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CRITICAL ANALYSIS OF STUDIES THAT HAVE CHANGED RECENT CLINICAL PRACTICE: ARRHYTHMIAS

ANÁLISE CRÍTICA DOS ESTUDOS QUE MUDARAM A PRÁTICA CLÍNICA RECENTE: ARRITMIAS

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ABSTRACT

The greatest advances in the treatment of cardiac arrhythmias, which have led to proposals of change and/or the incorporation of new drug or intervention treatment technologies, relate to atrial fibrillation, the most common sustained arrhythmia in medical practice, which is why we have placed more emphasis on it in this analysis. The latest studies to have revised, updated, and offered new perspectives on the principal global guidelines are those that involve comparisons of regimens that combine anticoagulation and antiaggregation of platelets in patients with atrial fibrillation within the context of coronary artery disease with planned or immediate intervention, as well of those that involve a catheter ablation strategy as an option at the beginning of treatment for atrial fibrillation in patients with heart failure with reduced ejection fraction.

Keywords: Arrhythmias, Cardiac; Atrial Fibrillation; Anticoagulants; Catheter Ablation.

RESUMO

Os maiores avanços no tratamento das arritmias cardíacas, que geraram propostas de mudança e/ou incorporação de novas tecnologias de tratamento medicamentoso ou intervencionista, referem-se à fibrilação atrial, arritmia sustentada mais frequente na prática clínica, razão pela qual demos maior ênfase a essa análise. Os últimos estudos que têm proporcionado revisões, atualizações e perspectivas das principais diretrizes mundiais são os que envolvem as comparações dos esquemas de combinações de anticoagulação e antiagregação plaquetária em pacientes com fibrilação atrial no contexto da doença arterial coronariana com intervenção planejada ou imediata, bem como os que envolvem a estratégia de ablação por cateteres com opção no início do tratamento da fibrilação atrial nos pacientes com insuficiência cardíaca com fração de ejeção reduzida.

Descritores: *Arritmias Cardíacas; Fibrilação Atrial; Anticoagulantes; Ablação por Cateter.*

INTRODUCTION

Regarding the theme "Arrhythmias", as in many other areas of Cardiology, several randomized and controlled studies have been published to answer the most controversial questions, whether in clinical intervention, or catheter and implantable device intervention.

In this chapter, due to the greater scope and importance, we chose to contribute to the critical analysis of studies related to the use of new oral anticoagulants in the context of patients with atrial fibrillation (AF) and intervention in coronary artery disease (CAD), as well as in AF ablation. in patients as a first option or when they are already in the heart failure stage with reduced ejection fraction (HFrEF).

I) More recent studies in the context of AF and CAD

Up to 10% of AF patients will require coronary angioplasty at some point in their lives. It is known that after implantation of a coronary stent or acute coronary syndrome (ACS), for a certain period of time, there is a need for the use of Dual Platelet Antiaggregation (DAPT), usually with ASA and another PYP12 inhibitory agent (whether clopidogrel, prasugrel or ticagrelor). While platelet antiaggregation protects against thrombotic phenomena such as acute stent thrombosis and new coronary ischemic events, its efficacy against cerebrovascular accident (CVA) is lower. The reverse observation holds true for oral anticoagulation.

Until recently, and as a recommendation of national[1] and international[2] guidelines, the only recommended combined antiaggregation plus antocoagulation strategy was triple therapy - always including warfarin and excluding new oral anticoagulants (NOACs) - with variable duration of 1-6 months, depending on the type of procedure performed and the thrombotic risk versus the patient's risk of bleeding.

Earlier studies had already explored the feasibility of a less aggressive course of antiaggregant/anticoagulant therapy

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such as ISAR-TRIPLE[3] and WOEST,[4] but these were studies which extrapolation of results ran into methodological and sample size problems. Three recent studies and their respective meta-analyzes,[5-8] however, have contributed to the change in therapeutic recommendations on the subject, especially when analyzing the safety of various therapeutic combinations in this scenario.

