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Angiotensin II Antagonists for Hypertension: Are There Differences in Efficacy?

Paul R. Conlin, J. David Spence, Bryan Williams, Arthur B. Ribeiro, Ikuo Saito, Claude Benedict, and Antonius M.G. Bunt

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We compared the antihypertensive efficacy of available drugs in the new angiotensin-II-antagonist (AIIA) class. The antihypertensive efficacy of losartan, valsartan, irbesartan, and candesartan was evaluated from randomized controlled trials (RCT) by performing a metaanalysis of 43 published RCT. These trials involved AIIA compared with placebo, other antihypertensive classes, and direct comparisons between AIIA. A weighted-average for diastolic and systolic blood pressure reduction with AIIA monotherapy, dose titration, and with addition of low-dose hydrochlorothiazide (HCTZ) were calculated. Weighted-average responder rates were also determined. The metaanalysis assessed a total of 11,281 patients. The absolute weighted-average reductions in diastolic (8.2 to 8.9 mm Hg) and systolic (10.4 to 11.8 mm Hg) blood pressure reductions (not placebo-corrected) for AIIA monotherapy were comparable for all AIIA. Responder rates for AIIA monotherapy were 48% to 55%. Dose titration resulted in slightly greater blood pressure reduction and an increase in responder rates to 53% to 63%. AIIA/hydrochlorothiazide combinations produced substantially greater reduction in systolic (16.1 to 20.6 mm Hg) and diastolic (9.9 to 13.6 mm Hg) blood pressure reductions than AIIA monotherapy and responder rates for AIIA/HCTZ combinations were 56% to 70%. This comprehensive analysis shows comparable antihypertensive efficacy within the AIIA class, a near-flat AIIA-dose response when titrating from starting to maximum recommended dose, and substantial potentiation of the antihypertensive effect with addition of HCTZ. Am J Hypertens 2000;13:418–426 © 2000 American Journal of Hypertension, Ltd.

KEY WORDS: **Hypertension, randomized controlled trials, efficacy, review, angiotensin-II-antagonists.**

A new class of antihypertensive drugs—angiotensin II antagonists (AIIA)—has emerged during the past 5 years. These agents specifically and selectively antagonize the effects of angiotensin II (AII) at the angiotensin type 1 (AT1) receptor. Prior clinical experience with angiotensin-converting enzyme inhibitors (ACE-I) suggested that this new class of drugs would be similarly effective for the treatment of hypertension.

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Losartan was the first of the AIIA to be approved for clinical use in hypertension, in 1994. Since then, three other agents, valsartan, irbesartan, and candesartan, have been introduced for clinical use; many others are at various stages of development. Differences in the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of these agents, such as gastrointestinal absorption, protein binding, volume of distribution, conversion of prodrug or active parent to active metabolite, oral bioavailability, competitive or noncompetitive antagonism of AII at AT1 receptors, receptor binding affinity, and elimination half-life, have been described.[1–7]

These differences have been cited as potentially important causes of differential clinical efficacy within the AIIA class, particularly with regard to the magnitude and duration of the antihypertensive response. In this regard, some recent publications have suggested differences in antihypertensive efficacy when AIIA were directly compared to each other in patients with hypertension.[8–11] This question of efficacy is potentially very important because if there are real and clinically meaningful differences in antihypertensive efficacy within the AIIA class, physicians would need to be aware of such differences to optimize therapeutic decisionmaking.

Independent interpretation of the available clinical data is confounded by the following problems: small trials, often conducted by the pharmaceutical manufacturer with a study design potentially set up in its favor; differences in methodology in describing the blood pressure (BP) reduction that hamper or preclude comparisons across studies; and a lack of sufficiently large, well-designed, independent head-to-head comparative studies. In the absence of optimal studies, an alternative way to objectively assess the antihypertensive efficacy of AIIA is to pool all of the existing randomized clinical trial (RCT) data and conduct a metaanalysis. We report the results of such an analysis and, in so doing, describe the antihypertensive efficacy of currently available AIIA from studies where these agents were compared with other classes of antihypertensive therapy and with each other.

