Randomized Trial of Warfarin, Aspirin, and Clopidogrel in Patients With Chronic Heart Failure

The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) Trial

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Background—Chronic heart failure remains a major cause of mortality and morbidity. The role of antithrombotic therapy in patients with chronic heart failure has long been debated. The objective of this study was to determine the optimal antithrombotic agent for heart failure patients with reduced ejection fractions who are in sinus rhythm.

Methods and Results—This prospective, randomized clinical trial of open-label warfarin (target international normalized ratio of 2.5 to 3.0) and double-blind treatment with either aspirin (162 mg once daily) or clopidogrel (75 mg once daily) had a 30-month enrollment period and a minimum of 12 months of treatment. We enrolled 1587 men and women ≥18 years of age with symptomatic heart failure for at least 3 months who were in sinus rhythm and had left ventricular ejection fraction of ≤35%. The primary outcome was the time to first occurrence of death, nonfatal myocardial infarction, or nonfatal stroke. For the primary composite end point, the hazard ratios were as follows: for warfarin versus aspirin, 0.98 (95% CI, 0.86 to 1.12; \( P = 0.77 \)); for clopidogrel versus aspirin, 1.08 (95% CI, 0.83 to 1.40; \( P = 0.57 \)); and for warfarin versus clopidogrel, 0.89 (95% CI, 0.68 to 1.16; \( P = 0.39 \)). Warfarin was associated with fewer nonfatal strokes than aspirin or clopidogrel. Hospitalization for worsening heart failure occurred in 116 (22.2%), 97 (18.5%), and 89 (16.5%) patients treated with aspirin, clopidogrel, and warfarin, respectively (\( P = 0.02 \) for warfarin versus aspirin).

Conclusion—The primary outcome measure and the mortality data do not support the primary hypotheses that warfarin is superior to aspirin and that clopidogrel is superior to aspirin. (Circulation. 2009;119:1616-1624.)

Key Words: anticoagulants ■ aspirin ■ clopidogrel ■ heart failure ■ warfarin

The role of antithrombotic therapy in patients with chronic heart failure has been a subject of debate for many years. Initial controlled clinical trials in cardiac patients were conducted to determine whether anticoagulation could reduce the high incidence of embolic events, particularly strokes, observed in these patients.1–3 These trials found substantial clinical benefit from anticoagulation, including reductions in embolic events and deaths. Because many patients in these trials had heart failure accompanied by atrial fibrillation and valvular disease, their relevance to current clinical practice for heart failure patients in sinus rhythm seems limited. Given that heart failure is associated with a hypercoagulable state and that both sudden deaths and deaths resulting from progressive heart failure may be caused by unrecognized atherothrombotic events, a clear rationale for anticoagulation in chronic heart failure exists.4–6 Although a posthoc analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trial indicated that warfarin therapy was associated with lower mortality and morbidity rates,7 no large prospective clinical trial limited
to heart failure patients in sinus rhythm has addressed this question.\(^8\)

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Many patients with chronic heart failure are treated with aspirin. A posthoc analysis of SOLVD has suggested that patients receiving aspirin may gain less benefit from angiotensin-converting enzyme (ACE) inhibition in terms of survival or hospitalization for worsening of heart failure.\(^9\) Meta-analyses of ACE inhibitor trials in patients with heart failure and left ventricular dysfunction after myocardial infarction (MI) have yielded mixed results but are generally consistent with some weakening of ACE inhibitor benefit.\(^10,11\)

Whether these findings should affect the use of this agent remains controversial. More recently, a study of 279 patients randomized to open-label aspirin 300 mg QD, warfarin (target international normalized ratio [INR] of 2.5 to 3.0), or no antithrombotic therapy found an excess of heart failure hospitalizations in the aspirin group compared with both warfarin and no antithrombotic agent patients.\(^12\) The finding that aspirin reduces the benefit of ACE inhibitors could relate to known adverse effects of prostaglandin inhibition in patients with heart failure.\(^13\) This may be more important in patients treated with ACE inhibitors because the hemodynamic effects of these agents are partially mediated by enhanced prostaglandin synthesis.\(^14–18\)

The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial was undertaken to determine the optimal antithrombotic agent for heart failure patients with reduced ejection fractions who are in sinus rhythm.\(^4\) Two primary hypotheses were addressed: that anticoagulation with warfarin is superior to antiplatelet therapy with aspirin in preventing major cardiovascular outcomes and that clopidogrel, an antiplatelet agent with a prostaglandin-independent mechanism of action, is superior to aspirin in this population. Aspirin was compared with clopidogrel rather than a placebo because it was not judged feasible or ethical to randomize heart failure patients with coronary artery disease to receive no antithrombotic therapy.

