New antithrombotics and clinical decision

Oral anticoagulation with dicoumarinics in patients with chronic atrial fibrillation is based on solid scientific evidences. In the meta-analysis of trials that assessed oral anticoagulation (OAC) with acenocoumarol or warfarin in comparison with placebo, the reduction of embolic events was notable: 64% with a confidence interval from 51% to 74%, (1) unusually high percentage with regard to any other intervention in cardiology.

OAC in atrial fibrillation reduces 2.7 events every 100 patients treated per year in primary prevention and 8.5 events every 100 patients/year in secondary prevention after an embolic accident. All this expressed in an absolute way.

However, OAC has multiple limitations and problems in the clinical practice:
1. It requires frequent controls, with the aim of keeping an INR between 2 and 3.
2. Levels < 2 are associated to high risk of embolisms and levels > 3, with high risk of hemorrhages.
3. The incidence of major hemorrhages is from 1.5 to 2% per year and it also increases the incidence of its more severe complication: intracranial hemorrhage.
4. Many patients and doctors do not use OAC to avoid frequent controls and bleeding risk.
5. Its effect is modified by an important number of drugs and food.

For the individual decision, risk of embolisms with the risk of hemorrhages is balanced. (2) In the practice, this may be assessed with CHADS and HAS-BLED scores. (3, 4) CHADS score gives 1 point for the history of congestive heart failure, hypertension, ≥ 75 years of age and diabetes, and 2 points for the history of ischemic cerebrovascular accident or systemic embolism. According to guidelines, patients with 1 or more points in the score should be treated with OAC.

HAS-BLED score has a maximum of 9 points and it gives 1 point for each of the following: non-controlled hypertension > 160 mm Hg, previous CVA, ≥ 65 years of age, kidney dysfunction, hepatic dysfunction, use of antiplatelet drugs or NSAIDS, history of bleeding, alcohol abuse and labile INR control.

In figure 1, the embolic risk according to CHADS score and the hemorrhagic risk according to HAS-BLED score are represented.

In an Argentine register of atrial fibrillation, (5) in 840 patients with an average age of 71 (85% of them with cardiovascular disease), the rate of OAC use was 48.5%. Excluding patients with contraindications, the rate was raised up to 57.6% and it was lower in older and female patients and also in patients with minor economic resources and social limitations. This register was performed by cardiologists in inpatients and outpatients. In patients’ reports in primary health care in the United States, the percentage of OAC indication in chronic atrial fibrillation was 35%. (6)

Despite these limitations, OAC is undoubtedly one of the therapeutics with major clinical impact and it has been supported during 60 years resisting with advantage comparative studies with different agents, among them the combination aspirin-clopidogrel which was inferior in its effectiveness with a similar incidence of hemorrhages. (7)

In the last two years, three randomized controlled trials of large dimensions with new antithrombotics, which have been compared with warfarin with a non-inferiority design, have been well-known with surprising beneficial results. (8-10)
The objective of this letter is to check the information of these three trials and to try to put, in a clinical perspective, the modification of the practice that will induce in the next years and the precautions their use.

**NON-INFERIORITY DESIGN OF TRIALS**

The classical design of intervention trials compares a new treatment against placebo or other previous treatment, with the hypothesis of showing advantages in terms of the so-called final points, that is, relevant clinical problems: mortality, morbidity, admissions and complications.

In many scenes of cardiovascular pathology, as the case of chronic atrial fibrillation, there are treatments consolidated in its benefit and the comparison against placebo in treatable patients is not ethical. New treatments may be compared to the previous ones with a classical design, in search for advantages in terms of the main final points, or with a design named of non-inferiority (equivalence). (11)

In non-inferiority trials, the new intervention would have a similar effect over the main event. The justification for the study is that since there is equality, other aspects would be profitable and they would justify its future use: convenient ways of administration, minor collateral effects or risk of complications.

Two key aspects for the design of these trials are the appropriate selection of the non-inferiority margin and the so-called proof of effect of the active control.

