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Meta-analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure, and augmentation index

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AIMS

Brachial systolic blood pressure (bSBP) exceeds aortic pressure by a variable amount, and estimated central systolic blood pressure (cSBP) may be a better indicator of cardiovascular risk than bSBP. We undertook a systematic review and meta-analysis to compare the effect of single and multiple antihypertensive agents on bSBP, cSBP and augmentation index (AIx).

Methods

A random effects meta-analysis was performed on 24 randomized controlled trials of antihypertensives with measurements of bSBP, cSBP and/or AIx. Separate analyses were performed for drug comparisons with or without placebo, and drug combinations.

Results

In the placebo *vs.* drug meta-analysis, antihypertensive therapy reduced bSBP more than cSBP and there was no statistically significant evidence of heterogeneity by drug class, although the number of individual studies was small. In placebo-adjusted drug *vs.* drug comparison, treatment with β-blockers, omapatrilat and thiazide diuretics lowered cSBP significantly less than bSBP (i.e. central to brachial amplification decreased), whereas other monotherapies lowered cSBP and bSBP to similar extents. Sample sizes were too small and effect estimates insufficiently precise to allow firm conclusions to be made regarding comparisons between individual drug classes. Antihypertensive combinations that included β-blockers decreased central to brachial amplification. β-Blockers increased AIx, whereas all other antihypertensive agents reduced AIx to similar extents.

CONCLUSIONS

A reduction in central to brachial amplification by some classes of antihypertensive drug will result in lesser reductions in cSBP despite achievement of target bSBP. This effect could contribute to differences in outcomes in randomized clinical trials when β-blocker- and/or diuretic-based antihypertensive therapy are compared with other regimens.

Introduction

Blood pressure (BP) is one of the principal modifiable risk factors for cardiovascular disease [1]. Mean and diastolic arterial pressure are relatively similar in all large elastic arteries [2], but systolic BP and pulse pressure in the brachial artery differ from the systolic BP and pulse pressure in other 'central' arteries, such as the aorta [2] and carotid artery [3]. This difference is thought to result from differential timing and magnitude of wave reflection attributed to differences in downstream impedance and arterial stiffness [4, 5]. Some studies have also found that measures of

central systolic BP (cSBP) and central pulse pressure are better predictors of target organ damage and cardiovascular disease than brachial systolic BP (bSBP) or brachial pulse pressure [6–13], and a recent meta-analysis showed borderline superiority of central pulse pressure compared with brachial pulse pressure in the prediction of cardiovascular events [14]. There is therefore a growing interest in using central BP as the target for treatment and monitoring in hypertension [15, 16].

Comparison of central and peripheral BP waveforms

The BP waveform at any site is thought to result from the interaction of forward- and backward-travelling waves. Forward-travelling waves are predominantly due to left ventricular ejection, while backward-travelling waves usually arise from wave reflection. Wave reflection occurs at sites of impedance mismatching, for example at arterial branches [17]. Some workers have also emphasized the role of arterial, particularly aortic, compliance (termed the 'Windkessel' or reservoir pressure) in the generation of the pressure waveform [18, 19]. The question of whether the Windkessel/reservoir and wave models are competing or complimentary ways of understanding the BP waveform remains disputed [20].

Differences in the magnitude, type (i.e. compression or decompression) and timing of waves account for the differences in systolic pressure and waveform morphology in the different large elastic arteries [5]. Systolic BP in the brachial and radial artery is consistently higher than in the aorta and carotid artery (termed central to brachial amplification). This amplification can mostly be explained by a large early reflected compression wave arising from the distal extremity of the upper limb [21], which is superimposed on the wave resulting from left ventricular contraction.

The complex pattern of wave interaction responsible for the BP waveform means that while bSBP and cSBP are related, the nature of this relationship is neither simple nor readily predictable. Typically, bSBP exceeds cSBP by around 10 mmHg, depending on age and sex [22], but in some individuals the difference between bSBP and cSBP can be in excess of 30 mmHg [23, 24]. The relationship between bSBP and central SBP is complex and highly variable and is influenced by numerous factors, including age [22], sex [22], height [25], heart rate [26] and disease, e.g. hypertension or diabetes [24].

Measurement of cSBP

The BP waveform can be recorded non-invasively by applanation tonometry [27], cuff-based techniques applied to the brachial artery [28, 29] or a volume-clamped photoplethysmographic device on the finger [30, 31]. The arterial distension waveform can be measured by ultrasound [32, 33] and provides an acceptable estimate of the BP waveform. Tonometry and ultrasound can be used on the carotid artery to obtain a BP waveform that is similar, although not identical, to the aortic BP waveform [3, 34] without the need for mathematical transformation. However, it is technically easier and more convenient to perform tonometry on the radial artery and estimate cSBP using some form of signal processing technique. Many studies have employed Fourier analysis to derive an individualized [3] or, more commonly, a generalized [35] transfer function that can be used to synthesise an approximation of the aortic BP waveform by differentially modifying the various frequency components of the BP waveform. This approach is widely used, but has been criticised for assuming that a single transfer function can be applied to all individuals in all circumstances [36]; differences in transfer functions result in different estimates of cSBP [37]. In addition, although many studies of antihypertensive agents have used radially derived estimates of central BP, there are few specific validation data for the transfer function technique in the presence of antihypertensive drugs.

