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Title:

Relative survival and excess mortality following primary percutaneous coronary intervention for ST-elevation myocardial infarction.

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Abstract

Background: High survival rates are commonly reported following primary percutaneous coronary intervention (PPCI) for STEMI with most contemporary studies reporting overall survival.

Aims: To describe survival following PPCI for STEMI corrected for non-cardiovascular deaths by reporting relative survival and investigate clinically significant factors associated with poor long term outcomes.

Methods and Results: Using the prospective UK PCI registry, PPCI cases (n=88,188; 2005-2013) were matched to mortality data for the UK populace. Crude 5-year relative survival was 87.1%for the patients undergoing PPCI and 94.7% for patients <55 years. Increasing age was associated with excess mortality up to 4 years following PPCI (56-65 years: excess mortality rate ratio (EMRR) 1.61, 95% CI 1.46-1.79; 66-75 years: 2.49, 2.26-2.75; >75 years: 4.69, 4.27-5.16). After 4 years, there was no excess mortality for ages 56-65 years (EMRR 1.27, 95% CI 0.95-1.70), but persisting excess mortality for older groups (66-75 years: EMRR 1.72, 95% CI 1.30-2.27; >75 years: 1.66, 1.15–2.41). Excess mortality was associated with cardiogenic shock (EMRR 6.10, 95% CI 5.72-6.50), renal failure (2.52, 2.27-2.81), left main stem stenosis (1.67, 1.54-1.81), diabetes (1.58, 1.47-1.69), previous MI (1.52, 1.40-1.65) and female sex (1.33, 1.26-1.41); whereas stent deployment (0.46, 0.42-0.50), radial access (0.70, 0.63-0.71) and previous PCI (0.67, 0.60-0.75) were protective.

Conclusions: Following PPCI for STEMI, long term cardiovascular survival is excellent. Failure to account for non-cardiovascular death may result in an underestimation of the efficacy of PPCI.

Keywords

PPCI, STEMI, Relative survival, Excess mortality, Cardiogenic shock, Renal insufficiency, Radial access, Risk stratification

Condensed abstract

After matching 88,188 cases of PPCI to the background UK death data, 5-year crude relative survival was 87% overall, and 94.7% among patients aged <55 years. After 4 years from PPCI, there was no excess mortality for patients aged 56-65 years, but older ages experienced ongoing excess mortality. Excess mortality was also significantly associated with renal failure and cardiogenic shock. Following PPCI relative survival was excellent, however, increasing age, renal failure and cardiogenic shock contribute to PPCI related mortality.

Introduction

The development of specialist heart attack centres, evolving pharmacology, second and third generation stent technology and increasing expertise has resulted in a decline in short term mortality following ST-elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (PPCI)[1, 2]. However, in the longer term non-cardiovascular death following PPCI is common and failure to account for this may underestimate the impact of PPCI on survival. Reported rates of death following PPCI are incongruent, with randomised studies suggest three year mortality rates of 3-8% and observational cohorts report one year mortality rates of around 10%[3-6]. Whilst variation in rates of death following PPCI may be due to unrepresentative cohorts, variable lengths of follow-up and different study designs, recently is has become apparent that the predominant cause of death following PCI may be non-cardiovascular and this may influence how mortality is attributed to PPCI [1].

Conventionally, the majority of studies of PPCI report all-cause mortality as the primary outcome [7]. Whilst this establishes the high

human cost and overall survival advantage it fails to estimate the underlying comorbidity in patients presenting with STEMI or estimate the efficacy of treatment with PPCI on cardiovascular outcomes. In turn, this has potential repercussions for the design and study of new treatments as well as informing patients as to the risks and benefits of the intervention. To overcome the limitations of all-cause mortality some studies report cause-specific mortality – addressing cardiac death rather than death due to any cause[8]. However, these data may be difficult to obtain or adjudicate on and are subject to bias by misclassification, for example lack of objectivity on death certificates or surmised cause of death without post-mortem studies [9]. An alternative method to estimate cause-specific outcomes is the technique of relative survival (RS), which compares outcomes between patients and an age and sex matched comparator group of the overall population – this provides the advantage of being able to correct for non-cardiac death and enables quantification of factors associated with excess deaths [10, 11].

