Heart, Lung and Circulation (2018) **27,** 666–682
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2017.06.721

ORIGINAL ARTICLE

Comparative Efficacy of Angiotensin II Antagonists in Essential Hypertension: Systematic Review and Network Meta-Analysis of Randomised Controlled Trials

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Received 21 January 2017; received in revised form 24 May 2017; accepted 23 June 2017; online published-ahead-of-print 14 July 2017

Background Evidence on the long-term clinical benefits of individual members of angiotensin II receptor blockers is limited given the lack of head-to-head studies. We conducted a network meta-analysis to determine the comparative efficacy of different members within this drug class with respect to outcomes of (i) blood pressure reduction (at 24 and 52 weeks) and (ii) prevention of cardiovascular disease (>104 weeks).

Methods A systematic literature review was conducted – Protocol registration: (PROSPERO – CRD42014007067) – to identify relevant literature from the following databases: Cochrane Library, PubMed, Medline and EMBASE; searched from inception to July 2016. Randomised controlled trials (RCTs) were included if they reported long-term effectiveness relating to blood pressure, mortality, myocardial infarction or stroke. Eligible studies included those with placebo or specific active-treatment comparators (either another angiotensin II receptor blockers or hydrochlorothiazide). A Bayesian random-effects network model was used to combine direct within-trial comparisons between treatment groups with indirect evidence from other trials.

Results Thirty-six studies were identified, representing 28 unique trials. Blood pressure reduction, based on 12 studies (n = 807) with fixed dosing regimen, was found to be similar amongst members of the angiotensin receptor blocker drug class at both 24 and 52 weeks. A network meta-analysis of five studies (n = 16,716) with a treat-to-target approach found that prevention of all-cause mortality, stroke and myocardial infarction was similar across the angiotensin-receptor blockers therapies initiated.

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Conclusions Current evidence is insufficient to show differences in any members within the angiotensin II receptor blocker drug class with respect to blood pressuring lowering effects or a reduction in cardiovascular diseases.

Keywords Angiotensin II type 1 receptor blockers • Systematic review • Meta-analysis • Blood pressure • Myocardial infarction • Stroke

Introduction

Hypertension is a prevalent medical condition that is a major modifiable risk-factor for cardiovascular disease. Although most clinical guidelines recommend an optimal blood pressure of <140/90 mmHg in low-to-moderate risk individuals and <150/90 mmHg in the elderly [1–3], meeting these targets can be challenging. Previous studies have shown that, in addition to lowering blood pressure, antihypertensive therapies confer protection against the development of cardiovascular disease [4,5]. However, these studies are only partially relevant clinically, given that care providers often do not simply face the issue of whether therapy should be initiated but rather which specific therapy should be prescribed. Existing systematic reviews and meta-analyses that compare across antihypertensive classes [6–10] can partly address this issue by providing clarity on the appropriateness of certain classes in different patient populations and under different indications. However, several agents may exist within a single drug class and an important question on selection still remains: can they all be considered equivalent?

Most, if not all, national guidelines for the management of hypertension recommend angiotensin II receptor blockers (ARBs) as first-line therapy [2,3,11,12]. ARBs inhibit the actions of angiotensin II through selective binding of type 1 (AT_1) receptors in vascular smooth muscle [13]. The results of treatment are effective reductions in blood pressure [14] and known ancillary properties independent of blood-pressure lowering, such as slowing the progression of renal disease [15–18]. Yet, debate remains unresolved regarding differences in the efficacy of agents within this drug class. Structural and chemical differences have been identified and some clinical studies have suggested that not all ARBs are equal, with newer agents having superior and more rapid blood pressure control when compared to losartan or valsartan at 4 and 8 weeks [19,20].

Clinically meaningful differences within this drug class would have implications for optimising therapeutic decision-making. Yet most studies are typically two-armed placebo-controlled trials that do not examine comparative effectiveness. Furthermore, meta-analyses attempting to address comparative effectiveness to date have been limited, as their analyses are constrained to direct evidence pooled from short-term (≤12 weeks) trials addressing only blood pressure outcomes [21–23]. In order to appropriately assess the question of intra-class superiority, the ideal approach would entail multiple treatment (network) meta-analyses in which both direct and indirect evidence is combined to generate an estimate of the comparative effectiveness of individual ARBs.

The purpose of this study is to provide a comprehensive and updated systematic review on the comparative effectiveness of ARBs in reducing blood pressure and cardiovascular event rates (i.e., myocardial infarction (MI), stroke, cardiovascular- and all-cause mortality) in patients with hypertension using network meta-analysis (NMA). We examine long-term effectiveness by comparing blood pressure outcomes at 24 and 52 weeks and cardiovascular event rates at >104 weeks.

Methods

Literature Search Strategy

We followed a pre-specified study protocol (CRD42014007067) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) consensus statement throughout the design, implementation, and reporting of this study [24].

We searched OVID Medline (1966 to present; In-Process and Other Non-Indexed Citations), EMBASE (1974 to July 2016), PubMed (for non-Medline records) and The Cochrane Library. A search filter was applied to restrict search results to randomised controlled trials, meta-analyses and systematic reviews. The search strategy used controlled vocabulary, including MeSH terms and keywords, related to ''hypertension''; ''angiotensin receptor blockers'' and the generic names of pharmacological agents (Appendix I). Additionally; the references of all retrieved articles and any relevant systematic reviews were hand-searched. We retrieved only English-language studies. An unrestricted timeframe was chosen to capture all relevant publications with the latest search performed as of 9 July 2016. We imported citations into reference management software for de-duplication and title/abstract screening.

Selection Criteria

Titles and abstracts were independently screened in duplicate to assess eligibility according to pre-defined inclusion/exclusion criteria. Potentially relevant studies then underwent full-text screening. To be included in this analysis, eligible trials had to fulfill the following criteria (Appendix II): randomised-control trial design; enrolling adult patients (≥18 years of age) with essential hypertension (no further restriction was imposed for age, gender or other co-morbidities); comparing ARBs to either another ARB, hydrochlorothiazide or a placebo regimen (with baseline concurrent drugs unrelated to hypertension permitted).

Outcomes of interest included either blood pressure, following at least 6 months of treatment, or adverse cardiovascular events (i.e. total and cardiovascular-related mortality, MI, stroke), following at least 2 years of treatment. Given the restriction for trials with longer durations, studies involving concomitant antihypertensive medication (e.g., usual antihypertensive treatment), step-care or combination therapy were included. Any disagreements were resolved by consensus between the independent screeners.

Study Quality Assessment

Two authors independently assessed risk of bias using the relevant components recommended by the Cochrane Collaboration.

Data Extraction Strategy

Data from each included trial were extracted by one reviewer using a structured form that was subsequently checked by a second reviewer. Disagreements were resolved by discussion. In this form, details on the trial design (e.g. timeframe, inclusion/exclusion criteria), trial population (e.g. age, gender proportion, baseline risk factors) and trial results (e.g. blood pressure measurements, absolute value and relative risk for cardiovascular and cerebrovascular events) were collected. Study authors were contacted to answer queries and provide additional information.

If a study resulted in multiple publications, data were extracted from both the primary and secondary papers. However, the analysis included only the main paper (defined as the one with the largest sample size) unless the secondary paper reported a different follow-up period or a separate outcome of interest.