The first one, PIONEER AF-PCI[5] (November 2016), with 2,124 patients from various centers worldwide, compared 3 therapy strategies in AF patients undergoing coronary stenting in a 1: 1: 1 randomization: (1) rivaroxaban 15mg (or 10mg if creatinine clearance between 30 and 50) + PYP12 inhibitor for 12 months; (2) rivaroxaban 2.5mg 12/12h + ASA 75-100mg 1xd + PYP12 inhibitor for 1, 6 or 12 months; or (3) warfarin with international standardized ratio (INR) target between 2 and 3 + ASA 75-100mg 1xd + PYP12 inhibitor also for 1, 6 or 12 months. The main endpoint was a safety outcome of clinically significant bleeding (major or minor TIMI or other bleeding requiring medical attention), and the secondary endpoint was major cardiovascular events (consisting of cardiovascular death, infarction, and CVA). The results favored the groups involving rivaroxaban,[5,8] with clinically relevant bleeding incidence of 16.8%, 18% and 26.7%, respectively, for groups 1, 2 and 3; this comparative analysis among them reached statistical significance of superiority. The incidence of major thromboembolic events was 6.5%, 5.6%, and 6.0% for groups 1, 2, and 3, respectively, with confidence intervals across the unit and therefore no significant difference between groups. The same was true for the incidence of stent thrombosis. This study, however, did not have sufficient power to assess this secondary outcome and this finding should therefore be considered as exploratory analysis only.

Possible critical considerations: (1) Off-label rivaroxaban doses lower than those recommended for prevention of thromboembolism were used in patients with AF (this was derived from observations of high bleeding rates at the usual doses in the ATLAS ACS-TIMI 46[6] study).

(2) The group "triple therapy with DAPT for 6 months" had a lower incidence of CVA than the rivaroxaban equivalent group, which may be due to chance, since in the 12-month group this finding was not maintained. (3) Stratification at 1, 6, or 12 months was at the discretion of the clinician and was, therefore, not randomized.

Then, this time with another NOAC, RE-DUAL PCI7 study (August/2017), also a multicenter study involving 2,725 AF patients who underwent coronary angioplasty, randomized the patients to 3 groups: (1) dabigatran 110mg 12/12h + PYP12 inhibitor; (2) dabigatran 150mg 12/12h + PYP12 inhibitor; and (3) warfarin with INR 2-3 target + PYP12 inhibitor + ASA 75-100mg 1xd (which was used for 1 month if conventional stent implantation and 3 months if drug-eluting stent implantation). Patients aged> 80 years outside the USA (or> 70 years in Japan) could not be randomized to group 1 for reasons of agreement with the package insert recommended in these other countries. Average follow-up was 14 months. The primary endpoint of this study was also a clinically relevant major or non-major bleeding safety outcome defined by the International Society on Thrombosis and Haemostasis (ISHT) classification. The main secondary outcome was a composite of thromboembolic events (infarction, stroke or systemic embolism, death or additional unplanned revascularization). The results favored the groups involving dabigatran[7,8], with a primary endpoint incidence of 15.4% x 26.9%, HR 0.52, 95% CI 0.42 to 0.63 (group 1 x group 3) and 20.2% x 25.7% HR 0.72, 95% CI 0.58 to 0.88 (group 2 x group 3), reaching a margin of superiority for the first comparison and not inferiority for the second. Thromboembolic outcomes were equivalent, with an incidence of 13.7% in the dabigatran groups and 13.4% in the triple therapy group, with $p = 0.005$ for noninferiority.

Possible Critical Considerations: (1) Ischemic events rates were numerically higher in the dabigatran 110mg + PYP12 inhibitor group. (2) A regimen of 1 to 3 months of ASA was used, and yet with a significant reduction in hemorrhagic outcome. (3) N of the study was lower than expected, which may have reduced the statistical power.

