Can Further Benefit Be Achieved by Adding Flosequinan to Patients With Congestive Heart Failure Who Remain Symptomatic on Diuretic, Digoxin, and an Angiotensin Converting Enzyme Inhibitor? 

Results of the Flosequinan-ACE Inhibitor Trial (FACET)

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Background. Angiotensin converting enzyme inhibitors, diuretics, and digoxin are each effective in treating congestive heart failure, but many patients remain symptom-limited on all three medications. This trial was designed to determine whether the addition of oral flosequinan, a new direct-acting arterial and venous vasodilator with possible dose-dependent positive inotropic effects, improves exercise tolerance and quality of life in such patients.

Methods and Results. In a randomized, double-blind multicenter trial, 322 patients with predominantly New York Heart Association class II or III congestive heart failure and left ventricular ejection fractions of 35% or less, who were stabilized on a diuretic, angiotensin converting enzyme inhibitor, and digoxin, were treated with 100 mg flosequinan once daily, 75 mg flosequinan twice daily, or matching placebo. Efficacy was evaluated with serial measurements of treadmill exercise time, responses to the Minnesota Living With Heart Failure Questionnaire (LWHF), and clinical assessments during a baseline phase and a 16-week treatment period. After 16 weeks, 100 mg flosequinan once daily produced a significant increment in median exercise time (64 seconds at 16 weeks) compared with placebo (5 seconds), whereas the higher-dose flosequinan group did not show a statistically significant increase. Flosequinan (100 mg once daily) also improved the overall LWHF score significantly compared with placebo; both active therapies decreased the physical component, but 75 mg flosequinan twice daily was associated with a trend toward worsening of the emotional component. Most clinical assessments tended to improve on active therapy.

Conclusions. These results indicate that additional symptomatic benefit can be attained by adding flosequinan to a therapeutic regimen already including a converting enzyme inhibitor. Because in the future most patients will fall into this category, flosequinan is a potential adjunctive agent in the management of severe congestive heart failure. However, because recent evidence indicates that the flosequinan dose studied in the present trial has an adverse effect on survival, the benefit-to-risk ratio must be assessed in individual patients. (Circulation 1993;88:492-501)

Key Words • heart failure • flosequinan • angiotensin converting enzyme • vasodilators

The management of congestive heart failure has evolved considerably over the past two decades. With the recognition that cardiac performance can be enhanced by modulating left ventricular preload and afterload, adjuncts to diuretics and digitalis glycosides that produce arterial and venous vasodilatation have been used with increasing frequency. In the first Veterans Administration Cooperative Studies Heart Failure Trial (V-HeFT),² the combination of oral hydralazine and isosorbide dinitrate, a commonly used direct

The main results of this study were presented at the 65th Annual Scientific Sessions of the American Heart Association, New Orleans, La; November 18, 1992. Correspondence to VAMC, Cardiology Section (111C), 4150 Clement St, San Francisco, CA 94121 (Dr Massie).
vasodilator regimen, was found to produce substantial hemodynamic improvement and to prolong survival. More recently, the angiotensin converting enzyme inhibitors have become the most widely studied and used vasodilators. As a result of the Captopril Multicenter Studies, 3, 4 CONSENSUS, 5 SOLVD, 6, 7 and SAVE, 8 these agents are now recognized to improve symptoms, prevent deterioration, and prolong survival in a wide range of patients with congestive heart failure. Thus, virtually all patients with significant left ventricular systolic dysfunction (ejection fractions of less than 35%), whether associated with clinical congestive heart failure or asymptomatic, are candidates for converting enzyme inhibitor therapy. Several recent studies have also confirmed the benefit of digoxin in patients with symptomatic congestive heart failure, 9-11 and diuretics remain an essential part of the therapeutic regimen for patients with clinical symptoms or evidence of fluid retention. 1 Consequently, most patients with symptomatic heart failure will be treated with agents from each of these classes, but because many will remain symptomatic, there is a need for treatments that can supplement what has now become standard triple-drug therapy.

Until recently, attention has focused on newer positive inotropic drugs, but results with phosphodiesterase inhibitors and sympathetic agonists have been discouraging. 12, 13 Little information is available on the use of direct-acting vasodilators in combination with angiotensin converting enzyme inhibitors. Nonetheless, this approach is potentially attractive because the converting enzyme inhibitors are relatively weak vasodilators 14, 15 but may prevent the neurohormonal activation and clinical tolerance that accompany some vasodilator drugs. 16-18 Furthermore, addition of a direct-acting vasodilator in patients receiving converting enzyme inhibitors produces incremental hemodynamic responses, 19 but it is not known whether this combination can produce further clinical benefit.