**Non-inferiority margin**

The hypothesis is that the treatment would be similar in its central effect to the previous one. In the case of new antithrombotics, the main assessed event is cerebral or systemic embolism. If the incidence of the main event is the same in both groups, the relative risk would be 1. To establish up to what level the margin of error or the confidence interval would be considered acceptable is complex.

This level is not arbitrary; it rises from a basic concept: when we compare a new treatment with a previous one, we do not know if the new treatment is superior to placebo. The effectiveness of the new treatment against placebo is established through a “mediator”, the old treatment named active control. If the result of the study is a $RR = 1$, but the confidence interval exceeds the benefit regarding placebo, we do not know if the new drug is better than the placebo.

Let us consider for an example, an absolute non-inferiority margin. For instance, let us suppose that an intervention reduced 2 events every 100 treated patients, with a CI from 1.5 to 2.5. In a design of non-inferiority, we could compare it with a new intervention and the incidence of events would be similar in both. In this case, the RR would be 1 and, expressed in absolute terms, the reduction of the absolute risk would be 0. If an absolute non-inferiority margin is 3, that is, the final result could be $ARR = 0$ (CI -3 to 3), we are accepting that the effect covers the risk with placebo, since the previous drug reduced the events only in 2 cases. The non-inferiority margin as minimum is established to preserve, if the worst comes to the worst, half of the effect of the previous study. In this example, we should establish the value of 1 event every 100 as a non-inferiority margin. The possible result would be an $ARR = 0$ (-1 to +1). We would preserve half of the effect that was 2 less events every 100. In order to achieve close confidence intervals, we should exponentially raise the number of patients.

The topic is a bit more complex in relative terms. Let us suppose that the study result is $RR = 1$ (CI 0.52). The new treatment had the same incidence of complications, but we do not know if the event is reduced to half or it may double the event. With this margin of error, we could not state that the new drug is non-inferior.

Usual studies in cardiology (12, 13) used non-inferiority margins of 1.15 – 1.20, so the CI could not exceed this value in its superior limit or, expressed in colloquial terms, if the worst comes to the worst, it could not result more than a 15% or 20% worst than the previous intervention.

In studies with antithrombotics, a non-inferiority margin of 1.42 to 1.46 in different trials was selected; new interventions would be associated, if the worst comes to the worst, to a 41% to 46% of increment of the event with regard to dicoumarinics would be accepted as a limit. (Figure 2).

Let us remember that the meta-analysis of OAC had shown a RR = 0.36 (0.74 – 0.51), so if the worst comes to the worst, this meta-analysis reduced to a 49% the incidence of events with regard to placebo. If we apply the established margin of 1.46 to 0.51 (that is, 46% worst), the result is 0.75. This 0.75 projected to placebo would involve that, if the worst comes to the worst, the new drug would reduce a 25% the risk or, expressed in other terms, it would maintain half of the worst effect of OAC that was a reduction of 49%.

This selection is debatable, but in the trials that we will discuss all the aforementioned is not relevant due to the effects of the new drugs were very beneficial. The superior limit of the confidence interval was far from 1.42 or 1.46 in the three cases that are summarized in table 1.

**Evidence of the effect of the active control**

Non-inferiority studies compare a new intervention against a consolidated one in its benefit which is made up as active control. In the new trial the active control is used in such a way that its original effectiveness is maintained. This is a basic requirement.

In the case of OAC, TTR was established as a parameter of appropriate use; the time that treated patients are maintained with an INR between 2 and 3 expressed in percentage terms. In original studies,
this percentage was 64%. The RE-LY study and the ARISTOTLE maintained that TTR, while the ROCKET study informed an inferior value (55%) which lead to intense debates about involvements of this finding that we will discuss later. To reach the non-inferiority against an active control, very decreased in its effect, (due to low dose, etc) does not guarantee the benefit of the new drug with regard to placebo.

After this methodological introduction, I will summarize the results from these three trials that will be discussed then.

