Efficacy and safety of a novel low-dose triple single-pill combination of telmisartan, amlodipine and indapamide, compared with dual combinations for treatment of hypertension: a randomised, double-blind, active-controlled, international clinical trial

Anthony Rodgers, Abdul Salam, Aletta E Schutte, William C Cushman, H Asita de Silva, Gian Luca Di Tanna, Diederick E Grobbee, Krzysztof Narkiewicz, Dike B Ojji, Neil R Poulter, Markus P Schlaich, Suzanne Oparil, Wilko Spiering, Bryan Williams, Jackson T Wright Jr, P Lakshman, W Uluwattage, P Hay, T Pereira, N Amarasena, G Ranasinghe, Chris Gianacas, Mathangi Shanthakumar, Xiaoqiu Liu, Nelson Wang, Sonali R Gnanenthiran, Paul K Whelton, on behalf of the GMRx2 Investigators

Lancet 2024; 404: 1536–46

See **Comment** page 1496

The George Institute for Global Health, University of New South Wales, Barangaroo, NSW, Australia (Prof A Rodgers PhD, A Salam PhD, Prof A E Schutte PhD, C Gianacas MBiostat, M Shanthakumar MSc, X Liu PhD, N Wang PhD, S R Gnanenthiran PhD); **Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal, India** (A Salam); **University of Tennessee Health Science Center, Memphis, TN, USA** (Prof W C Cushman MD); **Clinical Trials Unit, Faculty of Medicine, University of Kelaniya, Kelaniya, Sri Lanka** (Prof H A de Silva DPhil); **University of Applied Sciences and Arts of Southern Switzerland, Manno, Switzerland** (Prof G L Di Tanna PhD); **Julius Global Health, Julius Center for Health Sciences and Primary Care** (Prof D E Grobbee MD) **and Department of Vascular Medicine** (W Spiering PhD), **University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands; Medical University of Gdańsk, Gdańsk, Poland** (Prof K Narkiewicz PhD); **University of Abuja, Abuja, Nigeria** (D B Ojji PhD); **Imperial College London, London, UK** (Prof N R Poulter FMedSci, Prof A Rodgers); **The University of Western Australia, Perth, WA, Australia** (Prof M P Schlaich MD); **University of Alabama at Birmingham, Birmingham, AL, USA** (Prof S Oparil PhD);

Summary

Background Single-pill combinations (SPCs) of three low-dose antihypertensive drugs can improve hypertension control but are not widely available. A key issue for any combination product is the contribution of each component to efficacy and tolerability. This trial compared a new triple SPC called GMRx2, containing telmisartan, amlodipine, and indapamide, with dual combinations of components for efficacy and safety.

Methods In this international, randomised, double-blind, active-controlled trial, we enrolled adults with hypertension receiving between zero and three antihypertensive drugs, with a screening systolic blood pressure (SBP) ranging from 140–179 mm Hg (on no drugs) to 110–150 mm Hg (on three drugs). Participants were recruited from Australia, the Czech Republic, New Zealand, Poland, Sri Lanka, the UK, and the USA. In a 4-week active run-in, existing medications were switched to GMRx2 half dose (telmisartan 20 mg, amlodipine 2·5 mg, and indapamide 1·25 mg). Participants were then randomly allocated (2:1:1:1) to continued GMRx2 half dose or to each possible dual combination of components at half doses (telmisartan 20 mg with amlodipine 2·5 mg, telmisartan 20 mg with indapamide 1·25 mg, or amlodipine 2·5 mg with indapamide 1·25 mg). At week 6, doses were doubled in all groups, unless there was a clinical contraindication. The primary efficacy outcome was mean change in home SBP from baseline to week 12, and the primary safety outcome was withdrawal of treatment due to an adverse event from baseline to week 12. Secondary efficacy outcomes included differences in clinic and home blood pressure levels and control rates. This study is registered with ClinicalTrials.gov, NCT04518293, and is completed.

Findings The trial was conducted between July 9, 2021 and Sept 1, 2023. We randomly allocated 1385 participants to four groups: 551 to GMRx2, 276 to telmisartan–indapamide, 282 to telmisartan–amlodipine, and 276 to amlodipine–indapamide groups. The mean age was 59 years (SD 11), 712 (51%) participants self-reported as female and 673 (48·6%) male, and the mean clinic blood pressure at the screening visit was 142/85 mm Hg when taking an average of 1·6 blood pressure medications. Following the run-in on GMRx2 half dose, the mean clinic blood pressure level at randomisation was 133/81 mm Hg and the mean home blood pressure level was 129/78 mm Hg. At week 12, the mean home SBP was 126 mm Hg in the GMRx2 group, which was lower than for each of the dual combinations: –2·5 (95% CI –3·7 to –1·3, p<0·0001) versus telmisartan–indapamide, –5·4 (–6·8 to –4·1, p<0·0001) versus telmisartan–amlodipine, and –4·4 (–5·8 to –3·1, p<0·0001) versus amlodipine–indapamide. For the same comparisons, differences in clinic blood pressure at week 12 were 4·3/3·5 mm Hg, 5·6/3·7 mm Hg, and 6·3/4·5 mm Hg (all p<0·001). Clinic blood pressure control rate below 140/90 mm Hg at week 12 was superior with GMRx2 (74%) to with each dual combination (range 53–61%). Withdrawal of treatment due to adverse events occurred in 11 (2%) participants in the GMRx2 group, four (1%) in telmisartan–indapamide, three (1%) in telmisartan–amlodipine, and four (1%) in amlodipine–indapamide, with none of the differences being statistically significant.

Interpretation A novel low-dose SPC product of telmisartan, amlodipine, and indapamide provided clinically meaningful improvements in blood pressure reduction compared with dual combinations and was well tolerated. This SPC provides a new therapeutic option for the management of hypertension and its use could result in a substantial improvement in blood pressure control in clinical practice.

Funding George Medicines.

University College London, London, UK (Prof B Williams FMedSci); **University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH, USA** (Prof J T Wright Jr PhD); **Jaffna Teaching Hospital, Jaffna, Sri Lanka** (P Lakshman MD); **Karapitiya Teaching Hospital, Galle, Sri Lanka** (W Uluwattage FRCP); **Castle Hill Medical Centre, Sydney, NSW, Australia** (P Hay FRACGP); **Colombo South Teaching Hospital, Kalubowila, Sri Lanka** (T Pereira MD); **Teaching Hospital Sri Jayawardenapura, Sri Jayawardenapura, Sri Lanka** (N Amarasena MD); **Cardiology Institute, National Hospital, Colombo, Sri Lanka** (G Ranasinghe MD); **Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA** (Prof P K Whelton MD)

Correspondence to:
Prof Anthony Rodgers, The George Institute for Global Health, University of New South Wales, Barangaroo 2000, NSW, Australia
arodgers@georgeinstitute.org

Introduction

Globally, most people treated for high blood pressure do not have sustained blood pressure control, primarily due to continued use of low-efficacy regimens such as monotherapy.[1–4] Recent hypertension guidelines[3–6] recommend combinations of two blood pressure-lowering drugs as an initial treatment for most individuals. These recommendations were based on evidence that dual combinations give better blood pressure control, improve adherence, and reduce therapeutic inertia compared with monotherapy, without notable increases in adverse effects.[7–10] These guidelines also typically recommend earlier use of triple drug antihypertensive therapy, ideally as a single-pill combination (SPC). Currently available triple-drug SPCs are only indicated for substitution among individuals already taking all the three component drugs, or among those with inadequate blood pressure control on two of the component drugs.[11–13] Furthermore, there are no existing SPC products with low doses of an angiotensin-II receptor blocker, a calcium channel blocker, and a thiazide-like diuretic. To address this unmet need, a new triple SPC of telmisartan, amlodipine, and indapamide, named GMRx2, was developed. One crucial aspect of developing SPCs is to assess the contribution of each component drug to efficacy and safety. We therefore conducted a trial among adults with hypertension to compare GMRx2 with each of the three dual components for blood pressure-lowering efficacy and safety.