More recently, other approaches to estimate cSBP have been described, including identification of a late shoulder (SBP2) in the BP waveform that appears to correspond to cSBP [38], or use of a running-average filter [39]. All of these approaches are limited by uncertainties in methods used to calibrate the recorded waveforms and inaccuracies in the non-invasive determination of BP [38, 40].

Additional information can also be obtained from the BP waveform, in particular calculation of the augmentation index, with [41] or without [42] use of a transfer function. The central augmentation index (AIx) is often used as an index of aortic wave reflection, although it is also influenced by arterial stiffness and heart rate [43]. Nevertheless, it may provide some additional mechanistic insight into the haemodynamic response to antihypertensive agents.

The effects of antihypertensive medication on central BP

The relative efficacy of antihypertensive agents in randomized clinical trials has usually been assessed on the basis of their ability to lower brachial BP; however, because of the important influence of wave reflection, one might expect different classes of antihypertensive agents to have differential effects on aortic BP owing to their variable impact on vasodilator state and hence wave reflection. It is therefore plausible that reported differences in regression of target organ damage, such as regression of left ventricular hypertrophy [44], increased carotid intima–media thickness [45] or differences in cardiovascular event rates [46, 47] with different antihypertensive agents, despite almost equivalent lowering of brachial BP, could be attributable to differential lowering of cSBP, rather than pleiotropic mechanisms, because the left ventricle and carotid artery are exposed to central BP rather than brachial BP. In many studies and meta-analyses, however, there were small

residual differences in peripheral BP [9, 47] that might also explain differences in target organ damage or cardiovascular events.

In view of the importance of cSBP and increasing evidence that antihypertensive drugs may have a differential effect on cSBP compared with brachial systolic BP, we undertook a systematic review and meta-analysis. The aim of this systematic review was to compare the effects of different classes of single and multiple antihypertensive agents on bSBP, cSBP and AIx.

Methods

We identified original randomized controlled trials by an all-language search of all articles (any year up to May 2011) in the Cochrane Controlled Trials Register (CCTR), Medline and EMBASE. We subsequently screened the references of all retrieved articles to identify additional relevant publications. The following search strings and MESH terms were used: *central systolic blood pressure OR carotid systolic blood pressure OR aortic systolic blood pressure AND randomized controlled trial AND placebo*.

Study selection

We included any randomized controlled clinical trial in adults with hypertension (including isolated systolic hypertension) that compared the effects of at least one antihypertensive agent or a combination of antihypertensive agents with placebo, or with another antihypertensive agent, or combinations of antihypertensive agents, on brachial and central BP and, where available, AIx.

We excluded studies that investigated the effects on central BP of dietary factors, beverages or other agents that are not generally considered antihypertensive drugs. We also excluded studies where the duration of exposure to antihypertensive agent was less than 2 weeks. Studies were also excluded where only the changes in BP from baseline with treatment were reported, with no absolute values. Vasodilating β-blockers, such as nebivolol, were analysed as a separate drug class, because there is evidence that their haemodynamic effects differ substantially from first-generation β-blockers [48]. We took care not to include any study population more than once if it featured in more than one publication. Data for men and women that were presented separately in one publication [48] were pooled prior to inclusion in the analysis.

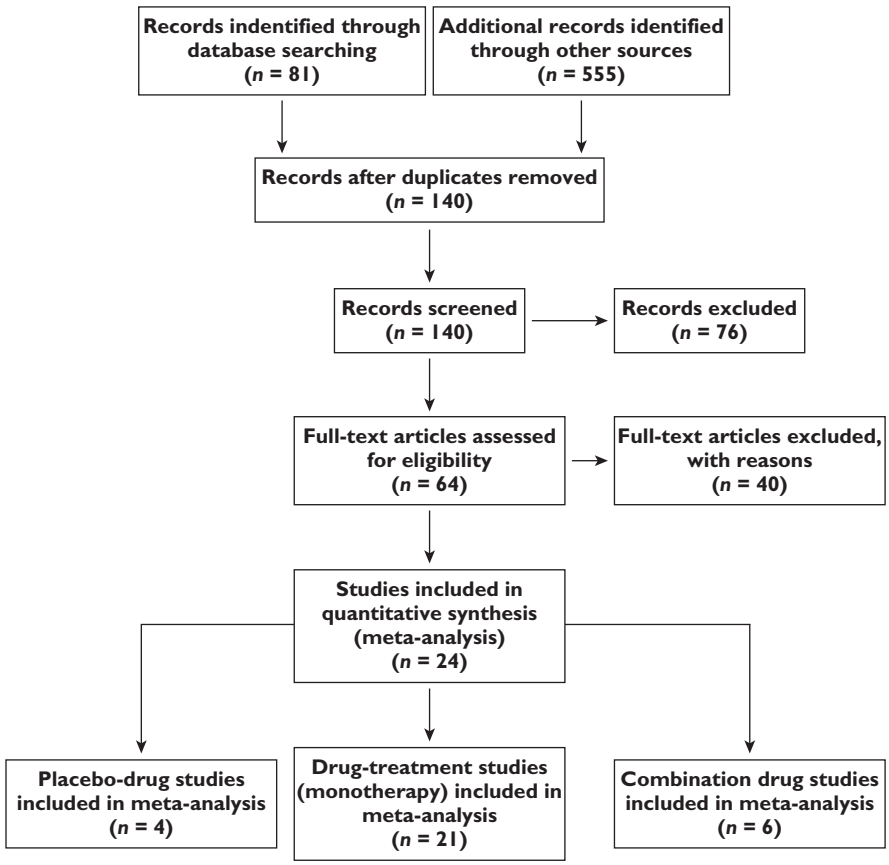

Figure 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

Data items and summary measures

We extracted brachial SBP, central SBP and AIx (if reported) from all studies. The AIx was defined as the percentage ratio of augmentation pressure divided by pulse pressure, where the augmentation pressure is the pressure difference between the shoulder and peak of the pressure waveform (systolic pressure), and pulse pressure is defined as the difference between systolic and diastolic pressures. Data were extracted into a data extraction form using standard QUOROM reporting guidelines [49]. Data were verified by two independent researchers, and any discrepancies were resolved by consensus.

