

Alma Mater Studiorum – Università di Bologna

**DOTTORATO DI RICERCA IN
SCIENZE CARDIO NEFRO TORACICHE**

Ciclo XXXV

Settore Concorsuale: 06/D1 - Malattie dell'Apparato Cardiovascolare e
Malattie dell'Apparato Respiratorio

Settore Scientifico Disciplinare: MED/23-Chirurgia Cardiaca

**TRADITIONAL RISK FACTORS AND LIFETIME
RISK OF ACUTE CORONARY EVENTS**

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Esame finale anno 2023

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ABBREVIATIONS AND ACRONYMS

ACE =angiotensin-converting enzyme

ACS= acute coronary syndromes

AHF= acute heart failure

ARB= angiotensin receptor blocker

BMI =body mass index

CABG= coronary artery bypass graft

CAD= coronary artery disease

CHD= coronary heart disease

CI= confidence intervals

GP=glycoprotein

HR=hearts rate

LMWH =low-molecular-weight heparins

NSTE-ACS= non-ST-segment elevation acute coronary syndrome

OR=odd ratio

PAD=peripheral artery disease

PCI =percutaneous coronary intervention

RR=risk ratios

SBP=systolic blood pressure

STEMI= ST-segment elevation myocardial infarction

RIASSUNTO

Obiettivo: L'obiettivo di questo studio è quello indagare l'associazione tra i quattro fattori di rischio tradizionali di malattia coronarica (ipertensione, fumo, ipercolesterolemia e diabete) e gli esiti della prima sindrome coronarica acuta (SCA).

Materiali e metodi: I dati sono stati estratti dal registro "International Survey of Acute Coronary Syndromes Archives". I partecipanti allo studio erano 70953 pazienti caucasici con prima SCA, ma senza pregressa malattia coronarica o scompenso cardiaco. Gli esiti primari erano l'età del paziente alla presentazione in ospedale e la mortalità per tutte le cause entro 30 giorni dal ricovero in ospedale. Le risk ratio (RR) per la mortalità tra i sottogruppi sono state calcolate utilizzando una strategia di bilanciamento mediante inverse probability weighting. I trend sono stati valutati mediante il coefficiente di correlazione di Pearson (r).

Risultati: Per le SCA fatali ($n=6097$), l'esposizione ad almeno un tradizionale fattore di rischio di malattia coronarica variava dal 77.6% nelle donne al 74.5% negli uomini. La presenza di tutti e quattro i fattori di rischio di malattia coronarica ha ridotto significativamente l'età al momento dell'evento SCA e della morte di quasi mezzo decennio rispetto all'assenza di qualsiasi fattore di rischio tradizionale di malattia coronarica. Ciò è avvenuto sia nelle donne (da 67.1 ± 12.0 a 61.9 ± 10.3 anni; $r = -0.089$, $P < 0.001$) che negli uomini (da 62.8 ± 12.2 a 58.9 ± 9.9 anni; $r = -0.096$, $P < 0.001$). Al contrario, si è osservato un'associazione inversa tra il numero di fattori di rischio tradizionali di malattia coronarica e la mortalità a 30 giorni. I tassi di mortalità nelle donne variavano dal 7.7% con quattro fattori di rischio tradizionali di malattia coronarica al 16.3% senza fattori di rischio tradizionali di malattia coronarica ($r = 0.073$, $P < 0.001$). I tassi corrispondenti negli uomini erano rispettivamente del 4.8% e dell'11.5% ($r = 0.078$, $P < 0.001$). I rapporti di rischio (risk ratio) tra gli individui con almeno un fattore di rischio di malattia coronarica rispetto a quelli senza fattori di rischio tradizionali di malattia coronarica erano RR: 0.72 (95%CI: 0.65 - 0.79) nelle

donne e 0.64 (95%CI: 0.59 – 0.70) negli uomini. Questa associazione permaneva anche tra i sottogruppi di pazienti gestiti con le opzioni terapeutiche raccomandate dalle linee guida.

Conclusioni: la stragrande maggioranza dei pazienti che muoiono per SCA presenta un'esposizione ai fattori di rischio tradizionali di malattia coronarica. I pazienti con fattori di rischio di malattia coronarica muoiono molto prima nella vita, ma hanno un rischio relativo inferiore di mortalità a 30 giorni rispetto a quelli senza fattori di rischio tradizionali di malattia coronarica, anche nel contesto di trattamenti clinici basati sull'evidenza durante il ricovero ospedaliero.

ABSTRACT

Objective: To investigate the association between the four traditional coronary heart disease (CHD) risk factors (hypertension, smoking, hypercholesterolemia, and diabetes) and outcomes of first acute coronary syndrome (ACS).

Methods: Data were drawn from the International Survey of Acute Coronary Syndromes Archives. The study participants consisted of 70953 Caucasian patients with first ACS, but without prior CHD. Primary outcomes were patient' age at hospital presentation and all-cause mortality within 30 days after hospital admission. The risk ratios (RRs) for mortality among subgroups were calculated using a balancing strategy by inverse probability weighting. Trends were evaluated by the Pearson's correlation coefficient (r).

Results: For fatal ACS ($n=6097$), exposure to at least one traditional CHD risk factor ranged from 77.6% in women to 74.5% in men. The presence of all four CHD risk factors significantly decreased the age at time of ACS event and death by nearly half a decade compared with the absence of any traditional CHD risk factors in both women (from 67.1 ± 12.0 to 61.9 ± 10.3 years; $r=-0.089$, $P<0.001$) and men (from 62.8 ± 12.2 to 58.9 ± 9.9 years; $r=-0.096$, $P<0.001$). By contrast, there was an inverse association between the number of traditional CHD risk factors and 30-day mortality. The mortality rates in women ranged from 7.7% with four traditional CHD risk factors to 16.3% with no traditional CHD risk factors ($r=0.073$, $P<0.001$). The corresponding rates in men were 4.8% and 11.5% ($r=0.078$, $P<0.001$), respectively. The risk ratios among individuals with at least one CHD risk factors vs. those with no traditional CHD risk factors were 0.72 (95% CI: 0.65 to 0.79) in women and 0.64 (95% CI: 0.59 to 0.70) in men. This association was consistent among patient subgroups managed with guideline recommended therapeutic options.

Conclusions: The vast majority of patients who die for ACS have traditional CHD-risk factor exposure. Patients with CHD-risk factors die much earlier in life, but they have lower relative

risk of 30- day mortality than those with no traditional CHD-risk factors, even in the context of equitable evidence-based treatments after hospital admission.

INTRODUCTION

Appreciation of the crucial role of traditional cardiovascular risk factors in the development of coronary artery disease have contributed to reduced risk of cardiovascular events and death from coronary heart disease (CHD). Extensive epidemiological research has established current cigarette smoking, diabetes, hypercholesterolemia, and hypertension as the main risk factors for the occurrence of CHD.¹

Still, there are patients who present with CHD, but without traditional risk factors. The proportion of such patients has been suggested to account for approximately 30% of those presenting to hospital with acute coronary syndromes (ACS).² Notably, earlier publications have also reported a close association between numbers of traditional risk factors and adverse outcomes after myocardial infarction.³ More recent research has found that mortality is higher in patients without traditional risk factors compared with their counterparts with at least one risk factor and has suggested that women have worse outcomes than men.⁴⁻⁶ These findings would imply that other factors play a major role in the development of CHD and that there is a substantial void in current understanding of the prevention and risk stratification of CHD, especially in women.

This perceived void has led to considerable research on nontraditional risk factors such as prediabetes, insulin resistance, abdominal obesity, psychosocial factors, poor nutrition, or physical inactivity and genetic causes of CHD. Yet, data on nontraditional risk factors and CHD mortality in the absence of conventional risk factors, are still limited. Moreover, it is difficult to discuss mortality post CHD acute events with no reference to how timely revascularization and medications on admission came into play.

To address these questions, we sought to determine the prevalence and consistency of the four traditional risk factor exposures across sexes and a range of adult ages in a broad multi-ethnic population of patients presenting to hospital for ACS as first manifestation of CHD. We also

investigated whether the impact of an increasing number of traditional CHD risk factors may correlate with younger age on hospital admission and lower mortality compared with the absence of risk factors.

MATERIALS AND METHODS

Study Design and Subjects

The study population consisted of 70953 Caucasian patients enrolled in the International Survey of Acute Coronary Syndromes (ISACS) Archives (*ClinicalTrials.gov*: NCT04008173) registry network for a first manifestation of ACS from October 2005 to January 2021 (**Figure 1**). Patients with prior CHD or heart failure of unknown origin were excluded.

