that inhibit platelet aggregation and delay blood coagulation. However, in the perioperative period, this activity may be inconvenient because blood coagulation needs to be partially or entirely completed for the surgical procedure to be successful. This creates a paradox that the involved professionals have to address during perioperative procedures using evidence to weigh the risk for bleeding against the risk for thromboembolic event and ensure patients' safety. We hope that the following recommendations help these professionals determine the lowest risk:

9.2. Indications for antiplatelet agents in cardiac surgery

9.2.1. ASA

The effect of ASA on the reduction of mortality, myocardial infarction, and cerebral thromboembolism in patients at risk for thromboembolic events, at the cost of higher risk for bleeding, has been demonstrated[1]. Doses of 75–100 mg are as effective as doses >300 mg, with lower risk for bleeding[2]. On the other hand, the variability of individual response to ASA and other antiplatelet agents has been shown. However, there is no practical clinical way of individualizing its administration and dosage.

In patients who are scheduled for cardiac surgery, the risk–benefit analysis of maintaining ASA in the preoperative period depends on the urgency of the situation, patient's cardiovascular risk, associated antithrombotic medications, and risk for bleeding[3].

Although in the past, the recommendation was to discontinue the use of ASA for 3–5 days before cardiac surgery, this practice has not been in use for some years in most healthcare centers[4]. The current guidelines of the American Heart Association/American College of Cardiology regarding revascularization surgery recommend the administration of ASA before the surgical procedure (as Class I) because there is evidence of an association with better postoperative outcomes[5]. In modern perioperative management, potential bleeding is rarely associated with continued administration of ASA (Table 1).

9.2.2. Thienopyridines

Ticlopidine is the first-generation thienopyridine. In the second generation, clopidogrel was introduced; it became the preferred agent for the associated lower incidence of blood dyscrasias and bone marrow toxicity[6]. More recently, prasugrel was introduced. Antiplatelet drugs of this class are associated with major bleeding in the postoperative period and should be avoided or specific measures should be taken in perioperative management. All these agents irreversibly inhibit platelet aggregation, and antidotes are not available. Thus, to restore platelet function, the use of these drugs needs to be discontinued, and one should wait for 5–7 days for the circulating platelet population to be renewed.

These drugs should receive separate comments because they exhibit specific characteristics (Table 2).

9.2.2.1. Ticlopidine

This first-generation thienopyridine reduces the incidence of stroke, myocardial infarction, and death by vascular causes and is more effective than ASA. The maximum

Table 1 – Recommendations for the use of ASA in the preoperative period of cardiac surgery

Class of recommendation	Indications	Level of evidence	References
I	ASA should be maintained in patients with ACS who will undergo myocardial revascularization surgery	B	4,5
IIa	Preoperative discontinuation of ASA could benefit patients at high risk for bleeding or transfusion complications or even those who refuse to receive transfusions, e.g., the followers of some religions, such as Jehovah's Witnesses	B	4,5
	In patients without ACS who undergo elective surgery, it is reasonable to discontinue ASA for reducing the risk of bleeding	A	4,5

ACS: acute coronary syndrome.

Table 2 – Recommendations for the use of thienopyridines in the preoperative period of cardiac surgery

Class of recommendation	Indications	Level of evidence	References
I	Thienopyridines (ticlopidine and clopidogrel) should be discontinued for 5–7 days before myocardial revascularization surgery	B	4,9,10
	Administration of unfractionated heparin and ASA is useful to prevent ischemic events after the discontinuation of clopidogrel in the immediate preoperative period	B	4,9,10
IIb	Platelet aggregation tests (point-of-care testing) can be useful to identify patients who are nonresponsive to clopidogrel	C	4,9,10

effect occurs after 3–5 days and lasts for up to 10 days after discontinuation. The adverse effects include diarrhea, allergic reaction, urticaria and erythema, and hemorrhagic (epistaxis, ecchymosis, menorrhagia) and hematolological (leucopenia, thrombocytopenia, pancytopenia) disorders[7].

In systematic reviews of large clinical trials, it was considered to be as effective as or more effective than ASA in preventing cardiovascular events. However, with the advent of clopidogrel, a drug of the same class and with less side effects, its use became secondary in clinical practice, mainly because of the occurrence of diarrhea and neutropenia[8].

9.2.2.2. Clopidogrel

This thienopyridine agent, a ADP P2Y12 receptor inhibitor, is the most widely used. It irreversibly inhibits platelet aggregation and should be discontinued 5–7 days before a surgical procedure to enable platelet renewal.

A recent multicenter analysis assessed the impact of exposure to clopidogrel for ≤ 5 days before myocardial revascularization surgery on the outcomes of reoperation, major bleeding, and hospitalization time in patients with ACS. The risk-adjusted reoperation rate (OR) was 9.80%, (95% CI 2.18–43.95, $p = 0.01$) in the clopidogrel group, in which the rate of reoperations was 6.4%, compared with 1.7% in the group without clopidogrel ($p = 0.004$)[9].

On the other hand, another recent analysis that compared the results obtained during three decades revealed that the management of surgical patients receiving clopidogrel had improved, which was demonstrated by the significant reduction in the occurrence of bleeding and mortality in recent years[10].

There is individual variability in the response to clopidogrel as a result of the genetic characteristics of patients. Therefore, a laboratory assessment should be performed (point of care testing) to determine its action in a specific patient[3].

In patients with recent ACS, stabilized with drug-based treatment, the preferred strategy is discontinuation for 5 days before the surgery, as mentioned above. During this period, the administration of ASA 100 mg/day and heparin is recommended. In patients at high risk for severe ischemic events (previous myocardial revascularization surgery, complex procedures, or with noncardiac comorbidities), the recommendation, which is rarely followed, is to perform antiplatelet therapy as "bridge to surgery" with drugs of short duration, i.e., GP IIb/IIIa inhibitors such as eptifibatide and tirofiban.

9.2.3. Glycoprotein (GP) IIb/IIIa inhibitors

This class of drugs inhibits the final step of platelet aggregation, preventing fibrinogen from binding to GP IIb/IIIa receptors and its conversion to fibrin. The available drugs are tirofiban, abciximab, and eptifibatide, all of which are intravenously administered. Their rapid activity onset, which occurs minutes after administration, and potency make them particularly effective for use in percutaneous coronary angioplasty and ACS but at the cost of higher risk for bleeding[11]. They vary with regard to the mechanism of action and duration of the effect.

Tirofiban and eptifibatide. These agents have short duration and a reversible effect. Tirofiban is a peptidomimetic, with an amino acid sequence similar to that of fibrinogen. Eptifibatide is a hexapeptide that has a three-amino-acid sequence similar to the bothropic ophidic venom[12].

Abciximab. This is a long-acting monoclonal antibody that inhibits thrombin generation. It has a short half-life in plasma and exhibits cross-reactivity with leukocyte receptors. It has a potent platelet-inhibiting activity, with gradual recovery 24–48 h after discontinuation[12].

The use of these agents combined with UH is recommended for a short preoperative period of time as "bridge to surgery" in patients with ACS who were using clopidogrel. The latter should be discontinued at least 5 days before the surgery. During this period, the use of ASA at a low dose (up to 100 mg) and heparin is recommended. An alternative, although not very much used, could be the administration of GP IIb/IIIa inhibitors to prevent ischemic events during the preoperative period but at the cost of higher risk for bleeding. In patients at high risk for bleeding, the alternative is to form this bridge using an intra-aortico balloon for 48–72 h before the surgical procedure[4]. In Brazil, the postclopidogrel bridge has been preferentially used with UH and ASA.

Patients who undergo surgery with the use of GP IIb/IIIa inhibitors require special measures and discontinuation of the medication at the time of the procedure, if not before. Eptifibatide and tirofiban have short half-lives of approximately 2 h, and there may be platelet aggregation recovery at the end of the revascularization surgery. With regard to abciximab, although it has a short half-life in plasma (10 min), dissociation from platelets gradually occurs, and with a half-life of 4 h, platelet function returns to normal after 24–48 h and a rebound effect may occur. If excessive bleeding occurs, the recommendations include fresh platelet transfusion and fibrinogen supplementation with fresh plasma or cryoprecipitate; these measures may be applied alone or in combination[13] (Table 3).

Table 3 – Recommendations for the use of glycoprotein IIb/IIIa inhibitors in the preoperative period of cardiac surgery

Class of recommendation	Indications	Level of evidence	References
I	In stable patients, GP IIb/IIIa inhibitors should be discontinued 48 h before revascularization surgery	B	4
IIa	In ACS and in patients at risk for ischemic events, tirofiban and eptifibatide can be maintained until surgery; they should be discontinued at the beginning of surgery, and precautions should be taken to reverse bleeding caused by platelet aggregation deficiency at the end of the surgery	B	4
IIb	Tirofiban and eptifibatide can be used as bridge to surgery in patients with ACS who discontinued clopidogrel before surgery	C	4

GP: glycoprotein; ACS: acute coronary syndrome.

9.2.4. P2Y12 receptor inhibitors

For complete aggregation to occur, both receptors (P2Y1 and P2Y12) have to be inhibited; however, P2Y12 is predominant, and its binding to adenosin results in increased production of thromboxane and prolonged antiplatelet activity[14-18].

The antiplatelet therapy recommended for patients with ACS and for those undergoing a coronary stent implant comprises ASA and a P2Y12 receptor inhibitor[19,20].

The new P2Y12 receptor inhibitors alter the conformation of this receptor, resulting in its reversible inhibition, unlike old platelet inhibitors such as ticlopidine and clopidogrel that irreversibly bind to platelets[21,22]. Platelet inhibition achieved by the new inhibitors prasugrel and ticagrelor has an earlier onset, on average 15–30 min after the initial dose vs. 1–2 h after the initial dose of clopidogrel, which has a higher effect (between 60% and 70% of inhibition 2–4 h after the initial dose vs. 30% 5 h after the initial dose of clopidogrel). Moreover, it exhibits a higher duration of action (up to 10 days vs. 7 days with clopidogrel)[23-30]. Patients with ACS treated with prasugrel are more protected against ischemic events than patients treated with clopidogrel. However, they exhibit higher risk for bleeding[31].

In the literature, some factors are associated with increased risk for postoperative bleeding, such as advanced age, preoperative anemia, emergency surgery, surgery with long extracorporeal circulation, and other comorbidities such as congestive heart failure, chronic obstructive pulmonary disease, and renal failure. In addition, one important factor associated with bleeding is the use of antiplatelet agents in the preoperative period. This type of drug is common in patients with coronary disease, particularly those with ACS. A series of studies have indicated that the use of P2Y12 receptor inhibitor is associated with major bleeding and that not even surgery without extracorporeal circulation seems to prevent this[9,32-34]. Three studies suggest that the use of P2Y12 receptor inhibitors associated with ASA decreases the incidence of ischemic events and does not increase the rate of bleeding, provided that the P2Y12 receptor inhibitors are discontinued at least 5 days before surgery[35-37]. Two recent studies have revealed that discontinuation 3 days before coronary surgery is sufficient[38,39].

In some series of studies, compared with clopidogrel, the two new P2Y12 receptor inhibitor agents prasugrel and ticagrelor did not exhibit an excessive increase in bleeding[40,41]. However, this fact is not associated with coronary surgeries, i.e., even if the increase in the incidence of bleeding with the use of these drugs has not been demonstrated, bleeding associated with myocardial revascularization surgery in patients using these new antiplatelet agents is increased[41]. Studies have shown up to fourfold higher likelihood of bleeding with the use of prasugrel than with the use of clopidogrel, and both ticagrelor and clopidogrel have been shown to exhibit the same risk for bleeding during surgery if the drug is administered up to 72 h before surgery[31,42].

The Society of Thoracic Surgery (STS), in a guideline published in 2011[3], recommends the discontinuation of P2Y12 receptor inhibitor agents at least 3 days before the surgical procedure. The previous recommendation was to wait for 5–7 days after the discontinuation of these drugs to perform surgery. However, many surgeons did not wait for this long[37], and because some studies[38,39] suggest that 3 days are sufficient, this is the current recommendation of STS.

ASA decreased the incidence of occlusion of venous grafts in the postoperative period. In the literature, there is a systematic review on the expansion of this concept to antiplatelet drugs[43]. Their systematic use after myocardial revascularization increases the incidence of reoperation caused by bleeding, and in view of currently available evidence, is not indicated. The use of P2Y12 receptor inhibitors is indicated in patients with some contraindication for the use of ASA in the postoperative period[44]. When its use is mandatory, it should be reintroduced 48 h after the end of surgery.

The American Heart Association, together with the American Association for Thoracic Surgery and STS, in their 2011 guideline for the management of antiplatelet drugs in myocardial revascularization surgery, recommend the discontinuation of ticagrelor 5 days before the surgery and discontinuation of prasugrel 7 days before the procedure. In cases of emergency reoperations, it is recommended that, if possible, these drugs be discontinued at least 24 h before surgery[5] (Table 4).

Table 4 – Recommendations for the use of receptor P2Y12 blockers in the preoperative of cardiac surgery

Class of recommendation	Indications	Level of evidence	References
I	There are no large studies comparing the use and the absence of prasugrel and ticagrelor during coronary surgery. Ticagrelor should be discontinued for 3–5 days before the surgery, and prasugrel should be discontinued for 7 days before the procedure	B	35-37
	In situations of urgency and emergency wherein the discontinuation of the P2Y12 receptor inhibitor does not occur, patients exhibit increased risk for bleeding; with ticagrelor, the risk is similar to that with clopidogrel, and with prasugrel, the risk is up to fourfold higher. If possible, prasugrel or ticagrelor should be discontinued 24 h before the procedure	C	31,42
IIa	The use of P2Y12 receptor inhibitors is indicated for patients with some contraindication for the use of ASA in the postoperative period. When their use is mandatory, they should be reintroduced 48 h after the end of the surgery	B	5,44
III	There is no advantage in early reintroduction or systematic use of P2Y12 receptor inhibitors in the postoperative period of myocardial revascularization	C	5,44

9.2.5. Cilostazol

This is a cAMP inhibitor with antiplatelet and vasodilating functions. It has been used with good results in patients with severe peripheral vascular disease and intermittent claudication[45] for the secondary prevention of stroke[46] and helps reduce intrastent restenosis in coronary disease[47,48]. It is used as part of the triple therapy associated with ASA and clopidogrel, and it decreases platelet aggregation in patients with AMI who undergo primary angioplasty[49]. Some studies have revealed that its combination with ASA does not increase the bleeding time[50].

Moreover, cilostazol affects the smooth muscle of vessels that appears to prevent the occurrence of hyperplasia[51,52]. This effect, in addition to preventing intrastent restenosis, decreases potential intimal hyperplasia that occurs at coronary anastomoses sites[53].

Onoda K et al.[54] revealed the benefits of combining cilostazol with ASA in patients undergoing myocardial revascularization without extracorporeal circulation. The authors mention that in surgeries without extracorporeal circulation, a state of hypercoagulation[55,56] occurs and that cilostazol is beneficial in the immediate postoperative period. In this study, both cilostazol and ASA were discontinued 7 days before the surgery (Table 5).

9.2.6. Dipiridamol and triple therapy

The articles on dipiridamol are outdated; the most recent publications are approximately 20 years old. In 1988, Teoh KH et al.[57] published a prospective and randomized study with 58 patients who underwent cardiac surgery with extracorporeal circulation. Forty patients who received dipiridamol, pre- and postoperatively, were compared with a control group of 18 patients. The preoperative administration of dipiridamol resulted in a significantly lower blood loss and lesser need for transfusion of blood concentrates. The authors concluded that dipiridamol leads to an increase in the number of platelets and reduces the postoperative risk for bleeding.

