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Editorial

Cardiocentro ERNESTO CHE GUEVARA SANTA CLARA CUBA

Anticoagulation is necessary when indicated in patients with atrial fibrillation

La anticoagulación es necesaria cuando está indicada en pacientes con fibrilación auricular

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In 2013, an editorial entitled "Ischemic atrial fibrillation: how to interpret its pathophysiology and the strategic decision of the treatment concerning the arrhythmia"[1] was written. Let's start the same way, because at that moment, the topic was anticoagulation in ischemic atrial fibrillation (AF) and at this time, the intention is to mention the need of anticoagulation in AF when required, referring to the original article Merino Barrera *et al.*[2], which is published in this issue of CorSalud.

The AF is currently the arrhythmia that generates the most scientific literature[1,3]. This interest is due to different reasons, among which are the persistence of ignorance of its mechanism and difficult behavior to follow. However, the biggest factor for the interest in this arrhythmia is its high prevalence and its great clinical and economic impacts[3]. It has been estimated that in Europe, the cost of each patient with AF may be between 450 and 3.000 euros annually[4].

Attempts in Latin America for characterization studies of the AF, seeking improvements in health care, have been countless, but perhaps isolated, as the work of Rosselli *et al*[5]. Not to exclude, for example, that countries like Argentina[6], Mexico[7] and Colombia[8] have developed guidelines or consensus, seeking guidance for the best treatment and monitoring of patients with AF. However, in Central American countries this does not happen in this way.

It is important to mention that Mexico has participated in the GARFIELD registry[9], considered to positively influence the most appropriate therapeutic approach in patients with non-valvular AF. Finally, joining efforts must be carried out in order to search for multicenter studies in Latin America, with very different economies from that of North America, in order to develop strategies for the appropriate prevention, diagnosis and follow-up of the AF.

It is unclear whether the presence of this arrhythmia increases mortality alone. There are studies that indicate it in patients with or without heart disease. This excess of mortality has been observed typically as a result of heart failure and thromboembolic complications produced by the AF. Recently, it has

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been reported to increase the risk of sudden death[10]. However, due to the lack of studies specifically aimed to know if the AF increases mortality independently, it cannot be rejected that this is only an «accompanying» marker of other factors that affect survival[10].

Nevertheless, other studies mention that the AF *per se* is not a potentially lethal arrhythmia, but patients with the disease have a five times greater risk of presenting a stroke, and when this complication takes place, the risk of death is twice as high in the next 12 months[11]. The percentage of stroke attributable to AF is only about 1,5% at 60 years old and reaches 23% at 80 years old. The consequences of stroke are more devastating than those of another origin. A European registry reveals higher mortality, dependency and disability at 3 months, with less probability to return home, greater impact on anterior cerebral territory and greater probability of clinical presentation with unfavorable neurological signs such as coma, aphasia, paralysis, swallowing disorders or incontinence[12]. With all the above and on the scientific evidences over the scale CHA_2DS_2-VASc, it is recommended oral anticoagulation (OAC), provided that aid is necessary, which promotes the benefits for the patient and for the economy of the different health systems[13]. However, the control of OAC is vital to avoid the risks of bleeding as a side effect of this therapy.

Dicoumarin-like agents have been used for over 6 decades, and in the present century, the new OAC has been successfully used in the treatment of patients with AF.

WARFARIN[12-14]

Advantages

Dicoumarin-like agents have a development of over 60 years. The failure rate is low when a suitable range of anticoagulation is reached. They have the advantage of a preclinical surrogate of bleeding and recurrence as the International Normalized Ratio (INR). The monthly monitoring of anticoagulation levels increases therapeutic adherence. The cost of treatment is low. Vitamin K uniformly reverses its effect and prothrombin complex concentrates prevent progression of intracranial hemorrhage when used early.

Disadvantages

The beginning and termination of its action is slow, making it necessary to use initial doses of low molecular weight heparin, if anticoagulation is required immediately. Experienced teams must be available, to achieve satisfactory time in therapeutic range (TTR). Interactions with food and medicine interfere in its pharmacological action and complicate the patient's quality of life. It cannot be used without laboratory controls for its unpredictable response and a narrow therapeutic range. This causes difficulties with patients, physicians that indicate the treatment and the laboratory processing the samples.