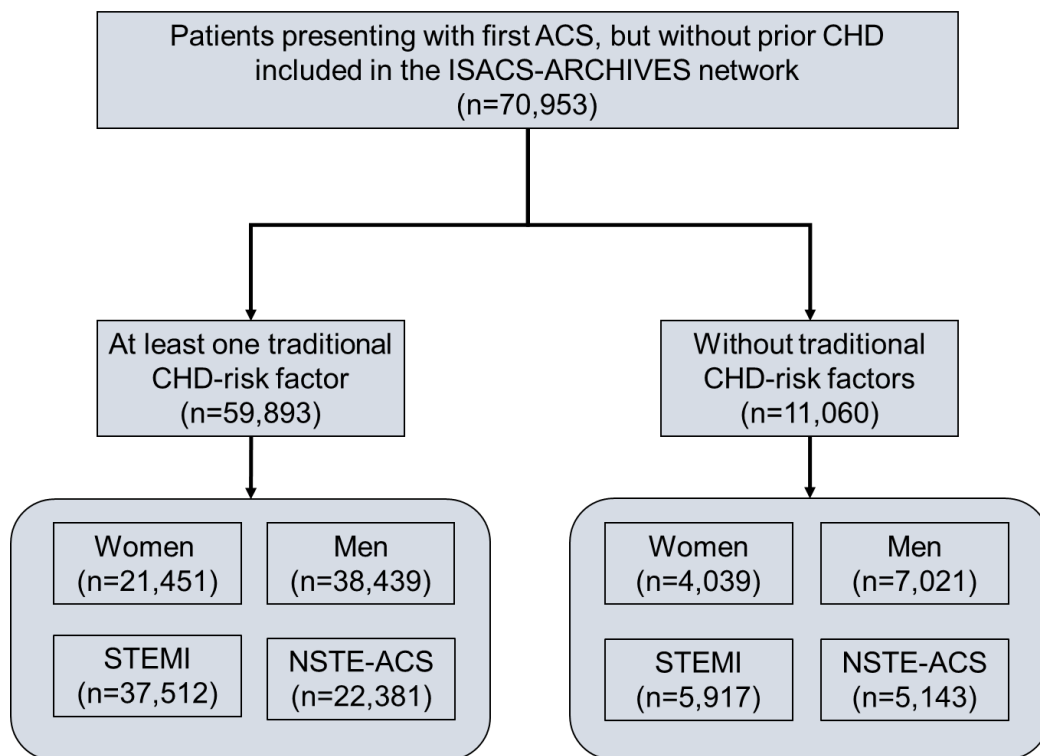


Figure 1. Study Flow Chart

Abbreviation: ACS=acute coronary syndromes, CHD=coronary artery disease, NSTEMI=non-ST-segment elevation acute coronary syndromes, STEMI= ST-segment elevation acute coronary syndromes

The design of the ISACS Archives has been previously described.^{7, 8} In brief, the ISACS Archives provide access to deidentified research cohorts in ACS. Registries enrolled in the ISACS Archives use data definition for the measures/experiments that are harmonized to the standard variables of the ISACS-TC (*ClinicalTrials.gov*: NCT01218776).⁹ Registries have independent source documentation. Because one of the aims of the current study was to

investigate the association between cardiovascular outcomes and time from onset of symptoms to hospital presentation, we identified two large clinical registries providing such information, namely, the ISACS-TC⁹ and the HORACS- RAACS¹⁰ (Department of Prevention and Control of Non-communicable Diseases of the Institute of Public Health of Serbia). The local research ethics committee from each hospital approved the study. Because patient information was collected anonymously, institutional review boards waived the need for individual-informed consent. This study complies with the Declaration of Helsinki.

Outcome measures

The primary outcome measure was all-cause mortality within 30 days of hospital admission. The 30-day window was selected to enrich the data over that acquired during the index hospitalization while mitigating survivor bias. To explore the multifaceted association between traditional CHD risk factors and mortality, we identified ST-segment elevation myocardial infarction (STEMI), acute heart failure and Shock Index on admission as secondary measures of outcome. The diagnosis of acute heart failure (AHF) was based on clinical symptoms or signs and radiographic evidence of pulmonary congestion. The presence and severity of acute heart failure at the time of hospital presentation was formally categorized by using the Killip classification.¹¹ The Shock Index was defined by the ratio of heart rate to systolic blood pressure on admission and categorized into two strata: <1.0, no or mild shock and ≥ 1.0 , moderate or severe shock.¹² Coronary artery bypass graft (CABG) was performed as a need for urgent surgery after percutaneous coronary intervention (PCI). As such, outcomes of CABG interventions were included in the subgroups of patients with reperfusion therapy and revascularization procedures.

Concomitant care and definitions

We also noted the type of medications given on hospital admission and during hospitalization (fibrinolysis, antiplatelet agents [aspirin and/or P2Y₁₂ inhibitors], heparins [unfractionated

heparin or low-molecular-weight heparins [LMWH], glycoprotein IIb/IIIa inhibitors [GP IIb/IIIa inhibitors], statins, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs] and β -blockers). All patients with a glomerular filtration rate <60 mL/min/1.73 m² for 3 months were defined as having chronic kidney disease. Smoking habits were self-reported. Persons who were active smokers at time of the index event and smoked regularly during the previous 12 months were classified as current smokers. Former smokers were defined as those patients who had a history of smoking tobacco but were not active smokers in the last 12 months. Hypertension, hypercholesterolemia, and diabetes were assessed by designation of medical history before admission in the database. Family history of coronary artery disease (CAD) was defined as death due to CHD before 55 years of age (for men) and 65 years of age (for women) in any first-degree relative or grandparent. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). Patients with BMI of 30 or greater were defined as obese. Delay to hospital presentation was calculated from the time of symptom onset to the time of hospital arrival. We characterized delay to hospital presentation using a dichotomous variable: delayed (≥ 120 minutes) versus early (<120 minutes) presentation according to the American College of Cardiology (ACC)/American Heart Association (AHA) practice guidelines.¹³

Statistical analysis

Patients were categorized according to their type and number of cardiovascular risk factors. Subgroups included age and sex. For the analyses on the effects of each individual risk factors, we divided the risk factors into dichotomous variables and grouped patients in those with and without the risk factor(s) under consideration. Baseline characteristics were reported as number (percentages) for categorical variables and mean \pm SD for continuous variables. We had complete data on mortality, sex, age, and index event. We used multiple imputation by chained equations (MICE) as the imputation method to treat missing data.¹⁴ To reduce the

imbalance of potential confounders between patients with and without traditional risk factors we compiled a set of baseline covariates. Variables included demographics (age and sex), traditional risk factors (diabetes, hypertension, hypercholesterolemia and current smoking) and nontraditional risk factors (former smoking, BMI, family history of CAD), prior medical history of cardiovascular disease (prior stroke and peripheral artery disease) and clinical findings on hospital admission (ST-segment shifts in anterior leads, systolic blood pressure on admission and heart rate on admission). We used an inverse probability weighting approach on the basis of propensity scores for confounding adjustment.¹⁵ Because of the instability that can be induced by extreme weights, stabilized weights were used that also preserve the original sample size. We created a threshold for weights to avoid the impacts of the outliers. Specifically, we used 0.01 as threshold of the propensity weighting. Standardized differences after weighting were calculated to ensure balanced treatment groups with respect to baseline characteristics. Groups were considered balanced when the standardized difference was <10%.¹⁶ We calculated the odd ratios (ORs) and the risk ratios (RRs) with their 95% confidence intervals (CIs) from logistic regression and inverse probability weighting models. We used the Pearson's correlation coefficient (r) to ascertain statistical significance of trends. Comparisons of outcomes between groups were assessed by 2-sided P values. A P value <0.05 was taken to indicate that the difference between the outcomes in subgroups was unlikely to have occurred simply by chance.

RESULTS

Baseline Characteristics

The demographic features, presenting characteristics, and treatment of patients with or without CHD traditional risk factors are shown in **Tables 1 and 2**.

Table 1. Baseline characteristics

	Traditional CHD risk factors N= 59893	Without traditional CHD risk factors N=11060	P value
Mean \pm SD age, years	62.6 \pm 11.8	64.4 \pm 12.3	<0.001
Women, n (%)	21451 (35.8)	4039 (36.5)	0.15
Risk factors			
Diabetes, n (%)	15988 (26.7)	0.0 (0.0)	<0.001
Hypertension, n (%)	44678 (74.6)	0.0 (0.0)	<0.001
Hypercholesterolemia, n (%)	29658 (49.5)	0.0 (0.0)	<0.001
Current smokers, n (%)	27860 (46.5)	0.0 (0.0)	<0.001
Former smokers, n (%)	1068 (1.8)	184 (1.7)	0.36
Family history of CAD, n (%)	19389 (32.4)	1609 (14.5)	<0.001
BMI \geq 30 kg/m ² , n (%)	12592 (21.0)	1446 (13.1)	<0.001
Prior history of CVD			
Prior stroke, n (%)	2415 (4.0)	327 (3.0)	<0.001
PAD, n (%)	1526 (2.5)	129 (1.2)	<0.001
CKD, n (%)	2897 (4.8)	387 (3.5)	<0.001
Clinical presentation			
STEMI, n (%)	37512 (62.6)	5917 (53.5)	<0.001
NSTE-ACS, n (%)	22381 (37.4)	5143 (46.5)	<0.001
ST-segment shifts in anterior leads, n (%)	12989 (21.7)	2074 (18.8)	<0.001
Time to admission <12 hrs, n (%)	44741 (74.7)	7895 (71.4)	<0.001
Time to admission <2 hrs, n (%)	13508 (22.6)	2238 (20.2)	<0.001
Mean \pm SD HR at admission, bpm	81.9 \pm 19.9	80.4 \pm 19.6	<0.001
Mean \pm SD SBP at admission, mmHg	139.2 \pm 28.2	131.1 \pm 29.5	<0.001

Table 1. Baseline characteristics, continued

Outcomes			
30-day mortality, n (%)	4631 (7.7)	1466 (13.3)	<0.001
Killip class ≥ 2 , n (%)	14789 (24.7)	2551 (23.1)	0.002
Shock index (moderate to severe), n (%)	2771 (4.6)	786 (7.1)	<0.001

Data are presented as number (%) or mean \pm standard deviation, unless otherwise specified.

