The effect of antihypertensive treatment on headache and blood pressure variability in randomised controlled trials: a systematic review

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Webfigure 1. Effect of class of antihypertensive agent on incidence of headache compared to other antihypertensive classes or placebo, different CCB classes analysed separately

Drug	Ν	Events Tris	s OR	95% CI	Headache	p-Val	pHet	rSBP	rDBP
Each dru	ave all	other classe							
Euchuru	y vs un	outer clusse							
ССВ	37093	4225 74	1.13	0.98 1.31	+●-	0.1013	0.0000	-0.7	-1.1
CCBND	5639	473 27	1.37	1.12 1.67	— • —	0.0036	0.6136	0.4	-1.3
Diuretic	8817	737 39	1.18	0.96 1.45	⊢ ∙−	0.1112	0.0940	-1.8	0.9
ARB	25064	2738 40	0.92	0.77 1.10	_ _	0.2698	0.0460	1.2	1.1
ACEI	22407	1858 77	0.89	0.76 1.04	+	0.1347	0.0035	-0.4	0.8
BB	7844	730 49	0.73	0.62 0.85		0.0002	0.8699	0.4	-0.7
Each drug	g vs pla	cebo							
ссв	6788	936 49	0.99	0.78 1.25		0.3966	0.0001	-10.9	-5.8
CCBND	2503	275 16	0.86	0.65 1.13		0.2202	0.6288	-9.0	-5.4
Diuretic	10181	1076 31	0.75	0.64 0.89		0.0011	0.3456	-12.4	-3.8
ARB	9352	1141 34	0.70	0.60 0.81	_--	0.0000	0.2915	-8.9	-4.8
ACEI	12557	772 50	0.71	0.60 0.84		0.0001	0.6267	-9.5	-4.7
BB	1916	190 16	0.47	0.33 0.68		0.0001	0.2989	-11.2	-7.8
				0.4	Odds Ratio (95% CI)	2.5			

Webfigure 2. Effect of class of antihypertensive agent on incidence of headache and variability in SBP compared to other antihypertensive classes or placebo, limited to trials of 26 weeks duration or less. A) Effect on incidence of headache. B) Effect on variability in SBP.

A)	Drug	N	Events Tris	S OR	95% CI	Headache	p-Val	pHet	rSBP rDBP
	Each dru	g vs all	other classe	5					
	ссв	10807	1171 68	1.12	0.94 1.34	↓ ●-	0.1782	0.0027	0.8 -0.4
	CCBND	4225	427 26	1.44	1.16 1.78	_ _	0.0014	0.6755	-0.6 -2.0
	Diuretic	5444	537 36	1.24	1.02 1.52	 ●	0.0418	0.3429	-1.3 1.4
	ARB	9288	647 37	0.88	0.73 1.06	_ ●+	0.1674	0.2186	-0.1 0.1
	ACEI	11908	984 70	0.88	0.73 1.06		0.1573	0.0049	-1.1 0.6
	BB	7052	713 47	0.74	0.62 0.87	_ — —	0.0005	0.8529	0.6 -0.5
	Each dru	g vs pla	cebo						
	ссв	5792	767 47	1.02	0.79 1.31		0.3941	0.0001	-10.9 -5.9
	CCBND	2503	275 16	0.86	0.65 1.13	• _	0.2202	0.6288	-9.0 -5.4
	Diuretic	3903	432 28	0.75	0.61 0.93	_ _	0.0126	0.4526	-7.8 -3.5
	ARB	8565	982 33	0.66	0.57 0.76		0.0000	0.6650	-8.9 -4.8
	ACEI	7508	704 48	0.72	0.61 0.86		0.0005	0.5943	-9.5 -4.7
	BB	1888	185 15	0.46	0.32 0.65 -		0.0000	0.3298	-11.1 -7.8
						 			
					0.4	Odds Ratio (95% CI)	2.5		

B)

Drug	N	Trls	VR	95% CI	SBP	p-Val pHet
Each drug vs all	other c	lasses				
_						
ССВ	1171		0.83	0.73 0.90		0.0067 0.0140
CCBND	427	7	0.90	0.70 1.13		0.2817 0.0276
Diuretic	537	8	0.93	0.49 1.10		- 0.3907 0.7836
ARB	647	13	1.10	0.91 1.29	_+●	0.2431 0.0612
ACEI	984	18	0.97	0.86 1.05		0.3622 0.0057
Beta-blocker	713	17	1.28	0.87 1.40	_ _	0.1840 0.5019
Each drug vs pla	icebo					
ССВ	767	8	0.71	0.48 0.89	_ _	0.0812 0.1932
CCBND	275	1		1.10	•	
Diuretic	432	2	0.89	0.34 1.30 -	•	0.3872 0.2879
ARB	982	6	1.02	0.75 1.18	_	0.3963 0.0988
ACEI	704	7	0.79	0.52 1.00	_	0.2258 0.2256
Beta-blocker	185	2	0.91	0.21 1.54 -		0.3957 0.9096
				-		
				0.4	Variance Ratio (95% CI)	2.5

Webfigure 3. Effect of class of antihypertensive agent on incidence of headache compared to other antihypertensive classes or placebo in trials reporting the incidence of new-onset headache or headache felt to be drug-related.