MATERIALS AND METHODS

Data Sources This analysis examines the antihypertensive efficacy of four currently available AIIA—losartan, valsartan, irbesartan, and candesartan—using Medline and Current Contents, through October 1998, as sources of data.

Types of Data Three categories of peer-reviewed data were considered: randomized, double blind, placebo-controlled trials of the various AIIA; RCT comparing the various AIIA with other established classes of antihypertensive therapy, such as ACE-I, calcium channel blockers (CCB), β-blockers (BB), and combinations of AIIA with thiazide diuretics, mainly hydrochlorothiazide (HCTZ); and the limited number of RCT in which the antihypertensive efficacy of different AIIA were compared directly with each other, so called "head-to-head" studies. The pooled data from all of the published RCT identified in these categories were subjected to a metaanalysis.

Study Selection The following criteria were used to determine the inclusion of a published RCT in the pooled metaanalysis:

Prospective, double-blind, randomized controlled methodology;

Placebo run-in period of 4 to 5 weeks;

Patient population defined as mild-to-moderate hypertension (DBP 95 to 115 mm Hg), with no concomitant diseases;

Population representative of the overall hypertensive population;

Clinical measurement of blood pressure using sphygmomanometer and cuff, not studies using only ambulatory blood pressure monitoring (ABPM);

Evaluated doses recommended in US, Japanese, and European product labels;

Treatment duration of at least 4 to 6 weeks with starting dose of AIIA before dose titration, then at least another 4 to 6 weeks until final assessment (total duration of double blind study was typically 8 to 12 weeks);

Use of the following dosing regimens: titration as needed (or elective titration), either from starting dose to maximum dose of monotherapy or from starting dose of monotherapy to a combination of starting dose AIIA with low-dose HCTZ; parallel-group comparisons of various doses as monotherapy or AIIA/HCTZ combinations; and forced titration of the dose.

Trials were excluded if they examined use of AIIA after demonstration of lack of response with a drug from another class, or if they used a dose of AIIA not recommended in the product label.

Data Extraction To analyze the pooled data, we corrected for the size of the different studies by assigning a greater weight to the results in proportion to the size of the study. To calculate the mean blood pressure reduction with the different agents, the pooled data were weighted for the study size using the following formula:

The absolute, ie, non–placebo-corrected, weighted average BP reduction was:

$$\frac{[(\text{BP reduction}_{(\text{study 1})} \times \text{Number of patients}_{(\text{study 1})} + \ldots + (\text{BP reduction}_{(\text{study n})} \times \text{Number of patients}_{(\text{study n})})]}{\text{Total number of patients}_{(\text{study 1} + \ldots + \text{study n})}}$$

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Statistical Analyses Data are presented as mean values with 95% confidence intervals (CI) calculated from the mean and standard deviation (SD) reported in the original publications. In publications where no SD was reported, we assumed an SD that was calculated from the weighted average of the same drug and dose. Comparisons of weighted average changes in blood pressure were compared using a *t* test with correction for multiple comparisons.

RESULTS

Pooled Metaanalysis of 43 Published RCT (N = 11,281) The number of patients included in the pooled analysis (Tables 1 and 2) was substantially larger for losartan than for the three other AIIA. The pooled analysis was grouped into three separate categories: AIIA monotherapy at starting dose; AIIA monotherapy with elective or forced dose titration from the starting to the maximum dose; and starting dose AIIA/HCTZ combinations. Because of lack of sufficient number of published trials, the higher dose AIIA/HCTZ combinations were not included.

Diastolic Blood Pressure Reduction The absolute weighted average DBP reduction at trough (non–placebo-corrected) for the starting doses of AIIA was 8.2 to 8.9 mm Hg (ie, maximum difference between individual AIIA was 0.7 mm Hg). The absolute weighted average DBP reduction at trough for AIIA monotherapy with dose titration was 9.5 to 10.4 mm Hg (ie, maximum difference between the individual AIIA was 0.9 mm Hg). AIIA monotherapy dose titration resulted in a modest incremental DBP reduction compared to the starting dose of AIIA, which suggests a relatively flat dose response curve across the AIIA class.

