Apixaban Compared with Warfarin for Stroke Prevention in Atrial Fibrillation: Implications of Time in Therapeutic Range

Running title: Gallego et al.; Implications of Time in Therapeutic Range

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Clinical guidelines\textsuperscript{1,2} advocate the use of oral anticoagulation, whether a vitamin K antagonist (VKA) or one of the novel agents, for stroke prevention in patients with atrial fibrillation (AF) who have one or more risk factor for stroke. The benefits of traditional oral anticoagulants (VKAs), in terms of a reduction in stroke and major bleeding events, are only experienced over a narrow therapeutic window (International Normalised Ratio (INR) of 2.0 to 3.0). Their intricate pharmacokinetic profile with a slow onset and offset of action and numerous drug-, food- and alcohol-interactions, as well as genetic, ethnicity, and age-related differences in dose response, necessitates regular INR monitoring\textsuperscript{3}.

The efficacy and safety of VKAs strongly depends upon the percentage of time in the therapeutic range (TTR) (INR 2.0 to 3.0), with maximum benefits evident when the TTR is 70\% and greater\textsuperscript{4-6}. It is well known that poor control of anticoagulation intensity increases the risks of both thrombotic and hemorrhagic events\textsuperscript{4-6}. These inherent limitations associated with VKAs have prompted the development of novel oral anticoagulants (NOACs), targeting a specific factor of the coagulation pathway, and providing a stable anticoagulation effect with a fixed dose. Over the past few years, NOACs have yielded encouraging results, demonstrating at least non-inferiority to warfarin for stroke and systemic embolism and major bleeding\textsuperscript{7} and for some endpoints, superior efficacy\textsuperscript{7} and/or safety\textsuperscript{7}. However, it has been suggested that the beneficial effect of the NOACs could be simply due to sub-optimal control of the INR among patients in the warfarin arms of these trials.

In this issue of \textit{Circulation}, this important issue is addressed by Wallentin et al\textsuperscript{8} in a post-hoc analysis of the ARISTOTLE cohort of 18,201 AF patients with $\geq$1 risk factor for stroke who were randomised to receive either apixaban 5mg twice daily or dose-adjusted warfarin for stroke prevention, in over 1000 clinical centres in 39 countries, followed up over a median of 1.8 years.
The present analyses examined the relationship between the stroke and systemic embolism, major bleeding, and death from any cause, with INR control, evidenced by percentage TTR quantified as both centre TTR (cTTR) and individual TTR (iTTR)\(^8\).

The overall median (interquartile range) TTR was 66.0\% (52.4\% to 76.5\%) but TTR varied substantially between countries, ranging from 49\% to 78\%, and across clinical centres within each country, which is consistent with one other clinical trial comparing a NOAC with warfarin;\(^9\) this variability was primarily driven by sub-therapeutic INRs (<2.0).\(^8\) Despite good anticoagulation intensity achieved with VKA therapy in this trial, overall apixaban was associated with fewer adverse events compared to VKA therapy.

The calculation of both centre and individual TTR employed in these post-hoc analyses was somewhat complex. For each patient receiving warfarin (with ≥2 INR results), individual TTR over the total treatment period was calculated by the traditional Rosendaal method and then each centre’s TTR was estimated and predicted using a model designed to address problems associated with measurement error (smaller sites with greater variability in averaged TTR than larger sites). Further, patient’s characteristics were then added to calculate iTTR. Thus, the analyses are based on these predicted cTTR and iTTR values, rather than on actual cTTR and iTTR per se.

For patients receiving warfarin, the rate of stroke (ischaemic, haemorrhagic, or unspecified) and systemic embolism and all-cause mortality was lowest in those with cTTR ≥71.2\%. There were no significant interactions between predicted cTTR and apixaban or warfarin. The post-hoc analyses for the primary endpoint of stroke and systemic embolism and mortality mirrored those from the main ARISTOTLE trial results\(^10\). The significant reduction in stroke and systemic embolism with apixaban compared to warfarin (HR 0.79 (95\% CI 0.66-0.95)
seen in ARISTOTLE\textsuperscript{10} remained regardless of the quartile of predicted cTTR, although there was no obvious directional effect. Similarly, the significant reduction in the risk of death from any cause with apixaban compared to warfarin (HR 0.89; 95% CI 0.80-0.998)\textsuperscript{10} was also consistent across all levels of predicted cTTR control\textsuperscript{8}.

Although major bleeding was significantly lower with apixaban compared to warfarin [HR 0.69; 95% CI0.60-0.80]\textsuperscript{10} overall and across quartiles of predicted cTTR\textsuperscript{8}, the benefit of apixaban was greatest at centres with the lowest predicted TTR. However, the rate of major bleeding appeared to be greatest in those centres with the best INR control (cTTR$>$71.2%), which could be explained by better compliance in bleeding event reporting at sites with high TTR. Despite this anomaly, a significant net clinical benefit in favour of apixaban was evident for those centres with the poorest cTTR ($\leq$60.5).