Drug	N	Events	Trls OR	95% CI		p-Val	pHet	rSBP rDBP
Each d	rug vs	all oth	er					
ссв	9702	858 28	8 1.08	0.82 1.42	——	0.3454	0.0015	-0.2 -1.0
Diuretic	1378	70 7	0.97	0.59 1.61		0.3969	0.6685	-0.3 1.6
ARB	4257	172 12	2 1.08	0.71 1.63	•	0.3739	0.1683	0.1 0.4
ACEI	10267	705 22	2 1.02	0.75 1.38	_	0.3958	0.0176	-0.1 0.7
вв	2482	175 13	3 0.72	0.52 0.99	•	0.0526	0.8161	1.2 0.1
Each di	rug vs	placeb	0					
ссв	3264	319 21	1 1.05	0.71 1.56	●	0.3886	0.0032	-9.4 -5.5
Diuretic	1955	305 7	0.66	0.51 0.85		0.0027	0.7617	-8.2 -3.4
ARB	1926	236 6	5 0.70	0.52 0.94		0.0251	0.9133	-10.0 -5.4
ACEI	3374	252 14	4 0.73	0.54 0.97	— •—	0.0409	0.5037	-9.5 -4.0
вв	1109	81 7	0.49	0.25 0.95 -	•	0.0424	0.1114	-11.4 -8.4
				0.4	Odds Ratio (95% CI)	2.5		

Webfigure 4. Effect of class of antihypertensive agent on difference in variability in DBP at follow-up compared to other antihypertensive classes or placebo.

Drug	N	Trls	VR	95% CI	DBP	p-Val pHet
Each drug vs all	other cl	asses				
ссв	4225	25	0.93	0.83 1.05	_	0.2086 0.0105
CCBND	473	8	0.97	0.76 1.24		0.3885 0.0353
Diuretic	1565	12	0.93	0.76 1.14		0.3143 0.0000
ARB	2738	14	1.14	1.09 1.20		0.0000 0.4210
ACEI	1858	20	1.06	0.92 1.22	—	0.2910 0.0125
Beta-blocker	978	18	1.02	0.85 1.21	_ - _	0.3929 0.0685
ССВ	936	9	0.75	0.59 0.95	_ _	0.0206 0.1604
ССВ	936	9	0.75	0.59 0.95		0.0206 0.1604
CCBND	275	1				
Diuretic	1076		0.79	0.47 1.34		0.2747 0.0000
ARB	1141		0.95	0.79 1.15		0.3487 0.1884
ACEI	772	7	0.85	0.70 1.04		0.1181 0.7516
Beta-blocker	190	2	0.97	0.29 3.28 -		0.3984 0.0586
				0.4	Variance Ratio (95% CI)	2.5

Webfigure 5. Effect of different non-dihydropyridine calcium channel blockers on on incidence of headache compared to other antihypertensive classes or placebo.

Drug	N	Events	s Trl s	OR	95	5% CI		Headache	p-Val	pHet	rSBP rDBP
Each a	drug v	s othe	er class	ses							
Amlod	19488	2390 2	24 0.	.82	0.75	0.89	•		0.0000	0.9372	-1.8 -1.4
Nitrend	815	152	51.	.98	1.18	3.32			0.0136	0.1885	-0.1 0.6
Felod	9593	876	8 1.	.36	1.18	1.57		_ ●−	0.0000	0.5049	0.0 -1.0
Israd	783	88	8 0.	.60	0.37	0.96 —			0.0396	0.5881	-2.4 -1.3
Nicard	589	73	31.	.25	0.76	2.06		<u> </u>	0.2680	0.6692	0.8 -0.4
Nifed	2190	281 1	16 1.	.66	1.15	2.40			0 .0097	0.1429	10.6 0.5
Each di	rug vs	placel	bo								
Amlod	2750	361 1	13 0.	.61	0.48	0.78			0.0001	0.4705	-14.7 -7.3
Nitrend	279	65	3 0.	.70 ·	0.22	2.23 —	-		0.3338	0.0268	-10.2 -4.8
Felod	1502	195 1	12 1.	.27	0.90	1.77	-		0.1547	0.4557	-10.2 -4.9
Israd	926	119	9 1.	29	0.74	2.25		· ·	0.2703	0.1155	-7.7 -5.2
Nicard	581	35	51.	.32	0.63	2.79			0.3058	0.4774	-15.1 -8.8
Nifed	591	142	51.	.48	0.57	3.82		·	0.2873	0.0012	-8.3 -5.0
						-		ļ	_		
						0.4	Odds Ratio	95% CI)	2.5		

