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Real role of β**-blockers in regression of left ventricular mass in hypertension patients** Bayesian network meta-analysis

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Abstract

Background: Left ventricular hypertrophy (LVH) is commonly present in patients with hypertension (HT). According to the expert consensus document from American, angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blockers (ARBs) were recommended as 1st-line therapeutic drugs. However, none noticed the different efficacy between fat-soluble and selective β 1-receptor blockers (FS- β -B) and other β -blockers on regression of LVH before. The aim of this analysis was to compare the efficacy of FS- β -B with the other 4 different classes of antihypertensive drugs (ACEI, ARBs, calcium channel blockers [CCBs], and diuretics) on regression of LVH.

Methods: Relative trials were identified in the PubMed, Web of Science, OVID EBM Reviews and Cochrane databases, and the relevant papers were examined. We performed both traditional and Bayesian meta-analysis of randomized controlled trials (RCTs) about the regression of LVH. Sensitivity analysis and regression analysis were performed to explore possible sources of heterogeneity. Inconsistency analysis was performed to check whether the analysis of the trials in the network was indeed consistent.

Results: A total of 41 RCTs involving 2566 patients with HT and LVH were included in this analysis. Bayesian network meta-analysis indicated no statistically significant differences between these groups: FS- β -B and ACEI (MD, -7.09; 95% Cl, -14.99, 1.27); FS- β -B and ARB (MD, -2.66; 95% Cl, -12.02, 6.31). Although FS- β -B showed greater efficacy when compared with diuretic (MD, 13.04; 95% Cl, 3.38, 22.59) or CCB (MD, 10.90; 95% Cl, 1.98, 19.49). The probabilities of being among the most efficacious treatments were: FS- β -B (72%), ARB (27%), ACEI (0.01%), CCB (0.00%), and diuretic (0.00%).

Conclusion: Evidence from our analysis reveals that FS- β -B have potential to become 1st-line therapeutic drugs in HT and LVH patients. However, the real efficacy of FS- β -B on regression of LVH should be confirmed by further large, high quality trials considering the limitation of the study number.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, FS- β -B = fat-soluble and selective β 1-receptor blockers, LVH = left ventricular hypertrophy, LVM = left ventricular mass, LVMI = left ventricular mass index.

Keywords: anti-hypertensive drug, Bayesian network analysis, β-blockers, hypertension, left ventricular hypertrophy

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1. Introduction

Left ventricular hypertrophy (LVH) is commonly present in hypertensive (HT) patients. It could strongly predict cardiovascular mortality and morbidity,^[1–3] and was associated with increased incidence of atrial fibrillation, left ventricular dysfunction, and heart failure.^[4–6]

There were several meta-analyses concerning the effect of 5 different classes of antihypertensive drugs on LVH.^[7–9] Although their conclusions had some differences, all of them agreed on a point that regression was worse with β -blockers and better with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARBs). On the basis of these previous clinical researches and meta-analyses, the expert consensus document on hypertension from American suggested that ACEI or ARBs should generally be used in hypertensive patients with LVH.^[10]

However, β -blockers used in majority of the clinical researches were not fat-soluble nor β 1-selective. And one newest study conducted by Caglar showed that nebivolol, one of the fatsoluble and selective β 1-receptor blockers (FS- β -B), had better effect on regression of LVH than ACEI.^[11] We hypothesized that FS- β -B, which including metoprolol, bisoprolol, and nebivolol,

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reduce left ventricular mass (LVM) to a greater extent than other antihypertensive agents.

The aim of the current network meta-analysis was to compare the efficacy of FS- β -B with other 4 different classes of antihypertensive drugs on LVH regression.

2. Methods

2.1. Ethical review

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.2. Search strategy

We searched PubMed, Web of Science, Cochrane Database, and OVID EBM Reviews (until December 2016) to identify clinical trials only published in English. The search terms included: "left ventricular mass," "left ventricular hypertrophy," "regression," and each class of antihypertensive drugs. For the FS- β -B we also performed searches for each drug separately, such as bisoprolol, nebivolol, and metoprolol. We also manually searched the previously published meta-analyses and bibliographies of the selected publications. Additionally, gray literature was identified by searching the related agencies and clinical trial registers. The reference lists of the original articles and reviews on the topic were examined to identify other eligible studies. A total of 41 randomized controlled trials (RCTs) were included (References supplemental appendix 1–41, http://links.lww.com/MD/B593).

2.3. Eligibility criteria

Selection criteria for inclusion in the meta-analysis were as follows: comparison of the effect of antihypertensive drugs, belonging to different drug classes (diuretics, β -blockers, calcium channel blockers [CCBs], ACEI, and ARBs), on left ventricular mass index (LVMI); initiation of drug treatment with monotherapy, with or without add-on therapy for better BP control; no other interventions or treatment, with interruption of all BP-lowering drugs before the run-in period; and availability of echocardiographic LVMI in \geq 70% of patients in \geq 1 visit after randomization (in case of multiple examinations, the last visit with <70% of analyzable data was taken).

Exclusion criteria were as follows: other β -blockers that were not FS- β -B, such as timolol, propranolol, atenolol, tertatolol, and carvedilol; only reported data of LVM instead of LVMI; hypertensive patients with cardiovascular or renal disease or other clinical conditions, such as diabetes; drug treatments provided for patients were different in all of the treatment arms; treatment duration of <2 months; missing the date of LVM at baseline and during treatment or at baseline with changes from baseline; and age <18 years.

And full publication in a peer-reviewed journal up to December 2016, with the exclusion of data repeats. Two reviewers (XFW and CJL) independently screened the studies to determine whether they satisfied the eligibility criteria. Disagreement between reviewers were resolved by consensus, and a 3rd reviewer (CYL) was consulted when necessary.

2.4. Data extraction

Two independent reviewers screened the data from the included studies using a predefined checklist for each study. Disagreements

between reviewers were resolved by discussion until a consensus was reached. Data extraction and presentation for this article followed the recommendations of the PRISMA group (References supplemental appendix 1–41, http://links.lww.com/MD/B593). The following data were extracted from each selected study whenever available: demographics and sample characteristics, LVMI, type, treatment duration and dose of antihypertensive drugs, and additional drug used. The primary endpoints in our meta-analysis were regression of LVH, determined by the LVMI.

2.5. Data analysis (traditional meta-analysis)

Traditional meta-analysis using the random-effects model was conducted. We computed the pooled mean difference (MD) and 95% credibility interval (CI) as well as the heterogeneity of the included studies. A random-effect model was used to calculate the pooled MD and 95% CI. I^2 statistic was used to indicate the proportion of heterogeneity between studies in total variation; the cut-off points for low, moderate, and high degrees of heterogeneity were 25%, 50%, and 75%, respectively. I^2 value <25% indicate no evidence of heterogeneity. Heterogeneity was considered significant when the P-value was less than 0.1.^[12] If between-study heterogeneity was observed in traditional metaanalysis, then we performed sensitivity analyses by excluding each study individually to explore the possible sources of heterogeneity. The regression analysis based on different duration of medication, treatment regimen (monotherapy or not, double dosage or not), published time, sample size, and study countries were conducted to investigate whether these conditions could influence the results. Traditional meta-analysis was performed with the REVMAN software (version 5.2; Cochrane Collaboration, Oxford, UK) and Stata 12 (StataCorp, College Station, TX).

2.6. Data analysis (network meta-analysis)

Network meta-analysis was conducted for mixed treatment comparisons in a Bayesian framework, and the pooled estimates were obtained using the Markov Chains Monte Carlo method. This approach is recommended by the National Institute for Health and Care Excellence (NICE) Decision Support Unit according to the technical support documents on evidence synthesis.^[13,14] We performed a random-effects network metaanalysis in GeMTC-GUI-0.14.3, which uses Bayesian Markov Chains Monte Carlo methods^[15,16] with 50,000 times random sampling. There were 3 parts in this analysis. First, in the network meta-analysis for the consistency model, we estimated all of the relative effects simultaneously by using the consistency constraint. For example, the parameter dBC was estimated from both direct evidence on BC and indirect evidence on AC and AB. The relative effect results for the consistency model were reported as an MD with a corresponding 95% CI. Then, we estimated the ranking probability for each drug. Rankings regarding treatment efficacy of the 5 drug classes were originally derived from Monte Carlo simulations and presented as the probability of possessing a specific ranking, in which the probabilities of different rankings of the same treatment were summed to 100%.^[17] Second, we performed the inconsistency analysis using the inconsistency model and the node-splitting model to check whether the analysis of the trials in the network was indeed consistent. In brief, the inconsistency factors, representing the discrepancy between the direct and indirect evidence, were added to the closed loops of the inconsistency model, that is, $dBC = dAC - dABb + \phi$

 $(\phi = \text{inconsistency factor})$. Therefore, the degree of inconsistency, by checking the size of an inconsistency factor within the cycle, was determined for a cycle (eg, ABC) rather than for individual pairwise comparisons.^[18] 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 can be considered as insignificant. Last, sensitivity analyses were performed to see if the efficacy hierarchies have changed.

3. Results

3.1. Search results

The search strategy revealed 547 potentially eligible references, and 20 additional records were identified by other means. After the duplicates were removed, 494 studies remained. When the titles were reviewed, 237 studies were excluded. When the abstracts or all content were reviewed in terms of the inclusion and exclusion criteria, 107 studies were excluded. The remaining 41 studies were all included in this meta-analysis (supplemental figure appendix 2, http://links.lww.com/MD/B592). Among these studies, all of them were from journal articles (full manuscripts acquired).

3.2. Study characteristics and baseline patient characteristics

Supplemental table appendix 1-2, http://links.lww.com/MD/ B593 describes key characteristics of the included studies (design, treatments, follow-up length, and the inclusion criteria of each trial) and the clinical and baseline characteristics of patients enrolled in each trial (age, male, BMI, LVM, etc.). Therapeutic methods in every study were different from each other. There are 22 studies used monotherapy, 13 studies combined with other antihypertension drug, and 6 studies did not mention this. Duration of hypotensor administration was different in these studies, ranging from 2 to 24 months. In these RCTs, 949 patients (36.98%) were assigned to ACEI (perindopril, enalapril, lisinopril, ramipril, etc.); 119 (4.64%) to FS-B-B therapy (atenolol, metoprolol, and nebivolol); 389 (15.16%) to diuretics therapy (hydrochlorothiazide, indapamide, perindopril, etc.); 375 (14.61%) to ARB (eprosartan, telmisartan, etc.); and 708 (27.59%) were randomized to CCB (nimodipine, nitrendipine, etc.). The construction of the network comparisons between different treatment strategies is shown in Fig. 1.

3.3. Traditional meta-analyses

Figure 2 (group 1–8) presents the results of the meta-analysis of the data about the regression of LVH between different classes of antihypertension drugs from the 41 included studies. There was not statistical difference between FS- β -B and ACEI (group1; P=0.36). By the way, only 1 study was included in the group 2 (FS- β -B and ARB).

Overall, heterogeneity was moderate, although for several groups the 95% CI included values that showed very high or significant heterogeneity, reflecting the small number of included studies for these pairwise comparison. For example, there were 2 groups which I^2 values were higher than 75%. They were group 1 (FS-β-B vs ACEI, $I^2=96\%$) and group 4 (CCB vs ARB, $I^2=88\%$). And only 3 studies were included in these groups, respectively.

