Impact of Antihypertensive Agents on Central Systolic Blood Pressure and Augmentation Index: A Meta-Analysis

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BACKGROUND

New evidence suggests that central systolic blood pressure (cSBP) and augmentation index (AI) are superior predictors of adverse cardiovascular outcomes compared to peripheral systolic BP (pSBP). We performed a meta-analysis assessing the impact of antihypertensives on cSBP and AI.

METHODS

PubMed, Cochrane Library, and CINAHL were searched until September 2014 to identify eligible articles. A DerSimonian and Laird random-effects model was used to calculate the weighted mean difference (WMD) and its 95% confidence interval (CI). Fifty-two and 58 studies incorporating 4,381 and 3,716 unique subjects were included for cSBP and AI analysis, respectively.

RESULTS

Overall, antihypertensives reduced pSBP more than cSBP (WMD 2.52 mm Hg, 95% CI 1.35 to 3.69; $I^2 = 21.9\%$). β -Blockers (BBs) posed a significantly greater reduction in pSBP as compared to cSBP (WMD

5.19 mm Hg, 95% CI 3.21 to 7.18). α -Blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, diuretics, renin-angiotensin aldosterone system inhibitors and nicorandil reduced cSBP and pSBP in a similar manner. The overall reduction in AI from baseline was 3.09% (95% CI 2.28 to 3.90; $I^2 = 84.5\%$). A significant reduction in AI was seen with angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, diuretics, renin-angiotensin aldosterone system inhibitors, BBs, α -blockers (ABs), nicorandil, and moxonidine reduced AI nonsignificantly.

CONCLUSIONS

BBs are not as beneficial as the other antihypertensives in reducing cSBP and AI.

Keywords: antihypertensive; augmentation index; blood pressure; central blood pressure; hypertension; meta-analysis.

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Elevated blood pressure (BP) is a leading modifiable risk factor for cardiovascular disease and continues to affect approximately 1 in 3 adults, or 66.9 million people, in the United States.¹ Traditionally, hypertension is diagnosed and treated by assessing the pressure at the brachial artery (peripheral BP),² but recent evidence suggests that central hemodynamics are better predictors of cardiovascular outcomes and mortality.^{3,4}

Central BP is indicative of the pressure directly exerted on target organs and often varies from peripheral BP.² Aortic and carotid arteries are more elastic than fibrous peripheral vasculature and the difference in peripheral and central pressures is thought to be a result of amplification due to wave reflections caused by the variance in arterial stiffness.^{2,5} As a result of arterial stiffness increasing with distance from the heart, peripheral systolic BP (pSBP) tends to be greater than central systolic BP (cSBP).⁶ Additionally, augmentation index (AI), which measures the degree of enhancement in the central pressure waveform due to reflected waves, has been shown to be an independent predictor of cardiovascular events.⁴

Recent technology has increased the availability of several noninvasive techniques to estimate central BP allowing for incorporation of these parameters in a multitude of patient populations and disease states.^{7–10} Differences between the various classes of antihypertensive agents regarding their effects on central hemodynamics have been identified.^{11,12} The Conduit Artery Function Evaluation (CAFE) study¹³ was one of the first trials to show differing clinical outcomes despite similar reductions in peripheral BP. In a previous meta-analysis, differing responses of β -blockers (BBs) and diuretics on central hemodynamics were implied but extrapolation of their finding was limited due to a modest number of included studies.¹² As a result of a greater number of new publications in the last few years assessing the effects of antihypertensives on central BP, we performed a meta-analysis analyzing the differential effects of antihypertensive agents on cSBP and AI. An assessment as such will help better determine the incorporation and place in therapy of the various antihypertensives in clinical practice.

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METHODS

Literature search

The online databases PubMed (MEDLINE), Cochrane Library (Central), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched until 26 September 2014 for relevant studies. The following terms were used: central BP, aortic BP, carotid BP, pulse wave velocity, AI, and antihypertensives. Studies were limited to clinical trials conducted in humans and published in the English language. In searching the literature and presenting results, the guidelines provided in the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement* were followed.¹⁴

Study eligibility and selection

Studies were included if they met the following criteria: (i) randomized, controlled trials in humans, (ii) reported data on pSBP and cSBP, (iii) reported data on AI, (iv) had a prescription antihypertensive medication intervention, and (v) had a duration of treatment ≥ 28 days. Studies were excluded if reporting incomplete or inappropriate data, used a non-prescription intervention or prescription intervention that

was not an antihypertensive, were duplicate publications, or published in a language other than English.

Two researchers independently conducted an initial screening of the studies based on the abstracts. The next phase involved an examination of the full text in reference to eligibility criteria. The final eligibility of the articles was determined through agreement between the 2 reviewers, with any disagreement resolved in consultation with a third reviewer. A summary of the review is presented in the PRISMA flow chart (Figure 1). Included articles were reviewed and relevant data were extracted.

Data extraction and quality assessment

All data were extracted through the use of a standardized data abstraction tool. The following information were retrieved from each article: author, year of publication, study design, study population, study intervention, dose and duration of treatment, sample size, type of device used to measure central hemodynamics, and relevant primary and secondary endpoint data. Baseline and post-intervention pSBP and cSBP and/or AI were extracted with SD, SEM, or 95% confidence intervals (CIs) (as available) and the change from baseline was calculated. If the change from baseline was reported, this information was recorded along with

RCT = randomized controlled trial, BP = blood pressure, AI = augmentation index, Rx = prescription, SD = standard deviation, SEM = standard error of the mean, CI = confidence interval

Figure 1. Study flow diagram.

