Atrial fibrillation: a spectrum of risk with a uniform treatment effect of novel anticoagulants?

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This editorial refers to ‘Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial,’† by S.M. Al-Khatib et al., on page 2464

The last several years have seen the completion of five pivotal outcomes trials evaluating three novel oral anticoagulants (NOACs) in > 55 000 patients with atrial fibrillation (AF) from around the world.1-5 Each of these studies has shown that the respective new agent is at least as efficacious as, if not superior to, warfarin in reducing stroke or non-central nervous system embolism; all three NOACs were shown to be superior to warfarin in reducing intracranial haemorrhage. The large, diverse populations enrolled across broad geographic regions and practice settings provide an opportunity to explore questions about the specific cohorts of patients with AF of clinical interest, the natural history of the disease, and the pragmatic challenges physicians confront each day in clinical practice.

The analyses from the ARISTOTLE study database by Al-Khatib and colleagues6 provide important information about outcomes in groups with different subtypes of AF and about treatment effects with apixaban compared with placebo in the same subtypes. We agree with the authors’ two primary conclusions: (i) patients with persistent or permanent AF have higher event rates (including rates of systemic embolus and bleeding complications) compared with patients with paroxysmal AF events after adjusting for baseline differences; and (ii) the effects of apixaban compared with warfarin in patients defined by AF subtype are consistent with the overall trial results (lower rates of embolus and less bleeding) without a statistically or clinically significant interaction. Similarly, within the ROCKET-AF trial,3 patients with paroxysmal AF had lower event rates and the results of the treatment comparison were consistent with the overall trial results. The differences among findings from ARISTOTLE6, ROCKET-AF,3 and RE-LY2 (with regard to the lower event rates with paroxysmal AF) are intriguing.

The authors point out a notable aspect of these analyses: the evaluation of treatment effect by duration of AF. It is critical for the reader to understand that this ‘duration of AF’ is not the duration of actual AF rhythm, but rather the length of time from the initial diagnosis of AF to randomization, as described in the statistical analysis section of the present article.6 The concept of duration of AF as defined by Al-Khatib and colleagues has substantial limitations, and results from these analyses should be interpreted with caution.

There is a growing body of literature about the prognostic importance of the actual burden of AF rhythm. Data suggest that subclinical AF and atrial arrhythmias detected by monitoring are associated with worse outcomes.7 More specifically, investigators have shown that the higher burden of AF rhythm as defined by the number of hours of actual abnormal rhythm is associated with worse outcomes.8 Importantly, the ongoing IMPACT randomized trial9 is formally testing whether management of anticoagulation therapy based on the burden of AF will affect clinical outcomes. Thus, ARISTOTLE is opening a window into a fascinating aspect of AF—namely, its temporal characteristics—that will be the subject of much new learning.

Ancillary or subgroup analyses from large clinical trial populations, such as the ones described in the report of Al-Khatib et al., are important and can provide valuable insights about the use of therapies. Greater confidence about specific observations is typically gained with larger sample sizes and cross-validation in independent populations, because individual trials are not designed with sufficient statistical power to examine the primary endpoint of interest in subgroups of a study population. Further, many qualitative interactions are simply ‘false positives’ generated by the multiple subgroup analyses performed in every large clinical trial.10,11 Less is known about the possibility of false-negative findings, although statistical power raises issues of similar importance to the performance of multiple comparisons.

We are entering an era in which the public will expect the results of human experiments to be made publicly available.12 Although multiple manuscripts reporting on individual subgroups will provide a critical contextual summary of the meaning of trial results, a superior approach would aggregate trial results across all therapies within a...
class at the level of the individual patient. We must work through the competing forces that challenge this important activity, while remaining mindful of the tremendous effort required, as well as the significant societal ramifications if broadly available data are mishandled or misused. The nascent ability to create large databases by aggregating individual trials and incorporating data from registries, electronic health records, and patient-reported outcomes promises to create a new ‘data fabric’ orders of magnitude more informative than current systems, but the rules of conduct for ensuring data transparency need considerable elucidation. Fortunately, we are quickly articulating the guiding vision, information technology infrastructure, and collaborative partnerships that will allow significant advances in the near future (www.nihcollaboratory.org).

These findings from the ARISTOTLE study reinforce the general message that NOACs are at least as good as warfarin in preventing arterial emboli and death, and superior in terms of causing less intracranial haemorrhage and lethal bleeding. These results are clear across multiple subgroups and populations. Patients, clinicians, and health systems must grapple with complex issues of comfort, convenience, and cost when deciding whether to offer anticoagulation therapy with warfarin or an NOAC—and, if the latter are chosen, which of the NOACs to use (Figure 1). However, the overall imperative to treat when the expected benefit outweighs the risk continues to grow, and together we should continue to develop more effective ways of providing the information that will enable informed choices.

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