# Blood pressure-lowering efficacy of antihypertensive drugs and their combinations: a systematic review and meta-analysis of randomised, double-blind, placebo-controlled trials

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## Summary

**Background** We aimed to quantify the blood pressure-lowering efficacy of antihypertensive drugs and their combinations from the five major drug classes.

**Methods** We conducted a systematic review and meta-analysis of randomised, double-blind, placebo-controlled trials involving adult participants randomly assigned to receive angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β blockers, calcium channel blockers, or diuretics. Eligibility criteria included follow-up duration between 4 weeks and 26 weeks, antihypertensive drug treatment fixed in all participants for at least 4 weeks before follow-up blood pressure assessment; and availability of clinic blood pressure for the calculation of mean difference in systolic blood pressure between treatment groups. Crossover trials with less than 2 weeks' washout between the crossover periods were excluded. Eligible studies published between database inception and Dec 31, 2022 were identified from searches of the Cochrane Central Register of Controlled Trials, MEDLINE, and Epistemonikos; searches were updated to include studies published between Jan 1, 2023, and Feb 28, 2025. The primary outcome was placebo-corrected reduction in systolic blood pressure. Blood pressure-lowering efficacy was estimated using fixed-effects meta-analyses standardised to mean baseline blood pressure across included trials. Drug regimens were categorised into low, moderate, and high intensity, corresponding to systolic blood pressure-lowering efficacy of <10 mm Hg, 10–19 mm Hg, and ≥20 mm Hg, respectively, from a baseline of 154 mm Hg. A model was developed to calculate efficacy for any combination of antihypertensives and validated on external trials of dual and triple combination antihypertensives. The study protocol was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY202410036).

**Findings** We analysed 484 trials including 104 176 participants (mean age 54 years [SD 8], 57 422 [55%] men, 46 754 [45%] women, and mean baseline systolic blood pressure 154/100 mm Hg). Mean follow-up duration was 8·6 weeks (SD 5·2). On average, monotherapy at standard dose reduced systolic blood pressure by 8·7 mm Hg (95% CI 8·2–9·2), and each doubling in dose conferred an additional 1·5 mm Hg (1·2–1·7) reduction. Dual combinations at one standard dose conferred a 14·9 mm Hg (95% CI 13·1–16·8) reduction in systolic blood pressure, with each doubling of doses of both drugs conferring an additional reduction of 2·5 mm Hg (1·4–3·7). Each 10 mm Hg decrease in baseline systolic blood pressure reduced pressure-lowering efficacy by 1·3 mm Hg (1·0–1·5) for monotherapies, although differences between drug classes were observed. Among 57 monotherapies at standard dose, 45 (79%) were classified as low intensity. Of 189 different drug–dose dual combinations, 110 (58%) were classified as moderate intensity, and 21 (11%) as high intensity. There were considerable differences in dose–response and baseline blood pressure–response relationships between and within drug classes. The efficacy model showed a high correlation between predicted and observed systolic blood pressures when validated on external trials ($r$=0·76, p<0·0001).

**Interpretation** These analyses provide robust estimates of the expected blood pressure-lowering effect for any combination of antihypertensive drugs, allowing their efficacy to be classified into low, moderate, and high intensity.

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## Introduction

High blood pressure is the leading modifiable risk factor for premature death globally.[1] Each mm Hg reduction in systolic blood pressure confers an approximately 2% reduction in the risk of major adverse cardiovascular events.[2,3] Thus, a therapy with increased efficacy of only a few mm Hg in comparison with an alternative would still be expected to confer clinically important additional reductions in cardiovascular events. The current management paradigm for hypertension relies on serial

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## Research in context

### Evidence before this study

Blood pressure control rates among people treated for hypertension are poor, even in settings where there is affordable access to the many dozens of different approved drugs and drug combinations. The current dominant paradigm is measure and reassess, aiming to monitor response on an individual basis so that treatment can be adjusted. However, this strategy is ineffective because intra-individual blood pressure variability is large, creating a highly unfavourable signal-to-noise ratio. Comprehensive evidence regarding blood pressure differences observed in placebo-controlled randomised trials should have a larger role in clinical decision making than it does at present. To date, this approach has not been widely adopted because estimates of blood pressure-lowering efficacy for different regimens of drugs and doses are not readily available. We conducted a literature search in MEDLINE and Cochrane Central Register of Controlled Trials for previous meta-analyses that reported the drug-specific and dose-specific short-term blood pressure reduction for antihypertensive drugs from all major classes and their combinations from database inception until Feb 1, 2025. We found one previous study first published in 2003 that reported the average blood pressure reduction according to drug class and select monotherapies, but no studies that provided comprehensive drug-specific and dose-specific estimates according to baseline blood pressure.

### Added value of this study

This systematic review and meta-analysis of 484 double-blind, placebo-controlled, randomised clinical trials quantifies the pressure-lowering efficacy of antihypertensives according to dose and baseline blood pressure. The review shows clinically significant differences in average blood pressure reduction, dose–response curves, and effect modification by baseline blood pressure between drugs and drug classes. These results allowed the development, to the best of our knowledge, of the first ever calculator to provide trial-derived estimates of blood pressure-lowering efficacy for any permutation of drugs from the major antihypertensive drug classes. We also introduce a new classification scheme, based on the magnitude of systolic blood pressure reduction, with low, moderate, and high intensity conferring reductions of <10 mm Hg, 10–19·9 mm Hg, and ≥20 mm Hg , respectively, for individuals with pretreatment systolic blood pressure of 154 mm Hg.

### Implications of all the available evidence

When choosing an antihypertensive drug regimen, clinicians should consider the intensity of the regimen depending on the desired blood pressure reduction. Our online efficacy calculator provides estimates of expected blood pressure-lowering efficacy according to double-blind randomised trial data.

blood pressure measurements before and after treatment to estimate blood pressure-lowering efficacy.[4,5] However, blood pressure is subject to substantial intra-individual variability due to both biological variation and measurement error.[6] This variability far exceeds inter-individual differences in treatment response, meaning that the blood pressure treatment response for a given individual in a typical clinical setting cannot be reliably measured.[7–10] Therefore, it has been suggested that instead of tailoring treatment to an individual's serial blood pressure measures, a better approach might be to simply assume the mean treatment effect from placebo-controlled randomised clinical trials. However, there is no reliable, comprehensive source for the evidence on these placebo-controlled effects.

