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DEBATE

Direct oral anticoagulants in atrial fibrillation: can data from randomized clinical trials be safely transferred to the general population? Yes

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Abstract Atrial fibrillation is the most common arrhythmia and is associated with significant morbidity and mortality. The current therapeutic options for patients at high thromboembolic risk include the vitamin K antagonists and the direct oral anticoagulants. These novel agents have been evaluated in more than 40,000 patients enrolled in four large randomized controlled trials for stroke prevention in non-valvular atrial fibrillation. When these results were pooled together, a greater efficacy profile, as well as a consistent reduction in life-threatening bleeding was shown in comparison to vitamin K antagonists. Randomized controlled trials offer the highest level of evidence on the efficacy and safety of an intervention; however, their results may not be directly applicable to the general population. The results of a number of post-marketing observational studies from the United States and Europe have been published. The results of these studies substantially confirm the findings of the randomized trials and show a favorable safety profile with the use of the direct oral anticoagulants even in unselected populations.

Keywords Atrial fibrillation · Factor Xa inhibitors · Thrombin inhibitors

Atrial fibrillation (AF) is the most common dysrhythmia and is associated with significant morbidity and mortality [1]. The presence of AF increases a risk of ischemic stroke approximately five times the non dysrhythmic person, and cardio-embolic strokes carry the highest fatality rates [2]. The risk of stroke in patients with AF is proportional to the number of risk factors which are summarized by the CHA_2DS_2-VASc score: congestive heart failure; hypertension; age ≥75 years (doubled); diabetes mellitus; previous stroke or systemic embolism (doubled); vascular disease; age 65–74 years; and female gender [3]. The current therapeutic options for patients at high thromboembolic risk include the vitamin K antagonists (VKAs) and the novel direct oral anticoagulants (DOACs). VKAs have been the only available oral anticoagulants for about 70 years, but they have several drawbacks, which led to their underuse in real-life AF patients [4]. The DOACs, instead, besides the target-specific action on thrombin (dabigatran) or on factor Xa (apixaban, edoxaban and rivaroxaban) and also have a predictable dose–response, which allows fixed dose regimens without the need for routine laboratory monitoring.

The DOACs have been evaluated in more than 40,000 patients enrolled in four large randomized controlled trials (RCTs) for stroke prevention in AF [5]. When these results are pooled together, a greater efficacy profile (19 % reduction in stroke or systemic embolism and 10 % reduction in all-cause mortality), as well as a consistent reduction in life-threatening bleeding (52 % lower risk of intracranial hemorrhages) is shown in comparison to VKAs [5].

RCTs offer the highest level of evidence of the efficacy and safety of an intervention; however, their results may not be directly applicable to the general population. In fact, RCTs have rigorous inclusion and exclusion criteria, therefore providing evidence for a selected population which is only partly representative of the AF population that we manage in everyday clinical practice [6]. Indeed, the DOACs are not approved for some categories of patients excluded from RCTs (such as patients with

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moderate-to severe mitral stenosis or patients with severe renal or liver failure), and their safety and effectiveness in other subgroups of fragile patients require additional information from phase IV clinical studies.

The results of a number of post-marketing observational studies, including the American Medicare database, or the Danish nationwide administrative registers, and of prospective registries, such as the Dresden registry, have already been published, and other large international registries are currently underway. [7–9]. Most of the current evidence from phase IV studies is on patients treated with dabigatran, since this was the first drug to be introduced on the market. The American and Danish administrative databases also include patients treated with warfarin, and, through propensity score matching, offer a comparison in the effectiveness and safety of the two therapeutic strategies [7, 8]. Of note, the Medicare database reflects current practice in the United States, where the Food and Drug Administration approved dabigatran 150 mg twice daily (BID), with strict criteria for reduction to a 75 mg BID dose that is recommended for patients with severe renal impairment, defined by a creatinine clearance between 15 and 30 ml/min [7], while the European Medicines Agency (EMA) approved dabigatran 150 mg and 110 mg BID and established a contraindication for patients with creatinine clearance <30 ml/min. Although comparative analysis from observational studies should be interpreted with caution, due to the potential risk of unmeasured confounders from non-random treatment allocation, the results of these studies have provided some important confirmations. For instance, in a large cohort of elderly Medicare beneficiaries, aged 65 years or older, initiating oral anticoagulant treatment for non-valvular AF, dabigatran 150 or 75 mg BID is associated, compared to warfarin, with reduced rates of ischemic stroke [1.13 vs 1.39/100 patient-years (pt-y); hazard ratio (HR) 0.80, 95 % CI 0.67–0.96] and mortality (3.26 vs 3.78; HR 0.86, 95 % CI 0.77–0.96) [7]. The effectiveness of dabigatran is also confirmed after pooling the data of 150 and 110 mg BID in the Dresden registry, where the on-treatment rate of stroke, transient ischemic attack, and systemic embolism is 1.9/100 pt-y and all-cause mortality is 3.8/100 pt-y [9]. These results are similar to the RE-LY trial: stroke or systemic embolism occurs in 1.54/100 pt-y for dabigatran 110 mg BID, 1.12 for dabigatran 150 mg BID, and 1.72 for warfarin [relative risk (RR) 0.89, 95 % CI 0.73–1.09 for dabigatran 110 mg BID vs warfarin; RR 0.65, 95 % CI 0.52–0.81 for dabigatran 150 mg BID vs warfarin]; and mortality rates are 3.75/100 pt-y for dabigatran 110 mg BID, 3.64 for dabigatran 150 mg BID and 4.13 for warfarin (RR 0.91, 95 % CI 0.80–1.03 for dabigatran 110 mg BID vs warfarin; RR 0.88, 95 % CI 0.77–1.00 for dabigatran 150 mg BID vs warfarin) [10, 11].