Using data from the United Kingdom PCI register (British Cardiovascular Intervention Society (BCIS) database), which includes all cases of PPCI in England and Wales; we aimed to

estimate the relative survival of patients following PPCI and investigate factors associated with their excess mortality.

Methods

Patients

We included all National Health Service hospitals (n=111) in England and Wales which provided care for patients aged 18-100 years with STEMI and who received PPCI between 1st January 2005 and 30th June, 2013 (n=88,188), (Figure 1). Patient-level data concerning demographics, cardiovascular risk factors, medical history and clinical and treatment characteristics at the time of hospitalisation were extracted from BCIS, whereby participation is mandated for all PCI operators and all National Health Service hospitals. Details of the BCIS registry have been described previously[12]. For multiple admissions, we used the earliest record, the diagnosis of STEMI was formulated by the attending clinician in line with the third universal definition of myocardial infarction[13].

Mortality and follow up

All-cause mortality data were extracted through linkage to the United Kingdom Office for National Statistics using each patient's unique anonymised National Health Service number. Patients were followed for five years from date of PPCI, with censoring at the end of follow-up on 31st December, 2013 (Appendix A). Survival time was defined as the duration between the date of the procedure and the date of death or censoring.

Relative survival

Relative survival was defined as the observed survival of PPCI cases divided by the expected survival of the comparable United Kingdom populace, and expressed as a relative survival rate (RSR). Observed survival was estimated using the actuarial method which calculates the survival in time intervals from the effective number of patients at risk in that particular interval. The expected survival was estimated by the Ederer II method [11]. For expected survival, country-specific population mortality rates of the United Kingdom were based on life tables from the Office for National Statistics and matched to the cohort by age, sex and year of procedure. A relative survival rate of

100% implies that cases of PPCI have survival rates equal to that of the matched, disease free background population.

Excess mortality

Excess mortality provides a measure of the additional hazard associated with a procedure or treatment and is expressed as a rate ratio (EMRR). For example, an EMRR of 1.5 for men/women indicates that men experience 50% higher excess mortality than women after accounting for the matched background rates of death. A multivariable model was built based on the following covariates: previous myocardial infarction, diabetes, chronic renal impairment (creatinine >2.26mg/dl or 200micromol/l), pre-procedural cardiogenic shock, flow in the infarct related artery, use of mechanical ventilation, number of stents deployed, number of vessels attempted, previous PCI and family history of coronary artery disease. The statistical model used collapsed life table data and generalised linear regression with a Poisson error structure. We checked for time-dependency and non-proportional hazards by fitting interaction terms between short-term follow up periods (<4 years and ≥4 years respectively) with age, which were significant (likelihood ratio test p=0.005). There was no evidence for non-proportional hazards for sex and calendar year by follow-up. Missing data were addressed using

multiple imputation by chained equations to create 20 imputed datasets and model estimates pooled over each imputation. All tests were two-tailed with 5% significance level and performed using Stata IC version 13.1 (StataCorp Texas USA).

Results

The PPCI cohort comprised 73.9% men, mean age 63.4 (SD 13.1) years; 41.1% were smokers and 13.4% had diabetes. Over half (56.1%) of cases were completed via radial access route, 7.4% presented with cardiogenic shock, 9.3% received more than three stents, 4.5% had >50% left main stem disease and 0.9% had a history of renal disease (Table 1).

Relative survival

Over 216,846 person-years follow-up (median follow up 2.5 years), in total 12,178 (13.8%) patients died. Overall (crude) relative survival was 92.8% (95% CI, 92.6-93.0%) at 3 months, 92.5% (92.3-92.7%) at 6 months, 92.3% (92.1-92.5%) at 1 year and 87.1% (86.6-87.7%) at 5 years. One year relative survival declined with increasing age

such that survival estimates for patients aged <55, 56-65, 66-75 and >75 years were 97.3%, 95.3%, 91.8% and 83.1% respectively (Figure 2). The corresponding 5 year estimates were 95.4%, 92.8%, 88.3% and 79.0%.