**Methods**

The WATCH trial design and baseline characteristics of enrolled patients have been described previously\(^4\) and are presented briefly here.

**Patient Population**

Patients were recruited between October 1999 and June 2002 from 142 centers in the United States, Canada, and the United Kingdom. Patients \(\geq 18\) years of age were eligible if they had symptomatic heart failure (New York Heart Association class II to IV) for \(> 3\) months before entry, had a left ventricular ejection fraction \(\leq 35\%\) measured within 3 months by any standard technique, were in sinus rhythm, and were treated with a diuretic and an ACE inhibitor for at least 60 days (unless not tolerated). For patients who could not tolerate an ACE inhibitor, treatment with hydralazine plus long-acting nitrates or an angiotensin II receptor antagonist was recommended. \(\beta\)-Blocker use was strongly encouraged. Other heart failure treatments were at the discretion of the investigators.

The primary exclusion criteria were contraindications or specific indications for any of the study medications, imminent procedures necessitating withdrawal or use of the study medications, heart failure from correctable causes, serious comorbid conditions expected to limit life expectancy, or other conditions that would interfere with protocol adherence.

All subjects provided written informed consent. The study protocol was approved by the Human Rights Committee of the Perry Point, Md, Department of Veterans Affairs (VA) Cooperative Studies Program Coordinating Center (CSPCC), by local regulatory authorities in Canada and the United Kingdom, and by the Institutional Review Board or Ethics Committee at each participating site.

**Study Design**

WATCH was a multinational, prospective, randomized trial in which patients were assigned to 1 of 3 treatment arms: aspirin 162 mg or clopidogrel 75 mg daily provided in a double blind, double-dummy manner or open-label warfarin titrated to a target INR of 2.5 to 3.0 with a designated acceptable range of 2.0 to 3.5. There was no loading dose for either clopidogrel or aspirin. Warfarin therapy, which was managed by either the investigative team or an anticoagulation clinic, was initiated at 4 mg daily except in subjects \(\geq 70\) years of age or taking amiodarone; they were started at 3 mg daily. INR was determined after 1 week, and dose was adjusted in increments of 1 mg as frequently as necessary to achieve an INR of 2.5 to 3.0. The target INR range of 2.5 to 3.0 was chosen because postinfarction trials achieving INR values in this range have shown superiority of warfarin over aspirin, whereas those with lower INR targets and values have not.\(^9,10–22\) Monitoring visits were at the discretion of the responsible practitioners but maximally at 6-week intervals.

Patients were seen at 3-month intervals, with interim telephone contacts at 6-week intervals. These calls were scripted to identify changes in clinical status, adverse events, study end points, and medication compliance.

**Study End Points**

The primary end point was the composite of all-cause mortality, nonfatal MI, and nonfatal stroke. Secondary end points included the 3 components of the primary end point and hospitalizations for heart failure. The primary safety end point was major bleeding episodes, defined as bleeding episodes leading to death or disability (including loss of neurological or special senses function), requiring surgical intervention, or associated with an acute decline of hemoglobin \(\geq 2\) gm/dL or transfusion of \(> 1\) U packed red cells or whole blood.

**Study Management**

An Executive Committee, consisting of investigators, heart failure researchers, and CSPCC and VA CSP Research Pharmacy Coordinating Center representatives, served as the decision-making body for the study. Operational aspects of the trial were overseen by the CSPCC, the study chairman’s office, and coordinating offices in Canada and the United Kingdom. The VA CSP Research Pharmacy Coordinating Center was responsible for obtaining, packaging, and distributing the study drug supplies; working with the regulatory agencies of the participating countries; and monitoring and reporting serious adverse events. An independent Data and Safety Monitoring Board was responsible for reviewing the study.

**Randomization and Blinding**

The CSPCC generated a randomization sequence for each site separately using varying block sizes of 3 or 6. The site coordinator/site investigator called the CSPCC to obtain a randomization number and treatment allocation. Study medication was obtained from the local pharmacy or dispensing unit on presentation of the signed consent form. Only patients randomized to aspirin or clopidogrel were blinded to treatment received. In an emergency, the blind could be broken by calling the VA CSP Research Pharmacy Coordinating Center, the study chairman, the regional coordinating center, or the CSPCC. A sealed envelope provided to the local pharmacy or dispensing unit could be opened as a default strategy. No attempt was made to...
assess the adequacy of blinding. The main outcome measures were adjudicated by an End Point Committee made up of members blinded to treatment allocation, including INR results.

