PDG91 OUTLYING STUDIES CAN CHANGE RANKING OF TREATMENTS AND COMPARATIVE EFFICACY ESTIMATES IN NETWORK META-ANALYSIS : FROM A COMPARATIVE STUDY OF ANTIHYPERTENSIVE DRUGS

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Backgrounds and Objectives

Network meta-analysis (NMA) is an evidence synthesis method for simultaneous comparison of multiple treatments using direct and indirect evidence for all the treatment comparisons of interest. However, in many NMA, some studies have characteristics that are markedly different from others, and potentially are inappropriate to be included. In addition, the inclusion of these "outlying" studies might lead to biases and, yielding misleading conclusions. The purpose of this study is to illustrate the influence of these outlying studies in practices of NMA, using a real data example of NMA for antihypertensive drugs [1].

Methods

Illustrative antihypertensive drugs data: The NMA for antihypertensive drugs are shown in Table 1. There were 26 clinical trials (N=223,313) that compared 7 antihypertensive drugs (AB: α-blockers, ACE: ACE inhibitors, ARB: angiotensin II receptor blockers, BB: β-blockers, CCB: calcium channel blockers, CT: conventional treatment, diuretics) and placebo. The outcome was the incidence of heart failure (HF).

Statistical analysis: All data analysis was conducted by Stata Version 15.0. We conducted the NMA using the contrast-based, multivariate random-effect model [2,3]. We estimated the comparative odds ratios (OR) and 95% confidence intervals (CI) based on the multivariate model. Also, we estimated the probability of each treatment to take a particular rank and the surface under the cumulative ranking curves (SUCRA) using the parametric bootstrap method [4]. Further, we assessed the inconsistencies on the network of evidence using the Dias's side-splitting method [5]. Then, we conducted sensitivity analyses that excluded candidates of outlying studies that had been detected by the inconsistency test.

Table 1 Antihypertensive drugs dataset

References	Treatments 1	2	3	No. of patients 1	2	3	No. of incidence of HF 1	2	3
ABCD	ACE	CCB		235	235		5	6	
ALLHAT2000	AB	Diuretics		9067	15268		514	851	
ALLHAT2002	CCB	Diuretics	ACE	9048	9054	15255	2203	1256	1334
AMBP2	ACE	Diuretics		1044	3039		69	78	
ASCOT-BPLA	CCB	BB		5639	5618		738	820	
CAPPP	ACE	CT		5492	5493		75	66	
CONVINCE	CCB	CT		8179	8297		126	100	
E-COST	ARB	CT		1053	995		35	41	
FEVER	CCB	Placebo		4841	4870		18	27	
HOPE	ACE	Placebo		4645	4652		417	535	
HYVET	Diuretics	Placebo		1933	1912		22	57	
INSIGHT	CCB	Diuretics		3157	3164		26	12	
Jikei Heart Study	ARB	CT		1541	1540		19	36	
LIFE	ARB	BB		4605	4588		153	161	
NICS-EH	CCB	Diuretics		204	210		0	3	
NORDIL	CCB	Diuretics		5410	5471		63	53	
ONTARGET	ACE	ARB		8576	8542		514	537	
RENAAL	ARB	Placebo		751	762		89	127	
SHELL	CCB	Diuretics		942	940		23	19	
STOP-2	CCB	CT		2196	2213		186	177	
Syst-China	CCB	Placebo		1253	1141		4	8	
Syst-Eur	CCB	Placebo		2398	2297		37	49	
TRANSCEND	ARB	Placebo		2954	2972		134	129	
UKPDS	ACE	BB		400	358		12	9	
VALUE	ARB	CCB		7649	7596		354	400	
VHAS	CCB	Diuretics		707	707		2	0	

AB: α-blockers, ACE: ACE inhibitors, ARB: angiotensin II receptor blockers, BB: β-blockers, CCB: calcium channel blockers, CT: conventional treatment

Results

NMA of antihypertensive drugs: Figure 1 shows the network of eligible comparisons for NMA. Table 2 and Figure 2 show summaries of the results of NMA. According to our NMA, diuretics, ACE, ARB and CT were significantly efficacious in HF prevention, compared with placebo. In addition, diuretics was significantly more efficacious than all the other treatments. These results were consistent to the original arm-based Bayesian analysis of Sciarretta et al. (2011).