Angiotensin II antagonists are frequently combined with low-dose diuretics to potentiate the antihypertensive effect. The absolute weighted average DBP reduction for AIIA at usual starting dose in combination with 12.5 mg HCTZ was 9.9 to 13.6 mm Hg (ie, the maximum difference between individual AIIA/HCTZ was thus 3.7 mm Hg). However, these data were based on substantially smaller numbers of patients. The incremental DBP reduction between the starting doses of AIIA and the AIIA/HCTZ combinations was substantial, indicating that combination therapy is a more effective strategy than monotherapy dose titration.

Systolic blood pressure reductions paralleled the DBP reductions. The absolute weighted average SBP reduction at trough for the starting doses of AIIA ranged from 10.4 to 11.8 mm Hg (ie, a maximum difference between AIIA of 1.4 mm Hg). The absolute weighted average SBP reduction for AIIA monotherapy with dose titration was 12.4 to 14.7 mm Hg (ie, a maximum difference between agents of 2.3 mm Hg). AIIA monotherapy dose titration provided a modest incremental SBP reduction compared with the starting dose of AIIA. The absolute weighted average SBP reduction for AIIA/HCTZ combination therapy was 16.1 to 20.6 mm Hg (ie, a maximum difference between individual AIIA/HCTZ of 4.5 mm Hg). Once again, these data were based on fewer numbers of trials. The incremental SBP reduction between the starting doses of AIIA and the AIIA/HCTZ combinations was again more substantial.

Responder Rates The responder rate, defined as DBP less than 90 mm Hg or a DBP decrease of 10 mm Hg or more, was approximately 50% for the recommended starting dose of all AIIA and increased to only 55% after AIIA monotherapy dose titration. The AIIA/HCTZ combinations, however, showed responder rates of approximately 70%, confirming the efficacy of this specific combination and the superiority of combination therapy when compared to monotherapy dose titration.

There were no statistically significant differences among the blood pressure responses of the four AIIA either as monotherapy or with dose titration for both systolic and diastolic blood pressures. Because there were fewer trials reporting responses to AIIA/HCTZ combinations, some of which did not report standard deviations, statistical comparisons could not be performed across this group.

The ranking of these four AIIA based on weighted average DBP and SBP reductions, and responder rates for monotherapy at starting dose, monotherapy titration, and the combination of AIIA/HCTZ, appeared to be random, with each agent ranking as the best or worst in one category or another (data not shown). Averages across all studies of a given AIIA at a given dose without correction for sample size showed results similar to the weighted averages presented here (data not shown).

DISCUSSION

This comprehensive analysis shows the comparable antihypertensive efficacy of losartan, valsartan, irbesartan, and candesartan when administered at their recommended doses. These four AIIA also show a near-flat dose-response curve when administered at doses recommended for the treatment of hypertension, which suggests that monotherapy dose titration offers limited benefit. As with other antihypertensive agents, combination of AIIA with low-dose diuretics significantly potentiated the blood pressure reduction and responder rates. Importantly, the blood pressures used in this analysis are trough blood pressures measured at the end of the 24-h dosing interval. This also

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TABLE 1. FORTY-THREE PUBLICATIONS USED FOR THE INTEGRATED ANALYSIS OF AIIA ANTIHYPERTENSIVE EFFICACY*