**SUMMARY OF CONTROLLED TRIALS WITH NEW ANTIHROMBOTICS**

RE-LY study (7): dabigatran versus warfarin in patients with atrial fibrillation

This study included 18,113 patients that were assigned randomly to three treatments: dabigatran in a low dose of 110 mg every 12 hours, dabigatran in a high dose of 150 mg every 12 hours and warfarin with the aim of maintaining the INR between 2 and 3. The study was opened for the treatments, but the interpretation of events was established blindly. With a non-inferiority design and an established margin of relative risk = 1.46. Inclusion criteria were atrial fibrillation with...
embolisms or previous CVA or, additionally, risk factors for embolisms: advanced age, heart failure or low ejection fraction, diabetes, hypertension and coronary artery disease. The average age was 71.5 years and the average CHADS was 2.1. The TTR, that is, the time with appropriate INR was 64%, similar to historical trials.

The main final point was the rate of CVA of any type or systemic embolism. Its incidence was 1.7% per year for the group treated with warfarin, 1.5% with dabigatran 110 mg [RR 0.91 (CI 0.74-1.11)] and 1.1% with dabigatran in a high dose [RR 0.66 (CI 0.53-0.82)]. Both doses showed non-inferiority, far from the established margin of 1.46 and the high dose could require superiority, with a reduction of 34% of the main final point with regard to warfarin. The incidence of intracranial hemorrhage was reduced with a low dose [RR 0.3 (CI 0.17 to 0.56)] and a high dose of dabigatran [RR 0.26 (0.14-0.49)] with regard to warfarin.

The incidence of bleedings had a more complex behavior: the incidence of total bleedings with dabigatran in a low dose was reduced, both doses were associated to a minor risk of major bleeding with life risk defined by the need of transfusing 4 units and the incidence of gastrointestinal bleeding increased 50% [RR 1.5 (1.2-1.9)] with a high dose of dabigatran, in all cases with regard to warfarin.

There was a tendency towards a minor mortality with dabigatran: the annual rate was 4.1% with warfarin, 3.8% with a low dose [RR 0.91(1.8-1.03)] and 3.6% with a high dose [RR 0.88 (0.77-1)].

The permanent suspension of the drug was greater with dabigatran and dyspepsia as a cause was 12% with dabigatran in a similar way for both doses versus 6% with warfarin. An unexplained finding was the increase of the incidence of myocardial infarction: 38% (0-91%) with a high dose and 35% (-2 to 87%) with a low dose which was not observed with other agents.

Briefly: a) dabigatran in a low dose was non-inferior in terms of CVA or embolisms and it had a minor and major total bleeding, and b) the high dose was superior to warfarin in the prevention of CVA or embolisms, with major gastrointestinal bleeding. Both were associated to minor intracranial hemorrhage.

ARISTOTLE study (8): apixaban versus warfarin in patients with atrial fibrillation

This study included 18.201 patients with inclusion criteria similar to the RE-LY study ones. Patients received apixaban 5 mg twice a day in a blind and double-masked experiment versus warfarin to reach an INR between 2 and 3. A non-inferiority margin of 1.42 was established. The average age was 70 years and the average CHADS was 2.1. The reached TTR was 62%. The annual incidence of the main final point, CVA or peripheral embolisms was 1.6% with warfarin and 1.27% with apixaban [RR 0.79 (0.66-0.95), that is, superior with the new treatment. The annual incidence of hemorrhagic CVA was 0.47% with warfarin and 0.24% with apixaban [RR 0.51 (0.35-0.75)]. Mortality was 3.94% per year with warfarin and 3.52% with apixaban [RR 0.89 (CI 0.81-0.98)]. The incidence of major bleeding was 3.09% with warfarin versus 2.13% per year with apixaban [RR 0.69 (0.6-0.8)] and the total bleeding was reduced, and the major bleeding was defined with the GUSTO and TIMI bleeding criteria. Gastrointestinal bleeding was 0.86% with warfarin and 0.76% per year with apixaban, with a tendency to non-significant reduction.

In short, apixaban was superior to warfarin in the prevention of CVA and embolisms with a minor rate of global and major bleeding, and mortality reduction.

