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Statistics on mortality following acute myocardial infarction in 842 897 Europeans

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Aims To compare ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) mortality between Sweden and the UK, adjusting for background population rates of expected death, case mix, and treatments.

Methods and results National data were collected from hospitals in Sweden [$n = 73$ hospitals, 180 368 patients, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART)] and the UK [$n = 247$, 662 529 patients, Myocardial Ischaemia National Audit Project (MINAP)] between 2003 and 2013. There were lower rates of revascularization [STEMI (43.8% vs. 74.9%); NSTEMI (27.5% vs. 43.6%)] and pharmacotherapies at time of hospital discharge including [aspirin (82.9% vs. 90.2%) and (79.9% vs. 88.0%), β-blockers (73.4% vs. 86.4%) and (65.3% vs. 85.1%)] in the UK compared with Sweden, respectively. Standardized net probability of death (NPD) between admission and 1 month was higher in the UK for STEMI [8.0 (95% confidence interval 7.4–8.5) vs. 6.7 (6.5–6.9)] and NSTEMI [6.8 (6.4–7.2) vs. 4.9 (4.7–5.0)]. Between 6 months and 1 year and more than 1 year, NPD remained higher in the UK for NSTEMI [2.9 (2.5–3.3) vs. 2.3 (2.2–2.5)] and [21.4 (20.0–22.8) vs. 18.3 (17.6–19.0)], but was similar for STEMI [0.7 (0.4–1.0) vs. 0.9 (0.7–1.0)] and [8.4 (6.7–10.1) vs. 8.3 (7.5–9.1)].

Conclusion Short-term mortality following STEMI and NSTEMI was higher in the UK compared with Sweden. Mid- and longer-term mortality remained higher in the UK for NSTEMI but was similar for STEMI. Differences in mortality may be due to differential use of guideline-indicated treatments.

Keywords Mortality • Acute myocardial infarction • SWEDEHEART • MINAP • Sweden • UK

1. Introduction

Outcomes of acute myocardial infarction (AMI) vary between and within countries, suggesting that the potential to reduce the burden of cardiovascular disease has not been realised.[1–3] International research may identify potentially modifiable factors associated with geographic variation in outcomes of patients with cardiovascular (and other) diseases through access to nationwide registries, shared resources, and specialized expertise.[4] Moreover, the study of clinical outcomes from countries which have similar population life expectancies, healthcare system access and disease registration processes enables variation attributable to the delivery of cardiovascular healthcare to be identified and characterized.

International comparison studies using population-based registries are rare and, to date, investigations of AMI outcomes have only considered short-term survival.[1–6] Nowadays, when survival from AMI is at its highest, it is essential that international comparisons investigate longer-term outcomes and that these are analysed in light of the high and potentially different proportion of patients who die from non-cardiovascular

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causes.[7] That is, deaths attributable to AMI may differ between countries, but this difference may not be identified when all-cause mortality is assessed.[8]

To date, no international comparative studies of mortality following ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI), have accounted for background population rates of expected death. Relative survival is a technique that enables country-specific correction for deaths with those of the disease of interest, and models time-dependent effects to express differences in mortality between groups over long follow-up periods.[9,10] Thus, it is particularly useful for international comparison studies of care and outcomes.[8–14] Given historical evidence of differing AMI mortality rates between Sweden and the UK, and taking advantage of their unique nationwide registry-based cohorts of AMI, we investigated the net probability of short- and long-term death by correcting for deaths from other causes and controlling for differences in demographics, comorbidities, and treatments across the two countries.

2. Methods

2.1 Study design and participants

We included all national healthcare hospitals in Sweden ($n = 73$) and in England and Wales ($n = 247$), which provided care for patients with AMI. Eligible patients were aged between 18 and 100 years and had been hospitalized following STEMI or NSTEMI between 1 January 2003 and 30 June 2013. For multiple patient admissions, we used the first recorded episode. Patient-level data concerning demographics, comorbidities, cardiovascular risk factors, and guideline-indicated treatments were extracted from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART), and the Myocardial Ischaemia National Audit Project (MINAP). SWEDEHEART and MINAP are population-based registries gathering outcome information from patients hospitalized for acute coronary syndrome in Sweden and the UK, respectively. Details of these two registries and data validation have been described previously.[15,16] AMI was classified by the attending Consultant as STEMI and NSTEMI according to the European Society of Cardiology (ESC), American College of Cardiology (ACC), and American Heart Association (AHA) guidelines.[17] Patients with unstable angina or missing subtype of AMI were excluded (*Figure 1*).

2.2 Case-mix covariates

To account for case-mix and cardiovascular risk, we adjusted for patient-specific information concerning age, sex, year of hospitalization, risk factors (diabetes mellitus, hypertension, smoking), prior cardiovascular diseases [myocardial infarction, heart failure, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, cerebrovascular disease, peripheral vascular disease (PVD)], other comorbidities [chronic renal failure, chronic obstructive pulmonary disease (COPD)], presenting clinical characteristics at hospitalization (systolic blood pressure, heart rate, ST-segment deviation), in-hospital course (cardiac arrest, use of loop diuretic), and guideline-indicated cardiovascular treatments. Class 1 guideline-recommended treatments included (i) prior to hospitalization [aspirin, β blockers, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB), and HMG Co-A reductase inhibitors (statins)]; (ii) during hospitalization [reperfusion treatment (primary PCI, fibrinolysis) and revascularization (primary PCI or CABG) surgery for patients with STEMI and (PCI or CABG surgery) for patients with NSTEMI],[18,19] and (iii) at the time of discharge from hospital (aspirin, β blockers, statins, ACEi/ARB, and P2Y12 inhibitors). Findings from data quality assessment and validation through regular chart review of randomly selected patients, including data on demographics, risk factors, and medical history, have shown 96.1% agreement in SWEDEHEART[15] and 89.5% in MINAP.[1]

2.3 Outcomes

The primary outcome was the standardized net probability of death (NPD) due to AMI estimated using relative survival, calculated as 1-mean relative survival. Relative survival was defined as the ratio of observed survival (all-cause survival) for STEMI or NSTEMI to (all-cause) survival that would be expected in the absence of AMI in the general population of Sweden and the UK, matched by age, sex, and year of hospitalization for each country.

