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Association of Clinical Factors and Therapeutic Strategies With Improvements in Survival Following Non–ST-Elevation Myocardial Infarction, 2003-2013

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IMPORTANCE International studies report a decline in mortality following non-ST-elevation myocardial infarction (NSTEMI). Whether this is due to lower baseline risk or increased utilization of guideline-indicated treatments is unknown.

OBJECTIVE To determine whether changes in characteristics of patients with NSTEMI are associated with improvements in outcomes.

DESIGN, SETTING, AND PARTICIPANTS Data on patients with NSTEMI in 247 hospitals in England and Wales were obtained from the Myocardial Ischaemia National Audit Project between January 1, 2003, and June 30, 2013 (final follow-up, December 31, 2013).

EXPOSURES Baseline demographics, clinical risk (GRACE risk score), and pharmacological and invasive coronary treatments.

MAIN OUTCOMES AND MEASURES Adjusted all-cause 180-day postdischarge mortality time trends estimated using flexible parametric survival modeling.

RESULTS Among 389 057 patients with NSTEMI (median age, 72.7 years [IQR, 61.7-81.2 years]; 63.1% men), there were 113 586 deaths (29.2%). From 2003-2004 to 2012-2013, proportions with intermediate to high GRACE risk decreased (87.2% vs 82.0%); proportions with lowest risk increased (4.2% vs 7.6%; $P = .01$ for trend). The prevalence of diabetes, hypertension, cerebrovascular disease, chronic obstructive pulmonary disease, chronic renal failure, previous invasive coronary strategy, and current or ex-smoking status increased (all $P < .001$). Unadjusted all-cause mortality rates at 180 days decreased from 10.8% to 7.6% (unadjusted hazard ratio [HR], 0.968 [95% CI, 0.966-0.971]; difference in absolute mortality rate per 100 patients [AMR/100], −1.81 [95% CI, −1.95 to −1.67]). These findings were not substantially changed when adjusted additively by baseline GRACE risk score (HR, 0.975 [95% CI, 0.972-0.977]; AMR/100, −0.18 [95% CI, −0.21 to −0.16]), sex and socioeconomic status (HR, 0.975 [95% CI, 0.973-0.978]; difference in AMR/100, −0.24 [95% CI, −0.27 to −0.21]), comorbidities (HR, 0.973 [95% CI, 0.970-0.976]; difference in AMR/100, −0.44 [95% CI, −0.49 to −0.39]), and pharmacological therapies (HR, 0.972 [95% CI, 0.964-0.980]; difference in AMR/100, −0.53 [95% CI, −0.70 to −0.36]). However, the direction of association was reversed after further adjustment for use of an invasive coronary strategy (HR, 1.02 [95% CI, 1.01-1.03]; difference in AMR/100, 0.59 [95% CI, 0.33-0.86]), which was associated with a relative decrease in mortality of 46.1% (95% CI, 38.9%-52.0%).

CONCLUSIONS AND RELEVANCE Among patients hospitalized with NSTEMI in England and Wales, improvements in all-cause mortality were observed between 2003 and 2013. This was significantly associated with use of an invasive coronary strategy and not entirely related to a decline in baseline clinical risk or increased use of pharmacological therapies.

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There has been a global decline in the rates of death following acute coronary syndrome; however, the extent to which this is due to use of guideline-indicated treatments for management of non-ST-elevation myocardial infarction (NSTEMI) is not known.[1-3] Randomized clinical trials provide evidence for reductions in morbidity associated with use of pharmacological and invasive coronary strategies among patients hospitalized with NSTEMI.[4,5] With the introduction of troponin assays, the detection of NSTEMI of lower clinical risk has increased, which may account for improved clinical outcomes in this population.[6,7]

However, there is a paucity of contemporary studies of sufficient duration and representation from a population perspective that enable a detailed evaluation of the association of baseline risk and guideline-indicated therapies with mortality among patients with NSTEMI.[1,8-10] The Myocardial Ischaemia National Audit Project (MINAP) is the only whole-country acute coronary syndrome registry, representing all hospitals in a single health system (the National Health Service of England and Wales) with prospective collection of detailed information about quality of care and clinical outcomes of patients for more than 15 years.[11,12] Thus, MINAP represents an opportunity to undertake phenotype- and treatment-specific studies of temporal changes in clinical outcomes for NSTEMI. Therefore, we aimed to investigate whether temporal improvements in 180-day mortality between 2003 and 2013 were associated with changes in patients' baseline clinical risk or use of guideline-indicated treatments for management of NSTEMI among patients in the UK National Health Service.

Key Points

Question Are temporal changes in clinical factors and therapeutic strategies associated with improvements in survival following non–ST-elevation myocardial infarction?

Findings In this prospective cohort study of 389 057 patients from 2003 to 2013, patient clinical risk decreased while use of guideline-indicated care increased. There was a significant decrease in 180-day all-cause mortality from 10.8% to 7.6% that was associated with increased use of an invasive coronary strategy after adjustment for changes in clinical risk and pharmacological therapies.

Meaning Invasive management may have been a contributor to declining mortality due to non–ST-elevation myocardial infarction between 2003 and 2013.