ROCKET study (9): rivaroxaban versus warfarin in patients with atrial fibrillation

The study included 14.264 patients in a blind experiment. Rivaroxaban was administered in a dose of 20 mg once a day with adjustments according to creatinine values and warfarin, in appropriate doses to reach an INR between 2 and 3. Rivaroxaban was indicated in a daily dose, since the half-life of the drug is similar to dabigatran, and in a recent trial in myocardial infarction, rivaroxaban was administered in two daily doses. (14) Inclusion criteria were CVA or embolism background and two or more risk criteria, and an average CHADS score of 3.45.

The discussion about the validity of this design exceeds the limits of this letter, but I will only use results by intention to treat analysis. The TTR was only 55%, under the historical value of 64% and from data obtained in the RE-LY and ARISTOTLE trials. The incidence of the main final point was 2.42% per year with warfarin and 2.12% with rivaroxaban [RR 0.88 (0.74-1.03)], confirming non-inferiority and close to significance due to superiority criteria.

In the analysis by protocol (no intention to treat), rivaroxaban was superior to warfarin. In the comparison with other events, the rates of myocardial infarction, peripheral embolism and ischemic CVA were almost the same with rivaroxaban or warfarin. Mortality was 4.91% per year with warfarin versus 4.52% per year with rivaroxaban [RR 0.92 (0.82-1.03)]. The rate of major bleedings was similar in both groups, with some heterogeneous behaviors: major bleedings with need of transfusion 2 units was high with rivaroxaban 1.65% versus 1.32% per year with rivaroxaban [RR 0.92 (0.82-1.03)], but they reduced lethal bleeding and intracranial hemorrhage: 0.74% per year with warfarin versus 0.49% per year with rivaroxaban [RR 0.67 (0.47-0.94)].

In short, rivaroxaban was non-inferior to warfarin in the prevention of CVA or peripheral embolism, without reaching superiority in the intention to treat analysis. The incidence of major bleeding was similar with advantages for rivaroxaban in the incidence of intracranial hemorrhage.
EVOLUTION OF DRUGS, APPROVAL CYCLE AND INITIAL EXPERIENCES

Dabigatran was approved unanimously at the end of the year 2010 by the Food and Drug Administration (FDA) from the United States for its use in atrial fibrillation, under the name Pradaxa, but only the high dose. It was also approved in the European Community. A postmarketing control has been requested to the pharmaceutical company. In the last months, the European Medicines Agency has shared in the need of reminding doctors the importance of the periodic control of creatinine levels, and different communities, such as the Australian and Japanese ones, have decided to reinforce the precaution to the users about bleeding risks. (15-17) A detail in particular is relevant for the practical use: when the transition from dicoumarinics to dabigatran takes place, there should be many days on hold to reduce the previous effect, if not the possibility of bleeding increases a lot. There exist 50 deaths associated to the use of dabigatran which probably reflect the low incidence of severe bleeding considering a number (470.000) of usual consumers of the drug, according to pharmaceutical industry sources. In the United States, 71 deaths per year in the last 14 years with warfarin were estimated which may constitute a base for the comparison with new antithrombotics in the future if their consumption is massive. (18)

NICE guidelines from Great Britain, elaborated by a group of professionals of different specialties with community participation, are usually more conservative than guidelines generated by specialists involved in trials and with connection to the industry. In the case of dabigatran, it is recommended “as an option” in this context for patients with inclusion criteria similar to the ones in the RE-LY trial. (19) The cost increase per QALY year is 10.000 dollars for a high dose and 30.000 dollars for a low dose. QALY is a concept that associates life year with quality of life, in such a way that the prevention of a disabling CVA is similar to the prevention of death.