Abbreviations: BMI=body mass index; CAD=coronary artery disease, CKD= chronic kidney disease, CVD=cardiovascular disorders, HR=heart rate; NSTE-ACS= non-ST-segment elevation acute coronary syndrome; NSTEMI= ST-segment elevation myocardial infarction, PAD=peripheral artery disease, SBP=systolic blood pressure; STEMI=ST-segment elevation myocardial infarction

Among patients with ACS, at least one of the four traditional risk factors were present in 84.2% of women and 84.6% men. For all traditional risk factors except current cigarette smoking, the prevalence was significantly higher in women than in men.

Table 2. Revascularization and Medications on Admission and during Hospitalization

	Traditional CHD risk factors N= 59893	Without Traditional CHD risk factors N=11060	P value
PCI for STEMI, n (%)	16456 (27.5)	2311 (20.9)	<0.001
Fibrinolysis for STEMI, n (%)	11113 (18.6)	1548 (14.0)	<0.001
CABG for STEMI, n (%)	765 (1.3)	134 (1.2)	0.56
Invasive cardiac procedures			
PCI (STEMI and NSTEMI-ACS), n (%)	22163 (37.0)	3266 (29.5%)	<0.001
CABG (STEMI and NSTEMI-ACS), n (%)	1301 (2.2)	197 (1.8)	0.005
Medications on Admission			
Aspirin and/or P2Y ₁₂ inhibitors, n (%)	56167 (93.8)	8499 (76.8)	<0.001
Unfractionated heparin, n (%)	33401 (55.8)	6121 (55.3)	0.40
LMWH, n (%)	27770 (46.4)	3215 (29.1)	<0.001
Heparins (all), n (%)	52477 (87.6)	7890 (71.3)	<0.001
GP IIb/IIIa inhibitors, n (%)	4284 (7.2)	754 (6.8)	0.20
Medications during hospitalization			
β -blockers, n (%)	40714 (68.0)	5268 (47.6)	<0.001
ACE inhibitors/ARBs, n (%)	43482 (72.6)	5185 (46.9)	<0.001
Statins, n (%)	47224 (78.8)	6616 (59.8)	<0.001

Abbreviations: ACE= angiotensin converting enzyme, ARB=angiotensin receptor blockers, CABG=coronary artery bypass graft, GP= glycoprotein, LMWH=low molecular weight heparins, NSTEMI-ACS= non-ST segment elevation acute coronary syndromes, PCI=percutaneous coronary intervention, STEMI=ST-segment elevation myocardial infarction.

Patients with no traditional risk factors had a lower rate of cardiac procedures and were less likely to receive medications on hospital admission and during hospitalization than those with at least one risk factor.

The prevalence and type of the four traditional risk factors changed with age (**Table 3**). The majority of patients with age less than 65 years (85.6% in women and 86.4% in men) had at least one traditional risk factor, with cigarette smoking being the most common in young men and hypertension in young women. Older patients had much lower rates of current cigarette smoking but typically higher rates of diabetes and hypertension, especially in women.

Table 3. Prevalence of Conventional Risk Factors by Age and Sex

	Age < 65 years		Age ≥ 65 years	
	Women N=10203	Men N=27582	Women N=15287	Men N= 17881
Individual risk factors				
Current smoking, n (%)	4395 (43.1)	15898 (57.6)	2231 (14.6)	5336 (29.8)
Hypercholesterolemia, n (%)	4923 (48.3)	12329 (44.7)	6160 (40.3)	6246 (34.9)
Hypertension, n (%)	6639 (65.1)	15506 (56.2)	11026 (72.1)	11507 (64.4)
Diabetes, n (%)	2241 (22.0)	4854 (17.6)	4712 (30.8)	4181 (23.4)
Number of risk factors				
0, n (%)	1474 (14.4)	3693 (13.4)	2565 (16.8)	3328 (18.6)
1, n (%)	2577 (25.3)	7750 (28.1)	4625 (30.3)	5690 (31.8)
2, n (%)	3346 (32.8)	8831 (32.0)	5131 (33.6)	5513 (30.8)
3, n (%)	2295 (22.5)	6057 (22.0)	2622 (17.2)	2846 (15.9)
4, n (%)	511 (5.0)	1251 (4.5)	344 (2.3)	504 (2.8)

Data are presented as number (%) or mean ± standard deviation, unless otherwise specified.

Prevalence of Traditional Risk Factors and Age at Hospital Presentation

As the number of traditional risk factors increased, there was an inverse relationship whereby median age at time of ACS event declined. The presence of all four CHD risk factors significantly decreased the age of ACS by nearly half a decade compared with the absence of any CHD risk factors in both sexes (women: from 67.1 ± 12.0 to 61.9 ± 10.3 years; $r = -0.089$,

95% CI: -0.077 to -0.101; P value<0.001 and men: from 62.8 ±12.2 to 58.9 ±9.9 years; $r=-0.096$, 95%CI: -0.087 to -0.106; P value<0.001). (**Figure 2**).

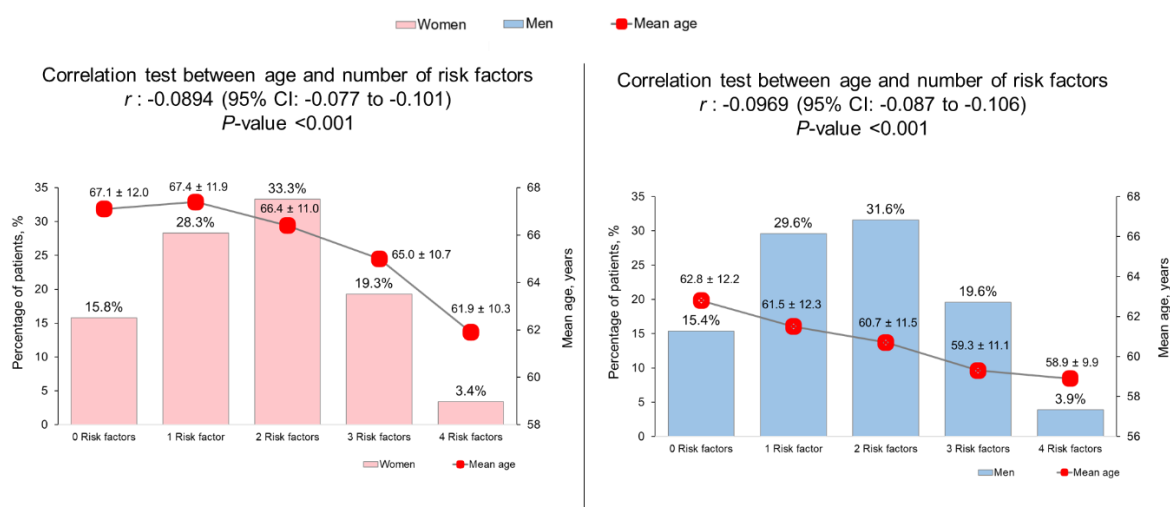


Figure 2. Prevalence of traditional CHD Risk Factors According to Age at Hospital Presentation in Women and Men

Abbreviations: CHD=coronary heart disease

Traditional Risk Factors and potential lifetime free of ACS.

To estimate years of potential lifetime free of ACS events lost in the presence of each traditional risk factor, we compared the observed patient age at time of ACS event for those with and without the risk factor under consideration (**Figure 3**).

On average, current smoking reduced the age at time of ACS event by about 7 to 10 years among men and women, for every risk factor combination (P value<0.001 for all combinations). Similarly, in the absence of current smoking, patients with hypercholesterolemia still lost an average of approximately 1 to 3 years compared with their expected life being free of hypercholesterolemia in both sexes. (P value<0.001 for all combinations). By contrast hypertension and diabetes in the absence of current smoking or hypercholesterolemia were associated with a survival advantage suggesting that these risk factors cannot negatively impact the lifetime risk for the occurrence of ACS.

