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REVIEW

Top Ten Breakthroughs in Clinical Hypertension Research in 2022

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Abstract

Hypertension is a major global public health concern whose disease burden affects an estimated 1.4 billion people worldwide and is associated with 10.8 million deaths annually. Despite substantial advances in medical care, the prevalence of hypertension has markedly increased, owing to population aging; poor treatment adherence; and increases in risk factors, such as excessive salt intake, and overweight and obesity. Consequently, the disability-adjusted life years have increased by 40%, primarily because of elevated risk of stroke, coronary atherosclerosis, heart failure, and kidney failure. Major outstanding problems associated with the treatment and management of hypertension include determining optimal blood pressure targets, developing innovative antihypertensive medications and devices, and implementing effective and feasible hypertension management strategies. To address these challenges, numerous clinical trials are currently underway. This article highlights the most influential ten clinical studies on hypertension in 2022. The rational use of antihypertensive medications is concluded to be important for effective hypertension management. Important considerations include medication types and dosing times; optimal blood pressure targets; the development of new drugs and therapeutic devices; specific community characteristics, such as village doctor-led care; and healthful diets.

Keywords: Hypertension; Clinical studies; Breakthrough; 2022

Nonstandard Abbreviations and Acronyms: ACC, American College of Cardiology; AHA, American Heart Association; BP, Blood pressure; CVDs, Cardiovascular diseases; DBP, Diastolic blood pressure; EBA, Endovascular baroreflex amplification; ESC, European Society of Cardiology; RDN, Renal denervation; SBP, Systolic blood pressure

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The Best Time to Take Antihypertensive Medication—TIME Study

The circadian rhythm of blood pressure (BP) shows a dipper pattern, defined by low BP during sleep and peaks after awakening. A non-dipper rhythm, including nocturnal and morning hypertension, is considered an important predictor of adverse cardiovascular outcomes [1, 2], and its management has been emphasized in The HOPE Asia network 2022 update consensus statement [3]. Moreover, taking antihypertensive medication in the evening has been demonstrated to normalize the circadian BP rhythm [4], thus leading to the hypothesis that evening

administration of antihypertensive medication may improve cardiovascular outcomes more effectively than morning administration. This hypothesis has been strongly supported by the MAPEC trial (RR = 0.33, 95% CI 0.19–0.55) and the Hygia trial (RR = 0.58, 95% CI 0.49–0.68) [5, 6]. However, the design of these trials was flawed, primarily because of issues with the randomization process. Furthermore, although significant differences were observed between the treatment and control groups after 1 year, the overall trial duration was 6.3 years, thus leading to ethical concerns. Consequently, the interpretation of the findings from these two studies remains debated in the scientific community [7, 8].

The results of the Treatment in Morning versus Evening (TIME) study, a prospective, pragmatic randomized controlled clinical study by Thomas M MacDonald, were presented at the European Society of Cardiology (ESC) Congress 2022. A total of 21,104 adults with hypertension who were taking at least one antihypertensive medication were recruited. The participants were randomly assigned to a morning (06:00–10:00) or an evening (20:00–00:00) medication administration group by a computer algorithm generated through a randomization process, with no restriction, stratification, or minimization randomization methods. Because of the nature of the intervention, neither patients nor investigators were blinded to the group allocation. However, the endpoint assessors were blinded to group allocation to minimize potential bias in the study results.

- The primary outcome was a composite of vascular death or hospitalization for non-fatal myocardial infarction or non-fatal stroke. The results indicated no statistically significant differences in cardiovascular outcomes between groups (HR = 0.95, 95% CI 0.83–1.10, P = 0.53).
- The secondary outcomes included the components of the primary outcome, all-cause mortality, and hospitalization or death from congestive heart failure. No statistically significant differences were found in any outcomes.
- Moreover, taking medication in the evening was found to be safe, because a lower incidence of falls and comparable incidence of fractures were observed the evening dosing group.
- Outcomes were assessed with an unadjusted Cox proportional hazards model, Yates' chi-square test, or t-test, as appropriate. The median follow-up time was 5.2 (IQR 4.9–5.7) years.

The results were published in *The Lancet* [9], which concurrently commented that the TIME study demonstrated that the optimal dosing time of antihypertensive medication should be decided jointly by patients and clinicians, according to each patient's lifestyle and situation, to achieve the best medication adherence and optimal BP control [10].

The findings of the TIME study markedly differed from those of the aforementioned MAPEC and Hygia trials; this discrepancy has prompted reevaluation of the optimal antihypertensive medication dosing time. In addition, two similar clinical trials, the BedMed (NCT02990663) and BedMed-Frail (NCT04054648) trials, are currently being conducted to investigate the effects of antihypertensive medication timing on morbidity and mortality in patients with hypertension. The BedMed-Frail trial specifically focuses on the frail population [11]. The findings of these studies are expected to provide valuable guidance for the development of future hypertension guidelines, which currently lack specific recommendations regarding the optimal timing of antihypertensive medication. However, the TIME study did not investigate the effects of different antihypertensive medications on cardiovascular outcomes associated with morning or evening dosing; such an investigation would enable more precise and detailed intervention guidance regarding the dosing time of hypertension medication. Thus, further investigations in this area are necessary.

Effects of Renal Denervation on Blood Pressure—Spyral HTN-ON MED Pilot Study With Long-Term Follow-up for 3 years

To achieve the target BP, multiple antihypertensive medications are frequently prescribed in numerous patients, thus often resulting in low adherence, drug intolerance, and high healthcare costs. Consequently, novel therapies are needed. With the rapid development of interventional techniques in recent years, transcatheter renal denervation (RDN) has emerged

as a potential approach for BP lowering. The unblinded clinical trials SYMPLICITY HTN-1 and HTN-2 have indicated significant decreases in systolic BP (SBP) 6 months after RDN, by 25 mmHg and 33 mmHg, respectively [12, 13]. However, the blinded and sham-controlled SYMPLICITY HTN-3 trial has demonstrated no significant differences in SBP and 24-hour ambulatory SBP at 6 months between patients who underwent RDN and sham surgery. The discrepant results observed between the SYMPLICITY HTN trials may be attributable to various factors, including differences in the trial design, patient populations, and execution of the RDN procedure. The rigorous design of the HTN-3 trial effectively eliminated regression to the mean, and the Hawthorne and placebo effects. However, the uncertain adherence to medication between groups and the suboptimal execution of the RDN procedure as a result of operators' limited experience in the HTN-3 trial might have introduced confounding effects, thereby hindering the ability to distinguish between the experimental and control groups, and leading to an absence of statistically significant results [14]. Therefore, caution is warranted in interpreting the 6-month follow-up results of the HTN-3 trial. Consequently, studies were subsequently conducted to further elucidate the role of RDN in the management of hypertension [15–19].

