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Review Article

Therapeutic adherence in hypertension: Current evidence and expert opinion from India

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ABSTRACT

Hypertension (HTN) is a globally prevalent non-communicable disease contributing significantly to cardiovascular (CV) morbidity and mortality. In achieving control of HTN, therapeutic adherence plays a crucial role. Studies from India identify varying rates of adherence to antihypertensive medications. Multiple factors determine treatment adherence in HTN. In India, factors such as lower socioeconomic status, health literacy, asymptomatic nature of disease, forgetfulness, cost of medications, and duration of HTN determine the adherence. An excellent physician-patient relationship incorporating adequate counseling along with the use of other methods can identify poor adherence. Improving adherence necessitates incorporating a multipronged approach with strategies directed at physicians, patients, and health systems. With innovation in therapeutics, the pharmaceutical sector can contribute significantly to improve adherence. Furthermore, increasing adherence to lifestyle interventions can help achieve better HTN control and improve CV outcomes. In the Indian context, more emphasis is necessary on patient education, enhanced physician-patient relationship and communication, increased access to health care, and affordability in improving therapeutic adherence in HTN.

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1. Introduction

Hypertension (HTN) affects multiple body systems and increases the risk of cardiovascular (CV) events such as myocardial infarction (MI), stroke, heart failure, renal dysfunction, and increased mortality risk. Globally, HTN affects nearly 1.3 billion people, and almost two-thirds of them belong to low- and middle-income countries (LMIC). Over the past two decades, the highest prevalence of HTN shifted from high-to middle-income countries (HMIC) to LMIC, attributed to multiple factors such as lifestyle changes.[1,2] HTN prevalence in India is 29.8 %. It varies from 27.6 % to 33.8 % in rural and urban settings.[3] Worldwide, the awareness, treatment, and control of HTN remain very low.[4–9] In India, unawareness of HTN may be seen in up to three-fourths of the individuals suffering from HTN, leading to uncontrolled HTN.[3] Though the trends over 25 years indicate improving HTN awareness levels in India, it remains much lower than that in the USA, UK, Australia, and Canada.[10,11] At the same time, the rate of non-compliance to HTN treatment has remained nearly constant over the past two decades.[12,13]

Control of HTN is essential to reduce the incidence of major adverse cardiovascular events (MACE) and associated deaths.[14] Poor adherence increases the risk of CV events and mortality.[15,16] Alternatively, higher adherence lowers the risk of CV events.[17] Thus, improving medication adherence should be the priority in any patient with HTN. Multiple factors such as type of treatment, comorbidities, cost, and physician-patient relationship affect adherence.[18,19] Various methods, such as drug prescription records, pill count, digital tools, increased physician-patient collaboration, and involvement of other healthcare professionals can help improve adherence.[22–25] Besides medication adherence, there is a wide variation in adherence to lifestyle therapy (diet, physical activity, salt, alcohol restriction, etc.). Ensuring compliance with such measures is also necessary.[20,21] As adherence is one of the critical determinants of HTN control, we must adopt measures to enhance adherence. Given general unawareness and lack of HTN control, improving adherence is crucial in the Indian context. This review discusses the current evidence on treatment adherence in HTN and provides practical tips for assessing and adopting strategies to improve adherence in the Indian setting.

2. Defining adherence to medications

Defining adherence is essential for routine as well as research purposes. Vrijens B et al have proposed a new taxonomy for adherence.[26] *Initiation* is the intake of the first dose of prescribed medication. *Discontinuation* is when the patient stops taking the prescribed medication irrespective of the reasons. When considered from initiation to the last dose, *implementation* represents the extent of taking actual dosing by the patient as per the prescribed dosing regimen. Further, the authors also identify another term as *persistence*. It is the time elapsed between initiation and the last dose before the medication discontinuation.[26]

3. Factors affecting adherence in hypertension

Multiple factors affect adherence in hypertensive individuals. Burnier and Egan, in their review, highlighted five major categories of such factors. These include sociodemographic, health-care team/system, therapy-related, condition-related, and patient-related factors (Fig. 1).[27] More than one factor may be the reason for suboptimal adherence. India-specific evidence on factors affecting adherence is summarized in Table 1 and briefly described below.

3.1. Adherence in hypertension: evidence from India

Current evidence in India shows variable adherence rates ranging from nearly 19 % to 96 % (Table 1).[16,17,28–35] The varying rates could be due to methodological differences in defining and assessing adherence. Besides, multiple factors that affect adherence (e.g., age, gender, literacy, socioeconomic status, duration of HTN, etc.) contributed to such differences in adherence rates. Another postulate is that the patients who were adherent to the treatment possibly had inherent motivation to respond to the questionnaire from the healthcare professionals. In contrast, the respondents with poor adherence may not have seen it necessary to participate in such studies.

