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EDITORIAL COMMENT

The Impact of Asymptomatic Atrial Fibrillation*

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Atrial fibrillation (AF) is associated with a substantial morbidity that is primarily related to troublesome symptoms, heart failure, and thromboembolic events. Drug and nonpharmacologic therapies that control rhythm or rate usually ameliorate the troublesome symptoms and heart failure, and randomized clinical trials have shown that oral anticoagulation with warfarin reduces the risk of thromboembolic events (1–5). However, when AF is thought to be completely suppressed or cured, usually equated with both the absence of clinical symptoms and the presence of only sinus rhythm documented with routine office electrocardiograms (ECGs) and an occasional 24-h ambulatory ECG or even an ECG event monitor for one month, physicians often stop anticoagulation in an effort to avoid the perceived unnecessary exposure of patients to the risks, burdens, and inconveniences of warfarin therapy. The question is whether such surveillance is sufficient to permit reliable conclusions about the suppression or cure of AF. The concern, of course, is that patients may have asymptomatic recurrences of AF, thereby exposing them to risk of ischemic stroke and other thromboembolic events.

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Although it has long been known that asymptomatic AF occurs (6), the magnitude of this problem is only beginning to be appreciated. Surveillance ECGs obtained at office visits are an insensitive method of detecting asymptomatic AF. Furthermore, a history of symptomatic AF in the past in no way guarantees that recurrences will be symptomatic (7,8). When routine transtelephonic recordings are performed, the incidence of asymptomatic AF recurrence may be as high as 50% (6,7). Recent studies have reported an even higher incidence of asymptomatic AF when pacemaker memory data are used for detection (9,10), and treatment of AF with drug therapy may contribute to this incidence by providing rate control during recurrence or by shortening the duration of the recurrence (11).

In this issue of the *Journal*, Israel et al. (12), using a sophisticated pacemaker to detect recurrent AF, confirmed a very high incidence of asymptomatic AF. Of particular note, this included episodes lasting more than 48 h in 17% of the patients studied. Additionally, even among those patients free of AF for more than three months, 16% subsequently had asymptomatic AF lasting more than 48 h. It may be argued that AF is more likely to be asymptomatic in pacemaker patients. Patients with complete atrioventricular block, for example, will not develop a rapid or irregular ventricular response rate. However, the message of Israel's study is that the overall recurrence rate of AF (symptomatic and asymptomatic) is remarkably high, often for relative long periods (>48 h), and occurs even after relatively long quiescent periods (3 months).

These findings, together with those of previous studies, have important implications. Clearly, great caution must be exercised when AF is judged "suppressed" or "cured." Certainly, as demonstrated by the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, in which 57% of the strokes in the rhythm control arm occurred in patients who had stopped taking warfarin, patients with risk factors for stroke whose AF is thought to be suppressed remain at considerable risk if warfarin is stopped (13). Presumably, this is largely explained by the occurrence of asymptomatic AF.

In light of this perspective, there are really two principal issues, the first of which is: Once there is an indication for warfarin in patients with a history of AF, should it ever be permanently stopped? The answer seems to be no. But how does this apply to patients after "successful" surgical Maze or catheter ablation procedures to cure AF? One would like to think that "cure" means never having to take warfarin again. However, with a dearth of data on the occurrence of asymptomatic AF in those patients, the admonition "once on warfarin, always on warfarin" may apply to virtually all patients with a history of AF and risk factors for stroke. Perhaps the only patients who do not need lifelong oral anticoagulation are those without associated risk factors for stroke and those whose AF occurred only in the context of a discrete and transient precipitating event (for example, after open heart surgery or thyrotoxicosis).

The considerable difficulties (prolonged dose titration, interaction with numerous drugs and foods, the need for anticoagulation monitoring, among others) in administering warfarin and maintaining an international normalized ratio in the therapeutic range lead to the second principal issue: Are there acceptable alternative therapies to warfarin to prevent thromboembolism? Potential alternatives are currently under investigation. During AF, most clots are thought to form in the left atrial appendage (14). Therefore, one approach is to occlude the left atrial appendage using endocardial catheter techniques (15). Another even more aggressive approach is to excise the left atrial appendage surgically (16,17). At present, these two approaches seem most applicable to patients at high risk for ischemic stroke who either cannot take warfarin or in whom warfarin has proven ineffective, and for whom cure of the atrial fibrilla-

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tion is not feasible. Perhaps the most important and practical alternative to warfarin therapy involves the new oral direct thrombin-inhibiting anticoagulants. Recently presented data from the Stroke Prevention Oral Thrombin Inhibitor in Atrial Fibrillation III (SPORTIF III) trial (18), a very large clinical trial of patients with AF at risk for ischemic stroke, demonstrated that compared with warfarin, the direct thrombin inhibitor ximelagatran was at least as effective in preventing stroke, had less bleeding, and had a favorable rate of major and minor bleeding. Moreover, compared with warfarin, ximelagatran does not require dose titration or adjustment, has rapid onset and offset of action, does not require monitoring for anticoagulation efficacy, and to date, has almost no documented interactions with foods or drugs. If the safety and efficacy of the oral direct thrombin inhibitors continue to be supported by subsequent studies, they should make it far easier for physicians to provide safe and effective oral anticoagulant therapy to patients with fibrillation who need it.

In summary, Israel et al. (12) have provided yet more authoritative data on the enormity of the problem of asymptomatic AF. The implications for treatment are clear, namely that apparent freedom from AF does not, per se, obviate the need for oral anticoagulation. The need to provide safe and effective oral anticoagulant therapy is crucially important, especially with the increasing numbers of patients with AF, most of whom are elderly and at risk for ischemic stroke (19).

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