In 1975, another study[58] compared 12 patients who underwent cardiac surgery with extracorporeal circulation and were treated with dipiridamol in the pre- and postoperative periods, with a control group of 38 patients. As observed in the first study, the results revealed an increase in the number of platelets, and increased bleeding in the postoperative period was not observed.

In 1986, Chesebro and Fuster[59] conducted a study wherein the efficacy of dipiridamol in preventing early occlusion of the saphenous vein bridge was assessed. The authors reported that the agent decreased platelet deposition in the graft during surgery and that its use in the preoperative period is important. Similar to other studies, they did not observe increased postoperative bleeding.

In 1978, another study[60] evaluated antithrombotic therapy in patients subjected to myocardial revascularization with the saphenous bridge and internal thoracic artery. In this series, the authors reported that there was a clear advantage in terms of reduction in the graft occlusion rate a year after the surgery in patients who received dipiridamol, without an increase in the incidence of bleeding immediately after the surgery[60,61].

The most recent article was published in 1993, and it refers to positive results in terms of reduction in the graft occlusion rate in the late postoperative period in patients who used dipiridamol. An increase in bleeding in the immediate postoperative period was not reported. In the 2011 guideline of STS[62,63] and the American Society of Anesthesiologists[3], dipiridamol is not mentioned as an agent responsible for increased postoperative bleeding.

With regard to triple therapy, there is no strong evidence to be considered; therefore, evidence regarding the individual drugs should be considered (Table 6).

Table 5 – Recommendations for the use of cilostazol in the preoperative period of cardiac surgery

Class of recommendation	Indications	Level of evidence	References
I	Few studies exist on cilostazol and cardiac surgery. This is a platelet inhibitor agent, and, as such, its use should be discontinued for at least 72 h before the surgery	C	5
IIa	There are no reports on increased bleeding in patients who require emergency surgery. Its use in the postoperative period, when associated with ASA, appears to provide some degree of protection with regard to graft occlusion, and it can be started in the immediate postoperative period	C	54

Table 6 – Recommendations for the use of dipiridamol and triple therapy in the preoperative period of cardiac surgery

Class of recommendation	Indications	Level of evidence	References
I	There are no reports of increased bleeding in patients using dipiridamol who require cardiac surgery	B	4,5
	With regard to triple therapy, discontinuation indications for each agent should be individually followed	B	60,61

9.3. Indications for anticoagulant agents in cardiac surgery

9.3.1. Heparin

Patients with ACS may require surgical treatment for myocardial revascularization. When they are administered heparin, they exhibit higher risk for postoperative bleeding and higher need for revision surgery and blood transfusion[64-73]. Therefore, the potential clinical benefit of using heparin in the preoperative period should be weighed against the risk for major postoperative bleeding and higher need for blood transfusion that may lead to an increase in clinical complications and death at 30 days[74,75]. Both blood derivative transfusion and revision surgery result in deterioration of the patient's clinical evolution and in increased costs and hospitalization time (Table 7).

9.3.2. Warfarin

The management of patients who use anticoagulant drugs in the perioperative period depends on the patient's risk for developing thromboembolic events when the use of the drug is discontinued and on the bleeding risk if anticoagulation therapy is not interrupted. Anticoagulation in the perioperative period is associated with a 3.0% increase in severe bleeding. It has been shown that INR (international normalization ratio) < 1.5 is not associated with perioperative major bleeding[76-78]. Adequate adjustment of anticoagulation therapy is important to minimize thrombotic and hemorrhagic events.

Discontinuation of anticoagulant therapy increases the risk for embolic phenomena such as stroke and thrombosis of mechanical prostheses, and this risk varies according to the presence of other comorbidities. These events can have devastating clinical consequences: stroke can lead to significant incapacity or death in 70% of patients; mechanical prosthesis thrombosis can be fatal in 15% of patients[76].

According to risks for embolic events in the perioperative period and the associated comorbidities, the risk will be stratified into high, moderate, and low[78] (Tables 8 and 9).

When aiming for rapid INR normalization, replacements of deficient factors include fresh frozen plasma (FFP) and a prothrombin complex concentrate [Resolution RDC n. 10, of January 23, 2004, of the *Agência de Vigilância Sanitária* (ANVISA) determines that "for the correction of hemorrhages caused by the use of coumarin anticoagulants or rapid reversal of the effects of coumarin anticoagulants, the product of choice is the prothrombin complex. Because this type of concentrate is not yet widely available in Brazilian hospitals, FFP is an acceptable alternative."][79].

The dosage of the prothrombin complex concentrate has not yet been standardized; however, its administration according to the patient's INR value is suggested (Tables 10 and 11).

9.3.3. Fondaparinux

Fondaparinux is a synthetic pentasaccharide that selectively inhibits factor Xa by binding to antithrombin. Fondaparinux has more affinity to antithrombin than the native pentasaccharide of UH or LMWH. This binding causes a conformational change in antithrombin that

Table 7 – Recommendations for the use of heparin in the preoperative period of cardiac surgery

Class of recommendation	Indications	Level of evidence	References
IIa	In patients who are on unfractionated heparin for acute coronary syndrome (ACS) or oral anticoagulation transition therapy or on antiplatelet drugs, it is recommended to discontinue unfractionated heparin 4-6 h before the surgery	C	4,5
	In patients using LMWH for ACS or in situations of oral anticoagulation transition or use of antiplatelet drugs, LMWH should be discontinued 24 h before the surgery	C	4,5

LMWH: low-molecular-weight heparin; SCA: acute coronary syndrome.

Table 8 – Classification of risk for embolic events in the perioperative period

Risk	Clinical situations
High	Mechanical prostheses: any mechanical prosthesis in the mitral position, old mechanical prosthesis in the aortic position, or stroke/TIA in the last 3 months
	AF with $CHADS_2 \geq 5$, associated with valve disease or with stroke/TIA in the last 3 months
	VTE in the last 3 months or associated with severe thrombophilia (protein C or S or antithrombin deficiency or presence of antiphospholipid antibody)
Intermediate	Aortic mechanical prostheses with AF, previous stroke/TIA, age > 70 years, HF, AH, or diabetes
	AF with $CHADS_2 = 3$ or 4
	VTE in the last 3–12 months, mild thrombophilia (factor V Leiden or factor II heterozygotic mutations), recurrent VTE, or active neoplasia
Low	Aortic mechanical prosthesis without risk factors for stroke
	AF with $CHADS_2 = 0–2$, without previous stroke/TIA

TIA: transient ischemic attack; VTE: venous thromboembolism; HF: heart failure; AH: arterial hypertension; AF: atrial fibrillation.

Table 9 – Recommendations for the use of warfarin in the preoperative period of cardiac surgery

Class of recommendation	Indications	Level of evidence	References
	Patients at high risk for thromboembolism		
I	Discontinue warfarin 5 days before the surgery and wait for INR < 1.5	C	4,5,76-78
	Start unfractionated heparin or full-dose LMWH when INR < 2.0	C	4,5,76-78
	Discontinue intravenous unfractionated heparin 4 h before the procedure and subcutaneous LMWH 24 h before	C	4,5,76-78
	Patients at intermediate risk for thromboembolism		
IIa	Depending on the patients' individual assessment, the recommendations made for high- or low-risk patients can be followed	C	4,5,76-78
	Patients at low risk for thromboembolism		
IIa	Discontinue warfarin 5 days before the surgery and wait for INR < 1.5 to perform the procedure	C	4,5,76-78
	In the preoperative period, unfractionated heparin or prophylactic LMWH can be used	C	4,5,76-78
	In the postoperative period, if indicated, use unfractionated heparin or prophylactic LMWH depending on the type of procedure and reintroduce the anticoagulant drug 12–14 h after the surgical procedure	C	4,5,76-78

INR: international normalization ratio; LMWH: low-molecular-weight heparin.

Table 10 – Recommendations for the use of warfarin in the preoperative period of cardiac surgery in situations of emergency and orientations for its reintroduction in the postoperative period

Class of recommendation	Indications	Level of evidence	References
I	In emergency surgery, the anticoagulant agent should be discontinued and intravenous vitamin K (2.5–5.0 mg) or oral vitamin K should be administered; replacement of deficient factors should be performed using the eprothrombin complex concentrate or FFP	C	4,5,76-78
	In elective surgery, the agent antivitamin K should be discontinued, and vitamin K1 should be used at a dose of 2.5–5 mg intravenously	C	4,5,76-78
	To reintroduce the agent in the postoperative period in patients at high risk for thromboembolism, reintroduce unfractionated heparin or LMWH at full dose as well as warfarin 12–24 h after the procedure and discontinue heparin only when INR is within the therapeutic range	C	4,5,76-78
	It is recommended to start the oral anticoagulant agent 12–24 h after the surgery (night or the following morning)	C	4,5,76-78

FFP: fresh frozen plasma; LMWH: low-molecular-weight heparin.

Table 11 – Dose of prothrombin complex concentrate to be administered for the reversal of oral anticoagulation according to the INR value

INR	Dose of prothrombin complex concentrate
2,0 – 3,9	25 U/Kg
4,0 – 5,9	35 U/Kg
≥ 6,0	50 U/Kg

INR: international normalization ratio.

enhances (by a factor of 300) the natural inhibitory effect of antithrombin against factor Xa. This is how fondaparinux functions as an anticoagulant[80-85].

Fondaparinux has been studied in coronary disease, including unstable angina and AMI, and in patients subjected to PCI[86,87].

In patients who are using fondaparinux and need elective surgery, the anticoagulant activity persists for approximately 3–5 half-lives after discontinuation of the agent; in patients with normal renal function, the anticoagulant activity persists for 2–4 days. A longer period would be necessary in patients with decreased renal function. There is no available antidote to reduce this waiting period. Some studies revealed that high doses of the recombinant factor VIIa (90 μg/kg) were able to normalize, up to 6 h, partially prolonged aPTT, endogenous thrombin potential, and prothrombin activation *in vivo* in healthy volunteers who received 10 mg of fondaparinux[85,88].

Recently, to make the use of fondaparinux safer, a variant antithrombin was developed as an antidote for heparin derivatives[89]. However, there are no systematic studies that include patients with bleeding (Table 12).

9.3.4. Bivalirudin

The safety and efficacy of bivalirudin have been investigated in a series of clinical trials in patients with ACS. compared with monotherapy with heparins, isolated or in combination with antiplatelet drugs, bivalirudin reduced the combined primary outcomes (death, myocardial infarction, and emergency revascularization). In addition, it significantly reduced hemorrhagic complications[87-96]. Based on the results of these studies and its beneficial effects, bivalirudin has been recommended, in the international guidelines, for use in patients with ACS treated in an invasive manner[91,92].

Bivalirudin has a linear anticoagulating dose–response behavior. The prothrombin time, aPTT, thrombin time, and activated clotting time linearly increase with an increase in the bivalirudin dose[97]. A dose of 0.2 mg/kg/h of bivalirudin increased the prothrombin time from 12 to 16 s, aPTT from 27 to 62 s, and thrombin time from 15 to 73 s[98]. The increase in the rate of bivalirudin infusion to 1 mg/kg/h resulted in a mean aPTT of 98 s, which returned to baseline within 4 h of infusion discontinuation[99] (Table 13).

9.3.5. Dabigatran

Dabigatran is a drug that directly inhibits the thrombin enzyme, responsible for converting fibrinogen into fibrin. Its use was approved by the European Medicines Agency in 2008 and more recently by ANVISA in Brazil and by the American FDA. It is an oral agent that can be used in a single daily dose, and there is no need to monitor its effect. However, dabigatran does not have an antidote[78].

Dabigatran has a half-life between 11 and 22 h in patients with normal renal function; in patients with renal impairment, the half-life can reach 35 h. Therefore, in procedures with a high bleeding risk, dabigatran should be discontinued between 2 and 6 days before the surgery[100,101].

In the case of acute intervention, dabigatran should be temporarily discontinued and the surgery should be postponed at least 12 h after the last dose. If it is not possible to postpone the surgery, hemorrhagic risk should be considered. This risk should be weighed against the urgency of the intervention (Table 14).

9.3.6. Rivaroxaban

This is an anticoagulant drug that directly inhibits activated factor X[102]. It is indicated for preventing VTE, stroke, and systemic embolism in patients with AF[102,103]. Rivaroxaban should not be used in patients with renal failure, in patients with liver disease associated with coagulopathy, and in patients using antimycotic drugs and protease inhibitors for HIV. It should not be administered to individuals younger than 18 years, pregnant women (because of the risk of toxicity as it crosses the placenta), and breastfeeding women (because the drug is excreted in the milk)[100]. Rivaroxaban has a mean half-life of 12 h and varies according to renal function[100]. In situations of emergency, where the anticoagulating effects of rivaroxaban need to be reversed, the 4-factor prothrombin complex concentrate can be used at a dose of 50 IU/kg. Other products such as plasma and cryoprecipitates do not reverse the anticoagulating effect of this agent[100] (Table 15).

9.3.7. Apixaban

Apixaban is one of the newest oral anticoagulant drugs that directly inhibits activated factor X. It has been shown to be effective and safe in the prevention and treatment of thromboembolism[75,81,82,87]. Few clinical studies exist, and the current recommendations are similar to those used for other direct inhibitors of activated factor X, such as dabigatran.

Table 12 – Recommendations for the use of fondaparinux in the preoperative period of cardiac surgery

Class of recommendation	Indications	Level of evidence	References
IIa	In patients with coronary disease who use the therapeutic dose of fondaparinux and need surgical treatment, it is recommended to discontinue the agents 4 days before the procedure (instead of 2 days before)	C	4,5,85,88

Table 13 – Recommendations for the use of bivalirudin in the preoperative period of cardiac surgery

Class of recommendation	Indications	Level of evidence	References
IIa	In patients with ACS who use bivalirudin and need surgical treatment for myocardial revascularization, it is recommended to discontinue the agent 4 h before the surgery, instead of discontinuing it at the surgical center	C	4,5,99
	In patients who exhibit thrombocytopenia induced by heparin (acute or subacute) in the presence of positive antibody and need emergency cardiac surgery, it is recommended to use bivalirudin instead of other anticoagulant agents (other than heparin)	C	4,5

ACS: acute coronary syndrome.

Table 14 – Recommendations for the use of dabigatran in the preoperative period of cardiac surgery

Class of recommendation	Indications	Level of evidence	References
IIa	In patients with normal renal function who need elective cardiac surgery, dabigatran can be discontinued 48 h before and adequate hemostasis is ensured	C	5,100,101
	In procedures with low risk of bleeding, dabigatran can be discontinued 24 h before the procedure	C	5,100,101
	In patients with compromised renal function (creatinine clearance < 50%), the discontinuation period varies between 4 and 6 days	C	5,100,101

Table 15 – Recommendations for the use of rivaroxaban in the preoperative period of cardiac surgery

Class of recommendation	Indications	Level of evidence	References
IIa	In patients with normal renal function who require cardiac surgery, rivaroxaban should be discontinued at least 24 h before the surgery	C	5,100,101
	In patients with compromised renal function (creatinine clearance < 50%), the discontinuation period should be 4 days	C	5,100,101

9.4. Management of antiplatelet agents in noncardiac surgeries

9.4.1. ASA

A large meta-analysis involving patients who underwent noncardiac surgery revealed that those receiving ASA exhibited up to 50% increase in the rate of perioperative bleeding. However, with the exception of neurosurgery and transurethral resection of the prostate, there was no increase in the occurrence of severe bleeding[104].

