Clarity regarding the role of antithrombotic treatments in patients with heart failure in the absence of atrial fibrillation remains elusive. In an era of an intensified search for personalized medicine, it is instructive to look back at the earliest evidence for a protective effect of anticoagulation, when little else had any promise to reduce morbidity and mortality in heart failure. It is now evident that those benefits were predominantly driven by effects in subsets of patients with atrial fibrillation and valvular disease. Sixty years later, the role of antithrombotic treatments in the remaining population remains uncertain. The Warfarin and Antiplatelet Therapy in Chronic Heart Failure Trial (WATCH), the results of which are published in the present issue, held the promise of providing clear support for one therapeutic approach above the others in reducing the incidence of adverse cardiovascular events. However, the primary WATCH findings provide no clear winner among warfarin, clopidogrel, and aspirin, with the limited statistical power preventing any clear conclusion. WATCH results do suggest that aspirin treatment increases the likelihood of heart failure hospitalization compared with the other approaches.

Evidence exists indicating that heart failure is often accompanied by a hypercoagulable state. Patients with reduced cardiac output may be predisposed to venous thrombosis and pulmonary embolus. In the sizable percentage of heart failure patients with ischemic heart disease, antiplatelet therapy is expected to decrease the incidence of recurrent coronary ischemic events, as it has been shown to do in the broader ischemic heart disease population. Among patients without known ischemic heart disease, there is suspicion that many adverse events, including worsening heart failure and sudden cardiac death, may be provoked by myocardial ischemia, raising the possibility that antithrombotic treatment may impact natural history in this population as well. On the other hand, hemorrhagic consequences of antithrombotic treatment would weigh against the net clinical benefit derived from preventing embolic or thrombotic events. The low rates of clinically definable thromboembolic events among patients with heart failure have limited the ability to demonstrate clinical benefit in this population.

Observational studies have supported the value of antithrombotic treatment. Analysis of data from patients with reduced left ventricular ejection fraction in the Studies of Left Ventricular Dysfunction (SOLVD) trial showed an association between warfarin treatment and reduction in both all-cause death and in the combined end point of death or heart failure hospitalization. These associations were not significantly influenced by symptom status, enalapril treatment, sex, age, severity of left ventricular ejection fraction reduction, presence of atrial fibrillation, or known presence of ischemic heart disease. Although there is no clear explanation for this finding, one possibility is prevention of coronary thrombosis, even in patients without known coronary occlusive disease. In the absence of randomized, controlled data, these observational findings have not been sufficient to support a clear guideline recommendation for warfarin anticoagulation for patients with heart failure in the absence of atrial fibrillation or other specific indication.

Aspirin use in heart failure is controversial. No randomized, controlled data specifically support a benefit from aspirin in patients with heart failure, with or without known ischemic heart disease. Practice guidelines have often recommended its use in the presence of ischemic heart disease on the basis of findings in non–heart failure populations. However, a number of reasons to question this practice exist. Aspirin, an inhibitor of prostaglandin synthesis, is far from a simple, specific antiplatelet agent. The commonly recommended low dose used in WATCH (162 mg/d) is presumed to be preferentially antithrombotic, irreversibly binding to platelets during the drug’s initial circulation, with subsequent rapid decline in blood levels. However, pretreatment with 75 mg of aspirin has been shown to inhibit the vasodilator effect of intra-arterial arachidonic acid in patients with heart failure, suggesting that the specificity of low-dose aspirin is incomplete and raising the possibility of a clinically relevant influence on vascular function, either directly or by inhibiting the prostaglandin-mediated effects of angiotensin-converting enzyme (ACE) inhibitors. We demonstrated an association between antiplatelet treatment (almost exclusively aspirin) and improved clinical outcomes in the combined SOLVD populations. However, we also found a strong interaction among antiplatelet treatment, enalapril randomization group, and outcome, with diminished aspirin-associated benefit in the enalapril group and diminished survival benefit from enalapril in patients receiving antiplatelet treatment. Analyses examining aspirin-related interactions across ACE inhibitor trials have tended to show retention of ACE inhibitor benefit, but have consistently shown some diminution of ACE inhibi-
Several factors limit the certainty of this conclusion. First, slow enrollment and early termination reduced the statistical power. However, as the authors point out, the 95% confidence limits exclude 20% differences between warfarin and aspirin and exclude a 20% difference favoring clopidogrel over aspirin for both the primary composite end point and total mortality. Importantly, there was no placebo group because the investigators viewed withholding antithrombotic treatment from patients with heart failure and coronary artery disease as unfeasible or unethical. The result is that we remain uncertain that any antithrombotic treatment influences outcome in this population.

