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Title: Association between time of hospitalization with acute myocardial infarction and in-hospital mortality

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Abstract

Aim

To study the association between time of hospitalization and in-hospital mortality for acute myocardial infarction (AMI).

Methods and Results

Patients admitted with ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) across 243 hospitals in England and Wales between 1st January 2004 and 31st March 2013 were included. The outcome measure was in-hospital mortality. Adjusted odds ratios for in-hospital mortality were estimated across six four-hourly time periods over the 24-hour clock using multilevel logistic regression, inverse-probability weighting propensity score and instrumental variable analysis. Among 615,035 patients (median age 70.0 years, IQR 59.0 - 80.0 years; 406,519 (66.0%) men), there were 52,777 (8.8%) in-hospital deaths. At night, patients with NSTEMI were more frequently co-morbid, and for STEMI had longer symptom-onset-to-reperfusion times. For STEMI, unadjusted in-hospital mortality was highest between 20:00 and 23:59 (four-hour period range 8.4% to 9.9%; OR compared with 00:00 to 03:59 reference 1.13, 95% CI 1.07 to 1.20), and for NSTEMI highest between 12:00 to 15:59 (8.0% to 8.8%; OR compared with 00:00 to 03:59 reference 1.07, 95% CI 1.03 to 1.12). However, these differences were only apparent in the earlier years of the study, and were attenuated by adjustment for demographics, co-morbidities and clinical presentation. Differences were not statistically significant after adjustment for acute clinical treatment provided.

Conclusions

There is little evidence to support an association between time of hospitalization and in-hospital mortality for acute myocardial infarction; variation in in-hospital mortality may be explained by case mix and the use of treatments.

Introduction

Hospital mortality rates for a number of medical conditions may be associated with the time of day at which at a patient presents to hospital and, in part, determined by their clinical presentation and extent of care received.[1-10] For example, thrombolysis times for stroke vary diurnally, and this is associated with higher rates of death.[10] In patients with acute myocardial infarction (AMI), admission to hospital at the weekend is associated with higher mortality and lower use of invasive coronary procedures.[6,11] Such reports have the potential to influence policy and, therefore, change how clinical practice may be provided across all medical disciplines.[12,13] To our knowledge, however, there are no studies assessing time of day effects on in-hospital mortality for patients with AMI.

Notably, there are few data sources which would enable a detailed evaluation of the impact of out-of-hour presentation and guideline-indicated therapies on mortality for AMI. The Myocardial Ischaemia National Audit Project (MINAP) is a whole country acute coronary syndrome registry,[14] 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 over 15 years, and represents an ideal conduit to undertake patient- and treatment-specific studies.[14-16] Thus, we aimed to use data from MINAP to investigate whether time of hospitalization with AMI among 615,035 patients was associated with in-hospital mortality, and if so, the magnitude of the relationship between this, treatment, and patient factors.

Methods

Data and patients

Participation in MINAP is 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 obligatory annual data validation exercise. Further details of MINAP have been published elsewhere.[14] The analytical cohort, derived from all patients with AMI admitted to hospital between 1st April, 2004 and 31st March, 2013, included 615,035 patients from 243 hospitals (supplementary eFigure 1). Patients were eligible for the study if they were aged 18 years or over with a diagnosis of ST-elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI). The diagnosis was the final diagnosis as 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 for the diagnoses of AMI.[17]

Study variables

We included demographic factors (age, sex, year of hospital admission), past medical history (coronary artery bypass grafting (CABG) surgery, percutaneous coronary intervention (PCI), chronic heart failure, diabetes mellitus, hypertension, hyperlipidaemia, previous myocardial infarction and smoking status), clinical presentation (heart rate, systolic blood pressure, troponin concentration, serum creatinine, cardiac arrest, elevated cardiac biomarkers and