Flosequinan, a direct-acting arterial and venous vasodilator, also has dose-dependent inotropic properties by an undefined mechanism. 20 It has been shown to increase exercise time in patients who are taking digoxin and diuretics but not converting enzyme inhibitors. 21-23 The present study was undertaken to determine whether the addition of oral flosequinan increases exercise time and improves the quality of life in patients who are maintained on a regimen including diuretics, digoxin, and an angiotensin converting enzyme inhibitor.

Methods

The Flosequinan–Angiotensin Converting Enzyme Inhibitor Trial (FACET) was a double-blind, placebo-controlled, randomized, parallel-group study of two dosages of oral flosequinan, and it was conducted in 33 centers within the continental United States. The study consisted of a single-blind placebo run-in, in which stability of symptoms, medications, and exercise tolerance was confirmed, and a subsequent 16-week double-blind treatment evaluation. The primary prespecified end point was the change in exercise tolerance at the end of the double-blind period. Prestated secondary objectives were to determine the effect of treatment on quality of life, as assessed by the Minnesota Living With Heart Failure (LWHF) questionnaire, 24 and the tolerability and safety of the treatments.

Patient Population

Men and women not at risk for pregnancy who were at least 18 years of age were eligible for the study. All patients were required to have at least a 12-week history of symptomatic heart failure, have a left ventricular ejection fraction of 35% or less by radionuclide angiography, and be able to exercise to an end point of dyspnea or fatigue. All patients must have received treatment with a converting enzyme inhibitor for at least 12 weeks and taken a minimum total daily dose of 37.5 mg captopril or 5 mg enalapril for at least 1 month before entry. Patients also were required to be on diuretic therapy for at least 12 weeks, and if present, digoxin therapy must have been ongoing for 12 weeks.

Principal exclusion criteria included congestive heart failure due to uncorrected primary valvular disease or obstructive or restrictive cardiomyopathy, acute myocardial infarction within 3 months, angina pectoris requiring chronic treatment, a serum creatinine level of more than 3 mg/dL, a total bilirubin level of more than 3 mg/dL, or associated medical or psychiatric conditions that might affect the outcome of the study. Exercise tolerance could not be limited by angina pectoris, primary pulmonary disease, peripheral vascular disease, orthopedic or rheumatological conditions, or neurological abnormalities. The following medications also were excluded: calcium channel blockers, β-adrenergic blockers, α-adrenergic blockers, long-acting nitrate preparations, disopyramide or class Ic antiarrhythmic agents, theophylline, oral or inhaled bronchodilators, or other investigational compounds.

Study Protocol

The study was conducted in three phases. First, patients apparently meeting study entry criteria were seen for an initial screening visit, during which informed written consent was obtained (according to the procedures of each site’s institutional review board); a complete medical history, physical examination, and baseline laboratory tests were performed; and the left ventricular ejection fraction was measured by radionuclide scintigraphy (unless a qualifying ejection fraction had been obtained within 12 weeks before screening). The LWHF questionnaire was administered on this visit for familiarization purposes.

Patients who met the eligibility criteria then entered a single-blind placebo run-in period, which was designed to establish a stable baseline of medication requirements, symptoms, and exercise capacity. The length of this phase was determined by the results of the exercise testing. Patients performed treadmill tests by the procedures outlined below at 1- to 2-week intervals. To qualify, each exercise test had to be between 3 and 14 minutes in duration, with the difference in the durations of the shortest and longest test not to exceed 60 seconds. In addition, if a trend toward an increase or a decrease in exercise time was observed during the three qualifying tests, the difference between any two consecutive tests could not be more than 45 seconds. If changes were made in medications administered for heart failure, the qualifying process was reinitiated. The duration of the baseline phase was required to be
between 3 and 12 weeks; the number of qualifying exercise tests ranged from 3 to 11. The final qualifying test was taken as the baseline measurement of exercise tolerance. In addition, the LWHF questionnaire was readministered during the baseline phase, and this test was used as baseline for comparison with subsequent treatment measurements.

