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THE EFFECT OF HOSPITAL ADMISSION DAY ON MORTALITY FROM MYOCARDIAL INFARCTION IN ENGLAND: A NATIONAL RECORD LINKAGE STUDY

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ABSTRACT

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Background: There are concerns that quality of medical care and availability of medical procedures may vary between weekdays and weekends. Acute myocardial infarction (AMI) is a life-threatening condition, which requires urgent specialized care and, potentially, invasive procedures. The specialized care and invasive procedures may not be equivalently available on weekends and weekdays, which may affect mortality from AMI. We tested the hypothesis that case fatality rates (CFRs) within 30 days from hospital admission for AMI did not differ between weekend and weekday admissions.

Methods: The National Health Service (NHS) provides health-care for all residents of England. We used datasets of English National Hospital Episode Statistics (HES) and mortality records supplied by, respectively, the NHS Information Centre and the Office for National Statistics. Linkage between the datasets was done using encrypted values of the unique HES identifier and of the unique NHS number supplemented with encrypted values of the patients' date of birth and postcode. We used the hospital admission and mortality data for England from 1999 to 2011 to calculate 30-day CFRs. We used chi-squared statistics to compare categorical variables and to test for statistical significance. We set the level of statistical significance at 0.01. Logistic regression analysis was used to quantify the effects of age, year of admission and day of the week of admission on the CFR. Statistical tests were carried out in SPSS Statistics version 20 for Windows.

Results: The study comprised 541,165 people. In patients admitted with AMI, CFRs for weekday and weekend admissions did not differ significantly: they were 11.5%

(45,629/397,173) on weekdays and 11.5% (16,566/143,992) on weekends, P-value=0.602. The 30-day CFR for all patients admitted to hospitals was 11.5%.

Conclusion: Overall, there was no evidence of a "weekend effect" on CFRs in patients hospitalized with AMI in England in 1999-2011. This indicates that the delivery of NHS care, at least in respect of CFRs for AMI in the period studied, was as effective for weekend as for weekday admissions.

Keywords: myocardial infarction; acute myocardial infarction; weekend-effect; weekend admission.

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LIST OF ABBREVIATIONS

ACEIs	Angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
ARBs	Angiotensin II receptor blockers
BBs	Beta-blockers
BMI	Body mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CFRs	Case fatality rates
CVD	Cardiovascular diseases
DAPT	Dual antiplatelet therapy
ECG	Electrocardiography
HES	Hospital Episode Statistics
LV	Left ventricular
MI	Myocardial infarction
MMP	Matrix-metalloproteinase
MRA	Mineralocorticoid receptor antagonists
NHS	National Health Service
NSTEMI	Non-ST elevation MI
OR	Odds ratio
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
STEMI	ST elevation MI

1. INTRODUCTION

Cardiovascular diseases are the leading cause of death in the world. Ischemic heart disease remains the world's biggest killer, accounting for 16% of the world's total deaths. The number of deaths for this disease has demonstrated the largest increase since 2000, rising by more than 2 million to 8.9 million deaths in 2019 (World Health Organization, 2020).

Among those with heart disease, the major contributor to mortality is acute myocardial infarction (MI). Patients with MI account for a large proportion of emergency hospital admissions (Purdy, Griffin, Salisbury, & Sharp, 2011) and are frequently admitted during weekends (Aylin, Yunus, Bottle, Majeed, & Bell, 2010). It is possible that during weekends hospital resources are limited. Decrease in hospital staff, and lack of senior physicians can lead to an increase in workload for a doctor and a time spent for one patient. As a result, specialized care and invasive procedures may not be equivalently available throughout the week. Indeed, earlier research have expressed concerns that the quality of medical care may vary between weekdays and weekends (Bell & Redelmeier, 2001; Clarke et al., 2010; Freemantle et al., 2015; Hong, Kang, & Lee, 2010; Kostis et al., 2007). However, studies about the "weekend-effect" are prone to confounders such as mixing the cases with larger proportion of critically ill patients admitted to hospital during the weekend with the potential to influence mortality rates values.

The existing evidence on the increased mortality occurring after hospital admission during the weekend is controversial. While the majority of studies suggest the existence of the "weekend effect", meaning that patients hospitalized on weekends tend to have higher mortality rates than those hospitalized during weekdays, there is also evidence to the contrary (Jneid et al., 2008; Kim et al., 2014).

Considering the acute and severe nature of the condition, any delays with referral to a healthcare facility might result in significant morbidity or even death. Given the universally high incidence of acute myocardial infarction, on a global scale the potential morbidity and mortality attributable to delay in healthcare access are staggering. This master's thesis studied the case fatality rates (CFRs) within 30 days from hospital admission for acute myocardial infarction and whether there is a difference between weekend and weekday admissions.

2. LITERATURE REVIEW

2.1. Overview

2.1.1. <u>Definition and classification</u>

Previously, there was a consensus to define myocardial infarction (MI) based on the symptoms, abnormal electrocardiography (ECG) changes and cardiac enzymes (Thygesen et al., 2012). In recent years, however, with the development of more sensitive diagnostic imaging techniques and tissue-specific biomarkers, it became possible to detect very small amounts of myocardial injury or necrosis. Apart from that, the improvement of the quality of treatment of patients with MI has led to minimizing the severity of myocardial injury or necrosis yet with little or no change of the clinical presentation of the disease. Considering this, it became evident that a new definition of MI was necessary (Thygesen et al., 2012).

In 2000, a new definition was presented which defined MI as any necrosis in the setting of myocardial ischemia (Thygesen et al., 2007). In the following years, another addition to the definition had been made which considered different conditions that might have led to an MI (Myocardial infarction redefined--a consensus document of the joint European society of cardiology/American college of cardiology committee for the redefinition of myocardial infarction 2000). However, continuous development of even more advanced diagnostic techniques and procedures required further adjustments to the definition of MI. With the invention of such procedures as percutaneous coronary intervention (PCI) which might itself lead to some extent of myocardial necrosis, the necessity of even more precise definition had become evident. Currently, the term acute myocardial infarction (AMI) should be used for an event of myocardial necrosis caused by an unstable ischemic syndrome (Anderson, J. L. & Morrow, 2017b).

AMI is classified according to the changes evident on ECG to an ST elevation MI (STEMI), where the elevation of ST-segment can be observed in two contiguous leads, and non-ST elevation MI (NSTEMI) with no elevation of ST-segment evident on ECG. In addition to these categories, MI is divided into six types (Thygesen et al., 2012):

a) Type 1 – Spontaneous Myocardial Infarction. It occurs due to atherosclerosis of the coronary vessels.
b) Type 2 – Myocardial Infarction Secondary to an Ischemic Imbalance. This is the type where myocardial necrosis is caused by the condition other than coronary artery disease (CAD) which leads to an imbalance between myocardial oxygen supply and/or demand. The examples may include MI caused by coronary vasospasm, endothelial dysfunction or MI in critically ill patients or patients undergoing major non-cardiac surgery (Thygesen et al., 2012).
c) Type 3 – Cardiac Death Due to Myocardial Infarction. Those patients who suffer cardiac death without the opportunity (due to fast progression) for ECG or biomarkers confirmation of myocardial necrosis fall into this category.
d) Type 4a – Myocardial Infarction Related to PCI. This type comprises MI that are associated with PCI.
e) Type 4b – Myocardial Infarction Related to Stent Thrombosis. Infarction that is due to thrombosis of a coronary stent represents this category.
f) Type 5 – Myocardial Infarction Related to Coronary Artery Bypass Grafting. This type includes MI that are associated with coronary artery bypass grafting (CABG). This is the procedure where either internal thoracic artery or great saphenous vein from the leg is used to restore normal blood flow to an obstructed coronary artery.

2.1.2. Etiology

The traditional belief was that parts of coronary artery affected by atherosclerosis would undergo progressive stenosis which would narrow the lumen of the vessel to such an extent that a platelet thrombus could cause the complete occlusion of the vessel. If it happens and the blood flow is arrested, ST-segment elevation myocardial infarction develops. If the occlusion of the vessel is incomplete or obstruction of blood flow is transient, non-ST elevation MI happens. However, numerous angiographic studies had been conducted which showed that the size of the atheromatous plaque did not cause such stenosis of the vessel that would obstruct blood flow. In addition, diagnostic angiographic techniques that were used to monitor after-effect of thrombolytic therapy showed that narrowing of the vessel caused by the thrombus itself was not the cause of the critical stenosis of the artery which led to an acute coronary syndrome (ACS) (Barbato et al., 2016; Hoffmann et al., 2006; Motoyama et al., 2009; Narula et al., 2008; Schoenhagen et al., 2003).

This provides the possibility, as there is no direct correlation between the degree of stenosis and the size of a plaque, of some compensatory mechanism to exist which allows to obscure the effect atheroma possesses on the blow flow. The outward expansion of the affected artery serves as the compensatory enlargement which prevents stenosis and masks the signs and symptoms of ischemia. However, when the growth of a plaque exceeds the ability of the artery to expand outward, the luminal stenosis of the vessels occurs (Arbab-Zadeh, Nakano, Virmani, & Fuster, 2012).

The commencing mechanism of AMI is either rupture or erosion of lipid-laden atherosclerotic plaque of the vessel. The most common cause of fatal ACS is physical disruption of atherosclerotic plaque (Davies, 1996; Falk, Shah, & Fuster, 1995). The plaque consists of a fibrous cap and the center rich in lipids, also known as necrotic core. The lipid core is filled with thrombogenic material (Libby, Peter, 2013). The fibrous cap serves as a barrier between blood with coagulation factors and thrombogenic material of the plaque. Any damage to this barrier would lead to interaction with the possibility of thrombus formation.

Studies showed that often, but not always, ruptured plaques which caused fatal MI had thin fibrous caps (50 to 65 μm thick) (Yonetsu et al., 2011). It means that the thickness of the fibrous cap could potentially serve as the predictor of fatal ruptures (Narula et al., 2013). Another finding was the presence of smooth-muscle cells at the sites of the ruptures of arterial walls (Davies, Richardson, Woolf, Katz, & Mann, 1993). This, in turn, signified the importance of understanding the mechanisms of the tensile strength of the fibrous cap. The structural protein responsible for the durability of the cap is an interstitial form of collagen which is synthesized in smooth-muscle cells of the artery (Libby, 2013).

This finding led to the hypothesis that a defect in the metabolism of collagen present in the plaque might contribute to further depletion of this protein with the potential to affect the tensile strength of the fibrous cap (Libby, P., 1995). To study this hypothesis, molecular mechanisms of collagen biosynthesis had become the primary focus of the research. In addition, the presence of inflammatory cells at the sites of the ruptured plaques and the use of inflammatory biomarkers as the predictors of the outcome of ACS also led to the assumption that certain inflammatory cells might play a role in affecting the integrity of collagen molecule (Amento, Ehsani, Palmer, & Libby, 1991; Rekhter et al., 1993).

