ASSESSING THE EFFECTIVENESS OF PRIMARY ANGIOPLASTY COMPARED TO THROMBOLYSIS AND ITS RELATIONSHIP TO TIME DELAY: A BAYESIAN EVIDENCE SYNTHESIS

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Abstract

Background: Meta-analyses of trials comparing thrombolysis and primary angioplasty following an acute myocardial infarction (AMI) have shown benefits for angioplasty. Choice of therapy needs to consider the relationship between this benefit and any time delay in initiating angioplasty.

Objective: To extend earlier meta-analyses of these alternative forms of reperfusion by considering both 1- and 6-month outcome data. To use Bayesian statistical methods to quantify more fully the uncertainty associated with the estimated relationships.

Methods: A systematic review and meta-analysis published in 2003 was updated with recently published trials. Data on key clinical outcomes and the difference between time-to-balloon and time-to-needle were independently extracted by two researchers. Bayesian statistical methods were used to synthesise evidence despite differences between trials in follow-up times and reported outcomes. Outcomes are presented as absolute probabilities of specific events and odds ratios (with 95% credible intervals (CrI)) as a function of the additional time-delay associated with angioplasty.

Results: A total of 22 studies were included in the meta-analysis, with 3,760 and 3,758 patients randomised to primary angioplasty and thrombolysis, respectively. The mean angioplasty-related time delay (over and above time to thrombolysis) was 54.3 minutes (S.E. 2.2). For this average delay, the mean event probabilities are lower for primary angioplasty for all outcomes. Mortality within 1 month is 4.5% following angioplasty and 6.4% after thrombolysis (odds ratio of 0.68 (95% CrI 0.46, 1.01)). For non-fatal re-infarction, the odds ratio is 0.32 (95% CrI 0.20, 0.51); and for non-fatal stroke it is 0.24 (95% CrI 0.11, 0.50). For all outcomes, the benefit of angioplasty decreases with longer delay from initiation.

Conclusions: The benefit of primary angioplasty, over thrombolysis, depends on the former's additional time delay. For delays between 30 and 90 minutes, angioplasty is superior, on average, for 1-month fatal and non-fatal outcomes. Thrombolysis may be the preferred option in terms of 6-month mortality only for delays at around 90 minutes and beyond but there is considerable uncertainty for longer time delays.

Keywords: Acute myocardial infarction, primary coronary angioplasty, thrombolytics, meta-regression.

INTRODUCTION

In the UK, at least 87,000 individuals under the age of 75 years suffer an acute myocardial infarction (AMI) each year.[1] The relationship between normal coronary artery blood flow and mortality after MI is well documented,[2] so early restoration of normal myocardial blood flow is a prime therapeutic goal for the management of MI. Pharmacological treatment with thrombolytic therapy and primary angioplasty are two different modes of reperfusion therapy for ST elevation AMI (STEMI).

Meta-analyses of the various randomised trials comparing thrombolysis and primary angioplasty have shown substantial benefits from angioplasty in terms of mortality, non-fatal re-infarction and stroke;[2-5] and they have also shown that angioplasty has lower recurrence rates and less residual stenosis.[6,7] Despite the apparent clinical superiority of primary angioplasty, thrombolytic treatment is the default treatment option in many countries because of practical limitations on the use of percutaneous interventions including a shortage of cardiac catheter facilities and appropriately skilled staff. The choice of appropriate management also needs to consider the possible time delay in initiating reperfusion with primary angioplasty compared to thrombolysis. The effect of this angioplasty-related time delay in reducing the mortality benefit of angioplasty relative to thrombolysis has been demonstrated using meta-regression methods.[8,9]

This work has been influential in clinical guidelines for the management of AMI.[10,11] For example, European guidelines suggest that primary angioplasty is the "preferred treatment if performed by an experienced team less than 90 minutes after first medical contact".[11] However, there are some limitations in the analyses informing these guidelines. A key meta-analysis only had abstracts available for some trials,[2] and inaccuracy in data extraction has been observed.[12] The quantification of the relationship between the benefit of angioplasty and time delay until its initiation did not quantify the uncertainty around this relationship, and the analysis was restricted to a sub-set of major clinical events.[8]

This paper seeks to build on these previous analyses by extending their scope and statistical rigor. It assesses how the treatment effect of angioplasty on fatal and non-fatal outcomes (re-infarctions and strokes) relates to the additional delay involved in initiating angioplasty. It also considers both the 1-month and the 6-month outcome data reported in randomised clinical trials. Furthermore, in using Bayesian statistical methods, the paper is able to quantify more fully the uncertainty associated with the estimated relationships.

METHODS

Search strategy and data extraction

To identify trials comparing intravenous thrombolysis and primary angioplasty in patients with STEMI, the analysis used an earlier review[2] as a starting point. To update this review, the following databases were searched: Cochrane Controlled Trials Register, UK National Research Register, Medline, Embase, Database of Abstracts of Reviews of Effects, UK National Health Service Economic Evaluation Databases, and Health Technology Assessment Database. The searches were restricted to English-language studies published between 2002 and 2004. The inclusion criteria were consistent with those used previously.[2,5] Full details of the search strategy are available in a technical report {note to

the editor: a technical report is submitted with this paper with a view to web-based publication}.

