It is Time to Replace Dicumarinics

Agonist

Vitamin K antagonists (acenocumarol and warfarin) have shown their ability to prevent atrial fibrillation (AF) systemic embolism (1, 2), reducing stroke rate by approximately 68% and mortality by 25%, and are among the drugs with the best cost-effectiveness profile.

Nobody doubts the efficacy of these agents; however, they have a series of limitations (3):
- The need for systematic laboratory monitoring
- Frequent pharmacological and dietary interactions.
- Slow therapeutic effect onset and offset.

Due to these limitations, their implementation ratio in clinical practice is far from an ideal percentage.

Bearing in mind these limitations and the numerous potential clinical applications of a new therapeutic class of agents, it seems reasonable to analyze their effect in prophylaxis and treatment of venous thromboembolism (VTE), AF and eventually acute ischemic syndromes. The research focused on two sites of the plasmatic coagulation cascade: thrombin and X factor.

Overall, these agents have the advantage of a fixed dosage, no laboratory monitoring, scarce or no interaction with drugs or diet, and faster antithrombotic onset and offset, (4) which are very attractive and novel benefits for our therapeutic aims.

The following agents are clinically used or in the course of clinical trials for the prevention of AF thromboembolism:
- Thrombin inhibitors: ximelagatran (discontinued due to hepatotoxicity), AZD 0837 (experimental agent which has not yet progressed to phase 2) and dabigatran, the first agent used in clinical practice.
- X factor inhibitors: apixaban (in approval phase by the FDA and EMEA), rivaroxaban (recently approved by the FDA and EMEA), edoxaban (in a clinical trial which has concluded enrollment) and betrixaban.

Tables 1 and 2 summarize clinical trial pharmacological profiles and differences in design.

In addition to efficacy and safety, better drugs need to be cost-effective, particularly in countries such as ours, with so many economical limitations, and hence costs considerations cannot be disregarded in our decision making.

Currently, dabigatran has been used for approximately 8 months in our country, while the other agents are not yet available. I will try to analyze them based on three concepts: efficacy, safety and costs. The first conclusion we can draw is that the risk profile is very different in the three concluded trials: ROCKET enrolled higher risk patients, while in RELY and ARISTOTLE the population had a similar risk profile; thus, in the absence of comparative studies, the conclusions that can be inferred from these indirect analyses loose consistency.

Not less important is their statistical design, which according to intention to treat (ITT) and with non-inferiority criteria, if they were more costly than traditional anticoagulants it would not be valid to speak only of non-inferiority. Ideally, superiority criteria should be attained, but always with more validated and of greater weight intention to treat than in treatment (IT) analyses.

   a) Dabigatran (5, 6): the 150 mg dose is superior to warfarin and the 110 mg dose is not inferior to warfarin; superiority is reached by ITT analysis, and mortality is significantly reduced only with 150 mg (0.05). It is difficult to say whether an open design decreases the validity of trial findings, taking into account that the gold standard is the randomized blind study; nevertheless, event adjudication was performed by an independent committee. It must be pointed out that the total therapeutic range (TTR) time is reasonable, as it is over 60% both in treated and naïve patients, a fundamental fact for comparative oral anticoagulation trials with non-inferiority purposes.
   b) Rivaroxaban (7, 8): it fulfills non-inferiority criteria for ITT analysis, of superiority only for IT and its TTR is close to 55%. The authors argue that in higher risk groups it is difficult to obtain an adequate TTR. Daily clinical experience does not support this concept and possibly attenuates this agent’s impact. It does not reduce mortality and its advantages are a once daily intake, which improves adherence and a lower renal excretion ratio compared to dabigatran.
   c) Apixaban (9): it meets superiority criteria for
ITT analysis, although it does not specifically reduce ischemic stroke as dabigatran at a 150 mg dose. Nevertheless, it significantly reduces global ACV, and provides another interesting result: it significantly decreases mortality, fulfilling the greater than 60% TTR criteria.

2. Safety: in this respect, I will analyze bleeding, specifically hemorrhagic stroke, and an adverse event, which though not severe is uncomfortable and leads to treatment discontinuation with accompanying risk: dyspepsia.

a) Dabigatran: at a 110 mg dose it is safer than warfarin, at a 150 mg dose it is as safe as warfarin, and both doses significantly reduce hemorrhagic stroke. Even though the 150 mg dose specifically increases gastrointestinal bleeding ratio, one would be tempted to find its cause in tartaric acid capsules which reduce gastric pH; however, it should be pointed out that the ROCKET study arrived to the same conclusion, as it is the highest bleeding region with any antithrombotic agent. Dyspepsia is a relatively common event (11%), both in clinical trials and clinical practice, and can be reduced with abundant water and food intake.