2.4 Observed survival

Data for all-cause survival were obtained through linkage to the National Population Registry (in Sweden) and the Office for National Statistics (in the UK) using each patient's unique identifier number. Patients were followed-up for their vital status after their hospitalization, with censoring at the end of follow-up on 30 June 2013 (Supplementary material online, *Table S1*). Survival time was the duration between the date of hospitalization and the date of death or censored at the end of the study period, as appropriate.

2.5 Expected survival

Expected survival was derived from death data for the general population of Sweden and England and Wales matched by age, sex, and year of hospitalization to that of the observed survival from the SWEDEHEART and MINAP patients, respectively. This was calculated using life tables produced by the Human Mortality Database of Sweden (http://www.mortality.org) and the Office for National Statistics in the UK (https://www.ons.gov.uk).

2.6 Statistical analyses

We used percentages to describe categorical variables and means and standard deviations (SDs) for continuous variables (all continuous variables were normally distributed). Differences in means for continuous variables and proportions for categorical variables were tested using *t* tests and two-sample tests.

We used flexible parametric survival models to calculate standardized NPD estimates. This approach uses restricted cubic spline functions to estimate the baseline cumulative hazard function. This enables cumulative hazards to be modelled by incorporating more than one time-dependent factor in the same model.[9] The base model (Model 1) was adjusted for age bands [≤55 years, 56–≤65 years, 66 to ≤75 years (reference), 76 to ≤85 years and >85 years], sex and year of hospitalization [categories 2003–05 (reference), 2006–08, 2009–11, and 2012–13]. We incrementally fitted case-mix factors which included prior cardiovascular diseases and other comorbidities (Model 2), cardiovascular risk factors, presenting and in-hospital clinical characteristics (Model 3), reperfusion and revascularization for STEMI and revascularization for NSTEMI (Model 4), and the use of guideline-indicated pharmacotherapies for AMI prior to admission and at discharge (Model 5). Given that differences in survival may be due to differences in patient characteristics and management between the two countries, we also calculated standardized NPD by applying the Swedish model parameters to the UK population.

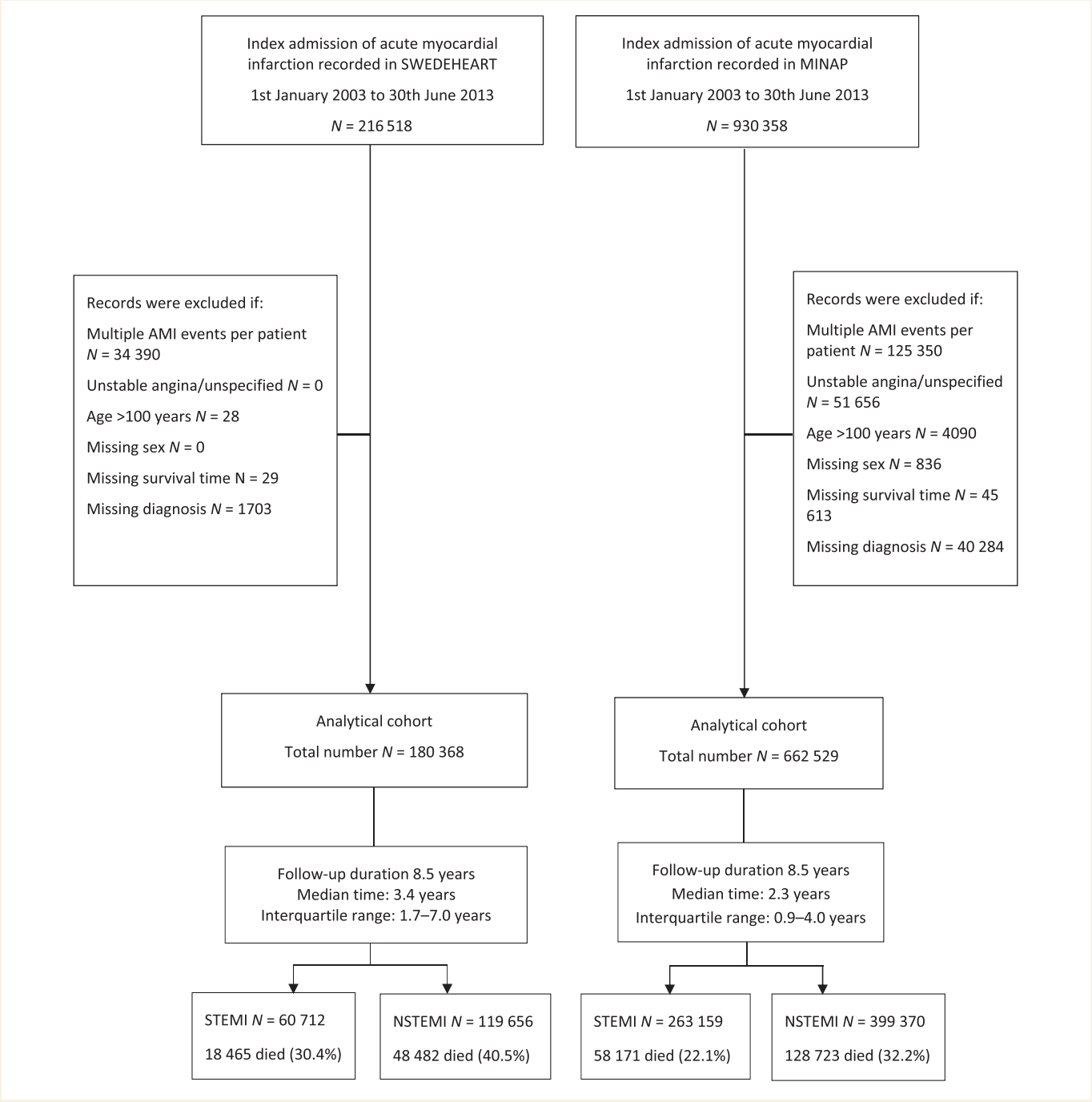

Figure 1 STROBE diagram of exclusion of cases from the SWEDEHEART and MINAP datasets, to derive the analytical cohort.