Till date, only one randomized, double-blind, and placebo-controlled study has been published on the perioperative use of ASA in noncardiac surgery. It included 220 patients with vascular disease who were already on ASA (i.e., patients on secondary prevention) and who were scheduled to have noncardiac surgical interventions. These patients were randomly assigned to stay on ASA or to discontinue this therapy in the perioperative period. The postoperative increase in troponin (primary goal) was lower in the group that stayed on ASA; however, the difference was not statistically significant, probably because of the number of patients in the study. However, there was a significant reduction in major cardiac events in patients who stayed on ASA in the perioperative period in comparison with patients who discontinued ASA (1.8% × 9.0%, $p = 0.02$). Although this was not one of the aims of the study, it did not demonstrate a difference in the rate of hemorrhagic complications between the groups[105].

In most situations, risk–benefit analysis of antiplatelet therapy in coronary patients who undergo noncardiac intervention favors the maintenance of ASA. Situations of exception include neurological surgery (in which even small bleedings can be catastrophic), transurethral prostatectomy (a procedure without primary hemostasis), and other circumstances wherein the risk of bleeding prohibits its use. In these cases, a minimum period of 7 days should be respected for reversal of the antiplatelet agent effect (Table 16).

9.4.2. Thienopyridines

In a systematic review of 37 studies on the use of thienopyridines in the perioperative period, Au et al.[106] concluded that this practice increased the need for reoperation because of bleeding [4.3% × 1.8% (OR 2.62, 95% CI 1.96–3.46)] and mortality [3.7% × 2.6% (OR 1.38, 95% CI 1.3–1.69)]. However, only six studies evaluated patients who underwent noncardiac surgery and, among these patients, the rate of events was too low to allow drawing definitive conclusions (six cases of bleeding that required reoperation among 230 patients and 14 deaths among 492 patients)[106].

In patients who underwent vascular surgery, although a greater number of studies was available, they included a small number of patients or events or they were observational and retrospective, which also did not allow drawing definitive conclusions. Burdess et al.[107] evaluated 113 patients with critical limb ischemia who underwent lower extremity revascularization, amputation, or femoral endarterectomy and who were randomized to receive clopidogrel 600 mg from 4 to 28 h before the surgery or a placebo at a dose of 75 mg/day after the surgery. All the patients were taking ASA. There was no difference in life-threatening major bleeding events between the groups: seven (14%) in the clopidogrel group and six (10%) in the placebo group ($p = 0.56$). However, the patients in the clopidogrel group exhibited an increase in the number of nonlife-threatening major bleeding events: 11 (22%) in the clopidogrel group and four (7%) in the placebo group ($p = 0.024$). Furthermore, 20 patients (40%) who received clopidogrel required transfusion of an erythrocyte concentrate, while only eight patients (14%) required this in the placebo group ($p = 0.0019$). There was no difference between the groups with regard to minor bleeding events ($p = 0.12$) or the duration of the surgery ($p = 0.6$) or hospitalization ($p = 0.72$)[107]. De Borst et al.[108] evaluated three different strategies for antiplatelet therapy in 102 patients before carotid endarterectomy.

Table 16 – Recommendations for the use of ASA in the preoperative period of noncardiac surgery

Class of recommendation	Recommendations	Level of evidence	References
I	Patients using ASA for secondary prevention undergoing noncardiac surgery should continue using ASA at a reduced dose (75–100 mg/day), with the exception of neurosurgery and prostate transurethral resection	B	104,105
	Patients using ASA for primary prevention should discontinue its use 7 days before the procedure	C	104,105

ASA: acetyl salicylic acid (aspirin).

The patients were divided into three groups: dipyridamole + ASA, dipyridamole + ASA + clopidogrel, and dipyridamole + ASA + dextran 40 mg. There was no difference among the groups with regard to the need for reoperation because of bleeding, which occurred in only five patients, thereby limiting the power of the study considerably[108].

Payne et al.[109] randomly assigned 100 patients, scheduled to undergo carotid endarterectomy, to receive 75 mg of clopidogrel or placebo in addition to ASA. There was no difference between the groups with regard to the need for blood transfusion ($p = 1.0$) and drainage volume ($p = 0.65$). However, there was an increase in the time to the closure of the surgical incision ($p = 0.004$) and a tendency for an increase in the occurrence of cervical hematoma (13% × 6%, $p = 0.47$) and in the need for revision surgery (11% × 6%) in the clopidogrel group, albeit without statistical significance[109]. Other observational studies that evaluated the use of clopidogrel in association with ASA in the perioperative period of carotid endarterectomy also included a small number of patients and events; therefore, no significant differences were observed between the groups[110]. Stone et al.[111] performed an observational study of 10,406 patients who underwent carotid endarterectomy, lower extremity revascularization, and conventional and endovascular abdominal aortic aneurysm repair. Among these patients, 2,010 (19.3%) did not receive antiplatelet therapy, 7,132 (68.5%) received ASA, 229 (2.2%) received clopidogrel, and 1,017 (9.7%) received double antiplatelet therapy. There was no difference between the groups with regard to reoperation because of bleeding (without antiplatelet therapy, 1.5%; ASA, 1.3%; clopidogrel, 0.9%; and ASA with clopidogrel, 1.5%; $p = 0.74$) or the need for transfusion (without antiplatelet therapy, 18%; ASA, 17%; clopidogrel, 0%; and ASA with clopidogrel, 24%; $p = 0.1$). Meanwhile, the number of patients who received clopidogrel in the groups that underwent aortic aneurysm repair was too small to allow drawing conclusions regarding the use of clopidogrel in this population[111].

Evidence is even scarcer for patients who underwent nonvascular surgery. A retrospective study compared 28 patients who received clopidogrel up to 6 days before undergoing general surgery with 22 patients in whom the treatment was discontinued 7 or more days prior to surgery. Patients who used clopidogrel exhibited a greater number of bleeding events that required transfusion than those who suspended clopidogrel 7 or more days before the surgery (21.4% × 9.5%); however, this difference was not statistically significant ($p = 0.53$). Approximately 32% of the patients in the clopidogrel group and 40% of the patients in the clopidogrel discontinuation group were taking ASA. None of the patients presented bleeding that required reoperation, and there was no difference between the groups with regard to mortality or duration of hospitalization[112].

Sim et al.[113] retrospectively evaluated 21 patients who were taking clopidogrel and underwent femoral fracture surgical repair and compared them with 114 control patients; those authors showed that there was no difference between the groups with regard to the need for transfusion or the presence of hematoma in the surgical wound[113]. Recently, Chechik et al.[114] evaluated 60 patients with femoral fracture who were taking clopidogrel; among them, 30 patients underwent surgery during treatment with this agent and 30 patients underwent surgery only 5 days after the treatment was suspended. There was no difference between the groups with regard to the need for transfusion or mortality, although there was a tendency for a greater number of clinical complications related to immobility (PTE, pressure ulcers, pulmonary edema, and sepsis) in the group in which surgery was delayed because of the use of clopidogrel[114]. These data are important because early surgery in patients with femoral fracture reduces mortality, and delaying the surgery because of the use of clopidogrel may be more damaging than beneficial. Furthermore, the discontinuation of the administration of antiplatelet therapy in patients with coronary disease increases the risk of ACS[115].

Another retrospective study compared 142 patients who were taking clopidogrel with 1,243 control patients who underwent colonoscopic polypectomy with regard to the occurrence of immediate and delayed bleeding. Seventy-seven patients (54%) in the clopidogrel group were also taking ASA. Although there was no difference between the groups with regard to immediate bleeding (2.1% × 2.1%), the patients who were taking clopidogrel exhibited a greater number of late bleeding events (3.5% × 1.0%, $p = 0.02$) and a greater need for hospitalization, transfusion, or additional intervention (2.1% × 0.4%, $p = 0.04$). We should consider that the eight patients in the clopidogrel group who exhibited bleeding were using ASA. In multivariate analysis, the independent variables that were related to bleeding were the use of double antiplatelet therapy (RR 3.69, 95% CI 1.6–8.52, $p = 0.002$) and the number of dried polyps (RR 1.28, 95% CI 1.19–138, $p < 0.001$)[116].

It is possible that isolated antiplatelet therapy using clopidogrel does not represent a great risk for bleeding; however, there is no current evidence in support of this contention.

The decision regarding the continuation or discontinuation of antiplatelet therapy should always be reached after a risk–benefit multidisciplinary discussion among the cardiologist/clinician, the anesthesiologist, and the surgeon (Table 17).

9.4.3. Patients with coronary artery stents

Approximately 5% of patients who undergo coronary angioplasty with stent placement require noncardiac surgery within 1 year[117]. The premature discontinuation of double antiplatelet therapy is the main risk factor for stent thrombosis, with a thrombosis-related mortality that can reach 45%[118]. Other risk factors for thrombosis of the drug-eluting Stents (DES) are advanced age, stent placement because of acute coronary syndrome (ACS), diabetes mellitus, reduced left ventricular ejection fraction, chronic renal failure, and angiographic characteristics (ostial lesions, long stents, bifurcations, and small vessels)[119]. Patients who undergo angioplasty with placement of stent must take ASA indefinitely, and thienopyridines should be used for a minimum of 1 month for conventional stents and 12 months for DES[120]. In approximately 30%–40% of patients in whom double antiplatelet therapy was prematurely discontinued, the reason for the discontinuation was surgical intervention[121].

The performance of noncardiac operations less than 2 weeks after angioplasty with conventional stent placement is associated with prohibitive rates of perioperative complications (AMI or hemorrhagic complications)[122]. Nuttall et al.[123] retrospectively evaluated 899 patients who underwent noncardiac surgery up to 1 year after angioplasty with conventional stent placement. Forty-seven patients (5.2%) exhibited a cardiovascular event (death, AMI, and need for revascularization). The rate of cardiovascular events was 10.5% when the surgery was performed less than 30 days after angioplasty, 3.8% between 31 and 90 days, and 2.8% after 91 days. Therefore, the risk for cardiovascular complications significantly decreased with every 30 days that passed between the angioplasty and the surgery ($p = 0.003$)[123]. In contrast, a study using the same design that evaluated 520 patients who underwent angioplasty with DES placement showed that the rate of cardiovascular events was constant during the first year after the angioplasty. A decrease in the rate of cardiovascular events was observed only after the first year after angioplasty with DES [124]. Therefore, elective noncardiac surgery should be postponed for at least 1 month after angioplasty with conventional Stent placement and 1 year after angioplasty with DES [78,121].

Eisenberg et al.[125] conducted retrospective analysis of 161 cases of DES thrombosis to determine the average time between the discontinuation of double antiplatelet therapy and thrombosis. The average time for the occurrence of stent thrombosis was 7 days after the simultaneous or sequential discontinuation of ASA and clopidogrel, whereas it was 122 days for patients who discontinued only clopidogrel therapy and continued taking ASA. Moreover, among the 94 patients who continued ASA therapy and discontinued clopidogrel therapy, Stent thrombosis occurred within the first 10 days only in six cases[125]. Therefore, in patients with an indication for the discontinuation of clopidogrel before a surgical procedure, this drug should be reintroduced as quickly as possible, preferably before 10 days after its discontinuation, to avoid stent thrombosis[78] (Table 18).

9.4.4. Glycoprotein (GP) IIb/IIIa inhibitors

A preliminary study evaluated the efficacy and safety of tirofiban as a bridging therapy in the perioperative period in patients with DES who underwent surgery within 1 year and thus required discontinuation of clopidogrel. The study included 30 patients who required emergency surgery with DES placement less than 6 months or less than 1 year prior

Table 17 – Recommendations for the use of thienopyridines in the preoperative period of noncardiac surgery

Class of recommendation	Recommendations	Level of evidence	References
I	Patients using clopidogrel/ticlopidine as primary prevention should discontinue these drugs 5 days before surgery	C	112
	In patients using clopidogrel/ticlopidine alone for secondary prevention, consider the risk of bleeding. When risk for bleeding is moderate or high, thienopyridine should be discontinued 5 days before the procedure	C	115
IIa	In secondary prevention, when risk for bleeding is low, the antiplatelet agent should be maintained in the perioperative period	C	115

Table 18 – Recommendations for the use of thienopyridines in the preoperative period of noncardiac surgery with recent coronary stent placement

Class of recommendation	Recommendations	Level of evidence	References
I	Maintain the use of ASA in the entire perioperative period*, discontinue thienopyridine 5 days before the surgery, and reintroduce it as soon as possible, preferably before the patient completes 10 days of discontinuation	C	78
IIa	Maintain double antiplatelet therapy in procedures with low risk for bleeding	C	78

**Except in neurosurgery and prostate transurethral resection.*

to the surgery but who had risk factors for stent thrombosis. Clopidogrel was discontinued 5 days before the procedure and tirofiban was started 4 days before the surgery. The infusion of tirofiban was stopped 4 h before the procedure (8 h if CrCl was less than 30 ml/min), restarted 3 h after the procedure, and discontinued 4 h after the administration of a dose of clopidogrel. Clopidogrel was restarted using a loading dose of 300 mg right after the patient was allowed oral ingestion. There were no cardiovascular events during hospitalization. One patient exhibited major bleeding (proctorrhagia on the 7th postoperative day) and required transfusion; this symptom was reversed after colonoscopic clipping. Two patients exhibited minor bleeding and required transfusion[126]. This was a pilot study that included few patients and no ischemic events, which does not allow recommending bridging therapy with tirofiban as a routine procedure; however, it can be used in patients at a very high risk of stent thrombosis.

It should be stressed that the use of UH or LMWH as bridging therapy for preventing stent thrombosis is not indicated because these agents not only protect against stent thrombosis but also yield a rebound prothrombotic effect after their discontinuation.

Abciximab is a universal platelet inhibitor with an action that lasts for 7 days; therefore, there is no indication for its use in the perioperative period in noncardiac surgeries, given its high risk of hemorrhage[118] (Table 19).

9.4.5. Cilostazol

Cilostazol has a half-life of approximately 10 h. In general, its administration is discontinued because of a high level of occurrence of side effects, such as headache and gastrointestinal disturbances. In addition, it is contraindicated in patients with heart failure because of its potential to induce ventricular arrhythmias[127].

No studies have evaluated the benefits or potential damaging effects of the use of cilostazol in the perioperative period of noncardiac surgeries. Based on the potential increase in bleeding and absence of evidence that corroborate the benefits of its continuation in this context, it is recommended that cilostazol be discontinued on the day before the planned noncardiac surgery (Table 20).

9.4.6. Dipyridamole

Similar to cilostazol, dipyridamole has a half-life of approximately 10 h. Although it exerts reversible effects on platelet function, dipyridamole is associated with an increase in the risk of bleeding, particularly when co-administered with ASA[128–130].

A study analyzed the rate of postoperative cerebral embolism detected by transcranian Doppler in 120 patients who underwent carotid endarterectomy and were on three different antiplatelet regimens, all of which included a combination of ASA and dipyridamole. There was no difference in embolic events between the groups (despite the low number of patients analyzed); however, a higher rate of bleeding than that usually detected in this type of procedure was observed in all the groups[128–130]. Because of a potential increase in risk for bleeding, it seems prudent to discontinue dipyridamole on the day before noncardiac surgery. Risk–benefit evaluation for the continuation of ASA must be performed at the individual level (Table 21).