Patients meeting the qualifying criteria during the single-blind placebo run-in phase were then entered into the double-blind treatment period, in which they were randomized to placebo, 100 mg flosequiban administered once daily, or 75 mg flosequiban administered twice daily. To maintain the blind, all patients took one pill twice a day, with both pills being active in the 75-mg twice-daily group, one pill being active in the 100-mg once-daily group, and neither pill being active in the placebo group. The first dose of the study medication was administered in the clinic, and the patient subsequently observed for 2 hours. The dosage of the study medication was reduced to 75 mg once daily or 50 mg twice daily for the two active therapy groups, respectively, if heart rate increased by more than 15 beats per minute on two consecutive visits or other adverse reactions linked to the study medications occurred. Patients were seen 1, 2, 4, 6, 8, 12, and 16 weeks after randomization for assessment of symptoms, medication changes, major cardiovascular physical findings, routine hematological and chemistry tests, and adverse reactions. The major efficacy parameters—exercise tolerance and responses to the LWHF questionnaire—were assessed after 4, 8, 12, and 16 weeks. Adjustments of concomitant medications during the double-blind period were allowed, but a minimum 5-day period on constant medication was required before each exercise test. The initiation of any antiarrhythmic agent during the double-blind period or the use of medications that were excluded at baseline also necessitated patient withdrawal.

**Study Procedures**

Treadmill exercise testing was the primary prespecified efficacy measurement. A modified Naughton treadmill protocol was used, in which the workload was increased every 2 minutes as follows: 1 mph/0% grade, 1.5 mph/0% grade, 2 mph/3.5% grade, 2 mph/7% grade, 2 mph/10.5% grade, 3 mph/7.5% grade, 3 mph/10% grade, 3 mph/12.5% grade, 3 mph/15% grade, and 3.4 mph/14% grade. During the baseline phase, patients were required to exercise to an end point of fatigue or dyspnea; all other exercise end points necessitated exclusion from the study. Patients were instructed to exercise to a symptom-limited maximum and to achieve approximately the same level of perceived exertion during all tests, but no specific encouragement was given to continue at any stage during the test.

Quality of life was assessed using the LWHF questionnaire, which was always administered before exercise testing and other assessments during the specified visits. A global assessment score and component scores were determined for physical symptoms and limitations and for psychoemotional reactions. In addition, both the subject and the clinician were asked to rate the patient’s overall status as very good, good, fair, poor, or very poor at each visit. The changes in these ratings compared with baseline were evaluated for each treatment group.

Twenty-four-hour ambulatory ECG monitoring was performed at the end of the single-blind placebo phase and after 4, 12, and 16 weeks of randomized therapy as a substudy in 13 centers (110 patients) to determine the effect of therapy on ventricular arrhythmias. The tapes were analyzed by an independent laboratory (Cardiodata, Inc), and the reports were reviewed by a consultant cardiologist; both were blinded to the patients’ treatment group. Worsening of ventricular arrhythmia was defined by criteria developed by Morganroth, as modified and expanded in the analysis of the Prospective Randomized Milrinone Survival Evaluation (PROSPECT). 

**Statistical Analysis**

The study was designed to provide a power of 0.80 to detect a 60-second difference in exercise duration between treatment groups at week 16 at a P=.05 level of significance. Based on variability estimates, 75 completing patients per treatment group were considered necessary, and therefore, assuming a 25% dropout rate, approximately 100 patients were entered into each treatment group. Comparisons of the demographic characteristics, clinical variables, and medications at baseline were performed using ANOVAs for continuous variables and contingency tables for categorical variables. All patients who entered the randomized phase were evaluated for side effects and clinical events according to the intent-to-treat principle. Patients with at least one exercise test or quality of life assessment were included in the efficacy analyses. Following the prespecified statistical plan and recommendations of the Food and Drug Administration, the conservative approach of carrying forward values from the last completed test was used for patients who did not complete the 16-week treatment phase.

The primary efficacy end point, the change in exercise tolerance at the completion of the double-blind treatment phase, was evaluated by comparing the change in exercise time from the final baseline test among the three treatment groups. As prespecified in the protocol, because this variable was not normally distributed, intergroup comparisons were performed using the non-parametric Kruskal-Wallis test and the Shirley-Dunn rank-sums test, respectively. Changes from baseline in the LWHF questionnaire score were compared among treatment groups using ANOVAs and Fisher’s least significant difference multiple comparison procedure. Differences in hospitalization rates and in nonparametric variables, such as clinical assessments, were examined using contingency table analyses and the \( \chi^2 \) statistics.

All differences were considered significant if the \( P \leq .05 \), and differences of borderline significance (\( .05<P<.10 \)) are indicated for informational purposes.

