

# Global Secondary Prevention Strategies to Limit Event Recurrence After Myocardial Infarction

## Results of the GOSPEL Study, a Multicenter, Randomized Controlled Trial From the Italian Cardiac Rehabilitation Network

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**Background:** Secondary prevention is not adequately implemented after myocardial infarction (MI). We assessed the effect on quality of care and prognosis of a long-term, relatively intensive rehabilitation strategy after MI.

**Methods:** We conducted a multicenter, randomized controlled trial in patients following standard post-MI cardiac rehabilitation, comparing a long-term, reinforced, multifactorial educational and behavioral intervention with usual care. A total of 3241 patients with recent MI were randomized to a 3-year multifactorial continued educational and behavioral program (intervention group; n=1620) or usual care (control group; n=1621). The combination of cardiovascular (CV) mortality, nonfatal MI, nonfatal stroke, and hospitalization for angina pectoris, heart failure, or urgent revascularization procedure was the primary end point. Other end points were major CV events, major cardiac and cerebrovascular events, lifestyle habits, and drug prescriptions.

**Results:** End point events occurred in 556 patients (17.2%). Compared with usual care, the intensive intervention did not decrease the primary end point significantly (16.1% vs 18.2%; hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.74-1.04). However, the intensive intervention decreased several secondary end points: CV mortality plus nonfatal MI and stroke (3.2% vs 4.8%; HR, 0.67; 95% CI, 0.47-0.95), cardiac death plus nonfatal myocardial infarction (2.5% vs 4.0%; HR, 0.64; 95% CI, 0.43-0.94), and nonfatal MI (1.4% vs 2.7%; HR, 0.52; 95% CI, 0.31-0.86). A marked improvement in lifestyle habits (ie, exercise, diet, psychosocial stress, less deterioration of body weight control) and in prescription of drugs for secondary prevention was seen in the intervention group.

**Conclusion:** The GOSPEL Study is the first trial to our knowledge to demonstrate that a multifactorial, continued reinforced intervention up to 3 years after rehabilitation following MI is effective in decreasing the risk of several important CV outcomes, particularly nonfatal MI, although the overall effect is small.

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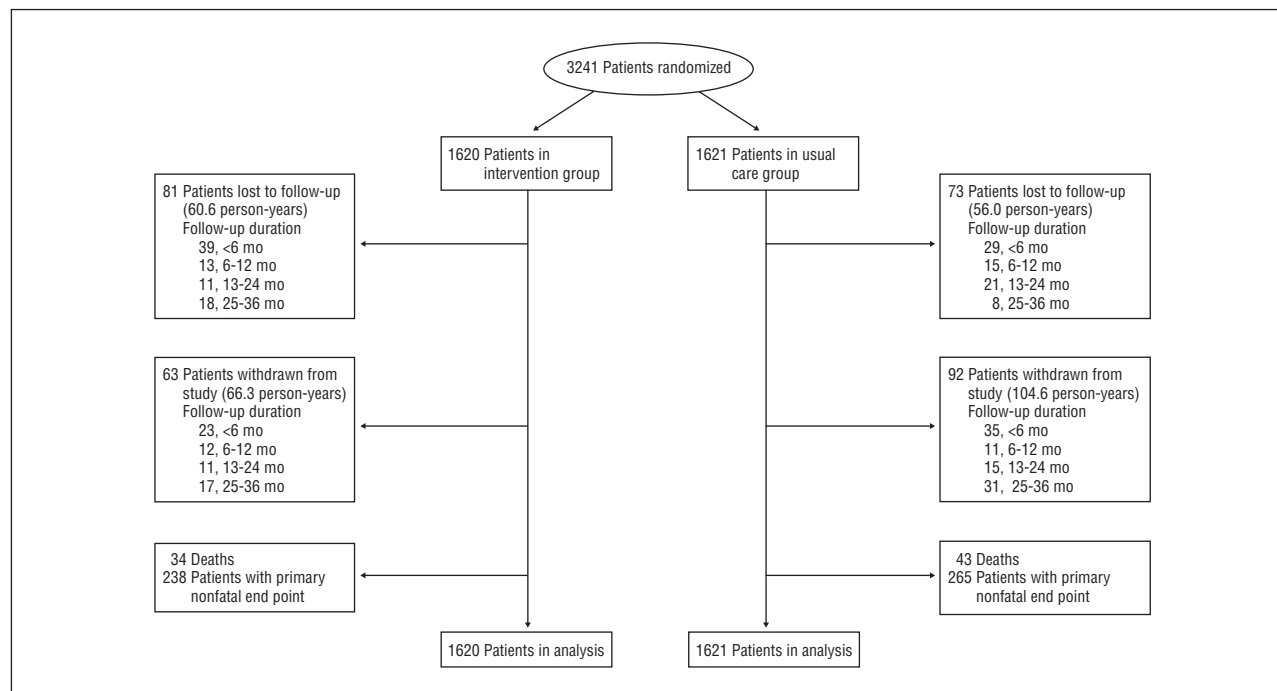
Group Information: A list of the GOSPEL Investigators is given at the end of this article.

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CARDIAC REHABILITATION programs (CRPs) after a diagnosis of coronary heart disease (CHD) have gradually evolved over the past 2 decades from an exercise-based intervention into a comprehensive, professional lifestyle program including smoking cessation, diet modification, control of cardiovascular (CV) risk factors, and behavioral interventions aimed at changing exercise, psychological stress, and vocational components of lifestyle habits.<sup>1-6</sup> Current CRP procedures rely on short-term interventions and are not adequately implemented because patients with CHD do not reach the therapeutic goals for their specific risk profile.<sup>7-10</sup>

Short-term approaches are, in fact, unlikely to yield long-term benefits, to have an impact on quality of life, or to decrease morbidity and mortality.<sup>10-14</sup> Finally, discontinuation of medication after myocardial infarction (MI) is frequent and occurs early after hospital discharge, although the issue of undertreatment has been addressed by only a few, small-scale studies.<sup>11,13,15,16</sup>

The Global Secondary Prevention Strategies to Limit Event Recurrence After Myocardial Infarction (GOSPEL) Study is a randomized controlled clinical trial designed to assess the efficacy of 2 strategies of secondary prevention with different duration and intensity of intervention following post-MI standard CRP.



**Figure 1.** Study flowchart.

## METHODS

The protocol of the GOSPEL Study has been published elsewhere.<sup>17</sup> In brief, the GOSPEL Study was a randomized trial performed in 78 Italian cardiac rehabilitation centers adopting a prospective, randomized, open-label, blinded, end point evaluation design and testing the efficacy of long-term, reinforced, multifactorial educational and behavioral intervention vs usual care after MI.

The institutional review boards of participating centers approved the protocol, and all patients provided written informed consent. Centers were selected for the study on the basis of documented experience in CRP, availability of expert personnel trained in counseling techniques, and a tradition of research in CV disease. The investigators underwent adequate training in the study procedures before the start of the trial. The study was independently managed and analyzed by the coordinating center.

