nature medicine

Article

https://doi.org/10.1038/s41591-025-03854-w

Comparison of dual therapies for hypertension treatment in India: a randomized clinical trial

Received: 2 December 2024

Accepted: 20 June 2025

Published online: 25 July 2025

Check for updates

A list of authors and their affiliations appears at the end of the paper

Evidence is lacking for guiding optimal combination hypertension therapy in South Asian patients. Here we investigated the blood pressure (BP)-lowering efficacy and safety of three commonly recommended antihypertensive dual combinations in a multicenter, single-blinded trial conducted in India. We randomized Indians aged 30–79 years (mean age, 52 years) with mean sitting systolic blood pressure (SBP) of 150–179 mmHg on no treatment or an SBP of 140–159 mmHg on monotherapy 1:1:1 to a single-pill combination of amlodipine–perindopril, perindopril–indapamide or amlodipine–indapamide. The primary outcome was the mean change in 24-hour ambulatory SBP at 6 months. Of the 1,981 participants (42% females) enrolled in the trial, 1,637 completed a 24-hour ambulatory BP measurement. All three drug combinations produced similar large reductions in the primary outcome, namely ambulatory (~14/8 mmHg) and office (~30/14 mmHg) BPs after 6 months, such that hypertension control rates (sitting BP < 140/90 mmHg) were achieved in approximately 70% of participants in all three groups. Furthermore, no significant differences in secondary outcomes, such as mean day and night ambulatory and office BPs and hypertension control rates, were observed among the study groups. Thus, in Indian patients, amlodipine–perindopril, perindopril–indapamide and amlodipine–indapamide were all equally well tolerated and equally highly effective in reducing 24-hour ambulatory and office BPs (ClinicalTrials.gov registration: NCT05683301).

Hypertension affects over 1.3 billion adults worldwide[1]. Elevated BP is the single largest contributor to the global burden of disease and mortality, annually causing 7.8% of the disability-adjusted life years lost and one in six deaths (10.9 million)[2]. It is critical that treatment and control rates of hypertension be improved given that its adverse effects are increasing in absolute terms[3]. Initiating dual combinations of BP-lowering therapy, ideally as single-pill combinations (SPCs), is one of the proposed mechanisms for improving BP management[3–6].

The usual dual combinations recommended are any two of a renin-angiotensin system blocker (angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)), a calcium channel blocker and a diuretic (thiazide or thiazide-like)[3–6]. Some randomized trial data are available to compare the cardiovascular protective effects of different combinations of BP-lowering agents[7–9]. However, the BP-lowering efficacy of the major drug classes appears to differ among ethnic groups[10–12], and the CREOLE trial[13] identified significant differences in BP lowering caused by three dual combinations of agents taken by Black patients with hypertension in sub-Saharan Africa.

Nevertheless, no robust data are available to inform optimal dual combinations for the treatment of hypertension in patients of South Asian origin, who constitute a quarter of the world's population. India has an enormous burden of hypertension, with an estimated 300

e-mail: dprabhakaran@ccdcindia.org

https://doi.org/10.1038/s41591-025-03854-w

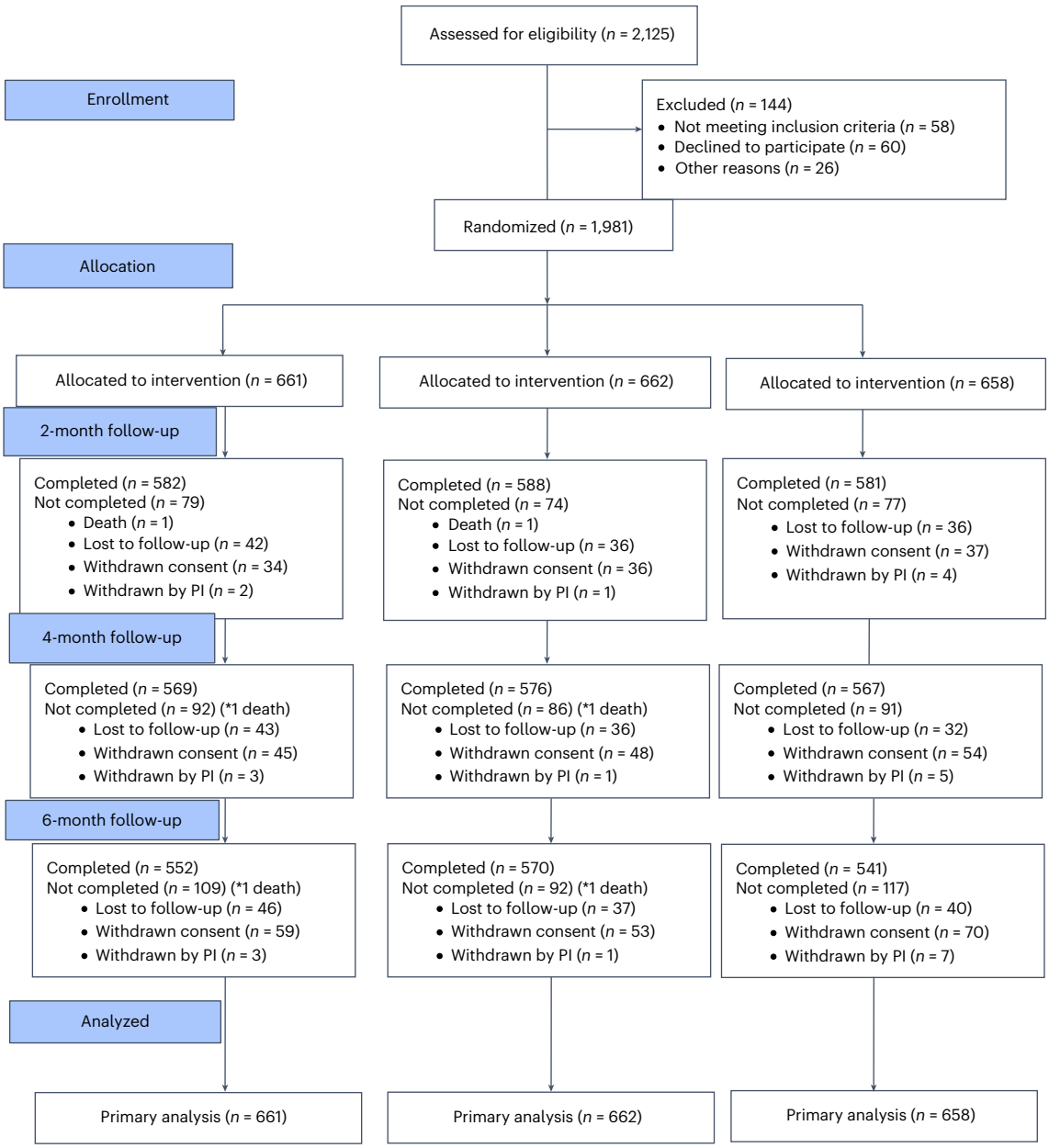


Fig. 1 | Design and follow-up of the TOPSPIN trial. The CONSORT flow diagram of the TOPSPIN trial. PI, principal investigator.

million individuals with high BP, among whom poor BP control in both rural (7–11%) and urban (11–20%) populations is reported[14–16].

We, therefore, conducted the Treatment Optimisation of blood Pressure with Single-Pill combinations in INdia (TOPSPIN) trial to compare the efficacy of amlodipine plus perindopril, amlodipine plus indapamide and perindopril plus indapamide in reducing the BP of Indian patients aged 30–79 years with hypertension.

Results

Study participants

We screened 2,125 patients with hypertension and randomized 1,981 participants. Of these, 661 participants received amlodipine and perindopril, 662 received perindopril and indapamide and 658 received amlodipine and indapamide as SPCs. At 6 months, 1,663 (84.0%) participants completed follow-up, with a 24-hour ambulatory blood pressure monitoring (ABPM) in 1,637 (82.6%). During follow-up, two participants died, 123 were lost to follow-up and 182 withdrew consent, and the treating physician withdrew the study medication in 11 participants (Fig. 1).

We included 1,981 participants in the primary analysis using multiple imputation for 344 participants who did not complete ABPM recording at 6 months. No difference was observed in the participant characteristics among those who completed and did not complete the ABPM measurement at 6 months (Extended Data Table 1). Overall, the participants had a mean age of 52.1±11.1 years; 42.1% were women; 18.6% had self-reported diabetes; and 58.1% had previously diagnosed hypertension. The baseline characteristics, 24-hour ambulatory and office BPs and laboratory parameters were similar across the groups (Table 1 and Extended Data Table 2). The demographic and clinical characteristics of those who did and did not provide 24-hour ambulatory recordings at 6 months were similar (Extended Data Table 1).

Treatment combinations and ambulatory BP

At 6 months, the unadjusted reduction in the primary outcome of 24-hour ambulatory SBP was 14.5 mmHg (95% confidence interval (CI): −16.0 to −13.2 mmHg) for amlodipine–perindopril; 13.3 mmHg (95%

https://doi.org/10.1038/s41591-025-03854-w

Table 1 | Characteristics of the study participants at baseline

Characteristic	Amlodipine–perindopril	Perindopril–indapamide	Amlodipine–indapamide
	(*n*=661)	(*n*=662)	(*n*=658)
Age			
Mean (years)	52.2±11.1	52.2±11.2	51.8±11.4
Distribution – no. (%)			
≥55 years	267 (40.4)	270 (40.8)	260 (39.5)
<55 years	394 (59.6)	392 (59.2)	398 (60.5)
Sex			
Females – no. (%)	278 (42.1)	265(40.0)	260 (44.2)
BMI (kg m^{-2})[a]	26.5±4.1	26.3±4.1	26.6±4.3
Current smoker – no. (%)	40 (6.1)	46 (6.9)	38 (5.8)
Diabetes – no. (%)[b]	125 (18.9)	125 (18.9)	120 (18.2)
Dyslipidemia – no. (%)[b]	48 (7.3)	47 (7.1)	49 (7.4)
Previously diagnosed hypertension – no. (%)[b]	393 (59.5)	384 (58.0)	372 (56.5)
BP (mmHg)			
Office systolic[c]	155.1±9.6	155.6±10.0	155.4±9.6
Office diastolic	92.3±10.8	91.9±10.6	91.8±11.1
24-hour ambulatory systolic[d]	135.9±16.9	135.4±17.1	135.3±17.0
24-hour ambulatory diastolic	85.0±11.0	84.2±10.8	84.2±11.0
Daytime ambulatory systolic	140.3±17.3	140.1±17.4	139.6±16.7
Daytime ambulatory diastolic	88.5±11.4	87.8±11.5	87.5±11.0
Nighttime ambulatory systolic	126.8±19.9	126.2±20.4	126.5±20.6
Nighttime ambulatory diastolic	78.4±12.8	77.7±12.4	77.8±13.2
Previous antihypertensive therapy – no. (%)			
ARB	225 (34.0)	195 (29.5)	193 (29.2)
Calcium channel blocker	103 (15.6)	127 (19.2)	120 (18.2)
Beta-blocker	40 (6.1)	35 (5.3)	31 (4.7)
ACE inhibitor	7 (1.1)	8 (1.2)	7 (1.1)
Diuretic	1 (0.2)	1 (0.2)	1 (0.2)

Plus–minus values are mean ± s.d. [a]BMI is the weight in kilograms divided by the square of the height in meters. [b]Self-reported. [c]Average of the last two of three office BP readings. [d]24-hour ambulatory BP was measured (one reading every 30 minutes) using a TM-2440 device (A&D Medical). Daytime ambulatory BP was estimated as the average of values between 9:00 and 21:00 and nighttime ambulatory BP as the average of values between 24:00 and 6:00.