In terms of safety, the rates of major bleeding with dabigatran range from 2.2 to 4.3/100 pt-y, with small differences according to the dose in both phase III clinical trials and in phase IV studies [7–12]. RCTs and registries unanimously report very low rates of intracranial hemorrhages (ranging from 0.1 to 0.3/100 pt-y), which are also significantly decreased compared to warfarin [7, 8, 10, 11]. Conversely, dabigatran 150 mg BID is associated with a trend toward higher rates of gastrointestinal bleeding, although the difference with the comparator is not always statistically significant [7, 8, 10, 11]. In a recent study, using nationwide Danish prescription and patient registries, the highest bleeding rates in a population of AF patients are seen with vitamin K antagonists-naïve warfarin initiators, and no difference in overall bleeding rates is detected between warfarin experienced patients and dabigatran patients [13]. Different findings are reported in a recently published analysis from the Medicare database; the rate of major bleeding is reported to be up to 9.0 % with dabigatran vs 5.9 % with warfarin (HR 1.58, 95 % CI 1.36–1.83) [14]. However, in this cohort, the definition of major bleeding also includes the need for emergency department stay, irrespective of hemoglobin loss or the need for transfusions, and baseline patients characteristics suggest a higher risk population treated with dabigatran (mean age 75 years, 33 % chronic kidney disease, and 29 % with seven or more comorbidities [14]).

Also mortality rates related to major bleeding after treatment with the DOACs are reported to be low. In the Dresden registry, mortality related to major bleeding is 5.1 % at 90 days in patients treated with rivaroxaban and 4.2 % in patients treated with dabigatran, with only few patients requiring the infusion of prothrombin complex concentrates [9, 15].

One of the advantages with the use of dabigatran in Europe is the availability of two doses, both proven to be effective and safe in phase III clinical trials, which allows physicians to choose the most appropriate treatment for each patient. The availability of these two doses is leading to a careful selection based on individual characteristics, resulting in different baseline characteristics between the two groups. In fact, real world patients prescribed with dabigatran 110 mg BID appear to be older and with more thromboembolic and bleeding risk factors than patients treated with dabigatran 150 mg BID [8, 9]. This selection may be the reason for the low event rates observed in both groups, as well as the reason for more major bleeding events reported in the group that receives the lower dose of dabigatran [8, 9].

In general, the availability of different drugs for the prevention of stroke in patients with AF leads to the selection of different populations for each compound. A recent analysis of the Danish database shows that patients

prescribed with warfarin are more likely to have chronic kidney disease, myocardial infarction, and heart failure, while patients prescribed with the DOACs are older, more frequently of female gender and with a prior stroke [16]. Moreover, apixaban and rivaroxaban users are at higher risk of both stroke and bleeding, compared with warfarin and dabigatran users [16]. These findings are certainly influenced not only by physicians' attempts to tailor anticoagulant treatment to the individual patient, but also by the approval criteria of regulatory agencies, and by the results of phase III clinical trials. For instance, patients enrolled in the ROCKET-AF trial have higher mean $CHADS_2$ score compared to RE-LY and ARISTOTLE trials (3.5 vs 2.1, respectively), which simultaneously corresponds to a greater prevalence of bleeding risk factors (such as older age and previous stroke) [5].

