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REVIEW PAPER

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Comparative efficacy of different types of antihypertensive drugs in reversing left ventricular hypertrophy as determined with echocardiography in hypertensive patients: A network meta-analysis of randomized controlled trials

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Abstract

Reversing left ventricular hypertrophy (LVH) can reduce the incidence of adverse cardiovascular events. However, there is no clear superiority–inferiority differentiation between angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers (BB), calcium channel blockers (CCB), and diuretics in reversing LVH in hypertensive patients. To provide further evidence for choosing the optimal antihypertensive drug for improving LVH, we performed a network meta-analysis of randomized controlled trials (RCTs) based on the Cochrane library database, Embase, and Pubmed, and identified 49 studies involving 5402 patients that were eligible for inclusion. It was found that ARB could improve LVH in hypertensive patients more effectively than CCB (MD −4.07, 95%CI −8.03 to −0.24) and BB (MD −4.57, 95%CI −8.07 to −1.12). Matched comparison of renin-angiotensin system inhibitors (RASi) showed that the effect of ACEI in reducing left ventricular mass index (LVMi) was not effective as that of ARB (MD −3.72, 95%CI −7.52 to −0.11). The surface under the cumulative ranking for each intervention indicated that the use of ARB was more effective among the different types of antihypertensive drugs (97%). This network meta-analysis revealed that the use of ARB in antihypertensive therapy could achieve better efficacy in reversing LVH in hypertensive patients.

1 | INTRODUCTION

Hypertension is a major risk factor for cardiovascular disease (CVD) and is significantly associated with increased morbidity and mortality from CVD.[1,2] Left ventricular hypertrophy (LVH) is a common target organ damage of hypertension, which can cause abnormal changes in the ultrastructure and energy metabolism of cardiomyocytes, resulting in adverse cardiovascular events such as abnormal cardiac contraction and diastolic function, and arrhythmia.[3-5] The left ventricular mass index (LVMi), which reflects LVH, plays an important role in predicting the risk of adverse cardiovascular events in the future.[6,7]

The European Society of Cardiology (ESC)/ European Society of Hypertension (ESH) 2018 Guidelines for Hypertension Diagnosis and Treatment indicate that antihypertensive therapy reverses LVH as represented by a reduction of CV events and mortality.[8,9] On the basis of preliminary clinical studies, the American expert consensus on hypertension points out that angiotensin receptor blockers (ARB)

The contributions of Jian-Shu Chen and Ying Pei in this study are consistent.

or angiotensin-converting enzyme inhibitors (ACEI) are generally used in hypertensive patients with LVH.[10]

Many current clinical studies have shown that there has been controversy over whether patients with hypertension can reverse LVH and the pros and cons of reversing LVH after treatment with antihypertensive drugs.[11,12] This also brings great confusion to clinical decision makers in the treatment of hypertensive LVH which antihypertensive drugs can obtain the maximum benefit. In addition, single randomized controlled trials or traditional meta-analysis cannot provide strong evidence support. At the same time, the lack of direct comparison between different antihypertensive drugs cannot evaluate the superiority–inferiority differentiation of different antihypertensive drugs in reversing LVH. The purpose of this network meta-analysis was to compare the efficacy of different types of antihypertensive drugs in reversing LVH in hypertensive patients.

2 | MATERIALS AND METHODS

2.1 | Search strategy for identifying eligible studies

We searched PubMed, Cochrane Library, and EMBASE databases up to May 2020 for evaluating the effects of different types of antihypertensive drugs on LVH in hypertensive patients by using the following search terms: (a) hypertension; (b) LVH; and (c) each class of antihypertensive drugs. We identify the grey literature by retrieving relevant institutions and clinical trial registries. All analyses were based on previously published studies and therefore did not require ethical approval and patient consent. The detailed search strategies are displayed in Figure 1.

2.2 | Eligibility criteria

Studies meeting the following criteria were considered for inclusion: (a) comparisons of six classes of antihypertensive drugs were performed and did not include any other non-drug treatment modality; (b) the shortest follow-up time was 3 months; (c) randomized controlled studies; and (d) LVMI was evaluated by echocardiography. Studies that did not meet these requirements were excluded.