CI: −14.7 to −11.9 mmHg) for perindopril–indapamide; and 13.9 mmHg (95% CI: −15.3 to −12.4 mmHg) for amlodipine–indapamide (Fig. 2).

No significant difference was observed in the primary outcome of mean change in ambulatory SBP adjusted for baseline value, stratification variables and sex among the three groups (Table 2). Similarly, the unadjusted reductions in 24-hour ambulatory DBP were similar across the groups (Fig. 2). Other secondary outcome measures of ABPM also revealed no significant difference in changes from baseline values between any two groups (Table 2). No differences were noted in the ambulatory BP in the complete case analysis (Extended Data Table 3). No significant interactions were apparent between any of the prespecified subgroups and the three treatment arms for the primary outcome except among body mass index (BMI) strata (Extended Data Figs. 1 and 2).

Treatment combinations and office BP

The unadjusted mean reduction in office SBP and DBP at 6 months was 30.4 mmHg (95% CI: −31.7 to −29.2 mmHg), 30.4 mmHg (95% CI: −31.6 to −29.2 mmHg) and 30.5 (95% CI: −31.7 to −29.2 mmHg) and 14.7 mmHg (95% CI: −15.8 to −13.6 mmHg), 14.0 mmHg (95% CI: −15.1 to −13.0 mmHg) and 13.9 mmHg (95% CI: −15.0 to −12.8 mmHg) in the amlodipine–perindopril, perindopril–-indapamide and amlodipine–indapamide groups, respectively.

At 2 months, participants who received amlodipine–perindopril had greater reductions in office DBP than participants who received perindopril–indapamide with a mean difference between groups of −1.25 mmHg (95% CI: −2.31 to −0.20), but there were no other significant differences among treatment groups at 2 months, 4 months and 6 months (Table 3).

We did not observe differences in the response rates or in conservative and more current office BP control rates among the treatment groups (Table 4 and Extended Data Table 4). At 6 months, based on office BPs, almost half of the participants were classified as responders; over two-thirds achieved conservative BP control targets; and over 40% achieved more current BP control targets (Table 4 and Extended Data Table 4).

Laboratory measures. The changes in various laboratory parameters are shown in Extended Data Table 5. A significant decrease was observed in fasting blood glucose and glycated hemoglobin levels in the amlodipine–perindopril group compared to the amlodipine–indapamide group. There were other clinically small but significant between-group differences in serum sodium, potassium, uric acid, urea and estimated glomerular filtration rate (eGFR), in keeping with established effects of ACE inhibitors and diuretics on these variables. Overall hypokalemia (<3.5 mmol l^{-1}) was detected at 6 months in 7.4% of participants for whom intervention was not required. However, differential effects across drug groups were apparent, with 15.2% of recipients of amlodipine plus indapamide having hypokalemia at 6 months.

Safety outcomes. A total of 51 participants experienced adverse events causing withdrawal of the study drug. Of these, 14 were in the amlodipine–perindopril group, 19 were in the perindopril–indapamide group and 18 were in the amlodipine–indapamide group. These participants reported a total of 77 adverse symptoms, of which dizziness (23 participants), pedal swelling (12 participants) and headache (10 participants) were the most common (Extended Data Table 6). Serious adverse events, defined as death or hospitalizations for any cause, occurred in 21 participants, but none was considered related to the study drugs.

Per-protocol analyses. Among the participants completing the 6-month follow-up, 1,307 (66.0%) were classified as adherent. We found no differences in the mean ambulatory BP changes among treatment groups in patients who were adherent (Extended Data Table 7).

Discussion

In this randomized trial of three commonly recommended dual combinations of antihypertensive agents, we found no differences in the ambulatory and office BPs of South Asian patients after 6 months of follow-up. Similarly, we found no differences in responder and control rates among the three treatment groups.

Our trial suggests that, in South Asian patients with untreated or uncontrolled hypertension while taking monotherapy, the use of any of the three dual combinations evaluated causes large reductions in 24-hour ambulatory and clinic BPs such that, at 6 months, the clinic BPs of approximately 70% of participants were controlled to less than 140/90 mmHg, and over 40% were controlled to less than 130/80 mmHg. The control rates are superior to most of those reported in patients worldwide[17–19].

These results contrast with those observed in the similarly designed CREOLE trial[13] involving Black patients in sub-Saharan Africa, where a calcium channel blocker combined with either an ACE inhibitor or a diuretic was superior to an ACE inhibitor and diuretic combination.

https://doi.org/10.1038/s41591-025-03854-w

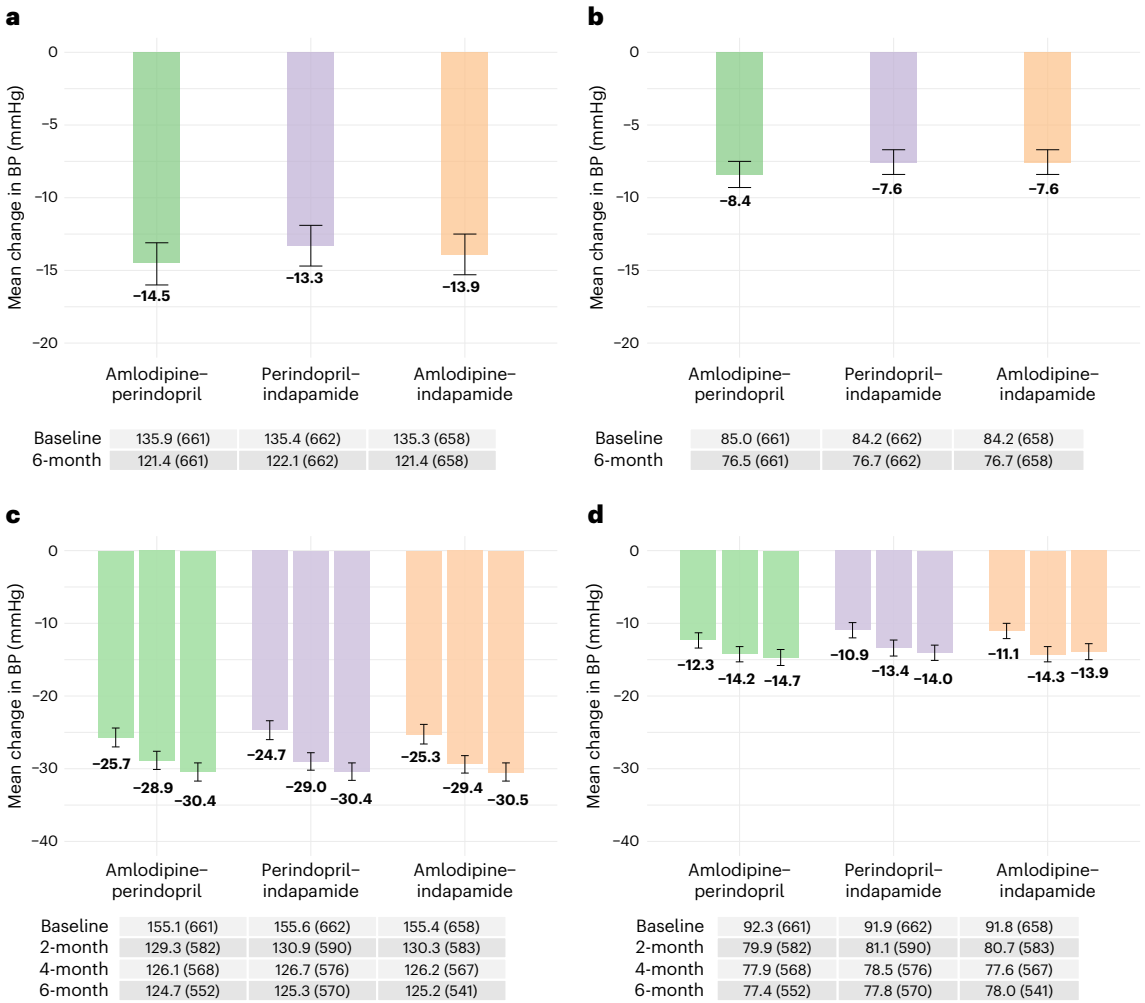


Fig. 2 | Unadjusted mean change in BP. a–d, Bar graphs with error bars showing ambulatory SBP (**a**), ambulatory DBP (**b**), office SBP (**c**) and office DBP (**d**). In **c** and **d**, the bars represent mean change in BP at 2 months, 4 months and 6 months. Error bars denote 95% CI.

However, in the South Asian context, the findings were compatible with several current guidelines that recommend using any dual combination from among a renin-angiotensin system blocker, a calcium channel blocker and a diuretic[3–6].

All three dual combinations were well tolerated, with less than 3% of participants having their therapy withdrawn due to side effects. However, an unknown proportion of those lost to follow-up may have been affected by side effects that were not reported. Notably, no serious cases of angioedema were reported. Furthermore, none of the 21 serious adverse events recorded was attributed to study drugs, and two-thirds of participants were classified as similarly compliant in all three groups, having consumed 80% or more of the prescribed medications throughout the trial.

Several clinically minor but statistically significant differential changes in laboratory parameters were apparent, particularly in renal function, potassium and uric acid on expected lines (Extended Data Table 5). Fasting blood glucose levels and glycated hemoglobin levels were lowest with the amlodipine–perindopril combination and were significantly lower than in the amlodipine–indapamide combination at 6 months. This finding may have clinical implications for this population with a high propensity to diabetes and a substantial burden of dysglycemia[20–22]. The differential effects of the three drug combinations on serum potassium highlights that routine monitoring of electrolytes should be carried out particularly among those taking a diuretic.

Similar reductions in 24-hour ambulatory BPs achieved in all three treatment groups were also observed in the per-protocol analyses, post hoc controlled multiple imputation analyses and prespecified subgroups of age strata, sex, diabetes status and previously diagnosed hypertension at baseline. Although borderline significant interactions among the treatment groups by BMI strata were apparent, the inconsistent differences observed most likely reflect the play of chance.

