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Editorial

Real-world assessment of direct oral anticoagulants and left atrial appendage closure in complex clinical situations

Evaluación en la vida real de los anticoagulantes orales de acción directa y el cierre de la orejuela en situaciones clínicas complejas

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Nonvalvular atrial fibrillation (NVAF) is a major health issue increasingly seen with progressive population aging.[1] Following the introduction of direct oral anticoagulants (DOAC), more patients at risk of stroke (previously not considered eligible for anticoagulation) receive this treatment; however, many patients with an indication for anticoagulation therapy still do not receive it for various reasons,[2] sometimes due to high hemorrhagic risk. In this context, highly favorable results have been published for left atrial appendage (LAA) closure in patients with contraindications for oral anticoagulants (OAC).[3]

Revista Española de Cardiología has recently published reports on 3 registries with patients diagnosed with NVAF.[4–6] The first, the FANTASIIA study,[4] compared the use of DOAC with vitamin K antagonists (VKA) in Spain between 2013 and 2014. The study included 2178 patients, with a mean age of 73.8 ± 9.4 years; 24.5% received DOAC and 75.5% received VKA. After a median follow-up of 32.4 months, patients receiving DOAC had fewer strokes (0.40 vs 1.07 patients/y; $P = .032$; relative risk [RR] = 0.42), fewer major bleeding episodes (2.13 vs 3.28 patients/y; $P = .0044$; RR = 0.76), fewer cardiovascular deaths (1.20 vs 2.45; $P = .009$; RR = 0.67), and fewer total deaths (3.77 vs 5.54; $P = .016$; RR = 0.86) than patients receiving VKA. For patients receiving DOAC, the RR was 0.82 for the total combined event of stroke, embolism, major bleeding, and death. The authors concluded that DOAC therapy was associated with a lower rate of all serious events.

The message is similar to that of other registries aiming to extrapolate the results of large randomized studies to the real world.[7] However, even in this setting, not all registries agree on this conclusion. For instance, a Danish registry[8] with 61 678 patients observed a decrease in serious bleeding events only with dabigatran and apixaban compared with warfarin, but not with rivaroxaban, and the US MarketScan claims data[9] (10 754 patients) showed no difference whatsoever in favor of DOAC. The registries also reached different conclusions regarding embolic events. In the Danish registry,[8] no differences were found between DOAC and warfarin in the reduction of ischemic stroke, and in the US MarketScan claims data,[9] only rivaroxaban (but not dabigatran or apixaban) was more effective than warfarin in reducing thromboembolic events.

In contrast, the FANTASIIA study[4] was a comparison in Spain and with acenocoumarol rather than warfarin, as pointed out by the authors.

Randomized studies have the advantage that they compare similar patients and are well-monitored and audited. However, their main limitation is that the results cannot be universally extrapolated to real-life patients, due to strict inclusion and exclusion criteria. In fact, it is estimated that the results are not applicable to at least 30% to 35% of the real-world population with the medical condition in question.[10] Conversely, registries usually have more methodological limitations, but may reflect how well the randomized study findings are replicated in real-world patients. For instance, it is known that bleeding risk increases dramatically as the patient meets more of the exclusion criteria.[11]

Although the message about using DOAC in the real world is still positive, there should be more events in registries than in the randomized studies because they have fewer exclusion criteria, at least theoretically. It is truly surprising, therefore, when registries report unequal and even lower event rates than those seen in randomized trials, a finding reported by the FANTASIIA registry (eg, a total mortality of 7.68 per 100 patients/y in patients treated with VKA in randomized trials vs 5.54 per 100 patients/y in the registry, and serious bleeding in 6.16 vs 3.28 per 100 patients/y in the randomized studies and in the registry, respectively).[12] This is indicative of more stringent selection criteria than in randomized trials, leading to the conclusion that these registries do not reflect what happens in the most complex real-world patients. The paradigm of this is the XANTUS trial,[13] which compared the results of rivaroxaban in clinical practice with the ROCKET-AF randomized trial.[14]