Methods

Data and Patients

MINAP is a comprehensive clinical database of patients hospitalized with acute myocardial infarction, mandated by the Department of Health for all hospitals in England and Wales. Data are collected prospectively at each hospital, electronically encrypted, and transferred online to a central database. Data entry is subject to routine error checking and a mandatory annual data validation exercise. Mortality data were obtained through linkage with Office for National Statistics death records, which occurs on an annual basis. Further details of MINAP have been published elsewhere.[11]

The analytical cohort was derived from all patients with NSTEMI admitted to 1 of 247 hospitals between January 1, 2003, and June 30, 2013 (eFigure 1 in the Supplement). Patients were eligible for the study if they were aged 18 years or older with a final diagnosis of NSTEMI. The final diagnosis was determined by local clinicians according to presenting history, clinical examination, and the results of inpatient investigations in keeping with the consensus document of the Joint European Society of Cardiology and American College of Cardiology.[13]

Patients who died in the hospital were excluded from the study because it was not possible to accurately ascertain their receipt of pharmacological therapies. Furthermore, patients with missing postdischarge mortality data were excluded from the analysis. A sensitivity analysis was conducted to assess the statistical effect of excluding those who died in the hospital (eAppendix 1 and eTables 2-4 in the Supplement).

Patient-level data included baseline Global Registry of Acute Coronary Events (GRACE) risk score (including age, cardiac arrest, ST-segment deviation, elevated enzyme levels, systolic blood pressure, heart rate, loop diuretic [substituted for Killip class], and creatinine), patient demographics (sex, index of multiple deprivation), comorbidities (history of diabetes, smoking, coronary heart disease, hypertension, myocardial infarction, angina, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease or asthma, chronic renal failure [defined as creatinine level chronically >200 μmol/L {>2.26 mg/dL}], congestive heart failure, previous percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery, and elevated cholesterol level [defined as an elevation of serum cholesterol requiring dietary or drug treatment]), pharmacological therapies at discharge (aspirin, β-blockers, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, $P2Y_{12}$ inhibitors, or aldosterone antagonists), use of an invasive coronary strategy (coronary angiography, PCI, or CABG surgery), and mortality (through linkage to the Office for National Statistics).

Ethical Approval

The National Institute for Cardiovascular Outcomes Research, which includes the MINAP database, has support under section 251 of the National Health Service Act of 2006 to use patient information for medical research without informed consent. Ethical approval was not required under current National Health Service research governance arrangements.

Statistical Analyses

Baseline characteristics were described using numbers and percentages for categorical data and means and standard deviations or medians and interquartile ranges for normally and nonnormally distributed continuous variables. For each patient, the probability of 180-day all-cause mortality after discharge was calculated using the GRACE risk score (range,

5-254.8; higher scores indicate greater risk).[14,15] Given international guidelines, patients were categorized according to their risk of 180-day mortality using their GRACE risk score into lowest risk (<70), low risk (70-87), and intermediate to high risk (≥88).[5,16] Temporal trends of patient and treatment characteristics were summarized by comparing data from the start of the study (2003-2004) to the end of the study (2012-2013) using χ^2 tests, *t* tests, and Wilcoxon rank sum tests. An ordered logistic regression model was fitted to determine the temporal trend in GRACE risk score category for each year of the study period, and results are presented as odds ratios.

A series of Royston-Parmar flexible parametric survival models[17] were fitted to determine the extent to which pharmacological treatments and an invasive coronary strategy (defined as coronary angiography, PCI, or CABG surgery) explained the association between baseline risk and survival trends. Flexible parametric survival models were selected in favor of Cox regression models to overcome violation of the proportional hazards assumption. Initially, a bivariable model was fitted to determine the overall temporal trend by year. Subsequently, the statistical effect of the GRACE risk score, comorbidity, pharmacological therapies at discharge, and an invasive coronary strategy on the yearly temporal trend was determined by incrementally adding these data to the model (see eTable 5 in the Supplement for sensitivity of the model to order of model building).

Multiple imputation by chained equations was used to produce 10 imputed data sets to minimize bias caused by missing data (eAppendix 2 and eTables 6-8 in the Supplement). Pooled estimates and accompanying 95% confidence intervals were generated according to Rubin's rules.[18] Improvements in model fit at each stage were determined by minimizing the Akaike information criterion and Bayesian information criterion ranges across all 10 imputations. The scale (proportional hazards, proportional odds, or normal) and complexity (number of degrees of freedom) for flexible parametric survival models were checked on the full multivariable model for each imputation (eTable 9 in the Supplement). To assess the potential statistical effect of clustering of patients within hospitals, a sensitivity analysis was conducted comparing estimates from a Cox model with and without the inclusion of a shared frailty term (eAppendix 3 and eTable 10 in the Supplement). To assess the potential for selection bias, an instrumental variable analysis with hospital rates of coronary angiography served to approximate a random assignment of patients to regional treatment groups that differed in their likelihood of receiving an invasive coronary strategy (eAppendix 4 and eTables 11 and 12 in the Supplement). In addition, a mediation analysis was conducted to determine the proportion of survival trends that were mediated by pharmacological therapies or use of an invasive coronary strategy in turn, while adjusting for confounding variables (eAppendix 5 and eFigures 3 and 4 in the Supplement).

All tests were 2-sided, and statistical significance was considered $P < .05$. Statistical analyses were performed in Stata version 14 (http://www.stata.com/) and R version 3.1.2 (https://cran.r-project.org/).

Results

The analytical cohort (n = 389 057) was drawn from 441 945 patients with NSTEMI admitted to 1 of 247 hospitals between January 1, 2003, and June 30, 2013 (eFigure 1 in the Supplement). A total of 31 321 patients (7.1%) who died in the hospital and 21 567 patients (4.9%) who had missing postdischarge mortality data were excluded from the analysis. The median follow-up time was 2.3 years (maximum, 8.4 years; 1 079 044 person-years). The median age for the NSTEMI cohort was 72.7 years (interquartile range, 61.7-81.2 years); 63.1% were male. Typically, individuals had high comorbidity: more than half had hypertension or were a current or ex-smoker and more than a quarter had diabetes, angina, or previous myocardial infarction (**Table 1**). Overall, 82.9% had an intermediate to high GRACE risk score, 9.7% had a low GRACE risk score, and 7.4% had a lowest GRACE risk score. During the full follow-up period, there were 113 586 deaths (29.2%) corresponding to 10.5 deaths per 100 person-years. At 180 days after hospital discharge, there had been 37 236 deaths (9.6%).