Sample Size and Statistical Analyses

The prespecified statistical analysis for the primary composite end point of death, nonfatal MI, and nonfatal stroke was a log-rank test of the Kaplan–Meier product limit estimator of time to first event based on intention-to-treat. The original sample size of 1500 patients for each of the 3 groups was determined using the method of Lakatos. This was based on a planned enrollment period of 3 years, a mean follow-up period of 3.5 years, and an estimated 18% annual event rate, which would have 90% power to detect a 20% between-group difference in annual event rates using a type I error rate of 0.017 (adjusting for the 3 pair-wise comparisons). The intent-to-treat log-rank test also was used to compare the effect of treatments on total mortality. Intent-to-treat χ² analyses were used to compare treatments on the dichotomous secondary outcome measures.

Early Termination

Because of slow enrollment, the study terminated prematurely in January 2002. As a result, recruitment ended in June 2002 (4 months early), and follow-up ceased 1 year later (16 months early). With the early termination, 1587 patients rather than 4500 were randomized. As a result, the difference in annual event rate that the study was powered to detect with the original parameters (power of 90% and a type I error rate of 0.017) increased from 20% to 40%. Power to detect the original 20% difference dropped from 90% to 41%.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Enrollment

Of the 1587 patients enrolled, 937 patients were from the United States (590 patients in 44 VA sites and 347 in 41 other US sites), 332 were from 28 Canadian sites, and 318 came from 29 sites in the United Kingdom. Patient baseline characteristics are shown in Table 1. Although screening information was not collected, the enrolled population was typical of trials involving patients with moderate to severe systolic heart failure. Although patients were required to have heart failure symptoms only for >3 months, Table 1 shows that 70% of the patients had a heart failure diagnosis for >2 years. The patient characteristics were well balanced among the 3 treatment groups. Among >70 baseline characteristics examined, the only intergroup difference that reached statistical significance (P=0.05) was the prevalence of diabetes, which was highest in the warfarin group (38%) and lowest in the clopidogrel group (31%).

Follow-Up and Protocol Adherence

The mean duration of follow-up was 1.9 years (median, 21 months), yielding 3073 patient-years of exposure. Figure 1 describes patient follow-up experience and vital status at the end of the study. Of the 1587 patients randomized, 523 received aspirin, 524 received clopidogrel, and 540 received warfarin. The figure indicates that there were 282 deaths, 13 patients terminated from the study because of a heart transplant, and 76 patients lost to follow-up, including 31 at 3 terminated early because of site regulatory issues. There were few differences between treatment groups. Of the 76 patients lost to follow-up, 22 were determined to be alive as of March 1, 2003.

Figure 1 also shows the reasons that patients were permanently discontinued from study drug. Although no difference existed between treatment groups regarding overall drug discontinuation, warfarin was discontinued by choice (32 patients) more frequently than aspirin (16 patients) or clopidogrel (19 patients). Warfarin patients also were more likely to have their study medication discontinued because of hemorrhage and increased bleeding risk but were less likely to have study medications stopped as a result of atrial fibrillation, embolic/occlusive events, and cardiovascular events. In addition, 52 (9.9%) of the aspirin patients, 48 (9.2%) of the clopidogrel patients, and 59 (10.9%) of the warfarin patients had their medications stopped temporarily during the study. For patients whose study medications were discontinued either permanently or temporarily, 81 (26.8%) discontinued clopidogrel or aspirin patients received nonstudy warfarin, 94 (55.6%) discontinued warfarin patients received nonstudy aspirin, and 72 (48.0%) discontinued clopidogrel patients received nonstudy aspirin.

On the basis of returned tablet counts, 80% of the prescribed double-blind aspirin and clopidogrel tablets were taken. When documented periods of temporary or permanent discontinuations were excluded, 93% of doses were used. After the initial 6-week titration phase, the mean INR value in the warfarin arm was 2.6±0.9, with 70.4% of measurements falling within the acceptable range (2.0 to 3.5), 20.3% falling below 2.0, and 9.3% falling above 3.5. The median INR was 2.5.

