JACC: HEART FAILURE
VOL. 5, NO. 6, 2017

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2017.03.003

FEATURED ARTICLE: DEAD LETTER OFFICE

Long-Term Effects of Flosequinan on the Morbidity and Mortality of Patients With Severe Chronic Heart Failure

Primary Results of the PROFILE Trial After 24 Years

Milton Packer, MD,[a] Bertram Pitt, MD,[b] Jean-Lucien Rouleau, MD,[c] Karl Swedberg, MD,[d,e] David L. DeMets, PHD,[f] Lloyd Fisher, PHD[g]

ABSTRACT

OBJECTIVES The purpose of this clinical trial was to evaluate the long-term effects of flosequinan on the morbidity and mortality of patients with severe chronic heart failure.

BACKGROUND Flosequinan was the first oral vasodilator to be used in the clinic to augment the effects of digitalis, diuretics, and angiotensin-converting enzyme inhibitors in heart failure. However, the drug activated neurohormonal systems and exerted both positive inotropic and chronotropic effects, raising concerns about its safety during long-term use.

METHODS Following a run-in period designed to minimize the risk of tachycardia, we randomly assigned 2,354 patients in New York Heart Association functional class III to IV heart failure and with an ejection fraction ≤35% to receive long-term treatment with placebo or flosequinan (75 or 100 mg/day) in addition to their usual therapy. The primary outcome was all-cause mortality.

RESULTS The trial was terminated after a recommendation of the Data and Safety Monitoring Board, because during an average of 10 months of follow-up, 192 patients died in the placebo group and 255 patients died in the flosequinan group (hazard ratio: 1.39, 95% confidence interval: 1.15 to 1.67; p = 0.0006). Flosequinan also increased the risk of disease progression, which was paralleled by drug-related increases in heart rate and neurohormonal activation. However, during the first month, patients in the flosequinan group were more likely to report an improvement in well-being and less likely to experience worsening heart failure. Similarly, during the month following drug withdrawal at the end of the trial, patients withdrawn from flosequinan were more likely than those withdrawn from placebo to report symptoms of or to require treatment for worsening heart failure.

CONCLUSIONS Although flosequinan produced meaningful symptomatic benefits during short- and long-term treatment, the drug increased the risk of death in patients with severe chronic heart failure. (J Am Coll Cardiol HF 2017;5:399–407) © 2017 by the American College of Cardiology Foundation.

From the [a]Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, Texas; [b]University of Michigan School of Medicine, Ann Arbor, Michigan; [c]Institut de Cardiologie, Université de Montréal, Montréal, Quebec, Canada; [d]Department of Molecular and Clinical Medicine, University of Goteborg, Goteborg, Sweden; [e]National Heart and Lung Institute, Imperial College, London, United Kingdom; [f]University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; and the [g]University of Washington School of Public Health, Seattle, Washington. This study was supported by a grant from Boots Pharmaceuticals. Each author had a consulting and/or research relationship with the sponsor at the time that the trial was ongoing; these relationships have been inactive for at least the past 5 years. Dr. Rouleau is a consultant for Novartis and Bayer. Dr. Swedberg is a consultant for Amgen, AstraZeneca, Novartis, and Servier. Dr. DeMets has received honoraria for serving on data monitoring committees for industry-sponsored trials, including the PROFILE trial.

Manuscript received January 18, 2017; revised manuscript received February 27, 2017, accepted March 2, 2017.

ABBREVIATIONS AND ACRONYMS

AMP = adenosine monophosphate

GMP = guanosine monophosphate

NYHA = New York Heart Association

In 1992, flosequinan was approved for the treatment of chronic heart failure in both the United Kingdom and the United States. Originally described purely as a peripheral arteriolar and venous vasodilator (1), this quinolone produced meaningful and sustained hemodynamic improvement in patients with heart failure (2–5) that was paralleled by decreases in cardiac wall stress (as reflected by a reduction in circulating natriuretic peptides [6–8]) and accompanied by beneficial effects on both symptoms and exercise tolerance (9–12). Following its commercial availability, uptake of the drug by physicians was rapid, and treated patients commonly reported early and dramatic increases in well-being and functional capacity. Flosequinan was the first oral agent to be used in the clinic to augment the effects of digitalis, diuretics, and angiotensin-converting enzyme inhibitors in chronic heart failure.

SEE PAGE 408

A distinctive feature of flosequinan in early clinical studies was its predilection to increase heart rate in sinus rhythm or the ventricular response in atrial fibrillation (9,12,13), and to enhance cardiac contractility (14–21). The positive inotropic and chronotropic effects of the drug were dose-dependent, were not inhibited by beta-blockers, and appeared to be related to increases in intracellular calcium without changes in cyclic adenosine monophosphate (AMP) or guanosine monophosphate (GMP) (14,16,18–22). This profile distinguished the action of flosequinan from that of hydralazine, which exerts direct vasodilator effects and indirect positive inotropic effects through changes in intracellular cyclic nucleotides and activation of the sympathetic nervous system, respectively, although it has little or only a modest effect on heart rate in patients with heart failure (19,23–27). The actions of flosequinan are also distinct from milrinone and other type III phosphodiesterase inhibitors, which produce positive inotropic, chronotropic, and vasodilator effects in heart failure through a cyclic AMP-dependent mechanism (19,28–32). In clinical trials in patients with chronic heart failure, hydralazine (when given in combination with isosorbide dinitrate) reduced all-cause mortality (33,34), whereas milrinone increased the risk of death (35). A meta-analysis of short-term, placebo-controlled trials with flosequinan reported a nonsignificant 52% increase in the risk of death (36), but this estimate was based on only 45 events that were recorded over a period of up to 16 weeks.