Some practical points should be considered when applying the results of RCTs to everyday clinical practice. First, many AF patients can develop an acute coronary syndrome (ACS) and become candidate for the combined treatment with dual antiplatelet drugs plus an oral anticoagulant. Despite several RCTs that evaluated the triple therapy with the DOACs in ACS patients, only rivaroxaban shows a significant benefit in the reduction of ischemic events, although at the price of an increased risk of bleeding [17]. It should be noted; however, that the dose of rivaroxaban licensed by the EMA for this indication (2.5 mg BID) is approximately one-fourth of the dose recommended for AF patients. Furthermore, the latest guidelines for the management of ACS patients recommend the use of one of the new P2Y12-receptor inhibitors (prasugrel or ticagrelor), but in RCTs, only clopidogrel was administered. Two RCTs specifically evaluating AF patients who undergo a percutaneous coronary intervention are ongoing, but so far data on the net clinical benefit of combining dual antiplatelet drugs and DOACs are extremely limited [18].

Second, many anticoagulated patients need to undergo interventional or surgical procedures. The pharmacological properties of the DOACs could simplify the perioperative management, since the rapid offset and onset of action overcome the need for bridging with low molecular weight heparin. A sub-analysis from the RE-LY trial reports similar rates of peri-procedural major bleeding between dabigatran and warfarin (3.8 % for dabigatran 110 mg BID, 5.1 % for dabigatran 150 mg BID and 4.6 % for warfarin), but 17 % of dabigatran-treated patients received heparin bridging anyway [19]. In the Dresden registry, the overall rates of peri-interventional major cardiovascular events and major bleeding with the DOACs are low (1.0 and 1.2 %, respectively) [20]. Approximately 30 % of DOACs-treated patients received heparin bridging, while the remaining underwent temporary short interruptions (48.6 %) or simply continued the DOACs (21.7 %). Major bleeding complications are higher in procedures with heparin bridging compared to procedures without heparin bridging (2.7 vs 0.5 %, $p = 0.010$), while no difference is found in major cardiovascular events (1.6 vs 0.8 %, $p = 0.265$) [20], thus supporting the lack of need for bridging therapy. However, due to the fact that peri-procedural management was left to the discretion of the attending physicians, a selection bias arising from the individual patients characteristics, as well as the type of procedures could have influenced the outcomes.

Third, a final major issue in real-life clinical practice is related to the persistence and the compliance with long-term anticoagulant treatments. The continuation of treatment for the prescribed duration (*persistence*) for rivaroxaban is similar in the Dresden registry and in the ROCKET-AF trial (81.5 vs 76.3 %, median treatment duration approximately 1.5 years) [21, 22]. Conversely, dabigatran discontinuation is considerably higher in the Dresden registry compared to the RE-LY trial (36.4 vs 21 %) at 2-year follow-up [9, 10]. However, the main reasons for discontinuation were represented by non-bleeding side effects, followed by physicians' preference for other anticoagulants. Indeed, most of these patients were switched to another oral anticoagulant drug.

The conformity to the prescribed treatment dose (*compliance*) with dabigatran in real-life was unexpectedly high. Previous research shows that compliance with chronic therapies declines significantly after the first 6 months of treatment [23]. However, although the lack of routine monitoring of the DOACs and the less intense surveillance compared to RCTs can lead to poorer compliance, adequate compliance with dabigatran (defined as at least 80 % of the time) is reported in 88 % of patients treated for at least 3 months and followed by a Canadian Thrombosis Center and in more than 75 % of patients in a Danish cohort during the first year of follow-up [24, 25].

In conclusion, data from phase IV studies seem to confirm the effectiveness and safety of the DOACs in real-life clinical practice. Major bleeding rates appear to be consistently low, reversal strategies are rarely required, and most of the time have favorable outcomes. The availability of different doses and different molecules allow physicians to tailor appropriate treatment strategies to the individual patient. Among AF patients prescribed with chronic anticoagulant treatment, medication persistence and compliance with the DOACs appear to be good. These data suggest that results from RCTs can be safely translated to the general population, provided an accurate selection of patients suitable for the DOACs and an adequate information and follow-up of each patient.

Compliance with ethical standards

Conflict of interest Dr. Riva has no relevant conflicts to declare in relation to this paper. Dr. Ageno has participated in advisory boards for Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb-Pfizer, and Daiichi Sankyo and has received travel or research support from Bayer HealthCare, GlaxoSmithKline, Pfizer-BMS, Daiichi Sankyo, and Boehringer Ingelheim.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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