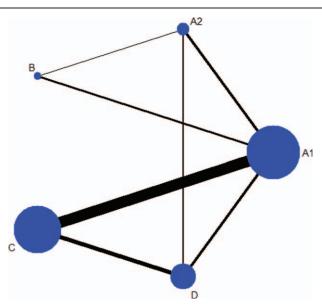


Figure 1. The construction of the network (A1=ACEI; A2=ARB; B=FS- β -B; C=CCB; D=diuretic). ACEI=angiotensin-converting enzyme inhibitor, ARB= angiotensin receptor blocker, CCB=calcium channel blocker, FS- β -B=fat-soluble and selective β 1-receptor blockers.

3.4. Bayesian network meta-analyses

We summarize the results of our random-effects network metaanalysis for the regression of LVH in Table 1. Pooled analysis of all of the included studies indicated that there were no statistical differences between these groups: FS- β -B and ACEI (MD, -7.09; 95% CI, -14.99, 1.27); FS- β -B and ARB (MD, -2.66; 95% Cl, -12.02, 6.31). Although FS- β -B showed greater efficacy when compared with diuretic (MD, 13.04; 95% CI, 3.38, 22.59) or CCB (MD, 10.90; 95% CI, 1.98, 19.49). Figure 4A showed the distribution of probabilities of each treatment being ranked at each of the possible 5 positions. The probabilities of being among the most efficacious treatments were: FS- β -B (72%), ARB (27%), ACEI (0.01%), CCB (0.00%), and diuretic (0.00%) (Table 2).

No significant changes of efficacy hierarchies emerged in sensitivity analysis when excluding studies published before 2000, with small sample size(n < 100), carried out in non-western countries, whose follow-up period were less than 1 year, or the study conducted by Gosse (supplemental table appendix 3, http://links.lww.com/MD/B593 and Fig. 4B) (References supplemental appendix 29, http://links.lww.com/MD/B593).

3.5. Comparisons between traditional meta-analyses and Bayesian network meta-analyses

Table 1 also presents the results of traditional pairwise metaanalyses. In general, the confidence intervals from traditional pairwise meta-analyses and the CIs from Bayesian network metaanalyses overlapped. By comparing with the results obtained from the Bayesian network meta-analysis, the results of the traditional meta-analysis were largely comparable.

3.6. Heterogeneity (traditional meta-analyses)

We performed sensitivity analyses by excluding each study individually to explore the possible sources of heterogeneity (Fig. 3). When we repeated the analysis after excluding the study

