Placebo controlled trial of felodipine in patients with mild to moderate heart failure

William A Littler, Desmond J Sheridan, on behalf of the UK Study Group

Abstract

Objective—To compare the effects of felodipine and placebo in patients with New York Heart Association functional class II or III and stable congestive heart failure despite treatment with an angiotensin converting enzyme inhibitor, diuretic, or digoxin, or any combination of these three drugs.

Patients and design—252 patients were randomised in a double blind, parallel group study after a 2-4 week placebo run-in to oral treatment with either felodipine extended release formulation or placebo 2.5-10 mg twice daily given in addition to existing background medication for a further 12 weeks.

Methods—Patients aged 18-75 years of either sex with chronic congestive heart failure due to ischaemic heart disease, hypertensive heart disease, or dilated cardiomyopathy with or without secondary mitral insufficiency that was stable during the preceding two months were included in the study. Treadmill exercise tests according to the modified Naughton protocol were performed at baseline, and after six, 11, and 12 weeks of treatment. Signs and symptoms of heart failure were assessed at every visit. Physical examination was performed and left ventricular ejection fraction measured at baseline and after 12 weeks.

Results—Mean (SD) baseline exercise test times increased from 434 (162) s and 480 (157) s for felodipine and placebo groups respectively to 541 (217) s and 591 (218) s at 12 weeks or the last visit. The change in exercise from baseline to last visit was 107 (141) s for patients given felodipine and 112 (128) s for those given placebo ($P > 0.20$). There was also no difference between treatments with respect to the other efficacy variables. There were few deaths in the study (felodipine $n = 3$, placebo $n = 2$). More patients who received felodipine were withdrawn from treatment ($n = 29$) than those who received placebo ($n = 17$). The most common adverse events of the 54 and 28 cited as reasons for withdrawal in the felodipine and placebo groups respectively were increased need for non-study heart failure treatment ($n = 10$; 8%)—that is, starting new medication or changes in the dosage of existing treatment for patients given felodipine, and

nausea ($n = 4$; 3%) for those given placebo. Patients withdrawn from the study due to increased need for non-study heart failure treatment rapidly stabilised and recovered.

Conclusion—Felodipine has not been shown to be of benefit in patients with mild to moderate heart failure.

(Br Heart J 1995;73:428-433)

Keywords: felodipine; heart failure; exercise testing

It has been established that the addition of various dilators, for example hydralazine, prazosin, and nitrates, of either the arterial resistance or venous capacitance vessels, or both, is of benefit to patients with congestive heart failure who are symptomatic on digitalis and diuretics alone. Calcium antagonists, which dilate the arterial resistance vessels, may therefore seem suitable for the treatment of heart failure. Many calcium antagonists, however, have negative inotropic effects in the heart which preclude their use.

Felodipine is a dihydropyridine calcium antagonist which is characterised by high vascular selectivity—that is, it is much more potent in its inhibition of contractile activity in vascular smooth muscle than in the myocardium. The in vitro ratio of vascular and myocardial potency for felodipine is greater than 118:1¹ and felodipine plasma concentrations resulting in pronounced reductions in total peripheral resistance in patients produce no negative inotropic effects² and no effects on cardiac conduction.³

The efficacy and tolerability of felodipine in patients with congestive heart failure have been studied in several open⁴⁻⁶ and double blind placebo controlled phase II studies.⁷⁻⁹ Thus Dunselman *et al*⁸ and Timmis *et al*^{6,10} demonstrated improved exercise capacity with felodipine in patients with heart failure, while Tan *et al*⁷ found no such improvement. In order to clarify this apparent discrepancy the present investigation was carried out with the principal purpose of assessing exercise capacity in a larger group of patients with mild to moderate heart failure.

Patients and methods

STUDY DESIGN

This was a double blind, placebo controlled, randomised parallel group investigation of

Department of Cardiovascular Medicine, Queen Elizabeth Hospital, Birmingham
W A Littler

Academic Cardiology Unit, St Mary's Hospital Medical School, London
D J Sheridan

Correspondence to: Professor W A Littler, Department of Cardiovascular Medicine, Queen Elizabeth Hospital, Birmingham B15 2TH.

