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FULL RESEARCH PAPER
Prevention in Practice

Long-term secondary cardiovascular prevention programme in patients subjected to coronary artery bypass surgery

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Aims Patients with coronary heart disease (CHD) are at very high risk of recurrent events. A strategy to reduce excess risk might be to deliver structured secondary prevention programmes, but their efficacy has been mostly evaluated in the short term and in experimental settings. This is a retrospective case–control study aimed at assessing, in the real world, the efficacy of a secondary prevention programme in reducing long-term coronary event recurrences after coronary artery bypass surgery (CABG).

Methods and results Programme participants (henceforth 'cases') were men and women aged <75 years subjected to CABG between 2002 and 2014, living within 100 km of the hospital. Key programme actions included optimization of treatments according to the most updated European preventive guidelines, surveillance of therapy adherence, and customized lifestyle counselling. Controls were analogous patients not involved in the programme because living farther than 100 km away, matched 1:1 with cases for gender, age at CABG, and year of CABG. Both groups ($n = 1248$) underwent usual periodic cardiology follow-up at our centre. Data on symptomatic or silent CHD recurrences were obtained from the hospital electronic health records. Cox analysis (adjusted for baseline differences between groups) shows that programme participation was associated with a significantly lower incidence throughout 5 years post-CABG of symptomatic [hazard ratio (95% confidence interval): 0.59 (0.38–0.94)] and silent [0.53 (0.31–0.89)] coronary recurrences.

Conclusion In a real-world setting, taking part in a structured longstanding secondary prevention programme, in addition to usual cardiology care, meaningfully lowers the risk of coronary recurrences.

Keywords Secondary cardiovascular prevention • Coronary heart disease • Coronary artery bypass graft • Implementation research • Real world

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Take-home messages

- Patients subjected to coronary revascularization have a significant residual coronary risk.
- The implementation in the real world of a comprehensive secondary cardiovascular prevention programme focusing on patient empowerment, decision sharing, and strengthening long-term adherence to a healthy lifestyle and drug therapy may, in addition to usual cardiology care, substantially reduce the risk of coronary recurrences after coronary bypass surgery.

Introduction

Patients with coronary heart disease (CHD) have a very high risk of recurrent cardiovascular (CV) events,[1] and each coronary recurrence further increases the likelihood of another one.[2] Coronary heart disease *per se* qualifies the patient for intensive secondary CV prevention, aimed to optimize the control of atherothrombotic risk factors and to reduce the risk of CV recurrence by fostering the adoption of a heart-friendly lifestyle and the appropriate utilization of evidence-based CV drugs.[1] Innovative pharmacological strategies aimed to aggressively reduce LDL-C levels,[3,4] or to target hypertriglyceridaemia[5] or inflammation[6] produced a modest absolute CV risk reduction, and, actually, the active intervention groups of the trials still remain at a high residual CV risk (cumulative incidence of events 10–12% at 3 years[3,4] and 15–20% at 5 years).[5,6] Even after coronary artery bypass graft (CABG) surgery, which patients often regard as a definitive healing treatment, the 5-year rate of recurrent coronary events in the real world is ∼15–20%.[7] Patients often perceive a coronary recurrence after CABG as a procedure failure, and they refer disappointment and discouragement.

In order to fulfil unmet needs in secondary prevention, several approaches may help, such as the development of CV drugs with an improved tolerability profile (which is a main determinant of compliance) or new compounds targeting risk factors so far considered poorly modifiable like lipoprotein (a).[8] Besides, a major barrier to an effective secondary prevention in the real-world setting is the progressively decreasing adherence to evidence-based therapies after the index event,[9–11] which also occurs in post-CABG patients.[12] Focused on this issue, implementation research seeks to develop and test ancillary strategies to reduce residual CV risk through new health system models aimed to optimize delivery of and long-term adherence to evidence-based interventions in the real world.

Different types of secondary CV prevention programmes have shown a positive impact on risk factor control and clinical prognosis.[13–15] However, most of them were short-term programmes and, to the best of our knowledge, none were focused on post-CABG patients. Moreover, previous reports refer to data gathered from selected patients in experimental settings such as randomized controlled trials.