In FANTASIIA, this is most likely due to inclusion criteria requiring that patients have taken OAC in a stable and continuous manner for at least 6 months prior to enrollment. In other words, it excluded patients hospitalized at that time, those with unstable anticoagulation in the previous 6 months, and those needing to discontinue and restart VKA to undergo invasive procedures involving bleeding risk. This is unquestionably the first bias of the

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study in terms of real-world events, as this period is known to be critical. Numerous studies have shown that patients bleed most in the first 6 months after starting anticoagulation therapy and that thromboembolic phenomena occur most often when this therapy is discontinued, even if only temporarily for surgeries, disruptions, or changes to antithrombotic therapy.[15]

Interestingly, the difference between thromboembolic events and bleeding events in randomized trials was only significant in patients who had not taken VKA previously, but was not significant (although there was a trend) in patients who had received VKA previously, despite totaling more than 31 000 patients in the meta-analysis.[12]

The authors themselves mention several important limitations of this registry, namely, a worse patient profile in the VKA group (higher rates of heart failure, kidney failure, and coronary disease), with equal $CHADS_2$ and HAS-BLED scores. Furthermore, the percentage of patients who switched treatment groups from the first to the third year from acenocoumarol to the other group was not negligible, with 64.6% originally receiving acenocoumarol dropping to 51.3%, and 31.8% originally receiving DOAC rising to 44.1% (38.67% increase in the DOAC group since the beginning of the study). As a result, some initial events that occurred in this 38.67% of patients may have been assigned to the acenocoumarol group after the patients had switched therapies. Last, when differences adjusted for confounding variables were applied, the differences were not significant, although a trend was evident.

One of the merits of the registry is that it reflects a tendency toward greater use of DOAC than VKA in Spain, rising from 5.4% in 2013 to 35.6% in 2018. The registry also reveals differences between autonomous communities: for example, the rate was 26.2% in the Principality of Asturias, but 56.8% in Cantabria. Improved control is obviously needed when VKA are used in Spain, as patients were within therapeutic range only 61.43% of the time.

In short, apart from the advantages of DOAC, the main message since their introduction is that the percentage of patients who should be receiving anticoagulation therapy has risen from 57% (2010-2011) to 70% (2014-2015), as reported by the GARFIELD-AF study.[16] Nevertheless, this registry revealed that 30% of patients who required anticoagulant therapy (OAC or DOAC) were not receiving it, a situation confirmed in up to 40% of patients with HAS-BLED score > 3. These findings were also reported by several contemporaneous registries (not named herein, due space constraints). Real-world approaches to treatment are complicated by other issues, such as inadequate dosing due to concerns about bleeding (increased risk of stroke), excess dosing due to failure to adjust for renal impairment (increased risk of bleeding), and lack of adherence in certain populations.

Two other recent publications in *Revista Española de Cardiología* address LAA closure in complex medical conditions, eg, treatment of patients aged $\geq$ 85 years or recurrent or resistant stroke (RS) despite OAC therapy.[5,6] These reports describe findings from an EWOLUTION substudy[17] and an Amplatzer Cardiac Plug multicenter substudy.[18]

The prevalence of NVAF can be as high as 18% in patients older than 80 years.[19] Very elderly patients, defined as age $\geq$ 80 years in most studies, are at greater risk of stroke, and are more likely to bleed due to a higher number of comorbidities, greater use of drugs (including anti-inflammatories and antiplatelets), problems with therapeutic adherence, and complications from falls. In fact, bleeding complications are seen in 9% to 13% of these patients in the case of both VKA and DOAC.[20] For this reason, these populations are underrepresented in most studies. Freixa et al.[21] (a substudy of the Amplatzer Cardiac Plug multicenter registry[18]) observed similar safety and efficacy results in patients aged < 75 years vs those aged ≥ 75 years. A study by Cruz-González et al.[5] split the groups at an even higher age of 85 years. This 10-year increase in the cut-off point is not a trivial issue. The HAS-BLED score does not discriminate by age brackets, but rather adds 1 point for age older than 065 years, regardless of whether the patient is 65 or 85 years old. This limitation is seen in recent studies, such as ENGAGE AF-TIMI 48,[22] which had 3 age brackets (< 65, 65-74, and ≥ 75 years) and reported a small increase in stroke events, but particularly in bleeding events, showing that age has a greater impact on bleeding vs stroke rates.