The 3-year follow-up results of SPYRAL HTN-ON MED, a randomized, single-blind, sham-controlled clinical study, were presented at the American College of Cardiology (ACC) Conference 2022. The study enrolled 80 patients meeting the inclusion criteria of SBP of 150–180 mmHg, diastolic BP (DBP) of at least 90 mmHg, mean 24-hour SBP of 140–170 mmHg, and taking one to three antihypertensive medications. The patients were randomly assigned to either a radiofrequency RND group (n = 38) or a sham group (n = 42).

- The primary outcome was the difference in 24-hour SBP at 6 months between the RDN group and the sham group. The RDN group, compared with the sham group, demonstrated a reduction of 7 mmHg (95% CI −12.0 to −2.1) in 24-hour SBP and 4.3 mmHg (95% CI −7.8 to −0.8) in 24-hour DBP [15]. After 3 years of follow-up, the RDN group exhibited reductions of 10.0 mmHg (95% CI −16.6 to −3.3) and 4.3 mmHg (95% CI −10.1 to −1.8) in 24-hour SBP and DBP, respectively compared to the sham group.
- The secondary outcome included assessment of changes in 24-hour, morning, daytime, nighttime, and office SBP changes at 24 and 36 months; statistically significant differences were observed in all these measures.
- Outcomes were assessed in SAS statistical software with T-tests or analysis of covariance, as appropriate.

The Lancet published results demonstrating that radiofrequency RDN consistently and significantly decreases BP in patients with hypertension without serious adverse events, independently of the antihypertensive medications taken. Moreover, after 3 years of RDN treatment, the observed 10 mmHg decrease in 24-hour SBP was sustained throughout the day and was associated with significantly lower rates of cardiovascular outcomes, thus suggesting that RDN may potentially be a viable alternative for patients with resistant hypertension, or those unwilling or unable to tolerate multiple antihypertensive medications [20, 21].

The results of several other RDN clinical trials were reported in 2022. The 6-month follow-up results of the Spyral HTN-ON MED Expansion study, which were presented at American Heart Association (AHA) Scientific Sessions 2022, indicated that the RDN group, compared with the sham group, had a significant reduction of 3.7 mmHg (P = 0.001) in nocturnal ambulatory SBP. However, the 24-hour SBP change between groups was 1.9 mmHg (P = 0.119), which didn't meet the primary endpoint. In addition, the 3-year follow-up results of the SYMPLICITY HTN-3 study were reported in *The Lancet* [22]. The difference between the RDN and sham groups was 22.1 mmHg (95% Cl −27.2 to −17.0) in SBP and 16.5 mmHg (95% CI −20.5 to −12.5) in 24-hour SBP, The distinct difference, in contrast with the negative results of 6-month follow-up, confirms the effectiveness and long-term durability of RDN. Furthermore, the 3-year follow-up results of the Global SYMPLICITY Registry study were reported in *JACC* [23]. After RDN, a sustained average 16.7 mmHg decrease in BP over 3 years and a higher amount of time spent in the therapeutic range of BP were observed compared

with the baseline, with lower major cardiovascular outcomes. Because of its demonstrated efficacy and safety, RDN is considered a viable antihypertensive therapy in the 2023 Hypertension Guidelines of China, Europe, and the Netherlands [24, 25].

However, several limitations should be considered before RDN becomes a standard treatment option for patients with hypertension. First, no clinically convenient and feasible method to detect renal sympathetic nerve activity is currently available. Therefore, the response to RDN in some patients is unsatisfactory. Second, the population of patients optimally suited for RDN has yet to be determined, because the mechanism and effects of RDN have not been fully elucidated. Third, the lack of standardized operation procedures, coupled with challenges in training operators and managing potential interventional complications, pose obstacles to the development of RDN.

Phase II Trial of the Aldosterone Synthase Inhibitor Baxdrostat on Resistant Hypertension—BrigHTN Study

Approximately 10% of individuals with hypertension are classified as having treatment resistance [26], such that their condition cannot be effectively controlled, even with the administration of multiple antihypertensive medications [27]. Aldosterone exacerbates hypertension by promoting sodium reabsorption in distal nephrons by increasing the number and opening frequency of epithelium sodium channels, thereby leading to volume expansion. Additionally, aldosterone damages various target organs, including vessels, kidneys, and the heart, via multiple mechanisms, such as upregulation of connective tissue growth factor and subsequent fibrosis; production of proinflammatory molecules contributing to organ and extracellular matrix remodeling; oxidative stress; and stimulation of cell migration, proliferation, and apoptosis [28]. Moreover, target organ damage may worsen hypertension. Previous studies have explored the effectiveness of mineralocorticoid receptor antagonists in the treatment of hypertension. However, limitations of these treatments have been identified to include adverse events, such as an augmented aldosterone response, hyperkalemia, and gynecomastia. In addition, mineralocorticoid receptor antagonists are not appropriate for patients with intermediate or advanced chronic kidney disease [29]. Therefore, researchers have focused on another mechanism: the inhibition of aldosterone synthase. Nevertheless, because of the 93% sequence similarity between the enzymes synthesizing aldosterone and cortisol, the development of highly selective inhibitors of aldosterone synthase has led to a bottleneck. However, in recent preclinical and phase I trials, baxdrostat, an oral small-molecule aldosterone synthase inhibitor, has been found to substantially decrease plasma aldosterone levels without a concomitant decline in cortisol levels; these findings have increased interest in, and focus on, the inhibition of aldosterone synthase [30].

The phase II results of the BrigHTN study, a multicenter, double-blind, dose-ranging randomized controlled trial, were presented at AHA Scientific Sessions 2022. A total of 275 patients with resistant hypertension, defined by a BP above 130/80 mmHg, who were taking at least three antihypertensive medications including a diuretic, were recruited. Patients were randomly assigned to receive baxdrostat at doses of 0.5 mg, 1 mg, or 2 mg once per day, or a placebo for 12 weeks.

- The study's primary efficacy endpoint was the change in mean seated SBP from baseline to the end of the 12-week treatment period. The results indicated that baxdrostat exhibited dose-dependent antihypertensive effect: the mean seated SBP decreased by 20.3 mmHg, 17.5 mmHg, 12.1 mmHg, and 9.4 mmHg in the baxdrostat group with doses of 2 mg, 1 mg, or 0.5 mg, and placebo, respectively. Moreover, the 2 mg baxdrostat group exhibited a significant antihypertensive effect, with placebo-adjusted SBP and DBP decreases of 11.0 mmHg (95% CI −16.4 to −5.5) and 5.2 mmHg (95% CI −8.7 to −1.6).
- The secondary outcomes included the change in the mean seated DBP with respect to baseline. The results indicated a difference in DBP between the baxdrostat 2-mg group and the placebo group of 5.2 mmHg (95% CI −8.7 to −1.6).
- Safety endpoints included adverse events, vital signs, and the results of physical examinations. Two patients developed high serum potassium levels exceeding 6.0 mmol/L, which did not recur after withdrawal and re-initiation of the drug.