AIIA Dose	First Author	n	DBP (mm Hg)			SBP (mm Hg)			Responders (%)
			Mean	SD	95% CI	Mean	SD	95% CI	
Losartan 50 mg	Trimarco[45]	72	−11.9	6.8	(−13.5, −10.3)	−14.6	11.8	(−17.4, −11.8)	
	Gradman[22]	79	−10.1	7.0	(−11.7, −8.5)	−13.0	12.7	(−15.8, −10.2)	
	Dahlof[30]	132	−9.0	7.7	(−10.3, −7.7)	−11.8	12.2	(−13.9, −9.7)	49
	Weir[46]	110	−8.9	7.5	(−10.3, −7.5)	−9.6	13.0	(−12.1, −7.1)	
	MacKay[47]	138	−8.8	7.6	(−10.1, −7.5)	−10.7	14.3	(−13.1, −8.3)	52
	Chan[28]	89	−8.8	7.7	(−10.4, −7.2)	−12.6	13.8	(−15.5, −9.7)	56
	Townsend[27]	132	−8.8	7.7	(−10.1, −7.5)	−8.6	13.8	(−11.0, −6.2)	
	Roca-Cusachs[48]	192	−8.7	7.7	(−9.8, −7.6)	−12.0	13.8	(−14.0, −10.0)	56
	Tikkanen[25]	200	−8.4	7.1	(−9.4, −7.4)	−10.6	13.0	(−12.4, −8.8)	51
	Wilson[29]	36	−8.4	5.9	(−10.4, −6.4)	−10.0	9.2	(−13.1, −6.9)	
	Oddou-Stock[8]	**534**	**−8.0**	**7.7**	**(−8.7, −7.3)**	**−10.5**	**13.8**	**(−11.7, −9.3)**	**44**
	Ikeda[49]	125	−7.7	9.0	(−9.3, −6.1)	−9.2	13.8	(−11.6, −6.8)	46
	Oparil[50]	97	−7.3	9.0	(−9.1, −5.5)	−6.1	14.4	(−9.0, −3.2)	
	Mallion[26]	109	−7.0	6.6	(−8.3, −5.7)	−9.3	11.9	(−11.6, −7.0)	46
	Byyny[51]	29	−6.7	7.8	(−9.7, −3.7)	−11.7	17.6	(−18.4, −5.0)	
	Andersson[9]	**83**	**−6.6**	**8.7**	**(−8.5, −4.7)**	**−11.1**	**21.2**	**(−15.7, −6.5)**	
	Oparil[11]	**192**	**−6.2**	**7.7**	**(−7.3, −5.1)**	**−8.3**	**13.8**	**(−10.3, −6.3)**	**44**
	Martina[52]	10	−4.0	7.2	(−9.2, 1.2)	−7.0	8.2	(−12.9, −1.1)	
Valsartan 80 mg	Hegner[36]	82	−13.4	7.7	(−15.1, −11.7)	−16.1	15.8	(−19.6, −12.6)	74
	Mallion[34]	94	−13.2	7.6	(−14.8, −11.6)	−17.2	11.9	(−19.6, −14.8)	61
	Corea[35]	84	−11.5	6.8	(−13.0, −10.0)	−13.1	14.8	(−16.3, −9.9)	67
	Holwerda[32]	136	−9.5	6.2	(−10.6, −8.4)	−12.4	12.7	(−14.5, −10.3)	55
	Oddou-Stock[8]	**545**	**−8.3**	**12.0**	**(−9.3, −7.3)**	**−11.0**	**17.5**	**(−12.5, −9.5)**	**46**
	Oparil[23]	150	−7.2	14.6	(−9.6, −4.9)	−8.6	25.1	(−12.6, −4.6)	43
	Black[33]	364	−7.1	14.7	(−8.6, −5.6)	−8.0	17.5	(−9.8, −6.2)	42
Irbesartan 150 mg	**Kassler-Taub[10]**	**129**	**−9.7**	**7.4**	**(−11.0, −8.4)**	**−12.1**	**13.1**	**(−14.4, −9.8)**	**60**
	Weber[53]	124	−9.7	7.2	(−11.0, −8.4)	−11.9	12.6	(−14.1, −9.7)	50
	Fogari[54]	53	−8.3	7.9	(−10.5, −6.1)	−11.4	12.4	(−14.8, −8.0)	55
