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CARDIOVASCULAR DISEASE

Incidence of cardiovascular events in patients with stabilized coronary heart disease: the EUROASPIRE IV follow-up study

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Abstract

The EUROASPIRE surveys (EUROpean Action on Secondary Prevention through Intervention to Reduce Events) demonstrated that most European coronary patients fail to achieve lifestyle, risk factor and therapeutic targets. Here we report on the 2-year incidence of hard cardiovascular (CV) endpoints in the EUROASPIRE IV cohort. EUROASPIRE IV (2012–2013) was a large cross-sectional study undertaken at 78 centres from selected geographical areas in 24 European countries. Patients were interviewed and examined at least 6 months following hospitalization for a coronary event or procedure. Fatal and non-fatal CV events occurring at least 1 year after this baseline screening were registered. The primary outcome in our analyses was the incidence of CV death or non-fatal myocardial infarction, stroke or heart failure. Cox regression models, stratified for country, were fitted to relate baseline characteristics to outcome. Our analyses included 7471 predominantly male patients. Overall, 222 deaths were registered of whom 58% were cardiovascular. The incidence of the primary outcome was 42 per 1000 person-years. Comorbidities were strongly and significantly associated with the primary outcome (multivariately adjusted hazard ratio HR, 95% confidence interval): severe chronic kidney disease (HR 2.36, 1.44–3.85), uncontrolled diabetes (HR 1.89, 1.50–2.38), resting heart rate $\geq$ 75 bpm (HR 1.74, 1.30–2.32), history of stroke (HR 1.70, 1.27–2.29), peripheral artery disease (HR 1.48, 1.09–2.01), history of heart failure (HR 1.47, 1.08–2.01) and history of acute myocardial infarction (HR 1.27, 1.05–1.53). Low education and feelings of depression were significantly associated with increased risk. Lifestyle factors such as persistent smoking, insufficient physical activity and central obesity were not significantly related to adverse outcome. Blood pressure and LDL-C levels appeared to be unrelated to cardiovascular events irrespective of treatment. In patients with stabilized CHD, comorbid conditions that may reflect the ubiquitous nature of atherosclerosis, dominate lifestyle-related and other modifiable risk factors in terms of prognosis, at least over a 2-year follow-up period.

Keywords Coronary heart disease · Guidelines implementation · Secondary prevention

Introduction

Secondary prevention in patients with existing coronary heart disease (CHD) aims at reducing the risk of recurrent events or death and to enhance quality of life. There is ample scientific evidence showing that appropriate preventive actions, preferably integrated into comprehensive prevention and rehabilitation programs, are effective to

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achieve these goals [1]. According to the recommendations of the Joint European Societies (JES), patients with coronary or other atherosclerotic disease should be given the highest priority regarding total cardiovascular disease reduction by means of lifestyle intervention, risk factor control and appropriate drug therapy [2]. Nevertheless, the EUROASPIRE surveys (EUROpean Action on Secondary Prevention through Intervention to Reduce Events), have since 1995 consistently found high prevalences of modifiable cardiovascular risk factors and revealed that a large majority of coronary patients in Europe is still failing to achieve the lifestyle, risk factor and therapeutic targets set by the JES guidelines [3].

The most recent EUROASPIRE IV study confirmed that translating current scientific knowledge into routine clinical practice through guidelines implementation is far from obvious [3]. Since trial circumstances in which evidence is obtained, may not always mirror a real-world clinical setting, observational studies are necessary to provide insights into daily practice and may help to understand how patients and their clinicians manage the disease. The objective of this study is to report on the incidence of total mortality and cardiovascular events during a period of 2 years following baseline screening of patients, who participated in the EUROASPIRE IV survey and to study the influence of a selection of common prognostic factors in this large cohort of patients with coronary artery disease seen in everyday clinical practice throughout Europe.

Methods

Patients

A detailed description of the EUROASPIRE IV cross-sectional study has been published elsewhere [3]. Briefly, 7998 coronary patients were recruited from cardiac centers and general hospitals serving the population in selected geographical areas in 24 European countries (Belgium, Bosnia Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, France, Germany, Greece, Ireland, Latvia, Lithuania, Netherlands, Poland, Romania, Russian Federation, Serbia, Slovenia, Spain, Sweden, Turkey, Ukraine and the United Kingdom). Centers were chosen to ascertain that any patient living within these areas presenting with acute symptoms of coronary disease, or requiring revascularization in the form of balloon angioplasty (PCI) or coronary artery surgery (CABG), had an approximately equal chance of being included. Within each hospital, consecutive male and female patients < 81 years of age at the time of the recruiting event or procedure, with the following diagnoses or treatments for CHD were identified retrospectively from diagnostic registers, hospital discharge lists or other sources: (1) elective or emergency CABG, (2) elective or emergency PCI, (3) acute myocardial infarction (AMI; ICD-10 I21), and (4) acute myocardial ischaemia (ICD-10 I20). The starting date for identification was ≥ 6 months and < 3 years prior to the expected interview date. These interviews and clinical examinations took place between May 2012 and April 2013. The overall participation rate was 49%. The average time between the hospital admission for the recruiting event or procedure and the baseline interview was 18 months.

