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Antihypertensive efficacy of angiotensin receptor blockers as monotherapy as evaluated by ambulatory blood pressure monitoring: a meta-analysis

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Aims Angiotensin receptor blockers (ARBs) are available in different dosages and it is common clinical practice to uptitrate if blood pressure goal is not achieved with the initial dose. Data on the incremental antihypertensive efficacy with uptitration are scarce. It is also unclear if antihypertensive efficacy of losartan is comparable with other ARBs.

Methods and results We systematically reviewed PubMed/EMBASE/Cochrane databases for all randomized clinical trials until December 2012 reporting 24 h ambulatory blood pressure (ABP) for most commonly available ARBs in patients with hypertension. Reduction in ABP with ARBs was evaluated at 25% of the maximum (max) dose, 50% of the max dose, and at the max dose. Comparison was made between 24 h BP-lowering effect of losartan 50 and 100 mg and other ARBs at 50% max dose and the max dose, respectively. Sixty-two studies enrolling 15 289 patients (mean age 56 years; 60% men) with a mean duration of 10 weeks were included in the analysis. Overall, the dose–response curve with ARBs was shallow with decrease of 10.3/6.7 (systolic/diastolic), 11.7/7.6, and 13.0/8.3 mmHg with 25% max dose, 50% max dose, and with the max dose of ARBs, respectively. Losartan in the dose of 50 mg lowered ABP less well than other ARBs at 50% max dose by 2.5 mmHg systolic ($P < 0.0001$) and 1.8 mmHg diastolic ($P = 0.0003$). Losartan 100 mg lowered ABP less well than other ARBs at max dose by 3.9 mm Hg systolic ($P = 0.0002$) and 2.2 mmHg diastolic ($P = 0.002$).

Conclusion In this comprehensive analysis of the antihypertensive efficacy of ARBs by 24 h ABP, we observed a shallow dose–response curve, and uptitration marginally enhanced the antihypertensive efficacy. Blood pressure reduction with losartan at starting dose and at max dose was consistently inferior to the other ARBs.

Keywords Angiotensin receptor blockers • Ambulatory blood pressure monitoring • Hypertension • Meta-analysis

Introduction

Hypertension is an asymptomatic condition and should remain so when treated. Angiotensin receptor blockers (ARBs) are known to provide a good blood pressure reduction with little, if any, adverse effects.[1] The magnitude and duration of antihypertensive response of various ARBs is thought to vary due to differences in pharmacokinetic and pharmacodynamic properties.[2] Conflicting results have been reported in several reviews and meta-analyses regarding the antihypertensive efficacy of various ARBs; some suggesting no difference within the class,[1,3] whereas others suggesting losartan being inferior.[4,5] Twenty-four hour ambulatory blood pressure (ABP) monitoring is considered as the most objective and accurate tool to assess antihypertensive efficacy and is shown to predict cardiovascular events even after adjusting for office blood pressure measurement.[6] Our objective was two-fold: (i) to evaluate the antihypertensive efficacy of ARBs as assessed by 24 h ABP at 25% maximum (max), 50% max, and max dose, and (ii) to evaluate ABP reduction with losartan compared with other ARBs.

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Methods

Search strategy

A systematic search was performed in PubMed, EMBASE, and Cochrane Central Register of Clinical Trials (Cochrane Library Issue 6, June 2012) using the key terms 'Angiotensin Receptor Blockers', 'ARBs', and names of all individual ARBs. We limited our search to randomized controlled trials in human subjects and in peer-reviewed journals until December 2012. No language restriction was applied. The reference lists of identified articles and bibliographies of original articles were also reviewed. Trials in the abstract form without a manuscript published were excluded for this analysis. Authors of the individual trials were contacted in case of inadequate data.

Selection criteria

To be included in the analysis, a trial had to fulfil the following criteria: (i) randomized clinical trials that assessed the antihypertensive efficacy by 24 h ABP comparing ARB with other antihypertensive drug classes

Table 1 Type of angiotensin receptor blockers with doses at 25% maximum, 50% maximum, and at maximum dose

Type of ARB	25% max dose (mg)	50% max dose (mg)	Max dose (mg)
Azilsartan	–	40	80
Candesartan	8	16	32
Irbesartan	75	150	300
Losartan	25	50	100
Olmesartan	5–10	20	40
Telmisartan	20	40	80
Valsartan	80	160	320

ARB, angiotensin receptor blocker; max, maximum.

Table 2 Baseline characteristics of the included trials

Trial, year	Number of patients	Men (%)	Age (years)	Follow-up (weeks)	Comparison group
Andersen *et al.*,[14] 2000	16	63	42	8	Losartan 50 mg vs. losartan 100 mg vs. placebo
Baguet *et al.*,[15] 2006	256	60	54	6	Candesartan 8 mg vs. losartan 50 mg vs. placebo
Bakris *et al.*,[16] 2001	406	56	53	8	Losartan 100 mg vs. verapamil 360 mg vs. enalapril 20 mg vs. placebo
Brunner *et al.*,[17] 2003	635	57	52	8	Candesartan 8 mg vs. olmesartan 20 mg
Byyny,[18] 1996	122	68	53	4	Losartan 50 mg vs. losartan 50 mg b.i.d. vs. losartan 100 mg vs. placebo
Chanudet and De Champvallins,[19] 2001	277	51	59	12	Losartan 50 mg vs. perindopril 2 mg/indapamide 0.625 mg
Chrysant *et al.*,[20] 2003	440	63	52	8	Olmesartan 20 mg vs. amlodipine 5 mg vs. placebo
Chung *et al.*,[21] 2000	263	53	57	12	Losartan 50 mg vs. mibefradil 50 mg Losartan 100 mg vs. mibefradil 100 mg
Crowe *et al.*,[22] 2003	17	NR	NR	8	Losartan 50 mg vs. losartan 100 mg
de Champlain *et al.*,[23] 2007	47	81	57	8	Valsartan 160 mg vs. amlodipine 10 mg
Destro *et al.*,[24] 2005	107	56	NR	8	Olmesartan 20 mg vs. valsartan 160 mg
Ding *et al.*,[25] 2004	61	77	61	6	Losartan 50 mg vs. telmisartan 40 mg
Duprez *et al.*,[26] 2011	108	54	78	4	Valsartan 160 mg vs. HCTZ 12.5 m vs. valsartan/HCTZ 160/12.5
Düsing *et al.*,[27] 2012	822	53	56	12	Telmisartan 80 mg vs. aliskiren 300 mg
Fagard *et al.*,[28] 2001	9	NR	46	6	Losartan 50 mg vs. enalapril 20 mg vs. placebo
Fogari *et al.*,[29] 2006	130	55	60	4	Olmesartan 20 mg vs. valsartan 160 mg
Fogari *et al.*,[30] 2008	126	55	60	8	Olmesartan 20 mg vs. telmisartan 80 mg
Galzerano *et al.*,[31] 2004	69	55	54	52	Telmisartan 80 mg vs. HCTZ 25 mg
Galzerano *et al.*,[32] 2005	82	57	60	44	Telmisartan 80 mg vs. carvedilol 25 mg
Guasti *et al.*,[33] 2002	22	NR	NR	8	Losartan 50 mg vs. enalapril 20 mg
Hermida *et al.*,[34] 2005	100	34	68	12	Valsartan 160 mg a.m. vs. valsartan 160 mg p.m.
Hermida *et al.*,[35] 2007	215	53	46.4	12	Valsartan 80 mg a.m. vs. valsartan 80 mg p.m.
Hermida *et al.*,[36] 2009	144	33	46.6	12	Olmesartan 20 mg a.m. vs. olmesartan 20 mg p.m.
Kawano *et al.*,[37] 2008	79	67	58.9	6	Irbesartan 100 mg vs. placebo
Kraiczi *et al.*,[38] 2000	40	100	57	6	Losartan 50 mg vs. atenolol 50 mg vs. HCTZ 25 mg vs. amlodipine 5 mg vs. enalapril 20 mg

