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Beyond secondary prevention drugs: Added benefit in survival and events of a healthy lifestyle in patients after an acute coronary syndrome

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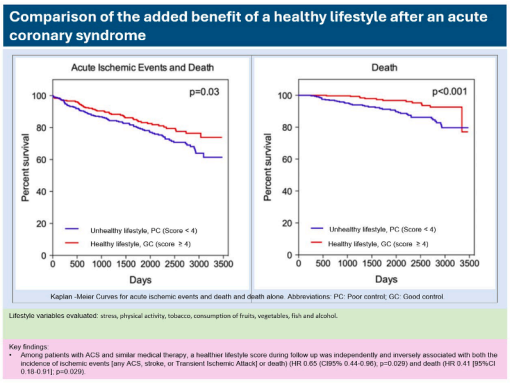
GRAPHICAL ABSTRACT



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ABSTRACT

Objective: To quantify the added clinical benefit of a healthy lifestyle following an acute coronary syndrome (ACS). Our study seeks to answer the question: Is adherence to medical therapy sufficient or a healthy lifestyle provides additional improvement?.

Methods: This is a prospective observational multi-center study of 685 ACS patients. At 6 months patients were asked about their post-ACS lifestyle and were given a score (range: 0–7) with the following items: Intake of ≥3 fruits and vegetables/day, ≥2 fish servings/week, ≤7 alcohol beverages/week, feeling stress <once/month, moderate-intense physical activity in leisure time, walking at work, and giving up tobacco. One point was assigned for each of these items. Mean follow-up was 4.89 (2.85–7.70) years.

Results: After adjusting for demographic variables, cardiovascular risk factors, characteristics of the index event, high-sensitivity C-reactive protein (hs-CRP), and drug therapy, multivariate Cox regression showed that the lifestyle SCORE was independently and inversely associated with both the incidence of the primary outcome (ischemic events [any ACS, stroke, or Transient Ischemic Attack] or death) (HR 0.65 (CI95 % 0.44–0.96); $p = 0.029$) and death (HR 0.41 [95 %CI 0.18–0.91]; $p = 0.029$). Statin therapy was also independently and inversely associated with the incidence of the primary outcome and death. Kaplan-Meier curves showed a higher event-free survival for both outcomes in patients with SCORE≥4 (healthy lifestyle) than in those with SCORE<4 (unhealthy lifestyle). Additionally, patients with a SCORE≥4 had a significantly greater decrease of total cholesterol and hs-CRP. For each 1-point increase in the score, there was a 35 % reduction in the incidence of the primary outcome (ischemic events or death) and a 59 % reduction in the incidence of death.

Conclusion: Among patients with ACS and similar medical therapy, a healthy lifestyle is an independent and added marker of a lower incidence of new ischemic events and death. It is also associated with a better lipid profile and lower inflammation after the ACS. As the prognosis of ACS has improved over the years due to better therapies; this study shows that lifestyle modifications continue to offer significant benefit at this point in time.

1. Introduction

Despite advances in drug treatment and secondary prevention programs, cardiovascular disease remains the leading cause of death in Western countries [1] There is overwhelming evidence that adopting a healthy lifestyle, combined with medication, significantly reduces cardiovascular risk in secondary prevention following coronary heart disease (CHD) [2,3]. As a result, it is recommended by all clinical practice guidelines [4]. However, the full extent and independent benefit of a healthy lifestyle, particularly after optimal medical therapy in secondary prevention, has not been widely reported.

Modern treatment with lipid-lowering agents, betablockers, antiplatelet, antihypertensive, and antidiabetic drugs modify lipid, glucose and blood pressure levels tend to overshadow any perceived benefit of lifestyle intervention beyond the effect of drug treatment. We believe that as prognosis of CHD improves, the benefit magnitude old interventions should be retested.

In fact, patients with CHD tend to exhibit a lower adherence to a healthy lifestyle than to pharmacological therapy [5–7].

Several articles assessing the level of adherence to a healthy lifestyle in patients with established CHD have reported alarming results, with only about 50 % of patients adhering to medical advice [8,9]. This highlights the continuous need to find evidence that reassures the crucial role of a healthy lifestyle, even in patients who are compliant with drug therapy.

The aim of the present study is to assess the independent incremental benefit of a combination of healthy lifestyle and optimized medical treatment after an acute coronary syndrome (ACS), specifically in reducing the occurrence of cardiac and cerebral acute ischemic events as well as overall mortality.

2. Methods

2.1. Patients

This prospective observational subs-study analysed the population of the BACS & BAMI (Biomarkers in ACS & Biomarkers in Acute Myocardial Infarction) study [10]. Briefly, BACS&BAMI was a study that included patients admitted to five hospitals in Madrid, Spain, with either non-ST elevation acute coronary syndrome (NSTEACS) or ST-elevation myocardial infarction (STEMI). The aim of that study was to test the prognostic value of a panel of plasma biomarkers.

Between July 2006 and June 2014, 2740 patients were discharged from the study hospitals with a diagnosis of NSTEACS or STEMI; 1483 patients were excluded due to the following prespecified criteria: age over 85 years, presence of disorders or toxic habits limiting survival, impossibility to perform cardiac revascularization, coexistence of other significant cardiopathy, impossibility to perform follow-up, clinical instability beyond the sixth day after the index event, refusal to participate in the study, and impossibility of the investigators to include them. From the included 1257 patients, 1230 completed the follow-up. From these, 685 had an adequate assessment of the lifestyle during the index event and six months after, including the risk factors reported in the INTERHEART study [11,12].

A total of 685 of patients discharged with a diagnosis of STEMI or non-STEMI or unstable angina were included in this study. On admission, clinical variables were recorded, and plasma was taken for analysis. Last follow-up visits were carried out in June 2016.

All patients were given standard healthy lifestyle advice following ESC guidelines on secondary prevention [4,13–16]. Patients were advised to follow healthy diet high in vegetables, fruits and whole grains, and to limit saturated fat and alcohol. They were also recommended to engage in 30–60 min of moderate physical activities most days, avoid stress and smoke cessation.

2.2. Ethics statement

The research protocol conforms to the ethical guidelines of the 1975 *Declaration of Helsinki* as reflected in a priori approval by the human research committees of the institutions participating in this study: Fundación Jiménez Díaz, Hospital Fundación Alcorcon, Hospital de Fuenlabrada, Hospital Universitario Puerta de Hierro Majadahonda, and Hospital Universitario de Mostoles. All patients signed informed consent documents. Date of approval by the Ethics Committee was 24th April 2007 (act number 05–07).