To increase the generalizability of the results, broad eligibility criteria were adopted. Patients enrolled in the GOSPEL Study who had had a recent MI (within <3 months) were routinely referred to a cardiac rehabilitation center, residential or ambulatory, irrespective of revascularization procedures received after the index event. Exclusion criteria were age older than 75 years, an unfavorable short-term outlook (eg, overt congestive heart failure, cancer), any systemic disease limiting exercise, and inability to participate in the trial for any logistic reason.

All patients completed a standard CRP lasting approximately 1 month and consisting of supervised exercise sessions and comprehensive lifestyle and risk factor management along with optimization of medical therapy. After completion of the standard CRP, the patients were randomized in a one-to-one fashion to either an intensive, 3-year-long, multifactorial intervention (intervention group) or usual care (control group). Randomization was centrally determined by fax at the coordinating secretariat using a computerized algorithm.

We planned the procedures of the trial to resemble as closely as possible the routine care after MI. Patients were required to perform follow-up visits at 6 months, 1 year, 2 years, 3 years,

and then yearly until December 2005, when the last randomized patients completed the planned 3-year program (**Figure 1**).

## EXPERIMENTAL INTERVENTION

The multifactorial, continued educational, and behavioral program was performed by a cardiac rehabilitation team composed of a specialist cardiac nurse, a physiotherapist, and a cardiologist (who was the supervisor). A clinical psychologist and occupational therapist could be recruited if needed.

A letter was sent to patients' family physicians informing them of the study and inviting their collaboration in the study objectives. Comprehensive cardiac rehabilitation sessions with one-to-one support were held monthly from month 1 to month 6, then every 6 months for 3 years. Each session consisted of 30 minutes of supervised aerobic exercise, plus lifestyle and risk factor counseling lasting at least 1 hour and reinforcement of preventive interventions lasting approximately 30 minutes. To improve adherence to lifestyle modification and help patients adopt a positive role in the care of their own health, a booklet explaining how to deal with exercise, diet, smoking cessation, and stress management was distributed. The mutual support of family members (eg, spouses) was encouraged in ad hoc meetings together with the patients to make correct lifestyle habits more likely to be maintained in the long run.<sup>18</sup>

The intervention was aimed at individualizing risk factor and lifestyle management, and pharmacological treatments were based on current guidelines.<sup>3,5</sup> The targets of the intervention strategy were to give up smoking, adopt a healthy Mediterranean diet,<sup>19</sup> increase physical activity up to at least 3 h/wk at 60% to 75% of the mean maximum heart rate, maintain body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of 25 or less, blood pressure of 140/85 mm Hg or lower ( $\leq 130/80$  mm Hg for patients with diabetes mellitus [DM]), total cholesterol level of 200 mg/dL or lower, low-density lipoprotein (LDL) cholesterol level lower than 100 mg/dL, blood glucose level of 110 mg/dL or lower, and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) level lower than 7.0% in subjects with DM.<sup>3-5,20,21</sup> Pharmacologi-

cal treatments, including antiplatelet agents, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs),  $\beta$ -blockers, statins, and omega-3 polyunsaturated fatty acids, were positively recommended to all patients. (To convert total cholesterol and LDL cholesterol to millimoles per liter, multiply by 0.0259; to convert HbA<sub>1c</sub> to a proportion of total hemoglobin, multiply by 0.01.)

## CONTROL GROUP

A letter was sent to family physicians recommending secondary prevention goals. After the standard, post-MI CRP, patients in the usual care group reported to their reference center only to undergo the 6-month and then annual scheduled assessments. After each assessment, a copy of the results of laboratory and exercise tests was forwarded to the family physician who was responsible for any further medical decisions.

## ASSESSMENTS AND PROCEDURES

Data collection procedures were the same for both groups. At baseline and at each follow-up visit, the following information was collected: vital signs and symptoms, BMI, 12-lead electrocardiogram, symptom-limited exercise stress test, check of compliance, and assessment of adverse events. Blood pressure was the mean of 2 measures taken 2 minutes apart with a manual sphygmomanometer. Laboratory analysis included fasting total cholesterol, high-density lipoprotein (HDL) and LDL cholesterol, triglyceride, fasting glucose, and HbA<sub>1c</sub> levels. An echocardiographic assessment of the left ventricular ejection fraction was performed at baseline.

Because the GOSPEL Study was designed as a large-scale, pragmatic trial with patients enrolled and followed by their own cardiologists in the real-world setting, it was deemed unlikely that full-scale questionnaires on food frequency and leisure time physical activity could be effectively administered in a busy clinical setting at multiple time points during 3 years of follow-up. Thus, a brief questionnaire was designed with food items selected to maximize detection of dietary variation among Italian adults.<sup>22,23</sup> Questions focused on the frequency of usual consumption of cooked vegetables, raw vegetables, fruits, fish, olive oil, and butter. Each item was scored on an ordinal scale from 1 to 4 based on frequency of consumption, and scores were summed to obtain a Mediterranean diet score (score range, 6 [worst] to 24 [best]) that was evaluated in prespecified indicator categories. Questionnaires on smoking habits, leisure time physical activity (3 items; score range, 3 [most unfit] to 12 [ $\geq 3$  h/wk of exercise]), and self/stress management (7 items; score range, 28 [inadequate self/stress management] to 7 [optimal self/stress management]) were administered at each visit by a trained nurse. A psychological and quality-of-life evaluation was performed using the Cognitive Behavioral Assessment Hospital form validated for the Italian population at baseline and after 1 year.<sup>24</sup> Information on the utilization of health care resources was collected from medical records at each study visit.

The primary combined end point included CV mortality, nonfatal MI, nonfatal stroke, hospitalization for angina pectoris or heart failure, and urgent unplanned revascularization procedure. Acute MI was defined as at least 2 of the following: chest pain of typical intensity and duration; ST-segment elevation or depression of 1 mm or more in any limb lead of the electrocardiogram, of 2 mm or more in any precordial lead, or both; or at least a doubling of necrosis enzymes. Diagnosis of nonfatal stroke required unequivocal signs or symptoms of persistent neurological deficit, with sudden onset and a duration of more than 24 hours. Diagnosis of fatal stroke was based on the same criteria. Alternatively, we used the diagnosis documented in hospital records or

on death certificates. Validation of the clinical events included in the primary end points was assured by the executive committee of the study blinded to the patient's group allocation. Secondary clinical end points were major CV events (ie, CV mortality plus nonfatal MI and nonfatal stroke), cardiac events (cardiac death plus nonfatal MI), and fatal plus nonfatal stroke. Additional analyses were performed for total mortality and sudden death. Secondary end points also included the modification of diet; physical activity; smoking habits; self/stress management; total blood cholesterol, LDL and HDL cholesterol, and triglyceride levels; glycemic control; BMI; and blood pressure. In addition to measuring the effect of the interventions on lifestyle habits, the latter variables were also used to measure the feasibility of the tested strategies (eg, adherence to or compliance with them).