Continued

Table 2 *Continued*

Trial, year	Number of patients	Men (%)	Age (years)	Follow-up (weeks)	Comparison group
Kuschnir *et al.*,[39] 2004	299	45	56	8	Losartan 50 mg vs. nifedipine 20 mg
Lacourciere and Asmar,[40] 1999	268	62	55	4	Losartan 50–100 mg vs. candesartan 8–16 mg vs. placebo
Lacourciere *et al.*,[41] 2006	812	67	53	14	Telmisartan 40–80 mg vs. ramipril 2.5–10 mg
Littlejohn *et al.*,[42] 2000	426	68	53	8	Telmisartan 80 mg vs. valsartan 80 mg
London *et al.*,[43] 2006	576	49	59	12	Candesartan 8 mg vs. amlodipine 5 mg vs. indapamide 1.5 mg
Mallion *et al.*,[44] 1999	223	67	56	6	Losartan 50 mg vs. telmisartan 40–80 mg vs. placebo
Matsumoto *et al.*,[45] 2009	35	54	61	4	Olmesartan 10 mg vs. amlodipine 2.5 mg
Meier *et al.*,[46] 2011	20	50	53	20	Losartan 100 mg vs. losartan 200 mg vs. losartan/lisinopril 100/20
Morgan and Anderson,[47] 2002	31	90	77	4	Candesartan 16 mg vs. felodipine 5 mg vs. placebo
Morgan *et al.*,[48] 2004	23	96	75	4	Candesartan 16–32 mg vs. lisinopril 20–40 mg vs. placebo
Munakata *et al.*,[49] 2004	41	49	54	12	Valsartan 80 mg vs. nifedipine 20 mg
Neutel *et al.*,[50] 1997	216	83	55	8	Valsartan 20 mg vs. valsartan 80 mg vs. valsartan 160 mg vs. valsartan 320 mg vs. placebo
Neutel *et al.*,[51] 2002	334	69	54	8	Olmesartan 5 mg vs. 2.5 mg b.i.d. vs. 20 mg vs. 10 mg b.i.d. vs. 40 mg b.i.d. vs. 80 mg vs. placebo
Neutel *et al.*,[52] 2003	714	57	55	6	Telmisartan 80 mg vs. losartan 50 mg/HCTZ 12.5 mg
Ogihara *et al.*,[53] 2009	862	68	57	12	Olmesartan 20 mg vs. azelnidipine 16 mg vs. olmesartan + azelnidipine 10–20/8–16
Palatini *et al.*,[54] 2010	654	61	54	9	Irbesartan 300 mg vs. aliskiren 300 mg vs. ramipril 10 mg
Parati *et al.*,[55] 2010	68	60	54	12	Losartan 100 mg vs. barnidipine 10 mg/losartan 50 mg
Pechere-Bertschi *et al.*,[56] 1998	20	65	54	12	Irbesartan 100 mg vs. enalapril 20 mg
Podzolkov *et al.*,[57] 2003	40	68	51	8	Losartan 50 mg vs. losartan 50 mg/HCTZ 12.5 mg
Poirier *et al.*,[58] 2004	57	70	59	8	Telmisartan 80 mg vs. amlodipine 10 mg vs. ramipril 10 mg
Povedano and Garcia De La Villa,[59] 2009	38	42	54	16	Olmesartan 40 mg a.m. vs. olmesartan 40 mg p.m.
Ragot *et al.*,[60] 2000	229	56	56	6	Losartan 50 mg vs. trandolapril 2 mg
Rajagopalan *et al.*,[61] 2007	404	53	64	12	Valsartan 160 mg vs. valsartan 160 mg/simvastatin 20 mg vs. valsartan 160 mg/simvastatin 80 mg
Sasso *et al.*,[62] 2002	64	NR	49	8	Irbesartan 150 mg b.i.d. vs. placebo
Smith *et al.*,[63] 2005	588	61	52	8	Irbesartan 150 mg vs. olmesartan 20 mg vs. losartan 50 mg vs. valsartan 80 mg
Stergiou *et al.*,[64] 2002	33	49	47	10	Losartan 50 mg vs. lisinopril 20 mg
Stergiou *et al.*,[65] 2003	36	78	50	10	Telmisartan 80 mg vs. lisinopril 20 mg
Suonsyrja *et al.*,[66] 2008	208	100	51	4	Losartan 50 mg vs. bisoprolol 5 mg vs. amlodipine 5 mg vs. HCTZ 25 mg
Tedesco *et al.*,[67] 1998	77	53	55	95	Losartan 50 mg vs. HCTZ 25 mg
Ubaid-Girioli *et al.*,[68] 2007	63	46	49.3	12	Irbesartan 150 mg vs. quinapril 20 mg vs. HCTZ 25 mg
Weber *et al.*,[69] 1995	122	68	53	4	Losartan 50 mg vs. 100 mg vs. 50 mg b.i.d. vs. placebo
Weir *et al.*,[70] 2011	246	50	52	8	Olmesartan 40 mg vs. losartan 100 mg
White *et al.*,[71] 2001	200	69	54	8	Eprosartan 600 mg vs. eprosartan 1200 mg vs. placebo
White *et al.*,[72] 2004	490	76	55	8	Telmisartan 80 mg vs. valsartan 160 mg
White *et al.*,[73] 2011	1291	54	56	6	Azilsartan 40 mg vs. olmesartan 40 mg vs. azilsartan 80 mg vs. valsartan 320 mg vs. placebo
Williams *et al.*,[74] 2006	801	60	54	14	Telmisartan 80 mg vs. ramipril 10 mg
Yasuda *et al.*,[75] 2005	87	41	62	12	Losartan 100 mg vs. amlodipine 10 mg

All studies had patient population with hypertension.
b.i.d., twice daily; HCTZ, hydrochlorothiazide; mg, milligrams; NR, not reported.

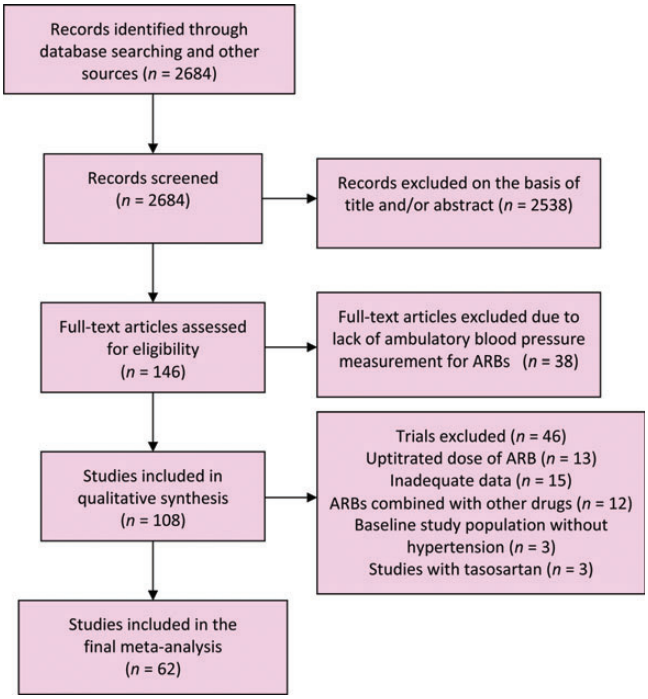

Figure 1 Selection of studies. ARBs, angiotensin receptor blockers.

