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The effect of door-to-balloon delay in primary percutaneous coronary intervention on clinical outcomes of STEMI: a systematic review and meta-analysis.

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Contents

Appendix 1. Study Protocol

This study was conducted according to the guidance from the Cochrane Handbook of Systematic Reviews.[1] Amendments to the initial published protocol [2] (PROSPERO ID: CRD42015026069) are presented in appendix 1. Original protocol (published)[2] is available online (since 2016 Aug 2) - doi: 10.1186/s13643-016-0304-7

eTable 1.1 List of discrepancies between the initial study protocol and the final analysis

	Original protocol	Amendment	Rationale
1	All eligible studies will be assessed for risk of bias (RoB) using the Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) tool (previously known as the Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NSRI))	Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS) [3]. Comparability between the two exposure groups (i.e. short vs. long D2B time group) were further scrutinized by comparing the confounding factors adjusted in each study against a list of predefined confounding domains identified using subject-matter knowledge and a review of literature.	After further assessing the nature of the study questions and the available evidence, along with an initial RoB assessment using the pre-determined ROBINS-I, we learned that the ROBINS-I tool although covers a wider scope of the RoB assessment, it is not as appropriate for use in investigation that study an exposure-outcome relationship. Many of the examined components were not directly relevant. In fact, ROBINS-I was designed primarily for study that examines an intervention-outcome relationship according to the descriptive paper (BMJ 2016;355:i4919). This is further evidenced by the recent development of the ROBINS-E* tool, which is a similar RoB assessment tool designed otherwise for exposure based study specifically. As our investigation of the time-outcome relationship in coronary intervention is a study that concern an "exposure" (time) rather than an "intervention", we made a decision to amend the protocol and used the NOS instead as the framework for RoB assessment. In addition to using the NOS for overall study quality assessment, we have further scrutinized the comparability between the exposure groups by comparing the confounding factors adjusted in each study against a list of predefined confounding domains identified using subject-matter knowledge and a review of literature. *https://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-e/
3	Pre-determined secondary endpoints included cardiac arrest (not resulting in death), tachy- and brady-arrhythmia, and cardiac wall aneurysm.	Pre-determined secondary endpoints included cardiac arrest (not resulting in death), tachy- and brady-arrhythmia, cardiac wall aneurysm and ejection fraction (EF).	After further discussion, we believe that EF is an important surrogate endpoint of HF.
4	-	Addition of the dose-response analysis (suggested by peers)	This analysis further clarifies the time-outcome relationship in addition to the dichotomous approach.

Appendix 2. MOOSE checklist

Criteria		Brief description of how the criteria were handled in the meta-analysis	Page No. / Location
Reporting of background			
√	Problem definition	Despite the significant improvement in D2B delay across many healthcare systems over the past decade[4, 5], recent studies in the US have shown that the overall mortality of patients undergoing pPCI at a population level remains unchanged.[6, 7] Because D2B time represents only a small fraction of the total ischemic time (i.e. the time from vessel occlusion to recanalization), it has been postulated that its improvement may not have a significant effect on the reduction of total ischemic time, especially in those with substantial pre-hospital delays. An opposing view has suggested that the increasing use of pPCI among higher risk patients over time as pPCI use in STEMI has expanded is the primary contributor to explain the lack of impact.[7] Despite many studies evaluating the D2B delay-outcomes relationship and this recent controversy[4, 8-15], there has been a lack of high-quality systematic review and meta-analysis assessing such relationship. Previously published reviews[16, 17] neither assessed the quality nor performed a quantitative synthesis on the evidence. Furthermore, the effects of patient risk level and the extent of pre-hospital delay on the D2B delay-outcomes relationship have not yet been explored above the level of individual studies.	3
√	Hypothesis statement	Thus, we perform a systematic review and meta-analysis to determine the relationship between D2B delay and mortality and other STEMI outcomes. We also examine the effect of potential effect modifiers such as pre-hospital delay and patients' risk profile on the relationship.	4
√	Description of study outcomes	Mortality and incident heart failure (HF) were the pre-defined primary outcomes of interest.	5
√	Type of exposure or intervention used	Door-to-balloon delay.	4-5
√	Type of study designs used	We only included prospective observational studies.	4
√	Study population	Adult with STEMI undergoing pPCI.	4
Reporting of search strategy			
√	Qualifications of searchers	The first author (FCY) performed the search. The credentials of the searchers are indicated in the author list.	0
√	Search strategy, including time period included in the synthesis and keywords	The search strategy is provided in appendix 3. No language restriction was applied.	4
√	Databases and registries searched	PubMed, EMBASE, ClinicalTrials.gov, WHO International Clinical Trials Registry, CINAHL Database, and The Cochrane Library.	4
√	Search software used, name and version, including special features	We did not used a search software. EndNote was used to merge retrieved citations and eliminate duplications.	4

Criteria		Brief description of how the criteria were handled in the meta-analysis	Page No. / Location
√	Use of hand searching	We hand-searched bibliographies of retrieved papers for additional references.	4
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart (eFigure 4.1). The citation list is available upon request.	4 & appendix 3
√	Method of addressing articles published in languages other than English	We placed no restrictions on language.	4
√	Method of handling abstracts and unpublished studies	We also have sourced proceedings for the past 20 years from the European Society of Cardiology (www.escardio.org), the American College of Cardiology (www.acc.org), the American Heart Association (www.aha.org), the EUROPCR (www.europcr.com) and the TCT (www.tctconference.com). ProQuest Dissertations and Theses Database was searched for additional grey literature.	4 & appendix 3
√	Description of any contact with authors	We contacted the authors by email to obtain additional data for the meta-analysis.	4
Reporting of methods			
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the "study selection" part of the methods section. Procedural details of data extraction are provided in appendix 4.	4 & appendix 4
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and possible effect modifiers of the association.	Appendix 4
√	Assessment of confounding	Conducted sensitivity analyses and meta-regression for the assessment of confounding.	5-6
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was evaluated by using the Newcastle-Ottawa quality assessment scale. The system allowed a total score of 0-9 points (9 representing the highest quality)	5-6
√	Assessment of heterogeneity	Heterogeneity of the studies were explored within two types of study designs using I^2 statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity.	6-7
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses and assessment of publication bias are detailed in the methods.	6-7

Criteria		Brief description of how the criteria were handled in the meta-analysis	Page No. / Location
√	Provision of appropriate tables and graphics	We included two tables for pooled effects of various outcomes and various subgroups, one forest plot for primary outcome and one meta-regression plot for the relationship between the main outcome and study level quality. We have also provided additional information as tables, figure and text in this appendix.	9, 11 and figures
Reporting of results			
√	Graph summarizing individual study estimates and overall estimate	Figures 1 and appendix 7: eFigure 7.1-7.11	Accompanying figures
√	Table giving descriptive information for each study included	Appendix 5, eTable 5.1-5.3	eTable 5.1-5.3, appendix 5
√	Results of sensitivity testing	In text and appendix 6.	10
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses	8-12
Reporting of discussion			
√	Quantitative assessment of bias	Subgroup analyses and sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies.	8-12
√	Justification for exclusion	We excluded studies if they lack adequate reported data for pooled analysis.	7
√	Assessment of quality of included studies	We discussed the results of the analyses.	8
Reporting of conclusions			
√	Consideration of alternative explanations for observed results	We discussed that potential unmeasured confounders may have caused residual confounding. We noted that the variations in the strengths of association may be due to true population differences, or to differences in quality of studies.	13
√	Generalization of the conclusions	D2B delay in pPCI is related to higher risk of adverse outcomes among STEMI patients. This relationship is congruent with our theoretical understanding of the pathophysiology of myocardial infarction. Hence, minimizing this delay should remain an important part of the quality improvement effort of contemporary STEMI care, especially in settings where D2B delay remains significant. Pre-hospital delays modify the effect of D2B time on outcomes, hence improving this segment of the delay chain should not be overlooked.	14
√	Guidelines for future research	We highlighted the current knowledge gaps in the limitation and hence future research should place focus on them.	14
√	Disclosure of funding source	This study received no funding.	15

Appendix 3. Search Strategies

Other Sources - conference proceedings and theses

- the European Society of Cardiology (www.escardio.org),
- the American College of Cardiology (www.acc.org),
- the American Heart Association (www.aha.org),
- the EUROPCR (www.europcr.com) and
- the TCT (www.tctconference.com).

ProQuest Dissertations and Theses Database were searched for additional grey literature.

A manual search was conducted on the reference list of relevant articles.

eTable 3.1 PubMed and The Cochrane Library

Search	Query
#11	Search (((((("Time Factors"[Mesh]) OR "Time-to-Treatment"[Mesh])) AND "Myocardial Infarction"[Mesh]) AND ((("Angioplasty, Balloon, Coronary"[Mesh]) OR "Myocardial Revascularization"[Mesh]) OR "Percutaneous Coronary Intervention"[Mesh])) AND "humans"[MeSH Terms] Filters: Publication date from 1977/01/01 to 2016/12/31
#10	Search (((((("Time Factors"[Mesh]) OR "Time-to-Treatment"[Mesh])) AND "Myocardial Infarction"[Mesh]) AND ((("Angioplasty, Balloon, Coronary"[Mesh]) OR "Myocardial Revascularization"[Mesh]) OR "Percutaneous Coronary Intervention"[Mesh])) AND "humans"[MeSH Terms]
#9	Search "humans"[MeSH Terms]
#8	Search (("Angioplasty, Balloon, Coronary"[Mesh]) OR "Myocardial Revascularization"[Mesh]) OR "Percutaneous Coronary Intervention"[Mesh]
#7	Search "Percutaneous Coronary Intervention"[Mesh]
#6	Search "Myocardial Revascularization"[Mesh]
#5	Search "Angioplasty, Balloon, Coronary"[Mesh]
#4	Search "Myocardial Infarction"[Mesh]
#3	Search ("Time Factors"[Mesh]) OR "Time-to-Treatment"[Mesh]
#2	Search "Time Factors"[Mesh]
#1	Search "Time-to-Treatment"[Mesh]

(5186 Records Found for PubMed & 823 Records Found for Cochrane Library)

eTable 3.2 EMBASE via Ovid

#	Search
1	heart infarction/
2	percutaneous coronary intervention/
3	transluminal coronary angioplasty/
4	2 or 3
5	time/

6	time to treatment/
7	5 or 6
8	1 and 4 and 7
9	limit 8 to (human and yr="1977 - 2016")

(523 Records Found)

eTable 3.3 CINAHL PLUS

Search ID#	Search Terms
S17	S4 AND S8 AND S15 ; Limiters- Publication Year: 1977-2015
S16	S4 AND S8 AND S15
S15	S9 OR S10 OR S11 OR S12 OR S13 OR S14
S14	MH "Revascularization"
S13	MH "Myocardial Revascularization"
S12	MH "Myocardial Reperfusion"
S11	MH "Angioplasty"
S10	MH "Angioplasty, Balloon"
S9	MH "Angioplasty, Transluminal, Percutaneous Coronary"
S8	S5 OR S6 OR S7
S7	MH "Coronary Disease"
S6	MH "Coronary Thrombosis"
S5	MH "Myocardial Infarction"
S4	S1 OR S2 OR S3
S3	MH "Treatment Delay"
S2	MH "Time Factors"
S1	MH "Time"

(1184 Records Found)

eTable 3.4 ClinicalTrials.gov

expert search syntax
(time OR door) AND (Percutaneous Coronary Intervention OR Myocardial Revascularization OR Angioplasty, Balloon, Coronary) AND (Myocardial Infarction OR STEMI) [DISEASE] AND EXACT Adult [AGE-GROUP]

(191 Records Found)

eTable 3.5 WHO ICTR

	In the	Key words
-	Condition	STEMI OR Myocardial Infarction OR Percutaneous Coronary Intervention OR Angioplasty OR Myocardial Revascularization
AND	Intervention	time OR door OR delay

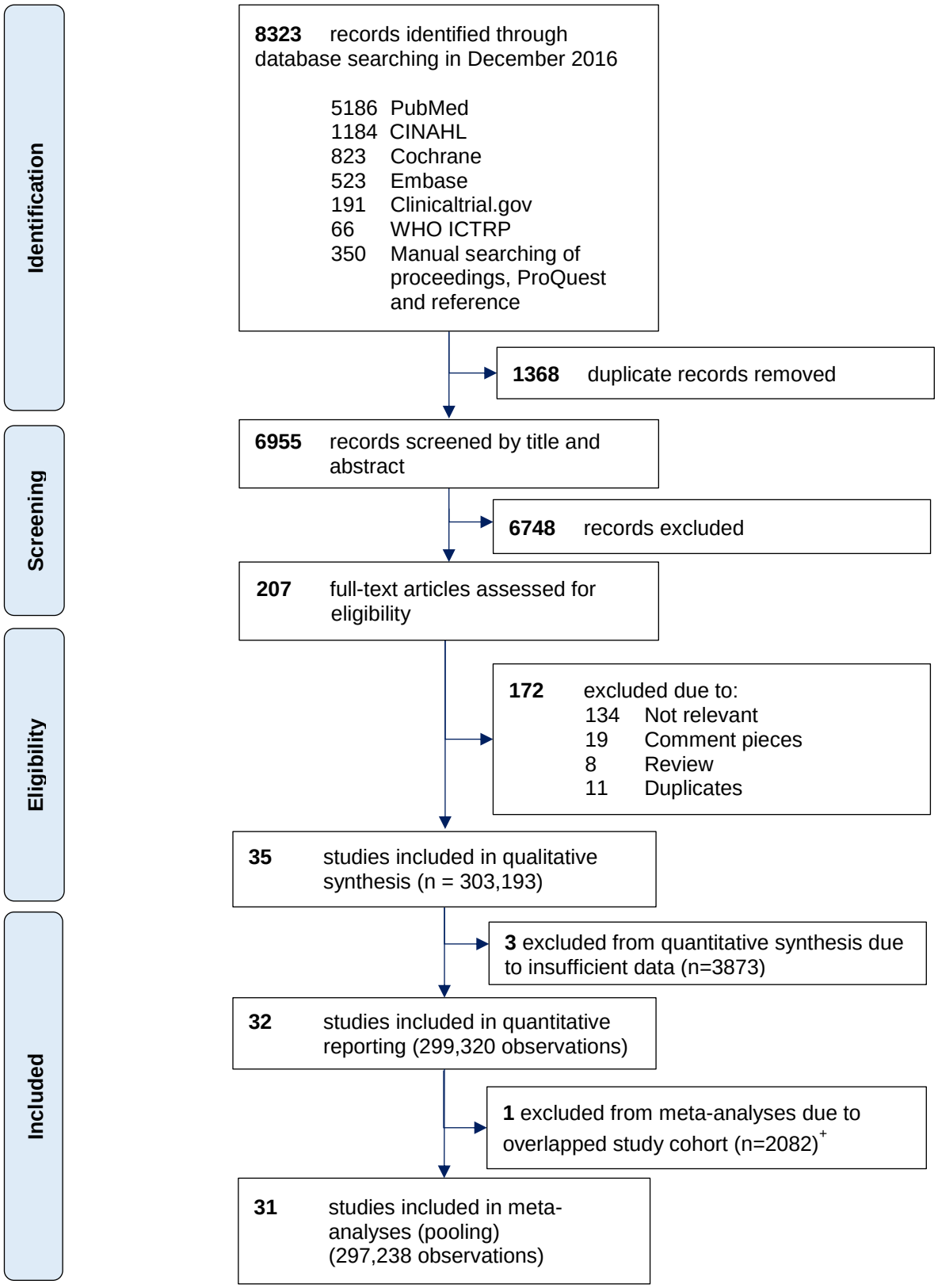
(66 records for 59 trials found)

Appendix 4. Data extraction

Two reviewers (F.C.Y and K.O.B) independently screened the titles and abstracts of retrieved citations to identify potentially relevant studies. Relevant data were abstracted using a standardized extraction form. The extracted data included study and subject characteristics, exposure, outcomes, and other relevant findings. We retrieved the unadjusted or the most adjusted odds ratios and their corresponding 95% confidence interval from each study. We also retrieved hazard ratio if reported. We considered hazard ratio to approximate the relative effect of similar outcomes reported in other studies that used odds ratios.[18, 19] Disagreement at any point in the review process was resolved by discussion. All extracted data were cross-checked between the two reviewers (F.C.Y and K.O.B). Further details of the data extraction and management process can be referred to in the published protocol.[2]

Appendix 5. Study Selection

eFigure 5.1. Flow diagram for study selection



+Two included studies were found to have a partially overlapped study cohort (see main text). The smaller study (n=2082) was excluded from the pooled analysis.

eTable 5.1 List of included studies and description of study characteristics.