There are various reasons for the non-adherence (Table 1). The predominant factors were lack of awareness of HTN and its complications, asymptomatic nature of the disease, and high treatment cost or low socioeconomic status. In a qualitative study from Jaipur, Gupta et al highlighted four major key themes associated with adherence, namely i) Patient experiences, ii) Patients' attitudes, iii) Health-system barriers, and iv) Healthcare professionals. In *patient experiences,* they observed that most of the interviewed patients lacked general awareness of HTN and had associated risk factors such as higher salt intake, lack of exercise, etc. The majority were unaware of the asymptomatic nature of HTN. In *patients' attitudes*, physician counseling had a substantial effect on lifestyle activities. In *health system barriers,* the long-distance residence from the hospital causing excess transportation cost and low income was the cause for skipping medications. In the fourth theme related to *healthcare professionals*, the study identified a relationship with the doctor as the most crucial factor for adherence.[36]

A meta-analysis of 44 epidemiological studies of adult populations reporting risk estimates of cardiovascular medication adherence with any CVD reported greater adherence to aspirin and anti-diabetic drugs than statins and antihypertensives (Fig. 2).[37] It is probably because of greater awareness of diabetes and the cost of aspirin. In addition to the factors discussed above, a negative perception of any therapy can deter adherence. Nielsen and Nordestgaard observed that negative statin-related news stories lead to reduced statin adherence and increased MI and CV mortality events.[38]

4. Detecting poor adherence

HTN treatment is lifelong, and any treatment interruption is not desirable. Qualitative methods such as interviews, questionnaires, and quantitative methods such as pill count, refill data, directly observed treatment (DOT), electronic monitoring can detect poor adherence. The use of other novel methods such as drug assay and digital medicine has also been suggested (Fig. 3).[27] Each of these methods has some unique advantages and disadvantages. A detailed discussion of such methods is out of the scope of this paper; they are briefly discussed here.

- The *interview method* is the simplest, cheapest, and highly feasible in a clinical setting. Physician interviews and questions the patients about medication adherence. However, this method lacks reliability and validity.
- A *questionnaire-based assessment* of adherence also offers an easy alternative. However, it can be time-consuming, and patients may or may not be willing to reply to such questionnaires.
- *Pill count* is a simple and easy method for detecting non-adherence. However, this can't be full-proof, and the patient can mislead with pill counts. A caregiver or family member's involvement in pill count can improve the reliability of this method.

