UvA-DARE (Digital Academic Repository)

Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure

Hampton, J.R.; Veldhuisen, D.J.; Kleber, F.X.; Cowley, A.J.; Ardia, A.; Block, P.; Cortina, A.; Cserhalmi, L.; Follath, F.; Jensen, G.; Kayanakis, J.; Lie, K.I.; Mancia, G.; Skene, A.M.

[Link to publication]

Articles

Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure

J R Hampton, D J van Veldhuisen, F X Kleber, A J Cowley, A Ardia, P Block, A Cortina, L Cserhalmi, F Follath, G Jensen, J Kayanakis, K I Lie, G Mancia, A M Skene, for the Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators

Summary

Background Drugs that improve symptoms in patients with heart failure must also be assessed for their effects on survival. Ibopamine stimulates DA-1 and DA-2 receptors and causes peripheral and renal vasodilatation; the drug improves symptoms of heart failure. We assessed the effect of ibopamine on survival in patients with advanced heart failure in a multicentre, randomised placebo-controlled study.

Methods Patients with advanced severe heart failure (New York Heart Association classes III and IV) and evidence of severe left-ventricular disease, who were already receiving optimum treatment for heart failure, were randomly allocated oral ibopamine 100 mg three times daily or placebo. The primary endpoint was all-cause mortality. The study was designed to recruit 2200 patients, and the minimum duration of treatment would be 6 months. We did intention-to-treat and on-treatment analyses; a post-hoc subgroup analysis was also done.

Findings After we had recruited 1906 patients the trial was stopped early, because of an excess of deaths among patients in the ibopamine group. 232 (25%) of 953 patients in the ibopamine group died, compared with 193 (20%) of 953 patients in the placebo group (relative risk 1·26 [95% CI 1·04–1·53], p=0·017). The average length of follow-up was 347 days in the ibopamine group and 363 days in the placebo group. In multivariate analysis, only the use of antiarrhythmic drugs at baseline was a significant independent predictor of increased fatality in ibopamine-treated patients.

Interpretation Ibopamine seems to increase the risk of death among patients with advanced heart failure who are already receiving optimum therapy, but the reasons for this increase are not clear. Our finding that antiarrhythmic treatment was a significant predictor of increased mortality in ibopamine-treated patients may be important, but exploratory analyses must be interpreted with caution.

Introduction

In patients with advanced heart failure, the relief of symptoms is important. However, drugs such as milrinone, enoximone, and flosequinan have been shown to improve symptoms at the expense of an increase in fatality.[1–3] Thus, evidence that a new drug improves the symptoms of heart failure is necessary but not sufficient for its acceptance into clinical use. Ideally, a new drug would increase survival and improve symptoms; at the least, it should have no effect on survival.

Dopamine agonists have properties that make them potentially useful for the treatment of heart failure. Ibopamine is an orally active compound hydrolysed in vivo to epinine (N-methyldopamine).[4] The active metabolite stimulates DA-1 and DA-2 receptors and causes renal and peripheral vasodilatation, and does not seem to have an inotropic effect.[5] Previous studies showed that in patients with heart failure, ibopamine reduced plasma concentrations of noradrenaline, renin activity, and aldosterone.[6–8] Clinical studies have reported that ibopamine improves symptoms and has an effect similar to captopril on exercise tolerance in patients with mild-to-moderate heart failure.[9,10] Ibopamine seemed to be a new class of drug that might make an important contribution to the management of patients with heart failure.

The Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II Study) was set up to investigate the effect of ibopamine on mortality and to collect sufficient data to show whether or not ibopamine treatment was safe.

Fatality rates among patients with severe heart failure are high, even if they receive optimum treatment. The PRIME II study was specifically designed to investigate the efficacy and safety of ibopamine in patients with advanced heart failure.

Methods

This multicentre, randomised study compared the effect of ibopamine 100 mg three times daily or placebo on all-cause mortality in patients with advanced heart failure. Secondary endpoints were cause of death, the need for cardiac transplantation, the number of and reason for hospital admissions, quality of life, symptom scores, and reasons for withdrawal from trial medication.

*Members of PRIME II are listed at end of paper

Cardiovascular Medicine, Queen's Medical Centre, University Hospital, Nottingham NG7 2UH, UK (Prof J R Hampton MD, A J Cowley MD); **University Hospital, Groningen, Netherlands** (D J Van Veldhuisen MD); **Universitatsklinikum Charite, Berlin, Germany** (Prof F X Kleber MD); **Department of Biostatistics, Zambon Group, Milan, Italy** (A Ardia PhD); **Academisch Ziekenhuis, Brussels, Belgium** (Prof P Block MD); **Hospital Central de Asturias, Oviedo University, Oviedo, Spain** (Prof A Cortina MD); **Hungarian Institute of Cardiology, Budapest, Hungary** (L Cserhalmi MD); **Universitatsspital, Zurich, Switzerland** (Prof F Follath MD); **Hvidovre Hospital, Hvidovre, Denmark** (G Jensen MD); **Bayonne, France** (J Kayanakis MD); **Academic Medical Centre, Amsterdam, Netherlands** (Prof K I Lie MD); **Università Degli Studi Di Milano, Italy** (Prof G Mancia MD); **and Nottingham Clinical Trial Data Centre, Nottingham, UK** (A M Skene PhD),

Correspondence to: Prof J R Hampton

Patients were randomly allocated ibopamine or placebo by means of a numbered pack system within each centre. Duration of treatment was for a minimum of 6 months. Ibopamine and placebo were identical in all respects. The allocation schedule was computer-generated by the data centre in blocks of four. The main code was held by the safety committee and by the drug-packaging department (but no other department) of the sponsor. The pharmacy of each participating centre held a series of individual sealed envelopes that corresponded to the drug kits allocated to that centre and contained a code break for each kit. These envelopes were returned to the sponsor at the end of the trial so that maintenance of blinding could be checked. Each centre was supplied with drug kits with a unique number. At randomisation, the investigator used the kit with the lowest available number.

We recruited patients with advanced heart failure from participating centres in Europe which had varying access to detailed investigation of left-ventricular function. Thus, the inclusion criteria were described in general and specific terms. Our protocol stated that "The typical included patient either will have required hospital admission for advanced congestive cardiac failure, or will have had symptoms of congestive heart failure at rest despite optimal therapy, within the 2 months before randomisation. However, hospitalised patients who cannot realistically be expected to be discharged are not eligible for the study." In addition, we used the following specific inclusion criteria:

Limitation of activities—Breathlessness or fatigue because of heart failure. We defined advanced heart failure as New York Heart Association (NYHA) classes III and IV. Investigators could classify heart failure between classes III and IV as an intermediate class III/IV.