## STATISTICAL ANALYSIS

We estimated the cumulative rate of the primary end point in the control group to be 30% over 3 years of follow-up by summing the incidence rates of the individual events included in the primary end point and discounting the final estimate to allow for multiple events in the same subject.<sup>25,26</sup> To detect a 15% risk reduction with the intensive approach vs usual care approach with 80% power and a 2-sided significance at the  $\alpha = .05$  level, at least 1600 patients in each arm had to be enrolled in the study. The analysis of secondary end points was planned as part of the protocol. Owing to the limited power of such analysis, no correction for multiplicity of comparisons was envisaged for the secondary end points. Statistical analysis was intention-to-treat, using Kaplan-Meier survival curves and log-rank tests. Hazards ratios (HRs) and 95% confidence intervals (CIs) were calculated by fitting Cox proportional hazards models. Continuous data are reported as means (SDs), categorical data as percentages. Mixed models for repeated measurements with treatment as fixed effect and time as random effect were used to test the change from baseline and any time during the course of the study.<sup>27-29</sup> The difference of continuous variables between intervention and control groups during and at the end of the study was adjusted for the values at baseline.

The significance level for all tests was set at  $P = .05$ . All  $P$  values are 2-sided. All statistical analyses were performed using SAS statistical software (version 9.1; SAS Inc, Cary, North Carolina).

## RESULTS

From January 2001 through December 2002, 3241 of 3778 eligible patients were randomized into the trial (Figure 1) and followed for 10 249.9 person-years. Vital status at the study end was ascertained for 3087 patients (95.2%). A total of 154 patients (4.7%) were lost to follow-up, and 155 (4.8%) withdrew their consent during the course of the study. These patients were followed by the GOSPEL investigators according to the procedures established in the protocol for a total of 116.6 and 170.8 person-years, respectively.

The median time from the index MI to randomization was 61 days. Baseline demographic and clinical characteristics were balanced across the 2 groups (**Table 1**) and define a relatively low-risk post-MI population, with 8.4% of patients older than 70 years and 7.3% with an echocardiogram-documented ejection fraction of less than 40%. Most of the patients were prescribed aspirin (84%),  $\beta$ -blockers (76%), statins (70%), or ACE inhibitors and ARBs (61%). Coronary revascularization procedures before randomization were performed in 67% of patients (Table 1).

A total of 119 patients (3.7%) withdrew from the program within the first 6 months of the study, 62 in the intervention group and 57 in the usual care group. At baseline, the characteristics of the patients who discontinued the program were comparable with those of patients who completed the final assessment visit (data not shown).

## CLINICAL END POINTS

**Figure 2** and **Table 2** show the full efficacy profile of the interventions. The intensive intervention decreased nonsignificantly the absolute risk of the combined primary end point by 2.1% (HR, 0.88; 95% CI, 0.74-1.04;  $P=.12$ ) compared with usual care. The intensive intervention decreased CV mortality plus nonfatal MI and stroke by 33% (95% CI, 0.47-0.95;  $P=.02$ ), cardiac death plus nonfatal MI by 36% (95% CI, 0.43-0.94;  $P=.02$ ), and nonfatal MI by 48% (95% CI, 0.31-0.86;  $P=.01$ ) with respect to usual care. Total mortality, sudden death, and total stroke decreased, although not significantly, by 21% ( $P=.29$ ), 38% ( $P=.24$ ), and 32% ( $P=.33$ ), respectively.

The intensive intervention decreased the other events in the primary end point to a variable extent and nonsignificantly ( $P$  values range from .22 to .67), the benefit ranging from 9% reduction of the risk of undergoing a percutaneous coronary intervention (PCI) procedure to 28% reduction of the risk of hospitalization for heart failure.

## LIFESTYLE HABITS

Lifestyle habits were similar in the 2 groups at baseline and improved in both groups during the study. The improvement was, however, significantly larger ( $P<.01$ ) in the intervention group for the scores for physical activity, stress, and dietary habits (**Figure 3**).

At baseline, the mean (SD) scores for physical activity were 6.7 (2.5) and 6.6 (2.4) in the intervention and usual care groups, respectively. At 6 months, it increased by 24.3% (mean score, 7.5 [2.2]) in the intervention group and by 18.2% (7.1 [2.3]) in the usual care group (Figure 3). Therefore, the 6-month score for physical activity was 6.1% higher in the intervention group ( $P<.01$ ). The difference in the level of physical activity from baseline between the 2 groups was maintained throughout the study (23.8% vs 18.8%; difference, 5%;  $P=.01$ ).

Overall, 26.1% of patients had Mediterranean-like dietary habits (score  $>19.0$ ) at baseline, which rose to 59.6% at 6 months. At baseline, the mean (SD) dietary score was 16.6 (2.8) in the intensive group and 16.6 (2.7) in the usual care group. At 6 months, it increased by 18% (mean score, 19.1 [2.2]) in the intervention group and 14.1% (18.6 [2.3]) in the usual care group. Therefore, the 6-month dietary score was 3.9% higher in the intervention group than in the usual care group ( $P<.001$ ). The difference in dietary habits from baseline between the 2 groups was maintained throughout the study (17.9% vs 14.5%; difference, 3.4%;  $P<.001$ ), the rate of patients with Mediterranean-like diet (score  $>19.0$ ) being higher in the intervention group than in the control group ( $P<.001$ ) (Figure 3).

Compared with baseline values, the percentage of subjects with better self/stress management (score  $<14.0$ )