The year of publication ranged from 1999 to 2016, and the patient cohorts included in the studies started since 1984. Nine studies took place in North America,[10-12, 14, 20-24] 9 in Europe,[25-33] 11 in Asia and Oceania[4, 15, 34-42] and 6 in multinational settings.[8, 9, 13, 43-45] All studies took place within the high-income country setting except one study.[37] No non-English language paper was found. The largest study [14] included 150,116 patients. Clinical registry, hospital databases and observational data from clinical trials were the main sources of data. All included studies had a cohort design. Summaries of the clinical characteristics of each cohort and the study characteristics are provided in appendix 4, eTable 4.1-4.3.

Reference	Pub Year	Data Source	Period	Country	No of site & sample size(n)	Outcomes assessed	Subgroup assessed	Adjusted variables
Yudi[34]	2016	MIG PCI registry	2004-2012	Australia	8; n=2539	30-day mortality, Reinfarction, and TVR 12-month mortality, Reinfarction, and TVR Long term incidence of death (median follow-up 509-1029 days)	High risk and low risk	Age, gender, DM, HPT, Dyslipidaemia, renal function, FHx of CAD, previous MI or HF, smoking status, cardiogenic shock, time from symptom onset to PCI, lesion location, bypass graft lesions, high risk lesion, use of GPIIb/IIIa, IABP use, drug-eluting stent use, stent length > 20 mm, and stent diameter < 2.5mm
Domenicantonio[25]	2016	Multiple admin and clinical databases	2009-2013	Italy	NA; n=3207	30-day mortality	No	Age, gender, clinical characteristics (SBP, heart comorbid, DM, CVA, Cancer), EMS vs direct presentation, time of admission
Wang[35]	2016	Single centre cohort	2009-2013	Taiwan	1; n=344	Mortality (unknown duration)	Younger and older age group	Age, Killip class

Reference	Pub Year	Data Source	Period	Country	No of site & sample size(n)	Outcomes assessed	Subgroup assessed	Adjusted variables
Solhpour[20]	2016	Database at Memorial Hermann Heart & Vascular Institute	2008-2013	US	2; n=786	30-day mortality	No	-
Sim[36]	2015	-	2009-2012	Singapore	1; n=1268	In-hospital mortality	No	Age, Gender, Ethnic, race, Socioeconomic status, type of AMI, mode of presentation, history of smoking, DM, HPT, hyperlipidaemia, prior MI, prior PCI, prior CABG, renal failure on dialysis, number of diseased vessel on coronary angiography, target vessel for PCI, left main disease, cardiogenic shock
Nallamothu[14]	2015	NCDR CathPCI Registry	2005-2011	US	600-1400; n=150116	In-hospital mortality	No	Age, Cardiogenic Shock on admission, Previous CHF, Prior Heart valve surgery, Cerebrovascular Disease, Heart valve disease, Chronic lung disease, Previous PCI, IABP Placement, EF(%), Pre-procedure TIMI flow, DM, SCAI lesion class, BMI, GFR, Dialysis, NYHA class, Infarct artery, Salvage status of PCI, Annual Median D2B
Wongpraparut[37]	2014	National PCI registry	2006	Thailand	29; n=161	In-hospital cardiogenic shock In-hospital mortality In-hospital MACE	No	-
Ho[38]	2014	Cohort study data	2008-2009	Taiwan	1; n=559	30-day mortality 30-day advanced CHF 30-day MACE	No	-
Helve[26]	2014	Clinical registry	2007-2012	Finland	1; n=500	90-day Mortality 90-day MACE	No	-
Brennan[4]	2014	MIG PCI registry	2006-2010	Australia	6; n=1926	12-month mortality 12-month recurrent MI 12-month MACE	No	Cardiogenic shock, eGFR, LMCA lesion, RCA lesion, chronic lung disease, DM, Age, Thienopyridine use, Chronic Lung Disease,

Reference	Pub Year	Data Source	Period	Country	No of site & sample size(n)	Outcomes assessed	Subgroup assessed	Adjusted variables
								Cardiogenic shock, History of MI, small vessel lesion, Type B2 or C lesion, single vs multi-vessel disease
Nakamura[39]	2012	J-AMI Registry	2011	Japan	213; n=2030	In-hospital mortality	No	-
Kodaira[40]	2013	JCD-KICS	2008-2011	Japan	> 1; n=214	In-hospital mortality In-hospital MACE In-hospital shock	No	-
Shiomi[15]	2012	CREDO-KYOTO AMI Registry'	2005-2007	Japan	26; n=3391	30-day mortality 30-day MACE 3-year incidence of death and MACE	Early presentation and delayed presentation	Age, Gender, BMI, HPT, DM, Insulin Rx, Smoking status, Heart failure, Ejection fraction, Severe MR, Prior MI, Prior CVA, PVD, eGFR, Haemodialysis, AF, Anaemia, Thrombocytopenia, COPD, Liver cirrhosis, Malignancy, Onset2Balloon, Onset2presentation, Killip class, IABP use, PCPS use, infarct related artery location, Total stent length, min stent size, DES use, thrombectomy, distal protection, medication at discharge
Heitzler[27]	2012	Croatian pPCI network cohort	2005-2007	Croatia	8; n=1190	In-hospital mortality 6-month mortality 6-month angina 6-month MACE	No	-
Towae[28]	2011	MITRAplus & OPTAMI registry	1994-2008	Germany	70-390; n=5078	In-hospital mortality 12-month mortality	No	Age, gender, diabetes, prior myocardial infarction, heart rate >100/min, blood pressure <100 mmHg, reduced left ventricular ejection fraction (LV EF <40%), cardiogenic shock, beta blocker, ace-inhibitors and, statins at discharge
Muller[29]	2011	Cohort study data	2004-2008	Germany	1; n=797	6-month mortality 6-month MACE	No	Age, SBP, Ant MI, Cardiogenic shock, Multivessel Disease, DM, Pre-dilation, Final TIMI flow, Stent number >/= 3

Reference	Pub Year	Data Source	Period	Country	No of site & sample size(n)	Outcomes assessed	Subgroup assessed	Adjusted variables
Lambert[21]	2010	Data extraction from medical chart	2006-2007	Canada	80; n=2356	30-day mortality 12-month mortality 1-year readmission for AMI 1-year readmission for CHF 1-year MACE	No	TIMI index, sex, anterior MI, 4 comorbidities (CHF, RF, PVD, cancer), arrival by ambulance and transfer status
Hannan[11]	2010	New York State PCI Reporting System Registry	2004-2006	US	NA	Long term incidence of death (median follow-up 413 days)	Early presentation and delayed presentation	Age, Gender, Ethnicity, EF, Co-morbid (carotid/cerebrovascular disease, Peripheral vascular disease, heart failure, COPD, DM, RF), shock, malignant ventricular arrhythmia, anatomical group, admission time
Brodie[43]	2010	CADILLAC trail & HORIZONS-AMI trail	1997-1999; 2005-2007	11 countries[a] & 9 countries[b]	199; n=4548	1-year incidence of death	Early presentation and delayed presentation	Age, Gender, DM, Prior MI, Ant MI, Killip class II-IV, Weight, TIMI risk score, Infarct location, 3-vessel disease LVEF index, TIMI flow pre-PCI, study difference, treatment assignment
Rathore[22]	2009	Cooperative Cardiovascular Project	1994-1996	US	NA; n=1932	30-day mortality 12-month mortality	No	Gender, race, age, presence of angina, time from onset to door, presentation characteristics (shock, cardiac arrest, SBP, heart rate), ECG findings on admission (LBBB, Q-wave MI, sum of ST elevation, infarct location), medical history (previous MI, CVA, CHF, COPD, DM, HPT, smoking, previous revascularization), annual MI volume of the treating hospital and presence of on-site surgical backup, annual MI volume, onsite surgical backup
Rathore[23]	2009	NCDR	2005-2006	US	> 600; n= 45687	In-hospital mortality	No	Patient Characteristics: Sex, race, age, findings at presentation (shock, renal failure, prehospital delay); Medical history (DM, LVEF, chronic lung disease); angiographic findings (LMD, proximal LAD, SCAI lesion classification); Procedural characteristics

Reference	Pub Year	Data Source	Period	Country	No of site & sample size(n)	Outcomes assessed	Subgroup assessed	Adjusted variables
								(pre-procedure IABP, use of non-stent device, use of thrombin inhibitors, time of day, weekend procedure); hospital characteristics (annual pPCI volume, teaching status, ownership, rural location)
Kong[30]	2009	British Cardiovascular Intervention Society database	2005-2008	UK	2; n=459	In-hospital mortality	High risk and low risk	-
Song[41]	2008	Korea Acute MI Registry	2005-2007	Korea	41; n=1416	30-day mortality 30-day MACE	High risk and low risk	-
Soon[42]	2007	Hospital patient database system	2001-2003	Singapore	1; n=199	30-days mortality 1-month MACE 6-month mortality 6-month MACE	No	-
Nallamothu[13]	2007	GRACE	Not mentioned	14 countries in Europe, North and South America, Australia and New Zealand	106; n=2173	6-month mortality	No	Age, cardiac arrest, Killip classification, SBP, pulse, creatinine, ST-changes, and elevated biomarkers and time from onset to presentation
Brodie[9]	2007	EMERALD Trial	2002-2003	US, Canada, France, Italy, Germany, Switzerland, Japan	38; n=450	6-month mortality 6-month re-infarction 6-month stroke 6-month MACE	No	-
McNamara[12]	2006	NRMI	1999-2002	US	1529; n=29222	In-hospital mortality	No	Age, gender, race/ethnicity, insurance status, medical history (current smoker, chronic

Reference	Pub Year	Data Source	Period	Country	No of site & sample size(n)	Outcomes assessed	Subgroup assessed	Adjusted variables
								renal insufficiency, previous AMI, HPT, FHx of CAD, hypercholesterolemia, CHF, previous CABG, previous PCI, COPD, stroke, angina, DM), presentation characteristics (time from onset to presentation, whether prehospital ECG done, admission time, admission day of week, chest pain at presentation, systolic BP, HR,HF on presentation), result of diagnostic ECG (number of lead with ST elevation, AMI location, ST depression, non-specific ST-T changes, Q wave), Calendar time.
Brodie[45]	2006	CADILLAC trial	1997-1999	9 countries (not specified)	76; n=1909	30-day mortality 30-day recurrent MI 12-month mortality 12-month recurrent MI Ejection fraction at follow-up	Early presentation and delayed presentation	Age, sex, DM, HPT, prior infarct, prior CABG, infarct location, Killip class, renal insufficiency.
Brodie[24]	2006	Hospital patient registry	1984-2003	US	1; n=2300	In-hospital mortality Long term incidence of death (median follow up time 84 months) Ejection fraction at follow-up	Early presentation and delayed presentation; High risk and low risk	Age, gender, DM, prior MI, prior CABG, ant MI, Killip class, HPT, smoking status
Zahn[31]	2004	ALKK PCI registry	1994-2000	Germany	80; n=4815	In-hospital mortality	No	Age, sex, location of infarction, cardiogenic shock, previous CABG, presence of LBBB, technical success; volume of pPCI at each hospital, year of inclusion
Juliard[32]	2003	Hospital patient registry	1988-2000	France	1; n=499	In-hospital mortality	No	Age, gender, risk factors for CAD, medical history and CV events, infarct type, presence of contraindication to thrombolysis, angiographic findings, ventricular arrhythmias, stent placement, use of GIIb/IIIa blocker

Reference	Pub Year	Data Source	Period	Country	No of site & sample size(n)	Outcomes assessed	Subgroup assessed	Adjusted variables
De Luca[33]	2003	Pooled data from 6 single centre clinical trials	1994-2001	The Netherland	1; n=1791	12-month mortality	High risk and low risk; Pre-procedural TIMI flow < 3 and > 2	-
Brodie[44]	2001	Stent PAMI trial	1995-1996	North America, Europe, Middle East & Asia, South America	62; n=1232	30-day mortality 6-month mortality	No	-
Cannon[10]	2000	NRMI-2	1994-1998	US	661; n=27080	In-hospital mortality	High risk vs low risk (Cardiogenic shock)	SBP, Age, Killip class, HR, Anterior MI, Hypercholesterolemia, DM, Thrombolytic contraindication, HPT, Prior CHF
Berger[8]	1999	GUSTO-IIb direct PTCA sub-study	1994-1996	N. America , Europe and Australia	57; n=565	30-day mortality	No	Age, SBP, baseline Killip class, smoking status, and diagnosis or treatment of cancer in the last 5 years

[a]The Netherlands, Italy, Spain, Germany, Israel, United Kingdom, Argentina, Poland, Austria, Norway, Sweden, Denmark;
[b]The Netherlands, Italy, Spain, Germany, Israel, United Kingdom, Argentina, Poland, Austria, Norway, Sweden, Denmark; pPCI= primary PCI;

eTable 5.2 Study cohort characteristics

		Study cohort characteristics				
Reference	**Year**	**Median D2BT(IQR)**	**Mean Age (SD)**	**Proportion Male**	**Proportion Anterior MI**	**Pre-hospital delay**
Yudi	2016	86.4	62(12.4)	77.4%	38.1%	202.4 mins
Domenicantonio	2016	Mean=70.9 (SD=27.9)	63.5(12.2)	77.6%	-	-
Wang	2016	-	-	88.2%	-	-
Solhpour	2015	-	56.5(11.5)	75.6%	56.9%	-
Ho	2014	-	60.5(12.6)	83.7%	54.4%	166.8 mins
Sim	2015	60.0	58(12)	86.0%	-	-
Nallamothu	2015	69(37)	60.9(13.0)	72.0%	55.9%	onset-to-admission : < 6 hrs: 82.1%; 6-12hrs: 6.4%; >12hrs: 6.1%; unknown: 5.5%
Wongpraparut	2014	115	61(13)	75.6%	-	-
Helve	2014	38.8	64.5(13.6)	67.4%	51.0%	Median = 177.3
Brennan	2014	-	62.9(12.7)	77.6%	-	Median STDT (IQR) = 95 min (65-157)
Nakamura	2012	42(38)	66.9(12.9)	77.1%	49.0%	median onset2door time = 135min(64-305) ; 82% arrived at hospital within 6 hrs
Kodaira	2013	104(60.5)	64.86775701	78.0%	34.1%	median time to presentation = 196min(255)
Shiomi	2012	90(60-132)	67.5(12.2)	74.0%	47.0%	median onset to presentation = 2.4 hrs (144 mins) (IQR = 1.1-5.1)
Heitzler	2012	108(10-540)	median=60; range=24-95	73.3%	42.6%	onset-to-door time(median)=130 min(range=15-1365)
Towae	2011	79.9	median=62.3	74.5%	-	-
Muller	2011	29(22-39)	64.7(12.5)	73.0%	48.0%	-
Lambert	2010	110(82-149)	60(median), 52-71(IQR)	74.0%	31.9%	-
Hannan	2010	-	-	-	-	-
Brodie	2010	107 (79-146)	60.2(11.9)	75.1%	40.0%	112 (IQR = 60-205)
Rathore	2009	128(92-178)	73(IQR= 69-78)	5530.0%	56.5%	symptoms < 6 hrs = 73.2%
Rathore	2009	83(62-109)	59(IQR=51-70)	7210.0%	55.0%	90.9% admitted < 6 hrs after onset