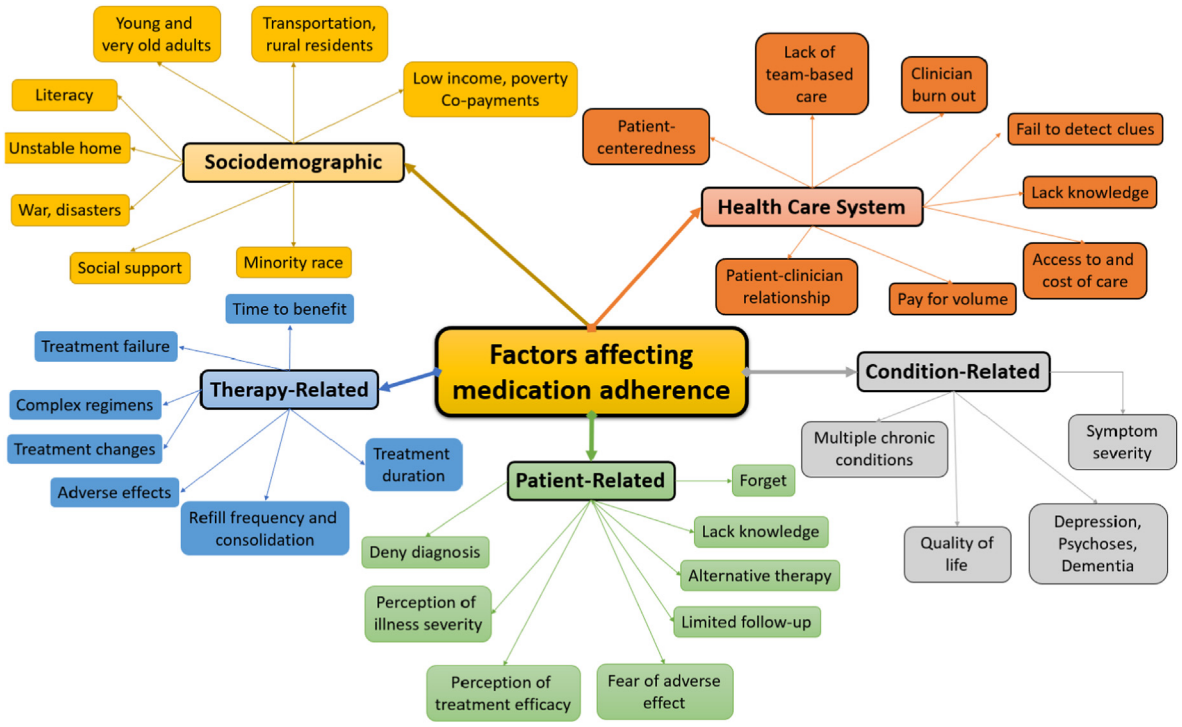

Fig. 1. Factors affecting adherence to medication.

Table 1
Literature evidence from India.

Author (year)	Region	Sample	Adherence rate	Factors for non-adherence or treatment interruption	Conclusion
Thomas et al (2011)[28]	South	608	50 %	- Medications are not working or medication will cause troubles - Difficulty in purchasing - Difficulty in getting refills on time - Problems in remembering the prescribed doses	Non-adherence is major limiting factor in achieving HTN control.
Rao et al (2014)[29]	South	287	82.2 %	- High treatment cost - Asymptomatic nature of the disease - Side-effects - Disinterest in taking medications	Treatment adherence is higher but is limited by cost and asymptomatic disease nature.
Nagarkar et al (2015)[13]	West	205	76.5 % (non-adherent)	- Aged below 57 years - Nuclear family - Not experiencing any symptoms related to HTN	Multiple factors affect adherence and need to look at such factors before changing treatment.
Bhandari et al (2015)[30]	East	348	73 %	- Need to purchase medications - Unsatisfied with current treatment - hypertension duration <5 years - Lower family income	Improved adherence help assist increase the rate of HTN control
Mallya et al (2016)[31]	South	200	96 % Interrupted treatment in past month: 13 %	- Forgetfulness - Not having any symptoms	High treatment adherence in HTN should be maintained and be optimized further.
Misra et al (2017)[32]	North	300	27.4 % - recall method 18.9 % - pill-count method	- Symptom-free period - Lower socioeconomic status	Awareness on low adherence rates need to be increased in patients with hypertension.
Balasubramanian et al (2018)[33]	South	189	High: 46 % Medium: 41.3 % Low: 12.7 %	- Poor knowledge of the HTN complications - Availing antihypertensive medications from the government pharmacy - Being asymptomatic at the time of diagnosis	Comprehensive strategies need to be adopted to address the issue of poor adherence.
Joshi et al (1996)[12]	Central	156	Non-adherence: 61 % - uncontrolled HTN 21 % - controlled HTN	–	Nonadherence rates are higher in patients with uncontrolled HTN.
Venkatachalam et al (2015)[34]	South	473	24.1 %	- Sedentary lifestyle - Smoking and alcohol intake	Patients who have active lifestyle were likely to be more adherent.
Choudhary et al (2016)[35]	West	958	54.6 %	–	Medication non-adherence may remain unrecognized that contributes to inadequate HTN control.

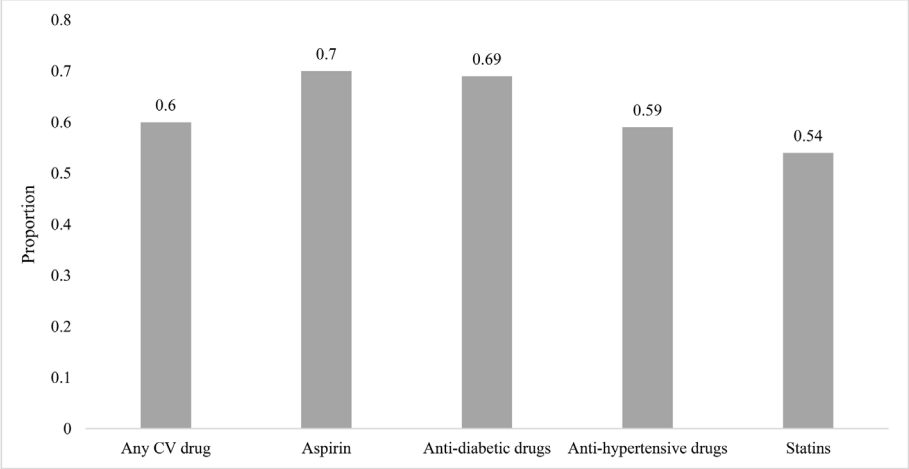

Fig. 2. Adherence rates to different cardiovascular medications.