Regarding safety, mortal risk hemorrhage should be analyzed (10) as one of the relative disadvantages of these agents, as there is no natural antidote; however, both doses reduce this event. Recently, Boehringer Ingelheim reported 260 deaths with its clinical use.

b) Rivaroxaban: it is as safe as warfarin regarding overall bleeding and significantly reduces hemorrhagic stroke, not referring dyspepsia as adverse event.

c) Apixaban: it reduces significantly both overall bleeding and hemorrhagic stroke and no dyspepsia is reported.

3. Cost-effectiveness: a series of cost-effectiveness analyses have been published only for dabigatran, as it is the only available drug for clinical use. Evidently, these analyses are difficult to extrapolate to our reality, and therefore, their impact is markedly reduced. Analyses based on direct comparisons of costs can be made as follows:

- Drug cost: the present monthly cost with dabigatran is $382.33. Comparatively, even though it is difficult to estimate a real cost as there is great variability in the values, the overall anticoagulant treatment cost, which includes the drug cost plus medical fees and laboratory monitoring, is below that of dabigatran. In addition, anticoagulants have medical security coverage, which in some cases reaches 100%, limiting the implementation of new therapies.

- Cost per year of life saved: it is the correct way of performing cost-effectiveness analyses, since besides drug and laboratory costs, we must consider the impact of this new therapeutic intervention on clinical events: stroke, bleeding, and obviously mortality, which is more difficult to demonstrate due to its low prevalence. Thus, reduction of stroke and bleeding would certainly influence final costs; however, these analyses are not very frequent in our country.

One interesting analysis (11) applying a cost-effectiveness theoretical model taking into account ischemic risk (measured by CHADS) and hemorrhagic risk leads to the following conclusions:

CHADS 0: only ASA is cost-effective

CHADS 1-2: warfarin, even in cases of high bleeding risk and poor TTR.

CHAD 3: dabigatran 150 mg unless TTR is 73.2%
One hundred and ten mg is not considered cost-effective, as it is not approved in the United States. Although this analysis would not be strictly applicable to our country, as our costs are different and the double dose scheme differs from that in the United States, it still seems logical even for our market.

If we applied a therapeutic selection criteria based exclusively on cost-effectiveness, the populations in which it would be more reasonable to apply dabigatran would be those of patients with poor adherence or low TTR, those with difficult geographical access to healthcare institutions and those under short treatment periods, such as cardioversion or ablation. The initial steps of their use should be cautious and safe, taking into account dose schemes and contraindications, and an even more careful use should be considered in elderly patients and in those with renal failure.

In conclusion, these new therapeutic options are welcome for their comparative pharmacological advantages as they would allow reduction of event ratio in patients with AF and expand the number of treated patients.

The obstacles for an unrestricted clinical use are unquestionably costs and possibly the logistical concerns with any new antithrombotic agent, sustained in part by initial alerts on bleeding events from regulatory agencies in Japan, Australia, New Zealand and the FDA which were reinforced at the beginning of 2012 by the serious events statistical report of the first trimester 2012 in the United States, (12) with 506 hemorrhagic cases vs. only 176 with warfarin. These alarms emphasize the greater vulnerability of elderly patients even with the therapeutic limitation of a single 150 mg dose, the increased cardiovascular events recently reported in a metaanalysis (13), though not observed in the RE-LY study population (14) and, finally, the more difficult management of trauma patients. (15)

Beyond question, independently of clinical trials, the passage to clinical experience will be fundamental and, certainly, the report of adverse events to regulatory agencies. These initial reports should be interpreted with extreme caution, similar to the one we must adopt in prescribing the new antithrombotic drugs, which in the light of evidence arise as an alternative to classical anticoagulants, as proclaimed in therapeutic guidelines, and not as yet as a first option drug. (16)

Conflict of interest
The author declare a relation with Astra Zeneca - BAGO

BIBLIOGRAPHY

Antagonist
MARCELO TRIVIMTSAC1

“It is time”, etching by Goya exhibited at the Museo del Prado. It has been interpreted as corresponding to “bishops and canon who lead an idle and relaxed life” at waking time.”