2.3 | Data extraction

Two researchers independently screened the literature, extracted and cross-checked the data. Any disagreement was resolved through discussion or judgment by a third party. Data extraction follows objective principles and faithful original data. We reported details of study design, participants, intervention, follow-up time, age, baseline systolic and diastolic blood pressure.

2.4 | Statistical analysis

Stata SE-64 and GeMTC-GUI-0.14.3 were used for statistical analysis. Continuous variables were analyzed using the mean difference (MD) with 95% CI. The significance level was set to 0.05.

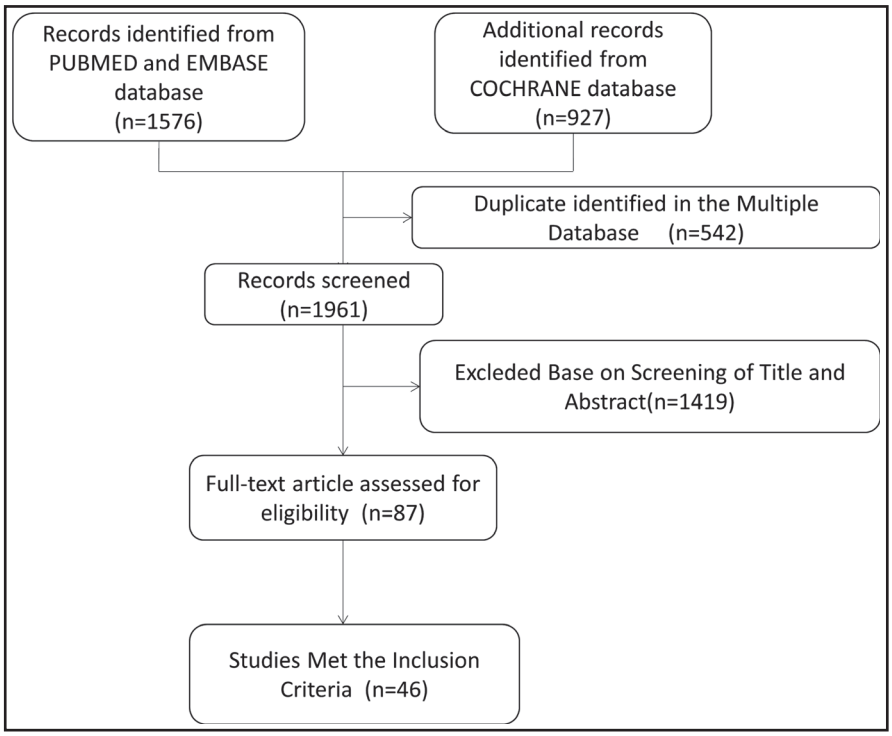

FIGURE 1 Flow diagram showing the study selection process

TABLE 1 Characteristics of the studies included in this Meta-analysis

Study (author, year)	Treatment class	Sample size	Mean age	LVMI (baseline)	SBP (mmHg)	DBP (mmHg)	Durations(months)
Futoshi 2005[13]	ARB/ACEI	10/11	59/59	151 ± 16/149 ± 16	157/156	97/97	10
Azizi 2014[14]	DIU/ACEI	46/40	56/55	97 ± 17/98 ± 27	150/150	90/90	3
Bilge 2005[15]	CCB/ACEI	14/13	46/49	122 ± 26/118 ± 23	151/161	101/103	6
Fogari 2005[16]	CCB/ACEI	60/61	61/60	116 ± 16/115 ± 15	148/148	89/90	24
Grandi 2008[17]	ARB/CCB	12/12	49/51	115 ± 19/146 ± 18	146/144	95/93	6
Neutel 2004[18]	CCB/ACEI	35/34	51/51	NA	156/160	93/91	6
Ogunyankin 2009[19]	CCB/DIU	18/20	54/55	NA	144/143	91/91	6
Okura 2013[20]	DIU/CCB	28/25	61/63	137 ± 34/146 ± 44	156/160	90/91	12
Scaglione 2007[21]	ARB/ACEI	19/19	56/56	47 ± 14/49 ± 10	162/159	94/98	6
Dahlof 2005[51]	DIU/ACEI	284/272	55/56	144 ± 30/143 ± 28	164/165	99/99	6
Fountoulaki 2005[47]	BB/ARB	20/20	54/56	98 ± 16/97 ± 13	156/153	99/98	3
Galzerano 2005[46]	ARB/BB	36/34	59/60	140 ± 13/135 ± 16	160/158	98/96	11