In addition, studies showed that interstitial collagen is a very stable molecule resistant to degradation by most proteolytic enzymes. However, some proteinases have interstitial collagenase activity allowing these enzymes to catalyze the degradation process of fibrous cap collagen. These enzymes belong to matrix-metalloproteinase (MMP) family and macrophages, cells that were found in abundance at the sites of the lesions which caused the majority of fatal ACS, are capable of producing all three human MMP collagenases – MMP-1, MMP-8 and MMP-13 (Galis, Sukhova, Lark, & Libby, 1994; Herman et al., 2001; Nikkari et al., 1995; Shah et al., 1995; Sukhova et al., 1999). Another study confirmed that the production of MMP by macrophages is regulated by T-lymphocytes which possess the ability to stimulate enzyme expression via T-cell-derived cytokine CD40 ligand (CD154) (Mach, Schönbeck, Bonnefoy, Pober, & Libby, 1997).

The net effect produces the cooperation between innate and adaptive immune system which facilitates degradation of interstitial collagen. This is the observation that links inflammatory process and weakening of fibrous cap that leads to plaque rupture and development of ACS (Libby, 2013). However, weakened fibrous cap is not the only factor that causes plaque rupture and progression of ACS, especially considering the fact that not all ruptured plaques necessarily display thin fibrous caps (Ohayon et al., 2008). Additional factors affecting transformation of the plaque may include calcifications within the intima of atherosclerotic plaque and coronary vasospasm. Microcalcifications dramatically increase circumferential stress of the cap which contributes to the rupture of the plaque (Yuliya Vengrenyuk et al., 2006). In case of plaque rupture, the blood contacts the necrotic core of the plaque rich in thrombogenic material precipitating thrombosis. In addition, tissue factor, a potent procoagulant produced by macrophages present at the site of the lesion, initiates thrombin generation, leading to platelet activation and aggregation (Drake, Morrissey, & Edgington, 1989; Wilcox, Smith, Schwartz, & Gordon, 1989).

2.1.3. Incidence of myocardial infraction and mortality

Acute myocardial infarction is the leading cause of hospital admissions worldwide (Moran et al., 2014). In US only, approximately 550,000 incident cases of AMI are registered every year (Mozaffarian et al., 2016). However, globally the incidence of AMI is declining, especially in high-income countries (Moran et al., 2014; Mozaffarian et al., 2016; Nichols, Townsend, Scarborough, & Rayner, 2014). By contrast, the burden of the disease is increasing in low- and middle-income countries. Currently, such countries account for more than 80% of all deaths due to cardiovascular diseases worldwide (Murray et al., 2012; Murray et al., 2015). In addition to improvement of health care and consequent increase of the prevalence of survivors of AMI, the globally increasing burden might be explained also by aging of world population and population growth (Moran et al., 2014). Stratification by the type of MI displays, on average, around 30% of hospitalizations due to STEMI and 70% due to NSTEMI, which indicates that the proportion of STEMI is declining during last decades (Yeh et al., 2010).

Cardiovascular diseases (CVD) are the leading cause of death in the world. In 2010, 29.6% of all deaths worldwide were caused by CVD, which means that every fourth death globally was due to CVD, including AMI (Lozano et al., 2012). It is more than deaths from all communicable disorders combined and twice more than the number of deaths caused by cancers (Nichols et al., 2014). Currently, though, global mortality trends are declining

(Benjamin et al., 2017). Mortality rates greatly depend on country as well as display significant differences when stratified by gender. Overall, data shows that 49% of deaths among women are attributable to CVD, while among men this figure equals 40%. This goes in contrast to deaths attributable from all cancers, which equals 20% for women and 24% for men (European cardiovascular disease statistics 2017 edition.2017).

In all countries, mortality rates increase with age (Isaksson et al., 2011). However, due to discrepancies among countries there are many cases where equal mortality rates can be observed for different age categories. For example, mortality rates among 55-59-year-old men in Belarus, Russia, Ukraine are higher than the equivalent rates among French men older than 75 years (Nichols et al., 2014). In Europe, the highest age-adjusted rates of CVD mortality can be observed in Russian Federation (915 for men and 517 for women per 100 000) and Belarus (893 for men and 428 for women per 100 000), while the lowest rates are shown by Denmark and Norway (less than 180 per 100 000 for men and less than 120 per 100 000 for women, respectively) (Nichols et al., 2014). Premature mortality rates also depend on the country and gender and might very almost 10-fold. Among men such countries as San Marino, France, Israel, with less than 65 deaths per 100 000 display the lowest rates while Russian Federation and Belarus, with the rate of over 560 deaths per 100 000 among men, display the highest rates. Among women, there were countries with the rate lower than 15 per 100 000 – Iceland, Israel and Italy versus Tajikistan, Turkmenistan and Uzbekistan with the rate of more than 120 deaths per 100 000 population (Nichols et al., 2014).

AMI case-fatality rates (CFR) display variations as well. In Europe, all countries except Estonia display a decreasing trend in AMI CFR (Rosengren & Ulin, 2017). Studies from China, however, report that no transition point was observed in CFR trends which remained stable for all patients except a mild increase in CFR for elderly women (Liu, Chen, Yu, Han, & Zheng, 2016). However, in general reductions in CFR among all countries have been documented during last years, with average of 3-6% change per year (Abildstrom, Rasmussen, Rosén, & Madsen, 2003; Nichols et al., 2014; Sulo et al., 2015).

2.2 Prognostic factors

2.2.1. Lifestyle-related factors

Global declines in mortality from CVD observed during last decades arise the question about the nature of the factors influencing this reduction. World Health Organization's multinational monitoring of trends in CVD project (MONICA) concluded that both lowering of case-fatality rates as well as incidence contributed to improving mortality across 38 studied countries (Harper, Lynch, & Smith, 2011). Currently, two features of the decline are distinguished: set of risk factors and treatments and set of social factors (Harper et al., 2011). Living conditions, education and occupation have the potential to influence the patterns of mortality from MI in the general population. The study conducted among Finnish population showed that household crowding can serve as a significant predictor of MI both in men and women. In addition, a rented childhood home correlated with mortality among women. However, growing up in a household with only one parent did not influence MI risk in both sexes (Kilpi, Silventoinen, Konttinen, & Martikainen, 2017).

The contribution of education, on the contrary, is more complicated in nature. It tends to influence other risk factors that have a huge impact on CVD mortality. One of the studies conducted in the United States demonstrated that a decrease of the proportion of people with 12 years of education or less resulted in reduction of the number of smokers across the same population which, in turn, led to improving CVD outcome. The researches proved that neither smoking nor education separately would not have influenced CVD outcome to such extent (Harper et al., 2011). Another study showed that increasing rates of women's education worldwide contributed heavily to the reduction of childhood mortality. Considering the role of early-life conditions in impacting future CVD risks (Loucks et al., 2012), improvement of educational level has the potential to demonstrate health benefits much later in time since the burden of CVD currently is shifting toward low- and middle-income countries (Murray et al., 2012; Murray et al., 2015). Occupation may also serve as a prognostic factor for MI.

Manual workers have higher incidence of MI especially among women. In addition, men with parents from agricultural or manual work background displayed higher mortality rates than men from administrative or professional occupation fields (Kilpi et al., 2017). The identification of the above-mentioned social factors assisted in improving the trends which have been observed currently in terms of cardiovascular outcomes and long-term survival of patients presenting with AMI. Nevertheless, people surviving MI display higher risk of adverse outcomes compared to general population (Johansson, Rosengren, Young, & Jennings, 2017).

Multimorbidity, defined as a presence of two or more chronic medical conditions in an individual (Wallace et al., 2015), is common among patients diagnosed with primary AMI and gravely impacts the prognosis of the disease (Barnett et al., 2012). Studies identified a lot of medical conditions that serve as risk factors of worsening the outcome of AMI. Hypertension is strongly associated with increasing adverse outcomes after AMI, in particular stroke, heart failure and cardiovascular death (Richards et al., 2002; Thune et al., 2008). GISSI-2 study showed that hypertension was associated with significantly higher in-hospital and 6-month mortality than normotensive patients (Fresco et al., 1996). In addition, patients with hypertension developing STEMI display higher risks of being affected by type 2 diabetes (Rembek, Goch, & Goch, 2010). However, diabetes mellitus itself increases mortality (Nauta, Sjoerd T., Deckers, Akkerhuis, & van Domburg, 2012). In addition, AMI mortality rates display an upgoing trend with increasing severity of hyperglycemia (Jw, Rt, M, & St, 2013) and with the decreasing renal function (Nauta, Sjoerd, Domburg, Nuis, Akkerhuis, & Deckers, 2013). Studies show that in elderly patients presenting with STEMI elevated glucose levels serve as early death predictors (Lazzeri, Valente, Chiostri, Picariello, & Gensini, 2011). Comorbidity with peripheral artery disease (PAD) among patients with MI worsens the outcome as well (Cotter et al., 2003; Golomb, Dang, & Criqui, 2006). In The Heart and Soul Study, a large prospective cohort study where 1024 participants had been followed for more than 15 years, it was found that PAD had statistically significant association with increased risk of both CV events incidence and worsening the prognosis (Grenon et al., 2013). The possible explanations and hypotheses that would explain increased adverse events associated with PAD include worse endothelial function, grave atherosclerotic burden and the presence of inflammation (Pasqualini et al., 2003).

Stroke in history also plays an important role in prediction both the occurrence and outcome of the MI. Cardiac arrhythmias are frequently associated with lesions specifically in cerebral hemisphere (Norris, Froggatt, & Hachinski, 1978). The tachyarrhythmias can, in turn, lead to hemodynamic instability which will both worsen stroke prognosis, but also increase the risk of cardiac ischemia (Kumar, Babu, & Subrahmanyam, 2012). Cortex itself alongside with its subcortical connections coordinate autonomic activity and possess the potential to generate cardiac arrhythmias under particular conditions, like hemispheric stroke. It is the left hemisphere that maintain parasympathetic regulation which reflects in cardioinhibitory function. This fact reflects the discovery that particular location of a stroke, left parietal lobe, is associated with higher risk of cardiac death and nonfatal MI. Moreover, the risk was independent of other cardiovascular risk factors. The effect of the location was also independent of size or mechanism of stroke (Rincon et al., 2008). In addition, the long-term risk of cardiac death is also increased following stroke (Kumar et al., 2012). Renal diseases and chronic obstructive pulmonary disease have also been identified as a potential risk factors influencing AMI prognosis (Rapsomaniki et al., 2016).

Another important determinant of AMI outcome, particularly STEMI, is coronary microcirculation. Although studies have shown that primary PCI reduce mortality rates in patients diagnosed with STEMI (Viana-Tejedor, Loughlin, Fernández-Avilés, & Bueno, 2015), a number of patients exist who experience impairment of myocardial perfusion even after recanalization of coronary artery leading to an increased risk of future cardiovascular events in this population (Niccoli, Scalone, Lerman, & Crea, 2016). The potential explanation might include ischemic or reperfusion injury, distal embolization of thrombotic material as well as individual susceptibility and pre-existing alterations (Joost et al., 2016; Niccoli et al., 2016).

2.2.2. Hospital admission days

High number of diseases tend to occur in some patterns, displaying seasonal or even weekly differences in incidence. Emergency medicine doctors acknowledge that the risk of certain diseases changes as the day progresses which is reflected by the types of emergency calls exhibiting distinct circadian patterns (Manfredini et al., 2002). AMI is not an exception, demonstrating variations in occurrence and mortality not only between seasons of the year or between days of the week, but even time of the day. The incidence of AMI is higher during winter compared with summer (Abrignani et al., 2009; Manfredini et al., 2009). December displayed the highest rates of 30-day mortality of patients with AMI compared to other months (Meine et al., 2005). Increased incidence during cold times of the year might be a consequence of higher levels of C-reactive protein in the blood, vasoconstriction and increased blood pressure (Abrignani et al., 2009).