**Table 1. Baseline Characteristics of the Patients Who Were Randomly Assigned<sup>a</sup>**

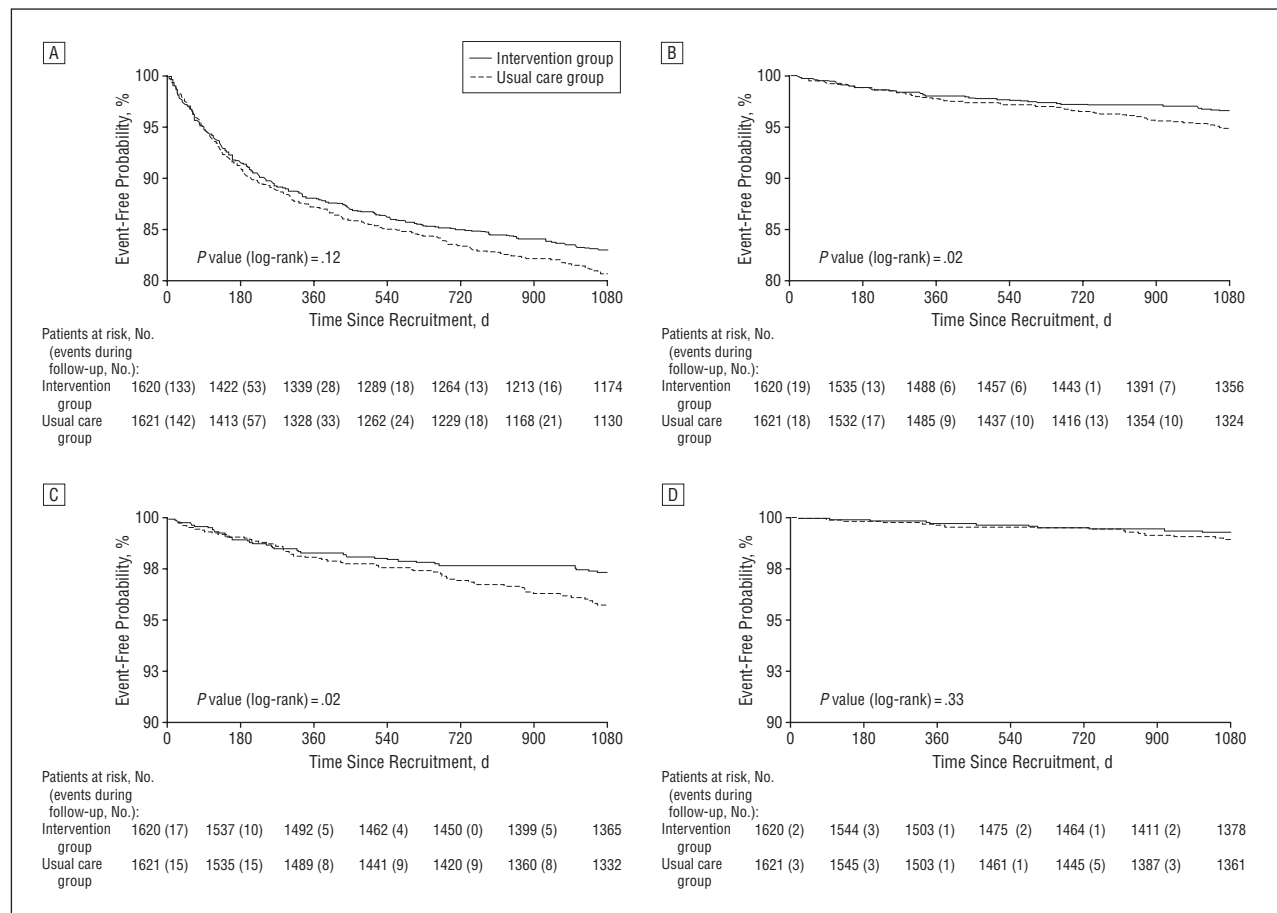
Characteristic	Total (N=3241)	Intervention Group (n=1620)	Usual Care Group (n=1621)
Age, mean (SD), y	57.9 (9.2)	57.8 (9.1)	58.0 (9.3)
>70 y	271 (8.4)	131 (8.1)	140 (8.6)
Female	444 (13.7)	229 (14.1)	215 (13.3)
<5 y of education	1072 (33.1)	541 (33.4)	531 (32.8)
Retired	1391 (42.9)	692 (42.7)	699 (43.1)
Post-MI findings			
Anterior MI	1117 (34.5)	580 (35.8)	537 (33.1)
Post-MI angina	196 (6.1)	94 (5.8)	102 (6.3)
Post-MI heart failure	143 (4.4)	71 (4.4)	72 (4.4)
NYHA classification III-IV on admission	8 (5.7)	2 (2.9)	6 (8.3)
Days from acute MI onset, mean (SD)	60.4 (20.2)	60.9 (20.3)	59.9 (20.2)
Risk factors or comorbidities			
Diabetes mellitus	500 (15.4)	245 (15.1)	255 (15.7)
Hypertension	1441 (44.5)	727 (44.9)	714 (44.1)
Hypercholesterolemia	1674 (51.7)	839 (51.8)	835 (51.5)
Overweight (BMI, 25-30)	1622 (50.1)	806 (49.8)	816 (50.3)
Active smoker	1380 (42.6)	688 (42.5)	692 (42.7)
Atrial fibrillation	134 (4.1)	72 (4.4)	62 (3.8)
Intermittent claudication	85 (2.6)	38 (2.4)	47 (2.9)
Ejection fraction			
Available	2793 (86.2)	1404 (86.7)	1389 (85.7)
Mean (SD), %	52.7 (9.9)	52.6 (9.7)	52.8 (10.0)
$\leq 40\%$	235 (7.3)	110 (6.8)	125 (7.8)
Post-MI invasive procedures			
Coronary angiography	2446 (75.5)	1217 (75.1)	1229 (75.8)
Nonsignificant stenosis	123 (5.1)	60 (5.0)	63 (5.2)
Left main stenosis	152 (6.2)	72 (5.9)	80 (6.5)
$\geq 1$ vessel	2160 (88.7)	1081 (89.1)	1079 (88.3)
CABG	866 (26.7)	453 (28.0)	413 (25.5)
PCI	1351 (41.7)	658 (40.6)	693 (42.8)
PCI/CABG	2180 (67.3)	1091 (67.4)	1089 (67.2)
Pharmacological treatments			
Aspirin	2721 (84.0)	1363 (84.1)	1358 (83.8)
Other antiplatelet agents	679 (21.0)	327 (20.2)	352 (21.7)
Calcium channel blockers	423 (13.1)	228 (14.1)	195 (12.0)
$\beta$ -Blockers	2468 (76.2)	1255 (77.5)	1213 (74.8)
Nitrates	1055 (32.6)	510 (31.5)	545 (33.6)
Diuretics	497 (15.3)	234 (14.4)	263 (16.2)
ACE inhibitors or ARBs	1975 (60.9)	982 (60.6)	993 (61.3)
Oral antidiabetic drugs	238 (7.3)	120 (7.4)	118 (7.3)
Insulin	101 (3.1)	53 (3.3)	48 (3.0)
Lipid-lowering agents	2258 (69.7)	1138 (70.3)	1120 (69.1)
PUFA	962 (29.7)	486 (30.0)	476 (29.4)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass grafting; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PUFA, omega-3 polyunsaturated fatty acids.