In this study, we assessed whether a long-term secondary prevention programme carried out in the real world, in addition to usual cardiology care, reduces the residual risk of post-CABG recurrent coronary events.

Methods

Study design

This case–control study analyses the real-world data obtained from institutional clinical databases, to compare the incidence of coronary recurrences throughout 5 years after CABG surgery between two patient groups matched for sex, age at CABG, and year of CABG: (i) patients who received a routine cardiology care follow-up (controls) and (ii) patients (henceforth 'cases') who, besides routine cardiology care follow-up, adhered to a structured, personalized secondary prevention programme run by a team of internal medicine specialists, nutritionists, and nurses.

The analysis focused on patients who underwent CABG surgery at our centre between 1 January 2002 and 31 December 2014. Patients younger than 75, with normal cognitive status (without senile dementia, Alzheimer disease, or schizophrenia), autonomous mobility, and without known active malignant diseases (except skin basalioma or non-invasive melanoma) at the time of CABG were considered. The study was approved by the Institutional Review Board and by the Ethics Committee of the centre (study code R1170/20-CCM 1232).

Programme candidates and features

Patients undergoing CABG surgery and living within 100 km of the centre were invited to join the secondary prevention programme during their hospital stay. Participation in the programme was free of charge, and patients were made aware that taking part in it was not intended to substitute but to complement their usual cardiology follow-up at our centre, typically every year. The candidates who adhered initiated the programme after the post-CABG rehabilitation period, i.e. 2–3 months after surgery.

The key components of the programme were optimization of CV drug treatments, surveillance of therapy adherence, precocious attention to ensuing CV symptoms and signs, and customized lifestyle counselling. Individual targets of intervention were identified (*Table 1*), and a personalized plan was designed to reduce residual CV risk. Internists and nutritionists who run the programme were instructed to optimize patients' therapy according to the most updated European consensus and recommendations on secondary CV prevention. In addition, a number of actions were taken to promote patient empowerment (*Table 1*). All clinical data and actions were recorded in an access-based database developed in-house for the purpose of the programme. Details about programme features are provided as Supplementary material online. The programme differed from traditional cardiac rehabilitation in that it did not include a structured supervised exercise component.

Control group

Control group candidates were patients subjected to CABG at our centre, not invited to participate in the programme because living farther than 100 km away from the hospital. This distance was arbitrarily chosen as the maximal acceptable to propose further periodic visits beyond those scheduled with their cardiologists. As indicated above, usual cardiology follow-up after CABG, carried out alike in cases and controls, involved systematic long-term periodic visits at our centre.

Collection of baseline clinical features

Since January 2002, cardiothoracic surgeons and anaesthesiologists of our centre systematically collected and registered comprehensive pre-surgery clinical data of patients subjected to any type of CV surgery into an institutional electronic database. Patients' baseline characteristics

Table 1 Programme targets and actions for patient empowerment

Targets of intervention
Lipid control
Blood pressure control
Glycaemic control in diabetics or pre-diabetics
Smoking cessation
Weight reduction
Improvement of diet quality
Increasing physical activity
Stress and depression management
Actions to promote patient empowerment
CV health education aimed to increase patients' literacy
Discussion on misbelieves/disvalues (e.g. fatalism) and truths and myths about the safety and efficacy of preventive interventions (e.g. 'garlic intake is a vaccine to any CV problem' and 'influenza vaccination is dangerous')
Encouragement of self-awareness and self-care
Shared decision-making about proposed preventive interventions
Promotion of adherence and persistence of healthy lifestyle habits (e.g. smoking cessation support, nutritional guidance, nudge to physical activity) and medicine intake

CV, cardiovascular.

were obtained from this source to ascertain whether cases and controls, although matched for sex, age at CABG, and year of CABG (see section Statistical analyses), differed at the time of CABG in clinical features that might represent confounding factors.

