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Determinants of excess mortality following unprotected left main stem percutaneous coronary intervention

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Complete List of Authors:	Alabas, Oras; University of Leeds, Division of Epidemiology and Biostatistics Brogan, Richard; University of Leeds, Division of Epidemiology and Biostatistics; York Teaching Hospital NHS Foundation Trust, Cardiology Hall, Marlous; University of Leeds, Division of Epidemiology and Biostatistics Almudarra, Sami; University of Leeds, Division of Epidemiology and Biostatistics Rutherford, Mark; University of Leicester, Department of Health Sciences Dondo, Tatendashe; University of Leeds, Division of Epidemiology and Biostatistics; University of Leeds, Division of Epidemiology and Biostatistics, Leeds Institute of Cardiovascular and Metabolic Medicine Feltbower, Richard; University of Leeds, Division of Epidemiology and Biostatistics; University of Leeds, Centre for Epidemiology and Biostatistics Curzen, Nick; University Hospital Southampton NHS F Trust, Wessex Cardiac Unit de Belder, Mark; The James Cook University Hospital, Middlesbrough, Cardiothoracic Division Ludman, Peter; University College London, National Institute for Cardiovascular Outcomes Research ; Queen Elizabeth Hospital, Department of Cardiology Gale, Chris; University of Leeds, Division of Epidemiology and Biostatistics
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Determinants of excess mortality following unprotected left main stem percutaneous coronary intervention

Authors:

OA Alabas[1], RA Brogan[1, 2], M Hall[1], S Almudarra[1], MJ Rutherford[3], TB Dondo[1], R Feltbower[1], N Curzen[4], M de Belder[5], P Ludman[6], CP Gale[1,2] on behalf of the National Institute for Cardiovascular Outcomes Research[7]

[1]MRC Bioinformatics Unit, Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM), University of Leeds, Leeds, UK

[2]Department of Cardiology, York Teaching Hospital NHS Foundation Trust, York, UK

[3]Department of Health Sciences. University of Leicester. Leicester, UK

[4]Department of Cardiology University Hospital Southampton NHS FT & Faculty of Medicine, University of Southampton

[5]Department of Cardiology South Tees Hospitals NHS Foundation Trust, UK

[6]Department of Cardiology Queen Elizabeth Hospital, Birmingham, UK

[7]National Institute for cardiovascular Outcomes Research (NICOR), University College, London, UK

Correspondence: Dr Oras Alabas, Research Fellow,
MRC Bioinformatics Unit,
Faculty of Medicine and Health, University of Leeds,
Leeds, LS2 9JT
Email: o.alabas@leeds.ac.uk
Tel: 0044 (0)113 343 8905

Study design:

Prospective population-based linked cohort study using data from the British Cardiovascular Intervention Society (BCIS) database, January 2005 to July 2014.

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Conflicts of interest:

Curzen N declares unrestricted research grants from Boston Scientific, HeartFlow, Haemonetics, Medtronic, St Jude Medical, and speaker fees/consultancy from St Jude Medical, HeartFlow, Haemonetics, Lilly/D-S. All other authors declare no conflicts of interest.

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Key questions

What is already known about this subject?

Mortality after PCI to the unprotected left main stem (UPLMS) is higher among emergency and urgent cases than elective cases and it is especially high among patients with cardiogenic shock. Following PCI, however, the dominant cause of death is non-cardiovascular.

What does this study add?

After adjusting for background population mortality, we found that long-term survival following UPLMS PCI for elective cases was excellent, approached that of the background populace and was significantly predicted by co-morbidity. For NSTEACS and STEMI without cardiogenic shock, the requirement for pre-procedural ventilation was the strongest determinant of excess mortality. For STEMI with cardiogenic shock, where survival was poor, the strongest determinant was TIMI flow.

How might this impact on clinical practice?

Greater attention to specific determinants of excess mortality, such as diabetes, renal failure and coronary anatomy, according to whether a case is emergent, urgent or elective will help improve survival following UPLMS PCI. Knowledge of clinical presentation-specific factors associated with excess mortality will allow better forecasting of outcomes for patients with UPLMS disease. The poor and persistently low survival among STEMI with cardiogenic shock requires greater clinical attention.

Abstract

Objective

For percutaneous coronary intervention (PCI) to the unprotected left main stem (UPLMS), there are limited long-term outcome data. We evaluated five year survival for UPLMS PCI cases taking into account background population mortality.

Methods

A population-based registry of 10,682 cases of chronic stable angina (CSA), non ST-segment elevation acute coronary syndrome (NSTEACS), ST-segment elevation myocardial infarction with (STEMI+CS) and without cardiogenic shock (STEMI-CS) who received UPLMS PCI from 2005 to 2014 were matched by age, sex, year of procedure and country to death data for the United Kingdom populace of 56.6 million people. Relative survival and excess mortality were estimated.

Results

Over 26,105 person-years follow-up, crude five year relative survival was 93.8% for CSA, 73.1% NSTEACS, 77.5% STEMI-CS and 28.5% STEMI+CS. The strongest predictor of excess mortality among CSA was renal failure (EMRR 6.73, 95% CI 4.06-11.15), and for NSTEACS and STEMI-CS was pre-procedural ventilation (6.25, 5.05-7.75 and 6.92, 4.25-11.26, respectively). For STEMI+CS, the strongest predictor of excess mortality was pre-procedural TIMI 0 flow (2.78, 1.87-4.13), whereas multivessel PCI was associated with improved survival (0.74, 0.61-0.90).

Conclusions

Long term survival following UPLMS PCI for CSA was high, approached that of the background populace and was significantly predicted by co-morbidity. For NSTEACS and STEMI-CS, the requirement for pre-procedural ventilation was the strongest determinant of

excess mortality. By contrast, among STEMI+CS, in whom survival was poor, the strongest determinant was pre-procedural TIMI flow. Future cardiovascular cohort studies of long-term mortality should consider the impact of non-cardiovascular deaths.

Keywords

Unprotected left main stem; percutaneous coronary intervention; relative survival; excess mortality; STEMI; NSTEACS; chronic stable angina; cardiogenic shock

Introduction

Improved stent technology, the *de novo* presentation of unprotected left main stem (UPLMS) coronary disease at primary percutaneous coronary intervention (PPCI) and evidence from randomised trials reporting good outcomes among higher risk patients has increased the number of patients who receive PCI to the UPLMS [1-3]. Among emergent, urgent and elective cases of UPLMS PCI, procedural success is high with evidence of over 95% technical success and excellent short-term outcomes [4].

However, there is a paucity of representative data regarding the longer-term outcomes following UPLMS PCI. In part, this is due to the inherent bias of small observational cohorts and difficulty in generalising results from the highly selected cohorts recruited into randomised trials, but also because long-term survival studies of UPLMS PCI typically report all-cause mortality [5, 6]. The latter point is of particular importance when, nowadays, the dominant cause of death after PCI is non-cardiovascular and if not accounted for, the efficacy of UPLMS PCI may be underestimated.

Whilst cause-specific mortality records can help ascertain the effect of an intervention on cardiovascular outcomes, this approach has its limitations. Cause-specific mortality records may be difficult to ascertain and when available are limited to trials or if obtained from administrative data can be biased by misclassification of the cause of death [7]. An alternative method to estimate cause-specific outcomes is relative survival, which adjusts for the expected rates of death in the general population. Using a relative survival approach and all cases of UPLMS PCI within the United Kingdom health care system, we aimed to report the rates of relative survival and then quantify the determinants of excess mortality among emergent, urgent and elective cases of UPLMS PCI. To achieve this, we matched cases of

UPLMS PCI from the British Cardiovascular Intervention Society (BCIS) national registry of PCI to lifetable data according to age, sex, year of procedure and country for the United Kingdom general populace of 56.6 million people. This allowed mortality and factors specifically associated with UPLMS disease and its treatment to be studied [8].