9.5. Management of anticoagulants in noncardiac surgeries

9.5.1. Heparin

9.5.1.1. Anticoagulation bridging therapy during the perioperative period

In the absence of randomized studies evaluating the risks and benefits of anticoagulation bridging therapy, the transition regimens of oral anticoagulation during the perioperative period considerably vary among different departments. Therefore, there is no established regimen for the management

Table 19 – Recommendations for the use of glycoprotein IIb/IIIa inhibitors in the preoperative period of noncardiac surgery

Class of recommendation	Indications	Level of evidence	References
IIb	Patients with a drug-eluting stent (DES) for less than 1 year and with risk factors for thrombosis who undergoing emergency surgery with intermediate or high risk for bleeding	C	126
	Patients with a DES for less than 1 year who undergoing emergency surgery with intermediate or high risk for bleeding when it is necessary to simultaneously discontinue ASA and clopidogrel	C	126

Table 20 – Recommendations for the use of cilostazol in the preoperative period of noncardiac surgery

Class of recommendation	Recommendations	Level of evidence	References
I	In patients with peripheral vascular disease who use cilostazol, discontinue use the day before the planned noncardiac surgery	C	128

Table 21 – Recommendations for the use of dipiridamol in the preoperative period of noncardiac surgery

Class of recommendation	Recommendationss	Level of evidence	References
I	In patients who use the combination of dipiridamol and ASA for the secondary prevention of cerebral ischemia, discontinue the use of dipiridamol the day before the planned noncardiac surgery	C	128-130

of anticoagulation during the perioperative period. The main goal of this bridging therapy is the maximal minimization of the risk for arterial thromboembolic events in patients with metallic prosthetic valves and risk for AF and to avoid the recurrence of previous thromboembolic events. Therefore, the indication for the transition from oral anticoagulation to parenteral or subcutaneous anticoagulation is based on two main factors: risk for thromboembolic events after the discontinuation of anticoagulation and risks for bleeding and the proposed surgery[78].

The existing directives recommend the estimation of the risk for thromboembolism and the evaluation of the risk for perioperative bleeding for managing perioperative anticoagulation[78,131]. The appraisal of the risk for perioperative thromboembolic events is mainly based on the three clinical conditions that result in the indication of oral anticoagulation: the presence of a mechanical prosthetic valve, presence of atrial fibrillation (AF), and previous history of ventous thromboembolism (VTE). Both the perioperative guideline of the Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia) and the latest update of the American College of Chest Physicians similarly classify the estimation of the risk of thromboembolic events during the perioperative period (Table 8)[78,131].

In general, in surgical procedures with a low risk for bleeding, it is not necessary to discontinue oral anticoagulation. The procedures can be performed at therapeutic INR[78,131]. In patients classified as being at low risk for thromboembolic events, there is no need to maintain full anticoagulation during the whole perioperative period because of the low incidence of arterial thromboembolic events in this population. The temporary discontinuation of oral anticoagulant therapy and the use of a prophylactic dose of heparin to prevent thromboembolic events during the perioperative period are indicated. In patients who are considered as being at high risk for thromboembolic events who are scheduled to undergo surgical procedures with moderate to high risk of bleeding, oral anticoagulation bridging therapy is recommended in the perioperative period. In patients at moderate risk, the two approaches mentioned above are used and well accepted. Usually, the indication for a transition from oral anticoagulant therapy is decided by medical evaluation.

9.5.1.2. Mechanical prosthetic valve

Patients with a mechanical prosthetic valve are considered as a group at high risk for thromboembolic events because the rate of events reaches approximately 8% in patients without anticoagulation therapy. The discontinuation of oral anticoagulant drugs in the perioperative period can lead to thromboembolic events such as stroke, systemic embolism, and/or prosthesis thrombosis.

There are no randomized clinical studies with adequate methods that have assessed strategies for anticoagulation bridging therapy in patients with a mechanical prosthetic valve. The existing studies that have evaluated perioperative anticoagulation in patients with mechanical prostheses are scarce and limited. The first studies comprised retrospective series and a single prospective study with a small number of patients who discontinued perioperative anticoagulation or were on unfractionated heparin (UH)[132-134]. Thus, perioperative anticoagulation was interrupted (patients with a mechanical prosthetic valve in the aortic position) or performed using UH (patients with a mechanical prosthetic valve in the mitral position). The results of these studies were very limited because there was no established system for anticoagulation management and the follow-up results were not adequately recorded[132-134].

In the absence of scientific evidence regarding the best strategy for perioperative anticoagulation management in patients with indication for bridging therapy, the adopted standard was patient hospitalization and transition to UH in the perioperative period. This choice of anticoagulation approach was confirmed by a Canadian study that assessed the preference for this type of heparin as anticoagulation bridging therapy in patients with a mechanical prosthetic valve, wherein the physicians preferred to use UH for its safety and effectiveness[135].

In recent years, this practice has been replaced by the use of low-molecular weight heparin (LMWH) because this form of treatment can be administered out of the hospital. Few studies have assessed the use of LMWH as perioperative anticoagulation bridging therapy in patients with a mechanical prosthetic valve. A review study by Spyropoulos et al.[136] included five studies assessing the efficacy and safety of changing anticoagulation therapy to LMWH in 749 patients with a mechanical prosthetic valve. The rate of cardioembolic complications was 0.4% and the bleeding rate was 2.8%, which showed that it was safe to use LMWH in patients with a mechanical prosthetic valve [136].

In patients for whom maintenance of perioperative anticoagulation is indicated, oral anticoagulation therapy with warfarin is usually discontinued 5 days before the surgical procedure and short-term heparin bridging therapy is initiated. This transition can be performed both with intravenous UH and with subcutaneous LMWH, at the therapeutic dose, and the last doses of heparin before the surgery should be in accordance with the half-life of the drug used. The use of UH as an oral anticoagulation bridging requires the patient to be hospitalized before the surgical procedure. In addition, the use of intravenous heparin requires monitoring of aPTT to adjust the therapeutic dose (with target aPTT between 1.5 and 2.5).

Its use is usually reserved for patients for whom the use of LMWH is contraindicated, such as patients with severe renal failure or those undergoing dialysis. Anticoagulation transition to LMWH appears to be a good alternative because it can be administered out of the hospital and there is no need to perform laboratory monitoring of the therapeutic level. However, its use should be avoided in some situations, particularly in patients with renal failure (CrCl < 30 ml/min).

There are no randomized studies in the literature comparing different perioperative anticoagulation management strategies and analyzing the best procedure for anticoagulation transition. Most existing studies are prospective and retrospective observational studies that evaluated different forms of anticoagulation transition.

The aim of the REGIME study was to assess perioperative anticoagulation management using two forms of heparin. This was a multicenter, prospective, and observational study involving 14 American and Canadian centers where information on perioperative anticoagulation was collected. The physician in-charge was responsible for deciding what type of bridging therapy would be used for the transition. The 901 patients were divided into two groups: one group received UH as an anticoagulation bridging (180 patients) and another group received LMWH administered twice daily (721 patients). The percentage of patients who received the dose of postoperative heparin was similar in both the groups (91.1% UH × 92.6% LMWH, $p = 0.49$). The rate of thromboembolic events was low in both the groups (2.4% in the UH group × 0.9% in the LMWH group). There was no statistically significant difference in the rate of major bleeding between the two groups (5.5% UH × 3.3% LMWH, $p = 0.25$). The group of patients who received anticoagulation bridging therapy with LMWH underwent more procedures as outpatients or was hospitalized for less than 24 h (63.6% × 6.1%, $p < 0.001$). Among the patients hospitalized for surgeries, the LMWH group was also hospitalized for a shorter time than the UH group (4.6 × 10.3 days, $p < 0.001$). Although this was the first study to compare anticoagulation transition therapies, it presented important limitations such as not being randomized and not having a control group. The results revealed that the two strategies were as effective and safe as the oral anticoagulation bridging therapy; however, LMWH had the advantage of being administered outside the hospital[137].

With the aim of assessing the efficacy and safety of LMWH as anticoagulation bridging therapy, Douketis et al.[138] conducted a study involving 650 patients with a mechanical prosthetic valve, AF, and history of stroke. Warfarin was discontinued 5 days before the surgical procedure, and the patients received anticoagulation transition therapy with dalteparin 100 IU/kg twice daily, which was started on average 3 days before the surgery. The last dose of preoperative dalteparin was administered at least 12 h before the surgery to avoid bleeding. In patients subjected to procedures classified as having high risk for bleeding, the postoperative dalteparin dose was not administered. The main outcomes analyzed were thromboembolism, major bleeding, and mortality. Oral anticoagulation was restarted the day after the surgery. In a mean follow-up period of 13.8 days, there was a low incidence of thromboembolic events (0.4%) and bleeding (0.7% and 1.8%) in this group[138].

Another multicenter prospective cohort study published in the same year also aimed to assess the safety and efficacy of bridging therapy with LMWH. The study included patients at high risk for arterial thromboembolism (patients with a mechanical prosthetic valve and AF). The study included 224 patients, 112 of which had a mechanical prosthetic valve and 112 had AF. The oral anticoagulant drug was discontinued 5 days before the surgery, and anticoagulation therapy transition was performed with LMWH, which was started 3 days before the surgery and was maintained for 4 days postoperatively. The preoperative dose of dalteparin administered was 200 IU/kg daily. On the day before the surgery, the patients received a dose of 100 IU/kg. In the postoperative period, warfarin was restarted on the first day after the surgery together with a dose of 200 IU/kg of dalteparin; patients at high risk for bleeding were administered a fixed dose of 5000 IU. The rate of thromboembolic events was 3.6% and that of bleeding was 6.7%. The authors concluded that the transition to LMWH was possible but that randomized and controlled studies were required to better define the strategy[139].

Further assessing the use of LMWH as anticoagulation bridging therapy, the PROSPECT study aimed to evaluate the safety of oral anticoagulation transition with a dose of 1.5 mg/kg of enoxaparin administered daily at home. This was a multicenter prospective cohort study with 260 patients with AF or VTE, and the primary outcome of the study was bleeding incidence. The rate of major bleeding observed in the study was 3.5%; however, analysis of bleeding risk according to the type of surgical procedure revealed that the bleeding rate was higher in the group of patients subjected to major surgeries (orthopedic, cardiovascular, and general surgeries) than in the group of patients subjected to minor procedures (20% vs. 0.7%)[140].

In 2009, a prospective cohort study analyzed patients who were on chronic oral anticoagulation therapy and were subjected to different regimens of anticoagulation bridging therapy in surgical procedures. Warfarin was discontinued 5 days before the surgery and LMWH was initiated (nadroparin or enoxaparin) 4 days before the surgery. The last dose of LMWH was administered at least 12 h before the surgery. Two strategies were adopted for anticoagulation therapy transition. The patients classified as being at high risk for thromboembolic events received bridging therapy with a full dose of LMWH twice daily. All the remaining patients classified as being at moderate or low risk received only a prophylactic dose of LMWH once daily. Of the 1,262 patients included in the study, 23.4% were considered as being at high risk for thromboembolic events and received transition therapy with a full dose of heparin, whereas 76.6% of patients received only a prophylactic dose of heparin. In terms of efficacy, only five cases of thromboembolic events occurred in the high-risk group, with an incidence of 0.4% (95% CI 0.1–0.9). The incidence of major bleeding, in this study was 1.2%, and it was higher in the high-risk group than in the

moderate/low risk group (2.7% vs. 0.7%, $p = 0.011$). The rate of minor bleeding was 4.2% and more significant in the group of patients who received transition therapy with full dose heparin[141].

A pharmacoeconomics study that compared the cost of both regimens of perioperative anticoagulation transition therapy revealed that the use of LMWH was the best choice because its cost was lower than that of intravenous heparin, given the possibility of administering the drug outside the hospital, with a reduction in hospitalization costs[77].

In conclusion, the studies showed a preference for anticoagulation bridging therapy with LMWH because of its ease of administration, without the need for patient hospitalization and therefore lower cost. On the other hand, when the use of LMWH is contraindicated, UH remains the indicated therapy.

9.5.1.3. Timing of heparin discontinuation before surgery

There are no studies assessing the heparin discontinuation time in the preoperative period. The indication is mainly based on the half-life of heparin. Because of its short half-life, with elimination between 30 and 120 min, it is safe to discontinue UH between 4 and 6 h before the surgery[131].

With regard to LMWH, observational clinical studies revealed that discontinuation of LMWH 12 h before the surgery did not increase bleeding during surgery. However, studies that assessed the substitute outcomes such as anti-Xa level dosage revealed that > 90% of patients who received the last dose of heparin 12 h before the surgery still exhibited the anticoagulating effect and > 34% of patients maintained a therapeutic level of anticoagulation. These findings are the basis for the current indication for LMWH to be discontinued at least 24 h before the surgery[131].

For restarting LMWH in the postoperative period, the effectiveness of hemostasis and risk for bleeding should be taken into account. In surgeries with high risk for bleeding, the reintroduction of LMWH should be performed at least 24 h after the end of the surgery, ideally 48–72 h. In procedures with low or moderate risk for bleeding, reintroduction can be performed within 24 h after the surgery[131] (Table 22).

9.5.2. Warfarin

The use of anticoagulant agents in the perioperative period depends on the patient's risk for developing thromboembolic events when the agent is discontinued and on the bleeding risk if anticoagulation therapy is not interrupted. Discontinuation of the anticoagulant drug increases the risk for embolic phenomena, such as stroke and mechanical prosthesis thrombosis, and this risk varies according to the presence of other comorbidities and risk factors[77,78,81,142]. These events can lead to devastating clinical consequences: stroke leads to significant incapacity or death in 70% of patients; mechanical prosthesis thrombosis is fatal in 15% of patients[77].

Similar to cardiac surgery, according to risks for embolic events in the perioperative period and comorbidities, risk should be stratified into high, moderate, and low risk, according to the recommendations of the Brazilian Society of Cardiology in the II Perioperative Guideline (Table 8)[78].

Table 22 – Recommendations for the use of heparin in the preoperative period of noncardiac surgery

Class of recommendation	Recommendations	Level of evidence	References
I	Unfractionated heparin and LMWH are effective and safe strategies for the prevention of VTE in the perioperative period of noncardiac surgery	A	78,131
	The use of unfractionated heparin for the prevention of VTE in the perioperative period should be started 2 h before the surgery and maintained in the postoperative period every 8 h or every 12 h, in the case of effective hemostasis	A	78,131
	Extended prevention using LMWH (4 weeks) should be started in patients at high risk for VTE, particularly those subjected to hip surgery	A	78,131,135
	In patients with indication for prevention of VTE, unfractionated heparin should be administered for a period of 5–7 days in general surgery and between 7 and 10 days in orthopedic surgery	C	78,131,135
	In patients receiving bridging therapy with a therapeutic dose of unfractionated heparin, it is recommended to discontinue this treatment 4–6 h before the procedure	C	78,131,135
	In patients with indication for the prevention of VTE, LMWH should be administered for a period of 7–10 days	C	78,131
IIa	The prevention of VTE with LMWH in the perioperative period can be started 12 h both before and after the procedure, with similar efficacy	C	78,131
	In patients receiving bridging with a therapeutic dose of LMWH, it is recommended to administer the last dose 24 h before the procedure	C	78,131,136
	In patients who receive bridging with a therapeutic dose of LMWH and undergoing interventions with high risk for bleeding, it is recommended to reintroduce LMWH 48–72 h after the intervention	C	78,131,136
IIb	The prevention of arterial or venous thromboembolic phenomena with LMWH in the perioperative period can be started in the postoperative period, between 4–6 h after the end of the surgery, in cases in which hemostasis is effective and risk for bleeding is low	C	78,131

LMWH: low-molecular-weight heparin; VTE: venous thromboembolism.