The PROFILE (Prospective Randomized Flosequinan Longevity Evaluation) trial was carried out to evaluate the long-term effects of flosequinan, which was administered in doses to minimize increases in heart rate, on the survival of patients with chronic heart failure.

METHODS

As originally designed, the PROFILE trial was carried out from October 1991 through March 1994 in the United States, Canada, and Scandinavia.

STUDY OVERSIGHT. The Steering Committee, in conjunction with the sponsor, developed and amended the protocol, oversaw the recruitment of patients and the analysis of data, and provided an independent interpretation of the results. A central committee blindly adjudicated the causes of death. Data were analyzed according to a pre-defined statistical analysis plan, and an independent statistician verified and replicated the analyses. The first author, who had unrestricted access to the data, prepared the drafts of the paper, which were then reviewed and edited by all authors. The authors collectively submitted the paper for publication, and assume responsibility for the accuracy and completeness of the analyses (Online Appendix).

STUDY PATIENTS. Patients were eligible if: 1) they had moderate or severe symptoms of heart failure (New York Heart Association [NYHA] functional class III or IV); 2) a left ventricular ejection fraction ≤35% within 3 months; and 3) had treatment with digitalis, diuretics, and an angiotensin-converting enzyme inhibitor for at least 2 months. During the previous 2 weeks, the doses of these 3 medications had to remain constant, and the patients could not have been hospitalized or received intravenous medications for heart failure. Treatment with a beta-blocker was allowed, but the ongoing use of other non-nitrate direct-acting vasodilators (e.g., hydralazine, calcium-channel blockers, pinacidil, or minoxidil) was not permitted.

Patients were excluded if they: 1) had heart failure due to active myocarditis, pericarditis, amyloidosis, hypertrophic cardiomyopathy, or uncorrected primary valvular heart disease; 2) had myocardial infarction or cardiac surgery within 2 months; 3) had a history of resuscitated sudden death, sustained ventricular tachycardia, or ventricular fibrillation (unless occurring within 24 h of an acute myocardial infarction), or received an implantable cardiac defibrillator that has not discharged within the last year; 4) were being considered for any cardiac surgery, including heart transplantation; 5) had a left ventricular ejection fraction >35% within 2 months; 6) had angina as

a symptom-limiting exercise, had severe or frequent angina, or had unstable angina or angina at rest within the last month; 7) received antiarrhythmic drugs known to have adverse effects on heart failure (encainide, flecainide, disopyramide, propafenone) within 2 weeks; 8) received positive inotropic agents known to have adverse effects on the heart (beta-agonists, theophylline, levodopa, amrinone, dobutamine, or dopamine) within 2 weeks; 9) had a heart rate <50 or >110 beats/min or a systolic blood pressure <85 mm Hg; 10) had a serum creatinine ≥3.0 mg/dl, serum potassium <3.5 or >5.0 mmol/l, or any liver function test >2 times the upper limit of normal; 11) received any investigational drug within 30 days or participated in a previous flosequinan study; or 12) had any condition that would interfere with the study conduct or drug absorption, or any illness other than heart failure than might limit life expectancy within 3 years.

The protocol was approved by the institutional review boards of all participating institutions, and written informed consent was obtained from all patients.

STUDY DESIGN. Following a screening period, patients entered an open-label test dose period lasting 2 to 3 weeks, during which they received flosequinan, in addition to their usual medications for heart failure. The initial dose was 100 mg once daily, which (if not tolerated) could be reduced to 75 mg once daily. At the end of the test-dose period, patients were eligible for randomization if they tolerated flosequinan (75 or 100 mg) without experiencing persistent or severe headaches, clinically significant hypotension, an increase in heart rate >10 beats/min above the baseline measurement, or an adherence rate to the study medication that was <75%. Patients tolerating open-label flosequinan were randomly assigned (double-blind; 1:1 allocation) to receive either oral flosequinan (at a dose of 75 mg or 100 mg once daily) or matching placebo.

Patients were evaluated as an outpatient every 2 to 3 months until the end of the study and were followed continuously for the occurrence of death or worsening heart failure, regardless of whether they continued to take the study medications. If adverse events occurred, the dose of the study medication was reduced (from 100 to 75 mg) or discontinued, or concomitant medications were adjusted; however, following randomization, increases in heart rate were not considered a reason for reduction of the dose or discontinuation of the study medication. If the patient's heart failure worsened, the dose of the study medication could be increased (if patients were taking <100 mg/day) or physicians could use any clinically indicated interventions, but patients were not permitted to receive open-label flosequinan.

STUDY ENDPOINTS. The primary endpoint for the PROFILE trial was all-cause mortality. Secondary endpoints included: 1) death due to cardiovascular reasons; 2) mortality due to sudden death or pump failure; 3) occurrence of hospitalization or the use of intravenous medications for heart failure; and 4) symptoms and functional status of heart failure. Pre-specified subgroup analyses included those that were based on: 1) the underlying cause of heart failure (ischemic vs. nonischemic); 2) ejection fraction above and below the median; 3) NYHA functional class (III vs. IV); and 4) heart rate during the test dose period above and below the median.

STATISTICAL ANALYSIS. The sample size for the study was estimated based on the primary endpoint of all-cause mortality. The plan was to enroll 3,400 patients based on the assumption that the 1-year mortality in the placebo group would be 20%, and that flosequinan would alter mortality by 20%. The trial was designed to continue until a total of 470 deaths had been observed. A Data and Safety Monitoring Board periodically reviewed the unblinded results and could recommend early termination of the trial if it observed a treatment effect that exceeded pre-specified boundaries; the monitoring boundaries were implemented by the Lan-DeMets method for an O'Brien-Fleming type alpha spending function, for an overall alpha level of 0.05 (37,38).