ST-segment depression on the ECG), the type of hospital admission (ambulance versus self-presented to hospital), investigations (ECG, coronary angiography), acute treatments (aspirin, thrombolysis or primary PCI for STEMI) and medications already taken or prescribed at time of hospitalization (aspirin, angiotensin converting enzyme inhibitors (ACEi)/angiotensin-receptor blockers (ARB), β blockers, and HMG Co-A reductase inhibitors (statins). Time of hospital admission was defined as the time of arrival of the ambulance at the hospital, or the accident and emergency department registration time for patients who self-presented to the department. It was categorised into six four-hour periods over the 24-hour clock (00:00 to 03:59; 04:00 to 07:59, 08:00 to 11:59, 12:00 to 15:59, 16:00 to 19:59, 20:00 to 23:59),[10] using 00:00-03:59 as the reference category representing the middle of the night. Time of symptom onset was also categorised as for time of hospital admission. Night-time was defined as 20:00 to 07:59, and day-time from 08:00 to 19:59. For each hospital we calculated its average annual volume and socioeconomic deprivation level (mean Townsend score) across all patients recorded in MINAP as attending that hospital during the study period.

Statistical Analyses

Baseline characteristics were described using numbers and percentages (with associated 95% confidence intervals [CI]) for categorical data, and medians and interquartile ranges (IQR) for continuous variables. We quantified the magnitude of variation in patient and treatment variables between time periods by calculating the coefficient of variation, CoV

(the ratio of the SD to the mean, multiplied by 100), and its confidence interval.[18, 19] CoV was used because it allows the dispersion of variables with different means to be compared.

The outcome was death in hospital due to any cause. Initially, the unadjusted association of four-hour periods with in-hospital mortality was calculated in a univariate logistic regression model, and results presented as odds ratios (OR, 95% CI). Subsequently, multilevel logistic models (with random intercepts for hospitals) were incrementally adjusted for 1) case mix (age, sex) and year of hospitalisation, 2) co-morbidities (CABG surgery, chronic heart failure, diabetes mellitus, hypertension, hyperlipidaemia, myocardial infarction, PCI) and smoking status, 3) clinical presentation (systolic blood pressure, heart rate, troponin I and T, creatinine, cardiac arrest, cardiac enzyme positive, and ST-segment depression), 4) acute treatments (ambulance transportation to hospital, thrombolysis, primary PCI, coronary angiography performed in hospital, pre-hospital ECG, and any ECG), 5) hospital medications taken at time of or pre hospitalization (aspirin, ACE inhibitor/ARB, beta blocker and statin). The average annual volume and socioeconomic deprivation level were fitted in the final models.

Multiple imputation by chained equations was used to produce 10 imputed data sets to minimize bias caused by missing data (Supplementary eTable 3). Pooled estimates and accompanying 95% CIs were generated according to Rubin's rules. Improvements in model fit at each stage were determined by minimizing the Akaike and Bayesian information criteria ranges across the 10 imputed datasets. Multiply imputed estimates were compared

with those from complete case data. We investigated whether the order of covariates in the multilevel model influenced the results by altering the order of covariate blocks entering or leaving the multilevel models through forward and backward model selection. The likelihood ratio test (LRT) was used to assess the significance of time of hospitalization in each model. To assess the association between daytime and night-time hospitalization and in-hospital mortality, inverse-probability weighting propensity score analysis was used to match the characteristics and treatments for patients admitted at daytime and night-time (supplementary eSection 3). To assess the potential of selection bias, an instrumental variable analysis was performed to include the hospital rates of guideline-indicated treatments as instrumental variables (supplementary eSection 3). Finally, sensitivity analysis was performed to investigate whether the time of symptom onset (rather than time of hospitalisation), and whether day time defined as 09:00 to 16:59 (rather than 08:00 to 19:59) altered the results (supplementary eSection 4).

All tests were 2-sided, and statistical significance was considered $p < 0.05$. Statistical analyses were performed in R version 3.3.1 (https://cran.r-project.org/).

Results

Among 615,035 patients with AMI (median age 70.0 years, IQR 59.0-80.0 years; 406,519 (66.0%) men), there were 52,777 (8.8%) in-hospital deaths. Patients were co-morbid: almost half had a history of hypertension, and nearly a quarter had diabetes, hyperlipidaemia or previous myocardial infarction (Table 1). The most frequent time of hospitalization was 12:00 to 15:59 for STEMI, with 59,867 (23.8%) STEMI admissions within this time interval, and 08:00 to 11:59 for NSTEMI, with 86,583 (23.8%) NSTEMI admissions (Table 1). In general, admission systolic blood pressure, heart rate and creatinine did not vary over the 24-hour clock (CoV between 0.9 and 2.0, supplementary eTables 1-2).