Methods

Patients, setting and inclusion criteria

Participation in BCIS is mandated for all operators and all National Health Service Providers in the United Kingdom. The sampling frame consisted of all cases from the 1st January 2005 to 1st July 2014 [9]. Data for every PCI performed, comprising 113 core fields [9] were collected prospectively, encrypted and transferred online to a central database at the National Institute for Cardiovascular Outcomes Research (NICOR). Patients included had PCI to a diseased UPLMS and were aged 18 to 100 years. Cases of UPLMS PCI were those in whom the left main stem was the target vessel and who did not have a patent graft to any left sided coronary artery (Figure 1) [9]. For those with multiple records, the first admission was used. According to the joint ESC/ACC consensus statement guidelines for definition for myocardial infarction, we grouped cases as chronic stable angina (CSA), non ST-elevation acute coronary syndrome (NSTEACS) and ST-elevation myocardial infarction (STEMI) [10]. To minimise bias due to the inclusion of patients with cardiogenic shock in the STEMI group, we subdivided STEMI cases into those with (STEMI+CS) and without cardiogenic shock (STEMI-CS); both groups only included patients who received primary PCI. The diagnosis of cardiogenic shock was clinical and included a systolic blood pressure <100 mmHg, pulse >100 bpm, in a patient who was cool and clammy or requiring inotropes, intra-aortic balloon pump or other cardiopulmonary support.

Mortality and follow up

All-cause mortality data for UPLMS PCI cases were extracted through linkage to the Office for National Statistics using each patient's unique pseudonymised National Health Service number. Patients were followed-up for their vital status up to 5 years after PCI, with censoring at the end of follow-up on 1st July, 2014 (Figure 1a, Appendix). 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 among cases of UPLMS PCI divided by the expected survival of the comparable United Kingdom populace and expressed as relative survival rates (RSR) [11]. A relative survival rate of 100% implies that cases of UPLMS PCI have survival rates equal to that of the matched disease free background population. Observed survival was estimated using the actuarial method which calculates the observed survival in time intervals from the effective number of patients at risk in that particular interval and the expected survival 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 matched to the cohort by single year of age, sex and year of procedure.

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). Evidence of excess mortality is observed

when the EMRR is greater than 1. For example, an EMRR of 1.5 for men/women indicates that men experience 50% higher excess mortality than women. The statistical model comprised generalised linear regression models, collapsed (life table) data, and a Poisson error structure [11]. First, we fitted a baseline model comprising age, sex and year of procedure. Each of the following covariates were then separately fitted into the baseline moactudel: previous myocardial infarction, previous PCI, diabetes mellitus, left ventricular systolic function, number of vessels attempted, number of stents, renal failure (defined as serum creatinine >200 µmol/L), cardiogenic shock pre- and post-procedure, degree of LMS stenosis pre and post procedure (the presence of stenosis was assigned if a vessel scored >50% on the effective stenosis), TIMI flow in the infarct related artery pre- and post-procedure, pre-procedural ventilation, use of GPIIb/IIIa inhibitors, use of intravascular ultrasound (IVUS) and fractional flow reserve (FFR). The proportional hazards assumption was tested by including interaction terms between the three baseline variables (age, sex, calendar year) and follow-up time, and using the likelihood ratio test; there were no time dependent effects ($p>0.05$) therefore no interaction terms were added. To mitigate bias due to missing data, we generated 20 multiply imputed datasets by chained equations [12]. All tests were two-tailed, the level of statistical significance pre-specified at 5% ($p<0.05$) and estimates derived with 95% confidence intervals (CI), statistical analyses were performed using Stata version 13.1 (StataCorp).

Ethics

Ethical approval was not required under NHS research governance arrangements. NICOR which includes the BCIS database (Ref: NIGB: ECC 1-06 (d)/2011*)* has support under section 251 of the National Health Service (NHS) Act 2006 to use patient information for medical research without consent.

Results

Among 10,682 cases of UPLMS PCI across 89 providers there were 3,799 (35.5%) CSA, 5,114 (47.8%) NSTEACS, 1,020 STEMI-CS and 749 STEMI+CS of whom 69.1% were male. Mean respective ages (SD) were 69.3 (11.2), 72.4 (12.1%), 68.0 (13.7) and 68.2 (12.7) years (Table 1). Over 26,105 person-years and median follow-up of 2 years, 2,872 (25.9%) died. The crude five year relative survival was 93.8% for CSA, 73.1% for NSTEACS, 77.5% for STEMI-CS and 28.5% for STEMI+CS (Figure 2). The number of cases in England, North of Ireland, Scotland and Wales were 9,736 (87.1%), 566 (5.2%), 439 (4.1%) and 387 (3.6%), respectively.

Table 1: Baseline characteristics for cases of UPLMS PCI by CSA, NSTEACS, STEMI-CS and STEMI+CS