Coronary recurrences during follow-up

Data on coronary outcomes after CABG of both groups were extracted from the centre's electronic archive containing the reports of cardiology follow-up visits. These reports, written and authenticated by the cardiologists, incorporate the information regarding clinical findings and events diagnosed and treated at our centre and in other hospitals. The last medical report filed in the centre's electronic archive, which resumes the patient clinical history and updates their health status, was fully explored to search for any predefined coronary outcome after CABG. For each patient, the time of censoring after CABG was the last visit in the hospital without CHD events or the earliest of the following: first recurrent non-fatal CHD event or fatal in-hospital CHD event. To avoid any bias in outcome adjudication, the researcher (L.V.) in charge of collecting data on coronary events from the cardiology reports was kept blinded regarding what criterion was used (place of residence) to discern between cases and controls. To maximize the chance to capture the impact of the programme on patients' medium and long-term prognosis, we excluded from the analyses patients with a follow-up post-CABG shorter than 1 year, regardless of the occurrence of coronary recurrences during such period (which are most likely related to technical problems in the anastomosis or early graft thrombosis). Events were considered 'valid outcomes' only when their wording aligned exactly with the predefined study outcomes (e.g. 'STEMI' and 'NSTEMI'). In the sporadic cases of events registered using wording not perfectly aligned with the predefined study outcomes, the diagnosis was corroborated or confuted through scrutiny of additional medical documents and/or consulting the responsible cardiologist. Data on coronary recurrences or vital status after the time of censoring were not enquired.

Predefined study outcomes

Primary outcome

The primary outcome of this study was any spontaneous post-CABG symptomatic (i.e. 'hard') coronary recurrence, including angina pectoris of any type (stable, unstable, or non-specified angina pectoris), acute myocardial infarction (AMI) (STEMI, NSTEMI, or non-specified AMI), followed or not by a revascularization procedure (percutaneous transluminal coronary angioplasty with or without stenting or redo-CABG), or cardiac death.

Secondary outcomes

As the rate of periodic cardiology tests (either stress tests or coronary imaging) in asymptomatic patients during follow-up might have differed in the two groups, potentially leading to unbalanced diagnostic test-driven procedures of coronary revascularization, asymptomatic (i.e. 'soft') coronary recurrences (induced silent myocardial ischaemia or significant silent coronary stenosis identified by coronary imaging followed or not by a new revascularization procedure) were analysed separately.

Moreover, data on levels of traditional risk factors and adherence to the main evidence-based drug therapies indicated for secondary CV prevention in the two groups during follow-up were obtained by searching the secondary prevention programme database (for cases) and the usual care cardiology reports (for controls).

Statistical analyses

To minimize between-group differences at baseline, cases and controls were matched by sex, age at CABG (±3 years), and year of CABG (±5 years). Continuous variables are presented as mean ± standard deviation and were compared using the *t*-test for independent samples. Categorical data were compared using the χ^2 test or Fisher's exact test, as appropriate.

Cox models were used to estimate crude and adjusted hazard ratios (HRs) and 95% confidence interval (CI) for coronary recurrences over 5 years of follow-up. Four different sets of covariates were considered: Model 1, unadjusted; Model 2, adjusted for previous CV events or interventions; Model 3, like Model 2 plus indexes of cardiac function; Model 4, like Model 3 plus EuroSCORE, CABG surgery procedure (CABG alone or CABG-valve combined surgery), and occurrence of immediate neurological complications. Kaplan–Meier analysis adjusted (Model 4) with conditional probability method[16] was used to generate time-to-event curves for coronary recurrences over 5 years in cases and controls. Sensitivity analyses were carried out by unadjusted Kaplan–Meier curves stratified for discrete baseline clinical features deemed as potentially relevant confounders (i.e. previous AMI and combined CABG-valve surgery). Log-rank tests were used to compare strata. All tests were two-tailed, and *P*-value <0.05 was required for statistical significance. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Between 1 January 2002 and 31 December 2014, 3062 patients were subjected to CABG surgery at our centre. Patients ≥75 years old at the day of CABG ($n = 435$) were excluded. Out of the remaining 2547 patients, 1066 lived farther than 100 km away from our centre and were considered potential controls, whereas 1481 patients resided within 100 km of our centre and were considered potential cases. Among the latter, 1062 (72%) agreed to join the programme,

