The Journal of Clinical Hypertension

WILEY

META-ANALYSIS OPEN ACCESS

Effectiveness and Safety of Using Standardized Treatment Protocols for Hypertension Compared to Usual Care: A Meta-Analysis of Randomized Clinical Trials

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Received: 9 September 2024 | **Revised:** 22 October 2024 | **Accepted:** 29 October 2024

Funding: This work was supported by the DBT/Wellcome Trust India Alliance Fellowship (Fellowship number IA/CPHI/20/1/505281) awarded to Abdul Salam.

Keywords: antihypertensive drugs | blood pressure | efficacy | meta-analysis | safety | standardized treatment protocol

ABSTRACT

Large gaps persist in the diagnosis, awareness, treatment, and control of hypertension globally. Standardized treatment protocols (STPs) have been widely proposed to guide hypertension treatment, particularly in primary healthcare settings. However, there has been no review that quantifies the effects of hypertension STPs on blood pressure (BP) reduction and control. We conducted a systematic review of randomized clinical trials (RCTs) among adults with hypertension, comparing hypertension STPs (intervention) with usual care (comparator) for effects on BP. Relevant RCTs were identified by searching multiple electronic databases. Random-effects meta-analyses were conducted to evaluate between-group differences in systolic BP reduction (primary outcome), diastolic BP reduction, BP control, and adverse events (AEs). Sixteen RCTs involving 59,945 participants (baseline mean BP: 149/91 mmHg) were included. Reductions in systolic and diastolic BP with STPs compared to usual care were 6.7 (95% CI 3.7–9.8) mmHg and 2.6 (1.2–4.1) mmHg, respectively ($p < 0.001$ for both). BP control achieved was 57% in the STP group compared to 24% in the usual care group ($p < 0.001$). The overall incidence of any AEs was 14.5% versus 13.5% (RR 1.27 [0.88–1.82]) with STPs and usual care, respectively. In summary, interventions involving hypertension STPs significantly reduce systolic and diastolic BP and improve BP control compared to usual care. STPs can, therefore, be an efficient strategy to implement evidence-based treatments and upscale treatment coverage, given the large untreated and uncontrolled hypertension burdens globally.

1 | Introduction

Globally, hypertension is the leading preventable risk factor for cardiovascular diseases, premature death, and disability [1, 2]. There are large gaps in the diagnosis, awareness, treatment, and control of hypertension. These gaps are larger in low- and middle-income countries (LMICs), where over two-thirds of the hypertension-attributed deaths occur [3]. Despite the availability of proven effective therapies, their use is suboptimal, and less than half of treated indi-

viduals achieve guideline-recommended blood pressure (BP) targets [4].

To address these gaps in implementing guideline-recommended treatment and achieving BP control, standardized treatment protocols (STPs) have been proposed to guide hypertension treatment, particularly in primary healthcare settings. STPs consist of simplified steps that specify the most preferred pharmacological and non-pharmacological treatments for a given health condition. For pharmacological treatment, STPs include the name of the drug, dosage form, strength, average dose, number of doses per day, and number of days of treatment [5, 6]. STPs may contribute to streamlining care by simplifying treatment options, reducing clinical variability outside the scope of evidence-based medicine, reducing therapeutic inertia, and improving patients' adherence to medicines. As such, STPs have the potential to improve the treatment and control of hypertension globally and are particularly imperative in LMICs [5, 6].

Key organizations and implementation programs, such as the World Health Organization's (WHO) HEARTS program (implemented in over 40 countries) and Resolve to Save Lives' Hypertension Control efforts (implemented in 38 countries) have been increasingly advocating the use of STPs for improving hypertension treatment and control [5, 6]. However, there has been no review that quantifies the effects of hypertension STPs (henceforth referred to as STPs) on BP reduction and control. We, therefore, aimed to evaluate the effectiveness of STP-based management compared to usual care among adults with hypertension for lowering BP and for safety.

2 | Methods

The protocol for this systematic review was registered on INPLASY (202380021) [7].