Optimum treatment for heart failure—Inhibitors of angiotensin-converting enzyme (ACE, unless tolerant), diuretics (furosemide 80 mg or more daily, if ACE inhibitors were not prescribed, or at least 40 mg daily in combination with an ACE inhibitor), and, if indicated, digoxin and other vasodilators.

Evidence of heart disease—One of the following: left-ventricular ejection fraction (LVEF) of less than 35% on radionuclide or contrast ventriculography, or on echocardiography; left-ventricular internal diastolic diameter of more than 6 cm on echocardiography; fractional shortening of less than 20% on echocardiography; a cardiothoracic ratio of more than 50% on standard posteroanterior chest radiography.

Demography—Men or women aged 18–80 years.

Consent—All patients had to give written informed consent to take part in the study.

The exclusion criteria were: obstructive valve disease, obstructive or restrictive cardiomyopathy, any potentially transient cause of heart failure (eg, acute myocarditis), a myocardial infarction during the previous 3 months, unstable angina, uncontrolled arrhythmias, current need for intravenous inotropic support, intolerance of dopamine or ibopamine, concomitant use of medication known to interact with these drugs (eg, metoclopramide, levodopa), pregnancy or lactation, inadequate contraception in women of childbearing age, and administration of another investigational drug within the previous 30 days.

Minimum follow-up was for 6 months. Patients who were withdrawn were followed up every 3 months until the end of the study. We assessed patients at the initial screening visit, at week 4, and then every 3 months until the end of the study, by which time the patients who had been recruited first had taken the study medication for more than 3 years. Haematological and biochemical assessments were done at baseline, months 1, 3, and 6, and then every 6 months. Records were kept of concomitant medication and of the number, duration, and cause of hospital admissions. Left-ventricular function was assessed at baseline only.
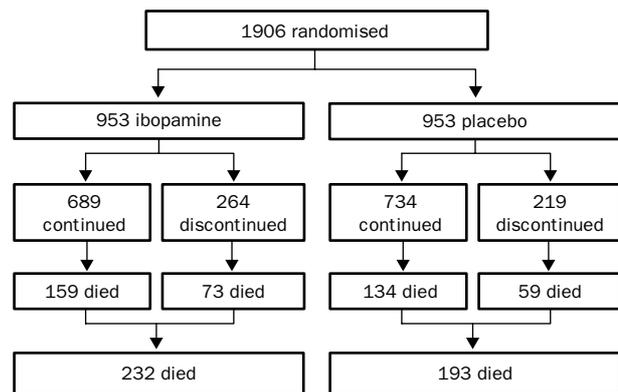

Figure 1: **Trial profile**
Continued=patients who took study medication until end of study or who died within 14 days of withdrawal.
Discontinued=patients who were withdrawn from treatment and did not die within 14 days of last tablet, or who were not formally withdrawn but had not taken study medication within 14 days of end of study.

We used three methods for the assessment of patients' symptoms at each follow-up visit. The investigating physician applied the NYHA classification according to the patient's description of his or her symptoms. The patient's general state was assessed on a simple five-point scale—good, good/fair, fair, fair/awful, and awful. Orthopnoea, dyspnoea, peripheral oedema, and fatigue were assessed on individual four-point scales. In addition, a detailed quality-of-life assessment based on the Nottingham Health Profile[11] and on a disease-specific questionnaire[2] was completed by all participating centres in the Netherlands, the UK, and Italy at baseline and months 3 and 12.

Since previous studies suggested that ibopamine led to an improvement of symptoms in patients with heart failure, and because the drug was licensed in several European countries, the primary objective of our trial was to exclude the possibility that the hazard ratio for ibopamine treatment relative to placebo was 1·2 or higher. Based on the assumption of an annual mortality rate of about 20% with an average follow-up of 22 months, we calculated that 2200 patients would be needed for 80% power to show that the upper 95% confidence limit of the hazard ratio was less than 1·2. No interim analyses were planned, except as required by the safety committee.

All patients were included in the intention-to-treat analysis of survival. The hazard ratio was estimated by fitting of a proportional hazard regression model. This method was also used for post-hoc exploratory analysis of the effect of the treatment in various subgroups.

The study followed the terms of the Helsinki Agreement; the protocol was approved by the ethics committees of all participating centres. The trial was designed and supervised by a steering committee on which a statistician from the sponsoring company was present as a non-voting member. The steering committee was responsible for all scientific aspects of the study design, analysis, and reporting. The safety monitoring committee monitored the safety of ibopamine relative to placebo and had access to uncoded information. This committee had access to the data and was permitted to conduct any interim analysis deemed necessary. In addition, the committee took account of any new information that might become available during the trial. Stopping rules were pre-defined by the safety committee—the study would be stopped if there was conclusive evidence of a benefit from ibopamine (one-sided p<0·001, against placebo); if ibopamine was associated with an increase in mortality and the 98% CI excluded the possibility of a hazard ratio of 1·0 (ie, one-sided p<0·01 against ibopamine treatment). The number of interim analyses was not prespecified, but these stopping rules are consistent with up to four or five interim analyses of the results at equal points during the follow-up. During the study, three formal analyses were done. Data on adverse events were reviewed every 3 months.

Data-handling under masked conditions was done at the Nottingham Clinical Trial Data Centre. Data were supplied to the safety committee on request. The treatment codes were held by the statistical representative of that committee. At the end of the study, the data centre was responsible for the statistical analyses on the instruction of the steering committee. A death classification committee, composed of representatives of the steering committee (AJC and FXK), who were unaware of treatment assignment, reviewed all available evidence on deaths. Deaths were classified according to the following criteria:

Sudden cardiac death—witnessed, instantaneous death in a patient who had no deterioration of heart failure for 1 week before death and no chest pain; or unwitnessed death in a patient who had no symptoms of heart failure for 1 week before death and no chest pain.

Progressive heart failure—shock, intractable heart failure that led to hospital admission, or deterioration of heart failure during the month before death.

Myocardial infarction—death during week after documented diagnosis of myocardial infarction, or death after suspected myocardial infarction.

