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Efficacy of an intensive prevention program in coronary patients in primary care, a randomised clinical trial

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Abstract

Background: Most studies that have analysed the effect of secondary prevention of coronary heart disease come from hospitals. Those that are community-based have been conducted mainly by nurses and follow-up was generally too short to show impact on cardiovascular events.
Methods: This is a multi-centre randomised controlled clinical trial in which patients in the intervention group received periodic postal reminders to see their general practitioner every three months during a 3-year follow-up. General practitioners reinforced healthy lifestyle recommendations to patients and reviewed drug therapies at these quarterly intervals. Patients in the control group received usual care.
Results: A total of 983 patients aged 30–79 were included. During the 3-year follow-up, 67 patients died and 156 experienced a non-fatal cardiovascular event. The event rates and all-cause mortality were similar in the intervention and control groups (24.0% and 23.5%, and 8.1% and 9.9%, respectively). Improvement in quality of life was similar in both groups. Blood pressure and high-density lipoprotein cholesterol were more frequently within recommended levels in the intervention group than in controls: odds ratio 1.63, 95% confidence interval 1.05–2.51, and odds ratio 2.61, 95% confidence interval 1.32–5.18, respectively.
Conclusions: Intensive secondary prevention conducted by general practitioners may improve long-term blood pressure control and increase high-density lipoprotein cholesterol in patients with stable coronary disease.

Keywords: Coronary heart disease; Secondary prevention; Primary care

1. Introduction

Coronary Heart Disease (CHD) is expected to remain the most important cause of death in western countries for decades [1]. Although Spain has among the world's lowest incidence and mortality rates of myocardial infarction (MI), the prevalence of risk factors is relatively high [2]. Approximately 70,000 acute coronary syndromes occurred in 2004 [3].

CHD mortality has decreased in the past three decades, owing in part to improved treatment of acute coronary syndromes in hospitals [4] and implementation of secondary prevention programs [5]. Risk-factor-specific [6–10] and comprehensive [11–15] interventions have reduced MI recurrences, mortality, and/or risk factor levels.

Community-based interventions have been managed mainly by nurses [13,14], follow-up was generally too

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[1] see the full roster of the ICAR investigators on the following website: www.regicor.org/ICAR_inv.

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short to show impact on mortality and cardiovascular events [13], and findings were inconsistent. Further research has been judged necessary [16].

We analyzed the efficacy of an intensive program of secondary prevention led by general practitioners (GP) to reduce cardiovascular recurrences and mortality and to improve risk factor control, lifestyle, and quality of life in patients with stable CHD.

2. Participants and methods

2.1. Design

The ICAR (*Intervención en la Comunidad de Alto Riesgo cardiovascular*/Community Intervention against High CHD Risk) study was a 23-centre community-based randomised clinical trial with more than 200 collaborating GPs in Catalonia, Spain.

2.2. Patients

Patients aged 30–79 who had suffered MI or angina with electrocardiographic signs of ischaemia in the 6 years prior to recruitment were eligible.

Those unwilling to participate or with terminal diseases, severe mental or physical disability, or unstable CHD within 1 month prior to recruitment were excluded. Primary care health facilities were allocated to control or intervention protocols by a random sequence generated by a computer program. This unit of randomisation was used to avoid contamination of clinical practice with non-intervened patients.