The analyses of predicted cTTR demonstrate that the benefit of apixaban on all the outcomes reported in these post-hoc analyses, with the exception of mortality, are more pronounced among those patients with cTTR $\leq$60.5%. Comparable results were reported in similar analyses of cTTR comparing dabigatran to warfarin\textsuperscript{9}: when compared to warfarin either doses of dabigatran reduced the risk of stroke and systemic embolism or major bleeding among patients with low cTTR ($<$57%). Nonetheless, it should be remembered that cTTR is primarily a reflection of differences in the quality of oral anticoagulant services, which is contingent on the provision of service, accessibility for patients, costs incurred attending for INR checks etc, all of which may be better in more affluent countries, and does not take into consideration individual differences in INR control.

Importantly, the present post-hoc analyses also examined the impact of predicted iTTR on outcomes. Among patients receiving warfarin the median (IQR) predicted iTTR was 66.0%
(60.0-70.2%)\(^8\). The rate of stroke and systemic embolism and mortality, net clinical benefit and the composite of the primary efficacy and safety endpoints among patients receiving warfarin were lowest among those with iTTR\(\geq71.3\%\). Although the rate of major bleeding was similar across quartiles of iTTR (around 3%), the rate was again seen to be highest in those with the best iTTR (\(\geq71.3\%\)). For the primary efficacy and safety endpoints there was a trend towards a significant interaction between predicted iTTR (0.06 and 0.078, respectively), suggesting that the efficacy and safety benefit of apixaban is attenuated, but still significant, when INR control is good (predicted iTTR \(\geq60\%\)).

These sub-analyses reported by Wallentin and colleagues\(^8\) highlight two important points. First, they reiterate and further emphasize the importance of achieving and maintaining the optimum INR (target 2.5, range 2.0-3.0) with the generally corresponding lower adverse event rates evident with good TTR, which corroborates previous findings by other secondary analyses of trial cohorts\(^9,11-12\), a retrospective observational study\(^13\) and systematic reviews and meta analyses\(^6,14\). Therefore, every effort should be made to achieve and sustain therapeutic anticoagulation control for patients receiving VKAs. Second, these results strengthen the main findings from the ARISTOTLE trial\(^10\) and demonstrate the superior efficacy and safety of apixaban over warfarin, even when compared to optimal anticoagulation with warfarin (TTR\(\geq70\%\)), suggesting that the benefits of NOACs are not simply a result of sub-optimal INR control in the trials\(^8,9\).

Finally, it is worth noting that perhaps the most important question resulting from the analyses of Wallentin et al is that of TTR prediction\(^8\). Until now, when prescribing oral anticoagulation, physicians have not been able to reliably predict which patients will be able to tolerate a VKA, who would be able to achieve and maintain steady INR control, and thus benefit
from VKA, and those cases in whom reaching a therapeutic dose would be difficult or impossible to achieve. Therefore efforts to identify those patients who may be more or less likely to achieve a good TTR should be concentrated on, as this would assist in the decision-making process about the most appropriate oral anticoagulant for each patient, given the greater choice of agents currently available.

Evident from the present analyses\(^8\) and previous meta-analyses\(^{14,15}\), demonstrates that the quality of oral anticoagulation is strongly related to the performance of coagulation centre and to clinical and demographic characteristics inherent to each patient. However, how these known characteristics can be applied in daily practice remains unclear.

Recently Apostolakis and colleagues\(^{16}\) have developed a score for predicting INR control using routinely available clinical information, namely Sex (females), Age (<60 years), Medical history (≥2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease), Therapy with interacting drugs (e.g., amiodarone for rhythm control) (presence of each scores 1 point), as well as current Tobacco use and Race/ethnicity (non-Caucasian) (presence of each scores 2 points). The score’s acronym, SAMe-TT\(_2\)R\(_2\), comprises these risk factors, with scores ranging from 0 to 8, and assesses the quality of INR control amongst AF patients demonstrating good discriminatory performance (c-statistics of 0.72 (95% CI 0.64-0.80) and 0.70 (95% CI 0.57-0.82) in the internal and external validation cohorts) between patients who do well on VKA (SAMe-TT\(_2\)R\(_2\) score = 0-1) and those who are at risk of sub-optimal anticoagulation control (i.e., SAMe-TT\(_2\)R\(_2\) score ≥2), who require more regular INR monitoring and other interventions to achieve appropriate anticoagulation control.

Whilst aiming for simplicity for everyday clinical use, clinical-based INR predictors may
ignore some crucial factors affecting the anticoagulation quality, such as genetic factors (related with VKA metabolism) and patient’s education. Improving the latter should be a major treatment goal to assure better medication regimen adherence, which may translate into fewer adverse events regardless of the OAC prescribed. With an increasing variety of therapeutic options when chronic oral anticoagulation is needed, finding an accurate way to predict who will adapt well to a VKA and who would better fit a NOAC should be a priority.

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