Efficacy and safety of dual combination therapy of blood pressure-lowering drugs as initial treatment for hypertension: a systematic review and meta-analysis of randomized controlled trials

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Objective: To assess the efficacy and tolerability of dual combination of blood pressure (BP)-lowering drugs as initial treatment for hypertension.

Methods: MEDLINE, Embase, CENTRAL were searched until August 2017 for randomized, double-blind trials of dual combination therapy vs. monotherapy in adults with hypertension who were either treatment naïve or untreated for at least 4 weeks. Regimens were classified with reference to usual daily 'standard-dose'; for example, $<1+<1$ for a combination of two drugs both at less than one standard-dose. Random-effects models were used for meta-analysis.

Results: Thirty-three trials (13 095 participants) with mean baseline mean BP 155/100 mmHg were included. Compared with standard-dose monotherapy, dual combinations of $<1+<1$, $1+<1$ and $1+1$ (i.e. low-to-standard dose), showed a dose–response relationship in reducing SBP [mean differences (95% confidence interval) of 2.8 (1.6–4.0), 4.6 (3.4–5.7) and 7.5 (5.4–9.5) mmHg, respectively], and in improving BP control [risk ratio (RR) (95% confidence interval) 1.11 (0.92–1.34), 1.25 (1.16–1.35) and 1.42 (1.27–1.58), respectively]. Withdrawals due to adverse events were uncommon with low-to-standard dose dual combinations, with no significant difference compared with standard-dose monotherapy [2.9 vs. 2.2%; RR 1.28 (0.85 to 1.92)]. There were fewer data for higher dose dual combinations, which did not appear to produce substantial additional efficacy and could potentially be less tolerable.

Conclusion: Compared with standard-dose monotherapy, initiating treatment with low-to-standard dose dual combination therapy is more efficacious without increasing withdrawals due to adverse events.

PROSPERO registration: CRD42016032822.

Keywords: antihypertensive drugs, hypertension, initial treatment, low-dose combination therapy, meta-analysis, systematic review

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; WDAE, withdrawals due to adverse event

INTRODUCTION

Recent hypertension guidelines have placed increased emphasis on initial use of combination therapy for most individuals [1,2], in contrast to previous ones that traditionally recommended stepped-care strategy with initial monotherapy [3,4]. This change in emphasis reflects several factors. Although most hypertensive patients need treatment with two or more drugs to achieve goal blood pressure (BP) [3,4] many do not receive such therapy mainly due to treatment inertia [5,6]. Concerns have also been expressed about the risks associated with prolonged times to control BP and whether the need for multiple clinic visits might adversely affect long-term adherence. These factors have intensified clinical interest in the use of combination therapy as initial treatment. However, concerns also remain about the evidence base to support such a strategy, in particular, in relation to risk of adverse events. Although previous reviews have demonstrated the increased efficacy of dual therapy compared with monotherapy [7], limited data were reported on tolerability and the reviews of *initial* combination therapy were limited to the combinations of amlodipine/benazepril [8], perindopril/indapamide [9]. There are no systematic reviews that examined the role of drug doses within different initial therapies of dual combinations. Given the critical impact of

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regimen tolerability, and the likely importance of doses on both efficacy and tolerability, this systematic review and meta-analysis sought to address these uncertainties.

METHODS

Literature search and selection of trials

The current review was registered with PROSPERO (CRD42016032822) before screening for eligible studies. MEDLINE, Cochrane Central Registry of Controlled Trials and Embase were systematically searched until August 2017 to identify relevant trials. The search strategy included Cochrane's highly sensitive search strategy for randomized controlled trials (RCTs) along with Medical Subject Heading and key words relevant to this review (Supplementary Table S1, http://links.lww.com/HJH/B86). We also identified 11 previously published reviews of initial combination therapy through MEDLINE search and screened their references to identify relevant trials.

Eligible studies were randomized, double-blind trials that compared dual combination with monotherapy at fixed doses for a duration of at least 4 weeks. All participants enrolled in the trials were hypertensive (SBP $\geq$ 140 and/or DBP $\geq$ 90 mmHg), treatment naïve and/or had prerandomization washout of previous antihypertensive therapy for at least 4 weeks. Crossover trials with less than 4 weeks' washout between treatments were excluded. Also excluded were trials with prerandomization active run-in, titration of doses based on BP level, and studies focusing on secondary hypertension. Trials were not excluded based on the presence or absence of any disease at baseline. There were no language restrictions.