In conclusion, this study first demonstrated significant antihypertensive effectiveness of baxdrostat in patients with resistant hypertension, without any adverse effects on cortisol levels or adrenocortical function, or causing severe hyperkalemia. The results were published in *NEJM* [31]. These results highlight the potential for baxdrostat to serve as a new treatment option for diseases including resistant hypertension and primary aldosteronism.

However, because baxdrostat was not compared with existing antihypertensive medications, and the renal function of all participants was normal, further studies are necessary to evaluate the long-term effectiveness and safety of this drug, and to identify patient populations in which its use would be appropriate.

Phase III Trial of Dual Endothelin Antagonist Aprocitentan on Resistant Hypertension—PRECISION study

Prior studies have shown the antihypertensive effects of endothelin receptor antagonists [32, 33]. These agents act by blocking the endothelin pathway, which is active primarily in endothelial cells and vascular smooth muscle cells, and is involved in cell proliferation and vessel vasoconstriction. Endothelin levels are known to be elevated in hypertension; diseases susceptible to resistant hypertension, such as obesity and obstructive sleep apnea; and complications associated with resistant hypertension, such as diabetes and chronic renal disease; moreover, the resulting changes in vascular tone contribute to the pathogenesis of hypertension and related cardiovascular diseases (CVDs) [34–37]. Aprocitentan is an oral antagonist of the dual endothelin A and B receptor. In a phase II clinical trial, aprocitentan monotherapy has been found to have more effective antihypertensive effects at doses of 10–25 mg compared to dose of 50 mg [38].

The phase III results of the PRECISION study, a multicenter, blinded randomized controlled trial, were presented at AHA Scientific Sessions 2022. A total of 730 patients with resistant hypertension were recruited, all of whom had a seated SBP above 140 mmHg and were taking at least three antihypertensive medications including a diuretic. The study comprised three parts. In part 1, participants were randomly assigned in a 1:1:1 ratio to receive aprocitentan at doses of 12.5 mg or 25 mg, or a placebo treatment in a double-blind period for 4 weeks. Then all participants took aprocitentan 25 mg for 32 weeks in part 2. Finally, in part 3, patients were randomly reassigned to two groups (1:1) to receive aprocitentan 25 mg or a placebo treatment in a double-blind period for 12 weeks.

- The primary and key secondary endpoints were SBP changes from baseline to week 4 and from medication withdrawal from baseline (at the beginning of part 3) to week 40. From baseline to week 4, SBP decreased by 3.8 mmHg (97.5% CI −6.8 to −0.8) in the 12.5 mg aprocitentan group and 3.7 mmHg (97.5% CI −6.7 to −0.8) in the 25 mg group, as compared with the placebo group. After 4 weeks of medication withdrawal, SBP increased by 5.8 mmHg (95% CI 3.7 to 7.9) in the placebo treatment group compared with the aprocitentan treatment group.

The study indicated that, despite its concurrent use with other antihypertensive medications, aprocitentan produced statistically and clinically significant decreases in BP among patients with resistant hypertension, and this effect was maintained for at least 1 year. The results were published in *The Lancet*, which commended the remarkably well-designed medication research protocol in this study. Notably, the study revealed that aprocitentan, because of its new pharmacological mechanism, may have the potential to serve as a novel option for more than 100 million patients with resistant hypertension worldwide. Moreover, the study also highlighted the long-term efficacy of aprocitentan. This durable treatment option may effectively prevent cardiovascular events, thus providing the first breakthrough in antihypertensive medication in 30 years.

Nonetheless, the effect of aprocitentan is modest, and its clinical value must be further evaluated by comparison with other fourth-line antihypertensive medications (such as spironolactone) [39, 40].

Best Time for Mild Chronic Hypertension Treatment During Pregnancy—CHAP study

Mild chronic hypertension during pregnancy has a prevalence ranging from 0.9% to 1.5%, and is associated with elevated risk of placental abruption, premature birth, low birth weight, and perinatal death,

as well as multiple maternal adverse events, such as heart failure, stroke, and acute kidney injury [41–43]. The treatment threshold for pregnant women with chronic hypertension varies among guidelines. Specifically, the American College of Obstetricians and Gynecologists (ACOG) guidelines recommend treatment when the BP is at or above 160/110 mmHg, whereas the cutoff in the ESC guidelines is 150/95 mmHg. The World Health Organization, in contrast, does not have a specific recommendation [41, 44, 45]. Doubts have been raised regarding potential harm to the fetus from reduced uteroplacental circulation and in utero exposure to antihypertensive medications during BP lowering, whereas the benefits to maternal health are unclear, thus futher investigations into therapies for BP between 140–159/90–109 mmHg are required. A previous study with small sample sizes has demonstrated the lack of utility of antihypertensive treatment for mild chronic hypertension during pregnancy [46], whereas a secondary analysis has indicated a higher risk of adverse outcomes among patients with mild chronic hypertension during pregnancy than those with normal BP, in a BP-dependent manner [47]. The 2015 randomized controlled study CHIPS has revealed that, in comparison with loosely controlled BP (DBP ≤100 mmHg), strictly controlled BP (DBP ≤85 mmHg) decreases the risk of severe maternal hypertension with no adverse effects on fetal growth; however, no statistically significant difference was observed in pregnancy outcomes within 28 days after delivery [48]. On the basis of the results, numerous associations have lowered the treatment threshold in their recommendations, except for ACOG and the Society for Maternal Fetal Medicine (SMFM), owing to doubts regarding the low statistical power of the CHIPS study, given that its sample size was smaller than anticipated, and it lacked long-term follow-up.

The results of an open-label, randomized trial with a larger sample size and improved regional and racial representation with respect to prior studies, the CHAP study, were presented at the ACC Conference 2022. A total of 2480 pregnant women with mild chronic hypertension and a single fetus of gestational age less than 23 weeks were included and randomly allocated to either an active treatment group (BP ≤140/90) or a standard treatment group (BP ≤160/105).

- The primary outcome was a composite of severe preeclampsia, medically indicated preterm births before 35 weeks, placental abruption, and fetal/neonatal death. Compared with the standard treatment group, the active treatment group maintained lower BP (129.5/79.1 mmHg vs. 132.6/81.5 mmHg) and had a lower incidence of the primary outcome (HR=0.82, 95% CI 0.74–0.92), particularly regarding decreased incidence of preeclampsia and medically indicated preterm births.