Limitations of this trial include that 17.4% of participants did not provide 24-hour ambulatory recording at 6 months. However, the demographic and clinical characteristics of those who did and did not provide 24-hour ambulatory recordings at 6 months did not differ. Furthermore, sensitivity analyses including only those who completed 24-hour ambulatory recordings at baseline and 6 months confirmed the findings of the primary analyses, which included all participants via multiple imputations. Additional limitations of this trial include that all possible two-drug combinations (including agents such as beta-blockers or ARBs) were not evaluated and the uncertainty of translating these equivalent BP-lowering data to having no differential impact of the three dual combinations on major adverse cardiovascular events. However, pending a much-needed cardiovascular outcome trial in South Asian patients, it seems reasonable to expect similar outcomes with the three combinations evaluated in this trial.

Another potential limitation of the trial was that the drug dosing was not wholly symmetrical across the treatment groups for the first

Table 2 | Adjusted mean between-group differences in changes from baseline in ambulatory BP

Ambulatory BP	Amlodipine–perindopril versus Perindopril–indapamide		Amlodipine–perindopril versus Amlodipine–indapamide		Perindopril–indapamide versus Amlodipine–indapamide	
	Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value
Model 1[a]						
Primary outcome						
24-hour systolic	−0.81 (−2.28 to 0.65)	0.27	−0.33 (−1.77 to 1.12)	0.65	0.49 (−0.96 to 1.94)	0.54
Secondary outcomes						
24-hour diastolic	−0.30 (−1.25 to 0.65)		−0.40 (−1.31 to 0.51)		−0.10 (−1.03 to 0.84)	
Daytime systolic	−0.98 (−2.55 to 0.60)		−0.65 (−2.2 to 0.89)		0.32 (−1.24 to 1.89)	
Nighttime systolic	0.00 (−1.80 to 1.80)		0.26 (−1.53 to 2.05)		0.26 (−1.49 to 2.01)	
Daytime diastolic	−0.42 (−1.53 to 0.69)		−0.50 (−1.60 to 0.59)		−0.09 (−1.22 to 1.05)	
Nighttime diastolic	0.17 (−0.92 to 1.26)		0.42 (−0.66 to 1.51)		0.25 (−0.82 to 1.33)	
Model 2[b]						
Primary outcome						
24-hour systolic	−0.88 (−2.35 to 0.59)	0.24	−0.31 (−1.76 to 1.14)	0.67	0.57 (−0.88 to 2.01)	0.49
Secondary outcomes						
24-hour diastolic	−0.39 (−1.34 to 0.55)		−0.48 (−1.39 to 0.43)		−0.08 (−1.02 to 0.85)	
Daytime systolic	−1.04 (−2.62 to 0.54)		−0.63 (−2.18 to 0.92)		0.41 (−1.16 to 1.98)	
Nighttime systolic	−0.06 (−1.86 to 1.75)		0.29 (−1.51 to 2.09)		0.34 (−1.41 to 2.10)	
Daytime diastolic	−0.52 (−1.63 to 0.60)		−0.56 (−1.66 to 0.55)		−0.04 (−1.17 to 1.09)	
Nighttime diastolic	0.08 (−1.01 to 1.16)		0.36 (−0.73 to 1.45)		0.28 (−0.80 to 1.35)	

[a]Model 1: The primary outcome analysis was performed using a multiple linear regression model adjusted for the ambulatory SBP at baseline, sex and stratification variables (age (<55 years and ≥55 years) and recruiting center) according to the intention-to-treat principle. A *P* value of 0.0167 was considered significant for adjustment for multiple hypothesis testing. [b]Model 2 was a sensitivity analysis performed with stratification variables (age and recruiting center), sex, respective baseline ambulatory BP values, presence of diabetes mellitus, BMI, heart rate and duration of hypertension.

Table 3 | Adjusted mean between-group differences in changes from baseline in office BP

Office BP	Amlodipine–perindopril versus perindopril–indapamide	Amlodipine–perindopril versus amlodipine–indapamide	Perindopril–indapamide versus amlodipine–indapamide
	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)
Systolic			
Month 2	−1.40 (−2.79 to 0.00)	−1.03 (−2.43 to 0.37)	0.37 (−1.02 to 1.76)
Month 4	−0.45 (−1.86 to 0.96)	−0.07 (−1.49 to 1.34)	0.37 (−1.03 to 1.78)
Month 6	−0.49 (−1.91 to 0.93)	−0.67 (−2.11 to 0.76)	−0.18 (−1.61 to 1.25)
Diastolic			
Month 2	−1.25 (−2.31 to −0.20)	−0.97 (−2.03 to 0.09)	0.29 (−0.77 to 1.34)
Month 4	−0.61 (−1.68 to 0.45)	0.34 (−0.73 to 1.41)	0.96 (−0.11 to 2.02)
Month 6	−0.37 (−1.44 to 0.71)	−0.51 (−1.61 to 0.58)	−0.15 (−1.23 to 0.93)

Office BP was measured at baseline and at 2 months, 4 months and 6 months (the average of the last two of three office BP readings is shown). The between-group differences in mean change in BP from baseline were estimated using a linear mixed-effects model adjusting for baseline value, gender and randomization stratification variables (age and site) as fixed effects and participant as a random effect, time-by-arm interaction.

2 months because indapamide sustained release (SR) is only available at a dose of 1.5 mg in an SPC with amlodipine. However, the BP-lowering efficacy of the indapamide SR 1.5 mg formulation is equivalent to the indapamide 2.5 mg formulation combined with perindopril[23,24]. Hence, between months 2 and 6, all medicines in the SPCs were at the usual maximum clinical dosage.

The study has important strengths. The three individual components of dual combinations evaluated in this trial—amlodipine, perindopril and indapamide—were used alone, in combination or with other drugs in several previous cardiovascular outcome trials[8–11]. These trials showed substantial benefit on various major cardiovascular endpoints and in different subgroups of patients (for example, diabetes, post-stroke and very elderly). Along with the BP-lowering efficacy reported here, these trials provide reassurance and support for the use of the dual combinations evaluated in this trial on South Asian patients, at least in the context of India.

The results of this trial may reasonably be extrapolated to a broad spectrum of Indian patients with hypertension because trial participants were recruited from 32 sites across the country with a wide age range (30–79 years); both men and women were well represented; and the trial included a mixture of treated and untreated patients.

In conclusion, in this trial involving South Asian patients in India, we found similar safety and efficacy in lowering ambulatory and office BPs with dual combinations of amlodipine–perindopril, perindopril–indapamide and amlodipine–indapamide. The study findings provide novel evidence to inform the choice of dual combination therapies for hypertension treatment among South Asians in India and potentially the diaspora.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-03854-w.

Table 4 | Secondary outcome analysis—office BP response and control rates

	Amlodipine–perindopril	Perindopril–indapamide	Amlodipine–indapamide
	n=661	*n*=662	*n*=658
	n (%)	*n* (%)	*n* (%)
Response rate[a]			
2-month	266 (40.2)	243 (36.7)	237 (36.0)
4-month	301 (45.5)	302 (45.6)	307 (46.7)
6-month	315 (47.7)	317 (47.9)	306 (46.5)
Proportion of responders[b]	266 (40.2)	260 (39.3)	248 (37.7)
Control rate[c] (<140 and 90 mmHg)			
2-month	424 (64.1)	411 (62.1)	417 (63.4)
4-month	464 (70.2)	478 (72.2)	470 (71.4)
6-month	470 (71.1)	486 (73.4)	454 (69.0)
Proportion with BP control[d]	440 (66.6)	457 (69.0)	429 (65.2)
Control rate[c] (<130 and 80 mmHg)			
2-month	221 (33.4)	196 (29.6)	199 (30.2)
4-month	267 (40.4)	266 (40.2)	285 (43.3)
6-month	282 (42.7)	274 (41.4)	262 (39.8)
Proportion with BP control[d]	194 (29.3)	195 (29.5)	191 (29.0)

Office BP was measured at baseline and at 2 months, 4 months and 6 months (the average of the last two of three office BP readings is used). [a]The response rate is the proportion of patients with a reduction in office SBP ≥20 mmHg and office DBP ≥10 mmHg at a given time. [b]The proportion of patients classified as 'responders' is defined as those who had a reduction of office SBP ≥20 mmHg and office DBP ≥10 mmHg at any of their office visits, with maintenance of this reduction at the 6-month office visit. [c]The control rate is the proportion of patients with an office BP of less than (140 and 90 mmHg or 130 and 80 mmHg) at a given time. [d]The proportion of patients who achieve BP control is defined as achieving target BP (less than 140 and 90 mmHg or 130 and 80 mmHg) at any of their office visits, with maintenance of this reduction at the 6-month office visit.

References

1. World Health Organization. Global report on hypertension: the race against a silent killer. *WHO* https://www.who.int/publications/i/item/9789240081062 (2023).
2. Brauer, M. et al. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* **403**, 2162–2203 (2024).
3. Whelton, P. K. 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* **71**, 1269–1324 (2018).
4. Unger, T. et al. 2020 International Society of Hypertension global hypertension practice guidelines. *Hypertension* **75**, 1334–1357 (2020).
5. McEvoy, J. W. et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur. Heart J.* **45**, 3912–4018 (2024).
6. Shah, S. N. et al. Indian guidelines on hypertension-IV (2019). *J. Hum. Hypertens.* **34**, 745–758 (2020).
7. Dahlöf, B. et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* **366**, 895–906 (2005).
8. Julius, S. et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* **363**, 2022–2031 (2004).
9. Jamerson, K. et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N. Engl. J. Med.* **359**, 2417–2428 (2008).
10. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* **288**, 2981–2997 (2002).
11. Gupta, A. K. et al. Ethnic differences in blood pressure response to first and second-line antihypertensive therapies in patients randomized in the ASCOT trial. *Am. J. Hypertens.* **23**, 1023–1030 (2010).
12. Materson, B. J. et al. Single-drug therapy for hypertension in men—a comparison of six antihypertensive agents with placebo. *N. Engl. J. Med.* **328**, 914–921 (1993).
13. Ojji, D. B. et al. Comparison of dual therapies for lowering blood pressure in black Africans. *N. Engl. J. Med.* **380**, 2429–2439 (2019).
14. Anchala, R. et al. Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension. *J. Hypertens.* **32**, 1170–1177 (2014).
15. Roy, A. et al. Changes in hypertension prevalence, awareness, treatment and control rates over 20 years in National Capital Region of India: results from a repeat cross-sectional study. *BMJ Open* **7**, e015639 (2017).
16. Varghese, J. S. et al. Hypertension diagnosis, treatment, and control in India. *JAMA Netw. Open* **6**, e2339098 (2023).
17. Zhou, B. et al. Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. *Lancet* **394**, 639–651 (2019).
18. Geldsetzer, P. et al. The state of hypertension care in 44 low-income and middle-income countries: a cross-sectional study of nationally representative individual-level data from 1.1 million adults. *Lancet* **394**, 652–662 (2019).
19. Beaney, T. et al. May Measurement Month 2019. *Hypertension* **76**, 333–341 (2020).
20. Deepa, M. et al. High burden of prediabetes and diabetes in three large cities in South Asia: the Center for cArdio-metabolic Risk Reduction in South Asia (CARRS) Study. *Diabetes Res. Clin. Pract.* **110**, 172–182 (2015).
21. Anjana, R. M. et al. Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). *Lancet Diabetes Endocrinol.* **11**, 474–489 (2023).
22. Oza-Frank, R. & Narayan, K. M. V. Overweight and diabetes prevalence among US immigrants. *Am. J. Public Health* **100**, 661–668 (2010).
23. Asmar, R. et al. Therapeutic benefit of a low dose of indapamide: results of a double-blind against placebo European controlled study. *Arch. Mal. Coeur Vaiss.* **88**, 1083–1087 (1995).
24. Ambrosioni, E. et al. Low-dose antihypertensive therapy with 1.5 mg sustained-release indapamide: results of randomised double-blind controlled studies. European study group. *J. Hypertens.* **16**, 1677–1684 (1998).