Statistical Analysis

Given the nature of the included studies, NMA was possible. This type of analysis, which combines both direct and indirect treatment comparisons, can summarise RCTs of several different treatment strategies and provide point estimates (and 95% confidence interval (CI)) of their association for a given endpoint. The NMA was conducted using a Bayesian random-effects generalised linear model [28] with a consistency assumption for the treatment effects. The generalised linear model framework allowed us to handle continuous and binary outcome variables. We used R software version 3.1.1 [29] with R package *gemtc* version 0.6 [30] to specify the model and interface with Just Another Gibbs Sampler (JAGS) software version 3.4.0 [31] to execute Bayesian estimation of the model parameters through a Markov chain Monte Carlo (MCMC) process. The default of vague prior distributions for treatment effect and heterogeneity parameters was chosen. As per convention [31], we set an adaption phase of 20,000 samples, a burn-in phase of 100,000 samples, and a thinning interval of 10, resulting in 10,000 samples being used for inference in the MCMC process. To ensure convergence for all model parameters, four chains were run and assessed by the Gelman-Rubin-Brooks plot and diagnostic test [32].

Results

5184 unique publications were identified, of which 5102 were excluded following title/abstract screening. Eighty-two documents underwent full-text screening of which 36 met the full inclusion criteria (Figure 1), representing 28 unique trials. Three clinical trials that were initially selected could not be subsequently included in the narrative synthesis as specific details regarding blood pressure were not available [19,33,34]. All remaining included studies reported on blood pressure reduction and, amongst these, five further reported on outcomes of cardiovascular morbidity and mortality (Table 1).

Table 1 summarises the general characteristics and baseline demographics of the studies identified in our systematic review. The majority of the studies were two-armed trials, with the exception of five three-arm trials. As the study objective was to assess long-term efficacy, mean study duration ranged from 24 to 243 weeks.

Heterogeneity between studies was observed in terms of the patient population (i.e., age, gender, co-morbidities) and the dosing regimen (i.e. fixed dosing or treat-to-target). A variety of patient populations were enrolled including: diabetes mellitus without [35–41] or with additional comorbidities [15–17,42–44]; metabolic syndrome [45–47]; and left-ventricular hypertrophy [48,49]. Certain studies focussed solely on the elderly [50–55]; while others centred on overweight and/or obese patients [42,43,49,56] (Table 1). Some of the identified studies evaluated the efficacy of ARBs in lowering blood pressure by either adhering to the same dosage strength throughout the study's duration [35,37,41–43,46,49,53,56–61] or by employing a forced dose-doubling regimen applied to all patients regardless of their treatment response [27]. However, a greater majority of the trials attempted to attain a particular blood pressure target using treat-to-target methodology. In the latter case, all patients received an ARB and the dosage of their respective ARB was doubled and/or additional antihypertensives were added in order to achieve a pre-defined blood pressure goal [15–17,36,38–40,44,45,47,48,52,54,57,62–65]. Blood pressure goals varied considerably across these studies: ranging from a systolic blood pressure between <130 to <160 mmHg and a diastolic blood pressure between <80 to <95 mmHg.

Although the treat-to-target studies are described narratively in this review, they were excluded from NMA for the outcome of blood pressure reduction specifically. As a large portion of patients in the placebo group received active treatment, this made it difficult to interpret the treatment effect attributable to ARB alone. In such studies, the difference in blood pressure reduction achieved would be smaller partly because background treatment with other antihypertensive drugs was permitted.

The quantitative NMA therefore addresses two separate questions according to the outcome: (i) in studies involving a fixed dosing regimen, what is the comparative effectiveness of individual ARBs in terms of controlling blood pressure following at least 24 weeks of treatment?; and (ii) in treat-to-target trials, what is the long-term comparative

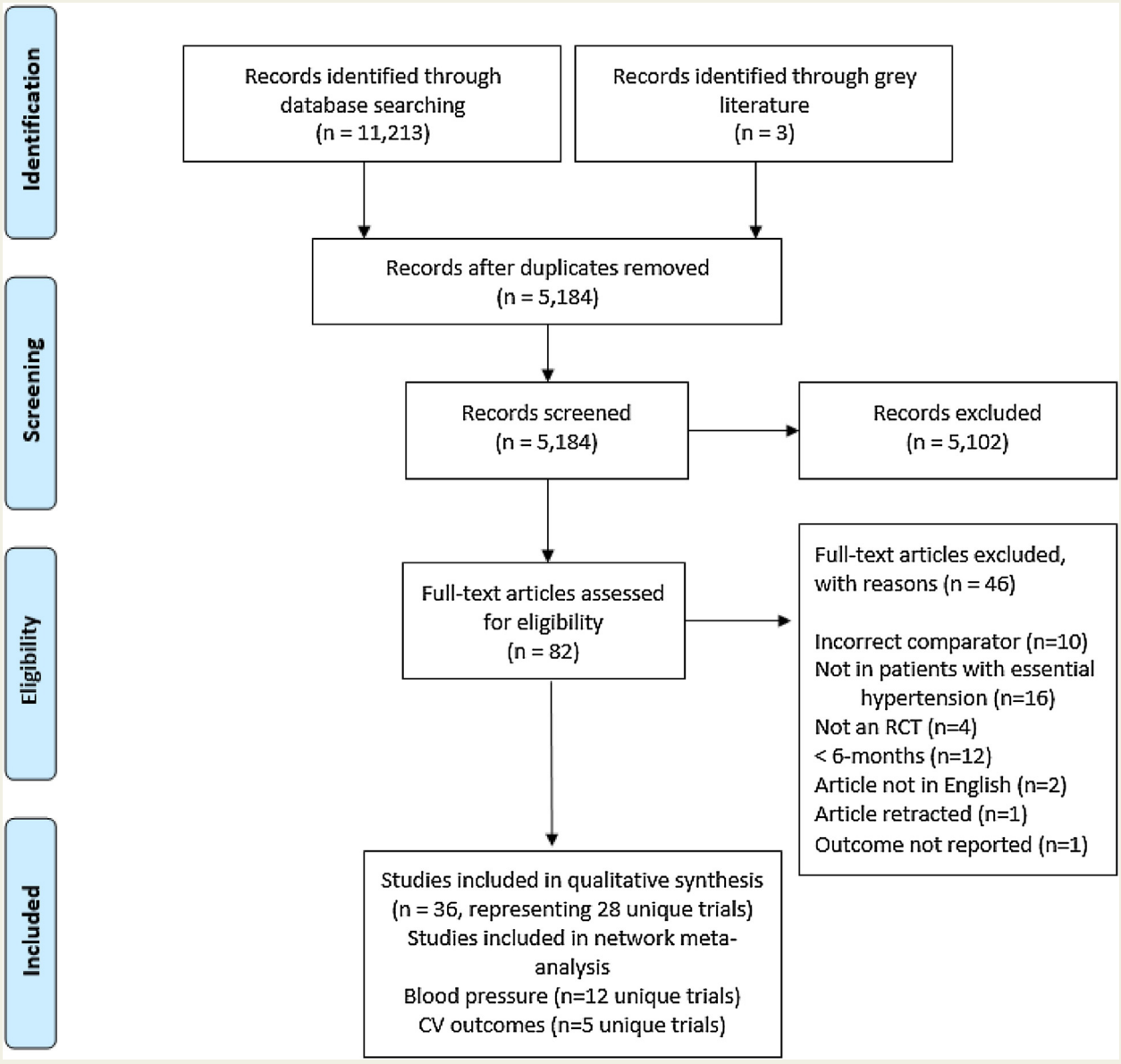

Figure 1 PRISMA Diagram of the Clinical Review Search Strategy.

effectiveness of ARB-initiated therapy alongside conventional antihypertensive treatment in preventing cardiovascular diseases following at least 2 years of treatment?

