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Stroke Prevention in Atrial Fibrillation in the Very Elderly: Anticoagulant Therapy Is No Longer a Sin

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It is well established that older individuals with atrial fibrillation (AF) are less likely to receive oral anticoagulant (OAC) therapy compared with their younger counterparts,[1,2] and when treated with vitamin K antagonists (VKAs), there is a relatively high rate of discontinuation resulting in a high rate of stroke or death.[3,4] This undertreatment of the very elderly represents a paradox because older patients are at higher risk of stroke and are more likely to need anticoagulant therapy compared with younger patients.[5,6] Why are physicians reluctant to prescribe therapy? There are many reasons for the undertreatment of AF in the elderly including physician-related factors, patient-related factors, and the practical aspects of therapy.[7] An overriding concern, however, is the fear of putting the patient at risk for major bleeding as a result of anticoagulant therapy, while the fear of leaving the patient open to stroke is of lesser concern.[4,7–9] This is sometimes expressed as the fear of creating a sin of commission versus a sin of omission (by doing something we should not do versus not doing something we should do).[10] The consequence of the latter (ie, stroke) is chalked up to the natural course of the disease. Until recently, studies to address the net benefit of anticoagulant therapy for stroke prevention in AF in the very elderly were lacking. Now we have substantial evidence in progressively older cohorts to put this issue to rest.

In elderly patients with AF, numerous trials have documented the increased risk of stroke while also showing an increased risk of bleeding with OAC therapy.[5,6] Until recently, only therapy with the VKAs was available where many factors come into play in how patients fare, including the all-important system of dose management of this complex drug to keep the patient in therapeutic range.[11] But even in the best of settings, such as randomized clinical trials or anticoagulation clinics, major bleeding is increased in the elderly when taking anticoagulants. Consequently, physicians may withhold therapy or prescribe aspirin, a clearly less effective antithrombotic, but one that physicians feel is less likely to cause major bleeding. Studies now show this to be a fallacy when applied to the elderly. Until recently, there was a dearth of studies that included "very old" patients, generally ≥80 or 85 years of age, but this void is quickly being filled.

In this issue of *JAHA*, Patti et al[12] provide evidence favoring treatment with anticoagulant therapy to prevent stroke or systemic embolism in the very elderly that outweighs the risk of major bleeding. They report on a subanalysis of the PREFER in AF Registry (PREvention oF thromboembolic events-European Registry in Atrial Fibrillation), a registry of over 7000 consecutive patients with AF from 461 centers in 7 European countries conducted between 2012 and 2014.[13] Although the report has limitations as a prospective registry, it has strength reflecting real-world antithrombotic therapy and it reports on a sizable number of very old patients ≥85 years of age (505) and compares them with 5907 patients <85 years. As expected, the older cohort was at greater risk for stroke and bleeding with more comorbidities and higher CHA_2DS_2VASc score than the younger cohort.

In all patients, those treated and not treated, the occurrence of stroke/transient ischemic attack/systemic embolism was substantially higher in the older than in the younger cohort (4.8% per year versus 2.3% per year, respectively; P=0.0006). Similarly, the older cohort had a higher rate of major bleeding than their younger counterparts, although this did not reach significance (4% per year versus 2.7% per year, respectively; P=0.11), unless those ≥85 years were compared with those <75 years where the rate was 1.9% per year; P=0.001. Fifty-one percent of all major bleeds were gastrointestinal, 9% intracerebral, and 43% other sites of bleeding. When comparing those treated with anticoagulants versus not treated or treated only with antiplatelet agents, there was a favorable odds ratio for reduced stroke/transient ischemic attack/systemic embolism in both the elderly cohort (0.64; P=0.37) and in those <85 years (0.74; P=0.26). This represented a greater absolute reduction of 2% in the elderly compared with 0.5% in those <85 years. In those ≥90 years