Accepted for publication 22 November 1994

twice daily dosing with felodipine in its extended release formulation (ER) when given in conjunction with existing treatment of heart failure (any combination of angiotensin converting enzyme (ACE) inhibitor, diuretic, or digoxin).

The study was conducted in 25 centres in the United Kingdom and consisted of a 2–4 week single blind placebo run-in trial to establish baseline measures, followed by randomisation of eligible patients to double blind treatment for a further 12 weeks. The primary end point was the change in exercise tolerance from randomisation (baseline) to the end of the double blind period. Secondary objectives were to assess changes in symptoms and left ventricular ejection fraction. Tolerability was evaluated by adverse event reporting and laboratory screening.

PATIENT POPULATION

Men and women aged 18–75 years were included if they had a left ventricular ejection fraction of equal to or less than 40% and heart failure that was stable during the preceding two months and was caused by ischaemic heart disease, hypertensive heart disease, or dilated cardiomyopathy with or without secondary mitral insufficiency. Patients had subjective and objective evidence of reduced effort tolerance, as demonstrated by New York Heart Association (NYHA) functional class II or III symptoms and an exercise duration (modified Naughton treadmill protocol) of between two and 12 min stopped because of dyspnoea or fatigue despite treatment for at least two months with an ACE inhibitor, diuretic, or digoxin, or any combination of these drugs. Patients were excluded if they had heart failure due to stenotic valve lesions, primary mitral or aortic insufficiency, or non-cardiac causes. Patients were also excluded, at inclusion if they had: exercise limited by claudication; unstable angina pectoris; a myocardial infarction, coronary bypass surgery or angioplasty within the previous three months; significant obstructive pulmonary disease limiting exercise capacity; uncontrolled atrial or ventricular arrhythmia within the previous four weeks; systolic blood pressure < 100 mm Hg; diastolic blood pressure > 114 mm Hg; medication with vasodilators which could not be withdrawn two weeks before entry (use of long acting nitrates was permitted if prescribed for angina and the dose was not changed during the study); severe concomitant disease interfering with assessment; primary liver or renal disorder (creatinine > 200 $\mu\text{mol/l}$); abnormal laboratory findings suggestive of unstable disease; known intolerance to dihydropyridines; child bearing potential; or conditions associated with poor compliance.

The study was conducted in accordance with the standards of the Helsinki declaration of 1975, as revised in 1983, and the protocol was reviewed by the ethics review boards of all participating institutions. All patients gave their written informed consent to participate in the study.

STUDY PROTOCOL

Patients who met the eligibility criteria were entered into the single blind run-in period of 2–4 weeks to establish a stable exercise tolerance. The duration of the run-in period was determined by how long it took to achieve reproducibility of exercise tests. Patients had to have two consecutive exercise tests each of 2–12 min in duration, and stopped because of dyspnoea or leg fatigue, to qualify for randomisation. The two tests could not differ in total exercise time by more than 15%. Patients were randomised on entry to the double blind period to receive either felodipine ER 2.5 mg or placebo administered twice daily. If the patient's condition did not contraindicate an increase in study medication then the dose was increased to 5 mg twice daily after two weeks. The dosage was doubled to a maximum of 10 mg twice daily for patients not achieving an increase of at least 120 s in total exercise time compared with that of the baseline test at six weeks. This dosage was continued to the end of the study but it could be reduced if considered clinically necessary.

Adjustments in concomitant medication were allowed only for those drugs not prescribed for the treatment of heart failure. Changes in all non-study medication prescribed for heart failure required withdrawal of the patient from the study.

The occurrence of any adverse events were recorded at each visit throughout the study. An adverse event was defined as any unfavourable, unintended event temporally associated with the administration of the study drug irrespective of whether or not it was considered to be drug related.