		Study cohort characteristics				
Reference	**Year**	**Median D2BT(IQR)**	**Mean Age (SD)**	**Proportion Male**	**Proportion Anterior MI**	**Pre-hospital delay**
Kong	2009	89(49-120) - 68(50-91)	63(14)	75.0%	44.4%	-
Song	2008	90 (65-136)	61.2(12.9)	75.0%	53.3%	onset2door time = 163 (IQR 90-285)
Soon	2007	110	56.0(11.6)	89.2%	57.2%	125mins
Nallamothu	2007	78(47-120)	61(IQR = 53-72)	7600.0%	-	120(IQR = 70-186)
Brodie	2007	-	median=58.1	79.8%	39.9%	-
McNamara	2006	102(54)	61.6	71.0%	36.4%	62% presented within 2 hrs of onset
Brodie	2006	120 (88.8-163.2)	-	73.0%	36.9%	O2D time = 106.8 mins (60- 205.8)
Brodie	2006	138(96-192)	59.8(11.2)	69.6%	38.2%	-
Zahn	2004	mean = 83 (SD = 122)	61.4(12.5)	74.4%	42.1%	180mins(SD=158)
Juliard	2003	median = 45 / mean = 54 (SD=28)	58.4(13.1)	80.0%	47.1%	median = 180 mins
De Luca	2003	55(36)	60.2(11.3)	79.2%	51.1%	-
Brodie	2001	113(81-162)	60.7(12.5)	74.4%	42.2%	median O2D = 115.0 mins
Cannon	2000	116(85-163)	61.5(0.1)	70.1%	39.4%	-
Berger	1999	76(61-95)	63.2(NA)	75.3%	-	-

eTable 5.3 Inclusion and exclusion criteria, definition of D2B delay of each included study

Author	Year	Inclusion Criteria	Exclusion Criteria	Definition of exposure (D2B delay)
Yudi	2016	All STEMI patients treated with primary percutaneous coronary intervention (PCI) between April 2004 and November 2012 in the MIG (Melbourne Interventional Group) registry	Patients treated with thrombolysis, rescue PCI or those who presented with an acute coronary syndrome (ACS) duration ≥24 h were excluded.	D2B time - not specifically defined; compared 2 groups (< 90 vs. >90)
Domenicantonio	2016	We selected patients aged 35–100 years, discharged with a diagnosis of STEMI (ICD-9-CM: 410.1–410.6, 410.8) between 1 January 2009 and 30 November 2013 who underwent PCI (ICD-9-CM: 00.66, 36.01, 36.02, 36.05–36.07) with a DTBT of less than 2 hours	Excluded – "invalid episode", uninsured individuals or non-Lazio residents, individual with invalid address, invalid D2B time, and mortality between 0-1 day.	D2B time - not specifically defined; compared between < 72 vs. > 72. The DTBT time interval were measured from the patient's first hospital "access".
Wang	2016	Consecutive STEMI patients who underwent PPCI from Jan 2009 through Sep 2013 at China Medical University Hospital in Taichung city in central Taiwan. All enrolled patients presented with typical ischemic chest pain and received PPCI within 12 h after symptoms onset.	Patients as below were excluded in this study: (1) chest pain symptoms onset N12 h before presenting at emergency room, (2) subjects who received thrombolytic agents as reperfusion therapy, (3) ST elevation on ECG without obvious coronary artery diseases, such as acute myocarditis, early repolarization, or Takotsubo cardiomyopathy and (4) Patients who didn't receive PPCI due to refusal, personal concerns, or physicians' clinical judgments.	D2B time - not specifically defined; compared both < 90 vs. >90 and < 60 vs. >60
Solhpour	2015	All patients with STEMI captured in the database	Patients transferred from other hospitals, those with prior MI or prior CABG, those undergoing rescue PCI for failed thrombolysis, patients who did not undergo PCI for their STEMI, patient without 30-day follow up information	D2B time - not specifically defined; analysed in 4 groups (< 30, 30-59, 60-89,>=90)

Author	Year	Inclusion Criteria	Exclusion Criteria	Definition of exposure (D2B delay)
Ho	2014	Patients of all ages presenting with STEMI < 12 hrs duration, underwent pPCI	-	Not defined; analysed in 3 different ways (< 30 vs > 30, < 45 vs > 45, < 60 vs > 60)
Sim	2015	Patient presented with STEMI and underwent pPCI	-	Not defined; analysed delayed (> 90 mins) vs non-delay (< 90 mins)
Nallamothu	2015	-	STEMI patients not undergoing pPCI (n=52,372); transfer patients (n=129,579); patients with D2BT < 15 mins and > 3 hrs (n=45,391) ; patients from hospitals that did not report data consistently (n=134,863)	Time from hospital arrival to first device use during pPCI (e.g. balloon or thrombectomy catheter) - per 10 mins decrease
Wongpraparut	2014	STEMI patients underwent pPCI	-	FMC to device time - time from arrival to ER to the initiation of first coronary balloon dilatation; analysed by < 90 min vs > 90 mins
Helve	2014	Diagnosed with STEMI, lived permanently in HUS district, given written consent, fulfilled STEMI criteria,	Those who did not received pPCI and those received fibrinolysis.	D2B time - not specifically defined; analysed in 2 groups (< 60 vs > 60 mins)
Brennan	2014	STEMI patients undergoing pPCI in 2006-2010	STEMI > 12 hr, rescue PCI and patients transferred from a non-PCI capable hospital	D2BT defined as the number of minutes from hospital arrival to first balloon inflation, thrombus aspiration or device deployment to establish reperfusion, dichotomized to </= 90 vs > 90
Nakamura	2012	-	Subjects without complete data (n=131)	D2B time - interval from arrival to initiation of primary PCI - 6 x 30 minute intervals; converted to < 90 mins vs > 90 mins, tested with Fisher test

Author	Year	Inclusion Criteria	Exclusion Criteria	Definition of exposure (D2B delay)
Kodaira	2013	-	Patients with cardiogenic shock or cardiopulmonary arrest (n=253); missing time to presentation or D2B time (n=620)	D2B time - time from hospital arrival till first balloon inflation: < 90 mins vs >/= 90 mins
Shiomi	2012	-	Patients who refused participation in the study when contacted at follow up	D2B time - time from arrival at the hospital to first balloon inflation during PCI: </= 90 mins vs > 90 mins
Heitzler	2012	Included both transferred and non-transferred STEMI patients treated by pPCI; STEMI definition according to European Cardiac Society criteria.	-	D2B time - from arrival to first hospital door to balloon inflation in pPCI; divided into 3 groups (< 90, 90-180, >180)
Towae	2011	STEMI with pre-hospital delay of less than 12 hrs	Those who received thrombolysis or not thrombolysed in any mean	Door-to-angiography - time from admission to hospital till the start of angioplasty (needle-entry) - 30 mins interval (<30min, 31-60, 60-120, . 120)
Muller	2011	STEMI patients treated by PCI (both primary and rescue) within 12 hrs after symptom onset, including transfer in patients	symptom onset > 12 hrs	D2B time defined as time between hospital arrival at PCI centre and first balloon inflation or primary stenting

Author	Year	Inclusion Criteria	Exclusion Criteria	Definition of exposure (D2B delay)
Lambert	2010	Patient with appropriate presenting symptoms of STEMI, a final diagnosis of AMI according to ICD 9, discharged between 1/10/2006-31/3/07 from all acute care Quebec hospitals, that treated at least 30 acute MI, with one of the following features : (1) received fibrinolysis in 4 hrs following triage at 1st ED; (2) sent to Cath lab in 4 hours following triage at first ED and had mentioned of STEMI in medical chart or evidence of STEMI on first ECG; (3) not receive fibrinolysis and not sent to Cath lab in 4 hrs after triage but has documented evidence of STEMI	Patients whose AMI occurred after their initial ED presentation	Timeliness of perfusion (combined fibrinolysis </= 30 mins (21.4%, n=392) & pPCI </= 90 mins (78.6%, n=1440)) defined as time from patient arrival at 1st hospital (door) to either start of fibrinolysis (needle) or first dilation (balloon).
Hannan	2010	New York state patients without previous revascularization who had undergone primary PCI for STEMI from Jan 2004 to Dec 2006 with O2D time < 12 hrs	Patients with invalid/missing D2B or O2D time (n=957)	D2B time - not specifically defined; D2B time categorized into < 90, 90-179, > 180
Brodie	2010	All patients randomized in the two RCT who underwent primary PCI and had DBT data available	-	D2B time - defined as time from hospital arrival until balloon inflation
Rathore	2009	Patients >/= 65 year olds who directly presented to the treating hospital within 12 hrs of symptom onset with an initial ECG that showed ST-segment elevation of LBBB and who subsequently underwent pPCI	Those who first received fibrinolysis and subsequently referred for PCI; those with missing time-to-treatment data	D2B time defined as the time in minutes from a patient's arrival at the hospital to first balloon inflation as documented in the patient's medical record; divided into 5 groups : < 60, 60-119, 120-179, 180-239, >/=240

Author	Year	Inclusion Criteria	Exclusion Criteria	Definition of exposure (D2B delay)
Rathore	2009	Patients who in 2005-2006, presented to a participating centre within 12 hours of symptom onset with lab and ECG evidence of ST elevation MI and subsequently underwent pPCI	1. those transferred from other hospitals (n=17992); 2. those first received fibrinolysis before PCI; 3. those under 18 or > 99 y/o; 4. those from hospitals that reported < 5 pPCI; 4. those with missing D2B time; 5. those D2B time < 15 mins & > 6 hours;	D2B time defined as the time in minutes from a patient's arrival at the hospital to first balloon inflation as documented in the patient's medical record; modelled D2B time as a continuous variable
Kong	2009	Consecutive patients receiving pPCI for STEMI over 3 years (2005-2008)	Missing D2B time	Not specifically defined
Song	2008	Patient with STEMI, presented within 12 hrs after symptom onset, were treated with pPCI, had completed a 30-day clinical follow up at the time of analysis	1. without ST elevation or LBBB on first ECG; 2. those with cardiogenic shock; 3. those with unknown time of symptom onset or missing data; 4. those with symptom onset-to-door time > 12 hrs	D2B time - time from arrival in the ED until initial balloon inflation
Soon	2007	Consecutive Patient with acute STEMI, admitted between June 2001- May 2003, underwent primary PCI	-	D2B time - interval between time of patient registration at ED and time of first balloon inflation or device deployment
Nallamothu	2007	Patient age >/= 18, admitted with STEMI, who presented to the admitting hospital within 6 hrs of symptom onset, and who received reperfusion therapy with either fibrinolytic therapy with a fibrin-specific agent or primary PCI.	Excluded patient receiving streptokinase	Not specifically defined

Author	Year	Inclusion Criteria	Exclusion Criteria	Definition of exposure (D2B delay)
Brodie	2007	Individuals eligible for enrolment were consecutive patients aged 18 years or older with AMI presentation more than 30 minutes but less than 6 hours after symptom onset, with 2 mm or more of ST-segment elevation in 2 or more contiguous leads or with presumably new left bundle-branch block, in whom primary or rescue (ie, after failed thrombolysis) PCI was intended.	Principal clinical exclusion criteria included major surgery or active bleeding within 6 weeks; aspirin, thienopyridine, or heparin allergy; neutropenia (<1000 neutrophils/mm3), thrombocytopenia (<100 000 platelets/mm3), hepatic dysfunction, or renal insufficiency (serum creatinine level >2.5 mg/dL [221 μmol/L]); cardiogenic shock; noncardiac condition with expected survival less than 1 year; and current participation in other investigations.	D2B time was time from arrival at the hospital until balloon inflation

Author	Year	Inclusion Criteria	Exclusion Criteria	Definition of exposure (D2B delay)
McNamara	2006	Patient with a diagnosis of AMI per the ICD-9 CM and any one of the following criteria: total creatine kinase or CK-MB that was 2 or more times the upper limit of the normal rage or elevations in alternative cardiac markers; ECG evidence of AMI or nuclear medicine testing, echocardiography, or autopsy evidence of AMI.	Patient transferred to or from another acute care institution (n = 341730, 41.1%); neither ST-segment elevation nor LBBB on first ECG (n=334013, 40.2%; AMI symptom onset after the admission date and time (n = 4305, 0.52%); with a non-diagnostic first ECG (n =14314, 1.7%); with diagnostic ECG that preceded hospital presentation by > 1 hr (prehospital ECG) or with time from door-to-diagnostic ECG that was more than 6 hrs or missing (n=6467, 0.8%); who did not receive primary PCI (n = 92772, 11.2%); with D2B time that were negative, more than 6 h or missing (0.1%); with unknown time of symptom onset (n = 4804, 0.6%)	D2B time - time from hospital arrival to balloon inflation, derived from the corresponding data/time noted in medical record and recorded in the NRMI CRF.
Brodie	2006	Patients with AMI of < 12 hrs who had either ST elevation or LBBBB or angiographically severe coronary stenosis associated with a regional wall motion abnormality	Patients with shock	D2B time was the time from hospital arrival until first balloon inflation
Brodie	2006	Consecutive patients with STEMI (patients with chest pain or hemodynamic compromised and with ECG ST segment elevation >/= 1mm in > 2 contiguous leads or LBBB and without severe co-morbid disease) treated with pPCI without previous	Missing D2B time (n=22)	D2B time was the time from arrival at the presenting hospital until balloon inflation

Author	Year	Inclusion Criteria	Exclusion Criteria	Definition of exposure (D2B delay)
		thrombolytic therapy from 1984 - 2003.		
Zahn	2004	All patients undergoing PCI for STEMI within 12 hrs after symptom onset were considered.	1. prehospital delay > 12 hrs; 2. non-primary PCI; 3. non-STEMI cases; 4. patients transferred from other hospitals for pPCI.	Door-to-angiography - time from admission to hospital till the start of angioplasty (needle-entry)
Juliard	2003	Consecutive patients admitted to CCU with a diagnosis of STEMI within 6 hrs of symptoms onset treated with emergency PTCA	1. with cardiogenic shock (n=60); 2. had spontaneously patent infarct vessel with TIMI grade 3 flow (n=28); 3. patients in whom PTCA failed to achieved TIMI 3 flow in the IRA (n=71)	Door-to-TIMI 3 time - defined by the delay between admission and final TIMI grade 3 flow in the infarct-related artery
De Luca	2003	All STEMI patients participated in any of the 6 clinical trials, presenting within 6 h from symptom onset or between 6-24 hr if they had continuous symptoms and signs of ischemia	-	D2B time - time from hospitalization to first balloon inflation
Brodie	2001	Patients with AMI < 12 hrs from symptom onset, no previous thrombolytic therapy and no cardiogenic shock	1. thrombolytic before PCI; 2. cardiogenic shock	D2B time was the time from arrival in the ED until initial balloon inflation

Author	Year	Inclusion Criteria	Exclusion Criteria	Definition of exposure (D2B delay)
Cannon	2000	Patients with onset of chest pain outside of a hospital within 24 hrs, which was associated with ST segment elevation of at least 0.1 mV in 2 or more ECG leads or LBBB and who underwent primary angioplasty	-	D2B time - time of arrival at the hospital to time of first balloon inflation of the primary angioplasty procedure (if balloon inflation time is not available, time of the start of the procedure will be used)
Berger	1999	Patients presenting to a participating hospital within 12 hours after symptom onset (chest pain lasting >/= 20 mins accompanied by ECG signs of >/= 0.2-mV ST segment elevation in >/= 2 contiguous leads or LBBB)	(Identical to those in the main GUSTO-IIb trial)	E2B time - time between enrolment in the study and the first angioplasty balloon inflation

Appendix 6. Quality Assessment of the Eligible Studies

eTable 6.1 Assessment of study quality using the Newcastle-Ottawa Scale (NOS)