	Guthrie[55]	98	−8.3	6.6	(−9.6, −7.0)	−9.1	12.1	(−11.5, −6.7)	53
	Oparil[11]	**178**	**−7.7**	**7.2**	**(−8.8, −6.6)**	**−11.1**	**12.6**	**(−13.0, −9.2)**	**50**
Candesartan 8 mg	Franke[56]	68	−10.5	9.9	(−12.9, −8.1)				69
	Andersson[9]	**77**	**−9.0**	**13.0**	**(−11.9, −6.1)**	**−14.0**	**23.7**	**(−19.4, −8.6)**	
	Reif[24]	60	−8.7	8.5	(−10.9, −6.5)	−9.9	14.0	(−13.5, −6.3)	
	Philipp[44]	131	−8.1	10.8	(−10.0, −6.2)	−11.4	20.1	(−14.9, −7.9)	47
Losartan 50–100 mg	Chan[28]	89	−13.2	8.2	(−14.9, −11.5)	−17.2	14.7	(−20.3, −14.1)	69
	Roca-Cusachs[48]	192	−11.5	8.2	(−12.7, −10.3)	−15.4	14.7	(−17.5, −13.3)	60
	Tiebel[57]	304	−11.4	9.5	(−12.5, −10.3)	−16.9	16.2	(−18.7, −15.1)	
	Dahlof[58]	298	−10.3	7.5	(−11.2, −9.4)	−13.6	13.7	(−15.2, −12.0)	60
	Gradman[22]	90	−9.9	6.9	(−11.3, −8.5)	−8.9	13.6	(−11.7, −6.1)	
	Oddou-Stock[8]	**534**	**−9.7**	**8.2**	**(−10.4, −9.0)**	**−12.9**	**14.7**	**(−14.2, −11.6)**	**55**
	Byyny[51]	28	−9.6	7.6	(−12.6, −6.6)	−11.0	14.5	(−16.6, −5.4)	
	Mallion[26]	109	−9.2	7.1	(−10.5, −7.9)	−9.5	14.0	(−12.2, −6.8)	51
	Kassler-Taub[10]	**131**	**−8.7**	**7.3**	**(−10.0, −7.4)**	**−11.3**	**13.0**	**(−13.6, −9.0)**	**56**
	Dahlof[30]	132	−8.6	8.8	(−10.1, −7.1)	−11.4	16.4	(−14.2, −8.6)	50
	Ikeda[49]	118	−8.6	8.3	(−10.1, −7.1)	−9.4	14.7	(−12.1, −6.7)	52
	Oparil[11]	**192**	**−7.9**	**8.2**	**(−9.1, −6.7)**	**−11.7**	**14.7**	**(−13.8, −9.6)**	**54**
Valsartan 80–160 mg	**Oddou-Stock[8]**	**545**	**−10.5**	**13.6**	**(−11.6, −9.4)**	**−13.8**	**24.0**	**(−15.8, −11.8)**	**62**
	Black[33]	162	−8.5	12.5	(−10.4, −6.5)	−10.9	21.9	(−14.3, −7.5)	46
	Oparil[23]	148	−7.3	14.7	(−9.7, −5.0)	−9.0	26.0	(−13.2, −4.7)	44
Irbesartan 150–300 mg	**Kassler-Taub[10]**	**134**	**−11.7**	**7.4**	**(−13.0, −10.4)**	**−16.4**	**13.1**	**(−18.6, −14.2)**	**69**
	Pool[21]	78	−11.6	7.5	(−13.3, −9.9)	−13.0	11.7	(−15.6, −10.4)	67
	Guthrie[55]	98	−10.5	8.0	(−12.1, −8.9)	−12.6	14.1	(−15.4, −9.8)	59
	Oparil[11]	**178**	**−10.2**	**7.6**	**(−11.3, −9.1)**	**−13.7**	**13.1**	**(−15.6, −11.8)**	**63**
	Kochar[59]	43	−10.2	7.6	(−12.5, −7.9)				49
	Weir[60]	79	−7.7	7.6	(−9.4, −6.0)	−12.0	13.1	(−14.9, −9.1)	