		CSA n=3799	NSTEACS n=5114	STEMI-CS n=1020	STEMI+CS n=749	Missing (%)[¥]
Demographics						
Mean (SD) age, years		69.3 (11.2)	72.4 (12.1)	68.0 (13.7)	68.2 (12.7)	135 (0.1)
Age greater than 80 years (%)		696/3799 (18.3)	1566/5111 (30.6)	231/1018 (22.7)	131/749 (17.5)	
Male (%)		2788/3765 (74.1)	3307/5091 (65.0)	732/1018 (71.9)	547/746 (73.0)	63 (0.6)
Medical History						
Previous MI (%)		1105/3446 (32.1)	1863/4630 (40.2)	161/956 (16.8)	125/673 (18.6)	982 (9.2)
Previous PCI (%)		1183/3779 (31.3)	971/5048 (19.2)	99/1006 (9.8)	80/733 (10.9)	120 (1.1)
Recent thrombolysis (%)		-	163/4447 (3.7)	19/956 (2.0)	10/729 (1.4)	757 (11.0)
Family history of CAD (%)		1611/3250 (49.6)	1783/4228 (42.2)	265/846 (31.3)	185/557 (33.2)	1811/16.9)
Diabetes mellitus (%)		755/3651 (20.7)	1184/4905 (24.1)	159/973 (16.3)	132/690 (19.1)	471 (4.4)
History of renal disease (%)		148/3757 (3.9)	464/5072 (9.2)	31/1017 (3.1)	29/745 (3.9)	93 (0.9)
Left ventricular systolic function (LVSD)						
Normal (EF ≥50%) (%)		1960/2667 (73.5)	1616/3527 (45.8)	125/380 (32.9)	43/350 (12.3)	3767 (35.2)
Moderate LVSD (EF 30-49%) (%)		466/2667 (17.5)	1183/3527 (33.5)	167/380 (44.0)	98/350 (28.0)	
Severe LVSD (EF<30%) (%)		241/2667 (9.0)	728/3527 (20.6)	88/380 (23.2)	209/350 (59.7)	
Angiographic findings						
LMS Stenosis	<50%	987/3500 (28.2)	962/4714 (20.4)	246/966 (25.5)	75/701 (10.7)	806 (7.5)
	≥ 50%	2513/3500 (71.8)	3752/4714 (79.6)	720/966 (74.5)	626/701 (89.3)	
Flow in IRA	TIMI 0 (%)	58/1197 (4.9)	101/1450 (7.0)	454/881 (51.5)	391/661 (59.2)	6501 (60.8)
	TIMI 1 (%)	30/1197 (2.5)	113/1450 (8.0)	82/881 (9.3)	91/661 (13.8)	
	TIMI 2 (%)	81/1197 (6.8)	209/1450 (14.4)	153/881 (17.4)	99/661 (15.0)	
	TIMI 3 (%)	1028/1197 (85.9)	1027/1450 (70.8)	192/881 (21.8)	80/661 (12.1)	
Procedure						
Requirement for mechanical ventilation		17/3270 (0.5)	217/4648 (4.7)	51/931 (5.5)	251/699 (35.9)	1145 (10.7)
Arterial access	Femoral (%)	2014/3722 (54.1)	2608/5038 (51.8)	420/1001 (42.0)	519/729 (71.2)	192 (1.8)
	Radial (%)	1693/3722 (45.4)	2398/5038 (47.6)	579/1001 (57.8)	208/729 (28.5)	
	Others (%)	15/3722 (0.4)	32/5038 (0.6)	2/1001 (0.2)	2/729 (0.3)	
Vessels attempted	LMS only (%)	1047/3799 (27.6)	1440/5114 (28.2)	282/1020 (27.7)	238/749 (31.8)	0
	LMS and another vessel (%)	2752/3799 (72.4)	3674/5114 (71.8)	738/1020 (72.4)	511/749 (68.2)	
Total number stents used	0 (%)	322/3786 (8.5)	267/5091 (5.2)	54/1018 (5.3)	68/743 (9.2)	46 (0.4)
	1 (%)	1118/3786 (29.5)	1617/5091 (31.8)	304/1018 (29.9)	259/743 (34.9)	
	>1(%)	2346/3786 (62.0)	3207/5091 (63.0)	660/1018 (64.8)	416/743 (56.0)	
Glycoprotein IIb/IIIa inhibitor		696/3565 (19.5)	1396/4855 (28.8)	559/969 (57.7)	453/729 (62.1)	566 (5.3)
Diagnostic device (IVUS)		1671/3611 (46.3)	1725/4860 (35.5)	225/968 (23.2)	64/728 (8.8)	515 (4.8)
Diagnostic device (FFR)		474/3611 (13.1)	237/4860 (4.9)	10/958 (1.0)	4/724 (0.6)	515 (4.8)
Procedural success						
LMS stenosis	<50%	3264/3451 (94.6)	4440/4629 (95.9)	909/958 (94.9)	629/695 (90.5)	953 (8.9)
	≥50%	187/3451 (5.4)	189/4627 (4.1)	49/958 (5.1)	66/695 (9.5)	
Flow in IRA	TIMI 0 (%)	26/1420 (1.8)	48/2729 (1.8)	56/899 (6.2)	63/677 (9.3)	4963 (46.4)
	TIMI 1 (%)	5/1420 (0.4)	9/2729 (0.3)	12/899 (1.3)	40/677 (5.9)	
	TIMI 2 (%)	19/1420 (1.3)	43/2729 (1.6)	44/899 (4.9)	107/677 (15.8)	
	TIMI 3 (%)	1370/1420 (96.5)	2629/2729 (96.3)	787/899 (87.5)	467/677 (69.0)	

Abbreviation: [¥], missing of the total=10,697; MI, acute myocardial infarction; PCI, percutaneous coronary intervention; CAD, cardiovascular disease; LVSD, Left ventricular systolic function; EF, ejection fraction; FFR, fractional flow reserve; LMS, Left main stem; IRA, infarct-related artery; TIMI, thrombolysis in myocardial infarction; *IVUS, intravascular ultrasound; -, not eligible*

Five year relative survival by age, sex and year

Five year relative survival was worse among the elderly (Figure 3). For cases of CSA aged <55 and > 75 years it was 96.3% vs. 96.2% and for NSTEACS 84.1% vs. 71.2%, STEMI-CS

90.1% vs.74.8% and STEMI+CS 41.2% vs.25.0% (Figure 3). For females and males, survival was 96.2% vs. 92.8% for CSA, 70.2% vs. 74.5% for NSTEACS; 60.0% vs. 55.8% for STEMI-CS and 36.4% vs. 25.8% for STEMI+CS (Figure 4). Between 2005/6 and 2009/10, survival rates improved; increasing for CSA (90.8% to 95.5%), NSTEACS (76.5% to 72.5%), STEMI-CS (72.2% to 76.4%) and with the greatest improvements among STEMI+CS (23.9% to 32.4%) (Figure 5).

Excess mortality by age, sex and year

For CSA, there was no evidence of excess mortality by age, sex or year of diagnosis. There was, however, significant excess mortality with increasing age (>75 compared with <55 years) for NSTEACS (EMRR 2.61, 95% CI 1.91-3.57) and STEMI-CS (3.49, 1.99-6.10), but not by sex and year of procedure. Among STEMI+CS excess mortality occurred with increasing age (1.73, 1.29-2.33), but not sex and there was a significant reduction in excess mortality for 20011/12 (0.54, 0.33-0.91) and 2013/14 (0.55, 0.33-0.91) compared with 2005/6 (Table 3a, Appendix).

Determinants of excess mortality

For CSA, excess mortality was associated with previous myocardial infarction (2.73, 1.77-4.21), diabetes (2.56, 1.64-3.97), moderate (2.43, 1.38-4.29) and poor left ventricular systolic function (3.90, 2.23 - 6.82), renal failure (6.73, 4.06-11.15) and pre-procedural stenosis severity (EMRR 1.82, 95% CI 1.02-3.23) (Table 2). There was a significant reduction of excess mortality associated with the use of IVUS (EMRR 0.46, 95% CI 0.28-0.76). Others variables such as the number of vessels attempted, the number of stents deployed and the use of a GPIIb/IIIa were not significantly associated with excess mortality.

For NSTEACS, excess mortality was associated with previous myocardial infarction (EMRR 1.55, 95% CI 1.34-1.80), diabetes (1.66, 1.43-1.95), moderate (2.34, 1.86-2.93) and poor left ventricular systolic function (3.65, 2.96-4.51), renal failure (3.25, 2.75-3.84), pre-procedural ventilation (6.25, 5.05-7.75) and pre-procedural LMS disease severity (2.09, 1.64-2.66). Reduced excess mortality was significantly associated with IVUS (EMRR 0.47, 95% CI 0.39-0.57) and FFR (0.44, 0.25-0.75).

Among cases of STEMI-CS, excess mortality was associated with diabetes (EMRR 1.69, 95% CI 1.15 - 2.48), renal failure (2.27, 1.20- 4.27), TIMI 1 flow versus normal flow (1.99, 1.01 - 3.92), pre-procedural ventilation (6.92, 4.25-11.26) and the LMS disease severity (1.60, 1.01- 2.41). Factors which were associated with reduced excess mortality were the deployment of one (0.31, 0.18-0.54) or more stents (0.32, 0.20-0.53), the use of GPIIb/IIIa inhibitors (0.42, 0.29-0.59) and the use of IVUS (0.43, 0.24-0.74).