Agabiti 2005[38]	BB/CCB	78/96	53/53	106 ± 23/104 ± 28	160/161	100/101	6
Schneider 2004[48]	ARB/BB	119/121	54/55	117 ± 27/119 ± 26	160/161	94/93	18
Richard 2004[40]	ARB/BB	457/459	NA	NA	NA	NA	12
Koldas 2003[45]	ACEI/CCB	20/20	60/59	202 ± 62/203 ± 56	173/180	99/95	3
Sakata 2003[39]	CCB/ACEI	30/30	NA	121 ± 32/127 ± 20	NA	NA	12
Dahlof 2002[49]	ARB/BB	115/110	57/57	149 ± 30/146 ± 31	165/169	98/99	9
Gaudio 2003[44]	ARB/CCB	30/30	50/53	141 ± 14/136 ± 17	168/168	107/108	6
Cuspidi 2002[42]	ARB/ACEI	91/105	53/53	141 ± 24/143 ± 28	163/162	102/101	12
Yoshida 2011[50]	CCB/ARB	22/22	57/57	102 ± 15/102 ± 17	162/159	NA	12
Richard 2001[36]	ACEI/CCB	148/155	64/63	131 ± 25/133 ± 25	172/171	98/98	12
Malmqvist 2001[57]	ACEI/BB	25/26	50/51	113 ± 23/116 ± 19	159/158	103/101	12
Kuperstein 2000[56]	ACEI/BB	10/11	NA	98 ± 9/101 ± 11	148/149	97/98	6
Nalbantgil 2000[43]	ARB/ACEI	20/20	54/53	162 ± 22/165 ± 24	166/165	101/100	6
Philippe 2000[41]	DIU/ACEI	206/206	55/54	144 ± 40/138 ± 36	172/172	101/102	12
Willem 2001[37]	CCB/ACEI	81/81	67/67	109 ± 20/114 ± 23	175/175	92/93	24
Sihm 2000[32]	CCB/ACEI/DIU	12/11/14	47/50/48	182 ± 52/152 ± 26	168/153/153	108/101/103	12
Martina 1999[25]	ARB/CCB	11/11	47/51	NA	154/145	102/100	4
Agabiti 1998[23]	CCB/DIU	15/17	50/56	142 ± 25/142 ± 26	156/159	102/102	6
Thurmann 1998[24]	ARB/BB	34/35	55/57	127 ± 23/127 ± 25	NA	NA	8
Hoglund 1998[27]	CCB/BB	33/33	52/53	117 ± 12/123 ± 18	163/163	104/103	6
Topouchian 1999[28]	CCB/ACEI	23/23	NA	52 ± 11/52 ± 11	156/160	96/101	3
Radevski 1999[29]	CCB/ACEI	47/48	53/43	146 ± 40/139 ± 36	179/181	118/117	4
Tedesco 1998[31]	ARB/DIU	44/33	54/56	139 ± 19/140 ± 23	157/158	96/97	6

(Continues)

TABLE 1 (Continued)