whereas 419 refused due to various reasons (i.e. perception of too many medical encounters, willingness to be assisted by a single doctor, a priori reluctance to receive advice for lifestyle modifications). Accepters and decliners were comparable at baseline for age, sex, and for most of the clinical features considered, except for a higher prevalence in decliners of renal impairment, history of peripheral arterial disease and use of statins, and for worse values of EuroSCORE and some indexes of cardiac function (Supplementary material online, *Table S2*). A total of 474 patients (240 cases and 234 potential controls) had a cardiology follow-up shorter than 1 year and were excluded from the analyses. Cases and controls with at least 1-year post-CABG follow-up, matched for sex, age at CABG, and year of CABG, yielded two groups of 624 patients each (*Figure 1*).

Supplementary material online, *Table S1* describes the detailed baseline features of matched patients and the surgical procedures carried out. Briefly, the study population was characterized by a prevalence of males (89%). The mean age at CABG was 62 ± 7 years. The groups did not differ in terms of traditional CV risk factors (smoking habits, dyslipidaemia, hypertension, diabetes) and overweight/obesity categories, severity of coronary disease (prevalence of stenosis >50% in the left main coronary artery and number of coronary arteries with haemodynamically significant stenosis), renal function, and intake of evidence-based drugs for secondary prevention of CV disease. Most surgical procedures were similar in both groups (use of extracorporeal circulation, type of grafts, combined intervention with carotid surgery, and use of vasoactive drugs during the intervention), as was the incidence of peri-procedural coronary events. Conversely, a history of previous AMI, coronary revascularization or peripheral artery disease, as well as combined CABG-valve surgery were more frequent in controls than in cases. The former