To examine differences in shorter- and longer-term NPD between the countries, we performed a landmark survival analysis.[20] Four landmarks were selected: (i) admission to 1-month post-discharge; (ii) 1–6 months; (iii) 6 months to 1 year; and (iv) 1 year to date of censorship (see Supplementary material online). The adjusted relative survival for each landmark can be interpreted as the proportion of patients alive after a given time of follow-up compared with the general population, whereby a ratio of 100% indicates that survival was equivalent to that of the general population during that landmark. For the admission to 1-month landmark analyses, pharmacotherapies at discharge were excluded from Model 5.

The proportional excess hazards assumption was assessed by including interaction terms between three baseline variables (age, sex, calendar year) and follow-up time and tested using the likelihood ratio test. All tests were two-tailed, the level of statistical significance pre-specified at 5% ($P < 0.05$) and estimates derived with 95% confidence intervals (CIs). *P*-values were calculated from *Z* values obtained from the difference between the main effect and 95% CIs at each time point between the two countries (see Supplementary material online). Missing covariates were imputed using the approach suggested for MINAP, imputing unrecorded as 'absent' or 'no'.[21]

A series of sensitivity analysis were included: (i) calculating non-standardized NPDs; (ii) using non-imputed covariate data; (iii) estimating all-cause mortality; and (iv) calculating NPDs in subset samples including (a) patients who received invasive treatment [(STEMI, reperfusion or revascularization) and (NSTEMI, revascularization)]; and (b) the latest cohort (2010–13). All statistical analyses were performed using Stata version 15.1 (StataCorp).

3. Results

There were 180 368 Swedish (33.7% STEMI) and 662 529 English and Welsh patients (39.7% STEMI). In Sweden compared with the UK, patients with STEMI were older [mean age 68.9 (SD 12.6) vs. 65.8 (SD 13.6) years]. Swedish patients more frequently had diabetes mellitus (15.6% vs. 12.2%), heart failure (4.6% vs. 1.8%), previous CABG surgery (3.4% vs. 2.1%), and cerebrovascular disease (7.5% vs. 4.7%). Swedish patients less frequently had COPD (5.0% vs. 9.8%) and were smokers (58.4% vs. 66.0%), but had more hypertension (40.2% vs. 36.3%). Patients with STEMI in Sweden more frequently had aspirin (90.2% vs. 82.9%), β-blockers (86.4% vs. 73.4%), $P2Y_{12}$ inhibitors (77.6% vs. 56.2%) at discharge from hospital, and revascularization (74.9% vs. 43.8%). However, statins (81.6% vs. 82.7%), ACEi or ARB (75.2% vs. 79.1%) at discharge from hospital, and receipt of reperfusion during hospitalization (75.7% vs. 78.9%) were higher in the UK (*Table 1*).

Patients with NSTEMI in Sweden, compared with the UK, less frequently had chronic renal failure (3.8% vs. 5.7%), COPD (7.8% vs. 14.6%), and cardiac arrest during hospitalization (2.4% vs. 4.7%). However, they more frequently had heart failure (12.2% vs. 6.5%), cerebrovascular disease (11.3% vs. 8.9%), and PVD (6.8% vs. 4.7%). Patients with NSTEMI in Sweden more frequently received aspirin (88.0% vs. 79.9%), β-blockers (85.1% vs. 65.3%), $P2Y_{12}$ inhibitors (63.7% vs. 50.7%) at discharge, and revascularization during hospitalization (43.6% vs. 27.5%) and had lower rates of prescription of statins (75.1% vs. 79.0%) and ACEi/ARBs (67.9% vs. 69.9%) at discharge (*Table 1*). See Supplementary material online, *Table S2* for information about missing data.

During the 8.5 years of study follow-up, amongst patients with STEMI there were 18 465 (30.4%) deaths after a median of 1.5 years post-AMI [25–75% interquartile range (IQR) 0.04–4.6] in Sweden, and 58 171 (22.1%) deaths after a median of 0.1 years (25–75% IQR 0.008–1.7) in the UK. Amongst patients with NSTEMI, there were 48 482 (40.5%) deaths after a median of 1.7 years post-AMI (25–75% IQR 0.3–4.3) in Sweden, and 128 723 (32.2%) deaths after a median of 0.5 years post-AMI (25–75% IQR 0.07–1.9) in the UK. The proportion of in-hospital deaths was higher in the UK than Sweden for NSTEMI (8.1% vs. 4.8%, $P = 0.001$), but similar for STEMI (9.3% vs. 7.6%, $P = 0.26$).

3.1 Adjusted standardized NPD

For STEMI, after controlling for demographics, previous medical history, and cardiovascular risk factors (Model 3) there was no significant difference in NPDs between Sweden and the UK {NPDs at all landmarks; between admission to 1 month [NPD (95% CI) 6.9 (6.7–7.1) vs. 6.7 (6.6–7.4)], 1–6 months [1.7 (1.6–1.9) vs. 1.7 (1.4–2.0)], 6 months to 1 year [0.8 (0.7–0.9) vs. 1.0 (0.7–1.3)], and >1 year [7.7 (7.0–8.5) vs. 8.2 (7.1–9.3)]}. However, after adjustment for reperfusion and revascularization (Model 4), NPDs were higher in the UK compared with Sweden at all landmarks; between admission to 1 month [8.6 (8.1–9.1) vs. 6.9 (6.7–7.1)], between 1 month and 6 months [2.4 (1.9–2.8) vs. 1.8 (1.6–1.9)], 6 months to 1 year [1.4 (0.9–1.8) vs. 0.8 (0.7–1.0)], and >1 year [10.7 (9.2–12.3) vs. 8.1 (7.3–8.9)]. NPDs remained higher in the UK compared with Sweden after adjustment for pharmacotherapies (Model 5) between admission to 1 month [8.0 (7.4–8.5) vs. 6.7 (6.5–6.9)] but were similar between 6 months to 1 year [0.7 (0.4–1.0) vs. 0.9 (0.7–1.0)] and >1 year [8.4 (6.7–10.1) vs. 8.3 (7.5–9.1)]. Only between 1 and 6 months was NPD higher in Sweden compared with the UK [1.8 (1.7–2.0) vs. 1.4 (1.1–1.7)] (*Figures 2 and 4* and Supplementary material online, *Table S3*).