		в			A1			Mean Difference		Mean Difference	
tudy or Subgroup	Mean		_	Mean	SD	Total	Weight			IV. Random, 95%	CI
iosse P1990	16	17.35	19	10	40.58	22	24.9%	6.00 [-12.67, 24.67]			
ARIN 2001 L CAGLAR2011	14 31.9	4 3.4	26 54	16 14.8	12	25 52	36.9%	-2.00 [-6.95, 2.95] 17.10 [15.90, 18.30]		1-	
otal (95% CI)			99			99	100.0%	7.29 [-8.42, 23.00]		+	
teterogeneity: Tau ² =	167.61;	Chi? = 55		f=2 (P	< 0.00						t de
est for overall effect: 2							and the		-1	60 -50 0 favours [ACEI] favour	50 100 s [FS-B-B]
roup2 B+A2		1			10			100000000		10-10-10-10	
Study or Subgroup	Mean	B SD 1	Total	Mean	A2 SD	Total	Weight	Mean Difference IV. Random, 95% Cl		Mean Difference IV. Random, 95%	
OUNTOULAKI2005		14.5	20		11.31		100.0%	-0.10 [-8.16, 7.96]			<u></u>
Total (95% CI)			20			20	100.0%	-0.10 [-8.16, 7.96]		+	
leterogeneity: Not app	licable								-50		25 50
lest for overall effect: 2	Z = 0.02	(P=0.9	8)						-90	-25 0 favours [ARB] favours	
group3 A1+A2		12			100			2010/2010/00/00		2010/2011	
Study or Subgroup	Mean	A1 SD	Total	Mean	A2 SD	Total	Weight	Mean Difference IV. Random, 95% C		Mean Difference IV, Random, 95%	
Anan, F2005	24	14.18	11	27	14.73	10	8.5%	-3.00 [-15.39, 9.39]			
Cuspidi, C2002	13.3	28.44	105	15	29.15	91	20.0%	-1.70 [-9.79, 6.39]			
anem2000 Jribe Flores2004	36.9	21.34	20 42	32.5	21.34	20 43	7.5%	4.40 [-8.83, 17.63] -1.49 [-6.01, 3.03]		-	
otal (95% CI)	0.00	2 = 0 =0	178	(D = 0	051 12	164	100.0%	-1.22 [-4.84, 2.40]	-		
feterogeneity: Tau ² = 0 fest for overall effect: 2) (In = ()	(00); P	- 0%			-50	-25 0 Favours (ARB) Favour	25 50
roup4 C+A2		100								- andra (- avour	a proved
		C			A2			Mean Difference		Mean Difference	
Study or Subgroup Gaudio,2003	Mean	SD 1	30	Mean 34,1		Total 30	Weight 36.9%	IV. Random, 95% Cl -15.10 [-22.98, -7.22]		IV. Random, 95%	CI.
Kazuhiro2011		41.58	28		13.62 35.17	30 29	26.3%	20.00 [-0.03, 40.03]		-	-
asunari2004		14.08	50		24.63	50		-25.00 [-32.86, -17.14]		-	
Fotal (95% CI)			108			109	100.0%	-9.52 [-27.15, 8.10]		-	
feterogeneity: Tau ² = 2				= 2 (P	= 0.000	2); 2 =	88%		-100	-50 0	50 100
Fest for overall effect: 2	= 1.06	(P = 0.28	9)						11.33	Favours [ARB] Favour	
group5 D+A2		D			AZ			Mean Difference		Mean Difference	
Study or Subgroup	Mean		Total	Mean	SD	Total	Weight	IV. Random, 95% Cl		IV. Random, 95%	
Galzerano2004		21.07	25	16	17.69	40		-12.00 [-21.91, -2.09]			
fedesco1998	5	22.07	28	11	20.07	42	48.7%	-6.00 [-16.18, 4.18]			
fotal (95% CI)		145	53	-			100.0%	-9.08 [-16.18, -1.98]	-	•	
Heterogeneity: Tau ² = 0 fest for overall effect: 2				(P=0	41); P	0%			-100	-50 0	50 100
			1							Favours [ARB] Favour	s [Diuretic]
and the second											
group6 D+C		D			c			Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total		SD		Weight	IV. Random, 95% CI		Mean Difference	
Study or Subgroup 1985Mace, P. J.	6	SD 1 21.52	8	19	SD 29.21	9	6.9%	IV. Random. 95% Cl -13.00 [-37.22, 11.22]	_		
Study or Subgroup 1985Mace, P. J. 1987Giles, T. D		SD		19	SD			IV. Random, 95% CI	_		
group6 D+C Study or Subgroup 1985Mace, P. J. 1987Giles, T. D 1993Senior, R. 1994Trenkwalder, P	6 2 18.9 0	SD 1 21.52 97.5 4.78 22.07	8 8 22 21	19 17 22.2 2	SD 29.21 38.35 6.41 27.84	9 7 19 21	6.9% 0.9% 38.0% 14.0%	IV. Random, 95% CI -13.00 [-37.22, 11.22] -15.00 [-88.29, 58.29] -3.30 [-6.81, 0.21] -2.00 [-17.19, 13.19]	-		
Study or Subgroup 1985Mace, P. J. 1987Giles, T. D 1993Senior, R. 1994Treniwalder, P 1996Dey, H. M	6 2 18.9	SD 1 21.52 97.5 4.78	8 8 22	19 17 22.2 2 11	SD 29.21 38.35 6.41	9 7 19 21 18	6.9% 0.9% 38.0% 14.0% 8.4%	IV, Random, 95% CI -13.00 [-37.22, 11.22] -15.00 [-88.29, 58.29] -3.30 [-6.81, 0.21] -2.00 [-17.19, 13.19] 5.00 [-16.51, 26.51]	-		
Study or Subgroup 1985Mace, P. J. 1987Giles, T. D 1993Senior, R. 1994Treniswalder, P 1996Dey, H. M 2000Shm, I 2000Shm, I 2002Rakic, D	6 2 18.9 0 16 30 13.35	SD 1 21.52 97.5 4.78 22.07 35.17 34.07 24.67	8 8 22 21 18 14 32	19 17 22.2 2 11 79 13.7	SD 29.21 38.35 6.41 27.84 30.51 45.74 14.98	9 7 19 21 18 12 17	6.9% 0.9% 38.0% 14.0% 8.4% 4.4% 20.3%	IV. Random. 95% CI -13.00 [-37.22, 11.22] -15.00 [-88.29, 58.29] -3.30 [-6.81, 0.21] -2.00 [-17.19, 13.19] 5.00 [-16.51, 26.51] 49.00 [-80.44, -17.56] -0.35 [-11.48, 10.78]	-		
Study or Subgroup 1985Mace, P. J. 1987Giles, T. D 1993Senior, R.	6 2 18.9 0 16 30	SD 1 21.52 97.5 4.78 22.07 35.17 34.07	8 8 22 21 18 14	19 17 22.2 2 11 79	SD 29.21 38.35 6.41 27.84 30.51 45.74 14.98	9 7 19 21 18 12	6.9% 0.9% 38.0% 14.0% 8.4% 4.4%	IV. Random. 95% Cl -13.00 [-37.22, 11.22] -15.00 [-68.29, 58.29] -3.30 [-6.81, 0.21] -2.00 [-17.19, 13.19] 5.00 [-16.51, 26.51] 49.00 [-80.44, -17.56]	-		
Study or Subgroup 1985Mace, P. J. 1993Geles, T. D. 1993Geles, T. D. 1994Trenkwalder, P. 1996Doy, H. M. 2000Shrin, I 2000ZRakic, D. 2013Takafumi Okura Total (95% CI)	6 2 18.9 0 16 30 13.35 22.4	SD 3 21.52 97.5 4.78 22.07 35.17 34.07 24.67 33.5	8 8 22 21 18 14 32 21 144	19 17 22.2 2 11 79 13.7 12.2	SD 29.21 38.35 6.41 27.84 30.51 45.74 14.98 43.85	9 7 19 21 18 12 17 20 123	6.9% 0.9% 38.0% 14.0% 8.4% 4.4% 20.3% 7.0%	IV. Random. 95% CI -13.00 [-37.22, 11.22] -15.00 [-88.29, 58.29] -3.30 [-6.81, 0.21] -2.00 [-17.19, 13.19] 5.00 [-16.51, 26.51] 49.00 [-80.44, -17.56] -0.35 [-11.48, 10.78]	-		
Study or Subgroup 985Mace, P. J. 987Gites, T. D. 1993Senice, R. 1994Forenkwadder, P. 1996Dey, H. M. 1900Shm, I. 1000Shm, I. 1002Rakic, D. 2013Takafumi Okura Total (95% CI) 104rogeneity: Tau ² = 3	6 2 18.9 0 16 30 13.35 22.4	SD 1 21.52 97.5 4.78 22.07 35.17 34.07 24.67 33.5	8 8 22 21 18 14 32 21 144 221	19 17 22.2 2 11 79 13.7 12.2	SD 29.21 38.35 6.41 27.84 30.51 45.74 14.98 43.85	9 7 19 21 18 12 17 20 123	6.9% 0.9% 38.0% 14.0% 8.4% 4.4% 20.3% 7.0%	IV. Random. 95% Cl -13.00 [-37.22, 11.22] -15.00 [-48.29, 56.29] -3.30 [-6.81, 0.21] -2.00 [-17.19, 13.19] 5.00 [-16.51, 26.51] 49.00 [-80.44, -17.56] -0.35 [-11.48, 10.78] 10.20 [-13.77, 34.17]	-100	IV. Random. 95%	
Study or Subgroup 1985Mace, P. J. 1987Giles, T. D. 1993Senior, R. 1994Trenkwatder, P. 1996Epy, H. M. 19002Rakie, D. 1903Takatumi Okura Total (95% CI) 1eterogeneity: Tau ² = 3 feet for ovenall effect; 2	6 2 18.9 0 16 30 13.35 22.4	SD 1 21.52 97.5 4.78 22.07 35.17 34.07 24.67 33.5	8 8 22 21 18 14 32 21 144 221	19 17 22.2 2 11 79 13.7 12.2	SD 29.21 38.35 6.41 27.84 30.51 45.74 14.98 43.85	9 7 19 21 18 12 17 20 123	6.9% 0.9% 38.0% 14.0% 8.4% 4.4% 20.3% 7.0%	IV. Random. 95% Cl -13.00 [-37.22, 11.22] -15.00 [-48.29, 56.29] -3.30 [-6.81, 0.21] -2.00 [-17.19, 13.19] 5.00 [-16.51, 26.51] 49.00 [-80.44, -17.56] -0.35 [-11.48, 10.78] 10.20 [-13.77, 34.17]	-	IV. Random. 95%	
Bildy of Subgroup 1985Mace, P. J. 1985Mace, F. D. 1993Tenior, R. 1994Tenika, R. 1994Tenika, M. 1995Day, H. M. 1902Rakic, D. 1902Rakic, D. 1903Takafumi Okura fotal (195% CI) 1eterogeneity: Tau ² = 3 feet or overall effect: Z group7 C+A1	6 2 18.9 0 16 30 13.35 22.4 0.18; Cl	SD 1 21.52 97.5 4.78 22.07 35.17 34.07 24.67 33.5 ht ² = 10.9 (P = 0.30	8 8 22 21 18 14 32 21 14 32 21 144 12, df =	19 17 22.2 2 11 79 13.7 12.2 7 (P =	SD 29.21 38.35 6.41 27.84 30.51 45.74 14.98 43.85 0.14); P	9 7 19 21 18 12 17 20 123 = 36%	6.9% 0.9% 38.0% 14.0% 8.4% 4.4% 20.3% 7.0%	IV. Random. 95% CI -13.00 [-37.22, 11.22] -15.00 [-88.29, 58.29] -3.30 [-6.81, 0.21] 5.00 [-16.51, 26.51] -0.05 [-11.48, 10.78] 10.20 [-13.77, 34.17] -3.66 [-10.64, 3.32] Mean Difference	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy or Subgroup 1995Mace, P. J. 1987Giles, T. D. 1993Terkwalder, P. 1994Terkwalder, P. 1994Terkwalder, P. 1994Terkwalder, P. 1994Terkwalder, D. 2003Takafumi Okura Total (1995-CI) Test for overall effect: Z group7 C+A1 Study or Subgroup	6 2 18.9 0 16 30 13.35 22.4 0.18: Cl = 1.03	SD 1 21.52 97.5 4.78 22.07 35.17 34.07 24.67 33.5 ht ² = 10.9 (P = 0.30 C n SD	8 8 22 21 18 14 32 21 144 32 21 144 12, df =	19 17 22.2 2 11 79 13.7 12.2 7 (P =	SD 29.21 38.35 6.41 27.84 30.51 45.74 14.96 43.85 0.14); P A1 SD	9 7 19 21 18 12 17 20 123 = 36%	6.9% 0.9% 38.0% 14.0% 8.4% 20.3% 7.0% 100.0%	IV. Random. 95% CI -13.00 [-37.22, 11.22] -15.00 [-86.29, 56.29] -3.30 [-6.81, 0.21] 5.00 [-16.51, 26.51] 5.00 [-16.51, 26.51] 40.00 [-60.44, -17.56] -0.35 [-11.46, 10.76] 10.20 [-13.77, 34.17] -3.66 [-10.64, 3.32] Mean Difference IV. Random. 95% CI	-100	V.Random.95%	CI 50 100 5 [Diuretic]
Budy of Subgroup 1985Mace, P. J. 1985Tolles, P. J. 1987Giles, T. D. 1994Terkwalder, P. 1994Terkwalder, P. 1994Terkwalder, P. 1994Terkwalder, P. 1994Toll, P. 1992Forkin, I. 10002Rakic, D. 1013Takafumi Okura Total (1995-Ci) 1002Rakic, D. 1013Takafumi Okura Total (1995-Ci) 1002Rakic, D. 1002Rakic, D. 1002	6 2 18.9 0 16 30 13.35 22.4 10.18. Cr (= 1.03) (= 1.03) Mean 3 2	SD 1 21.52 97.5 4.78 22.07 35.17 35.17 34.07 24.67 33.5 (P = 0.30 (P = 0.30) (P = 0.30) C n SD 8 39.74 3 7.21	8 8 22 21 18 14 32 21 144 12, df =	19 17 22.2 2 11 79 13.7 12.2 7 (P =	SD 29.21 38.35 6.41 27.84 30.51 45.74 14.98 43.85 0.14); P A1 SD 43.7.16 5.57	9 7 19 21 18 12 17 20 123 = 36%	6.9% 0.9% 38.0% 14.0% 8.4% 4.4% 20.3% 7.0% 100.0%	W. Random. 95% CI -13.00 [-37.22, 11.22] -15.00 [-18.22, 11.22] -15.00 [-18.25, 58.26] -3.30 [-6.61, 0.21] -2.00 [-16.51, 26.51] -2.00 [-16.51, 26.51] -3.66 [-10.64, 3.32] Mean Difference IV. Random. 95% C -4.00 [-0.3, 17.03] 2.00 [-2.66, 6.67]	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy of Subgroup 1985Mace, P. J. 1985Mace, P. J. 1997Giles, T. D. 1993Teinor, R. 1993Teinor, R. 1994Ternikwader, P. 1994Ternikwader, P. 1995Teinor, I. 10005Nin, I. 10007Rakic, D. 1013Takatumi Okura foat (95% Cl) 16terogeneity: Tau" = 3 foat (95% Cl) 16terogeneity: Tau" = 4 group7 C+A1 18tudy, or Subgroup_ 1995Chandi, L. S. 1995Chandi, A. M.	6 2 18.9 0 16 30 13.35 22.4 0.18. Cl = 1.03 1 	SD 1 21.52 97.5 4.78 22.07 35.17 34.07 24.67 33.5 hr ² = 10.9 (P = 0.30 C C n SD 8 39.74 3 7.21 0 16.7	8 8 22 21 18 14 32 21 144 52, df = 0) Total 67 14 18	19 17 22.2 2 11 79 13.7 12.2 7 (P =	SD 29.21 38.35 6.41 27.84 30.51 45.74 14.98 43.85 0.14); P A1 SD 37.16 5.57 17.06	9 7 19 21 18 12 17 20 123 = 36%	6.9% 0.9% 38.0% 14.0% 8.4% 4.4% 20.3% 7.0% 100.0% Weight 4.9% 11.3% 6.0%	IV. Random. 95% CI -13.00 (-37.22, 11.22) -15.00 (-16.22, 11.22) -15.00 (-16.52, 12.51) -2.00 (-17.19, 13.19) 5.00 (-16.57, 26.51) -0.00 (-16.44, -17.56) -0.3.66 (-10.64, 3.32) -3.66 (-10.64, 3.32) Mean Difference IV. Random. 35% CI -0.00 (-20.43, 17.03) -0.00 (-20.43, 1.03, 1.03)	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy, or Subgroup. 995Mace, P. J. 995Mace, P. J. 997Cites, T. D. 993Teriky, R. 994Terikwałce, P. 995Wardzi, Tau ² = 3 Feet for overall effect: Z group7 C+A1 Budy, or Subgroup_ 995Krpadis, H. G	6 2 18.9 0 16 30 13.35 22.4 0.18. Cl = 1.03 1 3 2 2 2 13.1	SD 1 21.52 97.5 4.78 22.07 35.17 34.07 24.67 33.5 hr ² = 10.9 (P = 0.30 C C SD 8 39.74 3 7.21 0 16.7	8 8 22 21 18 14 32 21 144 52, df = 0) Total 67 14 18	19 17 22.2 2 11 79 13.7 12.2 7 (P =	SD 29.21 38.35 6.41 27.84 30.51 45.74 45.74 45.74 45.74 45.74 43.85 0.14); P A1 5.57 17.06 5.57 17.06 15.72	9 7 19 21 18 12 17 20 123 = 36% 123 = 36%	6.9% 0.9% 38.0% 14.0% 8.4% 4.4% 20.3% 7.0% 100.0% Weight 4.9% 11.3% 6.0% 6.4%	W. Random. 95% CI 13.00 [-37.22, 11.22] -15.00 [-48.29, 58.29] -3.30 [-6.51, 02.7] -2.00 [-71.51, 31.9] 5.00 [-16.51, 26.51] 0.035 [-11.46, 10.76] 10.20 [-13.77, 34.17] -3.56 [-10.64, 3.32] Mean Difference U. Random. 