Webfigure 6. Effect of class of antihypertensive agent on incidence of headache and variability in SBP compared to other antihypertensive classes or placebo, excluding amlodipine. A) Effect on incidence of headache. B) Effect on variability in SBP.

A)

4)									
Drug	N	Events Trls	OR	95% CI	Headache	p-Val	pHet	rSBP	rDBP
Each d	rug vs	all other							
ссв	21956	2078 67	1.39	1.24 1.57		0.0000	0.2059	0.8	-0.9
Diuretic	8523	694 37	1.16	0.94 1.44	+∙-	0.1565	0.0801	-1.9	0.9
ARB	7764	569 31	0.84	0.68 1.03	_+	0.1008	0.1852	-0.4	0.0
ACEI	21009	1719 68	0.83	0.70 0.98		0.0319	0.0074	-0.7	0.7
BB	7348	691 45	0.71	0.60 0.84		0.0002	0.8018	0.3	-0.7
Each di	rug vs	placebo							
ссв	6541	850 52	1.12	0.90 1.39	_↓ ●	0.2390	0.0067	-9.2	-5.2
Diuretic	10181	1076 31	0.75	0.64 0.89	_	0.0011	0.3456	-12.4	-3.8
ARB	9352	1141 34	0.70	0.60 0.81	—	0.0000	0.2915	-8.9	-4.8
ACEI	12557	772 50	0.71	0.60 0.84	_	0.0001	0.6267	-9.5	-4.7
вв	1916	190 16	0.47	0.33 0.68 -	•	0.0001	0.2989	-11.2	-7.8
				0.4	Odds Ratio (95% CI)	2.5			
В)									
Drug	N	Trls	VR	95% CI		p-Val	pHet	rSBP	rDBP
Each a	lrug v:	s all other							
ССВ	19388	81	0.84	0.78 0.91	-	0.0001	0.0000	-0.8	-1.0
Diuretio			0.85	0.79 0.91		0.0000	0.0000	-2.5	0.1
ARB	14854	34	1.07	0.96 1.18		0.1829	0.0000	0.7	0.9
ACEI	57256	111	1.04	0.97 1.11	•	0.2075	0.0000	1.4	0.8
вв	21381	. 77	1.17	1.08 1.28	_ ←	0.0006	0.0000	1.3	0.7
Each a	lrug vs	s placebo							
ссв	11751		0.73	0.64 0.84		0.0000	0.0404	-5.8	-3.0
Diuretio			0.91	0.80 1.03	_ •+		0.0074		
					I				

Diuretic	12187	20	0.91	0.80 1.03
ARB	6756	13	0.93	0.87 1.00
ACEI	7074	43	0.94	0.82 1.08
BB	1210	19	1.04	0.88 1.23

0.5

Variance Ratio (95% CI)

2

0.0440 0.4800

0.3900 0.0000

0.6500 0.7800

-4.6 -2.4

-9.2 -4.5

-9.0 -5.5

Webtable 1. Trials included in meta-analyses.