Rivaroxaban was approved in November 2011 by the FDA. The advisory committee recommended it before the aforementioned approval with a divided vote, 9 in favor and 2 against. The history of this drug has been more traumatic and controversial:

a) The publication of the trial was delayed almost one year, when the usual is its spreading the same day, as it has been the case of dabigatran and apixaban. This reflects the complexity of the analysis of the results.

b) The doubtful decision to put in second order the intention to treat analysis and prefer results on treatment or on protocol. These studies of large dimensions are by definition pragmatic, that is, they should reflect the complexity of the drug’s use in the clinical practice and not the best result in patients that take it appropriately.

c) The complex finding of an abrupt increase of the number of CVA in the month after the withdrawal of rivaroxaban at the end of the trial: 22 episodes against 7 in the group that took warfarin. This was initially interpreted as a rebound effect, but meticulous analyses showed that it was the expected rate in patients that were without anticoagulant effect during some days.

d) The need of analyzing meticulously the low control level of the achieved INR in this study, 55% below the 64% of the historical meta-analysis and other present trials. This topic is crucial in non-inferiority trials: rivaroxaban would be non-inferior to warfarin that was badly used, which minimizes conclusions. In the analysis from FDA files, Robert Califf showed in elegant terms that this level had no impact in trial results, through multiple comparisons by quartile of INR levels, institutions, regions, etc. (20)

e) A day before the approval of the drug by the FDA, some staff members were opposed to the approval. For the drug defense, extensive expositions and comparative analyses were needed. The profusion of information presented to the FDA multiplies which is available in the reading of the published trial.

f) After the divided recommendation from the FDA committee, a NGO named Public Citizen started a public campaign to avoid the approval with arguments based on trial weaknesses. (21)

The advantage of the use in a single dose seems to be the most important strength of this drug.

We do not have information about its use in the clinical practice since it was approved a few weeks ago.

Apixaban was not approved for its use due to recent trial results, but the community impression is that the study obtained unbeatable results.

JOINT ANALYSIS

In Figures 3 and 4, I have illustrated the individual and global impact of trials over a series of events with clinical value with the meta-analysis technique. This analysis should not be considered as a definite one and it has multiple limitations: it is based on published harsh data and it considers the results of dabigatran in a high dose and in a low dose as two independent trials when actually both are compared with an only group treated with warfarin.

Accepting limitations, the use of this exploration is to reflect the degree of homogeneity and consistency among the effects of different drugs or doses about the results and their quantitative assessment.

When coming to the conclusion from a meta-analysis, statistical heterogeneity and inconsistency I² are relevant data: if the result is homogeneous and with low inconsistency, it indicates us that we may take the result of the meta-analysis as a class effect of this type of drugs. On the contrary, if we detect heterogeneity and inconsistency, the meta-analysis
does not help us and we should consider each drug or dose individually. (22)

The impact over the main final point CVA or embolism was RR = 0.82 (0.75-0.90), the proof of heterogeneity was not significant and inconsistency I² was 45%, low (Figure 3.a). In previous studies with warfarin, in similar patients, the absolute reduction of the same event, CVA or systemic embolism, was quantitatively very high: 2.7 less episodes per year. The additional contribution of antithrombotics does

Fig. 3. Graph with the meta-analysis technique of new antithrombotic effects over the incidence of CVA or embolism (a), ischemic CVA (a.1) and hemorrhagic CVA (a.2). A bar chart, which expresses the annual incidence of CVA or embolism in each treatment group and the annual absolute difference between both of them, is added. For a more detailed explanation, see the text.

Fig. 4. Graph with the meta-analysis technique of new antithrombotic effects over the incidence of death (b.1), major bleeding (b.2) and gastrointestinal bleeding (b.3). Each case is accompanied by a bar chart which expresses the annual incidence of the event in each treatment group and the annual absolute difference between both of them. For a more detailed explanation, see the text.
not exceed 0.3 episodes in average and only with dabigatran in a high dose, that contribution reaches 0.6 episodes per year. This is useful to put the treatment into perspective: the absolute contribution of the benefit is quantitatively small. In the same Figure, an important piece of information is observed (a.1): as a whole, drugs were not beneficial in the prevention of ischemic CVA [RR 0.95 (0.85-1.06)], but with statistical heterogeneity at the expense of the result with dabigatran in a high dose. In this case, the inconsistency was high, 87%. The major impact was over the hemorrhagic CVA (Figure 3, a.2) [RR 0.45 (0.37-0.53)], without heterogeneity and with moderate inconsistency, 56%. In quantitative terms, the reduction was 0.3 episodes in average per year every 100 treated patients, with a peak of 0.47 with apixaban and the lowest, 0.2 with rivaroxaban.