In conclusion, the CHAP study has indicated that active antihypertensive treatment (target BP ≤140/90) for mild chronic hypertension during pregnancy considerably decreases adverse pregnancy outcomes without increasing the risk of small-for-gestational-age infants. The results were published in *NEJM* [49].

The CHAP study has demonstrated that early-stage antihypertensive therapies are needed for mild chronic hypertension during pregnancy, thus leading to a decrease in the treatment threshold to 140/90 mmHg for pregnant women with chronic hypertension in the updated guidelines issued by SMFM and the Society of Obstetricians and Gynaecologists of Canada in 2022. The updated guidelines may result in more women receiving antihypertensive therapy during pregnancy, thus potentially improving outcomes for both mothers and infants. Healthcare providers should be aware of these updated guidelines, and should consider them when managing hypertension during pregnancy. However, although no statistical differences in neonatal outcomes were observed between groups, the potential long-term effects of active antihypertensive therapies on offspring exposed in utero remain unclear. Therefore, further follow-up studies are necessary to assess the effects on the health and well-being of the offspring. Such research will be crucial to ensure that interventions aimed at improving maternal and fetal health do not have unintended adverse effects on offspring in the long term, and to inform clinical decision-making in this area.

Comparison Between Chlorthalidone and Hydrochlorothiazide for Hypertension—DCP study

Thiazide diuretics, represented by chlorthalidone and hydrochlorothiazide, are the first-line medication recommended by current hypertension guidelines

[50]. Previous studies have illustrated the superiority of chlorthalidone to hydrochlorothiazide [51, 52], as also supported by the 2017 ACC/AHA Guidelines for High Blood Pressure [53], whereas several observational studies have recently demonstrated no significant difference between chlorthalidone and hydrochlorothiazide [54, 55]. However, hydrochlorothiazide is more commonly used by clinicians, owing to concerns regarding the hypokalemic effects of chlorthalidone. Thus, further evidence is urgently needed to elucidate current ambiguities.

At AHA Scientific Sessions 2022, the results of the Diuretic Comparison Project (DCP) study, a pragmatic, open-label trial, were presented. A total of 13,523 patients with hypertension, mainly veterans over the age of 65 years, were randomly allocated to a hydrochlorothiazide group (25 or 50 mg/d) or chlorthalidone group (12.5 or 25 mg/d).

- The primary outcome was a composite of noncancer deaths or nonfatal cardiovascular events, defined as nonfatal stroke, myocardial infarction, emergency revascularization for unstable angina, or acute heart failure. The results indicated that during a mean follow-up period of 2.4 years, the incidence of the primary outcome, as well as its components, was comparable (HR = 1.04, 95% CI 0.94–1.16) between the chlorthalidone group (10.4%) and the hydrochlorothiazide group (10.0%). Additionally, a subgroup analysis demonstrated that, among participants with a history of myocardial infarction or stroke, the primary outcome was reduced in the chlorthalidone group (HR = 0.73, 95% CI 0.57–0.94), whereas among those without such a history, chlorthalidone tended to increase the primary outcome (HR = 1.12, 95% CI 1.00–1.26).
- Regarding safety outcomes, the incidence of hypokalemia in the chlorthalidone group (6.0%) was higher than that in the hydrochlorothiazide group (4.4%). These findings confirmed clinicians' longstanding concerns. Moreover, new allergic or adverse reactions were more common in the chlorthalidone group (1.6%) than the hydrochlorothiazide group (0.3%), whereas no statistical difference was found in hospitalization for any cause. Thus, healthcare providers should consider the safety profiles of different diuretics when choosing treatment plans for their patients, and should take steps to minimize the risks of adverse reactions.

The results were published in *NEJM* [56]. The DCP study demonstrated that, compared with the clinically commonly used hydrochlorothiazide, chlorthalidone did not decrease the incidence of major cardiovascular outcomes or non-cancer deaths. This discovery challenges the established belief that chlorthalidone is the preferred treatment option, as supported by various guidelines. Therefore, in selecting the antihypertensive medication, consideration of each patient's medical history, renal function, complications, and other relevant factors is critical in making the most appropriate decision. However, a notable limitation is that this study focused on only participants 65 years of age or older, and the population was predominantly male. Age and sex are important factors influencing the response to antihypertensive therapy and the risk of adverse outcomes. Therefore, the findings of this study may not be directly applicable to younger adults and women, and caution should be exercised when extrapolating the results to these groups. Further studies in different patient populations are necessary to confirm the applicability of these findings.

Effectiveness of Blood Pressure Interventions Led by Village Doctors in Rural China—the CRHCP Study

Approximately 75% of patients with hypertension live in low- and middle-income countries with scarce resources, thus resulting in a low rate of hypertension control [57]. In rural China, only 5.5% of patients with hypertension have their BP under control [58]. Village doctors provide basic medical care in rural China and are likely to play a crucial part in the prevention and control of hypertension, if they are properly trained in areas including standardized BP measurement; health coaching on lifestyle modifications; and protocol-driven antihypertensive treatment involving a treatment algorithm, medication selection, contraindications of medications, and adjustment strategies [59, 60].

The China Rural Hypertension Control Project (CRHCP) study was a cluster randomized trial initiated by Yingxian Sun at the First Hospital of China Medical University. A total of 33,995 individuals over 40 years of age living in 326 Chinese villages, who had an untreated BP above 140/90 mmHg or treated BP above 130/80 mmHg, were enrolled and randomized (1:1) to an intervention group or a control

group receiving conventional antihypertensive medications. In the intervention group, patients received a comprehensive treatment approach initiated by village doctors, including the initiation of antihypertensive medication according to established guidelines, provision of discounted or free medications, guidance on home BP monitoring, health coaching on lifestyle modifications, and organization of social support groups. Follow-up assessments were conducted every 6 months to monitor BP levels and other associated conditions in participants. Notably, however, the study design had several limitations, including practical limitations regarding the recruitment of all patients in a village and variations in the sizes of the clusters. In addition, because the intervention in this study was conducted primarily through oral coaching and guidance by village doctors, the quality of communication between the doctors and patients, as well as patients' ability to understand and accept treatment, are crucial factors that might have influenced the effectiveness of the intervention. The uncontrollable communication among village doctors and patients between the intervention and control groups might have diminished the observed intervention effect. The phase I (18 months of follow-up) results were presented at AHA Scientific Sessions 2021 and published in *The Lancet*. The outcome of phase II (36 months of follow-up) was presented at AHA Scientific Sessions 2022 [61].

