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European Journal of Heart Failure xx (2006) xxx–xxx
The European Journal of Heart Failure
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The development of heart failure in patients with stable angina pectoris ☆

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On behalf of the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) investigators

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Received 7 April 2006; received in revised form 1 August 2006; accepted 5 September 2006

Abstract

Background: To describe the clinical characteristics of patients with stable angina pectoris who develop heart failure and the events preceding its onset.
Methods and results: Of 7665 patients with stable angina in the ACTION trial, which compared long-acting nifedipine to placebo, 207 (2.7%) developed heart failure (HF) during a mean follow-up of 4.9 years. Those who developed HF were significantly ($P<0.05$) older, more often had diabetes, had a more extensive history of cardiovascular disease, lower ejection fractions, a higher serum creatinine and glucose, a lower haemoglobin, and were more often on blood pressure lowering drugs. A cardiac event or an intervention ($n=155$), a significant non-cardiac infection ($n=19$) or poor control of hypertension ($n=12$) preceded the development of HF in 186/207 cases (90%). There was no obvious precipitating factor in the remaining 21 patients (10%). Myocardial infarction increased the risk of the development of new HF within one week more than 100-fold. Nifedipine reduced the incidence of HF by 29% ($P=0.015$).
Conclusions: The development of heart failure is uncommon in patients with stable angina, and even less so in the absence of an obvious precipitating factor.

Keywords: Angina pectoris; Heart failure; Randomised controlled trial; Calcium channel blockers

1. Introduction

Coronary heart disease commonly presents as stable angina, an acute coronary syndrome, sudden death, or sometimes as an arrhythmia. Heart failure is an unusual initial presentation, but may develop subsequently. Nevertheless, coronary heart disease is the leading cause of heart failure in the general population [1,2]. The development of heart failure in patients with hypertension or with asymptomatic coronary heart disease [3–9], or after an acute coronary syndrome or myocardial infarction [10–12] has been well-documented. There is sparse information available on the development of heart failure in patients with stable angina. An unsubstantiated notion is that some patients may develop heart failure over a period of time not following an overt clinical event, but because the function of the left ventricle becomes impaired as a result of intermittent, but repetitive myocardial ischaemia. In a small series of patients, all with stable angina, followed over a 5-year period, a significant reduction in left ventricular ejection fraction was demonstrated, but this change was not expressed as any change in clinical state [13].

☆ The ACTION trial was supported by Bayer Healthcare, AG, Wuppertal, Germany.
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doi:10.1016/j.ejheart.2006.09.002

Table 1
Clinical features at trial entry of patients with and without heart failure during follow-up

	Heart failure during follow-up		
	Yes (n = 207)	No (n = 7458)	
Age (years)	68.8 (8.4)	63.3 (9.3)	<0.001
Male gender	165 (80%)	5919 (79%)	0.9
Prior history			
Heart failure	19 (9.2%)	151 (2.0%)	<0.001
Atrial fibrillation	20 (10%)	293 (3.9%)	<0.001
Myocardial infarction	115 (56%)	3783 (51%)	0.2
Coronary angiogram performed	146 (71%)	5218 (70%)	0.9
1 vessel disease (% of CAG performed)	32 (22%)	1783 (34%)	0.002
≥ 2 vessel disease (% of CAG performed)	111 (76%)	3230 (62%)	<0.001
Coronary revascularisation	100 (48%)	3329 (45%)	0.3
Peripheral vascular disease[a]	43 (21%)	635 (9%)	<0.001
History of peripheral oedema	8 (3.9%)	242 (3.2%)	0.6
Current status			
Regular, frequent or daily anginal attacks	71 (34%)	2133 (29%)	0.07
Any diabetes mellitus	66 (32%)	1047 (14%)	<0.001
Diabetes mellitus treated with insulin	18 (8.7%)	165 (2.2%)	<0.001
Pulse rate (bpm)	66 (10)	64 (10)	0.006
Irregular pulse rate	13 (6.3%)	158 (2.1%)	<0.001
LV EF, core lab (%)	45 (7.2)	48 (6.4)	<0.001
LV EF, local value (%)	55 (8.2)	57 (9.6)	0.3
Haemoglobin <12.5 g/dl (men) or <11.5 g/dl (women)	17 (8.3%)	203 (2.8%)	<0.001
Glucose (mg/dl)	130 (64)	110 (42)	<0.001
Creatinine (mg/dl)	1.17 (0.28)	1.09 (0.21)	<0.001
Creatinine >1.5 mg/dl (men) or >1.4 mg/dl (women)	23 (11%)	260 (3.5%)	<0.001
Risk factors			
Current smoker	32 (15%)	1324 (18%)	0.4
Total cholesterol ≥5.0 mmol/l	121 (58%)	4694 (63%)	0.2
Body mass index ≥ 30.0 kg/m^2	62 (30%)	1682 (23%)	0.01
History of hypertension treated with drugs	108 (52%)	3090 (41%)	0.002
Blood pressure 140/90 mm Hg or higher	123 (59%)	3854 (52%)	0.03
Concomitant treatment			
ACE inhibitor or ARB	59 (29%)	1680 (23%)	0.04
Diuretic	44 (21%)	839 (11%)	<0.001
ASA or anti-platelet	174 (84%)	6602 (89%)	0.048
Vitamin K antagonist	17 (8.2%)	288 (3.9%)	0.002
Beta-blocker	164 (79%)	5935 (80%)	0.9
Organic nitrate	171 (83%)	5748 (77%)	0.06
Lipid-lowering	132 (64%)	5066 (68%)	0.2