- *Directly observed treatment* is a reliable and valid method. However, practical difficulties in implementation limit its routine clinical use.
- Other methods such as electronic monitoring, drug assay, and digital medicine can provide data on adherence reliably, but their use in clinical settings is limited. They are expensive and not practical for general use.

Recent European Society of Cardiology and European Society of Hypertension (ESC/ESH) guidelines also emphasized the concept of detecting poor adherence to drug therapy. Besides the methods mentioned above, guidelines identify that BP measurement with home-blood pressure monitoring can identify poor adherence to drug therapy.[39]

5. Strategies to improve drug adherence

World Health Organization (WHO) recognizes that improving patients' adherence might be the best investment to treat chronic conditions effectively.[40] ESC/ESH guidelines recommend various strategies to improve adherence (Table 2).[39] In addition, recent global hypertension practice guidelines from the International Society of Hypertension (ISH), 2020 recommend evaluating adherence at each visit and before escalating the antihypertensive treatment. Single combination pills, once-daily dosing, home BP monitoring, linking adherence behavior with daily habits, using electronic devices such as mobile phones as adherence aids, etc., are advised to improve adherence. A combination of counseling, self-monitoring, reinforcements, and supervision is an effective method for managing non-adherence.[41]

5.1. Physician level strategies

Physicians should engage in in-depth counseling about treatment and adherence strategies at each consultation. Physicians should seek frequent feedbacks on clinical and behavioral improvements. Resolve any barrier in adherence in discussion with patients. Time constraints may limit the implementation of this strategy.

The involvement of *healthcare personnel*, such as nurses or trained paramedics, can help improve therapy adherence.[39] A meta-analysis identified that nurse-collaborative interventions led to moderate improvement in adherence among discharged older adults.[42] A randomized trial ENURSIN assessing the efficacy of nursing intervention "Teaching: Individual" compared with usual care is underway to determine the impact of adherence in patients of HTN and/or type 2 diabetes.[43]

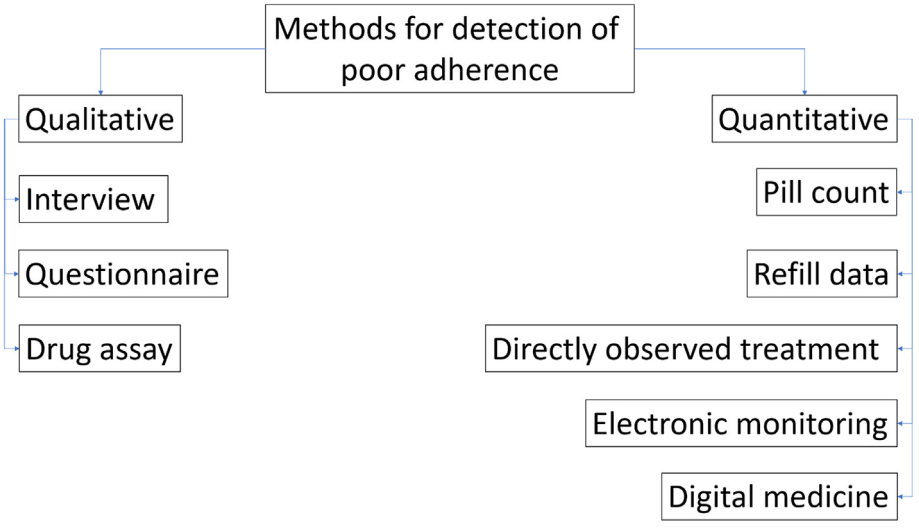

Fig. 3. Methods for the detection of poor adherence.

Table 2
Strategies to improve medication adherence.

Levels	Strategies
Physician level	Patient Counseling Feedback on clinical/behavioral improvement Identification of adherence related issues Involvement of healthcare personnel Improving health literacy of patients Reducing pill burden
Patient level	Self-monitoring of BP Telemonitoring – reminders, apps, etc. Motivation – Incentives in insurance premiums, priority physician visit, etc. Social support - Family engagement in treatment
Health system	Supporting the development of monitoring systems such as telemonitoring Availability of national prescription database Increased medication accessibility Increased population education and awareness about HTN and treatment
Pharma companies	Reminder packaging Development of digital medicine Monetary incentive in drug refills Patient educational activities

The health literacy of an individual can affect therapeutic adherence.[44] Physicians during the in-clinic counseling should spare more time in imparting knowledge on problems that can arise from poor medication adherence.