2.1 | Data Sources and Search Strategy

We used three sources to identify relevant randomized clinical trials (RCTs): (1) we conducted a systematic search of Embase from its inception to January 22, 2023 (full search strategy in Table S1); (2) we searched the DREAM (Double-blind randomized trials of effects of antihypertensive medicines) database of the George Institute for Global Health, which is developed by searching the Cochrane Central Register of Controlled Trials (until December 2022), MEDLINE (from 1946 to December 2022), and Epistemonikos (from inception to December 2022); (3) we reviewed six previous relevant systematic reviews of hypertension control interventions [8–13].

2.2 | Selection of Studies

Studies were included if they were RCTs among adult participants with hypertension, allocated to STP (as the only intervention or as a co-intervention) or usual care (comparator), and provided data to assess their effects on BP. We defined an STP as a series of steps recommended for the pharmacological management of hypertension, covering the information on the patient group (e.g., age, condition, race) for whom the STP is applicable, BP thresholds for initiating and intensifying pharmacological treatment, target BP, and BP-lowering class and/or drugs to be used at each step. Placebo-controlled trials and trials focusing on specific drugs (e.g., industry trials) or non-pharmacological interventions only, were excluded. One author reviewed records retrieved from the search to assess eligibility for inclusion, and a second author reviewed excluded records to ensure no eligible records were excluded. The inclusion of trials was based on consensus.

2.3 | Data Extracted

We extracted data on study design, participant characteristics, intervention, comparator, outcomes, and also characteristics of the STP. Outcomes data were BP values to be able to calculate the reduction in mean systolic and diastolic BP, its variability (standard deviation [SD]), BP control, and adverse events (AEs) in each group. For trials that did not report variability data for BP, it was imputed from the average of SDs from other included RCTs. BP control definition was as defined in the included trials. One author extracted data, and a second author checked them for accuracy.

2.4 | Risk of Bias Assessment and Certainty of Evidence

The risk of bias in the included trials was assessed using the Cochrane Risk of Bias tool version 1.0 by one reviewer, and a second reviewer verified the judgment of the first reviewer [14]. Disagreements between the two reviewers were resolved by discussion or adjudication by a third (senior) reviewer. Additionally, for cluster RCTs (cRCTs), we assessed (i) recruitment bias; (ii) baseline imbalance; (iii) loss of clusters; and (iv) incorrect analysis, as suggested in the Cochrane Handbook. Publication bias was assessed using funnel plots.

2.5 | Data Analysis

The primary outcome was the differences in the reduction in SBP. Secondary outcomes were the differences in the reduction in DBP, BP control, any AEs, and treatment-related AEs, from baseline to the maximum available follow-up week. DerSimonian and Laird random-effects meta-analyses were conducted for both continuous and dichotomous outcomes. The presence of statistical heterogeneity was assessed by *Q statistics* and quantified using the I^2 statistic (heterogeneity due to true variance in effects across trials). All meta-analyses were performed using Comprehensive Meta-Analysis (CMA) v2.0 (Biostat Inc., Englewood, NJ, USA). Three subgroup analyses were conducted to compare effects between (i) RCTs wherein STP alone was the intervention and those wherein STP was a co-intervention; (ii) individual RCTs and cRCTs; and (iii) RCTs with a follow-up duration of 6 months or lesser and those with more than 6 months. Three sensitivity analyses were conducted for reduction in systolic and diastolic BP: (1) excluding RCTs with a high risk of bias, (2) excluding one trial [15] with a very large treatment effect relative to effects in other included RCTs, and (3) conducting meta-analysis using

fixed effect model. The overall certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, and our evidence was classified as very low, low, moderate, or high. GRADEPro software was used to generate GRADE Evidence profile tables.

3 | Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure S1) reports the number of records identified, included, and excluded in the systematic review and meta-analysis. Sixteen RCTs comprising 16 comparisons and 59,945 participants were included [15–30]. The characteristics of the included trials are summarized in Table S2. All trials were parallel-group, and all but one was open-label. Ten trials (63%) were multicenter, four (25%) were cRCTs, and one was a nested 2 × 2 factorial trial. Eleven trials (69%) reported the STP, including drug classes at each step, used in the STPs, while the others only mentioned that an STP was used and did not provide the details. The mean age of the participants was 57 years, 40% were female, and the baseline mean SBP/DBP was 149/91 mmHg. Five (31%) trials involved comparison of STP alone with usual care, and the remaining trials compared multicomponent interventions with STP as a co-intervention with usual care. Six trials (37%) reported data on patients' adherence to antihypertensive drugs, which, on average, was 79% (range: 68%–100%) for the STP group and 60% (range: 39%–95%) for the usual care group.