**Results**

**Baseline Comparisons Between Treatment Groups**

Five hundred twenty-one patients entered the single-blind baseline phase. One hundred ninety-nine (38.2%) of these were not randomized, with the most common reasons for exclusion being exercise tolerance above the allowed limit (10.9%), an ejection fraction of more than 35% (4.0%), and noncompliance (2.9%). Three hundred twenty-two patients entered the randomized treatment phase.
TABLE 1. Baseline Characteristics of the Treatment Groups

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Placebo (n=110)</th>
<th>Flosequinan 100 mg once daily (n=110)</th>
<th>Flosequinan 75 mg twice daily (n=102)</th>
<th>All patients (n=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y±SD)</td>
<td>58±12</td>
<td>60±11</td>
<td>57±12</td>
<td>58±12</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>63</td>
<td>68</td>
<td>73</td>
<td>68</td>
</tr>
<tr>
<td>Men (%)</td>
<td>73</td>
<td>72</td>
<td>69</td>
<td>71</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (%)</td>
<td>46</td>
<td>41</td>
<td>37</td>
<td>41</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II (%)</td>
<td>53</td>
<td>51</td>
<td>54</td>
<td>53</td>
</tr>
<tr>
<td>Class III (%)</td>
<td>44</td>
<td>47</td>
<td>41</td>
<td>44</td>
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<tr>
<td>Class IV (%)</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretics (%)</td>
<td>99</td>
<td>96</td>
<td>94</td>
<td>96</td>
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<tr>
<td>Mean furosemide dose (mg)*</td>
<td>119</td>
<td>117</td>
<td>104</td>
<td>113</td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>86</td>
<td>91</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>Mean dose (mg)</td>
<td>0.22</td>
<td>0.22</td>
<td>0.22</td>
<td>0.22</td>
</tr>
<tr>
<td>Captopril (%)</td>
<td>60</td>
<td>53</td>
<td>65</td>
<td>59</td>
</tr>
<tr>
<td>Mean dose (mg)</td>
<td>87</td>
<td>83</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>Enalapril (%)</td>
<td>40</td>
<td>47</td>
<td>35</td>
<td>41</td>
</tr>
<tr>
<td>Mean dose (mg)</td>
<td>13.2</td>
<td>14.1</td>
<td>15.8</td>
<td>14.4</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association.
P=NS for all intergroup comparisons.
*Expressed as "furosemide equivalents," where 1 mg bumetanide equals 40 mg furosemide and 0.5 mg ethacrynic acid equals 1 mg furosemide. Drug doses are expressed as mean total daily dose.

Table 1 provides demographic information, baseline clinical characteristics, and medication history for the three treatment groups. Most patients were middle age or older caucasian men. Approximately 40% of the patients had known ischemic heart disease, as diagnosed by cardiac catheterization or documented prior myocardial infarction. Slightly more than half of the patients had New York Heart Association class II symptoms, and most of the remainder had class III symptoms. All patients were receiving diuretics, of which 96% received loop agents, with the mean daily dose exceeding 100 mg furosemide once daily or the equivalent in all groups. As required, all patients were receiving captopril or enalapril in moderately high dosages. Approximately 90% were on digoxin. With respect to all of these factors, the treatment groups were well balanced.

Table 2 compares the baseline measurements of vital signs, ejection fraction, exercise tolerance, and LWHF scores. There were no significant differences among the treatment groups.

**Effect of Treatment on Exercise Time**

Figure 1 illustrates the changes in exercise time in the three groups. At least one postrandomization exercise test was performed in 103 of 110 placebo patients, 101 of 110 100 mg flosequinan once daily patients, and 97 of 102 75 mg flosequinan twice daily patients. Using the

Table 2. Baseline Physical Findings and Assessments

<table>
<thead>
<tr>
<th>Vital signs</th>
<th>Placebo (n=110)</th>
<th>Flosequinan 100 mg once daily (n=110)</th>
<th>Flosequinan 75 mg twice daily (n=102)</th>
<th>All patients (n=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>81±13</td>
<td>81±13</td>
<td>81±11</td>
<td>81±12</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>115±18</td>
<td>116±16</td>
<td>116±17</td>
<td>116±17</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>72±10</td>
<td>73±10</td>
<td>74±9</td>
<td>73±10</td>
</tr>
<tr>
<td>Measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>23±8</td>
<td>23±7</td>
<td>23±8</td>
<td>23±8</td>
</tr>
<tr>
<td>Exercise time (s)</td>
<td>534±168</td>
<td>549±151</td>
<td>538±186</td>
<td>540±168</td>
</tr>
<tr>
<td>LWHF total score</td>
<td>38±23</td>
<td>44±24</td>
<td>47±25</td>
<td>43±24</td>
</tr>
<tr>
<td>LWHF physical score</td>
<td>18±10</td>
<td>20±10</td>
<td>22±11</td>
<td>20±11</td>
</tr>
<tr>
<td>LWHF emotional score</td>
<td>8±7</td>
<td>9±7</td>
<td>10±8</td>
<td>9±7</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute; BP, blood pressure; and LWHF, Minnesota Living With Heart Failure. Values are mean±1 SD.
P=NS for all intergroup comparisons.
carryforward approach, exercise time increased by 64 seconds in the 100 mg flosequinan once daily group at the end of the study compared with a 5-second increase in the placebo group ($P<.05$). An analysis limited to completers also showed a difference between the 100 mg flosequinan once daily group and the placebo group ($P=.05$). Favorable but statistically insignificant trends were seen with the 75 mg flosequinan twice daily group, and there was no significant difference between the two active therapy groups.

