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Antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention: triple versus dual therapy

Tratamento antitrombótico em pacientes portadores de fibrilação atrial e submetidos à revascularização coronária percutânea: terapia tripla *versus* dupla

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ABSTRACT – The ideal antithrombotic management in patients with atrial fibrillation undergoing elective percutaneous coronary intervention or in acute coronary syndrome has not been definitively established yet. Dual antiplatelet therapy (aspirin and P2Y₁₂ receptor inhibitors) reduces stent thrombosis and subsequent ischemic events. In turn, the presence of atrial fibrillation requires oral anticoagulation to prevent stroke and other thromboembolic complications. However, the combination of these two treatments, known as triple therapy, increases the risk of severe bleeding, with a negative prognostic impact. The use of direct anticoagulants, which reduce bleeding rates compared to warfarin, together with the maintenance of only one antiplatelet agent (P2Y₁₂ inhibitors), known as dual therapy, may be a safer alternative in these patients. In this article, we reviewed several randomized studies comparing triple *versus* dual therapy, as well as meta-analyses with such studies, and the approaches suggested by the most recent guidelines, discussing the advantages and disadvantages of these treatments, in terms of safety and efficacy in this important and growing subgroup of patients.

Keywords: Percutaneous coronary intervention; Atrial fibrillation; Anticoagulants; Platelet aggregation inhibitors

RESUMO – O manuseio antitrombótico ideal em portadores de fibrilação atrial e submetidos à intervenção coronária percutânea eletiva ou em síndrome coronária aguda não está definitivamente estabelecido. A dupla antiagregação plaquetária (aspirina e inibidores do receptor P2Y₁₂) reduz a trombose dos stents e os eventos isquêmicos subsequentes. Por sua vez, a presença de fibrilação atrial requer a anticoagulação oral para a prevenção de acidente vascular cerebral e outras complicações tromboembólicas. Entretanto, a combinação destes dois tratamentos, conhecida como terapia tripla, eleva o risco de sangramentos graves, com impacto prognóstico negativo. A utilização dos anticoagulantes diretos, que reduzem as taxas de sangramento relativamente à varfarina, juntamente da manutenção de apenas um antiplaquetário (os inibidores da P2Y₁₂), conhecida como terapia dupla, pode ser uma alternativa mais segura nesses pacientes. Neste artigo, revisamos os vários estudos randomizados comparando a terapia tripla *versus* a dupla, além de metanálises desses estudos e as condutas sugeridas pelas diretrizes mais recentes, discutindo as vantagens e desvantagens desses tratamentos, em termos de segurança e eficácia nesse importante e crescente subgrupo de pacientes.

Descritores: Intervenção coronária percutânea; Fibrilação atrial; Anticoagulantes; Inibidores da agregação de plaquetas

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INTRODUCTION

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias today, and its prevalence increases with age and the presence of risk factors, such as diabetes mellitus, hypertension (HTN) and dyslipidemia, being associated with increased mor-

tality.¹ Its treatment involves the use of oral anticoagulants administered chronically to prevent thromboembolic phenomena, such as stroke and systemic embolism.²

About 10% to 15% of AF patients also have stable or unstable coronary artery disease (CAD) and may potentially require percutaneous coronary intervention (PCI) with drug-eluting stenting (DES). The incidence of AF in ACS ranges from 2% to 23%, and the presence of AF, by itself, increases the risk of ACS with or without ST-segment elevation.³ PCI involves the use of dual antiplatelet therapy (DAPT), which is an association of aspirin with one of the P2Y₁₂ receptor inhibitors (clopidogrel, ticagrelor and prasugrel) for varying periods, depending on the clinical scenario and the anatomical complexity of the CAD. This therapy aims to reduce stent thrombosis and its major clinical consequences, namely death and acute myocardial infarction (MI).⁴⁻⁶

DEFINITION OF TRIPLE THERAPY

It is the association between anticoagulants and antiplatelet agents with the purpose of reducing, respectively, AF-related thromboembolic events and ischemic events associated with stents. However, this combination of drugs is correlated with the occurrence of potentially severe bleeding and the risk of death.^{7,8}

In a meta-analysis involving more than 80 thousand patients, Hansen *et al.* analyzed the risk of bleeding with the isolated use of aspirin, warfarin and clopidogrel, and also of the combinations of these drugs.^{9,10} In monotherapy, the risk of bleeding was low, with no significant difference between them. Nonetheless, any combination of these drugs significantly increased bleeding rates, ranging from 1.66 (aspirin and clopidogrel) to 3.70 (DAPT + warfarin).

