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Table A Thrombolytic and angioplasty treatment data (35 day mortality/ patients). Fourteen randomised controlled trials on thrombolytic treatments (Boland *et al,* 2003), and 22 RCTs comparing angioplasty to thrombolytic(Keeley *et al*, 2004): 35 day mortality / patient totals.

	SK	**t-PA**	**at-PA**	**SK+t-PA**	**r-PA**	**TNK**	**PCTA**
CI, 1993	9/130	6/123					
Cherng, 1992	5/63	2/59					
ECSG, 1985	3/65	3/64					
GISSI-2, 1990	887/10396	929/10372					
ISIS-3, 1992	1455/13780	1418/13746					
PAIMS, 1989	7/85	4/86					
TIMI-1, 1987	12/159	7/157					
White, 1989	10/135	5/135					
GUSTO-1, 1993	1472/20251		652/10396	723/10374			
KAMIT, 1991	4/107			6/109			
INJECT, 1995	285/3004				270/3006		
Zijlstra, 1993	11/149						2/152
Riberio, 1993	1/50						3/50
Grinfeld, 1996	8/58						5/54
Zijlstra, 1997	1/53						1/47
Akhras, 1997	4/45						0/42
Widimsky, 2000	14/99						7/101
De Boer, 2002	9/41						3/46
Widimsky, 2002	42/421						29/429
DeWood, 1990		2/44					3/46
Grines, 1993		13/200					5/195
Gibbons, 1993		2/56					2/47
GUSTO-3, 1997			356/4921		757/10138		
RAPID-2, 1996			13/155		7/169		
ASSENT-2, 1999			522/8488			523/8461	
Ribichini, 1996			3/55				1/55
Garcia, 1997			10/94				3/95
GUSTO-2, 1997			40/573				32/565
Le May, 2001			2/61				3/62
Bonnefoy, 2002			19/419				20/421
Schomig, 2000			5/69				3/71
Vermeer, 1999			5/75				5/75
Andersen, 2002			59/782				52/790
Kastrati, 2002			5/81				2/81
Aversano, 2002			16/226				12/225
Grines, 2002			8/66				6/71

SK- streptokinase; t-PA - tissue-plasminogen activator; at-PA – accelerated tissue-plasminogen activator; r-PA – reteplase; TNK – tenecteplase; PCTA - primary percutaneous transluminal coronary angioplasty.

Boland A., Dundar Y., Bagust A., Haycox A., Hill R., Mujica Mota R., Walley T., and Dickson R. Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation. *Health Technology Assessment* 2003;**7**:1-136.

Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;**361**:13-20.

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Mixed treatment comparisons: should they be more routine?

Web Extra Supplement

Statistical model

A previously published model [1 2] is presented in a more general form, to assist application to any mixed comparison evidence structure.

Assume that the seven treatments are labelled A,B,C,D,E,F,G, and that treatment A is the reference treatment for the meta-analysis - in this example Streptokinase. In each trial j we observe r_{jk} deaths on treatment k, in a sample of n_{jk}. We assume a binomial likelihood: $r_{jk} \sim \text{Bin}(p_{jk},n_{jk})$, where p_{jk} is mortality in trial j under treatment k. Our underlying model is:

$$\begin{aligned} \text{logit}(p_{jk}) &= \mu_{jb} && b=\text{A,B,C}\ldots \quad \text{if} \quad k = b \\ &\mu_{jb} + \delta_{jbk} && \text{if} \quad k \text{ alphabetically after } b \end{aligned}$$

μ_{jb} is the log odds of mortality on treatment b in trial j - a study-specific 'baseline' parameter, and δ_{jbk} is the trial-specific Log Odds Ratio of treatment k relative to treatment b. For example, if trial j compares treatments B and C, the B arm provides an estimate of $\text{logit}(p_{jB}) = \mu_{jB}$, while the C arm estimates $\text{logit}(p_{jC}) = \mu_{jB} + \delta_{jBC}$.