For STEMI+CS, excess mortality was associated with diabetes (EMRR 1.34, 95% CI1.04 - 1.72), renal failure (1.77, 1.13-2.75), pre-procedural ventilation (2.03, 1.66-2.50) and any degree of reduction of pre-procedural TIMI flow versus the normal flow (TIMI 0: EMRR 2.78, TIMI 1: 2.32, TIMI 2: 2.00). Factors significantly associated with reduced excess mortality were multivessel PCI (EMRR 0.74, 95% CI 0.61-0.90), deployment of stents versus no stent (one stent: 0.45, 0.32-0.62), more than one stent (0.42, 0.31-0.57) and IVUS (0.28, 0.17-0.46). Neither pre-procedural degree of LMS stenosis or GPIIb/IIIa inhibitors were associated with excess mortality.

Table 2: Factors associated with excess mortality for cases of UPLMS PCI by CSA, NSTEACS, STEMI-CS and STEMI+CS. Results are pooled estimates over 20 imputations.

Variable added to baseline	CSA (n=3799)	NSTEACS (n=5114)	STEMI-CS (n=1020)	STEMI+CS (n=749)
	EMRR	EMRR	EMRR	EMRR
Baseline model + Previous MI	2.73 (1.77- 4.21)*	1.55 (1.34 - 1.80)*	1.18 (1.79 - 1.77)	0.97 (0.75 - 1.26)
Baseline model + Diabetes	2.56 (1.64-3.97)*	1.66 (1.43 - 1.95)*	1.69 (1.15 - 2.48)*	1.34 (1.04 - 1.72)*
Baseline model + LVSD				
Good	1.00	1.00	∓	∓
Moderate LVSD	2.43 (1.38 - 4.29)*	2.34 (1.86 - 2.93)*		
Severe LVSD	3.90 (2.23 - 6.82)*	3.65 (2.96 - 4.51)*		
Baseline model + Renal Failure	6.73 (4.06 - 11.15)*	3.25 (2.75 - 3.84)*	2.27 (1.20 - 4.27)*	1.77 (1.13 - 2.75)*
Baseline model + Pre-procedure flow in IRA				
TIMI 3 (Normal flow) (reference)	1.00	1.00	1.00	1.00
TIMI 0 (No flow)	^	^	1.66 (0.96-2.87)	2.78 (1.87-4.13)*
TIMI 1 (Partial flow)			1.99 (1.01-3.92)*	2.32 (1.49 - 3.63)*
TIMI 2 (Slow flow)			1.40 (0.74-2.65)	2.00 (1.26-3.17)*
Baseline model + Vessels attempted				
One vessel	1.00	1.00	1.00	1.00
Multivessel PCI	1.52 (0.85 - 2.71)	0.90 (0.77 - 1.05)	0.88 (0.62 - 1.24)	0.74 (0.61 - 0.90)*
Baseline model + Number of stents				
No stent	1.00	1.00	1.00	1.00
One stent	1.25 (0.41 - 3.77)	0.93 (0.67 - 1.29)	0.31 (0.18 - 0.54)*	0.45 (0.32 - 0.62)*
More than one stent	2.20 (0.79 - 6.12)	0.92 (0.68 - 1.26)	0.32 (0.20 - 0.53)*	0.42 (0.31 - 0.57)*
Other interventions				
Baseline model + Pre procedural ventilation	^	6.25 (5.05 - 7.75)*	6.92 (4.25 - 11.26)*	2.03 (1.66-2.50)*
Baseline model+LMS stenosis pre-procedure	1.82 (1.02 - 3.23)*	2.09 (1.64 - 2.66)*	1.60 (1.01 - 2.41)*	1.03 (0.73-1.43)
Baseline model + GPIIb/IIa inhibitors	0.87 (0.51 - 1.49)	0.99 (0.84 - 1.17)	0.42 (0.29 - 0.59)*	0.83 (0.68 - 1.02)
Baseline model + IVUS	0.46 (0.28 - 0.76)*	0.47 (0.39 - 0.57)*	0.43 (0.24 - 0.74)*	0.28 (0.17 - 0.46)*
Baseline model + FFR	0.30 (0.08-1.19)	0.44 (0.25-0.75)*	^	^

Abbreviation: *, significance at 5% level; ∓, level of missingness detected >50% hence variable not imputed and excluded from model; *MI, acute myocardial infarction; cardiovascular disease; LVSD, Left ventricular systolic function; IRA, infarct-related artery; TIMI,* thrombolysis in myocardial infarction; *PCI, percutaneous coronary; LMS, Left main stem; IVUS, intravascular ultrasound;* ^, small number of cases; FFR, fractional flow reserve.

Discussion

This is the first population-based study estimating long-term relative survival for patients who received PCI to an UPLMS. Relative survival provides an objective measure of the proportion of patients dying from direct or indirect consequences of a disease without requiring a record of the precise cause of death [11]. To date, studies of UPLMS PCI have focused on observed survival and, therefore, reported outcomes include not only deaths related to the procedure, but also 'natural' deaths occurring in the cohort under study [2, 13, 14]. Our study provides new insights through the analysis of nationwide prospective, consecutive series registry data accounting for populace mortality data.

Specifically, we found that survival after UPLMS PCI for elective patients with CSA was very high (over 90% survived to five years) and approached that of the age, sex year and country matched disease-free general population. Whilst the presence of an acute coronary syndrome (either NSTEACS or STEMI) was associated with reduced longer-term survival, for NSTEACS and STEMI without cardiogenic shock survival was similar (about 75% survived to five years). By contrast, emergent cases of STEMI presenting with cardiogenic shock had very poor survival, which was evident immediately after PCI and persisted for many years (about 30% survived to five years). Data from this study provides real world evidence to substantiate the ACC/AHA guidelines which have upgraded PCI for UPLMS in specific circumstances from a class III to a class 1 or IIa procedure [15].

However, our study did identify an improvement among cases of STEMI with cardiogenic shock, and it is possible that operators and hospital services are more familiar with the urgent management of such cases. It is also possible that improved stents, deployment techniques (for complex anatomy) as well as more potent pharmacological treatments have, in part, facilitated the temporal improvements. Notwithstanding this, the 'accelerated failure'

and poor long-term survival among STEMI with cardiogenic shock was very clear. It appears, therefore, that the greatest gains for improved outcomes are among high risk cases of complex PCI. Survival for these cases was, however, constrained by co-morbidity, poor pre-procedural TIMI flow in the infarct related artery and the necessity for pre-procedural ventilation, but was associated with an improvement of about 50% with multivessel PCI. Given that trials testing the efficacy of the intra-aortic balloon pump have failed to reach their primary endpoints and that there is insufficient evidence for the use of percutaneous assist devices, a greater focus on technologies which support the myocardium (thereby allowing optimal infarct and non-infarct related PCI), improved stent design and enhanced operator experience is needed [16].

Whereas, for elective cases of UPLMS PCI, attention to co-morbidities (previous MI, diabetes and renal failure), optimisation of left ventricular systolic function and careful evaluation of pre-procedural stenosis severity (using IVUS or FFR) is likely to be key to maintaining the present rates of survival. Addressing these factors and using them to help predict a patients' clinical outcome will provide the opportunity for clinicians to discuss in greater detail the risks and benefits of the intended procedure. However, as survival rates are already very high among this group, future absolute gains are likely to be small.

For NSTEACS, factors that negatively impacted on long-term survival were prior myocardial infarction, diabetes, LMS stenosis >50%, moderate and poor left ventricular systolic function, renal failure, cardiogenic shock and the requirement for mechanical ventilation. As for elective cases, the use of IVUS and FFR was associated with a more than 50% reduction in excess mortality. Although our study design cannot determine a cause and effect relationship, this observation supports guideline recommendations that careful attention to the coronary anatomy and stent deployment are central to good outcomes. Even so, it is

possible that in our study, more stable, lower risk, patients were more likely to receive IVUS and FFR [17, 18].

