Atrial Fibrillation and Stroke Prevention in Aging Patients:

What’s Good Can be Even Better

Running title: Freedman et al.; Atrial Fibrillation, Stroke and Aging

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The most common arrhythmia in older adults is atrial fibrillation with an estimated prevalence of approximately 9% in adults aged 80 years or older and a concomitant increased burden of developing stroke. Additionally, over the past decade, both the incidence and prevalence of atrial fibrillation has markedly increased\(^1\) and, with it, the total number of patients potentially requiring long-term oral anticoagulation therapy for the prevention of stroke and systemic embolism. In 2009, the estimated number of atrial fibrillation diagnoses in the United States was 2,643,000 with equal distribution between men and women and 82% at ages 65 or older with that number increasing 10% between 1999 to 2005.\(^2\) The magnitude of the problem is exemplified by the fact that the risk of stroke in patients with atrial fibrillation increases with age and accounts for about 45% of embolic strokes, approximately 100,000 annually in the US.\(^3\)

The advent of the novel oral anticoagulants has strikingly shifted the goalposts in the field of stroke prevention. Large randomized trials of 4 agents involving 71,683 participants\(^4\) have demonstrated that these drugs are at least noninferior to warfarin for the prevention of stroke and systemic embolism and, in the case of of apixaban and higher doses of dabigatran, the trials demonstrated superiority over warfarin. In addition, these agents have demonstrated a consistent and striking impact on reducing intracerebral hemorrhage and major bleeding. Moreover, a recent meta-analysis demonstrated an overall reduction in mortality of approximately 10%.\(^4\)

A major issue in these studies is the increased bleeding and stroke rates in select populations. Among patients with atrial fibrillation treated with anticoagulation, the risk of was found to be higher among Asians, Blacks, and the elderly.\(^5\) Complicating the treatment for atrial fibrillation in the aging population is a higher risk of bleeding. This is another example of what we find often in medicine, namely; the greater the potential benefit the greater the risk. In the
case of atrial fibrillation, this is easily accounted for by the fact that many of the components of risk stratification scores for stroke are also incorporated into algorithm used to predict the risk of bleeding. This requires careful consideration to ensure both efficient and safe oral anticoagulation and, in the case of the “novel” oral anticoagulants, it is imperative that protocols be put into place to optimize their use in multiple situations; e.g. renal dysfunction, during procedures, following a bleeding episode, and using metrics to determine how to measure their effect. In addition, anticoagulants are widely underutilized in the community in general and, in particular, among the elderly. It appears that physicians are more concerned about bleeding in contrast to patients in whom the major fear is that of stroke.\textsuperscript{6,7} To compound the problem further, even among patients prescribed anticoagulants, there is a high rate of discontinuation. In the setting of cardiovascular disease, most elderly with atrial fibrillation who undergo percutaneous coronary intervention with stent placement receive dual rather than triple therapy at discharge.\textsuperscript{8}

Addressing the problem of atrial fibrillation in the aging population is a study by Halperin in the current issue of \textit{Circulation}.\textsuperscript{9} To examine atrial fibrillation in the elderly, this group utilized the ROCKET AF (Rivaroxaban Once-daily oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial using a prespecified secondary analysis comparing outcomes in patients aged >75 years with younger patients. The ROCKET AF trial, a randomized, double-blind, double-dummy study of rivaroxaban and warfarin in non-valvular atrial fibrillation, initially showed that this new oral factor Xa inhibitor was noninferior to warfarin.\textsuperscript{10} In the current analyses, there were 6229 patients aged >75 years with AF and >2 stroke risk factors who were randomized to warfarin or rivaroxaban. The primary endpoint was all strokes (ischemic or hemorrhagic) and
systemic embolism according to intention to treat. They found that older participants had higher rates of primary events (2.57% vs. 2.05%/100 pt-ys, and major bleeding (4.63% vs. 2.74%/100 pt-ys). Hemorrhagic stroke rates in patients >75 were similar to younger patients with no interaction between age and response to rivaroxaban. The conclusion was, as expected, older patients with atrial fibrillation have higher rates of stroke, embolic events and major bleeding, but the relative efficacy and safety of rivaroxaban compared with warfarin did not differ with age.

In general terms, these findings are consistent with benefit seen in previous subgroup analyses including the demonstration that, in patients with peripheral arterial disease in ROCKET AF, there was no statistically significant higher risk of stroke or systemic embolism and there was similar efficacy outcomes in patients treated with rivaroxaban and warfarin. These findings are also consistent with observations seen with other newer oral anticoagulants. The benefits of apixaban vs. warfarin have been shown to be consistent in patients with atrial fibrillation regardless of age. In fact, adjusting for the higher risk at older age, the absolute benefits of apixaban were reported greater in the elderly.

