HTNJ

January-March 2021 Vol. 7 No. 1

Hypertension Journal

Editorial Office

Editor-in-Chief

C Venkata S Ram

Hypertension Journal
SD-100, Ground Floor, Sector-45
Noida-201301, Uttar Pradesh, India
Contact No.: (+91) 8527814605
e-mail: editor@hypertensionjournal.in

Publishers Address

Branch Office:

Incessant Nature Science Publishers Private Limited
SD-100, Ground Floor, Sector-45
Noida-201301, Uttar Pradesh, India
Contact No.: (+91) 8527814605, (+91) 8368159278
e-mail: inspublishers@gmail.com, abhinav.kumar@inspublishers.com

Subscription Information:

For subscription related information, please contact: subscriptions@inspublishers.com Ph: +91 8368159278

Manuscript Submission:

Hypertension Journal (HTNJ) is also available online at www.hypertensionjournal.in

Manuscripts can be submitted electronically on the journal's website.

Advertisement Information:

For advertisement related information, please contact: advertisement@inspublishers.com

AIMS & SCOPE

Hypertension Journal is a peer-reviewed journal which highlights epidemiology, health implications and cardiovascular risk from hypertension in India/South-Asia. Hypertension is much more common than diabetes. It is vastly under diagnosed and poorly treated in India/South-Asia. There are excellent therapeutic options to treat hypertension, but the available resources are not fully utilized by doctors therefore neglecting this disorder. The journal will hereby promote the significance of hypertension and the urgent need to bring it under control. The medical community should be educated on hypertension evaluation, diagnosis, workup and management simultaneously bringing up the literature, research, guidelines and scientific advances related to hypertension and its disorders. We are hereby starting a high-quality journal dedicated solely to hypertension and thus promoting the awareness, evaluation and effective management in India/South-Asia. Dr C Venkata S Ram is a world authority on hypertension with lifelong work (research, clinical and publications).

This journal is an official publication of: **Current Medical Concepts.**

Endorsed by: The Indian Society of Hypertension and
The World Hypertension League

Hypertension Journal

Volume 7 | Issue 1 | January-March 2021

Contents

CASE REPORT

REVIEW ARTICLES

INDIAN SOCIETY OF HYPERTENSION
World Hypertension League
CURRENT MEDICAL CONCEPTS
HTNJ
CrossMark

Case Report

Confirming a Diagnosis of "Hypertension"

Raymond R. Townsend

Hypertension Program, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Abstract

Hypertension is the leading cause, worldwide, of premature death or surviving with disabilities due to damage to the heart, the brain, or the kidneys. Making a correct diagnosis of hypertension is an essential step in reducing the impact of elevated blood pressure (BP) on an individual's health. In this article, we will use a typical case to illustrate the steps involved in confirming a diagnosis of hypertension, along with the rationale for the usage of the current out-of-office BP measurement tools, to correctly identify and confirm elevated BP. The reader will be guided through an explanation of how to use the office BPs with, or without, complementary information from BPs readings obtained using at home devices, or through the use of an ambulatory BP monitors. The utility of these different approaches to how, and settings within which, BP is measured are also examined.

Keywords: Hypertension, home blood pressure monitoring, self-monitoring of blood pressure, ambulatory blood pressure monitoring, blood pressure measurement

Introduction

It's a busy day in the clinic. Returning from lunch you have a 45-year man in a clinic room as your first patient who may have "hypertension." You enter the room, introduce yourself, greet him reassuringly, and begin the visit.

Case Report

He feels fine, and says he is here today because his family has told him he needs to have this blood pressure (BP) problem evaluated. He has had a few BPs recorded over the years leading up to today. They are usually "a little bit high" but he always assumed that they were in error, because he feels well. He has a family history of hypertension, on the mother's side. He has three siblings, all younger, and none with a diagnosis of hypertension. He works in a nearby pharmaceutical plant as a laboratory technician. He does not smoke. He has no history of diabetes. His history is otherwise unremarkable.

His examination shows a man with a body mass index of 29.6 kg/m^2. He has seated BPs in his dominant (right arm) of 156/92 mmHg and 154/92 mmHg with a regular heart rate of 76 beats/min. On standing, his BP is 152/98 mmHg with a heart rate of 78 beats/min. His fundi show mild arteriolar narrowing. The rest of his physical exam is unrevealing.

Discussion

In the following paragraphs, I hope to conduct the reader through some of the common considerations faced by a practitioner making the diagnosis of hypertension in a patient. This will take the form of a narrative review and is based largely on the experiences of this author over the past 40 years of caring for patients with high BP.

Does he have "hypertension?"

How well does the BPs from a single office visit reflect a diagnosis of hypertension? This question was addressed by a UK study which sought to address the question of just "how many times do you need to check a BP in the office to feel reasonable confident that someone has hypertension?" Or at least confident that the clinic reflects the real BP. In the study mentioned,[1] 42 general practice providers in the

Address for correspondence:
Raymond R. Townsend, University of Pennsylvania, 3400 Spruce Street, 122 Founders Bldg, Philadelphia PA 19104, USA.
E-mail: townsend@upenn.edu

Received: 05-04-2021; Accepted: 15-04-2021
doi: 10.15713/ins.johtn.0213

Increasent Nature Science Publishers

United Kingdom were each asked to enroll the next three untreated patients who had an office diastolic BP of at least 90 mmHg to <110 mmHg. They recruited 110 new patients with suitably elevated diastolic BPs, and by a clever means of randomization, each patient was assigned a schedule of follow-ups over the next 8 weeks that would either occur at 4 and 8 weeks subsequently, or at 2, 4 6, and 8 weeks subsequently, or at 1, 2, 3, 4, and 8 weeks subsequently. It turns out, no matter what the follow-up assignment was, the same trend was evident in all three groups. Figure 1 shows pictorially what occurred during follow-up of these patients. Between the initial and subsequent visits, the systolic pressure declined by about 7 mmHg in all three groups and declined an additional 3 mmHg in all three groups at the third visit. After the third visit, there was little further change in systolic BP. The diastolic BP declined by about 5 mmHg between the initial and subsequent visit in all three groups, and although it declined an additional 2 mmHg between the second and third visit, there was little significant change in diastolic BP after the second visit. The fall in diastolic BP was not appreciably affected by the magnitude of the initial diastolic BP. However, those with higher systolic BPs tended to have a greater reduction in systolic BP in subsequent visits. Hence, it seems that two BP recordings taken and averaged for a single value, and repeated at occasions separated by 1–4 weeks between visits seemed like a valid way to use office BP readings to diagnose hypertension. Needless to say, in a patient presenting with greatly elevated BPs, for example, higher than 180/110 mmHg, therapy should begin right away, particularly if there is evidence of prior hypertension mediated organ damage (HMOD) such as left ventricular hypertrophy, heart attack, heart failure, prior stroke, or kidney function impairment. Comments in this article are basically meant to apply to uncomplicated, treatment naïve patients like our 45-year old patient.

So, does our patient have hypertension?

We are not sure yet

The ability to measure BP outside of a physician office has taught us that there are several patterns to BP in ambulatory people. Some patients have normal BPs within the office setting, as well as at home, or while wearing an ambulatory BP monitor (ABPM) that is configured to automatically take and record their BPs over 24–48 h. These people are considered "truly normotensive."

