Impact of call to balloon time on 30-day mortality in contemporary practice

Richard W. Varcoe[1] PhD MRCP

Tim C. Clayton[2] MSc

Huon H. Gray[3] MD FRCP

Mark A. de Belder[4] MA MD FRCP

Peter F. Ludman[5] MA MD FRCP

Robert A. Henderson[1] DM FRCP

on behalf of the British Cardiovascular Intervention Society (BCIS) and the National Institute for Cardiovascular Outcomes Research (NICOR)

[1] Trent Cardiac Centre, Nottingham University Hospitals NHS Trust, Nottingham

[2] London School of Hygiene and Tropical Medicine, London

[3] Wessex Cardiac Unit, University Hospital Southampton NHS Foundation Trust, Southampton

[4] The James Cook University Hospital, Middlesbrough

[5] Queen Elizabeth Hospital, University Hospital Birmingham NHS Foundation Trust, Birmingham

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Address for correspondence:
Richard Varcoe
Trent Cardiac Centre
City Hospital Campus
Nottingham University Hospitals NHS Trust
Hucknall Road
Nottingham
NG5 1PB
Phone: +44 115 969 1169 ext. 58389
Fax: +44 115 962 7968
Email: richard.varcoe@nuh.nhs.uk

Abstract

Objective

Studies reporting an association between treatment delay and outcome for patients with STEMI have generally not included patients treated by a PPCI service that systematically delivers reperfusion therapy to all eligible patients. We set out to determine the association of CTB time with 30-day mortality after PPCI in a contemporary series of patients treated within a national reperfusion service.

Methods

We analysed data on 16907 consecutive patients with STEMI treated by PPCI in England and Wales in 2011 with CTB times of 6 hours or less.

Results

The median CTB and DTB times were 111 and 41 minutes, respectively, with 80.9% of patients treated within 150 minutes of the call for help. An out of hours call time (58.2% of patients) was associated with a 10-minute increase in CTB time whereas inter-hospital transfer for PPCI (18.5% of patients) was associated with a 49-minute increase in CTB time. CTB time was independently associated with 30-day mortality ($p<0.0001$) with a hazard ratio of 1.95 (95% CI 1.54 to 2.47) for a CTB time of >180-240 minutes compared to ≤90 minutes. The relationship between CTB time and 30-day mortality was influenced by patient risk profile with a greater absolute impact of increasing CTB times on mortality in high-risk patients.

Conclusions

CTB time is a useful metric to assess the overall performance of a PPCI service. Delays to reperfusion remain important even in the era of organised national PPCI services with rapid treatment times and efforts should continue to minimize treatment delays.

Key Questions

What is already known about this subject?

Primary percutaneous coronary intervention (PPCI) is the treatment of choice for patients presenting with acute ST segment elevation myocardial infarction (STEMI) provided it can be delivered in a timely fashion. Delays to treatment are associated with outcome and most efforts have focused on improvements in door to balloon time (DTB).

What does this study add?

We have demonstrated a strong independent association between call to balloon time (CTB) and 30-day mortality in an organised national PPCI service with short treatment delays. This relationship is influenced by the patient's baseline risk profile such that those at highest risk are likely to benefit the most from reducing treatment delays.

How might this impact on clinical practice?

CTB time may more reliably assess the overall performance of a PPCI service as it includes the potentially modifiable components of both pre-hospital and hospital emergency care.

Introduction

National and international guidelines recommend that reperfusion therapy (fibrinolysis or primary percutaneous coronary intervention (PPCI)) for patients with acute ST segment elevation myocardial infarction (STEMI) is delivered as quickly as possible to restore coronary artery blood flow and limit myocardial necrosis. [1-3] In the United Kingdom (UK) the National Infarct Angioplasty Project (NIAP) recommended PPCI as the treatment of choice for patients with acute STEMI, provided it can be delivered in a timely fashion.[4] Following publication of the NIAP report in 2008 there has been a rapid roll-out of PPCI services across the UK and in 2011 over 95% of STEMI cases treated by reperfusion therapy underwent PPCI.[5]