Methods

Study design

In this international, randomised, double-blind, active-controlled, parallel-group trial, following a 4-week single-blind, active run-in, eligible participants were randomly allocated to a 12-week treatment period to investigate the efficacy and safety of GMRx2 compared with dual combinations of the component drugs in adults with high blood pressure. Participants were recruited from 83 clinics or hospital-based outpatient departments or primary care centres that provide hypertension care in Australia, the Czech Republic, New Zealand, Poland, Sri Lanka, the UK, and the USA. Ethics committee approvals were from: the Metro South Hospital and Health Services Human Research Ethics Committee in Australia; the Health and Disability Ethics Committees in New Zealand; the Ethics Committee of IKEM and Thomayer Hospital and Ethics Committee Edumed in the Czech Republic; the Bioethics Committee for Scientific Research at the Medical University of Gdańsk in Poland;

Research in context

Evidence before this study

We conducted an updated systematic review of randomised trials that compared triple-combination with dual-combination blood pressure-lowering drugs. Through searching MEDLINE, Cochrane Central Register of Controlled Trials, and the US Food and Drug Administration website from database inception to Dec 31, 2023, we identified randomised, double-blind trials involving adults with hypertension that compared triple versus dual combinations of antihypertensive drugs from five major classes (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β blockers, and diuretics) over a minimum of 4 weeks. Primary outcomes were reduction in blood pressure and withdrawal of treatment due to adverse events. Meta-analyses were conducted using a random-effects model. 24 trials (15533 participants) were included, and baseline systolic/diastolic blood pressure averaged 161/100 mm Hg in trials among people not on treatment and 150/94 mm Hg among people receiving dual therapy. Of the 58 triple-combination versus dual-combination comparisons, 53 (91%) involved one or more standard-dose or maximal-dose components. Overall, triple combination reduced clinic blood pressure by 5·1/3·7 mm Hg compared with dual combination (p<0·001 for both) and improved blood pressure control at 140/90 mm Hg from 54% to 69% (p<0·0001). Overall, mean final blood pressure was 134/83 mm Hg for triple versus 140/85 mm Hg for dual combination. Incidence of withdrawal of treatment due to adverse events was 4·2% versus 2·9% (relative risk 1·9 [95% CI 1·3–2·4], p=0·0042).

Added value of this study

This study provides the first large-scale comparison of triple half-dose versus dual half-dose combinations of any polypill, showing that the average triple versus dual blood pressure reduction of 4·6/2·8 mm Hg is clinically and statistically significantly superior. This trial also assesses the efficacy and tolerability of triple-combination therapy at baseline blood pressure levels considerably lower than those in previous trials. This is of relevance to the increasing emphasis in guideline recommendations on lower blood pressure targets and hence treatment initiation or intensification for individuals at lower blood pressure levels.

Implications of all the available evidence

Treatment with three or more blood pressure-lowering drugs is needed for many individuals to reach and maintain a target blood pressure of below 140/90 mm Hg and for most individuals to reach targets of below 130/80 mm Hg. The addition of a third drug to dual therapy leads to a clinically significant increase in blood pressure control rates and is well tolerated.

the Ethics Review Committee, Faculty of Medicine, University of Kelaniya, Sri Lanka; the South Central Oxford B Research Ethics Committee in the UK; and Advarra and the University of Tennessee Health Science Center Institutional Review Board in the USA. This study is registered with ClinicalTrials.gov, NCT04518293.

Participants

See Online for appendix 1

Full eligibility criteria are given in the protocol (appendix 1 pp 18–20). Participants were eligible if they were aged 18 years or older, had been diagnosed with hypertension, and provided signed consent to participate. Additionally, at the screening visit, clinic systolic blood pressure (SBP) had to be 140–179 mm Hg on no blood pressure-lowering drugs, 130–170 mm Hg on one blood pressure-lowering drug, 120–160 mm Hg on two blood pressure-lowering drugs, or 110–150 mm Hg on three blood pressure-lowering drugs. Following the 4-week active run-in on GMRx2 half dose (telmisartan 20 mg, amlodipine 2·5 mg, and indapamide 1·25 mg), participants were eligible for randomisation if their home SBP in the preceding week was 110–154 mm Hg, their adherence to the run-in medication was 80–120%, the treatment was tolerated, and the participants adhered to their home blood pressure monitoring schedule. During the first 15 months of trial conduct, the home SBP range for eligibility was 120–154 mm Hg, but the protocol was amended to allow an SBP of 110–154 mm Hg given the high proportion of individuals with SBP levels below 120 mm Hg during their run-in. Exclusion criteria included: treatment with four or more antihypertensive drugs, or use of antihypertensive drugs for indications other than hypertension (eg, heart failure); contraindication to the study medications; history of any established cardiovascular disease, uncontrolled diabetes, or kidney disease (eg, estimated glomerular filtration rate [eGFR] <60 mL/min per 1·73 m²); a known secondary cause of hypertension; childbearing potential; factors that would adversely affect trial participation, such as a physical or mental health condition, night shifts, or history of alcohol or drug abuse during the preceding 12 months; or an arm circumference that was too large or too small for the available blood pressure measurement cuffs.

Randomisation and masking

After a screening visit, eligible participants were switched from existing antihypertensive drugs to run-in on GMRx2 half dose. Following the run-in, eligible participants were randomly allocated (2:1:1:1) to continue GMRx2 half dose or to receive telmisartan 20 mg with indapamide 1·25 mg, telmisartan 20 mg with amlodipine 2·5 mg, or amlodipine 2·5 mg with indapamide 1·25 mg in a double-blind manner using capsules with an identical appearance for 6 weeks. At the week 6 visit, all of the doses were doubled (ie, to GMRx2 standard dose, telmisartan 40 mg with amlodipine 5 mg, telmisartan 40 mg with indapamide 2·5 mg, or amlodipine 5 mg with indapamide 2·5 mg) for a further 6 weeks, unless the investigator believed there was a specific contraindication for a particular participant, such as symptomatic hypotension or a very low home or clinic blood pressure (eg, SBP <100 mm Hg). Participants were advised to take one capsule of trial medication in the morning at approximately the same time each day (either before or after breakfast), immediately after taking their morning home blood pressure measurements. A random-sequence treatment allocation procedure was incorporated into an online electronic data capture application by the unmasked study statistician. Neither the investigators nor site staff had access to the randomisation sequence. Participants meeting the eligibility criteria for randomisation were randomly allocated in the online electronic data capture application. The application generated the randomisation record with the participant identification number, date, and time. After completion of the double-blind treatment period at week 12, participants were switched to non-trial medication as per local guidelines and practice.

Procedures

From the beginning of the run-in period until the end of the double-blind period, participants measured their blood pressure at home, following procedures outlined in printed instructions informed by American Heart Association recommendations[14] with reference to recent trials and clinical use given to the participants.[15,16] Each participant was supplied with a FORA D40g blood pressure machine (also known as Medisanté BP800 machine; Taidoc Technology, New Taipei City, Taiwan), which is a validated, electronic, automatic, digital upper-arm cuff monitor. Blood pressure readings were encrypted and transferred automatically to the trial database over the Global System for Mobile communication cellular network. Home blood pressure was to be measured: on four consecutive days immediately preceding a trial visit, and once a week on other weeks; in triplicate in the morning and in the evening; and in the morning immediately before the next trial medication dose. Blood pressure was measured with the participant in a seated position during all scheduled trial visits, using the same machine and a standard procedure, specified in the protocol (appendix 1 pp 21–23) and instruction manual.