3.1 | Risk of Bias Assessment

Results of risk of bias assessment in the included trials are summarized in Figure S2. Of the 16 included trials, none had a high risk of selection bias. For performance bias, 10 (62%) trials were marked as high risk, given that participants and personnel were not blinded in most trials. For detection bias, 9 (56%) trials were marked as high risk of bias. Two (12%) trials with uneven dropouts across groups were marked as high risk of attrition bias. Two (12%) trials that did not report data for SBP outcomes were marked as high risk of reporting bias. Further, for cRCTs, all but one trial had a high risk of recruitment bias, and two cRCTs had a high risk of loss of clusters and incorrect analyses. Funnel plots for SBP and DBP did not suggest publication bias (Figure S3).

3.2 | BP-Lowering Effects

For the primary outcome, the reduction in mean SBP with STPs compared to usual care was 6.7 (95% CI 3.7 to 9.8) mmHg (Figure 1). DBP reduction was 2.6 (1.2 to 4.1) mmHg. There was high heterogeneity in effects across RCTs for reduction in SBP (I^2 = 99%) and DBP (I^2 = 99%). There was no significant difference in the primary outcome between RCTs where STP alone was the intervention and RCTs where STP was a co-intervention, as well as individual RCTs and cRCTs (Tables S3A and S3B). Further, there was no significant difference between trials with follow-up duration of 6 months or lesser and those with more than 6 months (Table S3C).

In the sensitivity analyses for the difference in reduction in SBP and DBP (1) excluding RCTs (n = 10) with a high risk of bias for one or more domains of Cochrane risk of bias tool, reduction in SBP was 7.1 (95% CI 4.1 to 10.0) mmHg and DBP was 3.2 (95% CI 0.45 to 5.84) mmHg; (2) excluding the trial with very large treatment effect [15] relative to effects in other studies, reduction in SBP was 5.8 (95% CI 4.6 to 7.1) mmHg and DBP was 2.2 (95% CI 1.4 to 3.1) mmHg; and (3) with the fixed effect model, the reduction in SBP was 10.0 (95% CI 9.7 to 10.2) mmHg, and DBP was 3.4 (95% CI 3.3 to 3.5) mmHg.

BP control data was available from nine trials, and BP control definition varied across trials (Table S2). STPs achieved BP control in 57.0% of participants, compared to 23.9% in usual care (relative risk [RR] 1.27 95% [0.81 to 1.99], I^2 = 99) (Figure 2).

The GRADE of evidence was categorized as "low" certainty for SBP reduction and DBP reduction and "very low" certainty for BP control (Table S4).

3.3 | Safety

Only four (25%) and three (19%) trials reported data on any AEs and treatment-related AEs, respectively (Table S5). The incidence of any AEs was 14.5% versus 13.5% (RR 1.27 95% CI 0.88 to 1.82). The incidence of treatment-related AEs was 6.7% versus 3.0% (RR 1.83 95% CI 1.4% to 2.4%) in the STP group versus the usual care group, respectively (Figure 3). The GRADE of evidence was categorized as "very low" certainty for any AEs and treatment-related AEs (Table S4).

4 | Discussion

4.1 | Summary of Findings

In this systematic review and meta-analysis including 16 RCTs among adults with hypertension, STPs significantly reduced SBP and DBP and achieved higher BP control compared to usual care. There was no significant difference in findings when comparing RCTs of STP alone as an intervention or STP as a co-intervention versus usual care. The reduction in SBP remained significant after excluding RCTs with a high risk of bias and after excluding one RCT with a very large effect relative to other RCTs. Sparsely reported data on safety outcomes suggested no significant difference between STPs and usual care.