Study (author, year)	Treatment class	Sample size	Mean age	LVMI (baseline)	SBP (mmHg)	DBP (mmHg)	Durations(months)
Athanasios 1998[35]	CCB/ACEI	15/15	NA	140 ± 15/139 ± 15	NA	NA	6
Roman 1998[33]	ACEI/DIU	22/28	52/51	134 ± 20/93 ± 19	153/146	96/93	6
Scognamiglio 1997[22]	ACEI/CCB	36/37	58/57	87 ± 2/89 ± 2	165/167	100/101	9
Papademetriou 1997[34]	CCB/DIU	89/45	56/58	170 ± 36/165 ± 36	158/161	101/101	6
Yang 1995[58]	ACEI/CCB	26/27	48/49	162 ± 10/165 ± 12	162/160	105/102	12
Kirpizidis 1995[26]	ACEI/CCB	16/15	59/61	146 ± 17/146 ± 14	NA	102/103	6
Ernesto 1994[55]	BB/ACEI	8/9	NA	110 ± 6/125 ± 12	148/147	99/99	12
Trenkwalder 1994[30]	CCB/DIU	21/21	NA	138 ± 25/134 ± 21	194/195	102/101	3
Senior 1993[52]	DIU/CCB/ ACEI/ BB	23/22/11/20	56/60/49/59	151 ± 6/170 ± 7/142 ± 7/157 ± 8	167/168/ 172/166	102/103/ 106/102	6
Ranieri 1993[53]	BB/DIU	20/20	NA	113 ± 12/114 ± 15	165/162	106/106	6
Schulte 1992[54]	CCB/ACEI	20/20	NA	141 ± 6/148 ± 5	157/149	106/104	6

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blockers; CCB, calcium channel blocker; DIU, diuretic; LVMI, left ventricular mass index; NA, not available.

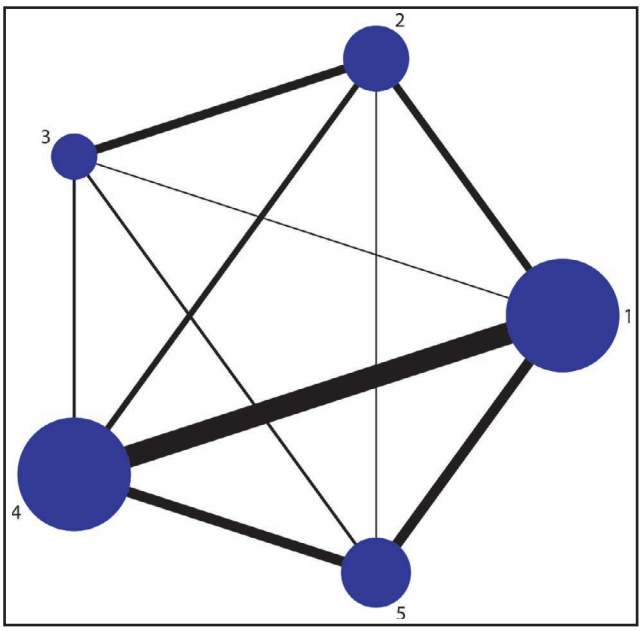

FIGURE 2 the construction of the network

A chi-square test was used to judge the heterogeneity between the results of each study (the test level was $\alpha = 0.10$). The specific steps are as follows:(a) if there was no statistical heterogeneity between the studies or the heterogeneity was small ($I^2 < 50\%$, $P > .1$), the fixed effect model was used for analysis; (b) if the heterogeneity was large($I^2 > 50\%$, $P < .1$), the heterogeneity source would be further determined by sensitivity analysis. Bayesian statistical method was used for network meta-analysis. We used the Markov Chains Monte Carlo methods to perform 20 000 tuning iterations and 5000 simulation iterations with 3 Markov chains. The convergence degree of the model was ensured according to the results of orbit diagrams and density diagram. We performed the node-splitting model to check whether the analysis of the trials in the network was indeed consistent. In addition, when the 95% CI of the median of the inconsistency factors included zero and if the inconsistency standard deviation was less than or equal to the random-effects standard deviation, the inconsistency was considered insignificant. According to the surface under the cumulative ranking, we evaluated the superiority–inferiority of multiple antihypertensive drugs in reversing LVH.

3 | RESULTS

3.1 | Study characteristics

Overall, the systematic review and network meta-analysis included 46 clinical studies involving 5074 hypertensive patients.[13-58] The follow-up time ranged from 3 months to 24 months with a mean of 7 months. The mean age of the participants was 55 (46- 67) years, and 61% of the patients were male. The mean baseline systolic blood pressure was 161 (143-180) mmHg. In these RCTs, 1332 patients (26.25%) were assigned to ACEI; 1040 (20.50%) to ARB; 967 (19.06%) to BB; 970 (19.12%) to CCB; and 765(15.08%) were randomized to DIU. The characteristics of the included studies and the associated patient characteristics are summarized in Table 1. The network