Risk of Bias Assessment

Table 2 presents the risk of bias assessment for the included studies. Nearly all were associated with an uncertain risk of selection bias given poor reporting on the methods of randomisation and the approach to preserve allocation concealment. A little over half of the studies reported blinding although, in the majority of the cases, the method by which blinding was ensured was not adequately described. The least-likely risk of bias was observed in terms of selective outcome reporting as most studies reported the results of the outcomes that were set out either in their methods or in published study protocols. Other sources of bias found in some studies included imbalance in the prognostic factors despite randomisation.

Efficacy: Blood Pressure Change

As previously mentioned, treat-to-target trials were excluded from the analysis of blood pressure given that such study designs do not aim to compare absolute blood pressure efficacy but, rather, the secondary effects of treatment, such as collateral benefits (e.g., reduction in cardiovascular morbidity and mortality), at the same or similar levels of blood pressure control. Consequently, treat-to-target trials have limited utility when evaluating blood pressure since a specific blood pressure target would have been pre-defined for all treatment arms within a trial.

Table 1 Characteristics and baseline data of included studies (secondary articles from main trial also presented).

First Author	Study name	Mean follow-up, wk	Number of participants analysed	Intervention, dose	Titration to reach BP goal		Demographic Details				Baseline Blood Pressure (mmHg)	
					Dose doubling?	Concomitant medication?	Mean age (SD)	Female (%)	BMI (SD)	Concomitant diseases	SBP (SD)	DBP (SD)
Brenner [14]	RENAAL	177	751	Losartan, 50 mg od	Yes	Yes	60 (7)	38.5	30 (6)	Diabetes + nephropathy	152 (19)	82 (10)
			762	Placebo			60 (7)	35.2	29 (6)		153 (20)	82 (11)
DeRosa [45,46]		52	95	Telmisartan, 40 mg od	NR	NR	56 −5	48	27.6 (1.1)	Diabetes + MS	135 (4)	86 (4)
			152	Irbesartan, 150 mg od			55 −4	52	27.7 −1.2		136 (4)	84 (3)
DeRosa [38]		52	40	Telmisartan, 40 mg od	NR	NR	54 −5	45	26.9 (1.2)	Diabetes	143 (5)	92 (3)
			39	Eprosartan, 600 mg od			55 −3	49	26.4 (1.3)		144 (5)	91 (4)
			40	Placebo			53 −5	50	26.2 −1.1		143 (4)	92 (4)
Foulquier [69]	TRANSCEND	243	2547	Telmisartan, 80 mg od	NR	Yes	NR	NR	NR		143.4	NR
			2551	Placebo	NR	Yes	NR	NR	NR		143.5	NR
Galzerano [62]		52	40	Telmisartan, 80 mg od	No	No	55 −8	43.9	NR		157 (8)	96 (6)
			25	HCTZ, 25 mg od			53 −7	46.4	NR		154 (10)	95 (7)
Hasegawa [66]	TALENT	52	29	Telmisartan, 40 mg od	Yes	Yes	59.1 (10.3)	31	25.7 (4.9)		152.1 (16.5)	90.0 (13.3)
			28	Losartan, 50 mg od			56.4 (10.1)	32.1	25.9 (4.8)		150.6 (10.6)	92.1 (12.3)
Lewis [15]	IDNT-2	104	579	Irbesartan, 75 mg od	Yes	Yes	59.3 (7.1)	35	31 (5.6)	Diabetes + proteinuria	160 (20)	87 (11)
			569	Placebo			58.3 (8.3)	29	30.5 (5.9)		158 (20)	87 (11)
Lindholm [70]	ALPINE	52	196	Candesartan, 16 mg od	No	Yes	54.5 (9.4)	52	27.8 (4.1)		154.7 (13.2)	96.8 (5.6)
			196	HCTZ, 25 mg od			55.4 (9.6)	53	28.1 (4.2)		155 (13.5)	97 (5.7)
Lithell [57]	SCOPE	194	2477	Candesartan, 8–16 mg od	Yes	Yes	76.4	64.8	27		166 (8.9)	90.3 (6.6)
			2460	Placebo			76.4	64.2	26.9		166.5 (9)	90.4 (6.6)
Papademetriou [54]	SCOPE (substudy)	167	754	Candesartan, 8 mg od	Yes	Yes	77.3	63.3	26.7		168.7	82.3
			764	Placebo			76.9	65.3	26.3		169.3	82.5
Saxby [53]	SCOPE (substudy: Single centre)	191	112	Candesartan, 8 mg od	Yes	Yes	76 (4)	48.2	NR		165 (8)	88 (7)
			116	Placebo			76 (5)	46.5	NR		166 (8)	89 (7)
Trenkwalder [56]	SCOPE (substudy: No add-on therapy)	191	1253	Candesartan, 8 mg od	No	No	76.4	67	NR		NR	NR
			845	Placebo					NR		NR	NR
Trenkwalder [58]	SCOPE (substudy: Pre-specified subgroup)	167	NR	Candesartan, 8 mg od	NR	NR	NR	NR	NR		NR	NR
			NR	Placebo			NR	NR	NR		NR	NR

Table 1. (continued).