Temporal Trends in Clinical Characteristics

Temporal trends in baseline clinical characteristics are shown in Table 1. Over the study period, the proportion of patients with NSTEMI who had diabetes, hypertension, cerebrovascular disease, chronic obstructive pulmonary disease or asthma, chronic renal failure, previous PCI, previous CABG surgery, or current or ex-smoking status increased (all $P<.001$ for trend). In contrast, the proportion of patients with previous myocardial infarction, angina, peripheral vascular disease, and congestive heart failure decreased (all $P<.001$ for trend). There was a reduction in the proportion of patients with NSTEMI who had an initial diagnosis of chest pain of uncertain cause (21.3% vs 13.4%; difference, 7.9%; 95% CI, 6.9%-8.9%; $P<.001$ for trend) and corresponding increase in the number of patients with an initial diagnosis of acute coronary syndrome or probable acute myocardial infarction (57.6% vs 72.8%; difference, 15.2%; 95% CI, 14.6%-15.9%; $P<.001$ for trend).

Temporal Trends in GRACE Risk Score

From 2003-2004 to 2012-2013, the proportions of NSTEMI in the intermediate to high GRACE risk category decreased (87.2% vs 82.0%; difference, 5.2%; 95% CI, 1.78%-8.62%); the proportions in the lowest GRACE risk category increased (4.2% vs 7.6%; difference, 3.4%; 95% CI, −5.9% to 12.7%); and the proportions at low risk increased (8.6% vs 10.4%; difference, 1.8%; 95% CI, −7.3% to 10.9%) ($P = .01$ for trend) (eFigure 2 in the Supplement). During the entire study period (2003-2013), patients were on average less likely to be at intermediate to high GRACE risk (odds ratio, 0.96; 95% CI, 0.96-0.97 per year) (**Table 2**). This temporal trend remained after adjusting for additional patient demographics, comorbidity, and pharmacological medications prescribed at hospital discharge. Over the study period, more patients who underwent an invasive coronary strategy were in the intermediate to high GRACE risk category (odds ratio, 1.01; 95% CI, 1.01-1.02 per year).

Table 1. Patient Characteristics by Year of Hospitalization[a]

Characteristics	Total Cohort, 2003-2013 (N = 389 057)	2003-2004 (n = 67 441)	2012-2013 (n = 56 649)	Difference, 2012-2013 – 2003-2004 (95% CI)	Missing Data, %
Age, median (IQR), y	72.7 (61.7-81.2)	72.8 (62.2-80.9)	72.0 (61.0-81.0)	0.80 (0.56 to 1.04)	0.2
Male, No. (%)	244 837 (63.1)	41 873 (62.3)	36 262 (64.1)	1.80 (1.12-2.48)	0.2
Deprivation, median (IQR), IMD score[b]	18.2 (10.6-31.5)	18.9 (11.0-32.8)	17.9 (10.4-31.4)	0.99 (0.77-1.21)	7.8
Systolic blood pressure, mean (SD), mm Hg	142.5 (28.4)	143.8 (29.6)	141.8 (27.1)	−2.01 (−2.38 to −1.65)	17.1
Heart rate, mean (SD), /min	83.3 (23.8)	84.6 (25.2)	81.2 (21.6)	−3.38 (−3.68 to −3.08)	16.9
Total cholesterol, median (IQR), mg/dL	185.6 (150.8-224.3)	193.4 (158.5-232.0)	177.9 (146.9-220.4)	15.08 (14.31 to 15.86)	39.5
Creatinine, median (IQR), mg/dL	1.04 (0.86-1.29)	1.20 (1.04-1.46)	0.98 (0.81-1.23)	0.22 (0.19 to 0.24)	42.6
Medical history, No. (%)					
Previous diabetes	81 469 (22.5)	9950 (20.6)	13 667 (24.5)	3.90 (2.83 to 4.97)	7.1
Current or ex-smoker	217 116 (60.3)	32 817 (55.7)	32 467 (59.8)	4.10 (3.34 to 4.86)	7.5
Family history of CHD	77 288 (31.7)	973 (37.3)	13 587 (29.5)	−7.80 (−10.93 to −4.67)	37.2
Hypertension	188 503 (52.8)	23 754 (47.3)	30 063 (55.5)	8.20 (7.35 to 9.05)	8.3
Previous MI	97 002 (27.1)	14 409 (28.6)	14 017 (25.8)	−2.80 (−3.83 to −1.77)	8.0
Previous angina	122 566 (34.6)	18 898 (37.8)	16 419 (30.5)	−7.30 (−6.31 to −8.29)	8.9
Peripheral vascular disease	18 324 (5.3)	2787 (5.8)	2673 (5.0)	−0.80 (−2.00 to 0.40)	11.5
Cerebrovascular disease	34 146 (9.8)	4311 (9.2)	5240 (9.7)	0.50 (−0.68 to 1.68)	10.6
COPD or asthma	56 708 (16.5)	7417 (15.9)	9058 (16.8)	0.90 (−0.23 to 2.03)	11.4
Chronic renal failure	21 938 (6.3)	1911 (4.0)	4161 (7.7)	3.7 (2.50 - 4.90)	10.4
Congestive heart failure	24 529 (7.0)	3835 (8.0)	3603 (6.7)	−1.30 (−2.48 to −0.12)	10.4
Previous PCI	32 663 (9.3)	2678 (5.7)	6642 (12.3)	6.60 (5.42 to 7.78)	10.1
Previous CABG surgery	27 637 (7.9)	2964 (6.2)	4793 (8.9)	2.70 (1.52 to 3.88)	9.8
Preadmission medications, No. (%)[c]					
Aspirin	130 185 (55.0)	19 310 (42.6)	16 915 (71.6)	29.00 (28.03 to 29.97)	7.6
β-Blocker	90 045 (32.5)	593 (50.1)	16 935 (32.7)	−17.40 (−21.49 to −13.31)	26.5
Statin	137 644 (48.2)	680 (57.6)	26 290 (48.4)	−9.20 (−12.96 to −5.44)	29
ACE inhibitor or ARB	113 345 (41.0)	588 (49.6)	22 025 (42.4)	−7.20 (−11.29 to −3.11)	28.9
$P2Y_{12}$ inhibitor	24 180 (14.5)	0	7602 (14.3)		57.3
Warfarin	21 544 (6.7)	3045 (7.4)	3168 (6.3)	−1.10 (−2.36 to 0.16)	17.9
Discharge medications, No. (%)[c]					
Aspirin	301 639 (97.1)	55 738 (95.9)	42 876 (98.4)	2.50 (2.30 to 2.70)	7.8
β-Blocker	244 962 (91.5)	41 066 (85.4)	37 610 (95.4)	10.00 (9.60 to 10.40)	8.3
Statin	297 045 (94.1)	51 834 (89.0)	42 541 (96.6)	7.60 (7.28 to 7.93)	9.1
ACE inhibitor or ARB	251 406 (87.6)	43 804 (81.1)	36 709 (92.6)	11.50 (11.05 to 11.95)	8.6
$P2Y_{12}$ inhibitor	127 356 (93.1)	0	38 854 (94.9)		54.9
Aldosterone antagonist	9702 (11.9)	0	3266 (13.7)		58.8
Admission diagnosis, No. (%)					
ACS or probable MI	252 456 (64.9)	38 843 (57.6)	41 243 (72.8)	15.20 (14.55 to 15.85)	
Chest pain, unknown cause	64 677 (16.6)	14 326 (21.3)	7563 (13.4)	−7.90 (−8.92 to −6.88)	0.01
Other	71 876 (18.5)	14 256 (21.1)	7843 (13.8)	−7.30 (−8.32 to −6.28)	
GRACE risk score category, No. (%)[d]					
Lowest (<70)	11 192 (7.4)	18 (4.2)	2496 (7.6)	3.40 (−5.92 to 12.72)	
Low (70-87)	14 695 (9.7)	37 (8.6)	3401 (10.4)	1.80 (−7.29 to 10.89)	61.2
Intermediate to high (≥88)	125 213 (82.9)	374 (87.2)	26 847 (82.0)	−5.20 (−8.62 to −1.78)	
Use of an invasive coronary strategy[e]	214 302 (63.3)	22 056 (42.7)	40 771 (78.6)	35.90 (35.14 to 36.66)	13.0

Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention.

SI conversions: To convert total cholesterol to millimoles per liter, multiply by 0.0259. To convert creatinine to micromoles per liter, multiply by 88.4.

[a] *P* values for linear trend across all study years (2003-2013) were all significant at the ≤.01 level.

[b] Index of Multiple Deprivation (IMD) scores range from 0.59 to 86.36; higher scores indicate greater deprivation.

[c] Only patients eligible to receive treatments were included in the denominator.

[d] Global Registry of Acute Coronary Events (GRACE) risk scores range from 5 to 258.4.

[e] Coronary angiography, PCI, or CABG surgery.

Table 2. Relationship Between Case Mix, Comorbidities, Pharmacological Therapies at Discharge, and Invasive Coronary Strategy and GRACE Risk Score Categorization, 2003-2013

Model[a]	Yearly Time Trend for Higher GRACE Score Categorization			AIC and BIC Ranges Over 10 Imputed Data Sets	
	Odds Ratio (95% CI)[b]	*P* Value	Absolute Difference in Odds (95% CI)[c]	AIC Range	BIC Range
Unadjusted yearly time trend	0.96 (0.96-0.97)	<.001	−0.037 (−0.040 to −0.034)	489 413.2-490 512.0	489 445.8-490 544.7
Yearly time trend adjusted for					
Sex and IMD	0.96 (0.96-0.970)	<.001	−0.037 (−0.040 to −0.034)	479 090.7-480 143.6	479 145.1-480 198.0
Sex, IMD, and comorbidities[d]	0.96 (0.95-0.96)	<.001	−0.045 (−0.050 to −0.042)	442 792.3-444 023.5	442 988-444 219.2
Sex, IMD, comorbidities, and pharmacological therapies at discharge[e]	0.98 (0.97-0.99)	<.001	−0.020 (−0.028 to −0.013)	261 326.3-261 947.5	261 573.6-262 194.9
Sex, IMD, comorbidities, pharmacological therapies at discharge, and invasive coronary strategy[f]	1.01 (1.01-1.02)	.001	0.014 (0.006 to 0.021)	252 226.8-252 967.1	252 494.7-253 235.1

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; GRACE, Global Registry of Acute Coronary Events; IMD, Index of Multiple Deprivation.

[a] Ordered logistic regression models performed after multiple imputation.

[b] The odds ratio indicates the likelihood of higher GRACE risk score categorization.

[c] Absolute difference in odds of higher GRACE risk score categorization between 2003 and 2013.

[d] Including history of diabetes, smoking, family history of coronary heart disease, hypertension, myocardial infarction, angina, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, chronic renal failure, congestive heart failure, percutaneous coronary intervention, coronary artery bypass graft surgery, elevated cholesterol (defined as elevation of serum cholesterol level requiring dietary or drug treatment).

