Does chronotherapy for essential hypertension matter by class? A systematic review and meta-analysis

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Abstract

Objectives The study was performed to evaluate the efficacy and safety of chronotherapy of hypertension with different medications monotherapy or a combination compared with traditional regimens Methods Three databases including PubMed, EMBASE and the Cochrane Library were searched, from the inception of each database to 10 April 2020. The Review Manager 5.4 was adopted for meta-analyses and subgroup analyses. The blood pressure delta (Δ) was used as mean of differences (MD) with 95% confidence intervals (CIs), and the estimated effect for events estimates the 95% CIs for frequency of events. The adults with essential hypertension were treated with chronotherapy and traditional regimens. Results Twenty-eight RCTs, recruiting 1865 patients in bedtime/evening dosing and 1867 in awakening/morning dosing, were enrolled in this quantitative review. Meta-analysis showed no significant differences for overall drug-related AEs (RR=0.81, P=0.17; I2=41%), but an obvious reduction of risk for overall withdrawals (RR=0.52, P=0.005; I2=0.0%) with bedtime dosing. No statistically significant differences were noted for clinic BP and diurnal BP, but 24-hour (48-hour) BP, nocturnal BP, morning BP, and non-dippers (%) showed obvious reductions, statistically. By class, there existed different efficacy between 2 administrations, with great decrease in nocturnal BP control and changes in circadian rhythm with RAAS blockers monotherapy, but an all-day control of BP for CCBs and diuretics. With regard to a combination, no significant differences in BP management were detected and the data about beta-receptor blockers were limited. Conclusions The safety and efficacy of chronotherapy in antihypertensive drugs might be based on the classes.

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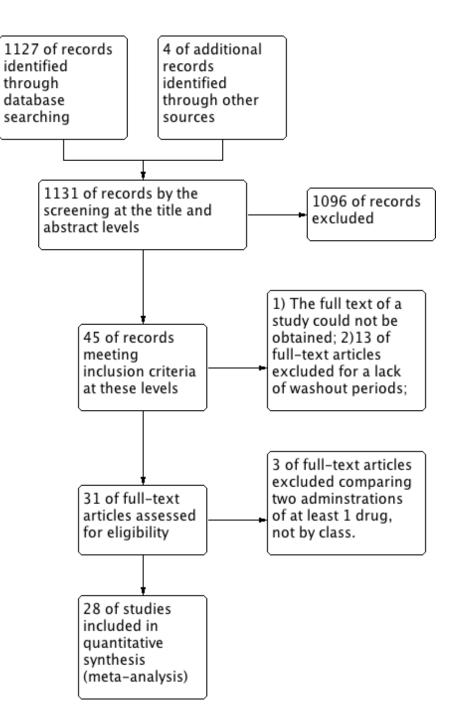
manuscript.pdf available at https://authorea.com/users/405719/articles/516597-doeschronotherapy-for-essential-hypertension-matter-by-class-a-systematic-review-and-metaanalysis

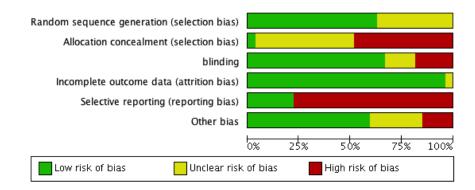
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Table 1 Included studies.pdf available at https://authorea.com/users/405719/articles/516597does-chronotherapy-for-essential-hypertension-matter-by-class-a-systematic-review-andmeta-analysis

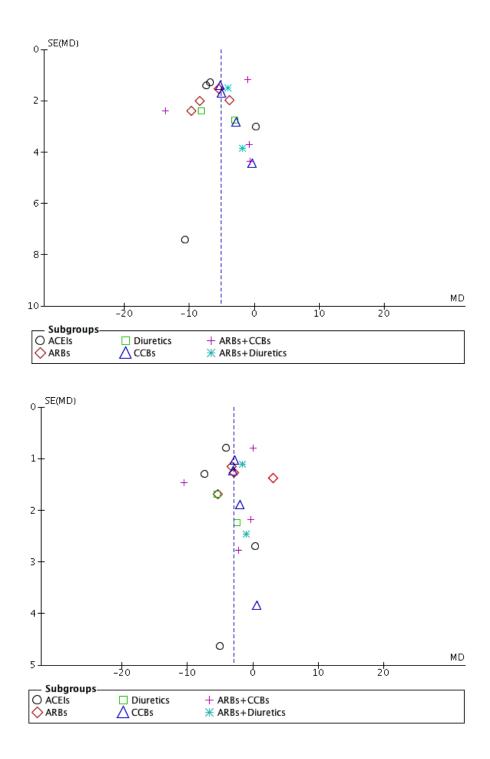
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Table 2 (safety profiles).pdf available at https://authorea.com/users/405719/articles/516597does-chronotherapy-for-essential-hypertension-matter-by-class-a-systematic-review-andmeta-analysis





	Random sequence generation (selection bias)	Allocation concealment (selection bias)	blinding	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Acelajado 2012	?	?	+	+	•	?