Outcomes

The primary efficacy outcome was difference between GMRx2 and each of the dual combinations in home seated mean SBP change from randomisation to week 12. At the outset of the trial, the primary outcome was clinic blood pressure, but this was switched, before randomisation began, to home blood pressure at the beginning of the COVID-19 pandemic. Secondary efficacy outcomes were differences in clinic blood pressure and home diastolic blood pressure (DBP) changes, and proportion of participants with blood pressure control

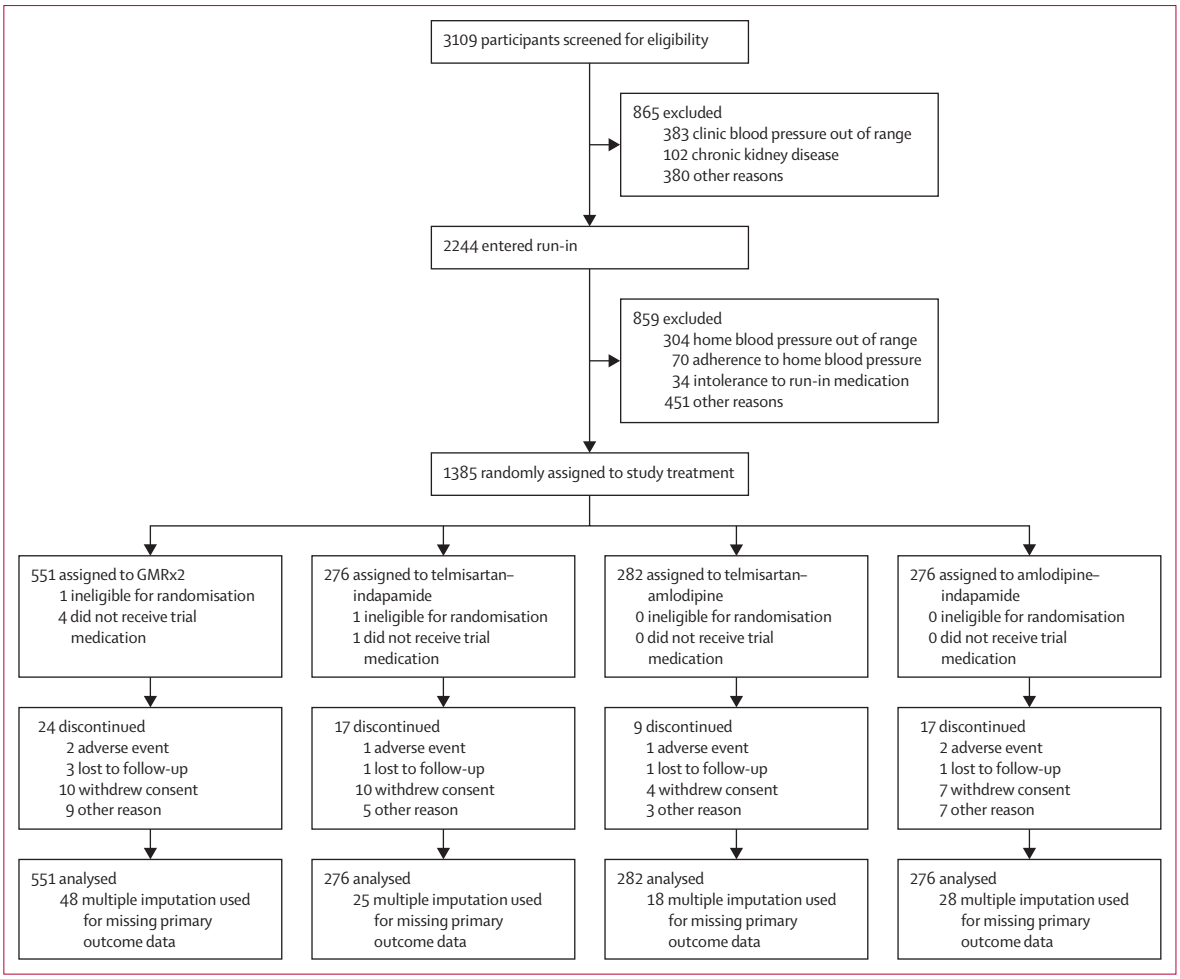


Figure 1: **CONSORT diagram**

(clinic blood pressure <140/90 mm Hg and <130/80 mmHg; home blood pressure <135/85 mm Hg and <130/80 mm Hg, including at trough), at weeks 6 and 12. The primary safety outcome was percentage of participants discontinuing trial medication due to an adverse event from randomisation to week 12. The secondary safety outcomes were proportion of participants discontinuing trial medication due to an adverse event from randomisation to week 6, and proportion of participants with serious adverse events, symptomatic hypotension, hyponatraemia or hypernatraemia, hypokalaemia or hyperkalaemia abnormalities, eGFR drop of more than 30%, or orthostatic hypotension or hypertension at weeks 6 and 12. Other than serious adverse events, only data on adverse events of special interest were collected. An adverse event of special interest was defined as the following set of adverse events: symptomatic hypotension; abnormal laboratory findings of sodium, potassium, uric acid, glucose, lipids, creatinine, or eGFR; headache; peripheral oedema; or any other symptom or laboratory abnormality that led to permanent discontinuation of trial medication.

Statistical analysis

A total of 1385 randomly assigned participants provided more than 97% power to detect a minimum clinically significant difference of 3 mm Hg in home mean SBP for each of the three comparisons of GMRx2 versus dual therapy, assuming an analysis of covariance-type approach, a common SD of home SBP of 11 mm Hg, and a correlation coefficient of 0·4. The overall power for all three comparisons was therefore more than 90% ($0 \cdot 97^3 = 0 \cdot 91$). A sample size of 1500 was originally planned. However, continued supply of study treatment became unfeasible due to COVID-19 pandemic-related delays; a review of study power, based on the prespecified statistical approach and a blinded assessment of the SD of the overall sample, indicated that 1385 participants would have sufficient statistical power. All tests were two-sided with a nominal level of α set at 5%. Because the purpose of the trial was to show effects on all three of the designated primary efficacy endpoint comparisons simultaneously (ie, superiority was required for all three GMRx2 *vs* dual comparisons for the trial to be regarded as positive), there was no need for adjustment of the