The trial-specific LORs are now drawn from a random-effects distribution: $\delta_{jbk} \sim N(d_{bk},\sigma_{bk}^2)$. To identify the means d_{bk} of these distributions, we take the six treatment effects of B, C, D, E, F, G relative to reference treatment A as our *basic* parameters. [3] These are given vague priors: $d_{AB}, d_{AC}, d_{AD}, d_{AE}, d_{AF}, d_{AG} \sim \text{N}(0,10000)$. The remaining 9 contrasts, *functional* parameters, can be expressed in terms of these basic parameters: $d_{BC} = d_{AC}-d_{AB}$; $d_{BD} = d_{AD}-d_{AB}$; $d_{CD} = d_{AD}-d_{AC}$; …. etc ….

The study effects are treated as unrelated nuisance parameters with vague priors: $\mu_{jb} \sim \text{N}(0,10000)$. Note that, with just two treatments A and B, the model is that typically proposed for Bayesian pair-wise meta-analysis. [4 5 6]

If $\sigma^2 = 0$ we obtain a fixed effects model. For random-effects, we make the assumption of *homogeneous variance*: $\sigma_{bk}^2 = \sigma^2$. A vague prior is provided for the common variance term, for example $\sigma \sim \text{Uniform}(0,2)$. Multi-arm trials on treatments A,B,C, for example, induce a covariance between δ_{jAB} and δ_{jAC}. Under homogeneous variance the covariance is $\sigma^2/2$ [1 2 7].

WinBUGS 1.4 Programmes for MTC analysis.

The fixed and random effects programmes on which this analysis was based can be downloaded from http://www.hsrc.ac.uk/Current_research/research_programmes/mpes.htm, where they appear as FE.odc and RE-3arm.odc respectively. Software to handle trials with more than 3 arms can also be found on this site. These programmes can be applied to any mixed treatment structure and only require the user to state the number of observations, studies and treatments in the data list. The programmes should only be used by those familiar with Bayesian methods and with WinBUGS 1.4 software [8]. The latter can be downloaded free of charge from http://www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml.

Data Structure

A declaration is required for the number of observations, N, number of studies, NS, and number of treatments, NT. For this dataset, there are 35 trials making pair-wise comparisons and one 3-arm trial:

list(N=73, NS=36, NT=7)

The data proper appear as vectors of length 73, set out in columns. Each row represents a single trial arm.

s[] indicates the study
t[] the treatment
r[] the numerator
n[] the denominator
b[] the comparator treatment (baseline) for that trial, such that b[i] ≤ t[i]
m[] takes the values 1,2 for 2-arm trials, 1,2,3 for 3-arm. This vector is only needed for random-effects models

The treatments are coded as follows:
1 = streptokinase
2 = tissue type plasminogen activator
3 = accelerated tissue type plasminogen activator
4 = streptokinase plus tissue type plasminogen activator
5 = reteplase
6 = tenecteplase
7 = percutaneous transluminal coronary angioplasty

s[]	t[]	r[]	n[]	b[]	m[]
1	1	1472	20251	1	1
1	3	652	10396	1	2
1	4	723	10374	1	3
2	1	9	130	1	1
2	2	6	123	1	2
3	1	5	63	1	1
3	2	2	59	1	2
4	1	3	65	1	1
4	2	3	64	1	2
5	1	887	10396	1	1
5	2	929	10372	1	2
6	1	1455	13780	1	1
6	2	1418	13746	1	2
7	1	7	85	1	1
7	2	4	86	1	2
8	1	12	159	1	1
8	2	7	157	1	2
9	1	10	135	1	1
9	2	5	135	1	2
10	1	4	107	1	1
10	4	6	109	1	2
11	1	285	3004	1	1
11	5	270	3006	1	2
12	1	11	149	1	1
12	7	2	152	1	2
13	1	1	50	1	1
13	7	3	50	1	2
14	1	8	58	1	1
14	7	5	54	1	2
15	1	1	53	1	1
15	7	1	47	1	2
16	1	4	45	1	1
16	7	0	42	1	2
17	1	14	99	1	1
17	7	7	101	1	2
18	1	9	41	1	1
18	7	3	46	1	2
19	1	42	421	1	1
19	7	29	429	1	2
20	2	2	44	2	1
20	7	3	46	2	2
21	2	13	200	2	1
21	7	5	195	2	2
22	2	2	56	2	1
22	7	2	47	2	2
23	3	3	55	3	1
23	7	1	55	3	2
24	3	10	94	3	1
24	7	3	95	3	2
25	3	40	573	3	1
25	7	32	565	3	2
26	3	2	61	3	1
26	7	3	62	3	2
27	3	16	419	3	1
27	7	20	421	3	2

```
28      3       5       69      3       1
28      7       3       71      3       2
29      3       5       75      3       1
29      7       5       75      3       2
30      3       59      782     3       1
30      7       52      790     3       2
31      3       5       81      3       1
31      7       2       81      3       2
32      3       16      226     3       1
32      7       12      225     3       2
33      3       8       66      3       1
33      7       6       71      3       2
34      3       522     8488    3       1
34      6       523     8461    3       2
35      3       356     4921    3       1
35      5       757     10138   3       2
36      3       13      155     3       1
36      5       7       169     3       2
END
```

