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Assessing the effectiveness of primary angioplasty compared with thrombolysis and its relationship to time delay: a Bayesian evidence synthesis

Christian Asseburg, Yolanda Bravo Vergel, Stephen Palmer, Elisabeth Fenwick, Mark de Belder, Keith R Abrams, Mark Sculpher

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Correspondence to: Dr M Sculpher, Centre for Health Economics, University of York, Heslington, York YO10 5DD, UK; mjs23@york.ac.uk

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Background: Meta-analyses of trials have shown greater benefits from angioplasty than thrombolysis after an acute myocardial infarction, but the time delay in initiating angioplasty needs to be considered.
Objective: To extend earlier meta-analyses by considering 1- and 6-month outcome data for both forms of reperfusion. To use Bayesian statistical methods to quantify the uncertainty associated with the estimated relationships.
Methods: A systematic review and meta-analysis published in 2003 was updated. 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 reported follow-up times and outcomes. Outcomes are presented as absolute probabilities of specific events and odds ratios (ORs; with 95% credible intervals (CrI)) as a function of the additional time delay associated with angioplasty.
Results: 22 studies were included in the meta-analysis, with 3760 and 3758 patients randomised to primary angioplasty and thrombolysis, respectively. The mean (SE) angioplasty-related time delay (over and above time to thrombolysis) was 54.3 (2.2) minutes. For this delay, mean event probabilities were lower for primary angioplasty for all outcomes. Mortality within 1 month was 4.5% after angioplasty and 6.4% after thrombolysis (OR = 0.68 (95% CrI 0.46 to 1.01)). For non-fatal reinfarction, OR = 0.32 (95% CrI 0.20 to 0.51); for non-fatal stroke OR = 0.24 (95% CrI 0.11 to 0.50). For all outcomes, the benefit of angioplasty decreased with longer delay from initiation.
Conclusions: The benefit of primary angioplasty, over thrombolysis, depends on the former's additional time delay. For delays of 30–90 minutes, angioplasty is superior for 1-month fatal and non-fatal outcomes. For delays of around 90 minutes thrombolysis may be the preferred option as assessed by 6-month mortality; there is considerable uncertainty for longer time delays.

In the UK, at least 87 000 people under the age of 75 years have 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 treatment for ST elevation MI (STEMI).

Meta-analyses of the various randomised trials comparing thrombolysis and primary angioplasty have shown substantial improvements in mortality, non-fatal reinfarction and stroke from the use of angioplasty[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 with 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 measure the uncertainty around this relationship, and the analysis was restricted to a subset 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 (reinfarctions and strokes) relates to the additional delay 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.

Abbreviations: AMI, acute myocardial infarction; CrI, credibility interval; OR, odds ratio; STEMI, ST elevation myocardial infarction

Table 1 Overview of trials, key end points and time to treatment for primary angioplasty (A) and thrombolysis (T)