The time interval between onset of symptoms due to STEMI and restoration of coronary blood flow is comprised of the 'patient delay' from onset of symptoms to the call for help, and the 'system delay' from the call for help to the delivery of reperfusion therapy. Several studies suggest that door to balloon (DTB) time (time from arrival in hospital to therapeutic instrumentation of the culprit coronary artery) correlates with in-hospital [6-9] and longer-term mortality [8,10,11] but this has not been confirmed in all studies.[12-17] By contrast, call to balloon (CTB) time (time from the call for help to therapeutic instrumentation of the culprit coronary artery) may be influenced by the modifiable elements of the 'system delay'.[18] CTB time includes the time from the call for help to arrival of emergency services through to delivery of PPCI in hospital. Hence, CTB time may provide a more reliable assessment of the overall performance of a reperfusion service.

Methods

The British Cardiovascular Intervention Society (BCIS) database records data from every PCI procedure in the UK, including patient demographics, clinical characteristics, procedural details and outcome data.[19] Definitions for these variables are published in the BCIS PCI dataset.[20]

Patient variables

We analysed the BCIS database to determine factors associated with CTB time and 30-day mortality in patients with acute STEMI in England and Wales treated by PPCI during 2011, three years after introduction of the national PPCI programme.

The CTB time was derived from the time of the call for help and the balloon time, which are recorded for each patient. The time of the call for help was defined as the time of the call for an ambulance for patients presenting in the community, or as the time of arrival at hospital for patients presenting directly to a hospital emergency department. For patients initially admitted to a hospital without PPCI capability, the call for help was defined by the first medical contact so that the CTB time included the time for transfer to a PPCI capable hospital. The balloon time was defined as the time of use of the first device in the coronary artery.

Patients were stratified according to their admission route; STEMI in the community admitted directly to a PPCI hospital (direct), STEMI in the community admitted to a non-PPCI hospital and then transferred to a PPCI hospital (transfer), STEMI whilst an in-patient in a non-PPCI hospital and then transferred to a PPCI hospital (non-PPCI IP), and STEMI whilst already an in-patient in a PPCI hospital (PPCI IP). Patients were also stratified into groups presenting 'in-hours' (weekday 0800h-1800h) or 'out of hours' (weekday 1800h-0800h and weekends).

The National Health Service (NHS) number was used to facilitate mortality tracking via the Office of National Statistics (ONS) in England and Wales. All-cause mortality at 30 days was determined from deaths reported to ONS, a statutory requirement in England and Wales.

Statistical analysis

Univariable associations of baseline, procedural and timing variables with CTB time were assessed using linear regression. Variables independently associated with CTB time were identified using a manual forward stepwise approach with a p-value of 0.01 as the criterion for inclusion in the final multivariable model. A manual approach was used rather than an automated stepwise procedure to allow for clinical judgement. The linear relationship of quantitative variables was considered and variables were grouped into appropriate categories as necessary.

To investigate the impact of CTB times and other factors on 30-day mortality, univariable and multivariable Cox models were fitted also using a manual forward stepwise approach, always including gender and CTB time. CTB time was not assumed to be linearly related to 30-day mortality across all times and hence was categorised into time intervals to reflect clinically relevant groups while ensuring sufficient numbers of patients in each group.

To estimate the impact of admission route, calls made 'out of hours', centre procedural volume, and the components of symptom to balloon time (symptom to call, call to door and door to balloon time), the Cox model was extended to include these variables, excluding CTB time as appropriate.

Data were missing for up to 14% of any one variable included in the models. In order to adjust for missing data, multiple imputation techniques with chained equations were used, assuming missingness is at random, with 10 imputations using all covariates in the model.[21]

To examine the relationship between CTB time and 30-day mortality for patients at different underlying risk, a multivariable model was created fitting CTB time as a continuous variable. The coefficients for this model were used to predict a patient's 30-day mortality risk assuming a CTB time of 60 minutes and patients at the 25^{th}, 50^{th} and 75^{th} centiles of risk were identified. By applying the coefficient for CTB time in the model to these risks, the predicted 30-day mortality at each of these centiles could be determined for any CTB time up to 360 minutes. The predicted 30-day mortality was plotted against CTB time to illustrate the association between CTB time and mortality risk at different levels of underlying risk.