STEMI

For STEMI, the proportion of patients with diabetes (range across all time periods 13.5% to 15.2%), previous PCI (5.1% to 6.0%), previous myocardial infarction (11.9% to 14.1%) and current smokers (65.1% to 69.5%) was highest at 00:00-03:59 compared with patients hospitalised during other time periods of the day; the greatest variation in co-morbidities being for patients with previous CABG surgery (CoV 8.9) (Supplementary eTable 1). For STEMI, the use of reperfusion was high and more frequent at night between 00:00-07:59 (range across all time periods 73.6% to 80.9%, CoV 3.7).

NSTEMI

For NSTEMI, at night patients more frequently had chronic heart failure (range across all time periods 6.7% to 8.8%), diabetes (21.1% to 25.4%), CABG surgery (6.9% to 8.6%) and previous myocardial infarction (23.2% to 30.5%), the greatest variation in co-morbidities being for patients with previous myocardial infarction (CoV 12.4, supplementary eTable 2). For NSTEMI, hospitalization via ambulance demonstrated wide variation, being more frequent at night (minimum 57.4% at 16:00 to 19:59, maximum 77.8% at 00:00 to 03:59, CoV 11.2). Similarly, electrocardiographic ST-depression (23.9% to 29.6%) was more frequent at night. The proportion of NSTEMI with cardiac arrest was highest in the evening and lowest during the early hours (minimum 0.9% at 00:00 to 03:59, maximum 1.5% at 20:00 to 23:59). Coronary angiography performed during the hospital stay was more frequent among NSTEMI who presented between 16:00 and 19:59 (41.9%).

STEMI versus NSTEMI

Overall, the use of an ambulance to attend hospital was high(64.8% to 70.7% for STEMI, 57.4% to 77.8% for NSTEMI), and varied less over the 24-hour clock for STEMI(CoV 8.8) than NSTEMI(CoV 24.7)(supplementary eTables 1-2). An ECG was performed less frequently at night for NSTEMI(74.8% to 77.3%), whereas for STEMI it varied little(78.2% to 79.3%). The proportion of patients who did not receive aspirin on admission to hospital was stable throughout the 24-hour clock, but higher for NSTEMI(6.0% to 6.4%) than STEMI(2.4% to 2.9%).

In-hospital mortality

For STEMI, unadjusted in-hospital mortality rates were the highest between 20:00 and 23:59 (all time periods range 8.4% to 9.9%; OR compared with 00:00 to 03:59 reference 1.13, 95% CI 1.07 to 1.20), and for NSTEMI between 12:00 to 15:59 (8.0% to 8.8%; OR compared with 00:00 to 03:59 reference 1.07, 95% CI 1.03 to 1.12). Unadjusted in-hospital mortality rates declined over the study period (for STEMI from 12.2%, 95% CI 11.9% to 12.5% in 2004/5 to 7.3%, 95% CI 7.1% to 7.6% in 2012/13; for NSTEMI from 12.9%, 95% CI 12.6% to 13.1% in 2004/5 to 5.8 %, 95% CI 5.6% to 5.9% in 2012/13) as did their variation over the 24-hour clock (for STEMI, from CoV 7.2 in 2004/5 to 5.4 in 2012/13; for NSTEMI, from CoV 6.2 in 2004/2005 to 3.1 in 2012/2013) (Figure 1).

For STEMI, adjustment for demographics, co-morbidities and clinical presentation resulted in no association between the time of hospitalization and in-hospital mortality for three of the five time periods (Table 2, Figure 2). With further adjustment for the use of acute treatments, there was no association between the time of hospitalization with STEMI and in-hospital mortality across the 24-hour clock. For NSTEMI, adjustment for demographics, co-morbidities and clinical presentation resulted in no association between the time of hospitalization and in-hospital mortality for two of the five time periods (Table 2, Figure 2). With further adjustments for the use of acute treatments as well as hospital medications taken at time of or pre- hospitalisation, there was no association between the time of hospitalization with NSTEMI and in-hospital mortality across the 24-hour clock. For each of STEMI and NSTEMI full adjustment for demographics, co-morbidities, clinical presentation,

treatments and medications resulted in no significant association between the time of presentation to hospital and in-hospital death (STEMI LRT p-value 0.062; NSTEMI LRT p-value 0.091) (Table 2, supplementary eTables 6-7).