Excess mortality

Up to 4 years following PPCI, compared with those less than 55 years old there was excess mortality among patients aged 55-65 years (EMRR 1.61, 95% CI 1.46-1.79), 66-75 years (2.49, 2.26-2.75) and >75 years (4.69, 4.27-5.16). After 4 years, there was no excess mortality for ages 56-65 years (EMRR 1.27, 95% CI 0.95-1.70), but ongoing excess mortality for ages 66-75 years (1.72, 1.30-2.27) and >75 years (1.66, 1.15-2.41) (Figure 3). Excess mortality was a third higher amongst females than males (EMRR 1.33, 95% CI 95% 1.26-1.41).

Clinical factors significantly associated with increased excess mortality were diabetes (EMRR 1.58, 1.47-1.69), renal failure (2.52, 2.27-2.81), pre-procedural ventilation (3.82, 3.56-4.12), pre-procedural cardiogenic shock (6.10, 5.72-6.50), left main stem stenosis >50% (1.67, 1.54-1.81) and previous MI (1.52, 1.40-1.65).

This contrasted with previous PCI (EMRR 0.67, 0.60-0.75), a family history of coronary artery disease (0.75, 0.69-0.81), the use of stents over balloon angioplasty (0.38, 0.34-0.41) and radial artery access (0.70, 0.63-0.71). The use of radial vs femoral access was associated with lower excess mortality in the elderly (EMRR <75 years, 95%.... 0.70, 0.65-0.76 and ≥75 years. 0.64, 0.59-0.69) (Figure 3)., The use of bare metal stents (BMS) was associated with lower excess mortality compared with POBA (EMRR 0.49, 95%…0.45-0.55) and DES superior to POBA (0.27, 0.24-0.29).

Discussion

This study of nearly 90,000 patients over five years of follow up addresses a key limitation of real world survival data for PPCI. For the first time in the literature, we report the long term relative survival for PPCI and investigate factors attributable to death from index STEMI and its treatment with PPCI.

The methods employed are relevant in the current era of high cardiovascular survival when the majority of deaths are remote from the date of intervention, not cardiovascular in origin and relate to the background risk of the population[8]. In particular, when studying the efficacy of an intervention amongst older age groups, lack of adjustment for increasing mortality amongst the general population can lead to underestimation of the interventions' efficacy. This study provides evidence for very high rates of five year relative survival – between 2005 and 2013 survival was 90% for the cohort and approached 96% for patients aged <55 years. After adjustment for baseline clinical characteristics and death with the matched general population, evidence for excess mortality was associated with increasing age, renal failure, pre-procedural cardiogenic shock, mechanical ventilation, presence of left main stem disease, previous MI and femoral access.

Overall, relative survival rates were lower early after PPCI, after which the hazards then decreased, this effect was most notably in the elderly. The survival for younger than 65 years old, 4 years after PPCI was the same as that of the age, sex, year and country matched background population. Previous studies report worse outcomes for the elderly at one (13.9% mortality), three (43.0%) and

five years (53.6%) with increasing age being an independent risk factor[14-16]. In our study, we found that the five year survival rate among patients over 75 years was 53%, and 79% when adjusted for the age, sex, year and country-specific background rates of death. These data suggest that despite the survival advantage conferred with PPCI for STEMI, the elderly fail to reach rates of survival comparable with their matched counterparts in the general population. We speculate that this may be due to a greater evidence-to-practice gap in secondary preventative care after hospital discharge among the elderly compared with the young [2, 17, 18].

We found that females had a third higher risk of excess mortality, consistent with other studies that have also shown that the femoral approach is associated with early mortality in this group[19-21]. Females also had an ongoing disadvantage, suggesting that although femoral access may be unfavourable in the short–term, other sex-specific factors including multimorbidity, mode of presentation and medications prescribed may influence longer-term outcome.