Other cardiovascular death—cardiovascular deaths not covered by the above definition.

Results

The first patient was randomly assigned study medication in September, 1992. In August, 1995, the safety committee, at its regular meeting to review data then available, found a significantly higher fatality rate among ibopamine-treated patients than among placebo-treated patients. Thus, the safety committee advised the steering committee to terminate the study. All patients were subsequently withdrawn from treatment.
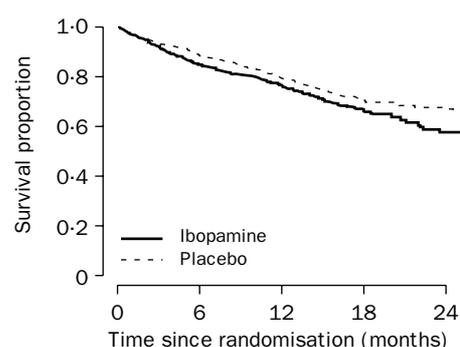
By August, 1995, we had recruited 1906 patients rather than the projected total of 2200, there were 953 patients in

Figure 2: **Kaplan-Meier survival curves for ibopamine and placebo groups**

	Ibopamine (n=953)	Placebo (n=953)
Mean (SD) age (years)	64·6 (9·6)	64·8 (9·5)
M/F	783/170	749/204
Diabetes	199 (20·9%)	195 (20·5%)
Mean (SD) duration of heart failure (months)*	42·5 (41·3)	45·0 (44·9)
Mean (SD) blood pressure (mm Hg)		
Systolic	121·6 (19·2)	121·7 (20·3)
Diastolic	75·5 (11·3)	74·7 (10·8)
Atrial fibrillation	230 (24·1%)	223 (23·4%)
NYHA class		
III	564 (59·2%)	574 (60·2%)
III/IV	299 (31·4%)	308 (32·3%)
IV	90 (9·4%)	71 (7·5%)
Current treatment for heart failure		
Mean (median) diuretic dose (mg)	117·3 (80)	118·8 (80)
Digoxin	620 (65·1%)	602 (63·2%)
Antiarrhythmic	213 (22·4%)	250 (26·2%)
ACE inhibitor	873 (91·7%)	875 (92·3%)
Aetiology		
Ischaemic heart disease	560 (58·8%)	560 (58·8%)
Valve disease	56 (5·9%)	39 (4·1%)
Cardiomyopathy	297 (31·2%)	303 (31·8%)
Hypertension	35 (3·7%)	44 (4·6%)
Other	5 (0·5%)	6 (0·6%)
Mean (SD) evidence of severity		
LVEF (%)	26·0 (8·5)	26·4 (9·6)
LVIDD (cm)	6·86 (0·92)	6·90 (0·99)
Cardiothoracic ratio (%)	57·9 (6·8)	58·2 (6·8)

*Median 30 months in both groups.
LVEF=left-ventricular ejection fraction; LVIDD=left-ventricular end internal diastolic diameter.

Table 1: **Baseline characteristics of patients**

each group (figure 1). The patients were recruited from 192 centres in 13 European countries.

Baseline characteristics (table 1)

The treatment groups were well matched in terms of age, sex, and medical history. Current treatment for heart failure at baseline was also similar: the median diuretic dose (furosemide or equivalent) was 80 mg daily in both groups (mean 117 mg [range 40–1600]). Of the 463 (24%) patients who were currently taking antiarrhythmic drugs, 403 (87%) were on amiodarone.

The distribution of causes of heart failure was similar in the two groups. About 60% of patients had ischaemic heart disease and about 30% had dilated cardiomyopathy. In the ibopamine and placebo groups, 55% and 53%, respectively, had a history of myocardial infarction. In addition, the groups were well matched with respect to left-ventricular function. LVEF was measured by at least one method in 1748 (92%) patients, and the mean value in both groups was 26%. A measurement of cardiothoracic ratio on chest radiographs was available in 1741 (91%) patients, and the mean value was 58% in both groups. Left-ventricular internal diastolic diameter was measured by echocardiography in 1432 (75%) patients, and the mean diameter in each group was 6·9 cm. Table 1 shows that our protocol was successful in defining a group of patients with heart failure at high risk of death.

Fatality

Although recruitment stopped within a few days of the safety committee's decision to terminate the trial, further deaths were reported. The steering committee decided that the intention-to-treat analysis should be based on the number of deaths that occurred up to the time when patients were told to stop taking study medication; deaths after this time were censored. This analysis showed that 232 (24·3%) patients in the ibopamine group and 193 (20·3%) in the placebo group died during the study. This excess of 39 deaths in the ibopamine group was significant (log-rank test p=0·017) and the risk of death with ibopamine relative to placebo was 1·26 (95% CI 1·04–1·53).

Figure 2 shows the proportion of patients who survived in each group. Survival seemed to be similar in both groups for the first 3 months, but thereafter the survival curves diverged to show a disadvantage with ibopamine treatment, which was most noticeable after 600 days.

| Cause of death	Ibopamine (n=953)	Placebo (n=953)
Sudden cardiac		
Witnessed	35	22
Unwitnessed	34	24
Total	69 (29·8%)	46 (23·8%)
Progressive failure		
Shock	79	60
Background of deterioration	30	28
Total	109 (47·0%)	88 (45·6%)
Myocardial infarction		
Proven	8	11
Suspected	7	10
Total	15 (6·5%)	21 (10·9%)
Other cardiovascular disease	17 (7·3%)	12 (6·2%)
Non-cardiovascular disease	15 (6·5%)	17 (8·8%)
Cardiac transplantation	2 (0·9%)	7 (3·6%)
Unclassifiable	5 (2·2%)	2 (1·0%)
Total	232	193

Table 2: **Causes of death**

The average length of follow-up was 347 days in the ibopamine group and 363 days in the placebo group; few patients were followed up for more than 2 years. The estimated 1-year mortality rates were 23·7% in the ibopamine group and 20·8% in the placebo group.

Eight ibopamine-group patients and seven placebo-group patients were lost to follow-up whilst continuing on study medication. 259 patients (27%) in the ibopamine group and 222 (23%) in placebo group were withdrawn from study medication before death or before the end of the study; of these patients, 16 and 20, respectively, were lost to follow-up after they had been withdrawn from treatment. All other patients were confirmed to have died or were contacted by the centre after the end of the study.