Cumulative survival curves were constructed by Kaplan-Meier survivorship methods, and differences between the curves were tested for significance by the log-rank statistic, stratified by NYHA functional class. Cox proportional hazards regression models were used to estimate flosequinan/placebo hazard ratios and their 95% confidence intervals. All survival analyses included all randomized patients, and all events were assigned to the randomized treatment group of the patients (according to the intention-to-treat principle). An adjusted p value, which took the interim analyses into consideration, was calculated for the primary endpoint; all other reported between-group differences had a nominal $p < 0.05$.

RESULTS

In April 1993, the Data and Safety Monitoring Board recommended the termination of treatment in patients assigned to receive 100 mg/day when the

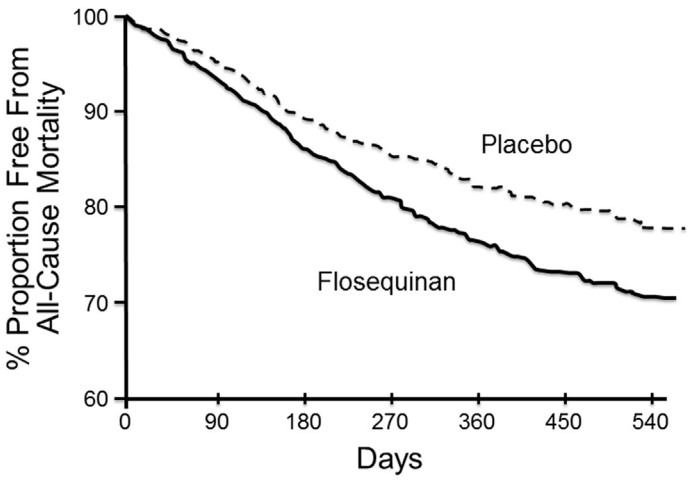
TABLE 1 Baseline Clinical Characteristics

	Placebo (n = 1,175)	Flosequinan (n = 1,170)
Age (yrs)	65.3 ± 10.7	65.6 ± 10.8
Men/women	941/234	910/260
Left ventricular ejection fraction	23 ± 7	23 ± 7
Etiology of heart failure (ischemic/nonischemic)	637/305	641/292
NYHA functional class (class III/IV)	1,032/143	1,025/145
Pulmonary rales (% present)	22%	20%
Peripheral edema (% present)	32%	31%
Dose of study medication at randomization (100 mg/75 mg)	937/238	964/206
Systolic blood pressure (mm Hg)	118 ± 19	118 ± 19
Heart rate (beats/min)	78 ± 12	79 ± 12
Weight (kg)	78 ± 17	78 ± 17
Serum sodium concentration (mmol/l)	138 ± 4	138 ± 4
Serum potassium concentration (mmol/l)	4.3 ± 0.5	4.3 ± 0.5
Blood urea nitrogen (mg/dl)	26 ± 15	26 ± 16
Serum creatinine concentration (mg/dl)	1.4 ± 0.4	1.4 ± 0.4

Values are mean ± SD, n, or %.
NYHA = New York Heart Association.

pre-specified boundary for harm had been crossed. Subsequently, in July 1993, a decision was made to terminate the participation of patients taking 75 mg/day, and the trial was closed.

FIGURE 1 All-Cause Mortality in the PROFILE Trial



Time-to-death Kaplan-Meier plots in the placebo and flosequinan groups. A total of 192 patients died in the placebo group and 255 patients died in the flosequinan group (hazard ratio: 1.39; 95% confidence interval: 1.15 to 1.67; p = 0.0006). The number of patients at risk at each time point can be estimated from a Data Safety Monitoring Board report (April 1993) as follows: 1,000 in each group at 1 month; 880 patients in each group at 3 months; 600 patients in each group at 6 months; 450 patients in each group at 9 months; 250 patients in each group at 12 months; and 100 patients in each group at 15 months. PROFILE = Prospective Randomized Flosequinan Longevity Evaluation.

Upon its completion, a total of 2,345 patients had been randomized into the trial (1,175 to the placebo group and 1,170 to the flosequinan group). The 2 treatment groups were similar with respect to baseline characteristics (Table 1); 6% to 8% of the patients were black, and <4% were taking beta-blockers. Of the 1,175 patients in the placebo group, 937 and 238 were randomized to 100 and 75 mg/day, respectively; of the 1,170 patients in the flosequinan group, 964 and 206 were randomized to 100 and 75 mg/day, respectively. The mean and maximum durations of follow-up were 308 and 609 days, respectively.

EFFECT OF FLOSEQUINAN ON MORBIDITY AND MORTALITY. By the intention-to-treat, 192 patients died in the placebo group and 255 patients died in the flosequinan group (hazard ratio: 1.39; 95% confidence interval: 1.15 to 1.67; p = 0.0006) (Figure 1). Time-to-first event plots for all-cause mortality or hospitalization for heart failure revealed an early difference in favor of flosequinan during the first 2 months, followed by a difference in favor of placebo thereafter (Figure 2). A similar pattern was seen in time-to-event plots for the use of intravenous medications for heart failure, with an intersection of the 2 treatment plots and reversal of the treatment effect at 4 to 6 months. The mode of death was cardiovascular in 400 patients (170 in the placebo group and 230 in the flosequinan group). Death due to pump failure occurred in 157 patients (62 in the placebo group and 95 in the flosequinan group), and sudden death occurred in 220 patients (94 in the placebo group and 126 in the flosequinan group).