95% CI 2.00 [-2.66, 6.66] -10.00 [-24.03, 1.03] -3.780 [-18.21, 2.41]	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy of Subgroup 1965Mace, P. J. 1967Clines, T. D. 1993Senior, R. 1994Tenkwalder, P. 1996Dey, H. M. 1996Dey, H. M. 1996Dey, H. M. 1996Dey, H. M. 1996Dey, H. M. 1997Wang, L. S. 1997Wang, L. S. 1997Wang, L. S. 1995Schulte, K. L. 1995Schulte, H. G. 1995Shimanob, H. G.	6 2 18.9 0 16 30 13.35 22.4 0.18: CP 10.18: CP	SD 21.52 97.5 4.78 22.07 35.17 34.07 33.5 hP ² = 10.9 (P = 0.30 C m SD 8 39.74 3 7.21 0 16.7 7 13.53 2 22.52 6 17.76	8 8 22 21 18 32 21 14 4 12, df = 10 10 10 14 18 15 16 9	19 17 2222 2 2 11 13.7 12.2 7 (P = 34 21 30 21 6 5 21.6 5 21.6 5 21.6 5 21.6 5 21.6 5 21.6 5 21.2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	SD 29.21 38.35 6.41 27.84 45.74 14.98 43.85 0.14); P 45.74 14.98 43.85 0.14); P 14.96 1 5.57 1 17.06 1 14.96 1 15.71 1 17.91 1 14.96 1 15.71 1 15.75 1 14.96 1 15.75 1	9 7 19 21 18 12 17 20 123 = 36% 10 5 16 5 16 5 16 5 16 5 16 5 10 10 10 10 10 10 10 10 10 10 10 10 10	6.9% 0.9% 38.0% 44.0% 8.4% 4.4% 20.3% 7.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 11.3% 6.0% 6.4% 5.0% 3.7%	W. Random. 95% CI -13.00 [-37.22, 11.22] -13.00 [-38.29, 58.29] -3.30 [-6.81, 0.21] 5.00 [-16.51, 26.51] 5.00 [-16.51, 26.51] 0.03 [-11.46, 10.76] 10.20 [-13.77, 34.17] -3.66 [-10.64, 3.32] Mean Difference // Random. 95% CI 2.00 [-26.6, 66.66] -10.00 [-21.03, 17.03] -200 [-26.6, 6.66] -10.00 [-24.03, 1.03] -3.00 [-38.45, 84] -8.70 [-38.45, 87, 71]	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy of Subgroup 1985Mace, P. J. 1985Mace, T. D. 1993Terior, R. 1994Terinkwałder, P. 1994Terinkwałder, P. 1994Terinkwałder, P. 1994Terinkwałder, D. 1907Zeakic, D. 1901Takafumi Okura Total (95% CI) 1901Wang, L. S. 1995Cand, A. M. 1995Krand, A. M. 1995Krand, A. M. 1995Krand, A. M. 1995Krand, M. 1995Krand, M. 1995Krand, M.	6 2 18.9 0 16 30 13.35 22.4 0.18: CP = 1.03 0 0.18: CP = 1.03 0 13.35 22.4 0.18: CP = 1.03 13 34 13 2 2 13 13 2 2 13 14 15 15 15 15 15 15 15 15 15 15 15 15 15	SD 21.52 97.5 4.78 22.07 35.17 34.07 24.67 33.5 M ² = 10.9 (P = 0.30 C n. SD 8.39.74 3.7.21 0.16.7 7.13.53 2.2.52 6.17.6 5.28	8 8 22 21 18 32 21 14 4 (2, df = 1) 10 10 10 10 10 10 10 10 10 10 10 10 10	19 17 22.2 2 11 79 13.7 12.2 7 (P = 34 2 1 3 3 4 2 11 3 3 4 2 11 7 9 13.7 12.2 2 11 7 9 13.7 12.2 2 11 79 13.7 12.2 2 11 79 13.7 12.2 2 11 79 13.7 12.2 2 2 11 79 13.7 12.2 2 2 11 79 13.7 12.2 2 2 11 79 13.7 12.2 2 2 7 7 9 13.7 12.2 2 7 7 9 13.7 12.2 2 7 7 9 13.7 12.2 2 7 7 9 13.7 12.2 2 7 7 9 13.7 12.2 11 1 7 9 13.7 12.2 11 1 7 9 13.7 12.2 11 1 7 9 13.7 12.2 11 1 1 7 9 13.7 12.2 11 1 1 1 1 1 1 2 1 1 1 1 1 1 1 1 1	SD SD 29.21 38.35 6.41 38.35 6.41 4.4.8 30.51 45.74 45.74 45.74 43.85 0.14); P 30.14); P 1 5.57 17.06 5.57 117.06 17.51 17.56 175.62	9 7 19 21 12 12 17 20 123 = 36% 123 = 36%	6.9% 0.9% 38.0% 8.4% 4.4% 20.3% 7.0% 7.0% 100.0% 100.0% 100.0% 4.9% 11.3% 6.0% 6.4% 5.0% 3.7% 3.0%	W. Random. 95% CI -15.00 [-37.22, 11.22] -15.00 [-48.22, 58.26] -3.00 [-48.1, 0.21] -2.00 [-16.51, 26.51] 5.00 [-16.51, 26.51] -0.00 [-16.41, 47.56] -0.02 [-13.77, 34.17] -3.46 [-10.64, 3.32] Mean Difference //. Random. 95% CI 4.00 [-0.03, 17.03] -0.00 [-21.03, 1.03] -7.00 [-18.42, 1.24] -8.00 [-10.42, 84, 5.84] -8.00 [-14.24, 28, 1.43]	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy, or Subgroup. 995Mace, P. J. 995Mace, P. J. 997Cites, T. D. 997Cites, T. D. 998Terikking, P. 999Terikking, P. 999Terikking, H. G. 999Khipmalok, H. G. 999Terikking, O.	6 2 18.9 0 16 30 13.35 22.4 0.18: CP 10.18: CP	SD 21.52 97.5 4.78 22.07 35.17 34.07 34.07 33.5 hi ² = 10.9 (P = 0.30 C C C N SD 8 39.74 3 7.21 0 16.7 7 13.53 2 22.52 6 17.76 5 28 4 35.59 4 35.59	8 8 22 21 18 32 21 14 4 12, df = 10 10 10 14 18 15 16 9	19 17 22.2 2 11 79 13.7 12.2 7 (P = 	SD 29.21 38.35 6.41 27.84 45.74 45.74 44.96 43.85 0.14); P A1 SE 5.57 17.06 5.57 17.06 5.57 17.06 5.57 17.06 15.72 115.62 17.51	9 7 19 21 12 17 20 123 = 36%	6.9% 0.9% 38.0% 8.4% 4.4% 20.3% 7.0% 100.0% 100.0% 100.0% 100.0% 11.3% 6.4% 5.0% 3.7% 3.0% 5.0%	IV. Random. 95% CI. -1300 [-37.22, 11.22] -1300 [-37.22, 11.22] -1500 [-88.29, 58.29] -3.30 [-6.81, 0.21] 5.00 [-16.51, 26.51] 9.00 [-60.44, 31.31] 5.00 [-16.51, 26.51] 0.35 [-11.46, 10.76] 0.35 [-11.46, 10.76] 0.36 [-10.64, 3.32] Mean Difference .V. Random. 95% CI -0.00 [-20.30, 17.03] 2.00 [-26.6, 6.66] -10.00 [-10.03, 1.03] -7.60 [-18.24, 2.41] -7.60 [-18.24, 2.41] -8.70 [-48.49, 7.19] 8.00 [-50.14, 28.14] 8.00 [-50.14, 28.14]	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy, or Subgroup. 996Mace, P. J. 996Mace, P. J. 997Cites, T. D. 9997Cites, T. D. 9997Cites, T. D. 9997Cites, T. D. 9997Cites, T. D. 9907Cites, N. D. 90002Rake, D. 90002Rake, D. 9013Takathmi Okuns 7otal (95% Cl) 16etocyanetic, Tau' = 3 9962Kinzida, Tau' = 5 9962Kinzida, K. L. 9962Kinzida, K. G. 996Xinzida, H. G. 996Xinzida, H. G. 996Xinzida, H. G. 9997Bandi, O. O. 997Parod, O. 9997Parod, O. 9997Bandi, O.	6 2 2 18.9 0 0 16 30 0 16 30 0 16 30 0 13.35 22.4 0 113.35 22.4 0 118: CI = 1.03 1 2 2 1 3 3 2 2 1 3 3 2 2 1 3 3 4 1 3 3 4 1 3 3 4 1 1 1 1 1 1 1 1	SD 152 21.52 97.5 4.78 22.07 33.5 34.07 24.67 33.5 m ² = 10.9 0.0 C S0.77 13.53 7.21 7 13.53 2 2.25 6 1.67 7 2.88 4.35.98 1.61.7 7 13.53 8 14.13 1 14.7	8 8 22 21 14 32 21 144 12, df = 10 10 10 10 10 35	19 17 22.2 2 11 79 13.7 12.2 7 (P =	SD 29.21 38.35 6.41 27.84 30.51 45.74 45.74 45.74 45.74 45.74 45.75 14.96 43.85 0.14); P 43.76 5.57 17.06 15.57 11.96 15.62 17.56 15.62 17.56 15.62 17.56 15.62 17.56 15.62 17.56 15.62 17.56 15.62 17.56 17	9 7 19 21 18 12 17 20 123 = 36% 123 = 36% 166 166 18 166 18 166 100 101 12 100 100 100 100 100 100 100	6.9% 0.9% 38.0% 8.4% 4.4% 4.4% 7.0% 100.0% 100.0% 100.0% 100.0% 100.0% 11.3% 6.0% 5.0% 3.0% 5.0% 3.0% 9.6%	IV. Random. 95% CI -13.00 [-37.22, 11.22] -15.00 [-48.29, 58.29] -3.20 [-47.18, 31.9] 5.00 [-16.51, 26.51] 9.00 [-60.44, -17.56] -0.35 [-11.46, 10.76] 0.20 [-13.77, 34.17] -3.66 [-10.64, 3.32] Mean Difference IV. Random. 95% CI -0.00 [-26.46, 5.63] -0.00 [-20.46, 5.64] -0.00 [-20.30, 17.03] 2.00 [-26.6, 6.66] -0.00 [-21.03, 1.03] -7.00 [-19.84, 5.84] -8.00 [-68.45, 8.41] -9.00 [-34.27, -37.3] -10.00 [-34.64, 3.41]	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy of Subgroup 985Mace, P. J. 985Mace, P. J. 993Terikka, T. D. 994Terkwalder, P. 994Terkwalder, P. 994Terkwalder, P. 994Terkwalder, P. 994Terkwalder, P. 994Terkwalder, P. 994Terkwalder, D. 1013Takafumi Okura fotal (995 C) fest for overall effect; Z group7 C+A1 Budy, or Subgroup 990Yang, L. S 990Schulte, K. L 9995Shimanoti, H. G 9997Sumidod, O 997Sumidod, O 997Sumidod, C 997Sumidod, C 997Sumidod, C 997Sumidod, C	6 2 18.99 0 13.35 22.4 00.18: CP 10.18: CP 10.18: CP 10.18: CP 10.18: CP 10.18: CP 10.18: CP 10.18: CP 10.18: CP 10.19: CP 10: CP 10: CP	SD 152 21.52 97.5 4.78 22.07 35.17 33.5 33.5 72 24.67 33.5 m² = 10.9 6 m² = 10.9 7.21 0 16.7 13.5 7.21 0 16.7 13.5 2.25.5 2.6 17.76 2.25.5 2.8 4.35.59 8.14.13 14.7 9 9 7.28	8 8 22 21 18 14 32 21 144 (2, df =)) Total 67 74 18 15 16 9 9 12 10 10 5 22	19 17 22.2 2 11 7.9 13.7 12.2 7.(P = 	SD 29.21 38.35 6.41 27.84 30.51 45.74 45.74 45.74 45.74 45.74 45.74 45.74 45.74 45.74 45.74 45.74 14.96 45.85 0.14); P 14.96 15.72 17.64 15.72 14.96 15.72 15.75 15.72 15.75 1	9 7 19 21 18 12 12 12 12 12 12 12 12 12 12 12 12 12	6.9% 0.9% 38.0% 4.4% 20.3% 7.0% 100.0% 4.4% 20.3% 7.0% 100.0% 4.9% 4.9% 4.9% 4.9% 4.9% 4.9% 4.9% 5.0% 3.7% 3.0% 0.5% 3.9% 3.9% 5.0% 3.9%	IV. Random. 95% CI -13.00 [-37.22, 11.22] -15.00 [-14.22, 11.22] -15.00 [-16.51, 26.51] -3.00 [-4.61, 0.21] -2.00 [-16.51, 26.51] 5.00 [-16.51, 26.51] -0.01 [-16.41, 47.56] -0.35 [-11.48, 10.78] -0.36 [-10.64, 3.32] Mean Difference IV. Random. 95% CI 4.00 [-0.03, 17.03] 2.00 [-26.6, 6.66] -10.00 [-21.03, 1.03] -7.00 [-18.21, 24.1] -8.00 [-4.64, 2.1.44] -8.00 [-4.64, 2.1.44] -9.00 [-4.52, 1.45] -9.00 [-4.52, 1.24] -10.00 [-21.03, 1.03] -7.00 [-18.24, 2.84] -8.00 [-4.64, 2.7, 2.73] -9.00 [-4.52, 1.24] -9.00 [-4.52, 1.24] -9.00 [-4.52, 1.24] -9.00 [-4.52, 1.27] -10.00 [-50.04, 2.81] -10.00 [-60.04, 2.81] -10.00 [-60.04, 2.81] -10.00 [-60.04, 2.7, -7.7] -10.00 [-60.04, 2.7, -7.7]	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy, or Subgroup. 995Mace, P. J. 995Mace, P. J. 9997Cines, T. D. 9997Cines, T. D. 9997Cines, C. 9997Cines, R. 9997Cines, C. 9997Cines, M. 90007Rake, D. 9007Rake, D. 9007Rake, D. 9097Cines, T. Gar, B. 9007Rake, D. 9097Cines, S. 9007Cines, L. 9095Cinud, S. K. 9995Cinud, A. M. 9995Cinud, A. M. 9995Cinud, A. M. 9995Cinud, A. M. 9997Parod, O. 9997Parod, O. 9997Parod, O. 9997Beatric, A. J. 9998Bethman, F. W. 9998Marolia, A. J. 9980Marolia, A. J.	6 2 2 18.9 0 0 16 30 0 16 30 0 16 30 0 13.35 22.4 0 113.35 22.4 0 118: CI = 1.03 1 2 2 1 3 3 2 2 1 3 3 2 2 1 3 3 4 1 3 3 4 1 3 3 4 1 1 1 1 1 1 1 1	SD 1 21 52 21.52 87.5 4.78 32.07 32.07 33.517 33.517 34.07 33.517 33.517 33.517 33.517 34.07 24.67 33.517 33.517 33.517 71.353 72.252 22.62 51.77 71.353 72.86 11.77 52.26 24.11 11.47 72.252 21.11 11.47 77.28 72.86 21.22 12.21 12.11 11.17	8 8 22 21 14 32 21 144 12, df = 10 10 10 10 10 35	19 17 22.2 2 11 79 13.7 12.2 7 (P = 	SD 29,21 38,35 6,41 27,84 30,51 45,74 45,74 45,74 45,74 45,74 45,74 45,74 45,85 0,14); P 45,85 17,06 15,57 17,06 15,57 17,06 14,96 1	9 7 19 21 18 12 20 123 = 36% 123 = 36% 123 = 36% 101 101 101 101 101 102 101 101 102 101 102 101 102 102	6.9% 0.9% 38.0% 14.0% 84.4% 20.3% 7.0% 100.0% 100.0% 100.0% 11.3% 6.4% 5.3% 3.0% 0.5% 3.9% 9.6% 10.0% 5.3%	IV. Random. 95% CI 15.00 [-37.22, 11.22] 15.00 [-16.22, 11.22] -15.00 [-16.51, 26.51] -3.00 [-40.24, 47.56] -3.00 [-40.44, 47.56] -0.02 [-15.57, 26.57] 10.20 [-16.57, 26.57] -3.66 [-10.64, 3.32] Mean Difference //. Random. 95% CI 4.00 [-0.04, 17.03] 2.00 [-26.66, 666] -10.00 [-18.21, 24.584] -8.00 [-19.24, 5.84] -8.00 [-59.18, 42.18] -8.00 [-59.18, 42.18] -9.10 [-54.27, -3.73] -10.00 [-51.26, 2.58] -17.00 [-19.24, 5.84] -8.00 [-59.18, 42.18] -8.00 [-59.18, 42.18] -8.00 [-50.18, 42.18] -8.00 [-50.16, 42.21, 43] -8.00 [-50.16, 42.21, 43] -13.73 [-19.27, -7.74]	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy, or Subgroup. 985Mace, P. J. 985Mace, P. J. 997Clines, T. D. 9992Tens/walder, P. 9992Tens/walder, Tau ² = 3 7eat (95% CI) 9992Tens/walder, Tau ² = 3 9992Tens/walder, Subgroup. 9992Candt, A. M. 9995Candt, A. M. 9995Candt, A. M. 9992Evandte, K. 9992Candt, A. M. 9992Candt, C. 9992Bethman, F. W. 9992Manotia, A. J. 9992Manotia, A. J. 9992Manotia, A. J. 9902Manotia, A. J. 9001Tenstar, W. F.	6 2 18.9 0 16.0 30 30 13.35 22.4 0.18. Cl. 3.3 2 2 2 2 2 13.3 3 4.4 2 2 18.8 19.9 9 5 5 23.4 18.2 19.5 19.5 19.5 19.5 19.5 19.5 19.5 19.5	SD 1:52 21:52 21:52 97:5 4.78 37:5 4.78 32:07 33:5 33:5 12 33:5 12 7:13:33 37:21 0:16:7 13:35 2:22:52 22:52 2:22:52 22:52 2:10:11 14:7 9:18:44 35:59 9:72:82 14:11 9:18:48 18:25	8 8 22 21 18 14 22 21 144 22 4 2 4 5 16 67 14 8 15 16 9 9 12 10 10 10 0 35 22 10 0 12 22 10 14 14 15 15 16 17 18 18 19 19 19 19 19 19 19 19 19 19 19 19 19	19 17 22.2 2 11 17 7 13.7 12.2 7 (P = 	SD 29,21 38,35 6,41 27,84 43,051 45,74 44,98 43,85 0,14); P 43,85 0,14); P 43,85 0,14); P 43,85 13,7,16 5,57 17,06 15,72 14,98 14,98 14,98 14,98 14,98 15,72 14,98 15,72 14,98 14,98 15,72 15,72 14,98 15,72 15,72 14,98 15,72 15,22 14,98 15,72 15,22 14,98 15,72 15,22 14,98 15,72 15,22 14,98 15,22 15,22 14,98 15,22 14,25 15,22 15,22 14,25 15,22 15,25	9 7 19 21 18 12 20 123 = 36% 123 = 36% 123 = 36% 10 10 10 10 10 10 10 10 10 10 10 10 10	6.9% 0.9% 38.0% 14.0% 8.4% 4.4% 20.3% 7.0% 100.0% 10.0% 6.6% 6.6% 6.6% 5.0% 3.9% 5.0% 3.9% 5.5% 11.0%	IV. Random. 95% CI 15.00 [-78.22, 11.22] -15.00 [-78.22, 11.22] -15.00 [-78.23, 11.319] -2.00 [-71.51, 31.319] 5.00 [-16.51, 26.51] 9.00 [-80.44, -17.56] -0.35 [-11.48, 10.78] 0.36 [-10.64, 3.32] -3.66 [-10.64, 3.32] Mean Difference IV. Random. 