Two researchers (YB, CA) independently extracted the clinical data. Outcomes of interest were mortality, non-fatal re-infarctions, fatal and non-fatal strokes, and hemorrhagic strokes, as well as any data regarding time delay to treatment initiation. Discrepancies were resolved by consensus, and a third researcher (SP) was consulted when necessary. Data were also extracted on the difference between time-to-balloon in angioplasty and time-to-needle in thrombolytic therapy. This definition emphasises the *differences* in times to initiation of treatment between the two reperfusion strategies, thus avoiding the problem of different timing definitions across studies. Mean times to treatment, together with their standard deviations, were preferred in the analysis, but medians and quartiles were used when these were not available. Where the earlier review[2] had used preliminary data from conference abstracts, these were updated with final trial reports; the earlier data extraction was also checked and any inaccuracies were corrected.

Statistical methods

The comparison in the meta-analysis was between primary angioplasty and thrombolysis (regardless of type of drug). Because only a limited number of trials reported 6-month data on fatal or hemorrhagic strokes, these endpoints were excluded from the meta-analysis. Thus three outcomes (death, non-fatal strokes, and non-fatal re-infarctions), for which sufficient data were available, were analysed using an intention-to-treat principle.

The analysis was undertaken using Bayesian statistical methods.[13-15] These methods were used because they are more suitable for synthesising evidence when there are differences between trials in, for example, follow-up times and reported outcomes. An important feature of Bayesian methods is that they use external evidence (so called 'prior distributions') which represent beliefs about the evidence and its uncertainty external to the data extracted from the trials. This analysis has used 'non-informative' prior distributions so that the data are dominant in the results presented. A sensitivity analysis was undertaken to verify that changing the specification of the prior distribution did not alter the results substantially. Bayesian methods also enable direct probability statements to be made about quantities of clinical interest, e.g. the probability that an intervention is superior to another. [13,14]

Full details of the statistical methods are presented in the technical report. Briefly, the meta-analysis models all outcomes of interest as probabilities on the log-odds scale, and results are reported in terms of the absolute probability of specific events and odds ratios (with 95% credible intervals (CrI)). It is assumed that baseline event rates (i.e. clinical events in the thrombolysis arms) vary randomly between trials, where the degree of variation is estimated from the data (a 'random effect' assumption). That is, although the patient populations in different trials are not identical, they are similar to each other. So the results of the analysis are only valid for patient populations similar to a hypothetical 'average' trial population.

For each outcome measure, the relative treatment effect of primary angioplasty compared to thrombolytic treatment is modelled as a 'random effect'; similar but not identical between trials. This *relative* treatment effect is estimated as a function of the time delay related to the initiation of angioplasty. This relationship is used to establish the extent to which any additional effectiveness of angioplasty is affected by the additional time it takes

to deliver the intervention compared to thrombolysis, whilst taking into account the uncertainty surrounding the average delay in each trial. When interpreting the results of such a 'meta-regression', caution is needed in extrapolating the relationship beyond the data on time delay observed in the trials. Also, it should be recognised that, at the extremes of the time delay data, uncertainty in the estimates relationship will be greater than around the mid-point.

A feature of the evidence base is that some trials report outcomes at 1 month follow-up, some at 6 months follow-up and some at both. In order that all these data can be used, outcomes at 1 month and 6 months are assumed to differ by a random effect.[16] This reflects the fact that clinical events are more likely to occur within the first month following AMI and, by allowing a relationship between outcomes at the two time-points, more of the data can be used in the analysis. Thus, those studies which do not report at 6 months can 'borrow strength' both from those that do and from their own results at 1 month.

RESULTS

Summary of the trial evidence

A total of 24 studies met the inclusion criteria. Two of the studies were subsequently excluded from the meta-analysis. One of these was excluded because it did not report times to treatment and, as such, could not provide data on the delay to primary angioplasty.[17] The SHOCK study[18] was also excluded because the primary comparison was between emergency revascularization without differentiating results by type of intervention (angioplasty 64%, surgery 36%), and hence this treatment strategy is not directly comparable with primary angioplasty in the other trials.

Table 1 lists the remaining 22 studies included. In comparison with the earlier review,[2] one additional trial[19] was identified which had not been published at the time. In addition, full trial results were available for three studies that had previously been reported in abstract form only.[20-22]

Table 1 lists the data extracted from the 22 trials. In total, these trials included 3,760 and 3,758 patients randomised to primary angioplasty and thrombolysis, respectively. Eight of the 22 trials used streptokinase as the form of thrombolysis, and 14 used t-PA. For angioplasty, 13/22 trials used coronary stents, and 8 studies used glycoprotein IIb/IIIa antagonists. The mean value of angioplasty-related time delay (over and above time to thrombolysis) was 54.3 minutes (S.E. 2.2). All trials reported outcomes at between 30 days and 6 weeks (both are referred to as '1 month' in the meta-analysis results) after the initial MI; 10 out of the 22 trials also reported outcomes at 6 months follow-up.

Table 1. Overview of trials and key endpoints and time to treatment for primary angioplasty (A) and thrombolysis (T).