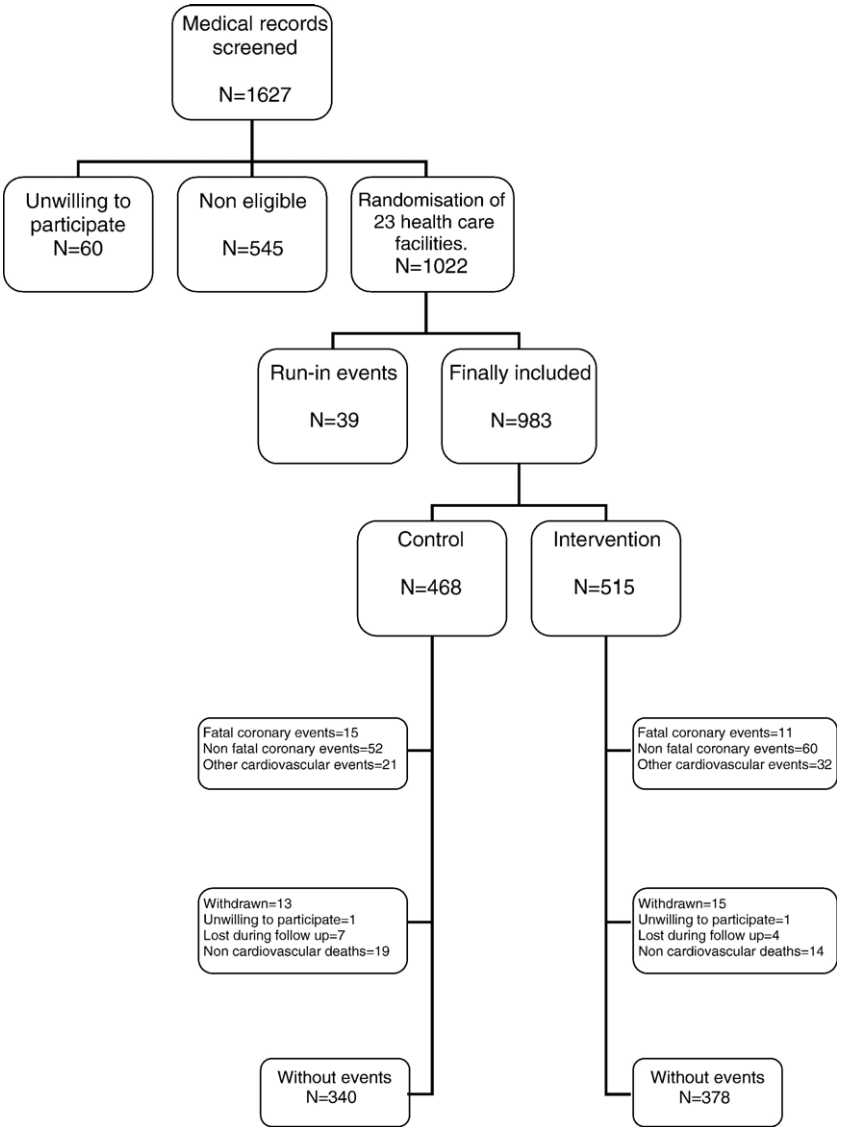

Fig. 1. Flow diagram showing the progress of the trial by treatment group in the ICAR (*Intervención en la Comunidad de Alto Riesgo cardiovascular*) clinical trial.

The study protocol was approved by two research ethics committees.

2.3. Sample size

Approximately 410 patients in each group guarantees a statistical power of 80% with an alpha risk of 0.05, given a difference ≥10% units in CHD events between the groups, assuming an event rate of 25% in the control group, based on previous observation [17], and a dropout rate <20%.

2.4. Baseline measurements

Demographic data, blood pressure, glucose, lipid levels, body mass index, smoking, treatment for secondary prevention, and history of hypertension, diabetes, hypercholesterolaemia, stroke, peripheral vascular disease, and previous CHD events were collected from medical records.

Socioeconomic status was coded as high (Class I–III: professional, intermediate, and skilled occupations) and low (Class IV–V: unskilled and manual occupations) status. Information about socioeconomic status, regular physical exercise, and smoking habit changes during the study was confirmed by personal, telephone, or mail questionnaire.

Lipid profile was considered within normal levels when total and LDL cholesterol levels were lower than 5.0 mmol/L and 3.0 mmol/L, respectively. Body mass index was optimal when levels were lower than 25 kg/m^2. Blood pressure and glycaemia were considered well controlled when systolic and diastolic levels were lower than 140 mm Hg and 90 mm Hg, respectively, and fasting blood glucose levels were lower than 6.10 mmol/L [18].

Only life-saving treatments (antiplatelet, beta-blocker, angiotensin-converting enzyme (ACE) inhibitor, and lipid-lowering drugs) were analysed [19].

The 12-Item Short-Form Health Survey questionnaire, validated for use in the Spanish population [20], was used to analyze quality of life and was administered at the beginning and end of the study.

2.5. Interventions

2.5.1. General practitioners

GPs in the intervention centres were instructed to strictly follow the most recent guidelines on cardiovascular prevention at that time and received a copy of the study protocol with detailed recommendations and treatment objectives [18]. They were reminded quarterly to measure blood pressure and weight and to provide patients in the intervention group with recommendations on healthy lifestyle, including materials about the traditional Mediterranean diet (pulses, fruits, vegetables, fish, and olive oil), physical exercise (GPs offered various options, such as walking and cycling), hypo-caloric diet, and counselling to quit smoking if applicable. GPs also were asked to adjust life-saving treatments (i.e., angiotensin-converting enzyme

Table 1
Baseline characteristics, endpoints, and risk factor control of patients of the ICAR (*Intervención en la Comunidad de Alto Riesgo cardiovascular*) clinical trial by intervention status