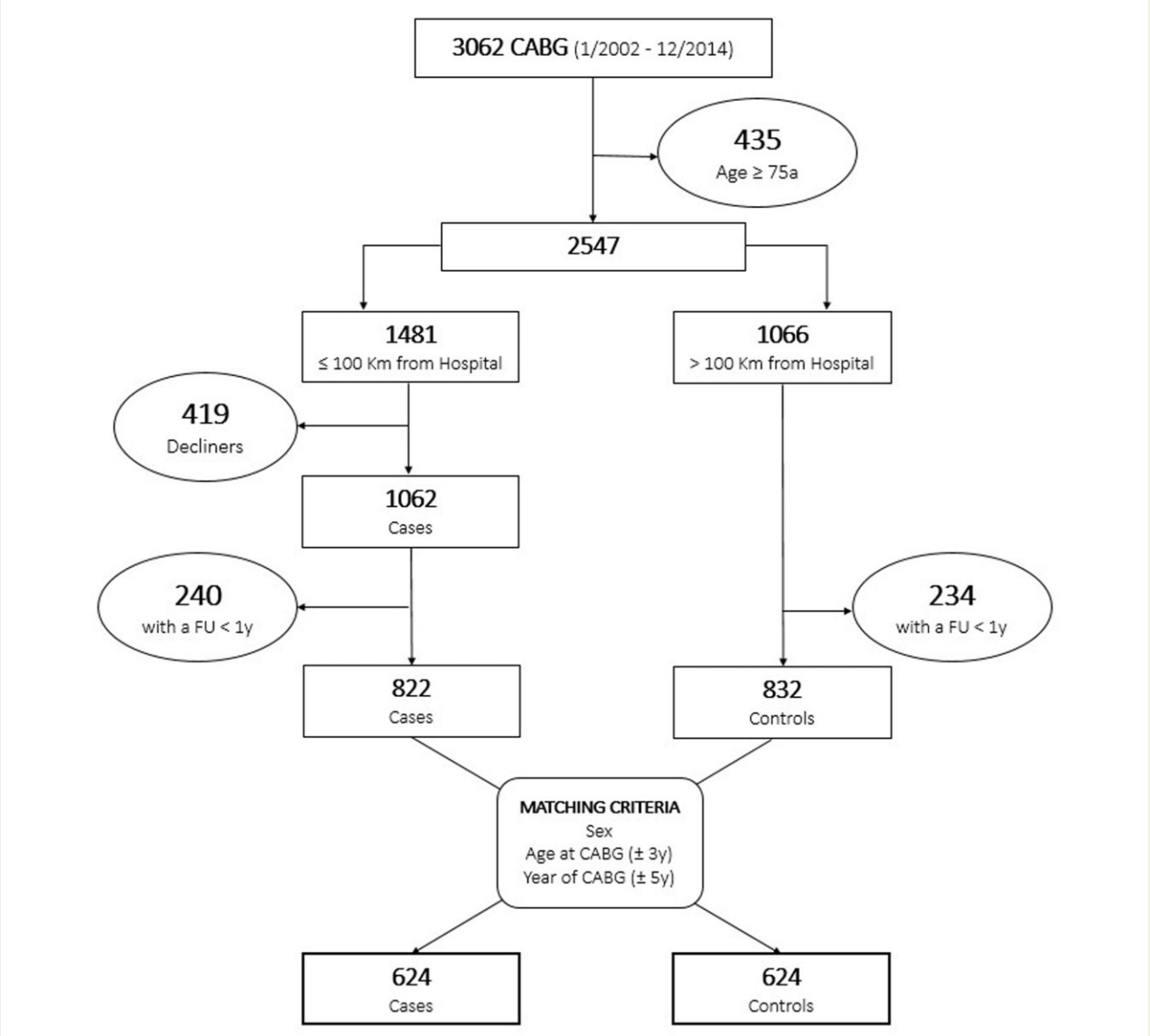

Figure 1 Study flowchart. CABG, coronary artery bypass surgery; FU, follow-up.

also had lower ejection fraction values and higher New York Heart Association categories and EuroSCORE values. The follow-up length did not differ between groups [cases: median (interquartile range): 2726 days (1642–3808); controls: 2688 days (1349–4064)].

The specific types of coronary recurrences occurring in each group are shown in *Table 2*. The incidence of hard coronary recurrences throughout 5 years after CABG was lower in cases than in controls. As shown in *Table 3*, participation in the prevention programme was associated with a significantly lower incidence of coronary recurrences in unadjusted Cox analysis (38% reduction), and the results were similar after adjusting for clusters or for all the between-group clinical differences identified at baseline (41% reduction in Model 4). The incidence of soft coronary recurrences throughout 5 years after CABG was also lower in the secondary prevention programme group than in the control group. Although this difference was not statistically significant in unadjusted Cox analysis, it was statistically significant in the fully adjusted Cox analysis (47% reduction in Model 4).

Figure 2 (upper panels) shows fully adjusted (Model 4) Kaplan–Meier curves illustrating the cumulative incidence of coronary recurrences during the 5-year follow-up in cases and controls. For both hard coronary recurrences (*Figure 2A*) and soft coronary recurrences (*Figure 2B*), the curves started to separate ~2 years after CABG surgery and kept diverging throughout the period of observation (log-rank test $P = 0.023$ for hard events and $P = 0.016$ for soft events).

A sensitivity analysis was carried out to assess whether the secondary prevention programme had an independent impact on prognosis in patients with clinical features suggestive of a different disease severity at baseline. *Figure 2* (lower panels) shows (*Figure 2C*) that cases (blue and red curves) had a significantly lower cumulative incidence of hard coronary recurrences than controls (black and green curves), especially when patients with a history of AMI are considered (red and green curves) (log-rank test $P = 0.02$), where the scissor starts after ~20 months only. The effect was less strong but still evident also considering the groups without previous AMI (black and blue curves). In these groups, indeed, the curves started to diverge ~3.5 years after CABG and did not reach statistical significance (log-rank test $P = 0.39$). Similar findings were observed in soft coronary recurrences (*Figure 2D*), but with a greater overlap than in hard events (log-rank test $P = 0.13$ for patients with a history of AMI and $P = 0.43$ for those without a history of AMI).

