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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

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ABSTRACT

OBJECTIVES The objective 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 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 Similarly, during the month following drug withdrawal at the end of the trial, patients withdrawn from flosequinan were more likely than those withdrawn from placebo to report symptoms of or to require treatment for worsening heart failure.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;■:■–■)

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

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ABBREVIATIONS AND ACRONYMS

AMP = adenosine monophosphate

GMP = guanosine monophosphate

NYHA = New York Heart Association

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.

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.

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