| Study | 1 month (4-6 weeks) | | | | | | | | 6 months | | | | | | | | Time (minutes) | |
| | N | | Death | | NF Reinfarction | | NF Stroke | | N | | Death | | NF Reinfarction | | NF Stroke | | Mean | Mean |
	(A)	(T)	N (A)/(T)	O.R. (95% CrI)	N (A)/(T)	O.R. (95% CrI)	N (A)/(T)	O.R. (95% CrI)	(A)	(T)	N (A)/(T)	O.R. (95% CrI)	N (A)/(T)	O.R. (95% CrI)	N (A)/(T)	O.R. (95% CrI)	(A)	(A)
Zijlstra et al 1993[23]§	70	72	0 / 4	0.1 (0 – 7.7)	0 / 9	0.1 (0.0 – 4.8)	0 / 2	0.2 (0.0 – 12.4)	-	-	-	-	-	-	-	-	61	30
Ribeiro et al 1993[24]§	50	50	3 / 1	3.1 (0.2 – 16)	4 / 5	0.7 (0.2 – 3.5)	-	-	-	-	-	-	-	-	-	-	238	179
Zwolle 1994§[19]	152	149	3 / 11	0.3 (0.2 – 2)	2 / 15	0.1 (0.0 – 1.7)	1 / 2	0.4 (0.0 – 8.1)	-	-	-	-	-	-	-	-	195	176
Berrocal et al 2003[20]§	54	58	5 / 6	0.9 (0.3 – 3.3)	1 / 2	0.5 (0.0 – 8.6)	-	-	-	-	-	-	-	-	-	-	82	15
Zijlstra et al 1997[25]§	45	50	1 / 0	2.3 (0 – 43)	0 / 8	0.0 (0.0 – 5.2)	1 / 2	0.5 (0.0 – 8.7)	45	50	1 / 0	2.2 (0.0 – 43.4)	0 / 8	0.0 (0.0 – 5.2)	1 / 2	0.5 (0.0 – 8.7)	68	29
Widimsky et al 2000[26]§	101	99	7 / 14	0.5 (0.3 – 1.8)	1 / 10	0.0 (0.0 – 2.7)	0 / 0	1 (0.0 – 50.4)	-	-	-	-	-	-	-	-	96	90
de Boer et al 2002[27]§	46	41	3 / 8	0.3 (0.1 – 2.4)	1 / 6	0.1 (0.0 – 3.5)	1 / 2	0.4 (0.0 – 7.9)	-	-	-	-	-	-	-	-	59	31
Widimsky et al 2003[21]§†	429	421	29 / 42	0.7 (0.5 – 1.4)	6 / 13	0.4 (0.2 – 1.8)	1 / 9	0.1 (0.0 – 3.0)	-	-	-	-	-	-	-	-	97	12
DeWood et al 1990[28]	46	44	3 / 2	1.5 (0.2 – 7.4)	-	-	-	-	-	-	-	-	-	-	-	-	126	84
Grines et al 1993[29]	195	200	5 / 13	0.4 (0.2 – 1.9)	5 / 13	0.3 (0.2 – 1.8)	0 / 3	0.1 (0.0 – 9.2)	188	190	7 / 15	0.4 (0.2 – 1.7)	-	-	-	-	60	32
Gibbons et al 1993[30]	47	56	2 / 2	1.2 (0.1 – 8)	-	-	-	-	47	56	3 / 2	1.8 (0.2 – 8.1)	0 / 2	0.2 (0.0 – 13.2)	-	-	277	232
Ribichini et al 1998[31]	55	55	1 / 3	0.3 (0.1 – 6.1)	1 / 2	0.4 (0.0 – 8.3)	0 / 0	1 (0.0 – 51.31)	55	55	1 / 4	0.2 (0.0 – 4.9)	2 / 2	1 (0.1 – 7.3)	-	-	53.2	36.5
Garcia et al 1999[32]	109	111	3 / 12	0.2 (0.1 – 1.9)	4 / 6	0.6 (0.2 – 3.0)	0 / 2	0.2 (0.0 – 12.3)	99	91	5 / 13	0.3 (0.2 – 1.7)	6 / 8	0.6 (0.2 – 2.5)	-	-	197	150
GUSTO IIb 1997[33]	565	573	32 / 40	0.8 (0.6 – 1.5)	25 / 37	0.6 (0.4 – 1.4)	1 / 5	0.2 (0.0 – 4.2)	565	573	-		-	-	-	-	228	180
Le May et al 2001[34]	62	61	3 / 2	1.5 (0.2 – 7.4)	3 / 5	0.5 (0.1 – 3.4)	1 / 1	1 (0.0 – 16.2)	62	61	3 / 2	1.5 (0.1 – 7.3)	4 / 10	0.3 (0.1 – 2.1)	1 / 3	0.3 (0.0 – 6.0)	77	15
Bonnefoy et al 2002[35]	421	419	20 / 16	1.3 (0.6 – 2.2)	7 / 15	0.4 (0.2 – 1.7)	0 / 4	0.1 (0.0 – 7.6)	-	-	-	-	-	-	-	-	190	130

Study																		
Schomig et al 2000[36]	71	69	3 / 5	0.6 (0.2 – 3.4)	2 / 4	0.4 (0.1 – 4.0)	-	-	71	69	3 / 9	0.2 (0.1 – 2.2)	-	-	-	-	65	30
Vermeer et al 1999[37]†	75	75	5 / 5	1 (0.3 – 036)	1 / 7	0.1 (0.0 – 3.4)	2 / 1	2 (0.1 – 15.3)	-	-	-	-	-	-	-	-	85	10
Kastrati et al 2002[38]	81	81	2 / 5	0.4 (0.1 – 3.5)	0 / 4	0.1 (0.0 – 7.6)	1 / 1	1 (0.0 – 16.2)	70	71	5 / 7	0.7 (0.2 – 2.8)	-	-	-	-	75	35
Aversano et al 2002[39]	225	226	12 / 16	0.7 (0.4 – 1.9)	11 / 20	0.5 (0.3 – 1.6)	3 / 8	0.3 (0.1 – 2.4)	225	226	14 / 16	0.8 (0.4 – 1.9)	12 / 24	0.4 (0.3 – 1.4)	5 / 9	0.5 (0.2 – 2.3)	101.5	46
Grines et al 2002[40]	71	66	6 / 8	0.7 (0.3 – 2.6)	1 / 0	1.8 (0 – 39.7)	0 / 3	0.1 (0.0 – 8.9)	-	-	-	-	-	-	-	-	174	63
Andersen et al 2003: Referral[22]*	567	562	37 / 48	0.7 (0.6 – 1.4)	11 / 35	0.2 (0.2 – 1.1)	9 / 11	0.8 (0.3 – 2.2)	-	-	-	-	-	-	-	-	90	20
Andersen et al 2003: Invasive[22]*	223	220	15 / 13	1.1 (0.5 – 2.3)	2 / 14	0.1 (0.0 – 1.8)	0 / 5	0.0 (0.0 – 6.6)	-	-	-	-	-	-	-	-	63	20

