Anticoagulation in Dilated Cardiomyopathy

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Patients with dilated cardiomyopathy have multiple factors that predispose to thromboembolic events. However, reports of the incidence of thromboembolic events in this population vary widely. There has never been a controlled study of long-term anticoagulation among patients with congestive heart failure due to dilated cardiomyopathy. In this report we review the available published data regarding the risk of thromboembolic events in patients with dilated cardiomyopathy, and the effectiveness and risks of anticoagulation in this population. Although many investigators have called for a prospective, randomized clinical trial to assess the risks and benefits of long-term anticoagulation in patients with dilated cardiomyopathy, a more practical approach may be to compile a national registry of patients with dilated cardiomyopathy to collect observational data on both the rate of embolic events as well as bleeding complications among patients with and without anticoagulation.

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There has never been a controlled study of long-term anticoagulation among patients with congestive heart failure (CHF) due to dilated cardiomyopathy. Reports of the incidence of thromboembolic events in this population vary widely. In this article, we summarize key studies, assess the risks and propose guidelines for anticoagulation among patients with dilated cardiomyopathy.

Incidence of Thromboembolism in CHF:
Smaller Studies

Factors that predispose to thromboembolic events in patients with CHF include low cardiac output, with relative stasis of blood in dilated cardiac chambers, poor contractility and regional wall motion abnormalities and concomitant atrial fibrillation. Early autopsy studies reported a very high frequency of thromboembolic events. In 1958, Spodick and Littman (1) reviewed reported autopsy cases of patients with CHF and found that 50% had evidence of thromboembolism (TE) at autopsy. Roberts et al. (2) in 1987 reviewed 152 consecutive patients with dilated cardiomyopathy and observed a 37% frequency of thromboembolic events.

More recently, investigators have reported a lower incidence of thromboembolic events. Fuster et al. (3), in a retrospective study of 104 patients with nonischemic dilated cardiomyopathy, reported an 18% frequency of thromboembolic events and an incidence of 3.5 clinically apparent events/100 patient-years. In 1993, Katz et al. (4) prospectively followed 264 patients with dilated cardiomyopathy and reported that the incidence of stroke was 1.7/100 patient-years. Finally, in 1995, Natterson et al. (5) retrospectively studied 224 patients awaiting heart transplantation (mean left ventricular ejection fraction [LVEF] 0.20) and found that only 6 (3%, or 3.2/100-patient years) had an episode of arterial embolization over a mean follow-up period of 301 days.

Incidence of Thromboembolism in CHF:
Large Therapeutic Trials

Several clinical trials involving patients with CHF reported on the incidence of TE in their study populations, but none evaluated anticoagulation or thromboembolic events as a primary end point. In the Vasodilators in Heart Failure (V-HeFT) trials (6,7), the overall rate of TE was between 2.2 and 2.5/100 patient-years (8). Patients with a lower LVEF and peak exercise oxygen consumption (MVo2) had a higher risk of stroke, but only the difference in MVo2 was statistically significant.

Although anticoagulation reduces the risk of stroke after acute (and especially anterior) myocardial infarction (9,10), this is not necessarily the case in chronic CHF, even when caused by ischemic cardiomyopathy. Based on data from V-HeFT, there appears to be no statistically significant difference in the rate of TE between patients with ischemic and nonischemic dilated cardiomyopathy.

In the Survival and Ventricular Enlargement (SAVE) trial (11), the incidence of stroke was 1.5/100 patient-years (12). Risk was increased in patients who were older (63 ± 9 vs. 59 ± 11 years, p < 0.001). In SAVE, like V-HeFT, patients with a lower LVEF had a higher rate of stroke. Patients with an LVEF ≤28% had a nearly twofold increase in relative risk of
stroke compared with patients with an LVEF >28% (relative risk [RR] 1.86, p = 0.01). For every 5% decrease in LVEF, there was an 18% increase in stroke rate. When balanced terciles based on LVEF were constructed, the total cumulative stroke rate was significantly higher in the tercile of LVEF 9% to 28% versus the tercile of LVEF >35%.

The most recent analysis (13) of the incidence of thromboembolic events in patients with cardiomyopathy comes from a retrospective review of Studies of Left Ventricular Dysfunction (SOLVD) data (14,15). This analysis, in contrast to the studies previously discussed, included only patients known to be in normal sinus rhythm at the time of randomization. Although the overall incidence of thromboembolic events was similar to that for other large clinical trials, an unexpected finding was that women were at increased risk for thromboembolic events compared with men (2.4 events/100 patient-years vs. 1.8 events/100 patient-years). Moreover, although a decrease in LVEF was not associated with an increased risk of TE in men, each 10% decline in LVEF was significantly associated with a 55% increased risk of TE among women. Women within the lowest two quartiles of LVEF had an incidence of TE almost twice that of men (Table 1). This finding may be due to gender differences in the clotting or fibrinolytic system, the effects of hormonal variations or simply chance.