Hypertension guidelines recommend antihypertensive drug classes and preferred drugs without specifying the expected efficacy in terms of mm Hg of blood pressure reduction.[4,5] This approach contrasts with that taken in other therapeutic areas, such as dyslipidaemia management, whereby lipid-lowering regimens are categorised according to expected LDL cholesterol lowering, with low-intensity, moderate-intensity, and high-intensity therapies reducing LDL cholesterol by <30%, 30–49% and ≥50%, respectively.[7] One reason for this discrepancy might be the many permutations of antihypertensive drug regimens, with thousands of possible drug–dose combinations. Knowing the expected efficacy of antihypertensive drugs and their combinations in advance would facilitate optimal prescribing, enabling rapid and cost-effective achievement of blood pressure targets.

Therefore, we conducted a systematic review and meta-analysis of randomised, double-blind, placebo-controlled trials to quantify the blood pressure-lowering efficacy of antihypertensive drugs from the five major classes (angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], β blockers, calcium channel blocker [CCBs], and diuretics) and their combinations. We also aimed to develop a calculator to estimate the mean expected reduction in blood pressure for any permutation of these antihypertensive drugs and doses according to baseline blood pressure.

## Methods

### Search strategy and selection criteria

This systematic review and meta-analysis was conducted following the guidance from the *Cochrane Handbook for Systematic Reviews of Interventions*[8] and is reported according to PRISMA guidelines.[9] For this review, we included randomised trials from our database, Double-blind, Randomised Trials of Effects of Antihypertensive Medicines (DREAM), which has been described previously.[10] We identified these randomised trials through

a systematic search of the Cochrane Central Register of Controlled Trials for randomised trials, MEDLINE, and Epistemonikos for eligible studies published between database inception and Dec 31, 2022. Searches were updated to include studies published between Jan 1, 2023, and Feb 28, 2025. We also searched reference lists of relevant previous systematic reviews and drug approval packages from the US Food and Drug Administration website for unpublished trials of antihypertensive drugs. The full search strategy is reported in the appendix (pp 3–8). The study protocol was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY202410036).

Trials published in English were included if they met the following criteria: they were randomised, double blind, and placebo controlled; they included adult participants (age ≥18 years) with or without hypertension; there was random assignment of participants to antihypertensive drugs from one or more of the five major classes (ACE inhibitors, ARBs, β blockers, CCBs, and diuretics) or to placebo; treatment and follow-up duration was between 4 weeks and 26 weeks; dose and choice of drug or drugs was fixed in all participants for at least 4 weeks before the assessment of follow-up blood pressure; and there was availability of clinic blood pressure for the calculation of mean difference in systolic or diastolic blood pressure between treatment groups. Crossover trials with less than 2 weeks' washout between the crossover periods were excluded.

### Screening and data collection

All identified trials in the literature search were screened for inclusion by two independent reviewers (among NW, AS, AK, RD, FH, KV, and PK), first at the level of title and abstract, and then at the level of full text. Data from the included trials were extracted independently by two reviewers (among NW, AS, AK, RD, FH, KV, and PK) with a standard data collection form. Any disagreements between the reviewers were resolved by consulting a third reviewer (AS, AR, or NW). Trial and participant characteristics, randomised treatment and dose, and blood pressure at baseline and follow-up were extracted. If blood pressure data were not reported numerically, they were extracted from figures using WebplotDigitizer.[11] We extracted data to compare monotherapy (treatment with a single antihypertensive drug class) and combination therapy (treatment with two or more antihypertensive drug classes) versus placebo, with or without background therapy. Background therapy was defined as treatment whereby all participants received the same antihypertensive drug or drugs regardless of their randomised group; this treatment was not considered part of the monotherapy or combination therapy classifications.

When possible, we used seated blood pressure measurements over standing or supine measurements. Missing SDs for blood pressure measurements were imputed with a stepwise approach as per the Cochrane handbook (appendix p 13).[8] No attempt was made to contact authors for missing data. Drug doses were standardised with the WHO daily defined dose and/or regulatory approved strengths (appendix pp 16–18).

### Data analysis

The primary outcome was reduction in clinic systolic blood pressure (difference in change in mean systolic blood pressure from baseline to the maximum available follow-up [minimum of 4 weeks]) with active treatment versus placebo. The secondary outcome was reduction in diastolic blood pressure. Risk of bias was assessed according to the Cochrane risk-of-bias tool version 2.[12]

See Online for appendix

The primary analysis focused on ACE inhibitors, ARBs, β blockers, CCBs, and thiazide or thiazide-like diuretics. Separate additional analyses of mineralocorticoid receptor antagonists (MRAs) and other diuretics (eg, loop) were conducted as a supplemental analysis. We standardised all treatment effects to a baseline blood pressure of 154/100 mm Hg (ie, the mean baseline blood pressure of all included trials) using drug-class-specific fixed-effects meta-regression models with inverse variance weighting, with blood pressure reduction as the dependent variable and baseline blood pressure and drug dose as covariates (appendix p 14). Inclusion of other variables, including mean age and percentage male sex, did not lead to substantial improvements in the final model.

Fixed-effects meta-analyses for each drug were conducted to estimate mean differences and 95% CIs standardised to baseline blood pressure. We opted for a fixed-effects meta-analysis to mitigate the risk of small-study bias and facilitate the exploration of underlying heterogeneity through key covariates, including baseline blood pressure, drug class classification, and specific medications and their dosages.[13] We also assessed blood pressure reduction for monotherapies and combination therapies at half, one, and two standard doses. Heterogeneity between studies was assessed with the $I^2$ test, with heterogeneity of 50% or more considered substantial.