As in Goya’s picture, dicumarinics (and those who manage the patients receiving them) have led a quiet life until the arrival of their competitors: the new oral anticoagulants

Thus, dabigatran, rivaroxaban and apixaban, the new stars in this billboard, are apparently determined to occupy a central and not a supporting role in the oral anticoagulation scenario.

Traditional oral anticoagulants (anti-vitamin K or dicumarinics) have demonstrated their efficacy in
numerous cardiologic indications beyond non-valvular atrial fibrillation (AF), which is the only accepted indication in this field for new anticoagulants. Thus, AF due to mitral valve stenosis and mechanical valve prosthesis are excluded from virtually all comparative studies, probably due to their higher emboligenous potential.

It is widely accepted that dicumarinics are not perfect drugs (Table 1): they require anticoagulation level control, they have a narrow therapeutic index, many drug interactions and a varying effect according to the diet, among others. Apparently, efficacy, defined by antithrombotic effect/hemorrhage, is also better for the new anticoagulants.

Three large studies have compared dicumarinics with the new anticoagulants: the RE-LY (1) study with dabigatran, two daily doses of 110 mg or 150 mg, the ROCKET-AF (2) study with rivaroxaban, one daily dose of 15 mg or 20 mg, and the most recent, ARISTOTLE (3) study with apixaban, 2.5 mg or 5 mg twice daily. The three studies showed differences favoring the new anticoagulants in the reduction of thrombotic and hemorrhagic events in comparison with traditional warfarin.

However, this difference, although statistically significant, might not be “clinically significant”. For some time, a publication demand from the New England Journal of Medicine (the journal where all researchers wish to publish) consists in showing comparative curves of two treatments at a real scale, in addition to the scale chosen for the figure. As can be seen in the real scale in Figure 1, there is virtually no difference between warfarin and apixaban when the lower part of the ARISTOTLE study figure is observed. In order to see the difference in the upper figure, the ordinate scale goes from 1 to 4!

There is approximately 20% relative risk reduction at 30 months (2 years and a half) that corresponds to an event reduction of approximately 3.5% to 2.5%, i.e. 1% less absolute risk. The difference at one year is even lower, 0.5%. Consequently, 200 patients must be treated during a year, out of which 199 will obtain no benefit. At first sight, it seems very poor.

Hence, the question of whether the difference is clinically significant. From a practical point of view, it is easier for clinical cardiologists to prescribe evidence-based new anticoagulants, saving the patient the need to control anticoagulation levels, food and drug interferences and hematology consults.

However, especially in countries like ours, always with limited resources, we have the medical responsibility to restrain health expenditure, using the most costly treatments when they are most useful. It has been estimated that in the United States, the additional cost of using dabigatran instead of warfarin exceeds US$1,000 annually and this cost doubles in Argentina (about $10,000 annually).

At this point it seems fair to admit that thanks to oral anticoagulants we have been able to know and learn from hematologists who have taught us to understand and manage hemostasis disorders. In this regard, my antagonist in this controversy, is my esteemed Marcelo Casey, one of the most outstanding hematologists specialized in hemostasis in our country, with whom I had the pleasure of working. If he supports the new anticoagulants, I have no doubt that in the future they will replace dicumarinics, but aside from my acknowledgement, this controversy refers to whether they should replace dicumarinics now and my position is no.

It so happens that new promising drugs in cardiology have been withdrawn from the market due to serious adverse effects not revealed until clinical use: mibefradil, cerivastatin and rimonabant are only some of the most outstanding examples in recent years. Controlled studies showed advantages for these drugs thus determining their use and sometimes their recommendation in guidelines, to be

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<td>Gastric intolerance</td>
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<td>Antidote</td>
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<td>Drug and food interactions</td>
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afterwards discontinued from clinical use. We must bear in mind that this might also occur with the new anticoagulants. However, I must admit that the first clinical experience is also favorable and most clinical cardiologists have begun to use them in some patients when the indication is clear.

In fact, we must be very careful in their prescription: these drugs notably increased bleeding when tested in acute coronary syndromes. (4) Recently, periprocedural use of dabigatran after pulmonary vein ablation to treat AF (generally non-valvular) has been seriously questioned due to the presentation of more embolic and hemorrhagic events than with warfarin. (5)

Continuing with dabigatran, the most used oral anticoagulant in Argentina, we must remember that gastric intolerance is a frequent, although not serious adverse event, and has prescription limitations in patients with renal failure. The experience in very old patients is scarce. Two of these three barriers do not seem to pose a problem with classic drugs, whereas age might raise a controversy, also for dicumarins, as I pointed out in my second controversy on AF (6) published in this Journal some years ago (the first one referred to the use of pre-cardioversion transesophageal echocardiography) (7)

Since we are mentioning Argentine references, I recommend the excellent review published by Raúl Altman and Héctor Vidal in the *Thrombosis Journal* last year (accessed freely in PubMed), where “the battle of oral anticoagulants from a clinical practice (the real world) perspective” is discussed. (8). It is always pleasing to find an outstanding fellow citizen cited in internationally renowned journals while performing a bibliographic search, especially when it has the level of this review.