First Author	Study name	Mean follow-up, wk	Number of participants analysed	Intervention, dose	Titration to reach BP goal		Demographic Details				Baseline Blood Pressure (mmHg)	
					Dose doubling?	Concomitant medication?	Mean age (SD)	Female (%)	BMI (SD)	Concomitant diseases	SBP (SD)	DBP (SD)
Makris [61]		26	45	Eprosartan, 600 mg od	No	No	55 (10)	55.6	23.96		148.77 (9)	95.31
			41	Losartan, 100 mg od			55 −9	46.3	23.97		148.56 (9.1)	95.24
Menne [39]	ROADMAP (substudy)	167	2043	Olmesartan, 40 mg od	No	Yes	58 (8.7)	52.9	31.3 (4.9)	Diabetes	138.4 (15)	81.7 (9.5)
			1977	Placebo			58.2 (8.5)	55.4	31.1 (4.9)		137.7 (14.4)	81.5 (9.1)
Minami [50]		24	20	Telmisartan, 40 mg od	NR	No	63.1 (11.6)	61.9	24.4 (3)	MS	NR	NR
			20	Losartan, 50 mg od			63.1 −11.6	61.9	24.4 (3)		NR	NR
Murakami [48]	ADIPO	24	9	Telmisartan, 40 mg od	No	Yes	61.4 (4.58)	66.7	27.2 (1.6)	MS	146.3 (3.6)	85 (3.8)
			10	Valsartan, 80 mg od			50.4 (4.75)	40	30.8 (2.4)		144.9 (4.8)	89.5 (3.6)
Nedogoda [52]		24	30	Telmisartan, 80 mg od	NR	NR	47.4 (9.2)	50	31.1 (3.1)	Majority: LVH (90%); hypercholesterolaemia (80%)	158 (3)	98 (3)
			30	Losartan, 100 mg od			46.7 (8.2)	50	29.4 (3.6)	Majority: LVH (97%) hypercholesterolaemia (87%)	157 (4)	98 (3)
Negro [59]		24	21	Irbesartan, 150 mg od	NR	NR	45 (9.3)	30.4	35.6 (2.8)		149.7 (4.7)	94.4 (4.2)
			22	Telmisartan, 80 mg od			46.7 (8.2)	34.8	36.4 (2.4)		151.7 (4.9)	97.7 (4.2)
Neldam [55]		24	123	Candesartan, 8 mg od	Yes	NR	78.5 −3.3	65	NR		178.9 (15.9)	101.8 (4.8)
			62	HCTZ, 12.5 mg od			78.1 (3.4)	58	NR		179.8 (16.5)	101 (4)
Parving [16]	IRMA2	104	195	Irbesartan, 150 mg od	Yes	Yes	58.4 −8	33.8	29.9 (3.8)	Diabetes + microalbuminuria	153 (14)	90 (9)
			194	Irbesartan, 300 mg od			57.3 (7.9)	29.4	30 (4.3)		153 (14)	91 (10)
			201	Placebo			58.3 (8.7)	31.3	30.3 (4.4)		153 (15)	90 (9)
Rossing [47]	IRMA2 (substudy:	104	13	Irbesartan, 150 mg od	No	Yes	62 −9	10	29 (2)	Diabetic + microalbuminuria	156 (15)	91 (11)
	Single centre)		15	Irbesartan, 300 mg od			56 −9	20	29 (4)		159 (16)	90 (9)
			15	Placebo			60 −7	30	28 (5)		157 (15)	89 (7)
Picca [51]		26	15	Losartan, 50 mg od	Yes	NR	48 −8	43.3	NR	Concentric LVH	164 (7)	105 (4)
			15	Valsartan, 80 mg od					NR		171 (8)	101 (6)
Rayner [67]		24	27	Losartan, 50 mg od	Yes	Yes	NR	60	NR		151 (8.4)	89.2 (8.4)
			25	Candesartan, 8 mg od			NR	59	NR		157 (16.7)	90.5 (7.84)
Rizos [49]		24	52	Telmisartan, 80 mg od	NR	NR	60 (10)	48.1	29 (4)	MS	153 (14)	91 (10)

Table 1. (continued).

First Author	Study name	Mean follow-up, wk	Number of participants analysed	Intervention, dose	Titration to reach BP goal		Demographic Details				Baseline Blood Pressure (mmHg)	
					Dose doubling?	Concomitant medication?	Mean age (SD)	Female (%)	BMI (SD)	Concomitant diseases	SBP (SD)	DBP (SD)
			48	Irbesartan, 300 mg od			60 (10)	54.2	29 (5)		151 (11)	90 (9)
			51	Olmesartan, 20 mg od			58 (12)	52.9	28 (4)		151 (11)	93 (8)
Sawaki [40]		52	14	Losartan, 25 mg od	NR	NR	54 (7)	57.1	24.3 (2.8)	Diabetes	134 (14)	78 (14)
			15	Placebo			54 (9)	46.7	24.5		131 (15)	82 (12)
Schram [42]		52	20	Candesartan, 8 mg od	Yes	Yes	60 (7)	45.8	28.8 (3.7)	Diabetes	151 (14)	94 (10)
Spoelstra-de-man [38]			19	HCTZ, 12.5 mg od			63 (6)	33.3	29.5 (3.5)		157 (13)	93 (9)
Sica [65]		24	323	Azilsartan, 20 mg od	Yes	No	57.8 (12.1)	49.8	30.8 (5.7)		158.1 (14.4)	91.2 (11)
			311	Azilsartan, 20 mg od			56.8 (10.7)	48.6	30.7 (5.3)		156.3 (12.5)	91.5 (10.5)
			322	Valsartan, 80 mg od			58.1 (10.9)	46.3	31.2 (5.8)		157 (14)	90.8 (11.3)
Solomon [68]	VALIDD	38	166	Valsartan, 160 mg od	Yes	Yes	61.1 (9.4)	53	30.1 (5.4)		143.5 (16.7)	85.4 (10.5)
			175	Placebo			60.2 (9.5)	49	30.7 (6.1)		144.1 (15.6)	87 (10.1)
Tedesco [63,64]		96–104	42	Losartan, 50 mg od	NR	NR	54 (9)	54.4	NR		157 (9)	96 (9)
			27	HCTZ, 25 mg od			56 (7)	45.4	NR		158 (10)	97 (7)
Tsutamoto [60]		52	25	Olmesartan, 20 mg od	No	No	68.2 (12.3)	40	NR		134 (15)	77 (9.7)
			25	Candesartan, uncertain			67.7 (7.8)	36	NR		130 (21)	73 (7.5)
Uzu [40]		24	14	Telmisartan, 80 mg od	NR	NR	57 (7)	NR	26.9 (3.7)	Diabetes	138 (11)	83 (7)
			14	Valsartan, 160 mg od			60 (10)	NR	26.6 (3.0)		134 (12)	80 (8)
Uzu [41]		24	16	Valsartan, 160 mg od	NR	NR	58 (10)	75	NR	Diabetes	NR	NR
			16	Losartan, 50 mg od + HCTZ			58 (10)	31.3	NR		NR	NR

Abbreviations: DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; LVH, left ventricular hypertrophy; MS, metabolic syndrome; SBP, systolic blood pressure.
ADIPO, Abdominal fat Depot Intervention Program of Okayama; ALPINE, Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation; IDNT-2, Irbesartan Diabetic Nephropathy Trial; IRMA2, Irbesartan in Patients With Type 2 Diabetes and Microalbuminuria; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention; SCOPE, Study on Cognition and Prognosis in the Elderly; TALENT, Telmisartan and Losartan Cardiac Evaluation Trial; TRANSCEND, Telmisartan Randomised AssessmeNt Study in ACE iNtolerant;VALIDD, Valsartan in Diastolic Dysfunction.

Table 2 Study Quality according to Cochrane Risk of Bias Tool (only the main study is presented) (+: low risk of bias;?: uncertain risk of bias; −: high risk of bias).