For all types of clinical presentations except STEMI with cardiogenic shock, we found that multivessel PCI was not associated with a survival advantage. For STEMI complicated by cardiogenic shock, multivessel PCI was associated with, on average, a lower relative excess mortality of 26%. This novel association warrants further large scale evaluation, especially when present data have failed to eliminate the clinical uncertainty about the most appropriate way to treat patients with multivessel disease. That is, whilst previous studies have not confirmed the benefit of more complete revascularisation in the context of cardiogenic shock, recent trials (among those without CS) have questioned the conventional view of lesion only revascularisation in STEMI [19, 20].

Strengths and limitations

Even though relative survival and excess mortality are novel concepts for the evaluation of cardiovascular outcomes, these techniques are well established in cancer epidemiology. Relative survival is an underused tool in cardiovascular outcome reporting [8], which in an era of evidence-based practice and an ageing 'survivorship' population merits further attention. The use of relative survival for this study has allowed higher resolution estimation of survival and excess deaths specifically due to UPLMS disease and its percutaneous treatment without requiring potentially unreliable 'cause of death' data.

Whilst this study has other strengths, including the size and quality of data, there were limitations. A high prevalence of the index disease among the general population will overinflate survival estimates [11]. Although cardiovascular disease is prevalent, this is unlikely to be the case for UPLMS disease *per se* – being identified at diagnostic

angiography in 4-6% of cases and estimated at 15 cases per 100,000 population/year [21]. Selection bias may have been introduced through the identification and consent of patients, which may lead to a healthier cohort than expected.

Conclusions

In the largest long-term outcomes study of UPLMS PCI, and after adjustment for non-cardiovascular death, survival for patients with CSA was excellent and approached that of the general population. This contrasted with emergency cases and, in particular, STEMI with cardiogenic shock where, despite temporal improvements, survival was poor. For NSTEACS and STEMI without cardiogenic, pre-procedural ventilation was the strongest determinant of excess mortality, in contrast to STEMI with cardiogenic shock where survival was poor and the strongest determinant was pre-procedural TIMI flow.

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Figure legends

Figure 1: Consort diagram of cohort derivation

Figure 2: Unadjusted five-year cumulative relative survival stratified by A: CSA, B: NSTEACS, C: STEMI-CS, D: STEMI+CS, by pre-determined time points

Figure 3: Unadjusted five-year cumulative relative survival stratified by A: CSA, B: NSTEACS, C: STEMI-CS, D: STEMI+CS, by age

Figure 4: Unadjusted five-year cumulative relative survival stratified by A: CSA, B: NSTEACS, C: STEMI-CS, D: STEMI+CS, by sex

Figure 5: Unadjusted five-year cumulative relative survival stratified by A: CSA, B: NSTEACS, C: STEMI-CS, D: STEMI+CS, by calendar year

Figure 1: Consort diagram of cohort derivation

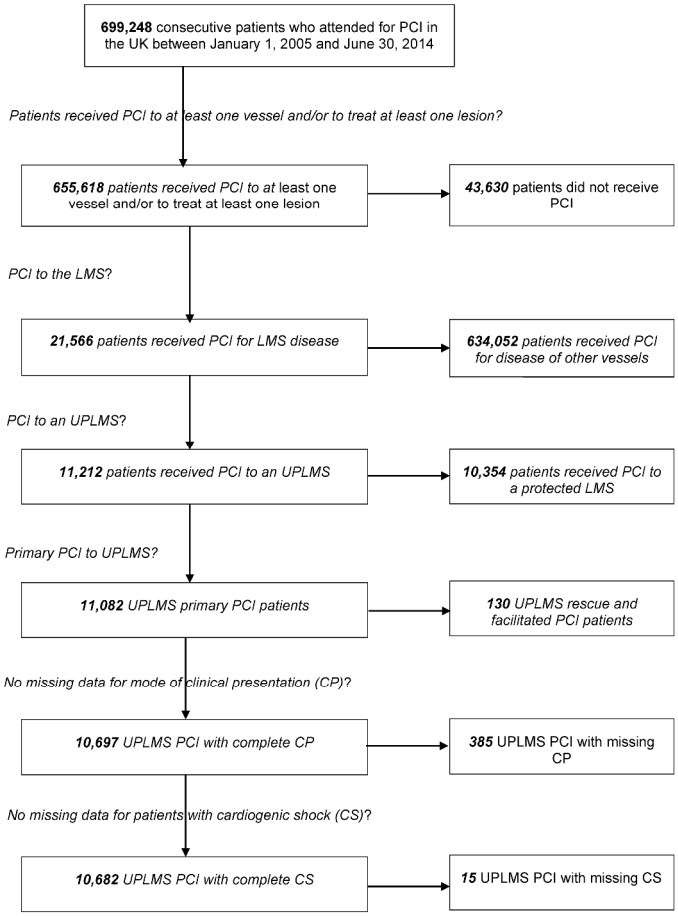

Figure 1
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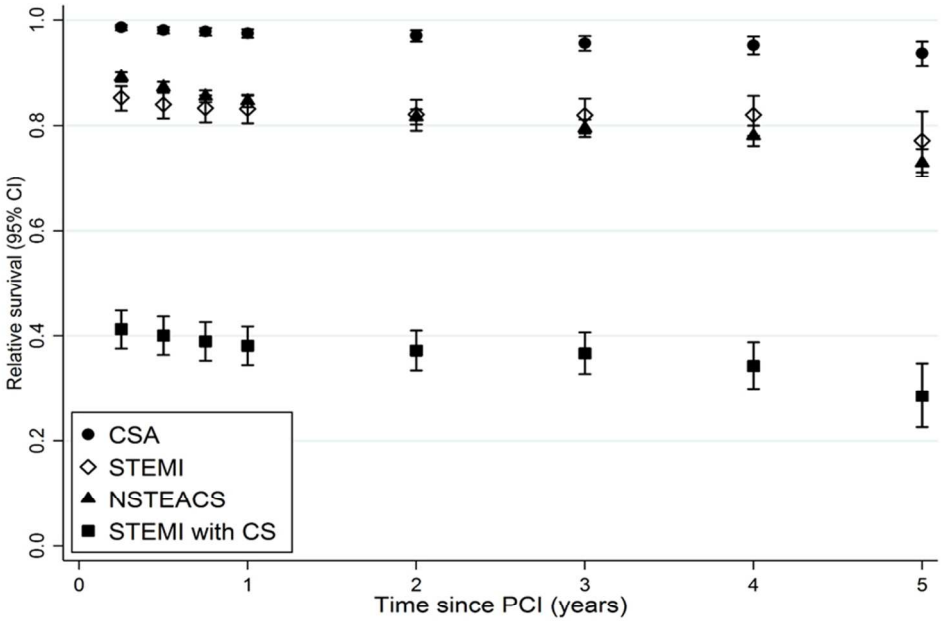