Reinf. = reinfarction; SD = standard deviation; CrI = credibility interval

* This trial consisted of two sub-trials, labelled 'Referral' and 'Invasive', and these are analysed as if they are two separate studies. † Includes a third group of patients who received thrombolytic therapy followed by transfer to angioplasty; these third comparators were excluded from the present analysis. § Trial used streptokinase as part the thrombolytic arm, all other trials used t-PA.

Meta-analysis

Table 2 shows the estimated probability of each outcome occurring within 1 month or 6 months after initial treatment with primary angioplasty or thrombolytics. These results are based on the average angioplasty-related time delay of 54.3 minutes reported in the trials, estimated as a weighted average, the weights being the total number of patients in each trial. For all outcomes, the mean probability of an event occurring is lower for patients randomised to primary angioplasty. In particular, mortality within 1 month is estimated to be 4.5% following angioplasty and 6.4% after thrombolysis, with an odds ratio of 0.68 (95% CrI 0.46, 1.01). For non-fatal re-infarction, the odds ratio is 0.32 (95% CrI 0.20, 0.51); and for non-fatal stroke it is 0.24 (95% CrI 0.11, 0.50). Table 2 also shows estimated results for the 6-month endpoints which are very similar to those at 1 month, indicating that the majority of events happen in the first month after randomisation.

As the additional time delay to initiation of primary angioplasty is modelled explicitly, it is possible to predict how particular angioplasty-related time delays influence the clinical superiority of angioplasty. For angioplasty delays of 30, 60 or 90 minutes, the absolute probability differences and the odds-ratios of angioplasty versus thrombolytic therapy are shown in Table 3. If angioplasty could be initiated within 30 minutes of possible thrombolysis, the absolute probabilities of mortality, non-fatal re-infarction and non-fatal stroke at 6 months would be, respectively, 3.7%, 4.6% and 1.7% lower than those with thrombolysis. For any of these outcomes, the benefit of angioplasty decreases with longer delay until its initiation.

This effect is shown in more detail in Figure 1. In terms of mortality, angioplasty is superior to thrombolysis, on average, at time delays up to 90 minutes. Moreover, in terms of the 1-month outcome of mortality, the probability that it is superior is 97%, for an additional delay of up to around 60 minutes. For the 6-month outcome of mortality, there is over 95% probability that angioplasty is superior for delays of up to around 45 minutes and 87% for delays up to around 60 minutes. However, this probability goes below 50% for delays at 90 minutes and beyond, where thrombolysis could therefore be the preferred option at least for the 6-month mortality outcome. For non-fatal re-infarction and non-fatal stroke, primary angioplasty is superior, on average, even if it requires an additional time of up to 2 hours to achieve reperfusion with that method. For both non-fatal outcomes at one month, there was over 95% probability that angioplasty is superior at additional delays of up to 90 minutes. For the corresponding 6-month outcomes, there was over 95% probability that angioplasty was superior at delays up to 80 minutes.

Table 2. **Estimated absolute probabilities of the occurrence of various endpoints 1 month or 6 months after angioplasty or thrombolytic therapy (mean and 95% CrI), together with the odds ratios (95% CrI) comparing primary angioplasty and thrombolysis and probabilities that angioplasty is superior. The results are for the average observed 'angioplasty-related time delay' (i.e. 54.3 minutes).**

1-month endpoints	Probability (angioplasty)	Probability (thrombolytics)	Odds ratio	Probability angioplasty superior
Death	4.5% (3.0%, 6.5%)	6.5% (4.5%, 9.0%)	0.68 (0.46, 1.01)	0.97
Non-fatal reinfarction	2.0% (1.2%, 3.1%)	6.1% (4.1%, 8.5%)	0.33 (0.20, 0.51)	1.00
Non-fatal stroke	0.5% (0.2%, 0.9%)	1.9% (1.0%, 3.2%)	0.26 (0.11, 0.50)	1.00
6-month endpoints	Probability (angioplasty)	Probability (thrombolytics)	Odds ratio	Probability angioplasty superior
Death	5.5% (3.4%, 8.8%)	7.7% (5.0%, 11.8%)	0.70 (0.42, 1.18)	0.93
Non-fatal reinfarction	2.6% (1.4%, 4.8%)	6.9% (4.4%, 10.7%)	0.33 (0.20, 0.67)	0.99
Non-fatal strokes	0.8% (0.2%, 1.0%)	2.8% (1.1%, 6.9%)	0.26 (0.08, 0.72)	0.99

Table 3. Absolute probability differences (thrombolysis minus angioplasty), odds ratios for the 6-month treatment effects of angioplasty compared to thrombolytic therapy (mean and 95% CrI) and probability that angioplasty is superior at assumed 'angioplasty-related time delays' of 30, 60 and 90 minutes.