Figure 2 illustrates the proportion of patients achieving at least a 60-second increase in exercise time compared with baseline. An increase of this magnitude was achieved by more patients in the 100 mg flosequinan once daily group than in the placebo group at each point in time, and the overall comparison was significant at $P\leq.05$ at weeks 8, 12, and 16. After correction for multiple comparisons, the difference remained significant at week 16 but was borderline ($P<.10$) at weeks 8 and 12. The results in the 75 mg flosequinan twice daily group fell in between at most time points but were not significantly different from those of placebo. Of note is that exercise tolerance improved similarly in the 100 mg flosequinan twice daily group in subsets defined by ejection fraction of 20% or less, 21% to 30%, and more than 30% and in patients classified as having ischemic and nonischemic etiologies.

**Effect of Flosequinan on Quality of Life**

Figure 3 illustrates the changes from baseline in the LWHF scores. The top panel illustrates the total score, which declined (indicating improvement) in the 100 mg flosequinan once daily group, was essentially unchanged in the placebo group, and showed an intermediate change in the 75 mg flosequinan twice daily group. The middle panel shows the score related to the physical component of the questionnaire. Improvement was seen in both active therapy groups at virtually all time points. The total LWHF score and the physical component

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**Fig 1.** Plot illustrating the changes in median exercise time compared with the final baseline test. The flosequinan 100 mg od (once daily) group showed an early and sustained increase compared with the placebo group that was statistically significant at the study end point. The flosequinan 75 mg bid (twice daily) group exhibited intermediate responses.

**Fig 2.** Plot of the proportion of patients exhibiting an increase in exercise test time (ETT) of at least 60 seconds; the proportion was higher in the flosequinan 100 mg od (once daily) group than in the placebo group at each point in time, but this was not true for the higher-dose flosequinan group. The difference between the flosequinan 100 mg od group and the placebo group was significant at 16 weeks (indicated by *). At 8 and 12 weeks, after correction for multiple comparisons, the P value was of borderline significance (0.05$<P<0.10$, indicated by #).

**Fig 3.** Plots of the changes in the Minnesota Living With Heart Failure scores are shown, with the total score shown at the top, the physical score shown in the middle, and the emotional score shown at the bottom. The flosequinan 100 mg od (once daily) group exhibited a significant improvement in both the total and physical scores compared with the placebo group. The flosequinan 75 mg bid (twice daily) group showed a significant improvement in the physical score but a nonsignificant worsening in the emotional component, resulting in a lack of improvement in the total score. Between-group differences that achieved statistical significance after correction for multiple comparisons are indicated by the asterisks.
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both declined in all patient subsets defined by baseline ejection fraction and New York Heart Association class. In contrast, changes in the emotional component of the score were small and insignificant, but interestingly, a trend toward improvement was seen in the 100 mg flosequinan once daily group, whereas a trend toward worsening was seen in the 75 mg flosequinan twice daily group.

**Additional Clinical Assessments**

Table 3 presents the results of the clinical assessments, as judged subjectively by the patient and physician. With flosequinan, there was a trend toward a greater proportion of patients feeling improved and fewer feeling worse, especially at the 75 mg twice daily dosage; this difference was of borderline statistical significance (P = .06). The physician classifications were very similar. New York Heart Association class tended to improve in more patients in the active therapy group at each point in time, but these differences did not achieve statistical significance.

Table 4 presents additional clinical outcomes. Deaths, hospitalizations, and hospitalizations for worsening heart failure occurred in similar proportions of patients in the three groups. Premature withdrawals for worsening heart failure occurred in 7.3% of the placebo patients, 1.8% of the 100 mg flosequinan once daily group, and 3.9% of the 75 mg flosequinan twice daily group.

Ninety-six percent of the patients were receiving loop diuretics. In these, the mean increase in furosemide dosage was 18.4 ± 6.8 mg in the placebo group compared with 3.5 ± 4.9 mg in the 100 mg flosequinan once daily group and 5.1 ± 3.8 mg in the 75 mg flosequinan twice daily group. These differences were of borderline statistical significance (P = .098). There was no change in the mean dose of angiotensin converting enzyme inhibitors in any of the three groups.