		Selection				Comparability		Outcomes				
Author	YearPub	1	2	3	4	1	2	1	2	3	Points on quality scale	Level of RoB
Wang	2016	*	*	-	*	*	-	-	*	*	6	M-H RoB
Domenicantonio	2016	-	*	*	*	*	*	*	*	*	8	Low RoB
Yudi	2016	*	*	*	*	*	-	*	*	*	8	Low RoB
Solhpour	2015	*	*	-	*	-	-	-	*	-	4	M-H RoB
Ho	2014	*	*	-	*	-	-	-	*	-	4	M-H RoB
Sim	2015	*	*	-	*	*	*	-	*	-	6	M-H RoB
Nallamothu	2015	*	*	*	*	*	-	*	*	*	8	Low RoB
Wongpraparut	2014	*	*	-	*	-	-	*	*	-	5	M-H RoB
Helve	2014	*	*	-	*	*	-	-	*	-	5	M-H RoB
Brennan	2014	*	*	*	*	*	-	*	*	-	7	M-H RoB
Nakamura	2012	*	*	*	*	-	-	*	*	*	7	M-H RoB
Kodaira	2013	*	*	*	*	-	-	*	*	*	7	M-H RoB
Shiomi	2012	*	*	*	*	*	*	*	*	*	9	Low RoB
Heitzler	2012	*	*	*	*	-	-	*	*	-	6	M-H RoB
Towae	2011	*	*	*	*	*	-	*	*	-	7	M-H RoB
Muller	2011	*	*	*	*	*	-	*	*	-	7	M-H RoB
Lambert	2010	*	*	*	*	*	-	*	*	-	7	M-H RoB
Hannan	2010	*	*	*	*	*	*	*	*	*	9	Low RoB
Brodie	2010	-	*	*	*	*	-	*	*	-	6	M-H RoB
Rathore	2009	*	*	*	*	*	*	*	*	*	9	Low RoB
Rathore	2009	*	*	*	*	*	*	*	*	*	9	Low RoB
Kong	2009	*	*	*	*	-	-	*	*	*	7	M-H RoB
Song	2008	*	*	-	*	-	-	*	*	-	5	M-H RoB
Soon	2007	*	*	*	*	-	-	*	*	*	7	M-H RoB
Nallamothu	2007	*	*	*	*	*	-	*	*	-	7	M-H RoB
Brodie	2007	-	*	*	*	-	-	*	*	*	6	M-H RoB
McNamara	2006	*	*	*	*	*	*	*	*	*	9	Low RoB
Brodie	2006	-	*	*	*	-	-	*	*	*	6	M-H RoB
Brodie	2006	*	*	-	*	*	-	*	*	*	7	M-H RoB
Zahn	2004	*	*	-	*	*	*	-	*	-	6	M-H RoB
Juliard	2003	*	*	-	*	*	-	-	*	-	5	M-H RoB
De Luca	2003	-	*	*	*	-	-	*	*	*	6	M-H RoB
Brodie	2001	-	*	*	*	-	-	*	*	*	6	M-H RoB
Cannon	2000	*	*	*	*	*	-	*	*	-	7	M-H RoB
Berger	1999	-	*	*	*	*	-	*	*	*	7	M-H RoB

Pub=publication, RoB=risk of bias, M-H=moderate-to-high

eTable 6.2 Important confounding domains for consideration

Domain	Example of variables
Pre-hospital delay	onset-to-door time (pre-hospital delay)
Demographics	Age, gender, ethnicity, smoking
Co-morbidities	stroke, Prior IHD/CABG, CHF, HPT, ESRF/Renal impairment/dialysis, PVD, DM, chronic lung diseases, prior PCI, prior valvular diseases/surgery, prior MI, dyslipidemia, renal transplant, sleep apnea, Rheumatoid diseases
Clinical state on admission	BP, PR, Killip class/shock, renal function, cardiac arrest prior to PCI, ejection fraction, BMI, function status/NYHA
Angiographic attributes	Lesion type (e.g. SCAI class, Lesion risk e.g. segment category left main, pLAD, etc., subacute thrombosis, multivessel disease, number of lesions, procedure AHA type (B2/C lesion), bifurcated lesion, dissected lesion
Process of care	IABP use, inotropes
Day-time factors	Day of admission, onset and admission time,
Hospital factors	Level of PCI specialization, Teaching status, ownership, geographical attributes (e.g. urban/rural, income level), volume

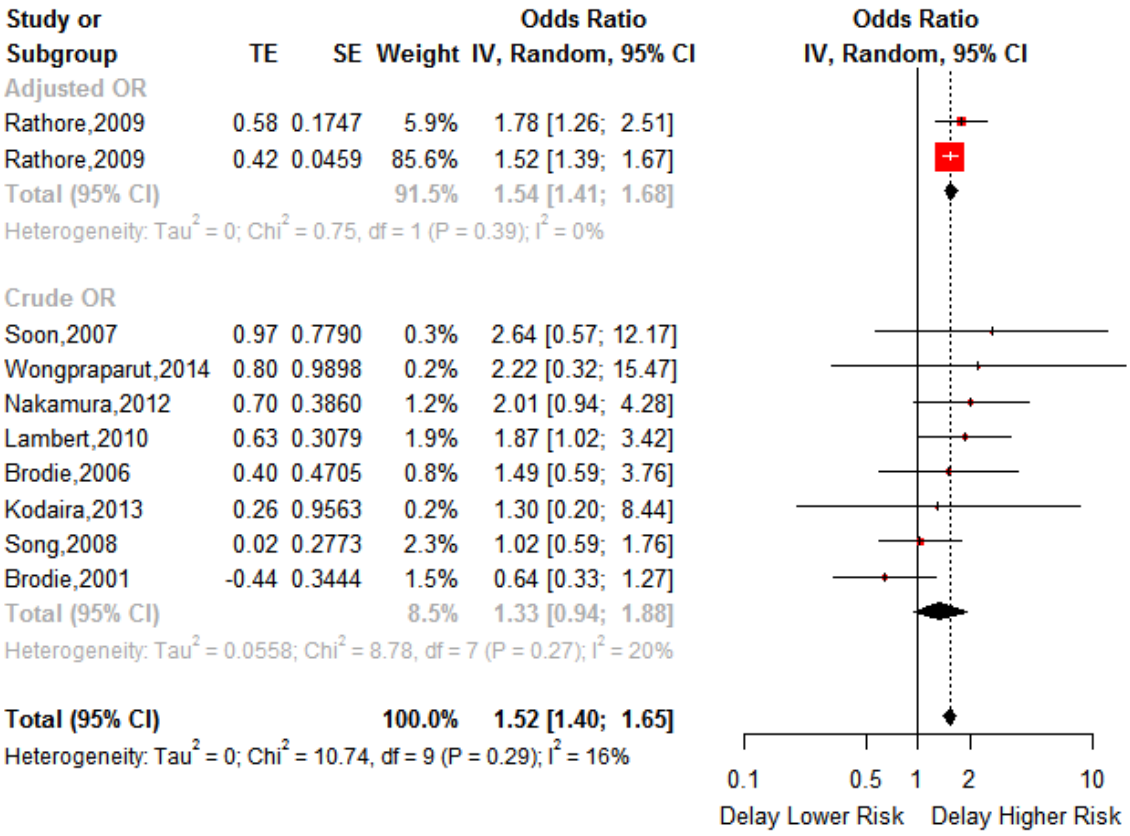
eTable 6.3 Assessment of completeness of confounding domains adjustment

		Confounding Domains							
Author	**Pub Year**	**Pre-hospital delay**	**Demographics**	**Co-morbid**	**Clinical state on admission**	**Angiographic attributes**	**Process of care**	**Day-time factors**	**Institutional factors**
Yudi	2016	+	+	+	+	+	+	-	-
Domenicantonio	2016	-	+	+	+	-	-	+	-
Wang	2016	-	+	-	+	-	-	-	-
Solhpour	2015	-	-	-	-	-	-	-	-
Ho	2014	-	-	-	-	-	-	-	-
Sim	2015	-	+	+	+	+	-	-	-
Nallamothu	2015	-	+	+	+	+	+	-	-
Wongpraparut	2014	-	-	-	-	-	-	-	-
Helve	2014	-	+	+	+	-	+	+	-
Brennan	2014	-	+	+	+	-	+	-	-
Nakamura	2012	-	-	-	-	-	-	-	-
Kodaira	2013	-	-	-	-	-	-	-	-
Shiomi	2012	+	+	+	+	+	+	-	-
Heitzler	2012	-	-	-	-	-	-	-	-
Towae	2011	-	+	+	+	-	-	-	-
Muller	2011	-	+	+	+	+	-	-	-
Lambert	2010	-	+	+	+	-	+	-	-
Hannan	2010	-	+	+	+	-	-	+	-
Brodie	2010	-	+	+	+	+	-	-	-
Rathore	2009	+	+	+	+	+	-	-	+
Rathore	***2009***	+	+	+	+	+	+	+	+
Kong	2009	-	-	-	-	-	-	-	-
Song	2008	-	-	-	-	-	-	-	-
Soon	2007	-	-	-	-	-	-	-	-
Nallamothu	2007	+	+	+	+	-	-	-	-
Brodie	2007	-	-	-	-	-	-	-	-
McNamara	2006	+	+	+	+	-	-	+	-
Brodie	2006	-	+	+	+	-	-	-	-
Brodie	2006	-	+	+	+	-	-	-	-

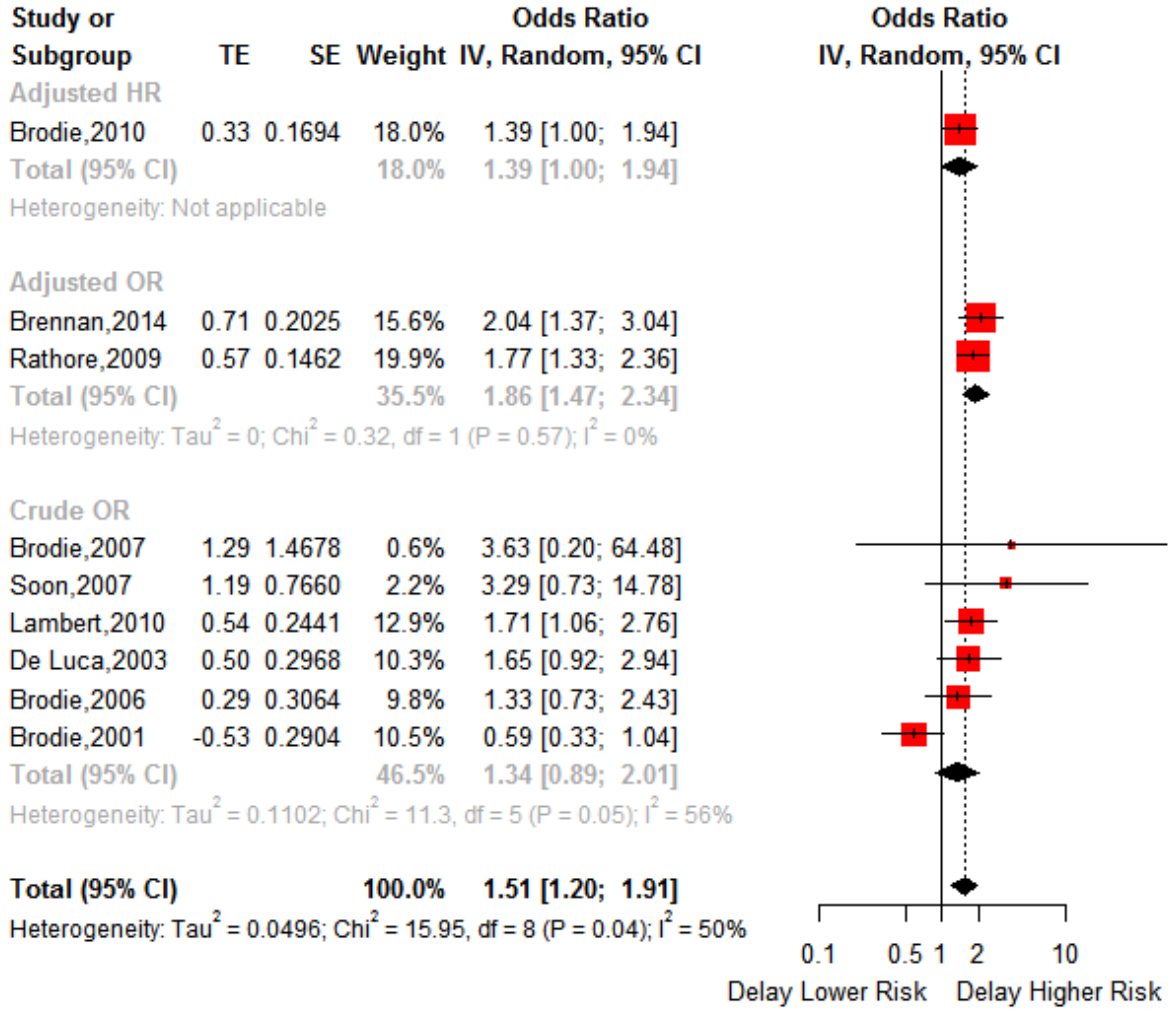
		Confounding Domains							
Author	**Pub Year**	**Pre-hospital delay**	**Demographics**	**Co-morbid**	**Clinical state on admission**	**Angiographic attributes**	**Process of care**	**Day-time factors**	**Institutional factors**
Zahn	2004	-	+	+	+	-	+	-	+
Juliard	2003	-	+	-	-	-	-	-	-
De Luca	2003	-	-	-	-	-	-	-	-
Brodie	2001	-	-	-	-	-	-	-	-
Cannon	2000	-	+	+	+	-	-	-	-
Berger	1999	-	+	+	+	-	-	-	-
Proportion of studies adjusted for this domain of potential confounding		***17.1%***	***65.7%***	***60.0%***	***62.9%***	***22.9%***	***22.9%***	***14.3%***	***8.6%***

Appendix 7. Graphical Presentation of Pooled Analyses and Sensitivity Analyses for Primary and Secondary Outcomes

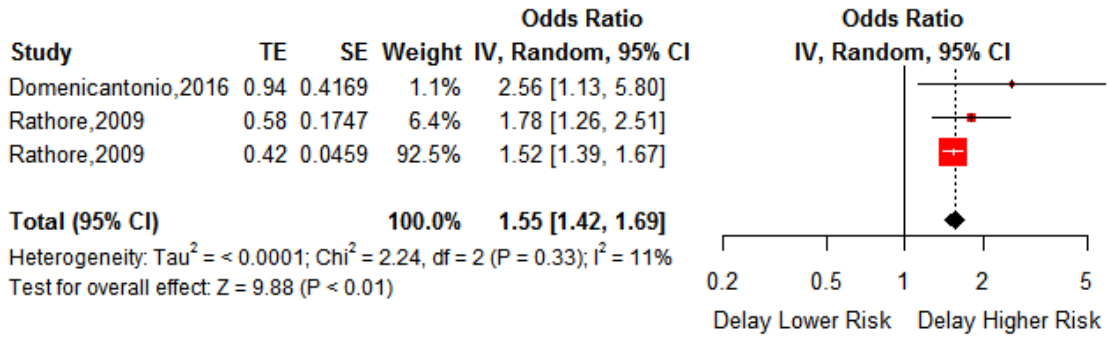
eFigure 7.1 Relative effect of shorter (< 90 mins) vs longer (> 90 mins) door-to-balloon times on short term STEMI mortality. (Primary Analysis)



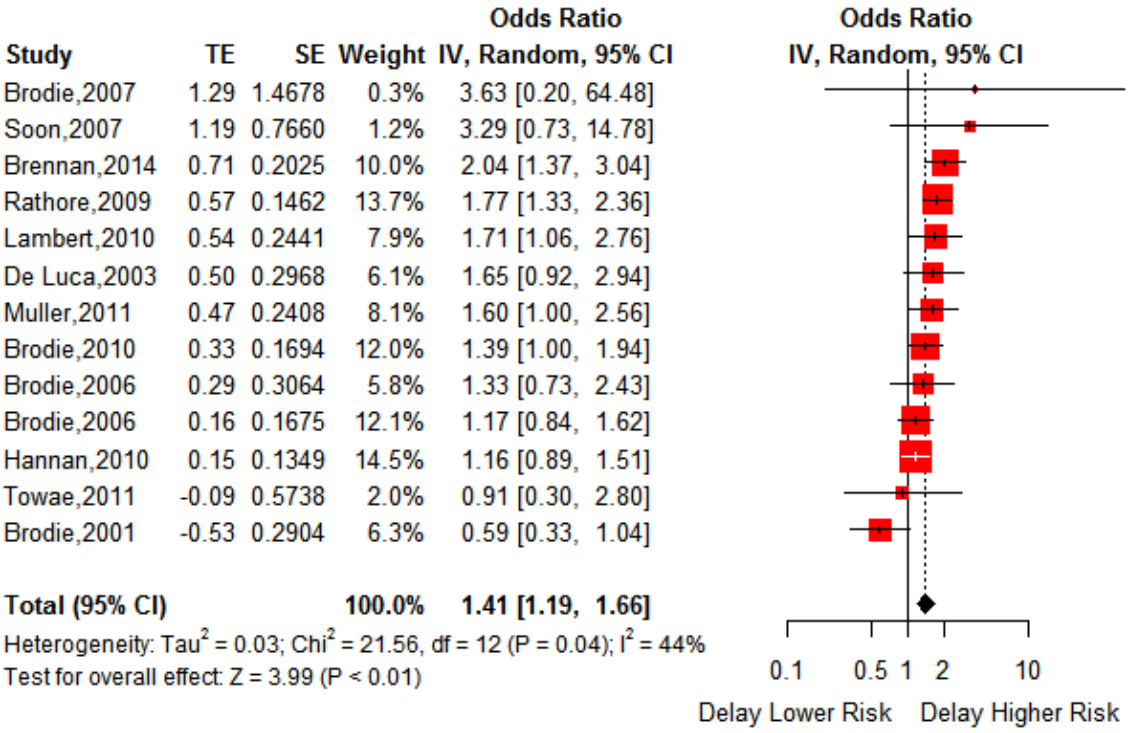
eFigure 7.2 Relative effect of shorter (< 90 mins) vs longer (> 90 mins) door-to-balloon times on medium-to-long term STEMI mortality. (Primary Analysis)