	1 Month (4–6 weeks)								6 Months								Time (min)	
	No		Death		NF Reinf		NF Stroke		No		Death		NF Reinf		NF Stroke		Mean	Mean
Study	(A)	(T)	No (A)/(T)	OR (95% CrI)	No (A)/(T)	OR (95% CrI)	No (A)/(T)	OR (95% CrI)	(A)	(T)	No (A)/(T)	OR (95% CrI)	No (A)/(T)	OR (95% CrI)	No (A)/(T)	OR (95% CrI)	(A)	(T)
Zijlstra *et al* 1993[23]‡	70	72	0/4	0.1 (0 to 7.7)	0/9	0.1 (0.0 to 4.8)	0/2	0.2 (0.0 to 12.4)	–	–	–	–	–	–	–	–	61	30
Ribeiro *et al* 1993[24]‡	50	50	3/1	3.1 (0.2 to 16)	4/5	0.7 (0.2 to 3.5)	–	–	–	–	–	–	–	–	–	–	238	179
de Boer *et al* 1994[19]‡	152	149	3/11	0.3 (0.2 to 2)	2/15	0.1 (0.0 to 1.7)	1/2	0.4 (0.0 to 8.1)	–	–	–	–	–	–	–	–	195	176
Berrocal *et al* 2003[20]‡	54	58	5/6	0.9 (0.3 to 3.3)	1/2	0.5 (0.0 to 8.6)	–	–	–	–	–	–	–	–	–	–	82	15
Zijlstra *et al* 1997[25]‡	45	50	1/0	2.3 (0 to 43)	0/8	0.0 (0.0 to 5.2)	1/2	0.5 (0.0 to 8.7)	45	50	1/0	2.2 (0.0 to 43.4)	0/8	0.0 (0.0 to 5.2)	1/2	0.5 (0.0 to 8.7)	68	29
Widimsky *et al* 2000[26]‡	101	99	7/14	0.5 (0.3 to 1.8)	1/10	0.0 (0.0 to 2.7)	0/0	1 (0.0 to 50.4)	–	–	–	–	–	–	–	–	96	90
de Boer *et al* 2002[27]‡	46	41	3/8	0.3 (0.1 to 2.4)	1/6	0.1 (0.0 to 3.5)	1/2	0.4 (0.0 to 7.9)	–	–	–	–	–	–	–	–	59	31
Widimsky *et al* 2003[21]†‡	429	421	29/42	0.7 (0.5 to 1.4)	6/13	0.4 (0.2 to 1.8)	1/9	0.1 (0.0 to 3.0)	–	–	–	–	–	–	–	–	97	12
DeWood *et al* 1990[28]	46	44	3/2	1.5 (0.2 to 7.4)	–	–	–	–	–	–	–	–	–	–	–	–	126	84
Grines *et al* 1993[29]	195	200	5/13	0.4 (0.2 to 1.9)	5/13	0.3 (0.2 to 1.8)	0/3	0.1 (0.0 to 9.2)	188	190	7/15	0.4 (0.2 to 1.7)	–	–	–	–	60	32
Gibbons *et al* 1993[30]	47	56	2/2	1.2 (0.1 to 8)	–	–	–	–	47	56	3/2	1.8 (0.2 to 8.1)	0/2	0.2 (0.0 to 13.2)	–	–	277	232
Ribichini *et al* 1998[31]	55	55	1/3	0.3 (0.1 to 6.1)	1/2	0.4 (0.0 to 8.3)	0/0	1 (0.0 to 51.31)	55	55	1/4	0.2 (0.0 to 4.9)	2/2	1 (0.1 to 7.3)	–	–	53.2	36.5
Garcia *et al* 1999[32]	109	111	3/12	0.2 (0.1 to 1.9)	4/6	0.6 (0.2 to 3.0)	0/2	0.2 (0.0 to 12.3)	99	91	5/13	0.3 (0.2 to 1.7)	6/8	0.6 (0.2 to 2.5)	–	–	197	150
GUSTO IIb 1997[33]	565	573	32/40	0.8 (0.6 to 1.5)	25/37	0.6 (0.4 to 1.4)	1/5	0.2 (0.0 to 4.2)	565	573	–	–	–	–	–	–	228	180
Le May *et al* 2001[34]	62	61	3/2	1.5 (0.2 to 7.4)	3/5	0.5 (0.1 to 3.4)	1/1	1 (0.0 to 16.2)	62	61	3/2	1.5 (0.1 to 7.3)	4/10	0.3 (0.1 to 2.1)	1/3	0.3 (0.0 to 6.0)	77	15
Bonnefoy *et al* 2002[35]	421	419	20/16	1.3 (0.6 to 2.2)	7/15	0.4 (0.2 to 1.7)	0/4	0.1 (0.0 to 7.6)	–	–	–	–	–	–	–	–	190	130
Schomig *et al* 2000[36]	71	69	3/5	0.6 (0.2 to 3.4)	2/4	0.4 (0.1 to 4.0)	–	–	71	69	3/9	0.2 (0.1 to 2.2)	–	–	–	–	65	30
Vermeer *et al* 1999[37]†	75	75	5/5	1 (0.3 to 036)	1/7	0.1 (0.0 to 3.4)	2/1	2 (0.1 to 15.3)	–	–	–	–	–	–	–	–	85	10
Kastrati *et al* 2002[38]	81	81	2/5	0.4 (0.1 to 3.5)	0/4	0.1 (0.0 to 7.6)	1/1	1 (0.0 to 16.2)	70	71	5/7	0.7 (0.2 to 2.8)	–	–	–	–	75	35
Aversano *et al* 2002[39]	225	226	12/16	0.7 (0.4 to 1.9)	11/20	0.5 (0.3 to 1.6)	3/8	0.3 (0.1 to 2.4)	225	226	14/16	0.8 (0.4 to 1.9)	12/24	0.4 (0.3 to 1.4)	5/9	0.5 (0.2 to 2.3)	101.5	46
Grines *et al* 2002[40]	71	66	6/8	0.7 (0.3 to 2.6)	1/0	1.8 (0 to 39.7)	0/3	0.1 (0.0 to 8.9)	–	–	–	–	–	–	–	–	174	63
Andersen *et al* 2003: Referral[22]*	567	562	37/48	0.7 (0.6 to 1.4)	11/35	0.2 (0.2 to 1.1)	9/11	0.8 (0.3 to 2.2)	–	–	–	–	–	–	–	–	90	20
Andersen *et al* 2003: Invasive[22]*	223	220	15/13	1.1 (0.5 to 2.3)	2/14	0.1 (0.0 to 1.8)	0/5	0.0 (0.0 to 6.6)	–	–	–	–	–	–	–	–	63	20

Reinf, reinfarction; CrI, credibility interval.