Table 1. Characteristics of included studies

Author, year	Patient population	Drug class(s)	Sample size	Study design	SBP/AI	Jadad
Baschiera <i>et al.</i> 2014 ¹⁶	Essential hypertension	RAAS-I vs. ACE-I	154	Parallel	SBP only	5
Bhagatwala <i>et al.</i> 2014 ¹⁷	Prehypertension	Diuretic	17	Non-controlled	SBP & AI	1
Kim <i>et al.</i> 2014 ¹⁸	Hypertension	ARB vs. BB	182	Parallel	SBP & AI	3
Peters <i>et al.</i> 2014 ¹⁹	Hemodialysis patients	ARB vs. placebo	41	Parallel	SBP & AI	4
Agnoletti <i>et al.</i> 2013 ²⁰	Essential hypertension	CCB vs. ARB vs. Diuretic vs. placebo	110	Parallel	SBP & AI	3
Briasoulis <i>et al.</i> 2013 ²¹	Type II diabetes	BB vs. nebivolol	61	Parallel	SBP & AI	2
Davis <i>et al.</i> 2013 ²²	Prehypertension	Nebivolol vs. placebo	25	Parallel	AI only	4
Dorresteijn <i>et al.</i> 2013 ²³	Obesity-related hypertension	RAAS-I vs. moxonidine vs. diuretic vs. placebo	30	Crossover	AI only	5
Eeftinck <i>et al.</i> 2013 ²⁴	Hypertension	Nebivolol + diuretic vs. BB + diuretic	22	Crossover	SBP & AI	3
Ihm <i>et al.</i> 2013 ²⁵	Essential hypertension	CCB vs. ARB	161	Parallel	SBP & AI	2
Kubota <i>et al.</i> 2013 ²⁶	Essential hypertension	RAAS-I vs. RAAS-I + diuretic	30	Parallel	SBP & AI	3
Kwon <i>et al.</i> 2013 ²⁷	Hypertension	ARB + diuretic vs. ARB + diuretic	28	Crossover	SBP & AI	3
Park <i>et al.</i> 2013 ²⁸	Hypertension	BB vs. BB	191	Parallel	SBP & AI	2
Radchenko <i>et al.</i> 2013 ²⁹	Essential hypertension	ARB + diuretic vs. BB + diuretic	59	Parallel	SBP & AI	2
Shahin <i>et al.</i> 2013 ³⁰	Intermittent claudication	ACE-I vs. placebo	14	Parallel	SBP & AI	5
Spanos <i>et al.</i> 2013 ³¹	Hypertension	RAAS-I vs. ARB	29	Parallel	SBP & AI	2
Studinger <i>et al.</i> 2013 ³²	Hypertension	BB vs. BB vs. nebivolol	60	Parallel	SBP & AI	5
Takami <i>et al.</i> 2013 ³³	Hypertension	ARB + CCB vs. ARB + CCB	52	Parallel	SBP & AI	3
Zhou <i>et al.</i> 2013 ³⁴	Essential hypertension	BB vs. BB	109	Parallel	SBP & AI	3
Frimodt-Moller 2012 <i>et al.</i> 35	CKD + hypertension	ACE-I + ARB	57	Parallel	SBP & AI	3
Hayoz <i>et al.</i> 2012 ³⁶	Postmenopausal women	ARB + diuretic vs. CCB + diuretic	125	Parallel	SBP only	3
Kanaoka <i>et al.</i> 2012 ³⁷	Essential hypertension	RAAS-I	17	Non-controlled	SBP & AI	1
Takenaka <i>et al.</i> 2012 ³⁸	CKD + hypertension	CCB vs. CCB	59	Parallel	SBP & AI	3
Viridis <i>et al.</i> 2012 ³⁹	Essential hypertension	RAAS-I vs. ACE-I	50	Parallel	SBP & AI	2
Vitale <i>et al.</i> 2012 ⁴⁰	Essential hypertension	ARB + diuretic vs. nebivolol + diuretic	65	Parallel	SBP & AI	4
Williams <i>et al.</i> 2012 ⁴¹	Marfan syndrome	BB vs. ACE-I vs. CCB	14	Crossover	SBP & AI	5
Ferdinand <i>et al.</i> 2011 ⁴²	Hypertension	RAAS-I + diuretic vs. CCB	324	Parallel	SBP only	5
Hefferman <i>et al.</i> 2011 ⁴³	Hypertension	BB vs. BB	24	Crossover	AI only	2
Kampus <i>et al.</i> 2011 ⁴⁴	Hypertension	BB vs. nebivolol	63	Parallel	SBP & AI	3
Kandavar <i>et al.</i> 2011 ⁴⁵	Hypertension	BB vs. nebivolol	41	Parallel	AI only	1
Kimura <i>et al.</i> 2011 ⁴⁶	CKD	Nicorandil	9	Non-controlled	SBP & AI	3
Matsui <i>et al.</i> 2011 ⁴⁷	Hypertension	ARB + CCB vs. ARB + diuretic	207	Parallel	AI only	3
Shah <i>et al.</i> 2011 ⁴⁸	Essential hypertension	BB vs. BB	41	Parallel	SBP & AI	1
Boutouyrie <i>et al.</i> 2010 ⁴⁹	Essential hypertension	ARB + CCB vs. BB + CCB	331	Parallel	SBP & AI	2
Doi <i>et al.</i> 2010 ⁵⁰	Hypertension	CCB vs. diuretic	37	Parallel	SBP & AI	2
Kinouchi <i>et al.</i> 2010 ⁵¹	Diabetes + hypertension	ARB vs. ARB + diuretic	25	Crossover	AI only	2
Mackenzie <i>et al.</i> 2009 ⁵²	Isolated systolic hypertension	ACE-I vs. BB vs. CCB vs. diuretic	59	Parallel	SBP & AI	2
Matsui <i>et al.</i> 2009 ⁵³	Hypertension	ARB + CCB vs. ARB + diuretic	207	Parallel	SBP only	3
Palombo <i>et al.</i> 2009 ⁵⁴	Essential hypertension	CCB	21	Non-controlled	AI only	1
Ahimastos <i>et al.</i> 2008 ⁵⁵	Peripheral arterial disease	ACE-I	20	Parallel	SBP & AI	2