(including other ARBs) or with placebo, (ii) patient population with hypertension, (iii) ARB used as monotherapy, (iv) no uptitration of ARB dose throughout the trial, and (v) trial duration of at least 4 weeks. Studies were excluded if ARB doses were uptitrated or if additional antihypertensive drugs were added to control the blood pressure. None of the included studies had patients with severe hypertension. Studies with tasosartan were excluded, since it was never marketed.

Data extraction

Two authors (H.M. and J.R.) searched the data independently and in duplicate. Disagreements were resolved by consensus. We extracted characteristics of each trial, duration of intervention and methods, baseline demographics, type of ARB used with the dose, 24 h ABP at baseline and after the intervention, for our analysis.

Quality assessment

The criteria used for quality assessment were sequence generation of allocation, allocation concealment, masking of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias, as recommended by the Cochrane Collaboration.[7]

Statistical analysis

The statistical analysis was done in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[8] using Review Manager (RevMan), version 5.1.7, the Cochrane Collaboration, 2012. Heterogeneity was assessed using the I^2 statistics. I^2 is the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error (chance) and we considered

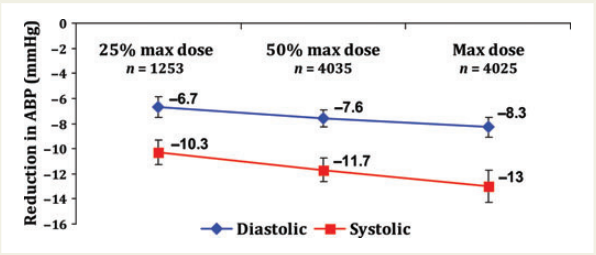

Figure 2 Antihypertensive efficacy of angiotensin receptor blockers at 25% maximum, 50% maximum, and the maximum dose. Error bars represent 95% confidence intervals. ABP, ambulatory blood pressure; *n*, number of patients; max, maximum.

$I^2 < 25\%$ as low and $I^2 > 75\%$ as high. Random-effects model of DerSimonian and Laird[9] was used to calculate the effect sizes if $I^2 > 25\%$. Analysis was performed on intention-to-treat basis. Data from changes in baseline blood pressure were combined using weighted mean difference method. For trials that did not provide complete information about variance for net change in BP, the information was obtained from confidence intervals (CIs), *P*-value, or from *t*-statistics. Variance was estimated from pre-test–post-test (parallel group and factorial design) and crossover designs as suggested by Follmann *et al.*[10] All the studies were stratified based on 25% max dose, 50% max dose, and the max dose of ARB as defined in hypertension guidelines of the Joint National Committee[11] (*Table 1*). Separate head-to head comparison was performed between losartan and other ARBs when data were available. Publication bias was estimated visually by funnel plots, and/or using Begg's test and the weighted regression test

of Egger *et al.*[12] Sensitivity analyses was performed for BP reduction at 50% max and max dose of ARBs based on the quality of study, mean baseline blood pressure (above vs. below mean BP), number of patients in the study (≤100 vs. >100), and study duration (≤8 vs. >8 weeks). We estimated difference between subgroups according to the tests of interaction.[13]

Results

Study characteristics

We identified 2684 articles, out of which 146 abstracts were retrieved and reviewed for possible inclusion. Sixty-two

