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Direct Oral Anticoagulants in the Management of Non-Valvular Oral Atrial Fibrillation: From Efficacy to Effectiveness

Mariano A Giorgi[1,2,3]*, Claudio Daniel Gonzalez[1] and Guillermo Di Girolamo[4,5]

[1]*Department of Pharmacology, School of Medicine. CEMIC University Institute, Autonomous City of Buenos Aires Argentina, South America*

[2]*Cardiology Section, Department of Medicine, Norberto Quirno Medical Education and Clinical Research Center "CEMIC", Autonomous City of Buenos Aires, Argentina, South America*

[3]*Health Economic and Outcome Research Unit. CEMIC University Institute, Autonomous City of Buenos Aires Argentina, South America*

[4]*Department of Toxicology and Pharmacology, Faculty of Medicine University of Buenos Aires, Autonomous City of Buenos Aires Argentina, South America*

[5]*Alberto C. Taquini Institute of Research in Translational Medicine, Faculty of Medicine University of Buenos Aires - CONICET, Autonomous City of Buenos Aires Argentina, South America*

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***Corresponding author:** Mariano A Giorgi, Instituto Universitario - CEMIC Health Economics and Technology Assessment Unit. Buenos Aires, Argentina, South America

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Abbreviations: DOACs: Direct Oral Anticoagulants; NVAF: Non-Valvular Atrial Fibrillation; VKA: Vitamin – K Antagonists; RCTs: Randomised Controlled Trials

Opinion

Since its introduction in the market more than a decade ago, Direct Oral Anticoagulants (DOACs) have become a standard of care worldwide for the prevention of thromboembolism in non-valvular atrial fibrillation (NVAF) [1-3] as an alternative to vitamin–K antagonists (VKA) (warfarin and other dicoumarins). Despite have been a mainstay anticoagulant since the 1950´s [4] with evidence from randomised controlled trials (RCTs) supporting a ~ 50% relative reduction in stroke risk compared with aspirin [5], warfarin has several limitations. One is the slow onset of the anticoagulatory effect due to its mechanism of action through the reduction of vitamin-K dependent coagulation factors [6]. Other is the variability achieving effective and safe levels of anticoagulation expressed as an International Normalized Ratio 2 to 3 [6] to avoid thrombotic and bleeding events, respectively, due to drug-drug pharmacokinetic interactions and polymorphisms in the VKOR and CYP 2C9 genes [7]. Aiming to overcome such limitations, the advent of DOACs (dabigatran, rivaroxaban, apixaban and edoxaban) offered different pharmacodynamic and pharmacokinetic properties, compared with warfarin, and changed the paradigm in the use of oral anticoagulation in NVAF [8]. Direct oral anticoagulants exert their effect through direct inhibition on thrombin (dabigatran [9]) or by inhibiting activated factor X –anti Xa – (apixaban [10], rivaroxaban [11], edoxaban [12]). Both direct mechanisms lead to an early onset of the anticoagulatory effect, no overlapping with parenteral anticoagulants is required and, they could be restarted 1 or 2 days after a surgical procedure [13]. Besides, in the need to suspend the anticoagulation (i.e., in the case of a scheduled surgical procedure) the effect is reversed more faster than with VKAs, there´s no need for bridging with parenteral anticoagulants and, no antidote is usually needed in such cases. Four large phase III clinical trials including dabigatran [14], rivaroxaban [15], apixaban [16] and edoxaban [17] proved the safety and efficacy of DOACs in the management of NVAF showing non-inferiority to warfarin in the prevention of thromboembolic events (i.e., stroke / pulmonary embolism). Data from a meta-

analysis of these RCTs revealed a 10% reduction in all-cause mortality, a 19% risk reduction in stroke or systemic embolism and a 51% reduction in haemorrhagic stroke compared with warfarin [18].

Despite the overall evidence from RCTs that supports the use of these drugs, there are some pending questions to be answered or solved. First, there´s limited availability to antidotes. In case of an urgent surgical procedure or a life-threatening bleeding there are two FDA-licensed antidotes, idarucizumab for dabigatran [19] and andexanet alfa for apixaban and rivaroxaban [20] and there´s no approved antidote for edoxaban. Besides, trial-based evidence to guide their use is very limited. Second, phase III trials have validated fixed dose schemes for almost all patients (including those with impaired renal function and the elderly). However, in certain groups of patients, such as those with extremely obesity [21], pregnant and lactating people [22] there´s scarce data regarding their safety and efficacy that supported the "one-size-fits-all" dose regimes. In the case of frail elderly and very elderly patients (which represents a considerable amount of anticoagulated NVAF patients) dose adjustments were based in subgroups analysis of RCTs for apixaban, dabigatran and rivaroxaban [23] and only edoxaban has a trial specifically designed to treat patients ≥ 75 years old [24]. Finally, although there´s usually no need to monitor their anticoagulant levels, in some cases (as in unexplained bleeding o in high-bleeding risk procedures) it could be useful to know it and define the need to administer an antidote. In such cases, there´s still debate regarding the availability of such tests, prompt results and reference levels of anti-Xa or cloting time essays for DOACs [25].

Years after their marketing authorisation, many observational, real-world studies (RWE) brought new data about the effectiveness of DOACs, assessing them in populations not previously included in phase III trials, reflecting the results in real clinical practice, and providing indirect head-to head comparison between DOACs. Since this type of research is subjected to some controversies regarding inclusion bias not all RWE studies provide high quality evidence [26]. We will mention two relevant examples of such type of research. Chan et al. [27] published a systematic review and meta-analysis of 18 observational studies with bias control methods (9 used propensity score matching, 2 propensity score weighting, and 6 multivariable logistic regression) showed that DOACS, compared with warfarin were associated with reduction in the risk of gastrointestinal bleeding (HR=0.66 [95%CI 0.46-0.95]; I2 60), all-cause mortality (HR=0.62 [95%CI 0.56-0.69]; I2 0) intracranial haemorrhage (HR=0.50 [95%CI 0.40-0.62]; I223) and in thromboembolic events (HR= 0.70 [9%CI5 0.63-0.78]; I2 66) [27] There were no differences between DOACs and warfarin regarding the risk of stroke and no significant differences were reported between DOACs. Another interesting example is the retrospective cohort study with propensity-score matching of patients at high gastrointestinal bleeding risk who were treated with oral anticoagulants for NVAF [28]. A significant lower risk of stroke and/or systemic embolism were observed with DOACs compared with warfarin. Regarding major bleeding, there were differences between DOACs with lower risk associated with apixaban and dabigatran compared with warfarin (for apixaban HR=0.59 [95%CI 0.56- 0.63] and for dabigatran HR=0.78 [95%CI 0.70-0.86]) [28]. Considering the amount and quality of data collected in the previous decade current evidence invigorates the findings from phase III trials and widens the spectrum of data to support a broader use of DOACs. Many questions remain unanswered by RCTs and good quality real-world evidence studies could provide evidence to fill those gaps.

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