The title and abstract of each record were screened to exclude clearly irrelevant studies. The full texts were retrieved and at least two reviewers (A.S., E.A., S.I., X.W.) independently identified eligible studies. Any disagreements in study selection were resolved by discussion or involvement of a third reviewer (A.R.), if necessary.

Outcomes

The primary outcomes were change in mean SBP and incidence of withdrawals due to adverse events (WDAEs). Secondary outcomes were change in mean DBP, proportion of participants achieving target BP (using individual study definitions) and incidence of dizziness.

Data extraction and risk of bias assessment in included trials

Two reviewers (A.S., E.A., S.I., X.W.) independently extracted relevant data on study design, participants, treatment and outcomes for each included trial using a standard piloted form. Risk of bias in included studies was assessed by two independent reviewers using the Cochrane Collaboration's risk of bias assessment tool [10].

Data management and analysis

Antihypertensive therapy in each randomized treatment group were defined in terms of 'standard-dose' of the drug(s), as reported in previous reviews [11,12], whereby the most common daily dose reported in Martindale [13], British National Formulary [14], Medical Information Management System [15] and WHO's defined daily dose [16] is taken as the standard dose (Table S2, http://links.lww.com/HJH/B86). Thus for example, in a dual combination, if both drugs were at less than standard-dose, the regimen would be classified and labelled as '<1 + <1' (low dose dual); if one drug at standard-dose and other drug at less than standard-does as '1 + <1' (standard-low dose dual); and if both drug at standard-dose as '1 + 1' (standard dose dual), so on and so forth. In trials with forced up titration of dose in all participants, we took the dose participants received prior to measurement of the outcome BP. If there were multiple treatment groups within a trial with same number of standard doses, they were combined to produce a single estimate.

Continuous outcomes (change in SBP and DBP from baseline) are summarized as mean difference along with 95% confidence intervals (CIs), and binary outcomes (BP control, WDAEs and dizziness) are summarized as the risk ratio (RR) along with 95% CI. We used random-effects model for meta-analysis. Heterogeneity in treatment effects was detected using the Chi-squared test and quantified by the I^2 statistic [17]. For each outcome two meta-analyses were performed: overall, and by doses of drugs in dual combination (defined by standard-dose). In overall meta-analysis, effect size from dual combination groups (and monotherapy groups, separately) within each trial were combined, irrespective of standard dose, and were compared. Data were analysed using comprehensive meta-analysis software [18]. Reporting (publication) bias and small study effect was investigated and reported using funnel plots [19].

RESULTS

Search results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram reports the number of records identified, included and excluded in the systematic review (Fig. 1). A total of 2251 records were identified by the initial search. After removing duplicates and clearly irrelevant records, 368 records were subjected to full text review. After excluding ineligible studies, 33 trials with 13 095 participants were included.

Characteristics of included trials

A summary of characteristics of included trials is reported in Supplementary Table S3, http://links.lww.com/HJH/B86. All included trials were parallel group and double-blind. The median duration of treatment was 8 weeks (minimum 4, maximum 26). Overall, 37% participants were female and the overall mean age was 53 years. BP measurement was done at trough in all but one trial, and predominantly in seated position. Mean baseline BP was 155/100 mmHg. In the 33 trials, there were in total 243 randomized groups and 29 trials included a placebo group. The most common dual combinations involved in the trials were of angiotensin-converting enzyme inhibitor (ACEI) + calcium channel blocker (15 trials, 6718 patients), ACEI + thiazide/like diuretics (six trials, 3145 patients) and AT1 blocker (ARB) + thiazide/like diuretics (five trials, 4545 patients). Overall, 23 trials reported data on BP control. Target BP definitions differed slightly across trials: DBP less than 90 mmHg in six, DBP 90 or less in two, DBP less