Data from publications comparing antihypertensive monotherapy with placebo were used to calculate weighted mean differences (WMD) between treatment and placebo by drug class (placebo *vs*. drug analysis) for each of bSBP and cSBP. In crossover studies where more than one drug class was compared with placebo, the number of participants in the placebo group was divided by the number of comparisons to avoid a unit of analysis error by multiple counting of placebo data [50]. In all but one of these placebo–drug trials, data for AIx were also available, and we calculated the WMD between treatment group and placebo for AIx in a similar way.

We also compared the effect of the different drug classes (drug *vs*. drug comparison analysis) on central to brachial amplification, i.e. the difference between cSBP and bSBP, in a further meta-analysis. As central to brachial amplification is highly variable between studies, we subtracted the central to brachial amplification on placebo from the data on drug to quantify the drug-related change in central to brachial amplification. Some studies lacked a placebo comparator and in order to include data from these trials, we imputed the placebo bSBP–cSBP difference based on the weighted mean of all placebo *vs*. drug trials included in the meta-analysis. We examined the effect of drugs on central to brachial amplification because in practice brachial BP is used to monitor the effect of antihypertensive treatment, and a differential effect of a drug on central to brachial amplification could result in different cSBP despite similar bSBP (e.g. [9]). Further meta-analyses were performed to compare the effect of different drug combinations (combination drug analysis) on the central to brachial amplification and also on AIx, using similar methodology.

Statistical analysis

As the underlying effect sizes can be expected to vary between studies, we performed a random-effects meta-analysis using Stata 11.2 (Stata Corp. College Station,

Table 1

Characteristics of included studies

Study id	Drug class or placebo studied	Sample size	Type of study	Tonometry site	Design	Comments	Reference
Asmar 2001b	P *vs.* ARB	27	Placebo controlled	Radial	Crossover	Hypertension + Diabetes	[63]
Asmar 2001a	ACEI + D *vs.* BB	471	Drug comparison, combination	Carotid	Parallel		[61]
Boutouyrie 2010	ARB + C *vs.* ARB + BB	393	Combination	Radial	Parallel		[64]
Chen 1995	ACEI *vs.* BB*	79	Drug comparison	Carotid	Parallel	cSBP not reported	[65]
Dart 2007	ACEI *vs.* D†	479	Drug comparison	Carotid	Parallel		[66]
Deary 2002	P *vs.* ACEI *vs.* C *vs.* ACEI *vs.* BB *vs.* AB *vs.* D	30	Placebo controlled, drug comparison	Radial	Crossover	Separate data for sexes	[49]
Dhakam 2006	BB *vs.* ARB	21	Drug comparison	Radial	Crossover		[67]
Dhakam 2008	P *vs.* BB *vs.* nebivolol	16	Placebo controlled, drug comparison	Radial	Crossover		[68]
Doi 2010	C *vs.* D	37	Drug comparison	Radial	Parallel		[69]
Ferdinand 2011	Aliskiren + D *vs.* CCB	53	Drug comparison, combination	Carotid	Parallel	African-American	[70]
Guerin 1992	BB *vs.* C	20	Drug comparison	Carotid	Parallel		[71]
Jiang 2007	ACEI *vs.* D	101	Drug comparison	Radial	Parallel		[72]
London 1994	C *vs.* ACEI	24	Drug comparison	Carotid	Parallel	End-stage renal disease	[73]
London 2004	ACEI + D *vs.* BB	181	Drug comparison, combination	Carotid	Parallel		[74]
Mackenzie 2009	C *vs.* ACEI *vs.* BB *vs.* D	59	Drug comparison	Radial	Parallel	Isolated systolic hypertension	[75]
Mahmud 2000	ARB	18	Drug comparison	Radial	Parallel		[76]
Mahmud 2005	D *vs.* spironolactone	24	Drug comparison	Radial	Crossover		[77]
Mahmud 2008	BB *vs.* nebivolol	40	Drug comparison	Radial	Parallel		[78]
Matsui 2009	ARB + C *vs.* ARB + D	207	Combination	Radial	Parallel		[79]
Mitchell 2002	ACEI *vs.* omapatrilat	167	Drug comparison	Carotid	Parallel		[80]
Morgan 2004	P *vs.* C *vs.* ACEI *vs.* BB *vs.* D	32	Placebo controlled, drug comparison	Radial	Crossover		[81]
Neal 2004	C *vs.* ACEI *vs.* BB	24	Drug comparison	Radial	Crossover	Liver transplantation	[82]
Schneider 2008	ARB *vs.* BB	156	Drug comparison	Radial	Parallel		[83]
Williams 2006	BB + D vs ACEi + CCB	2199	Combination	Radial	Parallel		[9]

Abbreviations: AB, α-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; C, calcium channel blocker; cSBP, central systolic blood pressure; D, thiazide diuretic; P, placebo. *Some patients received hydrochlorothiazide in addition to monotherapy. †Only 65% allocated ACEI received monotherapy.