185 ibopamine-treated and 141 placebo-treated patients were withdrawn because of adverse events; the excess of withdrawals in the ibopamine group was mainly due to gastrointestinal symptoms. Only three patients (two ibopamine, one placebo) were withdrawn because the investigator wished to use open-label ibopamine. The randomisation code was broken for eleven patients (four ibopamine, seven placebo).

The trial profile shows that at the time the study was stopped, 159 patients in the ibopamine group and 134 in the placebo group had died while on study medication or within 14 days of withdrawal from study medication (figure 1). Among the patients who continued to take study medication, four in the placebo group, compared with none in the ibopamine group died within 14 days of the end of the trial. These four patients are not included in

Figure 3: **Time to first hospital admission**
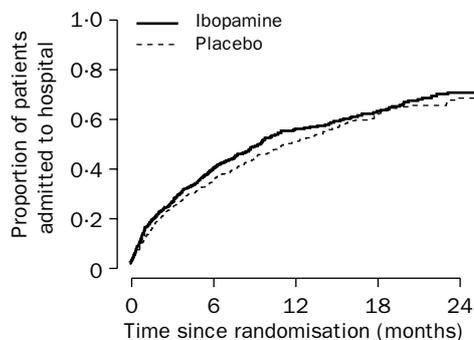
Number of patients at risk:
Ibopamine 953 399 200 96 35
Placebo 953 444 213 104 49

	% worse	% unchanged	% improved
Patients' self-assessment*			
Ibopamine	37	40	23
Placebo	39	40	21
NYHA class			
Ibopamine	14	42	44
Placebo	15	38	47
Orthopnoea			
Ibopamine	34	48	18
Placebo	32	50	18
Dyspnoea			
Ibopamine	51	36	13
Placebo	54	33	13
Peripheral oedema			
Ibopamine	21	56	23
Placebo	27	51	22
Fatigue			
Ibopamine	21	50	29
Placebo	24	47	29

*On five-point scale.

Table 3: **Changes in NYHA class, quality of life, and symptoms from baseline to last available assessment**

figure 2. There was a significant difference in Kaplan-Meier estimates of 1-year mortality between ibopamine-group patients and placebo-group patients who continued on treatment (19·5 vs 16·8%, p=0·017). Mortality rates in patients who were withdrawn from treatment were higher than those in patients who continued on treatment, but the difference between the ibopamine and placebo groups was not significant, because most withdrawals were made for clinical deterioration (25·3 vs 25·3%).

Overall, 21 patients in the ibopamine group and 22 in the placebo group underwent cardiac transplantation, of whom 13 and 16 had been previously withdrawn from the study. Of these 43 patients, two in the ibopamine group and seven in the placebo group died. All the patients who underwent cardiac transplantation were followed up until the end of the study; all deaths that occurred after transplantation were included in the intention-to-treat analysis. Study medication was discontinued before transplantation in some patients and at the time of surgery in others; for the on-treatment analysis these patients were classified as withdrawals. Alternative analyses that treated patients who underwent transplantation as censored observations or as deaths did not affect the significance levels.

Table 2 shows the causes of death as determined by the death classification committee. There was no significant difference in the causes of death between the groups.

Subgroups	1-year mortality		p
	Ibopamine (n=953)	Placebo (n=953)	
Sex			
Men	149 (24·6%)	114 (20·7%)	0·094
Women	25 (19·8%)	34 (20·9%)	
Duration of heart failure			
≤2 years	62 (19·9%)	74 (22·4%)	0·064
>2 years	112 (26·6%)	74 (19·5%)	
Antiarrhythmic therapy at baseline			
Yes	42 (26·7%)	33 (18·7%)	0·015
No	132 (22·8%)	115 (21·6%)	
NYHA class			
III	67 (16·1%)	73 (16·9%)	0·088
>III (III/IV or IV)	107 (34·8%)	75 (26·7%)	

Table 4: **Univariate analysis of 1-year mortality in selected subgroups of patients in whom excess mortality was associated with ibopamine treatment**
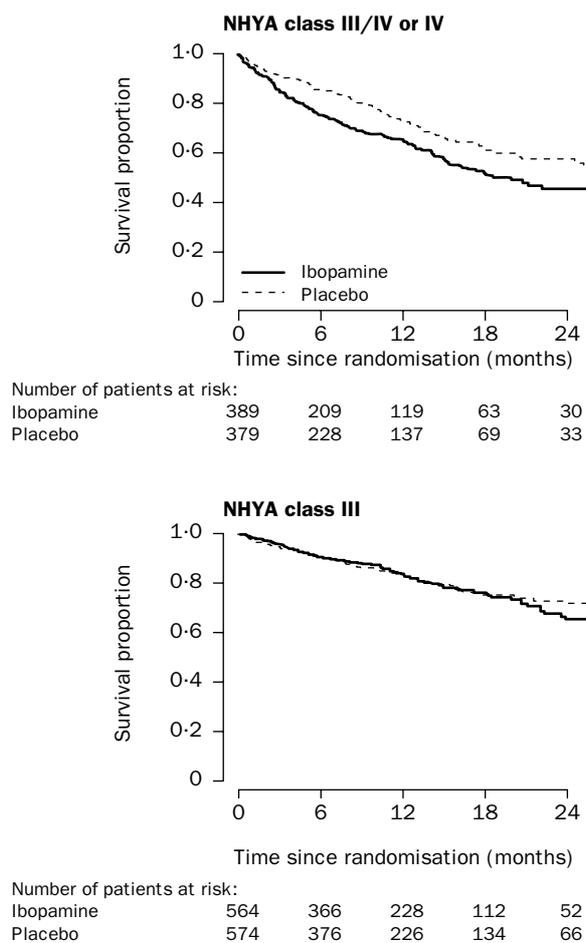
NHYA class III/IV or IV

Number of patients at risk:

Ibopamine	389	209	119	63	30
Placebo	379	228	137	69	33

NHYA class III

Number of patients at risk:

Ibopamine	564	366	228	112	52
Placebo	574	376	226	134	66

Figure 4: **Univariate analysis of survival by NYHA class at baseline**

No antiarrhythmic therapy at baseline

Number of patients at risk:

Ibopamine	740	447	273	140	64
Placebo	703	434	264	151	75

Antiarrhythmic therapy at baseline

Number of patients at risk:

Ibopamine	213	128	74	35	18
Placebo	250	170	99	52	29

Figure 5: **Univariate analysis of survival by use of antiarrhythmic therapy at baseline**

Secondary outcome endpoints

442 (46%) of the patients in the ibopamine group compared with 416 (44%) patients in the placebo group were admitted to hospital during the trial (relative risk 1·13 [95% CI 0·99–1·29]; figure 3). 215 (23%) ibopamine-group patients and 203 (21%) placebo-group patients were admitted on more than one occasion; the causes of admission were similar in both groups.