For NSTEMI, NPDs were higher in the UK compared with Sweden at all landmarks for Model 3 between admission to 1 month [NPD (95% CI) 6.6 (6.3–6.8) vs. 4.9 (4.8–5.1)], 1–6 months [4.3 (4.0–4.7) vs. 3.7 (3.5–3.8)], 6 months to 1 year [2.8 (2.5–3.2) vs. 2.2 (2.1–2.3)], and >1 year [21.0 (19.6–22.4) vs. 17.2 (16.5–17.9)]. NPDs remained higher in the UK after further adjustment for revascularization (Model 4) between admission to 1 month [7.9 (7.5–8.3) vs. 4.9 (4.8–5.1)], 6 months to 1 year [3.8 (3.3–4.2) vs. 2.3 (2.2–2.4)], and >1 year [25.8 (24.2–27.4) vs. 17.8 (17.1–18.5)], and pharmacotherapies (Model 5) between admission to 1 month [6.8 (6.4–7.2) vs. 4.9 (4.7–5.0)], 6 months to 1 year [2.9 (2.5–3.3) vs. 2.3 (2.2–2.5)] and >1 year [21.4 (20.0–22.8) vs. 18.3 (17.6–19.0)], but were similar between 1 and 6 months [3.8 (3.3–4.2) vs. 3.8 (3.7–3.9)] and [3.6 (3.3–4.0) vs. 3.8 (3.7–4.0)] for Models 4 and 5, respectively (*Figures 3 and 5* and Supplementary material online, *Table S3*).

3.2 Sensitivity analysis

Non-standardized NPDs were higher for STEMI and NSTEMI in the UK compared with Sweden at all landmarks and for all models (*Figures 2–5* and Supplementary material online,*Table S3*). Results from all-cause mortality analyses are presented in Supplementary material online, *Table S4* and *Figures S3–S7*. Results from the non-default imputed data were similar to the main analysis (Supplementary material online, *Figures S8* and *S9* and *Tables S5* and *S6*). NPDs for those who received invasive treatments are presented in Supplementary material online, *Tables S7* and *S8*. NPDs for model 5 using only the latest cohort (2010–13) were similar to findings from the main analysis (Supplementary material online, *Figures S10* and *S11*).

4. Discussion

We used registry-based nationwide cohorts within a relative survival framework to study international differences in care and short-, mid-, and longer-term outcomes for 842 897 patients hospitalized with AMI. This approach enabled the comparison of deaths in Sweden and the UK that were attributable to STEMI and NSTEMI (rather than using all-cause mortality that, nowadays, is driven predominantly by non-cardiovascular deaths, and which may vary between countries). We found that after adjusting for demographics, comorbidities, and treatments received, the standardized short-term mortality was significantly higher in the UK compared with Sweden for STEMI and NSTEMI. While mid- and long-term mortality remained higher in the UK for NSTEMI, it was similar in each country for STEMI.

Our data show that patients who received revascularization/reperfusion had a lower mortality than those who did not received treatment, in both Sweden and the UK (Supplementary material online, *Tables S7* and *S8*). Whilst the rates of reperfusion for STEMI were similar between the countries, there were higher rates of revascularization in Sweden. It is possible that, in addition to higher rates of use of pharmacotherapies, during the study period the more frequent use of primary PCI in Sweden