95% CI 4.00 [-80.47, 31.703] 2.00 [-26.6, 6.66] -10.00 [-21.03, 1.703] 2.00 [-26.6, 6.66] -10.00 [-31.03, 1.703] -10.00 [-31.03, 1.703] -10.00 [-34.27, 3.714] -10.00 [-34.27, 3.714] -10.00 [-34.27, 3.713] -200 [-48.45, 43.418] -17.03 [-18.24, 2.814] -10.60 [-31.73, 1.91.72, -77.41] -200 [-48.6, 10.26] -200 [-48.6, 10.26] -200 [-48.6, 10.26] -200 [-20, 2.04, 2.02] -200 [-20, 2.04, 2.02] -200 [-20, 2.04, 3.02] -200 [-20, 2.04, 3.02] -200 [-20, 2.04, 3.02] -200 [-20, 2.04, 3.02] -200 [-20, 2.04, 3.02]	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy of Subgroup 1985Mace, P. J. 1985Teiles, P. J. 1987Giles, T. D. 1994Terkwalder, P. 1994Terkwalder, P. 1994Terkwalder, P. 1994Terkwalder, P. 1994Terkwalder, P. 1002Rahic, D. 1013Takafumi Okura 1002Rahic, D. 1013Takafumi Okura 1002Rahic, D. 1002Rahic, D. 1002Rahic, D. 1002Rahic, D. 1002Rahic, D. 1002Rahic, D. 1002Rahic, D. 1002Rahic, D. 1002Rahic, H. G. 1995Sumindo, H. G. 1995Sumindo, H. 1995Sumindo, C. 1996Bahman, F. W. 1996Bahman, F. W. 1996Bahman, F. W. 1996Bahman, F. W. 1996Bahman, F. W. 1996Bahman, F. W. 1996Bahman, S. J. 1001Terenza, W. F. 1001Terenza, W. F. 1001Terenza, W. F.	6 2 18.9 0 16.0 30 30 13.35 22.4 0.18. Cl. 3.3 2 2 2 2 2 13.3 3 4.4 2 2 18.8 19.9 9 5 5 23.4 18.2 19.5 19.5 19.5 19.5 19.5 19.5 19.5 19.5	SD 1.52 21.52 21.52 87.5 4.78 87.5 4.78 22.07 22.07 22.07 22.07 22.07 24.67 33.5 33.5 n SD c n n SD c 10.16 n SD c 12.5 c 12.5 c 12.5 c 13.5 c 14.13 9 7.28 14.143 18.25 5 57.03	8 8 22 118 14 32 21 12 114 15 167 14 15 166 9 9 12 10 10 10 355 22 10 10 10 20 10 20 10 20 10 20 10 10 10 10 10 10 10 10 10 10 10 10 10	19 17 222 2 11 7 7 122 7 7 7 9 34 21 34 21 34 34 21 34 34 21 34 21 21 21 21 21 21 21 21 21 21	SD 29,21 38,35 6,41 27,84 43,051 14,96 43,85 0,14); P 443,85 0,14); P 43,76 14,96 145,74 14,96 15,75 17,06 14,96 14,96 14,55 117,06 14,96 14,55 117,06 14,55 117,06 14,55 117,06 14,55 117,06 14,55 117,06 14,55 117,06 110	9 7 7 19 21 16 12 17 20 123 = 36% 16 5 16 16 18 16 18 16 18 16 18 16 19 10 10 10 10 10 10 10 10 10 10 10 10 11 17 20 10 11 17 20 10 10 10 10 10 10 10 10 10 10 10 10 10	6.9% 0.9% 14.0% 4.4% 4.4% 4.4% 4.4% 4.4% 4.4% 4.4%	W. Random. 95% CI 1500 [-37.22, 11.22] -1500 [-16.22, 11.22] -1500 [-16.51, 26.51] -200 [-16.51, 26.51] -200 [-16.51, 26.51] -200 [-16.51, 26.51] -200 [-16.51, 26.51] -3.56 [-10.44, 17.56] -3.56 [-10.64, 3.32] Mean Difference //. Random. 95% CI -4.00 [-0.03, 17.03] 200 [-26.6, 6.66] -10.00 [-21.03, 10.03] 200 [-26.6, 6.66] -10.00 [-21.03, 10.03] 200 [-26.6, 7.19] -8.00 [-24.58, 7.19] -8.00 [-24.58, 7.19] -15.00 [-24.58, 7.19] -15.00 [-24.58, 7.21] -15.00 [-24.58, 7.21] -15.00 [-4.28, 10.26] -15.73]-19.72, -7.74 -2.00 [-14.28, 10.26] 2.20 [-24.57, 7.21] -3.00 [-10.26, 3.46] 2.20 [-24.57, 7.21] -3.00 [-10.26, 3.46]	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy, or Subgroup. 985Mace, P. J. 985Mace, P. J. 9807Clines, T. D. 9997Clines, T. D. 9997Clines, R. 9996Trowwardsr, P. 9996Trowwardsr, P. 9996Trowwardsr, M. 0003Pakie, D. 0013Takathumi Okuras Total (95% CI) steincogeneity: Tau" = 3 9704 (7 c4.1 Budy, C. S. 9995Cand, A. M. 9995Cand, A. J. 9001Drovenzu, R. B. 9001Drovenzu, R. F. W. 9001Drovenzu, R. F. M. 9001Brovenzu, R. F. M. 9003Kalos, L. 9003Kalos, L. K. 9003Kalos, L. K. 9003Kalos, L. K.	6 2 18.99 0 16.00 13.35 22.4 13.35 22.4 10.18: Cf 2 2 2 2 2 2 3.41 2 3.41 2 9.99 1 1.61 1.62 1.62 1.63 1.63 1.63 1.63 1.63 1.63 1.63 1.63	SD 152 21.52 21.52 87.5 4.76 87.5 4.76 22.07 33.55 33.5 7 33.5 7 C C C 16.7 7 13.53 22.52 22.65 8 39.74 4.35.59 8 8 14.33 1 14.7 7 22.9 18.4 35.59 9 18.4 8 18.25 5 57.03	8 8 22 118 14 32 21 12 114 15 167 14 15 166 9 9 12 10 10 10 355 22 10 10 10 20 10 20 10 20 10 20 10 10 10 10 10 10 10 10 10 10 10 10 10	19 17 22.2 2 11 79 70 70 70 12.2 70 12.2 13.7 12.2 14.3 12.2 14.3 12.2 14.3 17 14.2 12.2 14.3 17 14.2 14.3 17 14.2 14.3 1	SD 29.21 38.35 6.41 27.84 30.51 45.74 43.85 0.14); P 41 5.57 17.06 15.57 17.06 15.57 17.06 15.57 17.06 15.57 17.06 15.20 14.96 13.20 14.96 12.20 60.01	9 7 7 19 21 18 12 17 20 123 = 36% 167 16 67 16 68 16 16 16 10 10 10 10 10 10 10 10 10 10 10 10 10	6.9% 0.9% 14.0% 8.4% 4.4% 20.3% 7.0% 100.0% 11.0% 6.4% 11.0% 5.5% 9.6% 5.5% 9.6% 5.5% 9.0% 5.3%	IV. Random. 95% CI 15.00 [-78.22, 11.22] -15.00 [-78.22, 11.22] -15.00 [-78.23, 11.23] -5.00 [-16.51, 26.51] 5.00 [-16.51, 26.51] 0.20 [-17.19, 13.19] 5.00 [-16.51, 26.51] 0.35 [-11.48, 10.78] 0.36 [-10.64, 3.32] Mean Difference V. Random. 95% CI 4.00 [-20.43, 17.03] 2.00 [-26.6, 6.66] 1.00 [-31.03, 17.03] 2.00 [-26.6, 6.66] 9.00 [-80.44, 28.14] 8.00 [-10.34, 17.03] 1.00 [-34.08, 17.03] -10.00 [-31.03, 17.03] -200 [-28.46, 84.61] -3.00 [-48.27, 24.73] -10.00 [-41.03, 1.13] -10.00 [-31.42, 8.41] -10.00 [-31.42, 8.41] -10.00 [-41.33, 17.31] -20.0 [-48.64, 20.42] -3.00 [-48.27, 2-77] -10.00 [-31.42, 8.41] -13.73 [-19.72, -77.44] -14.60 [-8.004, 4.80] -200 [-48.61, 10.26] -200 [-48.61, 10.26] -200 [-48.61, 10.26] -200 [-48.61, 10.26] -200 [-48.61, 10.61] </td <td>-100</td> <td>IV. Random. 95%</td> <td>CI 50 100 5 [Diuretic]</td>	-100	IV. Random. 95%	CI 50 100 5 [Diuretic]
Budy, or Subgroup. 985Mace, P. J. 985Mace, P. J. 9807Ciles, T. D. 9997Cines, R. 9997Cines, R. 9997Cines, R. 9997Cines, R. 9997Cines, R. 9997Cines, R. 9997Cines, T. 9997Cines, G. 9997Cines, T. 9997Cines, G. 9997Cines, T. 9997Cines, C. 9997Cines, C. 9997Wang, L. S. 9995Cines, K. G. 9995Cines, K. G. 9995Cines, K. G. 9995Cines, M. G. 9995Cines, K. G. 9995Cines, K. G. 9995Cines, A. J. 9905Cines, A. J. 9905Cines, A. J. 9905Cines, A. J. 9901Trenstra, W. F. 9902Cines, A. K. 9901Trenstra, W. F. 9003Cines, A. K.	6 2 18.9 0 16.9 30 13.35 22.4 0.18: Crl 13.35 22.4 13.35 22.4 10.18: Crl 10.18: Crl 10.18: Crl 10.18: Crl 10.18: Crl 10.18: Crl 10.18: Crl 10.19 10.10	SD 152 21.52 21.52 87.5 4.76 87.5 4.76 22.07 33.55 33.5 7 33.5 7 C C C 16.7 7 13.53 22.52 22.65 8 39.74 4.35.59 8 8 14.33 1 14.7 7 22.9 18.4 35.59 9 18.4 8 18.25 5 57.03	8 8 22 21 14 12 21 144 12, df = 10 10 10 35 22 10 10 35 22 10 10 20 10 20 10 20 10 20 10 20 12 20 11 10 10 10 10 10 10 10 10 10 10 10 10	19 17 22.2 2 11 13.7 12.2 7 (P = 	SD 29.21 38.35 6.41 27.84 30.51 45.74 43.85 0.14); P 41 5.57 17.06 15.57 17.06 15.57 17.06 15.57 17.06 15.57 17.06 15.20 14.96 13.20 14.96 12.20 60.01	9 7 7 19 21 18 12 17 20 123 = 36% 17 123 = 36% 17 123 = 36% 16 16 16 16 16 10 10 10 10 10 10 10 10 10 12 11 17 17 20 17 19 19 21 17 19 21 17 20 19 19 21 17 20 19 19 21 17 20 19 19 21 17 20 19 19 21 17 20 19 19 20 10 21 17 20 19 20 10 20 20 20 20 20 20 20 20 20 20 20 20 20	6.9% 0.9% 14.0% 8.4% 4.4% 20.3% 7.0% 100.0% 11.0% 6.4% 11.0% 5.5% 9.6% 5.5% 9.6% 5.5% 9.0% 5.3%	IV. Random. 95% CI 1500 [-322, 1122] -1500 [-322, 1122] -1500 [-462, 29, 5628] -330 [-61, 124, 1319] 500 [-16, 51, 2651] 94, 900 [-80, 44, -17, 56] 94, 900 [-80, 44, -17, 56] 900 [-16, 51, 26, 51] 90, 16, 14, 48, 10, 76] 90, 26 [-14, 46, 13, 32] Mean Difference Mandom, 35% CI 4, 20 [-40, 43, 32] 10, 20 [-13, 77, 34, 17] 2, 00 [-26, 6, 66] 10, 00 [-10, 31, 103] -7, 00 [-18, 42, 144] -10, 00 [-21, 03, 1, 103] -7, 00 [-48, 42, 144] -10, 00 [-41, 03, 1, 103] -10, 00 [-41, 04, 12, 044] -10, 00 [-50, 16, 43, 13] -10, 00 [-50, 16, 43, 14, 26, 14] -10, 00 [-41, 42, 04, 26, 14] -13, 73 [-19, 72, -74] -200 [-44, 26, 1028] -200 [-44, 26, 1028] -200 [-44, 26, 14, 26, 14] -500 [-41, 31, 31, 31] -500 [-43, 16, 61] -500 [-51, 16, 671] -500 [-52, 14, 16, 61] -500 [-54, 16, 571]	-100	IV. Random. 95%	CI
Budy, or Subgroup. 985Mace, P. J. 985Mace, P. J. 987Ciles, T. D. 9997Cines, R. 9997Cines, R. 9990Treskwader, P. 9990Treskwader, P. 9990Treskwader, P. 9990Treskwader, P. 9990Treskwader, P. 9990Treskwader, Tau' = 3 9990Treskwader, Tau' = 3 9990Treskwader, Tau' = 3 9990Treskwader, S. 9990Treskwader, S. 9990Schuft, K. L. 9995Candi, A. M. 9997Lonbard, M. 9997Lonbard, M. 9997Suminon, T. 9995Behman, F. W. 9997Suminon, T. 9995Behman, F. W. 9997Suminon, T. 9995Behman, K. K. 1001Drevenus, R. J. 0001Terpata, W. F. 0003Bige, A. K. K. 10003Biger, C. 9997Lonbard, N. K. 1003Biger, S. C.	6 6 2 2 18.9 0 16.9 18.9 0 16 13.35 22.4 0.18. Cr 0.18. C	SD 1 21.52 21.52 27.5 37.5 35.17 34.07 33.5 33.5 m² = 10.9 0.16.7 6 17.76 6 17.76 5 22.85 6 17.76 5 55 8 14.7 9 7.81 14.8 14.25 5 57.03 7 2.94 4 20.54 4 20.54 4 20.54	8 8 8 14 12 21 144 12, df = 10 10 10 10 10 10 10 10 10 10 10 10 10	19 17 22.2 2 11 79 13.7 12.2 7 (P = 	SD SD 29:21 29:21 38:35 6:41 27:84 43:85 0.14): I2 74:57 43:85 37:16 55:17 17:06 15:57 14.98 17:17 15:62 17:51 12:36 12:20:66 60:1 20:66 60:1 13:37	9 7 7 19 21 12 12 17 20 12 12 17 20 12 12 12 12 12 10 12 10 10 10 10 10 10 10 10 10 10 10 10 10	6.9% 0.9% 0.9% 14.0% 4.4% 4.4% 4.4% 4.4% 100.0% 11.0% 100.0% 11.0% 100.0%	IV. Random. 95% CI 1500 [-322, 1122] -1500 [-322, 1122] -1500 [-462, 29, 5628] -330 [-61, 124, 1319] 500 [-16, 51, 2651] 94, 900 [-80, 44, -17, 56] 94, 900 [-80, 44, -17, 56] 900 [-16, 51, 26, 51] 90, 16, 14, 48, 10, 76] 90, 26 [-14, 46, 13, 32] Mean Difference Mandom, 35% CI 4, 20 [-40, 43, 32] 10, 20 [-13, 77, 34, 17] 2, 00 [-26, 6, 66] 10, 00 [-10, 31, 103] -7, 00 [-18, 42, 144] -10, 00 [-21, 03, 1, 103] -7, 00 [-48, 42, 144] -10, 00 [-41, 03, 1, 103] -10, 00 [-41, 04, 12, 044] -10, 00 [-50, 16, 43, 13] -10, 00 [-50, 16, 43, 14, 26, 14] -10, 00 [-41, 42, 04, 26, 14] -13, 73 [-19, 72, -74] -200 [-44, 26, 1028] -200 [-44, 26, 1028] -200 [-44, 26, 14, 26, 14] -500 [-41, 31, 31, 31] -500 [-43, 16, 61] -500 [-51, 16, 671] -500 [-52, 14, 16, 61] -500 [-54, 16, 571]	-100	IV. Random. 95%	50 100 50 CI
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Budy, or Subgroup. 1985Mace, P. J. 1985Mace, P. J. 1987Clines, T. D. 1997Clines, T. D. 1997Clines, T. D. 1998Darres/watcher, P. 1998Darres/watcher, P. 1998Darres/watcher, D. 1998Darres/watcher, D. 1998Darres/watcher, D. 1998Darres/watcher, D. 1998Darres/watcher, D. 1999Darres/watcher, D. 1999Darres/watcher, K. 1999Darres/watcher, K. 1999Darres/watcher, K. 1999Darres/watcher, K. 1999Darres/watcher, M.	6 6 9 18.9 0 16 30 13.35 22.4 00.18; Cl 2.2 13.3 3 2 2 2 2 2 2 2 3 4 1 3 3 2 2 4 13.3 5 2 2.4 Meaa 8 2 2 4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2 2.4 13.35 2.2 13.35 13.35 2.2 13.35 13.35 2.2 13.35 13.25 13.35 13.25 14.25 15	SD SD 21.52 21.52 21.52 97.5 4.76 35.17 33.5 7 24.67 33.5 33.5 7 0 16.7 13 7 21.52 13.5 0 16.7 13 7 21.52 14.14 14.7 9 7 23.9 4 30.55 5 57.03 7 23.9 4 20.54 4 20.54 4 20.54 4 20.54 4 20.54 4 20.54 4 20.54 4 20.54	8 8 8 14 12 21 14 12 21 14 12 21 14 12 21 14 12 21 14 18 15 16 67 14 18 15 16 16 10 10 10 10 10 20 20 10 11 14 14 12 21 14 14 14 14 22 21 14 14 14 22 21 14 14 14 22 21 14 14 14 22 21 14 14 14 14 22 21 14 14 14 14 14 14 14 14 14 14 14 14 14	19 17 22.2 2 11 79 13.7 12.2 7 (P = 	SD SD 29.21 29.21 27.84 38.35 6.41 27.84 27.84 30.51 45.74 45.74 45.74 45.74 45.74 45.74 45.74 14.96 43.85 0.14): I ² 14.96 43.85 15.72 14.96 15.72 14.92 14.95 12.92 14.95 20.66 20.61 12.32 20.60 60.07 13.37 0.0007)	9 7 7 19 21 12 12 12 7 20 12 12 12 12 12 12 12 12 12 12 12 12 12	6.9% 38.0% 38.0% 14.0% 8.4% 4.4% 7.0% 100.0% 11.3% 6.0% 5.0% 9.8% 9.8% 9.9% 9.9% 9.9% 9.9% 9.9% 9.9	IV. Random. 95% CI -13.00 [-37.22, 11.22] -15.00 [-48.29, 58.26] -3.00 [-48.29, 58.26] -3.00 [-48.1, 0.21] -3.00 [-48.1, 28.16] 5.00 [-16.51, 26.51] 10.20 [-13.77, 34.17] 10.20 [-13.77, 34.17] 10.20 [-13.77, 34.17] 10.20 [-13.77, 34.17] 2.20 [-2.66, 64.3, 3.32] IV. Random. 95% CI 4.00 [-9.03, 17.03] 2.20 [-2.66, 64.3, 1.03] -7.00 [-18.45, 18] -8.00 [-40.24, 25.48] -8.00 [-50.14, 26.14] -8.00 [-50.24, 7.217] -1.00 [-8.06, 4.86] 5.00 [-41.3, 31.31] 0.00 [-16.61, 16.61] 5.60 [-5.51, 16.71] -3.32 [-6.87, 0.24] Mean Difference	-100	N. Random. 95%	CI 50 10 50 10 50 10 50 10 50 10
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Figure 2. Results of traditional meta-analysis (A1 = ACEI; A2 = ARB; B = FS- β -B; C = CCB; D = diuretic). ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, FS- β -B = fat-soluble and selective β 1-receptor blockers.