*This trial consisted of two subtrials, labelled ''Referral'' and ''Invasive'', and these are analysed as if they are two separate studies.

†Includes a third group of patients who received thrombolytic treatment 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 tissue plasminogen activator.

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 the 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 (available at http://heart.bmj.com/supplemental).

Two researchers (YBV, CA) independently extracted the clinical data. Outcomes of interest were mortality, non-fatal reinfarctions, fatal and non-fatal strokes and haemorrhagic strokes, as well as any data about 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 treatment. 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 haemorrhagic strokes, these end points were excluded from the meta-analysis. Thus three outcomes (death, non-fatal strokes and non-fatal reinfarctions), 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—for example, the probability that one intervention is better than another.[13 14]

Full details of the statistical methods are presented in the technical report (http://heart.bmj.com/supplemental). Briefly, the meta-analysis models all outcomes of interest as probabilities on a log odds scale, and results are reported as the absolute probability of specific events and odds ratios (ORs; with 95% credible intervals (CrI)). It is assumed that baseline event rates (ie, 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 with 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 with thrombolysis, while 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 midpoint.

A feature of the evidence base is that some trials report outcomes at 1 month's 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 after an 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.

Table 2 Estimated absolute probabilities of the occurrence of various end points 1 month or 6 months after angioplasty or thrombolytic treatment, together with the odds ratios comparing primary angioplasty and thrombolysis and probabilities that angioplasty is superior

End points	Probability (angioplasty)* Mean (95%CrI)	Probability (thrombolytics)* Mean (95%CrI)	Odds ratio (95%CrI)	Probability angioplasty superior
At 1 month				
Death	4.5 (3.0 to 6.5)	6.4 (4.5 to 9.0)	0.68 (0.46 to 1.01)	0.97
Non-fatal reinfarction	2.0 (1.2 to 3.1)	6.1 (4.1 to 8.5)	0.32 (0.20 to 0.51)	1.00
Non-fatal stroke	0.5 (0.2 to 0.9)	1.9 (1.0 to 3.2)	0.24 (0.11 to 0.50)	1.00
At 6 months				
Death	5.5 (3.4 to 8.8)	7.7 (5.0 to 11.8)	0.70 (0.42 to 1.18)	0.93
Non-fatal reinfarction	2.6 (1.4 to 4.8)	6.9 (4.4 to 10.7)	0.33 (0.20 to 0.67)	0.99
Non-fatal stroke	0.8 (0.2 to 1.0)	2.8 (1.1 to 6.9)	0.26 (0.08 to 0.72)	0.99

*Results are given as percentages.
The results are for the average observed ''angioplasty-related time delay'' (ie, 54.3 minutes).

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

	Primary angioplasty-related time delay								
	30 Minutes			60 Minutes			90 Minutes		
End point	Probability difference* (95% CrI)	Odds ratio	Probability angioplasty is a better treatment	Probability difference* (95% CrI)	Odds ratio	Probability angioplasty is a better treatment	Probability difference* (95% CrI)	Odds ratio	Probability angioplasty is a better treatment
Death	−3.7 (−7.2 to −0.5)	0.54 (0.29 to 0.92)	0.98	−1.8 (−5.6 to +1.7)	0.77 (0.44 to 1.29)	0.87	+0.7 (−4.6 to +8.1)	1.15 (0.49 to 2.36)	0.44
Non-fatal reinfarction	−4.6 (−8.2 to −2.2)	0.30 (0.14 to 0.59)	0.99	−4.2 (−7.5 to −1.6)	0.39 (0.21 to 0.72)	0.97	−3.1 (−7.1 to +1.6)	0.55 (0.29 to 1.27)	0.93
Non-fatal stroke	−1.7 (−5.8 to −0.5)	0.47 (0.05 to 0.69)	0.99	−2.0 (−5.6 to −0.4)	0.56 (0.09 to 0.75)	0.98	−1.6 (−5.3 to +0.8)	0.79 (0.08 to 1.43)	0.93

*Results are shown as percentages.

