

# Papers

## Randomised trial of telephone intervention in chronic heart failure: DIAL trial

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### Abstract

**Objective** To determine whether a centralised telephone intervention reduces the incidence of death or admission for worsening heart failure in outpatients with chronic heart failure.

**Design** Multicentre randomised controlled trial.

**Setting** 51 centres in Argentina (public and private hospitals and ambulatory settings).

**Participants** 1518 outpatients with stable chronic heart failure and optimal drug treatment randomised, stratified by attending cardiologist, to telephone intervention or usual care.

**Intervention** Education, counselling, and monitoring by nurses through frequent telephone follow-up in addition to usual care, delivered from a single centre.

**Main outcome measure** All cause mortality or admission to hospital for worsening heart failure.

**Results** Complete follow-up was available in 99.5% of patients. The 758 patients in the usual care group were more likely to be admitted for worsening heart failure or to die (235 events, 31%) than the 760 patients who received the telephone intervention (200 events, 26.3%) (relative risk reduction = 20%, 95% confidence interval 3 to 34,  $P = 0.026$ ). This benefit was mostly due to a significant reduction in admissions for heart failure (relative risk reduction = 29%,  $P = 0.005$ ). Mortality was similar in both groups. At the end of the study the intervention group had a better quality of life than the usual care group (mean total score on Minnesota living with heart failure questionnaire 30.6 *v* 35,  $P = 0.001$ ).

**Conclusions** This simple, centralised heart failure programme was effective in reducing the primary end point through a significant reduction in admissions to hospital for heart failure.

### Introduction

Despite the considerable advances in treatment to improve outcomes in chronic heart failure this condition remains a growing health problem, reflected in high morbidity and mortality.<sup>1-5</sup> The already poor quality of life is often worsened by frequent admissions for decompensated heart failure.<sup>6-7</sup> This increased risk of readmission is often due to potentially preventable factors, such as non-adherence to drugs and diet, inadequate social support, and failure to seek prompt medical attention when symptoms worsen.<sup>8-9</sup> Intervention programmes based on comprehensive care and intensive follow-up by a multidisciplinary team have recently achieved a promising reduction in admissions and costs.<sup>10-17</sup> However, such evidence comes from small trials, done at single university centres, applying complex strategies to selected high risk populations.<sup>18</sup>

We designed a large multicentre, controlled trial—the randomised trial of telephone intervention in chronic heart failure (DIAL)—to test the hypothesis that a single centralised telephone intervention by trained nurses could reduce morbidity and mortality in patients with chronic heart failure compared with usual care.<sup>18</sup>

### Methods

#### Study design

We carried out a randomised, controlled, multicentre trial comparing a frequent centralised telephone intervention with usual care in patients with chronic heart failure. The design and rationale of the study have been reported previously.<sup>18</sup>

#### Eligibility criteria

The investigators, who are the attending cardiologists at each centre, screened patients previously included in a national multicentre chronic heart failure registry in Argentina. Patients had to be stable in ambulatory care, defined by no admissions in the previous two months, not needing more than one clinic visit a month, and with optimal heart failure treatment not modified for at least two months before inclusion (box).

#### Intervention

A detailed description of the intervention has been reported previously.<sup>18</sup> Briefly, all study patients were treated according to their attending cardiologists' criteria, with a follow-up visit at least every three months during the study period. At randomisation, patients allocated to the intervention received an education booklet. Nurses trained in the management of patients with chronic heart failure did frequent telephone follow-up from the telephone intervention centre. Telephone calls started within seven days after randomisation and were always from nurse to patient. The objectives of the first telephone call were to establish a good personal nurse-patient relationship, to check alternative telephone numbers or contacts, to arrange timing of the calls, and to determine the patient's clinical status and environment.

The purpose of the intervention was to educate and monitor the patient. The intervention was based on five main objectives: adherence to diet, adherence to drug treatment, monitoring of symptoms (especially progression of dyspnoea and fatigue), control of signs of hydrosaline retention (daily weight and oedema), and daily physical activity. To achieve these objectives, nurses followed a predetermined questionnaire and standardised intervention procedures. Nurses had special software with which they recorded data on every call. According to the telephone evalua-



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tion, nurses could adjust the dose of diuretic or recommend non-scheduled medical or emergency visits.

The first four telephone calls were made fortnightly, but they could be made more often according to the needs of the patient and the nurse's decision. After the fourth telephone call, the interval was automatically determined, on the basis of established criteria, using data recorded at each phone contact.