Some people have an office BP that is at, or above, the current threshold for a diagnosis of "hypertension" like our case, yet when monitored outside the office their BPs are lower than this threshold, and these people are considered to have "office hypertension" or, as it has several names, "white coat hypertension" or "white coat untreated hypertension" when they are not taking BP medication.[2]

Other people have the opposite finding from white coat. Their BPs are below the current hypertension threshold values, yet when outside the office, either during the day, or the night, or during both the day and the night, they are elevated. This pattern is generally known as "masked hypertension"[3] and is also called "masked uncontrolled hypertension" if they are on BP medication, or "masked untreated hypertension" when they are not taking BP medication.

Finally, there is the pattern where in-office and out-of-office BPs are high, and the patient is considered "truly hypertensive;" it is also known as "sustained hypertension" or "treated uncontrolled hypertension" when BPs levels remain elevated despite taking BP medicines. Figure 2 diagrams the four categories of BP using in-office and out-of-office findings.

How common are these patterns in India?

This question was recently addressed in a large study of Indian patients evaluated with 24 h ABPM.[4] The short answer is that

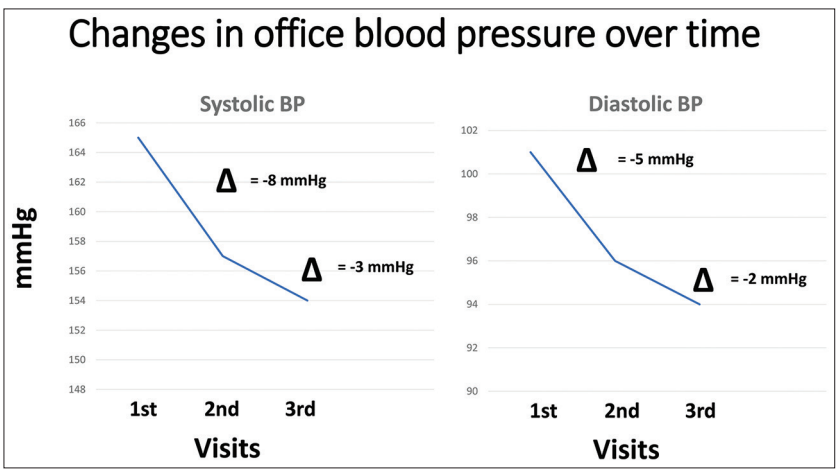


Figure 1: Unadjusted changes in-office blood pressure (BP) overtime in 110 patients attending primary care practices with a new diagnosis of hypertension, defined as a diastolic BP > 90 mmHg (and <110 mmHg). Adapted from Hartley *et al*., left panel shows changes in-office systolic pressures; right panel shows changes in-office diastolic BP

in 27, 472 adult Indian patients with ABPM data, 68% male, and about half taking BP medicines:

- 13% were normotensive (or controlled).
- 12% had white coat.
- 19% had masked.
- 56% were truly hypertensive (or uncontrolled).

These data indicate that it is possible for the office BPs to misrepresent what our patient's out-of-office BPs are about 31% of the time. Said another way, relying on the office BP alone can misclassify about 3 people in 10.

How will we further evaluate the BP in our patient?

We have several avenues available. To confirm elevated BP using the office values only, we could ask him to return in 2 weeks for another BP check, and then once more after that. In addition to measuring BP, we would also be assessing him to address these questions in hypertension evaluation:

- Is this person truly hypertensive? (when the answer is "yes," proceed to next point)
- Is their elevated BP primary, or is it a reflection of another issue in which elevated BP is a "symptom" (like aldosterone excess, or renal artery disease for example)?

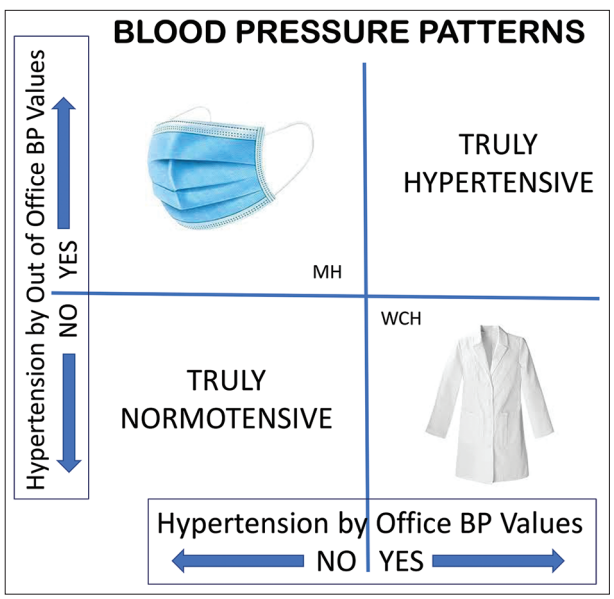


Figure 2: Patterns of blood pressure (BP) comparing values measured in an office setting with values obtained outside the office. The lower left and upper right indicate concordance with office and out-of-office values. When patients have office values below current hypertension thresholds, for example, either <130/80 mmHg or <140/90 mmHg depending on the country, yet have out-of-office BP above the hypertension threshold, they have masked hypertension (upper left box, "MH"). When patients have office values above current hypertension thresholds, for example, either >130/80 mmHg or >140/90 mmHg depending on the country, yet have out-of-office BP below the hypertension threshold, they have white coat hypertension (lower right box, "WCH"). For this illustration, patients are assumed to be untreated with BP medications

- Is there evidence of HMOD?
- Are there other CV risk factors, besides high BP, at play in this person?

For now, we will continue to pursue the first bullet point. The reader is referred elsewhere to address the second through the fourth bullet points.[5]

In addition to, or in place of, further office visits we could ask him to have his BP measured at home, or (when available), using an ABPM. So which is the BEST way to confirm the diagnosis of hypertension?

The answer to this last question will seem unsatisfying. All three are the BEST at some aspect of diagnosis. They differ from one another so much that they provide what can only be called complementary information. Table 1 provides some commentary to support this.

The value in-office BP as the diagnostic tool is based mainly on the sheer length of experience with this technique. Literally, all that we know about the consequences of high BP (e.g. death and HMOD), and the benefits of treating high BP are directly derived from the office BP experience. Both home and ABPM represent improvements on this, but cannot supplant the foundational aspects that office BP has provided in the diagnosis and management of high BP. That said, there is a need to use good technique when performing office BP measurements. The errors in not doing so, and there are many possibilities for error, almost always result in BP readings that are higher than the true BP for that individual.[6] Many societies have published guidance documents on the measurement of BP in humans.[7]

The value in home BP monitoring (HBPM), or as it is also known, self-measured (or monitored) BP (SMBP) is incremental to the office experience. The office values cannot identify white coat or masked effects; these rely on out-of-office measures like HBPM or SMBP (or ABPM – see below). As with office BP, good technique is equally important with home BP measurement. A useful graphic that provides a good summary of the necessary positioning and proper measurement technique for home BP measurement is available at

|| https://www.heart.org/-/media/files/health-topics/high-blood-pressure/how_to_measure_your_blood_pressure_letter_size.pdf?la=en Accessed April 12,2021 ||.