A further sensitivity analysis was carried out to assess whether the higher number of combined CABG-valve surgery interventions in controls than in cases influenced the results. To this purpose, patients undergoing the combined intervention ($n = 115$ controls and 73 cases) were excluded from the Cox analysis (Model 4). The results [HR (95% CI), hard events: 0.56 (0.34–0.90), soft events: 0.53 (0.31–0.92)] were practically identical to those obtained in the whole cohort.

At follow-up, cases had significantly lower numbers in traditional risk factors and significantly higher rates of adherence to anti-platelet compounds and statins than controls (Supplementary material online, *Table S3*). Cases preferentially received simvastatin, whereas atorvastatin was the most prevalent statin in controls. Moreover, rosuvastatin was more frequently used in cases than in controls. It is worth noting that 100% data were available for cases, while the record keeping of CV risk factors of controls in the usual cardiology reports was rather fragmentary.

Table 2 Coronary recurrences

Category of coronary recurrence	Cases[a] ($n = 624$)	Controls[a] ($n = 624$)
Spontaneous and symptomatic coronary recurrences—hard events, *n*		
Any kind of AMI	8	15
Fatal AMI	1	2
Non-fatal AMI (type unknown)	3	1
STEMI	0	2
NSTEMI	4	10
Stable or unstable angina	26	36
Total hard events	34	51
Asymptomatic coronary recurrences—soft events, *n*		
Silent inducible myocardial ischaemia	16	7
PTCA stenting of significant CHD found by imaging	11	31
Total soft events	27	38

AMI, acute myocardial infarction; CHD, coronary heart disease; NSTEMI, •••; PTCA, percutaneous transluminal coronary angioplasty; STEMI, •••.
[a]Event status was available for all patients.

Table 3 Efficacy of programme participation in reducing the risk of coronary recurrences

	HR (95% CI)
Hard events	
Model 1	0.62 (0.40–0.95)
Model 2	0.68 (0.44–1.02)
Model 3	0.61 (0.38–0.96)
Model 4	0.59 (0.38–0.94)
Soft events	
Model 1	0.65 (0.40–1.07)
Model 2	0.66 (0.40–1.09)
Model 3	0.55 (0.33–0.94)
Model 4	0.53 (0.31–0.89)

The table shows HR and 95% CI for coronary recurrences over 5 years of follow-up by Cox proportional hazard models. Model 1: unadjusted; Model 2: adjusted for previous acute myocardial infarction, coronary revascularization, and previous peripheral artery disease; Model 3: like Model 2 plus ejection fraction and NYHA classification; Model 4: like Model 3 plus EuroSCORE, CABG alone or CABG-valve combined surgery, and immediate neurological complications.
CABG, coronary artery bypass surgery; CI, confidence interval; HR, hazard ratio; NYHA, New York Heart Association.

Discussion

This study suggests that taking part after CABG surgery in a structured secondary CV prevention programme, in addition to usual cardiology care, is associated with a substantial reduction of the risk of recurrent coronary events. The effects on coronary outcomes observed in the unadjusted Cox regression analyses persisted after