This is especially relevant because less than 17% of patients had a history of bleeding in the DOAC randomized trials and registries,[12] whereas the rate was around 50% in LAA closure studies, such as the EWOLUTION study[17] mentioned earlier, and 70% in the Ibérico II registry[23]; the oldest patients had the highest rates of such clinical events in their history, leading to exclusion.[24]

Consequently, it is good news that the data presented here are positive in the sense that age does not affect the safety of the procedure, including events during the first 7 days. The positive effect of LAA closure is also evident in the 80% reduction in stroke rates, consistent with other large registries of this technique.[18,23] In terms of bleeding, during 24 months of follow-up, the oldest patients had twice as many serious or major bleeding episodes outside the procedure than other patients (5.1 per 100 patients/y when age ≥ 85 years vs 2.6 per 100 patients/y when age < 85 years), although the result was not significant due to the limited number of patients in the oldest patient subgroup. This increased risk was age-related, but may also have been influenced by postoperative treatment to prevent device thrombosis during the first 3 to 6 months. However, there was a decline in bleeding episodes compared with expected rates based on HAS-BLED score, although the drop was less spectacular in patients aged ≥ 85 years (12% vs 48%). In studies with longer follow-up periods, this rate was even more favorable because strict antithrombotic therapy had less influence in the first months of the implant, both in the general population and in the oldest subgroup.[23,25]

Last, the third study, also conducted by Cruz-González et al.,[6] involved another group of complex patients, namely, patients with stroke despite OAC (RS), in whom LAA closure could be an alternative or could enhance their treatment. The main message of this report is that LAA closure is safe and effective (with similar complications to those of other stroke-free patient groups), that it reduces stroke recurrence compared with expected rates according to risk scores (similar to the control group), and that there was a significant reduction in postprocedure bleeding.

Prior stroke is known to indicate a higher risk of new strokes, particularly of cardioembolic origin. This is still true in patients who have had stroke despite OAC therapy,[26] making it logical to advocate a switch to DOAC for patients who have experienced a stroke while taking VKA. However, apart from patients with poor international normalized ratio control, this patient group is also known to have more event recurrence with DOAC.[12]

Although randomized studies report that DOAC continue to be more effective than warfarin in patients with a history of stroke, similar to the stroke-free group, it is true that both DOAC and VKA are less effective in reducing stroke in these patients. In a meta-analysis of randomized trials with DOAC, patients with prior stroke accounted for 29.5% of trial patients (ROCKET AF contributed 52% of all such patients). In this patient subgroup, the recurrence rate for thromboembolic events during a mean follow-up of 2.2 years was 4.94% in the DOAC group and 5.73% in the VKA group (RR = 0.86) vs 2.33% and 2.98% (RR = 0.78) in the group without prior stroke. These figures represent twice as many thromboembolic events in this population, although the clinical impact may be weaker when expressed as the rate of events per patient-year.[12]

Once again, the inclusion criteria led to results that underestimated real-world clinical medicine because patients in the

acute poststroke phase were disqualified. In real-world studies, however, 1-year stroke recurrence is more likely in patients treated with OAC for secondary vs primary prevention, as shown in the Darlington registry[26] (8.6% vs 1.6%, respectively; $P < .001$) and in the RAF study, [27] with a recurrence rate of 7.6% for 90-day thromboembolic events and 3.6% for symptomatic cerebral bleeding. These figures could be somewhat better in the subgroup of patients treated with DOAC during this 90-day period, a subgroup in which combined stroke and cerebral bleeding events could drop to 5% between days 3 and 14.[28]