STUDY PROCEDURES

The primary efficacy variable, total exercise test time, was measured using the modified Naughton treadmill protocol in which workload is increased every 2 min as follows: 1 mph/0% grade, 1.5 mph/0% grade, 2 mph/3.5% grade, 2 mph/7% grade, 2 mph/10.5% grade, 3 mph/7% grade, 3 mph/10.5% grade, 3 mph/12.5% grade, 3 mph/15% grade, and 3.4 mph/14% grade. All exercise tests were performed in the morning 2–4 h after medication, the patient having not eaten at least 2 h before the test. Patients were told at the start of the test to exercise until they could do no more—that is, until exhaustion. Patients were asked to rate their leg fatigue and dyspnoea at the end of each stage according to the 10 point Borg rating scale.

Left ventricular ejection fraction was assessed at baseline and at the final visit using either radionuclide scanning or echocardiography. When a choice of method was available radionuclide testing was performed if possible. The same method of testing was used for each patient. Echocardiographic measurements were made from tracing end systolic and end diastolic images from an apical two or four chamber view.

STATISTICAL ANALYSIS

It was calculated that 115 patients per group would be needed to detect at least a 60 s difference in change in exercise duration between treatment groups with an approximate power of 95% and an α error of 5%. This prediction was based on historical data giving a standard deviation of 150 s for the change in exercise duration.

All evaluations were made according to the all patients treated, last value extended principle. As this analysis requires measurements to have been taken after randomisation, however, some patients who withdrew before any measurements were made were not included in the analysis.

The primary efficacy variable was change in exercise test time from randomisation to completion of the double blind treatment period. In analyses of exercise test time, the mean of

the last two tests in the run-in period were compared with, where available, the mean of the two tests performed at weeks 11 and 12 of the study. If only one test was available at weeks 11 or 12 then that test was used. Similarly the latest available value after randomisation before week 11 was used for patients terminating from the study. For all other variables the last value recorded in the run-in was used as the baseline value. The latest available post-randomisation value was used after randomisation.

Time until the end of exercise was analysed by using an analysis of covariance model including the factors treatment, centre, interaction between centre and treatment, and the baseline value as covariates. Blood pressure, heart rate, and body weight were evaluated in the same way. Left ventricular ejection fraction was analysed with a similar model but including method of measurement as an extra factor.

The Wilcoxon test with stratification according to baseline value (NYHA status, S_3 gallop, and orthopnoea) or the general association Cochran-Mantel-Haenszel statistic with baseline value as stratification variable (jugular venous distension, dyspnoea, and rales) were used for NYHA score, signs, and symptoms.

Disposition of patients in the study. Safety assessment includes the patient who had study treatment changed in the double blind period. AEs reported for this patient have been included under the appropriate treatment group. AE, adverse event.

Table 1 Baseline demography and clinical characteristics for 224 patients*

	Felodipine	Placebo	P value for between group tests
No of patients	113	111	
Mean (SD) age (years)	62.0 (7.9)	62.2 (8.6)	> 0.20
Sex (M/F)	90/23 (80/20%)	97/14 (87/13%)	0.119
Mean (SD) weight (kg)	75.9 (12.4)	76.0 (13.2)	> 0.20
Aetiology			
Ischaemic heart disease	87 (77%)	83 (75%)	> 0.20
Dilated cardiomyopathy	23	23	
Other	3	5	
No of patients receiving background ACE treatment	69 (61%)	68 (61%)	> 0.20
No of patients in NYHA class			
IIA	11	12	0.184
IIB	67 (59%)	75 (68%)	
III	33	24	
IV	1	0	
Mean (range) duration of diagnosis (months)	29.1 (31.7) (2-145)	42.4 (46.4) (2-298)	0.022
Mean (SD) left ventricular ejection fraction	25.6 (8.7)	27.6 (7.6)	> 0.20
No of patients assessed	97	98	

*All patients treated, last value extended analyser. ACE, angiotensin converting enzyme; NYHA, New York Heart Association.

Results

Mean (SD) baseline exercise test times increased from 434 (162) s and 480 (157) s for felodipine and placebo groups respectively to 541 (217) s and 591 (218) s at 12 weeks or the last visit. The change in exercise from baseline to last visit was 107 (141) s for patients given felodipine and 112 (128) s for those given placebo ($P > 0.20$). There was also no difference between treatments with respect to all other efficacy variables.