Collection of baseline data

Data collection at baseline was conducted by centrally trained research assistants according to standardized methods and instruments [3]. They reviewed individual medical records, interviewed and examined the patients at least 6 months after their acute hospital admission or procedure. Information on educational level, previous hospitalizations for cardiovascular events, smoking behavior, physical activity level, self-reported diabetes and the current use of prophylactic drugs, was obtained through patient interview. A low educational level was defined as 'primary school level only or less'. A patient was labeled as a smoker if he/she reported to be a current smoker or had an exhaled carbon monoxide level exceeding 10 ppm at the time of interview. Waist circumference was recorded using a metal tape measure at the level midway between the lower rib margin and the iliac crest at the end of a normal expiration. Abdominal overweight was defined as a waist circumference of ≥ 80 cm for women and ≥ 94 cm for men and central obesity as a waist circumference of ≥ 88 cm for women and ≥ 102 cm for men. In line with the level of physical activity recommended in the 5th JES guidelines, a positive answer to the question "Do you take regular physical activity of at least 30 min duration on average 5 times a week?" was regarded as target [4]. Blood pressure and resting heart rate were measured in a sitting position on the right arm using an automatic digital sphygmomanometer. Controlled blood pressure was defined according to the 5th JES guidelines as systolic blood pressure (SBP) < 140 mmHg and diastolic blood pressure (DBP) < 90 mmHg ($< 140/80$ mmHg in patients with diabetes mellitus) [4]. Blood pressure was considered severely raised if SBP exceeded 160 mmHg and/or DBP exceeded 100 mmHg. Uncontrolled blood pressures not exceeding these limits were considered mildly raised. Resting heart rate was considered elevated if > 75 beats per minute (bpm).

Venous blood was drawn for determination of serum total and high-density lipoprotein (HDL) cholesterol, triglycerides, serum creatinine and glycated haemoglobin

A1c (HbA1c). LDL cholesterol was calculated according to Friedewald's formula. Biochemical analyses were carried out at the central laboratory in Helsinki (Disease Risk Unit, National Institute for Health and Welfare, Helsinki, Finland). Glycated haemoglobin A1c levels were considered raised if exceeding the value of 6.5% (48 mmol/mol). Glomerular filtration rate (eGFR) was estimated from serum creatinine by means of the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) [5]. Severe chronic kidney disease (CKD) was defined as eGFR < 30 mL/min/1.73 m^2 while eGFR values between 30 and 60 mL/min/1.73 m^2 were defined as indicating moderate chronic kidney disease.

Symptoms of anxiety and depression were investigated by means of the Hospital Anxiety and Depression Scale (HADS) questionnaire [6]. The instrument, containing 14 items with four response categories each, permits calculation of both an anxiety score and a depression score. The total score on each subscale ranges between 0 and 21 with scores ≥ 11 indicating symptoms of a probable disorder.

Follow-up and outcomes

A follow-up, in the form of a one-page questionnaire, was performed after a minimum of 1 year after the baseline interview of the 7998 patients from 78 EUROASPIRE IV centres. The eligibility criterion was a follow-up rate of 90%. Twelve centres (440 patients) did not fulfill this requirement and were hence excluded from our analyses. Follow-up information was gathered from patients themselves, medical records, external registries or databases (mortality registers, municipal records and archives) or by contacting the patients' family or family doctor. The collected information comprised vital status, date and cause of death ('coronary heart disease', 'stroke', 'other vascular', 'cancer' or 'other causes') and the occurrence of new hospitalizations following the date of baseline interview. The primary cardiovascular outcome was defined as the incidence of fatal cardiovascular disease or hospitalization for non-fatal myocardial infarction, stroke or heart failure. Death from any cause ('all-cause mortality') was considered as secondary outcome. In case of several non-fatal events, the first occurring was taken into account.

Statistical methods

Power calculations suggested that 4677 patients were to be followed in order to precisely (i.e. confidence interval width 1%) estimate the anticipated cumulative 1-year incidence of the primary outcome (3%) at the 95% confidence level. Distributions of the baseline characteristics were summarized using means, standard deviations and proportions. Hazard ratios (HRs) for the primary and secondary outcomes, their 95% confidence intervals and statistical significances, were estimated according to the semi-parametric Cox model. The assumption of proportionality of hazards was checked using log(–log(survival)) plots. To allow regional variation in the form of the underlying hazard function, Cox regression models were stratified for country. First, hazard ratios and their significances were adjusted for age and gender. Then, all variables were then entered in a multivariate model to study their independent association with both outcomes. For the primary outcome, a backward elimination procedure (5% significance level) was additionally applied to derive a set of significant independent predictors. The goodness-of-fit of the models was assessed through the log-likelihood statistic. A type I error probability limit of $\alpha = 0.05$ was used to indicate statistical significance. All analyses were undertaken using SAS statistical software (release 9.3) at the Department of Public Health, Ghent University, Belgium.

Data management

Data management was undertaken by the EURObservational Research Programme at the European Heart House, Nice, France. All data were collected electronically through web-based data entry using a unique identification number for country, centre and individual. At the data management centre checks for completeness, internal consistency and accuracy were run. All data were stored under the provisions of the National Data Protection Regulations.

Ethical procedures

National coordinators were responsible for obtaining Local Research Ethics Committees approvals. Written, informed consent was obtained from each participant by the investigator by a signed declaration. The research assistants signed the Case Record Form to confirm that informed consent was obtained and stored the original signed declaration consent in the patient file.