We conducted the following prespecified subgroup analyses: diuretics classified as MRAs and other diuretics (loop diuretics and potassium-sparing diuretics); classification of CCBs as dihydropyridine and non-dihydropyridine; and presence or absence of background antihypertensive therapy. Sensitivity analyses were done for the primary outcome of mean reduction in systolic blood pressure according to drug class after exclusion of the following: comparisons with baseline imbalances in blood pressure (>5 mm Hg for systolic blood pressure); trials with fewer than 8 weeks of fixed antihypertensive drug treatment, in case there were any further treatment effects after 4 weeks; trials at moderate or high risk of bias; and trials with fewer than 50 participants. Finally, random-effects models were also used as sensitivity analyses.

Additionally, we developed an efficacy calculator using two hierarchical regression equations derived from

| | All trials |
|---|---|
| **Trial characteristics** | |
| Type of therapy* | |
| Monotherapy *vs* placebo | 466/484 (96%) |
| Combination therapy *vs* placebo | 88/484 (18%) |
| Trials by year of publication | |
| Before 1990 | 106/484 (22%) |
| 1990–99 | 218/484 (45%) |
| 2000–09 | 101/484 (21%) |
| After 2009 | 59/484 (12%) |
| Mean trial duration, weeks | 8·6 (5·2) |
| Trials with industry funding | 163/484 (34%) |
| Placebo-controlled comparisons | |
| Random assignment to monotherapy | 971/1219 (80%) |
| Random assignment to combination therapy | 248/1219 (20%) |
| Trials enrolling all patients with hypertension†‡ | 370/484 (76%) |
| Trials enrolling all patients with cardiovascular disease†§ | 48/484 (10%) |
| Trials enrolling all patients with diabetes† | 23/484 (5%) |
| Trials enrolling all patients with chronic kidney disease† | 5/484 (1%) |
| Intervention type* | |
| Angiotensin-converting enzyme inhibitors | 124/484 (26%) |
| Angiotensin II receptor blockers | 106/484 (22%) |
| β blockers | 77/484 (16%) |
| Calcium channel blockers | 143/484 (30%) |
| Diuretics¶ | 101/484 (21%) |
| Combination therapy | 88/484 (18%) |
| **Participant characteristics** | |
| Male participants | 57 422/104 176 (55%) |
| Female participants | 46 754/104 176 (45%) |
| Systolic blood pressure, mm Hg | 154 (12) |
| Diastolic blood pressure, mmHg | 100 (9) |
| Age, years | 54 (8) |

Data are n, n/N (%), or mean (SD). *Rows exceed 100% as some trials were included in more than one class. †Based on the trial inclusion criteria. ‡Hypertension was variably defined in the individual trials but included blood pressure ≥140/90 mm Hg and/or on antihypertensive treatment at baseline. §Including coronary disease, stroke, peripheral vascular disease, heart failure, and arrhythmia. ¶Includes thiazide or thiazide-like diuretics, mineralocorticoid receptor antagonists, and other diuretics.

***Table:*** **Trial and participant characteristics**

comparisons of monotherapy versus placebo (appendix p 14). The first regression equation was a linear-log dose–response regression equation for each unique monotherapy to estimate the mean difference and 95% CI for the baseline blood pressure of 154/100 mm Hg. We then adjusted the mean difference (and 95% CI) using regression models at the drug-class level according to the baseline blood pressure. The expected blood pressure reduction with combination therapy was calculated by adding the expected blood pressure reduction from derived meta-regression equations for the respective monotherapy components, accounting for a lower baseline blood pressure for the second and subsequent components (appendix p 14).[14] The efficacy calculator was validated with randomised comparisons of dual combination versus placebo. Given that only the monotherapy versus placebo comparisons were used to develop the efficacy calculator, the comparisons of dual combination versus placebo are external to the data used to derive the models. Additionally, we conducted a systematic literature search to identify randomised clinical trials of triple versus dual combination antihypertensives to assess the model's performance and the additive effect of three drugs compared with two drugs (appendix pp 9–11).

Consistency between the observed and expected efficacy of combination therapies was tested with Pearson's correlation coefficient (*r*) and the mean bias error. We conducted sensitivity validation analyses by testing the model on factorial trials of dual combinations and on different permutations of drug classes. Finally, we calculated mean and 95% prediction intervals for monotherapy, dual combinations, and triple combinations of the five most prescribed antihypertensives in the USA from the five major classes.[15] We classified treatment regimens conferring reductions in systolic blood pressure of <10 mm Hg, 10–19·9 mm Hg, and ≥20 mm Hg from a baseline systolic blood pressure of 154 mm Hg as low, moderate, and high intensity, respectively. All analyses were done with R version 4.1.2 and Stata version 18.1.[16,17]

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

The search strategy identified 39 582 records for screening after exclusion of duplicate studies, of which 484 trials were included in the analysis (appendix pp 71–72). 466 (96%) of the included trials compared monotherapy versus placebo, 83 (17%) compared a dual combination versus placebo, four compared a triple combination versus placebo, and one trial compared a quadruple combination versus placebo (table; appendix pp 19–35). Participants were randomly assigned to ACE inhibitors in 124 trials, to ARBs in 106, to β blockers in 77, to CCBs in 143, to thiazide or thiazide-like diuretics in 74, to MRAs in 23, and to other diuretics in nine trials. Mean treatment duration in the included trials was 8·6 weeks (SD 5·2). 104 176 participants were included in the analysis; mean age was 54 years (SD 8), 57 422 (55%) were men, and 46 754 (45%) were women. Baseline mean systolic blood pressure and diastolic blood pressure were 154 mm Hg (SD 12) and 100 mm Hg (9), respectively. Of the 484 trials, 389 (80%) were assessed as being at low

risk of bias, 91 (19%) as having some concerns for bias, and four (<1%) as being at high risk of bias, with the most common reason for bias being missing outcome data (appendix pp 36–54).