Ranking probability with SUCRA: Figure 3 summarizes the results of the treatment ranking based on the NMA results. These analyses have showed the ranking of the treatments was **diuretics-ACE-ARB-CT-CCB-BB-placebo-AB**.

Assessment of inconsistency: To assess the transitivity for the evidence on the network, we evaluated consistency between direct and indirect evidence for all possible treatment pairs by the side-splitting method [5]. As a result, we found a significantly inconsistent treatment pair, ARB vs. CT; the direct comparison OR estimate was 1.47 (95%CI: 1.021, 2.118), while the OR estimates for the indirect comparison was 0.92 (95%CI: 0.741, 1.135). The direct estimate indicated ARB was significantly more efficacious than CT, but the indirect estimate implied their treatment effects were not so different. The P-value of the test of inconsistency was 0.029 (Figure 4). On the other hand, we also evaluated inconsistencies using local [6] and global inconsistency [7] tests, but these tests could not find any significant inconsistencies that need to be considered for the impact on NMA (data not shown).

Sensitivity analysis: Finally, we conducted a sensitivity analysis, excluding three trials that involved ARB vs. CT (VALUE, E-COST, Jikei Heart Study) to assess how these studies affect the overall results. As shown in Table 3 and Figures 6, the comparative OR estimates and overall treatment rankings were markedly changed from the original analysis. First, the efficacy estimates of ARB got smaller, and that of ACE got larger. Second, CCB vs. placebo in the original analysis was not significantly different (OR 0.86, 95%CI 0.72, 1.04; P=0.113), but here there was significantly different (OR 0.81, 95%CI 0.65, 1.00; P=0.047); because the heterogeneity variance got smaller by excluding the three trials. In addition, the ranking of treatments also has been materially changed; the ranking was **diuretics-CT-ACE-CCB-ARB-BB-placebo-AB** (Figure 7). Further, by re-evaluating inconsistencies on the network, there were clearly no significant inconsistent pairs on the network. (Figure 8).

Discussion and Conclusion

As shown in the illustrative analyses, outlying studies possibly have influences to the overall conclusions of network meta-analyses. The significant inconsistent pair, ARB vs. CT, involved the Jikei Heart Study that was withdrawn by the misconduct, and the treatment effect of ARB would be overly estimated. The evidence obtained from network meta-analyses has been widely used for public health, clinical practices, health technology assessments, and policy making, thus they should be carefully evaluated in practices.

Analysis for original data

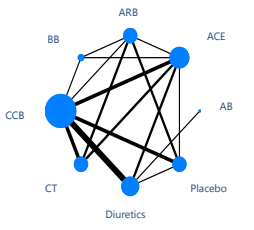

Figure 1 Network plot of the NMA of 26 clinical trials
The size of the treatment node (circle) is weighted by the number of patients, while the width of each is related to the number of studies.