<sup>a</sup>Data are given as number (percentage) except where indicated. Numbers do not always sum to group totals owing to missing information for some variables. Patients could have had more than 1 type of comorbidity, undergone more than 1 type of index procedure, or received more than 1 type of pharmacotherapy.

almost doubled at 6 months in both groups (48.1% vs 40.9%). At baseline, the mean (SD) scores for self/stress management were 16.3 (3.8) and 16.2 (3.8) in the intervention and usual care groups, respectively. At 6 months, this figure decreased by 12.1% (14.0 [3.4]) in the intervention group and 8.3% (14.5 [3.6]) in the usual





**Figure 2.** Cumulative Kaplan-Meier estimates of the rates of key study end points during the follow-up period among 3241 patients with recent myocardial infarction (MI). A, Data for the primary composite end point (cardiovascular mortality, nonfatal MI, nonfatal stroke, and hospitalization for angina pectoris, heart failure, or urgent revascularization procedure). The hazard ratio (HR) for the intensive intervention, compared with usual care, for the primary efficacy end point at the study end was 0.88 (95% confidence interval [CI], 0.74-1.04;  $P=.12$ ). B, Data for the secondary efficacy end point (death from cardiovascular causes, nonfatal MI, or nonfatal stroke). The HR for the intensive intervention, compared with usual care, for the primary efficacy end point at the study end was 0.67 (95% CI, 0.47-0.95;  $P=.02$ ). C, Data for the secondary efficacy end point (cardiac death plus nonfatal MI). The HR for the intensive intervention, compared with usual care, for the primary efficacy end point at the study end was 0.64 (95% CI, 0.43-0.94;  $P=.02$ ). D, Data for the secondary efficacy end point (fatal plus nonfatal stroke). The HR for the intensive intervention vs usual care, regarding the primary efficacy end point at the study end was 0.68 (95% CI, 0.32-1.47;  $P=.33$ ). The  $P$  values for the end points were calculated with the use of the Cox proportional hazards model.

**Table 2. Overall Efficacy Profile of Intervention vs Usual Care at the 3-Year Follow-up<sup>a</sup>**

Primary End Point <sup>b</sup>	Total (N=3241)	Intervention Group (n=1620)	Usual Care Group (n=1621)	HR (95% CI)	P Value <sup>c</sup>
Overall	556 (17.2)	261 (16.1)	295 (18.2)	0.88 (0.74-1.04)	.12
CV mortality	42 (1.3)	18 (1.1)	24 (1.5)	0.75 (0.41-1.38)	.35
Nonfatal MI	67 (2.1)	23 (1.4)	44 (2.7)	0.52 (0.31-0.86)	.01
Nonfatal stroke	24 (0.7)	11 (0.7)	13 (0.8)	0.84 (0.38-1.88)	.67
PCI	303 (9.4)	144 (8.9)	159 (9.8)	0.91 (0.72-1.14)	.39
CABG	95 (2.9)	45 (2.8)	50 (3.1)	0.90 (0.60-1.34)	.60
Hospitalization for HF	57 (1.8)	24 (1.5)	33 (2.0)	0.72 (0.43-1.22)	.22
Hospitalization for AP	171 (5.3)	80 (4.9)	91 (5.6)	0.88 (0.65-1.18)	.39
Other end points					
CV mortality, MI, and stroke	129 (4.0)	52 (3.2)	77 (4.8)	0.67 (0.47-0.95)	.02
Cardiac death and nonfatal MI	105 (3.2)	41 (2.5)	64 (4.0)	0.64 (0.43-0.94)	.02
Fatal and nonfatal stroke	27 (0.8)	11 (0.7)	16 (1.0)	0.68 (0.32-1.47)	.33
Sudden death	26 (0.8)	10 (0.6)	16 (1.0)	0.62 (0.28-1.37)	.24
Total mortality	77 (2.4)	34 (2.1)	43 (2.7)	0.79 (0.50-1.23)	.29

Abbreviations: AP, angina pectoris; CI, confidence interval; CABG, coronary artery bypass grafting; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

<sup>a</sup>Data are given as number (percentage), except where indicated.

<sup>b</sup>Defined as a composite end point comprising the first of any of these events: cardiovascular mortality, nonfatal MI, nonfatal stroke, and hospitalization for AP, HF, or urgent revascularization procedure. Patients could have had more than 1 type of end point.

<sup>c</sup> $P$  values were calculated with the use of the Cox proportional hazards model. The  $P$  value for the prespecified analysis for the primary end point was  $<.05$ .

care group. Therefore, the 6-month score for self/stress management adjusted for baseline was 3.8% lower in the intervention group ( $P < .001$ ). The difference in scores from baseline between the 2 groups was maintained throughout the study (14.1% vs 9.6%; difference, 4.5%;  $P < .001$ ). Similarly, the rate of patients with better self/stress management (score  $< 14.0$ ) was higher in the intervention group ( $P < .001$ ) (Figure 3).

At 6 months, the differences in levels of total blood cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides between the 2 groups were  $-2.3\%$  ( $P = .01$ ),  $2.4\%$  ( $P = .06$ ),  $-2.0\%$  ( $P = .02$ ), and  $-4.2\%$  ( $P = .02$ ), respectively (Figure 4). When we compared the mean levels in the 2 arms during the course of the study, the differences between the 2 groups in levels of total blood cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were  $-1.5\%$  ( $P = .04$ ),  $2.5\%$  ( $P = .25$ ),  $-1.2\%$  ( $P = .12$ ), and  $-3.2\%$  ( $P = .19$ ), respectively (Figure 4). Glycemic levels increased slightly over time in both groups to the same extent (data not shown). The HbA<sub>1c</sub> levels (Figure 5) showed no change in either group.

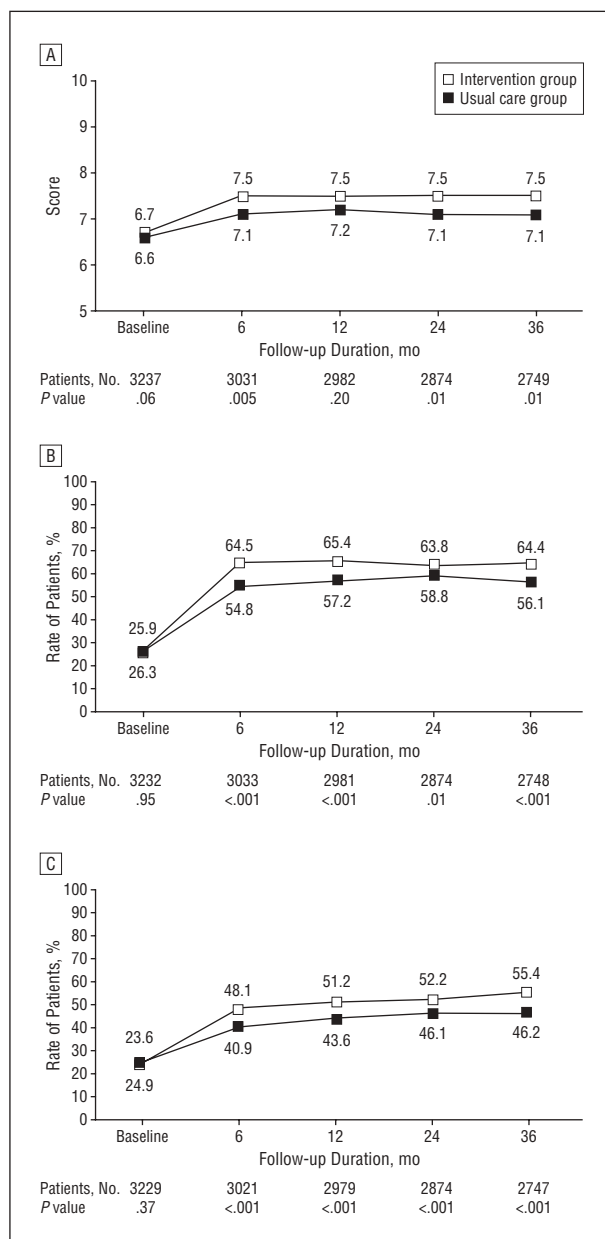
At baseline, the mean (SD) BMIs were 26.5 (3.5) and 26.6 (3.6) in the intervention and usual care groups, respectively. At 6 months, it increased by 0.7% (26.6 [3.5]) in the intervention group and 0.9% (26.8 [3.5]) in the usual care group (Figure 5); that is, there was a 0.2% lower increase in BMI in the intervention group ( $P = .17$ ). During the course of the study, BMI increased by 1.7% and 2.1% in the intervention and usual care groups, respectively, a difference that was statistically significant (0.4%;  $P = .03$ ).