The recommendations for discontinuation of warfarin in the perioperative period are shown in the tables below. In the case of surgery with reintroduction of the drug, urgency/emergency, or need for rapid reversal of the effect of warfarin, the recommendations mentioned for cardiac surgery should be followed (Table 23).

9.5.2.1. Procedures with low risk of bleeding

The following procedures are considered as exhibiting low risk for bleeding: cataract surgery, minor dermatological procedures, and dental procedures (e.g., hygiene, simple extraction, restoration, endodontic, and prosthetic procedures). In these cases, the recommendations in Table 24 should be followed.

9.5.3. Fondaparinux

There are two double-blind randomized studies that assessed the efficacy of fondaparinux as preventive therapy in the perioperative period of general surgery. In the first study, fondaparinux was compared with dalteparin in patients at high risk for VTE undergoing abdominal surgery. In total, 2,927 randomized patients were selected from 131 centers in 22 countries. Fondaparinux was administered 6 h after the end of the surgery. The first dose of dalteparin (2,500 IU) was administered 2 h before the surgery and the second dose was administered 12 h after the end of the surgery. On subsequent days, the administered dose of dalteparin was 5,000 IU per day. The primary outcome of efficacy was the occurrence of VTE (symptomatic or symptomatic). The safety outcome adopted in the study was major bleeding. The rate of VTE was 4.6% in the fondaparinux group and 6.1% in the dalteparin group, with a 24.6% reduction in relative risk (95% CI 9.0–47.9); however, the difference was not statistically significant ($p = 0.14$). There was no statistically significant difference in bleeding between the two groups (3.4% in the fondaparinux group vs. 2.4% in the dalteparin group, $p = 0.12$). The results revealed that fondaparinux was not superior to dalteparin as prevention therapy in general surgery; however, analysis of noninferiority revealed that it was at least as effective as LMWH[143].

In another double-blind, randomized, and placebo-controlled study on intra-abdominal general surgery, patients were randomly assigned to receive prevention therapy with fondaparinux at a dose of 2.5 mg started between 6 and 8 h postoperatively in combination with intermittent pneumatic compression or intermittent pneumatic compression alone. The primary outcome was the occurrence of venous

Table 23 – Recommendations for the use of warfarin in the preoperative period of noncardiac surgery

Class of recommendation	Recommendations	Level of evidence	References
I	To perform colonoscopy in which the biopsy of large-sized polyp (>1.2 cm in length) may be required, warfarin should be discontinued 5 days before the intervention	C	77,78,131
	Patients with PTE in the last 3 months, high-risk AF (previous stroke/TIA or multiple risk factors), and a mechanical prosthetic valve in the mitral position should receive bridging therapy with heparin	C	77,78,131
	In the postoperative period of procedures with high hemorrhagic risk, bridging therapy with heparin and reintroduction of warfarin should not be started before 48 h	C	77,78,131
IIa	In patients with low-risk AF (without stroke/TIA), warfarin can be discontinued without the need for bridging therapy with heparin	C	77,78,131
	In the postoperative period of noncardiac surgery in which there was adequate hemostasis, it is recommended to restart the treatment with warfarin between 12 and 24 h after the surgery	C	77,78,131
	In patients with a mechanical prosthetic valve, AF, or DVT associated with high risk for thromboembolism, bridging therapy with heparin is required	C	77,78,131
	In patients with a mechanical prosthetic valve, AF, or DVT associated with low risk for thromboembolism, bridging therapy with heparin is not necessary	C	77,78,131
	In patients with a mechanical prosthetic valve, AF, or DVT associated with moderate risk for thromboembolism, the decision of heparin bridging therapy will depend on the case and the associated risk factors.	C	77,78,131

AF: atrial fibrillation; PTE: pulmonary thromboembolism; TIA: transient ischemic attack; DVT: deep vein thrombosis.

Table 24 – Recommendations for the use of warfarin in the preoperative period of noncardiac surgery with low bleeding risk

Class of recommendation	Recommendations	Level of evidence	References
I	For some invasive procedures such as intra-articular injections, cataract, endoscopic procedures (including mucosal biopsy in individuals at low risk for bleeding and at high risk for thrombosis), it is not necessary to discontinue warfarin or perform bridging procedures. However, this recommendation is only valid for individuals with INR in the therapeutic range (between 2 and 3)	B	77,78,131

INR, international normalization ratio

thromboembolic events at the 10th day after the surgery. In total, 1,309 patients were selected from 50 centers. The group of patients that received fondaparinux exhibited a lower rate of VTE (1.7% vs. 5.3%, RR 69.8%, 95% CI 27.9–87.3, $p = 0.004$). Moreover, fondaparinux reduced the rate of proximal PVT by 86.2% ($p = 0.037$); however, there was no difference in the rate of symptomatic VTE or mortality between the two groups. Major bleeding was 1.6% in the fondaparinux group and 0.2% in the control group ($p = 0.006$). Among the cases of bleeding, there was no fatal bleeding or critical organ. Most bleeding resulted from surgical wounds[144].

These studies revealed that fondaparinux is effective in perioperative thromboprophylaxis, both in general and orthopedic surgeries. However, its use is associated with higher risk for bleeding.

In previous meta-analyses, thromboprophylaxis with UH was shown to be effective in the reduction of mortality[145], whereas the use of LMWH did not produce the same results[146]. For analyzing the effect of fondaparinux on mortality in studies on VTE prevention, the following meta-analysis was performed. Eight randomized, double-blind, phase III studies were included, with a total of 13,085 patients. The studies focused on the prevention of TEV using fondaparinux at a dose of 2.5 mg daily compared with that using LMWH (in five studies) or a placebo (in three studies). The main objective of the study was to analyze the effect of fondaparinux on mortality at 30 days; day 1 was the day of randomization. Of the eight studies included in meta-analysis, seven were performed in a perioperative context (abdominal or orthopedic surgeries), with a total of 12,236 patients, and one was performed with medical patients. The first dose of fondaparinux in the surgical studies was administered 6 ± 2 h after the surgery and the second dose was administered at least 12 h after the first dose and 24 h before the end of the surgery. The results of meta-analysis revealed a 21% reduction in the risk for mortality in the group that received fondaparinux in comparison with the control group; however, the reduction was not statistically significant (1.6% vs. 2.1%, RR 0.79, 95% CI 0.6–1.01, $p = 0.058$). This result was consistent both when fondaparinux was compared with LMWH (fondaparinux 1.5% × LMWH 1.9%, OR 0.78, 95% CI 0.58–1.06, $p = 0.11$) and with a placebo (2.0% vs. 2.6%, RR 0.77, 95% CI 0.46–1.26, $p = 0.3$). Thus, in the analyzed studies, fondaparinux did not have an effect on perioperative mortality[147].

Based on the previous meta-analysis, the authors analyzed of the association between the occurrence of bleeding and mortality at 30 days and identified the risk factors associated with the risk for bleeding. The risk factors identified as predictors of higher risk for bleeding were age, male gender, low weight, low CrCl, hip surgery or any type of surgery, absence of history of VTE, and treatment with fondaparinux. The mortality rate in the group with some type of bleeding was almost sevenfold higher than that in the group without bleeding (RR 6.83, 95% CI 4.57–10.22, $p < 0.001$), regardless of the prevention therapy administered. This was the first study to establish a relationship between bleeding and increased mortality in studies on the prevention of VTE[148].

The results of these studies showed that fondaparinux is effective as a thromboprophylactic strategy in the perioperative period in noncardiac surgery. In these studies, fondaparinux was as effective as or more effective than LMWH. However, the use of fondaparinux is associated with a higher rate of nonfatal bleeding and therefore with the need for more blood transfusions in the perioperative period.

No studies have assessed the use of fondaparinux as anticoagulation bridging therapy, probably because of its long half-life and risk for perioperative bleeding (Table 25).

9.5.4. Dabigatran

In patients with normal renal function, dabigatran can be discontinued 48 h before to ensure adequate hemostasis. In procedures with low risk for bleeding, dabigatran can be discontinued 24 h before the surgery. These procedures include catheterism, ablation, endoscopy, colonoscopy without polyp removal, simple laparoscopy, and small orthopedic surgical procedures[100]. In major elective surgical procedures in patients with normal renal function, it is recommended to discontinue the agent for 1–2 days[100]. In patients with compromised renal function, the discontinuation period should be longer[101].

In patients with moderate renal impairment, patients aged > 75 years, and those receiving amiodarone, it is recommended to reduce the standard dose to 150 mg/day (initial dose of 75 mg, followed by a standard dose of 150 mg, once daily)[78].

Precaution should be taken when the treatment is temporarily discontinued owing to interventions, and coagulation monitoring should be ensured. This should be taken into account in any procedure. A coagulation test can help determine whether hemostasis is still altered.

In the case of an acute intervention, dabigatran should be temporarily discontinued and the surgery should be postponed until at least 12 h after the last dose[100]. If it is not

Table 25 – Recommendations for the use of fondaparinux in the preoperative period of noncardiac surgery

Class of recommendation	Recommendations	Level of evidence	References
I	Prevention with fondaparinux may be initiated in the preoperative period, ideally 6–9 h before the end of the surgical procedure	A	143,144,147,148
IIa	Fondaparinux can be used for VTE prevention in situations in which the use of heparin is contraindicated, despite the higher risk for bleeding.	C	143,144,147,148

VTE: venous thromboembolism.

possible to postpone the surgery, risks for hemorrhage should be weighed against the urgency of the surgery[100].

Reintroduction of medication exclusively depends on risks for postoperative bleeding[100]. In the case of abdominal urological surgery with incomplete hemostasis, the agent should only be reintroduced when there are no signs of active bleeding. In the case of small procedures with good hemostasis, the agent can be started between 4 and 6 h after the procedure and the use of a half dose (75 mg), followed by maintenance of the usual dose, is suggested[100] (Table 26).

9.5.5. Rivaroxaban

Discontinuation of the agent should follow the same recommendations indicated for dabigatran. However, the adequate discontinuation time is shown in Table 27.

In emergency situations where reversal of the anticoagulation effect of rivaroxaban is required, 4-factor prothrombin complex concentrates can be used at a dose of 50 UI/kg[100]. Other products such as plasma and cryoprecipitates do not reverse the anticoagulating effect of this agent[100].

With regard to reintroduction of the agent in the postoperative period, a strategy similar to that used for dabigatran can be used for rivaroxaban. The drug should be started at a dose of 10 mg (first dose), and following this, the usual dose should be maintained[100].

9.5.6. Apixaban

Apixaban is one of the newest oral anticoagulant agents, and it has been shown to be effective and safe in the treatment of thromboembolism[149]. After an extensive literature review, most questions regarding the perioperative period could not be answered according to the class of recommendation and level of evidence because this agent has not yet been tested in clinical trials.

Table 26 – Recommendations for the use of dabigatran in the preoperative period of noncardiac surgery

Class of recommendation	Recommendations	Level of evidence	References
I	Patients with chronic use of dabigatran should discontinue the medication 24 h before the surgery. In case of moderate renal impairment (creatinine clearance < 50 ml/min) or surgery with high risk for bleeding, such as neurosurgery, dabigatran should be discontinued at least 48 h before the surgery	C	78,100,101
	In case of local anesthesia with an epidural catheter, wait at least 2 h after removing the catheter to administer the first prophylactic dose of dabigatran	C	78,100,101
IIb	Reintroduction of full anticoagulation with dabigatran should occur at least 24 h after the end of the surgery, once hemostasis is adequate	C	78,100,101

Table 27 – Recommendations for the use of rivaroxaban in the preoperative period of noncardiac surgery

Class of recommendation	Recommendations	Level of evidence	References
I	Patients with chronic use of rivaroxaban should discontinue the medication at least 24 h before the surgery	C	78,100
	In case of local anesthesia with an epidural catheter, wait at least 6 h after removing the catheter to administer the next prophylactic dose of rivaroxaban. In cases in which the epidural catheter is postoperatively maintained for analgesia, the removal should occur 18 h after the last dose	C	78,100
IIb	Reintroduction of full anticoagulation with rivaroxaban should occur at least 24 h after the end of the surgery, once hemostasis is adequate	C	78,100

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10. Specificities of antiplatelet and anticoagulant agents

10.1. Introduction

In recent years, advances have been made with regard to the treatment of heart diseases, particularly acute coronary syndromes (ACS,) and more recently, in the prevention of thromboembolic phenomena in atrial fibrillation (AF). Recent studies and new evidence have shown that cardiologists are increasingly familiarized with the new drugs.

The introduction of new antiplatelet and anticoagulant drugs makes it appropriate to study all the specificities of these agents and to review and update the older agents that are still in use in our daily practice.

In this chapter, we aim to review the mechanism of action, pharmacokinetics, therapeutic indications, precautions, contraindications, drug interactions, bleeding risk, and particularities of special groups to allow the reader to use these drugs with maximum efficacy and safety.

10.2. Specificities of antiplatelet agents

Table 1 – Specificities of aspirin (acetyl salicylic acid, ASA)

	Aspirin
Mechanisms of action	• Irreversible acetylation of the cyclooxygenase activity of prostaglandin H synthase-1 and prostaglandin H synthase-2, with more selectivity for prostaglandin H synthase -1
Pharmacokinetics	• Proximal upper gastrointestinal absorption (stomach and duodenum) • Plasma peak concentration at 15–20 min • Half-life of 20 min • Platelet inhibition at 40–60 min, persisting for 7 ± 2 days • Enteric presentations: absorption peak at 60 min; platelet inhibition at 90 min
Indications	• Ischemic stroke prevention and treatment, ACS, peripheral arterial disease, and sudden death prevention
Contraindications	• Active peptic ulcers • Hemorrhagic diatheses • Hypersensitivity to acetyl salicylic acid and others salicylates • History of asthma induced by salicylates and salicylate-like products • Use of high methotrexate dose • Last trimester of pregnancy
Precautions	• Previous gasatrointestinal ulcers
Drug and food interactions	• Increased effects of coumarins, digoxin, heparin, sulfonylureas, methotrexate, barbiturics, lithium, NSAID (ibuprofen and naproxen may revert Cox-1 inhibition), trimethoprim/sulfamethoxazole, triiodothyronine, and valproic acid • Reduced effects of diuretics, aldosterone, loop diuretics, probenecid, sulfinpyrazone, and uremia reducers • Alcohol enhances the effects of aspirin.
Adverse reactions	• Hemorrhagic manifestations • Gastrointestinal toxicity: nausea, vomiting, surfeit, epigastric pain, gastric ulcer • Hypersensitivity: respiratory disease worsened by ASA (dyspnea, bronchospasm), urticaria and angioedema, anaphylactic and anaphylaxis reactions
Platelet function tests	• No evidence for routine use
Hemorrhagic risk stratification	• Bleeding risk is dose-dependent (threefold higher with peptic ulcer history and twofold higher in men). • Use bleeding risk scores (example, CRUSADE)
Presence of thrombocytopenia	• Assess ischemia/ hemorrhage risk individually.
Influence of age, weight, and renal and liver functions	• Use carefully in children and patients with liver disease. • Dose adjustment for weight or renal function is not required.
Resistance	• Multifactorial etiology • Two- to fourfold higher risk of infarction, stroke, or death • There is no evidence supporting aspirin dose increase or replacement for other antiplatelet drug based on platelet function tests because of its multifactorial etiology.
Use of stomach protector	• Only in patients with known peptic ulcer • Recommended during double antiplatelet therapy
Desensitization	• Consider hypersensitivity manifestations with respiratory and cutaneous symptoms and secondary prevention of coronary events (indication for stent implant or recurrent cardiac events with simple antiplatelet therapy). • Apply desensitization protocol according to the indication of the allergy specialist.
Prevention of DVT in plane travels	• There is no consistent indication. See section 6, "Use of antiplatelet and anticoagulant agents in valve disease."