Table 1. Continued

Author, year	Patient population	Drug class(s)	Sample size	Study design	SBP/AI	Jadad
Alem <i>et al.</i> 2008 ⁵⁶	Stroke	Diuretic vs. diuretic	23	Parallel	AI only	4
Dhakam <i>et al.</i> 2008 ⁵⁷	Isolated systolic hypertension	BB vs. nebivolol	16	Crossover	SBP & AI	3
Karalliedde <i>et al.</i> 2008 ⁵⁸	Type II diabetes	ARB vs. CCB	131	Parallel	SBP & AI	4
Mahmud and Feely 2008 ⁵⁹	Hypertension	BB vs. nebivolol	39	Parallel	SBP & AI	3
Schneider <i>et al.</i> 2008 ⁶⁰	Essential hypertension	ARB vs. BB	156	Parallel	SBP & AI	2
Dart <i>et al.</i> 2007 ⁶¹	Hypertension	ACE-I vs. diuretic	479	Parallel	SBP only	2
Jiang <i>et al.</i> 2007 ⁶²	Essential hypertension	ACE-I vs. diuretic	101	Parallel	SBP & AI	3
Dhakam <i>et al.</i> 2006 ⁶³	Hypertension	BB vs. ARB	21	Crossover	SBP & AI	3
Rajagopalan <i>et al.</i> 2006 ⁶⁴	Normotensive	ARB vs. placebo	33	Crossover	AI only	3
Tsang <i>et al.</i> 2006 ⁶⁵	Isolated diastolic dysfunction	ACE-I vs. placebo	9	Parallel	AI only	4
Davies <i>et al.</i> 2005 ⁶⁶	Hypertension	BB vs. ARB	17	Crossover	AI only	2
Mahmud and Feely 2005 ⁶⁷	Essential hypertension	Diuretic vs. diuretic	24	Crossover	SBP & AI	2
Mitchell <i>et al.</i> 2005 ⁶⁸	Hypertension	Omapatrilat vs. ACE-I	159	Parallel	SBP & AI	3
de Luca <i>et al.</i> 2004 ⁶⁹	Hypertension	ACE-I + diuretic vs. BB	52	Parallel	SBP & AI	3
London <i>et al.</i> 2004 ⁷⁰	Essential hypertension	ACE-I + diuretic vs. BB	181	Parallel	SBP & AI	3
Neal <i>et al.</i> 2004 ⁷¹	Liver transplant + hypertension	CCB vs. BB vs. ACE-I	24	Crossover	SBP & AI	2
Deary <i>et al.</i> 2002 ⁷²	Essential hypertension	CCB vs. AB vs. ACE-I vs. BB vs. diuretic vs. placebo	30	Crossover	SBP & AI	1
Klingbeil <i>et al.</i> 2002 ⁷³	Essential hypertension	ARB vs. diuretic	40	Parallel	SBP & AI	5
Mahmud and Feely 2002(a) ⁷⁴	Hypertension	ARB vs. diuretic	11	Crossover	SBP only	2
Mahmud and Feely 2002(b) ⁷⁵	Hypertension	ARB vs. ACE-I	12	Crossover	SBP only	1
Asmar <i>et al.</i> 2001 ⁷⁶	Essential hypertension	ACE-I + diuretic vs. BB	144	Parallel	AI only	2
Dart <i>et al.</i> 2001 ⁷⁷	Hypertension	ACE-I vs. "usual care"	51	Parallel	SBP only	3
Spratt <i>et al.</i> 2001 ⁷⁸	Hypertension	ARB + diuretic	35	Non-controlled	SBP & AI	1
Chen <i>et al.</i> 1995 ⁷⁹	Essential hypertension	ACE-I vs. BB	79	Parallel	AI only	2
London <i>et al.</i> 1994 ⁸⁰	ESRD	ACE-I vs. CCB	24	Parallel	SBP & AI	4
Guerin <i>et al.</i> 1992 ⁸¹	Hypertension	BB vs. CCB	20	Parallel	AI only	2

Abbreviations: AB, α -blockers; ACE-I, angiotensin converting enzyme inhibitor; AI, augmentation index; ARB, angiotensin II receptor blocker; BB, β -blocker; CKD, chronic kidney disease; CCB, calcium channel blocker; ESRD, end stage renal disease; RAAS-I, renin-angiotensin-aldosterone-system inhibitor; SBP, systolic blood pressure.

SD, SEM, or 95% CIs (as available). When multiple usable arms were available within an individual study, the data were counted as another study in the meta-analysis model. Methodological quality was assessed using Jadad scores.¹⁵

Data synthesis and analysis

The weighted mean difference (WMD) for BPs was calculated as the difference between the mean change from baseline in pSBP and the mean change from baseline in cSBP (Δ pSBP – Δ cSBP). The WMD for AI was calculated as the difference in the mean change from baseline for each applicable intervention arm. A DerSimonian and Laird random-effects model was used to calculate the WMD and its 95% CIs with sample sizes halved to avoid artificial truncation

of the CIs. All statistical analyses were completed using StatsDirect Version 2.6.6 (StatsDirect, Cheshire, UK). SEM was converted to SD ($SE = SD/\sqrt{(\text{sample size})}$) and CIs were calculated ($CI = (\text{mean difference}) \pm [SEM \times 1.96]$) when necessary.

Publication bias was assessed using the Egger's statistic and visual inspection of funnel plots. Statistical heterogeneity was assessed using the I^2 statistic. To assess robustness, both the fixed and random effect models were utilized and reported. Subgroup analyses were performed to assess sources of clinical heterogeneity. Impact on cSBP and AI were assessed by analyzing data by individual antihypertensive class (α -blockers (ABs), angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), BBs, calcium channel blockers (CCBs), diuretics,

renin-angiotensin-aldosterone-system inhibitor (RAAS-I), nicorandil and moxonidine as well as combination interventions (ACE-I + ARB, ACE-I + diuretic, ARB + CCB, ARB + diuretic, BB + CCB, BB + diuretic, CCB + diuretic, neutral endopeptidase/ACE-I, RAAS-I + diuretic). In addition, subgroup analyses were performed by limiting to studies with a primary diagnosis of hypertension and excluding studies with Jadad scores <3.

RESULTS

A total of 52 studies incorporating 4,381 participants were including for the cSBP analysis and 58 studies incorporating 3,716 unique subjects were included for the AI analysis. Table 1 describes the study characteristics of the included studies. Fifteen of the included studies used a crossover study design while 46 used a parallel study design. Data for the following antihypertensives were available for analysis: ABs, ACE-Is, ARBs, BBs, CCBs, diuretics, RAAS-Is, nicorandil, moxonidine, and omapatrilat.

Overall, antihypertensives reduced pSBP more than cSBP (2.52 mm Hg, 95% CI 1.35 to 3.69; $I^2 = 21.9\%$) (Figure 2). This effect was maintained when limiting to patient populations with a primary diagnosis of prehypertension or hypertension (2.82 mm Hg, 95% CI 1.46 to 4.17, $I^2 = 29\%$). Additionally, utilizing the fixed-effects model (2.40 mm Hg, 95% CI 1.46 to 3.34) and limiting to Jadad scores ≥ 3 (2.57 mm Hg, 95% CI 1.32 to 3.82) did not change the outcomes (Table 2).

Subgroup analyses of individual drug classes showed a nonsignificant difference between pSBP and cSBP with ACE-Is, ARBs, CCBs, diuretics, and RAAS-Is (−2.40 mm Hg, 95% CI −4.89 to 0.08; 1.12 mm Hg, 95% CI −2.25 to 4.49; 1.01 mm Hg, 95% CI −2.17 to 4.19; 0.65 mm Hg, 95% CI −2.47 to 3.77; 1.09 mm Hg, 95% CI −4.80 to 6.99, respectively) (Table 2). BBs posed a significantly greater reduction in pSBP as compared to cSBP (5.19 mm Hg, 95% CI 3.21 to 7.18) (Table 2). Only one study was available for analysis of ABs and nicorandil, which showed no difference in the reduction between pSBP and cSBP (−0.12 mm Hg, 95% CI −14.30 to 14.06; −4.60 mm Hg, 95% CI −56.33 to 47.13; −4.90 mm Hg, respectively) (Table 2). None of the combination antihypertensive regimens revealed a significant difference in their effect on pSBP compared to cSBP (Table 2).