Table 2 League table representing summary estimates from NMA

AB	**0.60 (0.46,0.78)**	**0.63 (0.48,0.84)**	0.73 (0.53,1.01)	**0.65 (0.48,0.86)**	**0.64 (0.46,0.88)**	**0.51 (0.41,0.63)**	0.81 (0.60,1.10)
1.67 (1.29,2.16)	ACE	1.06 (0.91,1.21)	1.22 (0.98,1.51)	**1.17 (1.04,1.32)**	1.08 (0.92,1.26)	**0.85 (0.73,0.98)**	**1.36 (1.14,1.61)**
1.58 (1.19,2.08)	0.95 (0.83,1.08)	ARB	1.15 (0.94,1.41)	1.10 (0.97,1.26)	1.02 (0.86,1.21)	**0.80 (0.67,0.96)**	**1.28 (1.07,1.53)**
1.37 (0.99,1.89)	0.82 (0.66,1.02)	0.87 (0.71,1.06)	BB	0.96 (0.78,1.18)	0.88 (0.69,1.13)	**0.70 (0.54,0.89)**	1.11 (0.86,1.45)
1.43 (1.10,1.85)	0.86 (0.76,0.97)	0.91 (0.79,1.03)	1.04 (0.85,1.28)	CCB	0.92 (0.79,1.07)	**0.73 (0.62,0.85)**	1.16 (0.97,1.40)
1.55 (1.16,2.07)	0.93 (0.79,1.09)	0.98 (0.83,1.17)	1.13 (0.89,1.44)	1.08 (0.93,1.26)	CT	**0.79 (0.64,0.96)**	**1.26 (1.02,1.55)**
1.97 (1.60,2.43)	**1.18 (1.02,1.37)**	**1.25 (1.04,1.50)**	**1.44 (1.13,1.84)**	**1.38 (1.18,1.61)**	**1.27 (1.04,1.56)**	DIU	**1.60 (1.28,1.99)**
1.23 (0.91,1.67)	**0.74 (0.62,0.88)**	**0.78 (0.65,0.93)**	0.90 (0.69,1.17)	0.86 (0.72,1.04)	**0.79 (0.64,0.98)**	**0.62 (0.50,0.78)**	PLA

■Comparison ■Efficacy (mean with 95%CI) for the incidence of HF
The result of bold meant it had statistically significant.
DIU: diuretics, PLA: placebo

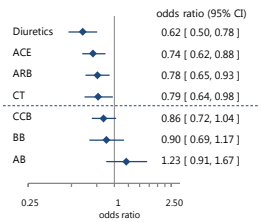

Figure 2 Forest plot of NMA with placebo considered as a referent treatment
Dotted lines indicate statistically significant intervention boundaries.

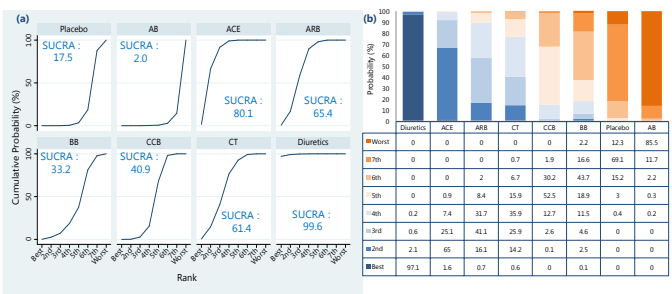

Figure 3 Results of ranking analysis
(a) Cumulative ranking probabilities for each treatment with SUCRA* (b) Probability ranking plots of each treatment
*SUCRA : the surface under the cumulative ranking curve value

	Study	Direct OR [95% CI]*	Indirect OR [95% CI]	*P*-value**
AB	vs. Diuretics	0.508 [0.412, 0.627]	[Not detected]	1.000
ACE	vs. ARB	1.049 [0.804, 1.368]	1.060 [0.862, 1.305]	0.950
ACE	vs. BB	0.838 [0.351, 1.999]	1.249 [0.995, 1.567]	0.384
ACE	vs. CCB	1.192 [0.983, 1.446]	1.135 [0.916, 1.408]	0.741
ACE	vs. CT	1.059 [0.828, 1.356]	1.106 [0.840, 1.457]	0.822
ACE	vs. Diuretics	0.917 [0.740, 1.136]	0.668 [0.468, 0.954]	0.148
ACE	vs. Placebo	1.281 [0.991, 1.656]	1.460 [1.144, 1.864]	0.469
ARB	vs. BB	1.056 [0.811, 1.376]	1.280 [0.950, 1.726]	0.344
ARB	vs. CCB	1.138 [0.870, 1.487]	1.087 [0.894, 1.321]	0.786
ARB	vs. CT	1.471 [1.021, 2.118]	0.917 [0.741, 1.135]	0.029
ARB	vs. Placebo	1.153 [0.906, 1.466]	1.515 [1.107, 2.073]	0.173
BB	vs. CCB	0.841 [0.616, 1.094]	1.099 [0.829, 1.456]	0.174
CCB	vs. CT	0.863 [0.713, 1.046]	1.083 [0.802, 1.462]	0.114
CCB	vs. Diuretics	0.715 [0.576, 0.887]	0.742 [0.533, 1.034]	0.853
CCB	vs. Placebo	1.469 [1.046, 2.006]	1.089 [0.937, 1.265]	0.218
Diuretics	vs. Placebo	2.600 [1.608, 4.267]	1.494 [1.314, 1.698]	0.029