The mechanisms that underlie the relation between death and bleeding are complex and include hypotension, anemia, adverse reactions to blood product transfusion, hypoxia, vasoconstriction, platelet dysfunction and, obviously, discontinuation and/or reversal of antithrombotic and antiplatelet therapies. Bleeding can also be related to possible occult neoplasms.¹¹

If the risk of bleeding with triple therapy (TT) is unquestionably high, besides its deleterious complications, why use it? ^{12,13} The ACTIVE-W study demonstrated that DAPT does not prevent the occurrence of stroke, systemic embolism and death from vascular causes in patients with AF, with a significantly higher incidence of these events in those patients who used only aspirin + clopidogrel (5.64% per year) *versus* those on oral anticoagulants (3.93% per year; relative risk reduction of 1.45, with $p=0.0002$).¹⁴

The ACTION Registry evaluated almost 5,000 patients aged >65 years, with acute MI, and AF undergoing PCI, and found that, among 27.6% of individuals who were discharged using TT, there was a lower incidence of ischemic

stroke (3.2% *versus* 4.7%; $p=0.002$) and significantly high rates of readmissions due to bleeding (17.6% *versus* 11%; $p=0.0001$) and intracranial hemorrhage (3.4% *versus* 1.5%; $p=0.001$) *versus* DAPT.¹⁵ Therefore, several studies were carried out to search for therapeutic alternatives, seeking a more favorable risk-benefit ratio, without increasing the occurrence of bleeding and ischemic events.¹⁶

RANDOMIZED STUDIES COMPARING TRIPLE THERAPY VERSUS DUAL THERAPY

WOEST

This was one of the first studies to analyze this issue. It was a multicenter, randomized and open study carried out with 573 high-risk patients (mean age 70 years, with AF, metallic valves or previous stroke), who underwent PCI and were divided into two groups: TT (aspirin + clopidogrel + warfarin) *versus* dual therapy (DT; clopidogrel + warfarin). The primary endpoint was the occurrence of any bleeding within 1 year after PCI (*Thrombolysis in Myocardial Infarction* – TIMI criteria).¹⁷

Any bleeding occurred in 19.4% in the DT group, and in 44.4% in the TT group (risk rate of 0.36; 95%CI 0.26-0.50; $p<0.0001$). The most frequent were minimal and minor, respectively, for TT and DT, with 16.7% and 6.5%, with $p<0.001$, and 27.2% and 11.2%, with $p<0.001$. There were no differences in major bleeding: 5.8% *versus* 3.3%, $p=0.159$.

As for the secondary endpoint (composite rate of death, stroke, MI, stent thrombosis and urgent target vessel revascularization), it was significantly lower in DT (11.3%) *versus* TT (17.7%), with a 0.60 risk rate, 95%CI 0.38-0.94, and $p=0.025$.

The authors concluded that DT was associated with a significant reduction in bleeding, without apparently increasing the rate of thrombotic events compared to TT.

Limitations of the study: small sample of patients included; significant reduction only in minimal/minor bleeding with no difference in major/intracranial bleeding; the study had statistical power for superiority on bleeding, but did not have power for non-inferiority testing of the secondary endpoint; the TIMI bleeding criteria could be replaced by more refined scores, such as the Bleeding Academic Research Consortium/International Society on Thrombosis and Hemostasis (BARC/ISTH) bleeding classification, and the follow-up was short (1 year).

Despite the limitations, the WOEST study was the first to indicate that discontinuing aspirin therapy could significantly reduce major bleeding, apparently without increasing ischemic complications.¹⁸

The advent of new anticoagulants which directly inhibit factor Xa (rivaroxaban, apixaban and edoxaban) or thrombin (dabigatran) has been a major advance, for enabling long-term anticoagulation (without tests or dose titration) and promoting a highly effective thromboembolic protection

with lower risk of bleeding (including intracranial hemorrhages), compared to warfarin.^{19,20}

Therefore, new studies using direct anticoagulants were conducted in patients with non-valvular AF with anticoagulation indication, undergoing elective PCI, or in ACS with stent implantation. Some of these studies are highlighted below.