Endpoint	Primary angioplasty-related time delay								
	30 minutes			60 minutes			90 minutes		
	Probability difference (95% CrI)	Odds ratio	Probability angioplasty is a superior treatment	Probability difference (95% CrI)	Odds ratio	Probability angioplasty is a superior treatment	Probability difference (95% CrI)	Odds ratio	Probability angioplasty is a superior treatment
Death	−3.5% (−7.2%, −0.5%)	0.54 (0.29, 0.92)	0.98	−1.8% (−5.6%, +1.7%)	0.77 (0.44, 1.29)	0.87	+0.7% (−4.6%, +8.1%)	1.15 (0.49, 2.36)	0.44
Non-fatal re-infarction	−4.8% (−8.2%, −2.2%)	0.30 (0.14, 0.59)	0.99	−4.2% (−7.5%, −1.6%)	0.39 (0.21, 0.72)	0.97	−3.1% (−7.1%, +1.6%)	0.55 (0.2,9 1.27)	0.93
Non-fatal stroke	−2.1% (−5.8%, −0.5%)	0.47 (0.05, 0.69)	0.99	−2.0% (−5.6%, −0.4%)	0.56 (0.09, 0.75)	0.98	−1.6% (−5.3%, +0.8%)	0.79 (0.08, 1.43)	0.93

Figure 1. Treatment effect of primary angioplasty relative to thrombolytic therapy, in terms of the absolute probability differences for each key outcome (death, non-fatal re-infarctions, non-fatal strokes) and point of follow-up (1-month, 6-month). The graphs show means and 95% CrIs plotted against the additional time delay to initiating primary angioplasty. Values above the x-axis indicate that angioplasty results in fewer clinical events. Each point represents a trial and their size is proportional to the trial sample size.
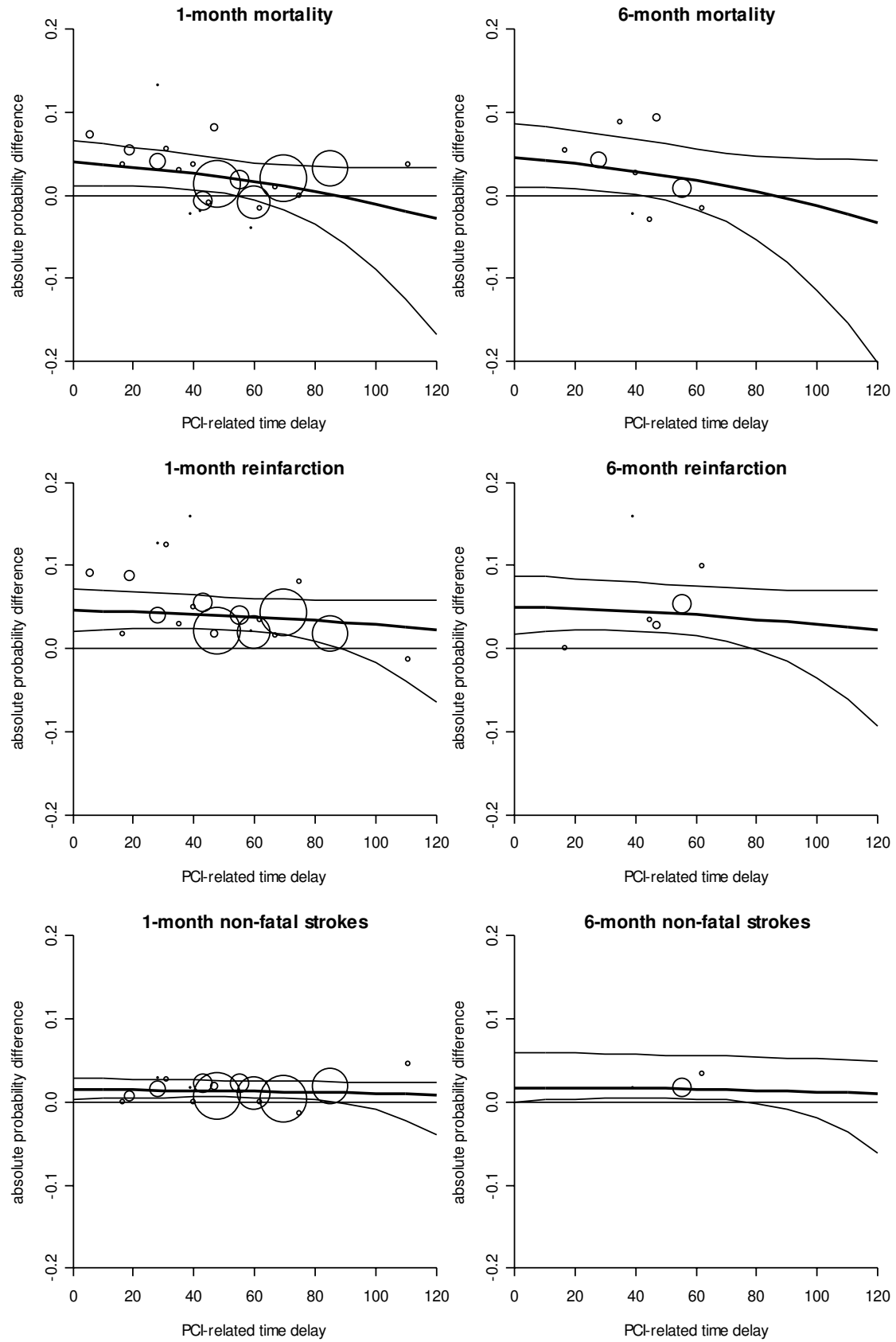
DISCUSSION

The contribution of this review is twofold. Firstly, it updates the most comprehensive recent meta-analysis of randomised trials comparing primary angioplasty and thrombolysis in patients with STEMI.[2] Secondly, it extends the evidence synthesis by evaluating the relationship between the treatment effects of angioplasty and time delay, expressed as the difference in times to initiation of treatment between the two reperfusion strategies. Furthermore, to our knowledge, this is the first study that explicitly models the measurement uncertainty associated with angioplasty-related time delay.