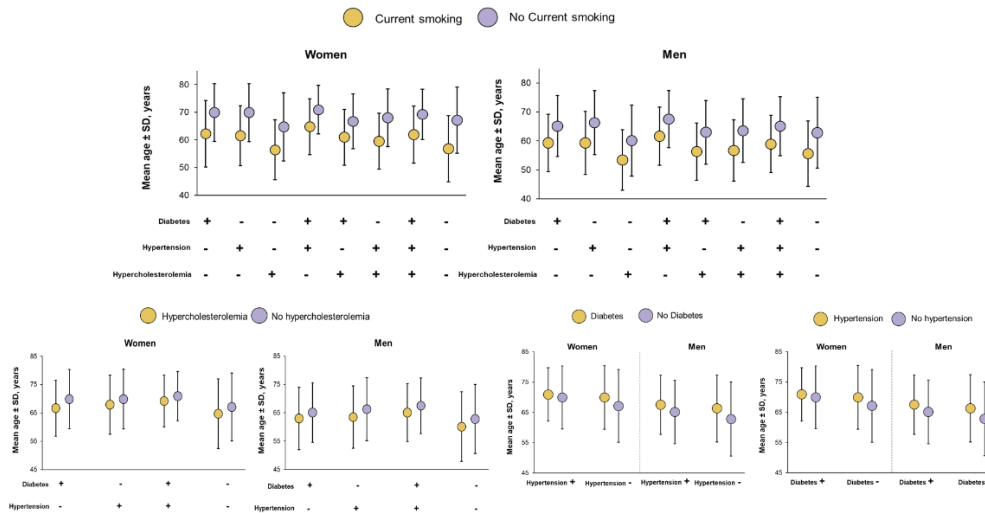


Figure 3. Relationship Between Age and Traditional CHD Risk Factor Combinations Stratified by Current Smoking Status (upper panel), Hypercholesterolemia (left lower panel), Diabetes (middle lower panel) and Hypertension (right lower panel) in Women and Men

Abbreviations: CHD=coronary heart disease.

Traditional Risk Factors and life expectancy free of ACS

To confirm the divergent associations that we observed in unadjusted analyses, we used multivariable regression modeling (Figure 4).

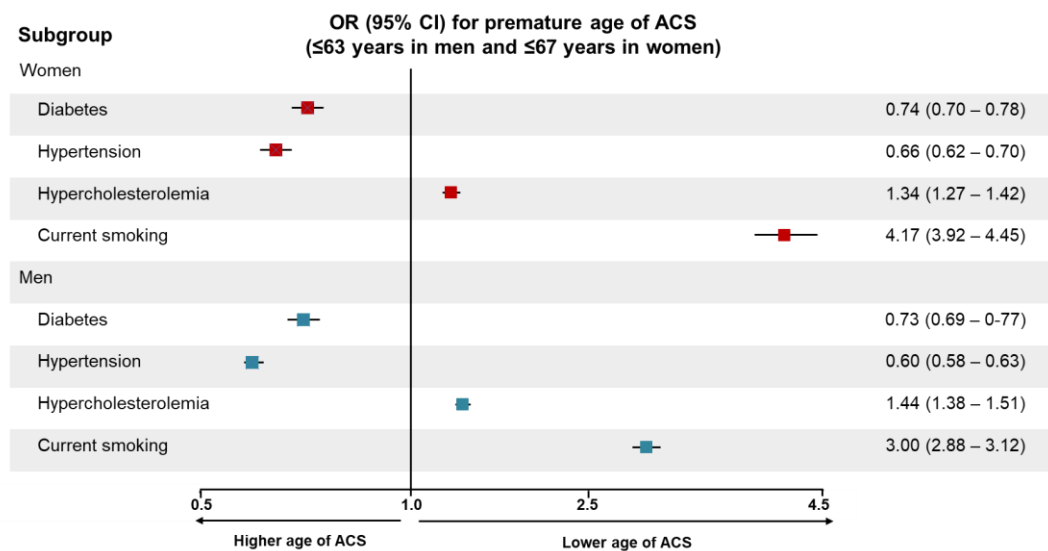


Figure 4. Multivariable Analysis of Traditional CHD Risk Factors Associated with Premature Age of ACS in Women and Men

Models adjusted for: diabetes, hypertension, hypercholesterolemia, current smoking, former smoking, family history of CAD, BMI, prior stroke, peripheral artery disease.

Abbreviations: ACS= acute coronary syndrome, CHD=coronary heart disease

The outcome of interest was “premature ACS”, which was calculated using the mean age at time of ACS of women (≤ 67 years) and men (≤ 63 years) with no risk factors. Patients who developed an ACS prior to these age thresholds were considered as having suffered “premature ACS”. The dependent variable was modelled using traditional and nontraditional risk factors as covariates. Nontraditional risk factors included family history of CAD, obesity and former smoking. Logistic regression models showed that patients who were current smokers had a more than three -fold increase in the odds of having a premature ACS (ORs: 4.17; 95%CI: 3.92 to 4.45 in women and 3.00; 95%CI: 2.88 to 3.12 in men). The corresponding ORs for patients with hypercholesterolemia were 1.34 (95%CI: 1.27 to 5.63) and 1.44 (95%CI, 1.38 to 1.51). By contrast, diabetes and hypertension were inversely associated with this endpoint.

Unadjusted mortality

For fatal ACS (n=6097), exposure to at least one traditional CHD-risk factor ranged from 77.6% in women to 74.5% in men. The timing of death is shown in **Figure 5**.

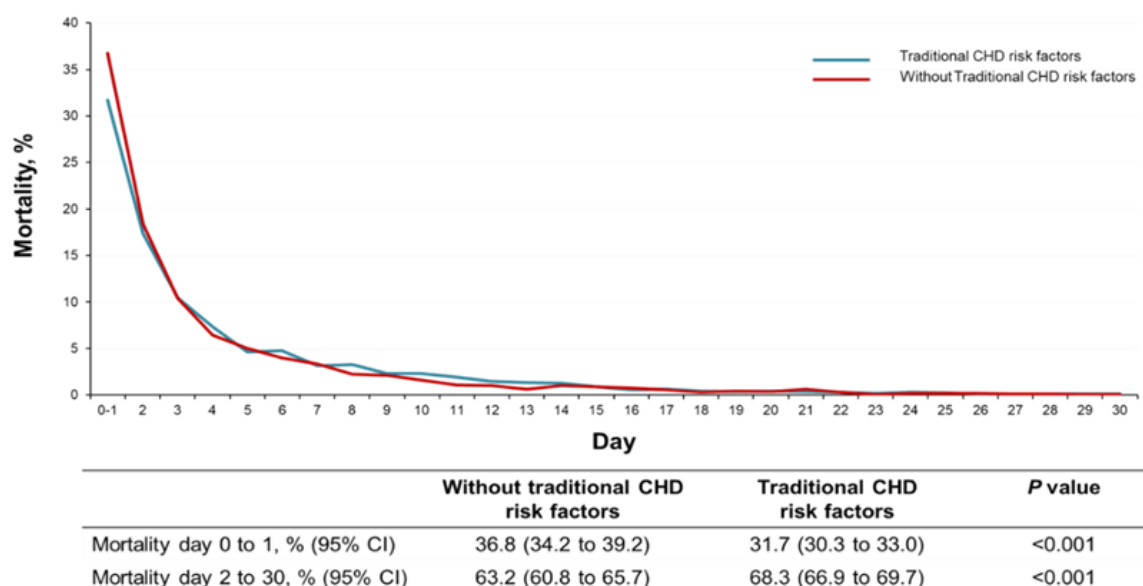


Figure 5. Mortality by Day, Stratified by the Presence of Traditional CHD Risk Factors.

Abbreviations: CHD=coronary heart disease

Of the patients with at least one traditional risk factor, 31.7% died on day 0 or day 1 (the day of presentation or the following day). The proportion of early deaths was significantly higher in patients with no traditional risk factors (36.8%; P value <0.001). After the first day, we observed similar or improved outcomes in patients with no risk factors compared with their counterparts with risk factors.

Overall, there was an inverse relationship between unadjusted 30-day mortality and the number of CHD risk factors. The mortality rates in women ranged from 7.7% with four CHD risk factors to 16.3% with no CHD risk factors ($r=0.073$, P value <0.001). The corresponding rates in men were 4.8% and 11.5% ($r=0.078$, P value <0.001). (**Figure 6**).

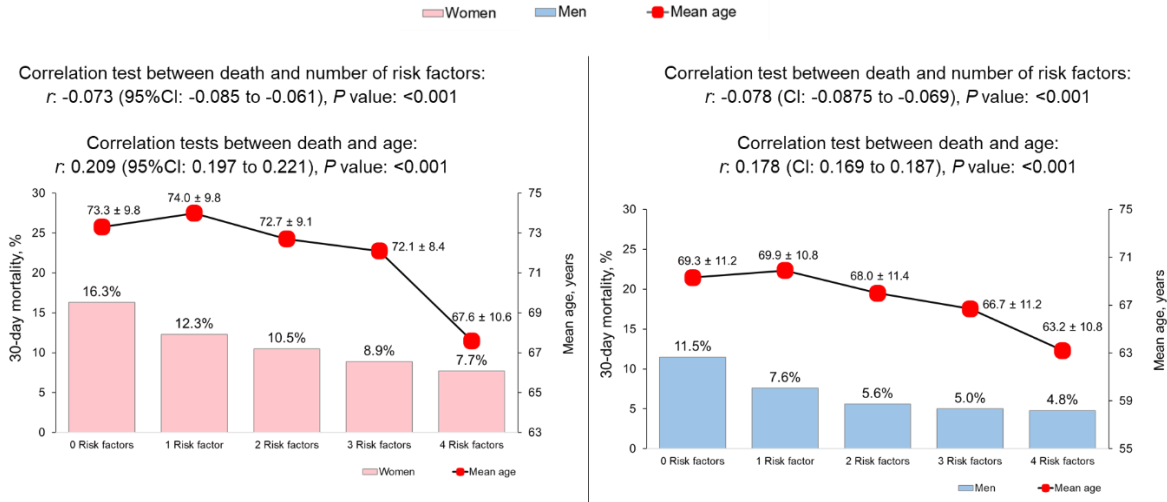


Figure 6. Prevalence of Traditional CHD Risk Factors and Death According to Age at Hospital Presentation in Women and Men

Abbreviations: CHD=coronary heart disease

We also observed a strict relationship between age of death and number of CHD risk factors. Men and women with two or more traditional risk factors were at higher risk of having death at younger age than their controls with no risk factors. Comparing patients with no risk factors vs those with four risk factors the age of death declined from 73.3 ± 9.8 to 67.6 ± 10.6 years ($r=-0.209$, 95%CI: 0.197 to 0.221; P value <0.001) in women and from 69.3 ± 11.2 to 63.2 ± 10.2 years ($r=-0.178$, 95%CI: 0.169 to 0.187; P value <0.001) in men.