On average, one standard dose of monotherapy was associated with a reduction of 8·7 mm Hg (95% CI 8·2–9·2) for systolic blood pressure and 5·6 mm Hg (5·3–6·0) for diastolic blood pressure (figure 1; appendix pp 55–58). The corresponding reduction in systolic blood pressure for one standard dose was 6·8 mm Hg (5·9–7·7) for ACE inhibitors, 8·5 mm Hg (7·8–9·3) for ARBs, 8·9 mm Hg (7·8–10·0) for β blockers, 9·5 mm Hg (8·4–10·6) for CCBs, 10·8 mm Hg (9·2–12·4) for thiazide or thiazide-like diuretics, and 8·4 mm Hg (6·0–10·7) for MRAs (figure 1; pp 55–58, 76). There was substantial heterogeneity for several meta-analyses by drug class ($I^2$ >50%), suggesting differences in efficacy between drugs within the same class. The use of background antihypertensives did not affect blood pressure reduction overall or for any drug class (p values for interaction were all >0·05; appendix p 77). Among the 57 different monotherapies at one standard dose, 45 (79%) were classified as having low-intensity efficacy, but there was substantial heterogeneity. When considering all 266 unique drug–dose options for monotherapies, 189 (71%) were classified as having low-intensity efficacy.

Lower pretreatment blood pressure was associated with less blood pressure reduction, varying by drug class (figure 2). Across all monotherapies, for each 10 mm Hg decrease in pretreatment blood pressure, on average, systolic blood pressure-lowering efficacy was reduced by 1·3 mm Hg (95% CI 1·0–1·5). Considering individual drug classes, each 10 mm Hg decrease in pretreatment systolic blood pressure was associated with 0·3 mm Hg (–0·3 to 1·0) less of a reduction with ACE inhibitors (the weakest association), 1·4 mm Hg (0·8 to 2·1) less with ARBs, 1·4 mm Hg (0·8 to 1·9) less with β blockers, 1·5 mm Hg (0·9 to 2·0) less with CCBs, 1·6 mm Hg (1·0 to 2·2) less for thiazide or thiazide-like diuretics, and 1·6 mm Hg (0·5 to 2·6) less for MRAs.

Blood pressure reduction increased modestly with increasing drug dose, with considerable heterogeneity between and within drug classes (appendix p 78). Overall, for monotherapy, each doubling of dose gave an additional 1·5 mm Hg (95% CI 1·2–1·7) reduction in systolic blood pressure and an additional 1·0 mm Hg (0·8–1·2) reduction in diastolic blood pressure. β blockers had the weakest dose–response relationship, with each doubling of dose conferring an additional 0·5 mm Hg (–0·1 to 1·1) reduction in systolic blood pressure, whereas CCBs had the steepest dose response, with each doubling of dose conferring an additional 2·6 mm Hg (1·9 to 3·2) reduction. Other drug classes were intermediate, with additional reductions per dose doubling of 1·6 mm Hg (1·1–2·1) for ACE inhibitors, 1·1 mm Hg (0·6–1·6) for ARBs, 2·0 mm Hg (1·4–2·6) for thiazide or thiazide-like diuretics, and 1·8 mm Hg (0·7–3·0) for MRAs.

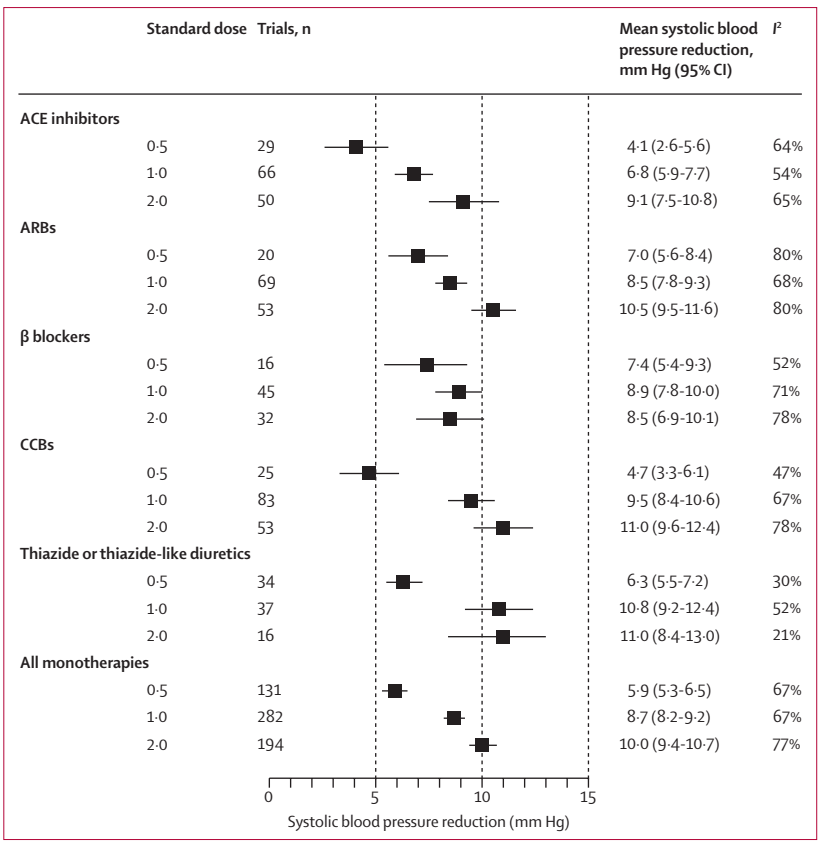


***Figure 1:*** **Mean placebo-corrected systolic blood pressure reductions by drug class and dose**
Boxes represent mean values, and whiskers represent 95% CIs. Estimates are standardised to a baseline systolic blood pressure of 154 mm Hg. ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blocker. CCB=calcium channel blocker.