The admission patterns for weekdays compared to weekends differ as well. A relative deficit of cases is observed during the weekends (Cram, Hillis, Barnett, & Rosenthal, 2004). This has the potential to influence the mortality rates, especially since it might mean that people wait till Monday and only critically ill are admitted during weekend. Nevertheless, currently no consensus is reached towards whether the mortality rates statistically differ when comparing weekdays versus weekends. Some studies convince no weekend excess in mortality is observed (Jneid et al., 2008; Kostis et al., 2007), while others suggest weekend admissions are associated with so-called “weekend effect”- higher mortality rates in patients hospitalized during weekends than those hospitalized during weekdays (Aylin, Yunus, Bottle, Majeed, & Bell, 2010; Bell & Redelmeier, 2001; Clarke et al., 2010; Freemantle et al., 2015; Hong, Kang, & Lee, 2010).

However, the common finding shared by the vast majority of studies is that the day of the week with the highest incidence of MI is Monday. A study where the information about the AMI incidence during 27-year period was analyzed showed a significant day-of-the-week variation, showed the peak of cases on Mondays and the low on Saturdays. The increase was similar for both men and women. However, no biological rhythms were detected (Collart, Coppieters, Godin, & Levêque, 2014). This was confirmed by the meta-analysis which revealed the odds ratio of 1.19 for the Monday excess of the incidence in MI (Witte, Grobbee, Bots, & Hoes, 2005).

2.3 Clinical implications

Myocardial infarction displays a wide range of complications which can generally be divided into several categories: Ischemic, Mechanical, Arrhythmic, Embolic and Inflammatory. Ischemic complications include reinfarction and angina. Pericarditis is the manifestation of the inflammatory type while the most abundant are mechanical complications, which comprise heart failure, cardiogenic shock, mitral valve dysfunction and aneurysms or cardiac ruptures (Cleveland clinic: Complications of acute myocardial infarction). Nevertheless, mechanical complications, particularly severe left ventricular (LV) dysfunction, account for most fatal outcomes (Cleveland clinic: Complications of acute myocardial infarction).

However, certain secondary preventive measures can prevent the progression of these complications, favor the outcome of MI and reduce its mortality rates. This includes both lifestyle-related interventions and medications. Smoking cessation is the most cost-effective of all secondary preventive measures (Chow et al., 2010). Due to the fact that smoking possesses strong pro-thrombotic effect, the benefit of smoking cessation can be observed in all patients with CAD, including MI. Meta-analyses show that a 36% reduction of mortality rate is attributable solely to smoking cessation (Critchley & Capewell, 2003). Overweight and obesity, defined as body mass index (BMI) ≥ 25 kg/m^2, is also associated with poorer outcomes and higher mortality compared to BMI ranging between 20 and 25 kg/m^2. In particular, abdominal fat is considered the most harmful type of fat. It means that maintaining normal weight or losing weight is beneficial to all people who suffered MI (Global BMI Mortality Collaboration, null et al., 2016). Physical activity and correspondent exercising program play a significant role as secondary prevention as well. Studies show a reduction of mortality rates in CAD up to 22% among individuals participating in exercise-based cardiac rehabilitation programme (Anderson, L. et al., 2016). Further, certain medications are proved both to reduce the rate of complications following MI and improve its outcome. However, an important barrier that should be considered when speaking about medications is adherence to treatment. Low treatment adherence prevents reaching treatment targets and is associated with worse outcomes (Simpson et al., 2006). Studies estimated that after a median of 2 years, the adherence to cardiovascular medications shows the level of 57% (Naderi, Bestwick, & Wald, 2012).

Several groups of medications decrease the mortality rates following MI and reduce the rate of its complications among which statins, beta-blockers (BBs), Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ACEIs and ARBs) and antiplatelet drugs (Setoguchi et al., 2008). ACE inhibitors are specifically recommended for patients suffering LV dysfunction or who have experienced heart failure in the early phase of AMI (ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (fourth international study of infarct survival) collaborative group.1995; Pitt et al., 2003; Yusuf et al., 2000). Small but significant reduction in mortality rates can be observed as soon as during the first week in patients taking ACEIs (ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (fourth international study of infarct survival) collaborative group.1995; Indications for ACE inhibitors in the early treatment of acute myocardial infarction: Systematic overview of individual data from 100,000 patients in randomized trials. ACE inhibitor myocardial infarction collaborative group.1998). Another medication that is proved to reduce morbidity and mortality of patients with LV dysfunction and heart failure is mineralocorticoid receptor antagonists (MRA). Eplerenone, a selective aldosterone receptor antagonist, has shown a 15% relative reduction in total mortality alongside with a 13% reduction in death and hospitalization for cardiovascular events combined (Pitt et al., 2003).

2.4 Treatment of myocardial infarction

2.4.1. General approach

The most crucial factors affecting AMI-associated morbidity and mortality are prehospital cardiac arrest and extension of necrosis. That is why initial steps of medical care, including rapid assessment, transportation and initiation of treatment, are fundamental in dealing with AMI (Anderson, J. L. & Morrow, 2017a).

The primary management includes bed rest with ECG monitoring alongside with antithrombotic therapy (Anderson & Morrow, 2017). ECG monitoring is necessary for early detection of life-threatening arrhythmias and defibrillation, if required (Diercks et al., 2006; Tubaro et al., 2011). In case ECG is equivocal, it should be repeated and, if possible, compared with previous recordings (Ibanez et al., 2018). Beta-blockers are usually initiated within first 24 hours after admission (Amsterdam et al., 2014; O'Gara et al., 2013). In addition, ACEIs or ARBs are recommended for all patients suffering from ACS, especially for those who present with MI, heart failure or ventricular dysfunction (Amsterdam et al., 2014; Anderson, J. L. et al., 2007; O'Gara et al., 2013). Depending on persistence of ischemic discomfort, congestive heart failure or profound hypotension that cannot be controlled, administration of nitroglycerin is favored (Amsterdam et al., 2014; O'Gara et al., 2013). In case of prominent pain syndrome, titrated intravenous opioids, morphine, should be used. Relief of pain is of vigorous importance not only because of the comfort of the patient, but also due to activation of the sympathetic nervous system that leads to vasoconstriction and increased workload of the heart (Hobl et al., 2014; Kubica et al., 2016; Parodi et al., 2015).

2.4.2. Approach to patients with STEMI

The primary therapeutic goal in patients presenting with STEMI is emergency reperfusion of ischemic myocardium. This is achieved by means of either percutaneous coronary intervention (PCI, angioplasty and stenting) or intravenous fibrinolytic therapy (Anderson &

Morrow, 2017). The preferred option is PCI, due to lower rates of reinfarction and early death. However, ideally it should be accomplished within 90 minutes from the first medical contact or within 120 minutes from STEMI diagnosis (Ibanez et al., 2018). In case PCI is delayed by more than 120 minutes, fibrinolytic therapy should become the treatment of choice (Anderson & Morrow, 2017).

2.4.3. Treatment of ACS without ST-segment elevation

The absence of elevation of ST-segment means the residual perfusion is still present in the ischemic zone (Anderson & Morrow, 2017). It defines the treatment approach to patients with NSTEMI. Such patients should receive dual antiplatelet therapy (DAPT), a combination of aspirin and a $P2Y_{12}$ inhibitor, and a parenteral anticoagulant (Ibanez et al., 2018).

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THE EFFECT OF HOSPITAL ADMISSION DAY ON MORTALITY FROM MYOCARDIAL INFARCTION IN ENGLAND: A NATIONAL RECORD LINKAGE STUDY

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ABSTRACT

Background: There are concerns that quality of medical care and availability of medical procedures may vary between weekdays and weekends. Acute myocardial infarction (AMI) is a life-threatening condition, which requires urgent specialized care and, potentially, invasive procedures. The specialized care and invasive procedures may not be equivalently available on weekends and weekdays, which may affect mortality from AMI. We tested the hypothesis that case fatality rates (CFRs) within 30 days from hospital admission for AMI did not differ between weekend and weekday admissions.

Methods: The National Health Service (NHS) provides health-care for all residents of England. We used datasets of English National Hospital Episode Statistics (HES) and mortality records supplied by, respectively, the NHS Information Centre and the Office for National Statistics. Linkage between the datasets was done using encrypted values of the unique HES identifier and of the unique NHS number supplemented with encrypted values of the patients' date of birth and postcode. We used the hospital admission and mortality data for England from 1999 to 2011 to calculate 30-day CFRs. We used chi-squared statistics to compare categorical variables and to test for statistical significance. We set the level of statistical significance at 0.01. Logistic regression analysis was used to quantify the effects of age, year of admission and day of the week of admission on the CFR. Statistical tests were carried out in SPSS Statistics version 20 for Windows.

Results: The study comprised 541,165 people. In patients admitted with AMI, CFRs for weekday and weekend admissions did not differ significantly: they were 11.5% (45,629/397,173) on weekdays and 11.5% (16,566/143,992) on weekends, P-value=0.602. The 30-day CFR for all patients admitted to hospitals was 11.5%.

Conclusion: Overall, there was no evidence of a "weekend effect" on CFRs in patients hospitalized with AMI in England in 1999-2011. This indicates that the delivery of NHS care, at least in respect of CFRs for AMI in the period studied, was as effective for weekend as for weekday admissions.

INTRODUCTION

Cardiovascular diseases are the leading cause of death in the world. Ischemic heart disease remains the world's biggest killer, accounting for 16% of the world's total deaths. The number of deaths for these diseases has demonstrated the largest increase since 2000, rising by more than 2 million to 8.9 million deaths in 2019 (World Health Organization, 2020) .

Among those with heart disease, the major contributor to mortality is acute myocardial infarction (MI). Patients with MI account for a large proportion of emergency hospital admissions(Purdy, Griffin, Salisbury, & Sharp, 2011) and are frequently admitted during weekends(Aylin, Yunus, Bottle, Majeed, & Bell, 2010). It is possible that during weekends hospital resources are limited. Decrease in hospital staff, and lack of senior physicians can lead to an increase in workload for a doctor and a time spent for one patient. As a result, specialized care and invasive procedures may not be equivalently available throughout the week. Indeed, earlier research have expressed concerns that the quality of medical care may vary between weekdays and weekends(Bell & Redelmeier, 2001; Clarke et al., 2010; Freemantle et al., 2015; Hong, Kang, & Lee, 2010; Kostis et al., 2007) . However, studies about the "weekend-effect" are prone to confounders such as mixing the cases with larger proportion of critically ill patients admitted to hospital during the weekend with the potential to influence mortality rates values.

The existing evidence on the increased mortality occurring after hospital admission during the weekend is controversial. While the majority of studies suggest the existence of the "weekend effect", meaning that patients hospitalized on weekends tend to have higher mortality rates than those hospitalized during weekdays, there is also evidence to the contrary(Jneid et al., 2008; Kim et al., 2014) .