Adjusted mortality

Given the concern of possible bias because patients with more severe presentation may have more adverse outcomes, we used inverse probability weighting models to reevaluate mortality and measures of severity of clinical presentation (**Table 4**).

Table 4. Inverse probability weighting: clinical factors and outcomes stratified by traditional CHD risk factors status

Characteristics	Traditional CHD risk factors (N=59893)	Without Traditional CHD risk factors (N=11060)	Standardized difference	P value
Mean ± SD age, years	62.9 ± 11.8	62.6 ± 12.7	0.021	0.17
Cardiovascular risk factors				
Family history of CAD, %	29.6	29.6	-0.0005	1.0
Former smokers, %	1.8	1.9	-0.0115	0.79
BMI ≥30 kg/m ² , %	19.8	20.0	-0.0062	0.75
Clinical history of CVD				
PAD, %	2.3	2.1	0.0126	0.61
Prior stroke, %	3.9	4.0	-0.0069	0.82
Clinical presentation on admission				
ST-segment shifts in anterior leads, %	21.2	21.4	-0.0044	0.76
Mean ± SD SBP at admission, mmHg	137.9 ± 28.4	138.4 ± 29.9	-0.0167	0.07
Mean ± SD HR at admission, bpm	81.7 ± 19.9	81.8 ± 20.2	-0.0041	0.27
Outcomes				
30-day mortality, %	8.1	11.4	-0.1125	<0.001
Risk Ratio (95% CI)	0.68 (0.64 – 0.73)		-0.1125	<0.001
Killip class ≥2, %	25.1	20.9	0.0995	<0.001
Risk Ratio (95% CI)	1.27 (1.21 – 1.33)		0.0995	<0.001
Shock index (moderate to severe), %	4.9	5.3	-0.0173	0.09
Risk Ratio (95% CI)	0.92 (0.84 – 1.01)		-0.0173	0.09
STEMI, %	62.8	53.3	0.1937	<0.001
Risk Ratio (95% CI)	1.48 (1.42 – 1.54)		0.1937	<0.001

Data are presented as percentages (%) or mean ± standard deviation, unless otherwise specified.

Abbreviations: BMI=body mass index; CAD=coronary artery disease, CVD=cardiovascular disorders, ECG=electrocardiogram, HR=heart rate; PAD=peripheral artery disease, SBP=systolic blood pressure; STEMI=ST-segment elevation myocardial infarction.

Baseline clinical characteristics were well balanced. Patients with at least one traditional risk factor had significantly lower rates of 30-day mortality (8.1% vs. 11.4%; RR: 0.68; 95%CI: 0.64 to 0.73) than patients with no traditional risk factors. By contrast, the rates of STEMI (62.8% vs. 53.3%, RR: 1.48, 95% CI: 1.42 to 1.54) and AHF on admission (25.1% vs. 20.9%; RR: 1.27; 95%CI: 1.21 to 1.33) were higher in the risk factor group than in patients without risk factors. There was no difference in Shock Index between patients with and without risk factors (4.9% vs. 5.3%; RR: 0.92; 95%CI: 0.84 to 1.01). In our sensitivity analyses, the adjusted RRs for the primary (**Figure 7**) and secondary outcomes were similar for men and women. These associations were also largely independent of younger or older age and type of risk factors combination.

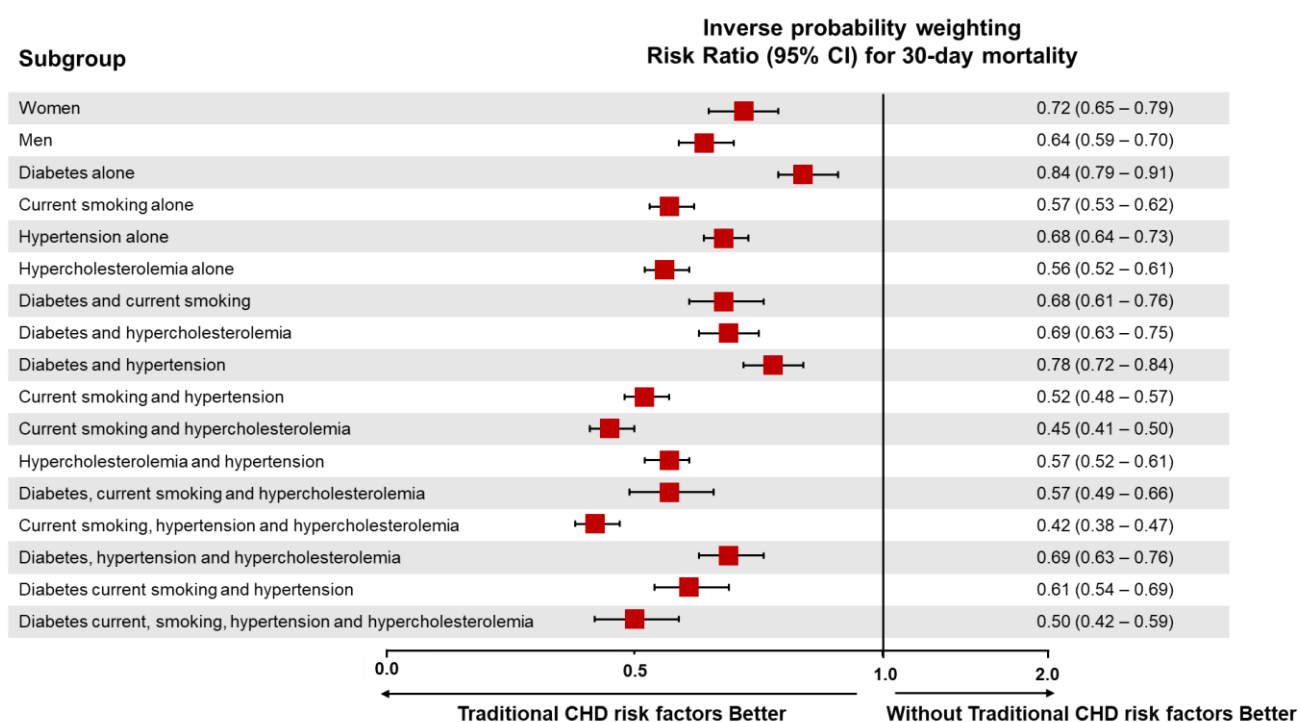


Figure 7. Primary outcome in sex, age, number, and type of traditional CHD risk factors subgroups. Risk ratios and confidence intervals were estimated with the use of inverse probability weighting models, with adjustment as in Table 4.

Abbreviations: CHD=coronary heart disease

Revascularization Procedures and Cardiovascular Morbidity

As ACS is a medical emergency and should be treated as such, further analyses were done in those patients who underwent reperfusion therapy in STEMI or revascularization strategies in NSTEMI-ACS (**Figure 8**). The mortality rate remained lower in patients with at least one traditional risk factor compared with their counterparts without risk factors in STEMI (7.0% vs. 10.8%; RR, 0.62; 95%CI, 0.55 to 0.70) regardless of the time to hospital presentation.

Comparable mortality patterns were also observed in patients with NSTEMI-ACS (2.6% vs. 3.8%; RR, 0.68; 95%CI, 0.48 to 0.97). The excess AHF on admission we observed in the overall population of ACS patients with at least one traditional risk factor persisted in STEMI (23.3% vs. 20.3%; RR, 1.19; 95%CI, 1.10 to 1.30), and NSTEMI-ACS (14.7% vs. 11.0%; RR, 1.40; 95%CI, 1.14 to 1.71).