Results

Follow-up data were available for 7471 (99%) of the 7558 eligible patients. In 60% of patients, information was obtained from the patient directly, in 29% from medical records, in 8% from an external registry or database while the family or family doctor was contacted in 3%. Average follow-up time, defined as the time between baseline interview and the date of vital status ascertainment or death, was 2.0 years (ranging from 1.6 to 2.5 years).

Baseline characteristics of the 7471 patients by gender are given in Table 1. Patients were 64.1 years on average and predominantly (76%) of male gender. The large majority (88%) of patients had undergone a coronary intervention (CABG or PCI). More than 40% had been hospitalized for an AMI. Peripheral artery disease was diagnosed in 6% of patients. Half of the male patients and two thirds of the female patients were found to be centrally obese. About 40% reported sufficient levels of physical exercise, men being more active than women. Despite a high

Table 1 Baseline characteristics of the study sample

	Men N = 5650	Women N = 1821	All N = 7471
Age at interview (years), mean (SD)	63.4 (9.6)	66.4 (9.0)	64.1 (9.5)
Low educational level (%)	15.7% (882/5606)	20.9% (378/1809)	17.0% (1260/7415)
Currently smoking (%)	17.0% (962/5650)	11.1% (202/1821)	15.6% (1164/7471)
Regular physical activity (%)	44.0% (2487/5650)	36.9% (672/1821)	42.3% (3159/7471)
Body mass index (kg/m^2), mean (SD)	28.9 (4.3)	29.6 (5.5)	29.1 (4.7)
Waist circumference (cm), mean (SD)	102.7 (11.9)	96.8 (13.3)	101.2 (12.5)
Abdominal overweight (%)	26.3% (1483/5641)	16.6% (301/1813)	23.9% (1784/7454)
Central obesity (%)	52.4% (2957/5641)	75.0% (1360/1813)	57.9% (4317/7454)
Symptoms of probable anxiety (%)	8.6% (464/5391)	18.3% (316/1729)	11.0% (780/7120)
Symptoms of probable depression (%)	6.1% (331/5391)	12.0% (207/1729)	7.6% (538/7120)
Previous hospitalizations			
PTCA (%)	66.9% (3762/5626)	62.4% (1129/1809)	65.8% (4891/7435)
AMI (%)	44.7% (2493/5580)	41.2% (736/1788)	43.8% (3229/7368)
CABG (%)	24.2% (1357/5612)	17.4% (314/1804)	22.5% (1671/7416)
Heart failure (%)	4.7% (260/5558)	5.6% (100/1788)	4.9% (360/7346)
Stroke (%)	4.5% (252/5559)	5.2% (93/1786)	4.7% (345/7345)
Previous peripheral artery disease (%)	6.4% (358/5571)	5.0% (89/1792)	6.1% (447/7363)
Using aspirin or other anti-platelets (%)	94.3% (5303/5624)	92.4% (1672/1810)	93.8% (6975/7434)
Using blood pressure lowering drugs (%)	95.3% (5360/5624)	95.8% (1734/1810)	95.4% (7094/7434)
Using lipid lowering drugs (%)	87.6% (4926/5624)	84.8% (1535/1810)	86.9% (6461/7434)
Systolic blood pressure (mmHg), mean (SD)	134.3 (18.9)	135.2 (19.5)	134.5 (19.1)
Diastolic blood pressure (mmHg), mean (SD)	79.1 (11.0)	78.2 (11.2)	78.9 (11.1)
Mildly raised blood pressure (%)	34.1% (1924/5638)	35.1% (637/1815)	34.4% (2561/7453)
Severely raised blood pressure (%)	11.1% (625/5638)	12.6% (228/1815)	11.4% (853/7453)
Resting heart rate (bpm), mean (SD)	66.2 (11.0)	68.1 (10.8)	66.7 (11.0)
Resting heart rate 60–74 bpm (%)	51.9% (2888/5561)	55.0% (966/1756)	52.7% (3854/7317)
Resting heart rate $\geq$ 75 bpm (%)	19.7% (1096/5561)	24.2% (425/1756)	20.8% (1521/7317)
Moderate chronic kidney disease[a] (%)	14.4% (767/5341)	23.0% (391/1699)	16.4% (1158/7040)
Severe chronic kidney disease[b] (%)	1.4% (72/5341)	1.9% (32/1699)	1.5% (104/7040)
Total cholesterol (mmol/L), mean (SD)	4.31 (1.06)	4.71 (1.25)	4.41 (1.12)
HDL cholesterol (mmol/L), mean (SD)	1.12 (0.26)	1.28 (0.32)	1.15 (0.29)
LDL cholesterol (mmol/L), mean (SD)	2.46 (0.88)	2.69 (1.04)	2.52 (0.92)
LDL-C 1.8–2.4 mmol/L (%)	39.6% (2036/5146)	35.7% (588/1647)	38.6% (2624/6793)
LDL-C $\geq$ 2.5 mmol/L (%)	39.4% (2028/5146)	48.6% (800/1647)	41.6% (2828/6793)
HbA1c (%) in patients with no DM, mean (SD)	5.74 (0.52)	5.75 (0.49)	5.74 (0.51)
HbA1c (%) in patients with DM, mean (SD)	7.13 (1.39)	7.33 (1.46)	7.18 (1.41)
Self-reported diabetes (%)	25.5% (1435/5625)	30.0% (543/1812)	26.6% (1978/7437)
No diabetes and HbA1c $\geq$ 6.5% (%)	4.2% (224/5298)	2.7% (46/1695)	3.9% (270/6993)
Diabetes and HbA1c $<$ 6.5% (%)	9.4% (498/5298)	10.0% (169/1695)	9.5% (667/6993)
Diabetes and HbA1c $\geq$ 6.5% (%)	16.0% (848/5298)	20.4% (345/1695)	17.1% (1193/6993)