Table 1: Comparison of techniques for diagnosing hypertension

	Office	ABPM	Home BP
For diagnosing hypertension	>100 years of experience	Largest # of out-of-office studies confirming hypertension	Practical, convenient, inexpensive
Value	Research showing benefit of treating BP is based on office readings	Better than office for predicting outcomes	Better than office for predicting outcomes
BP readings	Can be standardized per AHA and other societies	Reflect "real-world" activities: Eating, walking, sleeping, etc.	Can be standardized per AHA and other societies

With home BPs, the ideal period of monitoring is a week long, with two measurements in the morning (between 7 AM and 10 AM) and two in the evening (between 7 PM and 10 PM) daily. Once these are obtained, the 1st day readings are set aside, and the average of the ensuing 6 days is calculated. If one uses an office threshold of 140/90 mmHg to diagnose hypertension, then home values of >135/85 mmHg are considered "hypertensive."[8] If one uses an office threshold of 130/80 mmHg, the home values defining hypertension are also 130/80 mmHg.[8] Some authorities are comfortable with shortening the period of home BP measurement to five[9] or even 3 days.[10] The reader is referred to the excellent, balanced review of the different schedules of home BP recordings by Stergiou.[11] Although as few as 3 days are endorsed by the European Society, it is not optimal to use so short a period, and at least 5 days are preferred for diagnosing hypertension.

The value in ABPM is also incremental to the office BP readings. ABPM acquires multiple BPs, determined by how the monitoring device is configured, and represents a "real-world" collection of readings that spans the daytime activities and usually includes the night time (sleeping) readings. Unlike office or home readings, ABPM readings are not predicated on a period of rest before they are taken, nor is it necessary to sit, avoid exercise, etc. The ideal number of readings to acquire over a 24 h period is not universally agreed on, but many programs obtain clinical readings every 20 min while awake, and every hour while asleep, and generally require a minimum of 14 daytime and 6 nighttime readings to make diagnostic inferences. If one uses an office threshold of 140/90 mmHg to diagnose hypertension, then an average of the 24 h of ABPM values of >130/80 mmHg is considered "hypertensive."[8] If one uses an office threshold of 130/80 mmHg to diagnose hypertension, then an average of the 24 h of ABPM values of > 125/75 mmHg is considered "hypertensive."[8]

How do I choose which method (office, home, or ambulatory) to confirm the diagnosis of hypertension?

The answer to this question is a mix of pragmatism and availability. Sometimes, the patient's situation precludes buying or using a home BP monitor for economic or personal reasons. ABPM can be difficult to obtain due to the limited number of locations that offer this service. On the other hand, a home BP monitor can be of value for years to come when medications are started, titrated, or discontinued. Or when a patient loses weight, exercises, etc., to improve lifestyle factors associated with better BPs.

And, also on the other hand, the bulk of published evidence confirms the value of ABPM as an out-of-office confirmation of elevated BP.[12] Moreover, the nighttime values obtained during ABPM are, in health, about 10% or more lower than the daytime values.[13] When this fall in nocturnal BP is not present, this can be a clue to a patient at enhanced risk of HMOD.[14] A recent review comparing home and ABPM readings is recommended for further reading on the relative values of each modality,[15] as well as the recent report cited previously from a large sample of Indian patients undergoing 24 h ABPM.[4]

Why does all this matter? Why bother treating an asymptomatic disorder like elevated BP?

The goal in treating hypertension is to preserve the target organs – typically the heart, brain, and kidneys. When a person feels fine and has no evidence of HMOD, this represents "primary prevention." When a person already has sustained HMOD, for example, a prior stroke, then the practitioner engages in "secondary prevention." Whether the goal is primary, or secondary prevention, the patient is more likely to live longer with his or her organs functioning at the current level when BP is treated.[16,17] Moreover, the higher the BP level when beginning therapy, the greater the reduction in cardiovascular risk for the patient.[18] This, however, is not a license to "wait and see" arguing that if you delay treatment for a few years and allow the BP to rise further before treating it, the treatment "benefit" will be even greater. While the patient is being thus "monitored," but not treated, their vessels are thickening (vascular remodeling), and their heart is working harder (ventricular hypertrophy). This sets the stage for something epidemiologists call the "residual risk" associated with hypertension. A simple exercise will demonstrate this point [Figure 3 for the details].

Open an online ASCVD calculator such as the one at ||https://www.mdcalc.com/ascvd-atherosclerotic-cardiovascular-disease-2013-risk-calculator-aha-acc || and enter data from our patient, who is a 45-year-old male, Indian (i.e. other), a non-smoker, not diabetic, and using a total cholesterol value of 4.0 mmol/L and an HDL cholesterol value of 1.0 mmol/L you will find that for the systolic BP value of 156 mmHg the 10-year CV risk is 2.5%. If he had all the same values entered, but you entered a YES for the query about "Treatment for hypertension?" the value rises from 2.5% to 3.0%. The exercise is repeated for the same patient 10 years later in the figure, all things being otherwise the same (except age), and the differences in 10-year CV risk when his systolic pressure is 156 mmHg on medication versus off medication 10 years from now is even more evident.

One of the most memorable analogies I ever read about making the diagnosis of hypertension, and then acting on that diagnosis came from the pen of Dr. Tom Giles, a Cardiologist from Louisiana in the USA. He wrote: "We now perform routine colonoscopy instead of flexible sigmoidoscopy and mammography to supplement breast self-examination. Chronic increases in BP should be taken seriously. We have lived through the concept of 'essential hypertension' (the classic oxymoron) and that systolic BP should be (mm Hg) = 100 + age (years). After all, should our patients not benefit from the dedicated efforts of those contributing to hypertension research? We have observed the natural history of hypertension for too long."[19] The take home point here is that if you found a polyp on sigmoidoscopy, or if you were informed about a mass on mammography, would you just "monitor" it over the ensuing years?

Are there consequences to making a diagnosis of "hypertension?"

In addition to the kidney, heart, and brain consequences of hypertension, there are several psychological ones as well, and