Data are number of subjects (%) or mean (SD).
CAG, coronary angiogram; LV EF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; ASA, acetyl salicylic acid.
[a] Any baseline condition coded as ICD9 code 443.9.

In the ACTION trial [14–16] all clinical events were carefully documented in a large number of patients (n=7665) with stable angina over an average period of 4.9 years. The trial afforded a unique opportunity to compare the baseline characteristics and the precipitating factors (clinical events) in those patients who did, and those who did not develop heart failure, a prospectively defined end-point of the trial. In the trial patients who received long-acting nifedipine GITS (gastro-intestinal therapeutic system) were less likely to develop heart failure than those receiving placebo [15]. The precipitating factors in each arm of the trial were compared in an attempt to explain this reduction.

2. Methods

2.1. Design of ACTION

The design, methods and main results of the ACTION trial have been published previously [14,15]. Briefly, 7665 patients aged 35 years or older with stable angina requiring treatment were randomly assigned to treatment with either nifedipine (n=3825) or matching placebo (n=3840) in addition to their existing medication. Angina was likely to be caused by coronary heart disease because patients were also required to have either angiographically documented coronary artery disease (CAD), a past history of documented myocardial infarction, or a positive electrocardiogram on exercise or a positive exercise thallium myocardial perfusion scan. The left ventricular ejection fraction, usually measured by echocardiography, had to be at least 40%. Patients with a past history of heart failure could participate, but patients with clinically significant symptoms or signs of heart failure on assessment for entry to the study were excluded, as were patients who were on a daily dose of frusemide above 20 mg (or equivalent other diuretic), or were on combination therapy with an angiotensin-converting enzyme (ACE) inhibitor and a diuretic for heart failure. The details of the selection criteria and definitions have been described elsewhere [14].

The starting dose of nifedipine GITS or matching placebo was 30 mg once daily, increasing to 60 mg once daily within

Table 2
Cox proportional hazard model for outcome time to heart failure

	Hazard ratio		
	Z value	(95% CI)	P
Age per 10 years over 60	7.7	2.3 (1.8–2.8)	<0.001
EF per 5% decrease below 50	6.4	1.5 (1.3–1.7)	<0.001
ID diabetes	5.7	4.4 (2.6–7.3)	<0.001
Non-ID diabetes	4.3	2.1 (1.5–2.9)	<0.001
History of heart failure	4.0	2.7 (1.7–4.4)	<0.001
Peripheral vascular disease[a]	3.7	1.9 (1.4–2.7)	<0.001
Body mass index per kg/m^2	3.6	1.06 (1.03–1.10)	<0.001
Irregular pulse	2.4	2.0 (1.1–3.6)	0.01
Anaemia	2.6	2.0 (1.2–3.4)	0.008
Creatinine >1.5 mg/dl for men or >1.4 mg/dl for women	2.1	1.6 (1.0–2.6)	0.04
Allocated nifedipine	-2.1	0.74 (0.56–0.98)	0.03

CI, confidence interval; EF, ejection fraction; ID, insulin dependent.
[a] Any baseline condition coded as ICD9 code 443.9.