Table 2 – Specificities of clopidogrel

	Clopidogrel
Mechanisms of action	• Irreversible inhibition of the P2Y12 receptor
Pharmacokinetics	• Liver metabolism • Half-life of 8 h • A daily dose of 50–100 mg has stable platelet inhibition of 50%–60% after 4–7 days. • A loading dose of 300 mg has a more rapid action than a dose of 75 mg. • A loading dose of 600 mg has a total antiplatelet effect in 2–4 h. • Platelet function normalizes after 7–10 days of discontinuation.
Indications	• Prevention and treatment of ACS and ischemic stroke • Symptomatic peripheral arterial disease
Contraindications	• Hypersensitivity • Active pathological bleeding
Precautions	• Age > 75 years • Trauma or recent surgery • Recent pathological bleeding • Concomitant use of antiplatelet or anticoagulant agents • Cross hypersensitivity reaction with other thienopyridines may occur • Reported cases of TTP
Drug and food interactions	• Antiplatelet effect reduction with concomitant use of proton pump inhibitors (particularly with omeprazol)
Adverse reactions	• Hemorrhagic manifestations • Thrombocytopenia • TTP (usually in the first 15 days of use): rare • Neutropenia • Skin rash
Platelet function tests	• No evidence for its routine use • May be considered in patients who are already on clopidogrel and develop ACS or patients who will undergo very-high-risk intracoronary stent implant (late coronary patency or left coronary trunk), with dose increase to 150 mg/day if platelet aggregation inhibition is < 50%.
Hemorrhagic risk stratification	• Assess risk for ischemia/hemorrhage if there is a history of stroke/TIA, age > 65 years, weight < 60 kg, trauma, recent surgery or pathologic bleeding, active peptic ulcer, severe liver disease, and concomitant use of anticoagulants or NSAID. • Use bleeding risk scores (example, CRUSADE)
Presence of thrombocytopenia	• Assess the risk for ischemia/ hemorrhage individually.
Influence of age, weight, and renal and liver functions	• Use carefully in patients aged > 75 years, weighing < 60 kg, and having liver disease. • Dose adjustment is not necessary.
Resistance	• Multifactorial etiology (differences in pharmacokinetics, drug interactions, and receptor binding)
Use of stomach protector	• Only in patients with known peptic ulcer (avoid omeprazol)
Prevention of DVT in flights	• No indication

TTP: thrombotic thrombocytopenic purpura; ACS: acute coronary syndrome; NSAID: nonsteroid anti-inflammatory drug; DVT: deep venous thrombosis.

Table 3 – Specificities of ticlopidine

	Ticlopidine
Mechanisms of action	• Irreversible inhibition of the P2Y12 receptor
Pharmacokinetics	• Up to 90% of oral bioavailability • Peak plasma concentration at 1–3 h • Half-life of 24–36 h after a single dose and of 96 h after 14 days of use
Indications	• Ischemic stroke, TIA • ACS • Peripheral arterial disease • Hypersensitivity or adverse reactions with the use of clopidogrel
Contraindications	• Hypersensitivity • Active bleeding • Severe liver impairment • Neutropenia • Thrombocytopenia • Previous TTP or aplastic anemia

Continuation		
Precautions	•	Blood count every 2 weeks in the first 4 months • Discontinue use if neutrophils < 1,200/mm^3 or platelets < 80,000/mm^3. • Possible cross reaction with clopidogrel and prasugrel
Drug and food interactions	•	Avoid the use of NSAID (bleeding risk) • Reduction in teophylline clearance • 15% reduction in digoxin serum level • Increase in phenytoin serum level
Adverse reactions	•	Hypercholesterolemia • Neutropenia, thrombocytopenia • Aplastic bone marrow • TTP • Gastrointestinal toxicity: nausea, vomiting, surfeit, epigastric pain
Platelet function tests	•	No evidence for its routine use
Hemorrhagic risk stratification	•	Assess the risk of ischemia/hemorrhage if there is history of TIA or stroke, age > 75 years, weight < 60 kg, trauma, recent surgery or pathological bleeding, active peptic ulcer, severe liver disease, and concomitant use of anticoagulants or NSAID and if patients have hematological neoplasia • Use bleeding risk scores (example, CRUSADE)
Presence of thrombocytopenia	•	Discontinue if platelets < 80,000/mm^3
Influence of age, weight, and renal and liver functions	•	Restrict use in slight to moderate liver impairment and mild to moderate renal failure
Resistance	•	No description until this moment
Use of stomach protector	•	Only with a known peptic ulcer
Prevention of DVT in flights	•	No indication

AMI: acute myocardial infarction; TIA: transient ischemic attack; TTP: thrombotic thrombocytopenic purpura; ACS: acute coronary syndrome; NSAID: nonsteroid anti-inflammatory drug; DVT: deep venous thrombosis.

Table 4a – Specificities of glycoprotein IIb/IIIa inhibitors: tirofiban

		Tirofiban
Mechanisms of action	•	Low-molecular-weight nonpeptide reversible antagonist of the glycoprotein IIb/IIIa receptor
Pharmacokinetics	•	Intravenous use • Half-life of 1.9–2.2 h • Renal and biliary elimination • Antiplatelet activity > 90% after bolus infusion • Normal platelet function between 4–8 h after the end of infusion
Indications	•	High-risk unstable angina and AMI without ST-segment elevation (patients not previously treated with thienopyridines) • High-risk unstable angina and AMI without ST-segment elevation subjected to percutaneous coronary intervention with high thrombotic load and low risk for bleeding (previously treated with a thienopyridine) • AMI with ST-segment elevation referred for primary angioplasty (selected cases; example, high thrombotic load)
Contraindications	•	Hypersensitivity • Thrombocytopenia with previous exposure to a GP IIb/IIIa inhibitor • Active bleeding • Relevant recent bleeding (up to 30 days) • Hypertension not under control (SAP > 180 mmHg or DAP > 110 mmHg) • History or signs suggestive of aortic dissection • Pericarditis • Ischemic stroke in the last 30 days or history of hemorrhagic stroke • Intracranial pathology (neoplasia, arteriovenous malformation, cerebral aneurysm) • Coagulopathy (INR > 1.3), thrombocytopenia (< 100.0000/mm^3), and platelet function disorder • Trauma or recent surgery (up to 30 days) • Use of thrombolytic drugs in the last 48 h • Severe liver failure
Precautions	•	Administer with care in case of major bleeding in the last year, noncompressible puncture in the last 24 h, cardiogenic shock, thrombocytopenia (< 150,000/mm^3), anemia (Hb < 11 g/dl and Hct < 34%), retinal hemorrhage, and dialyzed patients • Monitor Hb, Hct, and platelets after 6 h of infusion and at least once daily after that
Drug and food interactions	•	Concomitant use with omeprazol and levothyroxine increases the clearance of tirofiban (without known clinical significance) • Increased risk for bleeding when associated with heparin, oral anticoagulants, and thrombolytic drugs

Continuation		
Adverse reactions	•	Hemorrhagic manifestations, edema, pelvic pain, vasovagal reaction, coronary dissection, dizziness, sweating, nausea, headache, fever, and shivers • Thrombocytopenia • Allergic reactions (urticaria, bronchospasm, anaphylaxis)
Platelet function tests	•	Currently not recommended for routine use
Hemorrhagic risk stratification	•	Assess ischemic/ hemorrhagic risk • Not indicated for patients at high risk for bleeding • Use bleeding risk scores (example, CRUSADE)
Presence of thrombocytopenia	•	Contraindicated for patients with a history of thrombocytopenia induced by GP IIb/IIIa inhibitors • Caution regarding patients with platelet count < 150,000/mm^3 • Contraindicated if platelet count < 100,000/mm^3
Influence of age, weight, and renal and liver functions	•	Higher risk for bleeding when ≥65 years • The dose should be correctly adjusted for weight (high doses increase hemorrhagic events) • Elimination decreased by 50% in renal impairment with glomerular filtration < 30 ml/min (adjust dose) • Eliminated during hemodialysis • Plasmatic clearance is not altered in mild and moderate liver impairment
Resistance	•	No reports
Use of stomach protector	•	Indicated for patients with history of gastrointestinal bleeding • Omeprazol increases the clearance of tirofiban (without known clinical significance)
DVT prevention in flights	•	No indication

GP: glycoprotein; AMI: acute myocardial infarction; INR: international normalization ratio; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; NSAID: nonsteroidal anti-inflammatory drug; DVT: deep vein thrombosis.

Table 4b – Specificities of glycoprotein IIb/IIIa inhibitors: abciximab

		Abciximab
Mechanisms of action	•	Fragment of monoclonal antibody that inhibits platelet aggregation by binding to the GP IIb/IIIa receptor
Pharmacokinetics	•	Intravenous use • Inhibits platelet aggregation in more than 80% 10 min after bolus administration • Plasma half-life of 10 min initially and of approximately 20 min subsequently • Platelet function recovered after 48 h • Low levels of GP IIb/IIIa receptor inhibition can be maintained for up to 15 days
Indications	•	High-risk unstable angina and AMI without ST-segment elevation subjected to percutaneous coronary intervention with high thrombotic load and low risk for bleeding (previously treated with a thienopyridine) • Infarction with ST-segment elevation referred for primary angioplasty (selected cases; example, high thrombotic load)
Contraindications	•	High risk for bleeding • Active pathological bleeding • Recent clinically significant gastrointestinal or genitourinary bleeding (6 weeks) • History of stroke (less than 2 years) or stroke with significant residual neurological deficit • Hemorrhagic diathesis • Use of warfarin in the last 7 days or INR > 1.2 • Thrombocytopenia (< 100,000/mm^3) • Recent major surgery or trauma (less than 6 weeks) • Intracranial pathology (neoplasia, arteriovenous malformation, cerebral aneurysm) • Hypertension not under control (SAP > 180 mmHg or DAP > 110 mmHg) • Presumed history or documented history of vasculitis • Hypersensitivity
Precautions	•	Monitor platelet count (before infusion, 2–4 h after bolus, and 24 h after bolus) • Discontinue medication if platelet count < 100,000/mm^3 or drop > 25% of the baseline value • Increased risk for bleeding when combined with oral anticoagulant agents, NSAIDs, and thienopyridines • Adequate adjustment of heparin dose (reduces the risk for bleeding) • Age > 75 years (no evidence of efficacy and safety)
Drug and food interactions	•	Increased risk for bleeding when associated with heparin, oral anticoagulants, and thrombolytic drugs
Adverse reactions	•	Hemorrhagic manifestations • Thrombocytopenia • Hypotension and bradycardia • Nausea, vomiting, and abdominal pain • Lumbar pain, chest pain, and pain in the catheterization puncture site • Peripheral edema • Allergic reactions (rarely anaphylaxis)

Continuation		
Platelet function tests	•	Not recommended for routine use
Hemorrhage risk stratification	•	Assess ischemic/hemorrhagic risk. • Not indicated for patients at high risk for bleeding • Use bleeding risk scores (example, CRUSADE).
Presence of thrombocytopenia	•	Contraindicated when platelet count < 100,000/mm^3
Influence of age, weight, and renal and liver functions	•	No need for dose adjustment in renal failure • No need for adjustment for age until 75 years (no evidence above this age) • Contraindicated in severe liver failure
Resistance	•	No reports
Use of stomach protector	•	Indicated if there is history of gastrointestinal bleeding • No known interaction with this class of drugs
Prevention of DVT in flights	•	No indication

GP: glycoprotein; AMI: acute myocardial infarction; INR: international normalization ratio; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; NSAID: nonsteroidal anti-inflammatory drug; DVT: deep vein thrombosis.

Table 5 – Specificities of prasugrel

		Prasugrel
Mechanisms of action	•	Pro-drug with one metabolism step in the liver; its active metabolite selectively and irreversibly binds to the P2Y12 receptors and inhibits platelet aggregation mediated by ADP
Pharmacokinetics	•	Rapid absorption after ingestion, with metabolism predominantly occurring in the intestine • Plasma peak of the active metabolite after 30 min of ingestion • The active metabolite has a half-life of approximately 7 h • Platelet function returns to normal between 7 and 9 days • Renal elimination of approximately 70%
Indications	•	Acute coronary syndrome (with established coronary anatomy and scheduled percutaneous coronary intervention)
Contraindications	•	History of ischemic stroke or TIA • Hypersensitivity • Active bleeding • Severe liver failure
Precautions	•	Caution with patients at high risk for bleeding: • Elderly (≥ 75 years) • Susceptibility to hemorrhage (recent trauma, recent surgery, recent gastrointestinal hemorrhage, or active peptic ulcer) • Low weight (< 60 kg) • Concomitant use of drugs that increase the hemorrhagic risk (oral anticoagulant drugs, clopidogrel, NSAIDs, and fibrinolytic drugs)
Drug and food interactions	•	Faster action when administered on empty stomach • Diet high in fats or calories, reduces the rate of absorption • Weak CYP2C9 inhibitor; can significantly interact with drugs that are exclusively metabolized via this route (example, cyclophosphamide and efavirenz) • Tablet contains lactose (caution with patients with a history of lactose and/or galactose intolerance; not recommended in severe hereditary conditions)
Adverse reactions	•	Hemorrhagic manifestations • Thrombocytopenia and TTP • Headache • Gastrointestinal disorders (nausea, vomiting, and flatulence) • Autonomic disorders (vertigo, pallor, and sweating)
Platelet function tests	•	Not yet recommended for routine use
Hemorrhage risk stratification	•	Assess ischemic/hemorrhagic risk • Not indicated for patients at high risk for bleeding • Use bleeding risk scores (example, CRUSADE)
Presence of thrombocytopenia	•	Assess ischemic/hemorrhagic risk
Influence of age, weight, and renal and liver functions	•	Patients aged > 75 years are at higher risk for bleeding and do not exhibit a net benefit (ischemic/hemorrhagic) from the use of a dose of 10 mg/day (a dose of 5 mg/day was not tested in large studies). • Patients < 60 kg are at higher risk for bleeding and do not exhibit a net benefit (ischemic/hemorrhagic) from the use of a dose of 10 mg/day (a dose of 5 mg/day was not tested in large studies). • No need for dose adjustment in renal failure • No need for adjustment in mild and moderate liver impairment; it is however contraindicated in severe liver impairment

Continuation		
Resistance	•	No reports
Use of stomach protector	•	Indicated for patients with a history of gastrointestinal bleeding
	•	The use of a proton pump inhibitor reduces the rate of absorption
Prevention of DVT in flights	•	No indication

TIA: transient ischemic attack; NSAID: nonsteroidal anti-inflammatory drug; TTP: thrombotic thrombocytopenic purpura; DVT: deep vein thrombosis.