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 thus 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 revascularisation without differentiating results by type of intervention (angioplasty 64%, surgery 36%), and hence this treatment strategy was 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 3760 and 3758 patients randomised to primary angioplasty and thrombolysis, respectively. Eight of the 22 trials used streptokinase as the form of thrombolysis, and 14 used tissue plasminogen activator. For angioplasty, 13/22 trials used coronary stents, and eight studies used glycoprotein IIb/IIIa antagonists. The mean (SE) value of angioplasty-related time delay (over and above time to thrombolysis) was 54.3 (2.2) minutes. 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; 10/22 trials also reported outcomes at 6 months' follow-up.

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 thrombolytic drugs. 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% after angioplasty and 6.4% after thrombolysis, with OR = 0.68 (95% CrI 0.46 to 1.01). For non-fatal reinfarction, OR = 0.32 (95% CrI 0.20 to 0.51); and for non-fatal stroke OR = 0.24 (95% CrI 0.11, 0.50). Table 2 also shows estimated results for the 6-month end points, which are similar to those at 1 month, indicating that most 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 treatment are shown in table 3. If angioplasty could be initiated within 30 minutes of possible thrombolysis, the absolute probabilities of mortality, non-fatal reinfarction 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.

Figure 1 shows this effect in more detail. For mortality, angioplasty is better than thrombolysis, on average, at time delays up to 90 minutes. Moreover, for 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 more than 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 might therefore be the preferred option at least for the 6-month mortality outcome. For non-fatal reinfarction 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 1 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.

DISCUSSION

The contribution of this review is twofold. First, it updates the most comprehensive recent meta-analysis of randomised trials comparing primary angioplasty and thrombolysis in patients with STEMI.[2] Second, 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 deal directly with 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% CI 0.58 to 0.85), which is similar to that reported here, although our estimate does not reach statistical significance. This lack of 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

