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Editorial

Current Evidence for New Oral Anticoagulants in the Treatment of Nonvalvular Atrial Fibrillation: Comparison of Substudies

Evidencias actuales de los nuevos anticoagulantes orales en el tratamiento de la fibrilación auricular no valvular: comparación de subestudios

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Above and beyond the encouraging findings of recent clinical trials (RE-LY, ROCKET-AF, ARISTOTLE y ENGAGE AF-TIMI 48),[1–4] which are discussed below, the arrival of the new oral anticoagulants (NOAGs) represents an improvement compared with standard treatment (vitamin K antagonists such as warfarin and acenocoumarol) in the prevention of thromboembolic complications in patients with nonvalvular atrial fibrillation (AF).

The NOAGs (dabigatran, rivaroxaban, and apixaban are currently available in Spain and edoxaban will probably receive approval) overcome many of the drawbacks traditionally associated with vitamin K antagonists (narrow therapeutic window, variable response, multiple interactions with food and other drugs, and slow onset and offset). The most immediate and obvious consequences of these limitations are the need for regular monitoring and continuous dose adjustments, in addition to the dietary restrictions, and scrupulous care when prescribing concomitant medication.[5] As a result, patients' quality of life has been greatly limited. The most important consequence, however, is that many patients with AF and a clear indication for anticoagulation are not receiving any therapy.[5,6] Moreover, even among patients taking vitamin K antagonists in Spain, approximately 35% to 40% have poorly controlled anticoagulation, in terms of the international normalized ratio (INR), with a major impact on the risk of both stroke and bleeding.[5–8] The NOAGs, with their broad therapeutic window, predictable anticoagulant response, lack of dietary restrictions, and limited drug-drug interactions, enable a constant and predictable anticoagulation, thereby obviating the need for regular monitoring of anticoagulant response and constant dose adjustments.

If these advantages were not enough, the different clinical trials point to additional benefits that are clearly of high clinical relevance. A recent metaanalysis of the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 studies found that, in comparison with warfarin, NOAGs significantly reduce the risk of stroke or systemic embolism (by 19%; $P < .0001$), all-cause death (by 10%; $P = .0003$), and intracranial bleeding (by 52%; $P < .0001$).[9] In addition, NOAGs showed a trend towards a reduction in major bleeding ($P = 0.06$), an important benefit in subjects with worse INR control (time in therapeutic window < 66%).

If the primary findings of the main clinical trials were not sufficiently strong evidence, in recent years substudies have further clarified the role of NOAGs in the treatment of patients with AF, particularly in specific situations. Table summarizes some of the most relevant substudies.[1–4,10–32] Given that the primary results of the ENGAGE AF-TIMI 48 trial were published only recently, no substudies have been published as yet. The information on certain clinical situations has therefore been extracted from the supplementary material for the original publication (the same applies to some specific instances with the other NOAGs). In general, the efficacy and safety of rivaroxaban, apixaban, and edoxaban, as well as most of the effects of dabigatran, were consistent with the findings obtained in the original studies, regardless of whether patients had a history of stroke or transient ischemic accident.[4,10–12] Moreover, although patients aged 75 years or older were at greater risk of bleeding, the benefits of NOAGs were age-independent.[4,13–15] Likewise, the efficacy and safety of NOAGs were robust and independent of the $CHADS_2$ score and history of kidney or heart failure.[2,4,16,17,21,23,27–29] In terms of INR control, the benefits (both in reduction of stroke/systemic embolism and safety) of all the NOAGs were robust and independent of mean INR control in the participating centers. With respect to overall vascular events, nonbleeding events, and mortality, the benefits of dabigatran were greater at sites with worse INR control than at those with adequate INR control. There was also a trend in favor of high-dose edoxaban in terms of lower risk of major bleeding in patients with worse INR control.[4,18–20] Although the efficacy and safety results were consistent regardless of the presence of history of coronary artery disease with apixaban and edoxaban, in the RE-LY study comparing dabigatran with warfarin there was a nonsignificant increase in the risk of myocardial infarction but not of other ischemic myocardial events. Thus, in general, dabigatran shows consistently positive effects in patients with

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Table
Results of the Main Substudies of the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 Clinical Trials