Table 6 – Specificities of ticagrelor

		Ticagrelor
Mechanisms of action	•	Selective and reversible inhibition of the ADP P2Y12 receptor
Pharmacokinetics	•	Oral absorption of approximately 1.5 h, without diet interference
	•	Onset of antiplatelet action after 30 min
	•	Maximum plasma concentration after 2 h
	•	Absolute bioavailability of approximately 36% (30%–42%)
	•	Half-life of 7 h (ticagrelor) and 9 h (active metabolite)
	•	Strong binding to plasma proteins (> 99%)
	•	Liver metabolism (CYP 3A4)
	•	Excretion via the gastrointestinal tract (biliary route); residual renal excretion
Indications	•	Acute coronary syndrome
Contraindications	•	Active pathological bleeding (example, peptic ulcer or intracranial bleeding)
	•	Severe liver disease (higher exposure to ticagrelor and reduction in the production of coagulation factors)
	•	History of intracranial hemorrhage
	•	Pregnant women, breastfeeding women (discontinue breastfeeding or the medication, according to risk and benefit for the mother) or children (regardless of age)
	•	Concomitant use of other CYP 3A4 inhibitors
Precautions	•	Moderate liver impairment
	•	Concomitant use of paroxetine, sertraline, and citalopram
Drug and food interactions	•	CYP 3A4 inhibitors: cetoconazol, itraconazol, voriconazol, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir
	•	ICYP 3A4 inducers: rifampicin, dexamethasone, phenytoin, carbamazepine, phenobarbital
	•	Simvastatin, lovastatin (serum levels may be increased)
	•	Digoxin (monitor serum levels)
	•	ASA: use of a maintenance dose of 100 mg daily; higher doses reduce the effect of ticagrelor
Adverse reactions	•	Dyspnea: this adverse effect occurs in approximately 14% of patients; it spontaneously improves without the need for drug discontinuation; other causes of dyspnea should be excluded before establishing that the symptom is caused by ticagrelor
	•	Bradycardia, sinusal pause, AF, hypertension, headache, dizziness, cough, asthenia, diarrhea, nausea, bleeding
	•	Laboratory: deterioration of renal function and increased uric acid
Platelet function tests	•	Not yet recommended for routine use
Hemorrhage risk stratification	•	Use bleeding risk scores (example, CRUSADE)
	•	Assess the clinical characteristics associated with higher risk for bleeding: elderly, history of hemorrhagic disorders, invasive procedures, use of concomitant drugs (anticoagulant drugs, fibrinolytic drugs, NSAIDs)
	•	Discontinue drug administration 5 days before surgical procedures
Presence of thrombocytopenia	•	No evidence of thrombocytopenia induced by ticagrelor
Influence of age, weight, and renal and liver functions	•	Elderly: no evidence of higher incidence of bleedings in the group aged > 65 years in the PLATO study
	•	Mild and moderate liver impairment require careful use, without dose adjustment; contraindicated in patients with severe liver impairment
	•	Renal impairment does not require dose adjustment; the group with renal impairment exhibited clear benefit from the use of ticagrelor; patients undergoing dialysis have not been studied
Resistance	•	No reports
Use of stomach protector	•	No interference with its action
Prevention of DVT in flights	•	No indication

ACS: acute coronary syndrome; ASA: acetyl salicylic acid (aspirin); AF: atrial fibrillation; NSAID: nonsteroidal anti-inflammatory drug; DVT: deep vein thrombosis.

Table 7 – Specificities of cilostazol inhibitors

	Cilostazol
Mechanisms of action	• Derivative of quinolone that acts as cellular phosphodiesterase inhibitor, particularly phosphodiesterase III, by inhibiting cyclic AMP degradation in platelets and blood vessels, resulting in a reduction in platelet aggregation and vasodilation
Pharmacokinetics	• Good oral absorption; increased rate of absorption when administered with fatty foods • Two active metabolites: 3,4-dehydro-cilostazol and 4-trans-hydroxi-cilostazol • Liver metabolism via cytochrome P450s (particularly CYP3A4 and, to a lesser extent, CYP 2C19) • Half-life of 11–13 h • Renal (74%) and fecal (20%) excretion • Binding to plasma proteins: 95%–98% (particularly albumin)
Indications	• Peripheral vascular disease and decreased intermittent claudication symptom • Prevention of thrombotic events in patients with peripheral arterial disease • Prevention of stroke recurrence • Under investigation for the prevention of restenosis of revascularized vessels, coronary or peripheral arteries
Contraindications	• Heart failure of any severity because it can trigger ventricular tachycardia • Hemostatic disorders or active pathological bleeding (example. hemorrhagic peptic ulcer or intracranial hemorrhage) • Pregnant women, during breastfeeding, and children • Hypersensitivity
Precautions	• Half-life increased in patients with renal failure • Thrombocytopenic patients: higher risk for bleeding • Thrombocytopenia, leucopenia, and agranulocytosis (rare)
Drug and food interactions	• Increased plasma concentration in association with diltiazem, cetoconazol, erythromycin, or CYP2C19 inhibitors such as omeprazol • Concomitant use of clopidogrel, other antiplatelet drugs: higher risk for bleeding
Adverse reactions	• Skin rash, bleeding, headache, diarrhea, dyspepsia, palpitations, tachycardia, dizziness, pancytopenia, abdominal pain, peripheral edema, myalgia, cough, pharyngitis, and rhinitis
Platelet function tests	• No description of clinical or experimental use
Hemorrhage risk stratification	• Precaution when used in combination with other antiplatelet drugs • Use bleeding risk scores (example, CRUSADE)
Presence of thrombocytopenia	• Rare event, may be associated with leucopenia and agranulocytosis
Influence of age, weight, and renal and liver functions	• Severe renal failure (creatinine clearance < 25 ml/min) • Severe to moderate liver impairment • Patients under dialysis were not evaluated; however, elimination by dialysis is improbable
Resistance	• No reports
Use of stomach protector	• Precaution with the associated use of omeprazol because it increases the plasma concentration of cilostazol
Prevention of DVT in flights	• No indication

DVT: deep vein thrombosis.

Table 8 – Specificities of dipiridamol

	Dipiridamol
Mechanisms of action	• Inhibition of cyclic phosphodiesterase; inhibition of adenosine reuptake; enhances the production of prostaglandin I2 and protection against its degradation
Pharmacokinetics	• Variable absorption, which can result in low systemic bioavailability • Formulations with modified release exhibit better bioavailability. • Bioavailability between 27% and 66% (absolute bioavailability of approximately 60%) • Widely distributed (lipophilic), particularly in the liver, lungs, kidneys, spleen, and heart; does not cross the blood–brain barrier; low placental barrier crossing and low excretion in maternal milk
Pharmacokinetics	• Very high protein binding (97%–99%), particularly to 1-alpha-acid-glycoprotein • Half-life of 1–12 h, mean of 10 h; time to reach the maximum concentration: approximately 75 min • Liver metabolism and biliary excretion as glucuronide conjugate and subjected to liver recirculation
Indications	• Prevention of cerebral thromboembolic events (stroke or TIA) • Prevention of thrombosis associated with cardiac prosthetic valves (combined with warfarin)
Contraindications	• Hypersensitivity • Children younger than 12 years (safety and efficacy not established)

Continuation	
Precautions	• Severe coronary artery disease, including unstable angina and recent myocardial infarction • Subvalvular aortic stenosis • Hemodynamic instability (example, uncompensated HF) • Patients with myasthenia gravis and in the presence of bronchospasm and angioedema • Pregnancy and breastfeeding (only if clearly indicated)
Drug and food interactions	• Rivaroxaban, dabigatran, colchicine, everolimus, NSAIDs, pentoxifylline • Adenosine (increases its plasma levels and the dose should be adjusted) • Increase in the hypotensive effect of antihypertensive drugs • Reduction in the anticholinesterase effects of the cholinesterase inhibitors
Adverse reactions	• More frequent: headache, dizziness, arterial hypotension, extrasystole, gastrointestinal intolerance (nausea, vomiting, diarrhea, abdominal pain) • Rare: angina, liver impairment, and hypersensitivity reactions (skin rash, urticaria, bronchospasm, angioedema, larynx edema, arthritis)
Platelet function tests	• No description of clinical or experimental use
Hemorrhage risk stratification	• No evidence of increased bleeding when associated with ASA or warfarin • Rare reports of increased bleeding associated with the postoperative period • Use bleeding risk scores (example, CRUSADE)
Presence of thrombocytopenia	• Rare reports of thrombocytopenia
Influence of age, weight, and renal and liver functions	• Plasma concentration is 50% higher in the elderly than in young individuals • No pharmacokinetic alterations in renal impairment • Administration of dipiridamol without restrictions in liver impairment, provided there are no signs of liver failure
Resistance	• No reports
Use of stomach protector	• No interference with its action
Prevention of DVT in flights	• No indication

HF: heart failure; stroke; TIA: transient ischemic attack; DVT: deep vein thrombosis; ASA: acetyl salicylic acid (aspirin).

10.3. Specificities of anticoagulant agents

Table 1 – Specificities of unfractionated heparin

	Unfractionated heparin
Mechanisms of action	• Enhances antithrombin III activity, increasing its affinity for thrombin (factor IIa) • Promotes the inactivation of thrombin and of factors IXa, Xa, XIa, and XIIa and plasmin • Inhibits the conversion of fibrinogen into fibrin
Pharmacokinetics	• Administered intravenously or subcutaneously • Binds to several plasma proteins, endothelial cells, macrophages, and von Willebrand factor, which contributes to the reduction in its bioavailability and variable anticoagulant activity • Plasma peak within 2–4 h after subcutaneous administration • Renal excretion • The biological half-life is dose-dependent (30 min for a bolus of 25 IU/kg, 60 min for a bolus of 100 IU/kg and 150 min for a bolus of 400 IU/kg)
Indications	• Prevention and treatment of thromboembolic conditions of any etiology and location • Treatment of ACS • During percutaneous coronary interventions • Treatment of disseminated intravascular coagulation • During extracorporeal circulation • During hemodialysis
Contraindications	• Active bleeding or severe coagulopathy • Recent cerebral hemorrhage • Severe thrombocytopenia
Contraindications	• Active ulcers • Severe liver and renal failure • Severe hypertension • Subacute bacterial endocarditis • Hypersensitivity

Continuation	
Precautions	• Patients with thrombocytopenia • Thrombocytopenia induced by heparin • Patients aged > 60 years; female patients, in particular, are at increased risk for bleeding
Drug and food interactions	• Digitalis, tetracyclines, nicotine, and antihistamines can partially antagonize the anticoagulating effects of heparin • Administration of intravenous nitroglycerin to patients under full heparinization regimen can decrease aPTT and cause a rebound effect after its discontinuation. Careful monitoring of aPTT should be performed in this situation • The concomitant use of oral anticoagulant drugs, antiplatelet drugs, and NSAIDs increases risk for bleeding. • Avoid the use of corticosteroids under prolonged treatment with heparin
Adverse reactions	• Hemorrhagic manifestations • Hypersensitivity reactions • Thrombocytopenia • Hyperkalemia • Elevated aminotransferases • Alopecia (prolonged use) • Osteoporosis (prolonged use)
Coagulation test	• Indicated only for patients under full heparinization regimen: assess aPTT every 6 h or every 4 h and maintain it between 50 and 70 s or the patient/control ratio between 1.5 and 2.5
Hemorrhage risk stratification	• Use bleeding risk scores (example, CRUSADE)
Presence of thrombocytopenia	• Discontinue its use in patients with thrombocytopenia induced by heparin • Discontinue and consider alternative treatment when platelet count < 100,000/mm³ • In case of thrombocytopenia of other etiologies, assess risks/benefits
Influence of age, weight, and renal and liver functions	• No need for specific dose adjustment in these populations. • The dose of UH should be guided by aPTT or by the activity of factor anti-Xa • Patients aged > 60 years are more sensitive to heparin and exhibit higher incidence of bleeding, and the dose required for anticoagulation is usually lower in this population
Resistance	• More than 35,000 IU/24 h are required to maintain aPTT at the therapeutic level • Associated with hereditary or acquired antithrombin deficiency, increase in proteins that bind to heparin, high levels of factor VIII and/or fibrinogen, and increased heparin clearance • More common in patients with fever, thrombosis, thrombophlebitis, infections leading to thrombosis, AMI, and cancer Also common after surgery
Use of stomach protector	• No interference with its action
Prevention of DVT in flights	• No indication

ACS: acute coronary syndrome; NSAID: nonsteroidal anti-inflammatory drug; UH: unfractionated heparin; AMI: acute myocardial infarction.

Table 2 – Specificities of low-molecular-weight heparin

	Low Low-molecular-weight heparin
Mechanisms of action	• Binds to antithrombin III, enhances its activity by inactivating the intrinsic and common factors of the coagulation cascade (factors IIa and Xa and, to a lesser degree, factors IXa, XIa, and XIIa) • The inhibition of generation of factor Xa and its activity reduces the generation of thrombin and consequently the conversion of fibrinogen into fibrin
Pharmacokinetics	• Bioavailability of 92% after subcutaneous administration • Factor Xa inhibition peak between 3 and 5 h • Elimination half-life between 3 and 6 h (in patients with preserved renal function) • Mainly renal elimination
Indications	• Prevention and treatment of DVT and PTE • Prevention of thromboembolic events in AF • Treatment of moderate- and high-risk ACS
Contraindications	• Active bleeding or severe coagulopathy • High risk for difficult-to-control bleeding • Active gastroduodenal ulcer • Recent cerebral hemorrhage • Acute bacterial endocarditis in patients with or without valve prosthesis • Hypersensitivity to heparin and its derivatives or to benzyl alcohol
Precautions	• Not for intramuscular administration • Not indicated for pregnant women in the first trimester or breastfeeding women • Use with caution in elderly patients, patients with low weight (men: < 57 kg, women: < 45 kg), liver or renal failure, coagulation disorders, thrombocytopenia induced by heparin, recent surgery or trauma, previous GIT ulcer or bleeding, diabetic retinopathy, arterial hypertension not under control, liquor puncture, and anesthesia via the spinal cord

Continuation	
Drug and food interactions	• The concomitant use of NSAIDs, antiplatelet drugs, oral anticoagulant drugs, thrombolytic drugs, and valproic acid increases risk for bleeding • In prolonged use, avoid combined use with corticosteroids.
Adverse reactions	• Hemorrhagic manifestations • Thrombocytopenia • Peripheral edema • Symptoms at the injection site (pain, nodulation, hematoma, rash, and itching) • Headache • Hyperkalemia • Elevation of aminotransferases • Hypersensitivity reactions
Coagulation test	• The levels of anti-Xa activation can be measured via monitoring of the anticoagulating effect in specific subgroups of patients (pregnant women, patients with renal failure, obesity, or low weight) • The levels of anti-Xa should be dosed approximately 4 h after the administration of the enoxaparin dose
Hemorrhage risk stratification	• Use bleeding risk scores (example, CRUSADE)
Presence of thrombocytopenia	• The use of LMWH is contraindicated in thrombocytopenia associated with the presence of a positive antiplatelet antibody laboratory test • Discontinue its use in patients with thrombocytopenia induced by heparin • Discontinue and consider alternative treatment when platelet count < 100,000/mm³ • In the case of thrombocytopenia of other causes, assess risks and benefits
Influence of age, weight, and renal and liver functions	• In patients aged > 75 years, the recommended dose of enoxaparin is 0.75 mg/kg every 12 h for full heparinization; the recommended dose is the same in patients with severe renal failure (if eGFR < 30 ml/min, the recommended dose is 1 mg/kg once daily) • Use with precaution in patients with liver failure
Resistance	• Described in thrombophilic syndromes
Use of stomach protector	• No interference with its action
Prevention of DVT in flights	• No consistent indication. See section 6, "Use of antiplatelet and anticoagulant agents in valve disease."