Although Keeley et al[2] do not directly address the issue of time delay, the main results in that study can be compared with those presented here for the average time delay of 54.3 minutes. For mortality at 1 month, Keeley et al found an odds ratio of 0.70 (95% confidence interval 0.58, 0.85), which is similar to that reported here, although our estimate does not reach statistical significance. This lack of statistical significance is likely to be due to differences in the data extraction,[12] the inclusion of additional evidence, and also because the measurement uncertainty in the time delay covariate is explicitly considered here. For the outcome of non-fatal re-infarction, the results here are similar to those of Keeley et al, in terms of both the magnitude and uncertainty of the odds ratio. The analysis of the stroke outcome is not comparable to that in Keeley et al which included all strokes compared to the non-fatal strokes considered here. Although a separate analysis of the longer-term follow-up data was undertaken by Keeley et al, these results were not presented in sufficient detail to allow a reliable comparison between the two sets of analyses at 6 months. Another reason why there will be slight differences between the two meta-analyses is that in ours the uncertainty in the between-study variability of the effect is appropriately taken in to account thus producing slightly wider CrIs than those obtained using Classical meta-analysis methods.[14,15]

Based on research undertaken during a similar period to our own, Boersma et al.[41] have also recently demonstrated, using individual patient data from 22 trials, that angioplasty is associated with significantly lower 30-day mortality, re-infarction and stroke relative to thrombolysis, regardless of delay in presentation. The main results in that study for the overall angioplasty-related delay of 55 minutes can be compared with those presented here for the average time delay of 54.3 at 1-month (Table 2) although there were minor differences in the trials included in the two studies. The absolute differences in the risks of non-fatal MI and stroke between angioplasty and thrombolysis at one month were very similar (4.3% vs 4.1% for non-fatal MI and 1.7% vs 1.4% for non-fatal stroke in Boersma et al and the current study, respectively). The estimated absolute reduction in mortality risk with angioplasty at one month was higher in the Boersma et al study: 2.6% versus 2%. As seen in previous studies,[8,42] the benefit of angioplasty in terms of mortality decreases the longer the time delay to initiation of angioplasty. However, none of these studies (including Boersma et al.[41]) quantify the uncertainty in this relationship fully. The comprehensive handling of uncertainty in the current analysis allows the precision associated with the relationship to be presented (Figure 1). The Bayesian approach also facilitates the presentation of results in terms of the probability of one intervention of being the superior treatment.

This is the first study to link explicitly short-term (1 month) with longer-term (6 months) outcomes using as much of the available clinical evidence as possible. Although none of the trial data indicate systematic differences between the relative treatment effect of primary angioplasty at 1 month and at 6 months, fewer data are generally available at 6

months resulting in greater uncertainty. It is, therefore, not surprising that the point estimates of the relative treatment effect of angioplasty are similar at the two time-points, but with greater uncertainty at 6-month endpoints. Thus, a probability of superiority of angioplasty in terms of the 6-month mortality endpoint of greater than 0.95 can be identified for delays of up to around 45 minutes only, whilst for delays at around 90 minutes thrombolysis appears to be superior. However, angioplasty appears to be superior for 6-month non-fatal outcomes, on average, for delays up to around 90 minutes. It should be noted, however, that the uncertainty in these relationships shown here is less than it would have been had only 6 month follow-up data been used in the analysis due to the paucity of the data.

The analysis suggests, therefore, that angioplasty performs better than thrombolytic therapy but this superiority is related to angioplasty-related time delay. It should be emphasised, however, that no trials have been identified which show a statistically significant advantage for thrombolysis at very long angioplasty-related time delays. Moreover, the PRAGUE-2 trial indicates that angioplasty performs better than thrombolysis even when it involves a patient transfer of up to 3 hours.[21] Without more evidence at long angioplasty-related time delays, the linear regression model estimated here will inevitably indicate that the relative treatment effect of primary angioplasty becomes negative at an unspecified delay. This is not because of data showing this effect, but simply because a consistent relationship has been observed for a range of relatively short time delays. In reality, for delays approaching 2 hours, this study can neither confirm nor refute whether angioplasty is better than thrombolytic treatment.

This study has some limitations. Firstly, the lack of individual patient data precludes the analysis of how the relative effect of angioplasty varies between patient sub-groups, and whilst this analysis has taken account of the uncertainty in the average time delay, thus reducing the possibility of ecological fallacy,[43] the presence of an ecological bias cannot be entirely eliminated. However, this is less of an issue when it is recognized that the aim of this study is to provide evidence to support population-based decisions using cost-effectiveness analysis as reported in the companion paper {ref to CE paper}. However, an analysis of individual patient data would also enable a more appropriate estimate of the impact or otherwise of time delay on outcome to be obtained.[44,45] Secondly, time-to-needle is a predictor of the success of thrombolytic treatment, but this effect could not be included in the analysis explicitly due to inconsistent reporting of the data in the trials. Hence the results are based on the *average* time-to-needle in the studies considered, which, at 75 minutes, was shown to be similar to the median call to needle time (67 minutes) in the UK (personal communication, Dr John Birkhead, UK Myocardial Infarction National Audit Project). Further research would be desirable to identify all external evidence on the effect of time-to-needle on outcomes and incorporate this into our analysis via appropriate prior distributions taking account of relevance and quality.[15] Thirdly, given this review was an update of those published earlier, neither the effect of publication bias, study quality or the influence of individual studies were formally assessed on the overall meta-analysis results. Fourthly, further exploration of whether the potential relationship between time-delay and effect (log odds ratio) is linear may be of merit.