Primary and Secondary End Points

Primary Composite End Point and Its Components

Figure 2A shows the event curves of the primary composite end point of all-cause mortality, nonfatal MI, or nonfatal stroke. For the warfarin versus aspirin comparison, the unadjusted hazard ratio (HR) was 0.98 (95% CI, 0.86 to 1.12; P=0.77). The HR for the clopidogrel versus aspirin comparison was 1.08 (95% CI, 0.83 to 1.40; P=0.57), and the HR for the warfarin versus clopidogrel comparison was 0.89 (95% CI, 0.68 to 1.16; P=0.39).

Figure 2B shows the event curves for all-cause mortality. The HR for warfarin versus aspirin was 0.98 (95% CI, 0.85 to 1.13; P=0.75); for clopidogrel versus aspirin, 1.04 (95% CI, 0.78 to 1.38; P=0.80); and for warfarin versus clopidogrel, 0.92 (95% CI, 0.69 to 1.23; P=0.58).

The numbers of primary end points were similar across treatment groups (Table 2), as were the numbers of deaths and nonfatal MIs. Although the numbers of nonfatal strokes were small (9, 11, and 1 in the aspirin, clopidogrel, and warfarin groups, respectively), both the aspirin-warfarin and the clopidogrel-warfarin differences reached nominal statistical significance (P<0.01 in both cases). Three of the nonfatal strokes (1 in each treatment group) were classified by the End Point Committee as hemorrhagic conversion. All others were nonhemorrhagic. There were 6 fatal strokes; 3, 1, and 2 in the aspirin, clopidogrel, and warfarin groups, respectively. For all strokes (fatal and nonfatal), the differences for the aspirin-warfarin and clopidogrel-warfarin com-
comparisons were not quite as significant (both $P<0.016$) as for nonfatal cases only (Table 2). However, when central nervous system bleeding was added to all strokes (Table 2), no significant differences were found for any of the treatment group comparisons.

Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Age, mean±SD, y</th>
<th>Aspirin (n=523)</th>
<th>Clopidogrel (n=524)</th>
<th>Warfarin (n=540)</th>
<th>Combined (n=1587)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>443 (85)</td>
<td>452 (86)</td>
<td>458 (85)</td>
<td>1353 (85)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>419 (80)</td>
<td>395 (75)</td>
<td>411 (76)</td>
<td>1225 (77)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>58 (11)</td>
<td>77 (15)</td>
<td>70 (13)</td>
<td>205 (13)</td>
</tr>
</tbody>
</table>

Cause of heart failure, n (%)

- Definite/probable ischemic CM†: 375 (72) | 376 (72) | 412 (76) | 1163 (73)
- Primary CM: 107 (20) | 126 (24) | 101 (19) | 334 (21)
- Other: 41 (8) | 22 (4) | 27 (5) | 90 (6)

Years diagnosed with heart failure, n (%)

- <1: 61 (12) | 62 (12) | 51 (9) | 174 (11)
- 1 to <2: 103 (20) | 93 (18) | 109 (21) | 305 (19)
- ≥2: 358 (69) | 367 (70) | 379 (70) | 1104 (70)

Comorbid illnesses, n (%)

- Prior MI: 302 (58) | 292 (56) | 322 (60) | 916 (58)
- Hypertension: 249 (48) | 249 (48) | 267 (49) | 765 (48)
- Diabetes: 178 (34) | 162 (31) | 206 (38) | 546 (34)
- Prior stroke: 23 (4) | 30 (6) | 34 (6) | 87 (5)
- PVD: 60 (11) | 53 (10) | 67 (12) | 180 (11)
- COPD: 44 (8) | 39 (7) | 41 (8) | 124 (8)

Baseline assessments

NYHA class, n (%)

- II: 219 (42) | 231 (44) | 249 (46) | 699 (44)
- III: 296 (57) | 284 (54) | 282 (52) | 862 (54)
- IV: 8 (1) | 9 (2) | 9 (2) | 26 (2)

Heart failure admission within 6 mo, n (%)

- 175 (34) | 184 (35) | 187 (35) | 546 (35)

Heart rate, mean (SD), bpm

- 72±13 | 72±13 | 72±12 | 72±13

Systolic BP, mean (SD), mm Hg

- 118±18 | 119±17 | 120±19 | 119±18

Ejection fraction, mean (SD)