We aimed to study hospital admissions and case fatality rates (CFR) for myocardial infarction to investigate if there is an impact of day of the week of admission on mortality rates in England. We hypothesized that 30 days case fatality rates of MI based on routine hospital admission records, linked to national mortality data, in patients admitted to National

Health Service hospitals with a diagnosis of MI would be the same for people hospitalized on weekdays compared to those hospitalized on weekends in England from 1999 to 2011.

METHODS

We used datasets of English National Hospital Episode Statistics (HES) and mortality records obtained from, respectively, the National Health Service (NHS) Information Centre and the Office for National Statistics. Linkage between the datasets was completed using encrypted values of the unique HES identifier and of the unique NHS number supplemented with encrypted values of the patients' date of birth and postcode(Methodology for creation of the & HES Patient ID (HESID),) .

Study population

We included records with any type of acute MI as a discharge diagnosis from 1999 to 2011. The discharge diagnosis was used because the diagnosis on admission cannot be accurate in every case due to the fact, that it is not confirmed by medical tests. We identified and used only the primary case of each episode. If the patient was admitted to hospital more than one time with the same diagnosis, we took only the first episode as an incident case. Emergency method of admission was selected as the only method of admission to exclude possible transfers from other hospital providers. The all-cause deaths were identified through death certificate records linked to our dataset.

The study comprised 541,165 patients aged 25 to 85 years: 65.75% men and 34.25% women. The information on age and sex of the patients was obtained from the hospital registers. Our database included only episodes with complete data – episodes with missing data were excluded during database preparation.

Case-fatality rates

The 30-day hospital case-fatality rate was calculated using the total number of hospital admissions with a discharge diagnosis of myocardial infarction as the denominator and all deaths from the day of admission to the 29th day after admission to the hospital or to the day of death, whichever came first, as the numerator. This was our primary follow-up period.

We have also analyzed CFR using two other follow-up periods: 1) from the next day after admission and 2) from the second day after admission till 29th day or until the day of death, whichever came first. Such an approach was intended to separate potentially fatal cases, for deaths during first hours or days of the disease might be the result of arrhythmias due to MI incompatible with life – which could affect the results.

We calculated 30-day CFRs for different days of the week, groups of days of the week and age groups both for all patients combined and separately for males and females.

Statistical analysis

We used hospital admission data from England between 1999 and 2011 to calculate the number and percentage of admissions to a hospital for myocardial infarction by days of the week and weekend. We compared the admission on weekends versus weekdays across different age groups in men and women. Chi-squared test was used to assess the difference in admission between weekends and weekdays in all age groups together for all patients combined and separately for men and women.

To study the differences in the outcome of MI based on various days of admission more precisely, we used two distinct age stratification groups: one with 5-year age intervals and another with broader,10 to 15-year age intervals.

Two models of logistic regression were fitted for each type of CFR. First, we calculated the univariable model and then multivariable model was calculated by using all variables of the univariable model mutually adjusted. The analyses were done among all subjects as well as stratified by sex across different age groups for three different CFRs.

Separate analyses were also done for patients aged 85 to 120 years. However, the findings did not significantly affect the main results, therefore we only included the results for age group between 25 and 85 years.

Analysis of "weekend-effect"

To assess the possible impact of admission days on mortality on weekdays and weekends, we first conducted all analyses with stratification by the day of the week. Then, patients hospitalized from Monday to Friday were combined into one group and those admitted from Saturday to Sunday in another group. We also re-defined weekend days and compared patients admitted Monday-Thursday to Friday-Sunday and Tuesday-Friday group to Saturday-Monday to see if the combinations of different weekdays had any effect on the mortality.

RESULTS

Hospital admission by day of the week

There were 541,165 people admitted to hospital with myocardial infarction in 1999-2011: 355,813 (65.75%) men and 185,352 women (34.25%), (Table 1). We observed relatively small, but statistically significant differences in the number of admissions between days of the week. The average number of hospitalized patients per day was 77,309 with the greatest number hospitalized on Monday – 84,874, comprising 15.7% of all admissions ($p < 0.001$). The day with the lowest admission rate was Sunday – 71,803, accounting for 13.3% of all hospitalizations ($p < 0.001$).

We conducted the same analyses also separately for men and women (Supplementary data, Appendix 1.1 and Appendix 1.2). However, subgroup analyses by gender did not demonstrate any significant differences with the aforementioned data, depicting Monday as the day when most admissions happened and Sunday – least number.

Table 1. Number and percentage of admission to hospital for myocardial infarction by day of the week and age group, 1999-2011[a]

Day of the week	Age Groups								All Ages	
	25-39 years		40-54 years		55-74 years		75-84 years			
	n	%	n	%	n	%	n	%	n	%
Monday	1566	15.8	13705	15.8	42927	15.9	26676	15.3	84874	15.7
Tuesday	1381	13.9	12437	14.3	39495	14.6	25565	14.7	78878	14.6
Wednesday	1404	14.1	11996	13.8	38666	14.3	25251	14.5	77317	14.3
Thursday	1386	13.9	12096	13.9	38489	14.2	25338	14.5	77309	14.3
Friday	1368	13.8	12255	14.1	39110	14.5	26062	15.0	78795	14.6
Saturday	1400	14.1	12030	13.9	35849	13.3	22910	13.2	72189	13.3
Sunday	1432	14.4	12273	14.1	35734	13.2	22364	12.8	71803	13.3
χ_6^2 *and P*	*19.37, 0.004*		*172.12, <0.001*		*921.57, <0.001*		*629.02, <0.001*		*1531.9, <0.001*	
Monday-Friday	7105	71.5	62489	72.0	198687	73.5	128892	74.0	397173	73.4
Saturday-Sunday	2832	28.5	24303	28.0	71583	26.5	45274	26.0	143992	26.6
χ_1^2 *and P*	*0.03, 0.874*		*13.82, <0.001*		*576.09, <0.001*		*566.61, <0.001*		*1022.48, <0.001*	
Total	9937	100.0	86792	100.0	270270	100.0	174166	100.0	541165	100.0

[a]Assuming an equal spread of admissions across days of the week, there would be 14.3% (1/7) of all admissions on each day and 28.6% (2/7) of all admissions on Saturday and Sunday.

Death in hospital in days after admission: day of the week of admission

We excluded the cases of MI with early fatal outcomes that could impact the effect of the day of the week. We defined cases of MI with early fatal outcomes as deaths that occurred during the first hours or days of the disease that might have been the result of incompatible with life post-MI arrhythmias.

We analyzed the data for patients who died on the day of admission, the day after, or 2 days after (Table 2). There was no statistically significant difference in same day deaths both between days of the week ($p=0.301$) and between weekdays and weekends ($p=0.353$). However, there was a statistically significant difference between different weekdays and between weekdays and weekends in deaths that occurred the day after admission ($p<0.001$). When comparing death 2 days after the admission, statistically significant difference was observed only in Monday-Friday versus Saturday-Sunday group ($p=0.014$). No evidence of an adverse "weekend effect" was observed in any other group.

The same analyses were conducted separately for men and women (Supplementary data, Appendix 2.1 and Appendix 2.2).

Table 2. Myocardial infarction and mortality by day of the week, 1999-2011[a]

Day of the week	Death in hospital in days after admission								Total	
	Same day death		1 day death		2 day death		3-29 days death			
Monday	1522	14.8%	1717	15.6%	983	14.7%	5215	15.2%	9437	15.2%
Tuesday	1474	14.3%	1615	14.7%	974	14.6%	4930	14.4%	8993	14.5%
Wednesday	1401	13.6%	1554	14.1%	977	14.7%	4906	14.3%	8838	14.2%
Thursday	1510	14.7%	1541	14.0%	934	14.0%	5057	14.8%	9042	14.5%
Friday	1497	14.5%	1620	14.7%	985	14.8%	5217	15.2%	9319	15.0%
Saturday	1443	14.0%	1467	13.4%	915	13.7%	4475	13.1%	8300	13.3%
Sunday	1459	14.2%	1474	13.4%	899	13.5%	4434	13.0%	8266	13.3%
χ_6^2 *and P*	*7.22, 0.301*		*29.98, <0.001*		*8.04, 0.235*		*127.28, <0.001*		*141.47, <0.001*	
Monday-Friday	7404	71.8%	8047	73.2%	4853	72.8%	25325	74.0%	45629	73.4%
Saturday-Sunday	2902	28.2%	2941	26.8%	1814	27.2%	8909	26.0%	16566	26.6%
χ_1^2 *and P*	*0.86, 0.353*		*17.56, <0.001*		*6.07, 0.014*		*108.87, <0.001*		*114.21, <0.001*	
Total	10306	100.0%	10988	100.0%	6667	100.0%	34234	100.0%	62195	100.0%

- [a]Assuming an equal spread of deaths occurring inside hospital across days of the week, there would be an expected 14.3% (1/7) of all deaths on each day.

30-day case fatality rates for different age groups

The 30-day CFR for all patients admitted to hospitals was 11.5% (Table 3). The lowest rate was in Monday admissions at 11.1%, while the highest rate was 11.8% for Friday admissions, (p=0.001).

In all age groups, there was no statistically significant difference in 30-day CFR between weekdays (Table 3). For the 25-39 years of age group, 30-day CFR was 2.0%, ranging from low 1.6% on Monday and Saturday to peak 2.4% on Wednesday (p=0.604). 40 to 54 group displayed 30-day CFR of 2.6%, varying from 2.4% to 2.8% (p=0.372). In 55-74 years of age group it was 8.8%, with narrow ranges from 8.6% to 8.9% (p=0.464). A dramatic increase in fatality rate was observed in 75-84 years of age group. The total CFR was 20.7% with the peak on Friday at 21.2% and the low on Monday at 20.1% (p=0.051).

Overall, we found no statistically significant difference in 30-day CFR between weekdays and weekends, with 11.5% versus 11.5% respectively (Table 3). When comparing weekends and weekdays by age groups, there was no statistically significant difference in any of them. 25-39 years of age group displayed the 30-day CFR of 2.0% for Monday-Friday period and 1.9% for Saturday-Sunday (p=0.713). The next age group, 40-54 years, showed the CFR of 2.5% and 2.7%, respectively (p=0.197). Considerably higher numbers, although lower than total CFR, were found in 55-74 age group, with 30-day CFR of 8.7% for Monday-Friday and 8.9% for Saturday-Sunday (p=0.177). The highest rate was observed in 75-84 years of age group: 20.6% for Monday-Friday and 21.0% for Saturday-Sunday, however the P-value of 0.105 showed that no statistically significant difference was present in this group as well.