The final limitation concerns the use of older streptokinase trials in the meta-analysis. Keeley *et al* were criticised[46] for including these trials in their meta-analysis because, by effectively averaging across the thrombolytic trials, the additional benefit of angioplasty may have been over-estimated. However, streptokinase is the most common form of

thrombolytic therapy used in many countries and is used in about a third of patients in the UK (personal communication, Dr John Birkhead, UK Myocardial Infarction National Audit Project). In the present meta-analysis, the differences between thrombolytic drugs were ignored with a focus on primary angioplasty or thrombolysis as two treatment groups. If only t-PA trials were analysed, the relative benefit of primary angioplasty is attenuated: 1-month odds-ratios for mortality are found to be 0.71 (95% CrI 0.44, 1.16); for non-fatal re-infarction, 0.41 (95% CrI 0.23, 0.71); and for non-fatal strokes, 0.23 (95% CrI 0.08, 0.57). Full details of this sensitivity analysis are reported in the technical report.

The policy implications of this analysis should be seen in the context of the relevant health care system. For example, US guidelines currently recommend that primary angioplasty should be used only within an angioplasty-related delay of less than 60 minutes.[10] The guidelines, however, seem to be based largely on the work of Nallamothu and Bates,[8] and may be premature because angioplasty appears to convey health benefits even when the delay is longer than 60 minutes. Even at delays longer than 1 hour, angioplasty is superior, on average, for all the 1-month outcomes included in this study, although there is considerable uncertainty associated with these estimates.

What size of treatment effect would be necessary with primary angioplasty to be considered worthwhile given the major changes in service organization necessary for its implementation? This issue is considered directly in the cost-effectiveness analysis submitted as a companion paper, which addresses whether the health benefits of primary angioplasty are sufficient to justify its additional cost. With respect to the absolute size of treatment effect with primary angioplasty, our analysis shows that the probability that primary angioplasty reaches at least a 1%, 2% and 3% improvement in survival at 1-month relative to thrombolysis is 0.82, 0.47 and 0.15, respectively, at the average angioplasty-related time delay. In short, the benefit of timely treatment is the key: If primary angioplasty can be delivered in a timely fashion, current evidence supports its use; if not, the choice of treatment probably depends on time from onset of symptoms to presentation[21, 41] and the availability of pre-hospital thombolysis.[35]

Decisions about appropriate methods of reperfusion should consider not only the effectiveness of each treatment option, but also their cost-effectiveness. With the quantification of both the expected treatment effects of angioplasty, with regard to several possible outcomes, and the uncertainties associated with these predictions, this meta-analysis using Bayesian methods lays the foundations for a robust cost-effectiveness analysis, in which other treatment strategies may be considered, and in which appropriate account is taken of statistical, clinical and methodological heterogeneity and all sources of uncertainty.[47]

Technical Appendix [Note to editor: this appendix could be web-based or published with the paper.]

The results of the 22 trials identified were formally combined using meta-analytic approaches. A Bayesian evidence synthesis is implemented[48] using specialist software (WinBUGS).[49] A random-baseline, random-effects approach is adopted for each outcome measure[50,51] that incorporates a linear regression of the treatment effect (log odds ratio) on the covariate "PCI-related time delay".[52] The model assumptions are described step by step below.

Multiple outcomes

In the trial search strategy we identified three clinical outcomes that are reported by a sufficient number of trials to inform an evidence synthesis: death, non-fatal strokes, and non-fatal re-infarctions. With such binomial outcomes, where an event either happens or does not happen, treatment effects can be modelled as absolute or relative risk differences or as log-odds.[53] For numerical convenience, we model all treatment effects on the log-odds scale. To reflect slight differences in recruitment criteria and patient mix, for each outcome the baseline event rates are assumed to vary randomly around a common mean.

Multiple time-points

While all trials report outcomes at the 1-month endpoint, a number of trials also report clinical events at the 6-month endpoint. However, any event that has occurred by 1 month will still have occurred by 6 months, so these endpoints are clearly related. Statistically, such a situation can be modelled by assuming that, for each treatment arm and outcome, the 1-month and the 6-month endpoints differ by a random effect, additive on the log-odds scale. We assume that these random effects are unrelated to the covariates that may explain some of the variation in the treatment effect of PCI compared to thrombolytic therapy.

Treatment effect of PCI relative to thrombolysis

For each trial and outcome, we model the treatment effect of PCI relative to thrombolysis as a random effect additive on the log-odds scale, respecting both the randomisation in the clinical trial and the heterogeneity of treatment effects measured by different trials. We assume that the same mean treatment effect of PCI, relative to thrombolysis, applies at both the 1-month and the 6-month time-point of each trial. This assumption is supported in the trial reports, which show that most clinical events occur within a few days from the initial episode (e.g. Aversano *et al*[29], Schomig *et al*[34], Le May et al[34], García *et al*[32]). We do not attempt to impute the 6-month data for those trials that did not report it and, therefore, the average treatment effect of PCI relative to thrombolytic therapy will be informed more strongly by the 1-month data that are reported more commonly. The mean treatment effect of PCI, relative to thrombolysis, is modelled in terms of the covariate "PCI-related time delay" (i.e. the additional time to PCI over and above thrombolysis) by linear regression [e. g. Berkey *et al* 1998[52]].