conducted by Sihm in the group6 (diuretic vs CCB) (References supplemental appendix 36, http://links.lww.com/MD/B593), the study conducted by Gaudio in the group 7 (CCB vs ACEI) (References supplemental appendix 16, http://links.lww.com/

MD/B593) and the study conducted by Caglar in the group 1 (FS- β -B vs ACEI) (References supplemental appendix 1, http://links. lww.com/MD/B593), we found that the pooled effect did not change, and the between-study heterogeneity decreased

The results of network and traditional meta-analysis for regression of LVH.									
A1	-1.22 (-4.84, 2.40)	7.29 (-8.42, 23.00)	-3.32 (-6.67, 0.24)	-4.91 (-11.70, 7.89)					
-4.31 (-10.03, 1.73)	A2	-0.10 (-8.16, 7.96)	-9.52 (-27.15, 8.19)	-9.08 (-16.18, -1.98) [*]					
-7.09 (-14.99, 1.27)	-2.66 (-12.02, 6.31)	В	NO	NO					
3.86 (0.02, 7.69)*	8.33 (2.08, 14.01)*	10.90 (1.98, 19.49)	С	-3.66 (-10.64, 3.32)					
5.99 (0.78, 11.57)*	10.30 (3.44, 16.97)*	13.04 (3.38, 22.59)*	2.12 (-3.25, 7.84)	D					