A total of 322 patients were enrolled into this study over a period from April 1990 to December 1991. The figure shows the disposition of these patients. The most common reasons for withdrawal in the run-in were exercise test times above the limit (21%) or beyond the 15% reproducibility limit (17%), or an ejection fraction of greater than 40% (23%).

Of the 252 patients randomised, 19 given felodipine and eight placebo withdrew from the study without a post-randomisation exercise test being performed and were thus not included in the analyses. One other patient was also excluded as the study medication was changed erroneously from placebo to felodipine. Table 1 provides demographic data and baseline characteristics for the 224 patients who were included in the efficacy analyses. Patients in the treatment and placebo groups were well matched except for the duration of heart failure, which was longer in the placebo group ($P = 0.022$).

EFFECT OF FELODIPINE ON EXERCISE TOLERANCE

Some 52% and 24% of patients had baseline

Table 2 Effect of felodipine on exercise time from baseline to last assessment

	Mean (SD) exercise time	
	Felodipine ER (n = 113)	Placebo (n = 111)
Baseline	434 (162)	480 (157)
Last visit	541 (217)	591 (218)
Change (baseline to final assessment)	107 (141)	112 (128)
Mean (SEM) (95% confidence interval) difference in change between treatments	-5.7 (17.7)	-40.6 to 29.3
P	> 0.20	

ER, extended release.

exercise test reproducibility between 0 and 5% and 5 and 10% respectively. Table 2 shows the changes in total exercise test time from baseline to last available value after randomisation. There was no significant difference between treatment groups with exercise test time increasing by nearly two minutes in each group.

A sub-analysis of change in exercise time stratified by baseline NYHA class (II or III) and background treatment (with or without an ACE inhibitor) suggested that patients in NYHA class III who were also taking an ACE inhibitor may have benefited from treatment with felodipine compared with that of the controls. Thus, mean (SD) exercise duration improved 125 (121) s in patients with NYHA class III receiving felodipine (n = 25) compared with 53 (89) s in those with the same functional class given placebo (n = 17).

EFFECT OF FELODIPINE ON BLOOD PRESSURE, HEART RATE, AND LEFT VENTRICULAR EJECTION FRACTION

Table 3 shows the effect of felodipine on haemodynamic variables and heart rate. At the end of treatment, standing systolic and diastolic blood pressures were significantly reduced by felodipine by 5.8 and 5 mm Hg respectively in comparison with those achieved with placebo. The results were similar for supine measurements. There was no significant difference in changes in heart rate compared with those of patients given

placebo. The change from baseline for left ventricular ejection fraction was +2.9 (8.6)% and +1.2 (7.0)% after felodipine and placebo respectively (P = 0.062).

EFFECT OF FELODIPINE ON CLINICAL SIGNS AND SYMPTOMS

There was no significant difference between treatments with respect to NYHA status, S₃ gallop, and orthopnoea.

Mean weight was about 76 kg at baseline in each group and remained unchanged throughout the study. For patients reporting oedema as an adverse event the mean weights at baseline were 75.85 (13.30) kg (n = 31) and 67.77 (17.30) kg (n = six) for the felodipine and placebo groups respectively. The mean changes in weight from baseline to last visit were +0.71 (2.08) kg in the felodipine group and +3.62 (4.89) kg for the placebo group.

ADVERSE EVENTS

Adverse events were reported by the majority of patients (felodipine n = 101, placebo n = 84). There were few deaths in the study (felodipine n = three, placebo n = two).

The most common adverse events reported in the study (table 4) were oedema (23%) in the felodipine group and dizziness or vertigo and dyspnoea (both 11%) in the placebo group. The numbers of patients withdrawn from the study were 29 from the felodipine group and 17 from the placebo group. The most common reasons for withdrawal in the felodipine and placebo groups, respectively, were increased need for non-study treatment because of worsening heart failure (8%) and nausea (3%). Such patients rapidly stabilised and recovered after withdrawal. These patients also seemed to have more severe heart failure at baseline (six of nine had NYHA class III or above) compared with those who remained in the study, otherwise no specific characteristics could be identified.