consumption of blood pressure lowering agents, the prevalence of raised blood pressure was 46%. Blood pressure levels were severely raised in 11% of patients. The prevalence of an elevated resting heart rate ($\geq$ 75 bpm) was 21%. Fasting LDL cholesterol was high ($\geq$ 2.5 mmol/L) in 42% of patients and only a fifth of the patients reached the LDL target of $<$ 1.8 mmol/L. A quarter of the patients reported to have been diagnosed with diabetes. The large majority of these patients had elevated HbA1c levels of $\geq$ 6.5%. Chronic kidney disease (eGFR $<$ 60 mL/min/1.73 m^2) was observed in 18% of patients with a minority (1.5%) found to have severe CKD.

During the entire follow-up period of 2 years on average, 222 deaths (3.0%) were registered of whom 128 (58%) were classified as cardiovascular. All-cause mortality rates were estimated as 15.1 and 13.5 per 1000 person-years in men and women respectively. The corresponding cardiovascular mortality rates were 8.2 and 9.7 per 1000 person-years. Regarding non-fatal events, 276 (3.7%) patients were hospitalized for heart failure, 177 (2.4%) for AMI and 142 (1.9%) for stroke. The incidence of the primary cardiovascular outcome was 42.0 per 1000 person-years (40.8 and 45.8 per 1000 person-years in men and women respectively). According to Kaplan–Meier estimates, 90% of patients were event-free after 2.5 years of follow-up (Supplementary Fig. 1).

In Table 2, the strength of the associations between baseline characteristics and events are shown after adjustment for age and gender. Adjusting for age, women were at significantly lower risk of all-cause mortality but not for the primary outcome. Educational level was strongly and inversely related to both all-cause mortality and incident cardiovascular events. Smoking was unrelated to the primary outcome although smokers had a higher total mortality risk. Patients taking regular physical activity had a significantly better survival and less cardiovascular events. The waist circumference was not significantly associated with adverse outcome. Symptoms indicating anxiety and in particular depression were predictive for both all-cause mortality and the primary outcome.

Subgroups of patients with a previous AMI, stroke, heart failure or peripheral artery disease as comorbid conditions were at increased risk for fatal and recurrent non-fatal cardiovascular events. Raised blood pressure was inversely related with all-cause mortality, but there was no significant association between blood pressure levels and total cardiovascular outcomes. Fitting systolic blood pressure as a quadratic effect in the model did not reveal a U-shaped relation between blood pressure and the incidence of cardiovascular events. Heart rate proved to be a strong and significant predictor for both outcomes with an increase in the cardiovascular incidence rate of 84% in patients with a resting heart rate exceeding 75 bpm. Patients using lipid-lowering drugs had 38% lower risk for total mortality and 29% less incident cardiovascular events. Irrespective of lipid-lowering treatment the LDL-C level was not significantly associated with mortality or with cardiovascular outcomes. This is further documented in Fig. 1 revealing that the lowest cardiovascular incidence rate was observed in patients with an LDL-C between 2.0 and 2.5 mmol/L. The association between self-reported diabetes and both fatal and non-fatal outcomes was strong. Patients with diabetes and hemoglobin A1c levels $\geq$ 6.5% were at particularly high risk for new cardiovascular events. Figure 1 further demonstrates the prognostic impact of raised HbA1c levels in patients with known diabetes. CKD was strongly related to adverse fatal and non-fatal events with patients being diagnosed with severe CKD being at particularly high risk for both mortality and cardiovascular events.

Multivariate Cox regression analyses confirmed the independence, strengths and directions of most of these relations with the primary outcome, with the exception of those for regular physical activity and symptoms of anxiety, both no longer reaching the level of statistical significance (Table 2). For total cardiovascular events, Fig. 2 displays the adjusted prognostic impact of baseline characteristics retained in the Cox model after applying the backward elimination procedure. Finally, in patients free from diabetes, only 4.5% had reached optimal risk factor levels at baseline (not smoking, waist circumference $<$ 102/88 cm in men/women, SBP/DBP $<$ 140/90 mmHg, LDL-C $<$ 1.8 mmol/L). After correction for age and gender, their risk for fatal and non-fatal cardiovascular events was not significantly different from risk in patients with at least one risk factor not on target [hazard ratio (95% CI) = 0.90 (0.40–2.03), P = 0.80].

Discussion

In this unselected cohort of coronary patients, cardiovascular event rates during follow-up were rather low in comparison with those observed in the REACH registry of patients with atherothrombosis [7]. In the subgroup of CAD patients in REACH, the 2-year cumulative incidence of major cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) was about 8%. In our study, the primary outcome (CVD death or non-fatal MI, stroke or heart failure) occurred in 8.3% of patients during the 2-years of follow-up; leaving out heart failure from the composite outcome diminished this 2-year cumulative incidence to 5.1%, a figure more in line with the incidence (annual rate 3.4%) observed in the Heart and Soul study [8]. The lower event rate observed in EUROASPIRE IV in comparison to REACH can partly be

Table 2 Associations between baseline characteristics and the development of new events