4.2 | Strengths and Limitations

To our knowledge, this is the first systematic review and meta-analysis comparing STPs with usual care, including nearly 60,000 participants with hypertension. However, results should be interpreted in the light of the following limitations. In most of the included trials (11 of 16), STP was a co-intervention, with only five trials comparing STP alone with usual care. To address this, we conducted subgroup analysis and found no statistically significant difference between these two sub-groups of trials. There was a high risk of bias for blinding participants and personnel (performance bias) and outcome assessment (detection

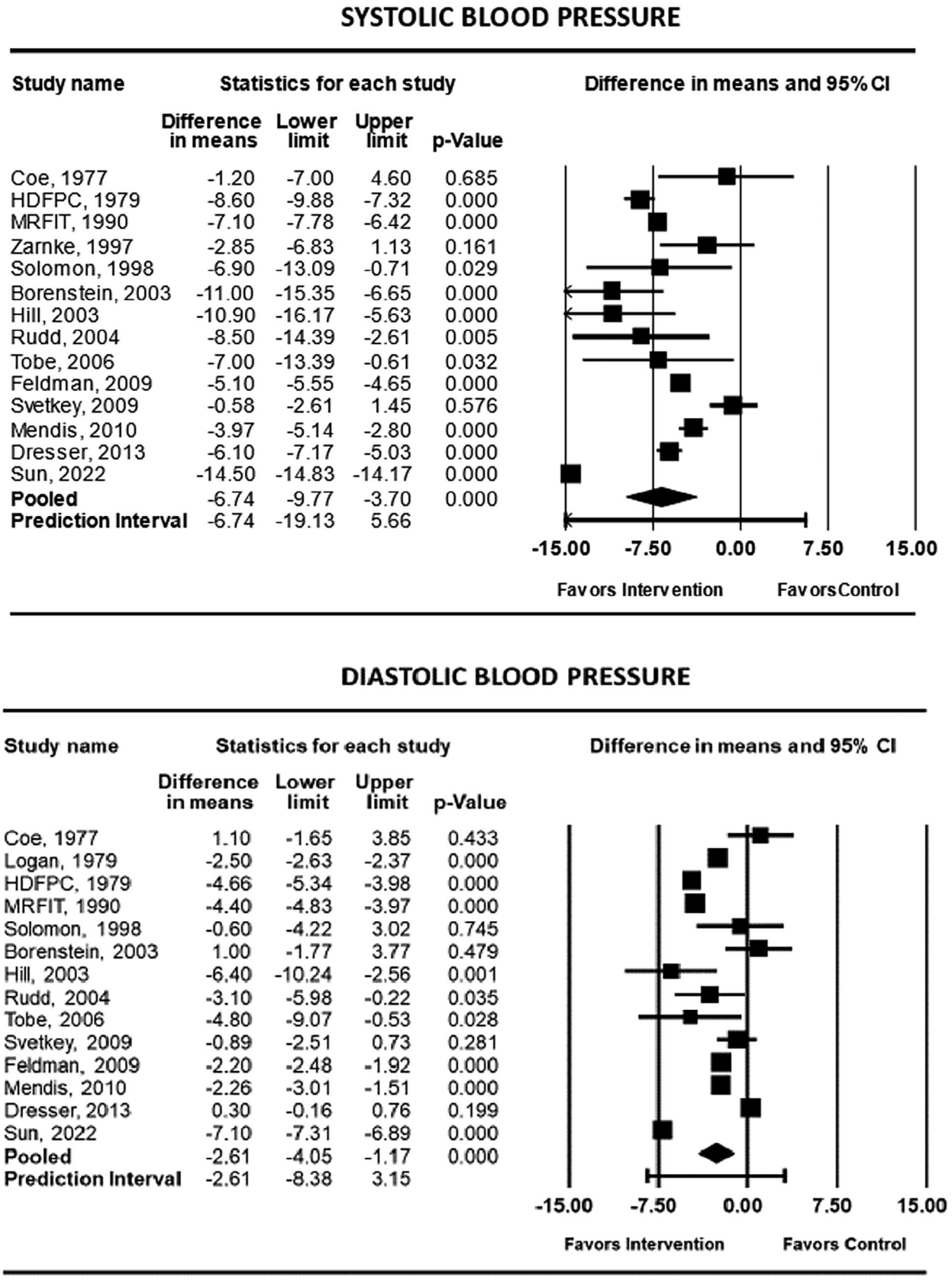

FIGURE 1 | Meta-analyses of trials comparing the reduction in (a) SBP and (b) DBP with STP compared to usual care.