First Author	Random sequence generation	Allocation concealment	Blinding of participants and study personnel	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Other sources of bias
Brenner [14]	?	?	?	?	−	+	−
DeRosa [45,46]	+	?	+	+	+	+	+
DeRosa [38]	?	?	?	?	?	+	+
Foulquier [69]	+	?	?	?	+	+	+
Galzerano[62]	?	?	?	?	−	+	+
Hasegawa [66]	?	?	−	+	+	−	−
Lewis [15]	?	?	?	?	?	+	−
Lindholm [70]	?	?	?	?	+	+	+
Lithell [57]	+	+	+ (patient) ? (study personnel)	?	+	+	+
Makris [61]	?	?	−	−	−	+	+
Menne [39]	+	+	+	+	?	+	+
Minami [50]	+	?	−	−	+	+	−
Murakami [48]	?	?	−	−	+	+	−
Nedogoda [52]	?	?	+ (patient) − (study personnel)	−	+	+	+
Negro [59]	?	?	−	−	+	+	+
Neldam [55]	?	?	?	?	−	+	+
Parving [16] Rossing [47]	?	?	+ (patient) ? (study personnel)	?	−	+	−
Picca [51]	?	?	?	+	+	+	+
Rayner [67]	?	?	−	−	+	+	+
Rizos [49]	?	?	−	?	?	+	+
Sawaki [40]	?	?	−	−	+	+	−
Schram [42]	?	?	+ (patient) ? (study personnel)	?	+	+	–
Sica [65]	?	?	?	?	−	+	+
Solomon [68]	+	?	?	+	+	−	+
Tedesco [63,64]	?	?	?	?	−	+	+
Tsutamoto [60]	?	?	−	−	?	+	+
Uzu [40]	+	+	−	?	?	+	−
Uzu [41]	+	+	−	?	?	+	+

Given this, only 12 unique trials involving a fixed dosing regimen were suitable for inclusion in the NMA on blood pressure (n = 807 patients) (Table 3). However, even amongst trials on the same ARB, different dosage strength may have been studied. Short-term pharmacological studies suggest a near flat dose-response within this class of drugs [66], but, to remain conservative, only the highest dose equivalent for each ARB was selected for the analysis [40,46,49,58–60]. As such, only half the number of patients (n = 460) were included in the NMA in which 407 and 53 patients received an ARB and a hydrochlorothiazide, respectively.

As treatment efficacy in terms of blood pressure control is dependent on the duration of therapy, two time points were explored: the efficacy at 24 weeks [41,46,49,58] and 52 weeks [59,60]. Figure 2 shows the network of treatment comparisons according to the time period assessed. At 24 weeks, five members of the ARB class were studied in which only six of the 15 possible pair-wise comparisons were studied directly. At 52 weeks, only two members of the ARB class could be studied, sharing the common comparator of hydrochlorothiazide. In both analyses, there was no evidence of non-convergence with the MCMC process. Pairwise between-study heterogeneity could not be assessed given that each direct pairwise comparison was informed by only a single study.

The results on blood pressure reduction from the pairwise comparisons between different members of the ARB class are presented in Figures 3 and 4 following 24 and 52 weeks of treatment, respectively. At both time points, the 95% credible

Table 3 Summary of study results (only main study presented).

First Author	Study name	Mean follow-up, wk	Number of analysed	Intervention, dose	Blood pressure			Clinical outcomes (no of subjects)			
					Definition	Δ SBP (mmHg)	Δ DBP (mmHg)	Mortality		Major CV event	MI	Stroke
								All-cause	CV-related			
Studies that report blood pressure outcomes only: titration and additional add-on therapy not permitted												
DeRosa [45,46]		52	95	Telmisartan, 40 mg od	Seated, trough	6 mths: −5 12 mths: −11	6 mths: −5 12 mths: −8					
			152	Irbesartan, 150 mg od		6 mths: −5 12 mths: −11	6 mths: −4 12 mths: −7					
DeRosa [38]		52	40	Telmisartan, 40 mg od	Seated	6 mths: −4 12 mths: −8	6 mths: −5 12 mths: −8					
			39	Eprosartan, 600 mg od		6 mths: −4 12 mths: −7	6 mths: −2 12 mths: −4					
			40	Placebo		6 mths: −1 12 mths: −2	6 mths: −1 12 mths: −2					
Galzerano [62]		52	40	Telmisartan, 80 mg od	Ambulatory	−24	−13					
			25	HCTZ, 25 mg od		−10	−8					
Makris [61]		26	45	Eprosartan, 600 mg od	Seated	−10.9	−12.9					
			41	Losartan, 100 mg od		−18	−13					
Nedogoda [52]		24	30	Telmisartan, 80 mg od	Ambulatory	−12	−7					
			30	Losartan, 100 mg od		−15	−12					
Negro [59]		24	21	Irbesartan, 150 mg od	Ambulatory	−16.6	−14.2					
			22	Telmisartan, 80 mg od		−17.1	−12.9					
Rizos [49]		24	52	Telmisartan, 80 mg od	Seated	−17	−10					
			48	Irbesartan, 300 mg od		−17	−8					
			51	Olmesartan, 20 mg od		−17	−10					
Sawaki [40]		52	14	Losartan, 25 mg od	Seated	3.4	4.6					
			15	Placebo		1.7	−1.1					
Sica [65]		24	323	Azilsartan, 20 mg od	Ambulatory	−14.9	NR					
			311	Azilsartan, 20 mg od		−15.3	NR					
			322	Valsartan, 80 mg od		−11.6	NR					
Tedesco [63,64]		96–104	42	Losartan, 50 mg od	Ambulatory	10 mths: −19 22 mths: −22	10 mths: −11 22 mths: −11					
			27	HCTZ, 25 mg od		10 mths: −7 22 mths: −11	10 mths: −5 22 mths: −7					
Tsutamoto [60]		52	25	Olmesartan, 20 mg od	Not reported	6 mths: −5 12 mths: −2.6	6 mths: −2 12 mths: −2					
			25	Candesartan, uncertain		6 mths: −3 12 mths: −2	6 mths: −2 12 mths: −2					
Uzu [40]		24	14	Telmisartan, 80 mg od	Ambulatory	−5	−2					
			14	Valsartan, 160 mg od		−3	−2					

Table 3. (continued).