	Control N=468	Intervention N=515	p
Age (Mean, [S.D.])	63.6 (10.3)	64.2 (9.8)	0.29
Sex (female) (%)	26.8	23.9	0.30
Previous co-morbidity (%)			
Diabetes	29.2	29.3	0.97
Hypertension	60.2	51.6	<0.01
Peripheral vascular disease	13.2	9.0	0.04
Hypercholesterolemia	64.2	61.6	0.41
Stroke	9.8	9.1	0.74
Any of above	84.2	85.2	0.65
Time (months) since the last CHD event [median (percentiles$_{25-75}$)]	44 (20.0)	44 (19.8)	0.86
Number of previous coronary events [median (percentiles$_{25-75}$)]	1 (1–2)	1 (1–2)	0.19
Social class (% low social class)	77.7	79.3	0.59
Quality of life SF-12 scores [mean, (S.D.)]			
Physical health summary score	43.3 (5.9)	43.4 (5.7)	0.74
Mental health summary score	46.6 (7.4)	45.8 (8.3)	0.17
Preventive drug therapy (%)			
Antiplatelet drugs	79.0	74.5	0.10
Beta-blockers	38.8	31.6	0.02
ACE inhibitors	29.6	23.0	0.02
Lipid-lowering drugs	54.8	52.9	0.56
Four of above	6.4	3.5	0.03
Cardiovascular risk factors [mean, (S.D.)]			
Weight (kg)	76.6 (11.0)	76.4 (11.9)	0.83
Body mass index (kg/m^2)	29.4 (4.3)	28.9 (3.9)	0.12
Systolic blood pressure (mm Hg)	134 (17)	130 (17)	<0.01
Diastolic blood pressure (mm Hg)	79 (10)	76 (10)	<0.01
Total cholesterol (mmol/L)	5.4 (1.1)	5.4 (0.9)	0.99
Low-density lipoprotein cholesterol (mmol/L)	2.68 (0.78)	2.68 (0.67)	0.99
High-density lipoprotein cholesterol (mmol/L)	1.24 (0.31)	1.29 (0.31)	0.03
Triglycerides (mmol/L) [median (percentiles$_{25-75}$)]	1.34 (1.05–1.90)	1.30 (0.91–1.78)	0.10
Fasting blood glucose (mmol/L) [median (percentiles$_{25-75}$)]	5.71 (5.16–7.10)	5.77 (5.16–7.32)	0.61
Glycosylated haemoglobin (%)[a]	6.9 (1.8)	7.4 (1.7)	0.12
Risk factor control (%)			
T-cholesterol<5.0 mmol/L and LDL-C<3.0 mmol/L	25.8	25.3	0.90
HDL-C>1.0 mmol/L in men or >1.2 mmol/L in women	69.1	75.0	0.10
Blood pressure<140/90 mm Hg	51.3	63.3	<0.01
Glucose<6.1 mmol/L	59.6	56.6	0.44
Body mass index<25 kg/m^2	12.6	13.9	0.61
Not smoking	86.6	86.2	0.84
Endpoints (%)			
All deaths	7.7	6.0	0.29
Cardiovascular deaths	3.6	3.3	0.77
All cardiovascular events	18.8	20.0	0.63

S.D.: Standard deviation; CHD: coronary heart disease; T-cholesterol: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; SF-12: Short-Form Health Survey Questionnaire; ACE: angiotensin-converting enzyme.

[a] In diabetic patients only.

inhibitors, aspirin, beta blockers and statins) to control risk factors according to the clinical practice guidelines, use the drugs recommended for secondary prevention if no contra-indications, and request two laboratory tests each year. GP adherence to protocol in the intervention group was monitored by quarterly reporting.

GPs in the control centres obtained blood pressure measurement, lipid profile, and glucose levels, as well as glycosylated haemoglobin in diabetic patients, at the end of the study.

2.5.2. Patients

All eligible patients were invited to participate. Those who signed the informed consent were included in the study. Patients in the intervention group received a mail reminder quarterly to consult with their GP Control group patients were only contacted on two occasions by telephone or mail to obtain clinical information, at the beginning and at the end of the study. Their GPs did not receive any letters reminding them to offer patients counselling and additional care.

Table 2
Centre-adjusted hazard ratios of cardiovascular event, cardiovascular mortality, or total mortality for patient characteristics (age, sex, intervention group, previous co-morbidity, socio-economic status, quality of life scores, treatments, and risk factor level and control) at baseline by left-truncated Cox model in the ICAR (*Intervención en la Comunidad de Alto Riesgo cardiovascular*) clinical trial