Asmar 2011	?	?	Ŧ	Ŧ		?
Calvo 2006	ŧ		Ŧ	ŧ	•	Ŧ
Hermida 2003	ŧ		÷	?		Ŧ
Hermida 2005a	+		+	÷		÷
Hermida 2005b	+	•	+	÷		Ŧ
Hermida 2007	Ŧ	•	Ŧ	Ŧ	•	•
Hermida 2007a	Ŧ	0	Ŧ	Ŧ		+
Hermida 2008	÷		÷	Ð		+
Hermida 2008a	÷		+	Ŧ		+
Hermida 2009	÷	+	?	÷	÷	+
Hermida 2009a	+	?	?	+	+	•



	Mean	J/Awake SD	ning Total	Mean	ng/Bedt SD		Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% Cl
4.2.1 ACEIs									
Hermida 2009	8.4	8.8	58	11.2	5.5	57	7.7%	-2.80 [-5.48, -0.12]	
Hermida 2009a	8.6	6.6	83	9.7	7.3	82	9.7%	-1.10 [-3.22, 1.02]	-+
Macciarulo 1999 Subtotal (95% CI)	11.81	15.22	40 181	15.19	15.1	40 179	2.0% 19.4%	-3.38 [-10.02, 3.26] -1.85 [-3.47, -0.24]	•
Heterogeneity: Tau ² = Test for overall effect:				(P = 0.5	56); I ² =	0%			
4.2.2 ARBs									
Hermida 2003	17	0	46	3.2	0	44		Not estimable	
Hermida 2005a	13.1	10.7	72	14.7	11.2	76	5.4%	-1.60 [-5.13, 1.93]	
Hermida 2005b	12.2	9.8	50	15.4	11.6	50	4.2%	-3.20 [-7.41, 1.01]	
Hermida 2007	7.8	6.6	107	8.7	6.4	108	11.5%	-0.90 [-2.64, 0.84]	
Hermida 2009b	13.8	9.5	67	13.9	11.1	66	5.4%	-0.10 [-3.61, 3.41]	
Ushijima 2015	5.1	9.1	11	0.9	16.4	12	0.8%	4.20 [-6.52, 14.92]	
Subtotal (95% CI) Heterogeneity: Tau ² =	0.00 [.] Chi ⁱ	2 = 2 33	353 df = 4	(P = 0.6)	58): I ² =	356	27.3%	-1.04 [-2.38, 0.30]	•
Test for overall effect:									
4.2.3 Diuretics			_			_			
Calvo 2006	6.2	10.2	30	11.2	10.3	28	2.9%	-5.00 [-10.28, 0.28]	
Hermida 2008 Subtotal (95% CI)	б.4	13.3	57 87	14.8	10	56 84		-8.40 [-12.73, -4.07] -7.03 [-10.38, -3.68]	
Heterogeneity: Tau ² = Test for overall effect:			df = 1	(P = 0.3	33); I ² =		0.5%	7.05 [10.50, 5.00]	•
4.2.4 CCBs									
Hermida 2007a	10.3	10.7	39	11.9	12.3	41	3.1%	-1.60 [-6.65, 3.45]	—-
Hermida 2008a	9	10	88	13	12	92	6.1%	-4.00 [-7.22, -0.78]	
Hermida 2009c	8.7	9.8	118	12.8	11.8	120	7.4%	-4.10 [-6.85, -1.35]	
Nold 1998	8.1	8.1	12	8.7	8	12	2.1%	-0.60 [-7.04, 5.84]	
Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect:				(P = 0.6	56); I ² =	265 0%	18.8%	-3.44 [-5.29, -1.59]	•
4.2.5 BBs									
Acelajado 2012	11.7	0		11.43	0	38		Not estimable	
						38		Not estimable	
Subtotal (95% CI)			38						
Heterogeneity: Not ap		able	38						
Heterogeneity: Not ap Test for overall effect: 4.2.6 ARBs+CCBs	Not applic								
Heterogeneity: Not ap Test for overall effect: 4.2.6 ARBs+CCBs Asmar 2011	Not applic	11	231	11	12	232	9.8%	0.00 [-2.10, 2.10]	-