	GMRx2 (N=551)	Telmisartan–indapamide (N=276)	Telmisartan–amlodipine (N=282)	Amlodipine–indapamide (N=276)
Age, years	59 (11)	59 (10)	59 (11)	59 (11)
Sex				
Female	276 (50%)	143 (52%)	145 (51%)	148 (54%)
Male	275 (50%)	133 (48%)	137 (49%)	128 (46%)
Weight, kg	79 (21)	79 (21)	78 (20)	78 (21)
Height, cm	165 (11)	165 (12)	165 (11)	164 (12)
BMI, kg/m²	29 (6)	29 (6)	29 (6)	29 (6)
Race				
American Indian or Alaskan Native	0	0	1 (<1%)	0
Asian	272 (49%)	132 (48%)	135 (48%)	134 (49%)
Black or African American	30 (5%)	13 (5%)	11 (4%)	16 (6%)
Native Hawaiian or Other Pacific Islander	2 (<1%)	3 (1%)	3 (1%)	1 (<1%)
White	246 (45%)	128 (46%)	132 (47%)	125 (45%)
Other	1 (<1%)	0	0	0
Ethnicity				
Non-Hispanic or Latino	487 (88%)	246 (89%)	250 (89%)	241 (87%)
Hispanic or Latino	63 (11%)	30 (11%)	31 (11%)	35 (13%)
Country				
Australia	54 (10%)	25 (9%)	26 (9%)	25 (9%)
Czech Republic	4 (<1%)	3 (1%)	2 (<1%)	2 (<1%)
New Zealand	8 (1%)	4 (1%)	4 (1%)	4 (1%)
Poland	4 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)
Sri Lanka	260 (47%)	128 (46%)	131 (46%)	127 (46%)
UK	138 (25%)	72 (26%)	73 (26%)	68 (25%)
USA	83 (15%)	42 (15%)	44 (16%)	49 (18%)
Education				
No formal education	10 (2%)	6 (2%)	2 (<1%)	1 (<1%)
Primary school	109 (20%)	61 (22%)	53 (19%)	51 (18%)
Secondary school	229 (42%)	100 (36%)	124 (44%)	126 (46%)
Tertiary education	133 (24%)	71 (26%)	79 (28%)	66 (24%)
Vocational training	70 (13%)	38 (14%)	24 (9%)	32 (12%)
Smoking				
Never	431 (78%)	198 (72%)	207 (73%)	211 (76%)
Ex-smoker	92 (17%)	64 (23%)	60 (21%)	50 (18%)
Current smoker	28 (5%)	14 (5%)	15 (5%)	15 (5%)
Alcohol consumption				
Currently drink alcohol	179 (32%)	96 (35%)	101 (36%)	105 (38%)
Standard drinks per week	7 (8)	9 (8)	8 (8)	7 (8)
Prescreening electrocardiogram				
Normal	402 (73%)	215 (78%)	214 (76%)	210 (76%)
Hypertension status				
Clinic blood pressure <140/90 mm Hg at screening	197 (36%)	96 (35%)	92 (33%)	104 (38%)
Clinic blood pressure <140/90 mm Hg at randomisation	356 (65%)	188 (68%)	181 (64%)	171 (62%)
Home blood pressure <135/85 mm Hg at randomisation	352 (64%)	168 (61%)	176 (62%)	160 (58%)

(Table 1 continues on next page)

type I error for the primary endpoint.[17] Additionally, the secondary efficacy parameters measured different aspects of the same underlying treatment effect, that is, the effect of GMRx2 compared with dual combinations on blood pressure, and do not show additional new treatment effects of the drug but rather clarify the effect already shown by the primary analysis. Therefore, no type I error adjustment was conducted to account for multiplicity for secondary efficacy endpoint analyses.

An independent data and safety monitoring board had responsibility for safeguarding the interests of participants by reviewing interim safety and efficacy data. A statistical analysis plan was finalised and published before database lock (appendix 2 pp 1–42). We used the estimand framework,[18] with a treatment policy strategy as a primary estimand, which most closely aligns to an intention-to-treat analysis in which all available and imputed data contribute towards the estimated treatment effects, irrespective of intercurrent events. The population for the primary estimand included adults with hypertension, the variable of interest was difference between baseline and week 12 home SBP, and the primary analysis was performed on the randomised set, which included all participants who were randomly assigned to treatment. Intercurrent events (that is, post-randomisation events that affect either the interpretation or existence of outcome data) were defined ahead of data lock in the statistical analysis plan.

Baseline characteristics by treatment group were summarised descriptively. To calculate home blood pressure averages, the first measurement from each of the home blood pressure triplicates was dropped and the remaining measurements were averaged for each participant (appendix 2 pp 1–42). The primary analysis was performed using a mixed model with repeated measures, including week 6 and week 12 measurements with baseline blood pressure, visit, treatment group, and visit by treatment group interaction as fixed effects, accounting for correlation within participants and clustering at the site level and variance estimated using a Huber–White sandwich estimator. For participants with missing primary outcome data, a Retrieved Data Multiple Imputation approach was employed,[19,20] with missing data imputed only from participants who were concordant with presence or absence of an intercurrent event. A total of 100 imputed datasets were used. Prespecified sensitivity and supplementary analyses included: use of only week 12 home blood pressure results; analysis adjusted for covariates; analysis after excluding participants with study treatment interruptions for supply-related reasons, complete cases with clinic blood pressure substitution for missing home blood pressure values; and a per-protocol analysis, excluding any participants with an intercurrent event or major protocol deviation. A two-dimensional multiple-imputation tipping point analysis was conducted to evaluate the effect of missing data under the assumption

of data not missing at random.[21] This involved imputing missing week 12 data for both the GMRx2 and active control groups, applying a shift parameter to assess when statistical significance was lost (p>0·05) for at least one comparison. Other continuous outcomes of difference in change in blood pressure were analysed as per the primary outcome. All continuous outcomes were reported along with 95% CI and the corresponding p value. The proportion of participants with blood pressure control was descriptively summarised and analysed using generalised estimating equations with the visit, treatment group, and visit by treatment group interaction as fixed effects and accounting for correlation within participant and clustering at the site level. Proportions by treatment group with 95% CI were presented along with the associated estimated risk difference and its corresponding p value. Other binary outcomes of efficacy and safety were analysed as per the percentage of participants with blood pressure control. Statistical analyses were conducted with SAS version 9.4 and R software.

Role of the funding source

The trial was designed by the Steering Committee, who were responsible for the study protocol. The funder and sponsor consulted with the US Food and Drug Administration to ensure the trial design was suitable to inform an application for regulatory approval, and provided comments on a draft of the publication. The Steering Committee had full access to all the data and had final responsibility for publication.

Results

The trial was conducted from July 9, 2021, to Sept 1, 2023. Trial conduct was affected by the COVID-19 pandemic in multiple ways, including slow enrolment and interruptions in recruitment due to issues with trial medication supply. A decision was made at the start of the trial for all episodes of COVID-19 to be classified as serious adverse events, but not all met the usual criteria for severity. 3109 participants were screened, of whom 2244 (72·2%) entered run-in and 1385 (44·5%) were randomly assigned (551 to GMRx2, 276 to telmisartan–indapamide, 282 to telmisartan–amlodipine, and 276 to amlodipine–indapamide), with the main reasons for screening and run-in failure related to blood pressure criteria (figure 1). During the single-blind run-in with the GMRx2 half dose, 25 (1%) participants had a serious adverse event, of which 18 were due to COVID-19, and only one due to increased uric acid was judged to be related to the study treatment. 72 (3%) participants discontinued trial treatment due to an adverse event.

The mean age of randomly assigned participants was 59 years (SD 11); 712 (51·4%) self-reported as female, and 673 (48·6%) as male. Baseline characteristics were similar across the groups (table 1). Mean screening clinic blood pressure for the randomly assigned participants, who were receiving an average of 1·6 blood pressure medications, was 142/85 mm Hg; and after the 4-week run-in average clinic blood pressure was 133/81 mm Hg and home blood pressure was 129/78 mm Hg. All but five eligible participants commenced randomised treatment, and at week 6 the proportion undergoing dose doubling was 442 (80%) of 551 in the GMRx2, 221 (80%) of 276 in the telmisartan–indapamide, 242 (86%) of 282 in the telmisartan–amlodipine, and 233 (84%) of 276 in the amlodipine–indapamide group. Of the 1385 participants who were randomly assigned, 1318 (95·2%) completed follow-up. Adherence, defined as the proportion of pills planned for the randomised phase that were taken, was 96% overall: 78 (95%) of 82 for GMRx2, 79 (98%) of 81 for telmisartan–indapamide, 79 (96%) of 82 for telmisartan–amlodipine, and 79 (95%) of 83 for amlodipine–indapamide.