All analyses were carried out with STATA version 13.1 (StataCorp, College Station, Texas).

Results

In 2011 the BCIS database recorded 79433 PCI procedures in England and Wales including 19534 procedures for patients with acute STEMI. We excluded patients with STEMI who were treated by fibrinolysis and subsequently underwent 'rescue' PCI, duplicate or repeat PPCI, missing call or balloon times, and CTB times greater than 6 hours. Our study cohort comprised 16907 patients with STEMI treated by PPCI (figure 1).

The baseline demographic, clinical, procedural and timing characteristics are shown in table 1. The mean CTB time was 121 minutes (median 111 minutes, IQR 90 to 139 minutes) and 80.9% of patients were treated within 150 minutes of the call for help (figure 2).

The mean DTB time for patients in the 'direct' cohort was 51 minutes (median 42 minutes, IQR 29 to 62 minutes). For patients in the 'transfer' cohort, the mean DTB time from first hospital admission was 133 minutes (median 123 minutes, IQR 95 to 161 minutes), but the mean DTB time from arrival at the PPCI centre was 39 minutes (median 34 minutes, IQR 25 to 47 minutes).

At 30 days 898 (5.3%) patients had died with 331 (2.0%) and 611 (3.6%) deaths at 24 hours and 7 days, respectively. Mortality rates at 30 days for patients with call to balloon times ≤90 minutes, >90-150 minutes, and >150 minutes were 3.5%, 4.8% and 9.4%, respectively (figure 3).

Table 1. Baseline demographic, clinical, procedural and timing factors

Variable		Number of patients	Call to balloon (mean mins)	Number of deaths at 30 days (%)
All patients		16907	121.4	898 (5.3%)
Age group, years	<55	4614 (27.3%)	117.8	103 (2.2%)
	55-≤60	2159 (12.8%)	117.5	72 (3.3%)
	60-≤65	2353 (13.9%)	118.6	92 (3.9%)
	65-≤70	2104 (12.4%)	120.0	96 (4.6%)
	70-≤75	1889 (11.2%)	124.4	106 (5.6%)
	75-≤80	1663 (9.8%)	127.5	129 (7.8%)
	80-≤85	1216 (7.2%)	130.2	132 (10.9%)
	>85	906 (5.4%)	130.7	167 (18.4%)
Gender	Male	12509 (74.1%)	119.6	583 (4.7%)
	Female	4379 (25.9%)	126.7	314 (7.2%)
Diabetes	No	14245 (86.8%)	120.3	652 (4.6%)
	Yes	2166 (13.2%)	127.4	179 (8.3%)
Hypertension	No	9630 (59.4%)	119.5	416 (4.3%)
	Yes	6581 (40.6%)	123.2	399 (6.1%)
Hypercholesterolaemia	No	9868 (60.9%)	120.8	495 (5.0%)
	Yes	6343 (39.1%)	121.3	320 (5.0%)
Smoking status	Never	5162 (33.7%)	122.2	281 (5.4%)
	Ex	3887 (25.4%)	122.1	195 (5.0%)
	Current	6278 (41.0%)	117.8	194 (3.1%)
Peripheral vascular disease	No	15681 (96.7%)	120.7	733 (4.7%)
	Yes	530 (3.3%)	128.6	82 (15.5%)
Cerebrovascular accident	No	15577 (96.1%)	120.6	740 (4.8%)
	Yes	634 (3.9%)	130.3	75 (11.8%)
Renal disease	No	15235 (98.7%)	120.9	708 (4.6%)
	Yes	205 (1.3%)	132.9	44 (21.5%)
Previous myocardial infarction	No	13904 (88.1%)	120.2	669 (4.8%)
	Yes	1876 (11.9%)	125.6	144 (7.7%)
Previous CABG	No	16174 (97.9%)	121.0	839 (5.2%)
	Yes	342 (2.1%)	134.7	24 (7.0%)
Previous PCI	No	15250 (92.0%)	121.1	783 (5.1%)
	Yes	1323 (8.0%)	121.6	72 (5.4%)
Cardiogenic shock pre-PCI	No	15750 (93.4%)	120.5	502 (3.2%)
	Yes	1109 (6.6%)	134.8	392 (35.3%)