Heterogeneity. Not ap, Test for overall effect: 4.2.6 ARBs+CCBs Asmar 2011 Hermida 2010	Not applic 11 17.3	11 13.4	231 50	24.8	10.2	52	3.6%	-7.50 [-12.13, -2.87]	+
Heterogeneity: Not ap Test for overall effect: 4.2.6 ARBs+CCBs Asmar 2011 Hermida 2010 Kario 2016	11 17.3 11.6	11 13.4 14.6	231 50 32	24.8 12.8	10.2 13.1	52 36	3.6% 2.0%	-7.50 [-12.13, -2.87] -1.20 [-7.83, 5.43]	
Heterogeneity. Not ap Test for overall effect: 4.2.6 ARBs+CCBs Asmar 2011 Hermida 2010 Kario 2016 Peng 2013	11 17.3 11.6	11 13.4	231 50 32 26	24.8	10.2 13.1	52 36 28	3.6% 2.0% 2.0%	-7.50 [-12.13, -2.87] -1.20 [-7.83, 5.43] -1.43 [-8.00, 5.14]	
Heterogeneity. Not ap, Test for overall effect: 4.2.6 ARBs+CCBs Asmar 2011 Hermida 2010 Kario 2016 Peng 2013 Subtotal (95% CI)	11 17.3 11.6 29.94	11 13.4 14.6 12.73	231 50 32 26 339	24.8 12.8 31.37	10.2 13.1 11.85	52 36 28 348	3.6% 2.0%	-7.50 [-12.13, -2.87] -1.20 [-7.83, 5.43]	
Heterogeneity: Not ap, Test for overall effect: 4.2.6 ARBs+CCBs Asmar 2011 Hermida 2010 Karlo 2016 Peng 2013 Subtotal (95% CI) Heterogeneity: Tau ² =	11 17.3 11.6 29.94 9.41; Chi ²	11 13.4 14.6 12.73 ² = 8.35,	231 50 32 26 339 df = 3	24.8 12.8 31.37	10.2 13.1 11.85	52 36 28 348	3.6% 2.0% 2.0%	-7.50 [-12.13, -2.87] -1.20 [-7.83, 5.43] -1.43 [-8.00, 5.14]	
Heterogeneity. Not agy Test for overall effect: 4.2.6 ARBs+CCBs Asmar 2011 Hermida 2010 Kario 2016 Peng 2013 Subtotal (95% CI) Heterogeneity. Tau ² = Test for overall effect: 4.2.7 ARBs+Diuretics	11 17.3 11.6 29.94 9.41; Chi ⁱ Z = 1.23	11 13.4 14.6 12.73 ² = 8.35, (P = 0.22	231 50 32 26 339 df = 3	24.8 12.8 31.37 (P = 0.0	10.2 13.1 11.85 04); I ² =	52 36 28 348 64%	3.6% 2.0% 2.0% 17.4%	-7.50 [-12.13, -2.87] -1.20 [-7.83, 5.43] -1.43 [-8.00, 5.14] -2.43 [-6.29, 1.43]	
Heterogeneity. Not ap. Test for overall effect: 4.2.6 ARBs+CCBs Asmar 2011 Hermida 2010 Peng 2013 Subtotal (95% Cl) Heterogeneity. Tau ² = Test for overall effect: 4.2.7 ARBs+Diuretics Hermida 2011	11 17.3 11.6 29.94 9.41; Chi ² 2 = 1.23	11 13.4 14.6 12.73 ² = 8.35, (P = 0.22 11.6	231 50 32 26 339 df = 3	24.8 12.8 31.37 (P = 0.0	10.2 13.1 11.85 04); I ² = 10	52 36 28 348 64%	3.6% 2.0% 2.0% 17.4% 6.8%	-7.50 [-12.13, -2.87] -1.20 [-7.83, 5.43] -1.43 [-8.00, 5.14] -2.43 [-6.29, 1.43]	