[e] Aspirin, β-blockers, statins, angiotensin-converting enzymes inhibitors or angiotensin receptor blockers, $P2Y_{12}$ inhibitors, and aldosterone antagonists.

[f] Coronary angiography, percutaneous coronary intervention, or coronary artery bypass graft surgery. Age, cardiac arrest, ST-segment deviation, elevated enzymes, systolic blood pressure, heart rate, loop diuretic, and creatinine were not individually included in the modeling process because they were all used in the calculation of the GRACE risk score.

Temporal Trends in Guideline-Indicated Treatments

The use of aspirin (95.9% vs 98.4%; difference, 2.5%; 95% CI, 2.3%-2.7%; *P*<.001 for trend), β-blockers (85.4% vs 95.4%; difference, 10%; 95% CI, 9.6%-10.4%; *P*<.001 for trend), statins (89.0% vs 96.6%; difference, 7.6%; 95% CI, 7.3%-7.9%; *P*<.001 for trend), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (81.1% vs 92.6%; difference, 11.5%; 95% CI, 11.1%-12.0%; *P*<.001 for trend), $P2Y_{12}$ inhibitors (0% vs 94.9%), and aldosterone antagonists (0% vs 13.7%) at discharge increased (**Figure 1**). The use of coronary angiography, PCI, or CABG surgery increased (*P* < .001) and in 2012-2013 reached rates of 71.5%, 33.3%, and 3.0%, respectively (Figure 1). Aspirin, $P2Y_{12}$ inhibitors, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins had a significant association with improved survival (eTable 1 in the Supplement).

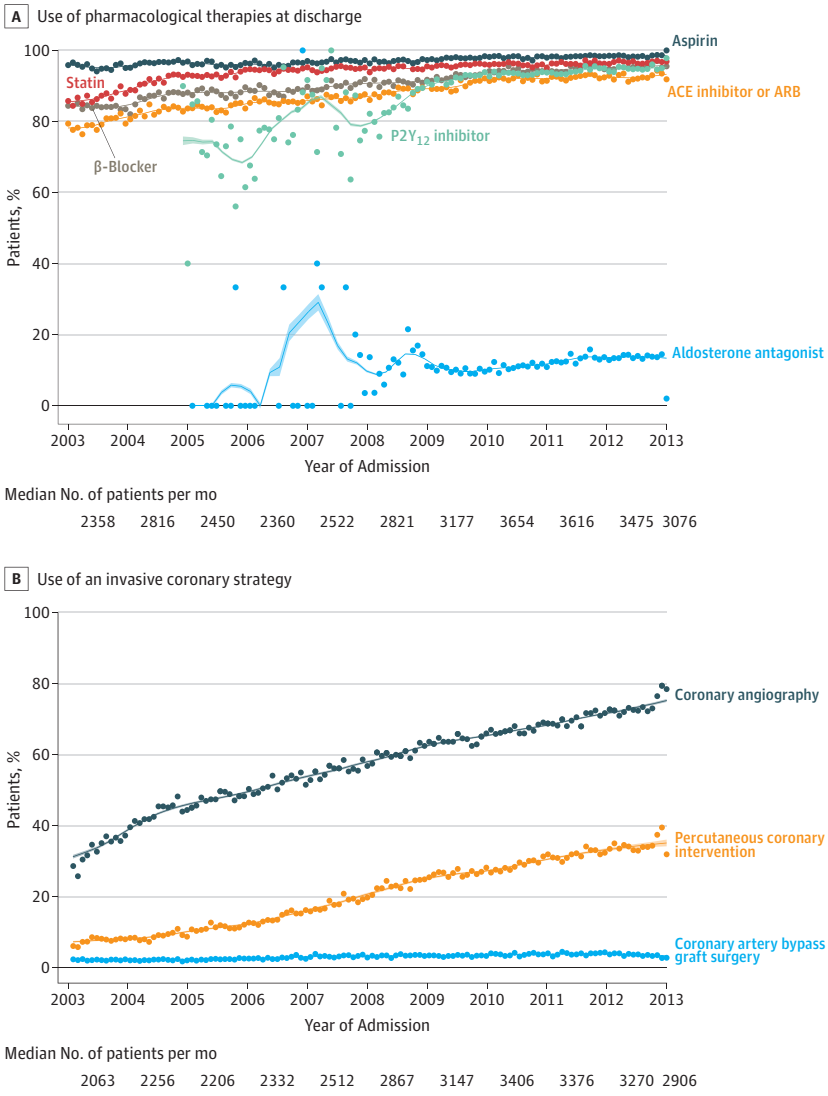
Temporal Trends in Mortality

From 2003-2004 to 2012-2013, unadjusted all-cause mortality rates at 30 days following hospital discharge decreased from 2.6% (95% CI, 2.5%-2.7%) to 2.0% (95% CI, 1.9%-2.1%) and at 180 days from 10.8% (95% CI, 10.5%-10.9%) to 7.6% (95% CI, 7.4%-7.8%). Over the study period, there was an absolute decrease in the adjusted mortality rate of 0.48 per 100 patients (95% CI, 0.25-0.72 per 100), corresponding to an average 3.2% relative improvement in survival per year (hazard ratio [HR], 0.968; 95% CI, 0.966-0.971). **Figure 2** shows that the decline in mortality at 30 and 180 days was greater for patients with NSTEMI who were at intermediate to high GRACE risk than for patients at lowest and low GRACE risk. In-hospital mortality decreased from 10.9% in 2003-2004 to 5.0% in 2012-2013 (difference, 5.9%; 95% CI, 4.8%-6.9%).