In the study conducted by Cruz-González et al.,[6] stroke reduction was effective in patients with RS and without prior stroke, although stroke rates were again higher in the group with prior stroke (2.6% and 1.2%, ie, 65% and 78% relative reduction compared with their CHA_2DS_2-VASc scores). These figures are fairly similar to those reported by the Ibérico II registry, with decreases of 74% and 81.6%, respectively, where the risk of 2-year stroke recurrence was higher in patients with prior stroke (RR = 2.5; $P = .043$). In other words, this population continues to be at higher risk. The indication for LAA closure due to RS in the registries ranged from 6.2% (Ibérico II registry[23]) to 11% (Amplatzer Cardiac Plug multicenter registry[6]).

The current study has several limitations. For instance, the time between the index event and LAA closure was not recorded, not all patients with prior OAC therapy were included, and there was no transesophageal echocardiogram (TEE) monitoring in the hours or days before the procedure in some patients.[6] Performance of TEE 24 to 72 hours before LAA closure is always important, but particularly in this subgroup of patients with RS, as they could be more susceptible to thrombus formation in the LAA before the procedure. Moreover, the problem can be underestimated in studies with fewer preimplantation TEEs (in this registry, 2.6 with preoperative stroke and 0.6 in the RS-free group) and fewer follow-up visits.

The presence of thrombus in the LAA represents a 3-fold risk of stroke.[29] The presence of thrombi in the LAA can range from 2% in populations at low risk (eg, younger patients admitted for cardioversion or ablation), up to 4.5% in populations at higher risk (even when adequately treated), and as much as 10% in populations at higher risk (eg, patients who are elderly or have signs of left ventricular dysfunction and high B-type natriuretic peptide or poor therapeutic adherence).[30] In this context, DOAC have not been shown to be superior to VKA in eliminating thrombi from the LAA (4.3% vs 2.2%) in patients who undergo cardioversion study.[31] Additionally, some patients are resistant due to genetic polymorphisms or have interactions with common drugs such as statins and dabigatran.[32] Familiarity with LAA anatomy may also play a part, with some publications describing that LAA with more small-lobe branches or cactus or cauliflower morphology are more closely associated with stroke (odds ratio = 2.5 and 2, respectively).[33]

In most studies, including the present study, it is not usually clear whether stroke recurrence in these patients is due to poor control with OAC or due to inherent resistance.[6] However, it may actually be a combination of both aspects. Other causes of thromboembolism, such as aortic plaque or thrombi outside the LAA, are factors that may have some influence and can be seen in up to a third of the populations at risk, thus potentially increasing the risk of recurrent stroke as much as 4-fold.[29]

Despite these limitations, this study appears to conclude that LAA closure may be a safe and beneficial technique in these patients, although it provides a local treatment for a problem that may be multifactorial. In this regard, LAA closure is presented as an indisputable treatment for patients with RS and bleeding, but also as an optional (or complementary and additional) treatment in patients with RS despite adequate treatment with OAC/DOAC.

In conclusion, this is a complex population, in which the anticoagulation decision must often consider the patient's inherent bleeding risk and expected life course, influenced by medical conditions and comorbidities that progressively arise, further complicating decision-making (eg, appearance of bleeding, need for stents due to coronary disease). On the other hand, data from LAA closure studies have shown that this approach is a reasonably safe option for these complicated patients. However, due to the complexity of randomized trials to compare DOAC or their alternatives with this interventional procedure in patients at high risk of bleeds or with contraindications for anticoagulants, there is clearly some scientific uncertainty that will hopefully be resolved in upcoming years.

CONFLICTS OF INTEREST

J.R. López-Mínguez is proctor for Abbott for LAA closures. The other authors have no conflicts of interest.

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