The patients' self-assessment scores of symptoms did not differ between the groups (table 3). Similarly, there was no apparent difference between the groups in the investigators' assessment of NYHA function class, dyspnoea, orthopnoea, peripheral oedema, or fatigue (table 3).

961 patients from the Netherlands, the UK, and Italy were included in the analysis of quality of life. There were no between-group differences in terms of the Nottingham Health Profile or the disease-specific questionnaire.

Subgroup analyses

Our study was not designed to assess the effect of ibopamine in any specific subgroup of patients, and no subgroups were identified a priori as being of particular interest. However, given the excess of deaths in the ibopamine group, we did various post-hoc analyses of subgroups to attempt to investigate the mechanism involved in this increased fatality.

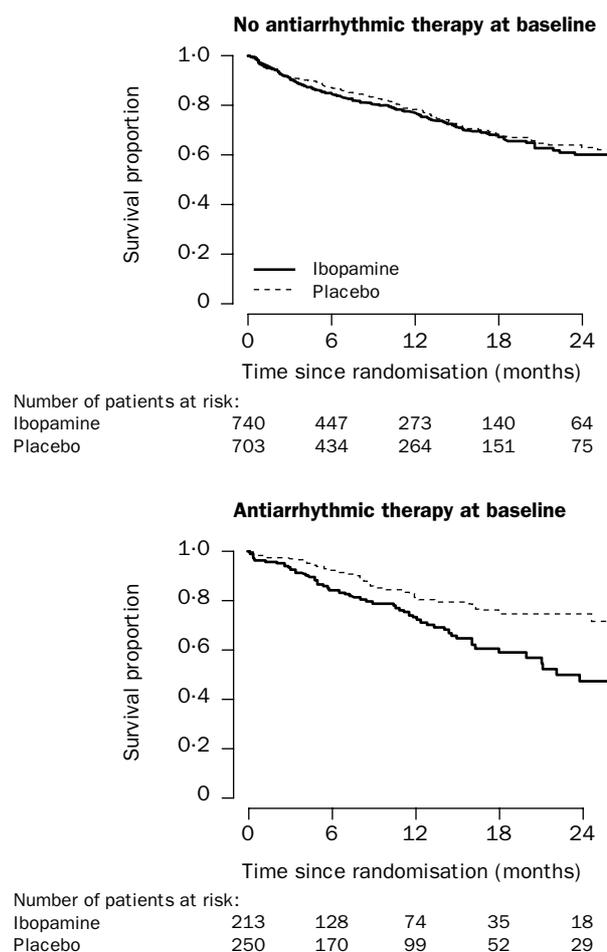Univariate analysis showed that the effect of ibopamine, relative to placebo, on mortality varied with subgroup for four factors: sex, NYHA class, duration of heart failure, and the use of antiarrhythmic drugs at entry to the study (p <0·1 in each group; table 4). For example, figure 4 compares survival in patients of NYHA class III and class III/IV by treatment group. Of the patients in NYHA class III, 97 (17·2%) of 564 ibopamine-group patients died versus 94 (16·4%) of 574 placebo-group patients (relative risk 1·06 [0·8–1·41]). By contrast, among patients of NYHA classes III/IV or IV, 135 (34·7%) of 389 ibopamine-group patients died versus 99 (26·1%) of 379 placebo-group patients (relative risk 1·48 [1·14–1·92]).

When the simultaneous effect of sex, NYHA class, duration of heart failure, and baseline use of antiarrhythmic drugs, was examined by multivariate analysis, the only factor that remained as an independent predictor of increased mortality from ibopamine was the use of an antiarrhythmic drug at baseline (figure 5).

Among the patients who did not use antiarrhythmic drugs at baseline, 172 (23·2%) of 740 ibopamine-group patients died versus 153 (21·8%) of 703 placebo-group patients (relative risk 1·1 [0·88–1·37]. By contrast, among those patients who used antiarrhythmic drugs at baseline, 60 (28·2%) of 213 ibopamine-group patients died versus 40 (16·0%) of 250 placebo-group patients (relative risk 1·95 [1·31–2·91]).

There were no significant subgroup effects for age, aetiology, previous morbidity, vital signs, LVEF, left-ventricular internal diastolic diameter, carthiothoracic

ratio, and use of digoxin, ACE inhibitors, or dose of furosemide.

Discussion

This is the fourth major study to report an association between active treatment and increased fatality in patients with heart failure.[1-3] Nevertheless, the adverse effect of ibopamine on survival reported here was unexpected. Ibopamine has properties expected to confer benefit to patients with heart failure, particularly vasodilatation and an appropriate effect on neurohormones, and is also thought not to have inotropic effects. The drug is well established in several European countries for the treatment of heart failure, and no previous study or any postmarketing surveillance suggested the possibility that ibopamine might increase fatality.

Most previous studies of ibopamine were of short duration in patients with mild to moderate heart failure; PRIME II was not designed to investigate the effect of ibopamine on survival in such patients. By contrast, we included only patients with advanced failure. We do not know whether ibopamine is safe in patients with less advanced heart failure. Furthermore, because this study was not designed to assess the effect of ibopamine in different subgroups of patients, the results of our post-hoc subgroup analyses must be interpreted with caution, although the main adverse effect of ibopamine was seen in patients with NYHA class III/IV or IV.

The role of the safety monitoring committee was crucial in this study. The predefined stopping rules were asymmetric: a high probability of benefit from treatment was required before the study would be terminated ($p < 0.001$), whereas the study would be stopped if ibopamine was harmful at a less significant level ($p < 0.01$). These limits were chosen because of the widespread use of ibopamine in several European countries, where it is thought to be a clinically useful drug.