DVT: deep vein thrombosis; PTE: pulmonary thromboembolism; AF: atrial fibrillation; ACS: acute coronary syndrome; GIT: gastrointestinal tract; eGFR: estimated glomerular filtration rate; LMWH: low-molecular-weight heparin.
**In these subgroups of patients, it is recommended to measure anti-Xa activity for therapeutic monitoring owing to high risk for bleeding.*

Table 3 – Specificities of fondaparinux

	Fondaparinux
Mechanisms of action	• Indirect inhibition of factor Xa via selective binding to antithrombin. Neutralization of factor Xa interrupts the blood coagulation cascade by inhibiting the generation of thrombin and thrombus formation, without actually inactivating thrombin
Pharmacokinetics	• Rapidly absorbed and bioavailability of 100% after subcutaneous administration • Peak of activity after 2 h and long half-life (17–21 h), which allows it to be administered once daily • Minimum and nonspecific binding to plasma proteins • Mainly renal excretion
Indications	• Prevention and treatment of venous thromboembolism • Treatment of ACS • Alternative as anticoagulant drug in thrombocytopenia induced by heparin
Contraindications	• eGFR < 20 ml/min • Active bleeding or hypersensitivity • Acute bacterial endocarditis • Pregnant women, breastfeeding women, and children • In patients weighing < 50 kg, use with caution
Precautions	• Use with caution in patients with eGFR of 30–50 ml/min and who already take medications that may increase risk for bleeding • Monitor platelet count • Patients who are scheduled for percutaneous coronary intervention should receive UH during the procedure to reduce the incidence of catheter thrombosis
Drug and food interactions	• No clinically relevant interactions
Adverse reactions	• Bleeding, local symptoms (injection site) such as rash, itching, skin necrosis or hematoma, anemia, hypokalemia, hypotension, dizziness, confusion, and insomnia
Coagulation test	• No indication for monitoring • Can prolong aPTT at high doses (7.5–10 mg) • The fondaparinux-specific anti-Xa test can help in special situations.

Continuation		
Hemorrhage risk stratification	•	Use bleeding risk scores (example, CRUSADE)
Presence of thrombocytopenia	•	Discontinue if platelet count < 100,000/mm^3
	•	Thrombocytopenia of 50,000–100,000/mm^3 may occur in up to 3.0% of patients; thrombocytopenia of < 50,000/mm^3 may occur in 0.2% of patients at a dose of 2.5 mg once daily
Influence of age, weight, and renal and liver functions	•	Use with caution in patients aged > 75 years or with eGFR of 30–50 ml/min
	•	In patients with eGFR of 30–50 ml/min, the dose should be reduced by 50% in the prevention of DVT
	•	Contraindicated if eGFR < 30 ml/min
	•	Avoid its use in patients with severe liver failure
	•	In the treatment of DVT/PTE, adjust dose according to weight
Resistance	•	No reports
Use of stomach protector	•	No interference with its action
Prevention of DVT in flights	•	No indication

ACS: acute coronary syndrome; eGFR: estimated glomerular filtration rate; UH: unfractionated heparin; DVT: deep vein thrombosis; PTE: pulmonary thromboembolism; UA/NSTEMI: unstable angina/acute myocardial infarction without ST-segment elevation; STEMI: ST-segment elevation acute myocardial infarction.

Table 4 – Specificities of warfarin

		Warfarin
Mechanisms of action	•	Competitively inhibits gamma-carboxylation of coagulation factors dependent on vitamin K (II, VII, IX, and X)
Pharmacokinetics	•	Rapid absorption via the oral route (90 min)
	•	Concentration peak: 2–8 h
	•	Half-life: 20–60 h
	•	Renal excretion: 92%
	•	Liver metabolism
Indications	•	Treatment of venous thromboembolism
	•	Prevention of thromboembolism in AF with or without valve disease, metal prosthetic valves, intracavitary thrombus, and other embolic risk conditions
Contraindications	•	Patients with severe liver disease, particularly associated with severe coagulopathy
	•	Presence of cerebral or aortic aneurysm with dissection
	•	Patients with active pathological bleeding
	•	Pregnant women (category D): should be avoided, particularly during the first and third trimesters
	•	Hypersensitivity
Precautions	•	Severe liver or renal disease
	•	Patients with vitamin K deficiency in their diet
	•	Patients with thrombocytopenia induced by heparin
	•	Thyroid disease
	•	Severe arterial hypertension not under control
	•	Bacterial endocarditis
	•	Congestive heart failure
	•	During 24 h before or after surgery, delivery, or invasive procedures
Drug and food interactions	•	One of the main problems of using warfarin is the numerous drug and food interactions; more than 200 drugs can interfere with warfarin, the main ones being the following:
	•	Increase the effect of warfarin: amiodarone, propranolol, ezetimibe, simvastatin, omeprazol, ciprofloxacin, fluconazol, and metronidazol
	•	Decrease the effect of warfarin: azathioprine, carbamazepine, barbiturates, and rifampicin
	•	ASA and NSAIDs increase the risk for bleeding
	•	Foods rich in vitamin K (vegetables, green tea, liver) decrease the activity of warfarin, and a diet with a constant intake of foods rich in vitamin K is indicated
	•	Acute alcohol intake decreases the metabolism of warfarin and increases its effect
Adverse reactions	•	Bleeding at any site (very dependent on the patient's sensitivity and on risk factors)
	•	Necrosis/skin gangrene
	•	Osteoporosis
	•	Hepatitis, jaundice, and cholestasis
Coagulation test	•	Prothrombin time/INR: the frequency of monitoring depends on the timing of the treatment, on the patient's sensitivity, and on INR instability
	•	CYP2C9 and VKORC1 genotyping can be performed before starting warfarin therapy
Hemorrhage risk stratification	•	The HAS-BLED score can be used
Presence of thrombocytopenia	•	Should be avoided in patients with platelet count < 80,000mm^3

Continuation		
Influence of age, weight, and renal and liver functions	•	Elderly patients, patients with low weight, and patients with liver failure are more sensitive and usually require lower doses and more frequent monitoring Dose adjustment according to renal function is not necessary; however, because risk for bleeding is increased, monitoring should be more frequent
Resistance	•	True warfarin resistance is rare and is defined as requirements greater than 70 mg/week to maintain INR within the therapeutic range Can be determined by polymorphisms in the VKORC1 gene (involved in pharmacodynamics) or in the CYP2C9 gene (involved in pharmacokinetics)
Use of stomach protector	•	Can increase the activity of warfarin
Prevention of DVT in flights	•	No evidence for its use
Procedure in case of overdose	•	INR 3.5–5.0: discontinue one dose, reduce weekly dose by 10%–20%, and repeat the test after a week INR 5–9: discontinue two to three doses, reduce weekly dose by 10%–20%, and repeat the test after 3–5 days INR > 9: hospitalization; discontinue the medication and administer vitamin K orally or intravenously. Repeat INR test daily and reintroduce warfarin when INR < 4, with 10%–25% reduction in weekly dose. In case of bleeding, administer fresh plasma, prothrombin complex, or recombinant factor VIIa

ASA: acetyl salicylic acid (aspirin); NSAID: nonsteroidal anti-inflammatory drug; INR: international normalization ratio; AF: atrial fibrillation.

Table 5 – Specificities of dabigatran

		Dabigatran
Mechanisms of action	•	This is a pro-drug whose active metabolite causes direct, competitive, specific, and reversible inhibition of free thrombin and fibrin-bound thrombin
Pharmacokinetics	•	Bioavailability: 6.5% Concentration peak: 30 min–2 h Half-life: 12–17 h Renal excretion: 80%
Indications	•	Prevention of VTE after surgery Prevention of VTE in AF without valve disease
Contraindications	•	Active bleeding or hemorrhagic diathesis Ischemic or hemorrhagic extensive stroke in the last 6 months Presence of prosthetic valve eGFR < 30 ml/min Patients younger than 18 years Concomitant use of cetoconazol
Precautions	•	Patients with high risk for bleeding Age > 75 years eGFR 30–50 ml/min Pregnant women (category C) Concomitant use of NSAIDs, antiplatelet drugs, and other anticoagulant drugs
Drug and food interactions	•	Less drug interactions than warfarin Increase their concentration: cetoconazol, amiodarone, verapamil, quinidine, clarithromycin Decrease their concentration: rifampicin, pantoprazol Food delays the drug's peak activity by 2 h
Adverse reactions	•	Hemorrhagic manifestations Dyspepsia (abdominal pain, nausea, vomiting) Increased aminotransferases Thrombocytopenia
Coagulation test	•	Does not require monitoring during the clinical treatment Changes in aPTT, thrombin time, and coagulation test with ecarin clotting time may occur. Increase in aPTT (in seconds): although not very sensitive, it may be useful in patients with active bleeding
Hemorrhage risk stratification	•	The HAS-BLED score can be used
Presence of thrombocytopenia	•	Should be avoided in patients with platelet count < 100,000/mm^3

Continuation	
Influence of age, weight, and renal and liver functions	• No influence of weight on dose • If eGFR 30–50 ml/min: • Prevention of VTE: reduce dose to 150 mg once daily • AF: 150 mg twice daily, monitor renal function, and take precaution with concomitant use of other medications • Not recommended if eGFR < 30 ml/min • Eliminated by dialysis • Liver function: dose adjustment is not necessary • Age: • Prevention of VTE: > 75 years, use 150 mg once daily • AF: > 80 years, use 110 mg twice daily
Resistance	• No data on resistance till date
Use of stomach protector	• The use of antacids and proton pump inhibitors can reduce its activity • Use dabigatran 2 h before the use of antacids
Prevention of DVT in flights	• No consistent indication. See section 6, "Use of antiplatelet and anticoagulant agents in valve disease."

VTE: venous thromboembolism; AF: atrial fibrillation; NSAID: nonsteroidal anti-inflammatory drug; eGFR: estimated glomerular filtration rate.

Table 6 – Specificities of rivaroxiban

	Rivaroxaban
Mechanisms of action	• Direct, selective, and reversible inhibition of factor Xa, preventing thrombin generation both in the free form and in already formed thrombi
Pharmacokinetics	• Good bioavailability: 80% • Concentration peak: 2–4 h • Half-life: 5–9 h (young) and 11–13 h (elderly) • Liver metabolism • Renal excretion (2/3)
Indications	• Prevention and treatment of VTE after surgery • Prevention of thromboembolism in atrial fibrillation without valve disease
Contraindications	• Active bleeding • Ischemic or hemorrhagic stroke in the last 6 months • Liver disease with associated coagulopathy • Moderate liver disease (CHILD B and C) • eGFR < 30 ml/min • Acute renal failure • Patients younger than 18 years • Concomitant use of cetoconazol and ritonavir
Precautions	• Patients with altered liver function but without coagulopathy • Severe arterial hypertension not under control • Pregnant women (category C) • Patients with lactose or galactose intolerance • Concomitant use of NSAIDs, antiplatelet agents, and other anticoagulant agents
Drug and food interactions	• Less drug interactions than warfarin • Increase its concentration: potent CYP3A4 and glycoprotein P inhibitors such as cetoconazol, itraconazol and protease inhibitors (ritonavir); grape juice • Reduce its concentration: CYP3A4 and glycoprotein P inducers such as rifampicin, carbamazepine, and phenytoin • Can be administered with food
Adverse reactions	• Hemorrhagic manifestations (mainly in patients with AF) • Nausea, syncope, itching, muscle spasm, pain in the extremities, and increased hepatobiliary damage markers
Coagulation test	• Does not require monitoring during medical treatment • Changes PT, aPTT, and factor anti-Xa activity may occur; these changes are dose-dependent • Increase in PT (s): may be useful in patients with active bleeding, good correlation with rivaroxaban dose • Changes INR should not be considered
Hemorrhage risk stratification	• The HAS-BLED score can be used • Factors that increase risk for bleeding: use of antiplatelet drugs, coagulation or platelet function disorders
Presence of thrombocytopenia	• Avoid using in patients with thrombocytopenia: increased risk for bleeding

Continuation		
Influence of age, weight, and renal and liver functions	•	No influence of gender, age, and weight on dose AF and eGFR 30–50 ml/min: reduce dose to 15 mg (once daily) Not recommended if eGFR < 30 ml/min Not eliminated by dialysis Not recommended if there is associated coagulopathy or cirrhosis (CHILD B and C) Mild liver impairment: no need for dose adjustment
Resistance	•	No data on resistance till date
Use of stomach protector	•	No influence on absorption or bioavailability of the drug
Prevention of DVT in flights	•	No consistent indication. See section 6, "Use of antiplatelet and anticoagulant agents in valve disease."

VTE: venous thromboembolism; eGFR: estimated glomerular filtration; NSAID: nonsteroidal anti-inflammatory drug; AF: atrial fibrillation; INR: international normalization ratio.

Table 7 – Specificities of apixaban

		Apixaban
Mechanisms of action	•	Selective and reversible inhibition of factor Xa
Pharmacokinetics	•	Bioavailability: approximately 50% Concentration peak: 3 h Half-life: 8–15 h Liver metabolism Renal and fecal excretion (27%)
Indications	•	Prevention and treatment of VTE after surgery Prevention of VTE in AF without valve disease
Contraindications	•	Active bleeding Ischemic or hemorrhagic stroke in the last 6 months Liver disease with associated coagulopathy eGFR < 15 ml/min Patients younger than 18 years Pregnant women Concomitant use of cetoconazol and ritonavir
Precautions	•	Patients with altered liver function but without coagulopathy eGFR 15–30 ml/min Patients with lactose or galactose intolerance Concomitant use of NSAIDs, antiplatelet agents, and other anticoagulant agents Concomitant use of phenytoin, carbamazepine, and phenobarbital
Drug and food interactions	•	Less drug interactions than warfarin Increase its concentration: cetoconazol, itraconazol, protease inhibitors (ritonavir), diltiazem, atenolol Reduce its concentration: rifampicin, carbamazepine, and phenytoin Can be administered with food
Adverse reactions	•	Hemorrhagic manifestations Anemia Nausea
Coagulation test	•	Does not require monitoring during the medical treatment Changes in PT, aPTT, and factor anti-Xa activity can occur Factor anti-Xa activity linearly correlates with drug concentration; it is less variable than the other tests and is important in the presence of active bleeding
Hemorrhage risk stratification	•	The HAS-BLED score can be used.
Presence of thrombocytopenia	•	Avoid its use in patients with platelet count < 100,000/mm^3
Influence of age, weight, and renal and liver functions	•	No influence of gender, age, and weight on dose Dose adjustment not required if eGFR > 30 ml/min Use with precaution in patients with eGFR 15–30 ml/min Not recommended if eGFR < 15 ml/min Not recommended if there is associated coagulopathy or cirrhosis (CHILD B and C) Mild liver impairment: dose adjustment not required
Resistance	•	No data on resistance till date
Use of stomach protector	•	No influence on the absorption or bioavailability of the drug
Prevention of DVT in flights	•	No evidence for its use till date

VTE: venous thromboembolism; AF: atrial fibrillation; eGFR: estimated glomerular filtration rate; NSAID: nonsteroidal anti-inflammatory drug.

Guidelines

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