- The primary outcome was a composite of myocardial infarction, stroke, heart failure requiring hospitalization, and CVD death. The primary outcome rate was substantially lower (HR = 0.64, 95% CI 0.58–0.70) in the intervention group (1.6%) than the control group (2.4%).
- The secondary outcomes included the components of the primary outcome and death due to all causes. The intervention group showed statistically significant decreases in all these outcomes, as compared with the control group, thus indicating a broad benefit of the intervention in decreasing the risk of cardiovascular events and death due to all causes.
- Moreover, the mean SBP in the intervention and control groups decreased by 30.9 mmHg and 7.8 mmHg, whereas the mean DBP decreased by 14.8 mmHg and 4.9 mmHg, respectively. The differences between groups in SBP and DBP were 23.1 mmHg (95% CI −24.4 to −21.9) and 9.9 mmHg (95% CI −10.6 to −9.3).

The results demonstrated the effectiveness and feasibility of implementing interventions led by village doctors to achieve target BP levels in poorly resourced villages, and may provide guidance for the development of government policies to allow trained village doctor-led interventions for uncomplicated hypertension in low- and middle-income countries, by using a standard protocol under supervision by physicians. This approach has the potential to significantly improve hypertension management and alleviate the burden of healthcare expenses, while increasing access to care for rural populations.

AHA 2022 has noted that this study empowered primary medical staff with enhanced capabilities through Chinese innovation, and the effects of the nearly 1% absolute risk reduction of primary outcome in the intervention group have notable implications for hypertension management in low- and middle-income countries worldwide with a high burden of hypertension.

The Chinese Heart-Healthy Diet on Hypertension—DECIDE-Diet Study

In 2017, an estimated 11 million deaths and 255 million disability-adjusted life years—a time-based measure that combines years of life lost because of premature mortality and time lived in states of less than full health or disability—were attributable to dietary risk factors [62]. Similarly, CVDs are significantly correlated with diets. Numerous studies have demonstrated that healthful diets [63], such as the Dietary Approaches to Stop Hypertension (DASH) diet and the Mediterranean diet, markedly decrease BP and CVD risk [64–67]. These diets emphasize the consumption of plant-based foods and olive oil, and limitation of red meat consumption. Despite the demonstrated health benefits of these diets, their implementation is often hindered by a perceived lack of flavor. Moreover, implementing Western-style diets in China, which has a high prevalence of CVDs, is challenging, because of the substantial differences in dietary patterns between Chinese and Western populations. Therefore, developing a healthful and palatable diet is imperative for the prevention and management of hypertension and CVDs in Chinese populations.

Circulation has reported the results of the Chinese Heart-Healthy (CHH) Diet pattern study, developed

by Yangfeng Wu at the Peking University Clinical Research Institute [68]. A total of 265 patients with SBP of 130–159 mmHg participated in the Exercise and Cardiovascular Health-Diet (DECIDE-Diet) study, a single-blind randomized trial. After a 7-day run-in period, participants were randomized to either a normal diet or CHH diet. The CHH diet included four major Chinese cuisines—Shandong, Huaiyang, Cantonese, and Szechuan—tailored to the geographic locations of the participants, and included nonrepetitive dishes in a cycle of at least 2 weeks. In contrast, the normal diet was developed on the basis of commonly consumed local foods. During the 28-day intervention period, the study achieved a high rate of participant compliance: 97% of the participants completed the study and consumed an average of 97% of the meals provided.

- The primary outcome was the change in SBP, which decreased by 5.0 mmHg (95% CI –6.5 to –3.5) in the normal diet group and 15.0 mmHg (95% CI –16.5 to –13.5) in the CHH diet group after 28 days. The differences observed for SBP and DBP between groups were 10.0 mmHg (95% CI –12.1 to –7.9) and 3.8 mmHg (95% CI –5.0 to –2.5).

Moreover, both diets were generally well received by participants, and the decrease in SBP by 1 mmHg cost only an additional CNY 0.4 (USD 0.06) per day. The author further estimated that adherence to the CHH diet was associated with a 20% decrease in CVD, a 28% decrease in heart failure, and a 13% decrease in all-cause mortality, thus indicating the efficacy, palatability, and cost-effectiveness of the CHH diet. These findings may provide valuable guidance for the Chinese government and other nations in developing guidelines and policies associated with health management.

However, the study has several limitations including confounding factors, such as the relatively short intervention time; enrollment below anticipated goals; and the controlled design. First, the intervention period was short, lasting only 4 weeks. Consequently, limited evidence suggesting a sustained hypertensive effect in the long term was found. Second, because whole food analysis was not used to measure nutrient composition, the intake of relevant nutrient components could not be ensured in the CHH diet. Third, the intended enrollment goals were not achieved because of the effects of the COVID-19 pandemic. Given the controlled design of this study, the generalizability of its findings to real-world scenarios warrants further validation.

Effectiveness of the Endovascular Baroreflex Amplification Technique on Hypertension—CALM-FIM Study with Long-Term Follow-up for 3 years

Despite the availability of various antihypertensive medications, 86% of patients with hypertension continue to experience uncontrolled hypertension, thus increasing their risk of developing CVDs. Therefore, investigating novel antihypertensive techniques and their potential effects on BP management is critical. Stimulating baroreceptors can lower BP by activating sympathetic and parasympathetic nerves [69]. Two antihypertensive techniques have been developed: baroreflex activation therapy and endovascular baroreflex amplification (EBA). MobiusHD, an implant for the internal carotid artery, belongs to the EBA category; this modality decreases BP through passive mechanical stimulation of baroreceptors, rather than using electrical stimulation as in baroreflex activation therapy [42, 70, 71].

The Controlling and Lowering Blood Pressure With the MobiusHD–First in Man (CALM-FIM) study was a prospective, open-label trial to assess the effectiveness of implanted MobiusHD in the unilateral internal carotid artery in 47 patients with resistant hypertension.

- The primary outcomes were the incidence of adverse events and changes in BP, 24-hour ambulatory BP, and antihypertensive medication use after implantation. The results of the 6-month follow-up, published in *The Lancet*, indicated that BP was lowered by 30/12 mmHg (95% CI −38 to −21/−17 to −8 mmHg), and ambulatory BP was lowered by 21/12 mmHg (95% CI −19 to −14/−16 to −7 mmHg) [72]. After 3 years, the BP decrease remained at 30/12 mmHg (95% CI −38 to −21/−17 to −8 mmHg).
- Regarding safety outcomes, the occurrence of five serious adverse events, including hypotension (n=2), hypertension (n=1), vascular access complications (n=2), and two transient ischemic attacks, were observed within 30 days

post-implantation. By 30 days post-implantation, six serious adverse reactions had occurred, including strokes (n=2), transient neurologic symptoms (n=1), hypertension (n=1), and hypotension (n=2).

The occurrence of these serious adverse events underscores the importance of continued monitoring and evaluation of the safety and effectiveness of this device. Although the adverse events observed in patients who underwent implantation of the MobiusHD device eventually resolved, the high incidence rate of these events has prompted concern regarding the safety of this method. Therefore, future studies should assess the long-term safety and efficacy of the MobiusHD device, to provide a more comprehensive understanding of its benefits and risks and to inform evidence-based clinical practice. The results were published in *JACC Cardiovascular Intervention* [73].