### Table 1. Incidence and Crude Relative Risk of Thromboembolic Events According to Gender and Left Ventricular Ejection Fraction Quartiles in Studies of Left Ventricular Dysfunction (SOLVD) Trial*

<table>
<thead>
<tr>
<th>LVEF</th>
<th>Incidence</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n = 5,457)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30%</td>
<td>1.70</td>
<td>1.00</td>
</tr>
<tr>
<td>21%–30%</td>
<td>1.83</td>
<td>1.08 (0.83–1.41)</td>
</tr>
<tr>
<td>11%–20%</td>
<td>2.01</td>
<td>1.21 (0.86–1.70)</td>
</tr>
<tr>
<td>10%</td>
<td>1.96</td>
<td>1.21 (0.80–3.92)</td>
</tr>
<tr>
<td>Women (n = 921)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30%</td>
<td>1.78</td>
<td>1.00</td>
</tr>
<tr>
<td>21%–30%</td>
<td>2.41</td>
<td>1.35 (0.74–2.47)</td>
</tr>
<tr>
<td>11%–20%</td>
<td>3.80</td>
<td>2.17 (1.10–4.30)</td>
</tr>
<tr>
<td>10%</td>
<td>4.20</td>
<td>2.43 (0.32–18.26)</td>
</tr>
</tbody>
</table>

*Adapted, with permission, from Dries et al. (13). CI = confidence interval; LVEF = left ventricular ejection fraction; RR = relative risk.

### Effectiveness of Anticoagulation

There has never been a controlled study of anticoagulation among patients with CHF. Accordingly, the effectiveness of anticoagulation must be judged by assessing observational data in patients with CHF who were treated with anticoagulant agents for a variety of reasons, such as atrial fibrillation, a previous thromboembolic event, or known left ventricular thrombus, or empirically. Additionally, most studies do not correct for the presence of a well-established risk for TE such as atrial fibrillation. Finally, neither the decision to initiate anticoagulant therapy nor the level of anticoagulation was specified or controlled as part of any study protocol.

In the study by Fuster et al. (3), there were 19 embolic events over 624 patient years in the 103 patients who were not treated with anticoagulant agents (3.5 events/100 patient-years), whereas none of the 32 patients who received warfarin (101 patient-years) had an embolic complication (p < 0.05). Natterson et al. (5) documented arterial embolization in 5 (4%) of 142 patients not receiving warfarin and in 1 (1%) of 82 patients receiving anticoagulation (p = 0.30). Of the nine patients who had a cerebral TE in the study by Katz et al. (4), 5 were receiving long-term anticoagulation; notably, however, 3 of these patients had left ventricular thrombus documented by two-dimensional echocardiography, and 1 had atrial fibrillation.

In contrast, the V-HeFT studies (6–8) failed to show any protective effect of anticoagulation; in fact, patients treated with anticoagulant agents had the same or higher rates of thromboembolic events. In V-HeFT I, the thromboembolic event rate in patients treated with anticoagulant agents (2.9/100 patient-years) was similar to that in patients not receiving anticoagulation (2.7/100 patient-years, p = NS). Ironically, V-HeFT II demonstrated that patients receiving anticoagulation had a higher thromboembolic event rate (4.9/100 patient-years) than those not receiving anticoagulation (2.1/100 patient-years), a difference that achieved statistical significance (p = 0.01). Because neither the decision to initiate anticoagulation nor the intensity of anticoagulation was controlled, it is likely that patients judged to be at highest risk for TE (e.g., those with atrial fibrillation or known LV thrombus or even patients with mechanical valve replacement) were treated with warfarin.

Although the SAVE trial (12) had an 81% risk reduction in stroke among patients receiving anticoagulant agents, anticoagulant therapy was not randomized, and its intensity was not controlled. In addition, aspirin use alone reduced the relative risk for stroke in the SAVE trial by 56%. Finally, the recent analysis of the SOLVD database (13) failed to show a reduction in thromboembolic events among either men (RR 0.97, 95% confidence interval [CI] 0.65 to 1.44, p = 0.87) or women (RR 1.34, 95% CI 0.56 to 2.71, p = 0.60) receiving anticoagulation.

### Risks of Anticoagulation

Although the rate of TE increases with CHF, especially in the elderly and in those with reduced LVEFs, controlled
clinical trials have not addressed the effectiveness or the risks of long-term anticoagulation in this patient population. Several studies (16–20) have found the incidence of major hemorrhage in patients receiving anticoagulation to range from 2.3 to 6.8/100 patient-years (Table 2). Intracranial bleeding is the most feared hemorrhagic event. van der Meer et al. (17) calculated a rate of intracranial bleeding of 0.62/100 patient-years, whereas the Stroke Prevention in Atrial Fibrillation (SPAF) II investigators (20) calculated an even higher rate of 0.9/100 patient-years.