Heterogeneity. Not agy Test for overall effect: 4.2.6 ARBs+CCBs Asmar 2011 Hermida 2010 Peng 2013 Subtotal (95% CI) Heterogeneity. Tau ² = Test for overall effect: 4.2.7 ARBs+Diuretict Hermida 2011	11 17.3 11.6 29.94 9.41; Chi ⁱ Z = 1.23	11 13.4 14.6 12.73 ² = 8.35, (P = 0.22	231 50 32 26 339 df = 3	24.8 12.8 31.37 (P = 0.0	10.2 13.1 11.85 04); I ² =	52 36 28 348 64%	3.6% 2.0% 2.0% 17.4% 6.8% 1.8%	-7.50 [-12.13, -2.87] -1.20 [-7.83, 5.43] -1.43 [-8.00, 5.14] -2.43 [-6.29, 1.43] -0.90 [-3.87, 2.07] -1.80 [-8.68, 5.08]	
Heterogeneity, Not ap. Test for overall effect: 4.2.6 ARBs-ACCBs Asmar 2011 Hermida 2010 Karlo 2015 Peng 2013 Subtotal (95% CI) Heterogeneity, Tau ² = Test for overall effect: 4.2.7 ARBs+Diuretics Hermida 2011 Huangfu 2015 Subtotal (95% CI) Heterogeneity, Tau ² =	Not applic 11 17.3 11.6 29.94 9.41; Chi ² 2 = 1.23 5 17 28.7 0.00; Chi ²	11 13.4 14.6 12.73 ² = 8.35, (P = 0.22 11.6 11.9 ² = 0.06,	231 50 32 26 339 df = 3 2) 104 20 124 df = 1	24.8 12.8 31.37 (P = 0.0 17.9 30.5	10.2 13.1 11.85 04); I ² = 10 10.5	52 36 28 348 64% 100 21 121	3.6% 2.0% 2.0% 17.4% 6.8%	-7.50 [-12.13, -2.87] -1.20 [-7.83, 5.43] -1.43 [-8.00, 5.14] -2.43 [-6.29, 1.43]	
Heterogeneity, Not ap. Test for overall effect: 42.6 ARBs-ACCBs Asmar 2011 Hermida 2010 Karlo 2015 Peng 2013 Subtotal (95% CI) Heterogeneity. Tau ² = Test for overall effect: 42.7 ARBs+Diuretics Hermida 2011 Huangfu 2015 Subtotal (95% CI) Heterogeneity. Tau ² = Test for overall effect:	Not applic 11 17.3 11.6 29.94 9.41; Chi ² 2 = 1.23 17 28.7 0.00; Chi ² Z = 0.75	11 13.4 14.6 12.73 ² = 8.35, (P = 0.22 11.6 11.9 ² = 0.06,	231 50 32 26 339 df = 3 2) 104 20 124 df = 1	24.8 12.8 31.37 (P = 0.0 17.9 30.5	10.2 13.1 11.85 04); I ² = 10 10.5	52 36 28 348 64% 100 21 121	3.6% 2.0% 2.0% 17.4% 6.8% 1.8%	-7.50 [-12.13, -2.87] -1.20 [-7.83, 5.43] -1.43 [-8.00, 5.14] -2.43 [-6.29, 1.43] -0.90 [-3.87, 2.07] -1.80 [-8.68, 5.08]	
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Heterogeneity, Not ap. Test for overall effect: 4.26 AR8s+CCBs Asmar 2011 Hermida 2010 Karlo 2015 Peng 2013 Subtotal (95% CI) Heterogeneity, Tau ² = Test for overall effect: 4.2.7 AR8s+Diuretics Hermida 2011 Heterogeneity, Tau ² = Test for overall effect: 4.28 CCBs+Diuretic2 Eng 2011	Not applic 11 17.3 11.6 29.94 9.41; Chi ⁱ Z = 1.23 17 28.7 0.00; Chi ⁱ Z = 0.75	$\begin{array}{c} 11\\ 13.4\\ 14.6\\ 12.73\\ ^2=8.35,\\ (P=0.22\\ 11.6\\ 11.9\\ ^2=0.06,\\ (P=0.45\\ \end{array}$	231 50 32 26 339 df = 3 2) 104 20 124 df = 1	24.8 12.8 31.37 (P = 0.0 17.9 30.5 (P = 0.8	10.2 13.1 11.85 04); I ² = 10 10.5 31); I ² =	52 36 28 348 64% 100 21 121 0%	3.6% 2.0% 2.0% 17.4% 6.8% 1.8% 8.6%	-7.50[-i2.13, -2.87] -1.20[-7.83, 5.43] -1.43[-8.00, 5.14] -2.43[-6.29, 1.43] -0.90[-3.87, 2.07] -1.80[-8.68, 5.08] -1.04[-3.77, 1.68]	