	Fatal CVD or non-fatal AMI, stroke or heart failure		All-cause mortality	
	Hazard ratio (95% CI) Adjusted for age and gender	Hazard ratio (95% CI) Multivariately adjusted	Hazard ratio (95% CI) Adjusted for age and gender	Hazard ratio (95% CI) Multivariately adjusted
Age at interview (per 10 years)	1.44 (1.31–1.58), $P < 0.0001$	1.39 (1.23–1.57), $P < 0.0001$	2.31 (1.93–2.75), $P < 0.0001$	2.42 (1.92–3.06), $P < 0.0001$
Female gender	1.05 (0.87–1.26), $P = 0.61$	0.86 (0.69–1.07), $P = 0.18$	0.71 (0.51–0.97), $P = 0.03$	0.56 (0.37–0.84), $P = 0.005$
Low educational level	1.40 (1.13–1.75), $P = 0.003$	1.31 (1.02–1.69), $P = 0.03$	1.81 (1.30–2.52), $P = 0.0005$	1.77 (1.20–2.59), $P = 0.004$
Currently smoking	0.91 (0.71–1.17), $P = 0.47$	1.02 (0.77–1.33), $P = 0.91$	1.60 (1.09–2.34), $P = 0.02$	1.39 (0.88–2.21), $P = 0.16$
Regular physical activity	0.81 (0.67–0.97), $P = 0.02$	1.00 (0.81–1.23), $P = 0.98$	0.61 (0.45–0.83), $P = 0.002$	0.73 (0.51–1.06), $P = 0.10$
Abdominal overweight[a]	0.86 (0.66–1.13), $P = 0.29$	0.79 (0.58–1.07), $P = 0.12$	0.77 (0.50–1.19), $P = 0.24$	0.80 (0.50–1.30), $P = 0.37$
Central obesity[a]	1.25 (0.99–1.57), $P = 0.06$	1.09 (0.84–1.42), $P = 0.50$	1.03 (0.71–1.48), $P = 0.89$	0.90 (0.59–1.38), $P = 0.63$
Using aspirin or other anti-platelet drugs	0.81 (0.60–1.08), $P = 0.15$	0.95 (0.67–1.34), $P = 0.77$	1.23 (0.72–2.10), $P = 0.44$	1.83 (0.94–3.58), $P = 0.08$
Using blood pressure lowering drugs	0.97 (0.64–1.47), $P = 0.90$	1.05 (0.64–1.72), $P = 0.85$	0.61 (0.35–1.05), $P = 0.07$	0.64 (0.33–1.26), $P = 0.19$
Using lipid lowering drugs	0.71 (0.57–0.87), $P = 0.001$	0.82 (0.64–1.06), $P = 0.14$	0.62 (0.44–0.86), $P = 0.004$	0.64 (0.42–0.97), $P = 0.04$
Previous hospitalizations: AMI	1.40 (1.19–1.65), $P < 0.0001$	1.27 (1.05–1.53), $P = 0.01$	1.58 (1.20–2.08), $P = 0.001$	1.43 (1.04–1.97), $P = 0.03$
Stroke	2.17 (1.67–2.82), $P < 0.0001$	1.70 (1.27–2.29), $P = 0.0004$	1.97 (1.28–3.03), $P = 0.002$	1.50 (0.91–2.47), $P = 0.11$
Heart failure	1.81 (1.36–2.41), $P < 0.0001$	1.47 (1.08–2.01), $P = 0.02$	1.38 (0.82–2.31), $P = 0.23$	1.07 (0.60–1.92), $P = 0.81$
CABG	1.19 (0.98–1.44), $P = 0.08$	1.10 (0.88–1.38), $P = 0.42$	1.33 (0.99–1.79), $P = 0.06$	1.28 (0.89–1.84), $P = 0.18$
PTCA	1.02 (0.85–1.22), $P = 0.84$	1.04 (0.84–1.28), $P = 0.73$	1.13 (0.85–1.52), $P = 0.40$	1.20 (0.84–1.70), $P = 0.32$
Previous peripheral artery disease	2.14 (1.66–2.77), $P < 0.0001$	1.48 (1.09–2.01), $P = 0.01$	1.95 (1.29–2.95), $P = 0.002$	1.15 (0.69–1.92), $P = 0.60$
Mildly raised blood pressure[b]	1.16 (0.98–1.38), $P = 0.09$	0.85 (0.69–1.05), $P = 0.13$	0.64 (0.47–0.87), $P = 0.005$	0.47 (0.32–0.69), $P = 0.0001$
Severely raised blood pressure[b]	1.04 (0.80–1.35), $P = 0.75$	0.84 (0.62–1.12), $P = 0.23$	0.82 (0.55–1.22), $P = 0.33$	0.67 (0.41–1.08), $P = 0.10$
Resting heart rate 60–74 bpm[c]	1.38 (1.10–1.72), $P = 0.006$	1.37 (1.07–1.76), $P = 0.01$	1.17 (0.83–1.67), $P = 0.37$	0.94 (0.64–1.38), $P = 0.74$
Resting heart rate $\geq$ 75 bpm[c]	1.84 (1.43–2.38), $P < 0.0001$	1.74 (1.30–2.32), $P = 0.0002$	1.73 (1.16–2.58), $P = 0.007$	1.40 (0.89–2.20), $P = 0.15$
Moderate chronic kidney disease[d]	1.37 (1.11–1.68), $P = 0.003$	1.23 (0.98–1.54), $P = 0.08$	1.40 (1.02–1.94), $P = 0.04$	1.07 (0.73–1.56), $P = 0.72$
Severe chronic kidney disease[e]	3.03 (1.96–4.70), $P < 0.0001$	2.36 (1.44–3.85), $P = 0.0006$	5.37 (3.04–9.46), $P < 0.0001$	5.35 (2.93–9.79), $P < 0.0001$
LDL-C 1.8–2.4 mmol/L[f]	0.85 (0.67–1.08), $P = 0.17$	0.95 (0.73–1.22), $P = 0.67$	0.87 (0.59–1.27), $P = 0.46$	0.99 (0.64–1.52), $P = 0.96$
LDL-C $\geq$ 2.5 mmol/L[f]	0.99 (0.78–1.25), $P = 0.92$	1.06 (0.82–1.38), $P = 0.65$	1.01 (0.69–1.48), $P = 0.98$	0.99 (0.63–1.54), $P = 0.95$
No diabetes and HbA1c $\geq$ 6.5%[g]	1.19 (0.77–1.83), $P = 0.44$	1.13 (0.70–1.83), $P = 0.62$	1.08 (0.50–2.33), $P = 0.84$	1.32 (0.57–3.06), $P = 0.51$
Diabetes and HbA1c < 6.5%[g]	1.50 (1.15–1.97), $P = 0.003$	1.44 (1.07–1.95), $P = 0.02$	1.43 (0.93–2.22), P = 0.11	1.74 (1.05–2.88), $P = 0.03$
Diabetes and HbA1c $\geq$ 6.5%[g]	2.28 (1.89–2.75), $P < 0.0001$	1.89 (1.50–2.38), $P < 0.0001$	1.82 (1.31–2.53), $P = 0.0003$	1.97 (1.32–2.95), $P = 0.001$
HADS Anxiety score $\geq$ 11[h]	1.36 (1.07–1.74), $P = 0.01$	1.21 (0.91–1.62), $P = 0.19$	1.43 (0.94–2.19), $P = 0.10$	0.88 (0.50–1.55), $P = 0.65$
HADS Depression score $\geq$ 11[h]	1.75 (1.37–2.22), $P < 0.0001$	1.36 (1.02–1.81), $P = 0.04$	1.91 (1.30–2.82), $P = 0.001$	1.30 (0.77–2.17), $P = 0.32$