The direction and magnitude of the unadjusted and adjusted estimated for the complete case analysis were consistent with the imputed data analysis (Supplementary eTable 4). Similarly, the order of covariates entering the model did not influence the final result (Supplementary eTable 5).

Propensity score and instrumental variable analysis

Propensity score analysis showed that for 2004-2013 in-hospital mortality was lower for STEMI hospitalised during the day (08:00-19:59, OR: 0.95, 95% CI: 0.93 to 0.97) compared with night (20:00-07:59). However, for the period 2008-2013 in-hospital mortality was not significantly different between daytime and night-time hospitalization (OR: 0.97, 95% CI: 0.94 to 1.01) (Supplementary eTable 8). The instrumental variable analysis showed the same trend and magnitude of association between in-hospital mortality and time of hospitalisation (Supplementary eTable 9). For NSTEMI, both propensity score analysis and instrumental variable analysis found no association between time of hospitalisation and in-hospital mortality for either the whole or the recent period (Supplementary tables 8-9). The same trend and magnitude of association was evident in both propensity score and instrumental variable analyses when day and night were redefined as 09:00-16:59 and 17:00-08:59 (Supplementary eTables 10-11).

Sensitivity analysis

A significant association between in-hospital mortality and time of symptom onset or day time defined as 09:00 to 16:59 (rather than 08:00 to 19:59) was observed in the period 2004-2007, but not in the period 2008-2013 (supplementary eSection 4, and eTables 14 and 17).

Discussion

In this study of over 600,000 patients hospitalized in England and Wales with AMI, at night patients more frequently were co-morbid, and for STEMI had longer symptom-to-reperfusion times. Although in-hospital mortality varied throughout the 24-hour clock and was higher for STEMI, the variation was small, decreased over time, and did not show a clear nocturnal peak. We found that adjustments for case mix removed much, but not all of the variation in mortality by time of admission, which was non-significant after further adjustment for the use of treatments. As such, there is little evidence to support an association between time of hospitalization and in-hospital mortality for acute myocardial infarction, and variation in in-hospital mortality may be explained by case mix and the use of treatments.

The recent literature highlights out-of-hour effects for several medical conditions, yet debate arises as to whether this may be due to reduced staffing, infrastructure and delivery of healthcare, or a more unwell patient population who present to hospital out of normal working hours.[1,2,20] Earlier work found that hospitalisation at the weekend with AMI was associated with higher mortality and lower use of invasive coronary procedures.[11] Our study extends this work to time-of-day effects, showing that in the later years of study there was minimal variation in the delivery of care and in-hospital mortality over the 24 hour clock for AMI.

Uniform and standardised provision of evidence-based care is associated with improved clinical outcomes for AMI.[21-24] For patients with NSTEMI, temporal improvements in survival were explained by an increase in the uptake of an invasive coronary strategy,[15] and for STEMI associated with the use of evidence-based pharmacotherapies and primary PCI.[25] The implementation of a national primary PCI programme has enabled 24/7 availability of guideline-recommended treatments in the UK,[15,26] although there remains variation across Europe.[27,28] Over the study period we found a decrease in absolute mortality, also noted by others,[23,29,30] but also a reduction in the variation in mortality associated with time of admission. Extrapolation of these findings suggests that for common medical emergencies, hospital-based population-wide delivery of high quality care is achievable and, if implemented, would contribute to temporal reductions and less variation in mortality.