The overall reduction in AI from baseline was 3.09% (95% CI 2.28 to 3.90; $I^2 = 84.5\%$) (Figure 3). When only the studies containing a patient population with a primary diagnosis of prehypertension or hypertension were analyzed, the change in AI from baseline was 2.75% (95% CI 1.79 to 3.71; $I^2 = 84.8\%$). Additionally, utilizing the fixed-effects model (2.45%, 95% CI 2.19 to 2.71; $I^2 = 84.5\%$) and limiting to Jadad scores ≥ 3 (3.68%, 95% CI 2.82 to 4.55; $I^2 = 64.1\%$) did not change the outcomes (Table 2).

Subgroup analyses of individual antihypertensive classes showed a significant reduction in AI with ACE-Is, ARBs, CCBs, diuretics, and RAAS-Is (5.61%, 95% CI 4.27 to 6.95; 5.28%, 95% CI 1.95 to 8.61; 5.36%, 95% CI 3.77 to 6.95; 3.24%, 95% CI 1.03 to 5.45; 3.39%, 95% CI 1.83 to 4.95, respectively) (Table 2). BBs had a nonsignificant reduction

Figure 2. Overall effect of antihypertensives on peripheral systolic blood pressure (pSBP) and central systolic blood pressure (cSBP).

Table 2. Antihypertensive class effect on peripheral systolic blood pressure minus central systolic blood pressure and augmentation index

Subgroup	Δ pSBP – Δ cSBP (mm Hg)			AI (%)		
	N (n)	Pooled WMD	95% CI	N (n)	Pooled WMD	95% CI
Overall (random-effects)	52 (4,381)	2.52	1.35 to 3.69	58 (3716)	3.09	2.28 to 3.90
Overall (fixed-effects)	52 (4,381)	2.40	1.46 to 3.34	58 (3716)	2.45	2.19 to 2.71
Jadad ≥ 3	31 (2,540)	2.57	1.32 to 3.82	33 (2381)	3.68	2.82 to 4.55
HTN diagnosis	40 (3,791)	2.82	1.46 to 4.17	44 (3226)	2.75	1.79 to 3.71
AB	1 (30)	–0.12	–14.30 to 14.06	1 (30)	3.95	–2.51 to 10.42
ACE-I	14 (677)	–2.40	–4.89 to 0.08	12 (330)	5.61	4.27 to 6.95
ARB	9 (393)	1.12	–2.25 to 4.49	11 (445)	5.28	1.95 to 8.61
BB	17 (963)	5.19	3.21 to 7.18	24 (1192)	0.32	–0.84 to 1.48
CCB	11 (510)	1.01	–2.17 to 4.19	12 (379)	5.36	3.77 to 6.95
Diuretic	10 (449)	0.65	–2.47 to 3.77	10 (268)	3.24	1.03 to 5.45
RAAS-I	5 (150)	1.09	–4.80 to 6.99	5 (100)	3.39	1.83 to 4.95
Nicorandil	1 (9)	–4.60	–56.33 to 47.13	1 (9)	7.10	–5.43 to 19.63
Moxonidine	N/A	N/A	N/A	1 (30)	0.30	–2.80 to 3.40
ACE-I + ARB	1 (57)	1.00	–17.19 to 19.19	1 (57)	2.00	–4.02 to 8.02
ACE-I + diuretic	2 (118)	0.29	–3.74 to 4.32	3 (188)	4.21	1.53 to 6.88
ARB + CCB	3 (324)	2.81	–3.31 to 8.94	3 (324)	4.60	3.09 to 6.10
ARB + diuretic	7 (350)	4.28	–3.27 to 11.82	7 (340)	3.46	1.66 to 5.27
BB + CCB	1 (162)	2.10	–2.21 to 6.41	1 (162)	2.81	1.16 to 4.46
BB + diuretic	3 (80)	10.60	–3.47 to 24.67	3 (80)	0.59	–4.19 to 5.36
CCB + diuretic	1 (62)	6.00	–0.08 to 12.08	N/A	N/A	N/A
NEP/ACE-I	1 (75)	–4.90	–12.22 to 2.42	1 (75)	8.00	5.26 to 10.74
RAAS-I + diuretic	2 (177)	–1.29	–8.90 to 6.31	1 (15)	2.30	–12.05 to 16.65

Abbreviations: AB, α -blockers; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, β -blocker; CCB, calcium channel blocker; HTN, hypertension; N, number of studies; n, sample size; NEP, neuroendopeptidase; RAAS-I, renin-angiotensin-aldosterone-system inhibitor; WMD, weighted mean difference.

in AI (0.32%, 95% CI –0.84 to 1.48) along with AB, nicorandil, and moxonidine (3.95%, 95% CI –2.51 to 10.42; 7.10%, 95% CI –5.43 to 19.63; 0.30%, 95% CI –2.80 to 3.40, respectively) (Table 2).

While the Egger's statistic showed a lack of publication bias ($P > 0.976$ for CBP and $P > 0.125$ for AI), it cannot be ruled out based on visual inspection of funnel plots (Figure 4).

DISCUSSION

Overall, antihypertensives significantly reduce pSBP more than cSBP and AI from baseline. An analysis by antihypertensive class showed that the significantly greater reduction of pSBP compared to cSBP was true only for BBs but not the other mono- or combination antihypertensive therapy groups. ACE-Is, ARBs, CCBs, diuretics, and RAAS-Is all significantly reduced AI from baseline, while BBs, ABs, nicorandil, and moxonidine did not.

In the Heart Outcome Prevention Evaluation study, a modest reduction of only 3.3 mm Hg in pSBP post-ACE-I therapy was associated with a 22% relative risk reduction in cardiovascular death, myocardial infarction, or stroke.⁸² However, the same magnitude of benefit should not be extrapolated post-BB therapy due to the significant difference evident in the reduction in pSBP and cSBP. As such, in a meta-analysis of 3,285 subjects, an increase in cSBP of 10 mm Hg corresponded to an 8.8% increased risk of total CV events.⁴ Our results are in line with previous evidence showing that BBs may be inferior to other antihypertensives in their ability to prevent cardiovascular events, specifically stroke.^{83–85} The diverse and variable mechanisms of action of BBs could attribute to this inferior ability.⁸⁶ BBs demonstrate antihypertensive action by decreasing cardiac output, inhibiting the release of renin and production of angiotensin II, and blocking presynaptic α -adrenoreceptors.⁸⁶ However, BBs also exhibit effects on glucose and lipid metabolism⁸³ and their long-term hemodynamic effect of increasing

Figure 3. Overall effect of antihypertensives on augmentation index (AI).

peripheral resistance may lead to their inefficacy in reducing morbidity and mortality.⁸⁷

Another important finding of this meta-analysis was the effect of antihypertensive classes on AI. A 10% increase in AI has been shown to increase risk of total cardiovascular events by 32% and total mortality by 38%.⁴ The significant reduction in AI with ACE-Is, ARBs, CCBs, diuretics, and RAAS-Is exhibits additional evidence of the beneficial effects of these drug classes.

