Atrial fibrillation (AF) continues to increase in incidence worldwide as people live longer in general and with co-existent cardiovascular diseases.\(^1\)\(^,\)\(^2\) In community-based studies, arrhythmia recurrence rates are frequent, and co-morbidities such as heart failure, stroke, and mortality remain pervasive despite different and evolving treatment approaches.\(^3\)\(^,\)\(^4\) In this context of an escalating disease incidence without consistent treatments that alter the natural history of the disease, two fundamental questions need to be considered. First, are community-based treatments appropriate and used correctly for the disease state and, if not, will improvement translate into better outcomes? Secondly, is our fundamental understanding of the disease correct? The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) is an ongoing study involving centres throughout the world that will ultimately include \(~\leq 52\) 000 patients. This registry will provide fundamental insight into practice patterns of AF treatments and AF-related outcomes.\(^5\) In an interim analysis of 17 162 patients, Bassand and colleagues\(^5\) presented antithrombotic use by stroke risk profiles and 2-year stroke, major bleeding, and death rates. Their outcomes provide understanding into the two fundamental questions that were proposed.

First, are used treatments appropriate for the disease state? In patients with a CHADS\(_2\)-VASc score of \(\geq 5\), \(~55–65\)% were on warfarin or a direct oral anticoagulant. Underuse of anticoagulants remains a pervasive worldwide problem in AF management.\(^6\) Despite the fact that an estimated 20–25% of patients that had coronary artery disease or peripheral artery disease may also benefit from an antiplatelet agent, \(~30\)% in each CHADS\(_2\)-VASc stratum of moderate to high risk were on an antiplatelet suggestive of overuse. Then, in patients with a CHADS\(_2\)-VASc score of 0, \(~40\)% were on warfarin or a direct oral anticoagulant despite no trial or observational study to support their use in this low-risk population. In addition, 30% of the low-risk patients were on an antiplatelet agent. Aspirin use in AF patients remains an area of controversy and has not been advocated in very low-risk patients in multiple society guidelines statements.\(^7\) A meta-analysis of 29 trials that included 28 044 AF patients examined the efficacy of aspirin for stroke or systemic embolism or mortality compared with either a control treatment or placebo.\(^8\) This meta-analysis found an overall 20% reduction in events with aspirin. A trended benefit was seen in most studies, but only one was statistically positive for a benefit with aspirin, the Stroke Prevention on Atrial Fibrillation (SPAF-I) trial, which reported a 42% reduction in stroke or systemic embolism.\(^9\) The answer to the first question is no; treatments for AF that may lower stroke rates are not consistently or appropriately used in the community.

Regarding the latter question of the disease mechanism, is it possible that AF is a risk marker of a distinct disease state severity rather than a risk factor for disease? If AF is primarily a risk marker, then its treatment is akin to treating only a fever in a patient with an infection. Although antipyretics will potentially improve symptoms early and increase quality of life, the infection that caused the fever, if unaddressed, will cause adverse outcome progression. However, if AF is a direct cause of stroke, heart failure, and mortality, then focused arrhythmia treatment should, if done safely and efficiently, significantly lower risk of these adverse outcomes.

The mechanistic paradox of whether AF is a risk marker of disease vs. a risk factor for disease is shown in Figure 1. If AF is a direct cause of stroke due the electrical instability of the atrium that leads to blood stasis, endothelial dysfunction, and hypercoagulability and, as a consequence, clot, then restoring sinus rhythm will reverse the risk. The implications are that AF and stroke are temporally related, and arrhythmia onset can be used to guide stroke risk management. Pill in the pocket anticoagulation approaches are feasible. Finally, maintaining sinus rhythm will lower stroke rates in a manner similar to other diseases such as heart failure. However, if AF is a marker of a systemic disease state severity, then atrial changes, both electrical and structural, also reflect this underlying disease process. Similarly, as atrial substrate worsens, there is a corresponding increase in stasis and hypercoagulability that impacts clot formation in the atrium, left atrial appendage, and elsewhere. The implications of this paradigm are that there is not a consistent temporal correlation of AF
and stroke. This is now becoming apparent as implantable technologies provide insight into the inconsistency of AF genesis and stroke events, and anticoagulation use tailored by device-detected arrhythmia does not lower thrombo-embolism rates.\textsuperscript{10,11} Next, only systemic approaches to the disease state will lead to durable favourable outcomes and they are directed at the core and the scope of the problem. Finally, diseases initially considered risks of AF will continue to be prevalent largely independently of the rhythm management itself.

In the GARFIELD-AF registry, death events outnumber stroke events 3:1. Although the CHADS\textsubscript{2}-VASc score predicted stroke events, it also predicted in an augmented manner with score increase, death and major bleeding. The same risk score significantly predicts stroke risk in patients without AF.\textsuperscript{12} As a risk score, CHADS\textsubscript{2}-VASc functions equally well to predict diverse endpoints in patients with and without the target disease in which it is used for stratification. Furthermore, the same risk factors when applied to people without AF are also strongly associated with the arrhythmia incidence.\textsuperscript{13} These findings highlight the underlying disease state that forms the foundation for arrhythmia genesis, derived from most of the variables that comprise the CHADS\textsubscript{2}-VASc score, which is a systemic vascular disease. This disease state is driven primarily by obesity, sedentary lifestyles, metabolic syndrome, and sleep apnoea. Unfortunately in many patients, AF is a manifestation of a systemic disease state and it draws attention away from the primary mechanisms that cause its incidence and disease state co-morbidities. Returning our attention to these mechanisms is probably the only way durably to treat and address the worldwide increasing rates of AF, stroke, and cardiovascular death.

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References