	Reference	Name	VR	OR
1.	ABC et al. Evaluation of candesartan cilexetil in black patients with systemic hypertension: the ABC Trial.Heart Dis.2000; 2: 392			Х
2.	Aberg et al. Different long-term metabolic effects of enalapril and atenolol in patients with mild hypertension. EGTA Group. J Hum Hypertens 1995; 9.2: 149		Х	
3.	Acbay et al. Effects of low-dose losartan treatment on persistent microalbuminuria in normotensive type 1 diabetic subjects. <i>J Endocrinol Invest</i> 2001; 24: 608		Х	
4.	Agabiti-Rosei et al. Cardiovascular structural changes and calcium antagonist therapy in patients with hypertension. J Cardiovasc Pharmacol 1994; 24 S A: S37		Х	Х
5.	Agabiti-Rosei et al. Efficacy and tolerability of moexipril and nitrendipine in postmenopausal women with hypertension. MADAM study group. Moexipril as Antihypertensive Drug After Menopause. <i>Eur J Clin Pharmacol</i> 1999; 55: 185		Х	
6.	Agabiti-Rosei et al. Evaluation of the Efficacy and Tolerability of Nebivolol versus Lisinopril in theTreatment of Essential Arterial Hypertension: A Randomized, Multicentre, Double-blind Study <i>Blood Press</i> 2003; 12 s 1: 30		Х	
7.	Agardh et al. Greater reduction of urinary albumin excretion in hypertensive type II diabetic patients with incipient nephropathy by lisinopril than by nifedipine. <i>J Hum Hypertens</i> 1996; 10: 185		Х	Х
8.	Ahmad et al. Effect of 5-year enalapril therapy on progression of microalbuminuria and glomerular structural changes in type 1 diabetic subjects. <i>Diabetes Clin Res</i> 2003; 60: 131		Х	
9.	Ahmad et al. Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. <i>Diabetes Care</i> 1997; 20: 1576		Х	
10.	Albergati et al. Comparison of the effects of carvedilol and nifedipine in patients with essential hypertension and non-insulin dependent diabetes mellitus. <i>J Cardiovasc Pharmacol</i> 1998; 19: 86		Х	
11.	ALLHAT Investigators. Diuretic Versus alpha-Blocker as First-Step Antihypertensive Therapy: Final Results From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) <i>Hypertension</i> 2003; 42: 239	ALLHAT I	Х	
12.	ALLHAT investigators. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288: 2981	ALLHAT II	Х	
13.	Amery et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1985; 1: 1349	EWPHE	Х	
14.	Andersson et al. The antihypertensive effect and tolerability of candesartan cilexetil, a new generation angiotensin II antagonist, in comparison with losartan <i>Blood Press</i> 1998; 7: 53		Х	Х
15.	Apperloo et al. Differential effects of enalapril and atenolol on proteinuria and renal haemodynamics in non-diabetic renal disease. <i>BMJ</i> 1991; 303: 821		Х	
16.	Applegate et al. A randomized controlled trial of the effects of three antihypertensive agents on blood pressure control and			Х

Investigators.Am J Cardiol.1999; 83: 272 31. Belz et al. [Cilazapril in essential hypertension. A placebo-controlled double-blind study to establish the dosage] X Medizinische Klinik 1986; 81: 524 X 32. Benetos et al. Efficacy, safety, and effects on quality of life of bisoprolol/hydrochlorothiazide versus amlodipine in elderly X patients with systolic hypertension. Am Heart J 2000; 140: E11 X 33. Berglund et al. Low Doses of Hydrochlorothiazide in Hypertension. Anfihypertensive and Metabolic Effects. Eur J Clin X pharmacol 1976; 10: 177 X 34. Bergstrand et al. Comparative study of metoprolol and alpha-methyldopa in untreated essential hypertension Eur J Clin X pharmacol 1976; 10: 375 S 35. Bielen et al. Comparison of the effects of isradipine and lisinopril on left ventricular structure and function in essential X hypertension Am J Cardiol 1992; 69: 1200 X				
different doses) in systemic hypertension. Am J Cardiol 1996; 78: 51 18. Armentano et al. Mechanical vs intrinsic components in the improvement of brachial arterial comparison of the effects of atenolol versus ramipril in hypertensive patients Medicina (8 Aires) 2001; 61 5.1: 535 X 19. Arora et al. Assessment of left ventricular changes in systemic hypertension—before and after therapy. Indian Heart J 1984; 36: 155 X 20. Asmar et al. Effect of bisoprolol on blood pressure and arterial hemodynamics in systemic hypertension. Am J Cardiol 1991; 68: 61 X 21. Asselbergs et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria Circulation 2004; 110: 2809 X 22. Aurell et al. Enalapril versus metoprolol in primary hypertension—effects on the glomerular filtration rate. Nephrol Dial transplant 1997; 12: 2289 X X 23. Baez et al. Antihypertensive effect of doxazosin in hypertensive patients: comparison with atenolol. Br J Clin Pharmacol 1996; 14: 527 X X 24. Bahena et al. Quinapril versus atenolol in the treatment of mild to moderate essential hypertension. Clin Ther 1992; 14: 527 X X 25. Bakris et al. Bakris Kidney Int 1998; 54: 1283 X X 27. Bakris et al. Optimapril versus atenolol for mike on arterial distensibility. Hypertension 1994; 23: 161 X 28. Bell et al. Effective dose range of candesartan cilexetil for systemic hypertension. Candesartan Cilexetil Study Investigators. Am J Cardiol.1999; 83: 272 X<				
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