2.3. Study design

At baseline, clinical variables were recorded, and twelve-hour fasting venous blood samples were withdrawn and collected in EDTA. A SCORE

was used to assess the lifestyle of the population. We examined seven items based on the INTERHEART study [11,12] in order to evaluate patients behaviors following the index event. These factors were evaluated based on patient's responses during the in person visit conducted at six months post-event, including: intake of ≥ 3 fruits and vegetables per day, ≥2 fish servings per week, drinking ≤ 7 alcohol beverages per week, feeling stress < once per month, moderate or intense physical activity in leisure time, at least walking at work, and cessation of tobacco use following the ACS. We assigned 1 point per item in a dichotomous matter, as each lifestyle factor was scored either as 0 (condition not met) or 1 (condition met). The total score ranged from 0 to 7, with a score of 7 indicating the healthiest lifestyle. A healthy diet was defined considering 2 variables of the questionnaire: ≥ 3 servings of fruits and vegetables per day, and ≥ 2 fish servings per week.

Part of this lifestyle assessment, was included in the INTERHEART study [11]. Furthermore, the Non-Laboratory INTERHEART SCORE has been established and validated in primary prevention and less frequently in secondary prevention in different countries [17,18].

Our scoring differs from the original, as it lacks some elements and has not been specifically validated, however it could serve as a simple and practical surrogate for assessing lifestyle.

At the end of follow-up, the medical records were reviewed, and patient status was confirmed by telephone contact. The primary outcome was the combination of acute ischemic events (STEMI, non-STEMI, unstable angina, transient ischemic attack [TIA], and stroke), and total death. The secondary outcome was total mortality. Non-STEMI was defined as rest angina lasting >20 min in the previous 24 h, or new-onset class III-IV angina, along with transient ST depression or T wave inversion in the electrocardiogram considered diagnostic by the attending cardiologist and troponin elevation. In the absence of troponin elevation, a diagnosis of unstable angina was made. STEMI was defined as symptoms compatible with angina lasting >20 min and ST elevation in at least two adjacent leads in the electrocardiogram without response to nitroglycerin, and troponin elevation.

A previous myocardial infarction was diagnosed in the presence of new pathological Q waves in the electrocardiogram along with a concordant new myocardial scar identified either by echocardiography or nuclear magnetic resonance imaging [19]. Stroke was defined as rapid onset of a neurologic defect attributable to a focal vascular territory lasting >24 h or confirmed by new cerebral ischemic lesions on imaging studies. TIA was defined as a transient stroke with signs and symptoms resolved within the first 24 h and without cerebral acute ischemic lesions at imaging techniques. Although all events were recorded for each case, patients were excluded from the Cox regression analysis after the first event. Then, although the total number of events is also described, patients that had more than one event were computed only once for these analyses.

2.4. Blood sample analysis

Plasma determinations were performed at the laboratories of Vascular Pathology and Biochemistry at Fundación Jiménez Díaz. The investigators who performed the laboratory studies were unaware of clinical data. Blood samples were centrifuged at 2500 g for 10 min and plasma was stored at −80 °C. Patients were seen every year at their hospitals. High-sensivity C-reactive protein (hs-CRP) was assessed by latex-enhanced immunoturbidimetry (ADVIA 2400 Chemistry System, Siemens, Munich, Germany), and troponin by immunometric immunoassay with a mice biotin-monoclonal antibody and a luminescent reaction (Ortho Clinical Diagnostics Vitros XT 7600, Raritan, NJ, U.S.A.). Lipids, glucose and creatinine determinations were performed by standard methods (ADVIA 2400 Chemistry System, Siemens, Munich, Germany). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

2.5. Statistical analysis

Quantitative data with a normal distribution are presented as the mean ± standard deviation (SD) and were compared using the Student's t-test. Data that did not follow a normal distribution are displayed as the median (interquartile range) and were compared using the Mann–Whitney test. Qualitative variables are shown as percentages and were compared with the Chi-square or the Fisher's test when appropriate.

Univariable Cox regression model was performed to analyse which variables were associated with the development of the outcomes. A large set of variables including age, sex, risk factors, lipids, and medication prescribed at discharge, among others were studied. Those variables showing a p value<0.05 were included in the multivariable analysis.

The Kaplan-Meier survival curves and long-rank test were used to compare time to the development of the primary and secondary outcomes in patients with a lifestyle score ≥4 (Good control group, GC), as compared with those with a score < 4 points (poor control group, PC).

Analyses were performed with SPSS 20.0 (SPSS Inc., New York), and variables with $p < 0.05$ were considered statistically significant.

3. Results

3.1. Study cohort

A total 685 patients with diagnostic at discharge of ACS (54.5 % STEMI, 33.9 NON-STEMI, and 11.7 % unstable angina) were included. All patients were given healthy lifestyle recommendations at discharge following ESC guidelines [4] on secondary prevention as mentioned before in the methods section of this article. Six months later, patients had a clinical, laboratory and lifestyle in person assessment by a cardiologist. The median follow-up was 4.89 (2.85–7.70) years.

3.2. Baseline characteristics at the time of the index event

Patients following a healthy lifestyle after the index ACS (score ≥4 [GC]) were younger, more frequently male, had reduced frequency of hypertension, and dyslipidemia (Table 1). Apart from smoking, they had a healthier lifestyle before the ACS in terms of stress, physical activity and consumption of alcohol, fish and fruit. The index event in this GC group was more frequently a STEMI. The mean eGFR was 82 (mL/min/1.73 m^2) in the GC group and 77 (mL/min/1.73 m^2) in the PC group. No differences were found in the percentage of patients with ejection fraction <40 % between the groups, in the number of vessels affected, the percentage of patients with complete revascularization. Prescribed medical therapy was also similar in both groups, with at least 97 % of patients receiving statins, 80 % betablockers, 96 % acetylsalicylic acid and 90 % anti-P2Y12. Details regarding baseline characteristics are shown in table 1.

To assess potential bias, we compared the baseline characteristics of this group with the 545 BACS-BAMI study patients excluded due to insufficient data for SCORE calculation. Both groups were largely similar, except the SCORE group had more STEMI cases, fewer drug-eluting stents, lower LDL, higher HDL, and greater use of statins, ACEI/ARB, and mineralocorticoid receptor antagonists. All other baseline characteristics were comparable (supplementary material)

3.3. Laboratory values at 6 months

The GC group had a greater decrease in total cholesterol and high-sensitivity C-reactive protein (hs-CRP) at 6 months. (Table 2) No significant differences were found for other lipoproteins.

3.4. Independent predictors of the primary outcome

One-hundred and thirty-seven patients (20 %) developed the

Table 1
Baseline characteristics of the studied population.

