NATIONAL TRAINING AND RESEARCH APPRAISAL GROUP

Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. Konstantinides et al. N Eng J Med 347, 1143-1150 (2002)

QUESTION	COMMENTS
1. (i) Was the assignment of subjects to treatments randomised? **(ii) Was the potential assignment concealed?**	i) Yes. Randomisation was done to create similar numbers on active and placebo by using a blocking device, stratified by centre. In each centre – and there were apparently 49 – for every six randomised, three would be on the active treatment and three on placebo. This should mean that when the study was stopped early the numbers on the two treatments should be similar. There was a difference of 20 which, given the numbers of centres, is probably reasonable. The study planned to recruit 434 patients in total – an average of about 9 patients per centre. It seems probably that some centres would recruit many more than that over the four plus years, which means that some centres will be contributing hardly any patients. That is not necessarily a problem but we have not been told of the breakdown of the different centres. ii) There is no information on concealed assignment – only that randomisation was done using a 'standard randomization protocol'. It seems there was great potential for the code to be revealed, especially as the size of the blocks was known.
2. Were all the subjects who entered the trial properly accounted for and attributed at its conclusion? (i) Was follow-up complete? (ii) Did the authors justify their choice of follow-up time?	i) Follow-up was at end of hospital stay or at 30 days, whichever was first. As this was an 'in-hospital' record of outcome it would be hoped that the outcome of all would be recorded. Figure 1 shows that one person was lost. This is not likely to influence the results in any way. ii) No, but 30 days seems reasonable as the active drug is designed to dissolve clots and one would expect that all clots not removed by drug action would have dissolved by normal body reactions. Figure 1 shows that the active drug appears to make the greatest difference only in the first 4 days. 30 days follow-up therefore seems appropriate for the primary end points, but probably not all of the secondary outputs
3. Were subjects, researchers and healthcare personnel 'blind' to the intervention or treatment?	One presumes so. There is mention of a 'matching' placebo and breaking a randomisation code.
4. (I) Were the subjects similar at the start of the trial? **(ii) Are here any**	i) Table 1 shows the similarities – all are similar apart from one ECG measurement. This could be chance but the p value is very low p= 0.002. This ECG change may influence outcome and is known prior to randomisation. This may offer the potential for pre

differences (e.g. in age, gender, health) likely to be important to the outcome (iii) Have the authors considered these?	trial selecting out of some patients ii) Table 3 shows that age and gender are important, but table 1 shows these are similar in the two groups iii) No need to adjust for these because the groups are similar
5. Aside from the intervention, were the subject groups treated equally?	Yes
6. Were data from the groups analysed according to randomisation? (i.e. "intention to treat" analysis	Yes – this is stated in the statistical analysis
7. Effect of intervention (i) What is the difference in measured outcome(s) between the groups? **(ii) How likely is this to be due to chance?**	i) 13.6% more patients experienced a primary end point on placebo (table 2), or expressed as an increased risk of 2.63 times more likely to experience a primary endpoint on placebo. There is a 13.6% lower incidence in the primary end point in patients on alteplase. ii) P = 0.006. One would expect a difference as great as the one seen here by chance alone on around 6 in 1000 times – very unlikely, therefore
8. (i) Is a confidence interval quoted for the intervention? **(ii) What does this imply?**	i) The confidence interval on the relative risk is 1.32 – 5.26. ii) This means that there is at least a 1.32 times increased risk of primary endpoint on placebo, and it could be as high as a 5.26 times increase in risk.
9. Were all the important outcomes considered? **Were potential harms as well as benefits reviewed?**	The primary endpoints of death or treatment escalation seem appropriate for the condition and relative length of the study. Secondary endpoints include consideration of potential downside of using thrombolytic therapy, such as a major haemorrhage
10. How relevant are the results of the study **(i) To various client groups?** **(ii) In different settings?**	The difference by adding alteplase is statistically significant, although the low end of the confidence interval is not that impressive, particularly as the methodology might be hiding bias. i) Note that the study is done in a highly defined group of patients with many exclusion criteria. The purpose of the refined group is to answer the question of whether thrombolysis should be extended to this particular subgroup. ii) Given the possible pre-existing bias, the non impressive effect

	size at the bottom of the confidence interval, and the acknowledgement that these patients are different that normal patients – because they have a significantly reduced mortality, regardless of treatment, and the fact that patients are in a trial with its inherent increased surveillance – this all suggests that this treatment may not translate to an increased benefit in the general population.
11. What is the NNT?	The NNT is 1/ARR (absolute risk reduction). 24.6% of patients experience the primary outcome on placebo, compared with 11% on alteplase – a 13.6% reduction. 1/136 = 7.35 – an NNT of 8. Treating 8 people with this condition with alteplase means that one less person will experience the primary outcome, in comparison with treating these people with a placebo
12. Does this paper justify the likely benefits as worth the potential harms and costs (if any)?	The research seems to be driven by the pharmaceutical company to increase use of thrombolytics. They have sacrified the usefulness of a pragmatic approach through considerable refining of the condition in order to demonstrate a 'theoretical' benefit. One of the authors is employed by Boehringer Ingelheim and they are involved in funding the study, providing statistical advice. Although the analysis was analysed independently, the authors had full access and participated in the analysis – is that independent? Until the benefits shown in this study are repeated in more typical patients, which show the sorts of outcomes expected of this diagnosis within the placebo group (8% mortality in comparison with 2.2% mortality), this proposed treatment benefit can only be considered as a possible hint that some benefit might be shown.