Clinical guidelines advocate the use of oral anticoagulation, whether a vitamin K antagonist (VKA) or 1 of the novel agents, for stroke prevention in patients with atrial fibrillation who have ≥1 risk factors for stroke. The benefits of traditional oral anticoagulants (VKAs), in terms of a reduction in stroke and major bleeding events, are experienced only over a narrow therapeutic window (international normalized ratio [INR] of 2.0–3.0). 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.

The efficacy and safety of VKAs depend heavily on the percentage of time in the therapeutic range (TTR; INR, 2.0–3.0), with maximum benefits evident when the TTR is ≥70%. It is well known that poor control of anticoagulation intensity increases the risks of both thrombotic and hemorrhagic events. 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 noninferiority to warfarin for stroke and systemic embolism and major bleeding and showing superior efficacy and/or safety for some end points. However, it has been suggested that the beneficial effect of the NOACs could simply be due to suboptimal control of the INR among patients in the warfarin arms of these trials.

In this issue of Circulation, this important issue is addressed by Wallentin et al in a post hoc analysis of the Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) cohort of 18,201 atrial fibrillation patients with ≥1 risk factor for stroke who were randomized to receive either apixaban 5 mg twice daily or dose-adjusted warfarin for stroke prevention in >1000 clinical centers in 39 countries and were followed up over a median of 1.8 years. The present analyses examined the relationship between stroke and systemic embolism, major bleeding, and death resulting from any cause and INR control, evidenced by the percentage of TTR quantified as both center TTR (cTTR) and individual TTR (iTTR).

The overall median TTR was 66.0% (interquartile range, 52.4%–76.5%), but TTR varied substantially between countries, ranging from 49% to 78%, and across clinical centers within each country, which is consistent with 1 other clinical trial comparing a NOAC with warfarin; this variability was driven primarily by subtherapeutic INRs (<2.0). Despite good anticoagulation intensity achieved with VKA therapy in this trial, overall, apixaban was associated with fewer adverse events compared with VKA therapy.

The calculation of both center and individual TTRs used 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 center’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). Furthermore, patient 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 rates of stroke (ischemic, hemorrhagic, or unspecified) and systemic embolism and all-cause mortality were 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 end point of stroke and systemic embolism and mortality mirrored those from the main ARISTOTLE trial results. The significant reduction in stroke and systemic embolism with apixaban compared with warfarin (hazard ratio, 0.79; 95% confidence interval, 0.66–0.95) seen in ARISTOTLE remained regardless of the quartile of predicted cTTR, although there was no obvious directional effect. Similarly, the significant reduction in the risk of death resulting from any cause with apixaban compared with warfarin (hazard ratio, 0.89; 95% confidence interval, 0.80–0.998) was also consistent across all levels of predicted cTTR control.

Although major bleeding was significantly lower with apixaban compared with warfarin (hazard ratio, 0.69; 95% confidence interval, 0.60–0.80) overall and across quartiles...
of predicted cTTR, the benefit of apixaban was greatest at centers with the lowest predicted TTR. However, the rate of major bleeding appeared to be greatest in those centers with the best INR control (cTTR >71.2%), which could be explained by better compliance in bleeding event reporting at sites with high TTRs. Despite this anomaly, a significant net clinical benefit in favor of apixaban was evident for those centers with the poorest cTTR (≤60.5).

The analyses of predicted cTTR demonstrate that the benefit of apixaban on all outcomes reported in these post hoc analyses, except mortality, is more pronounced among those patients with cTTR ≤60.5%. Comparable results were reported in similar analyses of cTTR comparing dabigatran and warfarin. Compared with warfarin, either dose 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 predicted iTTR was 66.0% (interquartile range, 60.0%–70.2%). The rate of stroke and systemic embolism and mortality, the net clinical benefit, and the composite of the primary efficacy and safety end points among patients receiving warfarin were lowest among those with iTTR ≥71.3%. Although the rate of major bleeding was similar across quartiles of iTTR (=3%), the rate was again seen to be highest in those with the best iTTR (≥71.3%). For the primary efficacy and safety end points, there was a trend toward 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 ≥60%).

These subanalyses reported by Wallentin and colleagues highlight 2 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 optimum INR control in the trials.8,9 Evidence from the present analyses8 and previous meta-analyses14,15 demonstrates that the quality of oral anticoagulation is strongly related to the performance of the coagulation center and to clinical and demographic characteristics inherent in each patient. However, how these known characteristics can be applied in daily practice remains unclear.

Recently, Apostolakis and colleagues16 have developed a score for predicting INR control using routinely available clinical information, namely sex (female), age (<60 years), medical history (≥2 of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, or hepatic or renal disease), therapy with interacting drugs (eg, amiodarone for rhythm control) (the presence of each score points 1), and current tobacco use and race/ethnicity (nonwhite) (the presence of each scores 2 points). This score, SAMe-TT2R2, comprises these risk factors, with scores ranging from 0 to 8, and assesses the quality of INR control among atrial fibrillation patients, demonstrating good discriminatory performance (c statistics of 0.72 [95% confidence interval, 0.64–0.80] and 0.70 [95% confidence interval, 0.57–0.82] in the internal and external validation cohorts) between patients who do well on VKA (SAMe-TT2R2 score=0–1) and those who are at risk of suboptimal anticoagulation control (ie, SAMe-TT2R2 score ≥2) who require more regular INR monitoring and other interventions to achieve appropriate anticoagulation control.

While 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 to VKA metabolism) and patient education. Improving the latter should be a major treatment goal to ensure 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.

Disclosures
Dr Gallego holds a grant from the Spanish Foundation Alfonso Martín Escudero. Dr Vílchez holds a research grant “Río Hortega” by the Instituto de Salud Carlos III. Dr Lane is in receipt of investigator-initiated educational grants from Boehringer Ingelheim and Bayer Healthcare and has been on the speakers’ bureau for Boehringer Ingelheim, Bayer Healthcare, and BMS/Pfizer. She is also on the steering committee for the AEGEAN study a phase IV trial funded by BMS/Pfizer.

References
Implications of Time in Therapeutic Range


**Key Words:** Editorials ■ anticoagulants ■ apixaban ■ atrial fibrillation ■ time in therapeutic range ■ warfarin
Apixaban Compared With Warfarin for Stroke Prevention in Atrial Fibrillation: Implications of Time in Therapeutic Range
Pilar Gallego, Juan Antonio Vilchez and Deirdre A. Lane

_Circulation_. 2013;127:2163-2165; originally published online May 2, 2013;
doi: 10.1161/CIRCULATIONAHA.113.003132
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/127/22/2163

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/