However, we also noticed opportunities where care quality could be enhanced. For STEMI, patients had longer symptom-to-reperfusion times at night, and less frequently received primary PCI suggesting that there are potentially modifiable delays to the seeking, access and provision of care. Equally, there was evidence for variation in coronary angiography according to when a patient presented to hospital with NSTEMI – and after adjustment for this, treatments and case mix, any variation in in-hospital was removed. Thus, although case mix accounts for some mortality variation, more uniform delivery of invasive coronary procedures could further reduce mortality rates from AMI.

This study has a number of strengths. In the UK, AMI data are collected from all acute hospitals, which includes demographic, co-morbidity, treatments and mortality data,[14] thereby allowing a sufficiently detailed time series analysis. Moreover, AMI is an ideal medical condition to investigate potential out-of-hour effects – given that it is a medical emergency with associated immediate risk of mortality and there are international guideline recommended treatments for STEMI and NSTEMI[31,32] which, if implemented, reduce mortality.[15, 30] Although MINAP is a single-health-system prospective observational cohort of AMI (designed to be representative of a population), there are limitations that must be considered. The study was reliant on accurate data recording. Not all cases of NSTEMI are recorded in MINAP,[33] and it is possible that there was selection bias in recording of patients according to time of hospitalization. We did not have access to more recent MINAP data, and due to General Data Protection Regulations were not permitted day of the week data. The use of high-sensitivity troponin assays may have contributed to an increased proportion of AMI in later years that may not previously have been diagnosed as such.[34, 35] However, this is unlikely to have had an effect for patients with STEMI in whom the findings were concordant with NSTEMI. In the UK about 60% of patients with out of hospital cardiac arrest have a cardiac aetiology,[36] and survivorship bias is possible. Nonetheless, this study was designed to investigate whether out-of-hours hospital admission (not pre-hospital cases) with AMI was associated with an increased mortality. To that effect, we recognise that circadian rhythms in platelet aggregation contribute to sudden cardiac death.[37] Pre-hospital delays to seeking help may have varied by time of hospitalization; even so, a sensitivity analysis by time of symptom onset found results consistent with the primary analysis of time of hospitalisation. We report all-cause rather than cardiovascular-specific

mortality, but for in-hospital mortality following AMI this is unlikely to affect the conclusions drawn.[38] Hospital facility and infrastructure factors have been shown to be significantly associated with the nationwide diffusion of primary PCI in the UK. Whilst we accounted for hospital level variables within the limitations of the dataset using propensity score analysis and instrumental variable analysis, residual confounding may exist including factors such as seniority of staff, staffing ratios and access to diagnostics, which are not recorded in MINAP. We acknowledge that such 'level 2 covariates' are potentially important factors in health service delivery and any associated outcomes. Finally, this is an observational study, and as such cannot demonstrate causation.

In conclusion, for patients hospitalized in England and Wales with AMI, there is little evidence to support an association between time of hospitalization and in-hospital mortality for acute myocardial infarction, in particular that of increased mortality out of hours. Moreover, any variation in in-hospital mortality associated with time of hospitalization was removed following adjustment for case mix and the use of treatments.

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Conflicts of interest

KAAF reports: grants and personal fees from Bayer, Janssen and AstraZeneca; personal fees from Sanofi, Regeneron and Verseon outside the submitted work. AT reports a travel grant from NovoNordisk outside the submitted work. CPG reports personal fees from AstraZeneca, Bristol Myer Squibb, Novartis and Vifor Pharma; travel grant from Bayer outside the submitted work. JW, MH, TBD, CW, PL, and MDB have nothing to disclose.

Ethical approval

The study was approved by the MINAP Academic Group.

Data sharing: Details of how to obtain additional data from the study (such as technical appendix, statistical programming) are available from the corresponding author at c.p.gale@leeds.ac.uk.