Dorairaj Prabhakaran[1,39] ✉, Ambuj Roy[2,39], Ambalam M. Chandrasekaran[1], Dimple Kondal[1], Somnath Mukherjee[1], Gaia Kiru[3], Kavita Singh[4], Hyndavi Salwa[1], Edmin Christa Sobitharaj[1], Ameeka Shereen Lobo[1], Gayatri Mahajan[1], Bishav Mohan[5], Aman Khanna[6], Amit Malviya[7], Satish G. Patil[8], Vinod K. Abichandani[9], Bhupinder Singh[10], Bal Kishan Gupta[11], Balsubramaiam Yellapantula[12], Shailendra Dandge[13], Shantanu Sengupta[14], Sunil Kumar[15], Neil Bardoloi[16], Nagendra Boopathy Senguttuvan[17], Rakesh Kumar Sahay[18], Suvarna Patil[19], Surender Deora[20], Rajpurohit Prahalad[21], Vijaya Parthasaradhi Sarvepalli[22], Justin Paul Gnanaraj[23], Mallika Khanna[6], Animesh Mishra[7], Kiran Aithal[8], Vipul Chavda[9], Victoria R. Cornelius[3], TOPSPIN Clinical Consortia* & Neil R. Poulter[3]

[1]Centre for Chronic Disease Control, New Delhi, India. [2]Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India. [3]Imperial Clinical Trials Unit, Imperial College London, London, UK. [4]Heidelberg University, Heidelberg, Germany. [5]DMC Heart Institute, Ludhiana, India. [6]Aman Hospital and Research Center, Vadodara, India. [7]North Eastern Indira Gandhi Regional Institute of Medical Sciences, Shillong, India. [8]Shri Dharmasthala Manjunatheshwara University, Dharwad, India. [9]Rudraksh Hospital, Rudraksha Speciality Hospital, Ahmedabad, India. [10]Department of Cardiology, All India Institute of Medical Sciences, Bhatinda, India. [11]Department of Medicine, S.P. Medical College and A.G. of Hospitals Bikaner, Bikaner, India. [12]Shalinitai Meghe Hospital and Research Center, Nagpur, India. [13]Mediciti Institute of Medical Sciences, Hyderabad, India. [14]Sengupta Hospital and Research Institute, Nagpur, India. [15]JSS Hospital, Mysuru, India. [16]Apollo Excelcare Hospital, Guwahati, India. [17]Sri Ramchandra Institute of Higher Education and Research, Chennai, India. [18]Osmania General Hospital, Hyderabad, India. [19]B.K.L. Walawalkar Rural Medical College, Sawarde, India. [20]All India Institute of Medical Sciences, Jodhpur, India. [21]Apollo Institute of Medical Sciences, Hyderabad, India. [22]Apollo Hospitals DRDO, Hyderabad, India. [23]Madras Medical College, Chennai, India. [39]These authors contributed equally: Dorairaj Prabhakaran, Ambuj Roy. *A list of authors and their affiliations appear at the end of the paper. ✉e-mail: dprabhakaran@ccdcindia.org

TOPSPIN Clinical Consortia

Aman Khanna[6], Mallika Khanna[6], Amit Malviya[7], Animesh Mishra[7], Kyrshanglang G. Lynrah[7], Kiran Aithal[8], Satish G. Patil[8], Vinod K. Abichandani[9], Vipul Chavda[9], Bishav Mohan[5], Gurpreet Singh Wander[5], Gautam Singal[5], Akash Batta[5], Ankush Mittal[5], Bhupinder Singh[10], Suraj Kumar[10], Deepak Chaudhary[10], Maninder Kansal[10], B. K. Gupta[11], Jigyasa Gupta[11], Balsubramaniam Yellapantula[12], Ankita Kapse[12], D. Shailendra[13], M. Sneha Manju[13], Shantanu Sengupta[14], M. Suchitra Uikey[14], Aniket Wazade[14], Sunil Kumar[15], Prathibha Pereira[15], K. M. Srinath[15], K. C. Shashidhara[15], Vinay Kumar[15], Ajay Hanumamthu[15], K. S. Poornima[15], Neil Bardoloi[16], Dhanjit Nath[16], Amitava Misra[16], Nagendra Boopathy Senguttuvan[17], Mohini Singh[17], Rakesh Kumar Sahay[18], S. Lekshmi[18], Said Jabir[18], Suvarna Patil[19], Sachin Surnar[19], Pranav Shamraj[19], Jyoti L. Iyer[19], Surender Deora[20], Deepti Mathur[20], Rajpurohit Prahalad[21], M. B. Shalini[21], S. V. Partha Saradhi[22], Justin Paul Gnanaraj[23], Rajendran Velayudham[23], Sudha Kulur Mukhyaprana[23], Hariharan Chellapandy[23], Vivek Jaganathan[23], Ramadevi Kanakasabapathi[23], E. Theranirajan[23], Debomallya Bhuyan[24], Barnali Bhuyan[24], Shoubhik Bhattacharjee[24], Sindhuja Kunapareddy[24], Ambuj Roy[3], Sandeep Singh[3], Sayavir Yadav[3], Kamar Ali[3], P. B. Jayagopal[25], Vinit Kr Shah[26], L. Sreenivasa Murthy[27], G. Pramod Bagali[27], P. V. Raghav Sarma[28], Chinta Srinivasarao[28], Sharan Badiger[29], Avinash V. Jugati[29], Saptarshi Bhattacharya[30], O. R. Kumaran[31], Anitha Kolukula[32], Harika Menti[32], H. C. Kalita[33], Hemant Thacker[34], Abhishek Subhas[34], Sudhir Varma[35], Harpreet Kalra[35], Sanchit Sood[35], Navjot Kaur[35], Prabh Simranpal[35], Taniya Aggarwal[35], Jabir Abdullakutty[36], Prashant Kr Sahoo[37], Sharmila Moharana[37], Yusuf A. Kumble[38] & P. N. Sandhya Rani[38]

[24]Nazareth Hospital, Shillong, India. [25]Lakshmi Hospital, Palakkad, India. [26]Apollo Hospitals, Ahmedabad, India. [27]Lifecare Hospital and Research Centre, Bengaluru, India. [28]Lalitha Super Specialties Hospital, Guntur, India. [29]BLDE Hospital, Vijayapura, India. [30]Indraprastha Apollo Hospitals, New Delhi, India. [31]Apollo Hospitals, Madurai, India. [32]Apollo Hospitals, Visakhapatnam, India. [33]Assam Medical College, Dibrugarh, India. [34]Bhatia Hospital, Mumbai, India. [35]Sadbhavna Medical and Heart Institute, Patiala, India. [36]Lisie Hospital, Kochi, India. [37]Apollo Hospitals, Bhubaneshwar, India. [38]Indiana Hospital and Heart Institute, Mangalore, India.

Methods

Trial design and oversight

TOPSPIN was a prospective, single-blind, randomized three-arm trial conducted in 32 centers across India (3 of the 35 centers did not recruit any participants (Supplementary Table 1)). The detailed protocol of the study is published elsewhere[25]. A Trial Operations Committee managed the day-to-day running; a Trial Steering Committee oversaw the study's progress; and a Data Safety and Monitoring Committee reviewed patient safety (see Supplementary Tables 2 and 3 for committee membership).

The study protocol was approved by the ethics committees of the participating centers and the coordinating center and was approved by the national regulatory authority.

Trial population and recruitment

Men and women 30–79 years of age were eligible if their sitting office SBP was between 140 and 159 mmHg on one antihypertensive medication or between 150 and 179 mmHg in drug-naive patients. Patients with a history of coronary artery and cerebrovascular diseases, congestive heart failure, serum creatinine above 1.5 mg dl^{-1}, current pregnancy and secondary hypertension were excluded (see the study protocol in the Supplementary Information for a full list of inclusion and exclusion criteria). All participants provided written informed consent. Three sitting office BP measurements were recorded using standard methods with a fully automated oscillometric device (HEM-7201; Omron). The mean of the last two office BP recordings was used for patient eligibility and subsequent evaluations. Standard biochemical tests were performed for all patients. A 24-hour ABPM with readings taken every 30 minutes was performed using a validated device (TM-2440; A&D Medical). A minimum of 34 valid readings were needed to qualify as an adequate ABPM, and inadequate recordings were repeated. The mean of all valid readings was used in the analysis.

Randomization and treatment

Eligible participants were randomly allocated to one of the three study arms in a 1:1:1 ratio using variable permuted block electronic randomization. The randomization was stratified by age (<55 years or ≥55 years) and recruiting center. The investigators were unaware of the trial group assignments (single-blind randomization). The pills provided to the patients were not identical because of cost and logistical reasons; however, repackaging them in opaque packs minimized potential bias. After randomization, the patients discontinued their previous antihypertensive medications without a washout period and received one of the following once-daily SPCs: amlodipine 5 mg plus perindopril 4 mg or perindopril 4 mg plus indapamide 1.25 mg or amlodipine 5 mg plus indapamide SR 1.5 mg. For the first 2 months, it was not possible to provide equivalent dosing of indapamide in combination with perindopril and with amlodipine because amlodipine 5 mg is only produced in combination with indapamide SR at a dose of 1.5 mg, whereas perindopril 4 mg is combined with the non-SR formulation of indapamide at 1.25 mg. At 2 months, the doses were up-titrated to amlodipine 10 mg plus perindopril 8 mg or perindopril 8 mg plus indapamide 2.5 mg or amlodipine 10 mg plus indapamide SR 1.5 mg if the office SBP was ≥120 mmHg. At 4 months, a beta-blocker (bisoprolol 5 mg) was added if the SBP was ≥160 mmHg or the DBP was ≥100 mmHg. Spironolactone 12.5 mg or doxazosin 2 mg was added in patients for whom a beta-blocker was contraindicated. A pill count was done to assess adherence at scheduled visits (2, 4 and 6 months). Participants taking 80% or more of the prescribed doses throughout the trial were defined as adherent.