A

Study or subgroup	Pre-treatment Mean	SD	Total	Post-treatment Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
1.5.1 Losartan								
Andersen *et al.*[14] (2000) (L = 50)	147	12	16	137	16	16	0.7%	10.00 (0.20, 19.80)
Baguet *et al.*[15] (2006) (L = 50)	140	16	89	131.8	16	89	1.9%	8.20 (3.50, 12.90)
Byyny *et al.*[18] (1996) (L = 50)	150.9	15.4	29	141.7	17.3	29	0.9%	9.20 (0.77, 17.63)
Chanudet and Dechampvallins[19] (2001) (L = 50)	143.7	14.2	77	134.9	14.2	77	2.0%	8.80 (4.31, 13.29)
Chung *et al.*[21] (2000) (L = 50)	148.4	12	137	139.4	12	137	2.7%	9.00 (6.16, 11.84)
Crowe *et al.*[22] (2003) (L = 50)	132.5	15.5	9	123	12	9	0.5%	9.50 (–3.31, 22.31)
Ding *et al.*[25] (2004) (L = 50)	140.9	13.7	30	129.7	15.6	30	1.1%	11.20 (3. 77' 18.63)
Fagard *et al.*[28] (2001) (L = 50)	148.3	13.7	9	138.9	13.1	9	0.5%	9.40 (–2.98, 21.78)
Guasti[33] (2002) (L = 50)	144	13	22	133	14	22	1.0%	11.00 (3.02, 18.98)
Kraiczi *et al.*[38] (2000) (L = 50)	147	12.6	16	140.1	12.6	16	0.9%	6.90 (–1.83, 15.63)
Kuschnir *et al.*[39] (2004) (L = 50)	152.3	15.7	99	143.5	15.7	99	2.0%	8.80 (4.43, 13.17)
Lacourciere and Asmar[40] (1999) (L = 50)	153	9.5	115	145.3	9.5	115	2.9%	7.70 (5.24, 10.16)
Mallion *et al.*[44] (1999) (L = 50)	148	12	57	140	12	57	2.0%	8.00 (3.59, 12.41)
Podzolkov *et al.*[57] (2003) (L = 50)	142.1	11.4	20	132.4	8.7	20	1.4%	9.70 (3.42, 15.98)
Ragot *et al.*[60] (2000) (L = 50)	138	13	82	130.6	14	82	2.1%	7.40 (3.26, 11.54)
Smith *et al.*[63] (2005) (L = 50)	152.3	12.2	150	143.3	12.2	150	2.7%	9.00 (6.24, 11.76)
Stergiou *et al.*[64] (2002) (L = 50)	137.2	10.5	33	130.7	12.8	33	1.5%	6.50 (0.85, 12.15)
Suonsyrja *et al.*[66] (2008) (L = 50)	135	10	228	125.1	10	228	3.2%	9.90 (8.06, 11.74)
Tedesco *et al.*[67] (1998) (L = 50)	155	9	44	133	11	44	2.1%	22.00 (17.80, 26.20)
Weber *et al.*[69] (1995) (L = 50)	150.9	15.4	29	141.7	15.4	29	1.0%	9.20 (1.27, 17.13)
Subtotal (95% CI)			**1291**			**1291**	**32.9%**	**9.59 (8.05, 11.14)**
Heterogeneity: $\tau^2 = 5.28$; $\chi^2 = 40.23$, df = 19 ($P = 0.003$); $I^2 = 53\%$								
Test for overall effect: $Z = 12.15$ ($P < 0.00001$)								
1.5.2 Other ARBs								
Brunner *et al.*[17] (2003) (O = 20)	145.7	11	312	133	11	312	3.2%	12.70 (10.97, 14.43)
Chrysant *et al.*[20] (2003) (O = 20)	153.9	13.8	188	141.7	13.8	188	2.7%	12.20 (9.41, 14.99)
de Champlain *et al.*[23] (2007) (V = 160)	147	14	24	134	12	24	1.1%	13.00 (5.62, 20.38)
Destro *et al.*[24] (2005) (O = 20)	146	5.7	52	131.4	5.8	52	3.0%	14.60 (12.39, 16.81)
Destro *et al.*[24] (2005) (V = 160)	146.4	5.3	55	130.7	5.1	55	3.1%	15.70 (13.76, 17.64)
Ding *et al.*[25] (2004) (T = 40)	143.9	12.4	31	129.3	14.1	31	1.3%	14.60 (7.99, 21.21)
Duprez *et al.*[26] (2011) (V = 160)	142.2	10.6	41	136.4	15.6	41	1.5%	5.80 (0.03, 11.57)
Fogari *et al.*[29] (2006) (O = 20)	152.5	9.8	65	137.5	5.9	65	2.7%	15.00 (12.22, 17.78)
Fogari *et al.*[29] (2006) (V = 160)	152.6	10.4	65	136.2	6.2	65	2.7%	16.40 (13.46, 19.34)
Fogari *et al.*[30] (2008) (O = 20)	153.1	10.3	63	139.2	7.8	63	2.5%	13.90 (10.71, 17.09)
Hermida *et al.*[34] (2005) (V = 160 a.m.)	139.6	10.2	50	127.4	9.3	50	2.2%	12.20 (8.37, 16.03)
Hermida *et al.*[34] (2005) (V = 160 p.m.)	138.4	11.5	50	123	11.6	50	1.9%	15.40 (10.87, 19.93)
Hermida *et al.*[36] (2009) (O = 20 a.m.)	129.5	8.7	73	115.7	10.1	73	2.6%	13.80 (10.74, 16.86)
Hermida *et al.*[36] (2009) (O = 20 p.m.)	130.4	9.9	71	116.5	12	71	2.3%	13.90 (10.28, 17.52)
Lacourciere and Asmar[40] (1999) (C = 16)	155.1	10.5	116	141.7	10.5	116	2.8%	13.40 (10.70, 16.10)
Mallion *et al.*[44] (1999) (T = 40)	151.5	12.6	57	140	12.6	57	1.9%	11.50 (6.87, 16.13)
Morgan and Anderson[47] (2002) (C = 16)	162.9	18.4	31	150	20.6	31	0.7%	12.90 (3.18, 22.62)
Morgan and Anderson[48] (2004) (C = 16)	159.4	9.6	23	146.6	10.1	23	1.5%	12.80 (7.11, 18.49)
Neutel *et al.*[50] (1997) (V = 160)	146.7	13.3	41	136.1	13.3	41	1.5%	10.60 (4.84, 16.36)
Neutel *et al.*[51] (2002) (O = 10 b.i.d.)	148	14.6	48	132.2	14.6	48	1.5%	15.80 (9.96, 21.64)
Neutel *et al.*[51] (2002) (O = 20)	149	16.1	45	132.5	16.1	45	1.3%	16.50 (9.85, 23.15)
Ogihara *et al.*[53] (2009) (O = 20)	157.3	12.6	211	145.2	12.6	211	2.9%	12.10 (9.70, 14.50)
Rajagopalan *et al.*[61] (2007) (V = 160)	142.1	13.2	137	132.9	13.2	137	2.6%	9.20 (6.07, 12.33)
Smith *et al.*[63] (2005) (I = 150)	151.6	11.3	146	140.3	11.3	146	2.8%	11.30 (8.71, 13.89)
Smith *et al.*[63] (2005) (O = 20)	152.1	10.4	147	139.6	10.4	147	2.9%	12.50 (10.12, 14.88)
Ubaid-Girioli *et al.*[68] (2007) (I = 150)	135.4	4.7	14	122	6.9	14	2.0%	13.40 (9.03, 17.77)
White *et al.*[71] (2001) (E = 600)	150	4	62	142.3	4	62	3.3%	7.70 (6.29, 9.11)
White *et al.*[72] (2004) (V = 160)	149	12	246	138.4	12	246	3.0%	10.60 (8.48, 12.72)
White *et al.*[73] (2011) (A = 40)	144	10	280	130.8	10	280	3.2%	13.20 (11.54, 14.86)
Subtotal (95% CI)			**2744**			**2744**	**67.1%**	**12.77 (11.74, 13.80)**
Heterogeneity: $\tau^2 = 4.67$; $\chi^2 = 90.22$, df = 28 ($P < 0.00001$); $I^2 = 69\%$								
Test for overall effect: $Z = 24.32$ ($P < 0.00001$)								
Total (95% CI)			**4035**			**4035**	**100.0%**	**11.74 (10.81, 12.66)**
Heterogeneity: $\tau^2 = 6.18$; $\chi^2 = 159.02$, df = 48 ($P < 0.00001$); $I^2 = 70\%$								
Test for overall effect: $Z = 24.80$ ($P < 0.00001$)								
Test for subgroup differences: $\chi^2 = 11.25$, df = 1 ($P = 0.0008$); $I^2 = 91.1\%$								

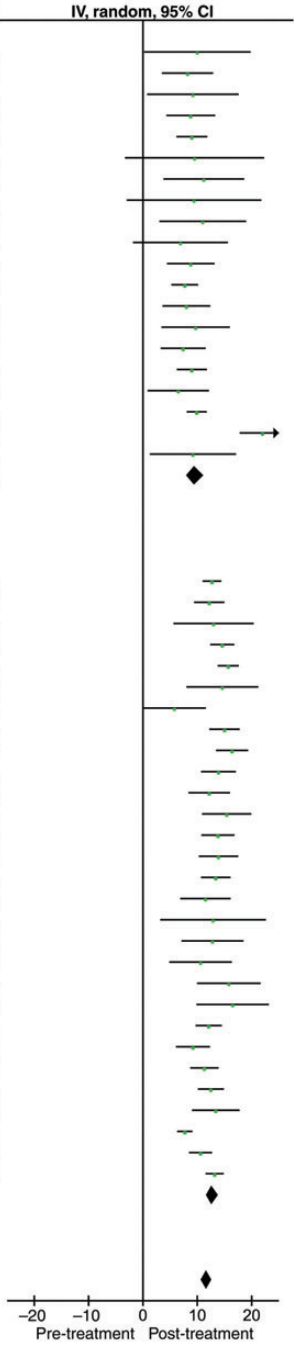

Figure 3 Forest plot showing reduction in ambulatory blood pressure for losartan and other angiotensin receptor blockers at 50% maximum dose. (*A*) Systolic. (*B*) Diastolic. The number in brackets represent angiotensin receptor blocker dose in milligrams. ABP, ambulatory blood pressure; ARB, angiotensin receptor blocker; b.i.d., twice daily; a.m., morning; p.m., evening; A, azilsartan; C, candesartan; E, eprosartan; I, irbesartan; L, losartan; O, olmesartan; T, telmisartan; V, valsartan.