In the AUGUSTUS[9] study (March/2019), 4,614 patients from 33 countries with AF with indication for anticoagulation and who, for some reason, needed DAPT (either by elective stent implantation or by ACS with or without stent implantation) participated. This is the largest clinical trial so far on the subject. Patients were randomized to a 2×2 factorial and followed for 6 months. This means that we had 4 groups in this work: [apixaban + ASA + PYP12 inhibitor], [apixaban + placebo + PYP12 inhibitor], [warfarin + ASA + PYP12 inhibitor] and [warfarin + placebo + PYP12 inhibitor], being the primary endpoint of the ISHT bleeding study, and the secondary endpoints were a composite of "death + hospitalization" and "death + ischemic event". It is noteworthy that all patients received ASA on the day of ACS or angioplasty and were only allocated to one of these groups after randomization (which was on average 6 days after inclusion in the protocol). Briefly, the results of this study favored the use of apixaban + PYP12 inhibitor alone (clopidogrel for 92.6% of patients) as a safer and not less effective strategy. Compared to warfarin, apixaban reduced by 31% (10.5 x 14.7%, HR 0.69; 95% confidence interval [CI], 0.58-0.81) bleeding events, even reaching the margin of superiority, with no statistically significant difference in relation to ischemic events - including finding lower stroke rates in the apixaban group. ASA, in turn, increased by 89% (16.1% x 9.0%, HR 1.89; 95% CI, 1.59-2.24; $P < 0.001$) the rate of major or minor clinically relevant bleeding, with no statistically significant difference in relation to ischemic outcomes compared with placebo. This study was also the first one designed to point out direct questions regarding the use of ASA as an antiaggregating therapy in the follow-up of these patients.

Possible critical considerations: (1) The incidence of embolic outcomes was numerically lower in the ASA group, leading to the existence of a subgroup of very high-risk thromboembolic patients who may still benefit from medication. (2) The TTR of patients in AUGUSTUS was slightly lower than in the other two studies. (3) Note that the average number of days for randomization was 6.6 and until then, patients probably used ASA.

The latest study with NOACs in this context is ongoing (ENTRUST-AF PCI)[10], and will explore edoxaban's performance in this scenario. Table 1 summarizes the top 3 studies in the context of AF and CAD.

This year's update of the US FA Guideline,[11] which was published before the AUGUSTUS study, makes a new

Table 1. Comparative table of the main randomized clinical trials with NOACs and DAPT.