On average, dual drug combination at one standard dose of each drug was associated with a 14·9 mm Hg (95% CI 13·1–16·8) reduction in systolic blood pressure and a 9·1 mm Hg (8·1–10·2) reduction in diastolic blood pressure (appendix pp 55–58). Doubling the dose of each individual component of the dual combination provided additional reductions in systolic blood pressure and diastolic blood pressure of 2·5 mm Hg (1·4–3·7) and 1·4 mm Hg (0·8–2·1), respectively. Among 37 different permutations of dual combinations at less than one standard dose per drug, 22 (59%) were classified as low-intensity and 15 (41%) were classified as moderate-intensity efficacy. Among 20 different permutations of dual combinations at one standard dose per drug, 16 (80%) were classified as moderate or high intensity. All 13 permutations of dual combinations at more than one standard dose per drug were classified as moderate intensity or high intensity. Among all 189 different dual combinations of any drug and dose, 110 (58%) were classified as having moderate-intensity efficacy and 21 (11%) as having high-intensity efficacy. For triple combination therapy, the mean reduction in blood

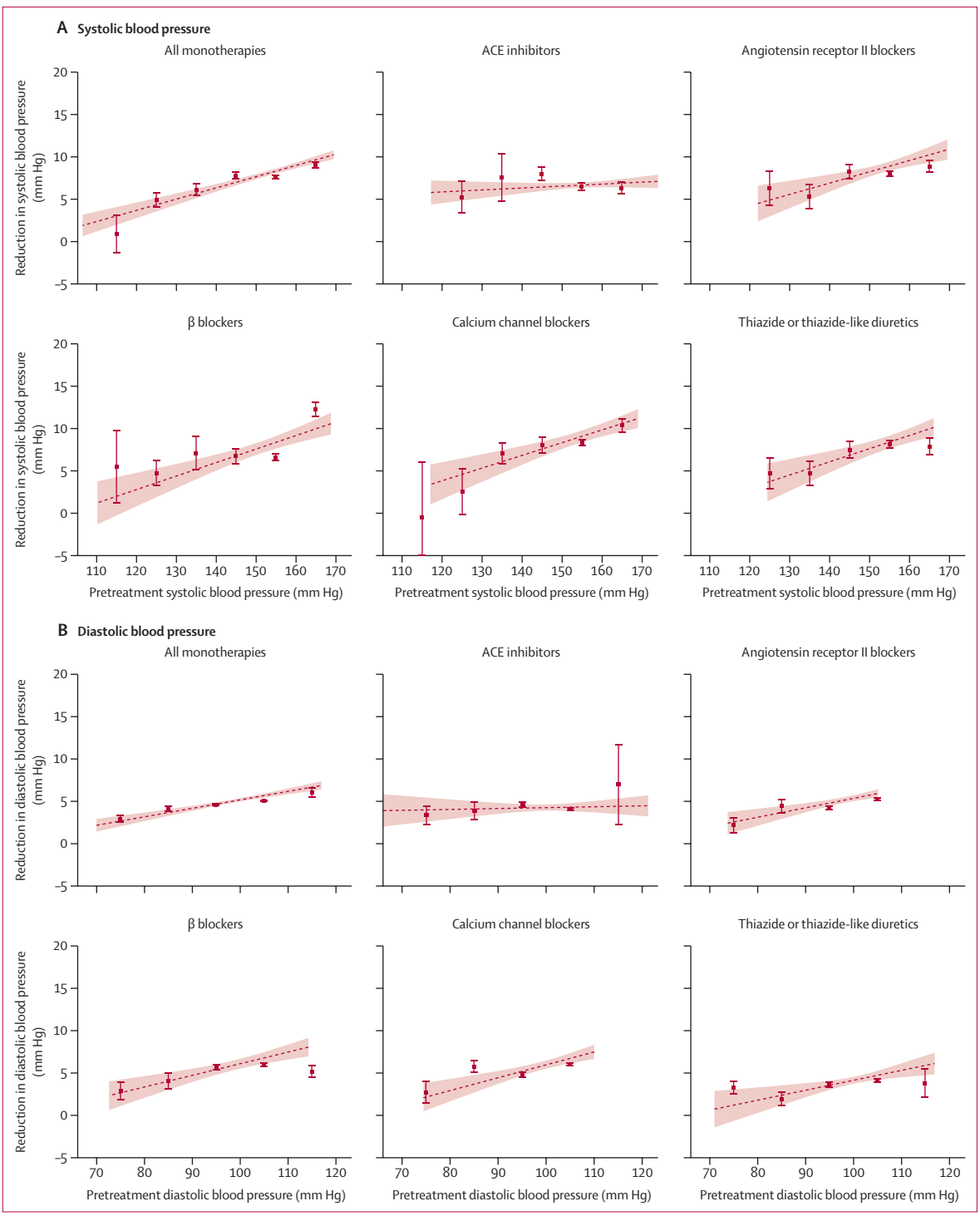


***Figure 2:*** **Associations between pretreatment blood pressure and reductions in systolic blood pressure (A) and diastolic blood pressure (B)**
Boxes represent mean reductions in systolic and diastolic blood pressure and whiskers represent 95% CIs from meta-analyses of available studies, with pretreatment systolic blood pressure strata of 110–119, 120–129, 130–139, 140–149, 150–159 and 160–169 mm Hg and pretreatment diastolic blood pressure strata of 70–79, 80–89, 90–99, 100–109, and 110–119 mm Hg. Regression lines and shaded areas represent meta-regressions and 95% CIs derived from all available trials. ACE=angiotensin-converting enzyme.

For the **online calculator** see www.bpmodel.org

pressure with quarter standard doses was 11·2 mm Hg (95% CI 8·4–14·1) for systolic blood pressure and 6·5 mm Hg (4·4–8·7) for diastolic blood pressure compared with reductions of 13·1 mm Hg (10·0–16·3) and 7·4 mm Hg (5·4–9·4), respectively, with half standard doses. For quadruple therapy with quarter standard doses (from one trial), the mean reductions in systolic blood pressure and diastolic blood pressure were 22·5 mm Hg (16·4–28·6) and 15·4 mm Hg (9·3–21·5), respectively.

Sensitivity analyses after exclusion of comparisons with baseline imbalances in blood pressure (appendix p 59), trials with less than 8 weeks of fixed treatment (appendix p 60), trials at moderate-to-high risk of bias (appendix p 61), and trials with fewer than 50 participants (appendix pp 62–63) showed consistent findings for mean reductions in systolic blood pressure by drug class. Consistent findings were also seen when using a random-effects meta-regression model (appendix pp 64–65).