Reducing pill burden is probably the most effective approach. Recent guidelines recommend using a single–pill combination (SPC) to achieve better medication adherence.[39,41] Compared to the multi-pill strategy, the use of fixed-dose combination treatment improves adherence. It lowers the composite outcome of death or hospitalization for acute myocardial infarction (AMI), heart failure, or stroke.[45] In addition, the use of SPCs increases medication persistence and lowers the rates of therapy discontinuation.[46]

5.2. Patient-level strategies

Self-monitoring of BP (SMBP) improves adherence to drugs in patients with HTN.[47] The involvement of the patient in his BP control increases adherence.

Use of technology: Telemonitoring with telephonic reminders and mobile apps for treatment reminders also improves adherence.[48,49]

Motivational strategies: Patients who achieve complete adherence and BP control can be eligible for incentives (e.g., some waiver in insurance premiums).[50] Also, physicians can prioritize appointments for highly adherent HTN patients.

Family or social support is also vital in achieving good adherence.[51] Engaging a relative during the patient consultation can help improve HTN awareness.

5.3. Health system-level strategies

At the health-system level, improved accessibility to medications, reimbursement of single–pill combination drugs, and improved HTN education and awareness movements for the general public should be the priority. In addition, supporting the development of monitoring systems (e.g., telemonitoring), increasing strategic collaboration with physicians and healthcare providers, developing a national prescription database accessible to physicians and pharmacists can be implemented to potentially improve the adherence and thereby control of HTN.[39]

The *cost* of medications is an important barrier to treatment adherence. In the United States, hypertensive patients have nearly $2000 higher annual expenditure compared to normotensives. Overall, healthcare costs associated with HTN account for almost $131 billion.[52] A survey from Ireland observed that nearly a third of hypertensive patients reported financial burden because of the cost of medications.[53] In India, the cost of medicines directly affects adherence. Antihypertensive SPCs can improve adherence. SPCs are recommended for effective HTN control. However, Negi and colleagues identified that the price of SPCs was higher than the equivalent combinations of separate pills.[54] In India, 80 % of healthcare expenditure is borne by patients.[55] Therefore, SPCs related cost concerns need to be addressed on priority. Under the Drug Price Control Order (DPCO), the essential medicine list includes major antihypertensive drugs.[56] Despite the cost limits of antihypertensives, Kumar and colleagues identified that nearly 40 % of the brands had a price above the recommended limit. It necessitates reassessment and monitoring for effective implementation of pricing policies in India.[57]

5.4. Role of pharma companies

Innovation in product packaging: Development of *reminder packaging* treatment improves adherence and persistence to the treatment. Pharmaceutical sectors can employ such packaging methods to add to improved treatment adherence.[58]

Patient education: Active engagement of patients and their relatives for educating about the treatment adherence by the medical representative can add to improved adherence. Targeting large population gatherings can be considered for educating about the importance of adherence.

6. Improving adherence to lifestyle interventions

Lifestyle interventions are an integral part of HTN management. Reduction in BP can range from 5 to 20 mmHg with interventions such as cutting down on salt, avoiding alcohol, increased physical activity, adopting unique dietary patterns (e.g., Dietary Approaches

Table 3
Practical tips for treatment adherence in management of hypertension.

Section	Practical tip
Defining adherence	We consider that in defining adherence, three quantifiable phases namely initiation, discontinuation, and implementation, should be adopted in routine practice as well as in designing adherence studies.
Factors associated with adherence	In the Indian context, medication adherence among patients of HTN is generally suboptimal in real-life situations. Multiple factors that are linked to the patients, physicians, and health-system may underlie poor adherence to antihypertensive therapy.
Detecting non-adherence	In the Indian context, we consider that physician counseling during the patient interview is probably the most important method to detect non-adherence. In conjunction with other methods such as pill count, etc. physicians should be able to detect any non-adherence during the patient's interview. A good physician-patient relationship can identify non-adherence accurately.
Strategies to improve adherence	In the Indian context, multiple strategies need to be adopted to improve therapeutic adherence as any single strategy may achieve optimal results. Reducing the pill burden with use of single–pill combinations available at lower costs is probably best strategy to improve medication adherence.
Adherence to lifestyle interventions	In the Indian context, besides medication adherence, it is equally essential to improve the patients' adherence to non-pharmacological interventions to achieve better control of HTN. Effective physician-patient interactions can help in achieving this objective.