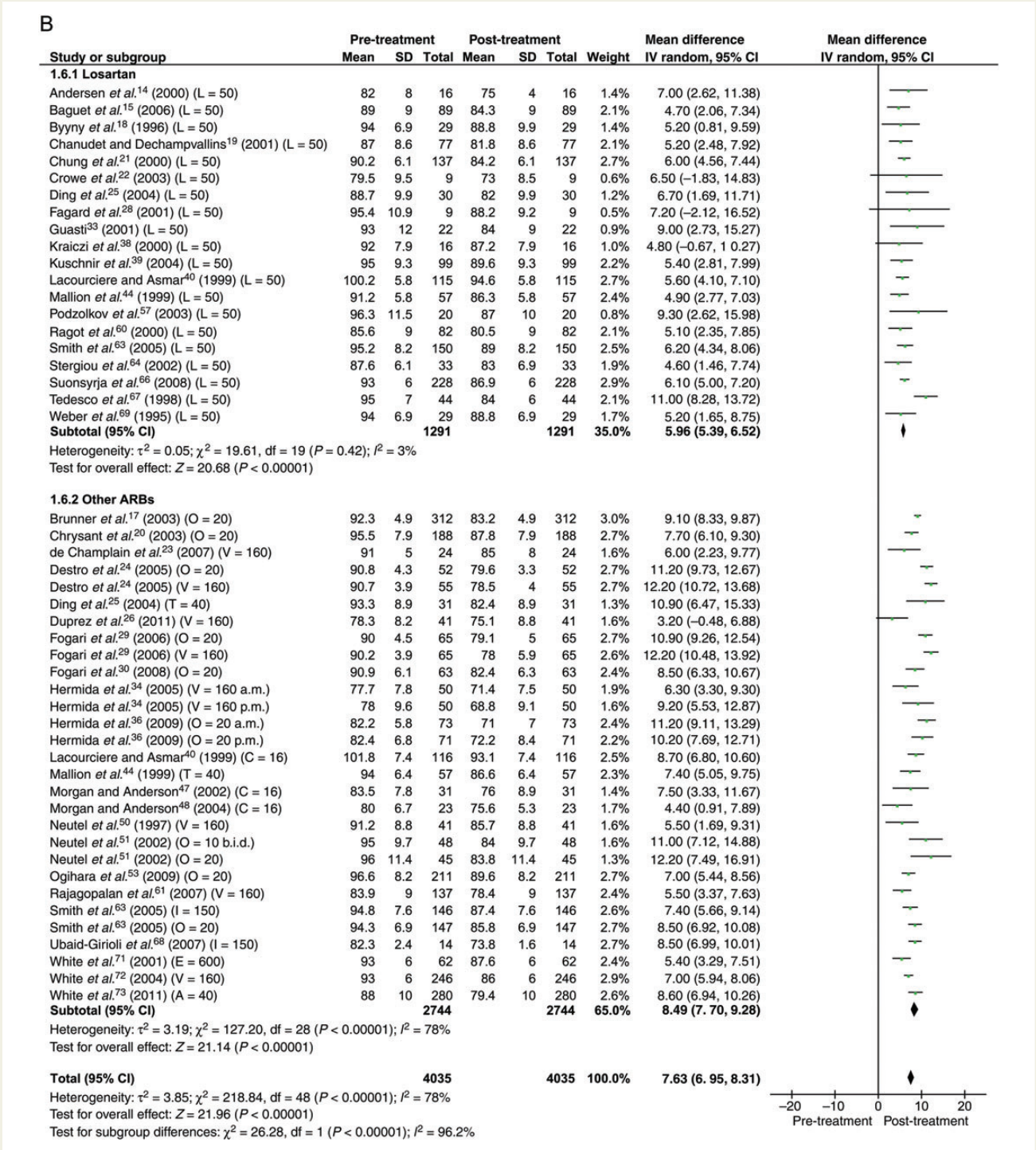

Figure 3 Continued.

studies[14–75] enrolling 15 289 patients (mean age 56 ± 7 years; 60% men) and the mean duration of 10 weeks fulfilled the inclusion criteria and were included in the analysis (*Table 2*). These 62 trials were with azilsartan ($n = 1$), candesartan ($n = 8$), eprosartan ($n = 1$), irbesartan ($n = 6$), losartan ($n = 25$), olmesartan ($n = 12$), telmisartan ($n = 14$), and valsartan ($n = 12$) (*Table 1*). Forty-six trials were excluded: uptitrated dose of ARBs ($n = 13$), inadequate data ($n = 15$), ARBs combined with other drugs ($n = 12$), baseline study population without hypertension ($n = 3$), and studies with tasosartan ($n = 3$) (*Figure 1*).

All the included studies were done in patients with mild to moderate hypertension. Of the 62 trials, 18 trials reported adequate generation of allocation sequence and adequate allocation concealment, and 39 reported adequate masking of participants,

personnel, and outcome assessors. On the basis of quality assessment, 18 were deemed as low-bias risk trials and the rest as high-bias risk trials.

Antihypertensive efficacy of angiotensin receptor blockers

Reduction in blood pressure was measured at three separate doses—25% max dose, 50% max dose, and at the max dose for all the ARBs (*Figure 2*).

Twenty-five per cent maximum dose of angiotensin receptor blockers

Data were available from 12 studies with the total of 1253 patients. Reduction in BP was 10.3 mmHg (95% CI: 9.3–11.3) systolic and 6.7 mmHg (95% CI: 5.8–7.5) diastolic with 25% max dose of ARBs.

Fifty per cent maximum dose of angiotensin receptor blockers

Data were available from 40 studies with the total of 4035 patients. With 50% max dose, the reduction in BP was 11.8 mmHg (95% CI: 10.8–12.7) systolic and 7.6 mmHg (95% CI: 7.0–8.3) diastolic (*Figure 3*).

Maximum dose of angiotensin receptor blockers

Data were available from 30 studies with the total of 4025 patients. With the maximum dose of ARBs, the reduction in BP was 13.0 mmHg (95% CI: 11.8–14.3) systolic and 8.3 mmHg (95% CI: 7.6–9.1) diastolic (*Figure 4*).

On comparing ARBs at 25% max dose with 50% max dose, there was a significant reduction of systolic ABP ($P = 0.04$), but not diastolic ABP ($P = 0.08$). On comparing ARBs at 50% max dose with the max dose, there was no significant difference in both systolic ($P = 0.11$) and diastolic ($P = 0.18$) ABP reduction. There was a significant