Although the CALM-FIM study demonstrated the efficacy of MobiusHD based on EBA, the study had several limitations. First, the study design lacked a control group, thus preventing accurate evaluation of the outcomes and adverse events associated with the treatment. Second, the study's observational design had the potential for confounding factors such as the Hawthorne effects, placebo effects, and regression to the mean. Furthermore, the study did not use urine or blood tests to assess medication compliance, thus posing challenges in ruling out the influence of medication differences among participants.

Therefore, although the study has provided preliminary evidence of the efficacy of MobiusHD, further trials with a more rigorous design are necessary to evaluate the benefit-risk profile of this technique.

Characteristics of Primary Care Institutions Associated with Hypertension Awareness, Treatment, and Control—China PEACE-Million Persons Project

China's primary medical and health care system consists of approximately 900,000 institutions and 3 million workers, and provides basic public health services on a nationwide scale. The quality of primary medical care is reflected by the awareness, treatment, and control rate of hypertension [74]. Over the past few years, China has implemented substantial investments and reforms to its primary care system, aimed at improving the quality of care provided. However, characteristics including financing methods, medical treatment patterns, and medical personnel capacity vary among regions [60], and the relationships between various characteristics of primary care institutions and the awareness, treatment, and control rates of hypertension remain unclear [75]. Understanding these relationships will be crucial for improving the quality of primary medical care and hypertension management in China's primary care system.

Research conducted by Xi Li and Jiapeng Lu from Fuwai Hospital Chinese Academy of Medical Sciences enrolled 433 primary care institutions from the Million Persons Project, which selected sites in all 31 provinces of mainland China through a convenience sampling strategy, to demonstrate the diversity of geographic distribution and demographics, risk factor exposure, and disease patterns. Among these sites, 660,565 patients with hypertension 35–75 years of age who had lived in the selected area for at least 6 of the prior 12 months were included.

Data were collected through standardized face-to-face interviews conducted by trained personnel using electronic questionnaires with real-time logic-checking capabilities. Univariate analyses of each institution-level were conducted with T-test or ANOVA. Moreover, multi-level logistic models with all participant-level variables were established. Institution-level variables with $P<0.05$ were retained in the final model. All these analyses were performed in SAS statistical software.

The results of standardized rates for hypertension awareness (8.2% to 81.0%), treatment (2.6% to 96.5%), and control (0% to 62.4%) were reported, and 10% of the awareness rate, 21% of the treatment rate, and 12% of the control rate were ascribed to primary care institutions. Characteristics of primary care institutions conducive to hypertension management included bonuses associated with performance (treatment rate OR=1.39, 95% CI 1.07–1.80), referrals through the online system (treatment rate OR=1.41, 95% CI 1.14–1.73; control rate OR=1.17, 95% CI 1.03–1.33), a family doctor service pattern (awareness OR=1.13, 95% CI 1.00–1.28; control rate OR=1.30, 95% CI 1.15–1.46), and a high proportion of practitioners (awareness OR=1.04, 95% CI 1.01–1.08; treatment rate

Table 1 Classification of Top Ten Breakthroughs in 2022 Clinical Studies of Hypertension.

Number	Classification	Research	Conclusion	Published/presented
1	Management of hypertension	TIME	No statistically significant difference was found between taking antihypertensive medication in the morning or evening.	Lancet [9]; ESC 2022
2		CHAP	Active antihypertensive treatment (target BP ≤140/90) for mild chronic hypertension during pregnancy considerably decreased pregnancy-related outcomes without elevating the risk of small-for-gestational-age infants.	NEJM [49]; ACC 2022
3		CRHCP	The effectiveness of hypertensive interventions led by rural physicians in poorly resourced villages is demonstrated.	Lancet [61]; AHA 2022
4		China PEACE Project	Evidence for the critical role of primary care institutions' characteristics in the quality of medical care is provided.	The Lancet Global Health [76]
5	Treatment of hypertension	Spyral HTN-ON MED Pilot	RDN consistently improved BP without serious adverse events, independently of the antihypertensive medication taken.	Lancet [21]; ACC 2022
6		BrigHTN	Baxdrostat considerably decreased BP in a dose-dependent manner.	NEJM [31]; AHA 2022
7		PRECISIN	Aprocitentan had antihypertensive effects at week 4, which were sustained until week 48.	Lancet [38]; AHA 2022
8		DCP	Compared with hydrochlorothiazide, chlorothiazide did not lessen the occurrence of major cardiovascular outcomes or non-cancer deaths.	NEJM [56]; AHA 2022
9		DECIDE-Diet	The efficacy, palatability, and cost-effectiveness of the Chinese Heart-Healthy diet are demonstrated.	Circulation [68]
10		CALM-FIM	The efficacy and safety of MobiusHD are corroborated through endovascular baroreflex amplification.	JACC Cardiovascular [73]

OR = 1.08, 95% CI 1.02–1.14). In contrast, characteristics detrimental to hypertension management included governmental allocation of resources, financial problems affecting daily work, and salaries associated with the numbers of outpatients and inpatients. The results have been published in *The Lancet Global Health* [76]. Considering the current situation in China, the training of primary care physicians must urgently be enhanced to increase the proportion of licensed practitioners, improve coordination between superior and subordinate hospitals, establish a robust network referral system, and optimize the incentive mechanism of performance bonuses. These strategies may also be relevant and applicable to other countries facing similar challenges.

However, this study had several limitations. The time mismatch between participant data (obtained from 2014 to 2021) and institutional characteristics data (obtained from 2016 to 2017) might have introduced bias in the observed associations, particularly given that some new policies were issued after 2017. Moreover, focusing on institutional characteristics without adjusting for individual health-care seeking behaviors might also have influenced the results of the analysis. Furthermore, the primary care institution characteristics included in the analysis, such as physician access to the clinical practice guidelines, might not have been comprehensive. Together, these limitations might have led to underestimation or overestimation of the effects of specific characteristics on hypertension management in primary healthcare systems, and affected the reliability and generalizability of the findings. Therefore, further studies including qualitative in-depth interviews and randomized controlled trials to assess these features would be essential and informative. In conclusion, this study highlighted the critical roles of primary care institution characteristics in the quality of medical care, and identified potential avenues for improving hypertension management in primary healthcare systems.

Conclusions

Hypertension is the most common chronic noncommunicable disease. The ten aforementioned clinical studies have offered valuable insights into the treatment and management of hypertension (Table 1). However, notable challenges in the management of hypertension remain to be addressed and elucidated in further research, to support evidence-based medicine, and achieve well-treated, controlled, and managed hypertension.