In addition to potentially offering benefit in terms of bleeding risk, newer oral anticoagulants may offer increased convenience for elderly patients, because of their more predictable pharmacologic profiles, a rapid onset of action, a broader therapeutic window, and no specific requirement for routine coagulation monitoring. Also, these therapies have far fewer food and drug interactions as compared with warfarin.

The question remains, even if reassured that the use of new oral anticoagulants is, at least, non-inferior in terms of risk/benefit, can we do better? Already, anticoagulants are recommended in patients with atrial fibrillation aged 75 years or above after assessing the bleeding risk using
the HEMORR2HAGES or HAS-BLED scores.\textsuperscript{14} Some suggest HAS-BLED has better predictive value in the elderly.\textsuperscript{15} However, can these scores be improved upon to assist with their use in the older patient? In the elderly, newer oral anticoagulants, all of which are renally excreted to a variable extent, should take into account renal function as well as and cognitive function specifically for adherence to treatment.\textsuperscript{16} It should be emphasized that renal function is a dynamic entity that requires frequent re-assessment. Furthermore, all but one of the 4 anticoagulants are prescribed twice daily and, given their shorter half-lives, compliance is a critical issue. Additional therapies including antiarrhythmic drugs should be used cautiously in elderly patients due to the frequency of metabolic abnormalities and higher risk of drug interactions.

Is there still a role for warfarin? Warfarin remains the drug of choice in patients with mechanical valves, left ventricular thrombi, rheumatic mitral valve disease and severe renal dysfunction. In patients on warfarin with a stable INR and easy access to an anticoagulation clinic or among whom home INR testing has been effective, there is certainly no compelling rationale for switching to a newer oral anticoagulant. In patients in whom compliance is an issue, the ability to check the INR is helpful. This is also the case in patients at a higher risk of bleeding in whom INR monitoring to maintain with a goal in the low therapeutic range is a reasonable option. It is also possible that newer medications such as Tercarferin, an orally active Vitamin K epoxide inhibitor, will have a role in select settings such as in valvular disease. Finally, cost will remain an issue for many, especially the elderly.

While more recent fundamental biological, diagnostic, and therapeutic developments raise hope that atrial fibrillation and/or the resulting stroke can be prevented or mitigated, many gaps do and will remain and likely will include older adults with a myriad of risks and
medications. Thus, the public health importance atrial fibrillation and stroke in elderly adults remains strong and should direct areas for investigation that may mitigate stroke-related morbidity. Clearly needed are innovative approaches that may ultimately facilitate the application of novel preventive, diagnostic, and therapeutic insights into the management of older adults with atrial fibrillation.17

Nonetheless, the search for new approaches should not divert attention away from improving on what is already in place. Firstly, the gap between those eligible for oral anticoagulants and those receiving these drugs must be closed. Second, it should also be emphasized that the data supporting aspirin as an alternative to warfarin are not strong and the recent ESC guidelines do not identify any role for aspirin in stroke prevention in atrial fibrillation. Aspirin may be a major contributor to bleeding in patients already on warfarin and in the elderly, in particular, the reasons for concomitant aspirin therapy need to carefully evaluated.18 Third, we should appreciate that the majority atrial fibrillation may be the consequence of risk factors causing increased arterial stiffness, diastolic dysfunction and atrial volume overload.19 Thus, it may be prudent to aim for aggressive risk factor modification as an intrinsic aspect in the management of atrial fibrillation.20

In summary, in this issue of Circulation, Halperin and colleagues, using data from the ROCKET AF trial demonstrate the utility of using rivaroxaban in older adults. Regardless of the medication chosen, however, older patients must always be treated cautiously due to an increased risk of stroke and bleeding, and additional challenges related to drug interactions. Despite the higher risk of primary events as well as risk due to the medications themselves, newer oral anticoagulants may be suitable alternatives to warfarin in older patients due to specific advantages; no need for regular monitoring, more rapid onset of action, and fewer drug
and food interactions. As additional data is gathered in this large and higher risk population, our
ability to guide optimal use in terms of risk/benefit as well as choose the optimal
medication/dosage and mitigate drug interaction, will expand and lead to better care of our older
patients. However, while there is no doubt about the benefits of oral anticoagulation in the
elderly, focus must be placed on reducing their risk.

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