Heterogeneity. Not ap Test for overall effect: 4.2.6 ARBs+CCBs Asmar 2011 Hermida 2010 Peng 2013 Subtotal (95% CI) Heterogeneity. Tau ² = Test for overall effect: Heterogeneity. Tau ² = Test for overall effect: Zubtotal (95% CI) Heterogeneity. Tau ² = Test for overall effect: Zeng 2011 Subtotal (95% CI) Heterogeneity. Not ap	Not applic 11 17.3 11.6 29.94 9.41; Chii Z = 1.23 17 28.7 0.00; Chii Z = 0.75 22.2 plicable	$11 \\ 13.4 \\ 14.6 \\ 12.73 \\ 2 = 8.35, (P = 0.22) \\ 11.6 \\ 11.9 \\ 2 = 0.06, (P = 0.45) \\ 16.6 \\ 16.6 \\ 11.9 \\ 16.6 \\ 10.00 \\ 1$	231 50 22 6 339 df = 3 2) 104 20 124 df = 1 5) 40 40	24.8 12.8 31.37 (P = 0.0 17.9 30.5 (P = 0.8	10.2 13.1 11.85 04); I ² = 10 10.5 31); I ² =	52 36 28 348 64% 100 21 121 0%	3.6% 2.0% 2.0% 17.4% 6.8% 1.8% 8.6%	-7.50[-i2.13, -2.87] -1.20[-7.83,5.43] -1.42 [-8.00, 5.14] -2.43 [-6.29, 1.43] -0.90 [-3.87, 2.07] -1.80 [-8.68, 5.08] -1.04 [-3.77, 1.68] -4.00 [-11.28, 3.28]	
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Heterogeneity. Not ap. Test for overall effect: 4.2.6 ARBs+CCEs Asmar 2011 Hermida 2010 Karlo 2016 Peng 2013 Subtotal (95% CI) Heterogeneity. Tau ² = Test for overall effect: 4.2.7 ARBs+Diuretics Hermida 2011 Heterogeneity. Tau ² = Test for overall effect: 4.2.8 CCBs+Diuretics Zeng 2011 Subtotal (95% CI) Heterogeneity. Not ap Test for overall effect:	Not applic 11 17.3 11.6 29.94 9.41; Chii 2 = 1.23 17 28.7 0.00; Chii Z = 0.75 22.2 plicable Z = 1.08 1.41; Chii	$11 \\ 13.4 \\ 14.6 \\ 12.73 \\ 2 = 8.35, (P = 0.22 \\ 11.6 \\ 11.9 \\ 2 = 0.06, (P = 0.45 \\ 16.6 \\ (P = 0.28 \\ 2 = 28.85 \\ 2 = 28.85 \\ 2 = 28.85 \\ 2 = 28.85 \\ 3 = 28.8$	231 50 32 26 339 (f = 3 2) 104 20 104 20 104 20 104 (f = 1 5) 40 40 40 5, df = 3	24.8 12.8 31.37 (P = 0.0 17.9 30.5 (P = 0.8 26.2	10.2 13.1 11.85 04); I ² = 10 10.5 31); I ² = 16.6	52 36 28 348 64% 100 21 121 0% 40 40 40 40	3.6% 2.0% 2.0% 17.4% 6.8% 1.8% 8.6% 1.7% 1.7%	-7.50[-i2.13, -2.87] -1.20[-7.83, 5.43] -1.42 [-8.00, 5.14] -2.43 [-6.29, 1.43] -0.90 [-3.87, 2.07] -1.80 [-8.68, 5.08] -1.04 [-3.77, 1.68] -4.00 [-11.28, 3.28] -4.00 [-11.28, 3.28]	-20 -10 0 10 20 (Morning/Awakening] [Evening/Bedtime]

Study or Subgroup	Morning Mean	/Awake SD	Total		ig/Bedi SD		Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