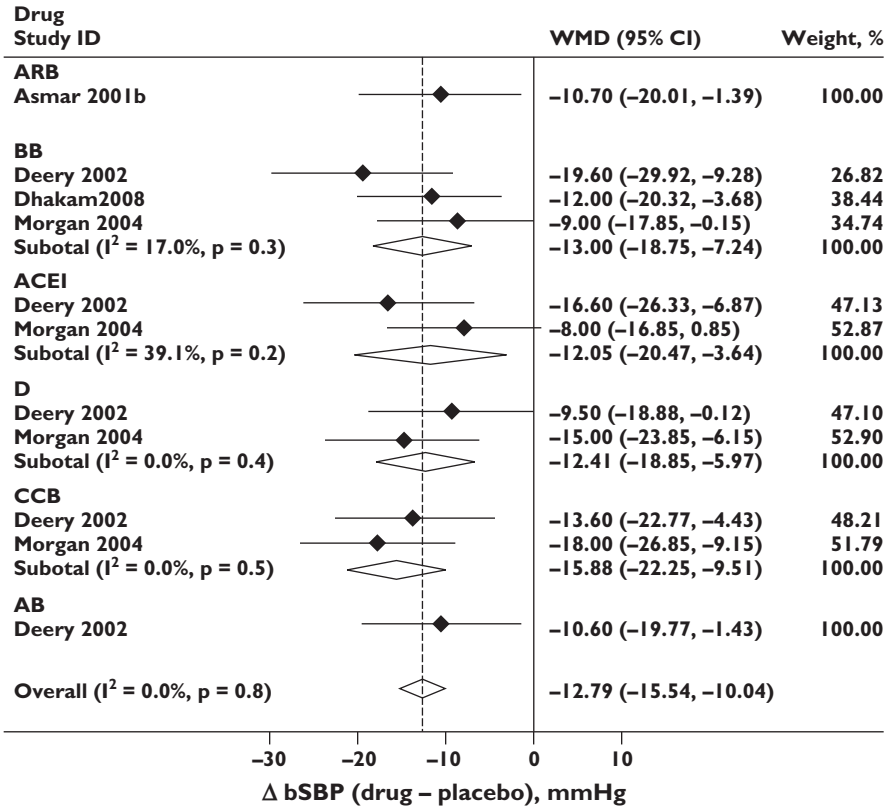

Figure 2

Effect of different classes of antihypertensive monotherapy *vs.* placebo on brachial systolic blood pressure (bSBP). Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; CI, confidence interval; D, thiazide diuretic; WMD, weighted mean difference

TX, USA). Study heterogeneity was assessed using Q and I^2 statistics [51]. Possible publication bias was assessed by inspection of funnel plots and use of Egger's test [52]. Weighted means or WMD of data are presented with their 95% confidence intervals in parentheses; $P < 0.05$ was considered statistically significant.

Results

A total of 24 individual studies involving 5071 participants were included in the meta-analysis (Figure 1 and Table 1). In eight of these studies, measurements were made at the carotid artery, while the others used the radial artery; of these, the Sphygmocor device was employed in all but one (Table 1). Data on the following drugs were available for analysis: α-blockers (AB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), β-blockers (BB), calcium channel blockers (CCB), nebivolol, omapatrilat, spironolactone and thiazide diuretics (D).

Effect of different classes of antihypertensives on bSBP and cSBP

Six drug classes (ARB, ACEI, BB, CCB, D and AB) were compared in placebo-controlled studies. Each class lowered bSBP and cSBP compared with placebo (Figures 2 and 3), although the reduction in bSBP was larger than that in cSBP [WMD −12.79 (−15.54, −10.04) *vs.* −9.60 (−12.61, −6.58) mmHg]. There was no evidence of publication bias (Egger's test $P = 0.2$ and 0.1, respectively, and Supporting Information Figure S1). For both bSBP and cSBP, differences between drug classes were relatively small and there was no statistically significant evidence of heterogeneity ($I^2 = 0\%$, $P = 0.8$ and $I^2 = 16.8\%$, $P = 0.3$, respectively), although the number of studies available for this analysis was limited (four studies). Different drug classes also lowered DBP to similar extents in placebo-controlled studies [overall difference between drugs and placebo = −6.4 (−8.3, −4.5) mmHg; $I^2 = 0\%$; $P = 0.7$]. There was again no evidence of publication bias (Egger's test $P = 0.3$ and Supporting Information Figure S1).

Effect of different classes of antihypertensives on central to brachial amplification

Figure 4 shows the placebo-adjusted differences between bSBP and cSBP (i.e. central to brachial amplification) for a total of nine drug classes as monotherapy; meta-analysis of the bSBP and cSBP data individually are shown in the supporting information (Figures S2 and S3). There was