to Stop Hypertension (DASH) diet), and weight loss.[59] In addition to lifestyle measures, community-based intervention with proactive home visits by trained government community health workers improves HTN control and lowers mortality.[60]

Besides drugs, adherence to lifestyle interventions is equally essential. Patients with HTN may have poor compliance with lifestyle changes.[34] Xu et al reported that physicians were more aggressive in recommending lifestyle change in obese than non-obese hypertensive patients. In contrast, obese patients were less adherent to such lifestyle changes than normal or underweight patients. Further, adherence to sodium and alcohol restriction was higher than physical activity and weight control.[20] It indicates that equal emphasis should be placed on appropriate lifestyle measures in HTN.

7. Take-home message

Non-compliance to treatment is associated with an increased risk of adverse CV events and mortality. Conscious efforts from treating physicians and patients are needed to improve treatment adherence and HTN control. Reducing the pill burden using SPCs made available at a lower cost is probably the best strategy to improve medication adherence. Table 3 provides some of the practical tips for improving treatment adherence in HTN.

8. Conclusion

HTN awareness, treatment accessibility/affordability and control are significant challenges in the Indian setting. Therapeutic adherence is a crucial factor in achieving HTN control, and it may get neglected in routine clinical practice. As multiple factors underlie poor adherence in patients with HTN, a holistic approach is necessary to identify and address the same. Strategies involving patients, physicians, and health systems are needed. In the Indian setting, increased HTN awareness, increased access to health care, and medications affordability are the need of the hour to improve treatment adherence and HTN control.