Conflict of interests

The authors declare no conflicts of interest.

REFERENCES

1. Kario K. Nocturnal hypertension: new technology and evidence. Hypertension 2018;71(6):997–1009.
2. Kario K. Morning surge in blood pressure and cardiovascular risk: evidence and perspectives. Hypertension 2010;56(5):765–73.
3. Kario K, Wang JG, Chia YC, Wang TD, Li Y, Siddique S, et al. The HOPE Asia network 2022 up-date consensus statement on morning hypertension management. J Clin Hyperten (Greenwich, Conn.) 2022;24(9):1112–20.
4. Sharma T, Mathur P, Mehta JL. Daytime or nighttime administration of antihypertensive medications? Am J Hypertension 2020;33(11):987–9.
5. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. Chronobiol Int 2010;27(8);1629–51.
6. Hermida RC, Crespo JJ, Dominguez-Sardina M, Otero A, Moya A, Rios MT, et al. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J 2020;41(48):4565–76.
7. Stergiou G, Brunstrom M, MacDonald T, Kyriakoulis KG, Bursztyn M, Khan N, et al. Bedtime dosing of antihypertensive medications: systematic review and consensus statement: International Society of Hypertension position paper endorsed by World Hypertension League and European Society of Hypertension. J Hypertens 2022;40(10):1847–58.
8. Turgeon RD, Althouse AD, Cohen JB, Enache B, Hogenesch JB, Johansen ME, et al. Lowering nighttime blood pressure with bedtime dosing of antihypertensive medications: controversies in hypertension - con side of the argument. Hypertension 2021;78(3):871–8.
9. Mackenzie IS, Rogers A, Poulter NR, Williams B, Brown MJ, Webb DJ, et al. Cardiovascular outcomes in adults with hypertension

with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial. Lancet (London, England) 2022;400(10361):1417–25.
10. Salah HM, Mehta JL. Best time for administration of antihypertensive medications: morning or evening? Lancet (London, England) 2022;400(10361):1383–5.
11. Garrison SR, Kolber MR, Allan GM, Bakal J, Green L, Singer A, et al. Bedtime versus morning use of antihypertensives for cardiovascular risk reduction (BedMed): protocol for a prospective, randomised, open-label, blinded endpoint pragmatic trial. BMJ Open 2022;12(2):e059711.
12. Symplicity HTNI. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension 2011;57(5):911–7.
13. Symplicity HTNI, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet (London, England) 2010;376(9756):1903–9.
14. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014;370(15):1393–401.
15. Kandzari DE, Bohm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet (London, England) 2018;391(10137):2346–55.
16. Azizi M, Sanghvi K, Saxena M, Gosse P, Reilly JP, Levy T, et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. Lancet (London, England) 2021;397(10293):2476–86.
17. Bohm M, Kario K, Kandzari DE, Mahfoud F, Weber MA, Schmieder RE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. Lancet (London, England) 2020;395(10234):1444–51.
18. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet (London, England) 2017;390(10108):2160–70.
19. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet (London, England) 2018;391(10137):2335–45.
20. Mahfoud F, Kandzari DE, Kario K, Townsend RR, Weber MA, Schmieder RE, et al. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. Lancet 2022;399(10333):1401–10.
21. Sarathy H, Salman LA. Can renal denervation replace medications for patients with hypertension? Lancet (London, England) 2022;399(10333):1363–5.
22. Bhatt DL, Vaduganathan M, Kandzari DE, Leon MB, Rocha-Singh K, Townsend RR, et al. Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 Trial. Lancet (London, England) 2022;400(10361):1405–16.
23. Mahfoud F, Mancia G, Schmieder RE, Ruilope L, Narkiewicz K, Schlaich M, et al. Cardiovascular risk reduction after renal denervation according to time in therapeutic systolic blood pressure range. J Am Coll Cardiol 2022;80(20):1871–80.
24. Barbato E, Azizi M, Schmieder RE, Lauder L, Bohm M, Brouwers S, et al. Renal denervation in the management of hypertension in adults. A clinical consensus statement of the ESC Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2023;44(15):1313–30.
25. Zeijen VJM, Kroon AA, van den Born BH, Blankestijn PJ, Meijvis SCA, Nap A, et al. The position of renal denervation in treatment of hypertension: an expert consensus statement. Neth Heart J 2023;31(1):3–11.
26. Noubiap JJ, Nansseu JR, Nyaga UF, Sime PS, Francis I, Bigna JJ. Global prevalence of resistant hypertension: a meta-analysis of data from 3.2 million patients. Heart (British Cardiac Society) 2019;105(2):98–105.
27. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension 2018;72(5):e53–90.
28. Imprialos KP, Bouloukou S, Kerpiniotis G, Katsimardou A, Patoulias D, Bakogiannis C, et al. Mineralocorticoid receptor antagonists in essential and resistant hypertension. Curr Pharm Des 2018;24(46):5500–7.
29. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet (London, England) 2015;386(10008):2059–68.
30. Freeman MW, Bond M, Murphy B, Hui J, Isaacsohn J. Results from a phase 1, randomized, double-blind, multiple ascending dose study