Pre-specified subgroup analyses did not identify a baseline characteristic that exerted an influence on the magnitude or direction of the difference between the 2 treatment groups. The hazard ratios for all-cause mortality for patients randomized to 75 or 100 mg were both >1.0 (i.e., 1.15 and 1.46, respectively). Based on this subgroup finding (with a small number of events in the 75 mg group), the investigators decided to selectively terminate the participation of patients receiving 100 mg/day in April 1993. Two months later, participation of the subgroup that received 75 mg/day was terminated because of an increased risk of hospitalizations for heart failure compared with those in the placebo group.

CLINICAL EFFECT OF FLOSEQUINAN DURING INITIATION AND WITHDRAWAL OF THERAPY. At the end of the first month of randomized treatment, compared with the placebo group, patients in the flosequinan group were more likely to report an improvement in well-being

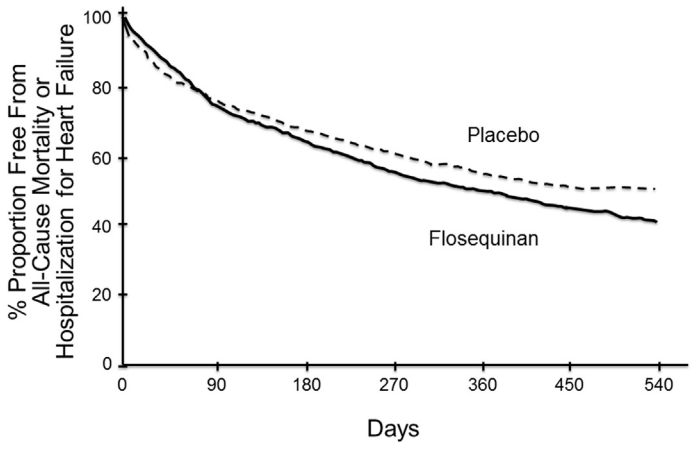
(38% vs. 15%) and less likely to report clinical deterioration (2.0% vs. 3.7%) (both nominal $p < 0.05$). During this time, the flosequinan group was less likely than the placebo group to require intravenous therapy for heart failure (3.0% vs. 7.7%), an emergency room visit for heart failure (1.7% vs. 3.5%), or a hospitalization for heart failure (3.3% vs. 7.5%) (all nominal $p < 0.05$). These effects were largely attributable to the responses seen in patients randomized to 100 mg/day.

At the time of the initial Data and Safety Monitoring Board recommendation to modify the trial (April 1993), 797 patients in the placebo group and 763 patients in the flosequinan were alive and taking 100 mg of the study medication. In all cases, treatment with placebo and flosequinan was stopped, and patients were followed for the next 28 days without knowledge of the treatment assignment. Information during this follow-up was available for 667 patients withdrawn from placebo and 614 patients withdrawn from flosequinan. During this interval after cessation of randomized treatment, patients who were withdrawn from flosequinan were more likely than those withdrawn from placebo to experience worsening heart failure (33.4% vs. 18.7%), an emergency room visit for heart failure (8.5% vs. 3.3%), or hospitalization for heart failure (10.9% vs. 4.9%), or to receive intravenous diuretics (11.6% vs. 5.7%), intravenous vasodilators (2.3% vs. 1.0%), or intravenous positive inotropic drugs (3.4% vs. 1.0%) (all nominal $p < 0.05$). In contrast, the proportion of patients who died from any cause or experienced clinical worsening for reasons other than heart failure was similar in the groups withdrawn from placebo or flosequinan.

ADVERSE EVENTS AND CHANGES IN PHYSIOLOGICAL AND LABORATORY VARIABLES. The most common adverse events during the test dose run-in period were headache (10.3%) and dizziness (2.9%). During the first month after randomization, compared with the placebo group, patients in the flosequinan group were more likely to report headache (3.6% vs. 2.8%), palpitations (1.2% vs. 0.4%), nausea (1.5% vs. 0.8%), diarrhea (1.0% vs. 0.5%), and taste alterations (1.0% vs 0.6%), but they were less likely to complain about heart failure (1.3% vs. 3.4%).

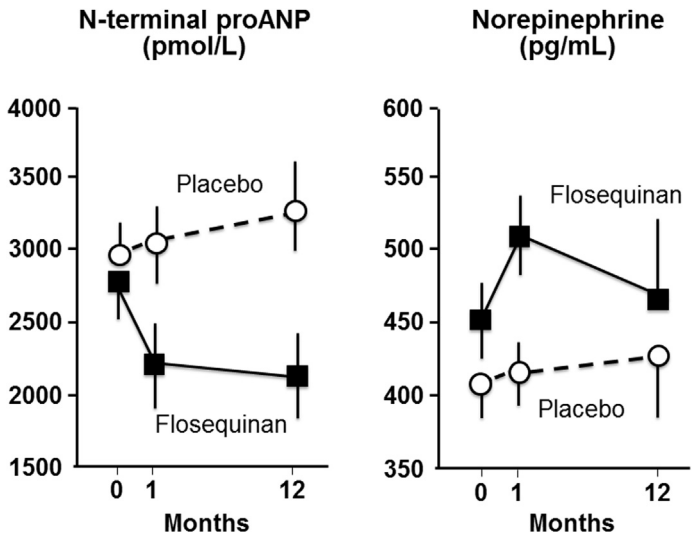
At 1 month, heart rate increased by approximately 5 beats/min in the flosequinan group compared with the placebo group, and this difference persisted during the entire follow-up period. This magnitude of the increase in heart rate was similar at both 75 and 100 mg/day doses of the drug; there was no relationship between changes in heart rate during the test

FIGURE 2 Combined Risk of All-Cause Mortality or Hospitalization for Heart Failure in the PROFILE Trial



Hazard ratios were not calculated. The number of patients at risk at each time point can be estimated from a Data Safety Monitoring Board report (April 1993) as follows: 1,000 in each group at 1 month; 880 patients in each group at 3 months; 600 patients in each group at 6 months; 450 patients in each group at 9 months; 250 patients in each group at 12 months; and 100 patients in each group at 15 months. PROFILE = Prospective Randomized Flosequinan Longevity Evaluation.