Association Between Changing Risk Profile and Improved Outcomes

The magnitude of the temporal survival improvements between 2003 and 2013 was similar when adjusted additively by baseline GRACE risk (difference in absolute mortality rate per 100 [AMR/100], −0.18 [95% CI, −0.21 to −0.16]; HR, 0.975 [95% CI, 0.972-0.977]), sex and socioeconomic status (difference in AMR/100, −0.24 [95% CI, −0.27 to −0.21]; HR, 0.975 [95% CI, 0.973-0.978]), comorbidities (difference in AMR/100, −0.44 [95% CI, −0.49 to −0.39]; HR, 0.973 [95% CI, 0.970-0.976]), and pharmacological therapies prescribed at hospital discharge (difference in AMR/100, −0.53 [95% CI, −0.70 to −0.36]; HR, 0.972 [95% CI, 0.964-0.980]) (**Table 3**). However, when use of an invasive coronary strategy (coronary angiography, PCI, or CABG surgery) was added, the temporal improvements in survival were reversed (difference in AMR/100, 0.59 [95% CI, 0.33-0.86]; HR, 1.02 [95% CI, 1.01-1.03]), suggesting that this variable significantly accounted for at least part of the reduction in NSTEMI mortality between 2003 and 2013 above that of reducing baseline risk, increasing comorbidities, and use of pharmacological therapies. After accounting for use of an invasive coronary strategy, apparent baseline survival worsened by an average of 2.0% per year. This result remained consistent in a sensitivity analysis whereby in-hospital deaths were included (HR, 1.020; 95% CI, 1.004-1.035) (eTable 4 in the Supplement). The finding that the increased use of an invasive coronary strategy was associated with temporal improvements in survival was consistent with mediation, which showed that 88.3% (95% CI, 55.3%-89.6%) and 9.9% (95% CI, 5.6%-10.6%) of this temporal change may be explained by increased use of an invasive coronary strategy and pharmacological therapies, respectively (eAppendix 5 in the Supplement).

Figure 1. Use of Pharmacological Therapies at Hospital Discharge and Use of an Invasive Coronary Strategy per Month, 2003-2013



ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers. Invasive coronary strategies included coronary angiography, percutaneous coronary intervention, and coronary artery bypass graft surgery. Curves were fitted using local polynomial smoothing. Median and range of patients per month for each year are based on complete case data for discharge medications and treatment only. Numbers of patients per month with use of pharmacological therapies ranged from 1092 to 3824 across all time periods. Numbers of patients per month with use of an invasive coronary strategy ranged from 1048 to 3591 across all time periods.

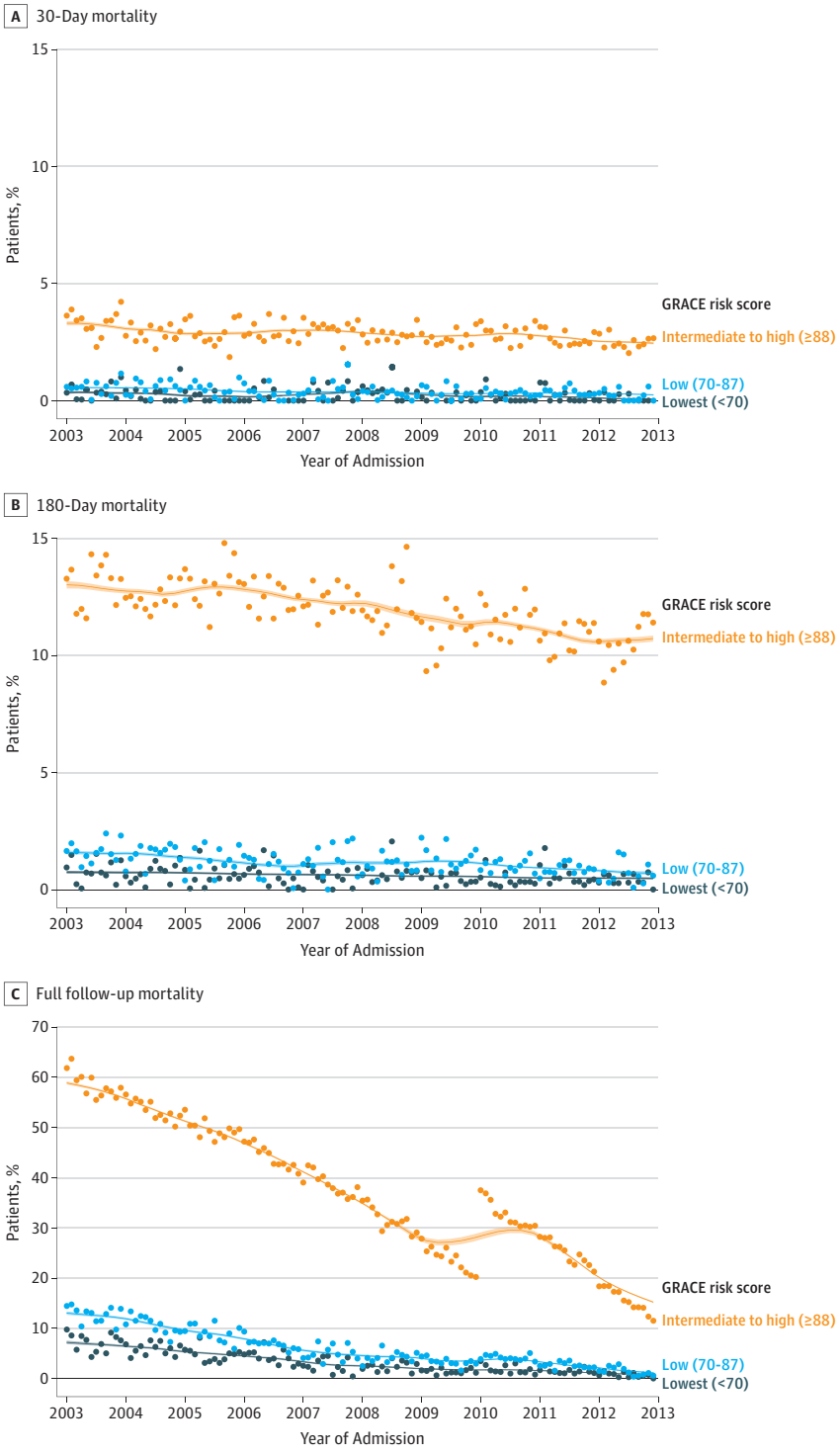
Within the instrumental variable analysis, use of an invasive coronary strategy was associated with a relative decrease in mortality of 46.1% (95% CI, 38.9%-52.0%) (eAppendix 4 in the Supplement). Furthermore, the estimate of the indirect contribution associated with an invasive coronary strategy through the provision of cardiac rehabilitation was small (3.6%; 95% CI, 3.0%-3.7%).