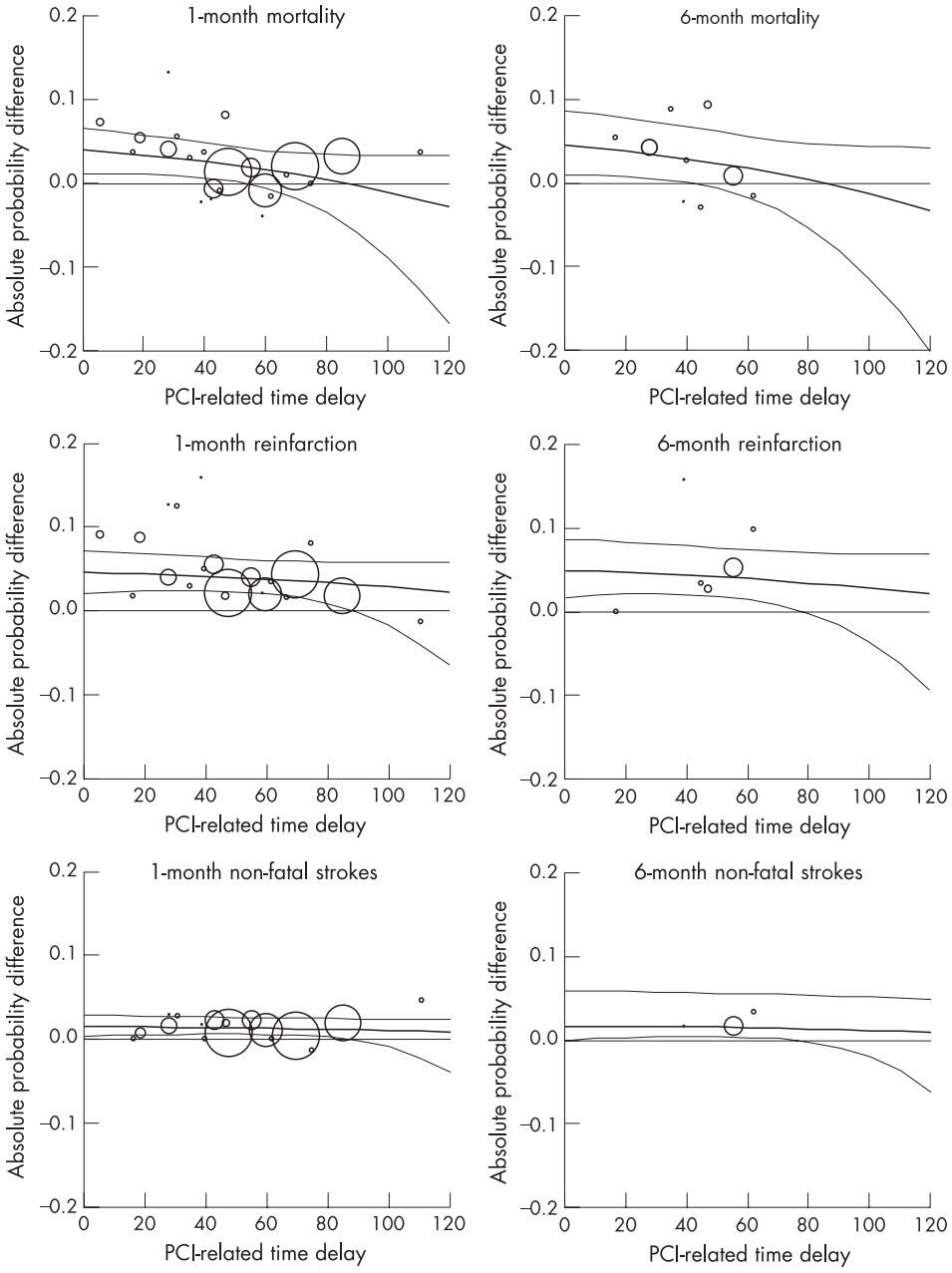

Figure 1 Treatment effect of primary angioplasty relative to thrombolytic treatment, shown as the absolute probability differences for each key outcome (death, non-fatal reinfarctions, non-fatal strokes) and point of follow-up (1 month, 6 months). The graphs show means and 95% credibility intervals plotted against the additional time delay to initiating primary angioplasty. Values above the 0.0 horizontal line indicate that angioplasty results in fewer clinical events. Each point represents a trial and their size is proportional to the trial sample size.

non-fatal reinfarction, the results here are similar to those of Keeley *et al*, for 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 with 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, reinfarction and stroke than 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 minutes 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 1 month were 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 1 month was higher in the study of Boersma *et al*: 2.6% versus 2%. As seen in previous studies,[8 42] the benefit of angioplasty for 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 (fig 1). The Bayesian approach also facilitates the

presentation of results as the probability of one intervention being the better 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 end points. Thus, a probability of the superiority of angioplasty measured by a 6-month mortality end point of greater than 0.95 can be identified for delays of up to around 45 minutes only, while for delays at around 90 minutes thrombolysis appears to be superior. However, angioplasty appears to be better for achieving 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 owing to the paucity of the data.

The analysis suggests, therefore, that angioplasty performs better than thrombolytic treatment, 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. First, the lack of individual patient data precludes an analysis of how the relative effect of angioplasty varies between patient subgroups, and although 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 a problem when it is recognised 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.[44] 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.[45 46]

Second, time-to-needle is a predictor of the success of thrombolytic treatment, but this effect could not be included in the analysis explicitly owing 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 by appropriate prior distributions taking account of relevance and quality.[15]

Third, given this review was an update of those published earlier, the effect of publication bias, study quality or the influence of individual studies on the overall meta-analysis results was not formally assessed.

Fourth, 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[47] for including these trials in their meta-analysis because by effectively averaging across the thrombolytic trials the additional benefit of angioplasty may have been overestimated. However, streptokinase is the most common form of thrombolytic treatment 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 tissue plasminogen activator trials are 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 to 1.16); for non-fatal reinfarction, 0.41 (95% CrI 0.23 to 0.71); and for non-fatal strokes, 0.23 (95% CrI 0.08 to 0.57). Full details of this sensitivity analysis are reported in the technical report (http://heart.bmj.com/supplemental).

The policy implications of this analysis should be seen in the context of the relevant healthcare 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 seems 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 for it to be considered worthwhile, given the major changes in service organisation necessary for its implementation? This question is considered directly in the cost-effectiveness analysis submitted as a companion paper, which examines whether the health benefits of primary angioplasty are sufficient to justify its additional cost.[44] 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 appropriate 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.[48]

Authors' affiliations
Christian Asseburg, Yolanda Bravo Vergel, Stephen Palmer, Mark Sculpher, Centre for Health Economics, University of York, UK
Elisabeth Fenwick, Public Health and Health Policy, Division of Community Based Sciences, University of Glasgow, UK

Mark de Belder, The James Cook University Hospital, Middlesbrough, UK
Keith R Abrams, Centre for Biostatistics and Genetic Epidemiology, Department of Health Sciences, University of Leicester, UK

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