Figure 2
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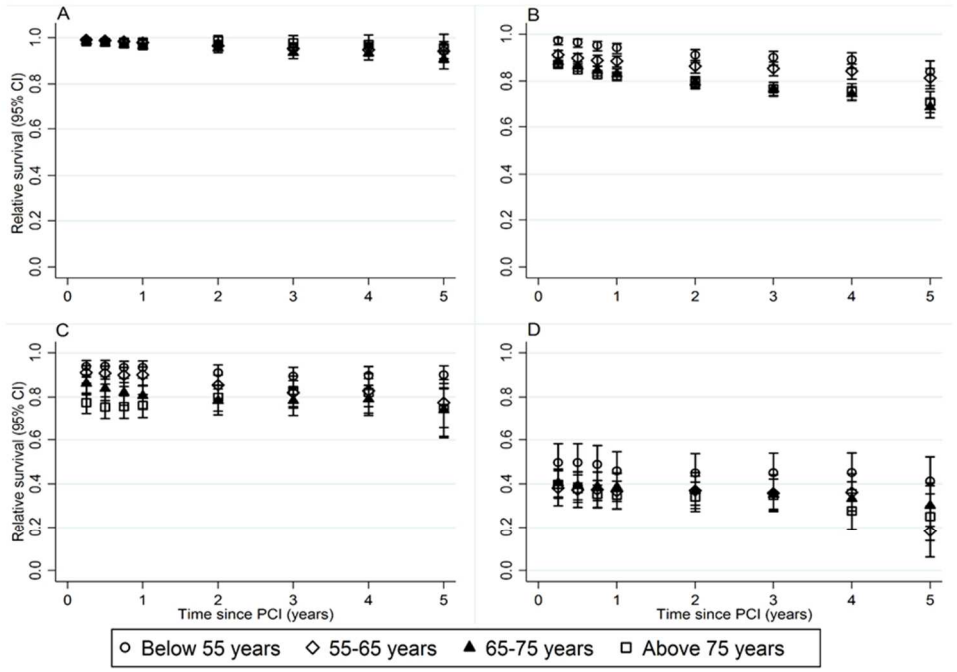

Figure 3
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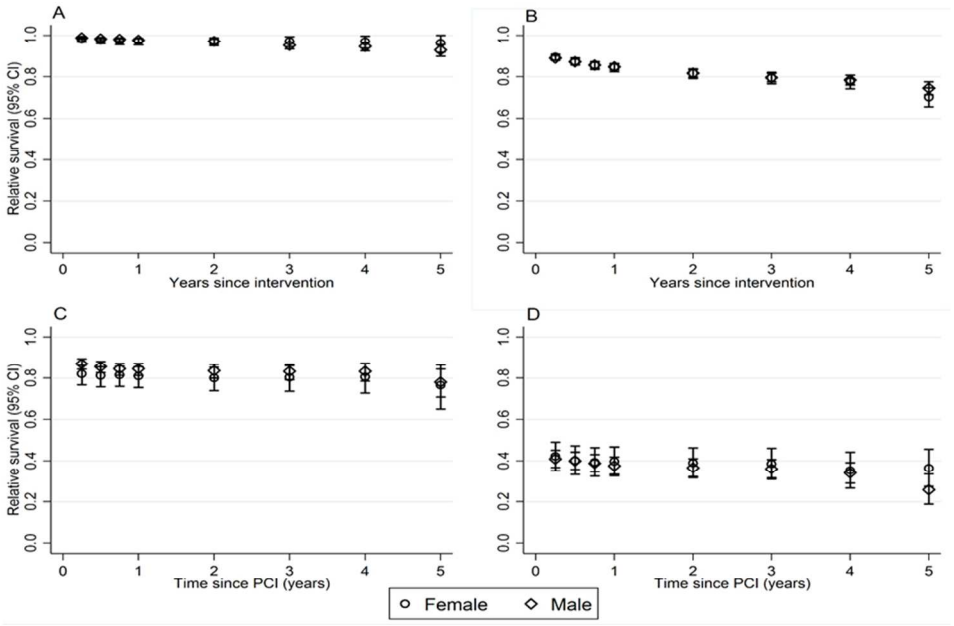

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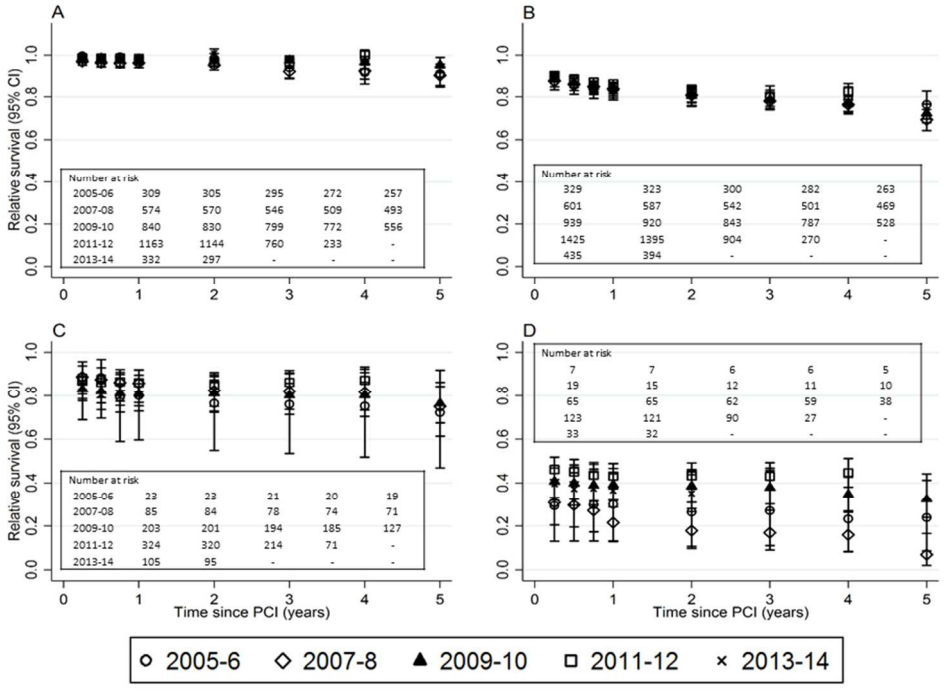

Figure 5
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Appendix

Section 1: Life table

Life table of the United Kingdom population mortality estimates was used to calculate expected survival. The latest published life table data available was for 2012; therefore 2012 population data was matched to 2013 and 2014 patient data without extrapolation (Table 1a).

Table1a: Years of procedure and years of follow-up included in the calculations of 5-year relative survival of UPLMS patients for the years 2005-2014. The numbers wihin the cells indicate the years following procedure.

Year of procedure	**Year of follow-up**									
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
2005	1	1/2	2/3	3/4	4/5	5/6	6/7	7/8	8/9	9/10
2006		1	1/2	2/3	3/4	4/5	5/6	6/7	7/8	8/9
2007			1	1/2	2/3	3/4	4/5	5/6	6/7	7/8
2008				1	1/2	2/3	3/4	4/5	5/6	6/7
2009					1	1/2	2/3	3/4	4/5	5/6
2010						1	1/2	2/3	3/4	4/5
2011							1	1/2	2/3	3/4
2012								1	1/2	2/3
2013									1	1/2
2014										1

Section 2: Multiple imputation

To avoid underestimation of the covariate-outcome association, the survival outcome was included in the imputation model in the form of the Nelson-Aalen estimate of the hazard function in addition to including the censoring indicator. Excess mortality estimates were averaged over the imputed data. Covariates with 50% or more missing data were excluded from the modelling, as was the case for LVEF function in the STEMI stratum. For each clinical phenotype separate imputed datasets were created. Multiple imputation of missing data made only small changes to point estimates generated from the models though, in general, improved their precision. Though, highlighting the possibility of bias in interpreting data from complete-case analyses (Table 2a).