Discussion

In this multicentre placebo controlled study felodipine had no significant effect on exercise tolerance or symptoms when administered to patients with persistent chronic heart failure

Table 3 Effect of felodipine and placebo on standing systolic and diastolic blood pressures, heart rate, and left ventricular ejection fraction

	Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)	Heart rate (beats/min)	Left ventricular ejection fraction (%)	
	n	Mean (SD)		Mean (SD)	n	Mean (SD)
Baseline						
Felodipine	113	127 (20)	80 (11)	85 (12)	97	26.7 (7.6)
Placebo	111	125 (19)	81 (11)	84 (14)	98	25.8 (8.1)
Last visit						
Felodipine	113	118 (15)	72 (9)	83 (13)	97	29.6 (10.9)
Placebo	111	123 (20)	78 (11)	83 (13)	98	27.0 (9.6)
Change						
Felodipine	113	-9 (17)	-8 (11)	-2 (11)	97	2.9 (8.6)
Placebo	111	-2 (15)	-3 (10)	-1 (14)	98	1.2 (7.0)
Mean (SEM) (95% confidence intervals) difference in change between treatments		-5.8 (1.9) (-9.5 to -2.2)	-5.0 (1.2) (-7.4 to -2.7)	-0.9 (1.4) (-3.8 to 1.9)		2.1 (1.1) (-0.1 to 4.4)
P		0.002	> 0.0001	> 0.20		0.062

Table 4 Most common adverse events reported by more than five patients in any treatment group*

	Felodipine ER (n = 132)	No of patients withdrawn	Placebo (n = 120)	No of patients withdrawn
	Total		Total	
Oedema	31 (23)	8 (6)	6 (5)	3 (3)
Dyspnoea (new or aggravated)	19 (14)	6 (5)	13 (11)	3 (3)
Dizziness/vertigo	10 (8)	0 (0)	13 (11)	2 (2)
Respiratory infection	9 (7)	0 (0)	12 (10)	0 (0)
Angina pectoris (new or aggravated)	13 (10)	2 (2)	8 (7)	2 (2)
Headache	9 (7)	0 (0)	10 (8)	2 (2)
Cardiac failure aggravated—that is, increased non-study treatment	10 (8)	10 (8)	3 (3)	1 (1)
Chest pain	8 (6)	0 (0)	0 (0)	0 (0)
Non-specific pain	5 (4)	2 (2)	7 (6)	0 (0)
Coughing	5 (4)	1 (1)	6 (5)	1 (1)
Nausea	2 (2)	1 (1)	6 (5)	4 (3)

Values in parentheses are percentages. *A single patient may report more than one adverse event and also more than one adverse event as the reason for withdrawal. Adverse events are listed in order of combined frequency of both treatment group. ER, extended release.

and receiving concomitant treatment with any combination of ACE inhibitor, diuretic or digitalis. Felodipine produced significant reductions in supine and standing blood pressure without adverse postural hypotensive effects and with no significant effect on heart rate. More patients receiving felodipine withdrew from the study due to increased need for non-study heart failure treatment, however, than those receiving placebo.

The present results differ from the findings of Dunselman *et al*⁸ and Timmis *et al*^{6,10} in which exercise capacity increased with felodipine, although symptoms improved only in the former study. The present findings, however, are similar to the results from the study by Tan *et al*⁷ in which despite an increase in cardiac index at rest and after exercise on felodipine no improvement in exercise tolerance or symptoms was observed.

The absence of a significant improvement in the present study may reflect (a) lack of efficacy in the group of patients selected, or (b) confounding aspects of the study population or study design. In this context it is worth noting that the majority of patients that were of NYHA class IIB (64%) were without symptoms and had good baseline exercise tolerance (481 (135) s in the felodipine group and 494 (152) s in the placebo group). The possibility exists, therefore, that heart failure in this group was not severe enough to benefit from further treatment. A remarkable feature of this study was the extent of the exercise test placebo response. This is a recognised feature of most clinical trials in heart failure, but was more marked in the present study. It remains unclear whether this is a result of real improvement in the patient's clinical condition associated with close medical supervision or of better performance due to familiarity and confidence in undertaking the exercise tests. Whatever the reason for this, the extent of the placebo response may have limited the sensitivity of the present study.