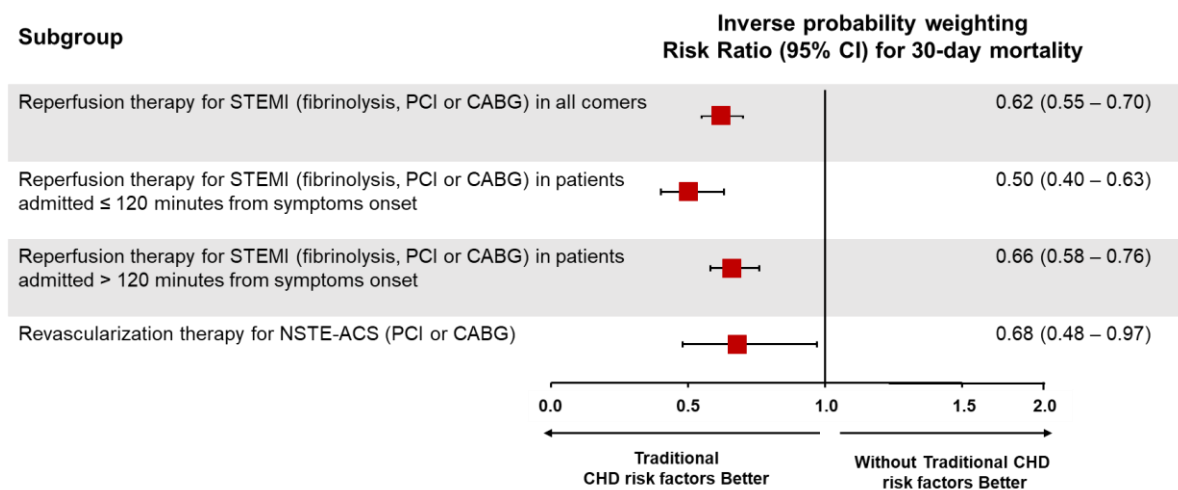


Figure 8. Primary outcome in STEMI patients undergoing reperfusion therapy and time to admission cut-offs, and NSTEMI-ACS undergoing revascularization therapy subgroups. Risk ratios and confidence intervals were estimated with the use of inverse probability weighting models, with adjustment as in Table 4.

Abbreviations: CHD=coronary heart disease, CABG=coronary artery bypass graft, NSTEMI-ACS=non-ST-segment elevation acute coronary syndromes, PCI=percutaneous coronary intervention, STEMI=ST-segment elevation myocardial infarction.

Additional analyses on medical therapies and outcomes

As noted in the descriptive **Table 2**, patients with no risk factors had lower prescription rates of recommended treatments on admission and during hospitalization compared with their

counterparts. Because the vast majority of deaths occurred in the first 48 hours, we investigated whether low use of evidence-based therapies given on hospital admission could have affected the RRs for outcomes of patients with vs those without CHD risk factors. The use of antiplatelet agents or heparins did not result in significant attenuations of the association between absence of traditional risk factors and reduced 30-day mortality compared with their counterpart (RRs: 0.84; 95%CI: 0.77 to 0.91 and 0.83; 95%CI: 0.77 to 0.90, respectively) (**Figure 9**). We also considered the possible contribution of GP IIb/IIIa inhibitors and indeed, this therapy resulted in a loss of the association between no risk factor status and lower survival (RR: 0.96; 95%CI: 0.73 to 1.26) (**Figure 9**). It should not go unnoticed, however, that the overall 30-day mortality in patients with no risk factors

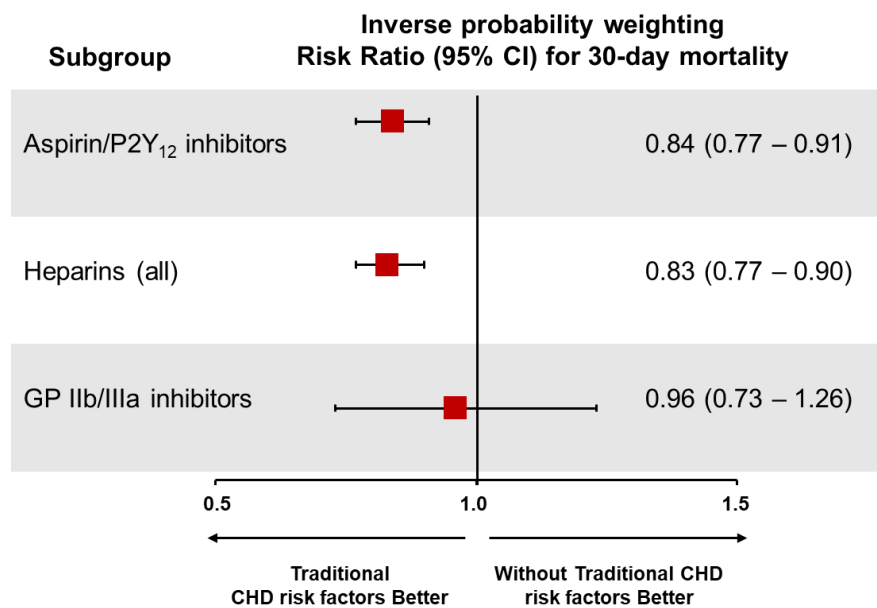


Figure 9. Primary outcome in antithrombotic therapy subgroups. Risk ratios and confidence intervals were estimated with the use of inverse probability weighting models, with adjustment as in Table 4 with addition of RAAS inhibitors, statins, β -blockers and (1) for aspirin use subgroup: GP IIb/IIIa inhibitors and heparins; (2) for heparins use subgroup: aspirin and GP IIb/IIIa inhibitors; (3) for GP IIb/IIIa inhibitors use subgroup: aspirin and heparins.

Abbreviations: CHD=coronary heart disease, GP=glycoprotein, RAAS=renin angiotensin aldosterone system

undergoing GP IIb/IIIa inhibitors use was too low (3.7% of 754 patients) for absolute interpretations. We did not analyze evidence-based therapies given during hospitalization as

timing of these treatments varied among patients and were not individually recorded. Patients receiving medications had to survive to the time of drug administration. Patients who died without receiving medications would have been classified as unexposed leading to immortal time bias.

DISCUSSION

This study indicates that the vast majority of patients presenting with ACS as first manifestation of CHD have traditional risk factor exposure, consistent with the results of previous studies.^{3, 17-20} For fatal ACS, prior exposure to at least one traditional CHD risk factor ranged from 74% to 77%. In addition, we observed that differences in traditional risk-factor burden translate into marked differences in the lifetime risk of ACS and subsequent mortality. This assumes particular importance in the presence of all four traditional risk factors, which was associated with up to 5-year younger age of mortality. By contrast, we observed a significant inverse relationship between the rates of mortality and the number of CHD risk factors. Patients who lacked traditional risk factors had higher risk of all-cause 30-day mortality compared with patients with risk factors. However, in these patients, deaths occurred later in life with substantially longer survivals compared with their counterparts. These observations raise significant clinical and methodological issues.

Because atherosclerosis typically develops later in women than in men, high risk factor prevalence in women would lead to the development of ACS at older age as in men with comparable burden. This hypothesis is substantiated by the results of the current study. The presence of all four CHD risk factors significantly decreased the age of hospital presentation for ACS and subsequent mortality by nearly half a decade compared with the absence of any CHD risk factors in both sexes. Among men the age of death declined from 63 to 59 years whereas among women the risk rose with older age, but still the presence of all four CHD risk factors shortened mean survival by 5 years, specifically from 67 to 62 years. In essence, patients with traditional risk factors have a significant survival disadvantage compared with those without risk factors.

A critically important feature of traditional risk factors is that each has a quantitatively different impact on the age of development of ACS. Cigarette smoking played a critical role reducing

the age at index event by about one decade in both men and women. Furthermore, cigarette smoking acted synergistically with the other traditional risk factors, greatly increasing the risk of ACS at premature age for each of these associations. A significant decrease, up to 3 years, in the age of ACS presentation in both sexes was also observed when patients showed a history of hypercholesterolemia. We did not find significant gains in the ACS event-free life expectancy with hypertension and diabetes. Thus, reductions in the prevalence of hypercholesterolemia and smoking cessation are measures of remarkable public health importance because these risk factors could reduce event-free survival from ACS.

Our data should not be interpreted as indicating that diabetes or hypertension have no overall effect on cardiovascular disease or health in general, because the data reported in the current investigation focused only on the occurrence of ACS as first manifestation of CHD. Thus, our estimates are not designed for clinicians to prioritize one prevention treatment over the other because cardiovascular disease outcomes and time of occurrence of outcomes vary substantially based on patients' individual burden of risk factors and the risk factors' differential effects on various manifestations of cardiovascular disease.²¹ As such, the lack of impact of hypertension and diabetes on the reduction of the age at time of ACS event may reflect an inherent survivor bias because patients with these risk factors may die at a much younger age than that expected for the occurrence of ACS in the context of other competing risks for death. Hypertension is associated with a substantially higher risk for heart failure and stroke^{22, 23} and is particularly prevalent among younger stroke patients.²⁴ As well, diabetes is associated with a wide range of incident cardiovascular diseases, but heart failure and peripheral arterial disease are the most common initial manifestations of cardiovascular disease.²⁵ The design of the study lend support to this hypothesis as patients with prior heart failure of unknown origin and prior CHD events were excluded from analyses. Nevertheless, our results may provide suggestions on how to inform the plan of prospective trials that often

include acute myocardial infarction as their primary event endpoint, because of a previous perception that acute outcomes are the first disease burdens in patients with hypertension and diabetes.