	PIONEER AF-PCI[5]	RE-DUAL PCI[7]	AUGUSTUS[9]
Base Characteristics			
Total Patients	2,124	2,725	4,614
Publication Year	Nov/2016	Aug/2017	March /2019
Consent withdrawal	0.4%	3.1%	1.3%
Time for randomization	Within 72 hours from the introducer removal, when INR reaches a value lower than 2.5	< 120 hours after angioplasty (study drug should be administered < 6 hours after introducer removal)	Within 14 days from ACS or Angioplasty (average 6.6 days)
Age	~ 70	~ 70	70.7
Female gender	~ 25%	~ 25%	~ 30%
Renal function	ClCr ~ 79	ClCr ~ 80	~ 90% with Cr < 1,5
Permanent AF	34%	18%	-
Persistent AF	20.7%	32%	-
Paroxysmal FA	44%	49%	-
CHADSVASC	26.7% with < 3	Average ~ 3.5	Average ~ 3,9
HASBLED	-	2.7	2.9
Previous VEA/TIA	-	~ 8.5%	~ 13.5% (also includes thromboembolic event)
Heart Failure	-	-	42%
Diabetes *Mellitus*	-	~ 37%	~ 36.5%
Acute Coronary Syndrome	~ 50%	~ 50%	~ 37% angioplasty ~ 23.9% clinical treatment
Conventional Stent	31.7%	24%	-
Drug-eluting stents	66%	83%	-
Clopidogrel	94%	88%	90%
Prasugrel	1,3%	-	1.1%
Ticagrelor	4.3%	12%	6.0%
TTR	65%	64%	59%
Safety endpoints (primary)			
Primary Endpoint	"Greater than clinically-relevant bleeding"	"Bleeding according to ISHT or non-major clinically relevant" Double (dabigatran 110mg) x Triple: HR 0.52 (0.42-0.63) and P for superiority < 0.001	"Bleeding according to ISHT or non-major clinically relevant" Apixaban x warfarin: HR 0.69 (0.58-0.81) and P < 0.001 for superiority
	Groups 1 and 2 x Group 3: HR 0.61 (0,5-0,75) e P < 0,001	Double (dabigatran 150mg) x Triple: HR 0.72 (0.58-0.88) and P for superiority 0.002	ASA x placebo: HR 1.89 (1.59-2.24) and P < 0.001 for superiority
Effectiveness endpoints (secondary)			
Composite effectiveness Endpoint (secondary)	"MACE"	"Thromboembolic event, death or unplanned revascularization"	"Death or hospitalization" (1) and "Death or ischemic event" (2)
	Group 1 x Group 3: HR 1.08 (0.69-1.68) and P 0.75 Group 2 x Group 3: HR 0.93 (0.59-1.48) and P 0.76	Double (110mg e 150mg) x Triple: HR 1.04 (0.84-1.29) and P 0.74	Apixaban x warfarin: (1) HR 0.83 (0.74-0.93) and P 0.002 (2) HR 0.93 (0.75-1.16) and P NS ASA x placebo: (1) HR 1.08 (0.96-1.21) and P NS (2) HR 0.89 (0.71-1.11) and P NT
Death/ Cardiovascular death	Death	Cardiovascular Death	Death
	Group 1 x Group 3: HR 1.29 (0.59-2.80) and P 0.52 Group 2 x Group 3: HR 1.19 (0.54-2.62) and P 0.66	Double (110mg) x Triple: HR 1.12 (0.76-1.65) and P 0.56 Double (150mg) x Triple: HR 0.83 (0.51-1.34) and P 0.44	Apixaban x warfarin: HR 1.03 (0.75-1.42) ASA x placebo: HR 0.91 (0.66-1.26)
Myocardial Infarction	Group 1 x Group 3: HR 0.86 (0.46-1.59) and P 0.62 Group 2 x Group 3: HR 1.75 (0.40-1.42) and P 0.37	Double (110mg) x Triple: HR 1.51 (0.94-2.41) and P 0.09 Double (150mg) x Triple: HR 1.16 (0.66-2.04) and P 0.61	Apixaban x warfarin: HR 0.89 (0.65-1.23) ASA x placebo: HR 0.81 (0.59-1.12)
Stent Thrombosis	Group 1 x Group 3: HR 1.20 (0.32-4.45) and P 0.79 Group 2 x Group 3: HR 1.44 (0.40-5.09) and P 0.57	Double (110mg) x Triple: HR 1.86 (0.79-4.40) and P 0.15 Double (150mg) x Triple: HR 0.99 (0.35-2.81) and P 0.98	Apixaban x warfarin: HR 0.77 (0.39-1.56) ASA x placebo: HR 0.52 (0.25-1.08)
VEA	Group 1 x Group 3: HR 1.07 (0.39-2.96) and P 0.89 Group 2 x Group 3: HR 1.36 (0.52-3.58) and P 0.53	Double (110mg) x Triple: HR 1.30 (0.63-2.67) and P 0.48 Double (150mg) x Triple: HR 1.09 (0.42-2.83) and P 0.85	Apixaban x warfarin: HR 0.50 (0.26-0.97) ASA x placebo: HR 1.06 (0.56-1.98)

AF: Atrial Fibrillation; VEA/TIA: Vascular Encephalic Accident and Transitory Ischemic Attack; TTR: *Time in Therapeutic Range* (Time in the NRR therapeutic time); ISHT: *International Society on Thrombosis and Hemostasis; ~: around.*

recommendation on the subject. In this case, with indication class IIa and B-R level of evidence, based on the results of the WOEST, PIONEER AF-PCI and RE-DUAL PCI studies, and also by retrospective cohort studies with ticagrelor and warfarin, it is recommended the use of double therapy (warfarin + clopidogrel, warfarin + ticagrelor, rivaroxaban 15mg 1xd + clopidogrel and dabigatran 150mg 2xd + clopidogrel) from the outset in patients undergoing coronary angioplasty in the context of ACS.

Thus, it is concluded that, despite some limitations, the above studies provide strong evidence that dual therapy from the outset in the treatment of patients with AF and with indication for PADD seems to be the safest, simplest and safer strategy in the prevention of thromboembolic events.

It is true, however, that some patients are likely to still benefit from a triple therapy period, probably those with a higher thromboembolic risk, but this patient and treatment time are not yet safely defined. The use of ticagrelor and prasugrel (especially the latter) still finds limited evidence, given the poor representation in these studies. Therefore, it is suggested that dual therapy involving rivaroxaban, dabigatran or apixaban, in addition to clopidogrel, should be considered the "standard therapy", however case-by-case individualization is appropriate.