Ventilated pre-PCI	No Yes	14354 (96.4%) 541 (3.6%)	119.2 156.4	595 (4.1%) 227 (42.0%)
Q wave on ECG	No Yes	11774 (81.8%) 2615 (18.2%)	118.6 129.0	534 (4.5%) 241 (9.2%)
TIMI flow pre-PCI	TIMI 0 TIMI 1 TIMI 2 TIMI 3	10403 (73.7%) 977 (6.9%) 1280 (9.1%) 1447 (10.3%)	119.0 121.2 124.6 129.7	608 (5.8%) 49 (5.0%) 58 (4.5%) 52 (3.6%)
TIMI flow post-PCI	TIMI 0 TIMI 1 TIMI 2 TIMI 3	842 (5.8%) 185 (1.3%) 692 (4.7%) 12850 (88.2%)	120.7 130.5 127.6 120.8	109 (12.9%) 40 (21.6%) 87 (12.6%) 552 (4.3%)
Multi-vessel disease (>75% stenosis)	1 vessel ≥ 2 vessels	11109 (70.5%) 4655 (29.5%)	119.3 124.2	410 (3.7%) 433 (9.3%)
Number of vessels attempted	Single Multi	15278 (90.9%) 1535 (9.1%)	120.8 126.6	684 (4.5%) 206 (13.4%)
Arterial access	Radial Femoral Joint/other	9065 (54.4%) 7173 (43.1%) 416 (2.5%)	119.5 123.7 127.9	282 (3.1%) 554 (7.7%) 47 (11.3%)
Call time	Weekday Weekend	12167 (72.0%) 4740 (28.0%)	119.2 127.1	670 (5.5%) 228 (4.8%)
Call time	0800-1800 1800-0000 0000-0800	9753 (57.7%) 3213 (19.0%) 3941 (23.3%)	118.2 124.5 126.8	529 (5.4%) 168 (5.2%) 201 (5.1%)
Out of hours	No Yes	7062 (41.8%) 9845 (58.2%)	114.8 126.1	389 (5.5%) 509 (5.2%)
Admission route	Direct Transfer Non-PPCI IP PPCI IP	12932 (77.2%) 3102 (18.5%) 372 (2.2%) 355 (2.1%)	112.4 162.8 123.1 88.3	655 (5.1%) 178 (5.7%) 27 (7.3%) 30 (8.5%)
Centre volume	<100 100-199 ≥200	1237 (7.3%) 1204 (7.1%) 14466 (85.6%)	108.1 117.7 122.9	92 (7.4%) 75 (6.2%) 731 (5.1%)

Symptom to call (mins)	≤10	2321 (14.2%)	121.4	207 (8.9%)
	>10-30	3206 (19.7%)	118.7	143 (4.5%)
	>30-60	2939 (18.0%)	118.8	131 (4.5%)
	>60-120	2821 (17.3%)	118.0	113 (4.0%)
	>120-180	1422 (8.7%)	119.8	68 (4.8%)
	>180-360	1727 (10.6%)	123.7	81 (4.7%)
	>360	1848 (11.3%)	126.9	108 (5.8%)
Call to balloon (mins)	≤90	4351 (25.7%)		150 (3.4%)
	>90-105	3061 (18.1%)		127 (4.1%)
	>105-120	2784 (16.5%)		120 (4.3%)
	>120-135	2052 (12.1%)		116 (5.7%)
	>135-150	1423 (8.4%)		82 (5.8%)
	>150-180	1412 (8.4%)		101 (7.2%)
	>180-240	1232 (7.3%)		135 (11.0%)
	>240-360	592 (3.5%)		67 (11.3%)

Diabetes: pre-hospital diagnosis
Hypertension: treated or untreated
Hypercholesterolaemia: total cholesterol >5.2 mmol/L or on lipid-lowering treatment
Renal disease: creatinine > 200 µmol/L, functioning transplant or renal failure on dialysis
CABG: coronary artery bypass graft surgery
PCI: percutaneous coronary intervention
TIMI: thrombolysis in myocardial infarction
Out of hours: Monday to Friday 1800-0800 hours, and weekends
Admission route:
Direct: STEMI in the community taken directly to PPCI hospital
Transfer: STEMI in the community taken to or self-presenting to non-PPCI hospital
Non-PPCI IP: STEMI whilst an inpatient in a non-PPCI hospital
PPCI IP: STEMI whilst an inpatient in a PPCI hospital
Centre volume: Number of PPCI cases by centre