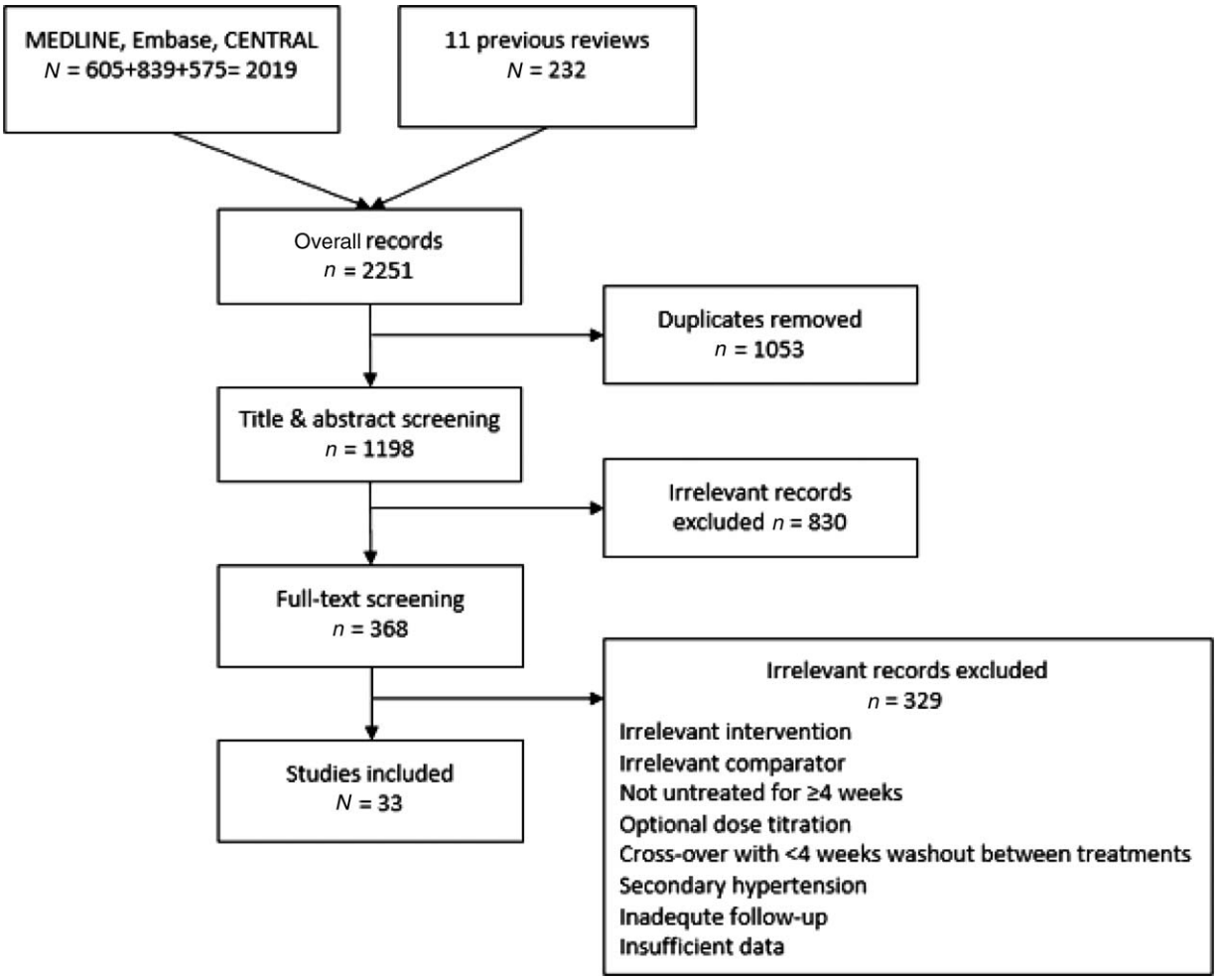

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart reporting identification and inclusion of studies.

than 90 or reduction of at least 10 of DBP from baseline in 10, SBP less than 140 and DBP less than 90 or less than 130 and less than 80 if diabetes in four, SBP less than 140 and DBP less than 90 or SBP at least 20 or DBP at least 10 from baseline in one.

A summary of risk of bias in each included trial is reported in Supplementary Fig. S1, http://links.lww.com/HJH/B86. Few trials adequately reported details of random sequence generation and allocation concealment. In most trials, a number of participants randomized, completed, withdrawn (along with reasons) and lost to follow-up were reported, and analyses were based on intention to treat. Most studies reported all relevant efficacy outcomes but not safety outcomes.