Variable	All cardiovascular events		Cardiovascular mortality		Total mortality	
	HR [95% confidence interval]	*p*	HR [95% confidence interval]	*p*	HR [95% confidence interval]	*p*
Age (years)	1.03 [1.01–1.05]	<0.01	1.08 [1.02–1.13]	<0.01	1.05 [1.02–1.09]	<0.01
Sex, female	1.33 [0.95–1.88]	0.10	1.01 [0.43–2.35]	0.99	0.68 [0.34–1.34]	0.27
Intervention group	0.97 [0.65–1.45]	0.87	1.02 [0.50–2.09]	0.96	0.85 [0.51–1.41]	0.53
Previous comorbidity						
Diabetes	1.70 [1.24–2.34]	<0.01	1.96 [0.95–4.05]	0.07	1.42 [0.83–2.42]	0.20
Hypertension	1.18 [0.86–1.61]	0.30	1.34 [0.64–2.82]	0.44	1.10 [0.65–1.86]	0.72
Hypercholesterolaemia	1.10 [0.79–1.53]	0.58	0.71 [0.34–1.47]	0.35	0.89 [0.52–1.51]	0.67
Peripheral vascular disease	1.90 [1.26–2.85]	<0.01	1.38 [0.48–3.97]	0.55	2.52 [1.35–4.68]	<0.01
Stroke	1.55 [0.96–2.50]	0.07	1.13 [0.34–3.76]	0.84	1.84 [0.90–3.76]	0.10
Low social class	1.25 [0.79–1.97]	0.35	3.08 [0.40–23.90]	0.28	1.81 [0.53–6.10]	0.34
Quality of life scores						
Physical summary score	0.98 [0.95–1.00]	0.10	1.00 [0.90–1.10]	0.94	0.98 [0.91–1.06]	0.63
Mental summary score	0.99 [0.97–1.01]	0.25	1.08 [0.98–1.18]	0.11	1.04 [0.98–1.11]	0.22
Preventive drug therapy						
Antiplatelet drugs	0.98 [0.66–1.44]	0.91	0.99 [0.40–2.43]	0.99	0.78 [0.43–1.43]	0.42
Beta-blockers	0.98 [0.71–1.36]	0.91	0.80 [0.37–1.73]	0.58	0.68 [0.39–1.19]	0.18
ACE inhibitors	1.11 [0.79–1.57]	0.56	3.01 [1.45–6.27]	<0.01	1.81 [1.07–3.08]	0.03
Lipid lowering agents	0.77 [0.57–1.06]	0.11	0.72 [0.35–1.48]	0.38	0.96 [0.57–1.61]	0.88
All	0.46 [0.17–1.24]	0.13	*	0.99	0.90 [0.28–2.89]	0.86

Cardiovascular risk factors	All cardiovascular events		Cardiovascular mortality		Total mortality	
	HR [95% confidence interval]	*p*	HR [95% confidence interval]	*p*	HR [95% confidence interval]	*p*
Weight	1.00 [0.98–1.01]	0.65	0.97 [0.93–1.01]	0.13	0.98 [0.95–1.00]	0.10
Body mass index	1.01 [0.96–1.05]	0.77	0.92 [0.82–1.04]	0.17	0.92 [0.84–1.00]	0.04
Systolic blood pressure	1.00 [0.99–1.01]	0.63	1.00 [0.97–1.02]	0.86	1.00 [0.98–1.02]	0.88
Diastolic blood pressure	0.98 [0.96–0.99]	0.02	0.98 [0.94–1.02]	0.40	0.99 [0.96–1.02]	0.46
Total cholesterol	1.00 [1.00–1.01]	0.28	1.00 [0.99–1.01]	0.82	1.00 [1.00–1.01]	0.29
Low-density lipoprotein cholesterol	1.00 [0.99–1.01]	0.43	1.00 [0.99–1.02]	0.78	1.00 [1.00–1.01]	0.37
High-density lipoprotein cholesterol	1.00 [0.98–1.01]	0.71	1.00 [0.96–1.04]	0.95	0.99 [0.96–1.02]	0.63
Triglycerides	1.41 [0.96–2.09]	0.08	1.92 [0.71–5.19]	0.20	1.71 [0.89–3.27]	0.11
Fasting blood glucose	1.01 [1.00–1.01]	<0.01	1.01 [1.00–1.02]	0.01	1.01 [1.00–1.01]	0.03
Glycosylated haemoglobin	1.11 [0.93–1.31]	0.24	1.39 [1.04–1.87]	0.03	1.18 [0.91–1.53]	0.20
Risk factor control						
Total cholesterol <5.0 and LDL-C <3.0 mmol/L	0.57 [0.35–0.92]	0.02	0.36 [0.08–1.58]	0.18	0.63 [0.27–1.43]	0.27
HDL-C >1.0 mmol/L in men or >1.2 mmol /L in women	0.90 [0.59–1.38]	0.64	1.04 [0.33–3.23]	0.95	0.89 [0.42–1.87]	0.76
Blood pressure <140/90 mm Hg	1.18 [0.83–1.68]	0.36	1.42 [0.62–3.22]	0.40	1.20 [0.67–2.14]	0.54
Glucose <6.1 mmol/L	0.69 [0.47–1.00]	0.05	0.55 [0.22–1.41]	0.21	0.64 [0.34–1.22]	0.18
Body mass index <25 kg/m^2	1.34 [0.84–2.15]	0.22	3.42 [1.35–8.71]	0.01	3.07 [1.57–5.97]	<0.01
Non-smokers	1.20 [0.71–2.04]	0.49	1.11 [0.33–3.02]	0.87	0.50 [0.26–0.96]	0.04

HR: hazard ratio; ACE: angiotensin-converting enzyme inhibitors; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; *not calculated because no patient died among those receiving all four treatments.