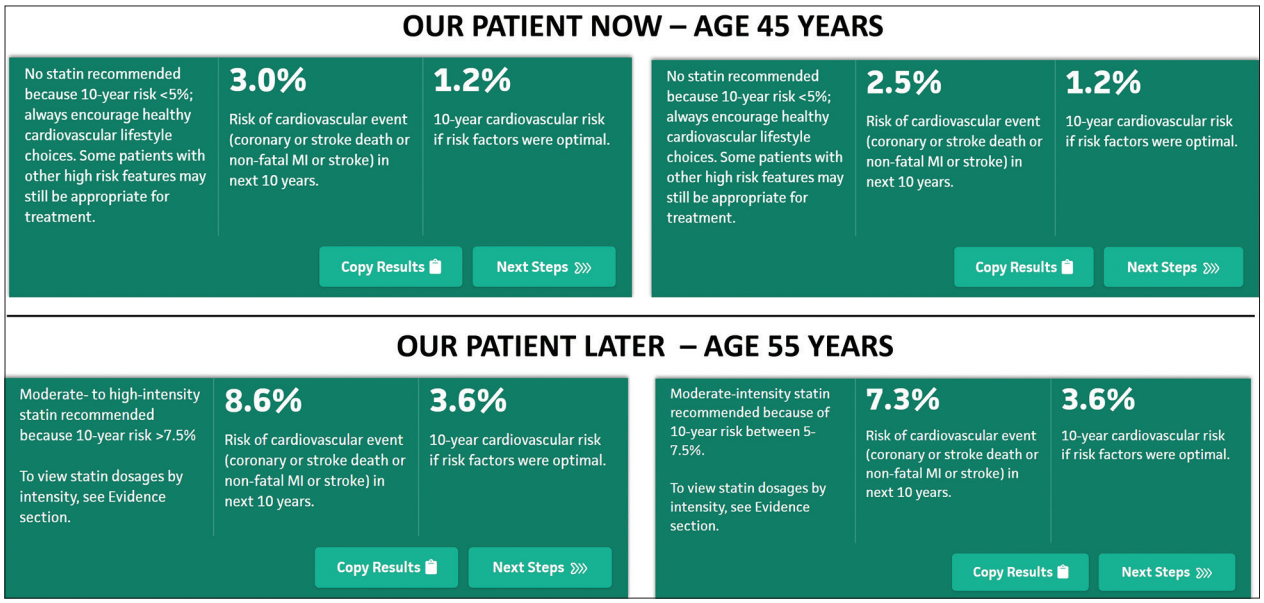


Figure 3: The results of using an online calculator of cardiovascular (CV) risk (https://www.mdcalc.com/ascvd-atherosclerotic-CV-disease-2013-risk-calculator-aha-acc Accessed March 30, 2021). The top two boxes show results for a 45-year-old man without diabetes, non-smoker, with reasonable cholesterol levels (4.0 mmol/L for total, 1.0 mmol/L for HDL). On the right of the top line is the 10-year risk of a CV event in a patient like the one presented in this review, whose systolic pressure is 156 mmHg. On the left of the top row is the same patient in all respects, except that the systolic pressure of 156 mmHg is in the presence of antihypertensive medication. The small but appreciable difference in risk of 0.5% over 10 years is called the "residual risk." On the lower row is the same patient, 10 years later, with the same smoking/diabetes/cholesterol status, and again the right hand panel is the 10-year CV risk with an untreated systolic pressure of 156 mmHg, and the left hand panel is the 10-year CV risk with a treated systolic pressure of 156 mmHg. Now, the residual risk of 1.3% is more than doubled compared with the difference in CV risk values at age 45 years

these may have an onset in the patient's life years before damage to the target organs is evident. In the rush to make a diagnosis and get a patient safely situated into a regimen of treatment meant to prolong life with functioning organs, we sometimes forget about the effect that applying a label like "hypertension" can have on a patient, a phenomenon sensibly known as the "labeling effect."[20] There is a considerable literature, spanning decades of the psychological consequences of receiving the label "hypertensive." Summarizing and hopefully doing justice to the field, when we label a patient as hypertensive they:

- Are more likely to be absent from work
- Score lower on indices of well being
- Show greater levels of psychological stress
- Are more likely to experience marital difficulties

along with other problems as outlined in the review by Wenger.[21] Hence, from a public health standpoint, as well as a private health standpoint, confirming the diagnosis is a vitally important issue.

Conclusion

As clinicians, it is challenging to find something we do that is more important from a global health perspective than finding and treating elevated BP. Making the correct diagnosis of hypertension, and instituting therapy, as early as possible reduces the time the vasculature is exposed to higher BP levels, reducing the burden of HMOD. The in-office BP is usually the first opportunity to candidly discuss both the importance of elevated BP and the benefits of treatment. Using good technique is essential to obtaining accurate BP measurement in, and outside of, the office setting. Keeping in mind that the labeling of a patient as hypertensive has psychological consequences for the patient, it is important to balance these concerns by the reasonable tolerability of most antihypertensive treatments, and pointing out the benefits of reducing the likelihood of heart attack, heart failure, stroke, and kidney disease progression which accompanies successful reduction of elevated BP.

Clinical Significance

The WHO has identified elevated BP as the world's most significant non-communicable disease.[22] Elevated BP is the most important contributor to premature death and premature damage to the brain, heart, and kidneys.[23] Clinical experience has shown the importance of proper technique to measure BP and reduce the likelihood of misdiagnosis. Decades of clinical trials have established the benefits of BP reduction, however, adherence to medication remains a significant challenge in high BP therapy.[24] In dealing with this last issue, adherence, it is particularly to confirm a diagnosis of hypertension early

to minimize future target organ damage, and to use the office visit as a means to support the patient as they are initiated on antihypertensive therapy. This is because some patients will experience medication side effects, some patients will be skeptical about benefits, and some patients will experience stressful psychological issues. Medical treatment is always an individualized risk-versus-benefit endeavor. The abundance of medication available, the clear message of benefit, and a caring attitude on the part of the clinician can make a huge difference in managing this globally important risk factor.

References

1. Hartley RM, Velez R, Morris RW, D'Souza MF, Heller RF. Confirming the diagnosis of mild hypertension. Br Med J (Clin Res Ed) 1983;286:287-9.
2. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? JAMA 1988;259:225-8.
3. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. Hypertension 2002;40:795-6.
4. Kaul U, Arambam P, Rao S, Kapoor S, Swahney JP, Sharma K, *et al*. Usefulness of ambulatory blood pressure measurement for hypertension management in India: The India ABPM study. J Hum Hypertens 2020;34:457-67.
5. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, *et al*. Clinical practice guidelines for the management of hypertension in the community a statement by the American society of hypertension and the international society of hypertension. J Hypertens 2014;32:3-15.
6. McFadden CB, Raymond R. Townsend, blood pressure measurement: Common pitfalls and how to avoid them. Consultant 2003;43:161-5.
7. Muntner P, Shimbo D, Carey RM, Charleston JB, Gaillard T, Misra S, *et al*. Measurement of blood pressure in humans: A scientific statement from the american heart association. Hypertension 2019;73:e35-66.
8. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Himmelfarb CD, *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: Executive summary: A report of the American college of cardiology/American heart association task force on clinical practice guidelines. Hypertension 2018;71:1269-324.
9. Nunan D, Thompson M, Heneghan CJ, Perera R, McManus RJ, Ward A. Accuracy of self-monitored blood pressure for diagnosing hypertension in primary care. J Hypertens 2015;33:755-62; discussion 762.
10. Parati G, Stergiou GS, Asmar R, Bilo G, de Leeuw P, Imai Y, *et al*. European society of hypertension guidelines for blood pressure monitoring at home: A summary report of the second international consensus conference on home blood pressure monitoring. J Hypertens 2008;26:1505-26.
11. Stergiou GS, Ntineri A. The optimal schedule for self-home blood pressure monitoring. J Hypertens 2015;33:693-7.
12. Piper MA, Evans CV, Burda BU, Margolis KL, O'Connor E, Whitlock EP. Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: A systematic review for the U.S. preventive services task force. Ann Intern Med 2015;162:192-204.
13. Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. N Engl J Med 2006;354:2368-74.
14. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. Hypertension 2011;57:3-10.
15. Townsend RR. Out-of-office blood pressure monitoring: A comparison of ambulatory blood pressure monitoring and home (self) monitoring of blood pressure. Hypertension 2020;76:1667-73.
16. Hypertension Detection and Follow-up Program Cooperative Group. Follow-up program cooperative, the effect of treatment on mortality in "mild" hypertension: Results of the hypertension detection and follow-up program. N Engl J Med 1982;307:976-80.
17. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA 1979;242:2562-71.
18. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-13.
19. Giles TD. Blood pressure--the better biomarker: delay in clinical application. J Clin Hypertens (Greenwich) 2007;9:918-20.
20. Johnston ME, Gibson ES, Terry CW, Haynes RB, Taylor DW, Gafni A, *et al*. Effects of labelling on income, work and social function among hypertensive employees. J Chronic Dis 1984;37:417-23.
21. Wenger NK. Quality of life issues in hypertension: Consequences of diagnosis and considerations in management. Am Heart J 1988;116(2 Pt 2):628-32.
22. Cohen DL, Townsend RR, Angell SY, DiPette DJ. The World Health Organization recognizes noncommunicable diseases and raised blood pressure as global health priority for 2025. J Clin Hypertens (Greenwich) 2014;16:624.
23. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: A systematic analysis for the global burden of disease study 2019. Lancet 2020;396:1223-49.
24. Berra E, Azizi M, Capron A, Høieggen A, Rabbia F, Kjeldsen SE, *et al*. Evaluation of adherence should become an integral part of assessment of patients with apparently treatment-resistant hypertension. Hypertension 2016;68:297-306.