Forest plot
0.25 1 2.50
odds ratio

Figure 4 Results of the side-splitting method to assess inconsistency
In the side-splitting plot ■ is the result of direct comparison, and
◆ is the result of direct comparison of indirect.
The red column indicates that there is statistically significant, i.e. the inconsistency. *CI : Confidence interval

Sensitivity analysis : excluding three trials (E-COST, Jikei Heart Study, VALUE)

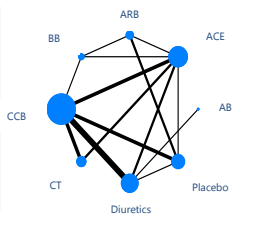

Figure 5 Network plot of the NMA of 23 clinical trials

Table 3 League table representing summary estimates from NMA

AB	**0.61 (0.45,0.81)**	**0.70 (0.50,0.97)**	0.76 (0.53,1.08)	**0.69 (0.51,0.93)**	**0.60 (0.43,0.83)**	**0.51 (0.40,0.64)**	0.85 (0.61,1.19)
1.65 (1.23,2.21)	ACE	1.15 (0.96,1.37)	1.25 (0.98,1.58)	1.14 (0.99,1.31)	0.99 (0.82,1.19)	**0.84 (0.71,0.99)**	**1.41 (1.17,1.69)**
1.44 (1.03,2.01)	0.87 (0.73,1.05)	ARB	1.09 (0.86,1.38)	0.99 (0.81,1.22)	0.86 (0.67,1.11)	**0.73 (0.58,0.93)**	**1.23 (1.03,1.46)**
1.32 (0.92,1.89)	0.80 (0.63,1.02)	0.92 (0.73,1.16)	BB	0.91 (0.72,1.15)	0.79 (0.60,1.05)	**0.67 (0.51,0.88)**	1.13 (0.86,1.47)
1.45 (1.08,1.95)	0.88 (0.76,1.01)	1.01 (0.82,1.24)	1.10 (0.87,1.38)	CCB	0.87 (0.73,1.03)	**0.74 (0.62,0.88)**	**1.24 (1.00,1.53)**
1.66 (1.20,2.31)	1.01 (0.84,1.22)	1.16 (0.90,1.49)	1.26 (0.96,1.66)	1.15 (0.97,1.36)	CT	0.84 (0.67,1.06)	**1.42 (1.10,1.84)**
1.97 (1.55,2.50)	**1.20 (1.01,1.41)**	**1.37 (1.08,1.73)**	**1.49 (1.14,1.95)**	**1.36 (1.14,1.61)**	1.18 (0.94,1.48)	DIU	**1.68 (1.33,2.13)**
1.17 (0.84,1.64)	**0.71 (0.59,0.86)**	**0.81 (0.68,0.97)**	0.89 (0.68,1.16)	**0.81 (0.65,1.00)**	**0.70 (0.54,0.91)**	**0.60 (0.47,0.75)**	PLA

■Comparison ■Efficacy (mean with 95%CI) for the incidence of HF
The result of bold meant it had statistically significant.
DIU: diuretics, PLA: placebo
The red column indicates that there is a change in statistical significance compared to the original analysis

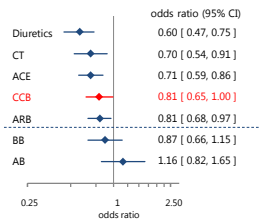

Figure 6 Forest plot of NMA with placebo considered as a referent treatment
Dotted lines indicate statistically significant intervention boundaries.
Red have changed significantly compared to the original data.