Factors associated with call to balloon time (table 2)

CTB time was independently associated with age and was 13 minutes longer for patients aged over 80 than for those aged under 55. CTB time was 4 minutes longer in female patients and 5 minutes in those with diabetes. A requirement for mechanical ventilation before PPCI was associated with the greatest absolute effect on CTB with an increase of 33 minutes.

CTB time was 10 minutes longer for patients presenting 'out of hours' than for patients presenting during normal working hours ('in-hours'). Patients initially admitted to a hospital without PPCI capability and then transferred to a PPCI centre had 49 minutes longer mean CTB times than patients admitted directly from the community to a PPCI service.

CTB time was 9 minutes shorter in centres doing fewer than 100 PPCI procedures compared to those doing 200 or more. Symptom to call time was not significantly associated with CTB time.

Factors associated with 30-day mortality (table 3)

In a univariable analysis each 30-minute increase in CTB time increased the hazard of 30-day mortality by around one fifth. In multivariable analysis there was strong evidence of an independent association between CTB time and 30-day mortality (trend test $p<0.0001$).

Advancing age was independently associated with a progressive increase in 30-day mortality such that patients aged over 80 were at over three-fold higher risk of 30-day mortality than patients under the age of 55. In a univariable analysis female gender was associated with higher 30-day mortality but this is explained by women presenting at older ages than men (average age at presentation 69 versus 62 years, respectively) and after multivariable analysis gender was not associated with 30-day mortality.

Table 2. Multivariable associations with call to balloon time

Variable		Difference in mean call to balloon time - minutes (95%CI)	P value
Age group, years	<55	0	<0.0001*
	55-≤60	1 (-2, 3)	
	60-≤65	2 (0, 4)	
	65-≤70	4 (2, 6)	
	70-≤75	8 (6, 11)	
	75-≤80	11 (8, 13)	
	80-≤85	13 (10, 15)	
	>85	14 (11, 18)	
Gender	Male	0	<0.0001
	Female	4 (2, 5)	
Diabetes	No	0	<0.0001
	Yes	5 (3, 7)	
Cardiogenic shock pre-PCI	No	0	0.0015
	Yes	5 (2, 8)	
Ventilated pre-PPCI	No	0	<0.0001
	Yes	33 (28, 37)	
Q wave on ECG	No	0	<0.0001
	Yes	8 (6, 10)	
TIMI flow pre-PPCI	TIMI 0	0	<0.0001*
	TIMI 1	2 (0, 5)	
	TIMI 2	6 (3, 8)	
	TIMI 3	10 (7, 12)	
Arterial access	Radial	0	0.0007*
	Femoral	2 (0, 3)	
	Joint/other	7 (2, 11)	
Out of hours	No	0	<0.0001
	Yes	10 (8, 11)	
Admission route	Direct	0	<0.0001
	Transfer	49 (47, 51)	
	Non-PPCI IP	9 (4, 13)	
	PPCI IP	-26 (-31, -22)	
Centre volume	≥200	0	<0.0001*
	100-199	0 (-2, 3)	
	<100	-9 (-12, -7)	

* Trend test; CI confidence interval

Diabetes, peripheral vascular disease, renal disease, Q waves on the presenting ECG, multi-vessel PCI, and femoral artery access were all independently associated with an increased risk of 30-day mortality. Cardiogenic shock and ventilation before PPCI had the greatest absolute independent effect on the hazard of 30-day mortality (table 3).

The 49-minute increase in CTB time associated with inter-hospital transfer was associated with an observed 18% increase in the hazard of 30-day mortality (95% CI 0.99 to 1.39) but the evidence was not strong (p=0.059) (table 4). The 10-minute increase in CTB time associated with an 'out of hours' call time was not associated with an increase in 30-day mortality.