[a]Versus normal waist

[b]Versus SBP/DB$P < 140/90$ mmHg (< 140/80 mmHg in patients with diabetes)

[c]Versus resting heart rate 60 bpm

[d]eGFR 30–59 mL/min/1.73 m^2

[e]eGFR < 30 mL/min/1.73 m^2

[f]Versus LDL-C < 1.8 mmol/L

[g]Versus no diabetes and HbA1c < 6.5%

[h]Versus HADS score < 11

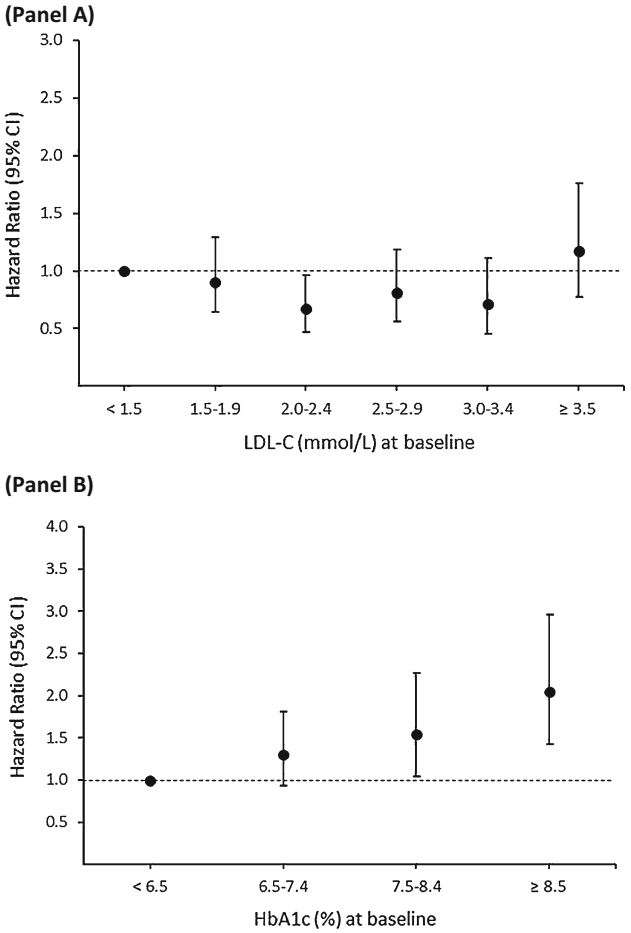

Fig. 1 **a** Age- and gender-adjusted association of baseline LDL-C levels with the incidence of new cardiovascular events in patients with established CHD; **b** age- and gender-adjusted association of baseline HbA1c levels with the incidence of new cardiovascular events in diabetes patients with established CHD