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References

1. World Health Organization. Hypertension. Fact sheet 13 September 2019. Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension. Accessed February 10, 2020.
2. Salem H, Hasan DM, Eameash A, et al. Worldwide prevalence of hypertension: a pooled meta-analysis of 1670 studies in 71 countries with 29.5 million participants. *J Am Coll Cardiol*. 2018;71, A1819.
3. Anchala R, Kannuri NK, Pant H, et al. Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension. *J Hypertens*. 2014;32:1170–1177.
4. Chow CK, Teo KK, Rangarajan S, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *J Am Med Assoc*. 2013;310:959–968.
5. Mohamed SF, Mutua MK, Wamai R, et al. Prevalence, awareness, treatment and control of hypertension and their determinants: results from a national survey in Kenya. *BMC Publ Health*. 2018;18, 1219.
6. Gebrihet TA, Mesgna KH, Gebregiorgis YS, et al. Awareness, treatment, and control of hypertension is low among adults in Aksum town, northern Ethiopia: a sequential quantitative-qualitative study. *PloS One*. 2017;12, e0176904.
7. Hien HA, Tam NM, Tam V, et al. Prevalence, awareness, treatment, and control of hypertension and its risk factors in (Central) Vietnam. *Int J Hypertens*. 2018, 6326984. Article ID.
8. Karmakar N, Nag K, Saha I, et al. Awareness, treatment, and control of hypertension among adult population in a rural community of Singur block, Hooghly District, West Bengal. *J Educ Health Promot*. 2018;7, 134.
9. Abdul-Razak S, Daher AM, Ramli AS, et al. Prevalence, awareness, treatment, control and socio demographic determinants of hypertension in Malaysian adults. *BMC Publ Health*. 2016;16, 351.
10. Gupta R, Gupta VP, Prakash H, Agrawal A, Sharma KK, Deedwania PC. 25-Year trends in hypertension prevalence, awareness, treatment, and control in an Indian urban population: Jaipur Heart Watch. *Indian Heart J*. 2018;70:802–807.
11. Zhou B, Danaei G, Stevens GA, 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*. 2019;394:639–651.
12. Joshi PP, Salkar RG, Heller RF. Determinants of poor blood pressure control in urban hypertensives of central India. *J Hum Hypertens*. 1996;10:299–303.
13. Nagarkar AM, Gadhave SA, Sharma I, Choure A, Morisky D. Factors influencing medication adherence among hypertensive patients in a tertiary care hospital, Pune, Maharashtra. *Natl J Community Med*. 2013;4:559–563.
14. Cushman WC, Whelton PK, Fine LJ, et al. SPRINT trial results: latest news in hypertension management. *Hypertension*. 2016;67:263–265.
15. Kim S, Shin DW, Yun JM, et al. Medication adherence and the risk of cardiovascular mortality and hospitalization among patients with newly prescribed antihypertensive medications. *Hypertension*. 2016;67:506–512.
16. Herttua K, Tabák AG, Martikainen P, Vahtera J, Kivimäki M. Adherence to antihypertensive therapy prior to the first presentation of stroke in hypertensive adults: population-based study. *Eur Heart J*. 2013;34:2933–2939.
17. Yang Q, Chang A, Ritchey MD, Loustalot F. Antihypertensive medication adherence and risk of cardiovascular disease among older adults: a population-based cohort study. *J. Am. Heart Assoc.* 2017;6, e006056.
18. Mekonnen HS, Gebrie MH, Eyasu KH, Gelagay AA. Drug adherence for antihypertensive medications and its determinants among adult hypertensive patients attending in chronic clinics of referral hospitals in Northwest Ethiopia. *BMC Pharmacol Toxicol*. 2017;18:27.
19. Mancia G, Zambon A, Soranna D, Merlino L, Corrao G. Factors involved in the discontinuation of antihypertensive drug therapy: an analysis from real life data. *J Hypertens*. 2014;32:1708–1715.
20. Xu KT, Ragain RM. Effects of weight status on the recommendations of and adherence to lifestyle modifications among hypertensive adults. *J Hum Hypertens*. 2005;19:365–371.
21. Elbur AI. Level of adherence to lifestyle changes and medications among male hypertensive patients in two hospitals in Taif; Kingdom of Saudi Arabia. *Int J Pharm Pharmaceut Sci*. 2015;7:168–172.
22. Vrijens B, Antoniou S, Burnier M, de la Sierra A, Volpe M. Current situation of medication adherence in hypertension. *Front Pharmacol*. 2017;8, 100.
23. Parati G, Omboni S, Compare A, et al. Blood pressure control and treatment adherence in hypertensive patients with metabolic syndrome: protocol of a randomized controlled study based on home blood pressure telemonitoring vs. conventional management and assessment of psychological determinants adherence (TELEBPMET Study). *Trials*. 2013;14:22.
24. Frias J, Virdi N, Raja P, et al. Effectiveness of digital medicines to improve clinical outcomes in patients with uncontrolled hypertension and type 2 diabetes: prospective, open-label, cluster-randomized pilot clinical trial. *J Med Internet Res*. 2017;19, e246.
25. Hedegaard U, Kjeldsen LJ, Pottegard A, et al. Improving medication adherence in patients with hypertension: a randomized trial. *Am J Med*. 2015;128:1351–1361.
26. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73:691–705.
27. Burnier M, Egan BM. Adherence in hypertension: a review of prevalence, risk factors, impact, and management. *Circ Res*. 2019;124:1124–1140.
28. Thomas D, Meera NK, Binny K, et al. Medication adherence and associated barriers in hypertension management in India. *CVD Prevent Contr*. 2011;6:9–13.
29. Rao CR, Kamath VG, Shetty A, Kamath A. Treatment compliance among patients with hypertension and type 2 diabetes mellitus in a coastal population of Southern India. *Int J Prev Med*. 2014;5:992–998.
30. Bhandari S, Sarma PS, Thankappan KR. Adherence to antihypertensive treatment and its determinants among urban slum dwellers in Kolkata, India. *Asia Pac J Publ Health*. 2015;27. NP74–84.
31. Mallya SD, Kumar A, Kamath A, et al. Assessment of treatment adherence among hypertensive patients in a coastal area of Karnataka, India. *Int J Commun Med Public Health*. 2016;3:1998–2003.
32. Misra P, Salve HR, Srivastava R, Kant S, Krishnan A. Adherence to treatment among hypertensive individuals in a rural population of North India. *Indian J Community Health*. 2017;29(2):176–181.
33. Balasubramanian A, Nair SS, Rakesh PS, Leelamoni K. Adherence to treatment among hypertensives of rural Kerala, India. *J Fam Med Prim Care*. 2018;7:64–69.
34. Venkatachalam J, Abrahm SB, Singh Z, Stalin P, Sathya GR. Determinants of patient's adherence to hypertension medications in a rural population of