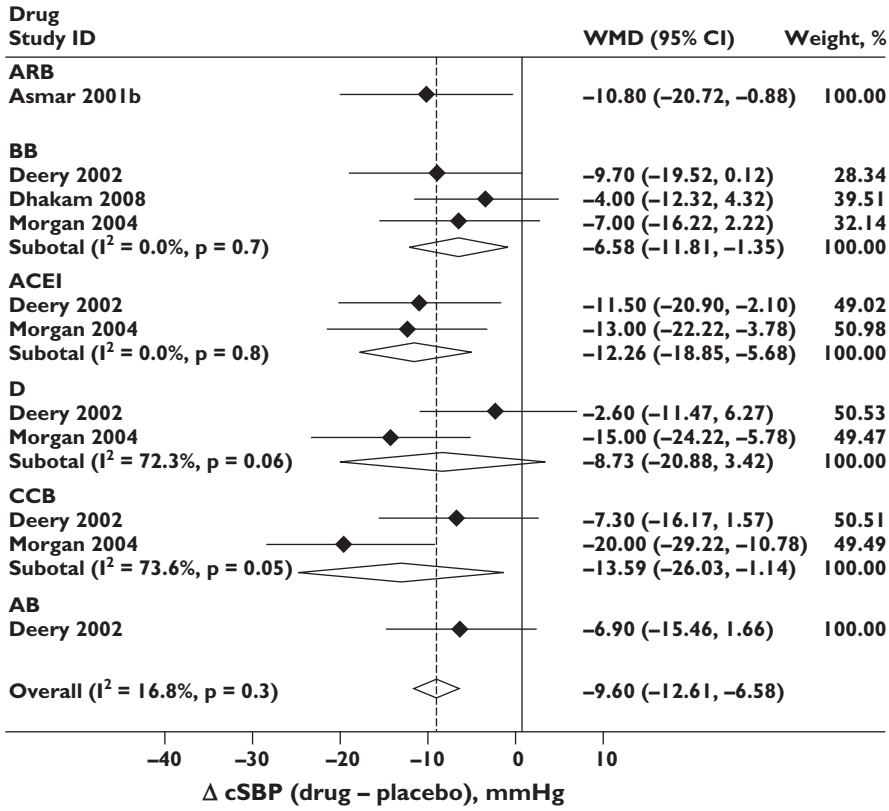

Figure 3

Effect of different classes of antihypertensive monotherapy *vs.* placebo on central systolic blood pressure (cSBP). Abbreviations are as for Figure 2

significant heterogeneity between drug classes (I^2 = 74%, $P < 0.001$). Treatment with BB ($P < 0.001$), D ($P = 0.02$) and omapatrilat ($P < 0.001$) resulted in significant changes in central to brachial amplification, whereas other drug classes had equivalent effects on bSBP and cSBP. There was no evidence of marked publication bias (Figure 4; Egger's test $P = 0.1$).

Further analysis of these data showed marked heterogeneity by site of measurement (I^2 = 74%, $P < 0.001$). However, when the meta-analysis was restricted to studies using radial tonometry the results for BB and D were not substantially different, with placebo-adjusted weighted mean differences between bSBP and cSBP for BB and D being 4.4 (1.7, 7.1) and 6.1 (−1.0, 13.1) mmHg, respectively.

Effect of different combinations of antihypertensive drugs on central to brachial amplification

Figure 5 shows the placebo-adjusted difference between bSBP and cSBP for seven combinations of antihypertensive drug class. There was significant heterogeneity between drug classes. Combinations of ACEI + D, ARB + BB and BB + D caused a greater reduction in bSBP than cSBP; ARB + CCB, ARB + D and ACEI + CCB reduced cSBP and bSBP to similar extents; while, in a single study, aliskiren + D caused a greater reduction in placebo-adjusted cSBP than bSBP. There was no evidence of publication bias (Egger's test P = 0.8 and Supporting Information Figure S1).

Effect of antihypertensives on AIx

Figure 6 shows a comparison of the effect of antihypertensive monotherapy (*vs.* placebo) on AIx. There was significant heterogeneity between drug classes; BB was associated with an increase in AIx, while the other classes reduced AIx to similar extents. There was no evidence of publication bias (Egger's test $P = 0.3$ and Supporting Information Figure S1).

Figure 7 shows the effect of six antihypertensive combinations on the placebo-adjusted difference in AIx. There was significant heterogeneity between drug classes. The combinations ACEI + D, ARB + BB and BB + D increased the placebo-adjusted difference in AIx; ARB + CCB had no overall effect on Aix, although the confidence limits of the estimate were very wide; and ACEI + D and ACEI + CCB reduced AIx. There was no evidence of publication bias (Egger's test P = 0.9 and Supporting Information Figure S1).