How to cite this article: Townsend RR. Confirming a Diagnosis of "Hypertension." Hypertens 2021;7(1): 1-6.

Source of support: Nil, **Conflicts of interest:** None

INDIAN SOCIETY OF HYPERTENSION
World Hypertension League
CURRENT MEDICAL CONCEPTS
HTNJ
CrossMark

Review Article

Endothelial Function and Cardiovascular Health

Mohsin Wali[1], C. Venkata S. Ram[2,3,4]

[1]Department of Medicine, Sir Ganga Ram Hospital and Ganga Ram Institute of Post Graduate Medical Education and Research, New Delhi, India, [2]Apollo Institute for Blood Pressure Management, World Hypertension League/South Asia Office, Apollo Hospitals, and Apollo Medical College, Hyderabad, Telangana, India, [3]Texas Blood Pressure Institute, University of Texas Southwestern Medical School, Dallas, U.S.A, [4]India Campus, Macquarie University, Medical School, Sydney, Australia

Abstract

Systemic vascular disease is a major public health issue all over the world. Vascular disease causes significant morbidity and excessive mortality. Risk factors for vascular disease like hypertension, diabetes, hyperlipidemia, and tobacco consumption inflict vascular disease by causing endothelial dysfunction. Endothelium, the innermost layer of the blood vessels governs vascular tone and vasomotion. Abnormal endothelial function promotes vasoconstriction and atherothrombosis. Thus, endothelial dysfunction predisposes to vascular disease affecting target organs --- brain, heart, and the kidneys, etc. Endothelial dysfunction, thus, is a precursor in the onset and progression of systemic vascular disease and atherosclerosis. Future interventions to prevent vascular disease should include modalities to preserve endothelial function and to reverse endothelial dysfunction. Endothelial function is critical to maintain holistic public health.

Key words: Cardiovascular Disease (CVD), Endothelium, homeostasis

Cardiovascular disease (CVD) is the leading global cause of premature mortality and excessive morbidity. A number of predisposing factors contribute to the pathogenesis of CVD. Etiological factors such as hypertension, diabetes, obesity, sedentary life style, tobacco consumption, and genetics participate in the onset and progression of CVD. Age and gender may also play an important role in the causation of CVD. An important critical fundamental basis for CVD is endothelial dysfunction. Circulatory homeostasis is regulated by the cells that line the vascular system – the endothelium.[1,2] Originally, endothelium was merely considered as an inactive physical barrier between the blood and vascular smooth muscle but it is now recognized as playing a central role in the development of vascular disease/atherosclerosis. While it is not absolutely clear whether it is the cause or consequence of CVD, endothelium is intimately linked to vascular pathology.[3,4] Given its (physical) location between the blood stream and vascular smooth muscle, endothelium is the locus for biological and mechanical actions of cardiovascular risk factors.

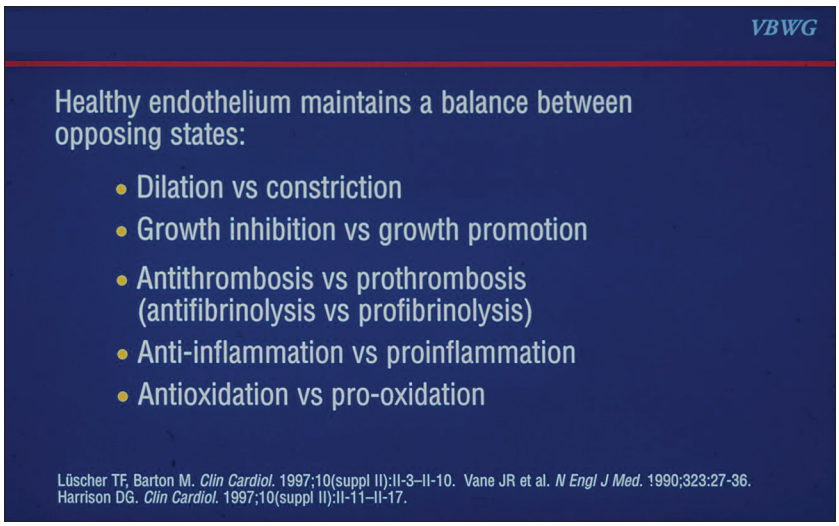
The endothelium is the largest organ in the body serving paracrine, endocrine, and numerous other regulatory functions in determining the cardiovascular health and CVD [Figure 1]. In response mechanical, biological, and endocrine stimuli, endothelium produces vasoactive substances which govern the vascular structure and function. The consequences of this phenomenon are vasoconstriction or vasodilation or thrombus formation.[5,6] Endothelium thus controls vascular remodeling, hemostasis, and inflammation. A principal function of the endothelium is to regulate vasomotor tone (contraction or dilation) [Table 1]. A prominent function of endothelium is nitric oxide (NO) metabolism and other vasodilatory substances such as prostacyclins.[7-9] The endothelium [Figures 2 and 3] also modulates vasoconstrictor components such as thromboxane A2, endothelin, and angiotensin II [Figure 4]. The vascular growth factors are also modulated by the endothelium. In other words, the endothelium is the maestro conducting the cardiovascular orchestra [Figures 5 and 6].

Address for correspondence:
C. Venkata S. Ram, Apollo Institute for Blood Pressure Management, World Hypertension League/South Asia Office, Apollo Hospitals, and Apollo Medical College, Hyderabad, Telangana, India. E-mail: drram_v@apollohospitals.com