Our findings significantly bolster the results of a previous meta-analysis ($n = 24$) driven by the incorporation of a larger number of recently published studies (44 additional studies plus 22 from previous meta-analysis). While their findings suggested a significantly differing effect on pSBP and cSBP with BB and diuretics, our results only suggest this to be significantly true post-BB therapy. Our meta-analysis also supports the notion that clinical practice should not be averse to appropriate diuretics use. Their results also suggested a significant increase in AI with BB therapy; this significance was not evident in the current meta-analysis. This may be due to the fact that they were limited by the availability of only 3 studies while our analysis incorporated 24 studies. BBs also have a direct impact on the heart rate, confounding the interpretation of the unadjusted AI. Future clinical trials should use heart rate adjusted AI to assess the efficacy of existing and novel drugs. While we included a total of 66 studies overall, the results for ABs, nicorandil, moxonidine, and certain combinations should be interpreted with caution due to the low sample sizes.

There are several limitations to this meta-analysis. The dosage of antihypertensives varied between the trials included in this meta-analysis. Many trials contained titration protocols and the total dose of antihypertensive that was ultimately used in each participant is unknown. Also, some study protocols allowed for the addition of diuretics when BP goals were not met with the study intervention alone. However, these confounders should play a limited role in the interpretation of our results as the change from baseline was assessed for all endpoints. Moreover, while studies were only included in the analysis if duration of treatment was at least 28 days, there was wide variance in the duration of the studies from 4 weeks^{17,24,41,43,46,48,56,59,74,75,81} to 4 years.⁶¹ Furthermore, the tonometry site for measurement of central hemodynamics varied amongst studies and a recent review of available techniques for measuring central BP cautioned that non-invasive cSBP estimation is device/technique-dependent.¹⁰

One study, the CAFE study,¹³ which was included in the previous meta-analysis, was not included in this analysis for not reporting baseline central BP data and also for not identifying which patients were on monotherapy or specific combinations of antihypertensives. This study however included 2,073 participants and had the ability to have a sizeable impact on our results.

The number of randomized, controlled trials including central hemodynamic endpoints has substantially increased in the past decade. However, many of these trials include small patient populations and are unable to individually show overall class effects of antihypertensives. This systematic review highlighted the need for further studies on some antihypertensive drug classes lacking evidence, such as ABs and RAAS-Is, and emerging agents, such as moxonidine and omapatrilat, which have an increasingly important role in

Figure 4. (A) Bias assessment plot for peripheral systolic blood pressure (pSBP) minus central systolic blood pressure (cSBP) and (B) augmentation index (AI).

the management of cardiovascular disease. Further, while we compared inter-antihypertensive class differences, the availability of more studies should allow for future meta-analyses assessing intra-class differences (e.g., dihydropyridine vs. non-dihydropyridine) and the impact of specific agents. The paucity of usable information limits this meta-analysis from performing detailed subgroup analyses.

It is well established that improving pSBP leads to better cardiovascular outcomes. The CAFE trial first demonstrated differing central hemodynamic effects with 2 different antihypertensive agents while having identical reductions in pSBP. The preponderance of current evidence suggests that central hemodynamic endpoints (cSBP and AI) are better predictors of long-term outcomes over pSBP. The results of this meta-analysis showed that BBs are less effective than other antihypertensives at reducing both cSBP and AI. Our results bolster the recommendations of the recently published guidelines for the management of high BP, which have deferred the initiation of BBs in the treatment algorithm.⁸⁸ Future trials are needed to determine the true magnitude of benefit of current and emerging pharmacological and lifestyle interventions in regards to central hemodynamic endpoints.

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DISCLOSURE

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REFERENCES

- Centers for Disease Control and Prevention. Vital signs: awareness and treatment of uncontrolled hypertension among adults—United States, 2003–2010. *MMWR* 2012; 61:703–709.
- Trudeau L. Central blood pressure as an index of antihypertensive control: determinants and potential value. *Can J Cardiol* 2014; 30:S23–S28.
- Cheng HM, Sung SH, Chuang SY, Pearson A, Tufanaru C, White S, Yu WC, Chen CH. Diagnostic performance of a stand-alone central blood pressure monitor: application of central blood pressure in the diagnosis of high blood pressure. *Am J Hypertens* 2014; 27:382–391.
- Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J* 2010; 31:1865–1871.
- Herbert A, Cruickshank JK, Laurent S, Boutouyrie P. Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors. *Eur Heart J* 2014; 35:3122–3133.
- O'Rourke MF. Pulsatile arterial haemodynamics in hypertension. *Aust N Z J Med* 1976; 6(Suppl 2):40–48.
- Horváth IG, Németh A, Lenkey Z, Alessandri N, Tufano F, Kis P, Gaszner B, Cziráki A. Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity. *J Hypertens* 2010; 28:2068–2075.
- Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension* 2001; 38:932–937.
- Weiss W, Gohlisch C, Harsch-Gladisch C, Tölle M, Zidek W, van der Giet M. Oscillometric estimation of central blood pressure: validation of the Mobil-O-Graph in comparison with the SphygmoCor device. *Blood Press Monit* 2012; 17:128–131.
- Narayan O, Casan J, Szarski M, Dart AM, Meredith IT, Cameron JD. Estimation of central aortic blood pressure: a systematic meta-analysis of available techniques. *J Hypertens* 2014; 32:1727–1740.
- Protogerou AD, Stergiou GS, Vlachopoulos C, Blacher J, Achimastos A. The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part II: Evidence for specific class-effects of antihypertensive drugs on pressure amplification. *Curr Pharm Des* 2009; 15:272–289.
- Manisty CH, Hughes AD. Meta-analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure, and augmentation index. *Br J Clin Pharmacol* 2013; 75:79–92.
- Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AL, Thurston H, O'Rourke M. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006; 113:1213–1225.
- Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151:264–269, W64.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17:1–12.
- Baschiera F, Chang W, Brunel P; AGELESS Study Group. Effects of aliskiren- and ramipril-based treatment on central aortic blood