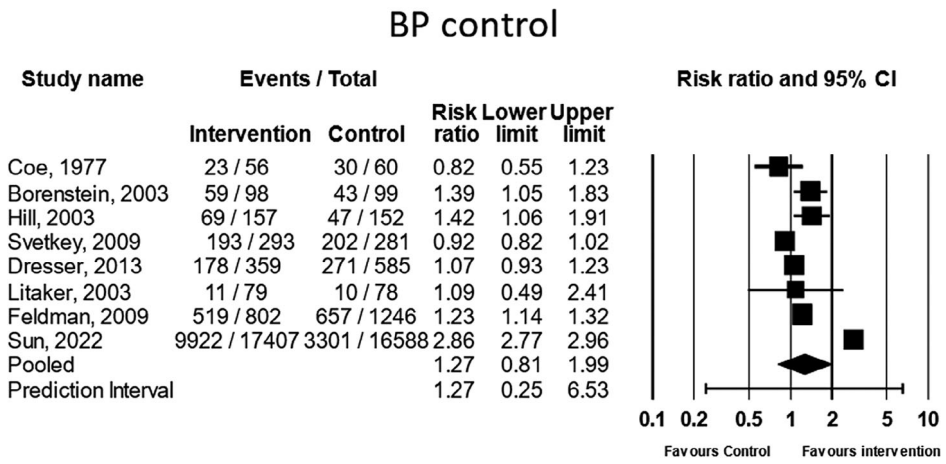

FIGURE 2 | Meta-analyses of trials comparing the proportion achieving hypertension control using STPs with those using usual care.

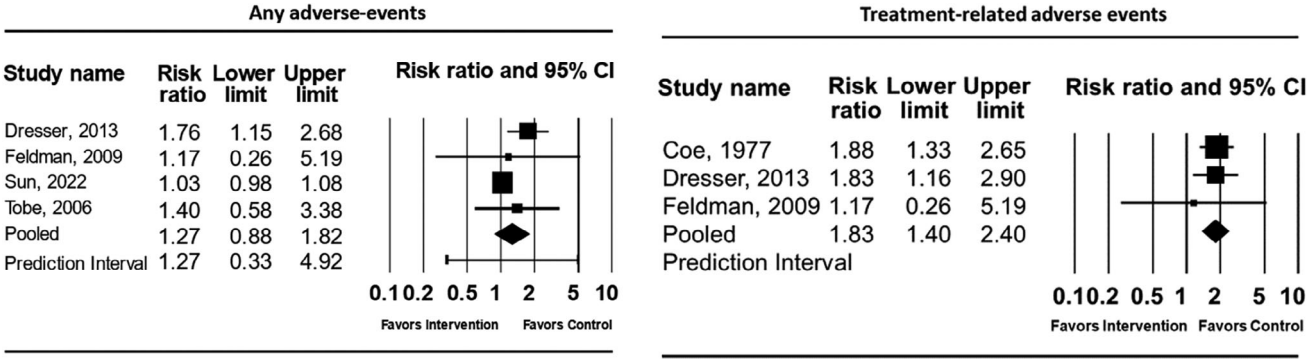

FIGURE 3 | Meta-analyses of trials comparing the incidence of (a) any adverse events and (b) treatment-related adverse events in STP and usual care groups.

bias). However, blinding is not feasible for STPs and usual care. Because of the sparsely reported safety data, it is difficult to draw definitive conclusions about the safety of STPs. We cannot completely rule out the likelihood of missing potential trials, as some may not have used the keywords used in our strategy. There was high heterogeneity in BP reduction across the included trials, primarily because of the clinical diversity (variability in participants, follow-up durations, and the nature of intervention and usual care across the included trials). However, none of the trials reported a higher reduction in SBP with usual care compared to STPs, indicating that the heterogeneity is restricted to the magnitude and not the direction of the effect. Lastly, for some RCTs, the usual care group received guideline-recommended care. In such cases, we assumed "guideline-based treatment" to be equivalent to "usual care." It is, however, possible that guideline-based treatment within a trial would result in enhanced usual care, potentially leading to underestimation of the effects of the STPs.