The expected blood pressure reductions according to baseline blood pressure for any combination of drugs and doses have been made available in an online calculator). The expected systolic blood pressure reductions obtained from the efficacy model were consistent with the reductions observed in an external set of trials of dual drug combination versus placebo ($r$=0·76, p<0·0001, mean bias error=1·2; figure 3). These findings were also consistent across different combinations of drug classes ($r$=0·58–0·90, p<0·0001, mean bias error=2·8–3·2; figure 3). Sensitivity analyses showed that the model performed well for factorial trials of dual combination versus placebo ($r$=0·79, p<0·0001, mean bias error=1·5; appendix p 79). A separate validation of randomised trials of triple versus dual combination therapy also showed good correlation between observed and predicted systolic blood pressure values ($r$=0·68, mean bias error=–0·74; appendix p 81). For some dual combinations of drug classes versus placebo, the observed reductions in systolic blood pressure were greater than the expected reductions; however, this trend was not evident in comparisons of triple versus dual drug combinations. Figure 4 outlines the predicted systolic blood pressure reductions with single, dual, or triple

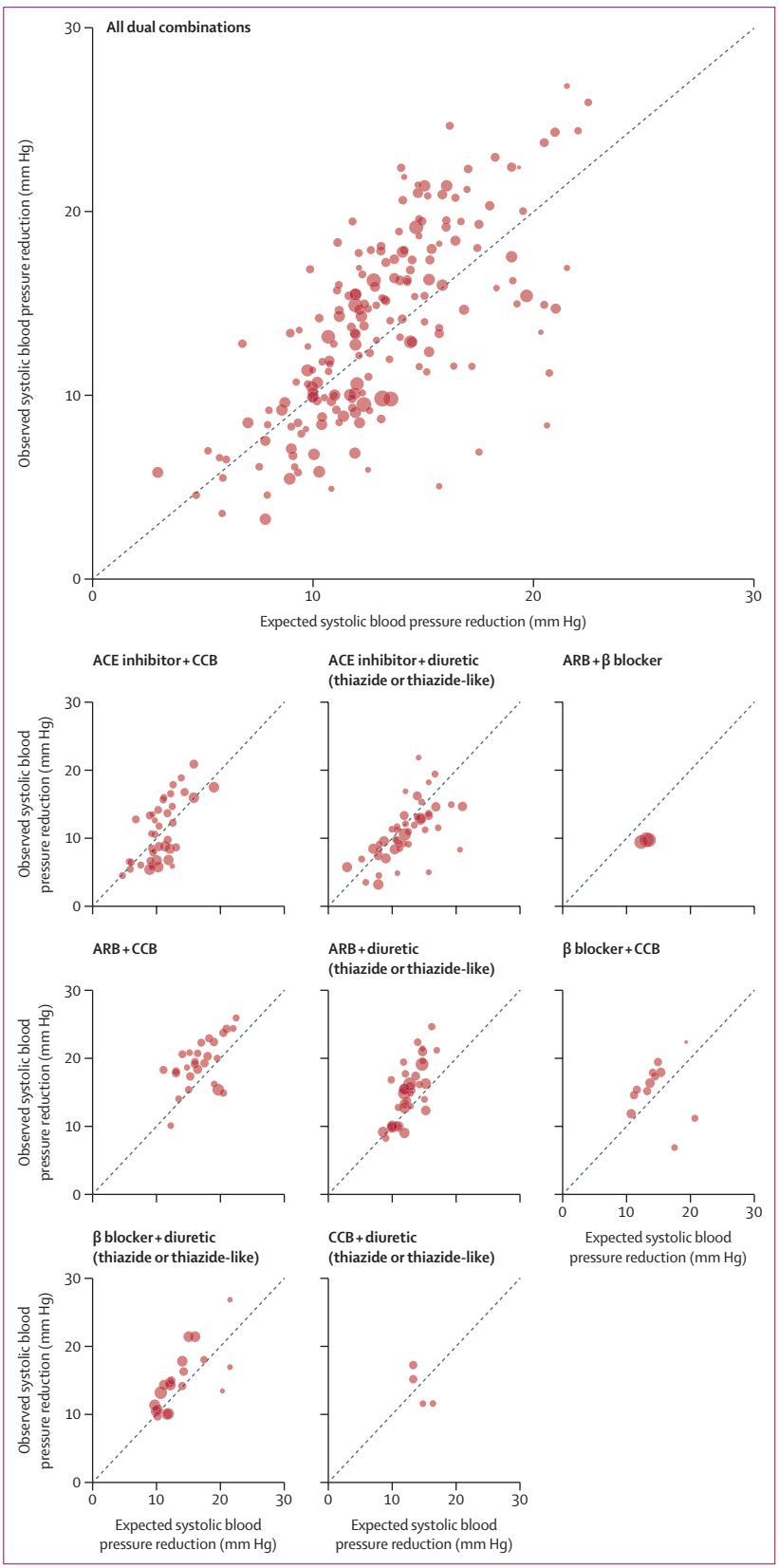


***Figure 3:*** **Expected and observed reductions in systolic blood pressure for dual drug combinations versus placebo**

Expected treatment effects were calculated with derived meta-regressions, adjusting for pretreatment systolic blood pressure and drug dose, and observed treatment effects are the placebo-corrected systolic blood pressure reductions reported in the trials. Circle size is proportional to the inverse variance weighting of each trial. Corresponding correlation coefficients: all combinations, $r$=0·76; ACE inhibitor + CCBs, $r$=0·63; ACE inhibitor + thiazide or thiazide-like diuretics, $r$=0·76; ARB + β blocker, $r$=0·92; ARB + CCB, $r$=0·57; ARB + thiazide or thiazide-like diuretic, $r$=0·73; β blocker + CCB, $r$=0·94; β blocker + thiazide or thiazide-like diuretic, $r$=0·75; CCB + thiazide or thiazide-like diuretic, $r$=0·86. ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blocker. CCB=calcium channel blocker.