References

1. Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. N Engl J Med 2001;**345**(9):663-8.
2. Freemantle N, Ray D, McNulty D, Rosser D, Bennett S, Keogh BE, Pagano D. Increased mortality associated with weekend hospital admission: a case for expanded seven day services? BMJ 2015;**351**:h4596.
3. Sorita A, Ahmed A, Starr SR, Thompson KM, Reed DA, Prokop L, Shah ND, Murad MH, Ting HH. Off-hour presentation and outcomes in patients with acute myocardial infarction: systematic review and meta-analysis. BMJ 2014;**348**:f7393.
4. Ruiz M, Bottle A, Aylin PP. The Global Comparators project: international comparison of 30-day in-hospital mortality by day of the week. BMJ Qual Saf 2015;**24**(8):492-504.
5. Meacock R, Anselmi L, Kristensen SR, Doran T, Sutton M. Higher mortality rates amongst emergency patients admitted to hospital at weekends reflect a lower probability of admission. J Health Serv Res Policy 2017;**22**(1):12-19.
6. Kwok CS, Al-Dokheal M, Aldaham S, Rushton C, Butler R, Kinnaird T, Zaman A, Zaman MJ, Timmis A, Mamas MA. Weekend effect in acute coronary syndrome: A meta-analysis of observational studies. Eur Heart J Acute Cardiovasc Care 2018:2048872618762634.
7. McKee M. The weekend effect: now you see it, now you don't. BMJ 2016;**353**:i2750.
8. Aylin P. Making sense of the evidence for the "weekend effect". BMJ 2015;**351**:h4652.
9. Bray BD, Steventon A. What have we learnt after 15 years of research into the 'weekend effect'? BMJ Qual Saf 2017;**26**(8):607-610.
10. Bray BD, Cloud GC, James MA, Hemingway H, Paley L, Stewart K, Tyrrell PJ, Wolfe CD, Rudd AG, collaboration S. Weekly variation in health-care quality by day and time of admission: a nationwide, registry-based, prospective cohort study of acute stroke care. Lancet 2016;**388**(10040):170-7.
11. Kostis WJ, Demissie K, Marcella SW, Shao YH, Wilson AC, Moreyra AE, Myocardial Infarction Data Acquisition System Study G. Weekend versus weekday admission and mortality from myocardial infarction. N Engl J Med 2007;**356**(11):1099-109.
12. Montano N, Papacci F, Cioni B, Di Bonaventura R, Meglio M. What is the best treatment of drug-resistant trigeminal neuralgia in patients affected by multiple sclerosis? A literature analysis of surgical procedures. Clin Neurol Neurosurg 2013;**115**(5):567-72.
13. NHS England. Five year forward view. London. https://www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf (accessed 12 Sep 2018) 2014.
14. Herrett E, Smeeth L, Walker L, Weston C, Group MA. The Myocardial Ischaemia National Audit Project (MINAP). Heart 2010;**96**(16):1264-7.
15. Hall M, Dondo TB, Yan AT, Goodman SG, Bueno H, Chew DP, Brieger D, Timmis A, Batin PD, Deanfield JE, Hemingway H, Fox KA, Gale CP. Association of Clinical Factors and Therapeutic Strategies With Improvements in Survival Following Non-ST-Elevation Myocardial Infarction, 2003-2013. JAMA 2016;**316**(10):1073-82.
16. Simms AD, Weston CF, West RM, Hall AS, Batin PD, Timmis A, Hemingway H, Fox K, Gale CP. Mortality and missed opportunities along the pathway of care for ST-elevation myocardial infarction: a national cohort study. Eur Heart J Acute Cardiovasc Care 2015;**4**(3):241-53.
17. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of

Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;**36**(3):959-69.
18. Reed GF, Lynn F, Meade BD. Use of coefficient of variation in assessing variability of quantitative assays. Clin Diagn Lab Immunol 2002;**9**(6):1235-9.
19. Vangel MG. Confidence Intervals for a Normal Coefficient of Variation. The American Statistician 1996;**50**(1):21-26.
20. Lilford RJ, Chen Y-F. The ubiquitous weekend effect: moving past proving it exists to clarifying what causes it. BMJ Quality & Safety 2015;**24**(8):480-482.
21. Gale CP, Allan V, Cattle BA, Hall AS, West RM, Timmis A, Gray HH, Deanfield J, Fox KAA, Feltbower R. Trends in hospital treatments, including revascularisation, following acute myocardial infarction, 2003–2010: a multilevel and relative survival analysis for the National Institute for Cardiovascular Outcomes Research (NICOR). Heart 2014;**100**(7):582-589.
22. Gale CP, Cattle BA, Woolston A, Baxter PD, West TH, Simms AD, Blaxill J, Greenwood DC, Fox KAA, West RM. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003–2010. European Heart Journal 2012;**33**(5):630-639.
23. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA, Jr., Granger CB, Flather MD, Budaj A, Quill A, Gore JM. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. JAMA 2007;**297**(17):1892-900.
24. Noman A, Ahmed JM, Spyridopoulos I, Bagnall A, Egred M. Mortality outcome of out-of-hours primary percutaneous coronary intervention in the current era. Eur Heart J 2012;**33**(24):3046-53.
25. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, James S, Kellerth T, Lindahl B, Ravn-Fischer A, Rydberg E, Yndigegn T, Jernberg T. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. Eur Heart J 2017;**38**(41):3056-3065.
26. Hall M, Laut K, Dondo TB, Alabas OA, Brogan RA, Gutacker N, Cookson R, Norman P, Timmis A, de Belder M, Ludman PF, Gale CP, National Institute for Cardiovascular Outcomes R. Patient and hospital determinants of primary percutaneous coronary intervention in England, 2003-2013. Heart 2016.
27. Widimsky P, Kristensen SD. Stent for Life Initiative: where are we standing and where are we going? European Heart Journal. Acute Cardiovascular Care 2012;**1**(1):48-49.
28. Andre R, Bongard V, Elosua R, Kirchberger I, Farmakis D, Hakkinen U, Fusco D, Torre M, Garel P, Araujo C, Meisinger C, Lekakis J, Malmivaara A, Dovali M, Pereira M, Marrugat J, Ferrieres J. International differences in acute coronary syndrome patients' baseline characteristics, clinical management and outcomes in Western Europe: the EURHOBOP study. Heart 2014;**100**(15):1201-7.
29. 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**(6):779-85.
30. Gale CP, Cattle BA, Woolston A, Baxter PD, West TH, Simms AD, Blaxill J, Greenwood DC, Fox KA, West RM. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003-2010. Eur Heart J 2012;**33**(5):630-9.

31. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevationThe Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal 2018;**39**(2):119-177.
32. Roffi M, Patrono C, Collet J-P, 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 elevationTask Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). European Heart Journal 2016;**37**(3):267-315.
33. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T, Timmis A, Hemingway H. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ : British Medical Journal 2013;**346**.
34. Eggers KM, Lindahl B, Melki D, Jernberg T. Consequences of implementing a cardiac troponin assay with improved sensitivity at Swedish coronary care units: an analysis from the SWEDEHEART registry. European Heart Journal 2016;**37**(30):2417-2424.
35. Eggers KM, Jernberg T, Lindahl B. High-sensitivity cardiac troponin T, left ventricular function, and outcome in non–ST elevation acute coronary syndrome. American Heart Journal 2018;**197**:70-76.
36. Hawkes C, Booth S, Ji C, Brace-McDonnell SJ, Whittington A, Mapstone J, Cooke MW, Deakin CD, Gale CP, Fothergill R, Nolan JP, Rees N, Soar J, Siriwardena AN, Brown TP, Perkins GD. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. Resuscitation 2017;**110**:133-140.
37. Brezinski DA, Tofler GH, Muller JE, Pohjola-Sintonen S, Willich SN, Schafer AI, Czeisler CA, Williams GH. Morning increase in platelet aggregability. Association with assumption of the upright posture. Circulation 1988;**78**(1):35-40.
38. 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**(2):85-91.

Figure legends

Figure 1. Crude in-hospital mortality rates by time of admission to hospital for STEMI and NSTEMI, stratified by biennial year of hospitalization.

Footnote: Dots represent in-hospital mortality rates per every 10 minutes of time of admission to hospital. Time data are fitted using cubic polynomials with trigonometric transformation to the time of hospitalization to ensure that the mortality at 00.05 and 23.55 is just ten minutes apart

Figure 2. Unadjusted and multivariable adjusted risk of in-hospital mortality according to time period of admission to hospital for STEMI and NSTEMI.

Take-home figure: Adjusted odds ratios for in-hospital mortality by time of hospitalisation, showing no significant difference across the six time-intervals of the 24-hour clock