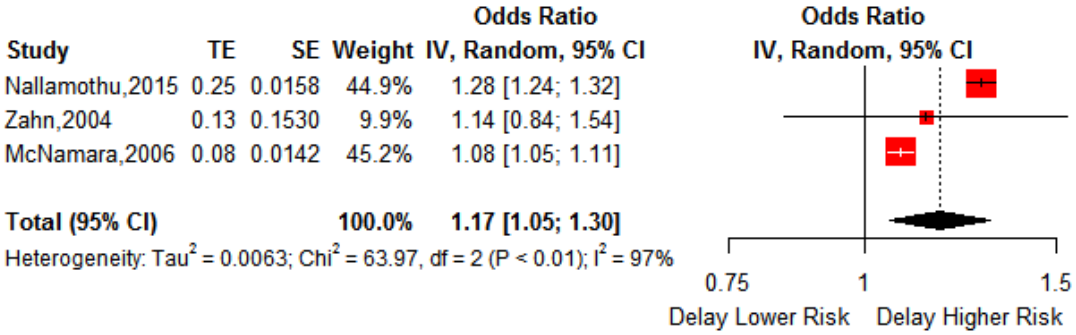
eFigure 7.3 Relative effect of shorter vs longer door-to-balloon times on short term STEMI mortality for studies of low risk of bias (NOS >7)



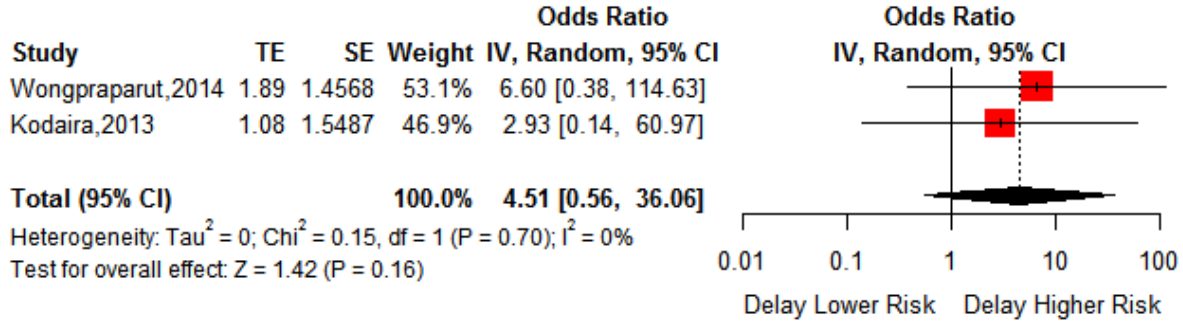
eFigure 7.4 Relative effect of shorter vs longer door-to-balloon times on medium-to-long term STEMI mortality. Included all studies that estimated the effect of D2B delay on medium-to-long term mortality regardless of D2B time definition and cut off point used.



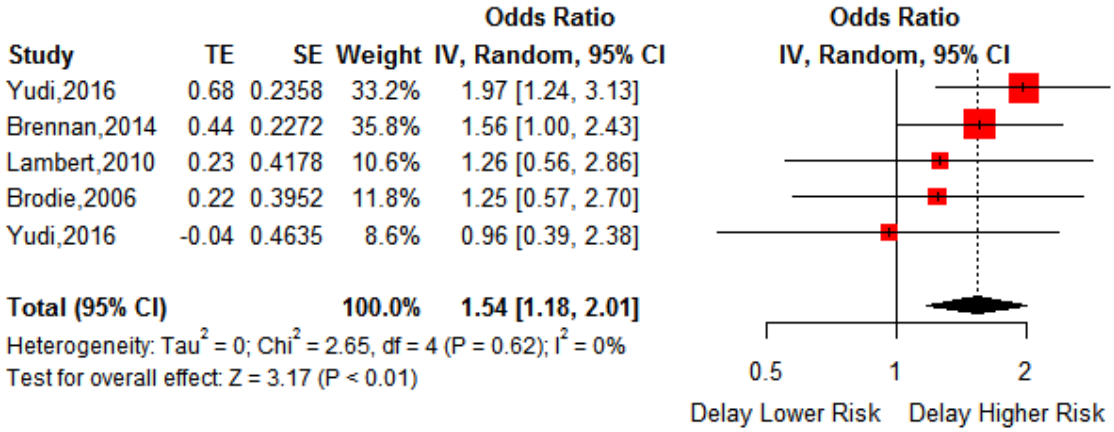
eFigure 7.5 Effect of door-to-balloon times by 30 minutes' increment on short term STEMI mortality.



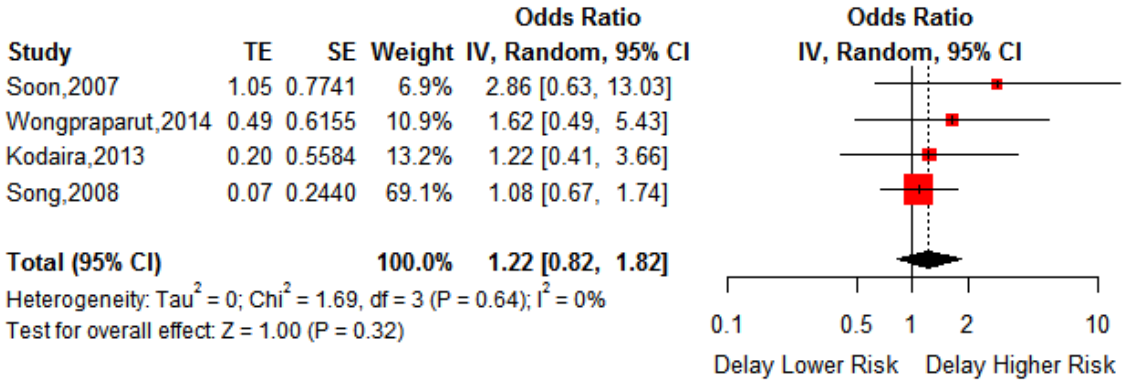
eFigure 7.6 Relative effect of shorter (≤ 90 mins) vs longer (> 90 mins) door-to-balloon times on In-hospital shock.



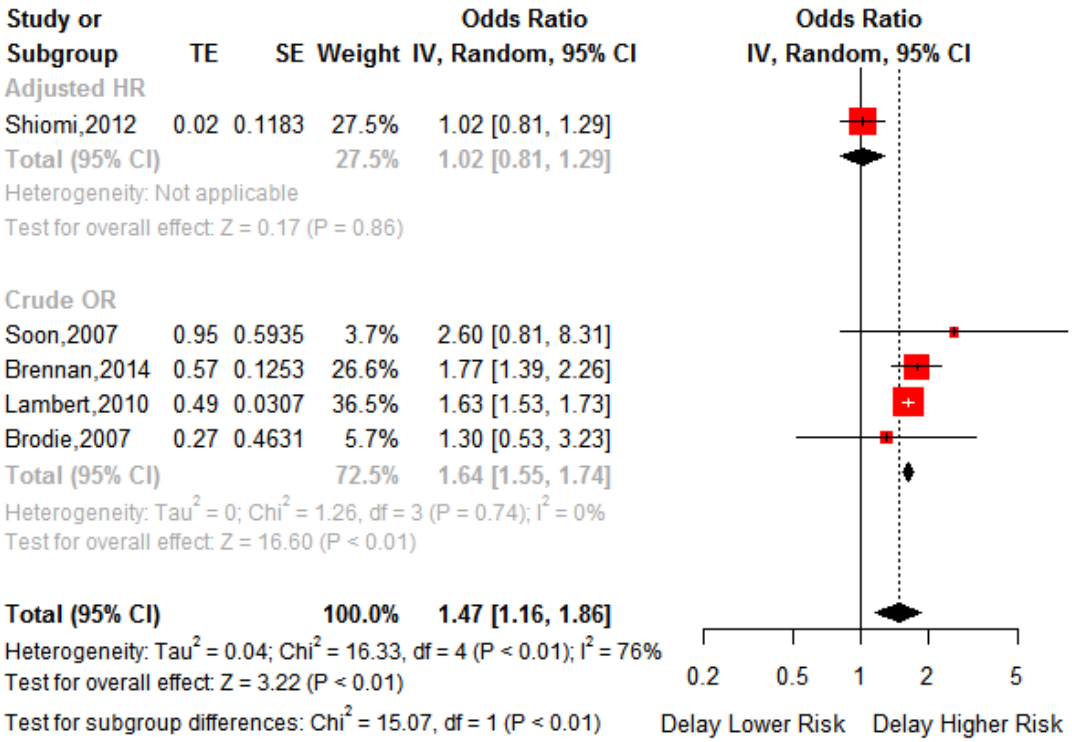
eFigure 7.7 Relative effect of shorter (≤ 90 mins) vs longer (> 90 mins) door-to-balloon times on 12-month recurrent infarction.



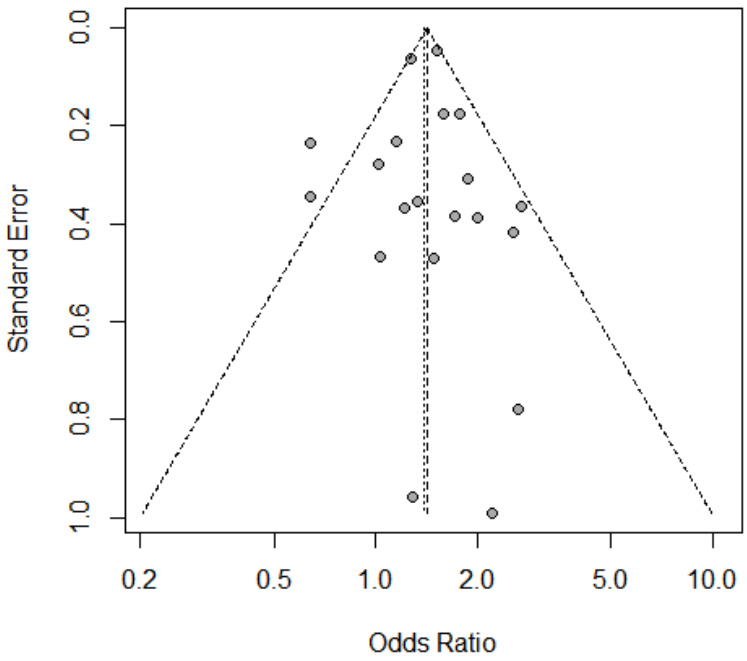
eFigure 7.8 Relative effect of shorter vs longer door-to-balloon times on short-term MACE.



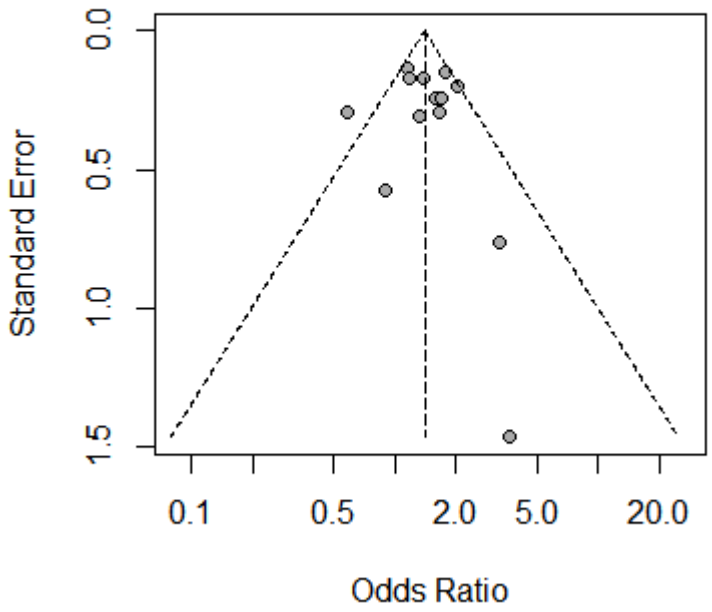
eFigure 7.9 Relative effect of shorter vs longer door-to-balloon times on medium-to-long term MACE.



eFigure 7.10 Funnel plot for studies of short-term mortality.

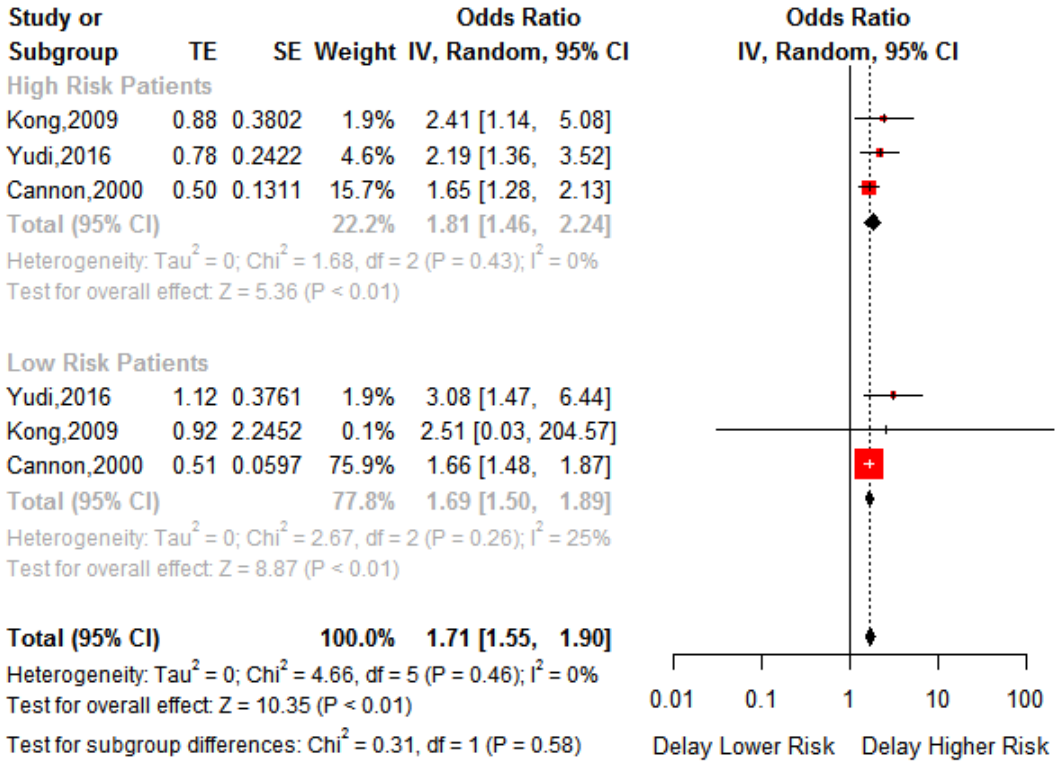


eFigure 7.11 Funnel plot for studies of medium-to-long term mortality.