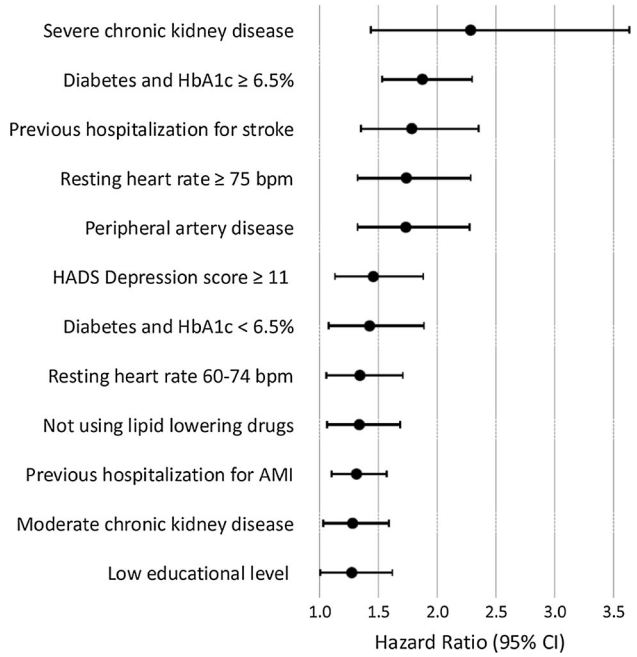

Fig. 2 Independent significant predictors of new cardiovascular events

explained by the fact that our cohort consisted exclusively of stabilized coronary patients in the age range 18–80 years seen at least 6 months after their recruiting event. REACH included patients being at least 45 years of age and no upper age limit was used; this resulted in a cohort with high rates of comorbidities and higher risk factor levels than in our study.

As expected, prognosis was clearly dependent on age but CVD incidence rates were not different between men and women in our study. The association of both outcomes with the patients' educational level was striking. In patients having completed primary school only or less, incidences of fatal and non-fatal events were significantly and independently raised. The present results give support to previous observations of an association between educational level and mortality in cardiovascular patients which could only be marginally explained by established risk factors such as smoking, other lifestyle behaviours or uncontrolled risk factor levels [9]. Cause remains an open question and may be attributed more generally to social determinants of health including health inequities, income level or living and working environments.

Importantly, our results show that the prognostic importance of chronic comorbidities (previous AMI, stroke, heart failure, CKD and PAD) reflecting disease severity outweigh the prognostic value of modifiable risk factors such as smoking, obesity, uncontrolled blood pressure, uncontrolled LDL cholesterol and insufficient levels of physical activity. Being a smoker at the time of the interview was not significantly related to the primary outcome according to our multivariate models. This may be partly because many long term smokers had stopped smoking in the time between hospitalization for the recruiting event and the time they were invited for the baseline visit resulting in a high residual risk in the ex-smokers category. A 2-year follow-up from this baseline may have been insufficient to reveal the longer term impact of smoking cessation. At baseline, 58% of patients were classified as centrally obese; however they were not at higher risk for subsequent cardiovascular events. The apparently lower risk in patients with abdominal overweight seems to be in line with several prospective cohort studies reporting a J-shaped relationship between body mass index and new events in patients with CHD or other chronic diseases, a phenomenon coined contentiously as the 'obesity paradox' [10, 11]. After adjustment for age and gender, we found that taking regular physical activity was

protective for both outcomes. However in multivariate analysis this effect dropped when adjusting for risk factors and comorbidities such as abdominal overweight or central obesity.

In our EUROASPIRE IV population of CHD patients, most of whom were taking aspirin or other anti-platelet therapies, antihypertensive drugs or statins, treated levels of blood pressure and lipids did not carry a residual prognostic impact on recurrent cardiovascular events or all-cause mortality. This important observation is consistent with the follow-up results from the REACH registry in which neither baseline blood pressure nor cholesterol levels carried a further residual risk for future development of fatal and non-fatal cardiovascular events [12]. Interestingly, we found that patients with mildly raised blood pressure were at significantly lower risk for all-cause mortality. Excluding fatal events occurring in the first 3 months following the baseline interview from the analysis, did not alter this result. Baseline LDL-C levels at interview in our study also had no prognostic impact regardless of statin use and this is consistent with a recent study from Israel [13]. This could partially be attributed to the fact that statins in many patients were only initiated at the time of the recruiting event—6 months to maximum 3 years prior to the baseline examination. In the 4S trial, the drop in LDL-C levels following simvastatin initiation lowered the risk of subsequent events mainly after 2 years following baseline examinations [14]. The lack of an incremental prognostic value of a 'treated LDL-C level' could also relate to the discussion whether the attained LDL-C level is important or rather the percent reduction; a patient with an attained LDL-C level of 2.5 mmol/L but coming from 5.0 mmol/L (50% reduction) may be at lower risk than a patient with an attained LDL-C of 1.5 mmol/L coming from 2.0 mmol/L (25% reduction). The use of lipid-lowering drugs was retained in our backwards elimination model as a significant protective factor (hazard ratio 0.76), fully in line with REACH registry data showing that the use of statins was associated with a 27% reduction in the incidence of cardiovascular events, irrespective of other risk factors (hazard ratio 0.73).

Interestingly, resting heart rate emerged as a strong and independent risk factor for both all-cause mortality and the occurrence of non-fatal cardiovascular events. In a secondary analysis, the strength of this association persisted in the subgroup of patients using beta-blockers at baseline and after excluding patients previously hospitalized for heart failure. Our findings confirm elevated heart rate as an important independent risk factor for cardiovascular events in CAD patients, both with and without diabetes [15, 16]. Although elevated heart rate is known to induce myocardial ischaemia, data from the SIGNIFY and BEAUTIFUL trials suggest that heart rate is not a modifiable risk factor in patients with CAD without heart failure, but rather a marker of risk [17, 18].