The only subgroup analysis requested by the safety committee was a comparison of the effect of treatment between patients who had NYHA class III and those with classes III/IV or IV. The safety committee was aware of the adverse effect of ibopamine in the patients with severe heart failure. Because there was no hypothesis that necessitated following the outcome in this, or in any other, subgroup, it was decided that the trial should continue if the adverse effect of ibopamine was limited to patients with severe heart failure and that the safety committee would recommend that the trial be stopped only if significant harm from ibopamine was shown in all patients, irrespective of NYHA class.

The mechanism underlying the adverse effect of ibopamine reported here is not known. Although subgroup analyses must always be viewed with caution, such analyses are a reasonable way of generating hypotheses when a trial is stopped early. Our post-hoc univariate analyses of various subgroups identified factors, particularly those linked to the severity of heart failure, that seemed to be associated with an unfavourable effect of ibopamine; and there was no difference between patients whose heart failure resulted from ischaemic heart disease and those with cardiomyopathy. In multivariate analysis, only the use of antiarrhythmic drugs at baseline emerged as an independent predictor for an adverse effect in ibopamine-treated patients. There is no known interaction between ibopamine and amiodarone or any other antiarrhythmic agent, and ibopamine is not thought to be proarrhythmic.[12] Since the subgroup of patients who received antiarrhythmics was identified as one of a wide variety of subgroups studied, and since there was no hypothesis about antiarrhythmic agents, the importance and underlying mechanism of this finding is unknown.

Two large substudies have been completed within the PRIME II protocol, but their results are not yet available. In one, the effect of ibopamine on a range of neurohormones was investigated: if the findings of this study support the results of previous investigations and show that the neurohormone profile is improved by ibopamine, the clinical results of PRIME-II may help define the importance of neurohormones in the progression of heart failure. The second substudy involves serial Holter electrocardiography monitoring, which should show whether ibopamine is proarrhythmic in patients with severe heart failure.

Restrictions have now been placed on the use of ibopamine in patients with severe heart failure in those countries where the drug is licensed.

Prime II Investigators
Writing Committee—J R Hampton, F X Kleber, D J van Veldhuisen.
Steering Committee and Country Coordinators—J R Hampton (chairman, UK), A J Cowley (UK), F X Kleber (Germany), K I Lie (Netherlands), G I Mancia (Italy), P Block (Belgium), A Cortina (Spain), L Cserhalmi (Hungary), F Follath (Switzerland), G Jensen (Denmark), J Kayanakis (France), D J van Veldhuisen (Netherlands), A Ardia (non-voting member, Italy).
Safety Monitoring Committee—D G Julian (London, UK), H E Kulbertus (Liége, Belgium), J G P Tijssen (statistical advisor, Amsterdam, Netherlands), A J M Craen (statistical assistant, Amsterdam, Netherlands).
Classification Committeee—A J Cowley, F X Kleber.
Sponsor (Zambon Group)—L Caresia (International Medical Manager), S Franchini (Drug Safety Unit Manager), T Pallotta (Clinical Trial Coordination Manager).
Nottingham Clinical Trial Data Centre—A M Skene, A Charlesworth, A Foxley, E Townsend, I Borland, S Stead, L Wolf.
Investigators—*Austria:* Karl Franzen Universität Graz, Graz (W Klein, N Watzinger), Krankenhaus der Barmherzzinger Brüder, Salzburgh (Auzinger G), Hamusch Krankenhaus, Wien (G Gaul, C Dornaus), Krankenhanstadt der Stadt Wien, Wien (J Slany, T Vanicek, G Krutisch); *Belgium:* VUB Vrije Universiteit Brussels, Brussels (P Block, P Dendale), Clinique St Jean, Brussels (P H de Salle), Cliniques Universitaires St Luc Bruxelles (De Kock), Ziekenhuis St Dimpna, Geel (J Vermeulen), Andre Dumont Kliniek, Genk (W Van Mieghem), Hopital St Joseph, Gilly (P Mengeot, F Piette), Hopital de Jolimont, La Louviere (J M Chaudron), Virga Jesse Ziekenhuis OCMW, Hasselt (R Geukens), Hopital de la Citadelle Liège, Liège (E Lecoq, J Boland), St Jozefziekenhuis, Mortsel (M Derveaux, B Vergauwem), Clinique La Dorcas, Tournai (G Jouret), St Augustinus Kliniek, Veurne (R Popeye); *Denmark:* Amtssygehuset I Glostrup, Glostrup (J Rokkedal Nielsen), Hvidovre Hospital, Hvidovre (G Jensen, W B Nielsen), Frederiksborg Amts Centralsygehus, Hillerød (F Pedersen, S G Jensen), Køge Hospital, Køge (S L Rasmussen), Centralsygehuset I Naestved, Naestved (Asbjørn Høegholm), Centralsygehuset Nykøbing Falster, Nykøbing Falster (B Sigurd, A Larkeborg); *France:* Clinique Saint-Hilaire, Agen (R Constans, J Leymarie, B Mouysset), Centre Hospitalier, Agen (J Daubeze, J Cherrier), Albi (G Lapeyre, T Bujaud, J F Masson, P Sigal), Bayonne (G Enjuto, A Chabanier, J L Glement, J G Kayanakis, P Doat, P Grenet, J P Bernis), Cages sur Mer (J M Dahan, M Essayagh), Hôpital Marie Madeleine, Forbach (J P Godenir, R Andriani), Hôpital General, Freyming-Merlebach (P Dambrine, A Gabriel, F Labaki), Hyeres (R Laquiere, J M Bouteau), Clinique de L'Union, L'Union (P Delpont, F Graffeille), Hôpital St Louis, La Rochelle (L Ledain, P Bru), Centre Hospitalier de la Seyne sur Mer, La Seyne sur Mer (J Beltran, M Proult, J F Guidicelli), CHG de Luneville, Luneville (W J L Weber), Hôpital Sainte-Blandine, Metz (N Baille), Clinique Claude Bernard, Metz (J L Neimann, A Hueber), Clinique du Pont de Chaume, Montauban (A Tardieu, R Salas, G Bonneric), Clinique Lavalette, Montpellier (G Levy, D Perez, J Baumelou, D Dupuy), Nice (A Schenowitz, R Kalle, J C Guiran), Clinique Les Franciscaines, Nimes (E Bosc), Centre Hospitalier, Niort (C Denis, C Cornuau), Clinique Bizet, Paris (D Marcadet P Tessier, A De Ratuld), Pau (A Goux), Centre Hospitalier Intercommunal de Poissy, Poissy (J C Kahn, B Baron, G Broutin, D Zannier), Remiremont (B Theil, F Coince), Hôpital de Rodez, Rodez (P Pouget), Hôpital d'Instruction des Armées Sainte-Anne, Toulon Naval (G V Dussarat, P Talard, C Bouchiat), Centre Hospitalier Universitaire de Rangueil, Toulouse (J P Bounhoure, M Galinier, P Toussaint), Toulouse (R Bahsoun, A Chantrelle, J P Baixas), Centre Hospitalier, Verdun (S Allam, P Muller); *Germany:* Klinik für Herz und Gefässerkrankugen, Bad Neustadt (G Kestrel, H Neuser), Charitè Berlin Humboldt-Universität, Berlin (F X Kleber, J Langel), Krankenhaus am Friedrichshain, Berlin (O J Tittelbach, D Zimmerman), DRK Krankenhaus, Berlin (H F Vöhringer, A Pilgrim), Franz-Vollhart-Klinik, Berlin-Buch (R Dietz), Herzzentrum Kaiser Wilhelm Krankenhaus, Duisburgh (J W Park), Medizinische Akademie, Erfurt (I Aβmann), Universitätsklinik, Essen (R Erbel, S Sack), Klinik der Alb-Ludwigs-Universitat, Freiburg (C H Holubarsch M Frey), Klinik am Eichert, Göppingen (A H Siegel, F Hofgäremer), Martin-Luther-Universität, Halle Wittenberg (W Teichmann, B Panzner), Kreiskrankenhaus Bergstrasse, Heppenheim