Funnel plots for the primary outcome of change in mean SBP for the three dual combinations of $<1+<1$, $1+<1$ and $1+1$ standard-dose, for which most data were available, compared with one standard-dose monotherapy and placebo, did not show asymmetry (Supplementary Fig. S2, http://links.lww.com/HJH/B86).

Efficacy

Blood pressure reduction

Compared with standard-dose monotherapy, overall, dual combinations reduced BP by 4.8/2.9 mmHg (both $P<0.01$; $I^2=72\%/82\%$). Dual combinations of $<1+<1$, $1+<1$ and $1+1$ (low-to-standard dose) showed a dose–response relationship in reducing BP by 2.8/0.7, 4.6/2.4 and 7.5/4.5 mmHg, respectively (all $P<0.01$, except for $<1+<1$ DBP $P=0.09$) (Fig. 2), with average reduction of 4.5/2.5 mmHg (Supplementary Fig. S3, http://links.lww.com/HJH/B86). High-dose dual combinations, beyond $1+1$ standard-dose, did not produce substantial additional BP reduction ($P=0.113/0.264$ for SBP/DBP for heterogeneity between low-to-standard and high-dose dual therapy) (Supplementary Fig. S3, http://links.lww.com/HJH/B86). In comparisons with less than standard dose monotherapy (<1) all dual combinations reduced BP significantly, whereas in comparison with high-dose monotherapies (all >1 standard-dose pooled), all dual combination significantly reduced BP except $<1+<1$, $>1+<1$ and $1+>1$ (Supplementary Fig. S4, http://links.lww.com/HJH/B86).

Compared with placebo, overall, dual combinations reduced BP by 12.8/7.9 mmHg (both $P<0.01$; $I^2=76\%/92\%$). Dual combinations of $<1+<1$, $1+<1$ and $1+1$ standard-dose again showed dose–response in reducing BP by 10.5/5.9, 12.0/7.1 and 14.8/10.7 mmHg, respectively (all $P<0.01$), with average BP reduction of 12.1/7.5 mmHg. High-dose dual combinations did not produce substantial additional BP reduction ($P=0.569/0.292$ for SBP/DBP for heterogeneity between low-to-standard and high-dose dual

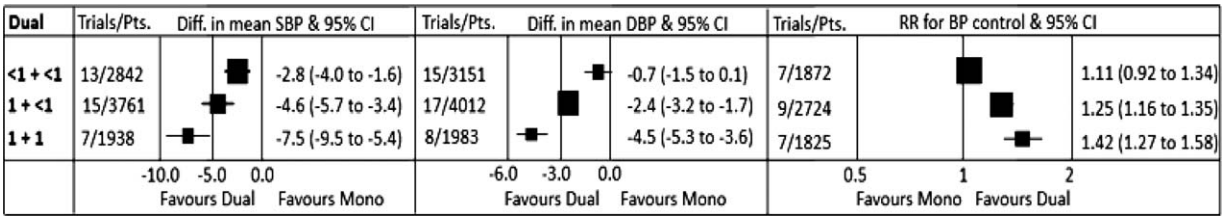

FIGURE 2 Blood pressure change and blood pressure control with dual combination vs. standard-dose monotherapy. Pts, patients.

therapy) (Supplementary Fig. S5, http://links.lww.com/HJH/B86).

There was no clear difference in the efficacy of dual combinations according to the drug class of the component drugs for SBP (Fig. 3 and Supplementary Fig. S6a–c, http://links.lww.com/HJH/B86).