Fixed effect model

```
model{

for(i in 1:N)  {   logit(p[s[i],t[i]])<-mu[s[i]]+ d[t[i]] - d[b[i]]                    # model
                   r[i]~dbin(p[s[i],t[i]],n[i])  }                                  #  binomial likelihood

for(j in 1:NS)  {   mu[j]~dnorm(0,.0001)}              # vague priors for 36 trial baselines

d[1]<-0
for (k in 2:NT)  {d[k] ~ dnorm(0,.001) }          # vague priors for 6 basic LOR parameters
```

Random-effects model including 3-arm trials

```
model{
sw[1] <- 0
for(i in 1:N)  {
      logit(p[i])<-mu[s[i]]+ delta[i]  * (1-equals(t[i],b[i]))                          #  model
      r[i]~dbin(p[i],n[i])                                                            #  binomial likelihood
       delta[i] ~ dnorm(md[i],taud[i])                                                # trial-specific LOR distributions
       taud[i] <- tau * (1 + equals(m[i],3) /3)                                       # precisions of LOR distributions
       md[i] <- d[t[i]] - d[b[i]]  +  equals(m[i],3) * sw[i]                          # means of LOR distributions
      }
for (i in 2:N)  {   sw[i] <- (delta[i-1] -  d[t[i-1]] + d[b[i-1]])/2}                # adjustment for 3-arm trials

for(j in 1:NS){ mu[j]~dnorm(0,.0001) }                                               # vague priors for 36 trial baselines

d[1]<-0
for (k in 2:NT)  {d[k] ~ dnorm(0,.0001) }                  # vague priors for 6 basic LOR parameters

sd~dunif(0,2)                                              #  vague prior for random-effects standard deviation
tau<-1/pow(sd,2)
}
```

1. *Additional code used in the analysis*

Some additional code has been be added to each program to :

1. Form a distribution for the log odds of mortality in the reference treatment, streptokinase, and add the LORs relative to streptokinase to this baseline to find the absolute efficacy T[k] of each treatment k, given that assumed baseline (Table 3). We have used the mean log odds of the mortality under streptokinase, averaged over the 19 trials in which it was used. Specific trials or cohort studies could equally well be used to define efficacy of the reference treatment.
2. Rank treatments in efficacy, and calculate the probability that each is best: best[] (Table 3).
3. Calculate all the pairwise odds ratios between the treatments in the MTC analysis: or[,] (Table 2),

```
# Absolute treatment effects based on the mean response to Treatment A over 19 trials
for (i in 1:N) {mu1[i] <- mu[s[i]] * equals(t[i],1)  }
for (k in 1:NT)   { logit(T[k])<- sum(mu1[])/19 +d[k] }


# Ranking and probability {treatment k is best}
for (k in 1:NT) { rk[k]<- rank(T[],k)
                  best[k]<-equals(rk[k],1)}

# All pairwise odds ratios
for (c in 1:(NT-1)) {  for (k in (c+1):NT)  { or[c,k] <- exp(d[k] - d[c] ) }}
```

Similar models for Mixed Treatment Comparisons can be programmed using non-Bayesian methods, for example in SAS, STATA, or S-PLUS software. Calculation of the probability that each treatment is best could then be achieved through bootstrap methods. [9]

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