The protocol design in the present study attempted to minimise within subject variability by recruiting only those patients with

exercise tests with a variation of less than 15%. This may have inadvertently introduced a bias in the baseline assessments. The remarkably high proportion of patients (52%) with consecutive exercise test durations within 5% during the baseline assessments indicate a constraint bias, which may have limited the sensitivity of the study.

While the present study showed no evidence of benefit in the patients selected, it is possible that other patient groups might benefit. This hypothesis finds some support from a subgroup analysis of the present results which shows that patients with NYHA class III heart failure who were already receiving an ACE inhibitor had greater improvement in exercise capacity with felodipine. The use of calcium antagonists as a class in patients with heart failure has produced mixed results. Early studies with "first generation" calcium antagonists have shown that treatment with those drugs is not appropriate for patients with heart failure presumably because of their negative inotropic effects and their activation of endogenous neurohormone systems.¹¹ A more recent study with amlodipine demonstrated good improvements in exercise and symptoms in patients with mild to moderate heart failure.¹² Like felodipine, amlodipine also exerts favourable neurohormonal effects in patients with heart failure.^{12,13} The ongoing V-HeFT III trial should further elucidate the role of felodipine in heart failure.¹¹

The most common adverse event for patients given felodipine was peripheral oedema (23%) and it was also the second most common adverse event cited as a reason for withdrawal from felodipine treatment (6%). This incidence is consistent with findings in hypertensive patients treated at these doses¹⁴ and as body weight in the felodipine group was essentially stable throughout the study period, it is most likely that the oedema observed was caused by vasodilatory action of the drug rather than fluid retention arising from worsening heart failure.

Ten patients on felodipine and one on placebo were required by the protocol to be withdrawn from the study because of aggravated symptoms of heart failure which required increases in non-study medication. These patients were rapidly stabilised after withdrawal. In many previously published studies¹⁵ such patients would not have been withdrawn but their non-trial medication would have been altered appropriately. The reason for having the present study design was to prevent changes in non-study medication confounding the interpretation of the main efficacy variable—that is, exercise test time.

In conclusion, the present study failed to demonstrate significant benefit in exercise duration or symptoms in patients with mild heart failure. There were few deaths in either group. More patients in the felodipine group were withdrawn because they needed increased non-study medication as a result of worsening heart failure. The study has identified previously unreported methodological

problems which may explain the high placebo response, highlighting the need for careful conduct of exercise tests as a measure of exercise capacity in patients with heart failure.

This study was supported by a grant from Astra Hässle AB, S 431 83 Mölndal, Sweden.

Study organisation steering committee: Professor W A Littler and Professor D J Sheridan; and Safety monitor: Professor L Wilhelmsen, Department of Medicine, Östra Hospital Gothenberg, Sweden.

Participating centres, principal investigators and registrars

W A Littler, M Salih, Queen Elizabeth Hospital, Birmingham; D J Sheridan, D O'Gorman, St Mary's Hospital Medical School, London; P C Adams, C Fraser, Royal Victoria Infirmary, Newcastle Upon Tyne; T D R Shaw, Western General Hospital, Edinburgh; J F J Bayliss, R Chamberlain-Webber, Hemel Hempstead General Hospital, Hemel Hempstead; R A Blackwood, P Robinson, Wexham Park Hospital, Slough; J C Cowan, D Coulshed, The General Infirmary, Leeds; R Greenbaum, A Cheng, Edgware General Hospital, Edgware; R J C Hall, University Hospital of Wales, Cardiff; M W Millar-Craig, S Vijan, Derbyshire Royal Infirmary, Derby; R E Nagle, M Payne, Selly Oak Hospital, Birmingham; D P Nicholls, Royal Victoria Hospital, Belfast; A F J Page, Norfolk and Norwich Hospital, Norwich; B L Pentecost, M Lynch, Birmingham General Hospital, Birmingham; J E F Pohl, P Verma, Leicester General Hospital, Leicester; M V J Raj, S Davies, Good Hope District Hospital, Sutton Coldfield; C J Reid, St Richard's Hospital, Chichester; P W L Siklos, West Suffolk Hospital, Bury St Edmunds; B Silke, Queen's University, Belfast; L B Tan, University of Leeds and Killingbeck Hospital, Leeds; D Waller, V Challenor, Southampton General Hospital, Southampton; R D Watson, I Ikram, Dudley Road Hospital, Birmingham; N H Stentiford, M M Kubik, Russells Hall Hospital, Dudley; R Sutton, Westminster Hospital, London; and W Ginks, S Ginks, The General Hospital, Jersey.