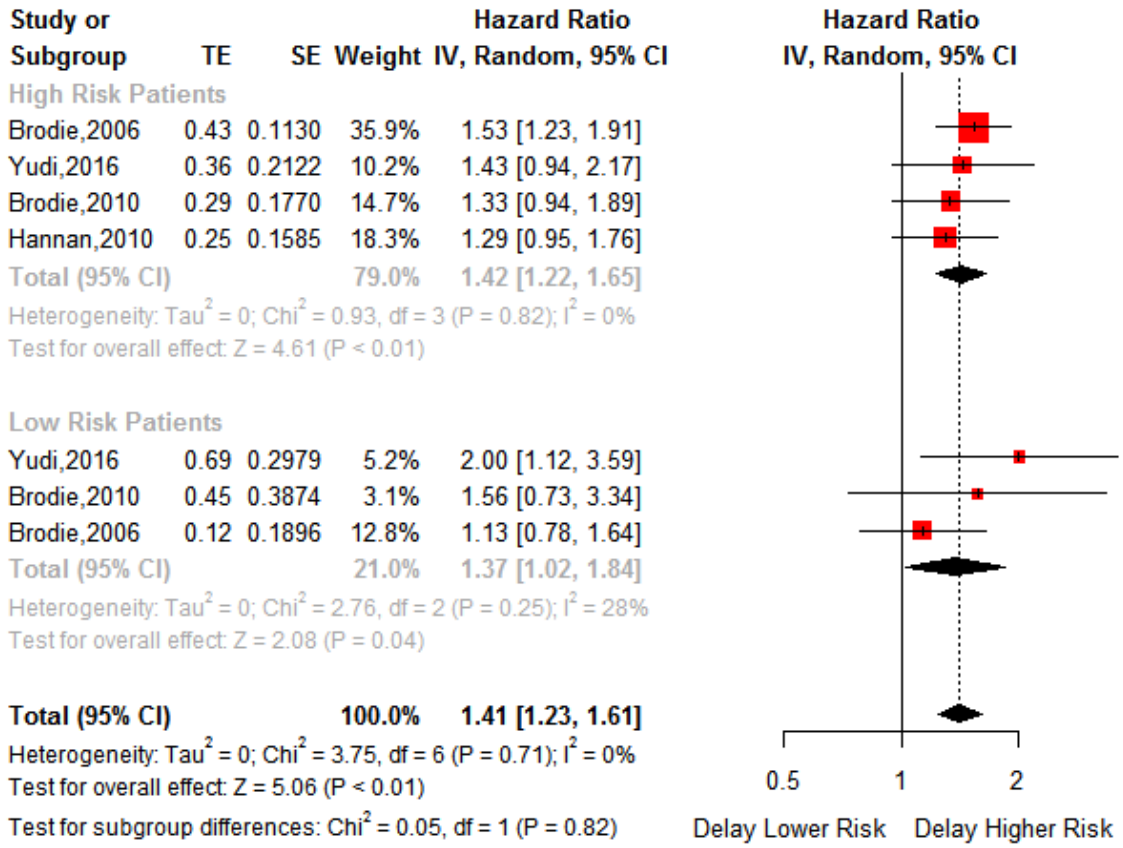
Appendix 8. Graphical Presentation of Subgroup Analyses

eFigure 8.1 Comparison of the relative effects (odds ratio) of shorter vs longer door-to-balloon times on short-term STEMI mortality by risk profile.



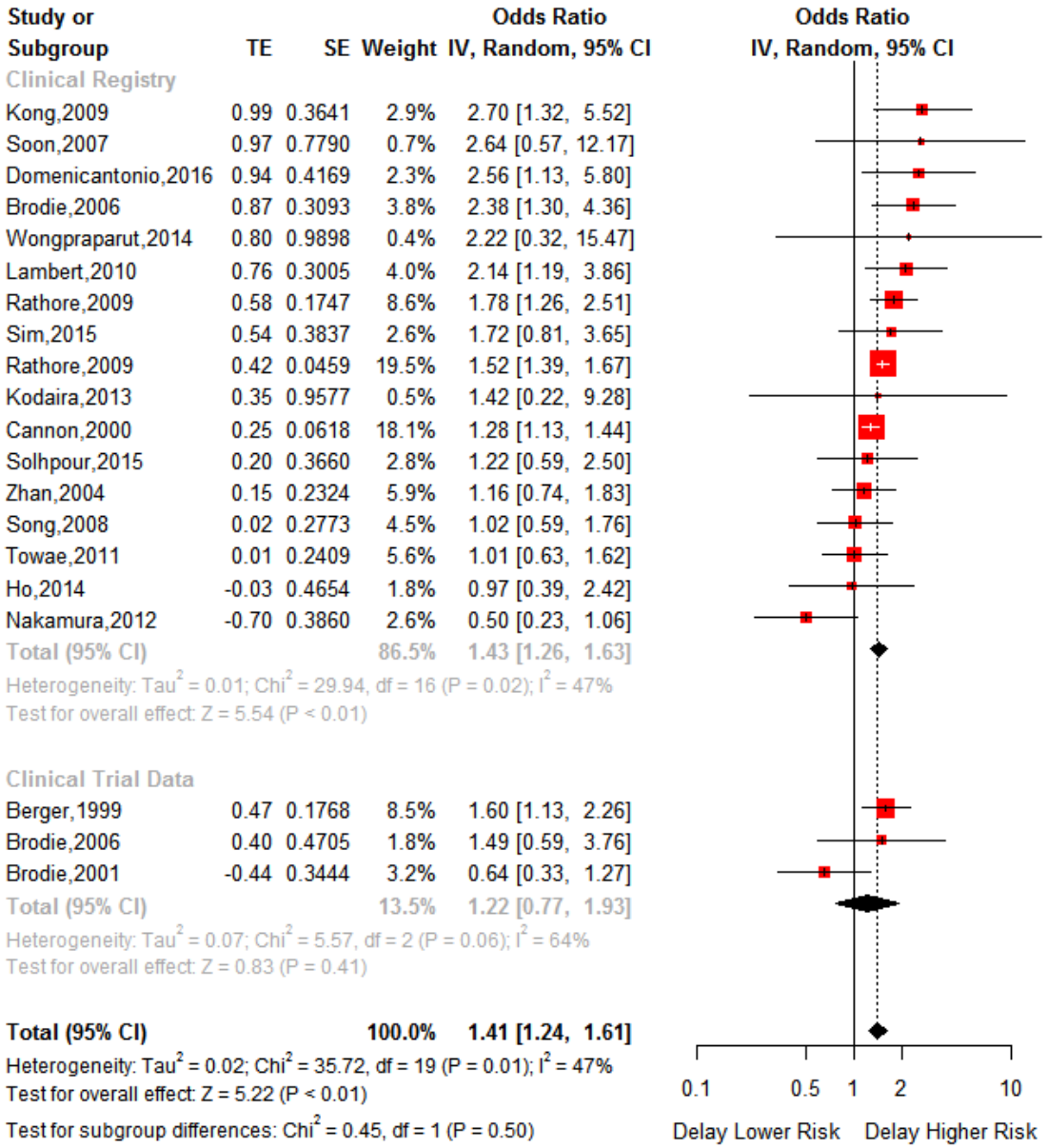
Note: refer to eTable 7.2 for definition of high risk vs. low risk subgroup

eFigure 8.2 Comparison of the relative effects (hazard ratio) of shorter (≤ 90 mins) vs longer (> 90 mins) door-to-balloon times on longer term mortality by risk profile

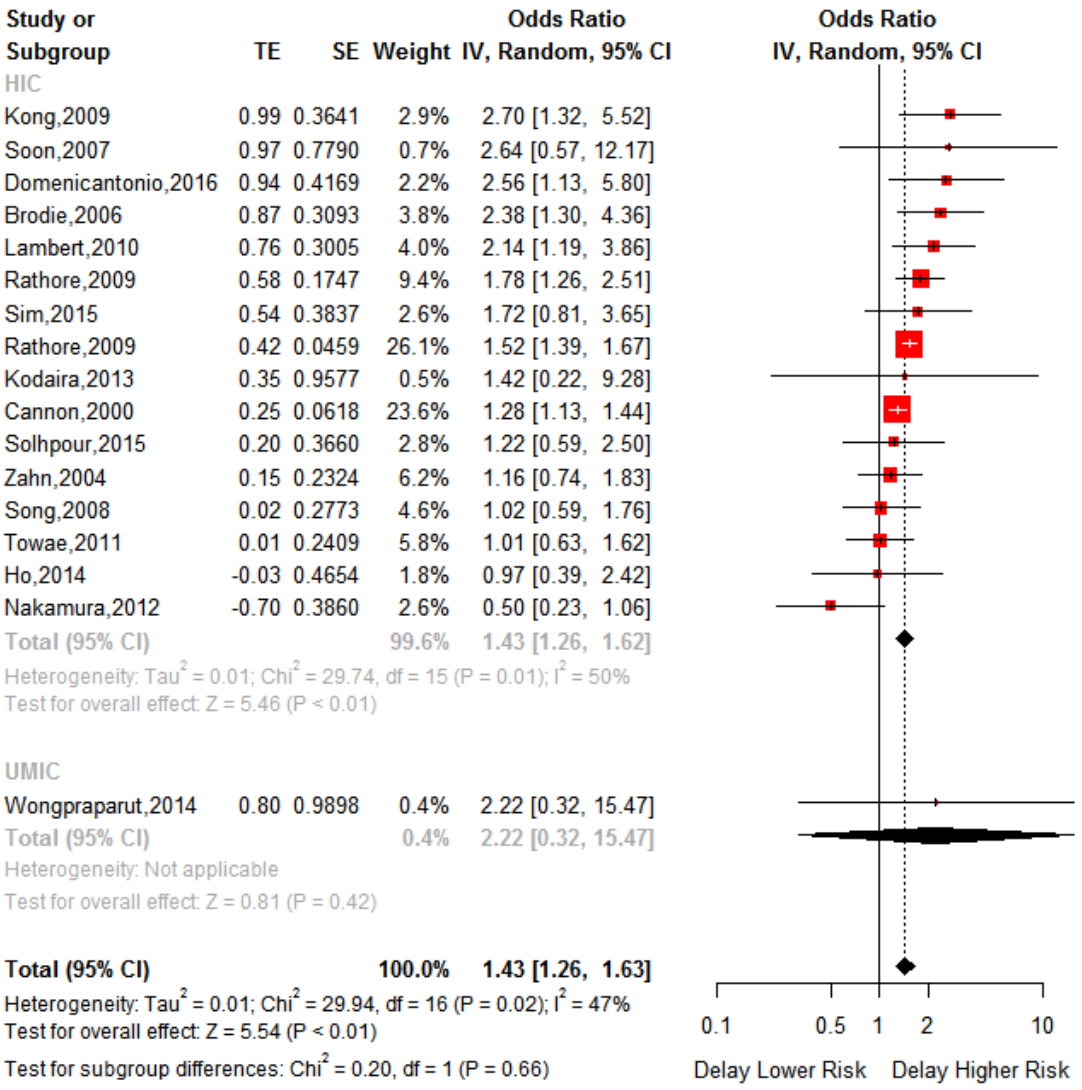


Note: Brodie, 2006 – median follow-up time = 83 months; Brodie, 2010 – 1-year mortality rate; Hanna, 2010 – median follow-up time = 413 days; Yudi, 2016 – mean follow-up time = 2.6 +/- 1.6 years. Refer to eTable 7.2 for definition of high risk vs. low risk subgroup.

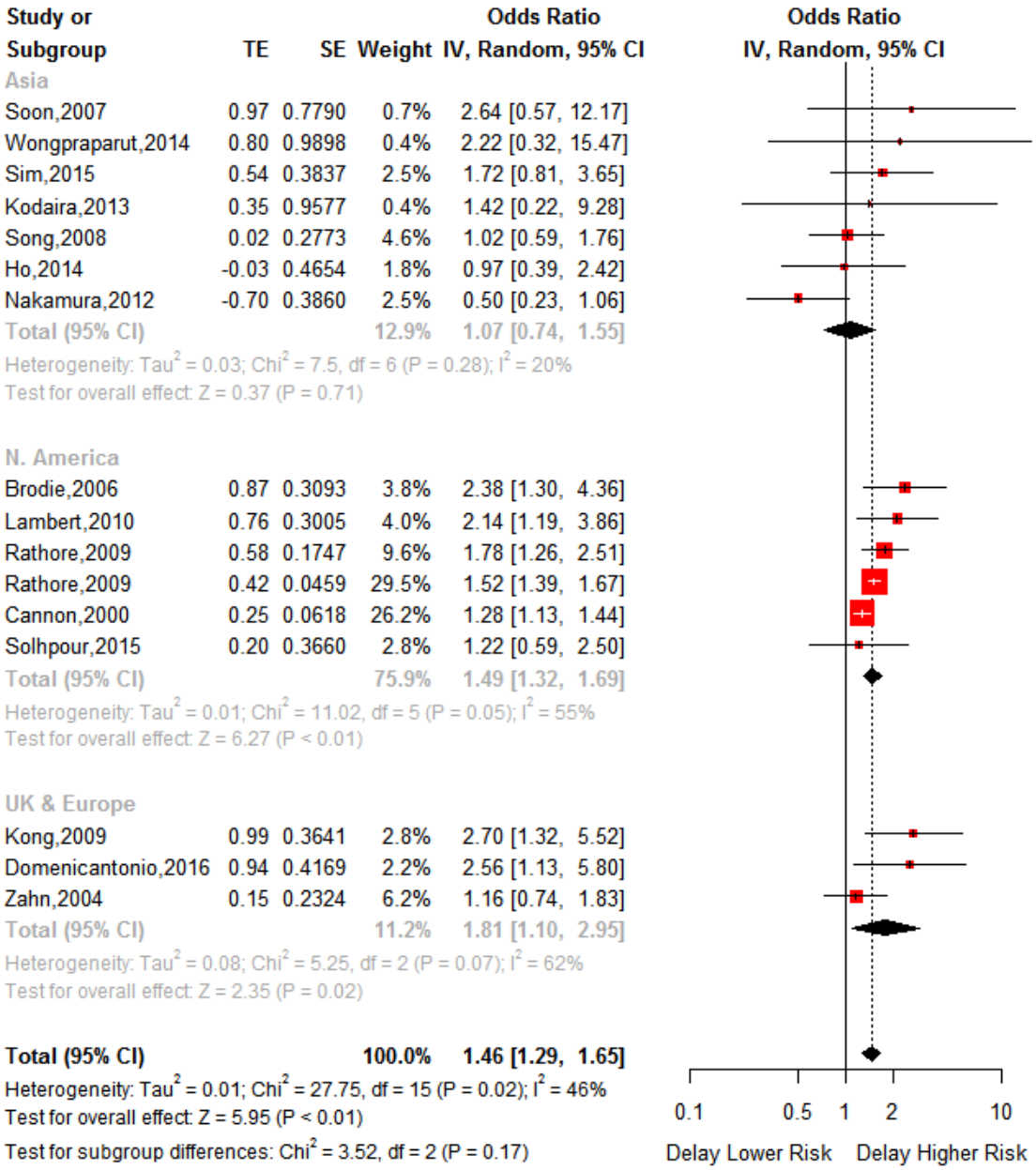
eFigure 8.3 Comparison of the relative effects of shorter vs longer door-to-balloon times on short-term STEMI mortality by data source.



eFigure 8.4 Comparison of the relative effects (odds ratio) of shorter (≤ 90 mins) vs longer (> 90 mins) door-to-balloon times on short-term STEMI mortality by setting (country income status). HIC = High income country; UMIC = Upper-middle income country.



eFigure 8.5 Comparison of the relative effects (odds ratio) of shorter (≤ 90 mins) vs longer (> 90 mins) door-to-balloon times on short-term STEMI mortality by geographical region.



Appendix 9. Dose-response analysis

The purpose of a dose-response meta-analysis in this study is to describe the overall functional relation of door-to-balloon time and short-term mortality risk. The dose-response analysis conducted in this study was based on the method previously formalized by Greeland and Longnecker.[46] This method aims to estimate a pooled dose-response curve from summarized dose-response data using two stage approach. In the first stage, the dose-response association between the log odds ratio and the door-to-balloon time in a study was estimated. In the second stage, the study-specific estimates of the dose-response association were combined using method of multivariate meta-analysis. We used the dosresmeta package[47] in R to performs these described procedures for the following two sets of dose-response meta-analysis.