PIONEER AF-PCI

This multicenter, randomized and open study was the first to evaluate a direct anticoagulant in the PCI scenario, aiming to analyze the safety of two doses of rivaroxaban *versus* TT (warfarin + clopidogrel + aspirin) in 2,124 patients with non-valvular AF, with no previous stroke/transient ischemic accident (TIA), who underwent PCI with stent implantation, and were randomized after 72 hours for three treatment strategies:²¹

1. WOEST-like strategy with low doses of rivaroxaban (15mg) + P2Y₁₂ inhibitor, without aspirin (group 1) for 12 months.
2. TT with very low doses of rivaroxaban (2.5mg b.i.d.) associated with DAPT, followed by 15mg rivaroxaban + low-dose aspirin after discontinuation of the P2Y₁₂ inhibitor (group 2).
3. TT (warfarin + DAPT) (group 3).

The primary endpoint of the study was the occurrence of major and minor bleeding (TIMI) and bleeding requiring medical care. The secondary endpoint included cardiovascular death, stroke and MI.

Both doses of rivaroxaban (groups 1 and 2) reduced the rates of major and minor bleeding, and bleeding requiring medical care, compared to the TT group (respectively: 16.8%, 18% and 26.7%, with $p < 0.001$), with the number needed to treat of 11 to 12 patients. The three groups had comparable rates of major adverse cardiac events (MACE) – respectively 6.5%, 5.6% and 6% ($p = \text{not significant}$), after 1 year.²¹

Limitations of the study: the recommended dose of rivaroxaban for prevention of stroke and thromboembolic events in patients with AF is 20mg per day. In the study, smaller doses were used, not approved for this purpose: 2.5mg administered twice a day, derived from the ATLAS-TIMI 51 study (treatment of patients with ACS without AF); and 15mg, used in the ROCKET-AF study in patients with chronic kidney disease (CKD). According to the authors, this represents real-world evidence in daily practice.²²⁻²⁴

There was also no statistical power to demonstrate superiority or non-inferiority in the efficacy endpoints (prevention of death/MI/stroke) in patients treated by PCI with stent implantation + AF. A superiority study with 90% power to detect a 15% relative difference between groups would require a population of approximately 14 thousand patients.

The stratification of groups 2 (2.5mg of rivaroxaban, twice a day) and 3 (TT), according to the duration of DAPT

(1.6 and 12 months), was not randomized, but determined by the attending physician, leading to selection bias, according to the characteristics of the patients. It is possible that patients with increased risk of bleeding may have been allocated for a shorter DAPT time.

RE-DUAL PCI^{25,26}

This multicenter, randomized and open study used two doses of dabigatran, as approved for the treatment of AF (110mg and 150mg, twice a day) in patients undergoing PCI with bare-metal and drug-eluting stents (DES). A total of 2,725 patients were selected, divided into three groups and randomized within 5 days after PCI: DT with dabigatran 150mg twice a day + P2Y₁₂ inhibitor (clopidogrel/ticagrelor) for 1 year; DT with dabigatran 110mg twice a day + P2Y₁₂ inhibitor (clopidogrel/ticagrelor) for 1 year and TT with warfarin (International Normalized Ratio – INR – between 2 and 3) + aspirin + clopidogrel for 1 year.

Aspirin was used for one month in patients treated with bare-metal stents (BMS) and for 3 months in those treated with DES. The primary endpoint was the occurrence of major or clinically relevant bleeding within 14 months.²⁷ The non-inferiority of DT with two doses of dabigatran *versus* TT was also analyzed with regard to the incidence of the composite efficacy endpoint (MI, stroke and systemic embolism), in addition to death and unplanned emergency revascularization.

The bleeding incidence rate was 15.4% in group DT with 110mg dabigatran *versus* 26.9% in TT (risk rate of 0.52; 95%CI 0.42-0.63; $p < 0.001$ for non-inferiority, and $p < 0.001$ for superiority). In DT with dabigatran 150mg, bleeding occurred in 20.2% *versus* 25.7% in TT (risk rate of 0.72; 95%CI 0.58-0.88; $p < 0.001$ for non-inferiority).

The incidence of the composite efficacy endpoint was 13.7% in the two combined groups of DT with dabigatran *versus* 13.4% for TT (risk rate of 1.04; 95%CI 0.84-1.29; $p = 0.005$ for non-inferiority).