4.2.1 ACEIs	wear	30	rotal	Mean	30	rotal	reight	14, Kanuoni, 55% CI	IV, Kaliuolii, 55% Ci
Hermida 2009	6.2	6.8	58	9.5	4.7	57	6.3%	3 30 LE 43 1 171	
Hermida 2009 Hermida 2009a	7	4.6	83	9.5 6.7	6.1	82	6.9%	-3.30 [-5.43, -1.17]	
								0.30 [-1.35, 1.95]	T
Macciarulo 1999 Subtotal (95% CI)	10.46	14.9	40 181	9.83	14.7	40 179	2.2% 15.4%	0.63 [-5.86, 7.12] -1.12 [-4.04, 1.81]	
	1.00 012			~ ~ ~	· · 2		13.4%	-1.12 [-4.04, 1.81]	-
Heterogeneity: Tau² = Test for overall effect:				(P = 0.0	13); 1° =	12%			
4.2.2 ARBs									
Hermida 2005a	8.5	8.6	72	14.7	8.2	76	5.5%	-6.20 [-8.91, -3.49]	
Hermida 2005b	6.3	7.7	50	15.4	9.4	50	4.7%	-9.10 [-12.47, -5.73]	—
Hermida 2007	7.9	7.9	107	8.7	8.1	108	6.3%	-0.80 [-2.94, 1.34]	-+
lermida 2009b	11.2	6.5	67	10.2	7.7	66	5.9%	1.00 [-1.42, 3.42]	
Jshijima 2015	3.7	5.8	11	2	8.6	12	2.5%	1.70 [-4.25, 7.65]	
Subtotal (95% CI)			307			312	24.8%	-2.84 [-6.70, 1.02]	-
Heterogeneity: Tau ² = Test for overall effect:				4 (P <	0.0000	1); 2 =	88%		-
4.2.3 Diuretics									
Calvo 2006	3.7	9.4	30	8	8.5	28	3.4%	-4.30 [-8.91, 0.31]	
Hermida 2008	3.4	9.6	57	9.5	7.4	56	4.9%	-6.10 [-9.26, -2.94]	—
Subtotal (95% CI)	2. 1	2.0	87	2.5	F . T	84	8.4%	-5.52 [-8.13, -2.92]	•
Heterogeneity: Tau ² = Test for overall effect:			df = 1	(P = 0.5	3); 12 =			,	•
4.2.4 CCBs									
Hermida 2007a	6.5	7.1	39	7.1	9.5	41	4.4%	-0.60 [-4.26, 3.06]	
Hermida 2008a	6	6.6	88	8	8.5	92	6.2%	-2.00 [-4.22, 0.22]	
Hermida 2009c	5.8	6.9	118	7.7	8.3	120	6.5%	-1.90 [-3.84, 0.04]	
Vold 1998	6.4	9.5	12	6.3	9.7	12	1.7%	0.10 [-7.58, 7.78]	
Subtotal (95% CI)	V. 1	2.2	257	0.5	2.1	265	18.7%	-1.70 [-3.04, -0.37]	▲
Heterogeneity: Tau ² =	0.00° CHI	- 0.67		/P = 0 9	- S1 12		2011/0	11.0 [510 1] 0151]	•
Test for overall effect:				(r = 0.c	10), 1 =	0/6			
4.2.6 ARBs+CCBs									
Asmar 2011	6	8.2	231	6	8.5	232	7.1%	0.00 [-1.52, 1.52]	+
Hermida 2010	13.4	8.3	50	13.5	9.5	52	4.6%	-0.10 [-3.56, 3.36]	
(ario 2016	5	7.2	32	6.4	6.2	36	4.9%	-1.40 [-4.61, 1.81]	
ena 2013	16.3	7.7	26	18.6	10	28	3.3%	-2.30 [-7.04, 2.44]	
ubtotal (95% CI)			339			348	19.8%	-0.37 [-1.61, 0.86]	•
Heterogeneity: Tau ² = Test for overall effect:				(P = 0.7	3); I ² =	0%			
1.2.7 ARBs + Diuretics									
4.2.7 ARBs + Diuretics Hermida 2011		81	104	12.1	65	100	6.4%	-0.60[-2.61 1.41]	
Hermida 2011	11.5	8.1	104	12.1	6.5 7.9	100	6.4% 3.5%	-0.60 [-2.61, 1.41]	
Hermida 2011 Huangfu 2015		8.1 6.9	20	12.1 18	6.5 7.9	21	3.5%	-2.10 [-6.63, 2.43]	