Correlated outcomes

We identify and model two sources of correlation between event rates. Baseline log-odds for the three outcomes are correlated across trials (e. g. high baseline mortalities may

systematically coincide with elevated or reduced rates of non-fatal strokes). Also, within each outcome, we model correlation of the four endpoints (1-month and 6-month endpoints on two treatment arms), but we allow the exact nature of these correlations to vary dependent on outcome [e. g. van Houwelingen *et al* 2002[51]]. We parameterise all the above correlations by multivariate normal distributions (on the log-odds scale).

Covariate "PCI-related time delay"

To model the measurement error in the covariate "PCI-related time delay", we model independently the delays associated with each treatment (time to needle/balloon) as measured in each trial, and calculate the value of the covariate by subtraction. For each treatment arm, the trial reports give a summary statistic (i.e. mean with standard error, or median with confidence interval), which we have interpreted to obtain a prior mean and variance under the assumption of normality. For those trials that do not report the variability in times to treatment,[26,28,37] we used the corresponding average values from the other trials. Because treatment effect in our model only depends on the "PCI-related time delay", i.e. the difference between the delays in the two arms of each trial, it is irrelevant whether a trial measures the time from occurrence of symptoms to reperfusion, or from randomisation to beginning of treatment as long as both arms of the trial are consistent, and assuming that there is no within-trial correlation.

Statistical Model

Table A1 shows the equations used in the analysis for each component of the model. Throughout, let j index the trials and i index the clinical endpoints. Also, let capital letters N, R stand for the 6-month endpoint data, and small letters n, r denote 1-month endpoint data from the trials, for the two arms $x = P,T$ (PCI or thrombolytics). Probabilities π are estimated on the log-odds scale. Baseline probability log-odds are denoted by μ. Random effects are modelled as additive on the log-odds scale, and the mean underlying probabilities shall be denoted by $\bar{\lambda}$. The log-odds differences between 1-month and 6-month probabilities are denoted by ω. Time delays, as measured in each trial arm, shall be written as δ, their means as $\bar{\delta}$, and the observed variance as v. The covariate "PCI-related time delay" is denoted by ∂, and the coefficients of the linear regression by α (intercept) and β (slope).

Wishart prior distributions were used for the covariance matrices, in which the degrees of freedom were set to the rank of the covariance matrix, whilst for means and regression parameters Normal or half-Normal prior distributions were assumed in which hyper-prior uniform distributions for the corresponding standard deviation were used.

Parameter Estimation

The parameters of the model were estimated using Markov Chain Monte Carlo (MCMC) methods as implemented in WinBUGS software 1.4.1.[49] Convergence was assessed via sensitivity analyses with respect to initial values, length of 'burn-in' and length of sample, using both visual inspection of trace plots, and by running multiple chains assessed by the Gelman-Rubin convergence statistic.[55] Final parameter estimates are based on a 'burn in' of 5,000 and a sample of 35,000 iterations.

Sensitivity analyses with respect to prior distributions, especially for the covariance matrices were also undertaken.

Table A1. The equations used in the analysis for each component of the model

Model component	Equations (for all i, j, x, where appropriate)
Trial data	$r_{i,j}^x \sim Bin\left(\pi_{i,j}^x, n_j^x\right)$ and $R_{i,j}^x \sim Bin\left(\Pi_{i,j}^x, N_j^x\right)$
Probabilities on logit scale	$\log\left(\pi_{i,j}^x \middle/ 1-\pi_{i,j}^x\right) = \lambda_{i,j}^x$ and $\log\left(\Pi_{i,j}^x \middle/ 1-\Pi_{i,j}^x\right) = \Lambda_{i,j}^x$
Correlated within-outcome errors	$\begin{pmatrix} \lambda_{i,j}^T \\ \lambda_{i,j}^P \\ \Lambda_{i,j}^T \\ \Lambda_{i,j}^P \end{pmatrix} \sim MVN\left(\begin{pmatrix} \overline{\lambda}_{i,j}^T \\ \overline{\lambda}_{i,j}^P \\ \overline{\Lambda}_{i,j}^T \\ \overline{\Lambda}_{i,j}^P \end{pmatrix}, X_i\right)$ where X_i is the between-time-point covariance matrix for the ith outcome and is assumed constant across trials.
Explain treatment effects	$\overline{\Lambda}_{i,j}^x = \overline{\lambda}_{i,j}^x + \omega_i^x$ to relate 1-month and 6-month outcomes, $\overline{\lambda}_{i,j}^P = \overline{\lambda}_{i,j}^T + \alpha_i + \beta_i \cdot \partial_j$ for the treatment effect
Random baselines	$\begin{pmatrix} \overline{\lambda}_{i=1,j}^T \\ \overline{\lambda}_{i=2,j}^T \\ \overline{\lambda}_{i=3,j}^T \end{pmatrix} \sim MVN\left(\begin{pmatrix} \mu_1 \\ \mu_2 \\ \mu_3 \end{pmatrix}, Y\right)$ where Y is the between-outcome covariance matrix for thrombolytic therapy and is assumed constant across trials.
time delay covariate	$\partial_j = \overline{\delta}_j^P - \overline{\delta}_j^T$
Measurement error in time delay	$\delta_j^x \sim N\left(\overline{\delta}_j^x, v_j^x\right)$

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