As we are talking about non-inferiority studies, the tendency to mortality reduction was important [RR 0.91 (0.86-0.96)] (Figure 4, b.1) which was homogeneous between studies and doses and with no inconsistency (0%). In quantitative terms; however, this reduction was small, 0.4 deaths every 100 patients treated per year.

One of the major advantages observed among trials was the reduction in major bleeding [RR 0.83 (0.78-0.88)] (Figure 4, b.2). This result was heterogeneous (p < 0.001) and with high inconsistency, 88%. Dabigatran in a high dose and rivaroxaban do not reduce the major bleeding as, whereas, dabigatran in a low dose and apixaban do it. This may be observed in the graphic.

The behavior of gastrointestinal bleeding was opposite: as a whole, drugs increase this complication [RR 1.25 (1.12-1.4)] (Figure 4, b.3), heterogeneous effect (p <0.005) and with high inconsistency, 87%. Dabigatran in a high dose as rivaroxaban are associated to an important increase of digestive hemorrhages; this does not happen with dabigatran in a low dose and apixaban. This is shown in the graphic.

**PROJECTION OF THESE RESULTS IN THE CLINICAL PRACTICE**

A through reading of trials and FDA debates for the approval of dabigatran and rivaroxaban and the intention to project them towards the clinical decision have given us several learnings.

We may not consider the obtaining of data from published trials as evidence-based medicine, since a lot of information is omitted or presented in a confused way. This is then clarified in debate records for the drug approval. To give an example, the basis of dabigatran approval included 200 pages of information about RE-LY study. Likewise, the relevance analysis of the relatively low level control of the INR in the ROCKET study required months of work and access to the database which is inaccessible for journals and doctors that are not involved in the research. In this sense, Richard Smith’s advice, which says that laboratories and research groups publish clinical trials with complete data in their own sites and that scientific journals are devoted to assess and criticize them with access to their databases, acquires important relevance. (23)

This situation would be more clear and reliable for readers.

The second learning was the internal debate in order to assume a conviction: do these results represent a revolution in the treatment of the pathology or a little advance?

There are reasons for both:

- **In favor:**
  - They are the first drugs that overcame dicoumarins in the prevention of embolisms with minor bleeding. They were superior in terms of mortality, reduction of cerebral hemorrhages, CVA and major bleedings.
  - They do not require coagulation controls, one of the obstacles that limits the access of this medication to sectors with less resources or control systems, or simply to patients that do not want to receive them in those conditions.
  - Against:
    - a) The quantitative impact is small.
    - Although results are significant due to giant proportions of trials, we should assess them in terms of their clinical relevance: the reduction of the main event of CVA or embolism is 0.5 events every 100 patients treated per year, mortality (0.4) and intracranial hemorrhage (0.3). As I mentioned before, the quantitative contribution of reduction of events of CVA was 2.7 every 100 patients treated with OAC as regards placebo, with an additional reduction of 0.3 or 0.4 with new agents. This is not trivial, since advantages may be sensitive to small modifications in their use in the real world with regard to the scene of clinical trials.
    - b) Short mean lifetime and sensitivity of the result at fulfillment level.

The requirement for drugs and doses was more effect the treatment more vulnerable to the non-fulfillment than warfarin. In this sense, data from CVA when stopping rivaroxaban have been didactic: in the transition into dicoumarins, a marked increase was observed, due to the short mean lifetime of these drugs. In other terms, new antithrombotics lose their protection 24 hours after their suspension. In this sense, the duplication reference of the incidence of dyspepsia with dabigatran as regards dicoumarins, a symptom that leads to the temporary suspension by patients’ decision, acquires relevance.

