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EDITORIAL COMMENT

If a Thing Is Worth Doing, it Is Worth Doing Well*

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There are few therapies as effective as oral anticoagulation for the prevention of atrial fibrillation (AF)-related stroke, yet the adherence and persistence to appropriate therapy are pitiful. Although the first oral anticoagulants were approved in the 1950s, they were not routinely offered to AF patients at risk of stroke until after a flurry of randomized clinical trials reported in the 1980s and 1990s.[1] These studies confirmed that, in contrast to aspirin, the major antiplatelet agent used then for thromboprophylaxis in AF, anticoagulation with warfarin was impressively more effective. There was, however, a major drawback; the use of anticoagulants was complicated by bleeding, including major and life-threatening bleeding events such as intracerebral hemorrhage. This risk was exacerbated by interactions with food and other medications and not sufficiently ameliorated by routine testing of anticoagulation status. Not surprisingly, this introduced doubt in the minds of physicians and patients about the overall benefit of therapy. Doctors failed to prescribe or used doses likely to be subtherapeutic and patients refused, abandoned, or underdosed their anticoagulant.

Much to the relief of many, so-called novel oral anticoagulants which directly inhibited the coagulant effect of thrombin or factor Xa were introduced about a decade ago.[2] These direct oral anticoagulants partially uncouple the beneficial antithrombotic effects and the harmful hemorrhagic consequences of anticoagulation and improve the net clinical benefit of therapy. This undoubted advantage stimulated an educational campaign to improve the status of stroke prevention for patients with AF at risk of stroke, which was aimed at both patients and doctors. To an extent, this was successful. The proportion of at-risk patients who were anticoagulated increased by some 10% to 15% due to a large increase in the prescription of direct oral anticoagulants, which much outweighed a reduction of vitamin K antagonist therapy, and a large decrease of antiplatelet monotherapy.[3] A stubborn minority, about 10% of at-risk patients, remain un-anticoagulated and although significantly less than with warfarin patients still abandon or purposefully underdose their prescribed anticoagulant.

Our failure to ensure that patients comply with their prescription may be seen as a therapeutic "scandal" since there is so much to gain from therapy but we seem incapable of persuading many of our patients to take the medication. Much effort has been devoted to education, gadgets and devices have been designed to remind the patient not to forget, and relatives and carers have been enlisted to help. However, the implication from the present study, by Tarn et al[4] in this issue of *JACC: Advances* is that reasons for nonadherence are complicated and variable. If we do not talk to our patients and ask them specifically why they fail to take their therapy we may not be able to address their concerns effectively.

There have been many studies that have cataloged differences between those who tend to adhere to therapy and those that do not. For example, the old are more reliable than the young. Those taking multiple medications can usually successfully add one more. For example, those at the highest risk of stroke, with a high CHA_2DS_2-VASc) score, tend to be more careful to take their medication on schedule. However, these descriptions of those who do best

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offer little obvious opportunity to improve the performance of those who do not.

Tarn et al[4] used a simple scheme to estimate the level of adherence: nonadherence is classified as mild with scores of 80 or above, poor if the scorer is <80 and poorest if the score was <60. Interestingly, the reasons for nonadherence varied between the groups, with forgetfulness scoring most highly in the mild group. Cost is more important for those with poor adherence, and bleeding is the biggest problem for those with the poorest adherence.

In their study, Tarn et al[4] asked the patients why they did not take the medication according to the prescription. The results confirmed some of our understanding and challenged others. Most patients feared a stroke more than a bleed, but some thought a 50% or more stroke risk was needed to justify anticoagulation. Fear of bleeding, the most important and main reason for developing new and better anticoagulants was not the major or only reason for most patients to disregard dosing instructions. The findings of this study expose the perceptions and misperceptions that encourage or discourage patients to adhere to therapy. With this knowledge, we should be able to tackle the problem more purposefully and successfully.

It is not easy for a patient, who is perhaps entirely asymptomatic, to accept or stick to treatment with a drug which although potentially beneficial in the long run, does not demonstrate any immediate symptomatic benefit but does pose a risk of fatal or life-threatening bleeding, which could happen at any time. The patients themselves, their relatives or friends, and sometimes their doctors counsel them against accepting the therapy or suggest an off-label, lower dose of the treatment. Patients are anxious about the need for this hazardous treatment for the rest of their lives since they often believe that eventually even rare but undoubtedly serious complications are bound to catch up with them.

On the other hand, other patients may dispute the value of anticoagulation, only acknowledging therapeutic benefit if the risk is high and can be virtually eliminated by the treatment. Of course, some lack of persistence or adherence to treatment stems from forgetfulness, particularly in elderly and/or cognitively impaired patients. Cost pressures may exist in healthcare economies where patients must afford the therapy themselves. This leads to intermittent treatment, dose or tablet splitting to prolong therapy at a lower cost, but with reduced effectiveness. These concerns and prejudices cannot be simply countered by an information leaflet, or a brief, peremptory explanation, however well-meaning. Carefully designed and targeted countermeasures are needed. It is incumbent on physicians and those caring for these vulnerable patients to engage the patients/family/friends and carers in a fulsome discussion about their fears and concerns about their treatment. Instigating such an approach may be far better in encouraging adherence.

Explaining to patients the real value of anticoagulation without overdoing the absolute benefits or underplaying associated hazards can be difficult, especially for hard-pressed doctors. Asking nurses, pharmacists, and others with more patience and time, and recruiting family members and friends to join in the overall educational effort may result in better outcomes. Acknowledging and providing as much help as possible cost-pressures may relieve overall anxiety and help the patients to continue their treatment.

Over the long term, there may be other solutions. Factor XI/XIa inhibitors much more fully separate inhibition of the intravascular or intrinsic thrombotic effect from the tissue factor-dependent or hemostatic coagulation effect within the vessel wall, extrinsic to the vessel lumen.[5] Under these circumstances, protection from intravascular thrombosis can be achieved without exposure to serious hemorrhagic penalties. This should improve the net clinical benefit and help more patients and their doctors to accept anticoagulation. Some of these new drugs are formulated for oral intake and may be vulnerable to hepatic disease or renal impairment. Drug-drug interactions may complicate these therapies. But, parenteral formulations of such fast-acting anticoagulants with prolonged elimination half-lives may need to be given only on a monthly basis and could also overcome any difficulties from comorbid hepatic or renal disease, patient-forgetfulness and lack of convenience.

Such an approach may possibly prove to be cost-effective for a healthcare system but it will undoubtedly be costly to individuals when they must pay the costs themselves. So, not only must our scientific aspirations be followed and potentially fulfilled, but the practical solutions stemming from the work of Tarn and colleagues must also be continued to overcome reluctance to carefully and properly use the highly effective medicines that are already in our therapeutic armamentarium. As Oscar Wilde put it “If a thing is worth doing, it is worth doing well.”

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