FIGURE 3 Changes in Neurohormonal Variables During Treatment With Placebo or Flosequinan



Changes in neurohormonal variables during short- and long-term treatment with placebo and flosequinan in a subgroup of patients randomized at centers in Canada (39) (mean ± SD). Number of patients contributing to the estimates is approximately 200 patients (100 in each group) at 1 month. The number of patients contributing to the estimates at 12 months is not known, but is <200, because repeat measurements of neurohormonal variables at this time were obtainable only in a subgroup of survivors. ANP = atrial natriuretic peptide.

dose run-in period or at 1 month after randomization and subsequent changes in the risk of death.

There were no differences between the 2 groups with respect to systolic or body weight; diastolic blood pressures were 1 mm Hg lower in the flosequinan group (compared with the placebo group) for the first 3 to 6 months. Compared with placebo, plasma levels of N-terminal pro–atrial natriuretic peptide were lower and levels of norepinephrine were higher at 1 month (both by ≈25%) (39); after 12 months, the between-group differences for N-terminal pro–atrial natriuretic peptide became more apparent (nominal $p < 0.05$), but the values for plasma norepinephrine in the 2 groups had converged (**Figure 3**).

At 1 month after randomization, flosequinan-treated patients had lower values for hemoglobin (by 0.2 g/dl), hematocrit (by 0.1 to 1.0), serum sodium (by 0.8 mmol/l), serum potassium (by 0.08 mmol/l), serum bilirubin (by 0.1 mg/dl), and alkaline phosphatase (by 10 U/l), and had increased values for serum cholesterol (by 10 mg/dl), serum creatinine (by 0.15 mg/dl), and platelet counts (by 20,000/ml) (all nominal $p < 0.05$). The decrease in serum potassium in the flosequinan group was no longer apparent after 1 month; in contrast, changes in all other values generally persisted for the duration of laboratory follow-up (i.e., 12 months).

DISCUSSION

The PROFILE trial demonstrated that long-term treatment with flosequinan increased the risk of death in patients with severe chronic heart failure who were receiving digitalis, diuretics, and angiotensin-converting enzyme inhibitors. This detrimental effect appeared to be related to both the dose of the drug and the duration of treatment. Flosequinan increased the risk of both pump failure deaths and sudden deaths, which were the 2 primary modes of death in patients with chronic heart failure. The magnitude of the adverse effect was larger than in other multicenter trials that were specifically designed to evaluate mortality and that reported a deleterious effect of a drug on survival based on a meaningful number of events (35,40,41). As a result of these findings, flosequinan was withdrawn from the U.S. market in July 1993.

The mechanisms by which flosequinan increased the risk of death could not be elucidated by the results of the trial. As in the case of other drugs that adversely affected survival in heart failure (35,40,41), this quinolone had positive inotropic effects, but agents that directly or indirectly enhance cardiac contractility (e.g., digoxin and hydralazine, respectively) do not necessarily increase mortality in patients with this disorder (33,34,42). However, flosequinan increased the activation of both the sympathetic nervous system and the renin-angiotensin-aldosterone system (43), and in this trial, short- and long-term treatment with the drug lowered serum sodium concentration, a phenomenon that signifies the occurrence of neurohormonal activation (44–47). Plasma norepinephrine increased during early treatment with flosequinan, which predicted an adverse outcome in our patients (39). (Our inability to demonstrate sympathetic activation at 12 months was likely related to the measurement of norepinephrine in a subgroup of survivors [39]). Although activation of the renin-angiotensin system by the drug should have been attenuated by the concomitant use of angiotensin-converting enzyme inhibitors, aldosterone might escape during long-term efforts to suppress angiotensin II (48). Therefore, the decrease in serum potassium seen during the first month of treatment with flosequinan might reflect increases in both catecholamines and aldosterone (45,49,50). Unfortunately, we did not interfere with the deleterious effects of these neurohormonal systems, because the trial was carried out before the widespread adoption of both beta-blockers and mineralocorticoid receptor antagonists for the treatment of chronic heart failure.

Flosequinan increases heart rate by an effect that is not related to sympathetic activation (20,39,51). Changes in heart rate have important prognostic significance in patients with heart failure (52–54); drug-induced differences in heart rate have been accompanied by differences in survival (54,55); and drugs that act directly to decrease heart rate (i.e., ivabradine) can have favorable effects on the morbidity and mortality of patients with this disorder (56). Concerns about the positive chronotropic effects of the drug were present throughout the development of flosequinan (4,9,13), and the importance of changes in heart rate was recognized by the investigators in the design of the PROFILE trial; patients in whom flosequinan increased heart rate by >10 beats/min during a run-in period were not enrolled. Despite the effort to minimize tachycardia, heart rate still increased in the flosequinan group by 5 beats/min. The magnitude of this chronotropic effect is important, but we found no relationship between changes in heart rate and the effects of flosequinan on survival. Furthermore, lower doses of flosequinan (75 mg/day) were associated with smaller increases in the risk of death but not a lower likelihood of tachycardia.