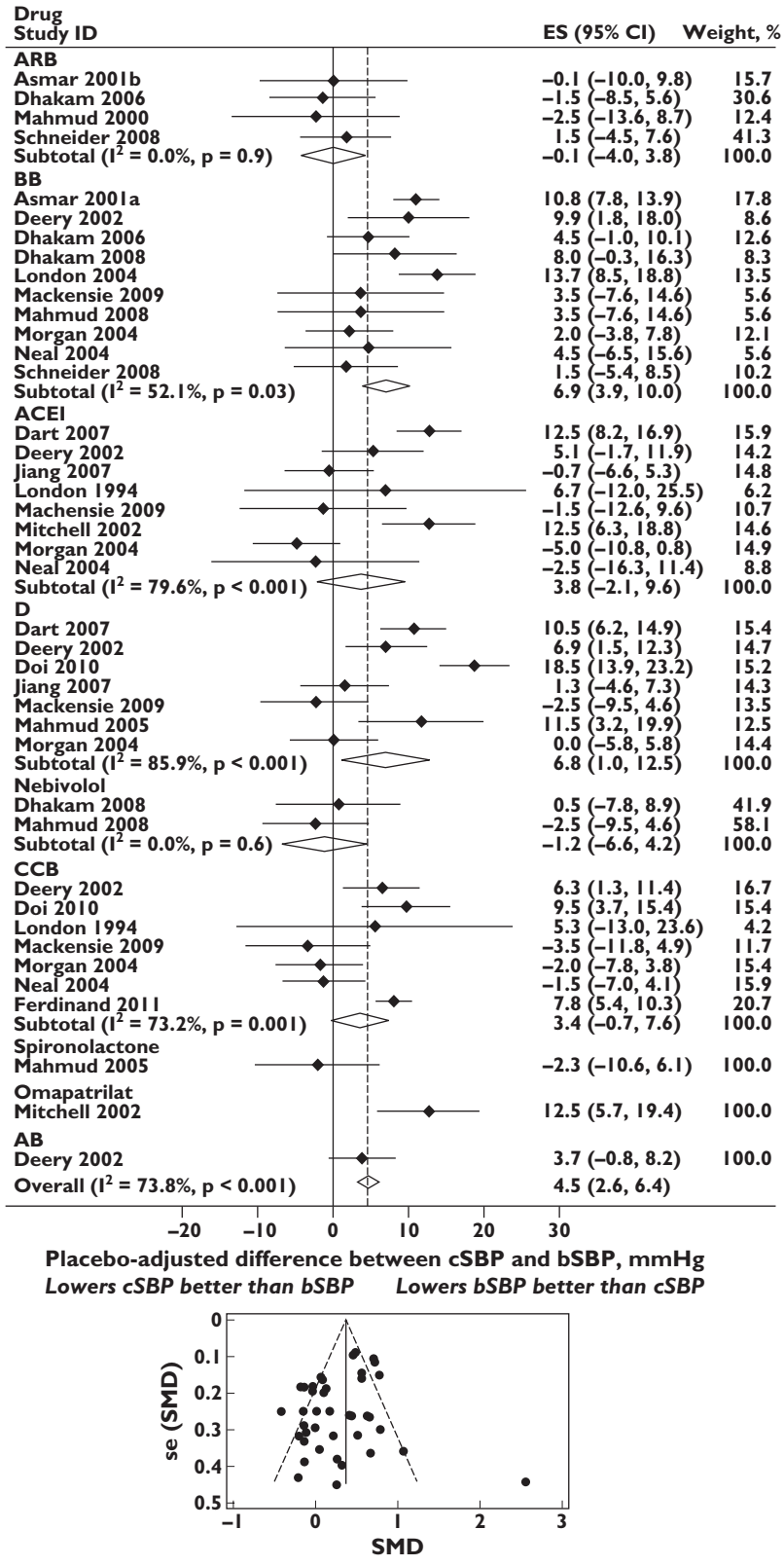

Figure 4

Effect of different classes of antihypertensive monotherapy on placebo-adjusted differences between central systolic blood pressure (cSBP) and brachial systolic blood pressure (bSBP). The funnel plot with pseudo 95% confidence limits is shown below. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; CI, confidence interval; D, thiazide diuretic; ES, effect size; se (SMD), standard error of the standardized mean difference; SMD, standardized mean difference

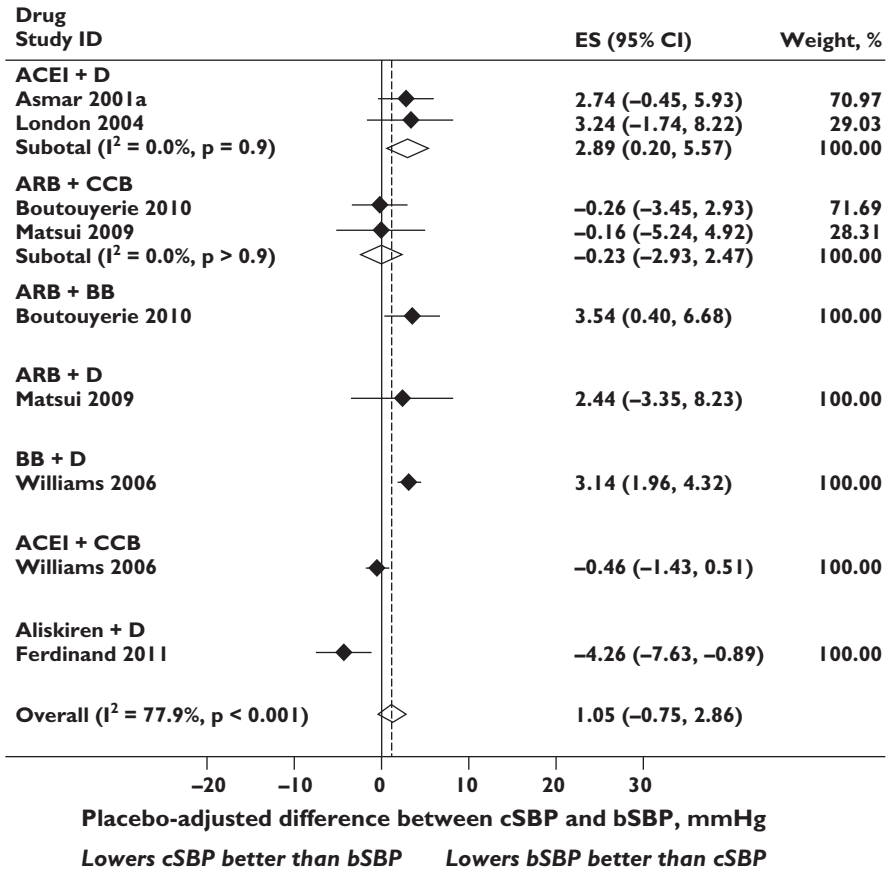

Figure 5

Effect of different combination of classes of antihypertensive drugs on placebo-adjusted differences between central systolic blood pressure (cSBP) and brachial systolic blood pressure (bSBP). Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; CI, confidence interval; D, thiazide diuretic; ES, effect size