Our study confirms the importance of an appropriate glycaemic control, expressed by a HbA1c $< 6.5\%$, in CHD patients with known diabetes. In our multivariate model, risk of the primary outcome in this particular group was found to be doubled in comparison to non-diabetic patients, confirming findings from several other studies in CHD populations such as the GAMI study and the Euro Heart Survey on Diabetes and the Heart [19, 20]. Since previously undetected glucose abnormalities, such as impaired glucose tolerance, are very common in patients with existing CHD and carry additional prognostic information, early detection and treatment is of primary importance. Several studies have demonstrated that a glucometabolic classification based on an oral glucose tolerance test, may be the preferred diagnostic procedure in patients at high risk such as those with established coronary heart disease [21].

At baseline, 6% of the EUROASPIRE IV patients reported to have been diagnosed with peripheral arterial disease. This figure is substantially lower than the PAD prevalence of 13% observed in the stable CAD outpatients from Europe enrolled in the CLARIFY registry [22]. In the GRACE registry, a history of PAD was seen in 10% of the patients with an acute coronary syndrome [23]. Our results are more in agreement with the observation made in the Spanish PAMISCA registry of ACS patients reporting a PAD prevalence of 7% [24]. The 50% cardiovascular risk excess associated with known PAD peripheral arterial disease in our cohort of CHD patients, warrants optimal risk factor control in patients with comorbid PAD to prevent future cardiovascular events. In a French sample of 710 patients with stable CHD, subclinical PAD (no history of PAD but abnormal ankle brachial index) was twice as common (26% vs. 12%) as clinical PAD (history of claudication or peripheral arterial interventions) [25]. Since asymptomatic PAD is associated with the same unfavourable cardiovascular prognosis as symptomatic PAD, systematic screening for asymptomatic PAD—using the ankle brachial index—is highly recommended in CHD patients.

Although impaired kidney function is associated with an elevated risk of adverse outcomes and mortality in the general population, relatively few studies have documented the prevalence and prognostic value of established chronic kidney disease in CHD patients [26, 27]. Overall, 18% of our EUROASPIRE IV patients were found to have CKD defined as eGFR < 60 mL/min/1.73 m^2. In the global CLARIFY register, a CKD prevalence of 22% was observed [28]. In a group of 6447 Dutch patients with known or suspected coronary artery disease, prevalence of CKD was 15% [29]. After a 7-year registration period,

hazard ratios for all-cause and cardiac mortality were high and very similar as the ones reported here.

Depression is quite common in patients with chronic diseases such as CHD and is consistently shown to be associated with adverse outcome [30]. The accumulating evidence has led the American Heart Association to release a statement that depression should be regarded as a common and strong prognostic factor in patients with acute coronary syndrome [31]. In our study, the association between symptoms of depression at interview and subsequent fatal and non-fatal CVD was only partly mediated by established risk factors and lifestyle. These results indicate the need for tailored psychosocial interventions in CHD patients with depressive symptoms. However, a recent meta-analysis demonstrated that interventions for comorbid depression may lead to a significant reduction in major cardiovascular events in the short term but concluded that this effect did not sustain in the longer term (> 12 months) [32].

The main strength of the EUROASPIRE surveys is our methodological approach with interviews and examinations done by centrally trained personnel using standardized instruments and with biochemical analyses done in a central laboratory, rather than relying on information found in medical records only. Also, our observations are based on a large sample of patients recruited from hospitals and cardiac centres from different geographical areas across Europe.

Our survey and current analyses have also limitations. The assumption that the EUROASPIRE patient cohort reflects the normal range of diversity in disease severity, comorbidities and socioeconomic background of stabilized CHD patients seen in everyday clinical practice, cannot be verified. Participation in the baseline examinations and interviews was low (49%) mainly because of restrictions imposed by local ethics committees and privacy laws in different countries on the way patients can be approached. But still, the low interview rate is very likely to have introduced selection and participation bias. Although our follow-up was 99% complete and information on events was mainly based on national mortality statistics and hospital and GP databases, the reliability and validity of our endpoints is not known, although this may have rather led to underestimations of the associations we have observed. Finally, the relatively short duration of our follow-up may have led to an underestimation of the longer-term impact of risk factors in particular those related to lifestyle.

In summary, this EUROASPIRE IV follow-up study shows that in stabilized CHD patients the severity of the underlying pathology, as reflected by comorbid conditions (previous AMI, stroke, heart failure or PAD, diabetes and CKD) dominates lifestyle-related (smoking, obesity, physical activity) and other modifiable risk factors (blood pressure, lipid levels) in the prognosis of future fatal and non-fatal cardiovascular events, at least over a 2-year follow-up period. This observation does not challenge the benefits of lifestyle intervention, risk factor management and cardioprotective drug therapies as evidenced by randomized controlled trials. However, patients participating in trials do not necessarily represent the generality of patients in the community because of stringent inclusion and exclusion criteria leading to selection. Registries such as the EUROASPIRE surveys collect clinical data on unselected patients regardless of their characteristics and therefore provide an everyday contemporary view on management and prognosis in daily clinical setting. The main conclusion from these survey data is the need to address CVD at an earlier stage in the clinical course of the disease through screening followed by appropriate interventions to prevent the initial development of CVD and associated co-morbidities; namely primary prevention.

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Compliance with ethical standards

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