II) More recent studies in the context of AF e HFrEF

Ablation of AF, arrhythmia with high prevalence and morbidity,[12,13] is currently one of the methods used in the rhythm control strategy of this pathology[14,15] It has long been known about its role in symptom control, especially in those patients of paroxysmal or persistent AF, with poor response to antiarrhythmic drugs or with contraindications and side effects to their use. Following this line of reasoning, the older AF Guidelines made it clear that the procedure should be aimed at the therapeutic management of symptomatic patients, as there was insufficient evidence for an indication of "harder" outcomes such as mortality, lower CVA rate and/or hospitalizations. In this sense, the document of the American Heart Association (AHA) and the European Society of Cardiology (ESC), published in 2014 and 2016, respectively, agreed on the good methodological quality for the indication of the procedure in this context.[16,17]

However, with the evolution of AF ablation, including the greater availability of electroanatomic mapping,[18,19] as well as the understanding of the need for pulmonary vein isolation,[20,21] it was thought that new perspectives on its results would be evident. Even in those at higher risk, such as patients with (HFpEF), since inadequate control of this arrhythmia can be deleterious.[22] Although it is well established that rhythm control with drugs is not superior to heart rate control in this population, the effect of ablation had not been adequately tested.[23] The hypothesis of the beneficial effects of the intervention had already been suggested by smaller studies,[24-27] however it was not until 2018 that the well-known New England Journal of Medicine published the CASTLE-AF study. Based on their results, it has been shown that rhythm control may be an option in the management of patients with AF and HFpEF.[28]

CASTLE-AF Study and Possible Critical Considerations: CASTLE-AF, a randomized, controlled, multicenter, open-label clinical trial, tested the hypothesis of superiority of AF ablation procedure (rhythm control) over drug control (rhythm and/or heart rate control), mortality and morbidity rate. For this, primary outcomes were defined as mortality from all causes and hospitalization for decompensated heart failure. It is noteworthy that prior to randomization there was a run-in phase where drug therapy, which alone could change the course of the disease, was optimized according to current recommendations. In addition, all patients underwent implantation of the cardio-defibrillator (ICD) or ICD with the cardiac resynchronization function (CRT) for the purpose of daily monitoring of heart rhythm and eventual treatment of life-threatening ventricular arrhythmias. The strategy chosen could not have been more accurate, by ensuring what is already established as therapy in reducing the mortality of HFpEF in the intervention group and the control group, reducing the chance of performance bias in the group undergoing ablation.

Another interesting aspect of the CASTLE-AF methodology was related to the statistical analysis, since from this information the real power of the study could be obtained. One of the main aspects was to analyze the plausibility of sinus rhythm restoration in reducing mortality and/or hospitalizations in patients with HFrEF already on standard therapy, since the loss of atrial output may be deleterious to these patients.[29,30] However, the CASTLE-AF estimate was to detect a difference of about 30% over these combined primary outcomes. For this difference, 65, 130 and 195 primary outcomes were planned throughout the study, within a sample size of 363 patients. More than half of the patients would be expected to have at least one outcome, which is inconsistent with the current mortality rate (7%) and hospitalization (32%) for HFrEF in outpatients. Not surprisingly, we observed that the incidence of outcomes was not as expected, so the study was discontinued after reaching 133 patients. Therefore, to continue our analysis, we must keep in mind that we are working on a small study that has not achieved an adequate number of outcomes, and this evidence should still be considered as exploratory.[31]

Regarding the results per se: in the characteristics of the sample, it was observed that the selection of patients was consistent with the study proposal, mostly patients in functional class (NYHA) II/III, with an average ejection fraction of 32%, with a small majority of non-ischemic patients. Approximately 60% of these patients had already failed antiarrhythmic drugs or had significant side effects, and 70% had persistent AF. Of the 179 patients assigned to interventional treatment, 84.4% underwent ablation and of these, 24.5% needed to undergo a new procedure. Of the drug group, composed of 184 patients, 9.8% underwent ablation during the study. It is interesting to note that this did not violate the study, since the analysis was made by intention to treat. Regarding primary outcomes, a lower incidence was observed in the intervention group (28.5%) compared to the control group (44.6%) - HR 0.62 (0.43 - 0.87). When looking at a combined outcome, one should consider whether the benefit was achieved by any of the components individually, leading to the total benefit on account of one of the components, however this is not what we observed when analyzing the mortality and hospitalization curves separately. Therefore, if we consider only this simple analysis, we consider that ablation reduces the incidence of primary outcome in this population by 38%.