- 0.24±0.07 | 0.25±0.06 | 0.25±0.06 | 0.25±0.06

Hemoglobin, mean±SD, g/dL

- 14.0±1.5 | 14.0±1.4 | 13.9±1.5 | 13.9±1.5

Creatinine, mean±SD, mg/dL

- 1.3±0.4 | 1.3±0.4 | 1.3±0.4 | 1.3±0.4

Baseline medications, n (%)

- ACE inhibitor: 458 (88) | 457 (87) | 474 (88) | 1389 (87)
- ARB: 55 (11) | 54 (10) | 57 (11) | 166 (10)
- Beta-blocker: 362 (69) | 368 (70) | 381 (71) | 1111 (70)
- Loop diuretic: 515 (98) | 519 (99) | 530 (98) | 1564 (99)
- Digoxin: 272 (52) | 264 (50) | 270 (50) | 806 (51)
- Spironolactone: 160 (31) | 143 (27) | 144 (27) | 447 (27)
- Warfarin: 5 (1) | 3 (1) | 7 (1) | 15 (1)

Current smoking, n (%)

- Yes: 85 (16) | 85 (16) | 95 (18) | 265 (17)
- Never: 110 (21) | 137 (27) | 110 (21) | 357 (23)
- Former: 324 (62) | 293 (57) | 325 (61) | 942 (60)

CM indicates cardiomyopathy; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; and ARB, angiotensin receptor blocker.

*Primarily, the cause of heart failure was considered valve disease or other in some patients.
†Definite ischemic cardiomyopathy was defined by the presence of prior MI, positive angiogram, or prior revascularization. Probable ischemic cardiomyopathy also included those with a stress-induced perfusion defect or wall motion abnormality.

When these primary analyses were considered for each gender group and each racial group (white, black, other) separately, similar results were seen. The only exception was for nonfatal strokes in women, in whom there were only 2 nonfatal strokes (0.9% of women).
Heart Failure Hospitalizations

In the aspirin group, 116 patients (22.2%) were hospitalized at least once for worsening heart failure compared with 89 patients (16.5%) in the warfarin arm (Table 2), a nominally significant increase ($P=0.019$). The total number of heart failure admissions also was greater with aspirin compared with warfarin (218 versus 155; $P<0.001$). When time to heart failure admission or death was considered, no differences were found. The HRs and 95% CIs were as follows: for aspirin versus control, 1.36 (95% CI, 1.04 to 1.79); for warfarin versus aspirin, 0.94 (95% CI, 0.84 to 1.04; $P=0.22$); for clopidogrel versus aspirin, 0.97 (95% CI, 0.78 to 1.21; $P=0.79$); and for warfarin versus clopidogrel, 0.90 (95% CI, 0.72 to 1.12; $P=0.37$).

Systemic Embolisms

There were only 10 total systemic (peripheral arterial, abdominal, renal, pulmonary, and other) embolisms (Table 2). Of these, 10, 4 were pulmonary embolisms. There were no significant differences between treatment groups. There was only 1 death, a warfarin patient with a pulmonary embolism.

Bleeding Events

Major bleeding episodes (Table 2) were more frequent in warfarin patients compared with clopidogrel ($P<0.01$) but not aspirin ($P=0.22$) patients. Six patients had 7 central nervous system bleeding episodes on warfarin compared with 3 patients on aspirin and 1 patient on clopidogrel. There also were more patients with minor bleeding episodes in the warfarin group than in the clopidogrel group ($P=0.025$) and a similar trend in the aspirin group ($P=0.054$).

Atrial Fibrillation and Gastrointestinal Intolerance

Atrial fibrillation occurred in 10% of patients at some time during their follow-up. There were no differences between treatment groups (10.3%, 10.3%, and 9.3% for aspirin, clopidogrel, and warfarin, respectively). Patients were routinely questioned about symptoms of gastrointestinal intolerance at each visit. There were 49.9% who reported dyspepsia or epigastric discomfort at some time, 41.2% who reported diarrhea, 29.2% who reported nausea or vomiting, and 22.5% who reported other symptoms of gastrointestinal intolerance. Differences between treatment groups were found only for diarrhea; fewer aspirin patients reported diarrhea than either clopidogrel (35.4% versus 43.9; $P=0.0048$) or warfarin (35.4% versus 44.4%; $P=0.0025$) patients.