The relationship between CTB time and predicted 30-day mortality at different levels of individual patient risk is shown in figure 4. For a patient at low risk (25^{th} centile of risk), an increase in CTB time from 60 minutes to 360 minutes is predicted to increase 30-day mortality by less than 1%, whereas such a treatment delay among higher risk patients (75^{th} centile of risk) is predicted to increase 30-day mortality by nearly 3% (figure 4).

Table 3. Multivariable associations with 30-day mortality

Variable		Hazard ratio (95%CI)	P value
Call to balloon (mins)	≤90	1	<0.0001*
	>90-120	1.14 (0.93, 1.39)	
	>120-150	1.26 (1.02, 1.56)	
	>150-180	1.21 (0.94, 1.57)	
	>180-240	1.95 (1.54, 2.47)	
	>240	1.41 (1.04, 1.90)	
Age group, years	<55	1	<0.0001*
	55-≤60	1.36 (1.00, 1.84)	
	60-≤65	1.62 (1.22, 2.15)	
	65-≤70	1.54 (1.17, 2.04)	
	70-≤75	2.15 (1.63, 2.83)	
	75-≤80	2.72 (2.08, 3.56)	
	80-≤85	3.88 (2.97, 5.06)	
	>85	6.36 (4.92, 8.23)	
Gender	Male	1	0.23
	Female	1.09 (0.94, 1.26)	
Diabetes	No	1	0.0001
	Yes	1.42 (1.19, 1.70)	
PVD	No	1	<0.0001
	Yes	2.02 (1.59, 2.58)	
Renal disease	No	1	0.0002
	Yes	1.86 (1.34, 2.57)	
Cardiogenic shock pre-PCI	No	1	<0.0001
	Yes	5.21 (4.40, 6.16)	
Ventilated pre-PCI	No	1	<0.0001
	Yes	3.76 (3.07, 4.60)	
Q wave on ECG	No	1	0.0003
	Yes	1.34 (1.14, 1.58)	
TIMI flow pre-PCI	TIMI 0	1.54 (1.13, 2.08)	0.0004*
	TIMI 1	1.38 (0.94, 2.04)	
	TIMI 2	1.06 (0.72, 1.56)	
	TIMI 3	1	
Number of vessels attempted	Single	1	<0.0001
	Multi	1.50 (1.26, 1.79)	
Multi-vessel disease (>75% stenosis)	1 vessel	1	<0.0001
	≥ 2 vessels	1.43 (1.23, 1.67)	
Arterial access	Radial	1	<0.0001*
	Femoral	1.41 (1.21, 1.64)	
	Joint/other	1.61 (1.17, 2.22)	

* Trend test, CI confidence interval

Table 4. Relationship between out of hours PPCI, admission route, centre volume and components of symptom to balloon time with 30-day mortality (multivariable analysis)

		CTB included in analysis		CTB excluded from analysis	
Variable		**Hazard ratio (95%CI)**	**P value**	**Hazard ratio (95%CI)**	**P value**
Out of hours	No	1		1	
	Yes	1.00 (0.87, 1.15)	0.99	1.04 (0.91, 1.20)	0.52
Admission route	Direct	1		1	
	Transfer	0.98 (0.81, 1.19)	0.85	1.18 (0.99, 1.39)	0.059
	Non-PPCI IP	1.57 (1.06, 2.32)	0.023	1.69 (1.15, 2.49)	0.007
	PPCI IP	1.39 (0.96, 2.02)	0.085	1.26 (0.87, 1.82)	0.22
Centre volume	≥200	1		1	
	100-199	0.93 (0.73, 1.19)	0.55	0.91 (0.71, 1.16)	0.46
	<100	0.99 (0.79, 1.24)	0.91	0.91 (0.73, 1.13)	0.39
Symptom to call (mins)**					
	≤10	1	0.58*	1	0.47*
	>10-30	0.81 (0.65, 1.01)		0.83 (0.66, 1.04)	
	>30-60	0.88 (0.70, 1.11)		0.90 (0.72, 1.13)	
	>60-120	0.82 (0.65, 1.04)		0.82 (0.65, 1.05)	
	>120-180	0.84 (0.63, 1.16)		0.88 (0.66, 1.17)	
	>180-360	0.94 (0.71, 1.23)		0.96 (0.73, 1.26)	
	>360	1.06 (0.83, 1.35)		1.08 (0.84, 1.38)	
Direct admission patients only* **					
Symptom to call (mins)*					
	≤10-30			1	0.38*
	>30-60			0.98 (0.77, 1.25)	
	>60-120			0.89 (0.69, 1.15)	
	>120-180			1.06 (0.78, 1.43)	
	>180			1.14 (0.91, 1.42)	
Call to door (mins)					
	≤60			1	0.0074*
	>60-90			1.07 (0.89, 1.28)	
	>90-120			1.36 (1.04, 1.77)	
	>120			1.40 (0.96, 2.04)	
Door to balloon (mins)					
	≤60			1	0.0008*
	>60-90			1.04 (0.84, 1.29)	
	>90-120			1.54 (1.16, 2.06)	
	>120			1.43 (1.07, 1.93)	

