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REVIEW ARTICLE

# NIH conference on dietary supplements, coagulation, and antithrombotic therapies Session V. Panel experts: Opinions and research priorities; supplements affecting antithrombotic therapies: A cardiologist's perspective. Dietary supplements and the management of atrial fibrillation

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Atrial fibrillation is the most common arrhythmia requiring treatment experienced by over two million patients in the U.S. each year [1,2]. The prevalence of atrial fibrillation increases with age: approximately 4% of persons over 60 years of age

and 9% of persons over 80 years of age experience either paroxysmal or chronic atrial fibrillation, sometimes unrecognized by the patient until an embolic event occurs due to clots dislodged from the fibrillating left atrium. In addition to age, risk factors for atrial fibrillation include hypertension, diabetes, obesity and most importantly, underlying heart disease (valvular heart disease; congestive, hypertrophic and constrictive cardiomyopathies;

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coronary artery disease) [3]. In many patients, however, atrial fibrillation may present without underlying heart disease in otherwise healthy people (“lone” atrial fibrillation). The morbidity and mortality risks of atrial fibrillation are largely determined by the nature and severity of underlying heart disease, but the most devastating consequence of the arrhythmia is stroke [4,5]. The annual risk of stroke in Framingham study participants with atrial fibrillation ranged from approximately 2% in persons aged 50 to 59 years to almost 24% in those aged 80 to 89 years, with greater risk in patients with associated structural heart disease [5].

Chronic anticoagulation by warfarin and other coumarin derivatives that antagonize vitamin K decreases the risk of stroke and other thromboembolic events [6–8]. This therapy, however, requires frequent monitoring because of: 1) the narrow therapeutic window (as measured by the internationalized normalized ratio-INR), above and below which are increased risks of bleeding and thromboemboli, respectively, and 2) fluctuations in INRs over time, in part because of changes in consumption of vitamin K-containing foods and effects of medications—and patients with heart disease often take many—on warfarin pharmacokinetics. As a result, patients taking warfarin must have INRs checked from a blood sample every few weeks, with adjustments in warfarin dosage often required to maintain INR values between 2–3 in patients without serious underlying heart disease, or higher in certain high-risk subgroups, such as patients with mechanical heart valves [8]. Even with frequent monitoring, major bleeding continues to impart significant morbidity with frequent hospitalizations and occasional mortality [9]. Because of the bleeding risks, physicians may be reluctant to initiate warfarin therapy for chronic use in some patients with atrial fibrillation who may be at risk for thromboemboli, especially if elderly. In addition, some patients may decline warfarin therapy because of the risks or the inconvenience of frequent monitoring [10].

Cardiologists have only recently become aware that dietary supplements may affect warfarin anticoagulation, either decreasing (e.g., St. John’s wort, ginseng, garlic, soy products) or increasing (e.g., ginkgo, ginger products, danshen) INRs [11]. Further, case reports of catastrophic bleeding or thrombotic events in patients taking warfarin and herbal dietary supplements suggest that on occasion, coadministration of warfarin and some dietary supplements may be clinically relevant [11]. Nonprescription supplement use by patients with heart disease (with or without atrial fibrillation) is

common, especially anti-oxidant vitamins, folate, fish oil and coenzyme Q10 [12–14]. Herbal supplement use is less clear, but may be as high as a third of patients by some estimates (possibly an underestimation, as some patients may not wish to tell health care professionals about nonprescription supplement use), and may also be common in anticoagulation clinics [12–15]. For patients on warfarin therapy, the widespread belief is that frequent INR checks will obviate concerns about supplement use, known or unknown, just as for changes in diet, as any change in the INR can be addressed by increasing or decreasing the warfarin dose before complications occur.

Under investigation are new drugs for chronic anticoagulation that target specific coagulation factors and are not protein cofactor dependent. Because of more predictable effects on hemostasis, agents such as the thrombin (factor II) inhibitor melagatran do not require laboratory monitoring, potentially representing a major advantage over warfarin with regards to patient acceptance and compliance, and physician enthusiasm for its use, if bleeding risk is low. The most widely investigated agent to date is ximelagatran, the orally active pro-drug for melagatran [16]. Based on favorable clinical trial data, ximelagatran is approved in several European countries for prevention of venous thromboemboli in patients undergoing knee or hip surgery. Other trials have shown efficacy of ximelagatran in treatment and secondary prevention of acute lower-extremity deep venous thrombosis, and prevention of thromboemboli after acute myocardial infarction. A series of clinical trials in the international Stroke Prevention with an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) program have shown efficacy comparable to warfarin therapy, with somewhat less bleeding risk [16]. Of concern is a 5–10% frequency of liver enzyme elevation, although the clinical implications of this finding are unclear as enzyme levels generally normalize with continued treatment. One clinical trial comparing ximelagatran with low-molecular-weight heparin and warfarin for treatment of deep venous thrombosis reported an increased incidence of coronary events (hospitalization for angina or myocardial infarction) in ximelagatran-treated patients compared with enoxaparin/warfarin-treated group [17]. Clinical trials of ximelagatran treatment in atrial fibrillation, with longer duration of treatment, have not reported an increased risk of coronary events [18]. Other agents that may achieve protection from stroke in patients with atrial fibrillation without need for chronic monitoring, such as the factor Xa inhibitor idraparinux (among others), are also under investigation.

Lessons learned from interactions between warfarin and dietary supplements, with adverse outcomes in some patients, may extend to coagulation factor-specific inhibitors and other novel approaches to anticoagulation. FDA approval of agents to prevent stroke and other thromboembolic risk that do not require monitoring would likely increase the acceptance of chronic anticoagulation therapy by patients in atrial fibrillation and, accordingly, the numbers of patients treated. If this results in less frequent interactions with health care professionals (as intended) and if important interactions with dietary supplements exist for these agents, adverse effects on hemostasis may not be recognized until serious bleeding or thrombosis occurs. Specific areas for research include: 1) better data on frequency of nonprescription supplement use by patients with cardiovascular disease, especially those on anticoagulant therapy, 2) impact of counseling by health care providers on supplement use, and 3) potential interactions between coagulation factor-specific inhibitors and the most commonly used supplements to determine implications for pharmacokinetics and hemostasis.

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