It is interesting to note that, in DT with the lowest dose of dabigatran (110mg twice a day), the rates of major bleeding were significantly lower (4.2%), and the rate of thromboembolic events was not significantly higher (1.8%) in comparison to the TT group. On the other hand, in DT with the highest doses of dabigatran (150mg twice a day), the rates of major bleeding were also significantly lower (2.8%), and the rate of major thromboembolic events was not significantly lower (1.0%) *versus* TT.

Based on the concept of net clinical benefit, there are two treatment options according to the risk of bleeding *versus* thromboembolic events: higher doses (150mg), in patients with high thromboembolic risk and low risk of bleeding, and smaller doses (110mg), in those with high bleeding risk and low thromboembolic risk.

The authors concluded that, in patients with AF undergoing PCI, the risk of bleeding was lower in those who used DT with dabigatran and a P2Y₁₂ inhibitor *versus* TT. Apparently, DT was not inferior to TT as to the risk of occurrence of thromboembolic events.

Limitations of the study: the population included was smaller than planned, limiting the power of the study to assess the efficacy endpoint, which was achieved by combining two doses of dabigatran, which, in turn, reduced its power to 83.6%. As to results, both for bleeding and for thromboembolic events, one might wonder what was the relative contribution of discontinuing aspirin and the oral anticoagulant used in DT *versus* TT, which could be obtained with a 2x2 factorial study.²⁸⁻³⁰ This is precisely the design of the AUGUSTUS study, which used apixaban.

AUGUSTUS

This was a multicenter, prospective, randomized study, with a 2x2 factorial design, whose objective was to evaluate the treatment of patients with AF and ACS or AF who underwent PCI + DES.³¹ All patients used P2Y₁₂ inhibitors (clopidogrel in 92.6%) and were randomized to two approaches: apixaban *versus* warfarin (open) and aspirin (81mg) *versus* placebo (double-blind), with a 6-month follow-up.

The primary endpoint was to verify the occurrence of major or not major clinically relevant bleeding (ISTH); the secondary endpoint was death or hospitalization, in addition to death and ischemic events (stroke, MI, definitive or probable stent thrombosis, and urgent revascularization).

A total of 4,614 patients were included, and patients with metallic valves, venous thromboembolism and mitral stenosis, severe CKD, history of intracranial hemorrhage, recent or planned cardiac surgery, coagulation disorders, and contraindications to the use of any class of anticoagulants were excluded.

The risks of stroke and bleeding were assessed, respectively, by two scores used in practice: CHA₂ DS₂-VASc and HAS-BLED^{32,33}

The dose of apixaban used was 5mg every 12 hours, or 2.5mg every 12 hours, if the patient had more than one of the following characteristics: age >80 years, weight ≤60kg, and creatinine >1.5mg/dL.

Major or clinically relevant bleeding occurred in 10.5% in the apixaban group, and in 14.7% in the warfarin group (risk rate of 0.69; 95%CI 0.58-0.81; p<0.001 for non-inferiority and superiority), and in 16.1% of patients who received aspirin *versus* 9.0% of patients who received placebo (risk rate of 1.89; 95%CI 1.59-2.24; p<0.001).

Patients treated with apixaban had a lower incidence of death or hospitalization as compared to those treated with warfarin (23.5% *versus* 27.4%; risk rate of 0.83; 95%CI 0.74-0.93; p=0.002), in addition to a similar incidence of ischemic events.

Patients on aspirin or placebo had a similar incidence of death or hospitalization. However, the incidence of death or ischemic events was numerically lower (6.5%) for aspirin *versus* placebo (7.3%; p=not significant)

The authors concluded that, in patients with AF and recent ACS or undergoing PCI and treated with P2Y₁₂ inhibitors, the use of apixaban without aspirin resulted in less bleeding and hospitalizations, with no significant differences in the incidence of ischemic events compared to those who used warfarin, aspirin or both.

On the one hand, one of the advantages of AUGUSTUS is its 2x2 factorial design, which dissociates the individual contribution of the use of direct anticoagulants and the discontinuation of aspirin therapy with regard to the risk of bleeding. Another advantage was the inclusion of patients with ACS treated clinically without PCI, and at a high ischemic risk.