CI confidence interval

* Trend test

** Among 16284 patients with symptom to call time available

*** Among 12497 direct admission patients with symptom to call time available

Discussion

We analysed data from a large contemporary series of patients with acute STEMI who were treated by a coordinated national PPCI service and identified several variables that were independently associated with CTB time and 30-day mortality. Some of these factors are unalterable (age, gender) but some are potentially modifiable (CTB time) suggesting scope to further improve the outcomes of PPCI.

Previous studies have generally reported a positive association between treatment delay and mortality after PPCI for STEMI, but inconsistencies in the evidence base may reflect differences in study design, data collection periods, and definitions of treatment delay and outcomes. Early studies from the United States reported median DTB times of over 100 minutes [6,9] and median symptom to balloon (STB) times of 234 minutes. [6] Recent studies have reported DTB times approaching 60 minutes but these improvements in STEMI care have not consistently been associated with improvements in outcome, [15-17] possibly because of the use of population rather than individual level treatment delays in some studies. [22]

DTB time may be a poor indicator of the overall impact of treatment delay on outcome, as it does not include pre-hospital care. The STB time is a measure of total ischaemic time, but symptom onset may be difficult to define accurately because of recall bias, prodromal anginal symptoms and silent or atypical presentations. By contrast CTB time is derived from two easily measured time points (time of call to emergency services or self-presentation at hospital, and time of therapeutic instrumentation of the culprit coronary artery), which are systematically recorded for all patients treated by PPCI in the UK. CTB time includes the potentially modifiable components of the system delay and may provide the best measure of the overall performance of a PPCI service.

In a previous study of 13,790 patients with STEMI, who were enrolled in the Swedish SCAAR registry from 2003-2008, the delay from first medical contact (FMC) to PPCI was associated with 1-year mortality and severe left ventricular systolic dysfunction at discharge from hospital. [23] The time of FMC, however, was defined by the time of the first electrocardiogram, which was recorded before arrival in hospital in only 51% of patients. Moreover the time of PPCI was determined by the start of the coronary arteriogram, rather than therapeutic instrumentation of the coronary artery. This may explain why the median time from FMC to PPCI in this study was only 70 minutes. Another study reported on 6,209 patients treated by PPCI from 2002-2008 at three centres in Western Denmark. CTB time was defined as the time from FMC with the emergency medical services to insertion of the guiding catheter before PPCI. CTB times following direct admission to the PPCI centre and following transfer from a local hospital were 97 and 139 minutes, respectively, and CTB time was independently associated with mortality at a median of 3.4 years.[11]In our study symptom to call time was not associated with 30-day mortality whereas call to door and door to balloon time were (table 4), suggesting pre-hospital and hospital based emergency care are equally important contributors to patient outcome.

In our study the relationship between CTB time and mortality was influenced by patient risk profile, such that an increase in CTB time was predicted to have substantially greater impact on 30-day mortality among patients at high risk relative to those at low risk. Several variables associated with CTB time were also associated with 30-day mortality, suggesting that patients most likely to experience delays to treatment may also be most likely to benefit from efforts to minimize treatment delay.