At 6 months, smoking was significantly more likely to have been discontinued in the intensive group than in the usual care group (80.2% vs 75.1%;  $P = .02$ ). When we compared the percentage of quitters over the whole course of the study, the efficacy of the intervention against smoking declined, and eventually the absolute difference between the 2 groups was “only” 4.2% ( $P = .60$ ).

Compared with the usual care group, the intervention group more frequently reached the blood pressure targets at 6 months (62.4% vs 59.5%) and at the end of the study (59.9% vs 55.8%), although the difference between the 2 groups was not statistically significant (Figure 5). The use of medications at baseline was similar in the 2 groups. During follow-up, a progressive decline in the rate of use of aspirin,  $\beta$ -blockers, and ACE inhibitors was seen in both groups (Figure 6). Such reduced prescription was more apparent in the usual care group. At the end of the study, the prescription of ACE inhibitors was significantly higher ( $P = .02$ ) in the intervention group than in the usual care group. The prescription of statins increased notably during the study, and at the end it was significantly higher ( $P < .001$ ) in the intervention group (84.2%) than in the usual care group (79.1%).

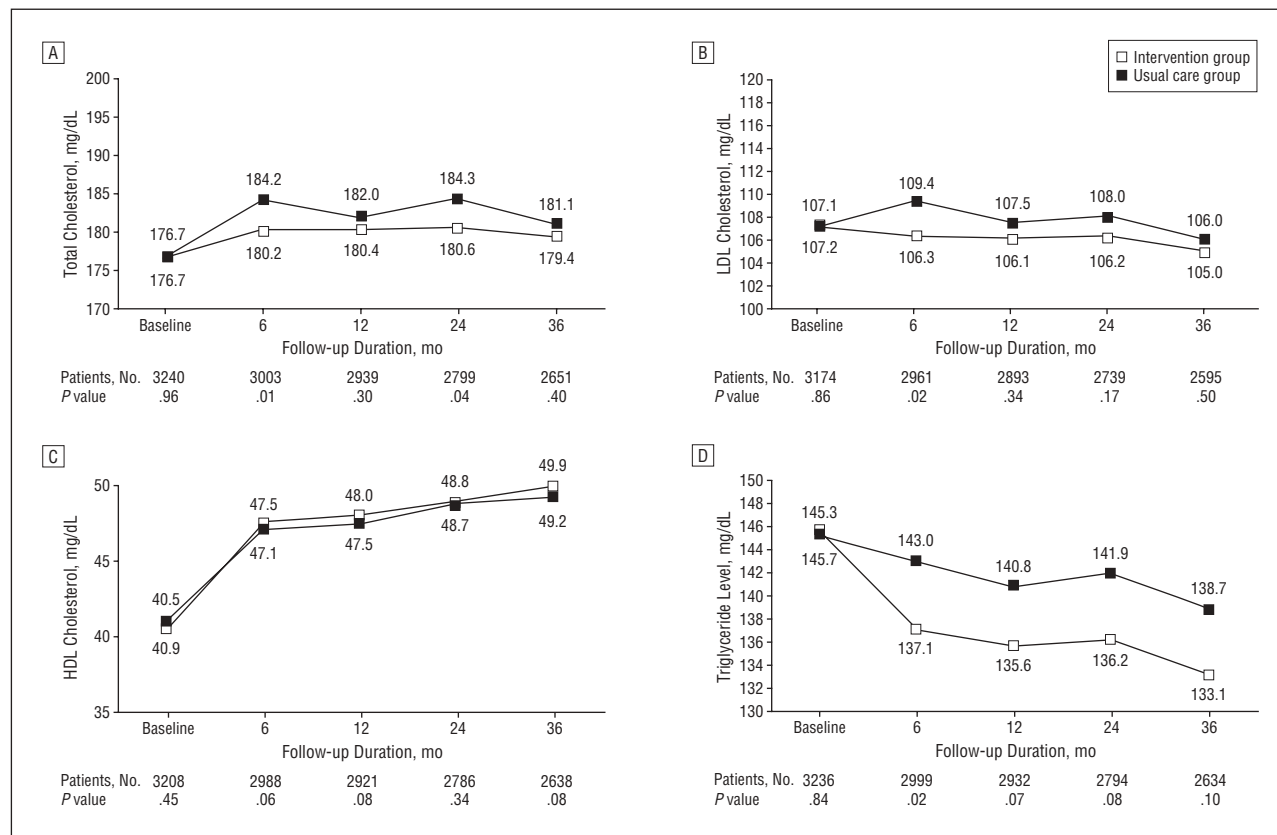
## COMMENT

The GOSPEL Study was designed to test a long-term preventive strategy after MI as well as to establish a high-level standard for secondary prevention. After 3



**Figure 3.** Lifestyle changes over 3 years for the intervention and the usual care groups. A, Physical activity score (range, 3.0-12.0). Time effect,  $P < .001$ ; time  $\times$  treatment,  $P = .01$ . B, Dietary habits, showing the rate of patients in the highest quartile (a score of  $\geq 19.0$  indicates a Mediterranean-like diet). Time effect,  $P < .001$ ; time  $\times$  treatment,  $P < .001$ . C, Stress score, showing the rate of patients in the lowest quartile (a score of  $\leq 14.0$  indicates a better self/stress management). Time effect,  $P < .001$ ; time  $\times$  treatment,  $P < .001$ .

years, the integrated, multifactorial, reinforced approach proved effective in countering the risk factors and medication adherence deterioration over time and was able to induce a considerable improvement in lifestyle habits. In line with such results, all the clinical end points were reduced by the intensive intervention. The primary end point was decreased nonsignificantly by 12% ( $P = .12$ ). However, the secondary outcome measures were significantly and importantly reduced: CV mortality, nonfatal MI, and stroke by 33% ( $P = .02$ ) and cardiac death plus nonfatal MI by 36% ( $P = .02$ ). In addition, total stroke and total mortality were decreased



**Figure 4.** Blood lipid concentrations during the 3 years of the study. A, Total cholesterol level. Time effect,  $P < .001$ ; time  $\times$  treatment,  $P = .04$ . B, Low-density lipoprotein (LDL) cholesterol level. Time effect,  $P = .003$ ; time  $\times$  treatment,  $P = .12$ . C, High-density lipoprotein (HDL) cholesterol level. Time effect,  $P < .001$ ; time  $\times$  treatment,  $P = .25$ . D, Triglyceride level. Time effect,  $P < .001$ ; time  $\times$  treatment,  $P = .19$ . To convert total, LDL, and HDL cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.