In a thinking exercise, if we consider an annual rate with no anticoagulation = 8.5% for patients with CHADS ≥ 3, we may estimate that the incidence is 0.02% per day without medication. Let us suppose that two days per month patients do not take the medication; that is, 24 days per year. This would not have relevance with dicoumarins, since their action...
is prolonged, but it would have relevance with new drugs: with 24 days per year multiplied by 0.02, the number of events would rise in 0.48, so the benefit over the main final point disappears. The adherence rate to drugs, which do not require controls, is low and in the PURE study, in patients with chronic coronary artery disease in countries with moderate incomes, half of the patients do not take the recommended drugs. (24)
c) High cost.
These drugs do not represent a solution for sectors of low resources without access to controls, since their cost is high.
d) The problem of gastrointestinal bleedings.
These drugs are associated with increase of gastrointestinal bleedings (Figure 4). In general, doctors perceive the global message of these drugs, “minor bleeding risk”. We should take into account that patients with history of bleeding with warfarin were excluded of these protocols and they are little represented in results.
e) Lack of antidotes.
With warfarin-acenocoumarol we may antagonize, in hours, the effect with vitamin K and when facing emergencies with the transfusion of prothrombin complex factors. There are few references in the bibliography about antidotes for these new antithrombotics. In a recent publication, the administration of prothrombin complex was effective to normalize parameters in patients treated with rivaroxaban. (25)
These concepts are summarized in table 2.

SOME PRACTICAL ASPECTS FOR THEIR CLINICAL USE

Over the base of the major rate of bleedings in the first days of transition from OAC to dabigatran and the major CVA rate in the transition from rivaroxaban to OAC, we may deduce two general rules:
a) If we want to pass from OAC to antithrombotics, warfarin or acenocoumarol suspension during two or three days is convenient. This may be shortened or extended according to the risk of CVA versus the risk of hemorrhages in the individual patient.
b) If we want to suspend the antithrombotic agent and pass to OAC; when the risk of CVA is high, the first days we should superimpose with heparin of low molecular weight similar to anticoagulation in venous thromboembolism.
In all cases, we should insist in the rigorous fulfillment of the daily doses and over the immediate risks about their suspension. This should be talked to patients at the moment of the initial selection of the treatment strategy.

CONCLUSIONS

Results from trials with new antithrombotics have opened the door to a change in the way of managing the prevention of embolic accidents in patients with chronic atrial fibrillation, with advantages against dicoumarinics after five decades of absolute hegemony. We are still in an initial period of community assessment about the effectiveness of these drugs in the real world of the clinical practice.
The fact that these drugs facilitate the control of patients with difficulties for the INR assessment is very hard due to cost reasons.
In patients that have good performance of dicoumarinics drugs, the advantage of their change to these new drugs is reduced and we should talk individually with each patient.
These drugs are an ideal alternative in patients that do not want to carry out controls or with unstable response to dicoumarinics,
All the observed advantages in trials may be vanished with small degrees of non-fulfillment of the medication, so that the decision of their use should include an appropriate discussion with patients and their families about their virtues and limitations and the critical importance of adherence, as well as attitudes when facing the detection of bleedings.

Table 2. Advantages and disadvantages of new antithrombotics

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<tr>
<th>Advantages</th>
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<tr>
<td>Significant reduction of embolic and mortality events</td>
<td>Reduced benefit in quantitative terms and sensitive to adherence level</td>
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<td>Reduction of major bleedings</td>
<td>Dyspepsia and gastrointestinal bleeding increase.</td>
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<td>Reduction of intracranial hemorrhages</td>
<td>Lack of antidote</td>
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<td>They do not require INR control</td>
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<td>Short mean lifetime and quick cessation of the effect</td>
<td>They require serialized measurements of creatinine</td>
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<td>Vulnerability when doses are not respected</td>
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BIBLIOGRAPHY


## APPENDIX

Table with incidence of individual events in studies and their relative risks

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<thead>
<tr>
<th>Event</th>
<th>RELY study Dabigatran</th>
<th>ARISTOTLE study</th>
<th>ROCKET study Rivaroxaban Data (intent to treat)</th>
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