Discussion

In this prospective observational cohort study of the management and outcome of patients with acute coronary syndrome using data for all hospitals in a single health care system, improvements in survival following NSTEMI were associated with use of an invasive coronary strategy. Among nearly 400 000 patients with NSTEMI hospitalized between 2003 and 2013, the temporal reduction in baseline acute coronary syndrome risk, increase in comorbidities, and use of guideline-indicated pharmacological therapies did not fully explain the relative 3.2% yearly improvement in survival. As seen in international registries, these improvements were significantly and independently associated with use of an invasive coronary strategy.[19]

International guidelines recommend use of pharmacological therapies and invasive coronary procedures according to baseline clinical risk.[4,5] This is a result of robust evidence from randomized clinical trials clearly showing that early intervention in moderate- to high-risk patients is associated with better outcomes.[20-22] Consequent evidence from large cohort studies across many countries shows a reduction in rates of death following acute coronary syndrome.[1,2,23,24] Yet there were concerns that improvements in outcomes were due to a lower-risk population. That is, the introduction of a higher-sensitivity

Figure 2. Crude All-Cause Mortality at 30 Days, 180 Days, and Full Follow-up (8.4 Years) per Month by GRACE Risk Score, 2003-2013



Median No. of patients per mo

Lowest	1	1	4	4	136	191	224	262	255	260	243
Low	2	2	5	4	169	242	270	317	347	350	324
Intermediate to high	18	15	34	48	1362	1709	1940	2292	2203	2175	1967

GRACE indicates Global Registry of Acute Coronary Events. Curves were fitted using local polynomial smoothing. Median and range of patients per month for each year are based on complete case data for GRACE risk score only. Numbers of patients per month with lowest, low, and intermediate to high GRACE risk scores ranged from 0 to 301, 0 to 395, and 1 to 2406, respectively, across all time periods.

troponin assay increases the diagnosis of type 1 acute myocardial infarction and has been associated with lower rates of death.[7,25-27] To date, however, studies reporting the decline in acute coronary syndrome mortality have not identified

Table 3. Temporal Trends by Year in Overall Survival Between 2003 and 2013 for Unadjusted and Adjusted Flexible Parametric Survival Models on the Proportional Odds Scale With 5 Degrees of Freedom After Multiple Imputation[a]

Model	Yearly Time Trend in Survival		AIC and BIC Ranges Over 10 Imputed Data Sets	
	Hazard Ratio (95% CI)[b]	Absolute Difference in Hazard, % (95% CI)[c]	AIC Range	BIC Range
Unadjusted yearly time trend	0.968 (0.966-0.971)	−1.81 (−1.95 to −1.67)	771 858.74-771 858.74	771 926.22-771 926.22
Yearly time trend adjusted for				
GRACE score[d]	0.975 (0.972-0.977)	−0.18 (−0.21 to −0.16)	733 789.36-734 273.24	733 876.12-734 360.01
GRACE score, sex, and IMD	0.975 (0.973-0.978)	−0.24 (−0.27 to −0.21)	732 794.96-733 291.51	732 891.37-733 387.91
GRACE score, sex, IMD, and comorbidities[e]	0.973 (0.970-0.976)	−0.44 (−0.49 to −0.39)	709 854.02-710 256.68	710 075.75-710 478.41
GRACE score, sex, IMD, comorbidities, and pharmacological therapies at discharge[f]	0.972 (0.964-0.980)	−0.53 (−0.70 to −0.36)	307 159.16-307 310.51	307 411.15-307 562.5
GRACE score, sex, IMD, comorbidities, pharmacological therapies at discharge, and invasive coronary strategy[g]	1.020 (1.012-1.029)	0.66 (0.38 to 0.93)	291 251.36-291 485.02	291 520.73-291 754.39
GRACE score, sex, IMD, comorbidities, pharmacological therapies at discharge, invasive coronary strategy, and GRACE score × follow-up time interaction (1 degree of freedom)[h]	1.020 (1.012-1.028)	0.59 (0.30 to 0.86)	291 349.97-291 478.24	291 628.02-291 756.29
GRACE score, sex, IMD, comorbidities, pharmacological therapies at discharge, invasive coronary strategy, and GRACE score × follow-up time interaction (2 degrees of freedom)	1.020 (1.012-1.029)	0.59 (0.33 to 0.86)	291 244.2-291 479.6[i]	291 530.95-291 746.35[i]
GRACE score, sex, IMD, comorbidities, pharmacological therapies at discharge, invasive coronary strategy, and GRACE score × follow-up time interaction (3 degrees of freedom)	1.020 (1.012-1.029)	0.59 (0.31 to 0.87)	291 245.6-291 481.05	291 541.03-291 776.49
GRACE score, sex, IMD, comorbidities, pharmacological therapies at discharge, invasive coronary strategy, GRACE score × follow-up time interaction (2 degrees of freedom), and sex × invasive coronary strategy interaction	1.020 (1.008-1.025)	0.49 (0.23 to 0.75)	291 862.21-292 097.55	292 148.96-292 384.29

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; GRACE, Global Registry of Acute Coronary Events; IMD, Index of Multiple Deprivation.