On the other hand, patients were included, on average, 6 days after ACS/PCI + DES, *i.e.*, the majority received aspirin for a short period of time before randomization. A greater number of coronary ischemic events was observed in patients who did not receive aspirin, although these rates were low (absolute increase of 0.5% for MI and 0.4% for stent thrombosis). The study also lacked statistical power to assess individual differences between the groups and it would be necessary to analyze the profile of patients, the time of occurrence of ischemic events and their relation with aspirin therapy discontinuation – other studies have shown a pattern similar to that of AUGUSTUS.^{26,34} The follow-up time was short (6 months), rendering difficult the assessment of mid- and long-term ischemic events in the group without aspirin. Finally, the sample size was insufficient to detect small and important differences in the occurrence of stent thrombosis and MI.

ENTRUST-AF PCI

Published in 2019, this was a randomized, multicenter, open, non-inferiority study, which included 1,506 patients with AF and indication for oral anticoagulation, who underwent PCI and were allocated to receive edoxaban 60mg daily associated with a P2Y₁₂ inhibitor (clopidogrel 75mg per day), for 12 months, *versus* warfarin + DAPT (aspirin 100mg per day + clopidogrel 75mg per day) for one to 12 months.³⁵ Patients were included in the study within 5 days after the PCI.

Smaller doses of edoxaban were used in the presence of one or more of the following factors: creatinine clearance ranging from 15 to 50mL/minute, weight ≤60kg, or concomitant use of P-glycoprotein inhibitors.

The primary endpoint was major or non-major clinically relevant bleeding at the end of 12 months; the secondary endpoint was cardiovascular death, MI, stroke, systemic embolism or definitive stent thrombosis.

Major or non-major clinically relevant bleeding occurred in 17% in the edoxaban group *versus* 20% in the warfarin group (risk rate of 0.83; 95%CI 0.65-1.05; $p=0.001$ for non-inferiority, and risk rate of 1.20; $p=0.12$ for superiority).

The authors concluded that, in patients with AF undergoing PCI, the use of edoxaban was not inferior to the treatment with warfarin with regard to the occurrence of bleeding and with no significant differences as to cardiovascular deaths, MI, stroke, ischemic embolism, and stent thrombosis (7% *versus* 6%).

META-ANALYSES

After the publication of these five studies comparing TT *versus* DT with direct anticoagulants at different doses and varied combinations with one or two antiplatelet drugs (usually with discontinuing aspirin therapy), meta-analyses and systematic reviews have been conducted to establish common findings, examine any differences and suggest recommendations for clinical practice.

One of them included four randomized studies mentioned here – PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST AF-PCI – with a total of 10,234 patients – in that, 5,496 on DT and 4,738 on TT.³⁶

The primary safety endpoint was the occurrence of major or non-major clinically relevant bleeding (ISTH) between 6 and 14 months. Other bleeding definitions also considered were those of the study itself and TIMI.³⁷ Secondary endpoints included overall and cardiovascular mortality, MACE defined by each study, MI, stroke, and stent thrombosis.

All four studies included patients with AF who underwent PCI. AUGUSTUS also evaluated a group with clinically treated ACS.

The primary safety endpoint (bleeding) was significantly lower in DT (13.4%) *versus* TT (20.8%), with a risk reduction of 0.66, 95%CI 0.56-0.78 and $p<0.0001$ for both types of bleeding (TIMI/ISTH).

DT also reduced intracranial hemorrhage rates by 67% compared to TT: 0.28% *versus* 0.86%, with a risk reduction of 0.33, 95%CI 0.17-0.65 and $p=0.001$.

As for the efficacy endpoints, there were no significant differences between DT and TT with regard to overall death (4.0% *versus* 3.7%; risk reduction of 1.10; 95%CI 0.91-1.34; $p=0.32$), cardiovascular death (2.6% *versus* 2.2%; risk reduction of 1.10; 95%CI 0.86-1.41; $p=0.44$), MACE (8.6% *versus* 8.0%; risk reduction of 1.08; 95%CI 0.95-1.23; $p=0.26$) and stroke (1.1% *versus* 1.1%; risk reduction of 1; 95%CI 0.69-1.45; $p=0.99$).