Unfortunately, older age increases the likelihood of major bleeding as well as the rate of TE among patients with CHF. In the van der Meer study (17), compared with patients <40 years old, each 10-year increase in age was associated with 46% more major bleeding. Fihn et al. (19) similarly found that even after adjustments were made for the intensity of anticoagulation, patients ≥80 years old had a fourfold greater risk of life-threatening or fatal bleeding. Finally, SPAF II (20) also found a significant increase in both the rates of intracranial bleeding and major bleeding in patients >75 years old.

Antiplatelet agents can cause bleeding complications, but this occurs far less frequently than with anticoagulant agents. Although low dose aspirin carries a risk of gastrointestinal hemorrhage, review of the various placebo-controlled aspirin trials suggests that the risk is especially increased when higher doses (>1,000 mg) are used (21).

Benefits of Aspirin Monotherapy

The efficacy of aspirin as an antithrombotic agent is well established. Among previously healthy male physicians, it reduced the incidence of myocardial infarction and death (22). Among patients with unstable angina, 75 mg of aspirin taken daily halves the rate of myocardial infarction and death (23). Aspirin also reduces the incidence of stroke and death in patients with a history of transient ischemic attacks (24) and reduces the rate of stroke and systemic embolism in patients with atrial fibrillation (25). Although there has never been a randomized trial of aspirin for TE risk reduction in patients with dilated cardiomyopathy, the clinical trials of patients with CHF suggest that aspirin monotherapy may be beneficial in this regard.

In V-HeFT I (8), the incidence of TE in patients receiving aspirin monotherapy was 0.5 events/100 patient-years compared with 2.7 events/100 patient-years in patients receiving no antiplatelet or anticoagulant agents (p = 0.07). Similarly, V-HeFT II (8) demonstrated that the incidence of TE in patients receiving aspirin was 1.6 events/100 patient-years compared with 2.1 events/100 patient-years in patients receiving no treatment, although this difference was not significant (p = 0.48).

In the SAVE trial (12), aspirin use significantly reduced the risk of stroke by 56%. The protective effect of aspirin was most pronounced in patients with an LVEF <28%; in this group, aspirin use was associated with a reduction in risk of stroke of 66% (p < 0.001). Similarly, the SOLVD trial (13) showed a beneficial effect of aspirin monotherapy, especially in women. The use of antiplatelet agents was associated with a 23% reduction in the risk of TE in men (p = 0.06); in women, antiplatelet monotherapy was associated with a marked 53% reduction in risk (p = 0.03). In the SOLVD trial (26), aspirin monotherapy was also associated with a 24% reduction in the risk of sudden death.

Recommendations

Although certain groups of patients with CHF have well defined indications for chronic anticoagulation (previous thromboembolic event, atrial fibrillation and the presence of newly formed left ventricular thrombus [27,28]), evidence from published reports does not demonstrate convincingly that the benefits of anticoagulation exceed the risks in other subgroups. Moreover, the fluctuating metabolic state of patients with dilated cardiomyopathy may predispose to bleeding complications. Patients with dilated cardiomyopathy often have a chronically low cardiac output that may impair hepatic and renal function. Furthermore, they often require multiple medications that may interact with warfarin.

Because of the potential for increased bleeding complications in patients with dilated cardiomyopathy, anticoagulant therapy, when indicated, should be administered under the most controlled circumstances. We recommend that, whenever possible, patients be monitored in properly managed anticoagulation clinics that can minimize bleeding complications (29,30).

The only clear-cut indications for anticoagulation in most patients with dilated cardiomyopathy are atrial fibrillation, a previous thromboembolic event or left ventricular thrombus. Recent analyses of the SAVE (12) and SOLVD (13) databases have shown that low dose aspirin may be quite useful in preventing TE and may be much less risky than warfarin. In patients with underlying coronary artery disease, aspirin probably confers additional benefit.

Although some investigators have called for a prospective, randomized clinical trial of long-term anticoagulation in patients with dilated cardiomyopathy (31,32), such a trial may not be feasible. The low rate of TE would necessitate an unrealistically large study size. One would also have to contend with resistance by physicians and their patients to the concept of randomization, primarily due to the strongly held beliefs of individual clinicians regarding anticoagulant therapy. Instead, a more practical initial approach might be to compile registries
of patients with dilated cardiomyopathy, in which observational data on embolic events as well as bleeding complications are collected for patients with and without anticoagulation. Such registries might be initiated not only within individual institutions but also among consortia of community hospitals, outpatient offices and health maintenance organizations to gain realistic insights into the outcomes encountered in various settings. While such data are being collected and analyzed, the most prudent approach will be risk stratification of patients with dilated cardiomyopathy to help determine which patients will have the largest net clinical benefit from long-term anticoagulation.

References