**Ambulatory ECG Monitoring**

One hundred ten patients underwent 24-hour ambulatory ECG monitoring at baseline and one to three times during the randomized treatment period. Five prespecified criteria for worsening of ventricular arrhythmia were used based on published approaches and on the experience of the PROMISE trial.26–28 As can be seen from Table 5, there was no trend toward worsening of ventricular arrhythmias in the active treatment groups.

Of the patients undergoing ambulatory monitoring, two died suddenly while they were not being monitored; both were in the placebo group. Four additional patients were withdrawn from the study because the investigator chose to initiate antiarrhythmic therapy for ventricular arrhythmia (two on placebo and one on flosequinan) or for atrial fibrillation (one on placebo). These decisions were made without the knowledge of results of the ambulatory ECGs.

**Side Effects and Adverse Reactions**

Adverse effects were reported in the majority of patients in all treatment groups. As can be seen in Table 6, the effects that appear to be drug related include palpitations, tachycardia, taste alteration, and headache. However, patient withdrawals due to adverse effects were equally distributed among the three treatment groups.

Sixty-nine patients had their study medication reduced (4.5% in the placebo group, 27.3% in the 100 mg flosequinan once daily group, and 33.3% in the 75 mg flosequinan twice daily group). Six percent and 10% of the dose reductions in the 100 mg once daily and 75 mg twice daily flosequinan groups, respectively, were due to heart rate changes that exceeded the prespecified upper limit of an increase of 15 beats per minute. Overall, heart rate increased by a mean of 6 beats per minute on

| TABLE 3. Change in Clinical Assessments at Week 16 or Last Evaluation |
|-------------------------|-------------------------|-------------------------|
|                         | Placebo (n=109)         | Flosequinan 100 mg once daily (n=110) | Flosequinan 75 mg twice daily (n=102) |
| Patient's global assessment* |  |  |  |
| Improved (%)            | 22.0                    | 31.8                    | 38.2                    |
| Worsened (%)            | 25.7                    | 17.3                    | 13.7                    |
| Physician's global assessment* |  |  |  |
| Improved (%)            | 18.4                    | 26.4                    | 36.3                    |
| Worsened (%)            | 24.8                    | 19.1                    | 17.7                    |
| NYHA class              |  |  |  |
| Improved (%)            | 22.0                    | 30.9                    | 39.3                    |
| Worsened (%)            | 14.7                    | 16.4                    | 15.7                    |

NYHA indicates New York Heart Association.

*P = .06 flosequinan 75 mg twice daily vs placebo.

†P = NS for NYHA class.

<table>
<thead>
<tr>
<th>TABLE 4. Other Clinical Outcomes for Patients in the Three Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=110)</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Deaths* (n, %)</td>
</tr>
<tr>
<td>Hospitalizations (all cause)* (n, %)</td>
</tr>
<tr>
<td>Hospitalizations for CHF* (n, %)</td>
</tr>
<tr>
<td>Withdrawals for worsening CHF* (n, %)</td>
</tr>
<tr>
<td>Mean increase in diuretic dosage (mg)†</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure.

*Patients with these outcomes using intent-to-treat principle.

†Quantified in "furosemide equivalents," where 1 mg bumetanide equals 40 mg furosemide and 0.5 mg ethacrynic acid equals 1 mg furosemide.

‡P < .10 vs placebo; all other comparisons are not significant.
TABLE 5. Worsening of Ventricular Arrhythmia on Ambulatory ECG Monitoring

<table>
<thead>
<tr>
<th>Symptomatic arrhythmia (n)</th>
<th>Placebo (n=40)</th>
<th>Flosequinan 100 mg once daily (n=32)</th>
<th>Flosequinan 75 mg twice daily (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New sustained VT (&gt;30 s) (n)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Increased VT length* (n)</td>
<td>8</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Increased VT frequency† (n)</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Increased PVC frequency‡</td>
<td>8</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Any criterion, n, %</td>
<td>15 (38)</td>
<td>8 (25)</td>
<td>14 (37)</td>
</tr>
</tbody>
</table>

*VT indicates ventricular tachycardia; and PVC, premature ventricular complexes.
No significant differences were present between treatment groups.
†Present if longest run of VT increased from baseline to any treatment recording as follows: if <5 beats at baseline to ≥10 beats on treatment or if >5 beats at baseline to ≥2 times baseline on treatment.
‡Present if frequency of PVC per 24 hours increased from baseline to treatment as follows: 0 to >5, 1 to >100, 2-5 to >50 times baseline, 6-50 to >20 times baseline, or >50 to >10 times baseline.
§Present if frequency of PVCs per hour increased from baseline to treatment as follows: 0 to >10, 1-50 to >10 times baseline, 51-100 to >5 times baseline, 101-300 to >4 times baseline, and >300 to >3 times baseline.