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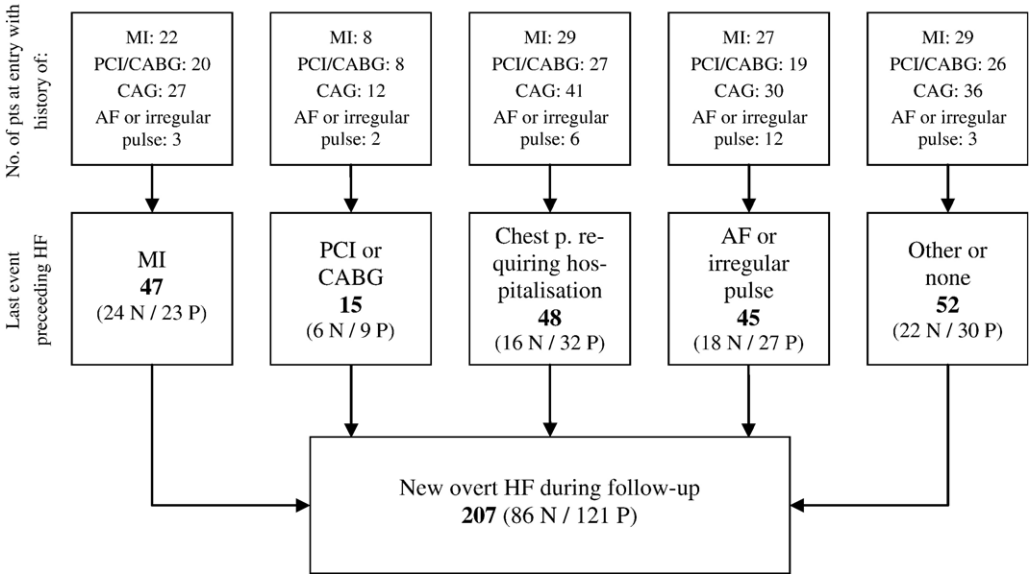

Fig. 1. Last clinical event during the trial before the onset of new heart failure and previous history at entry. HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CAG, coronary angiogram; AF, atrial fibrillation; p., pain; N, nifedipine; P, placebo.

six weeks. Physicians were encouraged to optimise risk factor modification and to treat symptomatic angina with appropriate medications. After baseline assessments and treatment allocation, patients were seen in the out-patient clinic at two weeks, six weeks and six months after randomisation; and from then onwards every six months. Between visits, patients were contacted by telephone.

2.2. Ascertainment of the development of heart failure

Data concerning events which occurred during follow-up were reported by investigators as either serious or non-serious adverse events. Serious adverse event (SAE) reports were grouped into clinical episodes. When the reports for any given episode suggested the occurrence of a major cardiovascular event, investigators were asked, irrespective of their own diagnosis, to provide further clinical information including the results of diagnostic tests performed. Based on the information received, each episode was classified by the Critical Events Committee (CEC) based on preset criteria. The CEC did not have access to the study medication code.

Patients were classified by the CEC as developing heart failure if they were hospitalised and met the preset criteria for the diagnosis. Patients needed to have symptoms compatible with the development of heart failure, and drug treatment for heart failure needed to have been introduced or changed. Patients were required to have physical signs compatible with the diagnosis of heart failure, or investigations reflecting abnormal left ventricular function. The diagnosis of heart failure was excluded if there was an alternative explanation for the patient's symptoms, or the results of left ventricular function tests were normal.

2.3. Selection of controls

For each case of new overt heart failure, two ACTION patients from the same centre were taken at random as potential controls who had not developed heart failure at the same point in time as the case. If the patient chosen as control had developed heart failure within the same time interval between randomisation and onset of heart failure as the case, or had already been chosen as control before, another ACTION patient from the same centre was selected at random. If less than two controls from the same centre could be determined in this manner, controls from the same country were selected. It was recognised that this procedure implied that a patient selected as control could become a case later on. Such patients were included in the analysis both as case and as control.

2.4. Information evaluated for cases and controls

For each case, all information collected during the course of the study prior to the development of heart failure was evaluated. The available information for each control was evaluated for the same duration of follow-up as for the case concerned. As potential precipitating factors for the development of heart failure, the following cardiac clinical events or interventions were considered: myocardial infarction, coronary revascularisation (coronary artery bypass surgery or percutaneous coronary intervention), chest pain requiring hospitalisation, and atrial fibrillation or an irregular pulse. In addition, the occurrence of cerebro-vascular accident, peripheral oedema, coronary angiography, peripheral arterial revascularisation, evidence of poor control of hypertension (defined either as hypertension reported as an adverse event or a blood pressure equal to or above 160/100 mm Hg measured at any

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Table 3
Clinical features and prior history of the cases developing heart failure compared with duration of follow-up matched controls without heart failure