First Author	Study name	Mean follow-up, wk	Number of analysed	Intervention, dose	Blood pressure			Clinical outcomes (no of subjects)				
					Definition	Δ SBP (mmHg)	Δ DBP (mmHg)	Mortality		Major CV event	MI	Stroke
								All-cause	CV-related			
Studies that report blood pressure outcomes only: titration and additional add-on therapy permitted to reach desired blood pressure goal												
Hasegawa [66]	TALENT	52	29	Telmisartan, 40 mg od	Seated	−21	−13					
			28	Losartan, 50 mg od		−18	−12					
Lindholm [70]	ALPINE	52	196	Candesartan, 16 mg od	Seated	6 mths: −20.9 12 mths: −21	6 mths: −12.8 12 mths: −13					
			196	HCTZ, 25 mg od		6 mths: −23.9 12 mths: −22.8	6 mths: −13.9 12 mths: −12.9					
Minami [50]		24	20	Telmisartan, 40 mg od	Ambulatory	Not calculable	Not calculable					
			20	Losartan, 50 mg od		Not calculable	Not calculable					
Murakami [48]	ADIPO	24	9	Telmisartan, 40 mg od	Seated	−9.5	−7.1					
			10	Valsartan, 80 mg od		−6.4	−2.9					
Neldam [55]		24	123	Candesartan, 8 mg od	Seated, trough	−16.3	−12					
			62	HCTZ, 12.5 mg od		−18.8	−11.4					
Parving [16]	IRMA2	104	195	Irbesartan, 150 mg od	Seated	−10	−7					
			194	Irbesartan, 300 mg od		−10	−8					
			201	Placebo		−9	−7					
Rossing [47]	IRMA2 (substudy: Single centre)	104	13	Irbesartan, 150 mg od	Seated, trough	−13	−8					
			15	Irbesartan, 300 mg od		−13	−8					
			15	Placebo		−11	−9					
Picca [51]		26	15	Losartan, 50 mg od	Supine	−27	−17					
			15	Valsartan, 80 mg od		−33	−16					
Rayner [67]		24	27	Losartan, 50 mg od	Seated	−18.3	−12					
			25	Candesartan, 8 mg od		−24	−10.1					
Schram [42]		52	20	Candesartan, 8 mg od	Seated	6 mths: −17 12 mths: −18	6 mths: −11 12 mths: −13					
			19	HCTZ, 12.5 mg od		6 mths: −21 12 mths: −20	6 mths: −11 12 mths: −10					
Spoelstra-de-man [38]		52	20	Candesartan, 8 mg od	Ambulatory	−26	−17					
			19	HCTZ, 12.5 mg od		−23	−18					
Solomon [68]	VALIDD	38	166	Valsartan, 160 mg od	Seated	−12.8	-7.1					
			175	Placebo		−9.7	−5.5					
Tsutamoto [60]		52	25	Olmesartan, 20 mg od	Not reported	6 mths: −5 12 mths: −2.6	6 mths: −2 12 mths: −2					
			25	Candesartan, uncertain		6 mths: −3 12 mths: −2	6 mths: −2 12 mths: −2					
Uzu [41]		24	16	Valsartan, 160 mg od	Ambulatory	Not calculable	Not calculable					
			16	Losartan, 50 mg od + HCTZ		Not calculable	Not calculable					

Table 3. (continued).

First Author	Study name	Mean follow-up, wk	Number of analysed	Intervention, dose	Blood pressure			Clinical outcomes (no of subjects)				
					Definition	Δ SBP (mmHg)	Δ DBP (mmHg)	Mortality		Major CV event	MI	Stroke
								All-cause	CV-related			
Studies reporting both blood pressure and final clinical outcomes: titration and additional add-on therapy permitted to reach desired blood pressure goal												
Brenner [14]	RENAAL	177	751	Losartan, 50 mg od	Not specified	12 mths: −6 24 mths: −9	12 mths: −4 24 mths: −5	155	NR	268	68	NR
			762	Placebo		12 mths: −3 24 mths: −9	12 mths: −2 24 mths: −5	158	NR	247	50	NR
Foulquier [69]	TRANSCEND	243	2547	Telmisartan, 80 mg od	Not specified	−7.4	NR	NR	193	NR	97	102
			2551	Placebo		−3.5	NR	NR	186	NR	130	125
Lewis [15]	IDNT-2	104	579	Irbesartan, 75 mg od	Seated	−20	−10	87		138		
			569	Placebo		−14	−10	93		144		
Lithell [57]	SCOPE	194	2477	Candesartan, 8–16 mg od	Seated	−21.7	−10.8	259	145	242	70	89
			2460	Placebo		−18.5	−9.2	266	152	268	63	115
Papademetriou [54]	SCOPE (substudy)	167	754	Candesartan, 8 mg od	Seated	−22.2	6	82	47	75	23	20
			764	Placebo		−20.2	−4.8	90	48	85	25	35
Saxby [53]	SCOPE (substudy:	191	112	Candesartan, 8 mg od	Seated	−24	−14	NR	NR	NR	3	4
	Single centre)		116	Placebo		−17	−12	NR	NR	NR	5	8
Trenkwalder [56]	SCOPE (substudy:	191	1253	Candesartan, 8 mg od	Seated	−21.8	−11	NR	NR	NR	NR	NR
	No add-on therapy)		845	Placebo		−17.2	−8.4	NR	NR	NR	NR	NR
Trenkwalder [58]	SCOPE (substudy:	167	NR	Candesartan, 8 mg od	Seated	Based on subgroup	Based on subgroup	Based on subgroup	Based on subgroup	Based on subgroup	Based on subgroup	Based on subgroup
	Pre-specified subgroup)		NR	Placebo		Based on subgroup	Based on subgroup	Based on subgroup	Based on subgroup	Based on subgroup	Based on subgroup	Based on subgroup
Menne [39]	ROADMAP (substudy)	167	2043	Olmesartan, 40 mg od	Seated	−12.1	−7	25	14	NR	NR	NR
			1977	Placebo		−8.2	−4.9	14	3	NR	NR	NR

Abbreviations: CV, cardiovascular; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; MI, myocardial infarction; SBP, systolic blood pressure.

ADIPO, Abdominal fat Depot Intervention Program of Okayama; ALPINE, Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation; IDNT-2, Irbesartan Diabetic Nephropathy Trial; IRMA2, Irbesartan in Patients With Type 2 Diabetes and Microalbuminuria; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention; SCOPE, Study on Cognition and Prognosis in the Elderly; TALENT, Telmisartan and Losartan Cardiac Evaluation Trial; TRANSCEND, Telmisartan Randomised AssessmeNt Study in ACE iNtolerant;VALIDD, Valsartan in Diastolic Dysfunction.

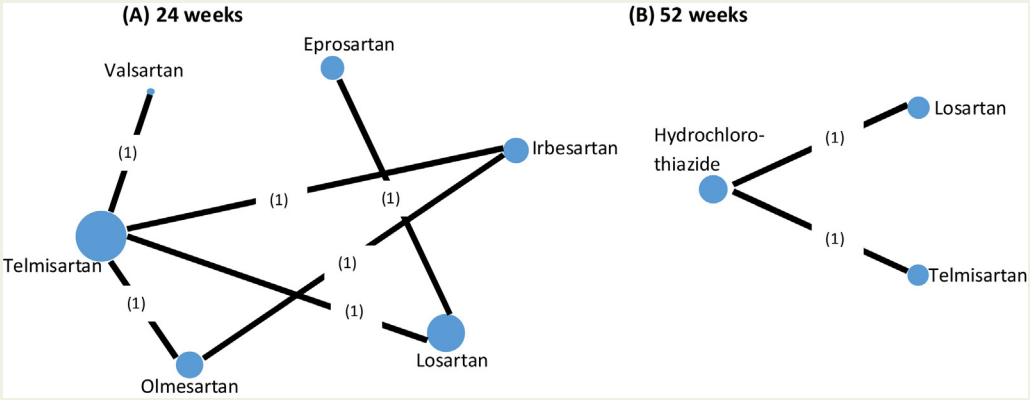

Figure 2 Network of the direct comparisons available reporting the efficacy of ARB on blood pressure reduction. The size of each treatment node is proportional to the number of analysed participants (sample size). The networks for systolic and diastolic blood pressure were the same.

interval indicates no difference between members of the ARB class.

An advantage to the Bayesian approach is its capability of estimating probabilities that each strategy would be the best treatment compared to the others. Common to NMA is a rank ordering which indicates the order in which the various treatments are most to least likely efficacious. However, we felt it was inappropriate and unlikely helpful to rank treatments because of the imprecision in the estimates generated by the NMA. This would lead to considerable uncertainty in the ranks. Rank probabilities for each treatment were similar [72] and presenting such results may potentially be misleading.