One last reference to the sociologic perspective. In addition to a reduced expenditure capacity, elderly subjects, the world’s growing population presenting more AF, encounter in solitude one of their worst ghosts. What better place than a waiting room in the company of their old anticoagulated peers to stimulate socialization and meetings with people of the third age, not very keen on employing Internet social networks in search of friends or a couple? This is an additional advantage of conventional oral anticoagulants, which in the absence of powerful sponsors have the potential for human relationships. With the new anticoagulants we shall have to find new options to amuse our elderly patients.

Turning more serious, the new anticoagulants represent a big step in AF antithrombotic treatment, although it is not yet the time to replace dicumarins.

**Conflict of interest declaration**

None declared

**BIBLIOGRAPHY**


**AGONIST’S REPLY**

First of all, I appreciate the complimentary concepts about me expressed by Marcelo, though I do not know if I deserve them.

We agree that it is beneficial to have new drugs, but as an option, not as first line drugs, logically, due to their cost-effectiveness. Then, in my humble opinion, we must try to select the ideal patients and even more, control them periodically. My zeal on dabigatran follow-up does not differ from the one I assume towards conventional anticoagulants, and that is my strong recommendation, its prevalent and detrimental renal excretion leads me to intensify the controls.

My ideal patients are those with any previous...
treatment, so that in case of a hemorrhagic complication this cannot be attributed to the new drug. Furthermore, why change if we are doing well? I do not find it contradictory or cost-effective considering the difficult geographic access to health centers and patients with large variability in INR, and I add electrical cardioversion, as it increases cost-effectiveness due to the extra cost of enoxaparine. Moreover, although in the case of ablation there are contradictory reports, with clear use guidelines I consider that it is not contradictory and it is cost-effective. Specifically, I know that ICBA has a good up to date experience.

I agree that the absolute risk reduction of these drugs is modest, but prudent and selective use maintains the advantages of easy administration, equal or better efficacy, greater safety and a clearer mortality reduction with apixaban and a more modest reduction with dabigatran.

Although it is true that the primary event absolute risk reduction in the ARISTOTLE study is not so impressive, in fact, that is the case for them all: to decrease mortality, reduce global hemorrhagic events without increasing gastrointestinal ones and have a low renal excretion appear as a more attractive option in eligible patients. Qualitatively, it seems interesting added to the logical class advantages of these drugs.

Dr. Marcelo Casey

ANTAGONIST’S REPLY

A controversy is a type of dialectic discussion, similar to that performed by the prosecutor and the defender in a trial, where generally both agree but take opposing positions. Our case is not an exception: as can be expected from two Marcelos, we have more points in common than differences.

As pointed out by Marcelo Casey: “… the prescription of these new antithrombotic drugs, arise in the light of evidence as an alternative to classical anticoagulants, as proclaimed in therapeutic guidelines, and not as yet as a first option drug”. If they are not the first choice, it is obvious that it is not time to replace dicumarinics. End of controversy.

Will they replace dicumarinics in the future? It is highly probable. They are equally or more effective as antithrombotics and with less hemorrhagic risks. With time the cost will steadily decrease and we will learn to prescribe them adequately and to manage their complications.

May the new anticoagulants extend their domain to other areas of cardiology and medicine such as pulmonary thromboembolism, valve prostheses or acute coronary syndromes? It is also probable, especially in the first two cases where coagulation seems to play a fundamental role. In acute coronary syndromes, closer related to platelet alterations, I have my doubts.

Which of the three renowned drugs will be the winner: dabigatran, rivaroxaban or apixaban? We might organize a round of bets. Rivaroxaban has, in my opinion, a slight advantage, being the only one with a single daily dose, an important issue for prolonged treatments, as well as a lower gastric intolerance than dabigatran. In conclusion, it is not yet time to replace dicumarinics, although the date is not far-off.

Dr. Marcelo TriviúMTSAC