Discussion

This systematic review and meta-analysis sought to compare the effects of different antihypertensive drug classes and their combinations on bSBP, cSBP and AIx. All classes of antihypertensive drugs reduced bSBP and cSBP compared with placebo, although the average reduction in bSBP was greater than the reduction in cSBP. An analysis restricted to placebo-controlled studies provided no evidence of heterogeneity between antihypertensive drugs classes on cSBP, although the number of trials included was small (four). A larger number of studies were available for a comparison of the effect of antihypertensive monotherapy on the placebo-adjusted difference between bSBP and cSBP. This analysis indicated that BB, omapatrilat and D lowered cSBP significantly less than bSBP (i.e. reduced central to brachial amplification), whereas other monotherapies lowered cSBP and bSBP to similar extents. Sample sizes and effect estimates were insufficiently precise to allow firm conclusions to be made regarding comparisons between individual drug classes with respect to differential lowering of bSBP and cSBP. Nevertheless, given the current practice of using brachial BP as a treatment target, these data imply that reductions in cSBP might be overestimated by as much as 7 mmHg when using BB or D as monotherapy. Combinations containing BB (ARB + BB and BB + D) were also less effective in lowering cSBP compared with bSBP by 3–4 mmHg.

Recently, the role of β-blockers in hypertension as has come under scrutiny [53], and evidence from meta-analyses suggests that β-blockers may be inferior to other first-line antihypertensive agents, particularly with regard to stroke [47]. If cSBP (the systolic pressure to which the brain is exposed) is more relevant to stroke, then based on the relationship between bSBP and CVD risk, a difference of 3 mmHg would be predicted to correspond to ~10% increased risk of stroke and could therefore be a contributor to less effective stroke prevention by BB. These observations also support suggestions that measurement of

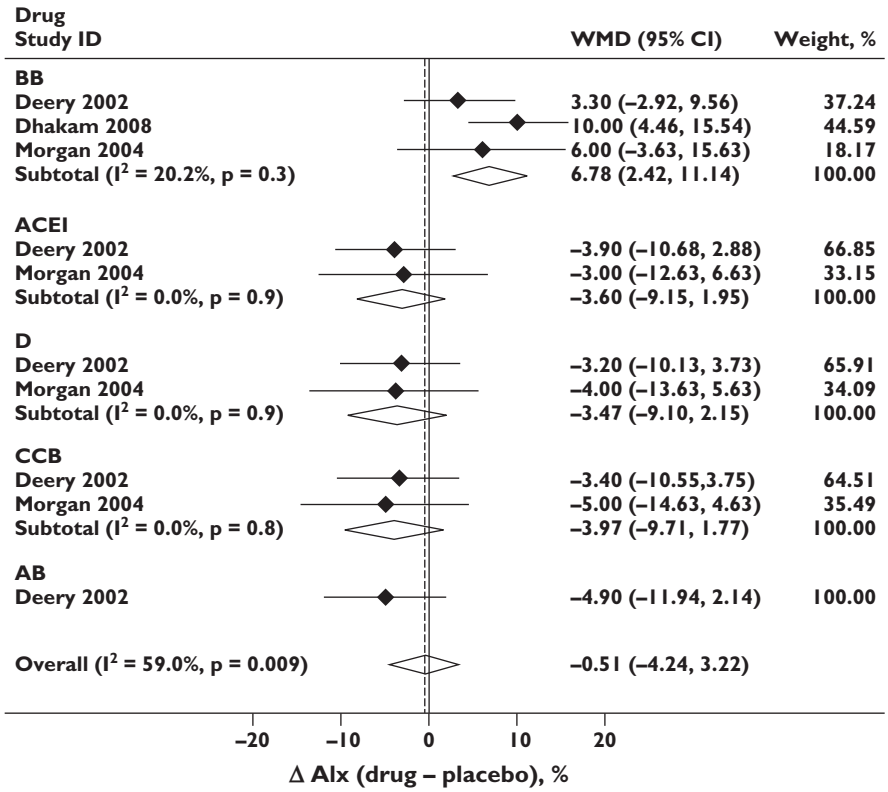

Figure 6

Effect of antihypertensive monotherapy compared to placebo on augmentation index (AIx). Abbreviations are as for Figure 2

central BP may offer advantages over brachial BP in CVD risk prediction and titration of therapy.

An implication of this meta-analysis is that it may be important to examine the effects of novel BP-lowering agents on central BP, as well as brachial BP. A similar consideration also applies to nonpharmacological treatments, such as weight loss, exercise, dietary change and reductions in salt and alcohol intake, and as yet there is limited information on this question [54–57]. We suggest that the effects of some vasoactive agents on cSBP might have been underestimated on the basis of conventional brachial sphygmomanometry and may be worthy of further study; organic nitrates [58] or phosphodiesterase type 5 inhibitors [59] spring to mind.