Other factors associated with excess mortality were major pre-existing medical conditions such as diabetes and renal failure as well

as the presence of acute STEMI-related scenarios including cardiogenic shock and mechanical ventilation[22]. Cardiogenic shock conferred a six-fold increased risk of death relative to the general population which persisted up to five years from the date of the procedure. This is likely related to degree of acute myocardial necrosis which persists even after successful revascularisation and its long term counterpart – chronic LV dysfunction. [23]. Our study cohort included those who had PPCI for STEMI but did not include those having facilitated or rescue PCI.

Previous myocardial infarction was associated with a 50% increase excess mortality. It is probable that this is a marker of infarction-mediated left ventricular dysfunction and/or pre-existent multi vessel coronary artery disease – each known to impact upon survival[24]. We found that a family history of coronary artery disease and previous PCI were each associated with improved outcomes. Whilst we cannot fully explain this, it may represent a healthy user bias – with those with a family history of cardiovascular disease and previous PCI being targeted for pharmacotherapeutic intervention or having healthier behaviour [25].

To date, there are a number of trials which have reported long-term mortality after PPCI[26-28]. Even though these studies demonstrate favourable outcomes, their interpretation is challenging because none have accounted for non-cardiovascular deaths or the greater background mortality rates among older patients[1, 7]. So far, studies which have reported short- and medium-term outcomes are limited because they are historic[27, 29, 30], from small cohorts[31] or have been derived from trials which may not be generalisable[26]. Furthermore, cohort studies may have underestimated the benefits of PPCI through not considering the impact of an ageing and increasingly co-morbid population. We respond to this by analysing national registry data within a relative survival framework to provide an alternative, objective and up-to-date measure of the proportion of patients dying from PPCI for STEMI.

Strengths and Limitations

The strengths of this study include a national dataset with consecutive cases, the depth of detail, robust mortality tracking and the ability to match cases to the background national population by age, sex, and year of procedure. Survival analysis using relative survival and excess mortality are novel concepts in cardiovascular

outcome evaluation and provide additional insight compared to the conventional Cox model or Kaplan Meier analysis[32]. However, biased estimates could be produced if the condition of interest is common and therefore mortality from the condition will also be represented in the background population. If the condition of interest is common this may affect the relative survival analysis, however, bias is negligible when assessing EMRR[10]. Rates of STEMI are around 100-400 per 100,000 population, our sensitivity analyses demonstrated that the estimates derived from standard survival techniques were aligned with those from the relative survival modelling, except among the elderly where the relative survival estimates were attenuated reflecting the background population rates of death associated with ageing (Appendix B).

A lack of information in the national life tables about co-morbidities directly related to PPCI may have introduced bias to the estimates because we could only match cases by age, sex, year of procedure and country. Whilst there were missing data we mitigated against potential bias using multiple imputation.

Conclusion

This nationwide study of survival following PPCI for STEMI standardised mortality to matched background population death data found that five year relative survival was very high. Among the elderly, however, there was evidence for significant persisting excess mortality which contrasted with younger age groups where survival rates approached those of the background population. Cardiogenic shock, pre-procedural ventilation, renal failure and the femoral vascular access route were associated with the highest long-term excess mortality after PPCI for STEMI.

Impact on daily practice

Primary PCI for STEMI is an effective treatment and most patients have excellent long-term outcomes. High risk groups have persisting excess mortality and require appropriate secondary prevention therapy and a targeted approach to reducing their risk of STEMI-related death. Further studies are required to elucidate the underlying mechanism of ongoing risk.

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Conflicts of interest statement

RAB, OA, MH, SA, TBD, MM, PDB, PB, MdB, and PL have no conflicts of interest. CPG has received consultancy and speaker bureau fees from AstraZeneca and Novartis. NC has received unrestricted research grants from Medtronic, Haemonetics, Boston

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Figure Legends

Table 1: PPCI cohort baseline characteristics

Figure 1: STROBE diagram of data flow

Figure 2: Five year relative survival following PPCI for STEMI, stratified by age

Figure 3: Factors associated with excess mortality following PPCI for STEMI

Appendices

Appendix A – Life table data

Appendix B – Sensitivity analysis

Appendix C - Abbreviations