(K A Zölch), Klinik III für Innere Medizin der Universität zu Köln, Köln (M Böhm D Hartmann), Kreiskrankenhaus Lüdenscheid, Lüdenscheid (D Boppert), Universitätsklinikum Mainz, Mainz (H Darious, W T Wittlinger, W Block), Ludwig Maximiliams Universität, München (I Theissen), Medizin Klinik des Städtischen Krankenhauses, Pforzheim (H P Helwing), Herz und Kreislaufzentrum, Rotenburg a.d. Fulda (F Loskot), Klinikum Sulh (M Wesser), Knappschaftskrankenhaus, Sulzback (G Rettig-Stuerner); *Hungary:* Hungarian Institute of Cardiology, Semmelweiss University of Medicine, Budapest (L Cserhalmi), Orzàgos Kardiològiai Intèetès Sote Kardiològiai Tanszèk, Budapest (L Cserhalmi), Bajcsy Hospital Cardiology IV, Budapest (G Buday), Haynal Imre University of Health Sciences Post Graduate Medical Faculty, Budapest (I Pràda), Albert Szent Gyorgyi University Medical School, Szeged (M Csanànyi, M Högye); *Italy:* Ospedale C Cantu di Abbiategrasso, Abbiategrasso (MI) (G De Vizzi, F Leali, G Signorini), Ospedale Cardioreumatologico Lancisi, Ancona (A Purcaro, M Mazzanti), Ospedale Gen, Regionale di Torrette, Ancona (P Russo, G Ferretti), Clinical Medica I-Presidio Ospedaliero, Bari (G Maiorano, F Bartolomucci), S Maugeri Foundation IRCCS, Cassano Murge, Bari (P Rizzon, D Scrutinio), Ospedale Civil, Belluno (P Pellegrini, J Dalle Mule), Ospedale Riuniti di Bergamo, Bergamo (G Tasca, M Senni), Universitádegli Studi, Spedali Civili, Brescia (L Dei Cas, M Mertra), Ospedale Brotzu, Cagliari (A Z Sanna, M Porcu), Ospedale Valduce, Como (M Santarone, G Tadeo), Ospedale Sante Croce, Cuneo (E Uslenghi, U Milanese), Ospedale Maggiore, Lodi (M Orlandi, A Oddone), Centro Auxologico Ospedale San Luca, Milano (G Leonetti, R Chianca), Ospedale San Geradro Dei Tintori, Monza, Milano (M Colombo, M Gelosa, G Mancia), Divisione di Cardiologia II Policlinico II, Napoli (M Chiariello), Seconda Universitá Napoli, Napoli (A Iancono, B Perna), Ospedale Monaldi, Napoli (N Mininni), Ospedale Maggiore della Caritá, Novara (A Monteverde), Policlinico San Matteo, Pavia (C Montemartini), UO Cardiologia Policlinico Monteluce, Perugia (M Cochieri, D Severini), Arcispedale S Maria Nuova, Reggio Emilia (U Guiducci, O Gaddi), CTO Centro Traumatologico, Roma (M Uguccioni, C Bianchi), Ospedale Villa San Pietro, Rome (F Ferri, P Delle Grotti), Policlinico Le Scotte, Siena (R Nami), Ospedale Le Molinette, Torino (Brusca Antonino), Fondazione Clinica del Lavoro, Tradate, Varese (R Tramarin, A Laporta), Ospedale di Circolo, Varese (G Binaghi, G Calveri); *Luxembourg:* Centre Hospitalier de Luxembourg, Luxembourg (C H Delagardelle); *Portugal:* Hospital Sao Francisco Xavier, Lisboa (A Sales Luis, F Ceia); *Spain:* Hospital Bellvitge, Barcelona (N Manito), Hospital Germans Trias I Pujol, Barcelona (V Valle Tudela, J Lupon), Hospital de Basurto, Bilbao (D Rodriguez), Hospital Reina Sofia, Cordoba (F Vallés Belsuéu, M Anguita), Clinical Puerta de Hierro, Madrid (L A Pulpon), Hospital Ramon Y Cajal, Madrid (V Barrios, E Asin Cardiel), Hospital Clinico San Carlos, Madrid (F Perez Gomez, J Zamorano), Hospital Costa del Sol, Marbella (E G Cocina), Hospital Central de Asturias, Oviedo (A Cortina, J L R Lambert), Hospital Virgen de la Macarena, Sevilla (J M Cruz Fernandez), Hospital Arnau de Vilanova, Valencia (J Sotillo), Hospital Clinico de Zaragoza, Zaragoza (A del Rio Ligorit, F Runcales); *Switzerland:* Ospedale San Giovanni, Bellinzona (A Gallino, C Marone), Kantonsspital Liestal, Liestal (C Cottier), Ospedale Civico Lugano, Lugano (T Moccetti), Kantonsspital, St Gallen (W Anghern, H Rickli), University Hospital, Zürich (F Follath, H D Brunner); *Netherlands:* Academic Hospital of the Free University, Amsterdam (O Kamp), Ziekenhuiscentrum Apeldoorn, Apeldoorn (E G Faber), Delfzicht Ziekenhuis, Delfzijl (S P M Twisk), Bronovo Hopital, Den Haag (H J J Kerkkamp, A M Marsman), Deventer Ziekenhuis, Deventer (D J A Lok, P W F Bruggink), Chr Ziekenhuis Nije Smellinghe, Drachten (M R van der Linde), Catharina Ziekenhuis, Eindhoven (H R Michels, C E E Hanekamp), Martini Hospital, Groningen (P J L M Bernink), University Hospital, Groningen (D J van Veldhuisen), Elkerliek Ziekenhuis, Helmond (P E F Bendermacher), St Streekziekenhuis Midden Twente, Hengelo (J J J Bucx), Ijsselland Ziekenhuis, Capelle a/d Ijssel (B J van den Berg), Leiden University Hospital, Leiden (V Cats Manger, E P Viergever), Academisch Ziekenhuis Maastricht, Maastricht (F W H M Bär, H Quint), Canisius Ziekenhuis Wilhelmina, Nijmegen (D P Hertzberger, T E H Hooghoudt), Cardiovascular Research Stichting Sticares, Rotterdam (W J Remme), Refaja Ziekenhuis, Stadskanaal (L M van Wijk), De Honte Hospital, Terneuzen (R Ciampricotti), St Elisabeth Ziekenhuis, Tilburg (W H Pasteuning, W F Wonnink de Jong), Maria Ziekenhuis, Tilburg (H A M van Kesteren), Academic Hospital Utrecht, Utrecht (C Klöpping), St Joseph Ziekenhuis, Veldhoven (A H Bosma), Ziekenhuis Velp, Velp (L H J van Kempen), St Jans Gasthuis, Weert (H J A M Penn), Ziekenhuis De Wezenlanden, Zwolle (J C A Hoorntje); *UK:* Royal United Hospital, Bath (R D Thomas, M Wicks), Queens University of Belfast, Belfast (G D Johnston, J Hughes), Royal Victoria Hospital, Belfast (D P Nicholls, S M Maguire), Selly Oak Hospital, Birmingham (M K Davies, M Salih), Blackpool Victoria Hospital, Blackpool (D H Roberts, G K Davis), Pilgrim Hospital, Boston (C Nyman), Darlington Memorial Hospital, Darlington (J J Murphy), General Hospital, Hartlepool (G Tildesley), Killingbeck Hospital, Leeds (L B Tan, J Al-Timman), Leicester Royal Infirmary, Leicester (D B Barnett), Fazakerley Hospital, Liverpool (R S Hornung, E Rodrigues), North Manchester General Hospital, Manchester (S P Hanley), Wythenshawe Hospital, Manchester (C Ward), King 's Mill Hospital, Mansfield (J M Rowley, D Nix), Ashford Hospital, Middlesex (P Wilkinson, J Marsh), Northampton General Hospital, Northampton (J S Birkhead, J O'Callaghan), University Hospital, Nottingham (A J Cowley), The Royal Alexandra Hospital, Paisley (I N Findlay), Queen Mary's Hospital, Sidcup (P Das Gupta), Stepping Hill Hospital, Stockport (P S Lewis, M Martin), Princess Royal Hospital, Telford (M E Heber, C Stiles), York District Hospital, York (R M Boyle, B S Wiseman).