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TABLE 1. CONTINUED.

AIIA Dose	First Author	n	DBP (mm Hg)			SBP (mm Hg)			Responders (%)
			Mean	SD	95% CI	Mean	SD	95% CI	
Candasartan 8–16 mg	Philipp[44]	36	−10.3	10.0	(−13.7, −6.9)	−12.6	19.1	(−19.1, −6.1)	69
	Andersson[9]	**80**	**−10.0**	**13.2**	**(−12.9, −7.1)**	**−16.0**	**24.4**	**(−21.4, −10.6)**	
	Meineke[61]	232	−10.0	10.0	(−11.3, −8.7)	−17.1	19.1	(−19.6, −14.6)	
	Zuschke[62]	90	−9.4	10.0	(−11.5, −7.3)	−11.1	19.1	(−15.1, −7.1)	
	McInnes[63]	96	−8.7	7.2	(−10.2, −7.2)	−14.3	16.3	(−17.6, −11.0)	47
	Reif[24]	59	−7.8	8.8	(−10.1, −5.5)	−10.7	14.7	(−14.5, −6.9)	54
Losartan 50 mg	Trimarco[45]	72	−13.9	7.3	(−15.6, −12.2)	−17.4	12.2	(−20.3, −14.5)	
HCTZ 12.5 mg	MacKay[47]	135	−13.2	6.6	(−14.3, −12.1)	−17.2	13.1	(−19.4, −15.0)	78
	Tiebel[57]	310	−13.2	7.7	(−14.1, −12.3)	−18.4	16.0	(−20.2, −16.6)	
	Critchley[64]	216	−12.6	7.3	(−13.6, −11.6)	−21.5	14.1	(−23.4, −19.6)	71
	Wilson[29]	31	−11.9	5.4	(−13.9, −9.9)	−16.0	11.6	(−20.3, −11.7)	
	Weir[46]	110	−11.6	7.6	(−13.0, −10.2)	−14.2	13.1	(−16.7, −11.7)	
	Dahlof[58]	300	−11.4	7.1	(−12.2, −10.6)	−17.1	12.4	(−18.5, −15.7)	70
	Oparil[11]	**192**	**−10.8**	**7.3**	**(−11.8, −9.8)**	**−13.9**	**14.1**	**(−15.9, −11.9)**	**65**
	Oparil[50]	97	−10.4	8.0	(−12.0, −8.8)	−11.3	16.5	(−14.6, −8.0)	
	Townsend[27]	132	−10.3	7.3	(−11.6, −9.0)	−11.3	14.1	(−13.7, −8.9)	
	Martina[52]	10	−9.0	7.9	(−14.7, −3.3)	−13.0	14.8	(−23.6, −2.4)	
Valsartan 80 mg	Mallion[34]	94	−15.5	7.5	(−17.0, −14.0)	−19.7	12.2	(−22.2, −17.2)	68
HCTZ 12.5 mg	Black[65]	96	−11.7	7.5	(−13.2, −10.2)				64
Irbesartan 150 mg	Phillips[66]	57	−13.2	7.5	(−15.2, −11.2)				69
HCTZ 12.5 mg	Weber[53]	124	−12.0	7.5	(−13.3, −10.7)	−16.1	14.3	(−18.6, −13.6)	65
Candesartan 8 mg	Philipp[44]	61	−10.2	9.4	(−12.6, −7.8)	−20.6	20.0	(−25.7, −15.5)	56
HCTZ 12.5 mg	McInnes[67]	237	−9.8	9.4	(−11.0, −8.6)				

** Per agent at a given dose, the studies were ranked by DBP reduction. The results from the four direct, head-to-head comparative trials within the AIIA class are indicated in bold. The 95% confidence intervals (95% CI) were calculated from the mean and standard deviation. For those studies, where no standard deviations (SD) were reported, we assumed the SD for the weighted average of the same drug and dose (SD underlined).*

AIIA, angiotensin II antagonists; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide.

provides some information with regard to efficacy in relation to the recommended dose interval for the AIIA for the treatment of hypertension.

The current pooled data analysis from 43 studies involving 11,281 patients treated with AIIA showed that the weighted average DBP/SBP reductions and responder rates for all four AIIA were comparable. This conclusion applied to studies of starting doses of AIIA, monotherapy dose titration, and combination therapy with starting doses of AIIA plus low-dose HCTZ. The dose-response was similar for all the AIIA and the observed differences were not clinically meaningful. For all four AIIA under consideration, titration to the AIIA/HCTZ combination produced the greatest antihypertensive effect.

There have been four published studies in which losartan has been compared directly with valsartan,[8] irbesartan,[10,11] and candesartan.[9] Some of these trials have suggested differences in efficacy or responder rates between the agents tested. The results of the present metaanalysis show no difference in blood pressure efficacy or responder rates. Because these direct comparative studies contribute less than 20% of all the available evidence on blood pressure efficacy, a metaanalysis of the sort provided in this paper might be regarded as a stronger basis for understanding the comparative efficacy of drugs in this class.