A

Study or subgroup	Pre-treatment Mean	SD	Total	Post-treatment Mean	SD	Total	Weight	Mean difference IV, random 95 % CI
1.7.1 Losartan								
Andersen *et al.*[14] (2000) (L = 100)	147	12	16	135	12	16	1.5%	12.00 (3.68, 20.32)
Bakris *et al.*[16] (2001) (L = 100)	147	10	118	137.7	10	118	3.6%	9.30 (6.75, 11.85)
Byyny *et al.*[18] (1996) (L = 100)	147.7	12.2	31	137.8	12.4	31	2.1%	9.90 (3.78, 16.02)
Byyny *et al.*[18] (1996) (L = 50 b.i.d.)	148.7	12.2	30	135.5	13.5	30	2.0%	13.20 (6.69, 19.71)
Chung *et al.*[21] (2000) (L = 100)	148.4	12	137	137.4	12	137	3.5%	11.00 (8.16, 13.84)
Crowe *et al.*[22] (2003) (L = 100)	127	18.5	8	117	13.5	8	0.6%	10.00 (–5.87, 25.87)
Lacourciere and Asmar[40] (1999) (L = 100)	153	10.7	115	143.7	10.7	115	3.5%	9.30 (6.53, 12.07)
Meier *et al.*[46] (2011) (L = 100)	139	17	20	129	17	20	1.1%	10.00 (–0.54, 20.54)
Parati *et al.*[55] (2010) (L = 100)	139	11	34	126.6	11	34	2.5%	12.40 (7.17, 17.63)
Weber *et al.*[69] (1995) (L = 100)	147.7	12.2	30	137.8	12.2	30	2.1%	9.90 (3.73, 16.07)
Weber *et al.*[69] (1995) (L = 50 b.i.d.)	148.7	12.2	31	135.5	12.2	31	2.1%	13.20 (7.13, 19.27)
Weir *et al.*[70] (2011) (L = 100)	141.1	13.4	123	135.5	13.4	123	3.3%	5.60 (2.25, 8.95)
Yasuda *et al.*[75] (2005) (L = 100)	158	15	44	146	13	44	2.2%	12.00 (6.13, 17.87)
Subtotal (95% CI)			**737**			**737**	**30.0%**	**9.80 (8.60, 11.00)**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 11.01$, df = 12 ($P = 0.53$); $I^2 = 0\%$								
Test for overall effect: $Z = 16.01$ ($P < 0.00001$)								
1.7.2 Other ARBs								
Düsing *et al.*[27] (2012) (T = 80)	146.9	9.5	408	134.6	12.7	408	4.0%	12.30 (10.76, 13.84)
Fogari *et al.*[30] (2008) (T = 80)	152.9	9.9	63	137.1	8.2	63	3.3%	15.80 (12.63, 18.97)
Galzerano *et al.*[31] (2004) (T = 80)	157	11	41	133	7	41	3.0%	24.00 (20.01, 27.99)
Galzerano *et al.*[32] (2005) (T = 80)	159.6	10.2	36	128.6	6.5	36	3.0%	31.00 (27.05, 34.95)
Hermida *et al.*[35] (2007) (T = 80 a.m.)	132.6	10	107	122.1	10.9	107	3.5%	10.50 (7.70, 13.30)
Hermida *et al.*[35] (2007) (T = 80 p.m.)	133	9.7	108	121.3	10.7	108	3.5%	11.70 (8.98, 14.42)
Lacourciere and Asmar[41] (2006) (T = 80)	148.2	11.6	405	133.4	11.6	405	4.0%	14.80 (13.20, 16.40)
Littlejohn *et al.*[42] (2000) (T = 80)	150.9	12.4	214	138.7	12.4	214	3.7%	12.20 (9.85, 14.55)
Mallion *et al.*[44] (1999) (T = 80)	151.2	11.8	54	137.9	11.8	54	2.8%	13.30 (8.85, 17.75)
Morgan and Anderson[48] (1999) (C = 32)	159.4	9.6	23	149.2	10.6	23	2.2%	10.20 (4.36, 16.04)
Neutel *et al.*[50] (1997) (V = 320)	148.4	13.7	45	134.1	13.7	45	2.3%	14.30 (8.64, 19.96)
Neutel *et al.*[52] (2003) (T = 80)	150.1	14.1	351	136.9	14.1	351	3.8%	13.20 [11.11, 15.29)
Palatini *et al.*[54] (2010) (I = 300)	145.4	12.1	222	132.3	12.1	222	3.7%	13.10 (10.85, 15.35)
Poirier *et al.*[58] (2004) (T = 80)	147.6	13.3	18	137.3	15.9	18	1.2%	10.30 (0.72, 19.88)
Sasso *et al.*[62] (2002) (I = 300)	161	12	32	146	12	32	2.2%	15.00 (9.12, 20.88)
Stergiou *et al.*[64] (2002) (T = 80)	138.4	9.7	36	126.5	11.1	36	2.6%	11.90 (7.08, 16.72)
T Povedano and Garcia De La Villa[59] (2009) (O = 40 a.m.)	138.5	9.3	38	124.8	7.1	38	3.1%	13.70 (9.98, 17.42)
T Povedano and Garcia De La Villa[59] (2009) (O = 40 a.m.)	138.5	9.3	38	124.1	6.9	38	3.1%	14.40 (10.72, 18.08)
Weir *et al.*[70] (2011) (O = 40)	140.6	13.5	123	131.4	13.5	123	3.3%	9.20 (5.83, 12.57)
White *et al.*[72] (2004) (T = 80)	150	12	244	138.2	12	244	3.8%	11.80 (9.67. 13.93)
White *et al.*[73] (2011) (A = 80)	145	10	285	130.7	10	285	4.0%	14.30 (12.66, 15.94)
Williams *et al.*[74] (2006) (T = 80)	147.6	12.9	397	133.1	12.9	397	3.9%	14.50 (12.71, 16.29)
Subtotal (95% CI)			**3288**			**3288**	**70.0%**	**14.16 (12.68, 15.65)**
Heterogeneity: $\tau^2 = 9.41$; $\chi^2 = 129.00$, df = 21 ($P = 0.00001$); $I^2 = 84\%$								
Test for overall effect: $Z = 18.69$ ($P < 0.00001$)								
Total (95% CI)			**4025**			**4025**	**100.0%**	**13.02 (11.75, 14.28)**
Heterogeneity: $\tau^2 = 9.83$; $\chi^2 = 174.12$, df = 34 ($P = 0.00001$); $I^2 = 80\%$								
Test for overall effect: $Z = 20.18$ ($P < 0.00001$)								
Test for subgroup differences: $\chi^2 = 20.01$, df = 1 ($P = 0.00001$); $I^2 = 95.0\%$								

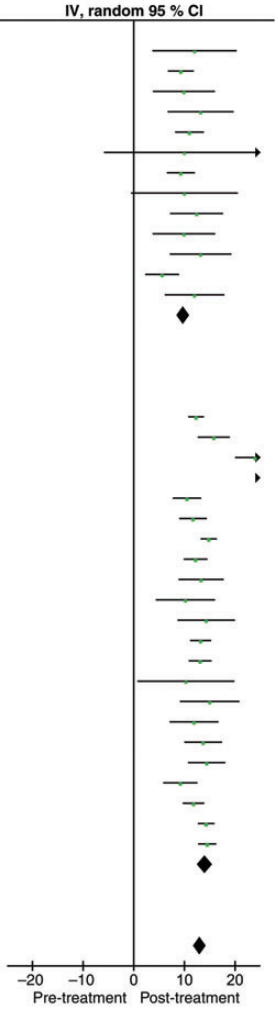

Figure 4 Forest plot showing reduction in ambulatory blood pressure for losartan and other angiotensin receptor blockers at maximum dose. (*A*) Systolic. (*B*) Diastolic. Abbreviations as in *Figure 3*.