Variables			Score <4. Unhealthy lifestyle; PC($N = 324$)	Score ≥ 4 Healthy lifestyle; GC ($N = 361$)	p
Sex (Male) (n, %)			235 (73 %)	288 (80 %)	**0.026**
Age (years)			63 (55–75)	58 (51–68)	**<0.001**
Race (Caucasian) (n, %)			312 (96 %)	346 (96 %)	0.762
Diabetes (n, %)			74 (23 %)	70 (19 %)	0.269
Hypertension (n, %)			203 (63 %)	190 (53 %)	**0.008**
Dyslipidemia (n, %)			208 (64 %)	203 (56 %)	**0.034**
Smoker (n, %)			102 (31 %)	180 (50 %)	**<0.001**
BMI			27.7 (25.3–30.4)	28.1 (25.3–30.5)	0.607
Fruit intake (servings per day)			2.2 (1.0–3.0)	2.5 (1.5–3.5)	**0.014**
Fish intake (servings per week)			2.0 (1.0–3.0)	2.5 (2.0–3.0)	**0.033**
Alcohol intake	0		133 (41.2 %)	138 (38.4 %)	**<0.001**
(Drinks per week)	1–7		71 (22.0 %)	136 (37.9 %)	
	8–14		60 (18.6 %)	46 (12.8 %)	
	≥15		59 (18.3 %)	39 (10.9 %)	
Stress	Never		52 (16.1 %)	93 (25.9 %)	**<0.001**
	< Once a month		43 (13.4 %)	69 (19.2 %)	
	≥ 1 every month		111 (34.5 %)	86 (24.0 %)	
	Permanent		116 (36.0 %)	111 (16.3 %)	
Physical activity at work	Not working		188 (58.0 %)	151 (42.1 %)	**<0.001**
	Sedentary		71 (21.9 %)	74 (20.6 %)	
	Walks in one floor		32 (9.9 %)	50 (13.9 %)	
	Climb stairs		13 (4.0 %)	50 (13.9 %)	
	Intensive		20 (6.2 %)	34 (9.5 %)	
Physical activity at leisure	Sedentary		72 (22.4 %)	79 (22.1 %)	**<0.001**
	Mild		176 (54.7 %)	136 (38.0 %)	
	Moderate		63 (19.6 %)	116 (32.4 %)	
	Intensive		11 (3.4 %)	27 (4.0 %)	
Previous Coronary Heart Disease (n, %)			70 (22 %)	58 (16 %)	0.063
Previous Cerebrovascular Accident (n, %)			11 (3.4 %)	9 (2.5 %)	0.484
Cardiovascular Event		NSTEACS	177 (55 %)	135 (37 %)	**<0.001**
		STEMI	147 (45 %)	226 (63 %)	
Number of Vessels Diseased (n)			1 (1–2)	1 (1–2)	0.753
Troponin (ng/mL)			9.79 (0.75–56.5)	18.7 (2.91–61.3)	**0.017**
eGFR (mL/min/1.73 m^2)			77 (60–91)	82 (66–94)	**0.006**
Ejection fraction <40 % (n, %)			47 (15 %)	49 (14 %)	0.701
Complete Revascularization			235 (73 %)	262 (73 %)	0.848
Type of revascularization		No	51 (16 %)	42 (12 %)	0.398
		Drug-eluting Stent	152 (47 %)	193 (53 %)	
		Bare-Metal Stent	97 (30 %)	101 (28 %)	
		Angioplasty	10 (3.1 %)	12 (3.3 %)	
		Coronary revascularization	14 (4.3 %)	13 (3.6 %)	
LDL-C (mg/dL)			114 (92–140)	114 (91–139)	0.657
Triglycerides (mg/dL)			131 (93–177)	120 (85–172)	**0.042**
HDL-C (mg/dL)			41 (35–49)	39 (32–48)	**0.021**
Non-HDL (mg/dL)			142 (118–171)	140 (115–168)	0.102
Glucose (mg/dL)			107 (96–130)	105 (96–120)	0.217
Hs-CRP (mg/L)			1.7 (0.9–3.3)	1.8 (0.8–3.2)	0.906
Acetylsalicylic acid (n, %)			310 (96 %)	346 (96 %)	0.914
AntiP2Y12 (n, %)			291 (90 %)	333 (92 %)	0.265
Statins (n, %)			313 (97 %)	354 (98 %)	0.234
Ezetimibe (n, %)			8 (2.5 %)	7 (1.9 %)	0.636
Insulin (n, %)			22 (6.8 %)	17 (4.7 %)	0.241
Oral antidiabetic drugs (n, %)			53 (16 %)	49 (14 %)	0.307
ACEI/ARB (n, %)			266 (82 %)	309 (86 %)	0.213
Aldosterone receptor blockers (n, %)			38 (12 %)	28 (7.8 %)	0.079
Betablockers (n, %)			260 (80 %)	301 (83 %)	0.288
Diuretics (n, %)			52 (16 %)	47 (13 %)	0.260

Quantitative variables are expressed as medians, interquartile ranges and percentage in relation to each group. Abbreviations: PC: poor control; GC: good control; BMI: body mass index; NSTEACS Non-ST elevation-acute coronary syndrome; STEMI: ST-elevation myocardial infarction; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; HDL: High density lipoprotein; Hs-CRP: High-sensitivity C-reactive protein; AntiP2Y12: P2Y12 receptor blockers; ACEI: Angiotensin-converting enzyme inhibitors; ARB: angiotensin 2 receptor blockers.

primary outcome. Of these: 74 (10.8 %) developed an ACS, 30 (4.4 %) a cerebrovascular accident, and 53 (7.7 %) died. Twenty patients developed two events, and the remaining patients developed a single event.

On univariate analysis, a healthier lifestyle SCORE, the use of statins and acetylsalicylic acid, and receiving complete revascularization at the index event, were inversely associated with the development of the acute ischemic events or death (Table 3). On the other hand, age, classical risk factors, previous CHD, and the number of diseased coronary arteries, were directly related with the development of the primary outcome.

On the multivariate analysis we included all variables that were statistically significant in the univariate analysis. The lifestyle SCORE and the use of statins were independent predictors of a decrease in the rate of development of the primary outcome. Hypertension, previous CHD, and insulin therapy were independently and positively associated with the outcome (Fig. 1.A, table 4).

We found that per each 1 point of increase in this score there was a 35 % reduction in the incidence of the primary outcome.

Table 2
Comparison of plasma levels changes at 6 months.

Variable	Score<4 (*N* = 324) Unhealthy lifestyle; PC	Score>4 (*N* = 361) Healthy lifestyle; GC	p
Cholesterol (mg/dL)	- 38 [−7.5-(−68)]	- 52 [(−16.5)-(−79)]	**0.040**
LDL-C (mg/dL)	- 30 [−8.5-(−61)]	- 41 [(−13.5)-(−64)]	0.096
HDL-C (mg/dL)	0 [6.0-(−6.0)]	- 2 [5.0-(−9.0)]	0.064
Triglycerides (mg/dL)	−17 [9.0-(−59)]	- 17 [7.5-(−58)]	0.551
Hs-CRP (mg/L)	−0.5 [(0.7-(−1.9)]	−1.1 [(−0.1)-(2.5)]	**0.001**

Abbreviations: PC: poor control; GC: good control; LDL: low-density lipoprotein; HDL: High density lipoprotein; Hs-CRP: High-sensitivity C-reactive protein.