DT was associated with a marginal increase in MI (3.6% *versus* 3.0%; risk reduction of 1.22; 95%CI 0.99-1.52; $p=0.07$) and a significantly higher risk of stent thrombosis (1.0% *versus* 0.6%; risk reduction of 1.59; 95%CI 1.01-2.50; $p=0.04$) compared to TT with warfarin.

Additional analysis with two doses of dabigatran revealed a higher risk of ischemic events (MI and stent thrombosis) for DT with the lowest dose (110mg) compared to DT with the highest dose (150mg).

The two main findings of this meta-analysis, encompassing the largest randomized studies with direct anticoagulants, are the fact that DT with direct anticoagulant significantly reduces major and clinically relevant bleeding, as well as intracranial hemorrhage *versus* TT, and that DT is associated with similar rates of MACE, overall/cardiovascular death and stroke and increased risk of MI (marginal) and stent thrombosis (significant) compared to TT.

Currently, the prevalence of cerebrovascular or cardiac ischemic events is very low relative to bleeding, and the four studies did not have statistical power to detect clinically significant differences between the two therapeutic strategies, with regard to efficacy (MACE).

Early suspension of aspirin therapy may reveal the importance of inhibition of cyclooxygenase-1 (COX-1) in preventing cardiovascular ischemic events and also insufficient inhibition of P2Y₁₂ receptors by clopidogrel in patients with known changes in the metabolism of this drug. Possibly other P2Y₁₂ inhibitors (ticagrelor or prasugrel) can minimize this risk, without increasing bleeding.^{38,39}

In conclusion, according to this meta-analysis, DT brings clinical benefits, with an undeniable reduction in bleeding, but this implies a small increase in ischemic events, which reinforces the concept of customized treatment. The risk-benefit balance should be considered, particularly in the early discontinuation of aspirin therapy after complex PCI and/or in the presence of ACS.

Another meta-analysis, published by Lopes et al., in 2019, analyzed the safety and efficacy of different antithrombotic therapies in patients with AF + ACS and/or PCI, including WOEST, PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS, with 10,026 patients.⁴⁰

The primary safety endpoint was major bleeding (TIMI), and the secondary safety endpoint included major and minor bleeding (TIMI), bleeding defined by study criteria individually, intracranial hemorrhage and hospitalization.

The primary efficacy endpoint included MACE defined by the studies and their individual components. Four treatments were compared, namely: warfarin + DAPT (TT); warfarin + P2Y₁₂ inhibitor; direct anticoagulant + DAPT, and direct anticoagulant + P2Y₁₂ inhibitor.

Three direct anticoagulants were analyzed: rivaroxaban, dabigatran and apixaban at different doses. The reference treatment was TT (warfarin + DAPT), present in all studies.

When compared to TT, the other three treatments had significantly lower risk rates (RR) for major bleeding (TIMI), being 0.58 (95%CI 0.31-1.08) for warfarin + P2Y₁₂ inhibitor, 0.49 (95%CI 0.30-0.82) for direct anticoagulant + P2Y₁₂ inhibitor, and 0.70 (95%CI 0.38-1.23) for direct anticoagulant + DAPT.

In turn, when compared with TT, the RR for MACE were all similar: 0.96 (95%CI 0.60-1.46) for warfarin + P2Y₁₂ inhibitor, 1.02 (95%CI 0.71-1.47) for direct anticoagulant + P2Y₁₂ inhibitor, and 0.94 (95%CI 0.60-1.45) for direct anticoagulant + DAPT.

Therefore, the best antithrombotic regimen to reduce all bleeding, including intracranial, was the use of direct anticoagulant + P2Y₁₂, with no differences in the occurrence of MACE.

The authors of this meta-analysis suggested TT should be generally avoided in patients with AF undergoing PCI and/or ACS.

Capodanno et al. published, in 2019, an excellent review on oral anticoagulation in patients with AF and associated PCI or ACS, considering important aspects,⁴¹ such as (1) revascularization procedure (assessing the real need for PCI — symptoms *versus* prognosis; preference for radial access — less bleeding; use of second generation DES — less thrombosis; and considering fractional flow reserve in elective cases, avoiding unnecessary procedures; performing pretreatment with clopidogrel, if PCI is decided or is likely (*ad hoc*), and use of periprocedural aspirin, to avoid acute and subacute stent thrombosis and its severe consequences) and (2) an assessment of the risk of ischemic events *versus* bleeding. This stratification is fundamental and must be individualized, because the choice for TT or DT depends on it. It can be qualitative (Chart 1) or quantitative with the use of scores (SYNTAX, GRACE, and HAS-BLED). It is not always easy to balance ischemia *versus* bleeding, since clinical, anatomical and procedural factors must be considered.