Table 2a: Excess mortality rate ratios with 95% Cis using complete case analysis

Variable added to baseline	CSA (n=3799)	NSTEACS (n=5114)	STEMI-CS (n=1020)	STEMI+CS (n=749)
	EMRR	EMRR	EMRR	EMRR
Baseline model + Previous AMI	2.88 (1.79-4.61)*	1.57 (1.34-1.82)*	1.57 (1.34-1.83)*	0.99 (0.77-1.28)
Baseline model + Diabetes	2.71 (1.67-4.41)*	1.68 (1.45-1.97)*	1.63 (1.11-2.39)*	1.35 (1.06-1.71)*
Baseline model + LV function				
Good	1.00	1.00	₸	₸
Moderate LVSD	2.99 (1.61-5.56)*	2.47 (1.94-3.15)*		
Severe LVSD	5.45 (2.92-10.18)*	4.07 (3.20-5.19)*		
Baseline model + Renal Failure	7.03 (4.12-12.02)*	7.04 (4.11-12.02)*	2.21 (1.17-4.18)*	1.70 (1.08-2.66)*
Baseline model + Pre-procedure flow in IRA				
TIMI 3 (Normal flow) (reference)	^	^	1.00	1.00
TIMI 0 (No flow)			1.66 (0.99-2.78)	2.66 (1.82-3.88)*
TIMI 1 (Partial flow)			2.00 (1.01-3.94)*	2.18 (1.40-3.39)*
TIMI 2 (Slow flow)			1.34 (0.72-2.52)	1.91 (1.23-2.97)*
Baseline model + Vessels attempted				
One vessel	1.00	1.00	1.00	1.00
Multi vessel PCI	1.65 (0.89-3.07)	0.88 (0.75-1.03)	0.86 (0.61-1.21)	0.74 (0.61-0.90)*
Baseline model + Number of stents				
No stent	1.00	1.00	1.00	1.00
One stent	1.11 (0.37-3.45)	0.91 (0.65-1.26)	0.31 (0.18-0.54)*	0.47 (0.34-0.65)*
More than one stent	2.03 (0.74-5.52)	0.91 (0.66-1.24)	0.32 (0.20-0.53)*	0.43 (0.32-0.59)*
Other interventions				
Baseline model + Pre procedural ventilation	^	6.47 (5.30-7.90)*	6.47 (5.30-7.90)*	2.08 (1.70-2.54)*
Baseline model+LMS stenosis pre-procedure	1.83 (0.99 - 3.35)	2.15 (1.68-2.75)*	2.15 (1.68-2.75)*	1.04 (0.76-1.43)
Baseline model + GPIIb/IIa inhibitors	0.95 (0.55-1.64)	0.95 (0.55-1.64)	0.41 (0. 29-0.58)*	0.83 (0.68-1.01)
Baseline model + Diagnostic device (IVUS use)	0.48 (0.28-0.82)*	0.47 (0.39-0.57)*	0.41 (0.24-0.71)*	0.28 (0.17-0.46)*
Baseline model + Diagnostic device (Pressure FFR use)	0.25 (0.05-1.23)	0.45 (0.26-0.77)*	^	^

Abbreviation: *, significance at 5% level; ₸, level of missingness detected >50%; *MI, acute myocardial infarction; cardiovascular disease; LVSD, Left ventricular systolic function; IRA, infarct-related artery; TIMI,* thrombolysis in myocardial infarction; *PCI, percutaneous coronary; LMS, Left main stem; IVUS, intravascular ultrasound; ^,* small number of cases; FFR, fractional flow reserve.

Section 3: Sensitivity analysis

Limited general populace information concerning comorbidities may have introduced bias to the estimates because we could only match cases by age, sex, year of procedure and country. However, we addressed this by i) running a baseline model which included covariates available both in the cohort and general population groups (Table 3a) and ii) performing a Poisson regression which found no substantial difference in estimates between all-cause mortality (MRR) (Table 3b) and excess mortality using the relative survival approach.

Table 3a: Excess mortality rate ratios, with 95% CIs using imputed data, baseline model

Baseline Model	CSA (n=3799)	NSTEACS (n=5114)	STEMI-CS (n=1020)	STEMI+CS (n=749)
	EMRR	EMRR	EMRR	EMRR
Age (years)				
< 55 (reference)	1.00	1.00	1.00	1.00
55-65	1.11 (0.56-2.20)	1.58 (1.11-2.25)*	1.85 (0.99-3.48)*	1.77 (1.28-2.45)*
65-75	1.64 (0.87-3.12)	2.46 (1.78-3.38)*	2.68 (1.48-4.85)*	1.66 (1.23-2.24)*
>75	1.26 (0.59-2.69)	2.61 (1.91-3.57)*	3.49 (1.99-6.10)*	1.73 (1.29-2.33)*
Sex				
Female (reference)	1.00	1.00	1.00	1.00
Male	1.20 (0.72-1.99)	0.98 (0.85-1.14)	0.81 (0.59-1.13)	1.04 (0.84-1.30)
Calendar year				
2005-06 (reference)	1.00	1.00	1.00	1.00
2007-08	0.97 (0.51-1.84)	1.06 (0.81-1.40)	0.88 (0.36- 2.18)	1.16 (0.69-1.96)
2009-10	0.47 (0.23-0.99)	1.01 (0.78-1.31)	1.09 (0.48-2.50)	0.63 (0.38-1.03)
2011-12	0.73 (0.39-1.36)	0.91 (0.71-1.19)	0.77 (0.33-1.76)	0.54 (0.33-0.91)*
2013-14	0.53 (0.20-1.41)	0.94 (0.70-1.27)	0.91 (0.39-2.16)	0.55 (0.33-0.91)*

Abbreviations: *, significance at 5% level .

Table 3b: Factors associated with Mortality Rate Ratios (MRR) for cases of UPLMS PCI by CSA, NSTEACS, STEMI-CS and STEMI+CS. Results are pooled estimates over 20 imputations.