	Cases of new HF (n = 207)	Matched controls (n = 414)[a]	Odds ratio	95% confidence interval	P
Mean age (SD), years	69 (8.4)	63 (9.4)	–	–	<0.001
Male	165 (80%)	331 (80%)	0.98	(0.63–1.6)	1.0
History of heart failure	19 (9.2%)	10 (2.4%)	4.4	(1.8–12)	<0.001
Diabetes	76 (37%)	88 (21%)	2.4	(1.6–3.7)	<0.001
Previous MI[b]					
Two or more	51 (25%)	40 (9.7%)	4.4	(2.5–∞)	<0.001[c]
One	94 (45%)	174 (42%)	1.7	(1.1–∞)	
None	62 (30%)	200 (48%)	1.0	(Ref. cat.)	
Last MI[b]					
Within 0–7 days ago	40 (19%)	0 (0.0%)	127	(23–∞)	<0.001[c]
Within 8–60 days ago	10 (4.8%)	0 (0.0%)	31	(5.0–∞)	
More than 60 days ago	95 (46%)	214 (52%)	1.3	(0.86–1.9)	
None	62 (30%)	200 (48%)	1.0	(Ref. cat.)	
Chest pain requiring hospitalisation					
Within 0–7 days ago	32 (15%)	1 (0.2%)	70	(12–2870)	<0.001[c]
Within 8–60 days ago	9 (4.3%)	6 (1.4%)	3.4	(1.1–12)	
More than 60 days ago	38 (18%)	68 (16%)	1.6	(0.95–2.6)	
None	128 (62%)	339 (82%)	1.0	(Ref. cat.)	
Episode of atrial fibrillation or irregular pulse[b]					
Within 0–7 days ago	26 (13%)	0 (0.0%)	84	(15–∞)	<0.001[c]
Within 8–60 days ago	8 (3.9%)	7 (1.7%)	3.5	(1.0–14)	
More than 60 days ago	39 (19%)	42 (10%)	2.4	(1.4–4.2)	
None	134 (65%)	365 (88%)	1.0	(Ref. cat.)	
Stroke, TIA or peripheral revascularisation[b]					
Within 0–7 days ago	1 (0.5%)	2 (0.5%)	1.0	(0.02–19)	<0.001[c]
Within 8–60 days ago	4 (1.9%)	1 (0.2%)	11	(1.1–565)	
More than 60 days ago	44 (21%)	34 (8.2%)	3.2	(1.9–5.6)	
None	158 (76%)	377 (91%)	1.0	(Ref. cat.)	
Peripheral oedema[b]					
Within 0–7 days ago	11 (5.3%)	0 (0.0%)	32	(5.2–∞)	<0.001[c]
Within 8–60 days ago	5 (2.4%)	5 (1.2%)	2.1	(0.48–9.2)	
More than 60 days ago	49 (24%)	89 (21%)	1.2	(0.80–1.9)	
None	142 (69%)	320 (77%)	1.0	(Ref. cat.)	
Coronary bypass surgery[b]					
Within 0–7 days ago	1 (0.5%)	0 (0.0%)	2.0	(0.05–∞)	<0.001[c]
Within 8–60 days ago	8 (3.9%)	0 (0.0%)	25	(3.9–∞)	
More than 60 days ago	77 (37%)	124 (30%)	1.5	(1.0–2.2)	
None	121 (58%)	290 (70%)	1.0	(Ref. cat.)	
Percutaneous coronary intervention[b]					
Within 0–7 days ago	7 (3.4%)	1 (0.2%)	13	(1.6–581)	<0.001[c]
Within 8–60 days ago	2 (1.0%)	1 (0.2%)	4.0	(0.21–236)	
More than 60 days ago	45 (22%)	110 (27%)	0.79	(0.50–1.2)	
None	153 (74%)	302 (73%)	1.0	(Ref. cat.)	
Coronary angiography[b]					
Within 0–7 days ago	5 (2.4%)	2 (0.5%)	4.4	(0.68–47)	<0.001[c]
Within 8–60 days ago	7 (3.4%)	9 (2.2%)	1.5	(0.43–4.8)	
More than 60 days ago	147 (71%)	313 (76%)	0.85	(0.53–1.4)	
None	48 (23%)	90 (22%)	1.0	(Ref. cat.)	
Evidence of poor control of hypertension					
Within 0–7 days ago	6 (2.9%)	2 (0.5%)	7.3	(1.28–76)	<0.001[c]
Within 8–60 days ago	10 (4.8%)	23 (5.6%)	1.1	(0.40–3)	
More than 60 days ago	76 (37%)	123 (30%)	1.5	(1.02–2)	
None	115 (56%)	266 (64%)	1.0	(Ref. cat.)	
Infection					
Within 0–7 days ago	16 (7.7%)	3 (0.7%)	11.1	(3.13–60)	<0.001[c]
Within 8–60 days ago	11 (5.3%)	12 (2.9%)	2.1	(0.79–6)	
More than 60 days ago	57 (28%)	125 (30%)	1.1	(0.67–2)	
None	123 (59%)	274 (66%)	1.0	(Ref. cat.)	

Data are number of patients (%) with each event. If a patient experienced more than one event of a particular kind, only the last event is tabulated according to its time of occurrence.
HF, heart failure; MI, myocardial infarction; TIA, transient ischaemic attack.
[a] Matched for time duration of follow-up until the onset of heart failure for cases and for centre.
[b] Either reported as a previous diagnosis or as an event at entry into the trial, or as a (serious) adverse event during follow-up.
[c] Global test for association (exact conditional logistic regression).