Blood pressure control

Compared with standard-dose monotherapy, dual combination improved BP control by about one-third [65 vs. 48%, RR 1.32 (1.20–1.45)] (Fig. S7, http://links.lww.com/HJH/B86). Dual combinations of $<1+<1$, $1+<1$ and $1+1$ standard-dose improved BP control by 11, 25 and 42%, respectively (all $P<0.05$ except for $<1+<1$) (Fig. 2) with an average of 27%. High-dose dual combination, beyond $1+1$ standard-dose, did not produce any substantial additional improvement in BP control ($P=0.220$ for heterogeneity between low-to-standard and high-dose dual therapy) (Supplementary Fig. S7, http://links.lww.com/HJH/B86). There was no difference in effects between subgroups of trials defined by definitions of target BP. For example, for the comparison of $1+<1$ vs. 1 standard-dose, involving nine trials (Fig. 2), the most common definition of target BP in four trials was DBP less than 90 mmHg or reduction of at least 10 mmHg in DBP, and the risk ratio (RR) for BP control was 1.28 (95% CI 1.10–1.48), whereas in five trials with slightly variable definition of target BP, overall RR was 1.23 (95% CI 1.10–1.36), $P=0.6$ for heterogeneity.

Compared with placebo, dual combination more than doubled BP control [60 vs. 24%, RR 2.54 (2.25–2.86)] (Supplementary Fig. S7, http://links.lww.com/HJH/B86).

Tolerability

Withdrawals due to adverse events

Overall, there was no difference in WDAEs with dual combinations compared with standard-dose monotherapy [incidence 2.7 vs. 2.4%; RR 1.19 (0.83–1.69)], or compared with placebo [incidence 2.8 vs. 3.0%; RR 0.76 (0.54–1.08)]. Dual combinations of $<1+<1$, $1+<1$, $1+1$ standard-dose did not differ with standard-dose monotherapy (Fig. 4), or placebo, and with sparse data a similar effect was seen for high-dose dual combinations (Supplementary Fig. S8, http://links.lww.com/HJH/B86).

Dizziness

Overall, there was higher incidence of dizziness with dual combination, compared with standard-dose monotherapy [incidence 5.4 vs. 3.2%; RR 1.54 (1.08–2.19)], and compared with placebo [incidence 4.0 vs. 2.3%; RR 1.81 (1.23–2.67)]. Dual combinations of $<1+<1$ standard-dose did not differ with standard-dose monotherapy, whereas there was an increase for $1+<1$ combinations (Fig. 4), with few data available for $1+1$ combinations. For high-dose dual combinations, compared with standard dose monotherapy, there was also an increase in dizziness [incidence 7.6 vs.

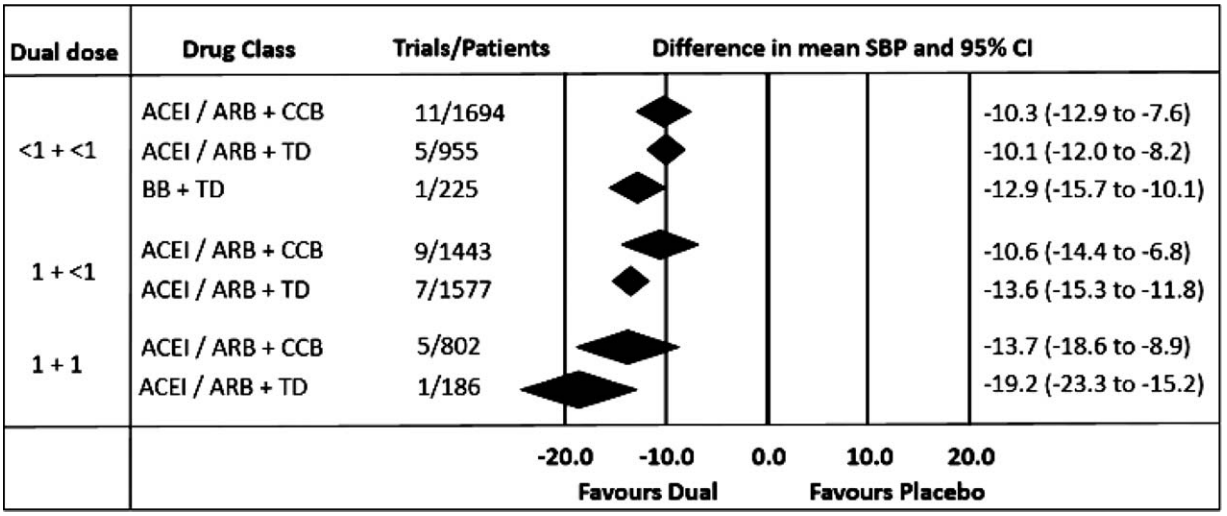

FIGURE 3 Change in SBP by class of antihypertensive drugs in dual combinations by dose, compared with placebo. ACEI, angiotensin converting enzyme inhibitor; ARB, AT1 blocker; CCB, calcium channel blocker; TD, thiazide diuretic.