Table 1: Patient characteristics and treatments for STEMI and NSTEMI, by country

	STEMI			NSTEMI	
	Sweden N=60,712	UK N=263,159	Difference in mean (CI)[a]	Sweden N=119,656	UK N=399,370
Mean (SD) age, years	68.9 (12.6)	65.8 (13.6)	3.1 (3.0 to 3.2)[b]	72.4 (12.0)	71.2 (13.4)
Male (%)	40 572 (66.8%)	185 404 (70.5%)	-3.6 (-4.21 to -3.12)[b]	74 402 (62.2%)	249 686 (62.5%)
Year of hospitalization					
2003-05	17 111 (28.2%)	64 866 (24.7%)	3.5 (2.8 to 4.3)[b]	34 153 (28.6%)	106 835 (26.8%)
2006-08	16 460 (27.1%)	74 064 (28.1%)	-1.0 (-1.2 to 0.3)	33 426 (27.9%)	105 525 (26.4%)
2009-11	16 480 (27.1%)	85 300 (32.4%)	-5.3 (-6.0 to -4.5)[b]	31 123 (26.1%)	129 402 (32.4%)
2012-13	10 661 (17.6%)	38 929 (14.8%)	2.8 (2.0 to 3.6)[b]	20 954 (17.5%)	57 608 (14.4%)
Cardiovascular risk factors					
Diabetes mellitus	9496 (15.6%)	32 120 (12.2%)	3.4 (2.6 to 4.2)[b]	26 894 (22.5%)	81 427 (20.4%)
Hypertension	24 425 (40.2%)	95 635 (36.3%)	3.9 (3.2 to 4.6)[b]	57 892 (48.4%)	191 025 (47.8%)
Current/ex-smoker	32 649 (58.4%)	154 692 (66.0%)	-7.6 (-8.2 to -7.0)[b]	58 838 (54.3%)	218 438 (59.7%)
Prior cardiovascular diseases					
Myocardial infarction	7624 (12.6%)	29 313 (11.4%)	1.4 (0.6 to 2.0)[b]	29 318 (24.5%)	96 254 (24.1%)
Heart failure	2795 (4.6%)	4708 (1.8%)	2.8 (2.0 to 3.7)[b]	14 552 (12.2%)	26 061 (6.5%)
PCI	3161 (5.2%)	12 068 (4.6%)	0.6 (-0.2 to 1.0)	10 620 (8.9%)	32 767 (8.2%)
CABG surgery	2041 (3.4%)	5547 (2.1%)	1.3 (0.4 to 2.1)[b]	11 192 (9.4%)	27 219 (6.8%)
Cerebrovascular disease	4521 (7.5%)	12 435 (4.7%)	2.7 (1.9 to 3.6)[b]	13 524 (11.3%)	35 487 (8.9%)
PVD	2120 (3.5%)	6617 (2.5%)	1.0 (0.1 to 1.8)[b]	8162 (6.8%)	18 560 (4.7%)
Other comorbidities					
Chronic renal failure	1089 (1.8%)	5442 (2.1%)	-0.3 (-1.2 to 0.6)	4513 (3.8%)	22 757 (5.7%)
COPD	3014 (5.0%)	25 707 (9.8%)	-4.8 (-7.6 to -5.9)[b]	9338 (7.8%)	58 349 (14.6%)
Presenting clinical characteristics					
Systolic BP, mean (SD) (mmHg)	140.6 (30.2)	135.4 (28.8%)	5.2 (4.9 to 5.5)[b]	149.2 (29.5)	141.2 (28.7%)
Systolic BP, ≤90mmHg	2587 (4.3%)	10 755 (4.1%)	0.2 (-0.7 to 1.0)	2247 (1.9%)	9868 (2.5%)
Heart rate, mean (SD) bpm	77.8 (21.5)	78.6 (21.3%)	-0.8 (-1.0 to -0.6)[b]	83.3 (24.3)	83.4 (23.8%)
Heart rate, >110 bpm	3498 (6.8%)	72 181 (27.4%)	-20.7 (-21.6 to 19.8)[b]	11 901 (11.7%)	105 062 (26.3%)
ST-segment deviation	56 750 (93.8%)	235 120 (92.7%)	1.1 (0.8 to 1.3)[b]	43 335 (36.9%)	110 305 (30.4%)
Prehospital treatment					
Aspirin	15 297 (25.5%)	33 798 (14.1%)	11.4 (10.6 to 12.2)[b]	51 088 (42.9%)	110 949 (30.1%)
β–blockers	16 345 (27.4%)	38 680 (22.2%)	5.2 (4.4 to 6.0)[b]	49 954 (42.1%)	90 740 (32.1%)
Statins	10 026 (16.7%)	55 912 (30.9%)	-14.2 (-15.0 to -13.4)[b]	33 583 (28.3%)	138 709 (47.5%)
ACEi or ARB	13 411 (25.3%)	47 630 (27.4%)	-2.1 (-2.9 to -1.3)[b]	40 492 (37.8%)	113 781 (40.3%)
$P2Y_{12}$ inhibitors	1645 (2.7%)	13 507 (13.9%)	-11.2 (-12.2 to -10.2)[b]	6657 (5.6%)	23 544 (14.0%)
In-hospital course					
Cardiac arrest	3756 (6.2%)	29 112 (12.0%)	-5.8 (-6.6 to -4.9)[b]	2839 (2.4%)	17 815 (4.7%)
Loop diuretic	13 884 (23.0%)	40 602 (20.3%)	2.7 (1.9 to 3.5)[b]	29 688 (25.0%)	102 643 (31.1%)
Hospital treatment					
Revascularisation	45 469 (74.9%)	102 880 (43.8%)	31.1 (30.6 to 31.6)[b]	52 144 (43.6%)	87 811 (27.5%)
Reperfusion	45 861 (75.7%)	191 425 (78.9%)	-3.2 (-3.7 to -2.8)[b]	Not applicable	Not applicable
Primary PCI	7956 (62.5%)	79 536 (33.2%)	29.3 (28.7 to 29.9)[b]	Not applicable	Not applicable
In-hospital fibrinolysis	37 880 (13.1%)	93 015 (38.8%)	-25.6 (-26.5 to -24.9)[b]	Not applicable	Not applicable
Guideline-indicated treatment at discharge					
Aspirin	54 177 (90.2%)	196 454 (82.9%)	7.4 (7.1 to 7.7)[b]	104 407 (88.0%)	289 196 (79.9%)
β–blockers	51 947 (86.4%)	172 781 (73.4%)	13.0 (12.6 to 13.4)[b]	101 053 (85.1%)	234 219 (65.3%)
Statins	49 043 (81.6%)	195 041 (82.7%)	-1.1 (-1.4 to -0.7)[b]	89 096 (75.1%)	248 089 (79.0%)
ACEi or ARB	42 442 (75.2%)	185 082 (79.1%)	-3.8 (-4.3 to -3.4)[b]	75 183 (67.9%)	262 521 (69.9%)
$P2Y_{12}$ inhibitors	46 695 (77.6%)	87 462 (56.2%)	21.4 (20.9 to 21.9)[b]	75 725 (63.7%)	120 455 (50.7%)

[a]Difference in means for continuous variables and proportions for categorical variables.
[b]Significance level <0.05.
ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease including asthma only for the UK; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

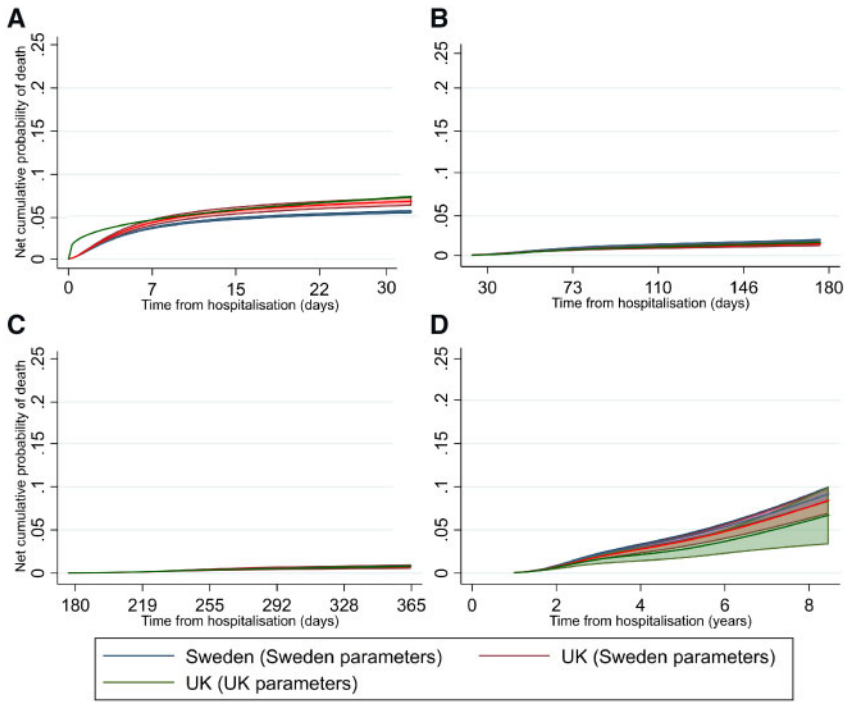

Figure 2 Adjusted standardized net cumulative probability of death for STEMI for (*A*) admission to 1-month post-AMI discharge; (*B*) 1–6 months; (*C*) 6 months to 1 year; and (*D*) over 1-year post-AMI.