ACTION follow-up visit), significant non-cardiac infection and the start or discontinuation of cardiovascular medications within one week prior to the development of heart failure were evaluated as potential precipitating factors. A comparison was made between cases and controls of the last blood pressure, heart rate, electrocardiogram and laboratory data either at baseline or at the last follow-up visit before the development of heart failure.

Except for chest pain requiring hospitalisation (which included refractory angina [14,15]), poor control of hypertension and any infection (which were only considered if they occurred during follow-up), no distinction was made between events that were reported (with date of past occurrence, if applicable) in the ACTION baseline case report form, and those that were reported during follow-up. The diagnoses of acute myocardial infarction, debilitating stroke, and refractory

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Table 4
Mean (SD) last observations prior to the onset of heart failure for cases which developed heart failure and for duration of follow-up matched controls without heart failure

	Cases of new HF (n = 207)	Matched controls[a] (n = 414)	P
Vital signs			
Systolic blood pressure (mm Hg)	139 (23)	135 (18)	0.02
Diastolic blood pressure: mean (mm Hg)	77 (10)	77 (9)	1.0
Pulse rate (bpm)	70 (14)	66 (10)	<0.001
Laboratory tests			
Glucose (mg/dl)	142 (76)	115 (47)	<0.001
Creatinine, men (mg/dl)	1.25 (0.4)	1.16 (0.5)	0.03
Creatinine, women (mg/dl)	1.03 (0.3)	0.98 (0.3)	0.4
Haemoglobin, men (mg/dl)	14.2 (1.5)	14.7 (1.1)	<0.001
Haemoglobin, women (mg/dl)	13.3 (1.3)	13.1 (1.2)	0.4

HF, heart failure.
[a] Matched for time duration of follow-up until the onset of heart failure for cases and for centre.

angina during follow-up were determined by the CEC using preset criteria [14,15].

2.5. Statistical analysis

All analyses were performed on an 'intention-to-treat' basis. A comparison of the baseline characteristics of patients who developed heart failure during follow-up with those who did not was made using chi-square tests for comparing categorical and two-sample t-tests for continuous variables. Multivariate Cox regression analysis with forward stepwise variable selection was used to determine which baseline characteristics were conditionally independent predictors of heart failure, retaining variables with a regression coefficient significant at the level of $P=0.05$.

To assess the impact of potential precipitating factors on the risk of heart failure, a comparison was made between those that developed heart failure and matched controls with the same duration of follow-up. Odds ratios for categorical variables were calculated by exact conditional logistic regression. To express odds ratios for clinical events preceding heart failure and their number or timing, "no event" was used as the reference category. For users of a drug during the week before heart failure occurred, non-users during the same week were used as the reference category. For patients in whom a drug was stopped during the week before heart failure, continuous users during the same week were used as the reference category. Similarly, for patients in whom a drug was started during the week before heart failure, non-users were used as reference category. The analyses of drug use were adjusted for the occurrence of potential clinical precipitating factors. For continuous variables, cases and controls were compared by standard t-tests.

Hazard ratios with 95% confidence intervals comparing the occurrence of heart failure among patients assigned nifedipine with those assigned placebo were obtained using Cox proportional hazards models with treatment allocation as the only covariate. Interaction tests for subgroup analyses were performed by Cox proportional hazards models.

3. Results

3.1. Proportion of patients developing heart failure

Of the 7665 patients who entered the study, 207 developed at least one episode of heart failure (2.7%) during a mean follow-up period until death or the end of the study of 4.9 years. The incidence rate was 0.55 per 100 patient years.

3.2. Comparison of baseline characteristics

In univariate comparisons, patients who developed heart failure (Table 1) were older at entry into the trial, more often had diabetes or a history of hypertension treated with drugs, and more often had a history of heart failure, atrial fibrillation, two or more vessel coronary disease, and peripheral vascular disease. Other significant baseline predictors of heart failure were an irregular pulse rate, a lower left ventricular ejection fraction or haemoglobin, a higher serum glucose or creatinine concentration, and a body mass index of at least 30 kg/m^2. Patients taking ACE inhibitors and diuretics in order to lower blood pressure, (patients given these drugs for heart failure were excluded from entry into the trial), were more likely to develop heart failure. By contrast, male gender, smoking, elevated cholesterol levels, a previous history of myocardial infarction, and previous revascularisation procedures were not associated with the development of heart failure.

As shown in Table 2, the strongest conditionally independent associations determined by Cox regression analysis between baseline characteristics and the development of heart failure during follow-up were for age, lower ejection fraction, a previous history of heart failure, anaemia and diabetes. Allocation to nifedipine was a significant

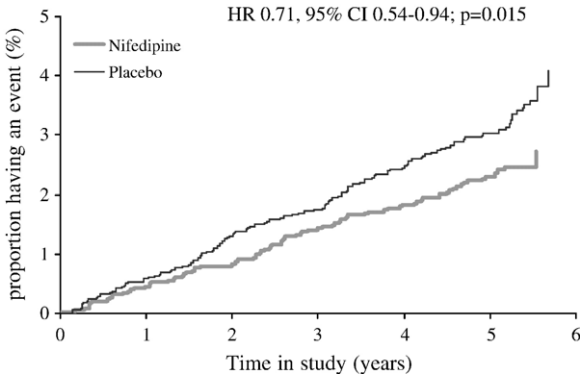

Fig. 2. Time to first occurrence of new heart failure.