Received: 23/03/2021; Accepted: 31/03/2021
doi: 10.15713/ins.johtn.0214

Indexed Nature Science Publishers

Table 1: Endothelial function/vascular health



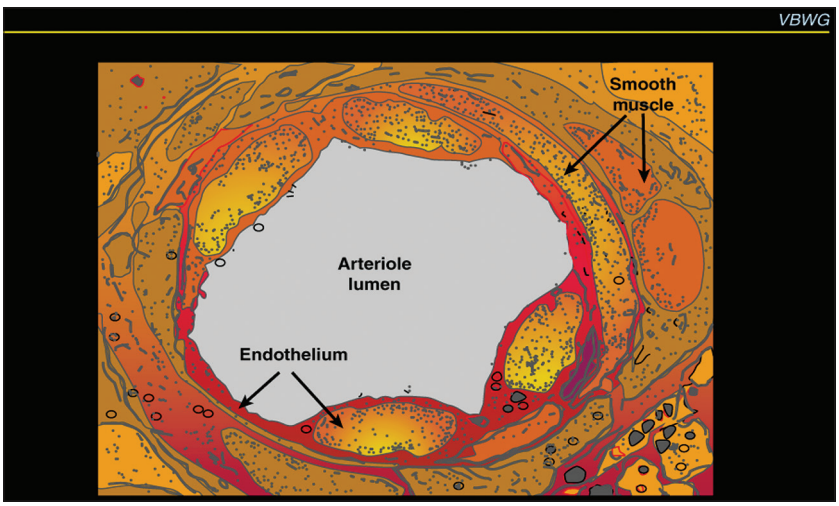


Figure 1: The endothelium: A living organ

Vasodilating Factors/Endothelium

NO

The seminal discovery by Furchgott of endothelium derived relaxing factor (EDRF) confirmed that normal endothelium is essential to induce vasodilation.[10] Subsequent research has led to uncovering that EDRF is NO. Endothelium produces NO by stimulating guanosine monophosphate (GMP). NO regulates vasomotor tone, myocardial contractility, cell permeability, vascular proliferation, and exerts anti-thrombotic effects. NO synthase produces NO from L-arginine. NO synthase in the endothelium is acNOS, an inducible enzyme. In the normally functioning endothelium, acNOS continually produces NO to maintain physiological vasodilation constantly.[11,12]

In addition, bradykinin and acetylcholine also stimulate ecNOS. Hypoxemia and vascular sheer stress are important stimuli for the release of NO. It is of interest to note that NO production is highest in the small arteries (resistance vessels) but NO activity is highest in the large diameter arteries. NO is involved in acto-regulation of blood flow in the arteries of all sizes, thus assuring required distribution of blood among various vascular networks. NO also modulates growth factors and vasoconstrictors. During atherogenesis, platelet-derived growth factor (PDGF) –β inhibits the activity of NO. Thus, positive and negative control mechanisms are present in the endothelium.

Prostacyclin and Bradykinin

Prostacyclin is elaborated in response to shear stress and other factors influencing NO. But when compared to NO, the contribution of prostacyclin to vasodilation is negligible. Endothelial cells produce and release bradykinin in response to

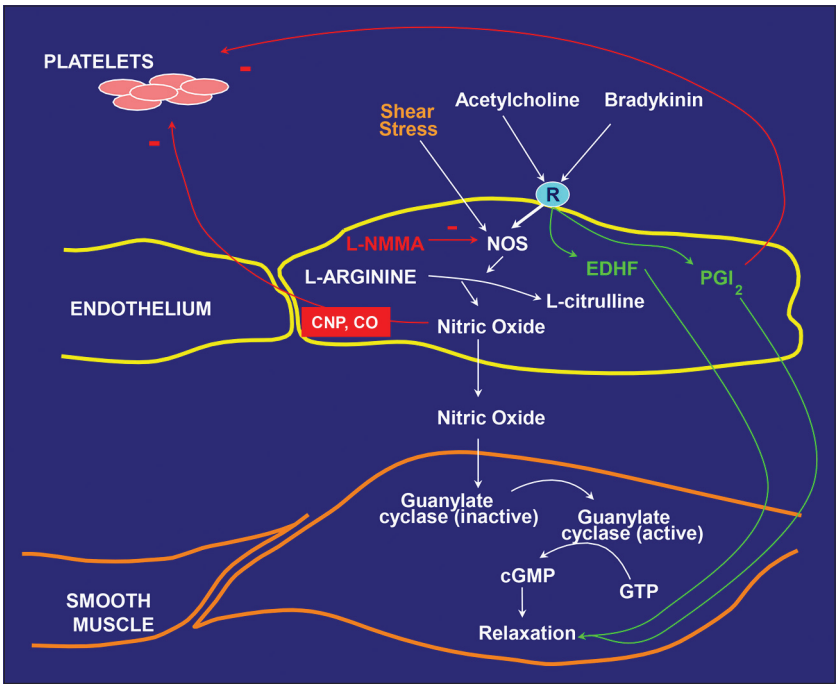


Figure 2: Cellular pathways of nitric oxide actions at the blood vessel

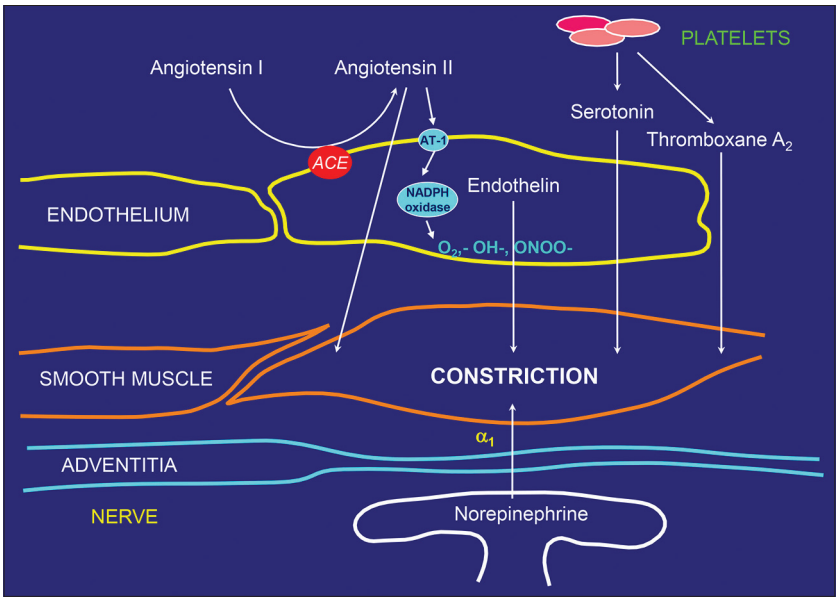


Figure 3: Cellular pathways of nitric oxide actions at the blood vessel

blood flow. Bradykinin in turn binds to β2 receptor to activate L-arginine – NO pathway Bradykinin has dual vasodilating properties – direct and indirect through stimulation of NO. Bradykinin causes nitrite release from coronary arteries. Bradykinin (like NO) also inhibits platelet aggregation and thrombosis. By stimulating tissue plasminogen activator (t–PA), bradykinin promotes an anti-thrombotic effect.

Vasocontracting factors/endothelium

Endothelium may prevent vasodilation or cause vasoconstriction through thrombin, acetylcholine, arachidonic acid, prostaglandin, H2, and high potassium levels as well as by hypoxia and vascular stretch. Examples of endothelium derived contracting factors include endoperoxides and thromboxane A2.