characterizing the pharmacokinetics and demonstrating the safety and selectivity of the aldosterone synthase inhibitor baxdrostat in healthy volunteers. Hypertens Res 2023;46(1):108–18.
31. Freeman MW, Halvorsen YD, Marshall W, Pater M, Isaacsohn J, Pearce C, et al. Phase 2 trial of baxdrostat for treatment-resistant hypertension. N Engl J Med 2022;388:395–405.
32. Krum H, Viskoper RJ, Lacourciere Y, Budde M, Charlon V. The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. Bosentan Hypertension Investigators. N Engl J Med 1998;338(12):784–90.
33. Nakov R, Pfarr E, Eberle S, HEAT Investigators. Darusentan: an effective endothelinA receptor antagonist for treatment of hypertension. Am J Hypertens 2002;15(7 Pt 1):583–9.
34. Clozel M. Aprocitentan and the endothelin system in resistant hypertension. Can J Physiol Pharmacol 2022;100(7):573–83.
35. Grubbs AL, Anstadt MP, Ergul A. Saphenous vein endothelin system expression and activity in African American patients. Arterioscler Thromb Vasc Biol 2002;22(7):1122–7.
36. Rossignol P, Massy ZA, Azizi M, Bakris G, Ritz E, Covic A, et al. The double challenge of resistant hypertension and chronic kidney disease. Lancet (London, England) 2015;386(10003):1588–98.
37. Solini A, Zoppini G, Orsi E, Fondelli C, Trevisan R, Vedovato M, et al. Resistant hypertension in patients with type 2 diabetes: clinical correlates and association with complications. J Hypertens 2014;32(12): 2401–10; discussion 2410.
38. Verweij P, Danaietash P, Flamion B, Menard J, Bellet M. Randomized dose-response study of the new dual endothelin receptor antagonist aprocitentan in hypertension. Hypertension 2020;75(4):956–65.
39. Schlaich MP, Bellet M, Weber MA, Danaietash P, Bakris GL, Flack JM, et al. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. Lancet (London, England) 2022;400(10367):1927–37.
40. Dechend R, Delles C. Endothelin antagonists and the quest for a new therapeutic option in resistant hypertension. Lancet (London, England) 2022;400(10367):1900–1.
41. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. Obstet Gynecol 2019;133(1):e26–50.
42. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122(5):1122–31.
43. Battarbee AN, Sinkey RG, Harper LM, Oparil S, Tita ATN. Chronic hypertension in pregnancy. Am J Obstet Gynecol 2020;222(6):532–41.
44. Sinkey RG, Battarbee AN, Bello NA, Ives CW, Oparil S, Tita ATN. Prevention, diagnosis, and management of hypertensive disorders of pregnancy: a comparison of international guidelines. Curr Hypertens Rep 2020;22(9):66.
45. Garovic VD, Dechend R, Easterling T, Karumanchi SA, McMurtry Baird S, Magee LA, et al. Hypertension in pregnancy: diagnosis, blood pressure goals, and pharmacotherapy: a scientific statement from the American Heart Association. Hypertension 2022;79(2):e21–41.
46. Sibai BM, Mabie WC, Shamsa F, Villar MA, Anderson GD. A comparison of no medication versus methyldopa or labetalol in chronic hypertension during pregnancy. Am J Obstet Gynecol 1990;162(4):960–6; discussion 966–7.
47. Ankumah NA, Cantu J, Jauk V, Biggio J, Hauth J, Andrews W, et al. Risk of adverse pregnancy outcomes in women with mild chronic hypertension before 20 weeks of gestation. Obstet Gynecol 2014;123(5):966–72.
48. Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med 2015;372(5): 407–17.
49. Tita AT, Szychowski JM, Boggess K, Dugoff L, Sibai B, Lawrence K, et al. Treatment for mild chronic hypertension during pregnancy. N Engl J Med 2022;386(19):1781–92.
50. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311(5):507–20.
51. Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. Hypertension 2011;57(4):689–94.
52. Roush GC, Holford TR, Guddati AK. Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses. Hypertension 2012;59(6)1110–7.
53. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, 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. J Am Coll Cardiol 2018;71(19): e127–248.
54. Hripcsak G, Suchard MA, Shea S, Chen R, You SC, Pratt N, et al. Comparison of cardiovascular and safety outcomes of chlorthalidone vs hydrochlorothiazide to treat hypertension. JAMA Intern Med 2020;180(4):542–51.
55. Edwards C, Hundemer GL, Petrcich W, Canney M, Knoll G, Burns K, et al. Comparison of clinical outcomes and safety associated with chlorthalidone vs hydrochlorothiazide in older adults with varying

levels of kidney function. JAMA Netw Open 2021;4(9):e2123365.
56. Ishani A, Cushman WC, Leatherman SM, Lew RA, Woods P, Glassman PA, et al. Chlorthalidone vs. hydrochlorothiazide for hypertension-cardiovascular events. N Engl J Med 2022;387(26):2401–10.
57. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation 2016;134(6):441–50.
58. MA Liyuan, WANG Zengwu, FAN Jing, HU Shengshou. Epidemiology and management of hypertension in China: an analysis using data from the Annual Report on Cardiovascular Health and Diseases in China (2021). Chin Gen Pract 2022;25(30):3715–20. (in Chinese)
59. Sidel VW. The barefoot doctors of the People's Republic of China. N Engl J Med 1972;286(24):1292–300.
60. Li X, Lu J, Hu S, Cheng KK, De Maeseneer J, Meng Q, et al. The primary health-care system in China. Lancet (London, England) 2017;390(10112):2584–94.
61. Sun Y, Mu J, Wang DW, Ouyang N, Xing L, Guo X, et al. A village doctor-led multifaceted intervention for blood pressure control in rural China: an open, cluster randomised trial. Lancet (London, England) 2022;399(10339):1964–75.
62. GBDD Collaborators. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England) 2019;393(10184):1958–72.
63. Wu Y, Benjamin EJ, MacMahon S. Prevention and control of cardiovascular disease in the rapidly changing economy of China. Circulation 2016;133(24):2545–60.
64. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med 1997;336(16):1117–24.
65. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N, Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99(6):779–85.
66. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018;378(25):e34.
67. Obarzanek E, Sacks FM, Vollmer WM, Bray GA, Miller ER 3rd, Lin PH, et al. Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. Am J Clin Nutr 2001;74(1):80–9.
68. Wang Y, Feng L, Zeng G, Zhu H, Sun J, Gao P, et al. Effects of Cuisine-Based Chinese Heart-Healthy Diet in Lowering Blood Pressure Among Adults in China: Multicenter, Single-Blind, Randomized, Parallel Controlled Feeding Trial. Circulation 2022;146(4):303–15.
69. van Kleef MEAM, Bates MC, Spiering W. Endovascular baroreflex amplification for resistant hypertension. Curr Hypertens Rep 2018;20(5):46.
70. Freeman R. Clinical practice. Neurogenic orthostatic hypotension. N Engl J Med 2008;358(6):615–24.
71. Bisognano JD, Bakris G, Nadim MK, Sanchez L, Kroon AA, Schafer J, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. J Am Coll Cardiol 2011;58(7):765–73.
72. Spiering W, Williams B, van der Heyden J, van Kleef M, Lo R, Versmissen J, et al. Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle clinical study. Lancet (London, England) 2017;390(10113):2655–61.
73. van Kleef M, Devireddy CM, van der Heyden J, Bates MC, Bakris GL, et al. Treatment of resistant hypertension with endovascular baroreflex amplification: 3-year results from the CALM-FIM study. JACC Cardiovasc Interv 2022;15(3):321–32.
74. Maimaris W, Paty J, Perel P, Legido-Quigley H, Balabanova D, Nieuwlaat R, et al. The influence of health systems on hypertension awareness, treatment, and control: a systematic literature review. PLoS Med 2013;10(7):e1001490.
75. Wong MC, Wang HH, Wong SY, Wei X, Yang N, Zhang Z, et al. Performance comparison among the major healthcare financing systems in six cities of the Pearl River Delta region, mainland China. PloS One 2012;7(9):e46309.
76. China PCG, Zhou T, Wang Y, Zhang H, Wu C, Tian N, et al. Primary care institutional characteristics associated with hypertension awareness, treatment, and control in the China PEACE-Million Persons Project and primary health-care survey: a cross-sectional study. Lancet Glob Health 2023;11(1):e83–e94.