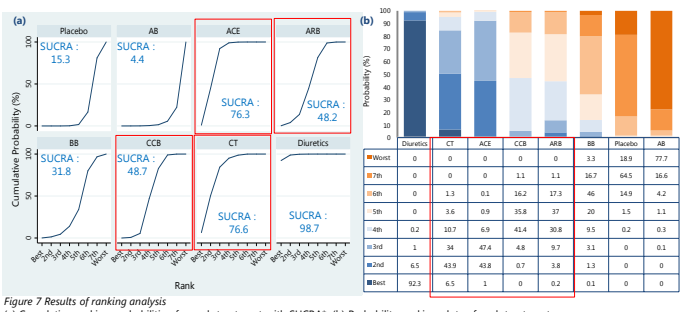

Figure 7 Results of ranking analysis
(a) Cumulative ranking probabilities for each treatment with SUCRA* (b) Probability ranking plots of each treatment
The red column indicates that there is a change in statistical significance compared to the original analysis
*SUCRA : the surface under the cumulative ranking curve value

	Study	Direct OR [95% CI]*	Indirect OR [95% CI]	*P*-value**
AB	vs. Diuretics	0.510 [0.400, 0.645]	0.000[Not detected]	1.000
ACE	vs. ARB	1.049 [0.818, 1.344]	1.272 [0.975, 1.660]	0.299
ACE	vs. BB	0.838 [0.349, 2.015]	1.288 [1.001, 1.656]	0.356
ACE	vs. CCB	1.190 [0.991, 1.485]	1.048 [0.826, 1.332]	0.410
ACE	vs. CT	1.065 [0.833, 1.362]	1.121 [0.841, 1.495]	0.321
ACE	vs. Diuretics	0.913 [0.744, 1.121]	0.641 [0.453, 0.906]	0.091
ACE	vs. Placebo	1.281 [0.986, 1.664]	1.553 [1.201, 2.008]	0.303
ARB	vs. BB	1.056 [0.773, 1.443]	1.123 [0.751, 1.681]	0.812
ARB	vs. Placebo	1.153 [0.906, 1.467]	1.375 [0.995, 1.898]	0.390
BB	vs. CCB	0.841 [0.617, 1.145]	1.011[0.708, 1443]	0.444
CCB	vs. CT	0.862 [0.704, 1.054]	0.904[0.603, 1.357]	0.238
CCB	vs. Diuretics	0.715 [0.574, 0.889]	0.795 [0.559, 1.130]	0.834
CCB	vs. Placebo	1.480 [1.040, 2.106]	1.105 [0.921, 1.325]	0.613
Diuretics	vs. Placebo	2.619 [1.573, 4.361]	1.531 [1.254, 1.869]	0.055

Forest plot
0.25 1 2.50
odds ratio

Figure 8 Results of the side-splitting method to assess inconsistency
In the side-splitting plot ■ is the result of direct comparison, and
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References
1 Sciarretta, S., Palano, F., Tocci, G., Baldini, R., and Volpe, M. (2011). Antihypertensive treatment and development of heart failure in hypertension: a Bayesian network meta-analysis of studies in patients with hypertension and high cardiovascular risk. Archives of internal medicine 171, 384-394.
2 White, I. R. (2011). Multivariate random-effects meta-regression: Updates to mvmeta. The Stata Journal 11, 255-270.
3 White, I. R., Barrett, J. K., Jackson, D., and Higgins, J. P. (2012). Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Research Synthesis Methods 3, 111-125.
4 Salanti, G., Ades, A. E., and Ioannidis, J. P. (2011). Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of Clinical Epidemiology 64, 163-171.
5 Dias, S., Welton, N. J., Caldwell, D. M., and Ades, A. E. (2010). Checking consistency in mixed treatment comparison meta-analysis. Statistics in Medicine 29, 932-944.
6 Chaimani, A., Higgins, J. P., Mavridis, D., Spyridonos, P., and Salanti, G. (2013). Graphical tools for network meta-analysis in STATA. PLoS One 8, e76654.
7 Higgins, J. P., Jackson, D., Barrett, J. K., Lu, G., Ades, A. E., and White, I. R. (2012). Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Research Synthesis Methods 3, 98-110.