The results of PPCI outside of normal working hours have been studied extensively. A meta-analysis of data from 1.9 million patients from 36 studies reported that ‘out of hours’ PPCI was associated with a 14.8-minute increase in DTB time and a 12% increase in the odds of in-hospital and 30-day mortality. [24] Three large registries also reported that out of hours PPCI

was associated with longer DTB times but these treatment delays had no impact on in-hospital mortality. [25-27]

In our study, an 'out of hours' call time was associated with an increase in CTB time of only 10 minutes, which did not translate into an increase in 30-day mortality. These data suggest that the increase in CTB time associated with 'out of hours' procedures was insufficient to impact 30-day mortality, and support current models of PPCI service delivery across England and Wales.

The shorter CTB times in 'low volume' centres (<100 PPCI procedures) may reflect opportunistic intervention in centres that do not provide a 24/7 service. Overall centre volume had no impact on 30-day mortality but this data requires cautious interpretation because it has limited statistical power.

In England and Wales a minority of patients with STEMI self-present to a non-PPCI hospital or are initially taken to the nearest emergency department because of diagnostic uncertainty. These patients experience a 49-minute increase in CTB time, which is associated with a 18% increase in the hazard of 30-day mortality. These data support the need for preferential transfer of patients with suspected STEMI directly to a hospital with PPCI capability to minimize delays to treatment.

In England and Wales over 80% of patients meet the national audit standard of a CTB time of less than 150 minutes. Recent guidance from the National Institute of Health and Care Excellence (NICE) recommended that PPCI should be the preferred reperfusion strategy provided that PPCI can be delivered within 120 minutes of the time at which fibrinolysis could be given. [28] For most patients the CTB time includes the time from the call for help to the arrival of an ambulance, the time to make a diagnosis and the time that would have been required to set up a fibrinolytic infusion. Cumulatively these delays are likely to exceed 30

minutes; hence the majority of patients in this study would have been compliant with the NICE guidelines. Long CTB times may be unavoidable in patients who present in geographically remote areas, in whom ambulance transfer is delayed or where there is diagnostic uncertainty at the time of presentation. Future research should focus on this subgroup and if CTB times cannot be shortened pharmaco-invasive treatment may be an alternative strategy. [29, 30]

Limitations

We assessed the impact of patient specific CTB times on 30-day mortality in a large cohort of patients undergoing PPCI in a single year. Substantial variation in observed and unobserved factors during this period is unlikely but residual confounding by factors not included in the multivariable analyses cannot be excluded.

Our data suggest that CTB time is a useful metric to evaluate the performance of PPCI services and has advantages over DTB time. Nevertheless, CTB time may not be a reliable surrogate for total ischaemic time because of variation in the duration and severity of symptoms before the person calls for help, and because the time of the first therapeutic intervention on the occluded coronary artery may not completely reperfuse the affected myocardium.

We report outcome at 30 days and most deaths after PPCI occur within this time window but longer term follow up data may provide additional information. In addition, our study only included patients treated by PPCI and is not applicable to patients with STEMI who are managed with fibrinolysis or do not receive reperfusion therapy, who may have worse outcomes. [5,31]

Conclusions

In this contemporary study of patients treated by PPCI within an established national system of STEMI care there was a strong independent association between CTB time and 30-day mortality. This relationship was influenced by patient risk profile and in high-risk patients an increase in CTB time of 90 minutes would be expected to increase 30-day mortality by around 1%.

Approximately 20% of patients have CTB times longer than 150 minutes and further research is required to determine the causes of treatment delay in this subgroup. Efforts to improve performance of PPCI services should ensure that all patients with STEMI are preferentially directed to a hospital with PPCI capability so that the route of entry into the healthcare system does not influence outcomes.

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Richard W.Varcoe and Tim C.Clayton had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

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Figure legends

Figure 1: Patient selection

Abbreviations: BCIS British Cardiovascular Intervention Society; PCI Percutaneous coronary intervention; PPCI Primary percutaneous coronary intervention; STEMI ST segment elevation myocardial infarction.

Duplicates refers to duplicate records

Repeat PPCI refers to a repeat PPCI procedure in the same year

Figure 2: Frequency of call to balloon times. Each bar represents a 15-minute interval

Figure 3: Kaplan-Meier plot of 30 day mortality by call to balloon time (with 90 and 150 minutes as cut-points)

Figure 4: Association between call to balloon time and 30-day mortality