Bleeding risk can be assessed by HAS-BLED, and its performance is modest and better compared to two other scores (HEMORR(2)HAGES and ATRIA)⁴⁴ and PRECISE DAPT.⁴³

Choice of antithrombotic therapy and duration

Direct anticoagulants should be preferred over warfarin, because they undoubtedly have lower bleeding rates (class effect). However, warfarin is still the best option in patients with moderate to severe mitral stenosis, in those with metallic prostheses and with CKD (clearance <15mL/minute).

The duration of TT after PCI varies from very short periods (periprocurement only) up to 3 to 6 months, while assessing the thrombotic risk *versus* the risk of bleeding.³

The antiplatelet drug of choice, in most cases, is clopidogrel, since it is effective in preventing stent thrombosis and its consequences (death and MI), and has a better safety profile, with reduced gastrointestinal bleeding, when compared to aspirin.^{44,45}

It is hypothesized the withdrawal of aspirin and the use of only clopidogrel may reveal the variability of the response to this drug, as well as the genetic changes, which make some subgroups resistant to its antiplatelet effect, with increased rates of thrombosis and MI. New P2Y₁₂ inhibitors (prasugrel and ticagrelor) can overcome these limitations, but they are approved only for use in ACS, have greater bleeding potential, and their use in the DT *versus* TT studies was quite limited (2% to 12%), because of the risk of bleeding when combined with direct anticoagulants.^{46,47}

Regarding the doses of direct anticoagulants, some of the studies mentioned here used lower doses when direct anticoagulants were combined with P2Y₁₂ inhibitors. Full doses, approved for the prevention of stroke and systemic embolism in patients with AF, should be resumed after discontinuing P2Y₁₂ inhibitors.

Observational studies have shown, in patients with stable CAD, the isolated use of direct anticoagulants is associated with lower bleeding rates, without increasing ischemic events. However, in the presence of clinical comorbidities and complex coronary anatomy, which predispose to the recurrence of thrombotic events, the maintenance of antiplatelet therapy (aspirin or clopidogrel) may be justified.⁴⁸

Chart 1. High risk characteristics of ischemic events and bleeding.

Criteria for increased risk of ischemic events	Criteria for high risk of bleeding
Previous stent thrombosis in regular use DAPT	Short life expectancy/old age
Stent in last remaining vessel	Bleeding neoplasm
Multivessel, diffuse CAD in diabetics	Poor adherence to treatment
CKD with clearance <60mL/minute	Compromised mental state
≥3 implanted stents	Severe CKD
Bifurcation treatment with 2 stents	Previous major bleeding
Stent length >60mm	Previous hemorrhagic stroke
Treatment of chronic occlusions	Alcoholism/anemia
	Bleeding while on DAPT

Source: adapted from Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al.; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39(3):213-60. <https://doi.org/10.1093/eurheartj/ehx419>. p. 92. Table 2; Criteria of High-Risk Features Tipping the Balance Toward More or Less Intense Antithrombotic Therapy for AF Patients Undergoing PCI.⁴⁴
DAPT: dual antiplatelet therapy; CAD: coronary artery disease; CKD: chronic kidney disease.

WHAT DO THE GUIDELINES RECOMMEND?

2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society

The recommendations of this guideline⁴⁹ regarding the use of TT (oral anticoagulant + aspirin + P2Y₁₂ inhibitor) in patients with AF and risk of stroke (CHA₂DS₂-VASc >2) undergoing PCI + stent by ACS are described in Chart 2.

Chart 2. Recommendations on the use of triple therapy in patients with atrial fibrillation associated with percutaneous coronary intervention after acute coronary syndrome.