Patients in the control group were followed by their attending cardiologists and received similar care to the intervention group.

### Outcomes

The primary end point was all cause mortality or admission to hospital for worsening heart failure. The secondary end points included total mortality, all cause hospital admission, admission for worsening heart failure, cardiovascular admission, quality of life measured using the Minnesota living with heart failure questionnaire, all cause mortality or overall admissions, and the combined end point of all cause mortality or cardiovascular

admission. The clinical events committee, which was blinded to the patients' treatment group assignment, adjudicated all outcomes.

### Sample size

Assuming an annual incidence of 30% for the primary end point in the control group and an  $\alpha$  error of 0.05, a sample of 1500 patients provided 85% power to detect a 23% relative risk reduction, including a 3% dropout rate. We continued the study until 400 primary events had been reported. Minimum follow-up for each patient was six months.

### Randomisation

All patients provided informed consent before enrolment in the national heart failure registry. We obtained additional informed consent only from the patients allocated to the intervention group. Those patients who did not consent to receive the intervention were analysed by intention to treat in their originally assigned group (Zelen criterion).<sup>19</sup>

Attending cardiologists selected an eligible patient and called the coordinating centre, where inclusion criteria were checked. We then used concealed randomisation lists to do permuted block randomisation stratified by attending cardiologist.

### Statistical methods

We based all analyses on the intention to treat principle. We used the log-rank test and relative risks and risk reduction to analyse the end points. We used the Cox proportional hazards model with interaction terms to estimate the adjusted effect and do subgroup analyses.<sup>20</sup>

We used the  $\chi^2$  test to compare adherence, drug use, and functional class between intervention and control groups and the independent samples *t* test to compare quality of life scores between groups. We considered a *P* value of less than 0.05 to be statistical significant in all comparisons.

### Results

The randomisation of 1518 outpatients from 51 centres began on 1 June 2000 and ended on 1 November 2001. A total of 760 patients were allocated to the intervention group and 758 to the control group. We stopped the trial on 1 August 2002 when 400 primary events had been reported. Another 35 events occurred before the closing date and were confirmed in the last meeting of the event committee.

The baseline characteristics of the two groups were similar (table 1). The mean age was 65 years, 71% were men, most patients were in New York Heart Association (NYHA) class II or III, and about 80% had left ventricular systolic dysfunction. Follow-up was completed in 1511 (99.5%) randomised patients (fig 1).

The mean length of follow-up was 16 (range 7-27) months. The primary outcome occurred in 200 (26.3%) patients in the intervention group and in 235 (31%) patients in the control group (relative risk reduction 20%, 95% confidence interval 3% to 34%,  $P=0.026$ ) (fig 2). We found no difference between the adjusted and unadjusted effect of the intervention for the primary outcome (adjusted for NYHA class, age, baseline treatment, comorbidity, and systolic dysfunction).

The reduction in the incidence of the primary end point was mostly due to a relative risk reduction in the incidence of admissions for heart failure of 29% (9% to 44%,  $P=0.005$ ): 128 (16.8%) in the intervention group as compared with 169 (22.3%) in the control group. The effect on all cause mortality was not

### Inclusion and exclusion criteria

#### Inclusion criteria

- Outpatients with stable heart failure diagnosed at least three months previously
- 18 years or older
- Optimal drug treatment

#### Exclusion criteria

- Telephone contact not available
- More than one medical visit within a month needed
- Clinical heart failure related to:
  - Restrictive or obstructive hypertrophic cardiomyopathy
  - Haemodynamically significant valvular lesion
  - Constrictive pericarditis or pericardial tamponade
  - Primary pulmonary hypertension or cor pulmonale
  - Congenital cardiac malformations
- Reversible cardiomyopathy secondary to:
  - Acute myocarditis
  - Toxic cardiomyopathy
  - Endocrine cardiomyopathy (thyrotoxicosis, untreated hypothyroidism, pheochromocytoma)
  - Thiamine deficiency
- Myocardial infarction or unstable angina within three months
- Cardiac surgery or angioplasty within three months or awaiting procedure
- Awaiting cardiac transplantation
- Symptomatic sustained ventricular tachycardia or history of ventricular fibrillation within three months, except patients with a defibrillator already implanted
- Regular pulse therapy with intravenous diuretics, vasodilators, or inotropic agents
- Symptomatic sinus sick syndrome, second or third degree atrioventricular block, except patients with permanent pacemaker implanted
- Stroke within three months before randomisation
- Any disease with less than one year of expected survival
- Pregnant women, or women of childbearing potential, not using an effective contraceptive method
- Known history of alcohol or drug misuse
- Severe disability from any cause
- Inclusion in another intervention study, within 30 days
- Chronic hospitalisation