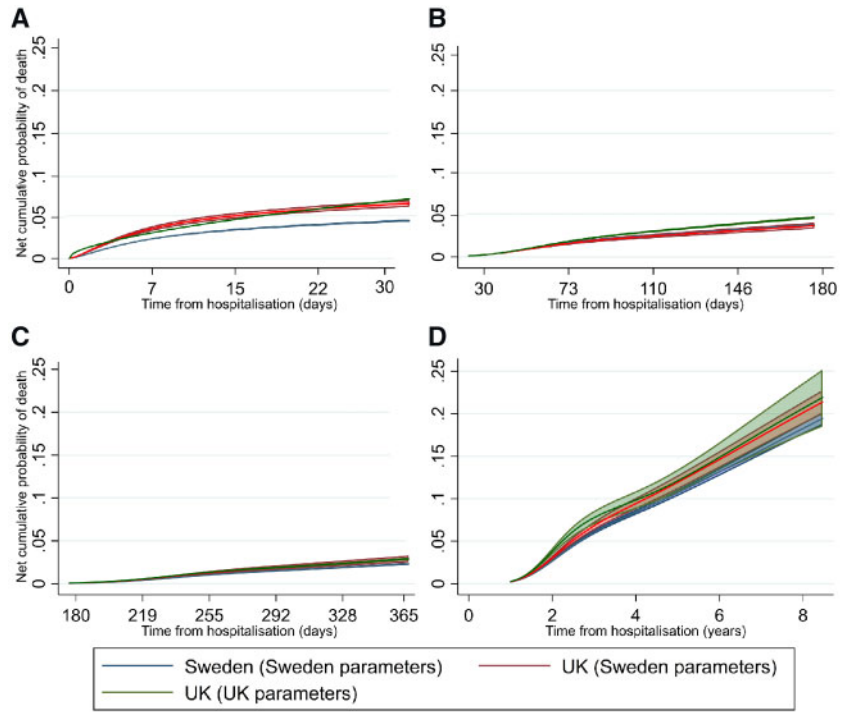

Figure 3 Adjusted standardized net cumulative probability of death for NSTEMI for (*A*) admission to 1-month post-AMI discharge; (*B*) 1–6 months; (*C*) 6 months to 1 year; and (*D*) over 1-year post-AMI.

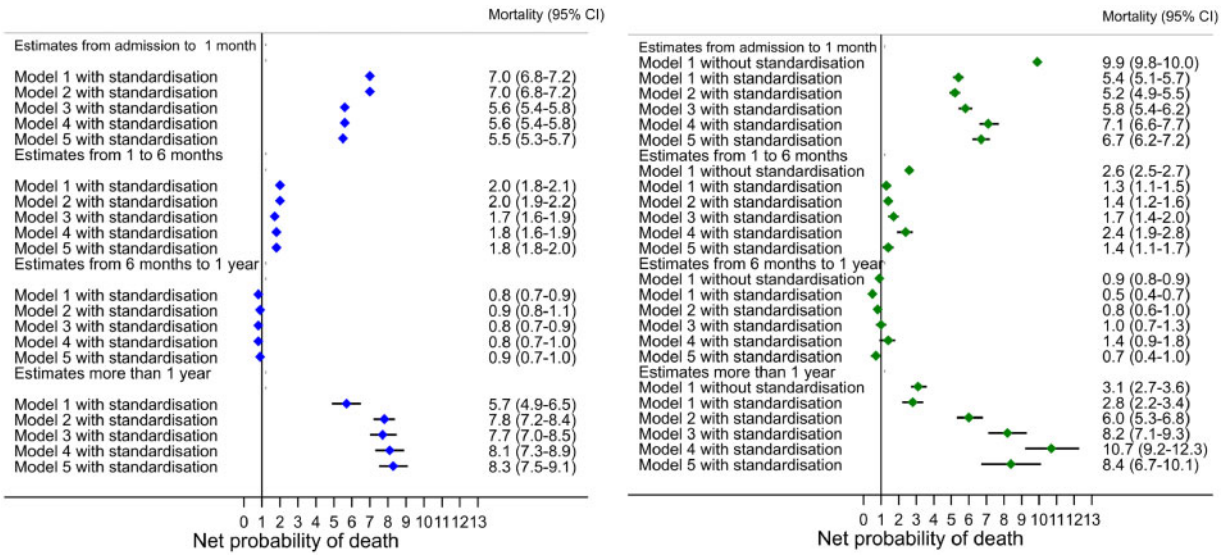

Figure 4 Adjusted net probability of death estimates with and without standardization for STEMI, in Sweden (*A*) and the UK (*B*).

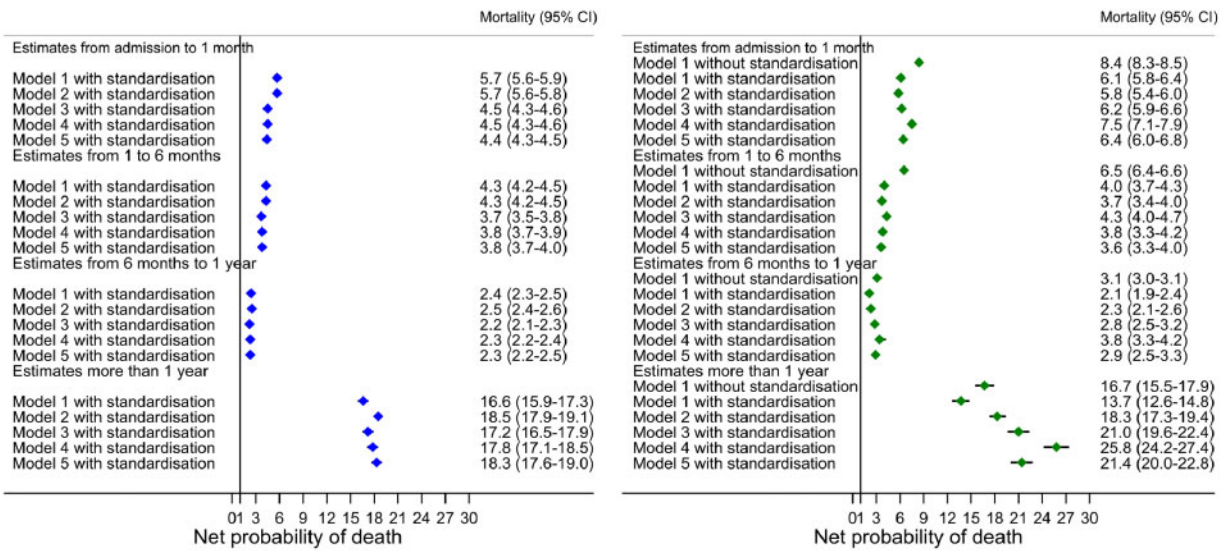

Figure 5 Adjusted net probability of death estimates with and without standardization for NSTEMI, in Sweden (*A*) and the UK (*B*).