Recommendation	Class
Preference for clopidogrel over prasugrel	Ia
DT with P2Y ₁₂ inhibitor (clopidogrel or ticagrelor) and adjusted dose of warfarin to reduce the risk of bleeding	Ia
DT with P2Y ₁₂ inhibitor (clopidogrel) and low dose of rivaroxaban (15 mg/day) to reduce the risk of bleeding	Ia
DT with P2Y ₁₂ inhibitor (clopidogrel) and dabigatran (150mg, twice a day) to reduce the risk of bleeding	Ia
If TT is chosen in patients with AF + PCI with or without drug-eluting stent, with ACS, consider transitioning to DT (oral anticoagulant and P2Y ₁₂ inhibitor) in 4-6 weeks	Ib

DT: dual therapy; TT: triple therapy; AF: atrial fibrillation; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome.

2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio Thoracic Surgery (EACTS)

In this guideline,³ the recommendation for ACS patients is to use triple therapy (aspirin + anticoagulant + P2Y₁₂ inhibitor) for a maximum of one week, after PCI without complications (regardless of the type of stent used), and dual therapy with anticoagulants (direct, whenever possible) + P2Y₁₂ inhibitor (preferably clopidogrel) for up to 12 months in patients at low risk of stent thrombosis, and/or if the risk of bleeding exceeds the ischemic risk (Class IB).

The same therapeutic regimen applies for PCI with no complications in elective patients for up to 6 months (Class IB).

If the risk of stent thrombosis outweighs the risk of bleeding, TT (aspirin + P2Y₁₂ inhibitor + anticoagulant) can be maintained for up to 30 days (Class IIA).

After 1 year in ACS and after 6 months in stable CAD, the anticoagulant monotherapy should be continued, un-

less the patient has recurrent ischemic events during this period.

Direct anticoagulants should be preferred over warfarin whenever possible (Class IA).

If warfarin is used in combination with antiplatelet therapy, the INR should be maintained between 2 and 2.5 (Class IIA).

2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The standard strategy recommended by this guideline⁵⁰ is the use of dual therapy with direct anticoagulants at the recommended doses for prevention of stroke associated with one of the antiplatelet agents, preferably clopidogrel, for up to 12 months, after a short period of TT (aspirin + clopidogrel + direct anticoagulant), usually one week after PCI.

The authors emphasized that, although none of the randomized studies have statistical power to detect small changes in the occurrence of ischemic events, when comparing dual *versus* triple therapy, some of them observed a non-significant increase in the risk of stent thrombosis and MI. Apparently, this risk was counterbalanced by the significant reduction in bleeding, having a neutral effect on the MACE and overall death rates.

The guideline points out that, in patients at high risk of bleeding, the dual therapy can be shortened to 6 months, by suspending the antiplatelet drug and maintaining only the oral anticoagulant. In turn, in patients at high ischemic risk, the triple therapy is given during one month, followed by dual therapy (anticoagulant + P2Y₁₂ inhibitor) for up to 12 months (Figure 1).

CONCLUSION

The choice between triple and dual therapy should be analyzed considering risks and benefits. In general, the dual therapy can be considered as a standard strategy with early discontinuation of aspirin (1 to 2 weeks) in stable patients and non-complex percutaneous coronary intervention. However, the triple therapy can be implemented for variable periods (1 to 6 months), particularly in patients at high ischemic risk, in complex percutaneous coronary interventions, with assessment of the risk of bleeding and, preferably, using direct anticoagulants, because they are safer.

New ongoing research may refine the management of these patients, by analyzing other variations of dual *versus* triple therapy, use of ticagrelor *versus* clopidogrel, and time of use of the dual antiplatelet therapy.

Source: adapted from Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2020 Aug 29;ehaa575. <https://doi.org/10.1093/eurheartj/ehaa575>. p. 32. Figure 8; Algorithm for antithrombotic therapy in non-ST-segment elevation acute coronary syndrome patients with atrial fibrillation undergoing percutaneous coronary intervention or medical management.⁽⁵⁰⁾

AF: atrial fibrillation; PCI: percutaneous coronary intervention; NSTEMI-ACS: non-ST segment elevation acute coronary syndrome; OAC: oral anticoagulation; DAPT: dual antiplatelet therapy.

Figure 1. Anticoagulation regimen in patients with atrial fibrillation and undergoing percutaneous coronary intervention in the presence of non-ST segment elevation acute coronary syndrome (modified from a European guideline for the management of non-ST segment elevation acute coronary syndrome).⁵²

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DECLARATION OF CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: MC; data collection: MC; data interpretation: MC and LFLT; text writing: MC; approval of the final version to be published: MC, LFLT and FF.

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