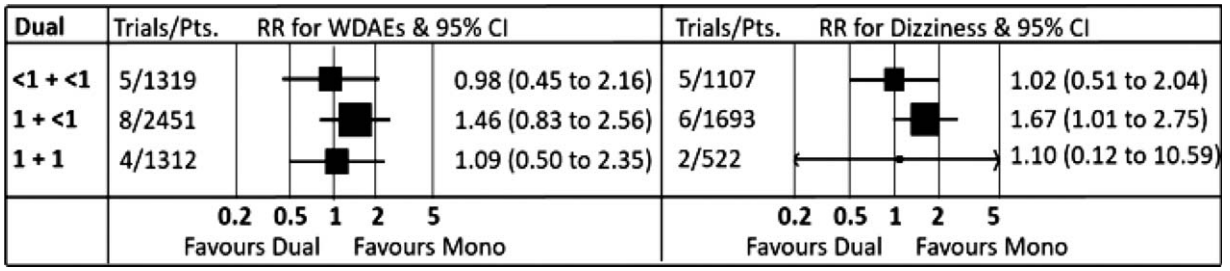

FIGURE 4 Incidence of withdrawals due to adverse events and dizziness with dual combination vs. standard-dose monotherapy. CI, confidence interval; Pts, patients; RR, risk ratio; WDAE, withdrawals due to adverse event.

4.0%, RR 1.78 (0.92–3.46)] (Supplementary Fig. S9, http://links.lww.com/HJH/B86).

DISCUSSION

The current systematic review demonstrated that dual combination of low-to-standard dose therapy improved BP control compared with standard-dose monotherapy, without an increase in WDAEs. There was an increase in dizziness (not resulting in drug withdrawal) with low-to-standard dose dual combinations, affecting approximately one in 50 people, whereas around one in six people benefitted in terms of an increase in hypertension control compared with standard-dose monotherapy. The effects did depend on the doses of drugs in dual combination, but did not appear to depend on the drug classes.

To our knowledge, this is the first systematic review of dose-related efficacy of initial combination therapy for hypertension, including over 13 000 participants who were treatment naïve or were untreated for at least 4 weeks. However, some limitations should be noted. Although our search was comprehensive, we could have missed some eligible trials because of use of terms other than those included in our search strategy, given there are no established standards to describe initial treatment. There were limited data to assess dose–response relationships for safety outcomes, and for efficacy and safety outcomes for high-dose dual combinations. Several analyses had a moderate to high degree of heterogeneity, indicating that summary findings should be treated with caution. Comparing the efficacy and tolerability of various BP-lowering drugs based on standard-doses may not account for all the variability in effects of different classes of antihypertensive drugs. Lastly, the use of low-dose combinations clearly results in a greater likelihood of BP control in short-term trials; however, there is less evidence that such an approach has favourable effects on important cardiovascular outcomes.

Recently, Laurent *et al.* [20] reported pooled analysis of individual participant data (IPD) from three trials (5496 participants) demonstrating low-dose dual combination of less than standard-dose of each drug (perindopril 3.5 mg + amlodipine 2.5 mg) compared with renin angiotensin system inhibitor monotherapies at standard-dose (perindopril 5 mg, irbesartan 150 mg and valsartan 80 mg) reduced BP by 2.4/1.7 mmHg. This is similar to the findings from our review, in which low-dose dual combination (<1 + <1) compared with standard-dose monotherapy reduced SBP by 2.8/0.7 mmHg.