| | | None | Losartan | | Lisinopril | | Metoprolol | |
|---|---|---|---|---|---|---|---|---|
| Hydrochlorothiazide | Amlodipine | 0 mg | 50 mg | 100 mg | 10 mg | 20 mg | 50 mg | 100 mg |
| 0 mg | 0 mg | | 7 (6–8) | 8 (7–9) | 7 (6–8) | 10 (7–11) | 7 (5–8) | 7 (6–8) |
| 0 mg | 5 mg | 9 (8–10) | 15 (13–16) | 16 (14–17) | 15 (13–16) | 18 (15–19) | 15 (13–16) | 15 (14–17) |
| 0 mg | 10 mg | 12 (10–15) | 18 (15–19) | 19 (16–21) | 18 (16–20) | 21 (17–22) | 18 (16–20) | 18 (16–21) |
| 12·5 mg | 0 mg | 6 (5–7) | 12 (11–13) | 13 (12–14) | 12 (11–13) | 15 (13–16) | 12 (11–13) | 12 (11–14) |
| 12·5 mg | 5 mg | 14 (13–15) | 19 (17–20) | 20 (18–21) | 20 (18–21) | 22 (19–24) | 19 (17–21) | 20 (17–21) |
| 12·5 mg | 10 mg | 17 (15–19) | 22 (19–24) | 23 (20–25) | 22 (20–24) | 25 (21–27) | 22 (19–24) | 22 (19–24) |
| 25 mg | 0 mg | 8 (7–9) | 14 (12–15) | 15 (13–16) | 14 (12–15) | 17 (15–18) | 14 (12–15) | 14 (12–15) |
| 25 mg | 5 mg | 16 (14–17) | 21 (19–22) | 22 (19–23) | 21 (19–22) | 24 (21–25) | 21 (19–22) | 21 (18–23) |
| 25 mg | 10 mg | 19 (17–21) | 23 (20–25) | 24 (21–26) | 24 (21–25) | 26 (22–28) | 23 (20–25) | 23 (20–25) |

**Efficacy**
Low intensity | Moderate intensity | High intensity

***Figure 4:*** **Predicted reductions in systolic blood pressure for different combinations of five antihypertensives at different doses as single, dual, or triple therapy for a baseline systolic blood pressure of 154 mm Hg**
Mean (95% prediction intervals) systolic blood pressure reduction was estimated by adding the expected blood pressure reduction from derived meta-regression equations for the respective monotherapy components, accounting for a lower baseline blood pressure for the second or third components. Different colours indicate efficacy intensity: low (red), moderate (yellow), and high (green) correspond to systolic blood pressure reductions of <10 mm Hg, 10–19·9 mm Hg, and ≥20 mm Hg, respectively, from a baseline of 154 mm Hg, with darker shades corresponding to greater reductions. Mean reductions are larger for higher baseline blood pressures and smaller for lower baseline blood pressures.

combinations of the five most prescribed antihypertensive drugs. Monotherapy was generally associated with low-intensity efficacy (systolic blood pressure reduction <10·0 mm Hg) with a few exceptions, such as amlodipine 10 mg, being classified as moderate intensity. All dual and triple therapies were associated with moderate-intensity (10·0–19·9 mm Hg) or high-intensity efficacy (≥20·0 mm Hg).

## Discussion

This systematic review and meta-analysis provides robust estimates of expected blood pressure reductions for antihypertensive drugs and their combinations from 484 double-blind placebo-controlled randomised trials, showing clinically relevant differences in expected efficacy by drug, dose, and baseline blood pressure. Given the many thousands of possible drug–dose permutations, we propose a high-level categorisation of treatment regimens, with low, moderate, or high intensity defined as systolic blood pressure-lowering efficacy of <10 mm Hg, 10–19 mm Hg, and ≥20 mm Hg, respectively, from a pretreatment systolic blood pressure of 154 mm Hg. We have also made available an online calculator that provides the trial-derived estimates of efficacy for any drug and dose combination.

Current hypertension guidelines do not refer specifically to the expected efficacy of different doses or combinations of antihypertensive drugs.[4,7] There are two main reasons for this omission. First, a widely held perception is that reliable blood pressure measurements are sufficient to assess individual treatment response, so the average response from trials is not required. However, as intra-individual blood pressure variability (whether with clinic, home, or ambulatory measurement) far exceeds inter-individual differences in treatment response, the signal-to-noise ratio is typically dominated by noise for individuals.[18–22] Second, there are thousands of drug–dose permutations, making the data challenging to collate and present in a digestible format. To address this complexity, the therapeutic intensity score—which estimates efficacy on the basis of the total sum of the standard dose of each antihypertensive drug—was developed.[23] However, this method incorrectly assumes that increasing the dose of a monotherapy is as efficacious as adding a second drug and does not capture any difference in efficacy across drugs or by baseline blood pressure or directly give an expected efficacy in terms of mm Hg reduction.[23] For these reasons, the therapeutic intensity score provides an inaccurate estimate of blood pressure-lowering efficacy compared with placebo-corrected randomised trial estimates and has not been widely adopted.[24] Our online calculator provides robust estimates of expected blood pressure reductions observed in randomised clinical trials according to baseline blood pressure and different doses and combinations of drugs.

Our overall results are broadly consistent with previous estimates of efficacy for specific drug classes. In 2003, Law and colleagues[14] reported that one standard dose of an antihypertensive drug conferred an average blood pressure reduction of 9/6 mm Hg and that each 10 mm Hg increment in baseline systolic blood pressure was associated with a 1·0 mm Hg greater reduction in systolic blood pressure. However, these previous analyses pre-dated many of the trials included in this review and present little information on variations in efficacy between drugs, drug classes, and baseline blood pressure. We identified differences in efficacy between drug classes and between drugs within the same class, many of which were clinically relevant in size since differences in blood pressure-lowering efficacy of even a few mm Hg translate to important differences in risk of major adverse cardiovascular events.[3] In terms of

potential effect modifiers, we did not find evidence for substantial heterogeneity according to background antihypertensive use. There was also no meaningful improvement in regression models after inclusion of trial-level average age or sex after accounting for baseline blood pressure, drug, and drug dose. These findings are supported by long-term blood pressure-lowering randomised trials showing that the benefits of blood pressure reduction on cardiovascular events are consistent across age, sex, and background blood pressure-lowering treatment.[25–28]