- 1 Ljung B, Nordlander M. Pharmacodynamic properties of felodipine. *Drugs* 1987;34(suppl 3):7-15.
- 2 Culling W, Rutledge MS, Sheridan DJ. Acute haemodynamic effects of felodipine during beta blockade in

- patients with coronary artery disease. *Br Heart J* 1984;52(4):431-4.
- 3 Amlie JP, Endresen K, Sire S. The effect of felodipine on the sinus and atrioventricular node in patients with ischaemic heart disease. *J Cardiovasc Pharmacol* 1990;15(suppl 4):S25.
- 4 Emanuelsson H, Hjalmarson Å, Holmberg S, Waagstein F. Acute haemodynamic effects of felodipine in congestive heart failure. *Eur J Clin Pharmacol* 1985;28:489-93.
- 5 Tweddel AC, Martin W, McGhie AI, Hutton I. Sustained haemodynamic effects of felodipine in patients with chronic cardiac failure. *Br J Clin Pharmacol* 1988;25:689-94.
- 6 Timmis AD, Smyth P, Kenny JF, Campbell S, Jewitt DE. Effects of vasodilator treatment with felodipine on haemodynamic responses to treadmill exercise in congestive heart failure. *Br Heart J* 1984;52:314-20.
- 7 Tan LB, Murray RG, Larsson Y, Littler WA. Felodipine in patients with chronic heart failure: discrepant haemodynamic and clinical effects. *Br Heart J* 1987;58:122-8.
- 8 Dunselman PHMJ, Kuntze CEE, van Bruggen A, Hamer H, Wesseling H, Lie KI. Felodipine in heart failure: double blind placebo controlled study in 23 patients. *Circulation* 1987;76(suppl 4):IV-179.
- 9 Kassis E, Amtorp O, Waldorff S, Fritz-Hansen P. Efficacy of felodipine in chronic congestive heart failure: a placebo controlled haemodynamic study at rest and during exercise and orthostatic stress. *Br Heart J* 1987;58:505-11.
- 10 Timmis AD, Campbell S, Monaghan MJ, Walker L, Hewitt DE. Acute haemodynamic and metabolic effects of felodipine in congestive heart failure. *Br Heart J* 1984;51:445-51.
- 11 Packer M. Calcium antagonists for congestive heart failure: evolving concepts in bridge building. *Cardiovascular Drugs and Therapy* 1993;7:95-6.
- 12 Packer M, Nicod P, Khandheria BR, et al. Randomised, multicentre, double-blind, placebo-controlled evaluation of amlodipine in patients with mild-to-moderate heart failure [abstract]. *J Am Coll Cardiol* 1991;17:247.
- 13 Kassis E, Amtorp O. Long-term clinical, hemodynamic, angiographic, and neurohumoral responses to vasodilation with felodipine in patients with chronic congestive heart failure. *J Cardiovasc Pharmacol* 1990;15:347-52.
- 14 Wester A, Lorimer AR, Westberg B. Felodipine extended release in mild to moderate hypertension. *Curr Med Res Opin* 1991;12:275-81.
- 15 Packer M, Narahara KA, Elkayam U, et al. Double-blind, placebo-controlled study of the efficacy of flosequinan in patients with chronic heart failure. *J Am Coll Cardiol* 1993;22:65-72.