References

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

2   Cowley AJ, Skene AM, on behalf of the Enoximone Investigators. Treatment of severe heart failure: quantity or quality of life? A trial of enoximone. *Heart* 1994; **72:** 226–30.

3   Massie BM, Berk MR, Brozena SC, et al. Can further benefit be achieved by adding fenequinan to patients wth congestive heart failure who remain asymptomatic on diuretics, digoxin and on angiotensin converting enzyme inhibitor? *Circulation* 1993; **88:** 492–501.

4   Itoh H. Clinical pharmacology of ibopamine. *Am J Med* 1991; **90** (suppl 5B): 36S–42S.

5   Rousseau MF, Raigoso J, Van Eyll C, et al. Effects of intravenous epinine administration on left ventricular systolic performance: coronary hemodynamics, and circulating catecholamines in patients with heart failure. *J Cardiovas Pharmacol* 1992; **19:** 155–62.

6   van Veldhuisen DJ, Girbes ARJ, van den Broek SAJ, de Graeff PA, van Gilst WH, Lie KI. Effects of ibopamine on the increase in plasma norepinephrine levels during exercise in congestive heart failure. *Am J Cardiol* 1993; **71:** 992–94.

7   Rousseau MF, Konstam MA, Benedict CR, et al. Progression of left ventricular dysfunction secondary to coronary artery disease, sustained neurohormonal activation and effects of ibopamine therapy during long-term therapy with angiotensin-converting enzyme inhibitor. *Am J Cardiol* 1994; **73:** 488–93.

8   van Veldhuisen DJ, Man in'T Veld AJM, Dunselman PHJM, et al. on behalf of the DIMT Study Group. Double-blind placebo-controlled study of ibopamine and digoxin in patients with mild to moderate heart failure: results of the Dutch Ibopamine Multicentre Trial (DIMT). *J Am Coll Cardiol* 1993; **22:** 1564–73.

9   Barabino A, Galbariggi G, Pizzorni C, Lotti G. Comparative effects of long-term therapy with captopril and ibopamine in chronic congestive heart failure in old patients. *Cardiology* 1991; **78:** 243–56.

10 Dohmen HJM on behalf of the PRIME-I Study Group. Efficacy and safety of captopril and ibopamine in mild to moderate heart failure: results of the PRIME-I Study. *Eur Heart J* 1995; **16:** 181 (abstr).

11 Hunt SM, McKenna SP. The Nottingham health profile user manual. Manchester: Galen Research, 1991.

12 van Veldhuisen DJ, Crijns HJ, Girbes ARJ, Tobe TJM, Wiesfeld ACP, Lie KI. Electrophysiologic profile of ibopamine in patients with congestive heart failure and ventricular tachycardia and relation to its effects on hemodynamics and plasma catecholamines. *Am J Cardiol* 1991; **68:** 1194–202.