TABLE 2 Direct comparison results of traditional meta-analysis

	Number of studies	SMD	I2	*p*	Models
ACEI vs					
ARB	4	0.04 (−0.21, 0.28)	0.00%	.741	fixed-effects models
BB	3	0.63 (−1.06,−0.20)	0.00%	.953	fixed-effects models
CCB	13	0.10 (−0.04, 0.25)	17.70%	.27	random-effects models
DIU	6	0.05 (−0.22, 0.33)	69%	.006	random-effects models
ARB vs					
CCB	4	−0.82 (−1.22,-0.42)	0.00%	.684	fixed-effects models
BB	6	−0.21 (−0.32,−0.10)	0.00%	.693	fixed-effects models
DIU	1	NA	NA	NA	NA
CCB vs					
BB	2	0.04 (−0.22, 0.29)	0.00%	.463	random-effects models
DIU	7	−0.16 (−0.44, 0.13)	28.8%	.230	random-effects models
BB vs					
DIU	2	0.20 (−0.68, 0.28)	61.50%	.107	fixed-effects models

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blockers; CCB, calcium channel blocker; DIU, diuretic; NA, not available; SMD, standardized mean difference.

comparison between different processing strategies is constructed as shown in Figure 2. The PRISMA checklist and PRISMA Protocol are presented in S1 Appendix and S2 Appendix respectively. A quality assessment of the included studies can be found in S3 Appendix.

3.2 | Traditional meta-analyses

The results of traditional meta-analysis showed that ARB was superior to CCB and BB in reversing LVH under fixed effect model, and the difference was statistically significant. The effect of ACEI on LVMI reduction was significantly better than that of BB. Table 2 presents the results of the meta-analysis of the data about the regression of LVH between different classes of antihypertension drugs.

3.3 | Bayesian network meta-analyses

In Network Meta-Analysis, consistency between direct and indirect comparisons was assessed by calculating inconsistency factors. For the comparison of different types of antihypertensive drugs to reverse LVH, the 95% confidence interval of inconsistency factors contained zero, indicating good consistency. In addition, there was no statistical difference in the consistency test by node-splitting method ($P > .05$), which also suggests that there is no inconsistency between direct comparison and indirect comparison. The results of network meta-analysis showed that ARB could effectively improve LVH in hypertensive patients, and its effect was better than that of CCB (MD −4.07, 95%CI −8.03 to −0.24) and BB (MD −4.57, 95%CI −8.07 to −1.12). ACEI were less effective, and ARB were more effect in reducing LVMI (MD −3.72, 95%CI −7.52 to −0.11). The results of our random-effects network meta-analysis for the regression of LVH are summarized in Table 3. The surface under the cumulative ranking for each intervention indicated that the use of ARB was more effective among the six types of antihypertensive drugs. The probabilities of being among the most efficacious treatments were as follows: ARB (97%), ACEI (43%), BB (24%), CCB (33%), and diuretics (53%) (Figure 3).

4 | DISCUSSION

The results of paired comparison of different types of antihypertensive drugs in the present network meta-analysis showed that BB and CCB were less effective in reversing LVH than ARB, and matched comparison of the renin-angiotensin system inhibitors (RASi) showed that ACEI was not effective as ARB in reducing LVMI.

The network meta-analysis is a comparison of various interventions in the same disease. Compared with the traditional meta-analysis, it can reduce the bias caused by only analyzing the results of direct comparison. After summarizing and quantifying different intervention measures, the biggest advantage of network meta-analysis is to sort according to the pros and cons of the outcome indicators, and finally get a relatively good treatment scheme for the same disease, which is more in line with the reality of clinical decision. It has more important application value for clinical decision.