Trial outcomes

The primary outcome was the difference among the treatment groups in the mean reduction in the 24-hour ambulatory SBP at 6 months adjusted for baseline ambulatory SBP. Secondary outcomes included a reduction in ambulatory DBP; mean change in the daytime (9:00 to 21:00) and nighttime (24:00 to 6:00) ambulatory BPs; change in office BP at 2, 4 and 6 months; the proportion of participants achieving conservative (<140/90 mmHg) or more current (<130/80 mmHg) BP control level at any of the office visits and maintained at 6 months; the proportion of 'responders' to treatment (defined as a reduction of SBP of ≥20 mmHg and DBP of ≥10 mmHg at any of the office visits and maintained at 6 months); and changes in laboratory investigations, fasting blood glucose, lipid profile, serum sodium, potassium, urea, creatinine and eGFR. The safety endpoint of the study was the occurrence of adverse or serious adverse events leading to withdrawal of the study drug at any of the follow-ups. Prespecified subgroup analysis for the primary outcomes were age (<55 years and ≥55 years), sex (male and female), self-reported history of diabetes at baseline and previously or newly diagnosed hypertension at baseline and BMI of <23, 23–24.9 and ≥25 kg m^{-2}.

Statistical analysis

With a planned sample size of 1,968 participants, the TOPSPIN trial had 85% power to detect a clinically meaningful difference of 3 mmHg in the 24-hour ambulatory SBP among the three groups. The assumptions included an s.d. of 15.0 mmHg, a two-sided significance level of 0.0167 (considered significant for adjustment of multiple hypothesis testing[26] for the three comparisons) and a 10% dropout rate.

Data from clinical sites were collected using Clinion software version 3.0, and statistical analyses were conducted at the research coordinating center using Stata version 16.0. Baseline characteristics and key safety outcomes were compared between the study groups using the chi-square test, Fisher's exact test, Wilcoxon rank-sum test and the two-sample *t*-test.

The primary outcome analysis was performed using a multiple linear regression model adjusted for the ambulatory SBP at baseline, age strata (<55 years and ≥55 years), recruiting center and sex according to the intention-to-treat principle. We performed multiple imputations for the primary analysis using multiple imputation chained equations for participants with a missing primary endpoint value. We generated 50 imputed datasets with a maximum of 1,000 iterations with linear imputation, including the treatment group, ambulatory SBP and DBP, office BP measurements, age, sex, recruiting center, BMI, presence of diabetes, duration of hypertension and pulse rate. This approach was repeated for the ambulatory DBP analysis[27,28]. We also performed analyses following the complete case scenario and per-protocol analyses, including only adherent participants.

We used a linear mixed-effect model to estimate the between-group mean difference in change in office BP measurement from baseline. The model included the participant as a random effect and age, site, sex and time-by-arm interaction as fixed effects. The same models were used for other continuous variable secondary outcomes. We compared the between-group differences in response and control rate, adjusting for age, recruiting center, sex and time-by-arm interaction using logistic regression. We did not plan for multiple comparison adjustments for secondary outcomes. Hence, we estimated the treatment effects in secondary outcomes as point estimates with 95% CIs (see the statistical analysis plan in the Supplementary Information).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Raw data cannot be publicly shared as per the Health Ministry Screening Committee of the Indian Government (National Regulatory Authority for human research with contributions from other countries), which mandates that no data can be shared beyond the borders without necessary approvals. Anonymized and tabulated or curated data will be made

available to bona fide researchers for the purpose of meta-analysis and similar research interests with necessary approvals. Requests may be made to D.P. (dprabhakaran@ccdcindia.org). All such requests will be responded to within a 2-week timeframe.

References

25. Kiru, G. et al. Treatment optimisation for blood pressure with single-pill combinations in India (TOPSPIN)—protocol design and baseline characteristics. *Int. J. Cardiol. Cardiovasc. Risk Prev.* **23**, 200346 (2024).
26. Hommel, G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika* **75**, 383 (1988).
27. Cro, S., Morris, T. P., Kenward, M. G. & Carpenter, J. R. Sensitivity analysis for clinical trials with missing continuous outcome data using controlled multiple imputation: a practical guide. *Stat. Med.* **39**, 2815–2842 (2020).
28. Austin, P. C., White, I. R., Lee, D. S. & van Buuren, S. Missing data in clinical research: a tutorial on multiple imputation. *Can. J. Cardiol.* **37**, 1322–1331 (2021).

Acknowledgements

We thank the members of the Trial Steering Committee and Data Safety and Monitoring Committee members of the TOPSPIN trial. We thank the TOPSPIN trial participants and their caregivers. The trial was supported by Imperial College London, the Centre for Chronic Disease Control, New Delhi and Servier International, France (unrestricted educational grant and in-kind logistical support). Servier had no role in the study's design, data collection, analysis or manuscript preparation.

Author contributions

D.P., A.R. and N.P. designed the study, coordinated the research and wrote the first draft of the paper. The TOPSPIN Clinical Consortia members conducted the trial in their hospitals. D.K. conducted the statistical analysis. V.R.C. reviewed the statistical analysis. S.M. and A.M.C. coordinated the conduct of the trial. All authors vouch for the accuracy and credibility of the data and the fidelity of the trial's conduct to the study protocol.

Competing interests

N.P. has received financial support from several pharmaceutical companies that manufacture BP-lowering agents. N.P. has received consultancy fees (Servier and Aktiia), funding for research projects and staff (Servier and Pfizer) and fees for arranging and speaking at educational meetings (AstraZeneca, Lri Therapharma, Napi, Servier, Sanofi, Eva Pharma, Pfizer, Emcure India, Dr. Reddy's Laboratories and Zydus). He holds no stocks or shares in any such company. D.P.'s institution, the Centre for Chronic Disease Control, has received research grants from Sun Pharmaceuticals, Lupin Limited and Intas Pharmaceuticals in India for capacity building of primary care physicians in cardiovascular diseases. The other authors declare no competing interests.

Additional information

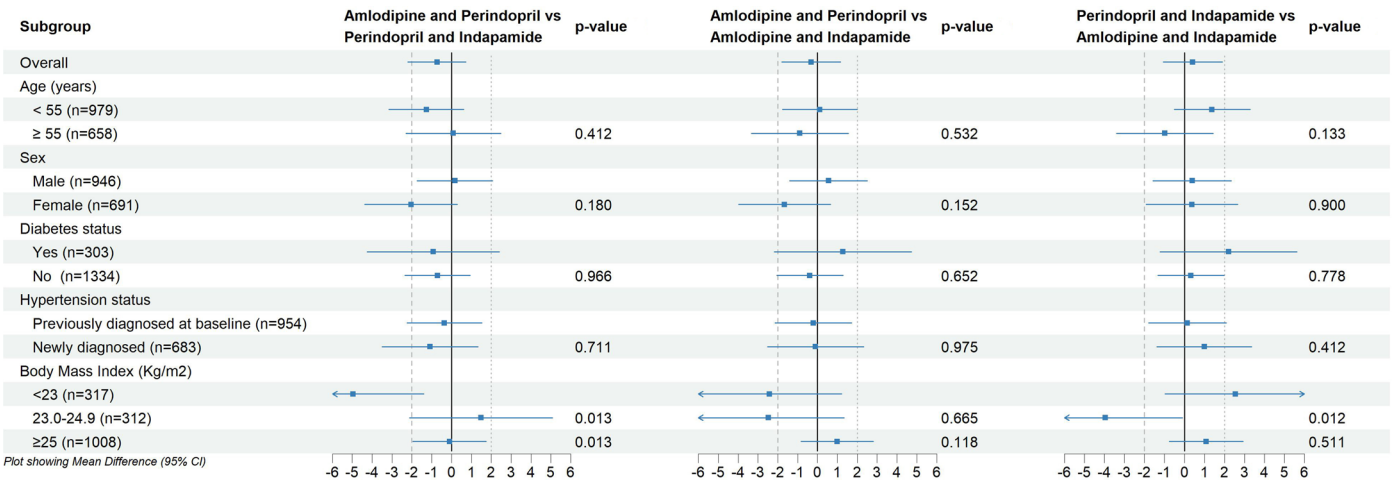
Extended data is available for this paper at https://doi.org/10.1038/s41591-025-03854-w.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-025-03854-w.

Correspondence and requests for materials should be addressed to Dorairaj Prabhakaran.

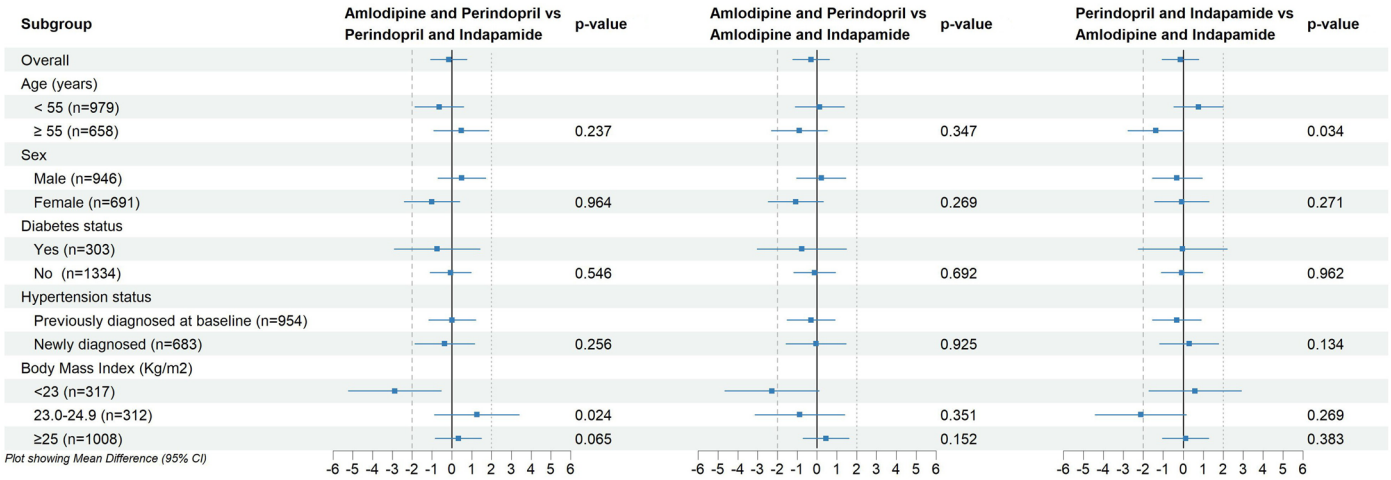
Peer review information *Nature Medicine* thanks David Flood, Andrew Moran, Gurpreet Singh Wander and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Michael Basson, in collaboration with the *Nature Medicine* team.

https://doi.org/10.1038/s41591-025-03854-w



Extended Data Fig. 1 | Changes in Ambulatory Systolic Blood Pressure by Pre-Specified Sub-Groups. Plots showing mean difference with 95% CI and p-value for interaction.