Table 3
Adjusted hazard ratio of cardiovascular event, cardiovascular mortality, or all mortality for the intervention group in the ICAR (*Intervención en la Comunidad de Alto Riesgo cardiovascular*) clinical trial

	Hazard ratio [95% confidence interval]	*P*
All cardiovascular events [a]	0.90 [0.56–1.45]	0.67
Cardiovascular mortality [b]	0.95 [0.46–1.98]	0.89
All-cause mortality [c]	0.79 [0.47–1.34]	0.38

[a] Adjusted for centre (as random effects factor), age, sex, peripheral artery disease, and diastolic blood pressure.
[b] Adjusted for centre (as random effects factor), age, sex, and angiotensin-converting enzyme inhibitors.
[c] Adjusted for centre (as random effects factor), age, sex, angiotensin-converting enzyme inhibitors, and peripheral artery disease.

2.6. Follow-up and endpoints

Patients were followed for 3 years or until an endpoint occurred. The main endpoints were admission for unstable angina, MI, heart failure, arrhythmias, stroke, or coronary artery revascularisation. Secondary endpoints were changes in cardiovascular risk factor control and quality of life. Subjects who developed severe physical or mental disability or presented non-CHD terminal diseases were withdrawn.

2.7. Statistical analysis

Data were analysed by intention to treat. Intervention and control groups were compared by Chi square and Student's *t* or Mann–Whitney tests as appropriate given the data distribution for categorical and continuous variables, respectively. Only triglycerides and fasting blood glucose did not follow a normal distribution.

Since the medical centre was the unit of randomisation, hazard rates of event occurrence were calculated for each patient characteristic to adjust for variability among centres.

Table 5
Adjusted odds ratio of good risk factor control (Panel A) or of receiving preventive drug therapy (Panel B), for intervention group, adjusted for age, sex, and baseline risk factor control status, among patients without events during follow-up in the ICAR (*Intervención en la Comunidad de Alto Riesgo cardiovascular*) clinical trial

	Odds ratio [95% confidence interval]	*p*
Panel A		
Good risk factor control		
Total cholesterol <5.0 mmol/L and LDL-C<3.0 mmol/L	0.99 [0.65–1.52]	0.97
HDL-C >1.0 mmol/L in men or >1.2 mmol/L in women	2.61 [1.32–5.18]	<0.01
Blood pressure <140/90 mm Hg	1.63 [1.05–2.51]	0.03
Glucose <6.1 mmol/L	1.04 [0.60–1.80]	0.89
Body mass index <25 kg/m^2	0.70 [0.30–1.65]	0.42
Non-smokers	0.55 [1.19–0.25]	0.13
Panel B		
Preventive drug therapy		
Antiplatelet drugs	1.13 [0.64–2.00]	0.66
Beta-blockers	1.21 [0.79–1.86]	0.39
ACE inhibitors	0.70 [0.47–1.06]	0.09
Lipid-lowering drugs	1.41 [0.86–2.31]	0.17
All	0.74 [0.43–1.28]	0.29

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ACE: angiotensin-converting enzyme.

Comparing outcomes in the intervention and control groups required adjustment for three sources of bias: differences in time to treatment (time to inclusion from the last CHD event), baseline characteristics of patients, and variability among centres (random effects). The first, which results from the fact that patients must survive a sufficient length of time to be recruited, was addressed by a left-truncated Cox regression model of time to event. The second source of bias was addressed in the centre-adjusted analysis by including in a multilevel Cox model age, sex, and those variables significantly related with the outcome (fixed factors at individual level). We also included in the model the random

Table 4
Differences in cardiovascular risk factor control levels and quality of life score changes between final follow-up and baseline values by intervention and control groups among patients without events during follow-up in the ICAR (*Intervención en la Comunidad de Alto Riesgo cardiovascular*) clinical trial