Prevention or reversal of LVH has been shown to reduce the risk of cardiovascular events in hypertensive patients.[59,60] Although

ACEI	−3.72 (−7.52, −0.11)	0.86 (−3.22, 4.94)	0.33 (−2.34, 2.98)	-1.09 (−4.42, 2.43)
3.72 (0.11, 7.52)	ARB	4.57 (1.12, 8.07)	4.07 (0.24, 8.03)	2.62 (−1.64, 7.07)
-0.86 (−4.94, 3.22)	-4.57 (−8.07, −1.12)	BB	-0.53 (−4.65, 3.60)	-1.93 (−6.31, 2.66)
-0.33 (−2.98, 2.34)	-4.07 (−8.03, −0.24)	0.53 (−3.60, 4.65)	CCB	-1.42 (−4.86, 2.08)
1.09 (−2.43, 4.42)	-2.62 (−7.07, 1.64)	1.93 (−2.66, 6.31)	1.42 (−2.08, 4.86)	DIU

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blockers; CCB, calcium channel blocker; DIU, diuretic.

TABLE 3 The results of network meta-analysis for regression of left ventricular hypertrophy

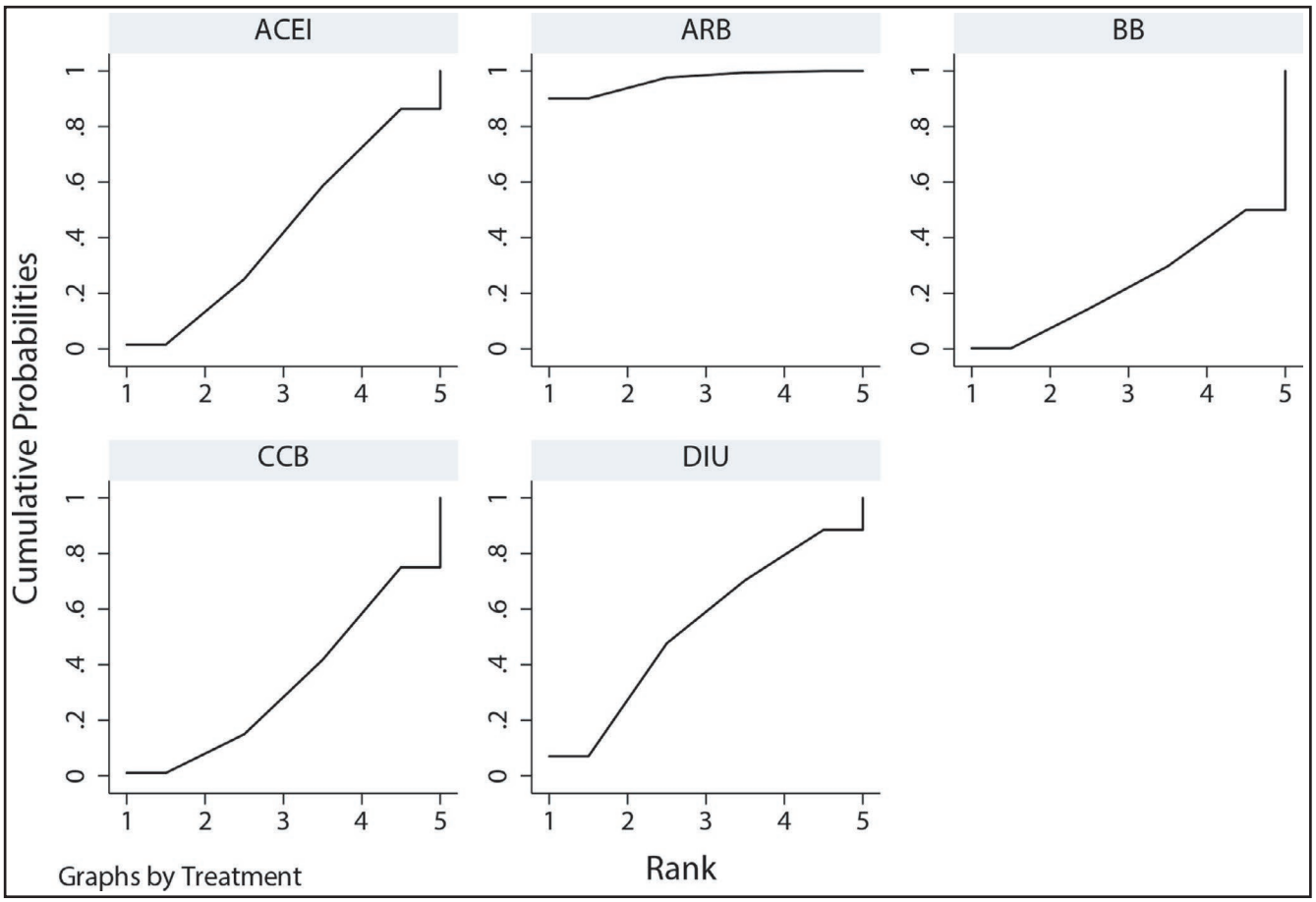

FIGURE 3 The surface under the cumulative ranking for each intervention

several clinical trials and meta-analyses have compared the effects of different classes of antihypertensive drugs on ventricular hypertrophy, the usefulness of the results is limited by their inadequate design and inappropriate methods.[61,62] Although meta-analyses can improve the statistical power and provide more accurate estimates of the effect value, the results depend largely on the criteria for inclusion in the study.[63,64] Molecular biology research has shown that LVH in hypertensive patients is a process evolving from quantitative change to qualitative change.[65,66] This process includes gene translocation of myosin heavy chain, encoding myosin, membrane protein, and energy metabolism of protein gene shift.[67-69] Brigitte et al have shown that it takes at least 100 days to reverse this process.[70] Therefore, the shorter intervention period in the previous meta-analysis was insufficient to evaluate the possibility of reversing LVH with various antihypertensive drugs.[61] Unlike previous meta-analyses, the shortest observation period in our study was three months, and network meta-analysis suggested that ARB might be the preferred antihypertensive drug to reverse LVH. Moreover, the results of network meta-analysis suggested that ARNI did not show any advantages in the treatment of LVH in hypertensive patients.

Nevertheless, as there are fewer clinical studies on the protective effect of ARNI on target organs of hypertension, larger RCTs are needed to confirm the role of ARNI in reversing LVH.