The present study confirmed the findings of previous placebo-controlled trials that showed that flosequinan produces immediate and meaningful symptomatic benefits in patients with chronic heart failure (9,12). Within 4 weeks of starting treatment, the drug not only improved patient well-being, but also reduced the risk of worsening heart failure. This pattern of response distinguished flosequinan from other agents used for the management of chronic heart failure (57). Treatments that modulate neurohormonal mechanisms (angiotensin-converting enzyme inhibitors, beta-blockers, and angiotensin receptor neprilysin inhibitors) may exert rapid effects on morbidity and mortality (58–60), but symptomatic benefits emerge slowly over a period of 3 months (61–63). In contrast, early during the course of treatment, positive inotropic drugs may improve symptoms and exercise tolerance, but they can increase the risk of clinical deterioration (31,37). In the PROFILE trial, the early symptomatic benefits of flosequinan were sustained after long-term treatment; withdrawal of the drug led to worsening of symptoms and an increased need for hospitalization and intravenous treatments for heart failure. These episodes were sufficiently severe that some patients requested and received treatment with flosequinan after completion of the trial, despite knowing that the drug increased the risk of death (64). Of note, the withdrawal of other positive inotropic agents led to worsening heart failure in some (but not all) studies (32,40,42,65,66). Yet, the occurrence of clinical deterioration following the withdrawal of treatment does not reliably inform the nature of the long-term effects of treatment on morbidity and mortality. Specifically, as in the PROFILE trial, worsening of heart failure following drug withdrawal did not imply a favorable long-term effect of treatment (34); conversely, the absence of clinical deterioration upon discontinuation of treatment does not imply a neutral effect on morbidity and mortality (40,66).

The effects of flosequinan on physiological and laboratory values also distinguished the drug from other agents used in the treatment of chronic heart failure. Drugs that cause systemic vasodilation by neurohormonal modulation (prazosin, carvedilol, angiotensin-converting enzyme inhibitor, angiotensin receptor neprilysin inhibitors) are associated with meaningful decreases in systolic blood pressure (33,55,62,67). In contrast, direct-acting vasodilators (flosequinan or the combination of hydralazine and isosorbide dinitrate) have been reported to have minimal effects on blood pressure in previous studies or in the present trial (12,33,55), possibly (in part) because these drugs have positive inotropic effects or activate neurohormonal systems (15,19,43). In addition, several interventions that reduce cardiac wall stress (as reflected in a long-term decrease in circulating natriuretic peptides) have been reported to have favorable effects on survival in heart failure (54,68,69), but flosequinan reduced blood levels of natriuretic peptides in the present study and in previous trials (6–8), but it also increased the risk of death. This finding indicated that changes in natriuretic peptides cannot be used as a surrogate endpoint for the effect of drugs on long-term morbidity and mortality in heart failure (70). Finally, in the PROFILE trial, treatment with flosequinan was associated with changes in numerous laboratory variables in a manner consistent with earlier controlled clinical trials, as reflected in the 1993 Food and Drug Administration approved labeling for the drug (36).

CONCLUSIONS

In demonstrating an adverse effect of flosequinan on the survival of patients with heart failure, the present trial both undermines and reinforces several prevailing concepts in the development of new therapeutic agents for this disorder. Our findings indicated that short- to intermediate-term effects of drugs (on clinical or surrogate endpoints) cannot be used to predict the long-term response to treatment. Furthermore, the effects of flosequinan in the trial underscore the importance of changes in heart rate in the progression of heart failure, but weaken the significance of changes in natriuretic peptides as a reliable biomarker for changes in morbidity and mortality. Our observations heighten concerns about the long-term risks of drugs that increase cardiac contractility (even through mechanisms that do not increase cyclic AMP), at least with respect to agents that exert both positive inotropic and chronotropic effects. Finally, our results raise the possibility that inhibiting the neurohormonal activation and the tachycardia produced by drugs like flosequinan (with beta-blockers, mineralocorticoid receptor antagonists, and ivabradine) might potentiate their usefulness while mitigating their risks.

ADDRESS FOR CORRESPONDENCE: Dr. Milton Packer, Baylor Heart and Vascular Institute, Baylor University Medical Center, 621 N. Hall Street, Dallas, Texas 75226. E-mail: milton.packer1526@baylorhealth.edu.

REFERENCES

1. Cowley AJ, Wynne RD, Hampton JR. The effects of BTS 49465 on blood pressure and peripheral arteriolar and venous tone in normal volunteers. J Hypertens Suppl 1984;2:S547–9.

2. Kessler PD, Packer M. Hemodynamic effects of BTS 49465, a new long-acting systemic vasodilator drug, in patients with severe congestive heart failure. Am Heart J 1987;113:137–43.

3. Kessler PD, Packer M, Medina N, Yushak M. Cumulative hemodynamic response to short-term treatment with flosequinan (BTS 49465), a new direct-acting vasodilator drug, in severe chronic congestive heart failure. J Cardiovasc Pharmacol 1988;12:6–11.

4. Gottlieb SS, Kukin ML, Penn J, et al. Sustained hemodynamic response to flosequinan in patients with heart failure receiving angiotensin-converting enzyme inhibitors. J Am Coll Cardiol 1993;22:963–7.

5. Cowley AJ, Wynne RD, Stainer K, Fullwood L, Rowley JM, Hampton JR. Flosequinan in heart failure: acute haemodynamic and longer term symptomatic effects. BMJ 1988;297:169–73.

6. Cavero PG, De Marco T, Kwasman M, Lau D, Liu M, Chatterjee K. Flosequinan, a new vasodilator: systemic and coronary hemodynamics and neuroendocrine effects in congestive heart failure. J Am Coll Cardiol 1992;20:1542–8.