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	Number of patients Nif / Pla	Number of patients with event (rate)* Nifedipine / Placebo		Hazard ratio†	$P^{\ddagger}$
All randomized	3840 / 3825	86 (0.46)	121 (0.65)		
Beta-blocker					
No	792 / 774	11 (0.29)	32 (0.86)		0.015
Yes	3033 / 3066	75 (0.50)	89 (0.59)		
Organic nitrate as required					
No	1668 / 1665	27 (0.33)	57 (0.71)		0.018
Yes	2157 / 2175	59 (0.56)	64 (0.60)		
Diuretic					
No	3390 / 3392	62 (0.37)	101 (0.61)		0.036
Yes	435 / 448	24 (1.17)	20 (0.93)		
ACE-I or ARB					
No	2966 / 2960	69 (0.47)	79 (0.54)		0.020
Yes	859 / 880	17 (0.41)	42 (1.01)		
Regular, frequent or daily anginal attacks					
No	2719 / 2742	50 (0.38)	86 (0.64)		0.060
Yes	1106 / 1098	36 (0.66)	35 (0.65)		
Ejection fraction < 45%					
No	2749 / 2744	40 (0.30)	71 (0.53)		0.078
Yes	1056 / 1074	46 (0.90)	50 (0.97)		
Hyponatraemia					
No	3378 / 3452	68 (0.41)	109 (0.65)		0.060
Yes	390 / 348	17 (0.92)	11 (0.66)		

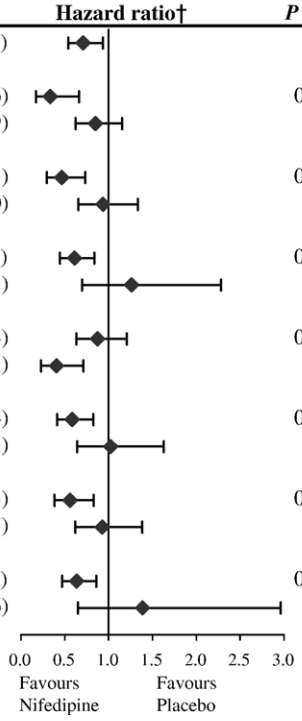

Fig. 3. Effect of nifedipine on new heart failure in subgroups. Nif, nifedipine, Pla, placebo; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker. * Rates as number of patients with event per 100 patient years at risk. †Comparison of nifedipine with placebo, with 95% confidence interval. ‡Test for interaction.

conditionally independent predictor of a reduced incidence of heart failure (HR 0.74, $P=0.03$).

3.3. Clinical events, physical signs and biochemical findings which might be associated with the development of heart failure

The last cardiac event or intervention during the trial that preceded the onset of heart failure is shown in Fig. 1. Only 52 patients (22 nifedipine, 30 placebo) - 25% of those who developed heart failure, or 0.7% of all those who entered the study - did not sustain any of the precipitating cardiac events or interventions shown. Of these 52, 19 (8 nifedipine, 11 placebo) had a significant infection and 12 (3 nifedipine, 9 placebo) had evidence of poor control of hypertension as the last event preceding the onset of heart failure. However, only five patients had infection and only one patient had poor control of hypertension as the last event in the week preceding the development of heart failure.

Potential precipitating clinical events are compared between the 207 cases of heart failure and 414 matched controls in Table 3. In total 9 patients included as controls developed heart failure subsequently. These were included in the analysis both as case and as control. Myocardial infarction, chest pain requiring hospitalisation (which included refractory angina as diagnosed by the CEC) and atrial fibrillation or irregular pulse during the last week before onset were frequent among cases of heart failure, but did not occur among controls (with the exception of one patient with chest pain requiring hospitalisation). Myocardial infarction within one week increased the risk of new overt heart failure more than 100-fold. All other events analysed increased the risk also, but to a lesser extent. Poor control of hypertension and infection within the same time period increased the risk 7.3-fold and 11-fold respectively.