100 mg flosequinan once daily and 9 beats per minute on 75 mg flosequinan twice daily (both P < 0.05 versus the placebo group, which did not change). The remaining dose reductions in patients on active flosequinan were due primarily to headache (11 and 16 in the 100 mg once daily and 75 mg twice daily groups, respectively). Supine and standing blood pressures decreased by mean values of 1.2/0.2 and 1.8/2.3 mm Hg at week 16 in the 100 mg once daily and 75 mg twice daily groups, respectively; standing pressure declined by 0.2/0.1 and 7.2/4.3 mm Hg, respectively. Hypotension or dizziness was the indication for decreasing the medication dosage in 1 placebo patient, 11 100 mg flosequinan once daily patients, and 9 75 mg flosequinan twice daily patients but led to patient withdrawal in only 2 patients from each group.

**Discussion**

Based on current practice and the results of recent trials, it appears that the treatment of most patients with congestive heart failure will consist of diuretics and angiotensin converting enzyme inhibitors and, in many patients, digoxin. Many, perhaps most, of these patients will remain or eventually become symptomlimited in their desired activities and could potentially benefit from an adjunctive agent that could enhance the effect of combination therapy. Two approaches are currently available: the addition of another positive inotropic agent or of a direct-acting vasodilator. Two recent major trials have examined the effect on survival of adding positive inotropic agents to regimens including angiotensin converting enzyme inhibitors. The European Xamoterol Study used a β-adrenergic agonist, and the PROMISE trial used a phosphodiesterase inhibitor. In both, mortality was increased in the active treatment groups, and therefore, chronic therapy with nonglycoside positive inotropic agents is lost much of its appeal. Because the angiotensin-converting enzyme inhibitors are effective vasodilators, it is not known whether the addition of another agent with this mechanism of action could be beneficial.

The present study demonstrates that oral flosequinan, a direct-acting arterial and venous vasodilator, which has dose-dependent positive inotropic effects, produces significant additional symptomatic benefit. The 100 mg once daily dosage (with dose reduction to 75 mg once daily in 27% of patients) significantly increased maximum exercise time over a 4-month period, with approximately 50% of treated patients exhibiting substantial (more than 60 seconds) increments in exercise capacity. Flosequinan (100 mg once daily) also improved quality of life as assessed by the LWHF questionnaire, particularly in the components that assessed symptoms and physical limitations. Interestingly, the 75 mg flosequinan twice daily dose did not produce as effective a response, although similar trends were apparent. The explanation for the lesser benefit of the higher dose may lie in the negative response observed in the emotional component of the LWHF score, which worsened despite a significant improvement in symptoms and other clinical assessments, perhaps reflecting the responses to a high incidence of palpitations, tachycardias, and headache. Another multicenter study of flosequinan without concomitant converting enzyme inhibitor therapy also showed a greater increment in exercise time with the 100 mg once daily dose of...
flosequinan\textsuperscript{20} than with the 75 mg twice daily dose, suggesting that at least in some patients, the higher dose is less effective.

Although one might anticipate difficulty in demonstrating benefit from adding flosequinan to patients already receiving three effective medications for heart failure including an angiotensin converting enzyme inhibitor, the results in the present trial are at least as favorable as those obtained in several previous studies in which flosequinan has been added to diuretic and digoxin without accompanying angiotensin converting enzyme inhibitor therapy.\textsuperscript{22,23} Thus, flosequinan should be useful in patients who remain symptomatic despite angiotensin converting enzyme inhibitor therapy as well as in those who cannot tolerate one. It is important that there does not appear to be a major problem with hypotension with the combination vasodilator regimen in the present study. Although approximately 10% of patients required dose reduction due to hypotension or other potentially blood pressure-related symptoms, only two patients in each group were withdrawn for this reason.

The potent vasodilating effect of flosequinan is well characterized,\textsuperscript{20,31,32} but despite considerable investigation, its mechanism of action is not fully understood. In experimental preparations, concentrations of flosequinan comparable to those observed during clinical treatment have been found to inhibit the production of inositol triphosphate and protein kinase C,\textsuperscript{20,32,33} particularly in response to endothelin-1-induced vasoconstriction,\textsuperscript{34} which could explain the vasodilator action of the drug.