Effectiveness

The embolic risk of the AF in prophylaxis decreases with dicoumarin-like agents in 64%, compared to placebo, especially with larger TTR to 65%. It is clearly superior to aspirin and, in that TTR, to dual antiplatelet therapy. For the prevention of ischemic stroke, it has only been clearly surpassed by the dabigatran in high doses. In patients without previous stroke, the number of them needed to treat for preventing a seizure is 37 and in secondary prophylaxis, 12; besides, the mortality for AF is reduced 26% annually.

Reliability

The most important side effect is the major bleeding. The main risk factors for bleeding are the high INR, poor training of the patient and the professional in charge, advanced age, comorbidities, pharmacogenetics with greater sensitivity, simultaneous use of antiplatelet agents, prolonged duration of treatment, presence of previous bleeding and lability in response. The HAS-BLED score quantifies some of these factors and, with a score of 0 to 9, shows an annual incidence of major bleeding between 1 and 12%, with an average of 1.5% annually. Other rates and scales, as ATRIA, do not offer significant advantages. The predictive ability of both is moderate and does not exceed 70% of bleedings.

Use in the real world

Despite the effectiveness of dicoumarin-like agents,

other records show that even in high-risk patients, only half of them receive warfarin and 50% of them are not in therapeutic range, and the other half is divided between any antithrombotic and one insufficient, such as aspirin. Swedish population data show that 25% of patients that do not receive anticoagulation for AF do not have contraindications for its use; in the rest, the risk of bleeding is the main cause for not prescribing blood anticoagulants. In addition, about 1 in 4 elderly patients starting treatment with warfarin suspended it when completing the first year, mostly for security problems.

NEW ORAL ANTICOAGULANTS[12,15-19]

Anticoagulants with more advanced clinical development are: dabigatran, rivaroxaban, apixaban and edoxaban. The dabigatran, first direct thrombin inhibitor, is used successfully since 2002 for prophylaxis of thromboembolism in patients undergoing hip surgery (17th International Congress on Thrombosis, Bologna, Italy, October 26-30, 2002). Others were subsequently incorporated into clinical practice, with its peak since 2009. Its main contribution has been to expand the number of patients with OAC.

Advantages

Fixed doses are used, the effect is immediate and predictable, and lacks important food and medication interactions.

Disadvantages

High direct costs for a population generally already retired and with limited financial resources. Lack of a laboratory method validated to ensure adherence or anticipate an increased risk of bleeding; it will be necessary to promote its indication by non-specialist doctors in anticoagulation, monitoring is more widely spaced and presuppose less care simultaneously when employing anti-inflammatory medication that increases the risk of bleeding; besides, lack of specific antidote, and there is little time experience in routine clinical practice.

Use in the real world

Several records show a gradual replacement of dicoumarin-like agents by the new OACs, especially in developed countries and in patients without treatment. Important clinical trials have demonstrated its effectiveness and safety. Apixaban, rivaroxaban and dabigatran have been compared with warfarin in patients with AF; the first, also with aspirin. The population of greater embolic risk was studied with rivaroxaban. The bleeding episodes have been controllable even in the absence of specific antidotes. The dropout rate of anticoagulation has failed to warfarin.

The most important findings are summarized as follows:

- Apixaban 5 mg and dabigatran 150 mg every 12 hours were more effective than warfarin.
- Rivaroxaban 20 mg every 24 hours was only superior to warfarin in the treatment's results.
- Dabigatran 110 mg every 12 hours and rivaroxaban 20 mg every 24 hours were equivalent to warfarin for the results to treat.
- As for major bleeding, apixaban was comparable to aspirin and warfarin, as doses of 110 mg of dabigatran. There is more prone to gastrointestinal bleeding with dabigatran 150 mg and rivaroxaban 20mg. All of them produced minor intracranial hemorrhage and showed a tendency to decrease mortality, but it was only significant with apixaban.

With all the exposed before, the OAC is reasonable and advisable, whenever necessary, in patients with AF. There may be risks, but the existence of scales as CHA_2DS_2-VASc and HAS-BLED[20] facilitates to identify patients in whom the risk/benefit ratio justifies the use of the OAC. The right and regular monitoring, when the therapeutic is with dicoumarin-like agents, is very important for decreasing the risk of bleeding.

The GARFIELD registry in Mexico is an example to follow in our region. The presence of qualified cardiologists in Latin American countries, trained in Cuba, in the *Escuela Latinoamericana de Medicina (ELAM)*, is a strength, no doubt, to join forces in conducting multicenter studies, which involve the creation of Latin American registries (and why not: a Latin American Registry of AF [RELAFA, after its acronym in Spanish]), to achieve the most adequate approaches for patients with this arrhythmia, and to

establish common scientific standards in its treatment.

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