explained some of the difference in mortality between the countries for STEMI. The higher NPDs found in Model 4 (after adjusting for revascularization and reperfusion) in the UK, but not Sweden primarily for STEMI patients could be, in part explained by differences in treatment provision between Sweden and the UK. For example, if in the UK patients who received invasive treatment were primarily those with a more severe presentation of AMI or those considered high-risk patients (who would therefore have also a higher risk of death regardless of the treatment administered) and in Sweden all patients were equally likely to receive the treatment regardless of presentation (so low-risk patients or with less severe AMI would also benefit from the treatment), then the estimates of mortality would increase after adjustment for invasive treatment in the UK (because of the higher risk of death among patients who received an invasive treatment) and not in Sweden. This explanation is also supported by the finding of a higher increase in mortality following adjustment for invasive treatment for STEMI than for NSTEMI (given all NSTEMI were also likely to have a 'more severe AMI', and therefore, differences in treatment provision between both countries would be smaller). A similar argument may be presented for NSTEMI, whereby earlier research found that delays to the uptake of guideline-indicated care for NSTEMI in the UK were associated with potentially avoidable deaths.[22]

Our results are consistent with, and extend findings from previous international comparisons of mortality.[1–3] For our investigation, however, we study much longer-term outcomes and present unbiased estimates of standardized NPD by applying the Swedish model parameters to the UK population variables—forcing the distribution of the case-mix covariates to be similar across the two countries and, thus, reducing the likelihood of bias in comparison. In addition, the use of a relative survival framework is relevant to, and recommended for, international comparisons studies[22] because it corrects estimates for expected mortality rates in the general population, thereby permitting a direct comparison of deaths due to AMI.

This study has important implications. We have found that for both STEMI and NSTEMI the higher mortality in the UK compared with Sweden was associated with differences in the delivery and/or uptake of invasive and guideline-indicated pharmacotherapies. The higher late mortality rates among NSTEMI in the UK compared with Sweden may also be influenced by differences in ongoing treatments in each country. However, nationwide data concerning the persistence of pharmacotherapies would be required to study this. This shows that even in high performing, high-income countries there are opportunities to improve care and therefore outcomes. Equally, such high-resolution interrogation of national health system performance was possible because Sweden and the UK each have registry-based nationwide cohorts which continuously collect data for clinically derived variables. This form of analysis would be challenging with administrative and/or geographically and temporally constrained cohorts.

Nevertheless, we acknowledge the study limitations. Relative survival relies on the assumption that the survival probability of the study group is similar to that of the reference (population) group. The main driver of the extent of the impact of this assumption will depend on the proportion of cardiovascular deaths to overall deaths in the population. We accounted for differentials in mortality for other causes in the countries by incorporating this information. This assumption could be called into question for older age groups who are more likely to have multiple comorbidities[23] and might have a higher proportion of deaths due to cardiovascular disease. This could explain the observed difference in long-term survival between the two countries for NSTEMI. Yet, our estimates were adjusted for comorbidities to minimize this bias and the analyses were performed separately for STEMI and NSTEMI, which, to an extent, also limits the potential impact of this bias. We did not correct for the prevalence of AMI in the general population and this may have overestimated the survival rates.[10,24] Moreover, given that cardiovascular and non-cardiovascular diseases are independent competing causes of death and that the prevalence of prior AMI in Sweden and England and Wales is small (9% and 6%, respectively; Supplementary material online, *Figures S1* and *S2*), further adjustment to address this would unlikely affect the results. Despite the fact that national hospital coverage is 100% for Sweden and the UK not all patients are captured. According to SWEDEHEART annual report 2017, 90% of patients with Acute Coronary syndrome are included in the registry.[25] In England and Wales, the majority of STEMI are likely to be captured but fewer NSTEMI are recorded due to complexity of diagnosis.[2] We adjusted the estimates for patient-specific information, risk factors, prior cardiovascular diseases, and guideline-indicated cardiovascular treatments administered pre-, intra-, and at discharge from hospital, but information on treatments provided during follow-up were not available in the dataset. Finally, the completeness and accuracy across the two registries are different although high.[2] However, our sensitivity analysis using default imputed covariate data showed that neither the direction nor the significance of the results changed compared to the findings from primary analysis (see Supplementary material online, *Figures S8* and *S9* and *Tables S5* and *S6*).

5. Conclusion

The observed differences in the delivery of guideline-indicated care between Sweden and the UK, coupled with a robust statistical technique for international comparisons of outcomes, suggests that disparities in the delivery of invasive coronary treatments and guideline-indicated pharmacotherapies are a contributing factor to differentials in AMI mortality between countries.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

Authors' contributions

C.P.G. and T.J. conceived the study. O.A.A. performed the data cleaning, analyses, and wrote the initial draft with support from M.J.R. and M.P.R. All authors contributed to critical revision of the manuscript and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. T.J. and C.P.G. are the guarantors.