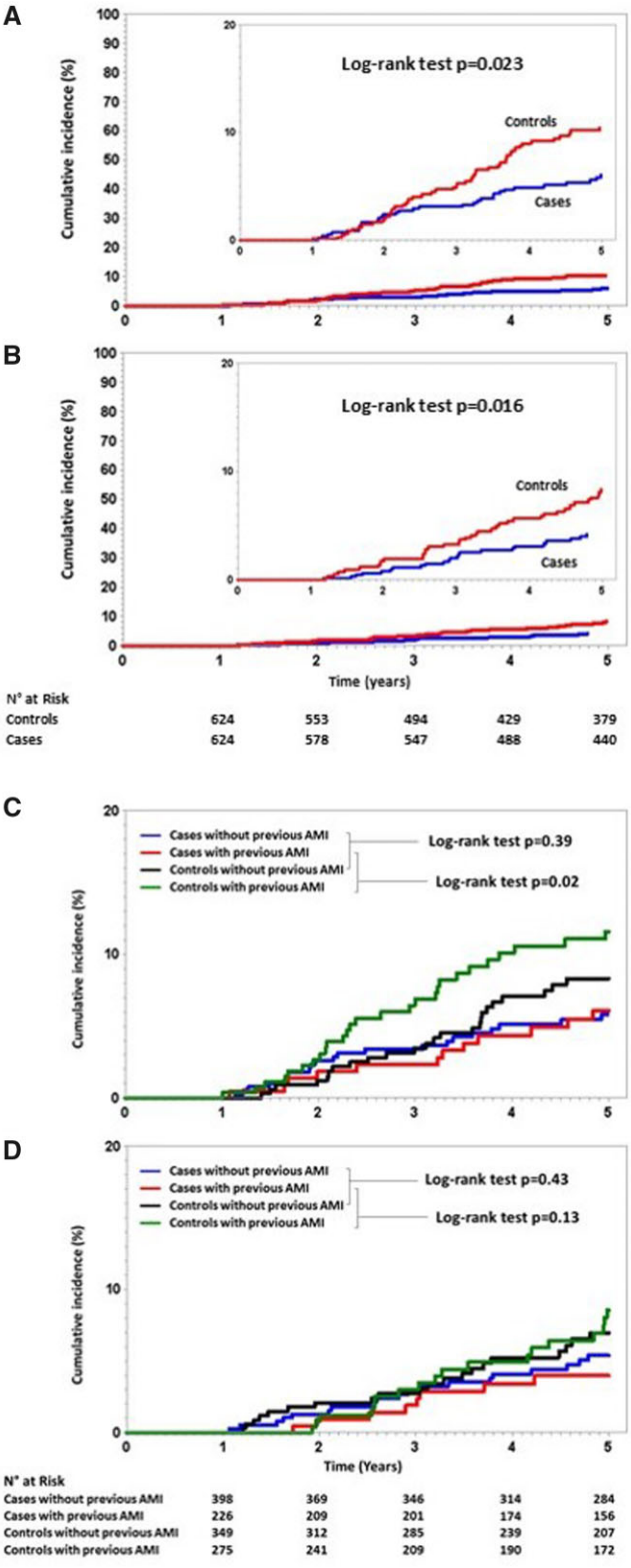

Figure 2 Programme participation and coronary outcomes. (*A* and *B*) Incidence of coronary recurrences in cases and controls during the 5-year follow-up. (*A*) Hard events; (*B*) soft events. (*C* and *D*) Incidence of coronary recurrences during the 5-year follow-up in cases and controls, stratified by history of previous acute myocardial infarction (AMI) at the time of coronary artery bypass surgery. (*C*) Hard events; (*D*) soft events.

adjustment for baseline differences possibly related to self-selection and referral biases, thus supporting an independent favourable effect of the programme. This interpretation is reinforced by a sensitivity analysis of the effect of the programme in patients with or without a history of AMI, a discrete condition suggestive of different disease severity at baseline. Remarkably, this analysis suggests a relatively earlier and greater benefit in patients with previous AMI, who have the highest risk of recurrences, than in those without.

We chose 'hard' (spontaneous and symptomatic) events as the primary outcome of the study to avoid classifying as 'recurrences' the procedures of coronary revascularization driven by results of stress tests or coronary imaging, potentially not evenly performed in cases and controls.

Based on the available data, cases had better control of several traditional risk factors and higher adherence to anti-platelets and statins than controls at follow-up. Although the rate of risk factor reporting in controls by our cardiologists was comparable of even higher than that reported in other studies,[17] the lack of complete data may nonetheless have introduced a bias, potentially influencing the differences observed. However, the significantly better figures in cases than in controls for different risk factors, all in the same direction, suggest a comprehensive favourable impact of the programme on patients' risk profile, which is in line with the main results we observed on coronary outcomes. The high adherence of cases to anti-platelets and statins at follow-up plainly differs with the progressive discontinuation of these drugs after an acute coronary episode reported in literature.[9,10] Our findings are in line with a recent systematic review on the determinants of the adherence to secondary prevention CV medications at the health system level, showing a meaningful role of patient counselling.[18]