Variable added to baseline	CSA (n=3799)	NSTEACS (n=5114)	STEMI-CS (n=1020)	STEMI+CS (n=749)
	MRR	MRR	MRR	MRR
Baseline model + Previous AMI	1.68 (1.40 - 2.01)*	1.39 (1.25 - 1.54)*	1.34 (0.99 - 1.82)	0.98 (0.76 - 1.25)
Baseline model + Diabetes	1.48 (1.20 - 1.82)*	1.45 (1.29 - 1.62)*	1.69 (1.24 - 2.30)*	1.32 (1.03 - 1.68)*
Baseline model + LV function				
Good	1.00	1.00	₸	₸
Moderate LVSD	1.66 (1.31 - 2.11)*	1.70 (1.47 - 1.96)*		
Severe LVSD	1.98 (1.49 - 2.64)*	2.21 (1.92 - 2.54)*		
Baseline model + Renal Failure	2.39 (1.78 – 3.21)*	2.46 (2.15 - 2.81)*	2.24 (1.31 - 3.80)*	1.69 (1.10 - 2.61)*
Baseline model + Pre-procedure flow in IRA				
TIMI 3 (Normal flow) (reference)	^	^	1.00	1.00
TIMI 0 (No flow)			1.23 (0.74 - 1.79)	2.37 (1.67 - 3.34)*
TIMI 1 (Partial flow)			1.48 (0.88 - 2.48)	2.02 (1.35 - 3.01)*
TIMI 2 (Slow flow)			1.19 (0.76 - 1.86)	1.72 (1.14 - 2.59)*
Baseline model + Vessels attempted				
One vessel	1.00	1.00	1.00	1.00
Multi vessel PCI	0.98 (0.81 - 1.19)	0.88 (0.79 - 0.98)*	0.86 (0.66 - 1.14)	0.75 (0.62 - 0.90)*
Baseline model + Number of stents				
No stent	1.00	1.00	1.00	1.00
One stent	1.08 (0.75 - 1.54)	1.00 (0.78 - 1.28)	0.39 (0.24 - 0.63)*	0.46 (0.33 - 0.63)*
More than one stent	1.21 (0.87 - 1.70)	0.94 (0.74 - 1.19)	0.38 (0.24 - 0.58)*	0.44 (0.32 - 0.60)*
Other interventions				
Baseline model + Pre procedural ventilation	^	4.37 (3.59 – 5.32)*	5.16 (3.25 - 8.19)*	1.94 (1.59 - 2.36)*
Baseline model + LMS stenosis pre-procedure	1.35 (1.08 – 1.68)*	1.71 (1.46 - 2.00)*	1.33 (0.96 - 1.84)	1.02 (0.74 - 1.41)
Baseline model + GPIIb/IIa inhibitors	0.89 (0.71 - 1.12)	0.91 (0.80 - 1.02)	0.46 (0.35 - 0.61)*	0.84 (0.68 - 1.02)
Baseline model + Diagnostic device (IVUS)	0.72 (0.59 - 0.87)*	0.60 (0.53 - 0.68)*	0.53 (0.36 - 0.78)*	0.33 (0.21 - 0.51)*
Baseline model + Diagnostic device (Pressure and FFR)	0.74 (0.54 - 1.01)	0.61 (0.44-0.84)*	0.98 (0.31-3.07)	^

Abbreviation: *, significance at 5% level; ₸, level of missingness detected >50%; *MI, acute myocardial infarction; cardiovascular disease; LVSD, Left ventricular systolic function; IRA, infarct-related artery; TIMI,* thrombolysis in myocardial infarction; *PCI, percutaneous coronary; LMS, Left main stem; IVUS, intravascular ultrasound;* ^, small number of cases; FFR, fractional flow reserve.

Table 4a: Factors associated with excess mortality for cases of UPLMS PCI by CSA, NSTEACS, STEMI-CS and STEMI+CS after excluding patients with previous PCI using imputed data

Variable added to baseline	CSA (n=2616)	NSTEACS (n=4143)	STEMI-CS (n=921)	STEMI+CS (n=669)
	EMRR	EMRR	EMRR	EMRR
Baseline model + Previous MI	3.33 (2.07-5.34)*	1.76 (1.49-2.08)*	1.03 (0.57-1.86)*	0.86 (0.59-1.26)
Baseline model + Diabetes	2.48 (1.50-4.08)*	1.59 (1.34-1.88)*	1.80 (1.19-2.74)*	1.31 (0.99-1.72)*
Baseline model + LVSD				
Good	1.00	1.00	^	^
Moderate LVSD	2.82 (1.41-5.66)*	2.25 (1.77-2.86)*		
Severe LVSD	4.28 (2.19-8.36)*	3.47 (2.72-4.42)*		
Baseline model + Renal Failure	4.31 (2.21-8.41)*	3.03 (2.51-3.66)*	2.22 (1.12-4.40)*	1.69 (1.01-2.81)*
Baseline model + Pre-procedure flow in IRA				
TIMI 3 (Normal flow) (reference)	^	^	1.00	1.00
TIMI 0 (No flow)			1.73 (0.98-3.04)	3.22 (2.05-5.03)*
TIMI 1 (Partial flow)			2.32 (1.14-4.70)*	2.78 (1.64-4.69)*
TIMI 2 (Slow flow)			1.34 (0.67-2.70)*	2.08 (1.24-3.49)*
Baseline model + Vessels attempted				
One vessel	1.00	1.00	1.00	1.00
Multivessel PCI	1.65 (0.85-3.18)	0.83 (0.70-0.98)*	0.82 (0.57-1.18)	0.73 (0.59-0.90)*
Baseline model + Number of stents				
No stent	1.00	1.00	1.00	1.00
One stent	0.84 (0.27-2.59)	1.29 (0.81-2.03)	0.27 (0.15-0.49)*	0.43 (0.30-0.61)*
More than one stent	1.56 (0.56-4.30)	1.15 (0.73-1.81)	0.27 (0.16-0.48)*	0.38 (0.27-0.53)*
Other interventions				
Baseline model + Pre procedural ventilation	∓	6.22 (4.95-7.82)*	5.98 (3.59-9.97)*	2.23 (1.80-2.77)*
Baseline model+LMS stenosis pre-procedure	2.07 (1.03-4.15)*	2.25 (1.69-2.99)*	1.69 (1.03-2.75)*	1.03 (0.72-1.48)
Baseline model + GPIIb/IIa inhibitors	0.96 (0.54-1.72)	0.96 (0.80-1.15)*	0.39 (0.27-0.57)*	0.90 (0.73-1.12)
Baseline model + Diagnostic device (IVUS use)	0.47 (0.27-0.82)*	0.45 (0.36-0.56)*	0.36 (0.19-0.68)*	0.21 (0.12-0.38)*
Baseline model + Diagnostic device (Pressure and FFR use)	0.49 (0.16-1.50)	0.42 (0.22-0.82)*	∓	∓

Abbreviation: *, significance at 5% level; ∓, level of missingness detected >50%; *MI, acute myocardial infarction; cardiovascular disease; LVSD, Left ventricular systolic function; IRA, infarct-related artery; TIMI,* thrombolysis in myocardial infarction; *PCI, percutaneous coronary; LMS, Left main stem; IVUS, intravascular ultrasound;* ^, small number of cases; FFR, fractional flow reserve.

STROBE checklist

	Item No	Recommendation	Page No
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract	Addressed on page 1
		Provide in the abstract an informative and balanced summary of what was done and what was found	Addressed on page 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Addressed on page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Addressed on page 6,7
Methods			
Study design	4	Present key elements of study design early in the paper	Addressed on page 7,8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Addressed on page 7
Participants	6	a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Addressed on page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Addressed on page 9
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Addressed on page 8,9
Bias	9	Describe any efforts to address potential sources of bias	Addressed on page 9, 17
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Addressed on page 7
Statistical methods	12	a) Describe all statistical methods, including those used to control for confounding	Addressed on page 8,9
		b) Explain how missing data were addressed	Addressed in appendix, page 2
		c) Cohort study—If applicable, explain how loss to follow-up was addressed	Addressed in appendix,

			page 1
		d) Describe any sensitivity analyses	Addressed in appendix, page 4
Results			
Participants	13	a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Addressed on Figure 1
		b) Give reasons for non-participation at each stage	Participation is mandatory
		c) Consider use of a flow diagram	Addressed in Figure 1
Descriptive data	14	a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Addressed in Table 1, page 11
		b) Cohort study—Summarise follow-up time (eg, average and total amount)	Addressed on page 8
Outcome data	15	Cohort study—Report numbers of outcome events or summary measures over time	Addressed on page 12
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Addressed on pages 10 to 14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Addressed on appendix
Discussion			
Key results	18	Summarise key results with reference to study objectives	Addressed on page 4, 15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Addressed on page 17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Addressed on pages 15 to 18
Generalisability	21	Discuss the generalisability (external validity) of the study results	Addressed on page 17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Addressed on page 2