	GMRx (N=551)	Telmisartan–indapamide (N=276)	Telmisartan–amlodipine (N=282)	Amlodipine–indapamide (N=276)
(Continued from previous page)				
Number of previous blood pressure treatments at screening				
0	65 (12%)	28 (10%)	27 (10%)	24 (9%)
1	193 (35%)	83 (30%)	110 (39%)	87 (32%)
2	217 (39%)	112 (41%)	105 (37%)	121 (44%)
3	76 (14%)	53 (19%)	40 (14%)	44 (16%)
SBP/DBP levels				
Clinic blood pressure at screening	142 (12)/85 (10)	142 (12)/85 (11)	142 (11)/86 (11)	141 (12)/85 (11)
Home blood pressure at randomisation	127 (10)/78 (9)	129 (11)/77 (9)	128 (10)/78 (9)	129 (10)/78 (9)
Clinic blood pressure at randomisation	133 (13)/81 (11)	132 (14)/81 (10)	133 (13)/81 (10)	133 (13)/81 (10)

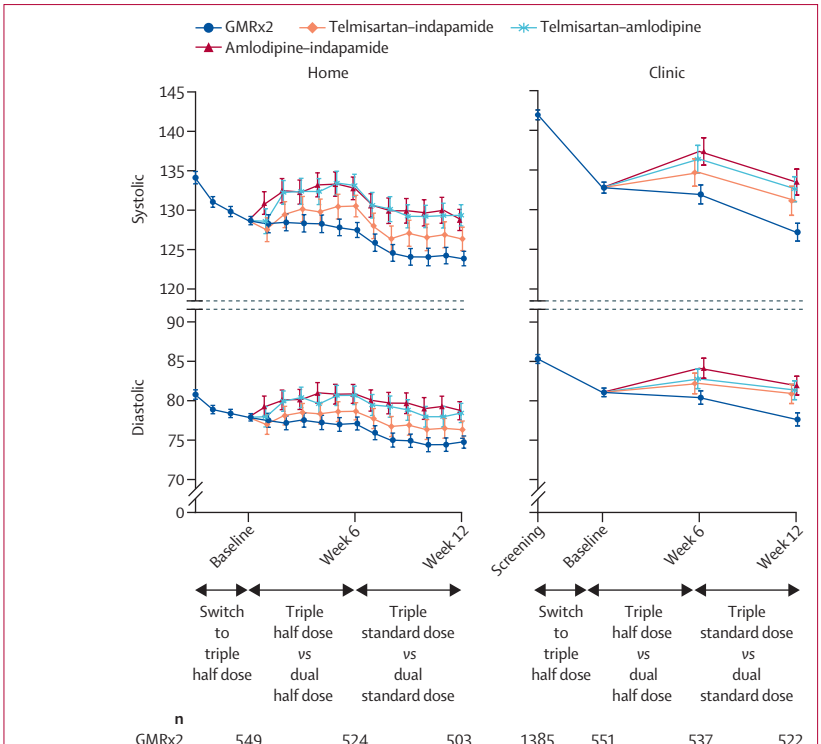
Data are n (%) or mean (SD). SBP=systolic blood pressure. DBP=diastolic blood pressure.

Table 1: **Baseline characteristics of randomly assigned participants**

See Online for appendix 2

At 12 weeks, the primary outcome (home SBP) was lower in the GMRx2 group compared with each of the dual-therapy groups: the least-squares differences in change in home seated mean SBP mm Hg from randomisation to week 12 was –2·5 (95% CI –3·7 to –1·3, p<0·0001) for GMRx2 versus telmisartan–indapamide, –5·4 (–6·8 to –4·1, p<0·0001) versus telmisartan–amlodipine, and –4·4 (–5·8 to –3·1, p<0·0001) versus amlodipine–indapamide (figure 2, table 2). The findings were not materially altered in all sensitivity analyses, including a tipping point analysis (appendix 3 pp 14–15). Findings were broadly consistent across predefined subgroups (appendix 3 p 3). Although there was statistically significant heterogeneity within subgroups defined by number of blood pressure medications at screening (GMRx2 *vs* telmisartan–indapamide), home SBP at randomisation (GMRx2 *vs* telmisartan–amlodipine), and BMI and region (GMRx2 *vs* amlodipine–indapamide), these findings should be considered in light of the 11 separate subgroup analyses

See Online for appendix 3



n							
GMRx2	549	524	503	1385	551	537	522
Telmisartan–indapamide	276	261	251	..	276	264	259
Telmisartan–amlodipine	282	270	264	..	281	276	272
Amlodipine–indapamide	276	259	248	..	276	264	258

Figure 2: **Home and clinic systolic and diastolic blood pressure over time**

	GMRx2 *vs* telmisartan–indapamide (N=827)	GMRx2 *vs* telmisartan–amlodipine (N=832)	GMRx2 *vs* amlodipine–indapamide (N=827)
Home systolic			
Week 6	−3·0 (−4·1 to −1·9)	−6·1 (−7·1 to −5·1)	−5·1 (−6·3 to −3·9)
Week 12	−2·5 (−3·7 to −1·3)	−5·4 (−6·8 to −4·1)	−4·4 (−5·8 to −3·1)
Home diastolic			
Week 6	−2·1 (−2·8 to −1·4)	−3·5 (−4·1 to −2·9)	−3·6 (−4·4 to −2·7)
Week 12	−2·1 (−3·0 to −1·2)	−3·4 (−4·1 to −2·6)	−3·6 (−4·6 to −2·6)
Clinic systolic			
Week 6	−3·5 (−5·3 to −1·7)	−5·0 (−6·7 to −3·3)	−5·4 (−7·3 to −3·4)
Week 12	−4·3 (−6·7 to −1·9)	−5·6 (−7·3 to −3·9)	−6·3 (−8·0 to −4·7)
Clinic diastolic			
Week 6	−2·3 (−3·4 to −1·2)	−2·4 (−3·4 to −1·5)	−3·8 (−4·9 to −2·7)
Week 12	−3·5 (−4·9 to −2·1)	−3·7 (−4·7 to −2·8)	−4·5 (−5·8 to −3·2)

Data are difference (95% CI). All differences in home and clinic blood pressure were p<0·0001 and all differences in clinic blood pressure were p<0·001.

Table 2: **Difference in change in home and clinic blood pressure from randomisation to week 6 (GMRx2 triple half-dose *vs* dual half-dose comparators) and week 12 (GMRx2 triple standard-dose *vs* dual standard-dose comparators)**

conducted for each of the three GMRx2 versus dual therapy comparisons.

Reductions in clinic SBP and DBP were also seen for all comparisons of GMRx2 versus dual combinations at each timepoint, and on average these were about 20% greater than those for home blood pressure. There was also broad consistency in the reductions in clinic SBP across different subgroups (appendix 3 p 4). For both clinic and home blood pressure, there was no clear difference between the size of the additional blood pressure reduction conferred by the GMRx2 half dose versus dual half doses and between the GMRx2 standard dose versus dual standard doses, at least for home blood pressure (table 2). For example, the average blood pressure differences for the GMRx2 half dose versus dual half doses at week 6 were 4·7/3·1 mm Hg for home blood pressure and 4·6/2·8 mm Hg for clinic blood pressure, and for the GMRx2 standard dose versus dual standard doses at week 12 they were 4·1/3·0 mm Hg for home blood pressure and 5·4/3·9 mm Hg for clinic blood pressure.

The least-squares difference in change in trough home mean SBP mm Hg from randomisation to 12 weeks was –1·9 (95% CI –3·2 to –0·6, p<0·0043) for GMRx2 versus telmisartan–indapamide, –5·6 (–7·0 to –4·2, p<0·0001) versus telmisartan–amlodipine, and –3·7 (–5·2 to –2·3, p<0·0001) versus amlodipine–indapamide, indicating effects were maintained at the end of the dosing interval. GMRx2 also conferred similar-sized reductions compared with each dual therapy in week 6 for home SBP, and there were also reductions in home DBP for all comparisons at both visits (all p<0·001; table 2).