Ischemic Versus Nonischemic Group Comparisons

Patients were divided into ischemic (definite or probable) and nonischemic groups, and analyses for the primary outcome measure, its components, and bleeding events were conducted for each group separately. For the ischemic patients, the only significant differences were for strokes; warfarin did better than aspirin (0.0% versus 1.6%; $P=0.01$) or clopidogrel (0.0% versus 2.7%; $P=0.0009$). For the nonischemic patients, the only significant finding was for major hemorrhage; clopidogrel patients (0.7%) had fewer major hemorrhages than warfarin patients (6.3%) ($P=0.0093$). The small sample sizes, especially for the nonischemic patients (total $n=424$ patients), most likely reduced the likelihood of finding other differences.

Discussion

With $>3000$ patient-years of follow-up, the WATCH trial is the largest randomized trial to date examining antithrombotic therapies in patients with chronic heart failure. Although the trial was discontinued prematurely, the WATCH results suggest that for the primary composite end point and all-cause mortality, major differences between anticoagulation with warfarin and antiplatelet therapy with either aspirin or clopidogrel are unlikely. Although the 327 primary end points observed were only 23% of the protocol-specified 1440 events, the 95% confidence limits around these results exclude 20% differences between warfarin and aspirin for both the primary composite end point and total mortality. Similarly, 90% CIs exclude a 20% difference favoring clopidogrel over aspirin for these end points. Therefore, these results do not support our 2 primary hypotheses that warfarin is superior to aspirin in preventing major cardiovascular outcomes and that clopidogrel is superior to aspirin in this population; indeed, our results exclude these hypotheses with a high degree of certainty.

For 2 prespecified secondary end points, nonfatal stroke and hospitalizations for worsening heart failure, some support is provided for the first hypothesis that warfarin may be superior to aspirin in preventing cardiovascular outcomes. These differences are not small and are potentially clinically important. Given the early study termination and the number of potential analyses, our results should be interpreted with caution. The trend for more minor bleeding in the warfarin group than the aspirin group also needs to be taken into
account when the use of warfarin is considered. We find no support from the secondary analyses that clopidogrel is superior to aspirin.

The relatively low incidence of stroke among our patients is noteworthy. For patients not assigned to warfarin, the incidence of stroke was only 1.0 event per 100 patient-years of follow-up, a finding consistent with observations from other trials conducted in the past 2 decades.\textsuperscript{26,27} Based on posthoc analyses of atrial fibrillation trials,\textsuperscript{28} this is far lower than for heart failure patients in atrial fibrillation for whom anticoagulation is strongly recommended. However, nonfatal strokes and all strokes were less frequent in the warfarin arm than in the groups assigned to either antiplatelet agent. These findings, which represent the first prospective, controlled data in patients required to be in sinus rhythm at baseline, are consistent with many physicians’ belief that anticoagulation may prevent stroke in patients with chronic systolic heart failure. These results should be tempered by the findings of more bleeding episodes with warfarin.

Compared with aspirin patients, the warfarin group experienced a 26% relative reduction (5.7% absolute decrease) in the proportion of patients hospitalized for heart failure. Taking into account multiple hospitalizations, warfarin was associated with a 40% reduction in heart failure admissions compared with aspirin (6.0 events per 100 patient-years

**Figure 2.** A, Plot of the proportion of patients experiencing the primary composite end point of death, nonfatal MI, or stroke during the course of the WATCH trial (warfarin vs aspirin, $P=0.77$; warfarin vs clopidogrel, $P=0.59$; aspirin vs clopidogrel, $P=0.39$). B, Plot of the proportion of patients who died during the course of the WATCH trial (warfarin vs aspirin, $P=0.75$; warfarin vs clopidogrel, $P=0.58$; aspirin vs clopidogrel, $P=0.80$).
One possible mechanism for this difference is that aspirin may interfere with the increase in prostaglandin levels that occurs in heart failure that is further enhanced by ACE inhibitors. Prostaglandins such as prostacyclin and prostaglandin E1 have vasodilator, natriuretic, and antiaggregatory activity, which appears to play a compensatory role in patients with heart failure. Although these data cannot be considered definitive, the magnitude of reduction potentially achievable by avoiding aspirin is similar to that observed with the most effective pharmacological therapies for heart failure such as ACE inhibitors and β-blockers.29–32 Moreover, the relative and absolute differences between warfarin and aspirin are similar to those observed in the Warfarin and Aspirin Study in Heart Failure.12 It should be kept in mind, however, that when an analysis of the time to first hospitalization or death was conducted, the differences disappeared.