- pressure in elderly with systolic hypertension: a substudy of AGELESS. *Vasc Health Risk Manag* 2014; 10:389–397.
17. Bhagatwala J, Harris RA, Parikh SJ, Zhu H, Huang Y, Kotak I, Seigler N, Pierce GL, Egan BM, Dong Y. Epithelial sodium channel inhibition by amiloride on blood pressure and cardiovascular disease risk in young prehypertensives. *J Clin Hypertens (Greenwich)* 2014; 16:47–53.
  18. Kim EJ, Song WH, Lee JU, Shin MS, Lee S, Kim BO, Hong KS, Han SW, Park CG, Seo HS. Efficacy of losartan and carvedilol on central hemodynamics in hypertensives: a prospective, randomized, open, blinded end point, multicenter study. *Hypertens Res* 2014; 37:50–56.
  19. Peters CD, Kjaergaard KD, Jensen JD, Christensen KL, Strandhave C, Tietze IN, Novosel MK, Bibby BM, Jensen LT, Sloth E, Jespersen B. No significant effect of angiotensin II receptor blockade on intermediate cardiovascular end points in hemodialysis patients. *Kidney Int* 2014; 86:625–637.
  20. Agnoletti D, Zhang Y, Borghi C, Blacher J, Safar ME. Effects of antihypertensive drugs on central blood pressure in humans: a preliminary observation. *Am J Hypertens* 2013; 26:1045–1052.
  21. Briasoulis A, Oliva R, Kalaitzidis R, Flynn C, Lazich I, Schlaffer C, Bakris G. Effects of nebivolol on aortic compliance in patients with diabetes and maximal renin angiotensin system blockade: the EFFORT study. *J Clin Hypertens (Greenwich)* 2013; 15:473–479.
  22. Davis JT, Pasha DN, Khandrika S, Fung MM, Milic M, O'Connor DT. Central hemodynamics in prehypertension: effect of the β -adrenergic antagonist nebivolol. *J Clin Hypertens* 2013; 15:69–74.
  23. Dorresteijn JA, Schrover IM, Visseren FL, Scheffer PG, Oey PL, Danser AH, Spiering W. Differential effects of renin-angiotensin-aldosterone system inhibition, sympathoinhibition and diuretic therapy on endothelial function and blood pressure in obesity-related hypertension: a double-blind, placebo-controlled cross-over trial. *J Hypertens* 2013; 31:393–403.
  24. Eeftinck Schattenkerk DW, van den Bogaard B, Cammenga M, Westerhof BE, Stroes ES, van den Born BJ. Lack of difference between nebivolol/hydrochlorothiazide and metoprolol/hydrochlorothiazide on aortic wave augmentation and central blood pressure. *J Hypertens* 2013; 31:2447–2454.
  25. Ihm SH, Jeon HK, Chae SC, Lim DS, Kim KS, Choi DJ, Ha JW, Kim DS, Kim KH, Cho MC, Baek SH; BELASCO trial investigators, Republic of Korea. Benidipine has effects similar to losartan on the central blood pressure and arterial stiffness in mild to moderate essential hypertension. *Chin Med J (Engl)* 2013; 126:2021–2028.
  26. Kubota Y, Takahashi H, Asai K, Yasutake M, Mizuno K. The influence of a direct renin inhibitor on the central blood pressure. *J Nippon Med Sch* 2013; 80:25–33.
  27. Kwon BJ, Jang SW, Choi KY, Kim DB, Cho EJ, Ihm SH, Youn HJ, Kim JH. Comparison of the efficacy between hydrochlorothiazide and chlorthalidone on central aortic pressure when added on to candesartan in treatment-naïve patients of hypertension. *Hypertens Res* 2013; 36:79–84.
  28. Park S, Rhee MY, Lee SY, Park SW, Jeon D, Kim BW, Kwan J, Choi D. A prospective, randomized, open-label, active-controlled, clinical trial to assess central haemodynamic effects of bisoprolol and atenolol in hypertensive patients. *J Hypertens* 2013; 31:813–819.
  29. Radchenko GD, Sirenko YM, Kushnir SM, Torbas OO, Dobrokhod AS. Comparative effectiveness of a fixed-dose combination of losartan + HCTZ versus bisoprolol + HCTZ in patients with moderate-to-severe hypertension: results of the 6-month ELIZA trial. *Vasc Health Risk Manag* 2013; 9:535–549.
  30. Shahin Y, Cockcroft JR, Chetter IC. Randomized clinical trial of angiotensin-converting enzyme inhibitor, ramipril, in patients with intermittent claudication. *Br J Surg* 2013; 100:1154–1163.
  31. Spanos G, Kalaitzidis R, Karasavvidou D, Pappas K, Siamopoulos KC. Efficacy of aliskiren and valsartan in hypertensive patients with albuminuria: a randomized parallel-group study. *J Renin Angiotensin Aldosterone Syst* 2013; 14:315–321.
  32. Studinger P, Tabák ÁG, Chen CH, Salvi P, Othmane TE, Torzsa P, Kapocsi J, Fekete BC, Tislér A. The effect of low-dose carvedilol, nebivolol, and metoprolol on central arterial pressure and its determinants: a randomized clinical trial. *J Clin Hypertens (Greenwich)* 2013; 15:910–917.
  33. Takami T, Saito Y. Azelnidipine plus olmesartan versus amlodipine plus olmesartan on arterial stiffness and cardiac function in hypertensive patients: a randomized trial. *Drug Des Devel Ther* 2013; 7:175–183.