The plan of encounters throughout the programme herein evaluated was tailored to the individual patient's clinical, cognitive, and psychological needs, according to real-world healthcare practice. Likewise, the programme operated a personalized approach aimed to achieve long-term control of the multiple CV risk factors usually present in patients subjected to CABG surgery. The observed reduction of hard CV event risk (41%) is similar to that previously obtained by a multi-target intervention in other patient groups at very high CV risk,[19] and it largely exceeds the effect of a more intensive vs. a less intensive control of a single consolidated risk factor, such as LDL-C, for example.[3,4] This suggests that, although cases may have received higher doses and/or more potent drugs against specific risk factors than controls to achieve 'goals', the overall benefit might be explained by the all-embracing attention to risk determinants (lifestyle, adherence to therapy, etc.).

Since a low adherence and persistence of patients to healthy lifestyle habits and drug therapies is a recognized barrier to an effective secondary CV prevention,[20,21] the programme paid special attention to undertaking and maintaining actions for patient empowerment.[22] This component of the intervention required a significant professional time not only to raise patients' CV health literacy, but also to deal with some misleading personal beliefs (e.g. 'my destiny only depends on God's will'), to solve fears and doubts (e.g. 'exercise is dangerous after CABG'), to dispel false myths (e.g. 'statins produce cancer'), and to provide support in the process of shared decision-making. Thus, besides delivering up-to-date preventive recommendations, the team strived to convey to each patient an attitude of co-responsibility in taking care of themselves, without formal contracts[23] or material incentives.[24] Many of the programme's actions entail communication and discussion between health providers and patients, without the need for a physical examination; therefore, trials investigating the potential contribution of an e-health component to a secondary CV prevention programme may be of value.

It is worth noting that hospital-based structured supervised exercise (namely 'rehabilitation') was not part of the programme, but just motivational actions to promote the autonomous long-term adoption of a physically active lifestyle, taking into account patients' changing possibilities, preferences, and self-imposed limits. Walking, dancing, and swimming were the activities more frequently accepted and adopted by cases. This policy may be pertinent, since long-term adherence to hospital-based rehabilitation is very low,[25,26] it requires dedicated spaces, equipment, and personnel, and it entails limited chances of considering each patient's physical activity preferences. Besides, previous data suggest that secondary prevention programmes with or without a component of structured supervised exercise are associated with similar clinical benefits.[13] Some patients received advice on behavioural strategies to cope with anxiety, stress, or depressive symptoms, and they were encouraged to consult a specialist, but, differently from other programmes, psychologists or psychiatrists were not part of the team. Smoking cessation was highly recommended, and personalized counselling and drug treatments to quit were provided, if accepted.

Thus, the efficacy of the programme in reducing the study outcomes may be ascribed to the summary result of a variety of actions and not to any single one, a fact inherent to any complex intervention.

This study has some limitations. First, controls had, at the time of CABG, some clinical features indicative of a greater disease severity that might have influenced the outcomes. This imbalance may be related to an admixture of, on one side, a preference by controls to undergo CABG surgery in our academic centre, even if farther than 100 km away from their residence, than in their local hospitals (referral bias), and, on the other, a self-selection of relatively healthy patients among candidates to the programme who accepted to take part in it (healthy user bias). These problems were faced in the statistical analysis by accounting for all the significant differences identified at baseline. However, unmeasured confounding factors may not be excluded. Second, although soft events were also less frequent in cases than in controls, we cannot be certain whether the number of diagnostic tests performed throughout the follow-up in both groups was well balanced. If not, more soft events might have been documented in a group subjected to more diagnostic tests. Yet, the consistent impact of the programme on both hard and soft outcomes suggests that also the reduction of the latter may be factual.

In conclusion, the results of this single-centre retrospective cohort study suggest that the participation in a personalized post-CABG comprehensive secondary CV prevention programme, delivered in the long term on top of usual cardiology care, associates with a meaningful risk reduction of the risk of subsequent coronary events. A randomized trial is warranted to confirm these findings.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Conflicts of interest: none declared.

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