Many physicians and patients are appropriately concerned about the safety of anticoagulation in heart failure patients because they usually are older, generally are taking multiple medications, and may have significant fluctuations in liver function, food intake, and drug absorption related to congestion.19,33,34 In that regard, warfarin treatment in our trial was associated with more frequent bleeding episodes compared with clopidogrel and a nonsignificant excess of bleeding compared with aspirin. However, warfarin-associated bleeding complications occurred at a frequency similar to that observed in anticoagulation trials in post-MI and atrial fibrillation patients. Although warfarin was related to a lower incidence of stroke compared with the other 2 drugs, when central nervous system bleeding and stroke were combined, these differences disappeared. Thus, the elevated risks for bleeding (major, minor, and central nervous system) versus the lower risk for stroke must be considered when warfarin is begun, especially given the low rates of embolic events.

Several limitations could have affected our results. The higher number of diabetic patients in the warfarin group, with their higher risks, could have underestimated the ability of warfarin to reduce thromboembolic events. However, the warfarin group had few such events in our study. Another concern is that patients with symptoms for only 3 months were enrolled. This may have resulted in a healthier subset of patients with lower event rates (e.g., ejection fraction may have improved after continuation of heart failure treatment), although 70% of our patients had been diagnosed for at least 2 years. An indication that our sample may have been a healthier subset of the patient population is the lower-than-expected event rate. Although our event rate was estimated to be 18% annually for our sample size estimates, as seen in

Table 2. Number of Patients With Events and Total Number of Events as Classified by End Point Committee

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Aspirin</th>
<th>Clopidogrel</th>
<th>Warfarin</th>
<th>P by χ2 (Patients With Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, n</td>
<td>%</td>
<td>Events, n</td>
<td>Patients, n</td>
</tr>
<tr>
<td>Death, nonfatal MI, or nonfatal stroke</td>
<td>108</td>
<td>20.7</td>
<td>...</td>
<td>113</td>
</tr>
<tr>
<td>All deaths reported</td>
<td>94</td>
<td>18.0</td>
<td>...</td>
<td>96</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>14</td>
<td>2.7</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>9</td>
<td>1.7</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>All strokes</td>
<td>12</td>
<td>2.3</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Hospitalization with decompensated congestive heart failure</td>
<td>116</td>
<td>22.2</td>
<td>218</td>
<td>97</td>
</tr>
<tr>
<td>All systemic embolisms</td>
<td>4</td>
<td>0.8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>All pulmonary embolisms</td>
<td>2</td>
<td>0.4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>19</td>
<td>3.6</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>CNS bleeds</td>
<td>3</td>
<td>0.6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>CNS bleeds or stroke</td>
<td>15</td>
<td>2.9</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Minor bleeds</td>
<td>123</td>
<td>23.5</td>
<td>711</td>
<td>119</td>
</tr>
<tr>
<td>Total patients</td>
<td>523</td>
<td>...</td>
<td>711</td>
<td>524</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system.
Figure 2A, it took almost 2 years to reach an 18% event rate. On the other hand, our study may be a truer reflection of heart failure patients in general. The early termination of the study, which reduced follow-up time by 16 months and reduced the number of events, made finding treatment differences more difficult as a result of low statistical power. Future studies with a longer follow-up time may be needed to find treatment differences. Finally, the target INR range of 2.5 to 3.0 for warfarin is relatively narrow and may limit generalizability to everyday practice. However, our medium INR was 2.5, and 70% of the actual INRs were between 2.0 and 3.5.

Given the absence of significant differences in the primary end point or in survival, this study does not justify a systematic avoidance of aspirin in patients with chronic heart failure in sinus rhythm. The WATCH results also do not provide supportive data to reinforce the recent recommendations of the Seventh Consensus Conference on Antithrombotic Therapy to avoid aspirin in patients with nonischemic dilated cardiomyopathy and in other heart failure patients with no evidence of or major risk factors for vascular disease. These results also provide no evidence to support the use of aspirin. Although the use of warfarin rather than aspirin or clopidogrel may have resulted in reduced strokes in our population, this benefit may be offset by increased risk from bleeding. Overall, our primary outcome measure and mortality results do not support our 2 primary hypotheses that anticoagulation with warfarin is superior to antiplatelet therapy with aspirin in preventing major cardiovascular outcomes and that clopidogrel is superior to aspirin in this population.

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References
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for the WATCH Trial Investigators

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