Efficacy: Final Clinical Outcomes

All trials reporting on final cardiovascular outcomes were included in the NMA (Table 3) [15,16,36,54,65]. These were all multi-national, two-armed, placebo-controlled RCTs that compared ARB-initiated therapy to usual antihypertensive therapy; adhering to treat-to-target designs in order to optimise blood pressure goals. Participants were balanced in gender (51.5% females) with the mean study duration being 2.68 years (range: 2.6–4.7). In total, 16,716 individuals were randomly assigned to either one of the five ARBs or to placebo, with subsequent titration and additional add-on therapy permitted to reach the desired blood pressure goal. For this NMA, placebo represented the bridging group.

Eprosartan	-2.06 (-9.62, 5.40)	-0.08 (-3.08, 2.93)	-0.06 (-7.20, 7.10)	-0.06 (-4.34, 4.20)	-0.03 (-9.76, 9.93)
3.14 (-14.55, 20.93)	*Irbesartan*	2.02 (-4.81, 8.94)	2.03 (-3.11, 7.12)	2.02 (-4.13, 8.21)	2.04 (-8.80, 13.03)
7.10 (-2.60, 17.05)	3.97 (-10.97, 18.57)	*Losartan*	0.01 (-6.55, 6.49)	0.02 (-3.06, 3.08)	0.05 (-9.20, 9.54)
3.13 (-14.35, 20.75)	-0.03 (-11.05, 11.06)	-3.99 (-18.42, 10.52)	*Olmesartan*	0.00 (-5.73, 5.82)	0.11 (-10.55, 10.65)
3.14 (-10.15, 16.53)	0.01 (-11.78, 11.62)	-4.00 (-13.10, 5.10)	-0.00 (-11.57, 11.43)	*Telmisartan*	0.03 (-8.77, 9.07)
5.22 (-13.80, 23.94)	2.03 (-16.01, 19.89)	-2.01 (-17.94, 14.19)	2.02 (-15.70, 19.70)	2.04 (-11.62, 15.53)	*Valsartan*

Figure 3 Relative treatment effects of ARBs at 24 weeks in terms of the absolute change [weighted mean difference (95% credible interval)] in systolic blood pressure (blue) and diastolic blood pressure (light green). To interpret: weighted-mean difference (WMD) <0 favours the column-defining treatment (e.g. eprosartan, compared to irbesartan, is associated with increase in blood pressure by +3.14/ + 2.06 mmHg.) To obtain WMDs for comparisons in the opposite direction, the reverse must be taken (eg. losartan, compared to irbesartan, is associated with a blood pressure changed of +2.02/ + 3.97 mm Hg). Significant results are bolded.

Losartan	-0.99 (-13.43, 11.31)	5.95 (-3.34, 15.27)
-1.99 (-27.91, 23.79)	*Telmisartan*	4.94 (-3.18, 13.11)
-12.00 (-30.33, 6.30)	-14.01 (-31.62, 3.93)	*Hydrochlorothiazide*

Figure 4 Relative treatment effects of ARBs at 52 weeks in terms of the absolute change [weighted mean difference (95% credible interval)] in systolic blood pressure (blue) and diastolic blood pressure (light green). To interpret: weighted mean difference (WMD) <0 favours the column-defining treatment (e.g. losartan, compared to telmisartan, is associated with change in blood pressure of −1.99/ + 0.99 mm Hg.) To obtain WMDs for comparisons in the opposite direction, the reverse must be taken. Significant results are bolded.

Figure 5 shows the network of eligible comparisons for the NMA. Of the 15 possible pair-wise comparisons between the five members of the ARB class and placebo, only five have been studied directly in individual trials. There was no evidence of non-convergence. Between-study heterogeneity could not be assessed given that each direct pairwise comparison was informed by a single study.

Figures 6 and 7 summarise the results of the Bayesian NMA. Across the outcomes of interest, the 95% credible intervals of the pairwise comparison of individual members within the ARB class suggests that members within the ARB class have no differences in treatment effects with respect to the risk of stroke, MI and mortality (i.e., all-cause of CV-related).

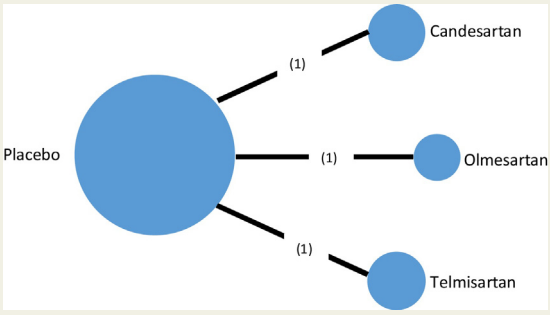

Figure 5 Network of the direct comparisons available reporting the efficacy of ARB-initiated therapy on prevention of cardiovascular-related mortality. The size of each node is proportional to the number of analysed participants (sample size). The network may differ depending on the outcome reported as not all studies reported on all final clinical outcomes of interest.

Candesartan	ND	1.31 (0.86, 2.02)	1.06 (0.58, 1.94)
1.59 (0.71, 3.51)	*Irbesartan*	ND	ND
1.11 (0.64, 1.91)	0.69 (0.39, 1.24)	*Placebo*	0.81 (0.53, 1.23)
1.51 (0.71, 3.19)	0.95 (0.44, 2.05)	1.36 (0.82, 2.27)	*Telmisartan*

Figure 6 Relative treatment effects [odds ratio (95% credible interval)] of ARBs on myocardial infarction (MI) (grey) and stroke prevention (light green). To interpret: odds ratio (OR) >1 favours the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken (eg. OR for MI in irbesartan compared with candesartan is 1/1.59 = 0.63). Significant results are bolded.
*ND, no data available to conduct a comparison for that particular outcome.

Discussion

In the absence of direct, head-to-head evidence comparing the long-term clinical efficacy of different members of the ARB class, a NMA was conducted. Our findings show that there was no difference in the comparative efficacy between agents with respect to blood pressure control or the incidence of cardiovascular events following long-term treatment.

These results summarise the experience so far from long-term clinical trials on this drug class by incorporating both direct and indirect comparisons, including those that have never been directly compared quantitatively in previous trials or reviews. Traditional meta-analyses published to date tend to selectively compare a few members within the drug class [67–72] and consider only the direct evidence within trials. Our study is unique in that it considers the totality of the available evidence base in conducting this analysis.