Because flosequinan is associated with dose-related increases in heart rate, it has been evaluated extensively for positive inotropic effects. In isolated muscle strips from normal animal and human hearts, flosequinan appears to have a dose-dependent, positive inotropic effect, although this is not always observed in the therapeutic concentration range.\textsuperscript{20,35-38} This is associated with a rise in intracellular Ca\textsuperscript{2+}, but it does not appear to be mediated by a cyclic AMP-dependent mechanism because it is not enhanced in the presence of forskolin in most studies.\textsuperscript{35,36,38} In muscle harvested from failing human hearts, conflicting findings have been observed. In one study, flosequinan did not increase contractility with or without forskolin stimulation.\textsuperscript{39} In a second report, a positive inotropic action was observed, although only at concentrations somewhat higher than the measured therapeutic range, and forskolin potentiation was present.\textsuperscript{39} These findings would be consistent with weak phosphodiesterase inhibitor activity.

In humans, data concerning the effect of flosequinan on myocardial contractility also are conflicting. In two acute hemodynamic studies, a positive effect was observed. In one, a 12% increase in dp/dt was observed 1 hour after a 100-mg oral dose.\textsuperscript{40} The second study used a large dose (150 mg IV) and reported an upward and leftward shift in the end-systolic pressure-volume relation as well as enhanced diastolic relaxation.\textsuperscript{41} In contrast, other laboratories found no change in end-systolic elastance after a lower intravenous dose\textsuperscript{42} and no change in dp/dt or noninvasive indexes of contractile function.\textsuperscript{33,44} Thus, both the relative importance and the possible mechanism of a positive inotropic effect of flosequinan remain uncertain. If positive inotropy is involved in the action of flosequinan, the greatest benefit of the low dose on both exercise time and quality of life is similar to the results of a recent trial with pimobendan,\textsuperscript{45} an agent with both phosphodiesterase inhibitor and calcium sensitizing actions, in which patients given the highest dose did not respond as well as those receiving a lower dose.

The positive chronotropic action of flosequinan, together with the question of positive inotropic effects, lends some importance to the analysis of ventricular arrhythmias. In this study, there was no trend toward an increase in any category of ventricular arrhythmias. This contrasts with the results with phosphodiesterase inhibitors. In particular, ambulatory ECGs obtained during the PROMISE trial showed an increase in each of the categories of nonsustained ventricular arrhythmia in patients treated with milrinone\textsuperscript{28,29} as well as a marked increase in the incidence of sudden death in the milrinone group.\textsuperscript{12}

Treatment with flosequinan generally was well tolerated in the present trial, as it was in previous studies that did not include a background of angiotensin converting enzyme inhibitor treatment. The predominant side effects of flosequinan were headache, tachycardia, dizziness, and hypotension. For the most part, these effects were mitigated by dose reduction, which was necessary in approximately 30% of the active treatment groups. The incidence of patient withdrawal for adverse reactions was comparable in the placebo and active treatment groups (9% versus 11% and 13%).

This trial was designed only to examine the effect of flosequinan on exercise tolerance, symptoms, and quality of life in heart failure patients who were relatively stable but still symptomatic or exercise-limited. It did not have adequate size or duration to assess the effect of flosequinan on disease progression or mortality, both of which can be prevented with angiotensin converting enzyme inhibitors. These latter agents remain the preferred vasodilator treatment for patients with all grades of congestive heart failure unless they are not tolerated or otherwise contraindicated.

Since the acceptance of this article, an international trial evaluating the effect of flosequinan on survival (The Prospective Randomized Flosequinan Longevity Evaluation, or PROFILE) was terminated because of an adverse effect on mortality in patients treated with flosequinan 100 mg once daily.\textsuperscript{46} Although the patients in PROFILE tended to be more symptomatic than those in FACET, the dosages of flosequinan and other medications were comparable. Thus, although the present article demonstrates symptom and exercise tolerance benefit with flosequinan 100 mg once daily, these results must be considered in light of the significantly increased mortality risk. The 75-mg twice-daily dose, which did not confer significant exercise tolerance benefit, cannot be justified by this study. Data concerning the 75-mg fall-back dosage are inadequate to determine the efficacy of a lower, potentially safer dose. The present study is the first multicenter trial in which the combination of an angiotensin converting enzyme inhibitor with a direct-acting vasodilator has been evaluated with clinical end points. Because the 100-mg once-daily dose of flosequinan studied in this trial has now been shown to have an adverse effect on mortality, the benefit-to-risk ratio of flosequinan must be carefully weighed in each patient, and lower dosages should be used, if possible.
Appendix

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References


Can further benefit be achieved by adding flosequinan to patients with congestive heart failure who remain symptomatic on diuretic, digoxin, and an angiotensin converting enzyme inhibitor? Results of the flosequinan-ACE inhibitor trial (FACET).

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