Much attention has recently focused on the group of ACS patients who present without traditional CHD risk factors because these patients have higher all-cause mortality from ACS than patients with at least one traditional risk factor.² A related assertion was that the mortality is higher in women than men in patients without traditional risk factors.²⁶ Our results are consistent with those of previous studies as we observed a strong inverse relationship between number of risk factors and 30-day mortality, even after adjustment for age, BMI, family history of CAD and prior cardiovascular comorbidities (RR: 0.68; 95% CI: 0.64 to 0.73). Yet, there are inaccuracies in the interpretation of the primary data that have been referenced to support the existence of sex difference in outcome.⁴ In fact, our study has shown that the adjusted RRs for all-cause mortality in patients with vs those without risk factors were similar for men (RR: 0.64; 95%CI: 0.59 to 0.70) and women (RR: 0.72; 95%CI: 0.65 to 0.79), which is concordant with the prior referred data. Thus, sex-based differences in outcomes exist among patients with ACS, but do not vary depending on the number of risk factors.^{27, 28}

Little is known about the group of ACS patients who present to hospital without traditional CHD risk factors and have excess mortality compared with their counterparts with at least one risk factor. This association persists despite the fact that patients with risk factors had more STEMI and higher Killip class on initial presentation. Thus, patients without risk factors cannot be considered too “sick” to provide an adequate history of CHD risk factors. As well, the association does not reflect undertreatment of patients with no risk factors, since in subgroup analyses, we considered patients in the context of equitable evidence-based

treatments after hospital admission, and subgroup findings were similar to the point estimates for the full matched cohorts.

In addition, prior work has been done comparing the mortality rates of ACS in patients with at least one risk factor versus those with no risk factors under the assumption that traditional risk factors contribute in a similar fashion to the outcomes of the acute manifestation of CHD. However, formal comparisons of the effects of cardiovascular risk factors on the rates of mortality in CHD are scarce. To address this concern, we performed a large number of sensitivity analyses. In each case, whether we re-stratified mortality into four distinct traditional risk factor groups or clusters of risk factors, mortality was still consistently higher among patients with no risk factors. Thus, although bias with case ascertainment will always be a concern, our sensitivity analyses suggest that bias alone is not a likely explanation of an inverse relationship between number and type of risk factors and mortality.

Possible mechanisms for the increased risk of death in the absence of traditional CHD risk factor exposure may involve several factors, which may include methodological issues as well as real differences in pathophysiology. First, and most concerning, would be the possibility that the increased mortality from ACS in the subgroup of patients with no traditional risk factors reflects an inherent survivor bias. Several studies have shown that diabetes is associated with out-of-hospital cardiac arrest and sudden cardiac death.²⁹ Selection bias, therefore, could have limited enrollment of the population to those who were healthier or less vulnerable to CHD. This concern cannot be ruled out by any retrospective analyses. Second, the presence of risk factors before ACS as first manifestation of CHD is often accompanied by medical management before hospital presentation. Primary preventive care such as use of aspirin^{30, 31} or statins^{7, 18, 32} may have attenuated the severity of ACS presentation and, thus, may have improved prognosis of the index event. This hypothesis is not fully supported by our data, as patients with risk factors presented with more STEMI and higher Killip class on

initial presentation than their counterparts. Furthermore, patients with no risk factors received fewer evidence-based medications and invasive cardiac procedures, and this undertreatment may have contributed to worse outcome. To address this issue, we selected patients who received the best medical treatment, including reperfusion and revascularization therapy, putting them on a more favorable survival track. We also stratified them into two distinct groups of clinical severity of disease on admission: STEMI and non-NSTE-ACS. Given that our primary results persisted after stratification, selection biases based on severity of illness or lack of treatment do not seem to affect the relationship we observed between risk factors and mortality.

There may be other potential explanations for differences in outcomes across groups with different numbers of risk factors. Patients with ACS in the no risk factor group may have had other nontraditional risk factors that may have influenced progression of atherosclerosis and adverse outcomes in ACS, such as prediabetes, obesity, former smoking, family history of CAD, psychosocial factors, or physical inactivity. However, in the current study, obesity, family history of CAD and former smoking were less represented in patients with no risk factors compared with their counterparts. Because incident prediabetes and physical activity are strongly and positively associated with obesity^{33, 34}, it is also unlikely that these risk factors may have contributed to yield some adverse outcomes in patients with no traditional risk factors. Although psychosocial risk factors may explain an individual's propensity to develop CHD, they mainly act as barriers to treatment adherence and efforts to improve lifestyle in the setting of populations with traditional risk factors.^{35, 36} It is, therefore, doubtful that the excess mortality in patients with no risk factors can be explained by some of them.

In summary, what is most striking in our results is that many of the explanations for the inverse association between the number of CHD risk factors and 30-day mortality in ACS—more comorbid conditions, delay in presentation, unequal treatment strategies were not found

to be the case, thus leaving us really with no explanation for the markedly increased mortality risk among patients with no risk factors. The only feature that differentiated mortality in ACS patients with vs those without risk factors was the rate of early death defined as death on the day of presentation or the following day. Early death accounted for 36.8 % of the total 30-day mortality in patients with no traditional risk factors, but significantly less (31.7%) for those with risk factors. By contrast, after the first day, we observed similar or improved outcomes in patients with no risk factors compared with their counterparts with risk factors. The increased early death, in the absence of higher Killip class on initial presentation suggests the likelihood of fatal arrhythmias as main determinant of death in the population of patients with no risk factors. The majority of patients who have ventricular arrhythmias after ACS do not survive till hospital arrival or they die soon after hospital admission.³⁷ This finding highlights the need for larger and better public health initiatives to identify measures of arrhythmic risk that have independent or added predictive power for mortality. In summary, the absence of traditional risk factor exposure should not necessarily be viewed as a guarantee of a favorable prognostic sign in ACS.

Our study has some limitations. This study was observational in nature and is therefore subject to potential confounding. Inverse probability weighting analyses minimized such confounding. We did not have a control group without ACS for comparison. However, previous work has shown that exposure to one or more of the traditional risk factors is also highly prevalent among individuals who do not develop clinical CHD.¹⁷ Exposure to the etiologic agents for CHD is, therefore necessary but not sufficient to cause acute clinical manifestation of the disease. Additionally, some of the risk factors were ascertained by the general practitioner, which might have led to errors in the dataset. Yet, the true prevalence of the traditional risk factors is certainly higher than that identified in our study, as approximately 30% of patients with hypertension, hypercholesterolemia and diabetes are

unaware that they have these risk factors.^{38, 39} Thus, detailed assessment for risk factors would almost certainly lead to higher prevalence rates than those reported in the current study. We acknowledge to have only limited data on medications given prior to the index event, and, as such, we did not use these numbers for the current analyses. Prior medications may have decreased the discriminatory power of traditional risk factors to accurately predict clinically relevant ACS. Nonetheless, the choice of including only patients with first ACS reduces the possibility that our population might have substantially altered lifestyles or risk factor levels before the index event. Finally, our study consisted solely of a population of European white patients. Application of these absolute lifetime risk estimates results to other race/ethnic groups is uncertain.

CONCLUSIONS

We believe these findings have important implications for clinical disease prevention and public health practice. Despite the fact that the risks of developing and dying from ACS are substantially higher than those for cancer, surveys continue to indicate that most people perceive that the risk of death from cancer is higher than that of cardiovascular disease.⁴⁰ People perceive cancer as something that inevitably reduce the length of their life. By contrast, they believe that the new advances in treatment of cardiovascular disease are lifesaving and would not reduce the length of their life. Thus, a substantial deficit in awareness of the relation between traditional risk factors as precursor of ACS and shorter survival exists. The data of the current analysis underscore the importance of considering all four traditional risk factors and the lifestyle behaviors causing them in lifetime risk estimation of ACS and subsequent mortality. Awareness of shorter survival in the presence of traditional risk factors may motivate lifestyle changes and adherence to preventive therapy both in women and men.

REFERENCES

1. Health benefits of smoking cessation : a report of the Surgeon General. 1990.
2. Vernon ST, Coffey S, D'Souza M, Chow CK, Kilian J, Hyun K, Shaw JA, Adams M, Roberts-Thomson P, Brieger D, Figtree GA. ST-Segment-Elevation Myocardial Infarction (STEMI) Patients Without Standard Modifiable Cardiovascular Risk Factors-How Common Are They, and What Are Their Outcomes? *J Am Heart Assoc* 2019;**8**:e013296.
3. Canto JG, Kiefe CI, Rogers WJ, Peterson ED, Frederick PD, French WJ, Gibson CM, Pollack CV, Jr., Ornato JP, Zalenski RJ, Penney J, Tiefenbrunn AJ, Greenland P, Investigators N. Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction. *JAMA* 2011;**306**:2120-2127.
4. Figtree GA, Vernon ST, Hadziosmanovic N, Sundstrom J, Alfredsson J, Arnott C, Delatour V, Leosdottir M, Hagstrom E. Mortality in STEMI patients without standard modifiable risk factors: a sex-disaggregated analysis of SWEDEHEART registry data. *Lancet* 2021;**397**:1085-1094.
5. Sia CH, Ko J, Zheng H, Ho AF, Foo D, Foo LL, Lim PZ, Liew BW, Chai P, Yeo TC, Yip JWL, Chua T, Chan MY, Tan JWC, Figtree G, Bulluck H, Hausenloy DJ. Comparison of Mortality Outcomes in Acute Myocardial Infarction Patients With or Without Standard Modifiable Cardiovascular Risk Factors. *Front Cardiovasc Med* 2022;**9**:876465.
6. Figtree GA, Vernon ST, Hadziosmanovic N, Sundstrom J, Alfredsson J, Nicholls SJ, Chow CK, Psaltis P, Rosjo H, Leosdottir M, Hagstrom E. Mortality and Cardiovascular Outcomes in Patients Presenting With Non-ST Elevation Myocardial Infarction Despite No Standard Modifiable Risk Factors: Results From the SWEDEHEART Registry. *J Am Heart Assoc* 2022;**11**:e024818.