In the first set of analysis, we estimated a log-linear dose-response model assuming a log-linear relation between door-to-balloon time and short-term mortality risk (odds ratio). The estimated model parameters are shown in eTable 9.1. Briefly, we found a significant log-linear dose-response association in between door-t-balloon time and mortality risk (p = 0.0052) and high level of heterogeneity (I^2 = 90.2%).

eTable 9.1 Result of the dose-response analysis using a log-linear random-effects model

	estimate	SE	z-score	P value	95% CI	
Dose	0.0031	0.0011	2.8932	0.0038	0.0010	**0.0052**

Chi2 model: X2 = 8.3709 (df = 1), p-value = 0.0038; Univariate Cochran Q-test for heterogeneity: Q = 71.2770 (df = 7), p-value = 0.0000; ***I-square statistic = 90.2%;*** *Estimation method: REML; Approximate covariance method: Greenland & Longnecker; 8 studies, 8 observations, 1 fixed and 1 random-effects parameters*

Next, we relaxed the linear assumption and modelled the relationship using a restricted cubic spline model[48] with 3 knots at 30%, 60% and 90% of the aggregated door-to-balloon time distribution. The rms package[49] was used to achieved this in the dose-response meta-analysis model. Random effect model was used to account for statistical heterogeneity. The estimated cubic spline model parameters are shown in eTable 9.2.

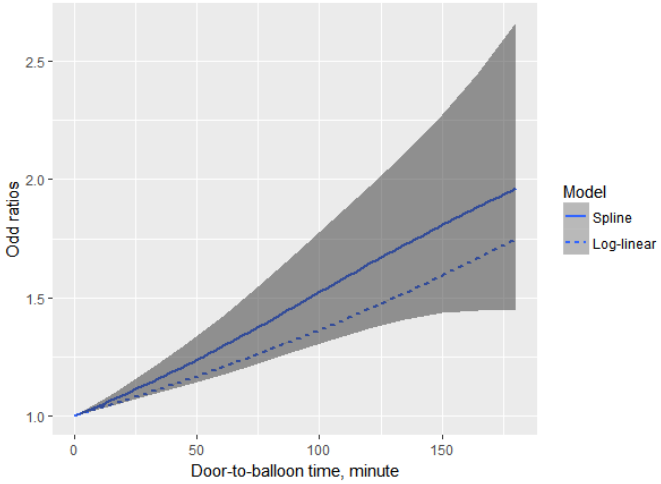
eTable 9.2 Result of the dose-response analysis using restricted cubic spline model

	estimate	SE	z-score	P value	95% CI	
Knot 1 (30%-60%)	0.0043	0.0008	5.2762	0.0000	0.0027	0.0058
Knot 2 (61% - 90%)	-0.0030	0.0038	-0.7928	0.4279	-0.0105	0.0044

Chi2 model: X2 = 28.5048 (df = 2), p-value = 0.0000; Multivariate Cochran Q-test for heterogeneity: Q = 50.3140 (df = 14), p-value = 0.0000; ***I-square statistic = 72.2%;***
8 studies, 16 observations, 2 fixed and 3 random-effects parameters

Then, a Wald test was used to compare the non-linear (spline model) and linear models (log-linear) to test for the probability of non-linearity. We found that the association in between door-to-balloon time and short-term mortality is likely not log-linear in fashion ($\chi^2 = 28.5$, $p < 0.001$). eFigure 9.1 shows the estimated odds ratios per door-to-balloon time arising from the log-linear and spline model. eTable 9.3 shows the estimated odds ratio of four specified door-to-balloon time points (60 minutes, 90 minutes, 120 minutes and 150 minutes) arising from the spline model using 30 minutes as the referent as reported in the main text.

eFigure 9.1 Comparison of cubic spline model and log-linear model for dose-response analysis



eTable 9.3 Estimated odds ratio of four door-to-balloon time points arising from the spline model.

Door-to-balloon time points	Estimated Odds Ratio	95% CI – Lower Limit	95% CI – Upper Limit
30	-	-	-
60	1.14	1.08	1.19
90	1.29	1.17	1.42
120	1.44	1.26	1.65
150	1.59	1.31	1.92

Notes:

The midpoint between the upper and lower boundaries of each category of time interval was used as the value of exposure ("dose"). The "response" variable is the log odds ratio for short-term mortality. We assigned the mid-point of the door-to-balloon time in each time interval category to the corresponding odds ratio for each study. The midpoint of each category was calculated by the average of the lower and upper bound. When the highest category was open ended we assumed the length of the open-ended interval to be the same as that of the adjacent interval. When the lowest category was open ended we set the lower boundary to zero.

Appendix 10. Meta-regression Model

eTable 10.1 Meta-regression Model Result

	estimate	SE	z-score	P value	95% CI		
(Intercept)	-0.1815	0.2216	-0.819	0.4128	-0.6159	0.2529	
Quality score	0.069	0.0274	2.5139	0.0119	0.0152	0.1227	*

Mixed-Effects Model (k = 20; tau^2 estimator: ML)

logLik = *-6.0111;* deviance = *22.4084;* AIC = *18.0222;* BIC = *21.0094;* AICc =*19.5222*

Appendix 11. Definition of Subgroup factors

eTable 11.1 Definition of high risk vs. low risk subgroup of each pooled study

Author	**Pub Year**	Subgroup Definition	
		High risk	**Low risk**
Yudi	2016	Killip class ≥ 2 or presented in cardiogenic shock or out-of-hospital cardiac arrest	Without any of the high-risk features
Brodie	2010	Modified TIMI score[+] ≥ 2	Modified TIMI score[+] < 2
Hannan	2010	One or more of these features: age ≥ 75, multi-vessel disease, EF < 30%, hemodynamic instability or shock, creatinine > 2.5 mg/dl or requiring dialysis	Without any of the high-risk features
Kong	2009	One or more of these features: cardiogenic shock, anterior MI, age ≥ 75, DM	Without any of the high-risk features
Cannon	2000	Cardiogenic shock = Yes	Cardiogenic shock = No
Brodie	2006	Killip class 3-4, age > 70, or anterior MI	Without any of the high-risk features

[+] age > 75 (3 points), age < 65 (2 points), Killip class > I (2 points), anterior MI (1 point), DM (1 point), weight < 67kg (1 point).

eTable 11.2 Subgroup definition of pre-hospital delay of each pooled study

			Definition	
			Early presentation	**Late presentation**
Author	**Pub Year**	**Data Source**	(Time from symptom onset to arrival at the presenting hospital)	
Brodie	2010	CADILLAC trial and HORIZONS-AMI trial	≤ 2 hours	> 2 hours
Hannan	2010	New York State PCI Reporting System Registry	< 2 hours	≥ 4 hours
Brodie	2006	Single institution cohort from 1984-2003	≤ 3 hours	> 3 hours

Appendix 12. GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	shorter D2B delay	Longer D2B delay	Relative (95% CI)	Absolute (95% CI)		
Short-term mortality												
13	observational studies	not serious [a]	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed			**OR 1.52** (1.40 to 1.65)	**2 fewer per 1,000** (from 1 fewer to 2 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Medium-to-long term mortality (follow up: range 31 days to 3 years)												
9	observational studies	serious [b]	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed			**OR 1.51** (1.20 to 1.91)	**2 fewer per 1,000** (from 1 fewer to 2 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Heart failure (assessed with: Readmission for heart failure and ejection fraction)												
3	observational studies	serious [c]	serious [d]	serious [e]	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed			-	see comment	⨁◯◯◯ VERY LOW	IMPORTANT
In-hospital shock												
2	observational studies	serious [f]	not serious	not serious	serious [g]	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed			**OR 4.51** (0.56 to 36.06)	**5 fewer per 1,000** (from 1 fewer to 36 fewer)	⨁⨁◯◯ LOW	IMPORTANT
12-month recurrent MI												
5	observational studies	serious [f]	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed			**OR 1.54** (1.18 to 2.01)	**2 fewer per 1,000** (from 1 fewer to 2 fewer)	⨁⨁◯◯ LOW	NOT IMPORTANT
Short-term MACE												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**shorter D2B delay**	**Longer D2B delay**	**Relative (95% CI)**	**Absolute (95% CI)**		
4	observational studies	serious [f]	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed			**OR 1.22** (0.82 to 1.82)	**1 fewer per 1,000** (from 1 fewer to 2 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Medium-to-long term MACE (follow up: range 1 months to 3 years)												
5	observational studies	serious [h]	very serious [i]	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed			**OR 1.47** (1.16 to 1.74)	**1 fewer per 1,000** (from 1 fewer to 2 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **MACE**: Major adverse cardiac event/composite endpoint

Explanations

a. 8 out of 10 studies reported only unadjusted effect

b. 3 out of the 9 studies reported only the unadjusted effect

c. Unadjusted effect

d. Definition of outcomes varied widely

e. 2 out of the 3 studies used the surrogate outcome of ejection fraction

f. All pooled estimates were unadjusted for the differences between comparison groups

g. Very wide confidence interval for the pooled effect estimates

h. Only 1 out of the 5 studies reported adjusted effect

i. Considerable statistical heterogeneity observed in pooled estimate

Appendix 13. Data

Author.1st	Year Pub	D2B time Ref	D2B time Comp	Outcome	Term	Subgroup	Coefficient	95%CI	Coeff. Type
Yudi	2016	</= 90	> 90	Mortality	Rate	High Risk Patients	0.7	0.47-1.08	Adjusted HR
Yudi	2016	</= 90	> 90	Mortality	Rate	Low Risk Patients	0.5	0.28-0.90	Adjusted HR
Domenicantonio	2016	</= 72	> 72	Mortality	30-days		2.564102564	1.22-6.25	Adjusted OR
Wang	2016	</= 90	> 90	Mortality	NA	High Risk Patients	(Unclear endpoints and no effect size reported)		
Wang	2016	</= 90	> 90	Mortality	NA	Low Risk Patients			
Solhpour	2015	< 90 mins	>/= 90 mins	Mortality	30-days		1.2184	0.5731-2.4061	Crude OR
Ho	2014	</= 60 mins	> 60	Mortality	30-days		0.9721	0.4048-2.5093	Crude OR
Ho	2014	</= 60 mins	> 60	Final TIMI Flow	30-days		1.3375	0.5261-3.8379	Crude OR
Ho	2014	</= 60 mins	> 60	CHF	30-days		0.96897	0.5743-1.6653	Crude OR
Ho	2014	</= 60 mins	> 60	MACE	30-days		1.2437	0.75498-2.0915	Crude OR
Sim	2015	< 90 mins	>/= 90 mins	Mortality	In-hospital		1.72	0.8-3.6	Adjusted OR
Nallamothu	2015			Mortality	In-hospital		0.92	0.91-0.93	Adjusted OR
Wongpraparut	2014			Shock	In-hospital		6.59597	0.9488-286.5654	Crude OR
Wongpraparut	2014			Mortality	In-hospital		2.223561	0.4475-21.6712	Crude OR
Wongpraparut	2014			MACE	In-hospital		1.6249	0.5347-5.9708	Crude OR
Helve	2014	</= 60 mins	> 60 mins	Mortality	90-days		(Not provided & have insufficient details to compute)		Adjusted OR

Author.1st	Year Pub	D2B time Ref	D2B time Comp	Outcome	Term	Subgroup	Coefficient	95%CI	Coeff. Type
Helve	2014	</= 60 mins	> 60 mins	MACE	90-days		(Not provided & have insufficient details to compute)		Adjusted OR
Brennan	2014	> 90 mins	</= 90 mins	Mortality	12-month		0.49	0.33-0.73	Adjusted OR
Brennan	2014	</= 90 mins	> 90 mins	Recurrent MI	12-month		1.5559	1.0006-2.4385	Crude OR
Brennan	2014	</= 90 mins	> 90 mins	MACE	12-month		1.7713	1.3872-2.2666	Crude OR
Nakamura	2012			Mortality	In-hospital		0.498136	0.24-1.09	Crude OR
Kodaira	2013			Mortality	In-hospital		0.7042314	0.10-4.27	Crude OR
Kodaira	2013			MACE	In-hospital		0.8172677	0.27-2.41	Crude OR
Kodaira	2013			Shock	In-hospital		0.3412885	0.01-4.33	Crude OR
Shiomi	2012	> 90 mins	</= 90 mins	MACE	Rate		0.98	0.78-1.24	Adjusted HR
Shiomi	2012	> 90 mins	</= 90 mins	MACE	Rate	Early Presenters	0.58	0.38-0.87	Adjusted HR
Shiomi	2012	> 90 mins	</= 90 mins	MACE	Rate	Late Presenters	1.57	1.12-2.18	Adjusted HR
Heitzler	2012	< 90 mins	> 90 mins	Mortality	In-hospital		(Insufficient information to compute the effect, CI & p-value)		Crude OR
Heitzler	2012	< 90 mins	> 90 mins	Mortality	6-month		(Insufficient information to compute the effect, CI & p-value)		Crude OR
Heitzler	2012	< 90 mins	> 90 mins	Angina	6-month		(Insufficient information to compute the effect, CI & p-value)		Crude OR

Author.1st	Year Pub	D2B time Ref	D2B time Comp	Outcome	Term	Subgroup	Coefficient	95%CI	Coeff. Type
Heitzler	2012	< 90 mins	> 90 mins	MACE	6-month		(Insufficient information to compute the effect, CI & p-value)		Crude OR
Towae	2011			Mortality	In-hospital		(Insufficient information to compute the effect, CI & p-value)		Adjusted OR
Muller	2011	D2BT < 30 mins	D2BT > 30 mins	Mortality	6-month		1.6	1.00-2.57	Adjusted HR
Muller	2011	D2BT < 30 mins	D2BT > 30 mins	MACE	Rate		1.5	1.13-1.99	Adjusted HR
Lambert	2010	D2NT </= 30 mins, D2BT </= 90 mins	D2NT > 30 mins, D2BT > 90 mins	Mortality	30-days		2.14	1.21-3.93	Adjusted OR
Lambert	2010	D2NT </= 30 mins, D2BT </= 90 mins	D2NT > 30 mins, D2BT > 90 mins	Mortality	12-month		1.61	1.00-2.66	Adjusted OR
Lambert	2010	D2NT </= 30 mins, D2BT </= 90 mins	D2NT > 30 mins, D2BT > 90 mins	Recurrent MI	12-month		1.26	0.56-2.88	Crude OR
Lambert	2010	D2NT </= 30 mins, D2BT </= 90 mins	D2NT > 30 mins, D2BT > 90 mins	CHF	12-month		2.02	0.92-4.40	Crude OR
Lambert	2010	D2NT </= 30 mins, D2BT </= 90 mins	D2NT > 30 mins, D2BT > 90 mins	MACE	12-month		1.57	1.08-2.30	Adjusted OR
Hannan	2010	<90	> 180	Mortality	Rate		1.26	0.82-1.93	Adjusted HR