Overall Results	
RE-LY[1]	Dabigatran 150 mg was superior to warfarin in reducing the risk of stroke and systemic embolism, but with similar rates of major bleeding.
	Dabigatran 110 mg was similar to warfarin in reducing the risk of stroke and systemic embolism, but with lower risk of major bleeding.
ROCKET-AF[2]	Rivaroxaban was not inferior to warfarin in preventing stroke or systemic embolism and its use was associated with lower risk of intracranial and fatal bleeding.
ARISTOTLE[3]	Apixaban was superior to warfarin in reducing the risk of stroke or systemic embolism, with lower risk of bleeding and death.
ENGAGE AF-TIMI 48[4]	Neither dose of edoxaban (30 mg or 60 mg) was inferior to warfarin in preventing stroke or systemic embolism (the 60 mg dose was superior in the modified intention-to-treat population during the treatment period) and both doses were associated with lower rates of bleeding and cardiovascular death.
Results According to History of Stroke/TIA	
RE-LY[10]	Most of the effects of both doses of dabigatran were consistent, regardless of prior history of stroke/TIA.
ROCKET-AF[11]	The efficacy and safety of rivaroxaban compared with warfarin were independent of history of stroke/TIA.
ARISTOTLE[12]	The effects of apixaban versus warfarin were consistent, regardless of prior history of stroke/TIA.
ENGAGE AF-TIMI 48[4,*]	The results for risk both of stroke or systemic embolism and of major bleeding were consistent for the 2 doses, regardless of history of stroke/TIA.
Results According to Age	
RE-LY[13]	Compared with warfarin, with the 2 doses of dabigatran, there was a lower risk of both intracranial and extracranial bleeding for individuals younger than 75 years, whereas those aged 75 years or older had fewer intracranial bleeding events but the same or higher number of extracranial bleeding events.
ROCKET-AF[14]	The effects of rivaroxaban compared with warfarin in terms of prevention of stroke or systemic embolism were independent of age ($\geq$ 75 years vs $<$ 75 years).
	Although patients aged 75 years or older had a higher risk of clinically relevant bleeds (most of which were not major), these were independent of treatment with rivaroxaban or warfarin.
ARISTOTLE[15]	The benefits of apixaban versus warfarin were consistent, regardless of patient age.
ENGAGE AF-TIMI 48[4,*]	For risk both of stroke or systemic embolism and of major bleeding, the results for the 2 doses of edoxaban were consistent, regardless of age ($\geq$ 75 years vs $<$ 75 years).
Results According $CHADS_2$ Score	
RE-LY[16]	Patients with higher $CHADS_2$ score had a higher risk of stroke or systemic embolism, bleeding, and death. However, compared with the original findings of the RE-LY study, there was no significant heterogeneity in the $CHADS_2$ score.
ROCKET-AF[2,*]	Both for the risk of stroke or systemic embolism and for major bleeding and clinically relevant minor bleeding, the effects of rivaroxaban compared with warfarin were consistent and independent of the $CHADS_2$ score.
ARISTOTLE[17]	In comparison with warfarin, apixaban significantly reduced the risk of stroke or systemic embolism, regardless of the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores. Likewise, treatment with apixaban was associated with a lower risk of major bleeding, regardless of $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED score.
ENGAGE AF-TIMI 48[4,*]	For risk of both stroke or systemic embolism and major bleeding, the results for the 2 doses of edoxaban were consistent, regardless of $CHADS_2$ score ($\leq$ 3 or $>$ 3).
Results According to INR Control	
RE-LY[18]	Compared with warfarin, the benefits of dabigatran 150 mg in reducing the risk of stroke, of dabigatran 110 mg in reducing the risk of bleeding, and of both doses in reducing the risk of intracranial bleeding were consistent and independent of the degree of INR control.
	In contrast, for overall vascular events, nonbleeding events, and mortality, the benefits of dabigatran were greater at sites with worse INR control than at those with acceptable INR control.
ROCKET-AF[19]	Compared with warfarin, the effects of rivaroxaban treatment in preventing stroke and systemic embolism were consistent, regardless of time in therapeutic window.
ARISTOTLE[20]	The benefits of apixaban compared with warfarin in terms of reducing the risk of stroke or systemic embolism, bleeding, and mortality appear to be independent of INR control.
ENGAGE AF-TIMI 48[4,*]	The risk of both stroke or systemic embolism and of major bleeding were consistent for both doses, regardless of time in therapeutic range ($>$ 66.4% or $\leq$ 66.4%), although there was a trend in favor of high doses of edoxaban in terms of lower risk of major bleeding for patients with worse control of INR (P = .06 for interaction).
Results According to History of Kidney Failure	
RE-LY[21]	The efficacy of both doses of dabigatran was in line with the primary findings of the RE-LY study, regardless of renal function.
	Both doses of dabigatran were associated with a lower risk of major bleeding in patients with glomerular filtration rate $\geq$ 80 mL/min.
ROCKET-AF[22]	Patients with atrial fibrillation and moderate kidney failure had a higher risk of stroke and bleeding than those with normal renal function. However, in an analysis according to renal function, there was no evidence of heterogeneity in treatment effect of the doses used.
ARISTOTLE[23]	In patients with atrial fibrillation and kidney failure, there was an increase in the risk of cardiovascular events and bleeding. Compared with warfarin, treatment with apixaban reduced the risk of stroke, death, and major bleeding, regardless of renal function.