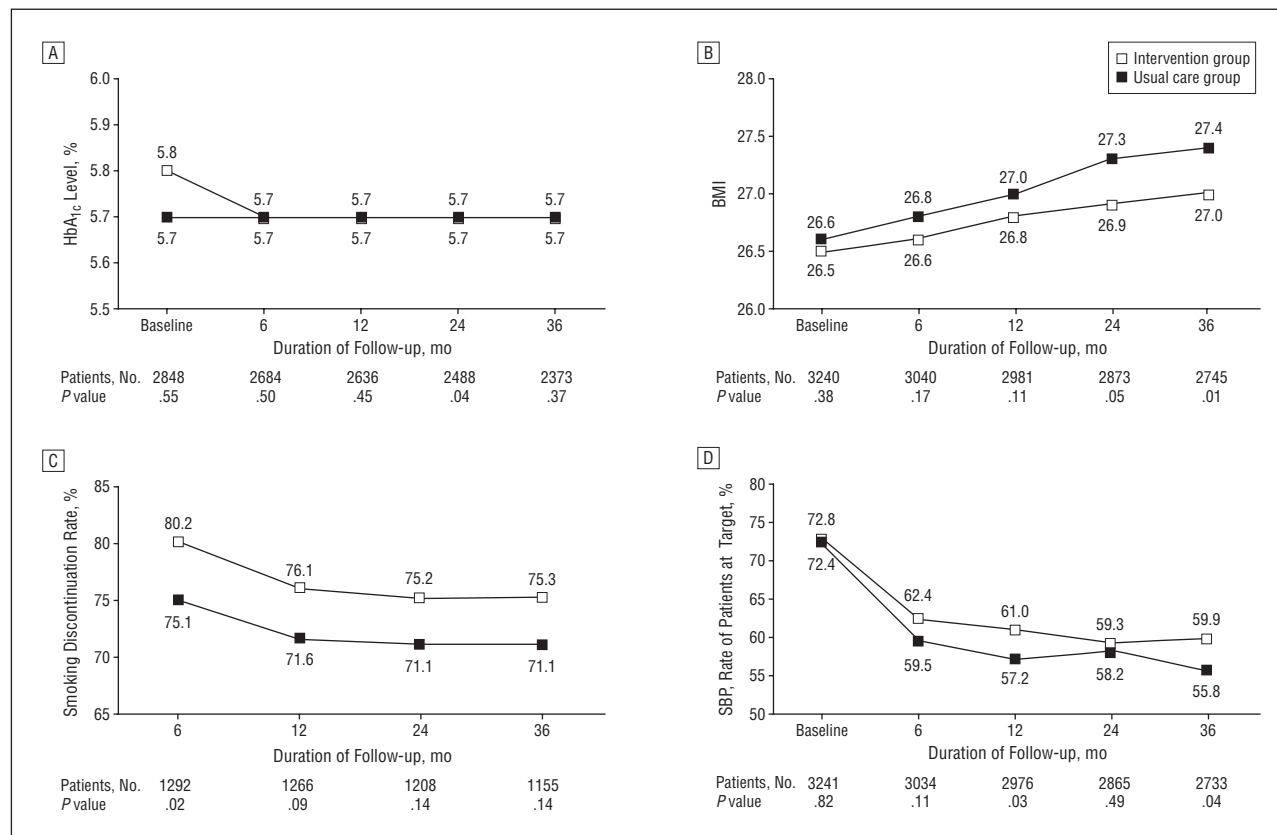
by 32% and 21%, respectively. The extent of the reduction for the individual events included in the primary end point varied from a statistically significant 48% ( $P < .01$ ) risk reduction for MI (1.4% vs 2.7%) to a non-significant 9% ( $P = .39$ ) relative risk reduction for PCI procedures (8.9% vs 9.8%).

The absence of a formal statistical significance for the primary study end point is not surprising. First, the incidence of the primary end point was much lower than expected (17% instead of 30%), probably because of the recent changes of therapy after MI in this population compared with the GISSI-Prevenzione population, which had been recruited almost 10 years before the start of the GOSPEL Study.<sup>25</sup> Second, the primary study end point was a combination of hard, but relatively rare events, such as nonfatal MI, the risk of which was halved, and PCI and CABG procedures, which were by far the most prevalent events but had a nonsignificant 10% reduction ( $P = .39$  and  $P = .60$ , respectively). Third, the rate of smoking cessation in our population of patients followed in cardiac rehabilitation centers is greater than that observed in the United States, and such a high background rate of smoking cessation may have minimized the potential effects of the intervention.

In any case, to our knowledge this is the first clinical trial showing, in a large sample of more than 3200 patients who experienced an MI, that an integrated, multifactorial, reinforced, and individually tailored second-

ary prevention program is effective in reducing major CV events. The reliability of this benefit is corroborated by the parallel benefit in preventing the long-term deterioration of several risk factors and lifestyle behaviors. Indeed, a greater proportion of patients in the intervention group achieved the expected targets for physical activity, healthy diet, stress management, weight reduction, triglyceride and HDL cholesterol levels, and blood pressure.

The GOSPEL Study results on the time-related worsening of the management of cardiac risk factors in CHD are consistent with those of prior studies and confirm that the gains for risk factors and lifestyle behavior achieved with the initial CRP in patients who experienced an MI are not maintained over the course of time.<sup>7,8,10-13</sup> Discontinuation of cardioprotective medications was also a common feature found in the first year after completion of CRP. Although international guidelines strongly recommend actions to reinforce the therapeutic alliance between patients and physicians,<sup>2-5</sup> the level of secondary prevention is far from optimal.<sup>1,3,7,9,11,12</sup> The positive changes in medication use we observed in the intervention group were relevant, although not massive and not always statistically significant, and included a larger use of aspirin, ACE inhibitors, and  $\beta$ -blockers. Of note, the rate of prescription of statins at 3 years was remarkably high in both groups (intervention group, 84.2%; usual care group, 79.1%).



**Figure 5.** Changes in risk factors over 3 years for the intervention and the usual care groups. A, Hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels. Time effect,  $P < .97$ ; time  $\times$  treatment,  $P = .19$ . B, Body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). Time effect,  $P < .001$ ; time  $\times$  treatment,  $P = .03$ . C, Smoking habits, showing the rate of smoking discontinuation among smokers at study entry. Time effect,  $P < .001$ ; time  $\times$  treatment,  $P = .60$ . D, Systolic blood pressure (SBP), showing the rate of patients at target according to the American Heart Association/American College of Cardiology guidelines.<sup>5</sup> Time effect,  $P < .001$ ; time  $\times$  treatment,  $P = .39$ .