Improvements in blood pressure control rates were seen for all GMRx2 versus dual therapy comparisons, at each timepoint, for home and clinic measures and for different threshold definitions (table 3, appendix 3 p 5). For example, the proportions of participants with clinic blood pressure below 140/90 mm Hg at week 12 were 407 (74%) of 551 for GMRx2, 167 (61%) of 276 for telmisartan–indapamide, 173 (61%) of 282 for telmisartan–amlodipine, and 146 (53%) of 276 for amlodipine–indapamide; the absolute differences were 13% (95% CI 6–20, p=0·0001) for GMRx2 versus telmisartan–indapamide, 13% (6–20, p=0·0003) for GMRx2 versus telmisartan–amlodipine, and 21% (14–28, p<0·0001) for GMRx2 versus amlodipine–indapamide. The size of the absolute improvement in various blood pressure control rates was broadly consistent, with point estimates of higher blood pressure control rates in GMRx2 versus comparator groups ranging from a 7% to a 23% absolute increase.

There was no statistically significant difference in the primary safety outcome of discontinuation of study treatment due to adverse events from randomisation to week 12. The absolute rates of discontinuation were 11 (2%) for GMRx2, four (1%) for telmisartan–indapamide, three (1%) for telmisartan–amlodipine, and four (1%) for amlodipine–indapamide; the absolute differences were 0·6% (95% CI –2·1 to 2·5) for GMRx2 versus telmisartan–indapamide, 0·9% (–1·5 to 2·8) for GMRx2 versus telmisartan–amlodipine, and 0·6% (–2·1 to 2·5) for GMRx2 versus amlodipine–indapamide (table 4).

17 (3%) participants in the GMRx2, seven (3%) in the telmisartan– indapamide, six (2%) in the telmisartan–amlodipine, and six (2%) in the amlodipine–indapamide

	Participants with blood pressure control				Risk difference		
	GMRx2 (N=551)	Telmisartan–indapamide (N=276)	Telmisartan–amlodipine (N=282)	Amlodipine–indapamide (N=276)	GMRx2 *vs* telmisartan–indapamide	GMRx2 *vs* telmisartan–amlodipine	GMRx2 *vs* amlodipine–indapamide
Clinic blood pressure control <140/90 mm Hg							
Week 6	346 (63%)	151 (55%)	148 (53%)	122 (44%)	8% (1–15), p=0·026	10% (3–18), p=0·004	19% (11–26), p<0·0001
Week 12	407 (74%)	167 (61%)	173 (61%)	146 (53%)	13% (6–20), p=0·0001	13% (6–20), p=0·0003	21% (14–28), p<0·0001
Clinic blood pressure control <130/80 mm Hg							
Week 6	167 (30%)	59 (21%)	65 (23%)	59 (21%)	9% (2–15), p=0·0046	10% (4–16), p=0·0007	12% (6–18), p<0·0001
Week 12	218 (40%)	76 (28%)	126 (45%)	123 (45%)	12% (5–19), p=0·0004	17% (10–23), p<0·0001	18% (11–24), p<0·0001
Home blood pressure control <135/85 mm Hg							
Week 6	346 (63%)	155 (56%)	74 (26%)	79 (29%)	7% (–1–14), p=0·067	18 (11–25), p<0·0001	18% (11–25), p<0·0001
Week 12	398 (72%)	176 (64%)	109 (39%)	91 (33%)	9% (2–16), p=0·015	15 (8–22), p<0·0001	16% (9–23), p<0·0001
Home blood pressure control <130/80 mm Hg							
Week 6	247 (45%)	90 (33%)	173 (61%)	146 (53%)	12% (5–19), p=0·0005	19% (12–25), p<0·0001	16% (9–23), p<0·0001
Week 12	308 (56%)	121 (44%)	56 (20%)	50 (18%)	12% (5–19), p=0·0010	17% (10–24), p<0·0001	23% (16–30), p<0·0001

Data are n (%) or risk difference (95% CI), p compared with GMRx2.

Table 3: **Home and clinic blood pressure control at week 6 (GMRx2 triple half-dose *vs* dual half-dose comparators) and week 12 (GMRx2 triple standard-dose *vs* dual standard-dose comparators)**

group had a serious adverse event (table 4). No deaths were reported during the study. 32 (6%) participants had symptomatic hypotension in the GMRx2 group compared with 11 (4%) in the telmisartan–indapamide, five (2%) in the telmisartan–amlodipine, and four (1%) in the amlodipine–indapamide group at week 12. Similarly, at week 6, 15 (3%) participants had symptomatic hypotension in the GMRx2, one (less than 1%) in the telmisartan–indapamide, three (1%) in the telmisartan–amlodipine, and two (less than 1%) in the amlodipine–indapamide group.

There were no between-group differences in measures of eGFR. Out-of-range sodium or potassium values occurred more frequently in the GMRx2 group compared with the telmisartan–amlodipine group (19·1% *vs* 8·5%, risk difference 10·6% [95% CI 5·4–15·1]) at week 12, but rates for the GMRx2 group were similar to those seen in the two dual-combination groups that included indapamide. Very few clinically significant electrolyte abnormalities occurred in any groups (appendix 3 pp 6–7). There was no significant difference in measures of orthostatic hypotension or hypertension between the groups when measured in clinic visits at week 6 or week 12.

	GMRx2 (N=551)	Telmisartan–indapamide (N=276)	Telmisartan–amlodipine (N=282)	Amlodipine–indapamide (N=276)
Treatment withdrawal due to adverse events	11 (2%)	4 (1%)	3 (1%)	4 (1%)
Adverse events of special interest	184 (34%)	75 (27%)	71 (25%)	79 (29%)
Symptomatic hypotension	32 (6%)	11 (4%)	5 (2%)	4 (1%)
Abnormal laboratory findings*	139 (25%)	59 (22%)	57 (20%)	69 (25%)
Headache	16 (3%)	8 (3%)	5 (2%)	5 (2%)
Peripheral oedema	7 (1%)	1 (0.4%)	6 (2%)	2 (<1%)
Other reason for discontinuation of trial medication	6 (1%)	0	2 (<1%)	1 (<1%)
At least one serious adverse event†	17 (3%)	7 (3%)	6 (2%)	6 (2%)

Data are n (%). Results are for people with one or more event type in the randomised phase, which included 6 weeks of half-dose combination therapy followed by 6 weeks of standard-dose combination therapy. Five participants did not start the study medication and not all were uptitrated at week 6. *Abnormalities of sodium, potassium, uric acid, glucose, lipids, creatinine, or estimated glomerular filtration rate. †All cases of COVID-19 were designated as serious adverse events, and these comprised 21 (57%) of 37 serious adverse events. There were no deaths and only one cardiovascular event: a non-ST segment elevation myocardial infarction occurring in the telmisartan–indapamide group.

Table 4: **Treatment withdrawal due to adverse events, adverse events of special interest, and serious adverse events from baseline to week 12**

Discussion

This trial was the first to assess the contributions of telmisartan, amlodipine, and indapamide as part of a triple half-dose as well as triple standard-dose combination therapy in hypertension. The trial assessed efficacy at lower levels of blood pressure than previous studies and showed that triple therapy was more effective than dual therapy, significantly reducing both home and clinic blood pressure and improving blood pressure control at both half and standard doses. Tolerability was good, with no increase in withdrawal due to adverse events.