	Control group *N*=340	Intervention group *N*=378	*p*
	Difference [95% confidence interval]	Difference [95% confidence interval]	
Cardiovascular risk factors			
Systolic blood pressure (mm Hg)	−2.0 [−4.6–0.6]	−1.1 [−3.4–1.3]	0.58
Diastolic blood pressure (mm Hg)	−3.5 [−5.1 to −2.0]	−0.7 [−2.1–0.7]	<0.01
Weight (kg)	0.9 [0.2–1.7]	1.1 [0.3–1.9]	0.79
Body mass index	0.3 [0.0–0.6]	0.4 [0.1–0.7]	0.70
Total cholesterol (mmol/L)	−0.29 [−0.47 to −0.11]	−0.38 [−0.53 to −0.23]	0.46
LDL-C (mmol/L)	−0.26 [−0.40 to −0.12]	−0.31 [−0.42 to −0.2]	0.58
HDL-C (mmol/L)	0.02 [−0.10–0.13]	0.05 [−0.09–0.19]	0.08
Fasting blood glucose(mmol/L)*	0.0 [−0.61–0.65]	0.05 [−0.65–0.56]	0.90
Triglycerides (mmol/L)*	−0.01 [−0.28–0.33]	0.01 [−0.29–0.3]	0.85
Quality of life SF-12 scores			
Physical summary score	4.4 [3.1–5.7]	4.6 [3.4–5.9]	0.80
Mental summary score	6.9 [5.9–8.0]	7.2 [6.0–8.4]	0.75

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; *[median (percentiles$_{25–75}$)]; SF-12: Short-Form Health Survey Questionnaire.

Table 6
Differences in medication prescription at baseline and at the end of follow-up by intervention status in the ICAR (*Intervención en la Comunidad de Alto Riesgo cardiovascular*) clinical trial

	Control group $N=340$				Intervention group $N=378$				p-value of increase differences
	Baseline	Final	Increase	p	Baseline	Final	Increase	p	
Antiplatelet drugs	82.5	88.1	5.6	0.04	75.0	88.4	13.4	<0.01	0.12
Beta-blockers	39.4	47.2	7.8	<0.01	34.8	46.9	12.1	<0.01	0.32
ACE inhibitors	30.1	41.2	11.1	<0.01	24.1	32.6	8.5	<0.01	0.44
Lipid-lowering agents	57.2	81.4	24.2	<0.01	56.1	81.9	25.8	<0.01	0.52
All	5.9	12.9	7.0	<0.01	3.8	9.2	5.4	<0.01	0.50

ACE: angiotensin-converting enzyme.

effects of variability among centres to control for the third source of bias, which implies accounting for the assumed lack of independence among individuals in each centre.

Kaplan–Meier survival curves were compared for the intervention and control groups using the log-rank test and also considering left truncation.

The baseline-value-adjusted odds ratios of risk factor control for the intervention group were estimated using binary logistic regression.

The differences in the baseline-to-final changes in risk factor levels and quality of life were compared between the intervention and control group by Student's t-test or Mann–