Author.1st	Year Pub	D2B time Ref	D2B time Comp	Outcome	Term	Subgroup	Coefficient	95%CI	Coeff. Type
Hannan	2010	< 90	>/= 90	Mortality	Rate	High Risk Patients	1.29	0.94-1.75	Adjusted HR
Hannan	2010	<90	>/= 90	Mortality	Rate	Early Presenters	1.29	0.95-1.77	Adjusted HR
Brodie	2010	>90	</= 90	Mortality	12-month		0.72	0.52-1.01	Adjusted HR
Brodie	2010	>90	</= 90	Mortality	12-month	Early Presenters	0.51	0.26-0.98	Adjusted HR
Brodie	2010	>90	</= 90	Mortality	12-month	Late Presenters	0.86	0.58-1.28	Crude HR
Brodie	2010	>90	</= 90	Mortality	12-month	High Risk Patients	0.75	0.51-1.02	Crude HR
Brodie	2010	>90	</= 90	Mortality	12-month	Low Risk Patients	0.64	0.30-1.37	Crude HR
Rathore	2009	</= 90	> 90	Mortality	30-days		1.7811	1.2749-2.5291	OR of adjusted mortality rate
Rathore	2009	</= 90	> 90	Mortality	12-month		1.77	1.3354-2.3684	OR of adjusted mortality rate
Rathore	2009	</= 90	> 90	Mortality	In-hospital		1.5227	1.3917-1.6661	OR of adjusted mortality rate
Kong	2009	> 90	</= 90	Mortality	In-hospital		0.37	0.18-0.75	Crude OR
Kong	2009	</= 90	> 90	Mortality	In-hospital	High Risk Patients	2.41	1.14-5.06	Crude OR
Song	2008	</= 90	> 90	Mortality	30-days		1.0209	0.5929-1.7580	Crude OR
Song	2008	</= 90	> 90	MACE	30-days		1.0767	0.6679-1.7380	Crude OR
Song	2008	</= 90	> 90	MACE	30-days	High Risk Patients	0.6726	0.3629-1.2337	Crude OR
Song	2008	</= 90	> 90	MACE	30-days	Low Risk Patients	4.7944	0.9476-46.6378	Crude OR
Soon	2007	< 90	>/= 90	Mortality	30-days		2.6441	0.7016-14.8691	Crude OR
Soon	2007	< 90	>/= 90	MACE	30-days		2.8568	0.7676-15.9577	Crude OR
Soon	2007	< 90	>/= 90	Mortality	6-month		3.2934	0.9032-18.1904	Crude OR
Soon	2007	< 90	>/= 90	MACE	6-month		2.5964	0.8998-9.2143	Crude OR

Author.1st	Year Pub	D2B time Ref	D2B time Comp	Outcome	Term	Subgroup	Coefficient	95%CI	Coeff. Type
Nallamothu	2007	< 90	>/= 90	Mortality	6-month		6-month mortality increased by 0.18% per 10-min delay in D2B time between 90-150 minute (95% CI = 0.08-0.35%)		NA
Brodie	2007	</= 90 mins	> 90 mins	Mortality	6-month		3.6314	0.5054-159.3615	Crude OR
Brodie	2007	</= 90 mins	> 90 mins	Recurrent MI	6-month		0.7848	0.2132-3.5660	Crude OR
Brodie	2007	</= 90 mins	> 90 mins	Stroke	6-month		0.7017	0.0362-41.7599	Crude OR
Brodie	2007	</= 90 mins	> 90 mins	Recurrent MI	6-month		1.058	0.3879-3.3524	Crude OR
Brodie	2007	</= 90 mins	> 90 mins	MACE	6-month		1.3036	0.5566-3.4188	Crude OR
McNamara	2006	-	Per 30 minutes interval	Mortality	In-hospital		1.08	1.05-1.11	Adjusted OR
Brodie	2006	< 90 mins	>/= 90 mins	Mortality	30-days		1.4938	0.6399-4.0467	Crude OR
Brodie	2006	< 90 mins	>/= 90 mins	Recurrent MI	30-days		0.8023	0.2614-2.9226	Crude OR
Brodie	2006	< 90 mins	>/= 90 mins	Mortality	12-month		1.3334	0.7519-2.4989	Crude OR
Brodie	2006	< 90 mins	>/= 90 mins	Recurrent MI	12-month		1.2456	0.6014-2.8312	Crude OR
Brodie	2006	D2B time as a continuous variables		Mortality	12-month	Early Presenters	1.24	1.05-1.46	Adjusted HR

Author.1st	Year Pub	D2B time Ref	D2B time Comp	Outcome	Term	Subgroup	Coefficient	95%CI	Coeff. Type
Brodie	2006	D2B time as a continuous variables		Mortality	12-month	Late Presenters	0.88	0.67-1.15	Adjusted HR
Brodie	2006	<90mins	90-120 mins	Mortality	In-hospital		1.34	0.67-2.67	Adjusted OR
Brodie	2006	<90mins	90-120 mins	Mortality	Rate		1.17	0.84-1.62	Adjusted HR
Brodie	2006	< 120 mins	>/= 120 mins	Mortality	Rate	Early Presenters	1.54	1.24-1.90	Unadjusted HR
Brodie	2006	< 120 mins	>/= 120 mins	Mortality	Rate	Late Presenters	0.95	0.62-1.45	Unadjusted HR
Brodie	2006	< 120 mins	>/= 120 mins	Mortality	Rate	High Risk Patients	1.53	1.22-1.90	Unadjusted HR
Brodie	2006	< 120 mins	>/= 120 mins	Mortality	Rate	Low Risk Patients	1.13	0.78-1.64	Unadjusted HR
Zahn	2004	</= 30 mins	> 60 mins	Mortality	In-hospital		1.16	0.74-1.84	Adjusted OR
Juliard	2003	D2T3 time per 15 min		Mortality	In-hospital		1.27	1.06-1.52	Adjusted OR
De Luca	2003	</= 90 mins	> 90 mins	Mortality	12-month		1.6453	0.8958-2.8672	Crude OR
De Luca	2003	-	-	Mortality	12-month	Low Risk Patients	Outcome was not related to D2B time; effect size, CI & p-value not provided; unadjusted estimates		NA

Author.1st	Year Pub	D2B time Ref	D2B time Comp	Outcome	Term	Subgroup	Coefficient	95%CI	Coeff. Type
De Luca	2003	-	-	Mortality	12-month	High Risk Patients	Outcome was not related to D2B time; effect size, CI & p-value not provided; unadjusted estimates		NA
De Luca	2003	-	-	Mortality	12-month	Preprocedural TIMI < 2	Outcome was not related to D2B time; effect size, CI & p-value not provided; unadjusted estimates		NA
De Luca	2003	-	-	Mortality	12-month	Preprocedural TIMI > 2	Outcome was not related to D2B time; effect size, CI & p-value not provided; unadjusted estimates		NA
Brodie	2001	< 90 mins	>/= 90 mins	Mortality	30-days		0.6445	0.3309-1.2767	Crude OR
Brodie	2001	< 90 mins	>/= 90 mins	Mortality	6-month		0.5886	0.3345-1.0443	Crude OR
Cannon	2000	<120 mins	> 120 mins	Mortality	In-hospital		1.28	1.13-1.44	Adjusted OR (PS)
Cannon	2000	<120 mins	> 120 mins	Mortality	In-hospital	With Cardiogenic shock	1.65	1.28-2.14	Crude OR
Cannon	2000	<120 mins	> 120 mins	Mortality	In-hospital	Without Cardiogenic shock	1.66	1.48-1.87	Crude OR

Author.1st	Year Pub	D2B time Ref	D2B time Comp	Outcome	Term	Subgroup	Coefficient	95%CI	Coeff. Type
Berger	1999	< 60 mins	61-75, 76-90, > 90	Mortality	30-days		1.6	1.13-2.26	Adjusted OR

References

1 R Core Team. R: A language and environment for statistical computing. R Foundation for statistical Computing. Vienna, Austria 2013.

2 Foo CY, Reidpath DD, Chaiyakunapruk N. The effect of door-to-balloon delay in primary percutaneous coronary intervention on clinical outcomes of STEMI: a systematic review and meta-analysis protocol. *Systematic reviews* 2016;**5**:130.

3 Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013.

4 Brennan AL, Andrianopoulos N, Duffy SJ, et al. Trends in door-to-balloon time and outcomes following primary percutaneous coronary intervention for ST-elevation myocardial infarction: an Australian perspective. *Intern Med J* 2014;**44**:471-7.

5 Krumholz HM, Herrin J, Miller LE, et al. Improvements in door-to-balloon time in the United States, 2005 to 2010. *Circulation* 2011;**124**:1038-45.

6 Flynn A, Moscucci M, Share D, et al. Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Arch Intern Med* 2010;**170**:1842-9.

7 Menees DS, Peterson ED, Wang Y, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. *N Engl J Med* 2013;**369**:901-9.

8 Berger PB, Ellis SG, Holmes DR, Jr., et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. *Circulation* 1999;**100**:14-20.

9 Brodie BR, Webb J, Cox DA, et al. Impact of time to treatment on myocardial reperfusion and infarct size with primary percutaneous coronary intervention for acute myocardial infarction (from the EMERALD Trial). *Am J Cardiol* 2007;**99**:1680-6.

10 Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *Jama* 2000;**283**:2941-7.

11 Hannan EL, Zhong Y, Jacobs AK, et al. Effect of onset-to-door time and door-to-balloon time on mortality in patients undergoing percutaneous coronary interventions for st-segment elevation myocardial infarction. *Am J Cardiol* 2010;**106**:143-7.

12 McNamara RL, Wang Y, Herrin J, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2006;**47**:2180-6.

13 Nallamothu B, Fox KA, Kennelly BM, et al. Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary percutaneous coronary intervention. The Global Registry of Acute Coronary Events. *Heart* 2007;**93**:1552-5.

14 Nallamothu BK, Normand SL, Wang Y, et al. Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: a retrospective study. *Lancet* 2015;**385**:1114-22.

15 Shiomi H, Nakagawa Y, Morimoto T, et al. Association of onset to balloon and door to balloon time with long term clinical outcome in patients with ST elevation acute myocardial infarction having primary percutaneous coronary intervention: observational study. *BMJ* 2012;**344**:e3257.

16 Chen HL, Liu K. Effect of door-to-balloon time on in-hospital mortality in patients with myocardial infarction: A meta-analysis. *International Journal of Cardiology* 2015;**187**:130-3.
17 Goel K, Pinto DS, Gibson CM. Association of time to reperfusion with left ventricular function and heart failure in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: a systematic review. *Am Heart J* 2013;**165**:451-67.
18 Sorita A, Ahmed A, Starr SR, et al. Off-hour presentation and outcomes in patients with acute myocardial infarction: systematic review and meta-analysis. *BMJ* 2014;**348**:f7393.
19 Li S, Shin HJ, Ding EL, et al. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2009;**302**:179-88.
20 Solhpour A, Chang KW, Arain SA, et al. Ischemic time is a better predictor than door-to-balloon time for mortality and infarct size in ST-elevation myocardial infarction. *Catheter Cardiovasc Interv* 2016;**87**:1194-200.
21 Lambert L, Brown K, Segal E, et al. Association between timeliness of reperfusion therapy and clinical outcomes in ST-elevation myocardial infarction. *Jama* 2010;**303**:2148-55.
22 Rathore SS, Curtis JP, Nallamothu BK, et al. Association of door-to-balloon time and mortality in patients > or =65 years with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol* 2009;**104**:1198-203.
23 Rathore SS, Curtis JP, Chen J, et al. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. *BMJ* 2009;**338**:b1807.
24 Brodie BR, Hansen C, Stuckey TD, et al. Door-to-balloon time with primary percutaneous coronary intervention for acute myocardial infarction impacts late cardiac mortality in high-risk patients and patients presenting early after the onset of symptoms. *J Am Coll Cardiol* 2006;**47**:289-95.
25 Di Domenicantonio R, Cappai G, Sciattella P, et al. The Tradeoff between Travel Time from Home to Hospital and Door to Balloon Time in Determining Mortality among STEMI Patients Undergoing PCI. *PLoS One* 2016;**11**:e0158336.
26 Helve S, Viikila J, Laine M, et al. Trends in treatment delays for patients with acute ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *BMC cardiovascular disorders* 2014;**14**:115.
27 Heitzler VN, Babic Z, Milicic D, et al. Evaluation of importance of door-to-balloon time and total ischemic time in acute myocardial infarction with ST-elevation treated with primary percutaneous coronary intervention. *Acta clinica Croatica* 2012;**51**:387-95.
28 Towae F, Juenger C, Mudra H, et al. The development of door-to-angiography time in the last 14 years for patients with acute ST-elevation myocardial infarction treated with primary coronary intervention: Determinants and outcome. Results from the MITRAplus and OPTAMI registry. *Acute Card Care* 2011;**13**:35-9.
29 Muller UM, Eitel I, Eckrich K, et al. Impact of minimising door-to-balloon times in ST-elevation myocardial infarction to less than 30 min on outcome: an analysis over an 8-year period in a tertiary care centre. *Clin Res Cardiol* 2011;**100**:297-309.
30 Kong PK, Connolly D, Varma C, et al. High-risk myocardial infarction patients appear to derive more mortality benefit from short door-to-balloon time than low-risk patients. *Int J Clin Pract* 2009;**63**:1693-701.
31 Zahn R, Vogt A, Zeymer U, et al. In-hospital time to treatment of patients with acute ST elevation myocardial infarction treated with primary angioplasty: determinants and outcome. Results

from the registry of percutaneous coronary interventions in acute myocardial infarction of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausarzte. *Heart* 2005;**91**:1041-6.
32 Juliard J-M, Feldman LJ, Golmard J-L, et al. Relation of mortality of primary angioplasty during acute myocardial infarction to door-to-Thrombolysis In Myocardial Infarction (TIMI) time. *The American Journal of Cardiology* 2003;**91**:1401-5.
33 De Luca G, Suryapranata H, Zijlstra F, et al. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. *Journal of the American College of Cardiology* 2003;**42**:991-7.
34 Yudi MB, Ramchand J, Farouque O, et al. Impact of door-to-balloon time on long-term mortality in high- and low-risk patients with ST-elevation myocardial infarction. *Int J Cardiol* 2016;**224**:72-8.
35 Wang YC, Huang YY, Lo PH, et al. Age-dependent impact of new ESC-Guideline recommended door-to-balloon times on mid-term survival in acute ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention. *Int J Cardiol* 2016;**222**:242-6.
36 Jun Sim EW, Ang AS, Tan MC, et al. TCTAP A-133 Treatment Delay in Door-to-Balloon Time in South-East Asian Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction: A Key Process Analysis of Patient Factors. *Journal of the American College of Cardiology* 2015;**65**:S66.
37 Wongpraparut N, Chotinaiwattarakul C, Panchavinnin P, et al. First medical contact to device time in the Thailand percutaneous coronary intervention (PCI) registry. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet* 2014;**97**:1247-53.
38 Ho YC, Tsai TH, Sung PH, et al. Minimizing door-to-balloon time is not the most critical factor in improving clinical outcome of ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention. *Crit Care Med* 2014;**42**:1788-96.
39 Nakamura M, Yamagishi M, Ueno T, et al. Current treatment of ST elevation acute myocardial infarction in Japan: door-to-balloon time and total ischemic time from the J-AMI registry. *Cardiovascular Intervention and Therapeutics* 2013;**28**:30-6.
40 Kodaira M, Kawamura A, Miyata H, et al. Door to balloon time: how short is enough under highly accessible nationwide insurance coverage? Analysis from the Japanese multicenter registry. *Int J Cardiol* 2013;**168**:534-6.
41 Song YB, Hahn JY, Gwon HC, et al. The impact of initial treatment delay using primary angioplasty on mortality among patients with acute myocardial infarction: from the Korea acute myocardial infarction registry. *J Korean Med Sci* 2008;**23**:357-64.
42 Soon CY, Chan WX, Tan HC. The impact of time-to-balloon on outcomes in patients undergoing modern primary angioplasty for acute myocardial infarction. *Singapore medical journal* 2007;**48**:131-6.
43 Brodie BR, Gersh BJ, Stuckey T, et al. When is door-to-balloon time critical? Analysis from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trials. *J Am Coll Cardiol* 2010;**56**:407-13.
44 Brodie BR, Stone GW, Morice MC, et al. Importance of time to reperfusion on outcomes with primary coronary angioplasty for acute myocardial infarction (results from the Stent Primary Angioplasty in Myocardial Infarction Trial). *Am J Cardiol* 2001;**88**:1085-90.

45 Brodie BR, Stone GW, Cox DA, et al. Impact of treatment delays on outcomes of primary percutaneous coronary intervention for acute myocardial infarction: analysis from the CADILLAC trial. *American heart journal* 2006:1231-8.
46 Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992;**135**:1301-9.
47 Crippa A, Orsini N. Multivariate Dose-Response Meta-Analysis: The dosresmeta R Package. *Journal of Statistical Software* 2016;**72**.
48 Orsini N, Li R, Wolk A, et al. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol* 2012;**175**:66-73.
49 Harrell FEJ. rms: Regression Modeling Strategies. R package version 5.1-1. 2017.