Kaplan-Meier curves showed that patients with a lifestyle score ≥4 had significantly less incidence of the primary outcome (Fig. 2.A).

3.5. Independent predictors of death

Fifty-three patients died. The cause of death was cardiovascular in eighteen cases (2.6 %), cancer in ten (1.5 %), infection in five (0.7 %), unknown in six (0.9 %), renal failure in two (0.3 %), pancreatitis in two (0.3 %), gastro-intestinal bleeding in one (0.1 %), and other in nine (1.3 %).

In univariable analysis, the lifestyle SCORE, together with eGFR, had an inverse association with the occurrence of death (Table 5). The use of betablockers, statins, acetylsalicylic acid and a complete revascularization at the index event were also protective. Age, smoking, hypertension, diabetes, and the presence of previous atherosclerotic disease, among others, were associated with the development of death (Table 5).

Multivariable analysis showed that the lifestyle SCORE was independently and inversely associated with the occurrence of death (Fig. 1.B, Table 6). Specifically, 1 point of increment in the lifestyle SCORE was associated with a 59 % reduction in the incidence of death. The use of statins was also an independent protective factor against death. Age, smoking, hypertension and insulin therapy were positively and independently associated with the incidence of death.

Kaplan-Meier curves showed that patients in the GC group had a lower incidence of death than those of PC group (Fig. 2B and Fig. 3)

4. Discussion

In our study, we show that adopting a healthy lifestyle (defined as low stress, abstinence from tobacco and alcohol, consumption of fruit, vegetables and fish, and physical activity at work and during leisure time) following an ACS is associated with a reduction in the incidence of subsequent acute ischemic events or death. This additional reduction is observed when these lifestyle modifications are combined with standard medical therapy, as opposed to medical therapy alone. The magnitude of the benefit had a linear inverse correlation, and each incremental in one of these items was associated with a 35 % reduction in the incidence of the primary end point and a 59 % reduction in the incidence of death.

Our results remained consistent even after adjustment for an extensive set of variables and suggest that a healthy lifestyle confers a clinical benefit that is additive to that of drug therapy.

The additional benefits of adopting a healthy lifestyle alongside standard treatment may be due in part to a reduction in inflammatory markers. In particular, patients who adopted a healthy lifestyle after ACS exhibited a noteworthy decrease in plasma levels of hs-CRP, indicating reduced systemic inflammation.

Although not directly explored in our study, previous investigations from our group have shown that consumption of a fat-enriched meal can induce the activation of nuclear factor κB (NF-κB), a pro-inflammatory transcription factor, in circulating monocytes [20]. Moreover, it is conceivable that improved vascular function may be another mechanistic pathway through which a healthy lifestyle exerts its beneficial effects. Research suggests that consumption of high-glycemic carbohydrates can impair flow-mediated vasodilation, particularly in

Table 3
Univariate Cox proportional hazard model for the incidence rates of acute ischemic events and death.

Variable		HR (95 % CI)	p
Sex (Male)		1.01 (0.69–1.49)	0.953
Age (years)		1.03 (1.01–1.04)	**<0.001**
Race (Caucasian)		1.11 (0.41–3.01)	0.837
Smoker		1.87 (1.29–2.72)	**0.001**
Diabetes		1.91 (1.33–2.72)	**<0.001**
Hypertension		2.25 (1.53–3.32)	**<0.001**
Dyslipidemia		1.49 (1.04–2.14)	**0.030**
BMI		1.02 (0.98–1.06)	0.252
Previous Coronary Heart Disease		1.95 (1.36–2.80)	**0.001**
Previous Cerebrovascular Accident		1.64 (0.77–3.51)	0.202
Cardiovascular Event (STEMI)		0.64 (0.45–0.91)	**0.012**
Number of Vessels Diseased (n)		1.25 (1.02–1.52)	**0.033**
Troponin (ng/L)		1.00 (0.99–1.00)	0.928
eGFR (mL/min/1.73 m^2)		0.98 (0.98–0.99)	**<0.001**
Ejection fraction <40 (n, %)		0.77 (0.45–1.31)	0.336
Complete Revascularization		0.47 (0.34–0.66)	**<0.001**
Type of revascularization	No	Ref.	——
	Drug-eluting Stent	0.83 (0.53–1.32)	0.438
	Bare-metal Stent	0.85 (0.52–1.40)	0.523
	Angioplasty	0.44 (0.10–1.85)	0.261
	Coronary revascularization	0.98 (0.40–2.38)	0.962
LDL-C (mg/dL)		0.99 (0.99–1.00)	**0.043**
Triglycerides (mg/dL)		1.00 (1.00–1.00)	0.105
HDL-C (mg/dL)		0.99 (0.98–1.00)	0.990
Non-HDL(mg/dL)		0.99 (0.99–1.00)	0.315
Glucose (mg/L)		1.00 (1.00–1.01)	**0.039**
Hs-CRP (mg/L)		1.01 (0.95–1.07)	0.779
Acetylsalicylic acid		0.54 (0.29–0.99)	**0.049**
AntiP2Y12		0.82 (0.49–1.36)	0.440
Statins		0.29 (0.16–0.53)	**<0.001**
Ezetimibe		2.48 (1.01–6.08)	**0.046**
Insulin		3.08 (1.82–5.21)	**<0.001**
Oral antidiabetic drugs		1.60 (1.06–2.41)	**0.024**
ACEI/ARB		0.68 (0.46–1.01)	0.057
Aldosterone receptor antagonist		1.00 (0.55–1.81)	0.997
Betablockers		0.73 (0.50–1.08)	0.115
Diuretics		1.81 (1.21–2.72)	**0.004**
SCORE (≥4 vs. <4)		0.69 (0.49–0.98)	**0.037**

Abbreviations: BMI: body mass index; STEMI: ST-elevation myocardial infarction; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; HDL: High density lipoprotein; Hs-CRP: High-sensitivity C-reactive protein; AntiP2Y12: P2Y12 receptor blockers; ACEI: Angiotensin-converting enzyme inhibitors; ARB: angiotensin 2 receptor blockers.

overweight or obese individuals [21]. It is plausible that the dietary and lifestyle modifications embraced by patients following ACS contribute to improved vascular function and to a reduction of inflammatory markers thereby reducing the risk of adverse cardiovascular events [22,23].

The majority of the evidence supporting the benefits of a healthy lifestyle is derived from primary prevention studies [24,18].

In secondary prevention, although several studies [25–28,9] have demonstrated that lifestyle modification reduces cardiovascular mortality, most of them primary focus on one or two individual risk factors at the time, and are not adjusted for multiple variables or compared with optimal medical therapy. This contrasts with the present work.