Despite similarities across the 3 groups in the primary end point, patients randomized to aspirin had the highest likelihood of hospitalization for heart failure. The aspirin and warfarin groups were nominally significantly different in terms of number of patients hospitalized for heart failure and number of heart failure hospitalization events, with the clopidogrel group being intermediate. A possibility not considered by the authors is that, in the absence of a placebo group, the heart failure–related findings represent a reduction by warfarin in the likelihood of heart failure exacerbation, potentially mediated through reductions in the incidence of pulmonary embolus or coronary thrombosis. More likely, these findings may be viewed as supporting the concern that the prostaglandin inhibitory effect of aspirin, even in low doses, exacerbates heart failure, either directly or by diminishing the ACE inhibitor benefit.

It is disappointing that the thoughtful design and hard work that went into WATCH did not translate into more definitive recommendations. Unfortunately, it is unlikely that placebo-controlled trials of antithrombotic treatment will ever be performed in patients with heart failure. Clinicians consider use of one or another of these agents to be an ethical imperative in patients with heart failure and ischemic heart disease, despite the absence of clear-cut, supportive, randomized, controlled data. A possible analogy is the common practice of prescribing statins in patients with heart failure and prior myocardial infarction despite absence of data supporting this practice in a heart failure population. Surprisingly, 2 recent randomized, placebo-controlled trials have failed to demonstrate a clear benefit of statins in patients with heart failure and coronary artery disease. The ongoing National Institutes of Health–sponsored Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) Trial, which is enrolling slowly, is comparing the effects of aspirin and warfarin on the combined end point of all-cause mortality and stroke in patients with a left ventricular ejection fraction <35%. Perhaps that study will provide further insight.

What guidance can we now give to clinicians? Patients with heart failure and either atrial tachyarrhythmias or a history of systemic or pulmonary emboli should be anticoagulated with warfarin unless there is a clear contraindication. Absent these specific risks, no firm evidence exists for benefit of anticoagulation on clinical outcomes. Clinicians might choose to follow observational findings that suggest that warfarin is beneficial in patients with heart failure, reduced left ventricular ejection fraction, and sinus rhythm, although most experts consider these findings insufficient to warrant a firm recommendation for this approach. Current clinical practice guidelines recommend antiplatelet therapy for patients with heart failure and coronary artery disease. However, there remains no clear, randomized, controlled data within a heart failure population to support or refute this recommendation. Although the WATCH findings suggest little or no overall benefit from warfarin compared with antiplatelet therapies, the higher frequency of heart failure hospitalizations in patients randomized to aspirin suggests an advantage to prescribing warfarin or clopidogrel rather than aspirin. This approach may warrant particular consideration in patients who continue to have symptoms and/or heart failure exacerbations while receiving aspirin along with appropriate heart failure treatment. It must be stressed, however, that neither WATCH nor other currently available randomized, controlled data mandate antithrombotic treatment across the broad population of patients with heart failure. Despite the difficulty in conducting such research, additional evidence clarifying the role of antithrombotic treatments could make a substantial impact on our effective management of patients with heart failure.

Disclosure

Dr Konstam is a consultant for Sanofi-Aventis in matters related to antiarrhythmic therapy but not antiplatelet therapy.

References

Antithrombotic Therapy in Heart Failure

Konstam


Key Words: Editorials ■ anticoagulants ■ aspirin ■ heart failure ■ platelets ■ thrombosis