Table 3. 30-day case-fatality rates (CFR) by day of the week for different age groups with myocardial infarction from 1999 to 2011

Day of the week	Age Groups														
	25-39 years[a]			40-54 years[b]			55-74 years[c]			75-84 years[d]			All Ages[e]		
	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)
Monday	1566	25	1.6	13705	334	2.4	42927	3707	8.6	26676	5371	20.1	84874	9437	11.1
Tuesday	1381	26	1.9	12437	320	2.6	39495	3414	8.6	25565	5233	20.5	78878	8993	11.4
Wednesday	1404	34	2.4	11996	284	2.4	38666	3338	8.6	25251	5182	20.5	77317	8838	11.4
Thursday	1386	26	1.9	12096	309	2.6	38489	3444	8.9	25338	5263	20.8	77309	9042	11.7
Friday	1368	30	2.2	12255	333	2.7	39110	3433	8.8	26062	5523	21.2	78795	9319	11.8
Saturday	1400	22	1.6	12030	309	2.6	35849	3174	8.9	22910	4795	20.9	72189	8300	11.5
Sunday	1432	31	2.2	12273	343	2.8	35734	3191	8.9	22364	4701	21.0	71803	8266	11.5
Monday-Friday	7105	141	2.0	62489	1580	2.5	198687	17336	8.7	128892	26572	20.6	397173	45629	11.5
Saturday-Sunday	2832	53	1.9	24303	652	2.7	71583	6365	8.9	45274	9496	21.0	143992	16566	11.5
Total	9937	194	2.0	86792	2232	2.6	270270	23701	8.8	174166	36068	20.7	541165	62195	11.5

- [a]Days of the week $\chi_6^2 = 4.54$, *P*-value = 0.604. Comparing weekend and weekday: Monday-Friday (2.0%) versus Saturday-Sunday (1.9%) $\chi_1^2 = 0.14$, *P*-value = 0.713.

- [b]Days of the week χ_6^2 = 6.48, *P*-value = 0.372. Comparing weekend and weekday: Monday-Friday (2.5%) versus Saturday-Sunday (2.7%) χ_1^2 = 1.66, *P*-value = 0.197.
- [c]Days of the week χ_6^2 = 5.64, *P*-value = 0.464. Comparing weekend and weekday: Monday-Friday (8.7%) versus Saturday-Sunday (8.9%) χ_1^2 = 1.82, *P*-value = 0.177.
- [d]Days of the week χ_6^2 = 12.56, *P*-value = 0.051. Comparing weekend and weekday: Monday-Friday (20.6%) versus Saturday-Sunday (21.0%) χ_1^2 = 2.63, *P*-value = 0.105.
- [e]Days of the week χ_6^2 = 24.42, *P*-value = 0.001. Comparing weekend and weekday: Monday-Friday (11.5%) versus Saturday-Sunday (11.5%) χ_1^2 = 0.03, *P*-value = 0.602.

CFR by day of the week groups and narrower age strata

The same analyses were also conducted with different combinations of weekdays. We compared patients admitted from Monday to Thursday with Friday-Sunday groups and Tuesday-Friday admissions with Saturday-Monday to assess the possible impact of admission days on mortality in weekdays and weekends. The data displayed similar results, with no statistically significant difference found in any age groups between various combinations of days groups, except 75-84 years of age group, where the 30-day CFR for Monday-Thursday period was 20.5% and for Friday-Sunday 21.1%, p=0.003 (Supplementary data, Appendix 3.1).

To study the differences in the outcome of MI based on various days of admission more precisely, we used narrower age stratification groups: one with 5-year age intervals. We calculated 30-days CFRs for different days of the week and different combinations of weekdays and found no significant difference in mortality between days, weekdays and weekends in patients of different age groups, however there were three age groups (65-69; 75-79; 80-84 years) which showed statistically significant difference between Monday-Thursday and Friday-Sunday days groups (P-value varies between 0.032 and 0.041), (Supplementary data, Appendix 3.2).

30-day CFRs by gender

The 30-day CFR for all men admitted to hospitals was 9.8%, with the lowest proportion (9.5%) on Monday and the highest (10.1%) on Friday (Table 4). However, analyses failed to demonstrate any statistically significant difference between days of the week (p=0.065). There was no statistically significant difference observed in CFRs between weekdays and weekends as well: 9.8% versus 9.7%.

The fatality rates for women revealed considerably higher numbers (Table 4). The total 30-day CFR for all females admitted to hospitals was 14.8%, ranging from low 14.3% on Monday to peak 15.3% on Sunday, displaying statistically significant difference between days of the week with p=0.006. However, when comparing weekdays with weekends, there was no statistically significant difference: Monday-Friday (14.7%) versus Saturday-Sunday (15.1%), p=0.055.

Table 4. 30-day case-fatality rates (CFR) by day of the week for different gender with myocardial infarction from 1999 to 2011

Day of the week	Males[a]			Females[b]			Both genders[c]		
	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)
Monday	56338	5352	9.5	28536	4085	14.3	84874	9437	11.1
Tuesday	51877	5088	9.8	27001	3905	14.5	78878	8993	11.4
Wednesday	50537	4946	9.8	26780	3892	14.5	77317	8838	11.4
Thursday	50386	4961	9.8	26923	4081	15.2	77309	9042	11.7
Friday	51398	5181	10.1	27397	4138	15.1	78795	9319	11.8
Saturday	47484	4622	9.7	24705	3678	14.9	72189	8300	11.5
Sunday	47793	4602	9.6	24010	3664	15.3	71803	8266	11.5
Monday-Friday	260536	25528	9.8	136637	20101	14.7	397173	45629	11.5
Saturday-Sunday	95277	9224	9.7	48715	7342	15.1	143992	16566	11.5
Total	355813	34752	9.8	185352	27443	14.8	541165	62195	11.5

N – total number of patients; n – number of patients who died

- [a]Days of the week $\chi_6^2 = 11.85$, P-value = 0.065. Comparing weekend and weekday: Monday-Friday (9.8%) versus Saturday-Sunday (9.7%) $\chi_1^2 = 1.08$, P-value = 0.298.
- [b]Days of the week $\chi_6^2 = 18.19$, P-value = 0.006. Comparing weekend and weekday: Monday-Friday (14.7%) versus Saturday-Sunday (15.1%) $\chi_1^2 = 3.69$, P-value = 0.055.
- [c]Days of the week $\chi_6^2 = 24.42$, P-value = 0.001. Comparing weekend and weekday: Monday-Friday (11.5%) versus Saturday-Sunday (11.5%) $\chi_1^2 = 0.03$, P-value = 0.602.

Potential confounders and multivariate modelling

We considered the effects of CFR on age, sex, year of admission and different groups of days of admission, adjusting each factor for the effect of each other. Table 5 demonstrates the results for all-ages analysis. The odds ratio (OR) for mortality within 30 days of admission was lower for males than females, increased substantially with increasing age and declined over time.

We compared different combinations of days as weekends and weekdays (using the latter as the reference category) to calculate OR (Table 5). For weekends defined as Saturday-Sunday, the OR was 1.02 (95% CI 0.98 – 1.06); for weekends defined as Friday-Sunday, the OR was 1.03 (95% CI 1.00 – 1.05); for weekends defined as Saturday-Monday, the OR was 0.98 (95% CI 0.96 – 1.01).

The same analyses were also conducted for 5-year age strata (Supplementary Data, Appendix 5.1). However, stratification into narrower age groups did not demonstrate any significant differences in OR for death within 30 days of admission between different days of the week.

Table 5. Determinants for 30-day CFR for myocardial infarction, 1999-2011, odds ratios with their 95% confidence intervals obtained from logistic regression with variations of weekend[a] definitions

Determinants	Odds Ratio	95% CI		P-value	30d CFR	Total
Age Groups		Lower	Upper			
25-39[b]	1.0				194	9937
40-54	1.32	1.14	1.53	<0.001	2232	86792
55-74	4.65	4.03	5.36	<0.001	23701	270270
75-85	12.45	10.79	14.36	<0.001	36068	174166
Sex						
Male	0.83	0.82	0.85	<0.001	34752	355813
Female[b]	1.0				27443	185352
Year of Admission						
1999[b]	1.0				7527	52282
2000	0.91	0.88	0.95	<0.001	6629	49485
2001	0.87	0.84	0.91	<0.001	6352	48459
2002	0.86	0.83	0.89	<0.001	6443	48998
2003	0.81	0.78	0.84	<0.001	5946	47260
2004	0.74	0.71	0.77	<0.001	5452	46487
2005	0.73	0.71	0.76	<0.001	5013	42931
2006	0.67	0.64	0.69	<0.001	4166	39561
2007	0.62	0.60	0.65	<0.001	3721	37662
2008	0.58	0.56	0.61	<0.001	3331	35291
2009	0.53	0.51	0.56	<0.001	2875	33356
2010	0.52	0.49	0.54	<0.001	2573	30536
2011	0.45	0.43	0.48	<0.001	2167	28857
Days of Admission						

Saturday-Sunday	1.02		0.98	1.06		0.42		16566	143992
Monday-Friday[b]	1.0							45629	397173
Friday-Sunday	1.03		1.00	1.05		0.059		25885	222787
Monday-Thursday[b]	1.0							36310	318378
Saturday-Monday	0.98		0.96	1.01		0.11		26003	228866
Tuesday-Friday[b]	1.0							36192	312299

[a]The results for the three variations of ‘weekend’ were obtained by running each variation separately

[b]Reference group

DISCUSSION

Main findings of the study

Overall, none of the analyses of CFRs comparing admissions by day of the week showed significant differences in mortality from MI, whether compared across separate days of the week or compared as weekdays versus weekends. We did not observe any systematic "weekend effect". Similar results were also demonstrated by the analyses of CFR stratifying patients by gender – no significant difference between weekdays and weekends.

Our 30-day CFR was 11.5%, which is consistent with the results of other studies(Roger et al., 2010; Van Doornum et al., 2015; Yeh et al., 2010) . We observed the difference in CFRs between genders with women having considerably higher rates: 14.8% versus 9.8% in males. During the period of the study mortality rates from MI were progressively decreasing, which is similar to the existing data(Roger et al., 2010; Van Doornum et al., 2015; Yeh et al., 2010) .

We hypothesized that the effects of CFR on age, sex, year of admission and different groups of days of admission might have been different when adjusting each factor for each separate effect. However, our findings remained similar with no significant differences in OR for death between different days of admission (Supplementary Data, Appendix 5.2).

Another finding of our study was the highest admission rate observed on Monday in different age groups in all patients combined and separately in males and females. It is a common finding in almost all research on the subject which is known as "Monday effect"(Bodis, Boncz, & Kriszbacher, 2010; Collart, Coppieters, Godin, & Levêque, 2014; Manfredini, 2009) , a phenomenon which does not have a conclusive answer.

What this study adds

We conducted a population-based study of survival of people with myocardial infarction during a 13-year period, based on HES datasets and mortality records supplied by Office for National Statistics, with selected only emergency admissions for the first episodes as incident cases. We had a large sample size comprising 541,165 patients aged 25 to 85 years: 355,813 men and 185,352 women. Our database included only episodes with complete data. Emergency method of admission was selected as the only method of admission to exclude possible transfers from other hospital providers. CFRs were analyzed using three different follow-up periods allowing us to see if there is an impact on the results of potentially fatal cases, for deaths during first hours or days of the disease might be the result of arrhythmias due to MI incompatible with life and not due to quality of medical help and health-care standards.

There was no evidence suggesting "weekend effect", meaning no increase in deaths of people admitted during Saturdays and Sundays. Our study provides national-level evidence that the NHS is able to provide uniformly reliable medical care with invasive procedures equivalently available throughout the week. Although our findings cannot be generalized to other clinical conditions in the NHS, one should consider MI as a marker disease of high standards of weekend medical care. It could also serve as a background condition for comparing the quality of acute care during "off hours" and effectiveness of health-care systems in general.

Study strengths and limitations

The National Health Service provides healthcare for all residents of England. We used datasets of English National Hospital Episode Statistics (HES) and mortality records obtained from, respectively, the National Health Service (NHS) Information Centre and the Office for National Statistics. Linkage between the datasets was completed using encrypted values of the unique HES identifier and of the unique NHS number supplemented with encrypted values of the patients' date of birth and postcode.