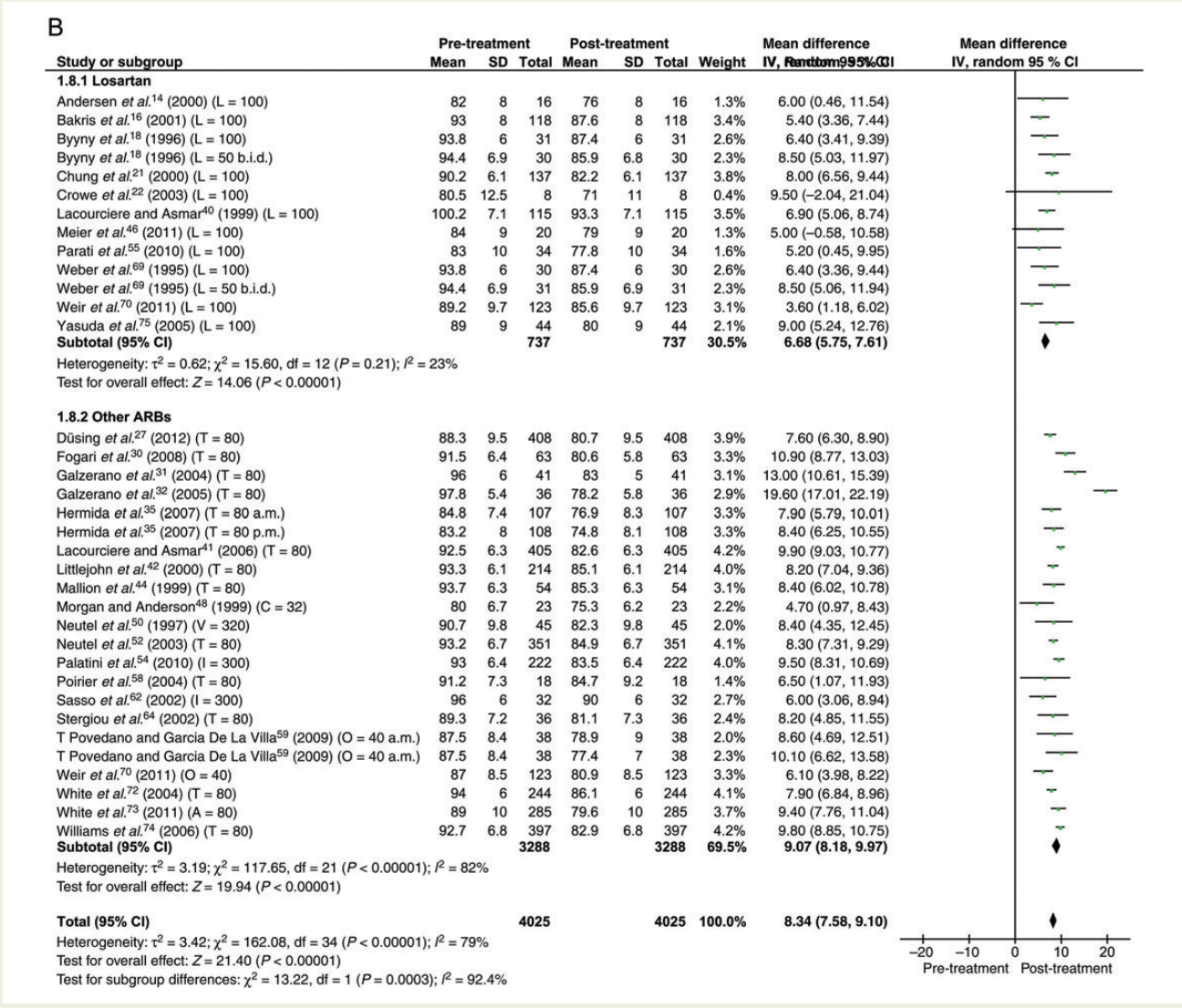

Figure 4 Continued.

reduction in both systolic ($P = 0.0008$) and diastolic ABP ($P = 0.004$) when ARBs at 25% max dose were compared with the ARBs at the max dose, but the four-fold increase in dose resulted in a meagre 2.7 mmHg (mean) decrease in systolic pressure. Since this is an indirect comparison, the data should be interpreted with caution.

Comparison of losartan 50 and 100 mg with other angiotensin receptor blockers at 50% maximum dose and at maximum dose

Head-to-head comparison between losartan and other ARBs was available in six studies (*Figure 5*). Losartan in the dose of 50 mg lowered ABP less well than other ARBs at 50% max dose by 2.5 mmHg systolic ($P < 0.0001$) and 1.8 mmHg diastolic ($P = 0.0003$). Losartan in the dose of 100 mg lowered ABP less well than other ARBs at max dose by 3.9 mmHg systolic ($P = 0.0002$) and 2.2 mmHg diastolic ($P = 0.002$) (*Figure 5*).

Significant heterogeneity was found to be present in most of the analyses and hence random variance model was used. There was no evidence of publication bias for any of the analyses. Sensitivity analysis performed to evaluate the role of baseline blood pressure on BP reduction showed no significant difference between the two subgroups (above vs. below mean BP) (*Table 3*). Similarly sensitivity analyses for various subgroups based on the risk of bias, number of patients, and study duration did not make any noticeable difference to any of the outcomes (data not shown).

Discussion

In the present analysis of the antihypertensive efficacy of various ARBs with 24 h ABP monitoring, we observed a shallow dose–

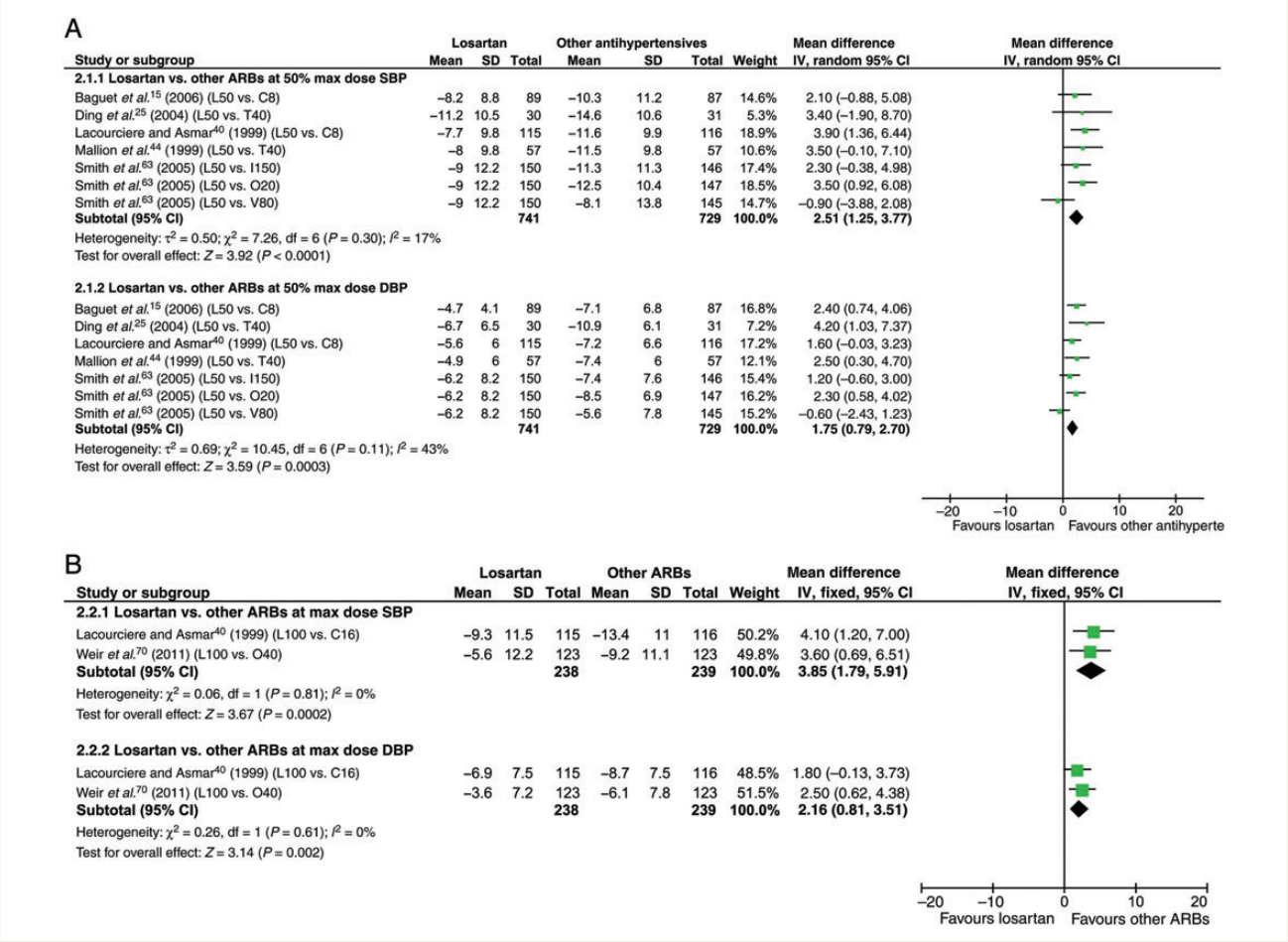

Figure 5 Forest plot showing 24 h ambulatory blood pressure reduction by losartan compared with other angiotensin receptor blockers. (*A*) Losartan 50 mg vs. other angiotensin receptor blockers at 50% maximum dose. (*B*) Losartan 100 mg vs. other angiotensin receptor blockers at max dose. DBP, diastolic blood pressure; SBP, systolic blood pressure; other abbreviations as in *Figure 3*.