Our findings have several implications for clinical practice. First, these results provide the basis for more evidence-informed prescribing, allowing clinicians to choose an antihypertensive regimen that will, on average, have the desired blood pressure-lowering efficacy. For example, for those patients with systolic blood pressure ≥20 mm Hg higher than the desired long-term average value, a high-intensity treatment regimen would be preferred.[29] Second, these results confirm and extend the conclusion that the key determinant of efficacy is the number of drug classes.[24,30] For example, doubling the dose of monotherapy increases efficacy by only 1–2 mm Hg, whereas adding a second drug class is around four times more effective. However, other factors are also relevant. For example, for patients with a baseline systolic blood pressure of 165 mm Hg, ramipril 5 mg and hydrochlorothiazide 25 mg are expected to confer average systolic blood pressure reductions of 6 mm Hg and 10 mm Hg, respectively; however, for those with a baseline of 135 mm Hg, both drugs would confer a reduction of 4–5 mm Hg. We found consistent blood pressure-lowering efficacy between trials with and without background antihypertensive treatment. This observation is consistent with previous findings that combination blood pressure-lowering can be reliably estimated by adding the effects of the individual components after adjusting for pretreatment blood pressure and extends that finding for multiple drug classes and triple therapy.[31]

Although blood pressure responses to antihypertensives can be heterogeneous,[32] we do not currently have the tools to ascertain these modest differences with adequate precision.[18–20,33] For patients willing and able to undergo repeated n-of-1, placebo-controlled crossover trials accompanied by repeated ambulatory blood pressure monitoring, it is possible to identify monotherapies that would improve systolic blood pressure lowering by an average of 4 mm Hg.[32] Nonetheless, monotherapy would still be in the low intensity category for the vast majority of patients. Finally, it is worth noting that the blood pressure-lowering estimates presented in this Article reflect short-term effects (mean trial duration of 9 weeks), which are the expected maximum blood pressure reductions with high levels of adherence. Adherence to blood pressure-lowering and other cardiovascular medicines often declines steeply over time.[34]

Several limitations should be considered. This study was a trial-level meta-analysis, which limited our ability to identify all potential effect modifiers, such as BMI and race or ethnicity. Future iterations of this model involving individual participant data would allow addition of other effect modifiers. Some studies have suggested that some antihypertensives, such as ACE inhibitors, might be associated with less blood pressure reduction in Black individuals than in individuals of other ethnicities, although findings are highly varied and include unbalanced comparisons.[35–41] For combination antihypertensive therapies, variations in blood pressure response among different racial or ethnic groups seem even less pronounced.[42,43] Analyses from large-scale randomised trials of blood pressure-lowering therapies have not identified any meaningful heterogeneity in terms of cardiovascular risk reduction between important subgroups such as age, sex, BMI, atrial fibrillation, race or ethnicity, and cardiovascular disease, suggesting that these factors are unlikely to be major effect modifiers.[3,25,26,44,45] The efficacy calculator provides estimates of the average expected blood pressure response, and inaccuracies inevitably exist. For example, the relationship between baseline blood pressure and treatment response appears non-linear for some drug classes. Although we were unable to improve model fit with non-linear regressions, access to individual patient data might improve future iterations of the model. Results for other antihypertensives, active comparisons, and tolerability will be assessed in subsequent updates. Finally, our systematic literature search was limited to studies published in English only.

In conclusion, this Article provides placebo-corrected blood pressure reductions for antihypertensives according to drug class, drug, dose, and baseline blood pressure, with an accompanying online calculator. We propose that these estimates should be used to classify blood pressure-lowering drug regimens in terms of intensity. These findings should have a role in informing prescribing decisions to mitigate the poor control rates among people treated for hypertension globally.[46]

#### Contributors

NW, AR, and AS—conception, design, data acquisition and interpretation, and drafting the manuscript. NW and RP—design, data analysis, and interpretation. KV, RD, FH, PK, HE, and RK—data acquisition and interpretation. AK—data management. NW, SRG, PKW, BE, AES, KR, OB, and AR—data interpretation. All authors had access to the data. All authors critically reviewed the manuscript. NW, RP, AS, and AR verified and had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

George Institute Ventures, the social enterprise arm of The George Institute for Global Health, has received investment to develop fixed-dose combination products, including combinations of blood pressure-lowering drugs. All staff employed by The George Institute have an institutional interest to declare with respect to George Institute Ventures; none of The George Institute staff have a financial interest in these investments or patents. NW is supported by the Heart Foundation post-doctoral fellowship 108288–2024_PDF. AES has received consulting fees and/or speaker honoraria from Omron Healthcare, Aktiia, Medtronic, Servier, Abbott, Sanofi, Sun Pharmaceuticals, and Novartis and is

supported by an investigator grant from the National Health and Medical Research Council of Australia (GNT 2017504). AR is employed by The George Institute for Global Health and Imperial College London and seconded part-time to George Medicines. The George Institute has submitted patent applications in respect of low fixed-dose combination products for the treatment of cardiovascular or cardiometabolic disease, with AR listed as one of the inventors (granted: US 10,369,156; US 10,799,487; US 10,322,117; US 11,033,544; and US 11,478,462; pending: US 17/932,982; US 18/446,268; US 17/598,122; and US 17/317,614); AR does not have a financial interest in these patent applications or investments. AR has served on a data and safety monitoring board for a trial sponsored by Idorsia and is supported by an investigator grant from the National Health and Medical Research Council of Australia (GNT 1160734). OB has an active research grant paid to his institution, The George Institute for Global Health, from Bayer and has received previous research grants to former institutions from Amgen, Servier, Novartis, and Pfizer. All other authors declare no competing interests.

### Data sharing

All study-level data underlying the results reported in this Article will be made available on reasonable request. Researchers who request access to the data should provide a methodologically sound proposal to the corresponding author. Data requestors will need to sign a data access agreement.

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