Notably, this study found that the effect of ACEI on LVH reversal was less effective than that of ARB. The reason underlying these differentials remains unclear, although potential explanations have been suggested. First of all, ACEI block the transformation of angiotensin I into angiotensin II, thus reducing the vessel wall tension and blood volume and achieving the purpose of lowering blood pressure.[71,72] On the one hand, ARB can effectively reduce blood pressure by blocking angiotensin (Ang) I receptor, inhibiting aldosterone secretion and eliminating water and sodium retention. On the other hand, ARB can increase the level of endogenous Ang II, that is, increase the level of angiotensin-converting enzyme (ACE)2 substrate, the homologous enzyme of ACE, thereby activating ACE2-Ang (1-7)-MAS receptor axis to exert cardiac protection.[73,74] Secondly, ARB also has vascular-protective and anti-inflammatory effects.[75] ARB can enhance pro-angiogenesis, which includes promoting the production of angiogenic factors and nitric oxide and reducing oxidative stress.[76] Finally, ARB is more prominent than ACEI in inhibiting collagen synthesis.[77] Studies in hypertensive heart failure (HF) rats have shown that ACEI reduces myocardial volume at the early stage of HF and myocardial length at the late stage. ARB is more effective in reducing the diameter of cardiomyocytes in the early and late stages of HF to near normal range.[78]

This meta-analysis provides new clues to support the hypothesis that patients with hypertensive cardiac hypertrophy may obtain better clinical benefits from the use of ARB as compared with other types of antihypertensive drugs. To improve the quality of life and long-term prognosis of patients with hypertensive cardiac hypertrophy, it is recommended that clinicians choose the optimal antihypertensive drugs to reverse LVH.

5 | CONCLUSION

In conclusion, the use of ARB in antihypertensive therapy can achieve better efficacy in reversing LVH in hypertensive patients. There is still a need for larger randomized controlled trials and longer-term follow-ups to clarify whether this better effect of ARB in lowering LVMI vs. other antihypertensive drugs could lead to better outcomes.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

All authors fulfill the criteria for authorship. Jing Yu and Jian-Shu Chen conceived and designed the research. Jian-Shu Chen, Ying Pei, and Cai-e Li acquired the data. Jian-Shu Chen and Qiong-ying Wang drafted the manuscript and made critical revision of the manuscript for key intellectual content. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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