Table 3 Sensitivity analysis based on baseline blood pressure

	Baseline mean BP (±SD)		Number of trials	Reduction in BP (95% CI)	Interaction *P*-value
25% max					
Systolic	147.3 ± 4.7	<147.3	6	10.03 (8.56–11.50)	0.63
		≥147.3	7	10.57 (8.94–12.20)	
Diastolic	93.2 ± 4.1	<93.2	6	7.44 (6.77–8.12)	0.09
		≥93.2	7	6.27 (5.18–7.37)	
50% max					
Systolic	146.6 ± 7.3	<146.6	21	11.79 (10.55–13.04)	0.99
		≥146.6	28	11.78 (10.45–13.10)	
Diastolic	90.1 ± 5.9	<90.1	19	7.22 (6.02–8.42)	0.56
		≥90.1	30	7.66 (6.92–8.59)	
Max dose					
Systolic	146.7 ± 7.8	<146.7	12	12.66 (11.62–13.70)	0.53
		≥146.7	23	13.32 (11.53–15.11)	
Diastolic	90.3 ± 4.9	<90.3	16	7.90 (7.29–8.52)	0.20
		≥90.3	19	8.71 (7.61–9.80)	

Interaction *P*-value comparing reduction in BP above and below baseline mean BP.
BP, blood pressure; CI, confidence interval; max, maximum; SD, standard deviation

response curve. Doubling the dose is a common clinical practice when proper blood pressure levels are not reached. In our analysis, doubling the dose merely increased the antihypertensive efficacy by <2 mmHg systolic or diastolic. Losartan had a similarly shallow dose–response curve and, in head-to-head comparisons with other ARBs, was significantly less efficacious at all doses.

The control of blood pressure in the USA remains far from adequate as was observed by the most recent NHANES data.[76] Thus, it becomes increasingly important to better control blood pressure with currently available drugs. Monotherapy remains the standard initial treatment for reducing blood pressure in many hypertensive patients. However, if specific blood pressure targets are not reached, most physicians will resort to uptitrating the drug to its max dose before switching to combination therapy. Indeed the American Joint National Committee VII[11] advocates uptitration as a primary approach, and combination therapy may be used initially only if a patient's blood pressure is distinctly above the therapeutic goal. British hypertension guidelines[77] of 2011 recommend starting monotherapy with either calcium channel blockers or ACE-inhibitors and then adding another antihypertensive agent if blood pressure is not under control. Our data make it clear that uptitration of monotherapy has little benefits for the antihypertensive regimen. Although ARBs may have a particularly shallow dose–response curve, the meta-analysis by Wald *et al.*[78] showed that the response was not much better among other antihypertensive drug classes with the exception of the calcium channel blockers. Wald *et al.* in this meta-analysis of more than 11 000 patients from 42 trials concluded that combining drugs from two different classes was approximately five times more effective in lowering blood pressure than doubling the dose. In fact, the most recent European Society of Cardiology guidelines on cardiovascular disease prevention[79] of 2012 recommend addition of drug from another class rather than uptitration for greater BP control. The guidelines also recommend treatment initiation with combination therapy in patients at high risk in whom early BP control is required.[79] In a meta-analysis of 354 trials,[80] reduction in blood pressure was only 20% lower with half standard dose compared with standard dose and was consistent among all antihypertensive agents. However, the dose-related adverse events were significantly lower with half standard dose compared with standard dose with thiazides, calcium channel blockers, and beta-blockers, but not with ACE-inhibitors and ARBs.[80] In the same meta-analysis, they showed that the reductions in BP were additive with low-dose combination therapy, but the adverse effects were less than additive compared with uptitration.[80] Several studies have shown that fixed combinations improve efficacy and adherence without increasing the overall adverse effects.[81] In a study comparing combination of valsartan and hydrochlorothiazide (HCTZ) with individual monotherapy, reduction in SBP/DBP was 16.7/8.6 mmHg with combination compared with 14.2/7.9 mmHg with valsartan alone and 9.0/3.9 mmHg with HCTZ alone.[26] Similarly, in a study comparing combination of olmesartan and azelnidipine with individual monotherapy, reduction in SBP/DBP was 22.1/13.5 mmHg with combination compared with 12.1/6.9 mmHg with olmesartan and 12.0/6.9 mmHg with azelnidipine.[53] Thus, antihypertensive combination therapy may be considered over uptitration of a single agent for better hypertension management. Angiotensin receptor blockers are available in fixed combinations with thiazide diuretics (HCTZ and chlorthalidone) as well as with calcium channel blockers (amlodipine).

Our analysis provides good evidence that antihypertensive efficacy of losartan is weaker compared with other ARBs and increasing the dosage from 50 to 100 mg contributes less to further BP reduction. The antihypertensive efficacy of losartan has been under fire ever since it was marketed.[82] Although all ARBs act by blocking angiotensin II receptor blocker, pharmacokinetic differences exist and may be the reason for the difference in antihypertensive efficacy. In a group of normotensive subjects comparing losartan with irbesartan and valsartan, losartan had the weakest angiotensin II antagonist effect; whereas irbesartan showed the slowest decay and longest duration of antagonist effects.[83,84] At 4 h, losartan blocked 43% of angiotensin II-induced systolic BP increase, compared with 51% with valsartan and 88% with irbesartan.[84] The results were similar when angiotensin II receptor blockade was assessed by the reactive rise in plasma angiotensin II levels and with an *in vitro* receptor assay.[84] In several head-to-head comparisons with other ARBs and meta-analyses, losartan lowered the blood pressure less well than other ARBs; however, for office blood pressure, this may be of questionable significance.[1] Its dose–response curve was so shallow that it was initially marketed in one dose only, and instead of uptitration from 50 to 100 mg, add-on therapy with HCTZ was advised.

Limitations

As with other meta-analyses, given the lack of data in each trial, we did not adjust our analysis for adherence to therapy. Also, the results are subject to limitations inherent to any meta-analysis based on pooling of data from different trials with different duration and different patient groups. We tried to minimize the effect of other antihypertensive drugs by excluding the studies that had second- or third-line agents added to control high BP. We also excluded studies that uptitrated the dose of ARB, since this study aimed at measuring 24 h BP at specifically 25% max, 50% max, and at the max dose. Blood pressure response to any drug depends on baseline blood pressure. However, we included only a rather homogeneous patient population with mild to moderate hypertension. Sensitivity analysis comparing studies with above baseline BP with those below baseline did not show a significant difference. Adequate data were not available to perform the head-to-head comparison between different ARBs except losartan.

Conclusion

As evaluated by 24 h ABP, uptitration of ARBs marginally enhances their antihypertensive efficacy. Antihypertensive efficacy of losartan at starting dose and at max dose is consistently inferior to other ARBs.

Authors' contributions

H.M. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: H.M., S.B., and F.H.M.; acquisition of data: H.M. and J.R.; analysis and interpretation of data: H.M., S.B., and F.H.M.; drafting of the manuscript: H.M., S.B., and F.H.M.; critical revision of the manuscript for important intellectual content: H.M., S.B., E.A., J.R., A.S., and F.H.M.; statistical analysis: H.M. and A.S.; study supervision: F.H.M. and H.M.

Conflict of interest: F.H.—*ad hoc* consultant/speaker for the following organizations: Novartis, Daiichi Sankyo, Pfizer, Takeda, Abbott, Medtronic, Servier, and Bayer. S.B.—advisory board: Daiichi Sankyo, Boehringer Ingelheim, Pfizer. H.M., E.A., J.R., A.S.: none.

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