**Table 1** Baseline characteristics. Values are numbers (percentages) unless stated otherwise

Characteristic	Intervention group (n=760)	Control group (n=758)	Total (n=1518)
Mean (SD) age (years)	64.8 (13.9)	65.2 (12.7)	65 (13.3)
Male	552 (72.6)	522 (68.9)	1074 (70.8)
Mean (SD) heart rate (beats/min)	73.7 (18.5)	75.7 (15.4)	74.7 (17.0)
Mean (SD) systolic blood pressure (mm Hg)	124 (25.2)	124.7 (23.5)	124.4 (24.4)
NYHA class III-IV	380 (50.0)	370 (48.8)	750 (49.4)
Sinus rhythm	543 (71.4)	549 (72.4)	1092 (71.9)
Hypertension	454 (59.7)	443 (58.4)	897 (59.1)
Diabetes mellitus	155 (20.4)	161 (21.2)	316 (20.8)
Previous heart failure admission	267 (35.1)	295 (38.9)	562 (37.0)
Previous infarction or angina	330 (43.4)	344 (45.4)	674 (44.4)
History of ventricular tachycardia/ fibrillation or sudden cardiac death	46 (6.1)	38 (5.0)	84 (5.6)
Left systolic dysfunction:			
Normal/mild (>40%)	164 (21.6)	149 (19.7)	313 (20.6)
Moderate/severe (<40%)	597 (78.6)	610 (80.5)	1207 (79.5)
Treatment at randomisation:			
Diuretic	624 (82.1)	633 (83.5)	1257 (82.8)
Digoxin	346 (45.5)	368 (48.5)	714 (47.0)
Amiodarone	222 (29.2)	220 (29.0)	442 (29.1)
Spironolactone	239 (31.4)	251 (33.1)	490 (32.3)
ACE inhibitor	593 (78.0)	615 (81.1)	1208 (79.6)
Angiotensin receptor blocker	111 (14.6)	92 (12.1)	203 (13.4)
β blocker	465 (61.2)	473 (62.4)	938 (61.8)

ACE=angiotensin converting enzyme; NYHA=New York Heart Association.

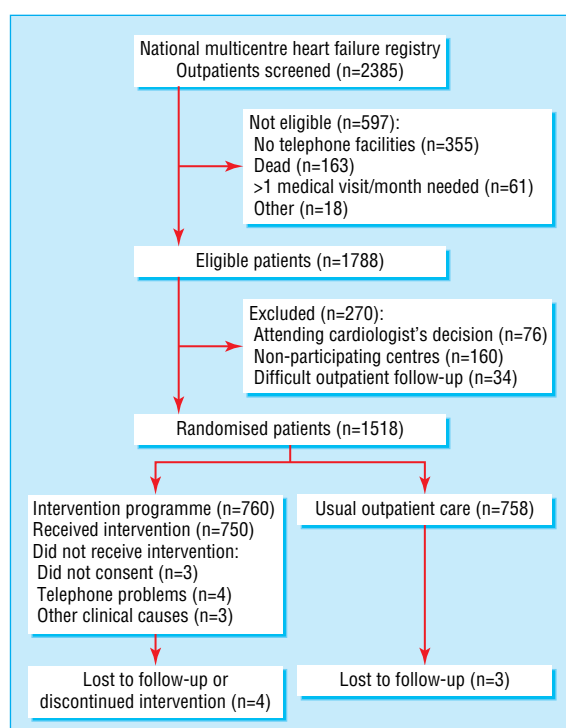
significant (relative risk reduction = 5%, -27% to 23%,  $P = 0.69$ ) (table 2).

The rate of all cause admissions was also lower in the intervention group: 261 patients were admitted at least once compared with 296 in the control group (reduction = 15%, 0.1% to 28%,  $P = 0.049$ ). Significantly fewer cardiovascular admissions were recorded in the intervention group than in the control group (183 *v* 228 patients, reduction = 24%, 7% to 28%,  $P = 0.006$ ) (table 2).