[a] No. of deaths=37 236 (9.6%); 178 451.5 person-years of follow-up.

[b] Hazard ratio of less than 1 indicates improved survival. All $P<.001$.

[c] Absolute difference in hazard per 100 patients between 2003 and 2013.

[d] Age, cardiac arrest, ST-segment deviation, elevated enzymes, systolic blood pressure, heart rate, loop diuretic, and creatinine were not individually included in the modeling process because they were all used in the calculation of the GRACE risk score.

[e] Including history of diabetes, smoking, coronary heart disease, hypertension, myocardial infarction, angina, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, chronic renal failure, congestive heart failure, percutaneous coronary intervention, coronary artery bypass graft surgery, and elevated cholesterol.

[f] Aspirin, β-blockers, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, $P2Y_{12}$ inhibitors, and aldosterone antagonists.

[g] Coronary angiography, percutaneous coronary intervention, or coronary artery bypass graft surgery.

[h] Fitted as a time-varying covariate.

[i] Final chosen model that minimized the AIC/BIC.

a reduction in baseline risk of death.[1] This study is one of the first to our knowledge to describe at scale the high but decreasing baseline acute coronary syndrome risk profile of patients with NSTEMI as well as their increasingly comorbid status.

During the study period, there was a significant reduction in the proportion of patients with NSTEMI who were given an initial diagnosis of chest pain of uncertain cause and a corresponding increase in the number of patients with an initial diagnosis of acute coronary syndrome or probable acute myocardial infarction. It is possible that this was related to the wider and earlier use of more sensitive cardiac biomarkers.[5] Earlier and more accurate diagnosis can lead to more appropriate and timely treatment, including a risk-determined invasive coronary strategy, with resultant improved outcomes.[5,28]

Although the findings were consistent with mediation of the reduction in mortality following NSTEMI by the use of an invasive coronary strategy, the use of pharmacological therapies prescribed at discharge offered little contribution to the change in the full survival effects. However, these findings should not be interpreted to indicate that medical therapies have no role in management of NSTEMI. In the cohort, aspirin, $P2Y_{12}$ inhibitors, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins each had a significant association with improved survival.

The majority (>80%) of patients in this NSTEMI cohort were at intermediate to high risk of death at 180 days. According to international guidelines, those at and above intermediate risk should receive an invasive coronary strategy; however, fewer than half of those with NSTEMI underwent coronary angiography. This finding is in keeping with the well-known risk-treatment paradox whereby the highest frequency of treatments were seen among patients in the lower risk category.[29] Moreover, a series of randomized studies have shown that the

greatest benefit from an invasive coronary strategy was seen among patients with higher-risk NSTEMI.[30-32]

To our knowledge, MINAP is the largest whole-country, single-health-system, prospective observational cohort of the quality of care and clinical outcomes across the spectrum of acute coronary syndrome. It is designed to be representative of the management of acute coronary syndrome in a clinical setting and has standardized criteria for defining case mix and treatments. However, there were limitations.

First, the study was reliant on accurate recording of data. Second, MINAP does not collect all cases of NSTEMI. Third, missing data could have biased the estimates. However, an imputation strategy to minimize bias was implemented following a previous comprehensive study of the nature of missing MINAP data.[33] Fourth, it is probable that other factors beyond the hospital stay (such as drug adherence and primary care visits) may also have influenced survival. Although data on primary care visits or drug adherence were not available, the findings were consistent with mediation analysis showing that only a small proportion of the change in survival was statistically accounted for by referral for cardiac rehabilitation—a multidimensional program that includes exercise programs, dietary advice, and smoking cessation advice if appropriate; drug adherence and psychological counseling; and follow-up for up to 3 months after NSTEMI.

Fifth, all-cause mortality was studied because cause-specific mortality data were not available. This is a limitation because noncardiovascular deaths may not be attributable to NSTEMI care. However, cause-specific mortality data might not always be reliable for cardiovascular-related causes of death. Moreover, most deaths within 180 days of discharge after NSTEMI would likely be cardiovascular related. Sixth, in-hospital deaths were excluded, which could have resulted in survivorship bias. Nonetheless, a sensitivity analysis revealed that exclusion of these cases did not affect the conclusions drawn. Seventh, the definition of an invasive coronary strategy included coronary angiography, which is a diagnostic procedure. Earlier work using MINAP data investigated the association between use of coronary angiography and better outcomes, whereby more than 40% of patients with NSTEMI underwent PCI.[34] Eighth, the results from this study could have been biased by selection of cases and mediated by factors other than those modeled. Sensitivity analyses were undertaken to quantify the potential bias and found that the resultant effect sizes were only modestly reduced. However, there may be some residual confounding from unmeasured factors. This study found odds of death associated with use of an invasive coronary strategy (odds of death, 0.54; 95% CI, 0.48-0.62) comparable with that observed in randomized clinical trial data (odds of death or myocardial infarction, 0.68; 95% CI, 0.56-0.82).[20] Ninth, this observational study cannot demonstrate causation, although adjustment was made for confounding factors based on available information in the study data set and was informed by external information from other studies.

Conclusions

Among patients hospitalized with NSTEMI in England and Wales, improvements in all-cause survival were observed between 2003 and 2013 that were significantly associated with use of an invasive treatment strategy and not entirely related to a decline in baseline clinical risk or increased use of pharmacological therapies.

ARTICLE INFORMATION

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