Wald and Law [7,21] with their meta-analysis of combination therapy compared with monotherapy reported that with a baseline SBP of about 155 mmHg, two drugs at half standard-dose (similar to <1 + <1 in our review) and two drugs at standard dose (1 + 1 in our review) compared with one drug at standard-dose would reduce SBP by 4.7 and 8.3 mmHg, respectively [7]. This is slightly higher than the findings in our review, in which <1 + <1 and 1 + 1 compared with one drug at standard dose reduced BP by 2.8 and 7.5 mmHg, respectively. However, this suggests that there are unlikely to be major differences in efficacy among treatments used for initial therapy among treatment naïve patients and those given to other patients who have recently received other treatment. These findings also extend previous results that combination therapy does not lead to an important increase in adverse events, with no increase in adverse events severe enough to warrant cessation of treatment [11]. In our review, given the small variation in important baseline characteristics of BP and age, it was not feasible to assess their association with efficacy and tolerability. A previous analysis of long-term RCTs of combination therapy suggested that the incidence of adverse events was the same for patients with baseline SBP in the range 140–159 and 130–139, and modestly increased for 120–129 mmHg [22]. However, we suggest an IPD meta-analysis would be ideal to assess effects in various subgroup groups of patients.

Three large pragmatic trials [23–25] have shown improved BP control with dual combination therapy compared with monotherapy but were not included in our review, because treatment regimens could be titrated during the course of follow-up [23,24] or because of publication after our literature search cut-off date [25]. In the STRATHE trial [23], a low-dose ACEI-thiazide combination therapy compared with sequential monotherapy and stepped-care therapy produced superior BP control without increase in adverse events. In the STITCH trial [24], a simple algorithm-guided therapy using low-dose ACEI/ARB-diuretic combination as initial treatment resulted in improved BP control, compared with guideline-based stepped care titration. More recently in the PATHWAYS-1 trial [25], combination of losartan and hydrochlorothiazide as initial treatment was superior to monotherapy with either drugs alone, with no difference in withdrawals due to adverse events. The PATHWAYS-1 trial [25] provided evidence against the hypothesis that initial combination gives better long-term results than initial monotherapy followed by combination therapy (the 'never catch-up

hypothesis'). However, it did demonstrate that initial combination was uniformly more effective than monotherapy, whether monotherapy was personalized by prediction of each patient's best drug (e.g. using renin levels or age) or by systematic crossover between monotherapy options. Finally, observational clinical practice data suggested benefits of initial combination therapy compared with monotherapy in terms of reduced discontinuation of antihypertensive therapy [26], and improved BP control [27].

The results of our review have implications for clinical practise and for research. First, we suggest initial combination therapy should be used much more widely. Concerns that initial combination therapy leads to an increase in adverse effects that result in treatment cessation are not supported by the evidence from randomized trials. Most guidelines at present typically recommend initiation of antihypertensive therapy with two drugs only when BP levels are 20/10 mmHg above goal – which for most patient groups in the US and European Guidelines would be those with BP levels above 150/90 mmHg. The European Guidelines state combination therapy should be used in 'most' patients with hypertension and clinicians should only consider monotherapy in patients with low-risk grade 1 hypertension or in the very old (>80 years) or frailer patients. These data support these recommendations, in particular among those at raised cardiovascular risk for whom the uncertainty, as well as delay, of achieving BP control with initial monotherapy would be of most clinical concern. Avenues for further research include assessment of optimal drug combinations for different populations [28] and assessment of efficacy and safety of combinations of three or more drugs at lower doses [12,29–32] as even with dual combination therapy around one-third of patients will not be controlled to 140/90 mmHg [21]. It will be necessary to evaluate operational issues, such as the effect of initial combination therapy on health delivery systems with particular interest in outpatient visit frequency and total pharmacologic costs, including the direct cost of the drugs and the indirect costs or savings related to changes in pharmacy labour, distribution and supply chain logistics. Most importantly there is a requirement for implementation research to assess optimal ways to increase the uptake and long-term maintenance of effective BP-lowering strategies, such as use of combination therapy as initial treatment. This approach, we believe, will provide further evidence for the inclusion of combination therapies for hypertension on the WHO's essential medicines list for adults, and on national essential medicines lists [33].

In conclusion, the current review suggests initiation of pharmacological treatment of hypertension with a low-to-standard-dose dual combination therapy is efficacious and well tolerated, compared with standard-dose monotherapy. The public health implications are considerable given the high burden of hypertension, the clinically important improvements in hypertension control rates afforded by combination therapy, and the large numbers of people globally with hypertension who are mostly treated with monotherapy and have uncontrolled BP.

ACKNOWLEDGEMENTS

Conflicts of interest

There are no conflicts of interest.

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