For instance, dietary adherence was often reported in a binary manner without specifying individual components, stress data was not consistently recorded, and the intensity of physical therapy was not reported. Additionally, data on inflammatory biomarkers were often not available. In our paper, we addressed these gaps by meticulously considering various lifestyle factors following the INTERHEART scale [11]. We included fish, fruits, vegetables, and alcohol consumption, stress management, the intensity of physical activity both at work and during leisure time, as well as measurement of hs-CRP plasma levels.

In a post-hoc analysis involving 18,809 patients with ACS from the OASIS-5 study, a significant reduction in the incidence of myocardial infarction at six months was observed following a healthy lifestyle. Smoking cessation alone was associated with a 43 % decrease, while adherence to a combined diet and exercise regime showed an even more substantial reduction of 48 % [5]. It is worth noting that adherence to a healthy lifestyle, encompassing these factors, was found to be less common than adherence to medical therapy alone. Diet was reported as adherence vs no adherence without specifying any of its components, and data on stress were not recorded. Data on inflammatory biomarkers were not available. In our paper, we have addressed these previously unexplored aspects.

Several studies have consistently shown the individual benefits of each lifestyle modification in patients with CHD. However, relatively few studies have focused on examining the detailed collective impact of multiple lifestyle modifications compared with similar medical therapy without lifestyle modifications.

Table 4
Stepwise Cox proportional hazard model for the incidence rates of acute ischemic events, and death.

Variable	Hazard Ratio	95 % CI	p
Hypertension	1.95	1.25–3.02	0.003
Previous Coronary Heart Disease	1.62	1.36–3.46	0.001
Statins	0.29	0.15–0.56	<0.001
Insulin	2.33	1.23–4.41	0.009
SCORE (≥4 vs. <4)	0.65	0.44–0.96	0.029

The Mediterranean diet has been shown to reduce the incidence of cardiovascular events after a myocardial infarction [29] in stable CHD [30] and also in primary prevention in subjects at high cardiovascular risk [31]. Indeed, clinical practice guidelines from the European Society of Cardiology recommend adopting a Mediterranean diet or a similar dietary pattern, along with measures such as limiting saturated fat and alcohol intake, smoking cessation, engaging in regular physical activity, and effective management of stress and depression. In spite of this, several studies show that a healthy lifestyle is not achieved in a large number of patients with CHD [5,32].

Smoking cessation after a CHD has been linked to a significant 36 % reduction in mortality compared with those who continue to smoke [33].

Additionally, physical activity has been consistently demonstrated to be effective in reducing the risk of cardiovascular events, with the degree of benefit increasing as exercise intensity rises [34,35]. Cardiac rehabilitation programs have been shown to be particularly effective in reducing mortality, likely due to their dual impact on treatment adherence and promotion of a healthy lifestyle, including exercise [36,37]. A meta-analysis found that exercise-based cardiac rehabilitation was associated with a 20 % reduction in cardiovascular mortality [38]. However, this study did not specifically report on alcohol and fruit consumption, the intensity of physical activity, or information on stress. In our study, smoking cessation and moderate to intense levels of physical activity, both at work and during leisure time, constituted components of a healthy lifestyle score linked to a reduced incidence of cardiovascular events and mortality. Furthermore, as our patients did not undergo an exercise training program, the benefit may be attributed to the healthy lifestyle itself.

In a cohort of 362 patients hospitalized for a CHD event within the previous 12 months, cognitive behavioral therapy was associated with a

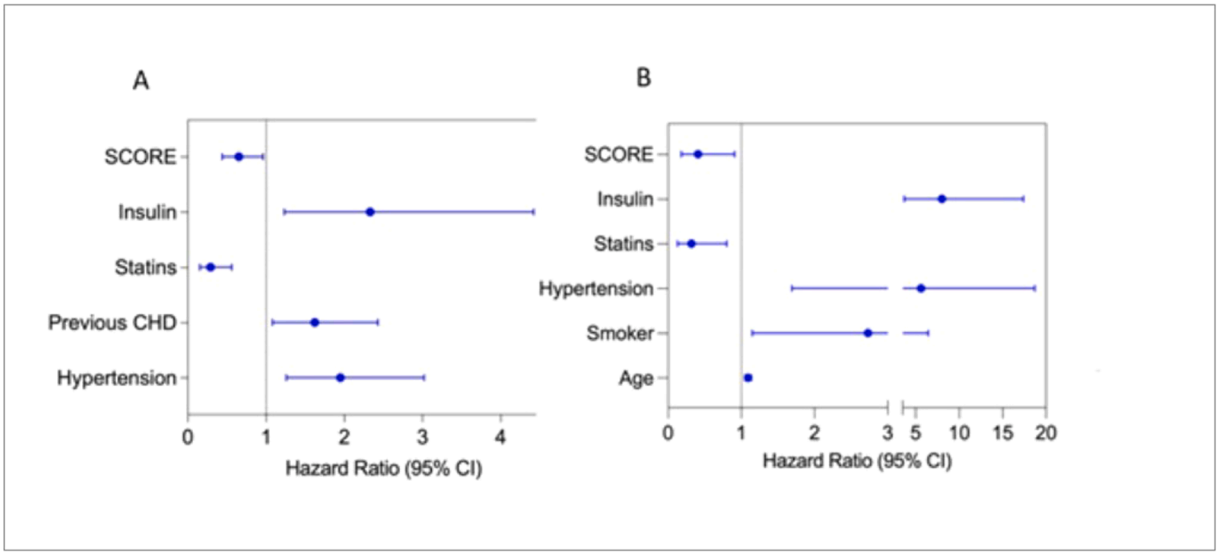

Fig. 1. A: Stepwise Cox proportional hazard model for the incidence rates of acute ischemic events and death. B: Stepwise Cox proportional hazard model for the incidence of death. Abbreviations: CHD: Coronary Heart Disease.