Data on the last follow-up observations obtained during the course of the trial prior to the onset of heart failure are shown in Table 4. The last measurement of vital signs and electrocardiogram preceded the onset of heart failure on the average by 3.7 months and the last laboratory tests by 11 months. A higher heart rate, higher blood sugar and, in men, a low haemoglobin were more common in those who developed heart failure than those who did not ($P<0.001$, Table 4). Systolic blood pressure ($P=0.02$), but not diastolic blood pressure, was higher. There were no statistically significant ($P<0.05$) differences for alanine and aspartate aminotransferases, alkaline phosphatase, bilirubin, total cholesterol, creatine kinase, haematocrit, uric acid and white blood cell count. The mean potassium level was the same in those who developed heart failure as in those who did not (4.4 mmol/l, SD 0.45) while there was a small but significant difference for sodium (140 mmol/l in those who developed heart failure, 141 mmol/l in those who did not, SD 2.8, $P=0.01$).

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3.4. Changes in drug treatment preceding heart failure

Changes of drug treatment during the last week were too infrequent both among cases and controls for reliable statistical evaluation, although stopping a calcium channel blocker (which included double-blind nifedipine), and starting ACE inhibitors or angiotensin-receptor blockers, or diuretics increased the risk of heart failure.

3.5. Comparison of those patients treated with nifedipine and placebo

Fewer patients developing heart failure had been assigned to nifedipine ($n=86$) than placebo ($n=121$, HR 0.71, 95% CI 0.54-0.94; $P=0.015$, Fig. 2). Subgroup analyses are shown in Fig. 3. Nifedipine appeared neutral in preventing heart failure in patients who were also taking a beta-blocker, an organic nitrate, or a diuretic while nifedipine was significantly more effective in those prescribed an ACE inhibitor or an angiotensin-receptor blocker. There was a trend for nifedipine to be more effective than placebo in preventing heart failure patients with less frequent angina, higher ejection fractions and higher plasma sodium concentration at baseline. In the nifedipine group 1405/3825 (37%) of patients developed peripheral oedema in the absence of heart failure compared to 517/3840 (13%) in the placebo group.

4. Discussion

The ACTION trial provided a unique opportunity to examine the natural history of patients who have stable angina pectoris focussing on the onset of new heart failure. The number of patients studied was larger ($n=7665$) and the duration of the follow-up (mean 4.9 years) was longer than in most previous studies [13,17]. There are several previous clinical trials which have allowed an insight into the natural history of patients with stable coronary artery disease [6–9], but few which selectively included only patients with the clinical syndrome of stable angina due to coronary artery disease [17–19]. These trials have been of shorter duration with fewer patients.

4.1. Incidence of heart failure

The development of heart failure is an unusual event in the course of the natural history of stable angina. Heart failure occurred in only 2.7% of patients over a mean period of 4.9 years in this study (incidence rate 0.55 per 100 patient years). Other cardiovascular events are equally uncommon in patients with stable angina. The incidence of death is 1.5 per 100 patient years at risk, and the incidence of any cardiovascular event, including cardiovascular death, myocardial infarction, refractory angina, new heart failure, debilitating stroke or peripheral revascularisation, is 4.1 per 100 patient years [15]. These low rates of cardiovascular events suggest that patients who have a clinical diagnosis of stable angina due to coronary artery disease can be reassured that their prognosis is good [15,17,18]. Comparison with other trials is difficult because of variability or uncertainty in the definition of heart failure [3,4]. In trials of patients with coronary heart disease or hypertension the incidence of heart failure is between 0.3 and 2 per 100 patient years [3–9], rising to about 10 per 100 patient years in trials after myocardial infarction or non-ST-elevation acute coronary syndromes [10–12].

4.2. Characteristics of patients developing heart failure

Not unexpectedly, the small group of patients, who developed heart failure, had important differences at baseline from those that did not. Patients who developed heart failure were older, and more often had a previous history of heart failure. Those who had the lowest left ventricular ejection fractions were more likely to develop heart failure. Patients who had an irregular pulse rate would also be expected to be more likely to develop heart failure because atrial fibrillation is an important precipitating factor for the development of heart failure. Taking ACE inhibitors or diuretics for hypertension, which was more frequent among patients who developed heart failure, could afford some protection against the development of heart failure. It has previously been established that patients who have had an episode of heart failure will relapse and develop fluid retention if diuretics are omitted subsequently [20].

Patients who had the most extensive coronary artery disease might be expected to be the most likely to develop heart failure. The extent of disease judged by coronary angiography did predict the development of heart failure in a univariate analysis (Table 1), but previous myocardial infarction, or previous revascularisation procedures which might reflect the extent of either myocardial damage or widespread coronary disease, did not. The presence of myocardial ischaemia as opposed to the extent of the pathological consequences of coronary disease on the left ventricle might also be expected to relate to the development of heart failure. Although there were no direct measurements of myocardial ischaemia during the study, surrogates of myocardial ischaemia, such as episodes of important angina separated those who developed heart failure from those that did not.