Being able to identify cases of MI based on discharge diagnosis rather than on diagnosis on admission allowed us to increase the accuracy of case selection. In addition, we were able to identify and use only the primary case of each episode. Possible transfers from other hospital providers were excluded by selection of emergency admission as the only method of admission to further increase the representativeness of the studied population.

Our database included only episodes with complete data – episodes with missing data were excluded during database preparation.

To increase the validity of the results, we used three different approaches to calculate CFR – from the day of admission, from the next day after admission and from the second day after admission to the 29th day or until the day of death, whichever came first. This enabled us to separate potentially fatal cases, for deaths during first hours or days of the disease might have been the result of arrhythmias due to MI incompatible with life – which could affect the results.

Moreover, 30-day CFRs were calculated for different days of the week, groups of days of the week (Monday-Friday vs Saturday-Sunday; Monday-Thursday vs Friday-Sunday; Tuesday-Friday vs Saturday-Monday). It enabled us to see if the combinations of different weekdays had any effect on the mortality. All analyses were done for all patients combined and separately for males and females. In addition, to study the differences more precisely, we used two distinct age stratification groups: one with 5-year age intervals and another with broader, 10 to 15-year age intervals.

Apart from that, two models of logistic regression were fitted for each type of CFR. First, we calculated the univariable model and then multivariable model was calculated by using all variables of the univariable model mutually adjusted.

One of the potential weaknesses of our study might be the assumption that the severity of the disease did not vary in any considerable ways between different days of the week. We observed a deficiency in the admission rates on Saturday and Sunday, the finding which might be the result of people preferring to wait until working week start instead of calling the ambulance on weekend. It might be due to the concerns about quality of medical care and availability of medical procedures during the weekend, which, in turn, might lead us to the conclusion that only extremely ill people call for medical help on Saturday or Sunday, resulting in the larger proportion of critically ill patients admitted to hospital during the weekend with the potential to influence mortality rates values. However, we did not have the ways of testing it directly.

On the contrary, Saturday and Sunday admission deficit might also indicate the fact of missed diagnoses. And taking into consideration the fact that we did not have the opportunity to check the rates of deaths outside hospitals, missed diagnoses might be the explanation of lower weekend admissions as well.

Another potential weakness of our study might be the lack of information about the exact time of day of admission. We were not able to differentiate admissions during day or night, as well as during on and off hours. Overall, it should not have had an impact on our results as we were comparing weekdays versus weekends, long periods of time that should have levelled off such differences.

The absence of the information about the type of MI, whether the diagnosis was ST-elevation MI (STEMI) or non-ST elevation MI (NSTEMI) might serve as a potential confounder of our study as well. Different subtypes of MI require different treatment approaches and while first-line help in STEMI is percutaneous coronary intervention (PCI) where door-to-balloon time plays crucial role in survival rate, NSTEMI requires different approach with oral anticoagulation, which is readily available in hospitals, as the mainstream of therapy. The published data suggests the incidence of NSTEMI is higher than STEMI, which may have had an impact on our results(McManus et al., 2011) .

CONCLUSION

We found no evidence of the excess of deaths from myocardial infarction in patients hospitalized during the weekends.

Supplementary Data

Appendix 1.1. Males. Number and percentage of admissions to hospital for myocardial infarction by day of the week and age group, 1999-2011

Day of the week	Age Groups								All Ages[e]	
	25-39 years[a]		40-54 years[b]		55-74 years[c]		75-84 years[d]			
	n	%	n	%	n	%	n	%	n	%
Monday	1293	15.7%	11234	15.9%	29904	16.0%	13907	15.5%	56338	15.8%
Tuesday	1159	14.1%	10046	14.2%	27399	14.6%	13273	14.8%	51877	14.6%
Wednesday	1184	14.4%	9613	13.6%	26701	14.3%	13039	14.5%	50537	14.2%
Thursday	1149	13.9%	9888	14.0%	26418	14.1%	12931	14.4%	50386	14.2%
Friday	1115	13.5%	9867	14.0%	27061	14.5%	13355	14.9%	51398	14.4%
Saturday	1157	14.0%	9850	14.0%	24819	13.3%	11658	13.0%	47484	13.3%
Sunday	1189	14.4%	10094	14.3%	24945	13.3%	11565	12.9%	47793	13.4%
Monday-Friday	5900	71.5%	50648	71.7%	137483	73.4%	66505	74.1%	260536	73.2%
Saturday-Sunday	2346	28.5%	19944	28.3%	49764	26.6%	23223	25.9%	95277	26.8%
Total	8246	100.0%	70592	100.0%	187247	100.0%	89728	100.0%	355813	100.0%

- [a]Days of the week $\chi_6^2 = 16.12$, *P*-value = 0.013. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 0.06$, *P*-value = 0.807.
- [b]Days of the week $\chi_6^2 = 167.2$, *P*-value < 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 3.52$, *P*-value = 0.061.

- [c]Days of the week $\chi_6^2 = 656.65$, P-value < 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 365.09$, P-value < 0.001.

- [d]Days of the week $\chi_6^2 = 363.43$, P-value < 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 318.12$, P-value < 0.001.

- [e]Days of the week $\chi_6^2 = 1032.04$, P-value < 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 561.23$, P-value < 0.001.

Appendix 1.2. Females. Number and percentage of admission to hospital for myocardial infarction by day of the week and age group, 1999-2011

Day of the week	Age Groups								All Ages[e]	
	25-39 years[a]		40-54 years[b]		55-74 years[c]		75-84 years[d]			
	n	%	n	%	n	%	n	%	n	%
Monday	273	16.1%	2471	15.3%	13023	15.7%	12769	15.1%	28536	15.4%
Tuesday	222	13.1%	2391	14.8%	12096	14.6%	12292	14.6%	27001	14.6%
Wednesday	220	13.0%	2383	14.7%	11965	14.4%	12212	14.5%	26780	14.4%
Thursday	237	14.0%	2208	13.6%	12071	14.5%	12407	14.7%	26923	14.5%
Friday	253	15.0%	2388	14.7%	12049	14.5%	12707	15.0%	27397	14.8%
Saturday	243	14.4%	2180	13.5%	11030	13.3%	11252	13.3%	24705	13.3%
Sunday	243	14.4%	2179	13.5%	10789	13.0%	10799	12.8%	24010	13.0%
Monday-Friday	1205	71.3%	11841	73.1%	61204	73.7%	62387	73.9%	136637	73.7%
Saturday-Sunday	486	28.7%	4359	26.9%	21819	26.3%	22051	26.1%	48715	26.3%
Total	1691	100.0%	16200	100.0%	83023	100.0%	84438	100.0%	185352	100.0%

- [a]Days of the week $\chi_6^2 = 8.24$, *P*-value = 0.221. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 0.02$, *P*-value = 0.878.
- [b]Days of the week $\chi_6^2 = 38.12$, *P*-value < 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 21.98$, *P*-value <0.001.

- [c]Days of the week $\chi_6^2 = 281.23$, P-value < 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 213.48$, P-value < 0.001.

- [d]Days of the week $\chi_6^2 = 278.68$, P-value < 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 249.65$, P-value < 0.001.

- [e]Days of the week $\chi_6^2 = 561.85$, P-value < 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 475.87$, P-value < 0.001.

Appendix 2.1. Males. Number and percentage of death for myocardial infarction by day of the week, 1999-2011[a]

Day of the week	Death in hospital in days after admission								Total[f]	
	Same day death[b]		1 day death[c]		2 day death[d]		3-29 days death[e]			
Monday	847	14.9%	925	15.9%	537	14.8%	3043	15.5%	5352	15.4%
Tuesday	824	14.5%	878	15.1%	540	14.9%	2846	14.5%	5088	14.6%
Wednesday	778	13.7%	813	13.9%	545	15.0%	2810	14.3%	4946	14.2%
Thursday	815	14.3%	810	13.9%	474	13.1%	2862	14.6%	4961	14.3%
Friday	841	14.8%	851	14.6%	548	15.1%	2941	15.0%	5181	14.9%
Saturday	792	13.9%	758	13.0%	495	13.6%	2577	13.1%	4622	13.3%
Sunday	783	13.8%	797	13.7%	489	13.5%	2533	12.9%	4602	13.2%
Monday-Friday	4105	72.3%	4277	73.3%	2644	72.9%	14502	73.9%	25528	73.5%
Saturday-Sunday	1575	27.7%	1555	26.7%	984	27.1%	5110	26.1%	9224	26.5%
Total	5680	100.0%	5832	100.0%	3628	100.0%	19612	100.0%	34752	100.0%

- [a]Assuming an equal spread of deaths occurring inside hospital across days of the week, there would be an expected 14.3% (1/7) of all deaths on each day.
- [b]Days of the week $\chi_6^2 = 5.69$, *P*-value = 0.459. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 1.98$, *P*-value = 0.16.
- [c]Days of the week $\chi_6^2 = 22.4$, *P*-value = 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 10.41$, *P*-value = 0.001.
- [d]Days of the week $\chi_6^2 = 11.15$, *P*-value = 0.084. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 3.73$, *P*-value = 0.053.

- [e]Days of the week $\chi_6^2 = 73.52$, P-value < 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 60.83$, P-value < 0.001.
- [f]Days of the week $\chi_6^2 = 92.93$, P-value < 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 70.11$, P-value < 0.001.

Appendix 2.2. Females. Number and percentage of death for myocardial infarction by day of the week, 1999-2011[a]

Day of the week	Death in hospital in days after admission								Total[f]	
	Same day death[b]		1 day death[c]		2 day death[d]		3-29 days death[e]			
Monday	675	14.6%	792	15.4%	446	14.7%	2172	14.9%	4085	14.9%
Tuesday	650	14.1%	737	14.3%	434	14.3%	2084	14.3%	3905	14.2%
Wednesday	623	13.5%	741	14.4%	432	14.2%	2096	14.3%	3892	14.2%
Thursday	695	15.0%	731	14.2%	460	15.1%	2195	15.0%	4081	14.9%
Friday	656	14.2%	769	14.9%	437	14.4%	2276	15.6%	4138	15.1%
Saturday	651	14.1%	709	13.8%	420	13.8%	1898	13.0%	3678	13.4%
Sunday	676	14.6%	677	13.1%	410	13.5%	1901	13.0%	3664	13.4%
Monday-Friday	3299	71.3%	3770	73.1%	2209	72.7%	10823	74.0%	20101	73.2%
Saturday-Sunday	1327	28.7%	1386	26.9%	830	27.3%	3799	26.0%	7342	26.8%
Total	4626	100.0%	5156	100.0%	3039	100.0%	14622	100.0%	27443	100.0%

- [a]Assuming an equal spread of deaths occurring inside hospital across days of the week, there would be an expected 14.3% (1/7) of all deaths on each day.
- [b]Days of the week $\chi_6^2 = 4.94$, *P*-value = 0.551. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 0.03$, *P*-value = 0.863.
- [c]Days of the week $\chi_6^2 = 11.52$, *P*-value = 0.074. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 7.22$, *P*-value = 0.007.

- [d]Days of the week $\chi_6^2 = 3.7$, P-value = 0.718. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 2.36$, P-value = 0.124.