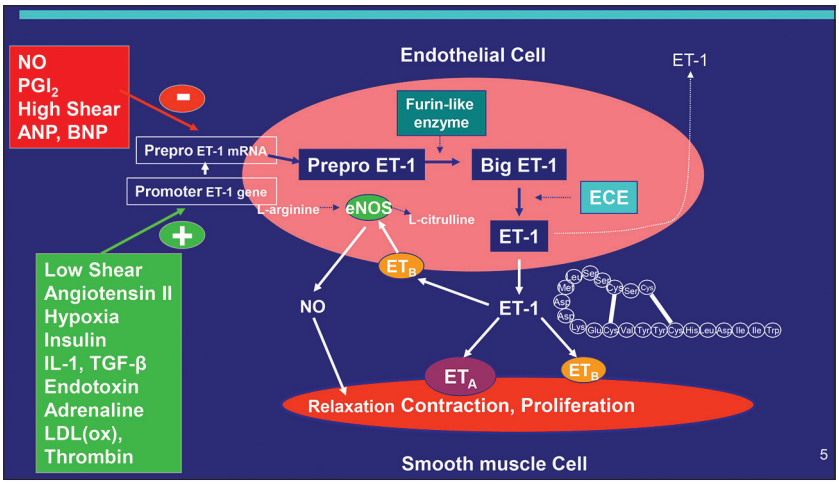


Figure 4: ET-1: Generation, action, and pathophysiology

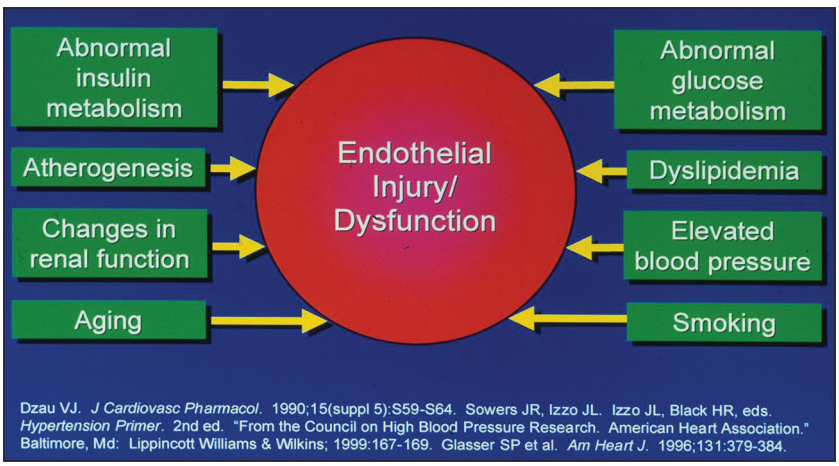


Figure 5: Known contributors of endothelia dysfunction

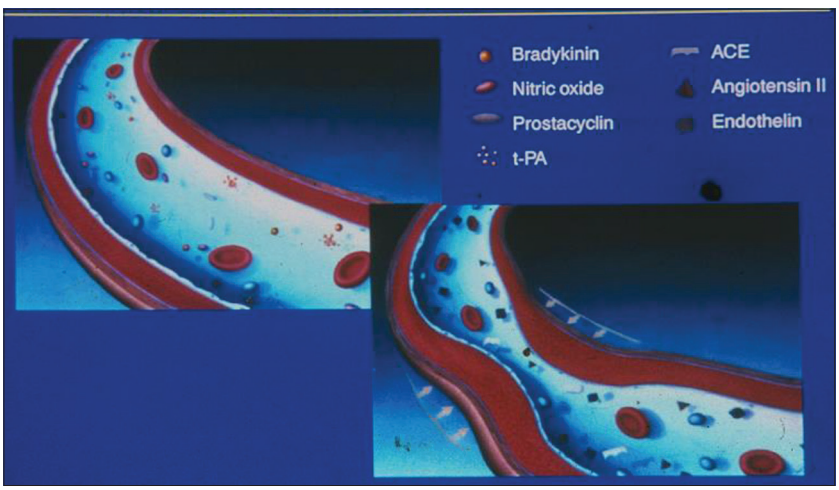


Figure 6: Vasodilation and vasoconstriction

Endothelin

Endothelin, a 21 – amino acid peptide is a potent vasoconstrictor. It is produced by the endothelin in response to thrombin, angiotensin II, arginine vasopressin, interleukin – I, and calcium Ionophores, etc. In healthy individuals, circulating levels of endothelin are very low. Endothelin production is influenced by cGMP-dependent inhibition, cAMP-dependent inhibition, and an inhibitory factor produced by vascular smooth muscle cells. Formation of NO by normal endothelium offsets the negative actions of endothelin.

Angiotensin II

Angiotensin II is a powerful vasoconstrictor produced by angiotensin converting enzyme present in the endothelial cells. In addition to causing direct vasoconstriction, angiotensin II stimulates endothelin and hence with resultant vasoconstriction.

Endothelium dependent – vasomotion

The pivotal role of endothelium --- dependent vasodilation in maintaining normal vasomotion is a well-established concept. It is well known that acetylcholine, an endothelium --- dependent factor causes coronary vasorelaxation in the normal vessels but causes paradoxical vasoconstriction in atherosclerosis arteries. The paradoxical vasoconstriction is explained by the loss of normal endothelial function in the diseased arteries. This pathological observation is seen well before the angiographic dissection of atherosclerotic lesions. Substances that inactive NO such as methylene blue and free hemoglobin blocks acetylcholine mediated vasodilation. In addition to NO, other endothelium derived vasodilators such as histamine and substance P cause coronary vessel dilation.[13] In summary, vascular endothelium plays a major role in maintaining vascular tone and tissue blood flow in health and in disease.

Vasculoprotective Properties of the Endothelium

Vascular growth

The endothelium produces a number of growth factors such as --- fibroblast growth factor, PDGF, angiotensin II, and endothelium. At the same time, the endothelial cells also produce growth inhibitors such as TGF -β, heparan sulfates, and heparin. Importantly, NO has significant anti-proliferative effects. NO inhibits vascular smooth muscle proliferation and fibroblast mitogenesis. Overexpression of NOs and precursors of NO inhibit and prevent endothelial injury. The superoxide generation by angiotensin II can be blocked by NO.

Anti-coagulant effects

The normal endothelium maintain a critical balance between the factors that regulate fibrinolysis and thrombosis.[14,15] The endothelium protects against thrombus formation by synthesizing glycosaminoglycans that bind to antithrombin. The endothelial cells synthesize thrombomodulin which transforms thrombin and converts it to an activator of protein C; these activated proteins have anticoagulant properties. In addition, protein C – causes fibrinolysis (through interaction with plasminogen activator inhibitor [PAI]). A vital fibrinolytic property of the endothelium is its ability to produce t-PA that converts plasminogen to plasmin. Endothelial cells synthesize PAI- 1 which determines the rate of fibrinolysis. The balance between t-PA and PAI-1 is tilted toward thrombosis by angiotensin II.

The endothelial cells can inhibit platelet aggregation and adhesion, prostacyclin produced by the endothelium also blocks platelet activation. Platelets also contain NO synthase which is turned on by platelet aggregation. NO blocks ADP-induced platelet adhesion and aggregation. In totality then, NO inhibits platelet adhesion to the vascular endothelial cells. The antithrombotic actions of endothelium are due to synergistic effects of NO and prostacyclin. The vasospasm and thrombus formation are prevented by joint actions of NO and prostacyclin.

Anti-inflammatory effects

Leukocyte adhesion is attenuated by NO produced by the endothelium.[16] NO also inactivates superoxide anion. Deficiency of NO causes vascular permeability and protein leakage hallmarks of vascular inflammation. An imbalance between NO and superoxide anion induces vascular inflammation by promoting leukocyte migration and mast cells. The endothelial cells normally prevent leukocyte adhesion, damaged endothelium expresses leukocyte adhesion molecules which is a pro-inflammatory state. Oxidized LDL cholesterol also causes an inflammatory reaction in the endothelium. The metabolic stress induced by hypertension and hyperlipidemia, for example, causes superoxide anion generation and vascular smooth muscle hypertrophy.