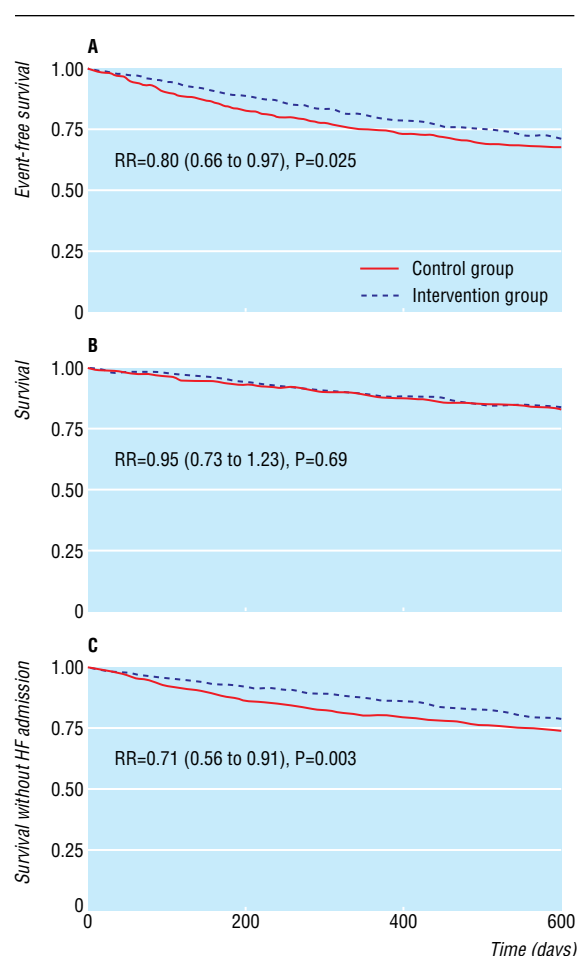
### Subgroup analyses

The reduction in the primary end point with the intervention was similar in direction and magnitude in all pre-specified

subgroups (for example, NYHA class, ventricular function, drug treatment) (fig 3). Although we observed no significant



**Fig 1** Flowchart of enrolment, randomisation, and follow-up of patients



**Fig 2** Kaplan-Meier curves for rate of death from any cause or admission to hospital for heart failure (panel A), rate of death from any cause (panel B), and rate of admission for heart failure (panel C). HF=heart failure; RR=relative risk (with 95% confidence interval)

**Table 2** Summary of primary and secondary end points. Values are numbers (percentages) unless stated otherwise

End point	Intervention (n=760)	Control (n=758)	Relative risk (95% CI)	P value
Primary end point:	200 (26.3)	235 (31.0)	0.80 (0.66 to 0.97)	0.026
Heart failure admission	128 (16.8)	169 (22.3)	0.71 (0.56 to 0.91)	0.005
All cause mortality	116 (15.3)	122 (16.1)	0.95 (0.73 to 1.23)	0.690
All cause admission	261 (34.3)	296 (39.1)	0.85 (0.72 to 0.99)	0.049
Cardiovascular admission	183 (24.1)	228 (30.1)	0.76 (0.62 to 0.93)	0.006
All cause admission and/or all cause mortality	299 (39.3)	339 (44.7)	0.86 (0.73 to 1.00)	0.057
Cardiovascular admission and/or all cause mortality	239 (31.4)	288 (38.0)	0.79 (0.65 to 0.95)	0.01

interaction between subgroups, the power to analyse each subgroup was limited.

**Quality of life and adherence**

A total of 1159 patients completed the Minnesota living with heart failure questionnaire at the final visit (excluding 238 deaths and 121 patients with visual defects, altered cognitive functions, or cerebrovascular events). Patients in the intervention group had better quality of life than control patients at the end of the study (mean total score in intervention group 30.6 v 35.0 in control group; mean difference = 4.4, 95% confidence interval 1.8 to 6.9, P = 0.001). We also found a difference in the physical score (11.2 v 12.8, P = 0.007) and emotional score (6.7 v 7.9, P = 0.002).

At the end of the trial, significantly more patients in the intervention group than the control group were taking  $\beta$  blockers (450 (59.2%) v 391 (51.6%), P = 0.003), spironolactone (207 (27.2%) v 172 (22.6%), P = 0.03), digoxin (254 (33.4%) v 217 (28.6%), P = 0.04), and furosemide (588 (77.3%) v 535 (70.5%), P = 0.007). A similar trend occurred in the use of angiotensin converting enzyme inhibitors (595 (78.3) v 575 (75.8%), P = 0.24). More patients in the control group stopped taking any

drugs (138 (18.2%) v 61 (8.0%), P < 0.001) and reported dietary transgressions (492 (64.9%) v 154 (20.2%), P < 0.001).