Kancheepuram District in Tamil Nadu, South India. *Indian J Community Med*. 2015;40:33–37.
35. Choudhary R, Sharma SM, Kumari V, Gautam D. Awareness, treatment adherence and risk predictors of uncontrolled hypertension at a tertiary care teaching hospital in Western India. *Indian Heart J*. 2016;68:S251–S252.
36. Gupta S, Dhamija JP, Mohan I, Gupta R. Qualitative study of barriers to adherence to antihypertensive medication among rural women in India. *Int J Hypertens*. 2019, 5749648. Article ID.
37. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J*. 2013;34:2940–2948.
38. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *Eur Heart J*. 2016;37:908–916.
39. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of hypertension (ESH). *Eur Heart J*. 2018;39:3021–3104.
40. World Health Organization. Improving adherence rates: guidance for countries. Available from: https://www.who.int/chp/knowledge/publications/Adherence_section2.pdf?ua=1. Accessed March 10, 2020.
41. Unger T, Borghi C, Charchar F, et al. International Society of Hypertension global hypertension practice guidelines. *Hypertension*. 2020;75:1334–1357, 2020.
42. Verloo H, Chiolero A, Kiszio B, Kampel T, Santschi V. Nurse interventions to improve medication adherence among discharged older adults: a systematic review. *Age Ageing*. 2017;46:747–754.
43. Romero Guevara SL, Parra DI, Rojas LZ. Teaching: individual" to increase adherence to therapeutic regimen in people with hypertension and type-2 diabetes: protocol of the controlled clinical trial ENURSIN. *BMC Nurs*. 2019;18:22.
44. Berkman ND, SheridanSL, Donahue KE. Low health literacy and health outcomes: a updated systematic review. *Ann Intern Med*. 2011;155:97–107.
45. Verma AA, Khuu W, Tadrous M, Gomes T, Mamdani MM. Fixed-dose combination antihypertensive medications, adherence, and clinical outcomes: a population-based retrospective cohort study. *PLoS Med*. 2018;15, e1002584.
46. Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. *Hypertension*. 2021;77:692–705.
47. Fletcher BR, Hartmann-Boyce J, Hinton L, McManus RJ. The effect of self-monitoring of blood pressure on medication adherence and lifestyle factors: a systematic review and meta-analysis. *Am J Hypertens*. 2015;28:1209–1221.
48. Friedman RH, Kazis LE, Jette A, et al. A telecommunications system for monitoring and counseling patients with hypertension: impact on medication adherence and blood pressure control. *Am J Hypertens*. 1996;9:285–292.
49. Morrissey EC, Casey M, Glynn LG, Walsh JC, Molloy GJ. Smartphone apps for improving medication adherence in hypertension: patients' perspectives. *Patient Prefer Adherence*. 2018;12, 813.
50. Hagihara A, Murakami M, Chishaki A, Nabeshima F, Nobutomo K. Rate of health insurance reimbursement and adherence to antihypertensive treatment among Japanese patients. *Health Pol*. 2001;58:231–242.
51. Morisky DE, DeMuth NM, Field-Fass M, Green LW, Levine DM. Evaluation of family health education to build social support for long-term control of high blood pressure. *Health Educ Q*. 1985;12:35–50.
52. Kirkland EB, Heincelman M, Bishu KG, et al. Trends in healthcare expenditures among US adults with hypertension: national estimates, 2003–2014. *J. Am. Heart Assoc*. 2018;7, e008731.
53. Dillon P, Smith SM, Gallagher P, Cousins G. Impact of financial burden, resulting from prescription co-payments, on antihypertensive medication adherence in an older publicly insured population. *BMC Publ Health*. 2018;18:1–9.
54. Negi S, Neupane D, Sahoo SK, et al. Prices of combination medicines and single-molecule antihypertensive medicines in India's private health care sector. *J Clin Hypertens*. 2021;23:738–743.
55. Kotwani A, Ewen M, Dey D, et al. Prices and availability of common medicines at six sites in India using a standard methodology. *Indian J Med Res*. 2007;125:645–654.
56. Ahmad A, Khan MU, Patel I. Drug pricing policies in one of the largest drug manufacturing nations in the world: are affordability and access a cause for concern? *J Res Pharm Pract*. 2015;4:1–3.
57. Kumar R, Kumar N, Ahmad A, et al. Cost comparison of antihypertensive drugs available in India with Drugs Prices Control Order price list. *Int J Res Med Sci*. 2019;7:101–105.
58. Dupclay L, Eaddy M, Jackson J, Raju A, Shim A. Real-world impact of reminder packaging on antihypertensive treatment adherence and persistence. *Patient Prefer Adherence*. 2012;6:499–507.
59. Vooradi S, Mateti UV. A systemic review on lifestyle interventions to reduce blood pressure. *J Health Res Rev*. 2016;3:1–5.
60. Jafar TH, Gandhi M, De Silva HA, et al. A community-based intervention for managing hypertension in rural South Asia. *N Engl J Med*. 2020;382:717–726.