7. Riegger GA, Kahles H, Wagner A, Kromer EP, Elsner D, Kochsiek K. Exercise capacity, hemodynamic, and neurohumoral changes following acute and chronic administration of flosequinan in chronic congestive heart failure. Cardiovasc Drugs Ther 1990;4:1395–402.

8. Dakak N, Makhoul N, Merdler A, et al. Haemodynamic and neurohumoral effects of flosequinan in severe heart failure: similarities and differences compared with intravenous nitroglycerin therapy. Eur Heart J 1993;14:836–44.

9. Packer M, Narahara KA, Elkayam U, et al. Double-blind, placebo-controlled study of the efficacy of flosequinan in patients with chronic heart failure. Principal Investigators of the REFLECT Study. J Am Coll Cardiol 1993;22:65–72.

10. Cowley AJ, McEntegart DJ. Placebo-controlled trial of flosequinan in moderate heart failure. The possible importance of aetiology and method of analysis in the interpretation of the results of heart failure trials. Int J Cardiol 1993;38:167–75.

11. Elborn JS, Riley M, Stanford CF, Nicholls DP. The effects of flosequinan on submaximal exercise in patients with chronic cardiac failure. Br J Clin Pharmacol 1990;29:519–24.

12. Massie BM, Berk MR, Brozena SC, et al. 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). Circulation 1993;88:492–501.

13. Massie BM, Shah NB, Pitt B, Packer M. Importance of assessing changes in ventricular response to atrial fibrillation during evaluation of new heart failure therapies: experience from trials of flosequinan. Am Heart J 1996;132 1 Pt 1:130–6.

14. Greenberg S, Touhey B. Positive inotropy contributes to the hemodynamic mechanism of action of flosequinan (BTS 49465) in the intact dog. J Cardiovasc Pharmacol 1990;15:900–10.

15. Corin WJ, Monrad ES, Strom JA, Giustino S, Sonnenblick ES, LeJemtel T. Flosequinan: a vasodilator with positive inotropic activity. Am Heart J 1991;121 2 Pt 1:537–40.

16. Perreault CL, Hague NL, Loh E, Hunneyball IM, Sim MF, Morgan JP. Differential inotropic effects of flosequinan in ventricular muscle from normal ferrets versus patients with end-stage heart failure. Br J Pharmacol 1992;106:511–6.

17. Burstein S, Semigran MJ, Dec GW Jr., Boucher CA, Fifer MA. Positive inotropic and lusitropic effects of intravenous flosequinan in patients with heart failure. J Am Coll Cardiol 1992;20:822–9.

18. Weishaar RE, Wallace AM, Kiser LM, et al. Assessment of flosequinan's direct effect on human arterial, venous, and cardiac muscle: comparison with other classes of agents used to treat heart failure. J Cardiovasc Pharmacol 1994;23:792–8.

19. Miao L, Perreault CL, Travers KE, Morgan JP. Mechanisms of positive inotropic action of flosequinan, hydralazine, and milrinone on mammalian myocardium. Eur J Pharmacol 1997;321:201–8.

20. Kelso EJ, McDermott BJ, Silke B. Actions of the novel vasodilator, flosequinan, in isolated ventricular cardiomyocytes. J Cardiovasc Pharmacol 1995;25:376–86.

21. Falotico R, Haertlein BJ, Lakas-Weiss CS, Salata JJ, Tobia AJ. Positive inotropic and hemodynamic properties of flosequinan, a new vasodilator, and a sulfone metabolite. J Cardiovasc Pharmacol 1989;14:412–8.

22. Jones RB, Frodsham G, Dickinson K, Foster GA. Effect of flosequinan on ischaemia-induced arrhythmias and on ventricular cyclic nucleotide content in the anaesthetized rat. Br J Pharmacol 1993;108:1111–6.

23. Hurrell DG, Perreault CL, Miao L, Ransil BJ, Morgan JP. Cellular mechanism of the positive inotropic effect of hydralazine in mammalian myocardium. Br J Pharmacol 1993;109:667–72.

24. Rabinowitz B, Parmley WW, Har-Zahav Y, et al. Correlation between effects of hydralazine on force and on the adenyl cyclase system of ventricular myocardium in dogs and cats. Cardiovasc Res 1986;20:215–20.

25. Songkittiguna P, Rand MJ. The mechanisms of the inotropic and chronotropic actions of hydralazine on rat isolated atria. Arch Int Pharmacodyn Ther 1982;255:269–80.

26. Chatterjee K, Ports TA, Brundage BH, Massie B, Holly AN, Parmley WW. Oral hydralazine in chronic heart failure: sustained beneficial hemodynamic effects. Ann Intern Med 1980;92:600–4.

27. Daly P, Rouleau JL, Cousineau D, Burgess JH, Chatterjee K. Effects of captopril and a combination of hydralazine and isosorbide dinitrate on myocardial sympathetic tone in patients with severe congestive heart failure. Br Heart J 1986;56:152–7.

28. Jaski BE, Fifer MA, Wright RF, Braunwald E, Colucci WS. Positive inotropic and vasodilator actions of milrinone in patients with severe congestive heart failure. Dose-response relationships and comparison to nitroprusside. J Clin Invest 1985;75:643–9.

29. DiBianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, Wright R. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. N Engl J Med 1989;320:677–83.

30. Grose R, Strain J, Greenberg M, LeJemtel TH. Systemic and coronary effects of intravenous milrinone and dobutamine in congestive heart failure. J Am Coll Cardiol 1986;7:1107–13.

31. Lowes BD, Higginbotham M, Petrovich L, et al. Low-dose enoximone improves exercise capacity in chronic heart failure. Enoximone Study Group. J Am Coll Cardiol 2000;36:501–8.

32. Metra M, Eichhorn E, Abraham WT, et al., ESSENTIAL Investigators. Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. Eur Heart J 2009;30:3015–26.

33. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547–52.

34. Taylor AL, Ziesche S, Yancy C, et al., African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049–57.

35. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med 1991;325:1468–75.

36. FDA approved label for Manoplax (flosequinan). Nottingham, UK: Boots Pharmaceuticals; 1993.

37. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549–56.

38. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659–63.

39. Moe GW, Rouleau JL, Charbonneau L, et al. Neurohormonal activation in severe heart failure: relations to patient death and the effect of treatment with flosequinan. Am Heart J 2000;139:587–95.

40. Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure.

Vesnarinone Trial Investigators. N Engl J Med 1998;339:1810–6.

41. Hampton JR, van Veldhuisen DJ, Kleber FX, et al. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Lancet 1997;349:971–7.

42. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–33.

43. Isnard R, Lechat P, Pousset F, et al. Hemodynamic and neurohormonal effects of flosequinan in patients with heart failure. Fundam Clin Pharmacol 1997;11:83–9.

44. McCurley JM, Hanlon SU, Wei SK, Wedam EF, Michalski M, Haigney MC. Furosemide and the progression of left ventricular dysfunction in experimental heart failure. J Am Coll Cardiol 2004;44:1301–7.

45. Mulder H, Schopman W Jr., van der Lely AJ, Schopman W Sr. Acute changes in plasma renin activity, plasma aldosterone concentration and plasma electrolyte concentrations following furosemide administration in patients with congestive heart failure–interrelationships and diuretic response. Horm Metab Res 1987;19:80–3.

46. Lilly LS, Dzau VJ, Williams GH, Rydstedt L, Hollenberg NK. Hyponatremia in congestive heart failure: implications for neurohormonal activation and responses to orthostasis. J Clin Endocrinol Metab 1984;59:924–30.

47. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. Circulation 1986;73:257–67.

48. Jungmann E, Störger H, Althoff PH, et al. Aldosterone and prolactin responsiveness after prolonged treatment of congestive heart failure with captopril. Eur J Clin Pharmacol 1985;28:1–4.

49. Johansson BW. Hypokalemia in cardiac decompensation. Acta Pharmacol Toxicol (Copenh) 1984;54 Suppl 1:103–6.

50. Dargie HJ. Interrelation of electrolytes and renin-angiotensin system in congestive heart failure. Am J Cardiol 1990;65:28E–32E.

51. Binkley PF, Nunziata E, Cody RJ. Influence of flosequinan on autonomic tone in congestive heart failure: implications for the mechanism of the positive chronotropic effect and survival influence of long-term vasodilator administration. Am Heart J 1994;128 6 Pt 1:1147–56.

52. Cubbon RM, Ruff N, Groves D, et al. Ambulatory heart rate range predicts mode-specific mortality and hospitalisation in chronic heart failure. Heart 2016;102:223–9.

53. Hamill V, Ford I, Fox K, et al. Repeated heart rate measurement and cardiovascular outcomes in left ventricular systolic dysfunction. Am J Med 2015;128:1102–8.

54. Fox K, Borer JS, Camm AJ, et al., Heart Rate Working Group. Resting heart rate in cardiovascular disease. J Am Coll Cardiol 2007;50:823–30.

55. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.

56. Swedberg K, Komajda M, Böhm M, et al., SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875–85.

57. Packer M. Beta-blockade in the management of chronic heart failure. Another step in the conceptual evolution of a neurohormonal model of the disease. Eur Heart J 1996;17 Suppl B:21–3.

58. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–35.

59. Krum H, Roecker EB, Mohacsi P, et al., Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. JAMA 2003;289:712–8.

60. Packer M, McMurray JJ, Desai AS, et al., PARADIGM-HF Investigators and Coordinators. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation 2015;131:54–61.

61. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Coll Cardiol 1983;2:755–63.

62. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Circulation 1996;94:2793–9.

63. Gottlieb SS, Fisher ML, Kjekshus J, et al., MERIT-HF Investigators. Tolerability of beta-blocker initiation and titration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Circulation 2002;105:1182–8.

64. van Veldhuisen DJ, Poole-Wilson PA. The underreporting of results and possible mechanisms of 'negative' drug trials in patients with chronic heart failure. Int J Cardiol 2001;80:19–27.

65. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med 1993;329:1–7.

66. Soran O, Young JD, Holubkov R, Loftus S, et al. Effect of inotrope withdrawal on morbidity and mortality in patients with chronic heart failure: results of the vesnarinone trial withdrawal substudy. VEST Withdrawal Substudy Group. J Card Fail 1999;5:195–200.

67. McMurray JJ, Packer M, Desai AS, et al., PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.

68. Fruhwald FM, Fahrleitner-Pammer A, Berger R, et al. Early and sustained effects of cardiac resynchronization therapy on N-terminal pro-B-type natriuretic peptide in patients with moderate to severe heart failure and cardiac dyssynchrony. Eur Heart J 2007;28:1592–7.

69. Brenyo A, Barsheshet A, Rao M, et al. Brain natriuretic peptide and cardiac resynchronization therapy in patients with mildly symptomatic heart failure. Circ Heart Fail 2013;6:998–1004.

70. Ferreira JP, Duarte K, Graves TL, et al. Natriuretic peptides, 6-min walk test, and quality-of-life questionnaires as clinically meaningful endpoints in HF trials. J Am Coll Cardiol 2016;68:2690–707.

KEY WORDS clinical trials, heart failure, placebo, survival, vasodilators

APPENDIX For a list of members of the Steering Committee, Biostatistical Center, Mortality Classification Committee, and the Data and Safety Monitoring Board, please see the online version of this paper.