Additional insight into some of the possible mechanisms responsible for differences between antihypertensive drug classes is provided by the meta-analysis of AIx. The BB class stands out in that it increases AIx, an effect that may, at least in part, be due to the reduction in heart rate [59], but may also relate to the detrimental effects of BB-based antihypertensive therapy on the magnitude of wave reflection [60, 61]. There was no evidence that D differed from other classes in terms of its effect on AIx, and this suggests that other explanations are needed to account for the effect of D on the difference between bSBP and cSBP observed in this meta-analysis.

This meta-analysis has several limitations. The number of studies that met inclusion criteria was small, and in particular, the comparison of placebo-controlled studies using monotherapy has limited power to exclude important between-class differences in cSBP. We believe this is the most likely explanation of the different conclusions drawn from the analysis of placebo-controlled studies as compared with the analysis of placebo-adjusted differences in bSBP and cSBP (for which more studies were eligible). We were also unable to assess the differences in effects on bSBP and cSBP between individual drug classes (for example, D *vs*. ACEI), and further studies are required to address this question. For many drug classes, there was clear evidence of heterogeneity within studies of the same drug class. Site of measurement contributed to this heterogeneity, but other unidentified sources of heterogeneity cannot be excluded. Given the small number of studies, particularly within each drug class, a robust assessment of publication bias was not achievable, and this too may influence some of the differences seen.

Although brachial BP remains the principal tool used for the clinical diagnosis and monitoring of hypertension, there is an increasing body of evidence demonstrating that central BP measurement may be a better prognostic marker in hypertension. In addition, there are newer cuff-based measurement methods that require minimal

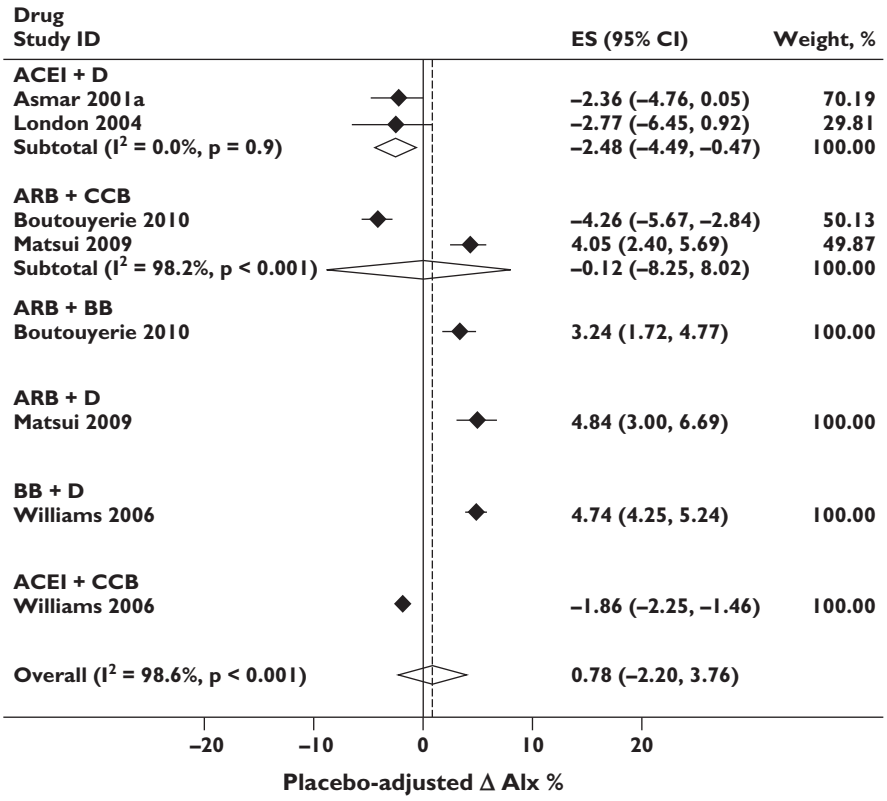

Figure 7

Effect of antihypertensive combinations on placebo-adjusted augmentation index (AIx). Abbreviations are as for Figure 5

additional training beyond conventional BP measurement, and will hopefully facilitate the transition of central BP measurement from research tool to clinical practice. This does not detract from the current importance of brachial BP, for which there are significantly more longitudinal data, and which is cheap and relatively simple to measure.

Conclusions

Brachial systolic pressure exceeds central or aortic systolic pressure owing to central to brachial amplification. β-Blockers, diuretics and combinations containing β-blockers tend to reduce central to brachial amplification, which implies that the achievement of target bSBP may be associated with lesser reductions in cSBP with these classes of agents. This could contribute to differences in outcomes in randomized clinical trials that compare β-blocker- and/or diuretic-based antihypertensive therapy with other regimens.

Competing Interests

There are no competing interests to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1
Funnel plots with pseudo 95% confidence limits for: (a) Effect of different classes of antihypertensive monotherapy *vs*. placebo on brachial systolic blood pressure (Figure 2); (b) Effect of different classes of antihypertensive monotherapy *vs*. placebo on central systolic blood pressure (Figure 3); (c) Effect of different combination of classes of antihypertensive drugs on placebo-adjusted differences between central systolic blood pressure and brachial systolic blood pressure (Figure 5); (d) Effect of antihypertensive monotherapy compared to placebo on augmentation index (Figure 6).

Figure S2
Effect of different classes of antihypertensive monotherapy on brachial systolic blood pressure (bSBP). Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; D, thiazide diuretic; ES, effect size.

Figure S3
Effect of different classes of antihypertensive monotherapy on central systolic blood pressure (cSBP). Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; D, thiazide diuretic; ES, effect size.