Hermida 2011 Huangfu 2015 Subtotal (95% CI) Heterogeneity: Tau ² =	11.5 15.9 0.00; Chi ²	6.9 = 0.35,	20 124 df = 1	18	7.9	21 121			•
Hermida 2011 Huangfu 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect:	11.5 15.9 0.00; Chi ² Z = 0.90 (6.9 = 0.35,	20 124 df = 1	18	7.9	21 121	3.5%	-2.10 [-6.63, 2.43]	•
4.2.7 ARBs+Diuretics Hermida 2011 Huangfu 2015 Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: 4.2.8 CCBs+Diuretics Zeng 2011 Subtotal (95% Cl)	11.5 15.9 0.00; Chi ² Z = 0.90 (6.9 = 0.35,	20 124 df = 1	18	7.9 5); I ² =	21 121	3.5% 9.9% 3.0%	-2.10 [-6.63, 2.43]	
Hermida 2011 Huangfu 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 4.2.8 CCBs+Diuretics Zeng 2011	11.5 15.9 0.00; Chi ² Z = 0.90 (11.7 blicable	6.9 = 0.35, P = 0.37 13.2	20 124 df = 1) 40 40	18 (P = 0.5	7.9 5); I ² =	21 121 0% 40	3.5% 9.9% 3.0%	-2.10 [-6.63, 2.43] -0.85 [-2.69, 0.99] -5.40 [-10.59, -0.21]	•
Hermida 2011 Hangfu 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: 4.2.8 CCBs+Diuretics Zeng 2011 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect:	11.5 15.9 0.00; Chi ² Z = 0.90 (11.7 blicable	6.9 = 0.35, P = 0.37 13.2	20 124 df = 1 ') 40 40	18 (P = 0.5	7.9 5); I ² =	21 121 0% 40 40	3.5% 9.9% 3.0% 3.0%	-2.10 [-6.63, 2.43] -0.85 [-2.69, 0.99] -5.40 [-10.59, -0.21] -5.40 [-10.59, -0.21]	* *
Hermida 2011 Huangtu 2015 Subtotal (95% CI) Heterogeneity. Tau ² = Fest for overall effect: 4.2.8 CCBs+Diuretics Eeng 2011 Subtotal (95% CI) Heterogeneity. Not app Fest for overall effect: Fotal (95% CI)	11.5 15.9 0.00; Chi ² Z = 0.90 (11.7 blicable Z = 2.04 (6.9 = 0.35, P = 0.37 13.2 P = 0.04	20 124 df = 1) 40 40 40	18 (P = 0.5 17.1	7.9 (5); I ² = 10.3	21 121 0% 40 40 40 1349	3.5% 9.9% 3.0% 3.0% 100.0%	-2.10 [-6.63, 2.43] -0.85 [-2.69, 0.99] -5.40 [-10.59, -0.21]	* *
Hermida 2011 Huangfu 2015 Subtotal (95% CI) Heterogeneity. Tau ² = Fest for overall effect: A.2.8 CCBs+Diuretics Zeng 2011 Subtotal (95% CI) Heterogeneity. Not app Fest for overall effect:	11.5 15.9 0.00; Chi ² Z = 0.90 (11.7 blicable Z = 2.04 (4.04; Chi ²	6.9 = 0.35, P = 0.37 13.2 P = 0.04 = 62.11	20 124 df = 1 1 40 40 40 40 8) 1335 3, df = 2	18 (P = 0.5 17.1	7.9 (5); I ² = 10.3	21 121 0% 40 40 40 1349	3.5% 9.9% 3.0% 3.0% 100.0%	-2.10 [-6.63, 2.43] -0.85 [-2.69, 0.99] -5.40 [-10.59, -0.21] -5.40 [-10.59, -0.21]	- <u>-</u> 20 - <u>10</u> - <u>10</u> - <u>20</u> [Morring/Awakening] [Evening/Bedtime]