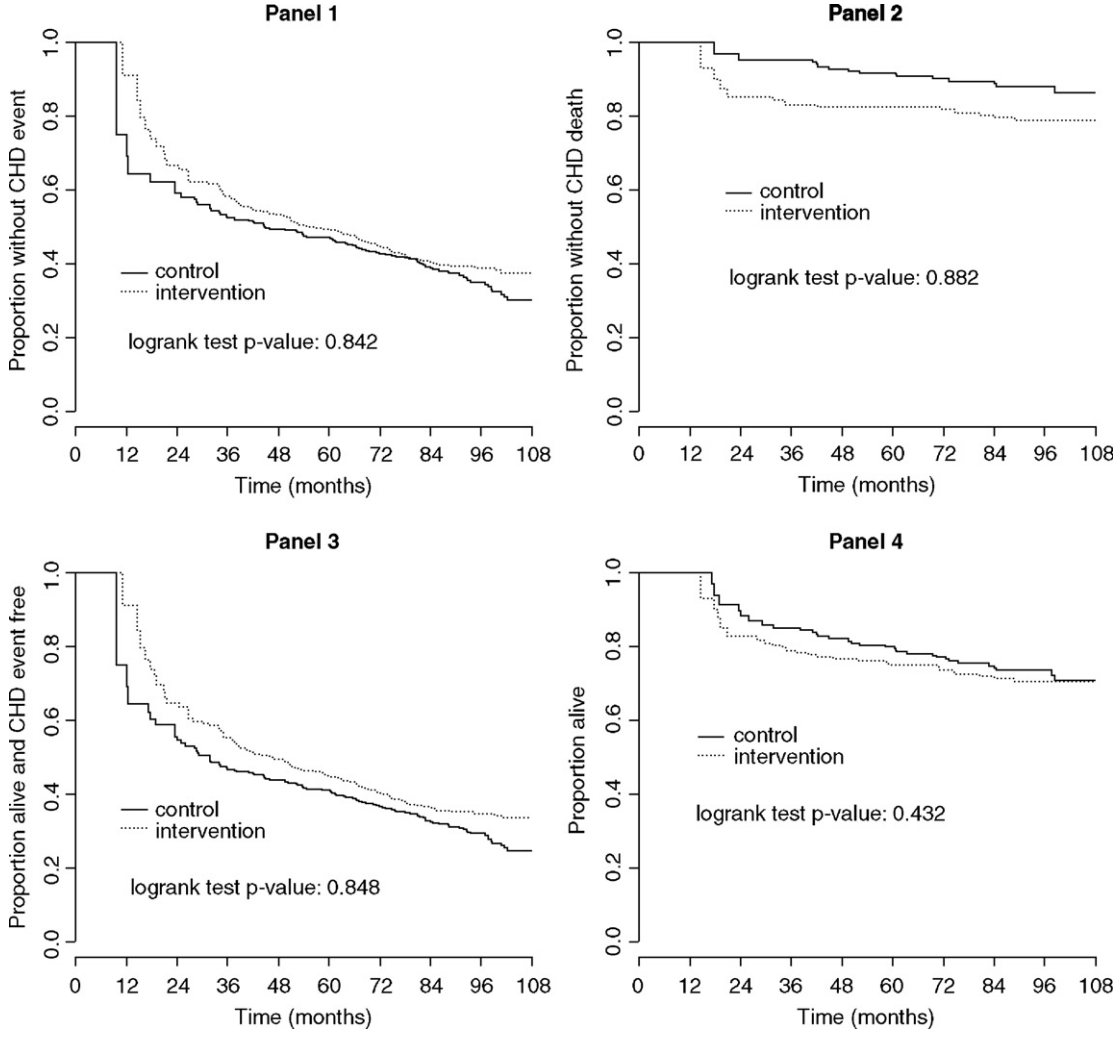

Fig. 2. Survival curves of total cardiovascular events (panel 1), cardiovascular death (panel 2), overall mortality and non-fatal cardiovascular events (Panel 3), and overall mortality (Panel 4), by intervention status in the ICAR (*Intervención en la Comunidad de Alto Riesgo cardiovascular*) clinical trial. Survival curves and log rank test for differences between intervention and control groups incorporate left-truncation.

Whitney *U*-test as appropriate. Normal distribution of these differences was verified by comparison with normal probability plots.

Statistical analyses were done with R 2.0 (R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-00-3, URL http://www.R-project.org) and SAS 8.2 (SAS Institute, Cary, NC, USA).

3. Results

Of 1627 patients screened, 545 were not eligible (147 presented no coronary event since 1993, 110 had a severe or terminal illness, 62 were older than 79 years, 190 had no CHD, 36 were dead prior to the recruitment time) and 60 were unwilling to participate. Of 1022 patients randomised, 39 presented an event during the 3-month run-in period. The flow diagram showing the progress of the trial by treatment group is presented in Fig. 1.

4. Baseline characteristics of patients in intervention and control groups

Mean age of patients was 63.9 years (S.D. 10.0) and 74.5% were men. Baseline characteristics were similar in all groups, but controls were more likely to have hypertension, peripheral vascular disease and lower levels of HDL cholesterol, and received more frequently beta-blockers and ACE inhibitors than the intervention group. Baseline control of cardiovascular risk factors was similar in both groups, except for blood pressure, that was better in the intervention group.

4.1. Follow-up

The median follow-up was 36 months. There were 67 deaths (32 cardiovascular) and a total of 156 study-related hospital admissions: 112 with a non-fatal CHD event (95 with MI or unstable angina and 17 for coronary revisualisation), 11 with heart failure, 6 with arrhythmic complications, and 27 with stroke. Only two patients were unwilling to continue their participation in the study, 11 (1.1%) were lost, and 28 withdrawn due to severe physical or mental disease (Fig. 1). Cardiovascular event and mortality rates during follow-up were similar in both groups (Table 1).

The risk of developing a cardiovascular event was higher in older and in diabetic patients, subjects with peripheral vascular disease, and those with higher fasting blood glucose levels; risk was lower when total and LDL cholesterol and glucose levels were within the recommended levels. The hazard ratio of cardiovascular mortality was significantly higher in older people, patients receiving ACE inhibitors, those with higher levels of fasting blood glucose and glycosylated haemoglobin, and in those with lower body mass index. Age, smoking, history of peripheral vascular disease, use of ACE inhibitors, body mass index, and fasting blood glucose at baseline were significantly related with at least one primary endpoint (Table 2).

The adjusted Cox models showed no differences in the hazard ratios of cardiovascular events, cardiovascular mortality, and all mortality (Table 3).

4.2. Quality of life

Although all quality of life scores increased at the end of follow-up, no significant differences between intervention and control groups were found for SF-12 physical and mental health summary scores.

4.3. Risk factor control

The levels of blood pressure, weight, fasting blood glucose, total and LDL cholesterol, and triglycerides among patients without events, adjusted by baseline values, were similar in both randomised groups at the end of follow-up. Diastolic blood pressure levels were better in the control group (Table 4) but patients in the intervention group achieved better blood pressure control and HDL cholesterol within recommended values than the control group (Table 5).