- [e]Days of the week $\chi_6^2 = 59.84$, P-value < 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 48.06$, P-value < 0.001.

- [f]Days of the week $\chi_6^2 = 57.59$, P-value < 0.001. Comparing weekend and weekday: Saturday-Sunday versus Monday-Friday $\chi_1^2 = 44.43$, P-value < 0.001.

Appendix 3.1. 30-day case-fatality rates (CFR) by day of the week for different age groups with myocardial infarction from 1999 to 2011

Day of the week	Age Groups														
	25-39 years[a]			40-54 years[b]			55-74 years[c]			75-84 years[d]			All Ages[e]		
	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)
Monday	1566	25	1.6	13705	334	2.4	42927	3707	8.6	26676	5371	20.1	84874	9437	11.1
Tuesday	1381	26	1.9	12437	320	2.6	39495	3414	8.6	25565	5233	20.5	78878	8993	11.4
Wednesday	1404	34	2.4	11996	284	2.4	38666	3338	8.6	25251	5182	20.5	77317	8838	11.4
Thursday	1386	26	1.9	12096	309	2.6	38489	3444	8.9	25338	5263	20.8	77309	9042	11.7
Friday	1368	30	2.2	12255	333	2.7	39110	3433	8.8	26062	5523	21.2	78795	9319	11.8
Saturday	1400	22	1.6	12030	309	2.6	35849	3174	8.9	22910	4795	20.9	72189	8300	11.5
Sunday	1432	31	2.2	12273	343	2.8	35734	3191	8.9	22364	4701	21.0	71803	8266	11.5
Monday-Friday	7105	141	2.0	62489	1580	2.5	198687	17336	8.7	128892	26572	20.6	397173	45629	11.5
Saturday-Sunday	2832	53	1.9	24303	652	2.7	71583	6365	8.9	45274	9496	21.0	143992	16566	11.5
Monday-Thursday	5737	111	1.9	50234	1247	2.5	159577	13903	8.7	102830	21049	20.5	318378	36310	11.4
Friday-Sunday	4200	83	2.0	36558	985	2.7	110693	9798	8.9	71336	15019	21.1	222787	25885	11.6

Tuesday-Friday	5539	116	2.1	48784	1246	2.6	155760	13629	8.8	102216	21201	20.7	312299	36192	11.6
Saturday-Monday	4398	78	1.8	38008	986	2.6	114510	10072	8.8	71950	14867	20.7	228866	26003	11.4
Total	9937	194	2.0	86792	2232	2.6	270270	23701	8.8	174166	36068	20.7	541165	62195	11.5

- [a]Days of the week χ_6^2 = 4.54, *P*-value = 0.604. Comparing weekend and weekday: Monday-Friday (2.0%) versus Saturday-Sunday (1.9%) χ_1^2 = 0.14, *P*-value = 0.713; Monday-Thursday (1.9%) versus Friday-Sunday (2.0%) χ_1^2 = 0.02, *P*-value = 0.883; Tuesday-Friday (2.1%) versus Saturday-Monday (1.8%) χ_1^2 = 1.32, *P*-value = 0.251.

- [b]Days of the week χ_6^2 = 6.48, *P*-value = 0.372. Comparing weekend and weekday: Monday-Friday (2.5%) versus Saturday-Sunday (2.7%) χ_1^2 = 1.66, *P*-value = 0.197; Monday-Thursday (2.5%) versus Friday-Sunday (2.7%) χ_1^2 = 3.79, *P*-value = 0.051; Tuesday-Friday (2.6%) versus Saturday-Monday (2.6%) χ_1^2 = 0.14, *P*-value = 0.711.

- [c]Days of the week χ_6^2 = 5.64, *P*-value = 0.464. Comparing weekend and weekday: Monday-Friday (8.7%) versus Saturday-Sunday (8.9%) χ_1^2 = 1.82, *P*-value = 0.177; Monday-Thursday (8.7%) versus Friday-Sunday (8.9%) χ_1^2 = 1.58, *P*-value = 0.209; Tuesday-Friday (8.8%) versus Saturday-Monday (8.8%) χ_1^2 = 0.17, *P*-value = 0.678.

- [d]Days of the week χ_6^2 = 12.56, *P*-value = 0.051. Comparing weekend and weekday: Monday-Friday (20.6%) versus Saturday-Sunday (21.0%) χ_1^2 = 2.63, *P*-value = 0.105; Monday-Thursday (20.5%) versus Friday-Sunday (21.1%) χ_1^2 = 8.75, *P*-value = 0.003; Tuesday-Friday (20.7%) versus Saturday-Monday (20.7%) χ_1^2 = 0.16, *P*-value = 0.691.

- [e]Days of the week χ_6^2 = 24.42, *P*-value = 0.001. Comparing weekend and weekday: Monday-Friday (11.5%) versus Saturday-Sunday (11.5%) χ_1^2 = 0.03, *P*-value = 0.602; Monday-Thursday (11.4%) versus Friday-Sunday (11.6%) χ_1^2 = 5.9, *P*-value = 0.015; Tuesday-Friday (11.6%) versus Saturday-Monday (11.4%) χ_1^2 = 6.7, *P*-value = 0.01.

Appendix 3.2. 30-day case-fatality rates (CFR) by day of the week for different age groups with myocardial infarction from 1999 to 2011

Day of the week	Age Groups														
	25-29 years[a]			30-34 years[b]			35-39 years[c]			40-44 years[d]			45-49 years[e]		
	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)
Monday	102	1	1.0	362	5	1.4	1102	19	1.7	2645	55	2.1	4508	84	1.9
Tuesday	87	2	2.3	341	5	1.5	953	19	2.0	2340	48	2.1	4062	89	2.2
Wednesday	96	3	3.1	311	5	1.6	997	26	2.6	2323	39	1.7	3958	83	2.1
Thursday	84	2	2.4	307	6	2.0	995	18	1.8	2240	44	2.0	3993	87	2.2
Friday	88	5	5.7	312	7	2.2	968	18	1.9	2273	43	1.9	3956	107	2.7
Saturday	101	1	1.0	339	8	2.4	960	13	1.4	2309	47	2.0	3949	104	2.6
Sunday	103	4	3.9	369	7	1.9	960	20	2.1	2395	51	2.1	4047	104	2.6
Monday-Friday	457	13	2.8	1633	28	1.7	5015	100	2.0	11821	229	1.9	20477	450	2.2
Saturday-Sunday	204	5	2.5	708	15	2.1	1920	33	1.7	4704	98	2.1	7996	208	2.6
Monday-Thursday	369	8	2.2	1321	21	1.6	4047	82	2.0	9548	186	1.9	16521	343	2.1
Friday-Sunday	292	10	3.4	1020	22	2.2	2888	51	1.8	6977	141	2.0	11952	315	2.6
Tuesday-Friday	355	12	3.4	1271	23	1.8	3913	81	2.1	9176	174	1.9	15969	366	2.3
Saturday-Monday	306	6	2.0	1070	20	1.9	3022	52	1.7	7349	153	2.1	12504	292	2.3
Total	661	18	2.7	2341	43	1.8	6935	133	1.9	16525	327	2.0	28473	658	2.3

N – total number of patients; n – number of patients who died

- [a]Days of the week χ_6^2 = 5.9, *P*-value = 0.434. Comparing weekend and weekday: Monday-Friday (2.8%) versus Saturday-Sunday (2.5%) χ_1^2 = 0.08, *P*-value = 0.774; Monday-Thursday (2.2%) versus Friday-Sunday (3.4%) χ_1^2 = 0.97, *P*-value = 0.324; Tuesday-Friday (3.4%) versus Saturday-Monday (2.0%) χ_1^2 = 1.25, *P*-value = 0.264.
- [b]Days of the week χ_6^2 = 1.6, *P*-value = 0.953. Comparing weekend and weekday: Monday-Friday (1.7%) versus Saturday-Sunday (2.1%) χ_1^2 = 0.45, *P*-value = 0.504; Monday-Thursday (1.6%) versus Friday-Sunday (2.2%) χ_1^2 = 1.03, *P*-value = 0.311; Tuesday-Friday (1.8%) versus Saturday-Monday (1.9%) χ_1^2 = 0.01, *P*-value = 0.915.
- [c]Days of the week χ_6^2 = 4.61, *P*-value = 0.594. Comparing weekend and weekday: Monday-Friday (2.0%) versus Saturday-Sunday (1.7%) χ_1^2 = 0.56, *P*-value = 0.455; Monday-Thursday (2.0%) versus Friday-Sunday (1.8%) χ_1^2 = 0.61, *P*-value = 0.436; Tuesday-Friday (2.1%) versus Saturday-Monday (1.7%) χ_1^2 = 1.11, *P*-value = 0.293.
- [d]Days of the week χ_6^2 = 1.69, *P*-value = 0.946. Comparing weekend and weekday: Monday-Friday (1.9%) versus Saturday-Sunday (2.1%) χ_1^2 = 0.37, *P*-value = 0.543; Monday-Thursday (1.9%) versus Friday-Sunday (2.0%) χ_1^2 = 0.11, *P*-value = 0.74; Tuesday-Friday (1.9%) versus Saturday-Monday (2.1%) χ_1^2 = 0.73, *P*-value = 0.394.
- [e]Days of the week χ_6^2 = 11.11, *P*-value = 0.085. Comparing weekend and weekday: Monday-Friday (2.2%) versus Saturday-Sunday (2.6%) χ_1^2 = 4.15, *P*-value = 0.042; Monday-Thursday (2.1%) versus Friday-Sunday (2.6%) χ_1^2 = 9.61, *P*-value = 0.002; Tuesday-Friday (2.3%) versus Saturday-Monday (2.3%) χ_1^2 = 0.06, *P*-value = 0.809.

Appendix 3.2. 30-day case-fatality rates (CFR) by day of the week for different age groups with myocardial infarction from 1999 to 2011 (cont.)

Day of the week	Age Groups											
	50-54 years[a]			55-59 years[b]			60-64 years[c]			65-69 years[d]		
	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)
Monday	6552	195	3.0	8635	345	4.0	10324	639	6.2	11264	1026	9.1
Tuesday	6035	183	3.0	7717	321	4.2	9301	558	6.0	10637	940	8.8
Wednesday	5715	162	2.8	7704	368	4.8	9082	547	6.0	10237	877	8.6
Thursday	5863	178	3.0	7353	323	4.4	9027	565	6.3	10236	895	8.7
Friday	6026	183	3.0	7709	354	4.6	9208	555	6.0	10340	971	9.4
Saturday	5772	158	2.7	7239	307	4.2	8544	537	6.3	9300	864	9.3
Sunday	5831	188	3.2	7495	332	4.4	8443	519	6.1	9317	855	9.2
Monday-Friday	30191	901	3.0	39118	1711	4.4	46942	2864	6.1	52714	4709	8.9
Saturday-Sunday	11603	346	3.0	14734	639	4.3	16987	1056	6.2	18617	1719	9.2
Monday-Thursday	24165	718	3.0	31409	1357	4.3	37734	2309	6.1	42374	3738	8.8
Friday-Sunday	17629	529	3.0	22443	993	4.4	26195	1611	6.2	28957	2690	9.3
Tuesday-Friday	23639	706	3.0	30483	1366	4.5	36618	2225	6.1	41450	3683	8.9
Saturday-Monday	18155	541	3.0	23369	984	4.2	27311	1695	6.2	29881	2745	9.2
Total	41794	1247	3.0	53852	2350	4.4	63929	3920	6.1	71331	6428	9.0

N – total number of patients; n – number of patients who died

- [a]Days of the week χ_6^2 = 2.98, *P*-value = 0.812. Comparing weekend and weekday: Monday-Friday (3.0%) versus Saturday-Sunday (3.0%) χ_1^2 = 0.001, *P*-value = 0.99; Monday-Thursday (3.0%) versus Friday-Sunday (3.0%) χ_1^2 = 0.03, *P*-value = 0.861; Tuesday-Friday (3.0%) versus Saturday-Monday (3.0%) χ_1^2 = 0.002, *P*-value = 0.968.