Higher systolic (but not diastolic) blood pressures, the presence of diabetes mellitus and known prior peripheral vascular disease (but not higher cholesterol levels or smoking), were risk factors that were more likely to lead to the development of heart failure. Of these, the presence of diabetes or prior peripheral vascular disease might reflect more extensive coronary artery disease. The importance of diabetes has been demonstrated in other large recent trials [21].

4.3. Events leading to the development of heart failure

A number of clinical events are known to lead to the development of heart failure in patients with coronary artery disease. These include the acute coronary syndromes due to

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the adverse effect that these incidents have on left ventricular function. The same is true for the development of paroxysmal atrial fibrillation, as loss of atrial systolic function leads to important reductions in cardiac output which may be the harbinger of heart failure. These suppositions have been borne out during this study, as a substantial proportion (155/207 or 75%, Fig. 1) of patients had episodes of myocardial infarction, angina, coronary revascularisation or atrial fibrillation before developing heart failure. The exact timing of the development of heart failure following such events varied from patient to patient but was usually close to the event. Fifteen patients developed heart failure following revascularisation procedures carried out during follow-up. Development of heart failure in these patients may be explained by damage to the left ventricle during these procedures, analogous to the insult of acute myocardial infarction.

Changes in drug treatment, particularly the withdrawal of diuretics, may lead to the development of heart failure or to its exacerbation [20]. Changes in therapy during the week prior to onset of heart failure were infrequent. Hence, the present analysis does not allow any conclusions in this regard.

4.4. Do patients with stable angina "lapse" into heart failure without any precipitating events?

An intriguing aspect of this study was the development of heart failure in a small number of patients (52 or 0.7% of all patients entering the study, 25% of all 207 who developed heart failure) who had no preceding cardiac event or intervention during the trial (Fig. 1). This suggests that patients with stable angina may just lapse into heart failure. A possible explanation is that such patients are those who had the most severe continuing myocardial ischaemia with a slow progressive loss of myocytes over time. Such a hypothesis cannot be confirmed by available information in this study and is largely an argument of exclusion of alternative explanations. Speculation exists as to whether a sudden rise in blood pressure or an episode of non-cardiac infection might precipitate heart failure. That is an unlikely explanation. Of the 19 patients among the 52 patients without any cardiac event preceding heart failure who had infection as the last event preceding its onset, only five had this in the preceding 7 days, while of the 12 patients who had evidence of poor control of hypertension as the last event, only one had this within the same time interval. These observations suggest that hypertension and infection are unusual precipitating factors for heart failure in patients with stable angina, although these factors may have been more common in the past. The contribution of hypertension is more likely to be a consequence of hypertension being a risk factor for the premature development of coronary heart disease.

4.5. Effect of nifedipine on frequency of clinical events leading to heart failure

Nifedipine significantly reduced the incidence of heart failure, a predefined end-point in the ACTION trial, by comparison with placebo. A reduction in the incidence of heart failure by a calcium channel blocker (CCB) has not been reported previously and this result was therefore unexpected. Findings suggesting that CCBs may increase the incidence of heart failure may be the result of misclassifying peripheral oedema (a known side effect of nifedipine which in the ACTION trial was almost three times as common in patients assigned to nifedipine than in those assigned to placebo) as denoting heart failure. In the ACTION trial strict criteria for diagnosing heart failure, which required more than just the presence of peripheral oedema, were used. This may in part explain the reduction in incidence of heart failure in the ACTION trial by contrast with other studies where the definition of heart failure was either not predefined or less stringent [3,4].

A number of hypotheses can be put forward to attempt to explain how nifedipine achieved this effect. It is unlikely that the reduction of myocardial infarction by nifedipine plays a role ([15], Table 1 and Fig. 1). A more likely explanation is that nifedipine achieves a reduction of heart failure by its anti-anginal effect, which in turn reduces the need for coronary interventions ([15] and Fig. 1). An appealing concept is that nifedipine by its anti-anginal action reduced ischaemic episodes and thereby preserved the number of myocytes. This would be a slow effect and only become evident over years. In addition, the blood pressure lowering effect of nifedipine may play a role. Blood pressures were lower in ACTION patients assigned to nifedipine than in those assigned to placebo [15,16].

5. Conclusions

The development of heart failure in patients with stable angina is unusual. Patients who do so are the elderly, those who have diabetes or hypertension, and those with concomitant peripheral vascular disease, important angina, a previous history of heart failure and worse left ventricular systolic function.

The development of heart failure without a precipitating clinical event is rare. The most frequent clinical precipitating events are worsening angina, acute myocardial infarction and atrial fibrillation.

Nifedipine reduces the development of heart failure in patients with stable angina. The mechanism by which this occurs is likely to relate to its anti-anginal and blood pressure lowering effects.

Acknowledgements

We thank all the patients who participated in this trial and all the ACTION investigators and study nurses/coordinators whose work made the trial possible. The study was supported by Bayer Healthcare AG, Wuppertal, Germany.

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