https://doi.org/10.1038/s41591-025-03854-w



Extended Data Fig. 2 | Changes in Ambulatory Diastolic Blood Pressure by Pre-Specified Sub-Groups. Plots showing mean difference with 95% CI and p-value for interaction.

https://doi.org/10.1038/s41591-025-03854-w

Extended Data Table 1 | Comparison of baseline demographic and clinical characteristics of participants with and without ABPM at 6 months

Characteristic	Participants with ambulatory blood pressure (N=1637)	Participants without ambulatory blood pressure (N=344)
Age		
Mean – yr	52.1±11.2	51.8±11.4
Distribution – no. (%)		
≥55 yr	658 (40.2%)	139 (40.4%)
<55 yr	979 (59.8%)	205 (59.6%)
Gender		
Female – no. (%)	691 (42.2%)	143 (41.6%)
Body-mass index (kg/m^2)†	26.5±4.2	26.4±4.0
Current smoker – no. (%)	169 (10.3%)	29 (8.4%)
Diabetes – no. (%)‡	303 (18.5%)	67 (19.5%)
Dyslipidemia – no. (%)‡	117 (7.1%)	27 (7.8%)
Blood pressure – mmHg		
Office systolic§	155.5±9.7	154.8±9.9
Office diastolic	91.9±10.8	92.3±11.1
24-hour ambulatory systolic¶	135.4±17.0	136.0±17.0
24-hour ambulatory diastolic	84.4±11.0	84.8±10.5
Daytime ambulatory systolic	140.0±17.0	140.0±17.6
Daytime ambulatory diastolic	88.0±11.4	87.7±10.9
Nighttime ambulatory systolic	126.4±20.4	127.3±19.8
Nighttime ambulatory diastolic	77.8±12.8	78.5±12.4
Previous antihypertensive therapy – no. (%)		
ARB	497 (30.4%)	101 (29.4%)
Calcium-channel blocker	269 (16.4%)	72 (20.9%)
Beta-blocker	96 (5.9%)	9 (2.6%)
ACE inhibitor	13 (0.8%)	7 (2.0%)
Diuretic	3 (0.2%)	0 (0.0%)

Plus–minus values are means±s.d. †BMI is the weight in kilograms divided by the square of the height in meters. ‡Self-reported history §Average of the last two of three office BP readings ¶24-hour ambulatory BP was measured (one reading every 30 minutes) using a TM-2440 device (A&D Medical). Daytime ambulatory BP was estimated as the average of values between 9:00 and 21:00 and nighttime ambulatory BP as the average of values between 24:00 and 6:00.

https://doi.org/10.1038/s41591-025-03854-w

Extended Data Table 2 | Baseline laboratory parameters

Laboratory parameter	Amlodipine-Perindopril (N=661)	Perindopril-Indapamide (N=662)	Amlodipine-Indapamide (N=658)
Sodium (mmol/L)	138.9±3.0	139.0±3.2	139.1±3.3
Potassium (mmol/L)	4.3±0.4	4.3±0.5	4.3±0.5
Urea (mg/dL)	22.9±7.9	23.0±8.5	23.1±8.0
Uric acid (mmol/L)	4.9±1.9	4.8±1.9	4.8±1.8
Serum creatinine (mg/dL)	0.8±0.2	0.9±0.2	0.8±0.2
Urine albumin creatinine ratio	48.7(187.7)	58.0(166.4)	41.0 (133.0)
eGFR (CKD EPI 2009) equation code, mean (SD)	94.3±18.4	94.0±19.1	94.3±18.4
Fasting blood glucose (mg/dL)	115.6±47.7	111.5±40.7	111.3±44.0
Glycated hemoglobin (%)	6.4±1.7	6.3±1.5	6.3±1.6
Total cholesterol (mg/dL)	187.3±41.9	184.9±41.3	186.4±41.1
LDL (mg/dL)	114.3±35.8	114.0±36.6	115.1±35.7
HDL (mg/dL)			
Male	44.3 ± 11.3	44.2 ± 10.6	44.1 ± 10.9
Female	46.9 ± 10.7	47.0 ± 12.0	47.5 ± 11.7
Triglycerides (mg/dL)	163.3±96.1	160.3±128.1	153.3±86.4
Hemoglobin (g/dL)	13.6±1.8	13.7±1.8	13.5±1.9
White blood cells (10*9)/L	7791.9 (3164.6)	7665.5 (2825.1)	7407.1 (1898.2)

Values are presented as mean±s.d. or median (interquartile range).

https://doi.org/10.1038/s41591-025-03854-w

Extended Data Table 3 | Adjusted mean between-group differences in changes from baseline in ambulatory BP (complete case analysis)

Ambulatory Blood pressure	Amlodipine-Perindopril vs. Perindopril-Indapamide	Amlodipine-Perindopril vs. Amlodipine-Indapamide	Perindopril-Indapamide vs. Amlodipine-Indapamide
	Mean Difference (95% CI)	Mean Difference (95% CI)	Mean Difference (95% CI)
Model 1†			
Primary outcome			
24-hour systolic	-0.73 (-2.2, 0.73)	-0.32 (-1.81, 1.16)	0.41 (-1.07, 1.89)
Secondary Outcomes			
24-hour diastolic	-0.15 (-1.07, 0.76)	-0.30 (-1.23, 0.62)	-0.15 (-1.07, 0.77)
Daytime systolic	-0.95 (-2.54, 0.63)	-0.67 (-2.28, 0.93)	0.28 (-1.32, 1.88)
Nighttime systolic	0.12 (-1.65, 1.89)	0.31 (-1.48, 2.11)	0.20 (-1.59, 1.99)
Daytime diastolic	-0.30 (-1.38, 0.78)	-0.50 (-1.59, 0.6)	-0.20 (-1.29, 0.89)
Nighttime diastolic	0.19 (-0.89, 1.27)	0.39 (-0.7, 1.48)	0.20 (-0.89, 1.28)
Model 2‡			
Primary outcome			
24-hour systolic	-0.84 (-2.31, 0.63)	-0.31 (-1.8, 1.18)	0.53 (-0.95, 2)
Secondary Outcomes			
24-hour diastolic	-0.28 (-1.2, 0.63)	-0.39 (-1.32, 0.54)	-0.11 (-1.03, 0.81)
Daytime systolic	-1.04 (-2.63, 0.54)	-0.64 (-2.25, 0.97)	0.41 (-1.19, 2.00)
Nighttime systolic	0.02 (-1.75, 1.80)	0.34 (-1.46, 2.14)	0.31 (-1.48, 2.1)
Daytime diastolic	-0.42 (-1.51, 0.66)	-0.56 (-1.66, 0.54)	-0.13 (-1.22, 0.96)
Nighttime diastolic	0.06 (-1.02, 1.14)	0.29 (-0.8, 1.39)	0.23 (-0.86, 1.32)

†Model 1 was performed using a multiple linear regression model adjusted for the ambulatory SBP at baseline, age (<55 years and ≥55 years), clinical site and sex among participants who completed the follow-up. ‡Model 2 was a sensitivity analysis performed with stratification variables (age and clinical site), sex, respective baseline ambulatory BP values, presence of diabetes mellitus, BMI, heart rate and duration of hypertension among participants who completed the follow-up.

https://doi.org/10.1038/s41591-025-03854-w

Extended Data Table 4 | Adjusted mean differences in BP response and control between the groups

	Amlodipine-Perindopril vs. Perindopril-Indapamide	Amlodipine-Perindopril vs. Amlodipine-Indapamide	Perindopril-Indapamide vs. Amlodipine-Indapamide
	Mean Difference (95% CI)	**Mean Difference (95% CI)**	**Mean Difference (95% CI)**
Response rate†			
2 month	4.43 (-1.11, 9.98)	4.98 (-0.57, 10.53)	0.55 (-4.94, 6.04)
4 month	0.72 (-4.9, 6.34)	-1.41 (-7.02, 4.21)	-2.12 (-7.73, 3.48)
6 month	1.21 (-4.4, 6.82)	0.53 (-5.13, 6.18)	-0.68 (-6.32, 4.96)
Proportion of responders‡	1.19 (-4.3, 6.69)	2.85 (-2.64, 8.35)	1.66 (-3.82, 7.14)
Control rate§ (<140 and 90 mmHg)			
2 month	2.91 (-2.12, 7.94)	1.53 (-3.48, 6.53)	-1.38 (-6.45, 3.68)
4 month	-1.74 (-6.07, 2.59)	-1.46 (-5.81, 2.9)	0.28 (-3.98, 4.54)
6 month	-0.64 (-4.73, 3.45)	1.3 (-2.95, 5.54)	1.94 (-2.24, 6.11)
Proportion with blood pressure control¶	-2.4 (-7.12, 2.32)	1.77 (-3.08, 6.63)	4.17 (-0.59, 8.93)
Control rate§ (<130 and 80 mmHg)			
2 month	4.54 (-0.81, 9.89)	3.95 (-1.41, 9.31)	-0.59 (-5.88, 4.7)
4 month	0.59 (-5.04, 6.21)	-3.31 (-8.95, 2.34)	-3.89 (-9.53, 1.75)
6 month	2.68 (-3.02, 8.38)	2.75 (-3.01, 8.5)	0.07 (-5.67, 5.8)
Proportion with blood pressure control¶	0.27 (-5.03, 5.56)	0.56 (-4.75, 5.86)	0.29 (-4.99, 5.57)

Office BP was measured at baseline and at 2 months, 4 months and 6 months (average of the last two of three office BP readings). The between-group differences in mean change in BP from baseline to 6 months were estimated using a linear mixed-effects model adjusting for baseline value and randomization stratification variables (age and site) as fixed effects and participant as a random effect, time-by-arm interaction. †The response rate is the proportion of patients with a reduction in the office SBP ≥20 mmHg and office DBP ≥10 mmHg at a given time. ‡ The proportion of patients classified as 'responders' was defined as those who had a reduction of office SBP ≥20 mmHg and office DBP ≥10 mmHg at any of their clinic visits and maintained at the 6-month clinic visit. §The control rate is the proportion of patients with an office BP of less than (140 and 90 mmHg or 130 and 80 mmHg) at a given time. ¶The proportion of patients who achieve BP control is defined as achieving target BP (140 and 90 mmHg or 130 and 80 mmHg) at any of their clinic visits and maintained at the 6-month clinic visit.

