Letter to the Editor

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Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction (PRAGUE-2 trial)

To the Editor

We read with interest the results of the PRAGUE-2 trial\(^1\) and its editorial.\(^2\) Widimsky et al. compared the effects of transport for primary percutaneous coronary angioplasty (PCI) and immediate thrombolysis (TL) for patients with acute myocardial infarction (AMI), in the randomized trial PRAGUE-2.\(^3\) The authors concluded that long distance transport from a community hospital to a tertiary PCI centre in patients with AMI is safe. The strategy markedly reduces the mortality in patients presenting >3 h after symptoms onset.

Some methodological issues may affect these conclusions. The primary outcome of the study was total death at 30 days. The analysis by intention to treat showed no significant reduction in death, 6.8% in PCI vs 10.0% in TL group (P=0.12). However the authors emphasize that per protocol analysis showed a significant reduction in death, 6.0% in PCI vs 10.4% in TL group (P<0.05). Per protocol analyses are prone to bias and are not recommended for reporting the primary outcome of the study. In addition they performed a post hoc subgroup analysis comparing patients randomized <3 h and >3 h after symptoms to avoid bias. Adequate analysis of the subgroup effect should be performed with an interaction test that was not reported in the paper. This small study of 850 patients may be not large enough to detect a moderate but clinically important reduction of total death by primary PCI. Similarly, the DANAMI-2 was a single small country study that showed a non-significant death reduction of 6.6% in PCI vs 7.6% in TL group (P=0.35).\(^4\) A formal meta-analysis published recently included 7739 AMI patients.\(^3\) The rate of death was 7% in primary PCI vs 9% in TL group (RR 0.73, 95% CI 0.62–0.86 P=0.001). This contrasts to the informal meta-analysis by Zijlstra in the editorial with data from 6478 patients. The rate of death was 5.5% in primary PCI vs 7.8% in TL group (RR 0.70, 95% CI 0.57–0.85 P<0.001). Zijlstra concluded that primary PCI for AMI patients should be applied widely in urban areas in Europe.

Meta-analysis of small RCTs are prone to publication bias because trials with positive results are more likely to be published than those with inconclusive results. A funnel plot is a graph of plots of the trials’ effect estimates against the sample size to assess the validity of meta-analysis. In the absence of publication bias the plot will resemble a symmetrical inverted funnel. A funnel plot analysis of the RCTs comparing primary PCI vs TL shows an asymmetric funnel suggesting publication bias (Fig. 1). We believe that definitive recommendations in clinical guidelines should rely on data from large RCTs because they provide a better estimation of the treatment effects. At the present time we believe that the aggregate data for the benefit of primary PCI over thrombolysis is small and promising but it would be helpful if more randomized data from large trials was available.

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**References**


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**Fig. 1** Funnel plot showing asymmetry of the funnel for relationship between odds ratios and sample size. Sixteen studies lie on the left of funnel and seven on the right, suggesting publication bias.\(^5\)

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\(^{a}\) Correspondence to: Dr A. K. Taneja, Clinical Trials and Evaluation Unit, Royal Brompton and Harefield NHS Trust, Sydney Street, London SW3 6NP, UK. Tel: +44 2073158827; Fax: +44 2073158829.

E-mail address: a.taneja@rbh.nthames.nhs.uk (A.K. Taneja).

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Dego Perez de Arenaza
Anil K. Taneja
Marcus Flather
Royal Brompton and Harefield Hospital
London
UK