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of age, the absolute risk reduction was even greater at 4.6%. What is most important is the finding that major bleeding was not significantly different in either cohort between those treated compared with those not treated with anticoagulants; in the elderly, 4.2% versus 4.0%, respectively; P=0.77; in those <85 years, 3.4% versus 2.9%, respectively; P=0.74. Similar findings were seen in an exploratory analysis of those ≥90 years. When comparing those on anticoagulant therapy versus those only on antiplatelet therapy in the very elderly, the incidence of major bleeding was similar (4.1% versus 3.9%, respectively), but higher than in those without any antithrombotic therapy (4.1% versus 2.8%). Finally, net clinical benefit (thrombosis+bleeding+myocardial infarction) significantly favored treatment in the very elderly (P=0.036). Although not the focus of this report, an incidental finding is that 78% of the very elderly were receiving anticoagulants and over 80% of the entire cohort with a CHA_2DS_2VASc score ≥2 received anticoagulants, thus documenting the changing nature of contemporary physician prescribing behavior. This suggests a greater willingness to treat patients with AF even in the very old compared with studies from the 1990s and early 2000s. This trend has been seen in other recent registries as well[14] and indicates an overall improvement in complying with professional guidelines. The older cohort, however, was also treated more frequently with antiplatelet drugs compared with younger patients (15% versus 11%, respectively), a therapeutic intervention that is both less effective and not any safer.

What are the take-home messages from this prospective observational registry? First, it focuses on the very elderly and confirms the higher risk of stroke and major bleeding compared with a younger cohort. Second, it shows that the benefit of treating such patients with anticoagulants outweighs the risk of major bleeding. Third, it supports evidence that antiplatelet therapy with aspirin is associated with a similar risk of major bleeding as with OAC. Fourth, and as an incidental finding, it suggests that contemporary physician prescribing patterns for stroke prevention in AF in the very elderly are changing, with a greater willingness to anticoagulate such patients.

These results support other recent studies of anticoagulant therapy in the very elderly.[15–18] The BAFTA trial (Birmingham Atrial Fibrillation Treatment of the Aged Study) compared VKA therapy with antiplatelet therapy as stroke prevention in 973 patients 75 years or older.[15] Investigators showed a significant reduction in stroke, systemic embolism, or intracranial hemorrhage with VKA therapy (1.8% versus 3.8%; relative risk 0.48, 95% CI 0.28–0.80; P=0.003). At the same time, extracranial hemorrhage was no different between groups (VKA 1.4% versus aspirin 1.6%). In a very large cohort of 4093 patients ≥80 years of age treated with OAC for a variety of indications, Poli et al[18] found a major bleeding rate of only 1.87%, which compares very well with the bleeding rate in the BAFTA trial. Ogilvie et al,[19] in a meta-analysis of outcomes of OAC therapy compared with aspirin therapy in real-world patients outside of clinical trials, further confirmed the benefit of OAC and the lack of improved safety with antiplatelet therapy.

What do these findings mean in the age of the new direct oral anticoagulants (DOACs), which are rapidly gaining market share for stroke prevention in AF? In the Patti et al trial,[12] DOACs had only a small penetration (approximately 6% in each group), limiting an analysis of their performance in the elderly. But in subanalyses of elderly cohorts in the phase 3 AF trials of the DOACs compared with warfarin, the effectiveness and safety of DOACs compared with warfarin was maintained[20–22] and potentially even greater with similar safety when compared with aspirin.[23] To be sure, the use of DOACs in the very elderly requires special attention to a number of clinical issues such as renal function, drug–drug interactions, tolerability, and others,[24] but most of these are easily manageable. Accordingly, the DOACs, with their improved safety performance, have the potential to change the equation even further, providing a greater net clinical benefit in the very elderly compared with the VKAs.

As other editorials on this topic have proclaimed,[25,26] it is time for all physicians to recognize that although the very elderly with AF have a higher risk of stroke and major bleeding than those who are younger, the increase in the risk of stroke is greater than the increase in the risk of major bleeding, thus presenting the opportunity for an even greater potential for stroke reduction versus a risk of major bleeding. Secondly, antiplatelet therapy with aspirin is not only less effective, it is also no safer than OAC therapy in the very elderly. It is gratifying to see from this registry that physicians are more willing to employ anticoagulant therapy in these high-risk patient populations, suggesting that they are beginning to understand that acts of omission are far more serious than acts of commission and that it is no longer a sin to treat the very elderly with anticoagulant therapy.

Disclosures

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