  34. Zhou WJ, Wang RY, Li Y, Chen DR, Chen EZ, Zhu DL, Gao PJ. A randomized controlled study on the effects of bisoprolol and atenolol on sympathetic nervous activity and central aortic pressure in patients with essential hypertension. *PLoS One* 2013; 8:e72102.
  35. Frimodt-Møller M, Kamper AL, Strandgaard S, Kreiner S, Nielsen AH. Beneficial effects on arterial stiffness and pulse-wave reflection of combined enalapril and candesartan in chronic kidney disease—a randomized trial. *PLoS One* 2012; 7:e41757.
  36. Hayoz D, Zappe DH, Meyer MA, Baek I, Kandra A, Joly MP, Mazzolai L, Haesler E, Periard D. Changes in aortic pulse wave velocity in hypertensive postmenopausal women: comparison between a calcium channel blocker vs angiotensin receptor blocker regimen. *J Clin Hypertens (Greenwich)* 2012; 14:773–778.
  37. Kanaoka T, Tamura K, Ohsawa M, Wakui H, Maeda A, Dejima T, Azushima K, Haku S, Mitsushashi H, Yanagi M, Oshikawa J, Uneda K, Aoki K, Fujikawa T, Toya Y, Uchino K, Umemura S. Effects of aliskiren-based therapy on ambulatory blood pressure profile, central hemodynamics, and arterial stiffness in nondiabetic mild to moderate hypertensive patients. *J Clin Hypertens (Greenwich)* 2012; 14:522–529.
  38. Takenaka T, Seto T, Okayama M, Kojima E, Nodaira Y, Sueyoshi K, Kikuta T, Watanabe Y, Inoue T, Takane H, Ohno Y, Suzuki H. Long-term effects of calcium antagonists on augmentation index in hypertensive patients with chronic kidney disease: a randomized controlled study. *Am J Nephrol* 2012; 35:416–423.
  39. Virdis A, Ghiadoni L, Qasem AA, Lorenzini G, Duranti E, Cartoni G, Bruno RM, Bernini G, Taddei S. Effect of aliskiren treatment on endothelium-dependent vasodilation and aortic stiffness in essential hypertensive patients. *Eur Heart J* 2012; 33:1530–1538.
  40. Vitale C, Marazzi G, Iellamo F, Spoleitini I, Dall'Armi V, Fini M, Volterrani M. Effects of nebivolol or irbesartan in combination with hydrochlorothiazide on vascular functions in newly-diagnosed hypertensive patients: the NINFE (Nebivololo, Irbesartan Nella Funzione Endoteliale) study. *Int J Cardiol* 2012; 155:279–284.
  41. Williams A, Kenny D, Wilson D, Fagenello G, Nelson M, Dunstan F, Cockcroft J, Stuart G, Fraser AG. Effects of atenolol, perindopril and verapamil on haemodynamic and vascular function in Marfan syndrome - a randomised, double-blind, crossover trial. *Eur J Clin Invest* 2012; 42:891–899.
  42. Ferdinand KC, Pool J, Weitzman R, Purkayastha D, Townsend R. Peripheral and central blood pressure responses of combination aliskiren/hydrochlorothiazide and amlodipine monotherapy in African American patients with stage 2 hypertension: the ATLAAS trial. *J Clin Hypertens (Greenwich)* 2011; 13:366–375.
  43. Heffernan KS, Suryadevara R, Patvardhan EA, Mooney P, Karas RH, Kuvin JT. Effect of atenolol vs metoprolol succinate on vascular function in patients with hypertension. *Clin Cardiol* 2011; 34:39–44.
  44. Kampus P, Serg M, Kals J, Zagura M, Muda P, Karu K, Zilmer M, Eha J. Differential effects of nebivolol and metoprolol on central aortic pressure and left ventricular wall thickness. *Hypertension* 2011; 57:1122–1128.
  45. Kandavar R, Higashi Y, Chen W, Blackstock C, Vaughn C, Sukhanov S, Sander GE, Roffidal LE, Delafontaine P, Giles TD. The effect of nebivolol versus metoprolol succinate extended release on asymmetric dimethyl-arginine in hypertension. *J Am Soc Hypertens* 2011; 5:161–165.
  46. Kimura T, Kitamura H, Inoue K, Kawada N, Matsui I, Nagasawa Y, Obi Y, Shinzawa M, Sakata Y, Hamono T, Rakugi H, Isaka Y. Effects of nicorandil on the reduction of BNP levels in patients with chronic kidney disease. *Clin Exp Nephrol* 2011; 15:854–860.
  47. Matsui Y, Eguchi K, O'Rourke MF, Ishikawa J, Shimada K, Kario K. Association between aldosterone induced by antihypertensive medication and arterial stiffness reduction: the J-CORE study. *Atherosclerosis* 2011; 215:184–188.
  48. Shah NK, Smith SM, Nichols WW, Lo MC, Ashfaq U, Satish P, Johnson JA, Epstein BJ. Carvedilol reduces aortic wave reflection and improves left ventricular/vascular coupling: a comparison with atenolol (CENTRAL Study). *J Clin Hypertens* 2011; 13:917–924.
  49. Boutouyrie P, Achouba A, Trunet P, Laurent S; EXPLOR Trialist Group. Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: the EXPLOR study. *Hypertension* 2010; 55:1314–1322.
  50. Doi M, Miyoshi T, Hirohata S, Kamikawa S, Usui S, Kaji Y, Sakane K, Ogawa H, Ninomiya Y, Kusachi S. Combination therapy of calcium channel blocker and angiotensin II receptor blocker reduces