Some trials have suggested that certain agents within the ARB class can lower blood pressure to a different extent [14,19,73–77] and occasionally, traditional meta-analyses have appeared claiming superiority of one agent over another on certain outcomes [22,67–69,71]. However, these meta-analyses are limited, given issues of selection bias and inappropriate methods of pooling data which violate randomisation (i.e., such as combining results from a single arm of a trial). Our study lends support to existing meta-analyses that have shown comparable blood pressure lowering capacity amongst different agents within the ARB class [23,70,72,78,79]. This includes, specifically, one of the largest pooled meta-analyses to date on this topic by Conlin et al. [23]. A total of 11,281 patients were studied by combining 43 trials on four ARBs (i.e. candesartan, irbesartan, losartan, valsartan) and it was found that the effectiveness of the individual ARBs, following 4 to 6 weeks of administration,

Candesartan	ND	ND	5.45 (0.37, 87.59)	1.06 (0.18, 6.18)	1.10 (0.10, 13.33)
1.06 (0.39, 2.91)	*Irbesartan*	ND	ND	ND	ND
0.93 (0.35, 2.47)	0.87 (0.31, 2.39)	*Losartan*	ND	ND	ND
0.55 (0.17, 1.70)	0.51 (0.16, 1.61)	0.59 (0.19, 1.84)	*Olmesartan*	0.20 (0.02, 1.55)	0.20 (0.01, 3.08)
0.96 (0.49, 1.93)	0.91 (0.43, 1.87)	1.04 (0.52, 2.12)	1.76 (0.72, 4.43)	*Placebo*	1.04 (0.18, 5.91)
ND	ND	ND	ND	ND	*Telmisartan*

Figure 7 Relative treatment effects [odds ratio (95% credible interval)] of ARBs on all-cause (grey) and CV-related (light green) mortality. To interpret: odds ratio (OR) >1 favours the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are bolded.
*ND, no data available to conduct a comparison for that particular outcome.

in lowering blood pressure was similar across agents [23]. Amongst individual agents, the absolute weighted mean diastolic and systolic blood pressure reduction ranged from 8.2 to 8.9 mmHg and from 10.4 to 11.8 mmHg, respectively (i.e., this represents a maximum difference between individual ARBs of 0.7 mmHg and 1.3 mmHg for diastolic and systolic blood pressure respectively). The NMA technique employed in our analysis goes beyond traditional meta-analysis in that it allows dissection of the association of individual members of this drug class on blood pressure by considering all evidence simultaneously together. Furthermore, our NMA studied a longer treatment period (i.e., ≥24 weeks) and found that the effectiveness of individual members of the ARB class in lowering blood pressure remained similar to what has been reported following a shorter duration of treatment (i.e., 8 to 12 weeks [23]).

Treatment for hypertension is considered preventative as elevated blood pressure does not manifest, in itself, as a symptomatic illness. Rather, hypertension is of concern due to its role as a modifiable risk factor for cardiovascular events. To address whether members of the ARB class had differing effect on the risk of cardiovascular disease, a second NMA on these outcomes was conducted. This is novel as no previous studies have done such a comparison within the ARB drug class. Given that all long-term trials reporting final clinical outcomes were treat-to-target designs, it is important to understand that the original studies, in fact, involved a comparison between ARB-initiated antihypertensive treatment versus non-ARB initiated antihypertensive treatment.

Two main conclusions can be drawn from the analysis of the final clinical outcomes. Firstly, the data provides no clear evidence of any differential effects between individual members of the ARB class with respect to prevention of major cardiovascular diseases. In addition, as the common treatment group linking this network was placebo (which, in such study designs reflect usual antihypertensive management), the findings suggest that ARB, as a class, had similar efficacy to non-ARB initiated anti-hypertensive therapy across the final clinical outcomes that were studied. To explore whether ARB-initiated treatment led to other beneficial outcomes over conventional hypertensive therapy without an ARB, a potential analysis of interest would be to compare the number of additional antihypertensive drugs required to achieve blood pressure control. However, this outcome was found to be poorly and inconsistently reported across studies and no further analysis was feasible. The hypothesis is that, if patients on ARB-initiated therapy required fewer drugs to achieve the desired blood pressure target than conventional non-ARB therapy, this may prove to be clinically meaningful to patients since this may lower treatment burden, increase compliance and lead to cost-savings.

Strengths and Limitations

Hypertension is a relatively asymptomatic illness. It is therefore important to ensure that the downstream benefits of preventing a primary clinical event are balanced against the potential side effects from treatment [78]. We did not investigate safety outcomes in this study. As the safety profile of ARBs, as a class, have been described as placebo-like with low rates of severe adverse events [20], we did not analyse tolerability or safety.

As in other meta-analyses, given the lack of data within each trial, we did not adjust our analyses for compliance to the assigned treatment. Despite an understanding that the risk for hypertensive-related cardiovascular complications is dependent on both an individual's blood pressure and the duration in which blood pressure is adequately controlled, compliance was difficult to assess given the lack of reporting. To better address the impact of compliance on the efficacy of particular drugs, a meta-regression could have been

performed. In such an analysis, patient-level data including important covariates such as the degree of compliance would be combined by regression techniques to better understand the impact of each covariate on the outcomes of interest. However, adding covariates to the models would increase model complexity and is ill-advised in situations where there are small networks of trials. Furthermore, it would have required access to patient-level data from all trials involved.

Finally, it is worth noting that our current analyses are challenged by scant primary data on blood pressure lowering, cardiovascular event rates, and related mortality. However, no current minimums are set for the number or sample size of trials included in NMA [81,82], and clinically informative insights have been gained from similar high-quality investigations [83] examining the clinical benefits of antihypertensive treatment. Still, our findings must be cautiously interpreted. Although there was no evidence of non-convergence in any of the network models, the precision of our estimates may have been affected by the small number of studies involved in each network. Additionally, the wider credible intervals produced by our analyses suggest that our analyses may lack power. Our outcomes of interest are also based on a small number of events, making it possible for calculated odds ratios to have been considerably affected by even small differences between studies in how events were classified. There was also no evidence available on the long-term efficacy of azilsartan and eprosartan that could be incorporated into this NMA.

Our review also has several strengths. Among them are a protocol-driven approach adherent with best practice in systematic review conduct and reporting; a comprehensive literature search of multiple electronic databases; attempts to contact authors to solicit missing data; double data abstraction; quality assessment of the primary studies using validated tools; and, appropriate methods for combining effect estimates. Our NMA offers one of the most comprehensive compilations of data specifically on the topic of comparative ARB effectiveness, providing a balanced analysis of the evidence base.

Conclusions

Our findings demonstrate that, overall, ARBs were capable of lowering blood pressure and that the evidence, albeit limited, suggest no difference between members within this class in terms of their ability to control blood pressure. No individual ARB offered significantly greater protection from cardiovascular morbidity and mortality. Additional well-designed, long-term, head-to-head comparative trials may be required to better address whether the efficacy between individual members in this drug class indeed varies given the potential lack of power in this analysis. Until such studies are conducted, prudence is advised, as there is no evidence to support any preferential claims. Even compared to non-ARB based treatment, there is little support for the superiority of ARB-initiated therapy. Rather, this study highlights the general role of blood pressure lowering therapies to reduce the incidence of cardiovascular disease risks, independent of which agent is used.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

Data used to conduct the analyses is available in supplemental files.

Competing Interests

The authors have no competing interests to declare.

Funding

BT was supported by an Award from the Father Sean O'Sullivan Research Centre, St. Joseph's Healthcare Hamilton and the CIHR Drug Safety and Effectiveness Cross-Disciplinary Training program. LA was supported by the Comprehensive Research Education for Medical Students Scholar Program at the University of Toronto. The remaining authors have no potential conflicts of interest to disclose.

Authors' Contributions

BT conceived and designed the study. BT, LA, CF conducted the study. BT and AB conducted the analysis under the guidance of EP, ML, and DOR. All authors read, edited and approved the final version of the manuscript and agree to be accountable for the work.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.hlc.2017.06.721.

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