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References

1. Chung SC, Gedeborg R, Nicholas O, James S, Jeppsson A, Wolfe C, Heuschmann P, Wallentin L, Deanfield J, Timmis A, Jernberg T, Hemingway H. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. *Lancet* 2014;**383**:1305–1312.
2. McNamara RL, Chung SC, Jernberg T, Holmes D, Roe M, Timmis A, James S, Deanfield J, Fonarow GC, Peterson ED, Jeppsson A, Hemingway H. International comparisons of the management of patients with non-ST segment elevation acute myocardial infarction in the United Kingdom, Sweden, and the United States: the MINAP/NICOR, SWEDEHEART/RIKS-HIA, and ACTION Registry-GWTG/NCDR registries. *Int J Cardiol* 2014;**175**:240–247.
3. Chung SC, Sundstrom J, Gale CP, James S, Deanfield J, Wallentin L, Timmis A, Jernberg T, Hemingway H. Comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and United Kingdom: population based cohort study using nationwide clinical registries. *BMJ* 2015;**351**:h3913.
4. Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M, Wilkins E, Wright L, Vos R, Bax J, Blum M, Pinto F, Vardas P, Goda A, Demiraj AF, Weidinger F, Metzler B, Ibrahimov F, Pasquet AA, Claeys M, Thorton Y, Kusljugic Z, Smajic E, Velchev V, Ivanov N, Antoniades L, Agathangelou P, Táborský M, Gerdes C, Viigima M, Juhani PM, Juilliere Y, Cattan S, Aladashvili A, Hamm C, Kuck K-H, Papoutsis K, Bestehorn K, Foussas S, Giannoulidou G, Varounis C, Kallikazaros I, Kiss RG, Czétényi T, Becker D, Gudnason T, Kearney P, McDonald K, Rozenman Y, Ziv B,

Bolognese L, Luciolli P, Boriani G, Berkinbayev S, Rakisheva A, Mirrakhimov E, Erglis A, Jegere S, Marinskis G, Beissel J, Marchal N, Kedev S, Xuereb RG, Tilney T, Felice T, Popovici M, Bax J, Mulder B, Simoons M, Elsendoorn M, Steigen TK, Atar D, Kalarus Z, Tendera M, Cardoso JS, Ribeiro J, Mateus C, Tatu-Chitoiu G, Seferovic P, Beleslin B, Simkova I, Durcikova P, Belicova V, Fras Z, Radelj S, Gonzalez Juanatey JR, Legendre S, Braunschweig F, Kaufmann UP, Rudiger-Sturchler M, Tokgozoglu L, Unver A, Kovalenko V, Nesukay E, Naum A, de Courtelary PT, Martin S, Sebastiao D, Ghislain D, Bardinet I, Logstrup S. European Society of Cardiology: cardiovascular disease statistics 2017. *Eur Heart J* 2018;**39**:508–579.

5. Rapsomanik ET, Yang E, Blin P, Hunt P, Chung S, Stogiannis D, Pujades-Rodriguez M, Timmis A, Denaxas SC, Danchin N, Stokes M, Thomas-Delecourt F, Emmas C, Hasvold P, Jennings E, Johansson S, Cohen DJ, Jernberg T, Moore N, Janzon M, Hemingway H. Using big data from health records from four countries to evaluate chronic disease outcomes: a study in 114 364 survivors of myocardial infarction. *Eur Heart J Qual Care Clin Outcomes* 2016;**2**:172–183.
6. Mandelzweig L, Battler A, Boyko V, Bueno H, Danchin N, Filippatos G, Gitt A, Hasdai D, Hasin Y, Marrugat J, Van de WF, Wallentin L, Behar S. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. *Eur Heart J* 2006;**27**:2285–2293.
7. Spoon DB, Psaltis PJ, Singh M, Holmes DR Jr, Gersh BJ, Rihal CS, Lennon RJ, Moussa ID, Simari RD, Gulati R. Trends in cause of death after percutaneous coronary intervention. *Circulation* 2014;**129**:1286–1294.
8. Alabas OA, Gale CP, Hall M, Rutherford MJ, Szummer K, Lawesson SS, Alfredsson J, Lindahl B, Jernberg T. Sex differences in treatments, relative survival, and excess mortality following acute myocardial infarction: national cohort study using the SWEDEHEART registry. *J Am Heart Assoc* 2017;**6**:1–12.
9. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med* 2004;**23**:51–64.
10. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. *Stata J* 2009;**9**:265–290.
11. Nelson CP, Lambert PC, Squire IB, Jones DR. Flexible parametric models for relative survival, with application in coronary heart disease. *Stat Med* 2007;**26**: 5486–5498.
12. Alabas OA, Allan V, McLenachan JM, Feltbower R, Gale CP. Age-dependent improvements in survival after hospitalisation with acute myocardial infarction: an analysis of the Myocardial Ischemia National Audit Project (MINAP). *Age Ageing* 2014;**43**:779–785.
13. Hall M, Alabas OA, Dondo TB, Jernberg T, Gale CP. Use of relative survival to evaluate non-ST-elevation myocardial infarction quality of care and clinical outcomes. *Eur Heart J Qual Care Clin Outcomes* 2015;**1**:85–91.
14. Alabas OA, Hall M, Dondo TB, Rutherford MJ, Timmis AD, Batin PD, Deanfield JE, Hemingway H, Gale CP. Long-term excess mortality associated with diabetes following acute myocardial infarction: a population-based cohort study. *J Epidemiol Community Health* 2017;**71**:25–32.
15. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, Stenestrand U, Wallentin L. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart* 2010;**96**:1617–1621.
16. Herrett E, Smeeth L, Walker L, Weston C. The myocardial ischaemia national audit project (MINAP). *Heart* 2010;**96**:1264–1267.
17. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation* 2012;**126**:2020–2035.
18. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;**33**:2569–2619.
19. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *G Ital Cardiol (Rome)* 2016;**17**:831–872.
20. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. *J Clin Oncol* 1983;**1**:710–719.
21. Pinto P, Rothnie KJ, Lui K, Timmis A, Smeeth L, Quint JK. Presentation, management and mortality after a first MI in people with and without asthma: a study using UK MINAP data. *Chron Respir Dis* 2018;**15**:60–70.
22. Dondo TB, Hall M, Timmis AD, Gilthorpe MS, Alabas OA, Batin PD, Deanfield JE, Hemingway H, Gale CP. Excess mortality and guideline-indicated care following non-ST-elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2017;**6**:412–420.
23. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T, Micheli A, Sant M, Weir HK, Elwood JM, Tsukuma H, Koifman S, Ga ES, Francisci S, Santaquilani M, Verdecchia A, Storm HH, Young JL. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008;**9**:730–756.
24. Talback M, Dickman PW. Estimating expected survival probabilities for relative survival analysis–exploring the impact of including cancer patient mortality in the calculations. *Eur J Cancer* 2011;**47**:2626–2632.
25. https://www.ucr.uu.se/swedeheart/arsrapport-2017/swedeheart-annual-report-2017 (15 May 2019, date last accessed).