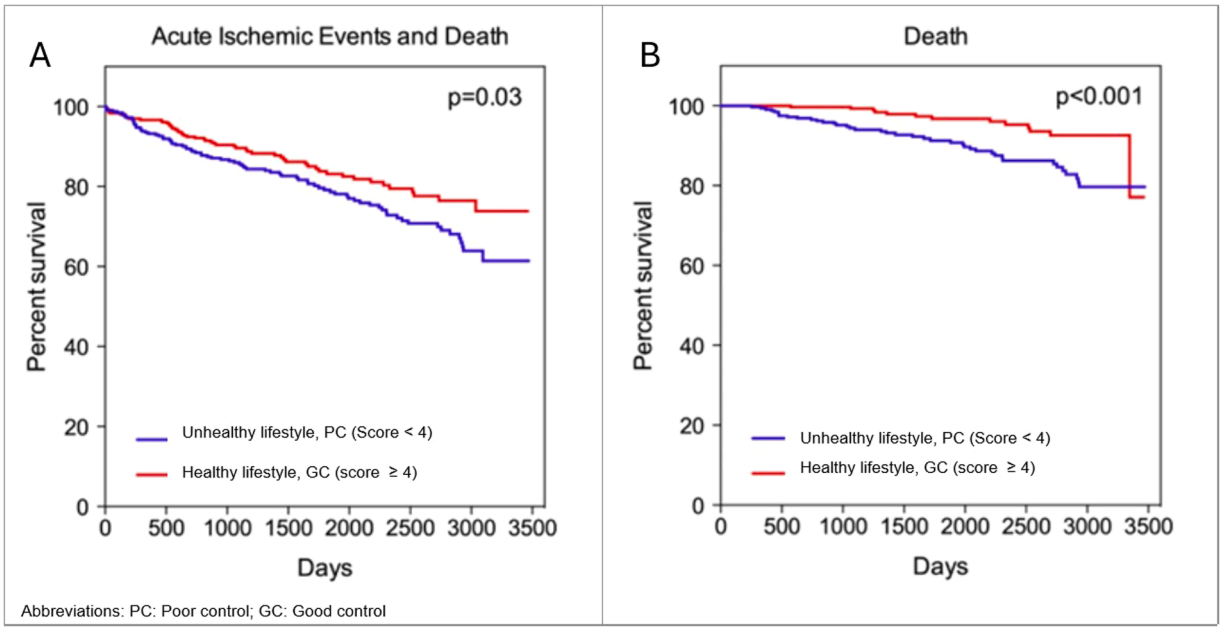

Fig. 2. Kaplan -Meier Curves for A: Acute ischemic events and death and B. Death alone.

Table 5
Cox proportional hazard model for the incidence rates of death.

Variable		HR (95 % CI)	p
Sex (Male)		0.87 (0.48–1.58)	0.642
Age (years)		1.10 (1.07–1.13)	**<0.001**
Race (Caucasian)		21.1 (0.15–29,907)	0.410
Smoker		2.31 (1.19–4.50)	**0.013**
Diabetes		3.00 (1.74–5.15)	**<0.001**
Hypertension		6.70 (2.67–16.8)	**<0.001**
Dyslipidemia		1.15 (0.66–2.02)	0.626
Previous Coronary Heart Disease		1.89 (1.07–3.34)	**0.029**
Previous Cerebrovascular Accident		4.13 (1.76–9.66)	**0.001**
Cardiovascular Event (STEMI)		1.03 (0.60–1.78)	0.910
Number of Vessels Diseased (n)		1.25 (0.92–1.71)	0.156
Troponin (ng/L)		1.00 (1.00–1.00)	0.165
eGFR (mL/min/1.73 m^2)		0.97 (0.95–0.98)	**<0.001**
Ejection fraction<40 % (n, %)		2.22 (1.16–4.24)	**0.016**
Complete Revascularization		0.57 (0.33–0.99)	**0.046**
Type of revascularization	No	Ref.	——
	Covered Stent	1.09 (0.53–2.26)	0.817
	Standard Stent	0.88 (0.39–1.98)	0.752
	Angioplasty	0.73 (0.09–5.73)	0.763
	Coronary revascularization	0.50 (0.06–3.89)	0.505
LDL-C (mg/dL)		0.99 (0.98–0.99)	**0.002**
Triglycerides (mg/dL)		1.00 (1.00–1.00)	0.712
HDL-C (mg/dL)		1.00 (0.97–1.02)	0.918
Glucose (mg/L)		1.01 (1.00–1.01)	**0.006**
Hs-CRP (mg/L)		1.06 (0.98–1.14)	0.135
Acetylsalicylic acid		0.42 (0.18–0.98)	**0.044**
AntiP2Y12		0.73 (0.34–1.55)	0.406
Statins		0.18 (0.08–0.38)	**<0.001**
Ezetimibe		1.19 (0.16–8.63)	0.863
Insulin		6.92 (3.53–13.6)	**<0.001**
Oral antidiabetic drugs		2.23 (1.23–4.07)	**0.009**
ACEI/ARB		1.43 (0.69–2.94)	0.334
Aldosterone receptor blockers		2.93 (1.47–5.86)	**0.002**
Betablockers		0.44 (0.25–0.78)	**0.005**
Diuretics		2.63 (1.44–4.79)	**0.002**
SCORE (≥4 vs. <4)		0.34 (0.18–0.63)	**0.001**

Abbreviations: STEMI: ST-elevation myocardial infarction; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; HDL: High density lipoprotein; Hs-CRP: High-sensitivity C-reactive protein; AntiP2Y12: P2Y12 receptor blockers; ACEI: Angiotensin-converting enzyme inhibitors; ARB: angiotensin 2 receptor blockers.

reduction in the risk of recurrent cardiovascular events and acute myocardial infarction [39]. Similarly, among 237 women hospitalized for myocardial infarction or coronary revascularization in the previous four months, psychosocial intervention targeting stress reduction was linked to a lower total mortality after 7.1 year follow-up [40]. Moreover, a comprehensive review encompassing 35 studies and involving 10,703 patients with CHD revealed consistent results [40]. In the current study, we incorporated a low level of stress, as determined by the INTERHEART scale [11], as a defining component of a healthy lifestyle. This was independently associated with a reduced incidence of cardiovascular events. Given the increasing incidence of mental health issues, including stress in our study holds even greater significance.

While moderate alcohol consumption was once believed to confer protection against CHD, current clinical guidelines advise against alcohol consumption [4]. Large recent studies have demonstrated that alcohol consumption is positively associated with the risk of stroke, CHD, and heart failure in the general population [41]. In addition, mendelian randomization studies suggest that abstainers have the lowest risk of cardiovascular disease, and that any alcohol intake may contribute to increases in body mass index and blood pressure [42,43,41].

Future research efforts could focus on validating the score used in this study, which includes fewer items than the original INTERHEART score [24].

As the prognosis of ACS has improved over the years due to better therapies; and as new and often costly drugs continue to emerge, demonstrating further incremental gains in survival has become increasingly challenging. A good example is the REDUCE-AMI [44] study that recently found that beta-blockers may not provide incremental survival advantages in patients with stable coronary artery

Table 6
Cox proportional hazard model for the incidence rates and death.

Variable	Hazard Ratio	95 % CI	p
Age, years	1.09	1.05–1.14	<0.001
Smoker	2.73	1.15–6.47	0.023
Hypertension	5.62	1.69–18.7	0.005
Statins	0.32	0.13–0.80	0.015
Insulin	8.01	3.67–17.4	<0.001
SCORE (≥4 vs. <4)	0.41	0.18–0.91	0.029

disease and preserved ejection fraction. Our study shows that lifestyle modifications continue to offer significant benefit. Low-cost lifestyle modification showed similar rates of mortality reduction as some medical therapy. This evidence with its detailed assessment of multiple lifestyle factors, which has not frequently been reported in recent years, challenges the perception that new and effective drugs reduce the relevance of lifestyle recommendations itself.