7. Bugiardini R, Yoon J, Mendieta G, Kedev S, Zdravkovic M, Vasiljevic Z, Milicic D, Manfrini O, van der Schaar M, Gale CP, Bergami M, Badimon L, Cenko E. Reduced Heart Failure and Mortality in Patients Receiving Statin Therapy Before Initial Acute Coronary Syndrome. *J Am Coll Cardiol* 2022;**79**:2021-2033.
8. Bugiardini R, Yoon J, Kedev S, Stankovic G, Vasiljevic Z, Milicic D, Manfrini O, van der Schaar M, Gale CP, Badimon L, Cenko E. Prior Beta-Blocker Therapy for Hypertension and Sex-Based Differences in Heart Failure Among Patients With Incident Coronary Heart Disease. *Hypertension* 2020;**76**:819-826.
9. Bugiardini R, Badimon L, Investigators I-T, Coordinators. The International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC): 2010-2015. *Int J Cardiol* 2016;**217 Suppl**:S1-6.
10. Vasic A, Vasiljevic Z, Mickovski-Katalina N, Mandic-Rajcevic S, Soldatovic I. Temporal Trends in Acute Coronary Syndrome Mortality in Serbia in 2005-2019: An Age-Period-Cohort Analysis Using Data from the Serbian Acute Coronary Syndrome Registry (RAACS). *Int J Environ Res Public Health* 2022;**19**.
11. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC, Jr., Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, American College of C, American Heart Association Task Force on Practice G, Canadian Cardiovascular S. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004;**110**:e82-292.

12. Mutschler M, Nienaber U, Munzberg M, Wolf C, Schoechl H, Paffrath T, Bouillon B, Maegele M, TraumaRegister DGU. The Shock Index revisited - a fast guide to transfusion requirement? A retrospective analysis on 21,853 patients derived from the TraumaRegister DGU. *Crit Care* 2013;**17**:R172.
13. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**61**:e78-e140.
14. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software* 2011;**45**:1 - 67.
15. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015;**34**:3661-3679.
16. Dongsheng Y, Dalton JE. A unified approach to measuring the effect size between two groups using SAS®: SAS global forum 2012: statistics and data analysis. SAS Global Forum. 2012: 335-2012. Available from: <https://support.sas.com/resources/papers/proceedings12/335-2012.pdf> .
17. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, Wilson PW. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA* 2003;**290**:891-897.
18. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, Investigators IS. Effect of potentially modifiable risk

- factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**:937-952.
19. Khot UN, Jia G, Moliterno DJ, Lincoff AM, Khot MB, Harrington RA, Topol EJ. Prognostic importance of physical examination for heart failure in non-ST-elevation acute coronary syndromes: the enduring value of Killip classification. *JAMA* 2003;**290**:2174-2181.
 20. Rosengren A, Dotevall A, Eriksson H, Wilhelmsen L. Optimal risk factors in the population: prognosis, prevalence, and secular trends; data from Goteborg population studies. *Eur Heart J* 2001;**22**:136-144.
 21. Glynn RJ, Rosner B. Methods to evaluate risks for composite end points and their individual components. *J Clin Epidemiol* 2004;**57**:113-122.
 22. Bulpitt CJ, Beevers DG, Butler A, Coles EC, Hunt D, Munro-Faure AD, Newson RB, O'Riordan PW, Petrie JC, Rajagopalan B, et al. The survival of treated hypertensive patients and their causes of death: a report from the DHSS hypertensive care computing project (DHCCP). *J Hypertens* 1986;**4**:93-99.
 23. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990;**335**:827-838.
 24. George MG, Tong X, Bowman BA. Prevalence of Cardiovascular Risk Factors and Strokes in Younger Adults. *JAMA Neurol* 2017;**74**:695-703.
 25. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, Deanfield J, Smeeth L, Timmis A, Hemingway H. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet Diabetes Endocrinol* 2015;**3**:105-113.

26. Lonnebakken MT. The risk of no risk in STEMI. *Lancet* 2021;**397**:1039-1040.
27. Cenko E, Yoon J, Kedev S, Stankovic G, Vasiljevic Z, Krljanac G, Kalpak O, Ricci B, Milicic D, Manfrini O, van der Schaar M, Badimon L, Bugiardini R. Sex Differences in Outcomes After STEMI: Effect Modification by Treatment Strategy and Age. *JAMA Intern Med* 2018;**178**:632-639.
28. Cenko E, van der Schaar M, Yoon J, Manfrini O, Vasiljevic Z, Vavlukis M, Kedev S, Milicic D, Badimon L, Bugiardini R. Sex-Related Differences in Heart Failure After ST-Segment Elevation Myocardial Infarction. *J Am Coll Cardiol* 2019;**74**:2379-2389.
29. Kucharska-Newton AM, Couper DJ, Pankow JS, Prineas RJ, Rea TD, Sotoodehnia N, Chakravarti A, Folsom AR, Siscovick DS, Rosamond WD. Diabetes and the risk of sudden cardiac death, the Atherosclerosis Risk in Communities study. *Acta Diabetol* 2010;**47 Suppl 1**:161-168.
30. Bugiardini R, Pavasovic S, Yoon J, van der Schaar M, Kedev S, Vavlukis M, Vasiljevic Z, Bergami M, Milicic D, Manfrini O, Cenko E, Badimon L. Aspirin for primary prevention of ST segment elevation myocardial infarction in persons with diabetes and multiple risk factors. *EClinicalMedicine* 2020;**27**:100548.
31. Force USPST, Davidson KW, Barry MJ, Mangione CM, Cabana M, Chelmow D, Coker TR, Davis EM, Donahue KE, Jaen CR, Krist AH, Kubik M, Li L, Ogedegbe G, Pbert L, Ruiz JM, Stevermer J, Tseng CW, Wong JB. Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement. *JAMA* 2022;**327**:1577-1584.
32. Bergami M, Cenko E, Yoon J, Mendieta G, Kedev S, Zdravkovic M, Vasiljevic Z, Milicic D, Manfrini O, van der Schaar M, Gale CP, Badimon L, Bugiardini R. Statins for primary prevention among elderly men and women. *Cardiovasc Res* 2022;**118**:3000-3009.

33. Neeland IJ, Turer AT, Ayers CR, Powell-Wiley TM, Vega GL, Farzaneh-Far R, Grundy SM, Khera A, McGuire DK, de Lemos JA. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. *JAMA* 2012;**308**:1150-1159.
34. Badimon L, Bugiardini R, Cenko E, Cubedo J, Dorobantu M, Duncker DJ, Estruch R, Milicic D, Tousoulis D, Vasiljevic Z, Vilahur G, de Wit C, Koller A. Position paper of the European Society of Cardiology-working group of coronary pathophysiology and microcirculation: obesity and heart disease. *Eur Heart J* 2017;**38**:1951-1958.
35. Albert MA, Glynn RJ, Buring J, Ridker PM. Impact of traditional and novel risk factors on the relationship between socioeconomic status and incident cardiovascular events. *Circulation* 2006;**114**:2619-2626.
36. Vaccarino V, Badimon L, Bremner JD, Cenko E, Cubedo J, Dorobantu M, Duncker DJ, Koller A, Manfrini O, Milicic D, Padro T, Pries AR, Quyyumi AA, Tousoulis D, Trifunovic D, Vasiljevic Z, de Wit C, Bugiardini R, Reviewers ESCSDG. Depression and coronary heart disease: 2018 position paper of the ESC working group on coronary pathophysiology and microcirculation. *Eur Heart J* 2020;**41**:1687-1696.
37. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. *Circulation* 1992;**85**:I2-10.
38. Nieto FJ, Alonso J, Chambless LE, Zhong M, Ceraso M, Romm FJ, Cooper L, Folsom AR, Szklo M. Population awareness and control of hypertension and hypercholesterolemia. The Atherosclerosis Risk in Communities study. *Arch Intern Med* 1995;**155**:677-684.
39. Franse LV, Di Bari M, Shorr RI, Resnick HE, van Eijk JT, Bauer DC, Newman AB, Pahor M, Health A, Body Composition Study G. Type 2 diabetes in older well-functioning people: who is undiagnosed? Data from the Health, Aging, and Body Composition study. *Diabetes Care* 2001;**24**:2065-2070.

40. Blackwell DL, Villarroel MA. Tables of summary health statistics for U.S. adults: 2015 National Health Interview Survey. Hyattsville, MD: National Center for Health Statistics; Available from <http://www.cdc.gov/nchs/nhis/SHS/tables.htm>