Taking into account the lower baseline blood pressure levels in this trial, these results are broadly consistent with the findings in previous trials (see Research in context panel), in which standard or maximal dose triples on average conferred a 5·1/3·7 mm Hg additional SBP/DBP reduction compared with dual therapy.[22] The relevance of the smaller difference between triple therapy and a renin angiotensin system-diuretic dual combination for home blood pressure is uncertain, given this was not clearly seen for clinic SBP in this or previous

triple-combination versus dual-combination trials[22] or expected from other large trials comparing dual combinations.[23] Similarly, the relevance of the subgroup findings for home blood pressure are uncertain given the number of subgroup analyses conducted and inconsistency for home and clinic blood pressure; for example, the lowest p value for heterogeneity for home SBP analyses suggested lesser reduction with BMI lower than 30 kg/m² versus 30 kg/m² or higher for the GMRx2 versus amlodipine–indapamide comparison, but the same comparison with clinic SBP showed a numerically greater reduction for those with BMI lower than 30 kg/m². The tolerability findings are also broadly consistent for the standard-dose comparisons, with around a 1% absolute excess observed in this trial compared with a 2% excess in past trials but overlap in CIs.

Strengths of this trial included randomisation, double blinding, and enrolment of enough participants to provide adequate statistical power to assess the treatment effects on home as well as clinic blood pressure in a broad array of participants with hypertension, including those taking between zero and three antihypertensive drugs at baseline. The trial provided evidence at blood pressure levels lower than those studied in previous trials, for which baseline blood pressure levels averaged 169/103 mm Hg among untreated populations and 150/95 mm Hg for those uncontrolled on dual antihypertensive therapy.[22] In contrast, our trial mean clinic blood pressure was 133/81 mm Hg at baseline and 142/85 mm Hg when participants began a triple half-dose run-in. This contrast means the trial generated evidence on efficacy and tolerability at blood pressure levels of current interest, given the increasing guideline recommendations for blood pressure targets below 130/80 mm Hg and the recognition that mean SBP levels of around 125 mm Hg are required to reach more than 80% of blood pressure levels below 140/90 mm Hg.[24] Conversely, the trial included comparatively few participants with very high levels of blood pressure, which is an important minority of the population with hypertension. This makes direct comparison with previous trials challenging, because the extent of blood pressure reduction is strongly associated with the initial blood pressure level.

In terms of weaknesses, the trial design did not allow a direct randomised comparison between half-dose and standard-dose combinations, or with other drugs and doses that are in common use, because the primary aim was to satisfy regulatory requirements related to evaluation of each component's contribution to efficacy and safety. The proportion of screened participants who were randomly assigned was comparatively low, which might affect generalisability, although this proportion varies widely across hypertension trials, with similar proportions seen in other regulatory approval trials.[25] The potential for non-uptitration after 6 weeks of half-dose regimens is likely to have led to underestimation of the difference between standard-dose regimens, because half-dose regimens were particularly effective at lowering blood pressure in some participants who were not then uptitrated. In addition, the use of an active run-in to optimise trial power meant that initial tolerability findings did not have a comparator, and the relatively high proportion of screened participants who were not randomised could affect generalisability. Further shortcomings relate to challenges with trial conduct as a result of the COVID-19 pandemic. For home blood pressure, although extensive training and instruction materials were provided and participants who did not adhere to the measurement protocol were excluded after run-in, home blood pressure measurement fidelity was not directly checked. It is possible, therefore, that some home blood pressure measures were not optimal, eg, performed with a suboptimal technique. Given this was a blinded trial, this shortcoming would tend to result in bias to the null. The availability of clinic blood pressure assessments also mitigates this issue, because these were conducted by trained staff using the same machine and procedure. Finally, 24 h blood pressure data were not available, although morning home blood pressure data did provide evidence of efficacy at the end of the interdosing period.

The clinical and public health implications of these findings are considerable, given that high blood pressure is a leading cause of global disease burden and fewer than one in four treated individuals reaches blood pressure goals.[26,27] The safety profile was reassuring, with no excess of serious adverse events and most cases of electrolyte imbalance and symptoms of hypotension being mild to moderate, in keeping with a placebo-controlled comparison of this combination.[28] Although standard clinical and laboratory monitoring is still required, in general, the expected benefits from blood pressure lowering in terms of cardiovascular event reduction reliably outweigh these adverse reactions in those at heightened cardiovascular risk.[29] The importance of reaching and maintaining lower blood pressure targets substantially increases the relevance of affordable, effective, and safe triple SPCs, because such targets are rarely possible with monotherapy and often not reached with dual therapy. Recent large trials with cardiovascular endpoint outcomes that have been successful in reaching intervention group targets (which in all cases involved SBP <130 mm Hg) all used an average of two to three drugs per participant in the intervention group.[30–36] Modern hypertension treatment algorithms, such as those recommended by WHO,[37] also all have triple therapy, usually as a third treatment step, and all recommend SPCs in preference to separate pills where possible to improve adherence. The 2024 European Society of Cardiology Guidelines recommend initial low-dose dual therapy followed by low-dose triple therapy for most individuals.[38]

Further research is required to assess the efficacy of this new treatment option in several areas. First, more pragmatic trials and implementation-focused research are needed that compare this strategy with usual care; one such trial in Nigeria has recently shown promising results.[39] Subsequent research should assess the potential for integration with other important strategies, such as team-based care and interventions that improve adherence and cost-effectiveness, for example extended dispensing intervals.[40] Research is also needed in priority populations, such as those with chronic kidney disease, minority populations, and others at raised cardiovascular risk.

In conclusion, a novel triple-combination SPC of telmisartan, amlodipine, and indapamide at half and standard doses was more effective in lowering blood pressure than dual combinations and was well tolerated. Increased availability of SPCs can be expected to improve adherence compared with separate pills, and interventions such as the one tested here can facilitate clinically relevant improvements in efficacy for the large number of people with hypertension whose blood pressure remains uncontrolled after dual-combination therapy.

Contributors

AR wrote the first draft with input from AS, AES, and PKW. Statistical analyses were conducted by GLDT, CG, MS, XL, and the Veristat team. The Steering Committee had full access to all data. All authors commented on the draft manuscript and were responsible for the decision to submit for publication.

Declaration of interests

AR, AS, AES, CG, MS, XL, and NW are employed at The George Institute for Global Health (TGI), which holds an interest in George Medicines via its social enterprise arm, George Institute Ventures. None of the TGI staff has a personal financial interest in George Medicines. AR is seconded part-time to George Medicines. TGI holds patents for ultra-low-dose, fixed-dose combination products for the treatment of hypertension and diabetes, and AR is listed as one of the inventors (granted: US 10 369 156, US 10 799 487, US 10 322 117, US 11 033 544, US 11 478 462; pending: US 17/932 982, US 18/446 268, US 17/598 122, US 17/317 614, US 17/527 084, US 17/527 085, US 17/527 087). AR does not have a financial interest in these patents. None of the other authors has a financial interest in George Medicines or has received funding for their independent contribution to the GMRx2 programme. AR reports consulting fees as a data and safety monitoring board member for Idorsia; and a fellowship grant from the National Health and Medical Research Council of Australia (GNT 1160743). AES reports consulting fees or speaker honoraria from OMRON Healthcare, Aktiia, Medtronic, Servier, Abbott, Sanofi, Sun Pharmaceuticals, Novartis, and Skylabs; being co-chair of the National Hypertension Taskforce Australia; being a board member for Hypertension Australia and the Australian Cardiovascular Alliance; and an investigator grant from the National Health and Medical Research Council of Australia (GNT 2017504). DBO reports speaker honoraria from Novartis, AstraZeneca, Servier, Swipha, and Boehringer Ingelheim for speaking at educational meetings. KN reports speaker and consulting honoraria from Bausch Health, Berlin-Chemie/Menarini, Egis, Idorsia, Janssen, Gedeon Richter, Gilead, Krka, Novo Nordisk, Polpharma, Recordati, Sandoz, and Servier; and honoraria from or participation on advisory boards for Polpharma and Zentiva. MPS reports consulting fees or travel and research support from Medtronic, Abbott, Recor, Novartis, Servier, Pfizer, and Boehringer Ingelheim; and being current President of Hypertension Australia and Treasurer of the World Hypertension League. WCC reports institutional grants from Recor and George Medicines; and consulting fees from Alnylam Pharmaceuticals. NRP reports consultancy fees from Servier and Aktiia; support for research projects and staff from Servier and Pfizer; support for arranging and speaking at educational meetings from AstraZeneca, LRI-Therapharma, Napi, Servier, Sanofi, EVA Pharma, Pfizer, Emcure, Dr Reddy's Laboratories, and Zydus; and support by the National Institute for Health Research Senior Investigator Awards, Biomedical Research Centre funding, and the British Heart Foundation Research Centre Excellence Award. DEG reports funding to his department as part of the EU Horizon Hypermarker project. BW reports trial steering committee appointments for Novartis and AstraZeneca; lecture fees for Servier and Novartis; and an unremunerated role as President of the International Society of Hypertension. JTW reports institutional grants from the National Institutes of Health, the Ohio Department of Medicaid, and the Agency for Healthcare Research and Quality; travel support and participation on an advisory board for Medtronic; being chair of the data safety monitoring board for the IMPACTS MIND Trial at Tulane University; and being on the Northeast Ohio Neighbourhood Health Center Community Board of Directors. All other authors declare no competing interests.