- [b]Days of the week χ_6^2 = 8.04, *P*-value = 0.235. Comparing weekend and weekday: Monday-Friday (4.4%) versus Saturday-Sunday (4.3%) χ_1^2 = 0.35, *P*-value = 0.851; Monday-Thursday (4.3%) versus Friday-Sunday (4.4%) χ_1^2 = 0.34, *P*-value = 0.56; Tuesday-Friday (4.5%) versus Saturday-Monday (4.2%) χ_1^2 = 2.32, *P*-value = 0.128.

- [c]Days of the week χ_6^2 = 1.31, *P*-value = 0.971. Comparing weekend and weekday: Monday-Friday (6.1%) versus Saturday-Sunday (6.2%) χ_1^2 = 0.29, *P*-value = 0.591; Monday-Thursday (6.1%) versus Friday-Sunday (6.2%) χ_1^2 = 0.03, *P*-value = 0.873; Tuesday-Friday (6.1%) versus Saturday-Monday (6.2%) χ_1^2 = 0.46, *P*-value = 0.498.

- [d]Days of the week χ_6^2 = 6.89, *P*-value = 0.331. Comparing weekend and weekday: Monday-Friday (8.9%) versus Saturday-Sunday (9.2%) χ_1^2 = 1.51, *P*-value = 0.219; Monday-Thursday (8.8%) versus Friday-Sunday (9.3%) χ_1^2 = 4.6, *P*-value = 0.032; Tuesday-Friday (8.9%) versus Saturday-Monday (9.2%) χ_1^2 = 1.92, *P*-value = 0.166.

Appendix 3.2. 30-day case-fatality rates (CFR) by day of the week for different age groups with myocardial infarction from 1999 to 2011 (cont.)

Day of the week	Age Groups											
	70-74 years[a]			75-79 years[b]			80-84 years[c]			All ages[d]		
	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)	N	n	CFR(%)
Monday	12704	1697	13.4%	13705	2480	18.1	12971	2891	22.3	84874	9437	11.1
Tuesday	11840	1595	13.5%	13071	2404	18.4	12494	2829	22.6	78878	8993	11.4
Wednesday	11643	1546	13.3%	12918	2382	18.4	12333	2800	22.7	77317	8838	11.4
Thursday	11873	1661	14.0%	12947	2375	18.3	12391	2888	23.3	77309	9042	11.7
Friday	11853	1553	13.1%	13380	2563	19.2	12682	2960	23.3	78795	9319	11.8
Saturday	10766	1466	13.6%	11627	2186	18.8	11283	2609	23.1	72189	8300	11.5
Sunday	10479	1485	14.2%	11301	2098	18.6	11063	2603	23.5	71803	8266	11.5
Monday-Friday	59913	8052	13.4%	66021	12204	18.5	62871	14368	22.9	397173	45629	11.5
Saturday-Sunday	21245	2951	13.9%	22928	4284	18.7	22346	5212	23.3	143992	16566	11.5
Monday-Thursday	48060	6499	13.5%	52641	9641	18.3	50189	11408	22.7	318378	36310	11.4
Friday-Sunday	33098	4504	13.6%	36308	6847	18.9	35028	8172	23.3	222787	25885	11.6
Tuesday-Friday	47209	6355	13.5%	52316	9724	18.6	49900	11477	23.0	312299	36192	11.6
Saturday-Monday	33949	4648	13.7%	36633	6764	18.5	35317	8103	22.9	228866	26003	11.4

Total	81158	11003	13.6%	88949	16488	18.5	85217	19580	23.0	541165	62195	11.5

N – total number of patients; n – number of patients who died

- [a]Days of the week $\chi_6^2 = 8.67$, *P*-value = 0.193. Comparing weekend and weekday: Monday-Friday (13.4%) versus Saturday-Sunday (13.9%) $\chi_1^2 = 2.72$, *P*-value = 0.099; Monday-Thursday (13.5%) versus Friday-Sunday (13.6%) $\chi_1^2 = 0.12$, *P*-value = 0.727; Tuesday-Friday (13.5%) versus Saturday-Monday (13.7%) $\chi_1^2 = 0.89$, *P*-value = 0.346.

- [b]Days of the week $\chi_6^2 = 6.28$, *P*-value = 0.392. Comparing weekend and weekday: Monday-Friday (18.5%) versus Saturday-Sunday (18.7%) $\chi_1^2 = 0.45$, *P*-value = 0.503; Monday-Thursday (18.3%) versus Friday-Sunday (18.9%) $\chi_1^2 = 4.2$, *P*-value = 0.04; Tuesday-Friday (18.6%) versus Saturday-Monday (18.5%) $\chi_1^2 = 0.22$, *P*-value = 0.643.

- [c]Days of the week $\chi_6^2 = 8.54$, *P*-value = 0.201. Comparing weekend and weekday: Monday-Friday (22.9%) versus Saturday-Sunday (23.3%) $\chi_1^2 = 2.01$, *P*-value = 0.151; Monday-Thursday (22.7%) versus Friday-Sunday (23.3%) $\chi_1^2 = 4.19$, *P*-value = 0.041; Tuesday-Friday (23.0%) versus Saturday-Monday (22.9%) $\chi_1^2 = 0.04$, *P*-value = 0.847.

- [d]Days of the week $\chi_6^2 = 24.42$, *P*-value = 0.001. Comparing weekend and weekday: Monday-Friday (11.5%) versus Saturday-Sunday (11.5%) $\chi_1^2 = 0.03$, *P*-value = 0.602; Monday-Thursday (11.4%) versus Friday-Sunday (11.6%) $\chi_1^2 = 5.9$, *P*-value = 0.015; Tuesday-Friday (11.6%) versus Saturday-Monday (11.4%) $\chi_1^2 = 6.7$, *P*-value = 0.01.

Appendix 5.1 Determinants for 30-day CFR for myocardial infarction, 1999-2011, odds ratios with their 95% confidence intervals obtained from logistic regression with variations of weekend[a] definitions

Determinants	Odds Ratio	95% CI		P-value	30d CFR	Total
Age Groups		Lower	Upper			
25-29[b]	1.0			<0.001	18	661
30-34	0.65	0.38	1.14	0.136	43	2341
35-39	0.69	0.42	1.14	0.146	133	6935
40-44	0.72	0.44	1.16	0.174	327	16525
45-49	0.84	0.52	1.35	0.471	658	28473
50-54	1.07	0.67	1.72	0.778	1247	41794
55-59	1.59	0.99	2.54	0.054	2350	53852
60-64	2.26	1.42	3.62	0.001	3920	63929
65-69	3.37	2.10	5.38	<0.001	6428	71331
70-74	5.30	3.31	8.47	<0.001	11003	81158
75-79	7.68	4.81	12.28	<0.001	16488	88949
80-84	10.28	6.43	16.43	<0.001	19580	85217
Sex						
Male	0.88	0.87	0.90	<0.001	34752	355813
Female[b]	1.0				27443	185352
Year of Admission						
1999[b]				<0.001	7527	52282
2000	0.91	0.88	0.95	<0.001	6629	49485
2001	0.87	0.84	0.90	<0.001	6352	48459
2002	0.86	0.82	0.89	<0.001	6443	48998
2003	0.80	0.77	0.83	<0.001	5946	47260
2004	0.73	0.70	0.76	<0.001	5452	46487
2005	0.73	0.70	0.76	<0.001	5013	42931

2006		0.66		0.63	0.69		<0.001		4166		39561
2007		0.62		0.59	0.65		<0.001		3721		37662
2008		0.58		0.55	0.60		<0.001		3331		35291
2009		0.53		0.51	0.56		<0.001		2875		33356
2010		0.51		0.49	0.54		<0.001		2573		30536
2011		0.45		0.43	0.47		<0.001		2167		28857
Days of Admission											
Saturday-Sunday		1.01		0.98	1.05		0.467		16566		143992
Monday-Friday[b]		1.0							45629		397173
Friday-Sunday		1.03		1.00	1.05		0.048		25885		222787
Monday-Thursday[b]		1.0							36310		318378
Saturday-Monday		0.98		0.96	1.01		0.194		26003		228866
Tuesday-Friday[b]		1.0							36192		312299

[a]The results for the three variations of ‘weekend’ were obtained by running each variation separately

[b]Reference group

Appendix 5.2. Determinants of 30-day CFR for myocardial infarction, 1999–2011, odds ratios with their 95% confidence intervals obtained from logistic regression with variations of weekend[a] definition

Determinants	OR	95% CI		P-value
Age groups		Lower	Upper	
25-39[b]	1.0			<0.001
40-54	1.33	1.14	1.54	<0.001
55-74	4.83	4.19	5.57	<0.001
75-84	13.12	11.37	15.13	<0.001
Age groups				
25-29[b]	1.0			<0.001
30-34	0.67	0.38	1.17	0.156
35-39	0.70	0.42	1.15	0.159
40-44	0.72	0.45	1.17	0.183
45-49	0.85	0.53	1.36	0.487
50-54	1.10	0.69	1.76	0.696
55-59	1.63	1.02	2.61	0.042
60-64	2.33	1.46	3.73	<0.001
65-69	3.54	2.21	5.66	<0.001
70-74	5.60	3.51	8.95	<0.001
75-79	8.13	5.09	12.99	<0.001
80-84	10.66	6.67	17.03	<0.001
Sex				
Male	0.62	0.61	0.63	<0.001
Female[b]	1.0			
Year of Admission				
1999[b]				<0.001
2000	0.92	0.89	0.95	<0.001
2001	0.90	0.87	0.93	<0.001

2002		0.90		0.87	0.93		<0.001
2003		0.86		0.83	0.89		<0.001
2004		0.79		0.76	0.82		<0.001
2005		0.79		0.76	0.82		<0.001
2006		0.70		0.67	0.73		<0.001
2007		0.65		0.63	0.68		<0.001
2008		0.62		0.59	0.65		<0.001
2009		0.56		0.54	0.59		<0.001
2010		0.55		0.52	0.57		<0.001
2011		0.48		0.46	0.51		<0.001
Days of Admission							
Saturday-Sunday		1.00		0.98	1.02		0.868
Monday-Friday[b]		1.0					
Friday-Sunday		1.02		1.00	1.04		0.015
Monday-Thursday[b]		1.0					
Saturday-Monday		0.98		0.96	1.00		0.01
Tuesday-Friday[b]		1.0					

[a]The results for the three variations of ‘weekend’ were obtained by running each variation separately

[b]Reference group

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