A1 = ACEI, A2 = ARB, B = FS- β -B, C = calcium channel blocker, D = diuretic. Red font represent the results of network meta-analysis and black font represent the results of traditional meta-analysis. Drugs are reported in alphabetical order. Results are the mean differences (MDs) in the column-defining treatment compared with the MDs in the row-defining treatment. For regression of LVH, MDs > 0 favor the column-defining treatment (ie, the first in alphabetical order). Significant results are marked(*). To obtain MDs for comparisons in the opposite direction, opposites should be taken (eg, the MD for B compared with A1 is 7.09 [-1.27, 14.99]).

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, FS-β-B = fat-soluble and selective β1-receptor blockers, LVH = left ventricular hypertrophy.

significantly (I^2 = 36.0% to 0%, I^2 = 52.0% to 17%, and I^2 = 96.0% to 0%, respectively). These 3 studies could be the source of the heterogeneity. First, in the group 2, the study conducted by Sihm was the only one that added other antihypertensive drugs into original drug therapy. Second, the study conducted by Gaudio was the only one that employed magnetic resonance imaging instead of echocardiography to measure the LVMI in the group 3. Last, the cause of the significant heterogeneity in the group 1 might lie in the limitation of the study number included. Just only 3 studies were included.

Besides, when we excluded the study conducted by Gosse in the group 8 (References supplemental appendix 29, http://links.lww. com/MD/B593), the pooled result changed and the betweenstudy heterogeneity decreased significantly (P=0.16-0.001; $I^2=73\%-5\%$). The possible causes were listed as follows. First, the drug used in this study was indapamide rather than hydrochlo-rothiazide. They were grouped together in a single class of antihypertensive drug (diuretic). Indapamide had calciumantagonistic effect, not only diuretic effect. Second, a total of 131 patients (25.9%) prematurely discontinued the study. The missing rate was higher than other studies in group 8. Considering the significant heterogeneity, we performed sensitivity analysis by excluding this study in our network metaanalysis.

Moreover, the regression analysis based on different duration of medication, treatment regimen, published time, sample size, and study countries showed that there was no one factor influenced our results (supplemental table appendix 4, http:// links.lww.com/MD/B593).

3.7. Model inconsistency (Bayesian network metaanalyses)

In the network meta-analysis, the disagreement between direct and indirect comparison was concerning and was examined by calculating the inconsistency factors. For all comparisons in the regression of LVH, the 95% CI of inconsistency factors from all cycles included zero (Table 3), and the node-splitting method showed no significant inconsistency within the networks for any of these outcomes, which suggested that the results in the network were consistent between direct and indirect evidence (Table 4).

4. Discussion

To our knowledge, this is the first and only one Bayesian network meta-analysis that included most updated studies to evaluate all of the 5 classes of antihypertensive drugs on regression of LVH. The key point of this analysis was whether the accepted idea, β -blockers were associated with less regression for LVH patients than ACEI or ARB, was right. Using the network meta-analysis of randomized controlled trials, the indirect comparisons between drugs were made possible, and the relative differences between different classes of antihypertensive agents could be determined. In this Bayesian network meta-analysis, the probability ranking analysis suggested that FS- β -B was the preferred agent for the regression of LVH.

The mechanisms underlying the beneficial effects of FS-β-B remain unknown and may be multifactorial. First, adrenergic system plays an important role in the development of LVH and heart failure (HF).^[19,20] Simply, adrenergic receptors belong to the guanine nucleotide-binding G protein-coupled receptor (GPCR) superfamily. So far, 7 mammalian isoforms of GPCR kinases (GRK1-GRK7) have been identified. GRK2 and GRK5 are the predominantly expressed isoforms in the heart. Both of them could inhibit NF-kB transcriptional activity which was relevant in the development of LVH.^[21] Second, according to a recently published updated clinical and pharmacological evaluation edited by Maung-U,^[22] there were several differences between FS-B-B and other B-blockers. On the one hand, lipophilic compounds are rapidly adsorbed in the gastrointestinal tract and cell membrane, and are extensively metabolized in the liver (1st-pass metabolism), resulting in a shorter half life, a faster response time when compared to other β -blockers.^[23] On the other hand, B1-receptors mainly exist in heart, while B2receptors mainly exist in bronchus and vascular smooth muscle. The reduced inhibitory effect on β 2-receptor makes the selective β1-blockers less likely to cause peripheral vasoconstriction, so that it could bring better antihypertensive effect than other β-blockers. Third, previous fundamental research showed that cardiac-specific overexpression of B1-receptors in mice caused cardiomyocyte hypertrophy.^[24,25] However, the consequences of overexpression of B2-receptors were more complex. A 200-fold overexpression of \u03b32-receptors in the murine heart was accompanied by increased heart rate and left ventricular contractility.^[26] A 350-fold overexpression of β 2-receptors in mouse models was associated with dilated cardiomyopathy, heart failure, and mortality.^[27] For these reasons, selective β 1receptor blockers might show better regression on LVH. Last, the more pronounced effect of FS-B-B may not be ascribed only to the reduction of blood pressure, but other factors might have concurred. For example, nebivolol, a new generation β -receptor blocker, had a vasodilator property that mediated by the Larginine/NO pathway. Besides, differently from classical β-blockers, nebivolol has been demonstrated to have antiproliferative activity,^[28–32] attributable to the increase of NO bioavailability also at coronary and cardiac level.^[33,34] NO is involved on LV fibrotic component regression.[32,35] This property might have played an important role in the regression