Only 2.3% and 1.5% of patients in the control and intervention groups, respectively, reported an increase in physical exercise during the study. This was not statistically significant.

4.4. Medication for secondary prevention

A significant increase was observed in the use of all life-saving drugs in the intervention and control groups, but increase differences between groups were not significant. The greatest variation was observed in the percentage of lipid-lowering drugs, with higher usage in the intervention group (Table 6). After adjusting for preventive drug therapy use at baseline, no significant differences between intervention and control groups were found (Table 5).

4.5. Survival analysis

The 3-year Kaplan–Meier survival rate of all cardiovascular events was 24.0% and 23.5% in the intervention and control groups, respectively. Similarly, cardiovascular mortality was 4.3% and 4.7%, non-fatal cardiovascular events 8.1% and 9.9%, and total mortality 27.0% and 27.6%; none of the rates improved with the intervention (Fig. 2).

5. Discussion

Our intensive cardiovascular prevention program shows better blood pressure control and increased high-density lipoprotein cholesterol in patients with stable coronary disease. Nevertheless, no reduction in mortality or in cardiovascular events at 3 years was found.

The absence of physical activity changes in the intervention group may be related to the fact that only encouragement and a brochure were provided at each quarterly contact, as

well as to participants' mean age, which was close to 68 years by the end of the study.

Despite the potential for increasing secondary prevention in general practice [21], the efficacy of simultaneous lifestyle and drug interventions to reduce CHD morbidity and mortality remains unclear. In both the intervention and control groups, important improvements were observed in the percentage of life-saving treatments (antiplatelet, beta-blockers, ACE-inhibitors and lipid-lowering drugs) prescribed. A trend toward preventive prescriptions, described in recent years [22], may have reduced the impact of the intervention; the intensity of drug therapy, measured by the consumption of all four life-saving drugs, doubled in both groups.

All participating GPs, including those in the control centres, may have been influenced by other sources of information on CHD prevention. It is also important to note that the high mean age of the population and the presence of co-morbid situations would generate multiple prescriptions and may limit the number of drugs prescribed for cardiovascular prevention. In addition, primary health care protocols in Spain, which include systematic care of diabetic and hypertensive patients, may have attenuated the effect of the intervention. However, the limited improvement in risk factor control obtained in the intervention group concurs with the results of other programs led by GPs, hospitals, or nurses [21,23].

The study was conducted in a "real-life" environment. Although even more intensive measures might yield better results, it might be unrealistic to implement them in primary care with current resources and GP workload. It seems difficult to improve the stable CHD patient's outcome without specific secondary prevention clinics and higher costs [14].

Overall mortality and cardiovascular event rates were similar in both groups. This concurs with other secondary prevention clinical trials conducted in recent years [24]. Quality of life scores at baseline were lower than those of the normative population [20], as in other studies after MI [25]. The improvement in quality of life observed at the end of follow-up in both groups also has been observed after a CHD event [26].

5.1. Study characteristics

Our GP-led clinical trial was conducted on patients younger than 80 years, with the intervention integrated into daily practice. Health care facility was the unit of randomisation to avoid contamination of clinical practice with non-intervened patients.

Baseline differences between groups (despite randomisation) in hypertension, HDL cholesterol, and peripheral artery disease prevalence were adjusted for in the Cox regression models.

Our study was designed in 1999 to analyse whether a 3-year intensive cardiovascular prevention program based on the evidence then available would result in improved CHD event and mortality rates, quality of life, and risk factor control. We cannot rule out that, even being among the longest trials to date in secondary prevention in primary care, 3 years may be insufficient to observe an intervention effect on stable CHD patients.

However, it is also possible that the specific intensive program adds no further benefit to that obtained by usual care. Another possibility is that even more intensive interventions with both patients and professionals than our study's quarterly reminders about risk factors and laboratory tests may be required to improve secondary prevention outcomes in primary care. Unfortunately, this is not a feasible option for most National Health Systems.

The fact that patients included in the study were clinically stable could limit the effect of the interventions. However, management of unstable coronary patients is not recommended in the primary care setting.

The external validity of the present findings is guaranteed by a very low withdrawal and lost-to-follow-up rates. The results should be safely applied to stable CHD patients seen in primary care.

6. Conclusions

There is little evidence about the efficacy of specific strategies for the follow-up of stable coronary disease patients. Recommendations of expert committees have suggested annual evaluations after the first year [27]. At minimum, our study shows that a 3-year intensive secondary prevention program, managed quarterly by GPs, resulted in better long-term blood pressure control and increased HDL cholesterol in patients with stable coronary disease.

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