**Discussion**

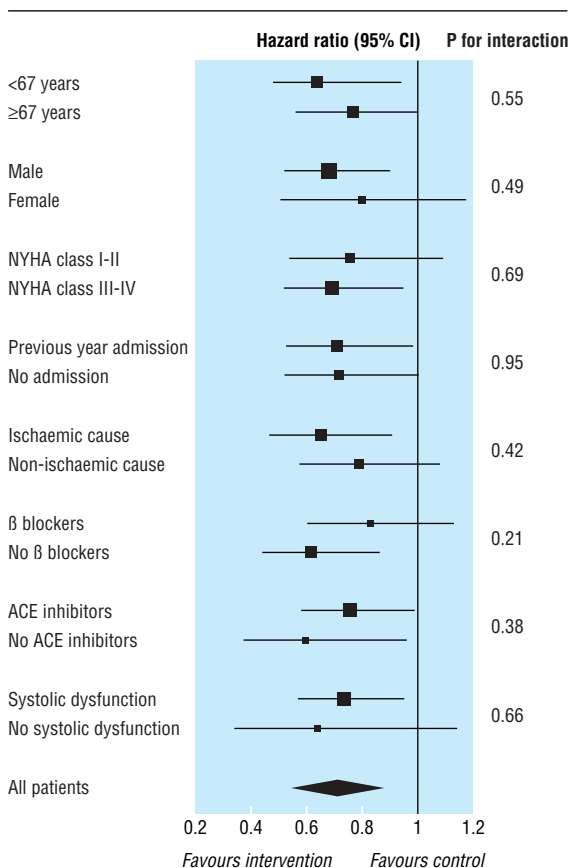
We have shown that a telephone intervention programme provides clear clinical benefits in patients with chronic heart failure. This strategy was effective in reducing the primary end point, mainly owing to a reduction in admissions for worsening heart failure. The number of heart failure patients who needed to be called in a year to prevent one admission for worsening heart failure was 16. In addition, all cause and cardiovascular admissions were significantly decreased and quality of life was better at the end of the study in the intervention group. The benefit was not significantly different in subgroup analyses, but a trend to a more favourable effect was observed in sicker patients.

This is the first multicentre randomised trial including more than 1500 patients followed for more than a year. It supports the hypothesis that heart failure management programmes represent useful tools to achieve clinical benefit in chronic heart failure. Although previous small studies showed promising results with a reduction in all cause and heart failure admissions, these results might have low external validity because they were achieved in highly selected populations, with short follow-up, and by applying complex and costly interventions.<sup>10-17</sup> In contrast, our study found similar results by applying a simple programme in a large and non-selected population of outpatients with heart failure, in very different clinical settings.

The improved adherence to diet and drug treatment among the patients assigned to the intervention group may explain, at least in part, the results obtained. The reported effect was additive to drug treatment, considering that most patients received optimal heart failure treatment prescribed by cardiologists.

Although we consider that the observed benefit is a direct consequence of the intervention, some other potential explanations should be explored. Firstly, the end points may have been misclassified. To deal with this potential bias, we created an independent and blinded endpoint committee. Moreover, we did not notice a shift from heart failure admissions to other cause admissions, because the overall admissions also fell significantly. Secondly, owing to the open design of the trial, it might be argued that the benefit was a result of a deliberate intensification of medical follow-up or drug treatment in the intervention group. However, the number of total medical visits was similar in both groups and the drug treatment prescribed by physicians did not differ.

Although multidisciplinary and complex strategies could provide greater advantage, the results of our simple intervention were still similar to those of other reported combined strategies. In fact, our intervention would be justified as it is equally effective at a reasonably low cost. The impact of these interventions could be greater in patients followed up only by non-specialised physi-



**Fig 3** Subgroup analysis: admission to hospital for heart failure

### What is already known on this topic

Multidisciplinary management programmes in post-admission patients with heart failure have suggested a reduction in hospital admissions and costs

This evidence, however, comes from small trials, at single university centres, applying complex strategies to selected high risk populations

### What this study adds

In this large scale multicentre trial, a telephone intervention by nurses reduced readmissions for worsening heart failure

A simple and centralised intervention is feasible and effective in heart failure outpatients with different risks in diverse clinical settings and geographical locations

cians, where interaction with the programme could also help to improve patterns of heart failure practice.

### Conclusion

The clinical course and prognosis of chronic heart failure can be much improved on top of optimal drug treatment through comprehensive programmes based on simple strategies that overcome barriers among patients and effective health care. This kind of intervention should become a useful tool in heart failure patients, to enhance the transfer of evidence from clinical trials to the daily clinical practice.

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