Before moving on to the new recommendations of the Guidelines on the subject, we will recap what we have analyzed throughout our reasoning. Because it is an early-interrupted, small, low-outcome, open-ended study, CASTLE-AF cannot be interpreted as definitive evidence of the superiority of rhythm control by ablation vs. drug control in patients with AF and HFrEF. Because it is open, it is not possible to guarantee that there was no greater attention to the treatment of patients in the intervention group (performance bias), which is a confounding factor, since optimized therapy, added to cardiac devices, reduces mortality and leads to improvement in patients with HFrEF. In addition, the power of the study was compromised by stopping early recruitment with a low number of outcomes.

Approximately one year after the publication of CASTLE--AF, the new AHA AF guideline was published (2019)[32] In this new publication, AF ablation was included in HFrEF patients with the intention of reducing mortality and hospitalization for decompensated heart failure. Despite the new recommendation, they are clear about the limitations of the study, with indication IIb class and B-R evidence level. In interpreting this new recommendation, when taking the approach to clinical practice, we must consider that we are facing a still limited indication class, generated by one (1) study of moderate quality of evidence. In analyzing the main limitations on the subject in the Guideline, we note that our mental process of study interpretation is in line with AHA interpretation.

Despite the interest in the treatment of AF, especially in those patients at higher risk, it is not possible to say that the rhythm control strategy is capable of reducing larger outcomes. However, after the exploratory outcome of CASTLE-AF, new publications may perhaps show the real role of AF ablation in patients with HFrEF. It is important to stress that these patient profiles require that the ablation technique be performed in experienced centers with great ability to manage possible immediate complications and with high reproducibility among the other equivalent centers. CABANA Study and Possible Critical Considerations: CABANA study recently tested the hypothesis and superiority of reduced (all-cause) mortality from AF ablation as the first choice of treatment compared to drug control (rhythm or heart rate control) in patients without heart failure.[33] Despite the great expectation cast on its results, CABANA study was extended longer than expected and the outcome of the primary endpoint was similar to the control group. Does this mean that AF ablation does not reduce mortality? Not necessarily, as this was an undersized study. Despite the initial planning of 3,000 patients, with an estimated 12% mortality in the control group and 30% reduction in events in the intervention group, a sufficient number of outcomes was not observed throughout the study. As a result, the secondary outcome (death, "disabling" CVA, major bleeding, and/or cardiac arrest) was elevated to primary outcome. Therefore, in these 2 points (protocol violation and low number of outcomes), we can already say that whatever the study result, we cannot guarantee its veracity. An interesting reflection is on the estimated 12% death in the control group; Since we are dealing with a patient on anticoagulation with medications that control HR: would ablation for sinus rhythm restoration be so effective as to lead to a reduction in mortality of this magnitude? CABANA was published as early as 2019 and therefore there has not yet been time to incorporate its findings into the main Guidelines. On the other hand, issues such as reduced hospitalizations and recurrences had better outcomes in the ablation group as secondary outcomes. We should be aware of the upcoming guidelines and whether there will be changes after the outcome of this study, but the trend is toward class I indication level, taking into account patient preference and the expertise and experience of the electrophysiology center.

In conclusion, the major advances in the incorporation of treatment strategies in the area of cardiac arrhythmias are related to the management of the most frequent sustained arrhythmia in clinical practice, AF, both in terms of clinical management with new oral anticoagulants in the context of CAD, and in the intervention aspect of catheter ablation in HFrEF and as a first option in patients with AF without HF. All of these studies have some treatment bias or proposed statistical power, but point to the inexorable evolution towards better treatment and understanding of the pathophysiological aspects of this complex and fascinating cardiac arrhythmia.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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