It is possible that additional data that are perceived to be negative by commercial sponsors of specific therapies may not be published. By necessity, our pooled analysis of published trials would not be able to include the data from any such negative studies, which inevitably would introduce a publication bias. Nevertheless, the volume of data recorded in our analysis strengthens the hypothesis that there are no clinically meaningful differences in antihypertensive efficacy within the AIIA class.

Review articles on AIIA[1–7] and separate pooled analyses for irbesartan[18,19] and candesartan[6,20] reported results consistent with the weighted average SBP/DBP reductions and response rates reported here. Man in 't Veld calculated placebo-corrected DBP reductions of 5 mm Hg for 150 mg irbesartan and 6 mm Hg for 300 mg irbesartan, and non–placebo-corrected DBP reductions of 9.2 mm Hg for 150 mg irbesartan and 10.3 mm Hg for 300 mg irbesartan.[19]

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TABLE 2. SUMMARY OF WEIGHTED AVERAGE ANTIHYPERTENSIVE EFFICACY FROM 43 PUBLISHED DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIALS WITH STARTING DOSE AIIA MONOTHERAPY, AIIA MONOTHERAPY DOSE TITRATION, OR AIIA/HCTZ COMBINATION THERAPY AND CROSS ALL PRODUCTS*

	N	% of Total	DBP (mm Hg)	95% CI	SBP (mm Hg)	95% CI	Responders (%)
AIIA monotherapy starting dose							
Losartan 50 mg	2359	50%	−8.2	(−8.5, −7.9)	−10.4	(−10.9, −9.8)	48
Valsartan 80 mg	1455	31%	−8.8	(−9.4, −8.2)	−10.9	(−11.8, −10.0)	49
Irbesartan 150 mg	582	12%	−8.7	(−9.3, −8.1)	−11.2	(−12.2, −10.2)	53
Candesartan 8 mg	336	7%	−8.9	(−10.1, −7.7)	−11.8	(−14.0, −9.7)	55
Across products	4732	100%	−8.5		−10.8		49.5
AIIA monotherapy titration							
Losartan 50–100 mg	2217	52%	−10.0	(−10.3, −9.6)	−13.1	(−13.7, −12.5)	56
Valsartan 80–160 mg	855	20%	−9.6	(−10.5, −8.7)	−12.4	(−14.0, −10.8)	56
Irbesartan 150–300 mg	610	14%	−10.4	(−11.0, −9.8)	−13.8	(−14.9, −12.8)	63
Candesartan 8–16 mg	593	14%	−9.5	(−10.3, −8.7)	−14.7	(−16.2, −13.1)	53
Across products	4275	100%	−9.9		−13.3		56.6
Starting dose AIIA/HCTZ combination							
Losartan 50 mg/HCTZ 12.5 mg	1605	71%	−12.0	(−12.3, −11.6)	−16.5	(−17.2, −15.8)	70
Valsartan 80 mg/HCTZ 12.5 mg	190	8%	−13.6	(−14.6, −12.5)	−19.7	(−21.4, −18.0)	66
Irbesartan 150 mg/HCTZ 12.5 mg	181	8%	−12.4	(−13.5, −11.3)	−16.1	(−18.2, −14.0)	66
Candesartan 8 mg/HCTZ 12.5 mg	298	13%	−9.9	(−11.0, −8.8)	−20.6	(−22.9, −18.3)	56
Across products	2274	100%	−11.9		−17.3		68

** The 95% confidence intervals (95% CI) were calculated from the mean and standard deviation. Responder rates were typically the percent of treated patients who achieved a diastolic blood pressure < 90 mm Hg or had a decline in diastolic blood pressure by ≥ 10 mm Hg.*

Abbreviations as in Table 1.

Elmfeldt et al reported placebo-corrected DBP reductions of 6 mm Hg for 8 mg candesartan and 8 mm Hg for 16 mg candesartan.[20] Reductions in SBP and response rates were also comparable to the current integrated analysis.

This analysis suggests that AIIA lower blood pressure with similar efficacy when administered at their usual recommended doses for the treatment of hypertension. At these recommended doses, the dose response for blood pressure reduction with all AIIA is relatively flat and, in general, efficacy is enhanced significantly by adding low-dose (12.5mg) HCTZ to the initial dose of AIIA rather than escalating the dose of the AIIA.

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