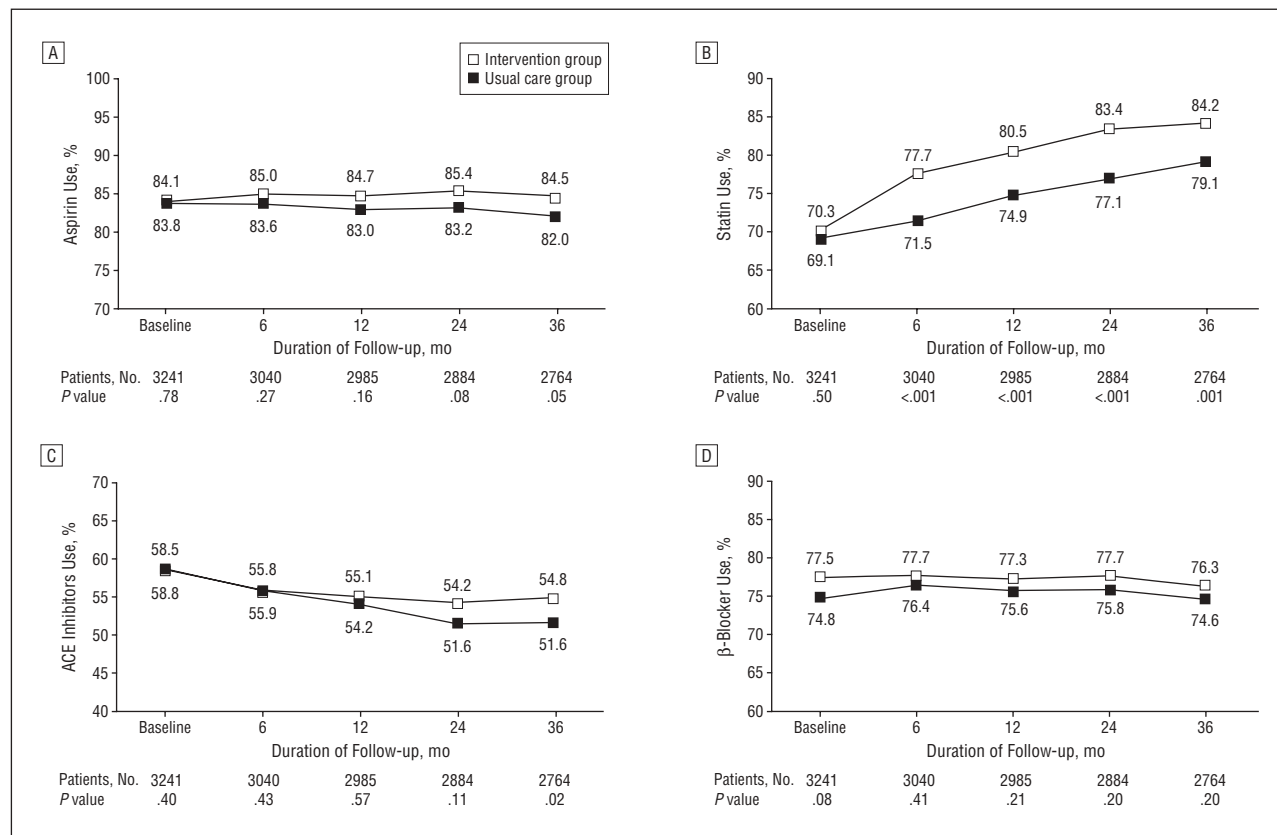
Several potential limitations warrant mention. The GOSPEL Study enrolled a broad, relatively low-risk population, with only a small proportion of patients either older than 70 years or with an echocardiogram-documented ejection fraction of less than 40%, and most of these had undergone revascularization after MI. The usual care group in the GOSPEL Study does not represent the real world of patients with recent MI because most patients in the real world do not receive standard CRP after acute MI. However, the GOSPEL trial was aimed at comparing 2 different rehabilitation strategies, not post-MI rehabilitation vs post-MI abandon of patients. Accordingly, it is possible that the annual assessment visits provided to the patients allocated to usual care (which are not routine in clinical practice) may have improved the prescription of medications and adoption of correct lifestyle habits, hence decreasing post-MI risk and so possibly downplaying the benefit of the intervention. The proportion of patients lost to follow-up and/or who dropped out of the study could seem high, but the peculiarity of the study, necessitating compliance to demanding lifestyle interventions, such as maintenance exercise, should be kept in mind. Moreover, a systematic external monitoring aimed at rescuing nonattendant patients was not implemented because this would have been inherently in contrast with an intervention program based on the convinced cooperation of the patients. These patients were maintained in the analysis, gave their con-

tribution to the study person-time, and were right-censored at the point at which their last clinical information was known to the investigators. In any case, the proportion of patients lost to follow-up or withdrawn from the study was the same in the 2 groups. Therefore, this factor was probably random with respect to the outcome.

A prolongation of the follow-up would have increased the rate of events and the power of the study to observe a long-term benefit on atherothrombotic events in the intervention group. However, the GOSPEL Study was a pragmatic study, promoted by a scientific association, funded by the industry only to assure its coordination, and conducted in the framework of clinical practice within a nation-wide hospital network. Considering this scenario, follow-up prolongation to increase the rate of study events was discussed by the steering committee but was considered unfeasible and therefore not implemented.

Misclassification of lifestyle exposures may have occurred. Because data were collected prospectively, such errors would likely be random with respect to the outcome and would cause, if anything, underestimation of the observed associations. Moreover, because of the more intensive educational intervention, there may have been a stronger tendency for patients in this group to give positive answers on the lifestyle questionnaires than those in the usual care group. Finally, some of the study sec-





**Figure 6.** Secondary prevention drug prescription in the intervention and the usual care groups. A, Aspirin use. Time effect,  $P < .09$ ; time  $\times$  treatment,  $P = .37$ . B, Statins use. Time effect,  $P < .001$ ; time  $\times$  treatment,  $P = .001$ . C, Angiotensin-converting enzyme inhibitor use. Time effect,  $P < .001$ ; time  $\times$  treatment,  $P = .001$ . D,  $\beta$ -Blocker use. Time effect,  $P < .01$ ; time  $\times$  treatment,  $P = .86$ .

ondary end points were self-reported and were not collected in an otherwise verifiable fashion.

In conclusion, the nonsignificant reduction of the primary end point, the significant reduction of major CV events, the reduction of the other clinical end points, the relevant improvement of lifestyle habits, CV risk factors, and prescription of pharmacological treatments all indicate the importance of an intensive, comprehensive, long-term secondary prevention program after MI. To our knowledge, the GOSPEL Study is the first large-scale trial to demonstrate that such a multifactorial continued reinforced intervention following MI is effective.

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