5. Limitations

Due to the study's design, plasma withdrawal for analysis was required at discharge no later than six days after admission to ensure homogeneity of results. Consequently, there was a limited number of patients with a left ventricular ejection fraction below 40 % in our series. Therefore, these results should not be extrapolated to populations with a high percentage of patients with moderate or severe left ventricular systolic dysfunction. In addition, due to the limited sample size, we were unable to compare subgroups of patients with a very healthy lifestyle (with a score of 6 to 7) to those with a very low score, where potentially more significant differences could have emerged. Additionally, specific data regarding the type of diet, such as intermittent fasting or a low-calorie diet, were not recorded in this study. Similarly, information about the specific type of exercise, such as anaerobic, strength training or high-intensity workouts, was not acquired. Further studies in this population could delve into these specifics to identify the optimal benefits.

Moreover, due to the study's design, we were unable to determine which specific variables within the score have the greatest impact on protecting against recurrent events or death. Furthermore, patients were asked about their lifestyle six months after the event, but their habits were not monitored throughout the entire follow-up period. However, the reported lifestyle following an ACS was a strong independent predictor of future outcomes, as it may be a surrogate marker of the lifestyle the patients will follow in the next years. As with any study on lifestyle interventions, we acknowledge the potential for response bias. However, compliance was assessed though in person interview during follow up visits with the patient cardiologist, ensuring a more direct and reliable evaluation.

Our cohort did not participate in a cardiac rehabilitation program, as this service was not available in all participating hospitals at the time of the study. While the benefits of cardiac rehabilitation are well-established, our study specifically focused on self-reported lifestyle behaviors. In our view, it is crucial to assess the sustainability and positive impact of healthy lifestyle habits once patients are no longer under the direct supervision of a medical team.

Lastly, we did not formally assess the presence of depressive symptoms. However, patients with such symptoms were not excluded from the study, and our conclusions remain applicable to this population.

6. Conclusions

In patients following an ACS, healthy lifestyle modification decreases the incidence of ischemic events and death, and it also reduces mortality rates compared with patients receiving medical therapy alone. It is also associated with improved lipid profiles and reduced inflammation. This additional benefit demonstrates an inverse linear correlation: the

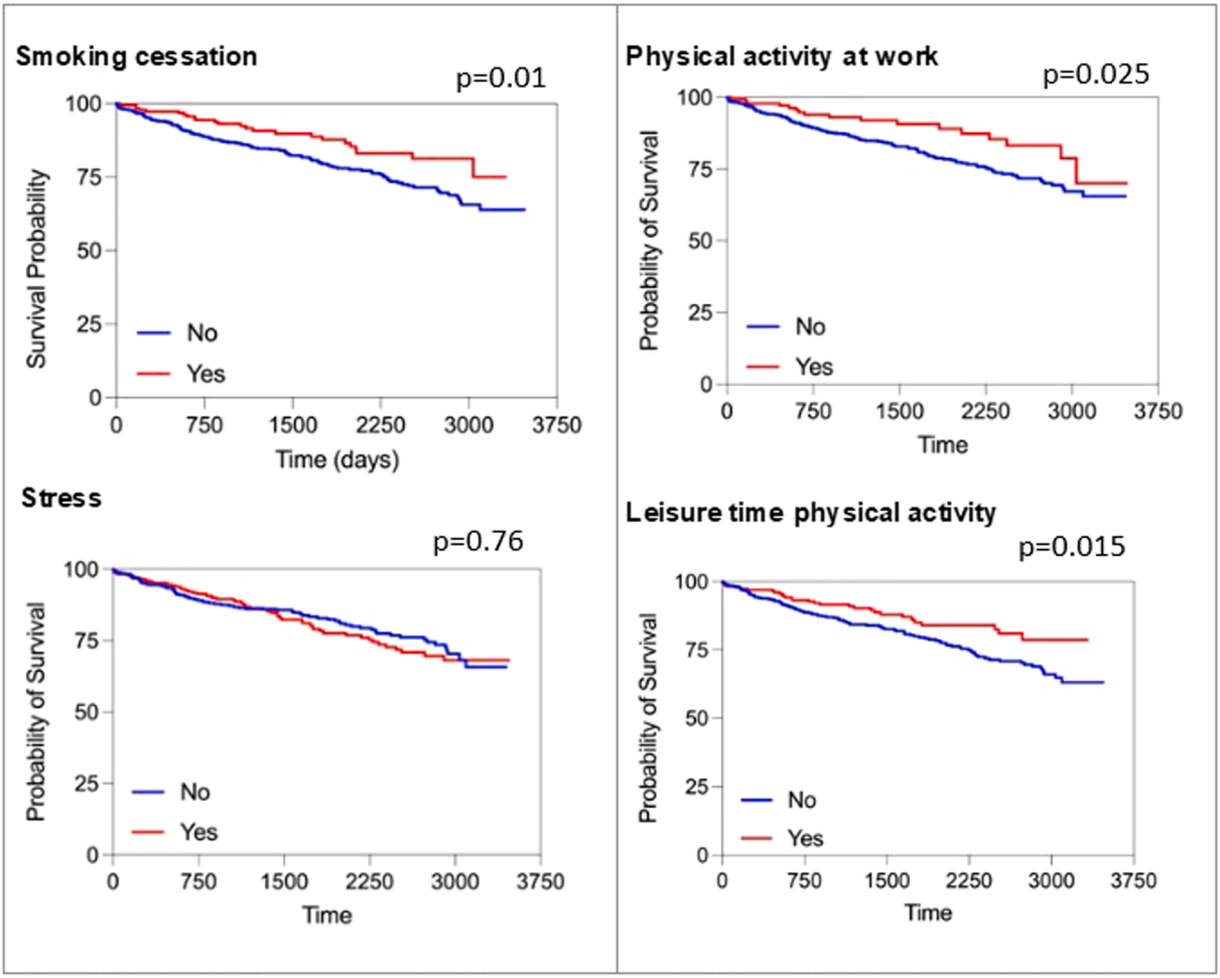

Fig. 3. Kaplan-Meier curves for Smoking cessation, physical activity at work and during leisure and stress.

healthier the lifestyle, the lower the incidence of cardiovascular events and death. Furthermore, the degree of added benefit is similar to that of medical therapy.

Authors agreement

Agree to submit the manuscript to the American Journal of preventive cardiology. The manuscript is original, unpublished, and not under consideration elsewhere. These authors contributed equally to this work as co-senior authors

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CRediT authorship contribution statement

Ester Cánovas Rodríguez: Writing – original draft. **Andrea Kallmeyer:** Writing – review & editing. **Nieves Tarín:** Writing – review & editing. **Carmen Cristóbal:** Writing – review & editing. **Ana Huelmos:** Writing – review & editing, Investigation, Data curation. **Ana María Pello Lázaro:** Writing – review & editing. **Álvaro Aceña:** Writing – review & editing. **Carlos Gutiérrez-Landaluce:** Writing – review & editing. **Óscar González-Lorenzo:** Writing – review & editing. **Jairo Lumpuy-Castillo:** Writing – review & editing. **Joaquín Alonso:** Writing – review & editing. **Lorenzo López-Bescós:** Writing – review & editing. **Jesús Egido:** Writing – review & editing. **Óscar Lorenzo:** Writing – review & editing. **Luis M. Blanco-Colio:** Writing – review & editing. **José Tuñón:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors have not conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100923.