https://doi.org/10.1038/s41591-025-03854-w

Extended Data Table 5 | Six-month and mean change in laboratory parameters

	Amlodipine-Perindopril	Perindopril-Indapamide	Amlodipine-Indapamide	Amlodipine-Perindopril vs. Perindopril-Indapamide	Amlodipine-Perindopril vs. Amlodipine-Indapamide	Perindopril-Indapamide vs. Amlodipine-Indapamide
	mean±SD	mean±SD	mean±SD	Mean Difference (95% CI)	Mean Difference (95% CI)	Mean Difference (95% CI)
Fasting blood glucose, mg/dL	110.6±40.0	111.3±46.1	114.9±46.6	-2.47 (-6.61, 1.67)	-5.69 (-9.88, -1.5)*	-3.22 (-7.38, 0.94)
Glycated hemoglobin (%)	6.0 ± 1.3	6.1 ± 1.3	6.2 ± 1.6	-0.15 (-0.27, 0.03)	-0.20 (-0.32, -0.08)*	-0.06 (-0.18, 0.06)
Total cholesterol, mg/dL	178.6±40.8	179.0±41.8	180.9±43.4	-2.09 (-6.03, 1.85)	-0.93 (-4.92, 3.06)	1.16 (-2.81, 5.13)
Triglycerides, mg/dL	157.4±85.8	156.0±88.4	153.9±76.9	0.05 (-8.29, 8.4)	1.63 (-6.81, 10.07)	1.58 (-6.82, 9.97)
HDL-C, mg/dL						
Male	46.7 ± 12.0	46.6 ± 13.6	48.3 ± 13.9	-0.77 (-2.54, 1.00)	0.02 (-1.80, 1.85)	0.79 (-1.02, 2.61)
Female	43.9 ± 12.0	44.8 ± 14.6	44.0 ± 10.8	-0.10 (-2.23, 2.02)	-1.61 (-3.72, 0.50)	-1.51 (-3.61, 0.58)
LDL-C, mg/dL	108.3±34.9	109.0±36.9	110.9±35.5	-2.03 (-5.53, 1.47)	-0.8 (-4.34, 2.74)	1.24 (-2.28, 4.75)
Serum sodium, mmol/L	138.6±3.3	138.2±3.5	139.1±3.3	0.43 (0.06, 0.81)*	-0.39 (-0.77, -0.01)*	-0.83 (-1.2, -0.45)*
Potassium, mmol/L	4.3±0.5	4.2±0.5	4.0±0.5	0.1 (0.04, 0.15)*	0.31 (0.26, 0.37)*	0.22 (0.16, 0.27)*
Urea, mg/dL	23.4±9.6	25.7±10.7	23.5±8.0	-1.99 (-3.03, -0.94)*	0.08 (-0.98, 1.13)	2.06 (1.01, 3.11)
Uric acid, mmol/L	5.0±1.6	5.7±1.8	5.3±1.7	-0.72 (-0.89, -0.54)*	-0.31 (-0.48, -0.13)*	0.41 (0.23, 0.59)*
Creatinine, mg/dL	0.9±0.3	0.9±0.3	0.8±0.3	-0.03 (-0.06, 0)	0.02 (-0.02, 0.05)	0.05 (0.01, 0.08)*
Urine albumin creatinine ratio†	40.7(76.3)	45.2(102.0)	41.6(144.3)	-2.97 (-21.27, 15.32)	10.57 (-8.00, 29.14)	13.54 (-4.97, 32.06)
Estimated GFR, mL/min/1.73m2 (CKD EPI 2009)	93.4±21.4	90.4±22.8	94.4±21.5	2.55 (0.46, 4.63)*	-1.33 (-3.44, 0.78)	-3.88 (-5.98, -1.78)*

*Comparisons that were statistically significant

https://doi.org/10.1038/s41591-025-03854-w

Extended Data Table 6 | Serious adverse events and adverse events leading to drug withdrawal

Adverse symptoms	Amlodipine-Perindopril (N=661)	Perindopril-Indapamide (N=662)	Amlodipine-Indapamide (N=658)
Serious adverse events*	8	8	5
Adverse events			
Number of participants reporting an adverse event	14	19	18
Total adverse symptoms	23	25	29
Pedal Swelling	5	3	4
Dry Cough	4	3	2
Dizziness	5	11	7
Headache	3	4	3
Angioedema	1	0	1
Urine frequency increased/ decreased	1	0	1
Weakness	0	1	2
Breathlessness	1	1	1
Fall	1	0	1
Electrolyte imbalance	1	0	1
Others	1	2	6

*Serious adverse events were defined as death or all-cause hospitalizations.

https://doi.org/10.1038/s41591-025-03854-w

Extended Data Table 7 | Adjusted mean between-group differences in changes from baseline in ambulatory BP (per-protocol analysis)

Ambulatory Blood pressure	Amlodipine-Perindopril vs. Perindopril-Indapamide	Amlodipine-Perindopril vs. Amlodipine-Indapamide	Perindopril-Indapamide vs. Amlodipine-Indapamide
	Mean Difference (95% CI)	**Mean Difference (95% CI)**	**Mean Difference (95% CI)**
Model 1†			
Primary outcome			
24-hour systolic	-0.68 (-2.32, 0.95)	-0.21 (-1.87, 1.45)	0.48 (-1.17, 2.13)
Secondary Outcomes			
24-hour diastolic	-0.03 (-1.04, 0.97)	0.11 (-0.91, 1.13)	0.14 (-0.87, 1.16)
Daytime systolic	-0.78 (-2.55, 0.99)	-0.48 (-2.28, 1.32)	0.30 (-1.49, 2.09)
Nighttime systolic	0.02 (-1.94, 1.98)	0.38 (-1.61, 2.37)	0.36 (-1.62, 2.35)
Daytime diastolic	-0.45 (-1.65, 0.75)	-0.30 (-1.52, 0.92)	0.15 (-1.06, 1.36)
Nighttime diastolic	0.17 (-1.02, 1.37)	0.67 (-0.54, 1.88)	0.49 (-0.71, 1.7)
Model 2‡			
Primary outcome			
24-hour systolic	-0.70 (-2.33, 0.94)	-0.15 (-1.82, 1.52)	0.55 (-1.1, 2.2)
Secondary Outcomes			
24-hour diastolic	-0.12 (-1.13, 0.88)	0.02 (-1.00, 1.05)	0.15 (-0.87, 1.16)
Daytime systolic	-0.78 (-2.55, 1)	-0.38 (-2.2, 1.43)	0.39 (-1.4, 2.19)
Nighttime systolic	0.04 (-1.93, 2.01)	0.48 (-1.53, 2.48)	0.44 (-1.55, 2.43)
Daytime diastolic	-0.54 (-1.75, 0.66)	-0.38 (-1.6, 0.85)	0.17 (-1.05, 1.38)
Nighttime diastolic	0.09 (-1.11, 1.28)	0.58 (-0.64, 1.8)	0.49 (-0.71, 1.7)

†Model 1 was performed using a multiple linear regression model adjusted for the ambulatory SBP at baseline, age (<55 years and ≥55 years), clinical site and sex among participants who adhered to the study protocol. ‡Model 2 was a sensitivity analysis performed with stratification variables (age and clinical site), sex, respective baseline ambulatory BP values, presence of diabetes mellitus, BMI, heart rate and duration of hypertension among participants who adhered to the study protocol.

nature portfolio

Corresponding author(s): Dorairaj Prabhakaran

Last updated by author(s): 02-12-2024

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☐	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Clinion Software Version 3.0
Data analysis	Stata Version 16.0

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Raw data cannot be publicly shared as per the Health Ministry Screening Committee (HMSC) of the Indian Government (National Regulatory Authority for human research with contributions from other countries), which mandates that no data can be shared beyond the borders without necessary approvals. Anonymized and tabulated or curated data will be made available to bona fide researchers for the purpose of meta-analysis and similar research interests with necessary approvals. Requests may be made to Prof. Prabhakaran - dprabhakaran@ccdcindia.org. All such requests will be responded to within a two-week time frame.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	The trial participants included men and women (female 42.1%) with a mean age of 52.1± 11.1 years
Reporting on race, ethnicity, or other socially relevant groupings	The trial was conducted only in south-asian ethnicity i.e., only Indians
Population characteristics	Participants had a mean BMI of 26.5 (SD 4.2) kg/m2. At baseline, 58 % had a diagnosis of hypertension, while 42 % were newly diagnosed. Diabetes was present in 18.6 % of the cohort, and 7.3 % had dyslipidaemia. The prevalence of current smoking was low, at 6.2 %. Symptoms such as dyspnea (5.7 %), orthopnea (4.3 %), and palpitations (3.4 %) were uncommon. There was no history of coronary heart disease or stroke among participants.
Recruitment	The trial recruited hypertensive patients from outpatient clinics at 35 hospitals across India from August 2022 to February 2024. Men and women between 30 and 79 years were eligible if their sitting office systolic blood pressure was between 140 and 159 mmHg on one antihypertensive medication or 150 and 179 mmHg in drug naïve patients. Patients with a history of coronary artery and cerebrovascular diseases, congestive heart failure, serum creatinine above 1.5 mg/dl, current pregnancy and secondary hypertension were excluded.
Ethics oversight	Ethics committee approval were obtained from the Centre for Chronic Disease Control, New Delhi, Imperial College London and all the participating clinical sites. Participating Clinical sites Aman Hospital and Research Center, Vadodara, Gujarat North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong, Meghalaya Shri Dharmasthala Manjunatheshwara Medical College, Dharwad, Karnataka Rudraksha Multispeciality Hospital, Ahmedabad, Gujarat Dayanand Medical College & Hospital, Ludhiana, Punjab All India Institute of Medical Sciences, Bathinda, Punjab Sardar Patel Medical College, Bikaner, Rajasthan Shalinitai Meghe Hospital & Research Centre, Nagpur, Maharashtra MediCiti Institute of Medical Sciences, Hyderabad, Telangana Sengupta Hospitals & Research Institute, Nagpur, Maharashtra JSS Hospital, Mysore, Karnataka Apollo Excelcare Hospital, Guwahati, Assam Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu Osmania General Hospital, Hyderabad, Telangana B.K.L. Walawalkar Rural Medical College, Sawarde, Maharashtra All India Institute of Medical Sciences, Jodhpur, Rajasthan Apollo Institute of Medical Sciences, Hyderabad, Telangana Apollo DRDO Hospitals, Hyderabad, Telangana Madras Medical College, Chennai, Tamil Nadu Nazareth Hospital, Shillong, Meghalaya All India Institute of Medical Sciences, New Delhi, Delhi Lakshmi Hospital, Palakkad, Kerala Apollo Hospitals, Ahmedabad, Gujarat Lifecare Hospital & Research Centre, Bengaluru, Karnataka Lalitha Super specialties Hospital, Guntur, Andhra Pradesh BLDE Hospital, Vijayapura, Karnataka Indraprastha Apollo Hospitals, New Delhi, Delhi Apollo Hospitals, Madurai, Tamil Nadu Apollo Hospitals, Visakhapatnam, Andhra Pradesh Assam Medical College, Dibrugarh, Assam Bhatia Hospital, Mumbai, Maharashtra Sadbhavna Medical and Heart Institute, Patiala, Punjab Lisie Hospital, Kochi, Kerala Apollo Hospitals, Bhubaneshwar, Odisha Indiana Hospital & Heart Institute, Mangalore, Karnataka Aman Hospital and Research Center, Vadodara, Gujarat North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong, Meghalaya Shri Dharmasthala Manjunatheshwara Medical College, Dharwad, Karnataka Rudraksha Multispeciality Hospital, Ahmedabad, Gujarat Dayanand Medical College & Hospital, Ludhiana, Punjab All India Institute of Medical Sciences, Bathinda, Punjab Sardar Patel Medical College, Bikaner, Rajasthan Shalinitai Meghe Hospital & Research Centre, Nagpur, Maharashtra MediCiti Institute of Medical Sciences, Hyderabad, Telangana Sengupta Hospitals & Research Institute, Nagpur, Maharashtra JSS Hospital, Mysore, Karnataka Apollo Excelcare Hospital, Guwahati, Assam

Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu
Osmania General Hospital, Hyderabad, Telangana
B.K.L. Walawalkar Rural Medical College, Sawarde, Maharashtra
All India Institute of Medical Sciences, Jodhpur, Rajasthan
Apollo Institute of Medical Sciences, Hyderabad, Telangana
Apollo DRDO Hospitals, Hyderabad, Telangana
Madras Medical College, Chennai, Tamil Nadu
Nazareth Hospital, Shillong, Meghalaya
All India Institute of Medical Sciences, New Delhi, Delhi
Lakshmi Hospital, Palakkad, Kerala
Apollo Hospitals, Ahmedabad, Gujarat
Lifecare Hospital & Research Centre, Bengaluru, Karnataka
Lalitha Super specialties Hospital, Guntur, Andhra Pradesh
BLDE Hospital, Vijayapura, Karnataka
Indraprastha Apollo Hospitals, New Delhi, Delhi
Apollo Hospitals, Madurai, Tamil Nadu
Apollo Hospitals, Visakhapatnam, Andhra Pradesh
Assam Medical College, Dibrugarh, Assam
Bhatia Hospital, Mumbai, Maharashtra
Sadbhavna Medical and Heart Institute, Patiala, Punjab
Lisie Hospital, Kochi, Kerala
Apollo Hospitals, Bhubaneshwar, Odisha
Indiana Hospital & Heart Institute, Mangalore, Karnataka

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	we recruited 1981 people with hypertension. To detect a clinically meaningful difference of 3.0 mmHg between arms in the 24-h mean ASBP assuming an SD in 24-h ASBP of 15 mmHg with 85 % power and adjusting for three comparisons using a two-sided significance level of 0.0167, we needed a minimum of 590 participants per arm. Factoring in a 10 % dropout rate, we were required to recruit a total of 1968 participants (656 participants per arm) to achieve 590 evaluable participants per group.
Data exclusions	None
Replication	TOPSPIN is a original research and first of its kind in the world. It is not a replication of any other studies.
Randomization	Using a blocked design, randomisation was stratified by age (<55 or ≥55 years) and trial site - Computer generated built on Redcap.
Blinding	Participants and investigators were blinded to the treatment received.

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	*Briefly describe the study type including whether data are quantitative, qualitative, or mixed-methods (e.g. qualitative cross-sectional, quantitative experimental, mixed-methods case study).*
Research sample	*State the research sample (e.g. Harvard university undergraduates, villagers in rural India) and provide relevant demographic information (e.g. age, sex) and indicate whether the sample is representative. Provide a rationale for the study sample chosen. For studies involving existing datasets, please describe the dataset and source.*
Sampling strategy	*Describe the sampling procedure (e.g. random, snowball, stratified, convenience). Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient. For qualitative data, please indicate whether data saturation was considered, and what criteria were used to decide that no further sampling was needed.*
Data collection	*Provide details about the data collection procedure, including the instruments or devices used to record the data (e.g. pen and paper, computer, eye tracker, video or audio equipment) whether anyone was present besides the participant(s) and the researcher, and whether the researcher was blind to experimental condition and/or the study hypothesis during data collection.*

Timing	*Indicate the start and stop dates of data collection. If there is a gap between collection periods, state the dates for each sample cohort.*
Data exclusions	*If no data were excluded from the analyses, state so OR if data were excluded, provide the exact number of exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.*
Non-participation	*State how many participants dropped out/declined participation and the reason(s) given OR provide response rate OR state that no participants dropped out/declined participation.*
Randomization	*If participants were not allocated into experimental groups, state so OR describe how participants were allocated to groups, and if allocation was not random, describe how covariates were controlled.*

Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	*Briefly describe the study. For quantitative data include treatment factors and interactions, design structure (e.g. factorial, nested, hierarchical), nature and number of experimental units and replicates.*
Research sample	*Describe the research sample (e.g. a group of tagged Passer domesticus, all Stenocereus thurberi within Organ Pipe Cactus National Monument), and provide a rationale for the sample choice. When relevant, describe the organism taxa, source, sex, age range and any manipulations. State what population the sample is meant to represent when applicable. For studies involving existing datasets, describe the data and its source.*
Sampling strategy	*Note the sampling procedure. Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient.*
Data collection	*Describe the data collection procedure, including who recorded the data and how.*
Timing and spatial scale	*Indicate the start and stop dates of data collection, noting the frequency and periodicity of sampling and providing a rationale for these choices. If there is a gap between collection periods, state the dates for each sample cohort. Specify the spatial scale from which the data are taken*
Data exclusions	*If no data were excluded from the analyses, state so OR if data were excluded, describe the exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.*
Reproducibility	*Describe the measures taken to verify the reproducibility of experimental findings. For each experiment, note whether any attempts to repeat the experiment failed OR state that all attempts to repeat the experiment were successful.*
Randomization	*Describe how samples/organisms/participants were allocated into groups. If allocation was not random, describe how covariates were controlled. If this is not relevant to your study, explain why.*
Blinding	*Describe the extent of blinding used during data acquisition and analysis. If blinding was not possible, describe why OR explain why blinding was not relevant to your study.*

Did the study involve field work? ☒ Yes ☐ No

Field work, collection and transport

Field conditions	35 tertiary care hospitals with primary care feeder clinics in India
Location	India
Access & import/export	Not applicable
Disturbance	Not applicable

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used — *Describe all antibodies used in the study; as applicable, provide supplier name, catalog number, clone name, and lot number.*

Validation — *Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer's website, relevant citations, antibody profiles in online databases, or data provided in the manuscript.*

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s) — *State the source of each cell line used and the sex of all primary cell lines and cells derived from human participants or vertebrate models.*

Authentication — *Describe the authentication procedures for each cell line used OR declare that none of the cell lines used were authenticated.*

Mycoplasma contamination — *Confirm that all cell lines tested negative for mycoplasma contamination OR describe the results of the testing for mycoplasma contamination OR declare that the cell lines were not tested for mycoplasma contamination.*

Commonly misidentified lines (See ICLAC register) — *Name any commonly misidentified cell lines used in the study and provide a rationale for their use.*

Palaeontology and Archaeology

Specimen provenance — *Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.*

Specimen deposition — *Indicate where the specimens have been deposited to permit free access by other researchers.*

Dating methods — *If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.*

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight — *Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.*

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals — *For laboratory animals, report species, strain and age OR state that the study did not involve laboratory animals.*

Wild animals — *Provide details on animals observed in or captured in the field; report species and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.*

Reporting on sex — *Indicate if findings apply to only one sex; describe whether sex was considered in study design, methods used for assigning sex. Provide data disaggregated for sex where this information has been collected in the source data as appropriate; provide overall*

	numbers in this Reporting Summary. Please state if this information has not been collected. Report sex-based analyses where performed, justify reasons for lack of sex-based analysis.
Field-collected samples	*For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.*
Ethics oversight	*Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.*

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT05683301
Study protocol	https://doi.org/10.1016/j.ijcrp.2024.200346
Data collection	Data was collected by trained clinical research coordinators and site-investigators at baseline, two months, four months and six months. We used a validated electronic clinical data management system - CLINION Software Version 3.0 for transfer of data from the 35 participating clinical sites to the research coordinating centre. The study participant recruitment was conducted between August 2022 to February 2024 and the past participant was followed till August 2024.
Outcomes	The primary outcome was the difference among the treatment groups in the mean reduction in the 24-hour ambulatory systolic blood pressure at six months adjusted for baseline ambulatory systolic blood pressure. Secondary outcomes included a reduction in ambulatory diastolic blood pressure; mean change in the daytime (9 a.m. to 9 p.m.) and nighttime (12 midnight to 6 a.m.) ambulatory blood pressures; change in office blood pressure at 2, 4, and 6 months; the proportion of participants achieving conservative (<140/90 mmHg) or more current (<130/80 mmHg) blood pressure control level at any of the office visits and maintained at six months; the proportion of "responders" to treatment (defined as a reduction of systolic blood pressure of ≥20 mmHg and diastolic blood pressure of ≥10 mmHg at any of the office visits and maintained at 6 months); changes in laboratory investigations, fasting blood glucose, lipid profile, serum sodium, potassium, urea, creatinine and estimated glomerular filtration rate (eGFR). The safety endpoint of the study was the occurrence of adverse or serious adverse events leading to withdrawal of the study drug at any of the follow-ups. Pre-specified sub-group analysis for the primary outcomes were age (<55 and ≥ 55 years), sex (male and female), self-reported history of diabetes at baseline and previously or newly-diagnosed hypertension at baseline, and body mass index (BMI - <23, 23-24.9 and ≥25 Kg/m2).

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
☒	☐	Public health
☒	☐	National security
☒	☐	Crops and/or livestock
☒	☐	Ecosystems
☒	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
☒	☐	Demonstrate how to render a vaccine ineffective
☒	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☒	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☒	☐	Increase transmissibility of a pathogen
☒	☐	Alter the host range of a pathogen
☒	☐	Enable evasion of diagnostic/detection modalities
☒	☐	Enable the weaponization of a biological agent or toxin
☒	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links
May remain private before publication.

For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.

Files in database submission

Provide a list of all files available in the database submission.

Genome browser session
(e.g. UCSC)

Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

Methodology

Replicates

Describe the experimental replicates, specifying number, type and replicate agreement.

Sequencing depth

Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.

Antibodies

Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.

Peak calling parameters

Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.

Data quality

Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.

Software

Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.

Flow Cytometry

Plots

Confirm that:

☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	*Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.*
Instrument	*Identify the instrument used for data collection, specifying make and model number.*
Software	*Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.*
Cell population abundance	*Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.*
Gating strategy	*Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.*

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	*Indicate task or resting state; event-related or block design.*
Design specifications	*Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.*
Behavioral performance measures	*State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).*

Acquisition

Imaging type(s)	*Specify: functional, structural, diffusion, perfusion.*
Field strength	*Specify in Tesla*
Sequence & imaging parameters	*Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.*
Area of acquisition	*State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.*

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software	*Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).*
Normalization	*If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.*
Normalization template	*Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.*
Noise and artifact removal	*Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).*

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

(See Eklund et al. 2016)

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.