Data sharing

Documentation around the analyses presented here will be made available to qualified scientific and medical researchers, upon researcher's request, as necessary for conducting legitimate research. Participant data will be de-identified and will be shared via a secure means. Requests for data will only be reviewed after approval of the product in the USA and EU, and after George Medicines approval of its Data Access Request and receipt of its executed Data Sharing Agreement. A request form can be obtained by email to the corresponding author or to info@george-medicines.com.

Acknowledgments

We thank all the people who participated in this trial. This study was funded by George Medicines.

References

1 Chow CK, Teo KK, Rangarajan S, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* 2013; **310:** 959–68.

2 Benjamin IJ, Kreutz R, Olsen MH, et al. Fixed-dose combination antihypertensive medications. *Lancet* 2019; **394:** 637–38.

3 Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018; **71:** e13–115.

4 Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018; **39:** 3021–104.

5 Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *J Hypertens* 2020; **38:** 982–1004.

6 WHO. Guideline for the pharmacological treatment of hypertension in adults. Geneva: World Health Organization, 2021.

7 Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med* 2009; **122:** 290–300.

8 Salam A, Kanukula R, Atkins E, et al. 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. *J Hypertens* 2019; **37:** 1768–74.

9 Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SAE, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. *Hypertension* 2009; **53:** 646–53.

10 Mourad JJ, Waeber B, Zannad F, et al. Comparison of different therapeutic strategies in hypertension: a low-dose combination of perindopril/indapamide versus a sequential monotherapy or a stepped-care approach. *J Hypertens* 2004; **22:** 2379–86.

11 Calhoun DA, Lacourciere Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. *Hypertension* 2009; **54:** 32–39.

12 Chrysant SG, Izzo JL Jr, Kereiakes DJ, et al. Efficacy and safety of triple-combination therapy with olmesartan, amlodipine, and hydrochlorothiazide in study participants with hypertension and diabetes: a subpopulation analysis of the TRINITY study. *J Am Soc Hypertens* 2012; **6:** 132–41.

13 Mourad J-J, Amodeo C, de Champvallins M, Brzozowska-Villatte R, Asmar R. Blood pressure-lowering efficacy and safety of perindopril/indapamide/amlodipine single-pill combination in patients with uncontrolled essential hypertension: a multicenter, randomized, double-blind, controlled trial. *J Hypertens* 2017; **35:** 1481–95.

14 Muntner P, Shimbo D, Carey RM, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. *Hypertension* 2019; **73:** e35–66.

15 Stergiou GS, Parati G, Imai Y, et al. Guidelines for home blood pressure monitoring. In: Stergiou GS, Parati G, Mancia G, eds. Home blood pressure monitoring. Cham: Springer, 2020: 165–70.

16 Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015; **386:** 2059–68.

17 US Food and Drug Administration. Multiple Endpoints in Clinical Trials. Guidance for Industry. 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials (accessed Sep 30, 2024).

18 US Food and Drug Administration. E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical (accessed Sep 30, 2024).

19 Huque MH, Carlin JB, Simpson JA, Lee KJ. A comparison of multiple imputation methods for missing data in longitudinal studies. *BMC Med Res Methodol* 2018; **18:** 1–16.

20 Van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res* 2007; **16:** 219–42.

21 Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. *Pharm Stat* 2013; **12:** 337–47.

22 Salam A, Atkins E, Hsu B, Webster R, Patel A, Rodgers A. Efficacy and safety of triple versus dual combination blood pressure lowering therapy—a systematic review and meta-analysis of randomized controlled trials. *J Hypertens* 2019; **37:** 1567–73.

23 Ojji DB, Mayosi B, Francis V, et al. Comparison of dual therapies for lowering blood pressure in Black Africans. *N Engl J Med* 2019; **380:** 2429–39.

24 Egan BM, Li J, Wagner CS. Systolic Blood Pressure Intervention Trial (SPRINT) and target systolic blood pressure in future hypertension guidelines. *Hypertension* 2016; **68:** 318–23.

25 Giles TD, Weber MA, Basile J, et al. Efficacy and safety of nebivolol and valsartan as fixed-dose combination in hypertension: a randomised, multicentre study. *Lancet* 2014; **383:** 1889–98.

26 Murray CJL, Aravkin AY, Zheng P, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396:** 1223–49.

27 Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation* 2016; **134:** 441–50.

28 Rodgers A, Salam A, Schutte AE, et al. Efficacy and safety of a novel low-dose triple single-pill combination compared with placebo for initial treatment of hypertension. *J Am Coll Cardiol* 2024; published online Aug 31. http://doi.org/10.1016/j.jacc.2024.08.025.

29 Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet* 2014; **384:** 591–98.

30 ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; **362:** 1575.

31 Sprint Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; **373:** 2103–16.

32 Brook RD, Brook AJ, Jamerson K, Levy PD, Kaciroti N. Worse blood pressure levels and control during nonsummer months in rigorously treated patients with hypertension: the ACCOMPLISH trial. *J Am Heart Assoc* 2023; **12:** e030696.

33 SPS3 Study Group. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013; **382:** 507–15.

34 He J, Ouyang N, Guo X, et al. Effectiveness of a non-physician community health-care provider-led intensive blood pressure intervention versus usual care on cardiovascular disease (CRHCP): an open-label, blinded-endpoint, cluster-randomised trial. *Lancet* 2023; **401:** 928–38.

35 Sun Y, Mu J, Wang DW, et al. A village doctor-led multifaceted intervention for blood pressure control in rural China: an open, cluster randomised trial. *Lancet* 2022; **399:** 1964–75.

36 Zhang W, Zhang S, Deng Y, et al. Trial of intensive blood-pressure control in older patients with hypertension. *N Engl J Med* 2021; **385:** 1268–79.

37 Moran AE, Gupta R, Global Hearts Initiative Collaborators. Implementation of Global Hearts hypertension control programs in 32 low- and middle-income countries: JACC International. *J Am Coll Cardiol* 2023; **82:** 1868–84.

38 McEvoy JW, McCarthy CP, Bruno RM, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J* 2024; published online Aug 30. http://doi.org/10.1093/eurheartj/ehae178.

39 Ojji DB, Salam A, Sani MU, et al. Low-dose triple-pill vs standard-care protocols for hypertension treatment in Nigeria: a randomized clinical trial. *JAMA* 2024; published online Aug 31. http://doi.org/10.1001/jama.2024.18080.

40 Marklund M, Cherukupalli R, Pathak P, et al. Hypertension treatment capacity in India by increased workforce, greater task-sharing, and extended prescription period: a modelling study. *Lancet Reg Health Southeast Asia* 2023; **10:** 100124.