- augmentation index in hypertensive patients. *Am J Med Sci* 2010; 339:433–439.
51. Kinouchi K, Ichihara A, Sakoda M, Kurauchi-Mito A, Itoh H. Safety and benefits of a tablet combining losartan and hydrochlorothiazide in Japanese diabetic patients with hypertension. *Hypertens Res* 2009; 32:1143–1147.
  52. Mackenzie IS, McEniery CM, Dhakam Z, Brown MJ, Cockcroft JR, Wilkinson IB. Comparison of the effects of antihypertensive agents on central blood pressure and arterial stiffness in isolated systolic hypertension. *Hypertension* 2009; 54:409–413.
  53. Matsui Y, Eguchi K, O'Rourke MF, Ishikawa J, Miyashita H, Shimada K, Kario K. Differential effects between a calcium channel blocker and a diuretic when used in combination with angiotensin II receptor blocker on central aortic pressure in hypertensive patients. *Hypertension* 2009; 54:716–723.
  54. Palombo C, Malshi E, Morizzo C, Rakebrandt F, Corretti V, Santini F, Fraser AG, Kozakova M. Arterial wave reflection during antihypertensive therapy with barnidipine: a 6-month, open-label study using an integrated cardiovascular ultrasound approach in patients with newly diagnosed hypertension. *Clin Ther* 2009; 31:2873–2885.
  55. Ahimastos AA, Dart AM, Lawler A, Blombery PA, Kingwell BA. Reduced arterial stiffness may contribute to angiotensin-converting enzyme inhibitor induced improvements in walking time in peripheral arterial disease patients. *J Hypertens* 2008; 26:1037–1042.
  56. Alem M, Milia P, Muir S, Lees K, Walters M. Comparison of the effects of diuretics on blood pressure and arterial stiffness in patients with stroke. *J Stroke Cerebrovasc Dis* 2008; 17:373–377.
  57. Dhakam Z, Yasmin, McEniery CM, Burton T, Brown MJ, Wilkinson IB. A comparison of atenolol and nebivolol in isolated systolic hypertension. *J Hypertens* 2008; 26:351–356.
  58. Karalliedde J, Smith A, DeAngelis L, Miranda V, Kandra A, Botha J, Ferber P, Viberti G. Valsartan improves arterial stiffness in type 2 diabetes independently of blood pressure lowering. *Hypertension* 2008; 51:1617–1623.
  59. Mahmud A, Feely J. Beta-blockers reduce aortic stiffness in hypertension but nebivolol, not atenolol, reduces wave reflection. *Am J Hypertens* 2008; 21:663–667.
  60. Schneider MP, Delles C, Klingbeil AU, Ludwig M, Kolloch RE, Krekler M, Stumpe KO, Schmieder RE. Effect of angiotensin receptor blockade on central haemodynamics in essential hypertension: results of a randomised trial. *J Renin Angiotensin Aldosterone Syst* 2008; 9:49–56.
  61. Dart AM, Cameron JD, Gatzka CD, Willson K, Liang YL, Berry KL, Wing LM, Reid CM, Ryan P, Beilin LJ, Jennings GL, Johnston CI, McNeil JJ, Macdonald GJ, Morgan TO, West MJ, Kingwell BA. Similar effects of treatment on central and brachial blood pressures in older hypertensive subjects in the Second Australian National Blood Pressure Trial. *Hypertension* 2007; 49:1242–1247.
  62. Jiang XJ, O'Rourke MF, Zhang YQ, He XY, Liu LS. Superior effect of an angiotensin-converting enzyme inhibitor over a diuretic for reducing aortic systolic pressure. *J Hypertens* 2007; 25:1095–1099.
  63. Dhakam Z, McEniery CM, Yasmin, Cockcroft JR, Brown MJ, Wilkinson IB. Atenolol and eprosartan: differential effects on central blood pressure and aortic pulse wave velocity. *Am J Hypertens* 2006; 19:214–219.
  64. Rajagopalan S, Kariisa M, Dellegrottaglie S, Bard RL, Kehrer C, Matlow S, Daley W, Pitt B, Brook R. Angiotensin receptor blockade improves vascular compliance in healthy normotensive elderly individuals: results from a randomized double-blind placebo-controlled trial. *J Clin Hypertens (Greenwich)* 2006; 8:783–790.
  65. Tsang TS, Barnes ME, Abhayaratna WP, Cha SS, Gersh BJ, Langins AP, Green TD, Bailey KR, Miyasaka Y, Seward JB. Effects of quinapril on left atrial structural remodeling and arterial stiffness. *Am J Cardiol* 2006; 97:916–920.
  66. Davies J, Carr E, Band M, Morris A, Struthers A. Do losartan and atenolol have differential effects on BNP and central haemodynamic parameters? *J Renin Angiotensin Aldosterone Syst* 2005; 6:151–153.
  67. Mahmud A, Feely J. Aldosterone-to-renin ratio, arterial stiffness, and the response to aldosterone antagonism in essential hypertension. *Am J Hypertens* 2005; 18:50–55.
  68. Mitchell GF, Lacourcière Y, Arnold JM, Dunlap ME, Conlin PR, Izzo JL Jr. Changes in aortic stiffness and augmentation index after acute converting enzyme or vasopectidase inhibition. *Hypertension* 2005; 46:1111–1117.
  69. de Luca N, Asmar RG, London GM, O'Rourke MF, Safar ME; REASON Project Investigators. Selective reduction of cardiac mass and central blood pressure on low-dose combination perindopril/indapamide in hypertensive subjects. *J Hypertens* 2004; 22:1623–1630.
  70. London GM, Asmar RG, O'Rourke MF, Safar ME; REASON Project Investigators. Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: comparison with atenolol. *J Am Coll Cardiol* 2004; 43:92–99.
  71. Neal DA, Brown MJ, Wilkinson IB, Byrne CD, Alexander GJ. Hemodynamic effects of amlodipine, bisoprolol, and lisinopril in hypertensive patients after liver transplantation. *Transplantation* 2004; 77:748–750.
  72. Deary AJ, Schumann AL, Murfet H, Haydock S, Foo RS, Brown MJ. Influence of drugs and gender on the arterial pulse wave and natriuretic peptide secretion in untreated patients with essential hypertension. *Clin Sci (Lond)* 2002; 103:493–499.
  73. Klingbeil AU, John S, Schneider MP, Jacobi J, Weidinger G, Schmieder RE. AT1-receptor blockade improves augmentation index: a double-blind, randomized, controlled study. *J Hypertens* 2002; 20:2423–2428.
  74. Mahmud A, Feely J. Effect of angiotensin II receptor blockade on arterial stiffness: beyond blood pressure reduction. *Am J Hypertens* 2002; 15:1092–1095.
  75. Mahmud A, Feely J. Reduction in arterial stiffness with angiotensin II antagonist is comparable with and additive to ACE inhibition. *Am J Hypertens* 2002; 15:321–325.
  76. Asmar RG, London GM, O'Rourke ME, Mallion JM, Romero R, Rahn KH, Trimarco B, Fitzgerald D, Hedner T, Duprez D, De Leeuw PW, Sever P, Battagay E, Hitznerberger G, de Luca N, Polónia P, Bénétos A, Chastang C, Ollivier JP, Safar ME; REASON Project Investigators (PREterax in regression of Arterial Stiffness in a contrOLled double-bliNd Study). Amelioration of arterial properties with a perindopril-indapamide very-low-dose combination. *J Hypertens Suppl* 2001; 19:S15–S20.
  77. Dart AM, Reid CM, McGrath B; Tonometry Study Group. Effects of ACE inhibitor therapy on derived central arterial waveforms in hypertension. *Am J Hypertens* 2001; 14:804–810.
  78. Spratt JC, Webb DJ, Shiels A, Williams B. Effects of candesartan on cardiac and arterial structure and function in hypertensive subjects. *J Renin Angiotensin Aldosterone Syst* 2001; 2:227–232.
  79. Chen CH, Ting CT, Lin SJ, Hsu TL, Yin FC, Siu CO, Chou P, Wang SP, Chang MS. Different effects of fosinopril and atenolol on wave reflections in hypertensive patients. *Hypertension* 1995; 25:1034–1041.
  80. London GM, Pannier B, Guerin AP, Marchais SJ, Safar ME, Cuche JL. Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease. Comparative effects of ACE inhibition and calcium channel blockade. *Circulation* 1994; 90:2786–2796.
  81. Guerin AP, Pannier BM, Marchais SJ, Metivier F, Safar M, London GM. Effects of antihypertensive agents on carotid pulse contour in humans. *J Hum Hypertens* 1992; 6(Suppl 2):S37–S40.
  82. Sleight P, Salim Y, Pogue J, Tsuyuki R, Diaz R, Probstfield, J. Heart Outcomes Prevention Evaluation (HOPE) Study. Blood-pressure reduction and cardiovascular risk in HOPE study. *Lancet* 2001; 358:2130–2131.
  83. Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005; 366:1545–1553.
  84. Wiyosong CS, Bradley HA, Volmink J, Mayosi BM, Mbewu A, Opie LH. Beta-blockers for hypertension. *Cochrane Database Syst Rev* 2012; 11:3–80.
  85. Larochelle P, Tobe SW, Lacourcière Y. β -Blockers in hypertension: studies and meta-analyses over the years. *Can J Cardiol* 2014; 30:S16–S22.
  86. López-Sendón J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, Tendera M, Waagstein F, Kjekshus J, Lechat P, Torp-Pedersen C; Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on beta-adrenergic receptor blockers. *Eur Heart J* 2004; 25:1341–1362.
  87. Messerli FH, Grossman E, Goldbourt U. Are β -Blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. *JAMA* 1998; 279:1903–1907.
  88. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Oggedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311:507–520.