References

[1] GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Lond Engl 2018;392:1736–88.
[2] Ambrosetti M, Abreu A, Corrà U, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the Secondary prevention and rehabilitation section of the european association of preventive cardiology. Eur J Prev Cardiol 2021;28:460–95.
[3] Ekblom O, Ek A, Cider Å, et al. Increased physical activity post-myocardial infarction is related to reduced mortality: results from the SWEDEHEART registry. J Am Heart Assoc 2018;7:e010108.
[4] Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227–337.
[5] Chow CK, Jolly S, Rao-Melacini P, et al. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. Circulation 2010;121:750–8.
[6] Easthall C, Taylor N, Bhattacharya D. Barriers to medication adherence in patients prescribed medicines for the prevention of cardiovascular disease: a conceptual framework. Int J Pharm Pract 2019;27:223–31.
[7] Pedretti RFE, Hansen D, Ambrosetti M, et al. How to optimize the adherence to a guideline-directed medical therapy in the secondary prevention of cardiovascular diseases: a clinical consensus statement from the European Association of Preventive Cardiology. Eur J Prev Cardiol 2023;30:149–66.
[8] Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: a European society of cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol 2016;23:636–48.
[9] Teo K, Lear S, Islam S, et al. Prevalence of a healthy lifestyle among individuals with cardiovascular disease in high-, middle- and low-income countries: the Prospective Urban Rural Epidemiology (PURE) study. JAMA 2013;309:1613–21.
[10] Tuñón J, Blanco-Colio L, Cristóbal C, et al. Usefulness of a combination of monocyte chemoattractant protein-1, galectin-3, and N-terminal probrain natriuretic peptide to predict cardiovascular events in patients with coronary artery disease. Am J Cardiol 2014;113:434–40.
[11] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet Lond Engl 2004;364:937–52.
[12] McGorrian C, Yusuf S, Islam S, et al. Estimating modifiable coronary heart disease risk in multiple regions of the world: the INTERHEART Modifiable Risk Score. Eur Heart J 2011;32:581–9.
[13] Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407–77.
[14] Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119–77.
[15] Collet J-P, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42:1289–367.
[16] WHO guidelines on physical activity and sedentary behaviour 2020.
[17] Joseph P, Yusuf S, Lee SF, et al. Prognostic validation of a non-laboratory and a laboratory based cardiovascular disease risk score in multiple regions of the world. Heart Br Card Soc 2018;104:581–7.
[18] Selvarajah S, Kaur G, Haniff J, et al. Comparison of the framingham risk score, SCORE and WHO/ISH cardiovascular risk prediction models in an Asian population. Int J Cardiol 2014;176:211–8.
[19] Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol 2018;72:2231–64.
[20] Blanco-Colio LM, Valderrama M, Alvarez-Sala LA, et al. Red wine intake prevents nuclear factor-kappaB activation in peripheral blood mononuclear cells of healthy volunteers during postprandial lipemia. Circulation 2000;102:1020–6.
[21] Lavi T, Karasik A, Koren-Morag N, et al. The acute effect of various glycemic index dietary carbohydrates on endothelial function in nondiabetic overweight and obese subjects. J Am Coll Cardiol 2009;53:2283–7.
[22] Dod HS, Bhardwaj R, Sajja V, et al. Effect of intensive lifestyle changes on endothelial function and on inflammatory markers of atherosclerosis. Am J Cardiol 2010;105:362–7.
[23] Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med 2004;351:2599–610.
[24] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet Lond Engl 2004;364:937–52.
[25] Clark AM, Hartling L, Vandermeer B, et al. Meta-analysis: secondary prevention programs for patients with coronary artery disease. Ann Intern Med 2005;143:659–72.
[26] de Waure C, Lauret G-J, Ricciardi W, et al. Lifestyle interventions in patients with coronary heart disease: a systematic review. Am J Prev Med 2013;45:207–16.
[27] Iestra J, Knoops K, Kromhout D, et al. Lifestyle, Mediterranean diet and survival in European post-myocardial infarction patients. Eur J Cardiovasc Prev Rehabil Off J Eur Soc Cardiol Work Groups Epidemiol Prev Card Rehabil Exerc Physiol 2006;13:894–900.
[28] Sdringola S, Nakagawa K, Nakagawa Y, et al. Combined intense lifestyle and pharmacologic lipid treatment further reduce coronary events and myocardial perfusion abnormalities compared with usual-care cholesterol-lowering drugs in coronary artery disease. J Am Coll Cardiol 2003;41:263–72.
[29] de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99:779–85.
[30] Delgado-Lista J, Alcala-Diaz JF, Torres-Peña JD, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. The Lancet 2022;399:1876–85.
[31] Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018;378:e34.
[32] De Bacquer D, Astin F, Kotseva K, et al. Poor adherence to lifestyle recommendations in patients with coronary heart disease: results from the EUROASPIRE surveys. Eur J Prev Cardiol 2022;29:383–95.
[33] Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. JAMA 2003;290:86–97.
[34] Sattelmair J, Pertman J, Ding EL, et al. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation 2011;124:789–95.
[35] Kyu HH, Bachman VF, Alexander LT, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ 2016;354:i3857.
[36] Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease: cochrane systematic review and meta-analysis. J Am Coll Cardiol 2016;67:1–12.

[37] De Schutter A, Kachur S, Lavie CJ, et al. Cardiac rehabilitation fitness changes and subsequent survival. Eur Heart J Qual Care Clin Outcomes 2018;4:173–9.
[38] Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. Am J Med 2004;116:682–92.
[39] Gullikson M, Burell G, Vessby B, et al. Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: secondary Prevention in Uppsala Primary Health Care project (SUPRIM). Arch Intern Med 2011;171:134–40.
[40] Orth-Gomér K, Schneiderman N, Wang H-X, et al. Stress reduction prolongs life in women with coronary disease. Circ Cardiovasc Qual Outcomes 2009;2:25–32.
[41] Wood AM, Kaptoge S, Butterworth AS, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet Lond Engl 2018;391:1513–23.
[42] Holmes MV, Dale CE, Zuccolo L, et al. Association between alcohol and cardiovascular disease: mendelian randomisation analysis based on individual participant data. BMJ 2014;349:g4164.
[43] Millwood IY, Walters RG, Mei XW, et al. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China. Lancet Lond Engl 2019;393:1831–42.
[44] Yndigegn T, Lindahl B, Mars K, et al. Beta-blockers after myocardial infarction and preserved ejection fraction. N Engl J Med 2024;390:1372–81.