4.3 | Findings in the Context of Other Evidence

Several other studies have previously summarized the benefits and advocated using STPs for hypertension [31–34]. STPs appear to be particularly effective in achieving specific targets. The Hypertension Detection and Follow-Up Program (HDFP) was one of the earliest large hypertension control trials—involving 10 940 persons with high BP, demonstrating STP-based care was associated with achieving BP targets more consistently than referred or usual care. Recently, SPRINT, a randomized trial of 9361 individuals with SBP ≥130 mm Hg and an increased CVD risk, demonstrated that intensive treatment using STPs (targeting an SBP ≤120 mm Hg) was associated with lower cardiovascular mortality and morbidity when compared with usual treatment (target SBP ≤140 mm Hg) [35]. Although our meta-analysis did not include this trial, as the BP targets were different in the two groups, SPRINT also demonstrates the utility of STPs in achieving specific targets.

The World Health Organization's (WHO) HEARTS technical package recommends evidence-based STPs in its strategic approach to improving cardiovascular health [34]. Recent quality improvement interventions of these STPs have facilitated the development of "clinical pathways" for hypertension in several countries in the Region of the Americas. The India Hypertension Control Initiative (IHCI) aims at improving hypertension treatment and control in public clinics in India, and STPs are one of the key interventions. Results from the IHCI demonstrated the feasibility of implementing STP-based hypertension treatment and significant improvement in hypertension control [36]. Additional evidence from the Bangladesh HEARTS trial [37] further buttresses the positive effect of interventions, including STPs, on lowering SBP and DBP and improving BP control

compared to usual care, as well as the feasibility of implementing them in rural public clinics. We previously assessed the global availability of hypertension STPs, critically appraised them, and identified deficiencies, highlighting the need for improvement for alignment with guideline recommendations [38].

4.4 | Implications for Practice and Research

The results of our systematic review—demonstrating clear benefits to implement STPs for the effective treatment of hypertension—have potential implications for clinical practice and for research, especially since several organizations, including the WHO, are increasingly advocating STPs in their hypertension control efforts. STPs help streamline and simplify treatment, reduce undesirable clinical variability outside the scope of evidence-based practice, and optimize drug procurement [9]. Further, STPs also facilitate team-based care by allowing appropriately trained non-physician health workers to initiate or titrate hypertension medicines per protocol, and enable multiple actors to participate in hypertension management and adhere to the standardized approach [31–33]. STPs ensure that patients are managed safely and efficiently, and only those with resistant hypertension or complications are referred to specialists. The effect of using STPs in clinical practice is likely to extend beyond specific hypertension control programs and result in significantly improved treatment and control of hypertension.

There is limited evidence on the cost-effectiveness of implementing STPs. A 2022 study from India estimated that scaling up STP-based treatment through hypertension control programs at <$4 per patient annually is a potentially cost-effective intervention [39]. For optimal large-scale implementation, there is a need for further economic evaluations to demonstrate the benefits of investing in STPs.

5 | Conclusion

Hypertension STPs significantly reduce SBP and DBP and achieve higher BP control compared to usual care. STPs can, therefore, be an efficient strategy to implement evidence-based treatments and upscale treatment coverage, considering the large burden of untreated and uncontrolled hypertension globally. Given the limited certainty of evidence, larger trials comparing STP alone with usual care are warranted.

Author Contributions

A.S. conceived the study idea. A.S. developed the search strategy, and G.S. and R.D. conducted the screening and extracted the data. G.S. and A.S. wrote the first draft of the manuscript, with inputs from V.J., A.E.S., B.B., D.P., and A.E.M. All authors reviewed and approved the final version of the manuscript.

Acknowledgments

Open access publishing facilitated by University of New South Wales, as part of the Wiley - University of New South Wales agreement via the Council of Australian University Librarians.

Ethics Statement

This systematic review was approved by The George Institute Ethics Committee (Project Number: 17/2024).

Conflicts of Interest

V.J. has received grant funding from GSK, Baxter Healthcare, and Biocon and honoraria from NephroPlus, Zydus Cadilla, Travere, Astra Zeneca, Vera, Visterra, Bayer, and Boehringer Ingelheim under the policy of all honoraria being paid to the organization. Other authors declare no conflicts of interest.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.