group1 B+A1		в			A1			Mean Difference	Mean Difference
Study or Subgroup	Mean		Total	Mean		Total	Weight	a set of a second of the set of the second se	
Gosse P1990		17.35	19	10	40.58	22	6.6%	6.00 [-12.67, 24.67]	
KARIN 2001	14	4	26	16	40.58	25	93.4%		
ARIN 2001	31.9	3.4	20	14.8	2.9	20 52	93.4%	-2.00 [-6.95, 2.95] 17.10 [15.90, 18.30]	
- CHOLANZOTT	31.8	3.4	04	14.0	2.3	92	0.0%	11.10 [13.80, 16.30]	
fotal (95% CI)			45			47	100.0%	-1.47 [-6.26, 3.31]	1
Heterogeneity: Tau ² = 0 Test for overall effect: 2				1 (P = 0	(,42); I*	= 0%			-100 -50 0 50 100 favours [ACEI] favours [FS-B-B]
group6 D+C									
		D			C			Mean Difference	Mean Difference
Study or Subgroup	Mean		Total		1.		Weight	IV. Random, 95% CI	IV. Random. 95% Cl
1985Mace, P. J.		21.52	8	19	29.21	9	1.7%	-13.00 [-37.22, 11.22]	
1987Giles, T. D	2	97.5	8	17	38.35	7	0.2%	-15.00 [-88.29, 58.29]	
1993Senior, R.	18.9	4.78	22	22.2	6.41	19	81.7%	-3.30 [-6.81, 0.21]	
1994Trenkwalder, P	0	22.07	21	2	27.84	21	4.4%	-2.00 [-17.19, 13.19]	
1996Dey, H. M	16	35.17	18	11	30.51	18	2.2%	5.00 [-16.51, 26.51]	
000Sihm, I	30	34.07	14	79	45.74	12	0.0%	49.00 [-80.44, -17.56]	
2002Rakic, D	13.35	24.67	32	13.7	14.98	17	8.1%	-0.35 [-11.48, 10.78]	+
013Takafumi Okura	22.4	33.5	21	1000	43.85	20	1.7%	10.20 [-13.77, 34.17]	<u> </u>
Total (95% CI)			130			111	100.0%	-2.78 [-5.95, 0.39]	•
Heterogeneity: Tau ² = 0	00 CH	2 = 2 70	and the second second	(P=0)	18-12-			and famous anost	
Fest for overall effect: Z				0 - 04	197, P =				-100 -50 0 50 1 Favours [CCB] Favours [Diuretic]
proup7 C+A1									Pavours [Coop] Pavours [Dimetic]
groups or Al		с			A1			Mean Difference	Mean Difference
Study or Subgroup	Mean		D Tota	Mean		Total	Weight		
1991Wang, L. S		8 39.74			a second and a	and a second	and the second		
1992Schulte, K. L	23	Contraction of the second							
1995Grandi, A. M	20							the second s	
			S		10000	1 000			
1995Kirpizidis, H. G		7 13.5			15.72		a manager of the		
1995van Leeuwen, J. T		2 22.5							
996Shimamoto, H	34.6				3 17.51				
1997Lombardo, M	25								
1997Parodi, O	-	4 35.5	9 10) 4	74.51	10			
1997Sumimoto, T	18.8	8 14.13	3 10	37.8	3 20.19	10	3.0%	-19.00 [-34.27, -3.73]	
1998Beltman, F. W	11	1 14.3	7 35	12.6	5 13	36	12.4%	-1.60 [-8.06, 4.86]	+
1998Gaudio, C	9.99	9 7.2	8 22	23.72	12.36	22		Not estimable	
1998Manolis, A. J	13	2 14.1	1 10	14	14.53	11	4.4%	-2.00 [-14.26, 10.26]	
001Devereux, R. B	16.9	9 18.4	4 122	14.3	20.6	113	17.2%		
001Terpstra, W. F	23.8	8 18.2	5 61	27.2	20.66	63	11.4%	the second s	
003Koldas, L.		5 57.0		and the second					
005Bilge, A. K	17			1. Sec.		1000			
005Sabharwal, N. K		4 20.5							
fotal (95% CI)			452			453	100.0%	-1.45 [-4.18, 1.29]	4
Heterogeneity: Tau ² = 4	80: Ch	= 18.0			0.26): P	1000	2	an one of the state of a state of a state of the	++ ++
Test for overall effect: Z					and the second sec				-100 -50 0 50 1 Favours [ACEI] Favours [CCB]
group8 D+A1									
		D			A1			Mean Difference	Mean Difference
Study or Subgroup	Mean	10000	Total	1222			Weight	IV. Random, 95% Cl	IV. Random. 95% CI
Dahlof, B1992	13.3	8.74	11	21.6	7.81	12	34.4%	-8.30 [-15.10, -1.50]	
Fagard, R. H1997	28	77.02	11	40	85.63	14	0.4%	-12.00 [-75.90, 51.90]	
Gosse, P 2000	7.3	25.8	205	3	25.8	206		Not estimable	
Roman, M. J1998	0.8	21.8	28	8.7	20.1	22	11.7%	-7.90 [-19.55, 3.75]	
Senior, R1993	7.67	5.79	9	12	6.36	9	50.4%	-4.33 [-9.95, 1.29]	-
Sihm2000		34.07	14	54	23.9	11	3.1%	-24.00 [-46.76, -1.24]	
fotal (95% CIL			73			68	100.0%	-6.75 [-10.74, -2.76]	•
Total (95% CI)		-		10 - 0			100.076	-0.10[-10.14, -2.10]	
leterogeneity: Tau ² = (1.00; Ch			(P=0	.53); P =	0%			-100 -50 0 50 1
Test for overall effect: 2									

Figure 3. Sensitive analysis of traditional meta-analysis (A1 = ACEI; A2 = ARB; B = FS- β -B; C = CCB; D = diuretic). ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, FS- β -B = fat-soluble and selective β 1-receptor blockers.

Table 2 Ranking.									
Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5				
A1	0.01	0.10	0.85	0.03	0.00				
A2	0.27	0.66	0.06	0.10	0.00				
В	0.72	0.23	0.03	0.10	0.00				
С	0.00	0.00	0.03	0.75	0.21				
D	0.00	0.00	0.01	0.20	0.78				

Ranking indicates the probability to be the best treatment, the 2nd best, the 3rd best, and so on, among the 5 antihypertensive drugs. A1=ACEI, A2=ARB, B=FS- β -B, C=CCB, D=diuretic. ACEI=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, CCB=calcium channel blocker, FS- β -B=fat-soluble and selective β 1-receptor blockers.

of LV fibrotic component, that characterizes LVH.^[36,37] In addition, nebivolol reduces large arterial stiffness and central blood pressure,^[38,39] which have a pathogenetic role in promoting LVH.^[39,40] One previous meta-analysis concluded that nebivolol achieved similar or better rates of treatment response and BP normalization than other drug classes, with significantly better tolerability than losartan, other β -blockers, and all antihypertensive drugs combined. This meta-analysis suggested that nebivolol, one of the FS- β -B, is likely to have advantages over existing antihypertensives and may have a role in the 1st-line treatment of hypertension.^[41]

The information revealed in our meta-analysis will be useful for clinicians and will enable them to select the optimal antihypertensive agents to regress the LVH in hypertensive patients. Especially in Asia, where LVH caused by hypertension was common.^[42,43]

5. Conclusion

In our study, FS- β -B were estimated to have a 72% chance of being the best for regression of LVH. Although there were no statistical difference between FS- β -B and ARB/ACEI. The clinical evidence related to the FS- β -B in regression of LVH was insufficient considering the limitation of the study number. So, more studies are needed with FS- β -B to find out if they do indeed Table 3 Inconsistency factors.

Cycle	Median (95% Crl)		
A1, A2, B	-0.33 (-13.64, 8.83)		
A1, A2, C	-0.76 (-12.25, 5.09)		
A1, A2, C, D	-0.85 (-14.48, 5.23)		
A2, C, D	-0.41 (-12.83, 7.03)		

A1=ACEI, A2=ARB, B=FS- β -B, C=CCB, D=diuretic. ACEI=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, CCB=calcium channel blocker, FS- β -B=fat-soluble and selective β 1-receptor blockers.

reduce LVM to a greater extent than other antihypertensive agents do and if this effect would lead to a better prognosis.

6. Limitation

As with any meta-analysis, several limitations should be highlighted. First, there were significant heterogeneity in group 4 (CCB vs ARB) in traditional meta-analyses. It might be contributed to the limitation of the study number considering that only 3 studies were included in these groups. So, even after we performed sensitivity analysis, we could not find out the sources of heterogeneity in group 4. Second, most of the patients were prescribed with different treatment regimens, such as the dosage, combination antihypertensive drugs, and duration. Our results were influenced inevitably by these confounding factors. Although we conducted regression analysis to control these factors. Third, different drugs were grouped together in a single class of antihypertensive drug, such as indapamide and hydrochlorothiazide. And that might be the reason why the study conducted by Gosse brought about significant heterogeneity and influenced the result of traditional meta-analysis in group 8. Although no significant change in efficacy hierarchies emerged in sensitivity analysis after excluding the study conducted by Gosse. Last, network meta-analysis was simply a statistical method, and its clinical literature evidence level might not be that

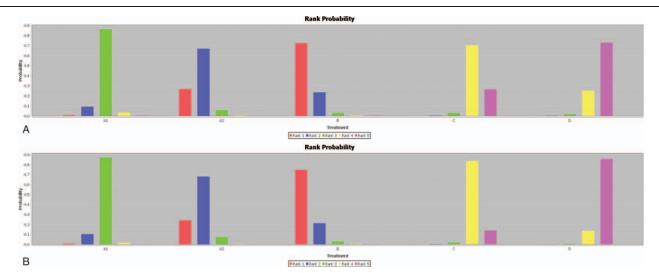


Figure 4. (A) Rangking (A1=ACEI; A2=ARB; B=FS- β -B; C=CCB; D=diuretic). (B) Sensitivity analysis of network meta-analysis (A1=ACEI; A2=ARB; B=FS- β -B; C=CCB; D=diuretic). ACEI=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, CCB=calcium channel blocker, FS- β -B=fat-soluble and selective β 1-receptor blockers.

Study	Direct effect	Indirect effect	Overall	Р	
A1 + A2	0.83 (-7.33, 8.93)	7.64 (-0.75, 15.23)	4.31 (-1.73, 10.03)	0.23	
A1 + B	7.80 (-1.92, 16.79)	3.65 (-13.99, 20.87)	7.09 (-1.27, 14.99)	0.67	
A1 + C	-3.46 (-8.08, 1.02)	-5.47 (-13.76, 3.20)	-3.90 (-7.69, -0.02)	0.68	
A1 + D	-4.76 (-12.69, 2.61)	-7.01 (-15.10, 0.59)	-5.56 (-11.57, -0.78)	0.68	
A2 + B	-0.12 (-16.34, 16.27)	3.77 (-7.56, 15.30)	2.66 (-6.31, 12.02)	0.69	
A2 + C	-13.58 (-22.78, -3.20)	-5.41 (-12.57, 1.79)	-8.18 (-14.01, -2.08)	0.19	
A2 + D	-8.96 (-21.30, 3.19)	-10.88 (-19.10, -2.46)	-10.30 (-16.97, -3.44)	0.81	
C + D	-4.03 (-12.40, 4.02)	-0.48 (-8.72, 6.93)	-2.12 (-7.84, 3.25)	0.53	

A1=ACEI, A2=ARB, B=FS-β-B, C=CCB, D=diuretic. ACEI=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, CCB=calcium channel blocker, FS-β-B=fat-soluble and selective β1-receptor blockers.

good. But, the point was the clinical significance it reflected, especially for the question that nobody paid attention to.

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