NO and anti-atherosclerotic effects

Besides blocking the leukocyte-endothelial interaction, NO also prevents other mechanisms involved in atherosclerosis. NO inhibits vascular smooth muscle hypertrophy and migration and eliminates oxidative modification of LDL. NO deficiency results in vascular dysfunction and thrombus formation. Low levels of NO may stimulate angiotensin and block bradykinin production. NO blocks adhesion molecules and chemotactic proteins. For all these reasons, NO is considered as an natural anti-atherogenic molecule.[17,18]

Exposure to vascular shear stress augments NO activity, thereby inhibiting monocyte adhesion to the blood vessel wall and promoting vasodilation. On the other hand, low shear stress is accompanied by reduced NO activity, exaggerated vasoconstriction, and platelet aggregation. Regions of low shear stress are vulnerable to atherosclerosis (typically seen in the arterial branches or bifurcations). Non-aligned cells are found in low shear stress areas whereas aligned cells are found in high shear stress areas. These observations emphasize that endothelial functions are sensitive to hemodynamic changes in the circulatory state.[19,20]

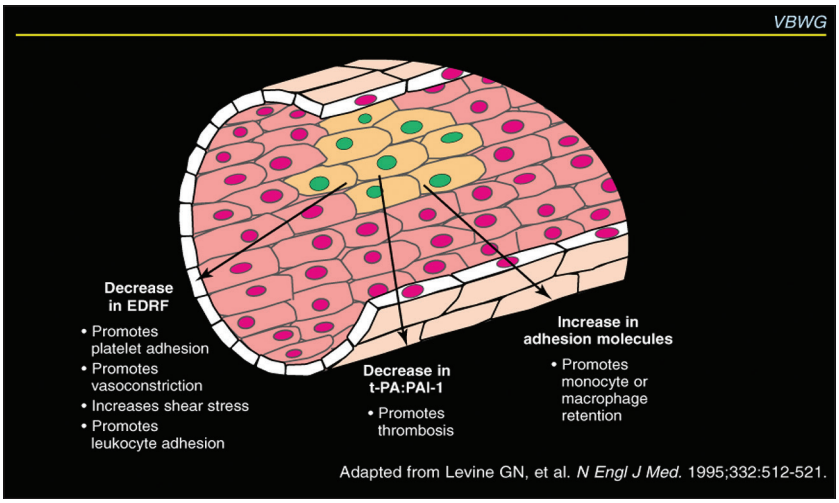


Figure 7: Dysfunctional endothelial cells in dyslipidemia and atherosclerosis

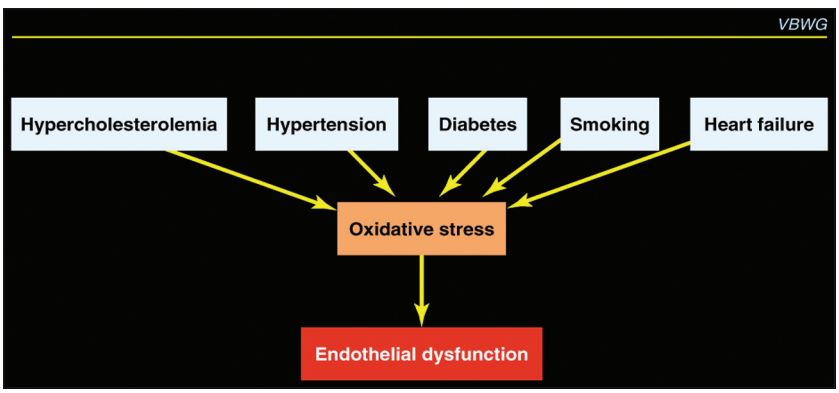


Figure 8: Risk factors and endothelial dysfunction mediator role of oxidative stress

Summary

The endothelium is an important organ which governs and maintains cardiovascular homeostasis. Located strategically between the blood stream and vascular smooth muscle, it plays a critical role in maintaining cardiovascular health. Normal endothelial function is responsible for physiological blood flow, oxygenation, and prevention of thrombus formation. Endothelial dysfunction predisposes to vasoconstriction, hypoxemia, and thrombus formation leading to ischemia and infarction of the tissue. Endothelial damage has widespread pathophysiological consequences and implications. Abnormal endothelial function promotes vascular inflammation and vascular hypertrophy. The end result of endothelial dysfunction is vascular insufficiency and target organ damage. Risk factors which predispose to endothelial damage include – hypertension, diabetes, hyperlipidemia, tobacco consumption, obesity, sedentary life style, and genetic factors [Figures 7 and 8]. To prevent vascular disease and to protect endothelial function, risk factors should be identified early and treated aggressively. In addition to the control of risk factors, vascular health can be maintained by therapies which promote NO release. Thus, a broad spectrum therapeutic approach is required to maintain endothelial integrity and cardiovascular health. Understanding of endothelial physiology and pathophysiology is necessary to preserve and to protect global public health.

References

1. Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. N Engl J Med 1990;323:27-36.
2. Rubanyi GM. The role of endothelium in cardiovascular homeostasis and diseases. J Cardiovasc Pharmacol 1993;22 Suppl 4:S1-14.
3. Meredith IT, Yeung AC, Weidinger FF, Anderson TJ, Uehata A, Ryan TJ. Role of impaired endothelium-dependent vasodilation in ischemic manifestations of coronary artery disease. Circulation 1993;87 Suppl 5:V56-66.
4. Lerman A, Burnett JC Jr. Intact and altered endothelium in regulation of vasomotion. Circulation 1992;86 Suppl 3:III12-9.
5. Vaughan DE. Thrombotic effects of angiotensin. J Myocard Ischemia 1995;7 Suppl 1:44-9.
6. Radomski MW, Palmer RM, Moncada S. The antiaggregating

properties of vascular endothelium: Interactions between prostacyclin and nitric oxide. Br J Pharmacol 1987;92:639-46.
7. Loscalzo J, Welch G. Nitric oxide and its role in the cardiovascular system. Prog Cardiovasc Dis 1995;38:87-104.
8. Groves P, Kurz S, Just H, Drexler H. Role of endogenous bradykinin in human coronary vasomotor control. Circulation 1995;92:3424-30.
9. Muller-Estrl W. Kininogen, kinins and kinships. Thromb Haemostat 1989;61:2-6.
10. Furchgott RF, Zawadski JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373-6.
11. Radomski MW, Palmer RMJ, Moncada S. Comparative pharmacology of endothelium-derived relaxing factor, nitric oxide, and prostacyclin on platelets. Br J Pharmacol 1987;92:181-7.
12. Kubes P, Granger DN. Nitric oxide modulates microvascular permeability. Am J Physiol 1992;262:H611-5.
13. Crossman DC, Larkin SW, Fuller RW, Davies GJ, Maseri A. Substance P dilates epicardial coronary arteries and increases coronary blood flow in humans. Circulation 1989;80:475-84.
14. Radomski MW, Palmer RM, Moncada S. An L-arginine/nitric oxide pathway present in human platelets regulates aggregation. Proc Natl Acad Sci U S A 1990;87:5193-7.
15. Kubes P, Suzuki M, Granger DN. Nitric oxide: An endogenous modulator of leukocyte adhesion. Proc Natl Acad Sci U S A 1991;88:4651-5.
16. Alexander RW. Hypertension and the pathogenesis of atherosclerosis. Oxidative stress and the mediation of arterial inflammatory response: A new perspective. Hypertension 1995;25:155-61.
17. Cooke JP, Tsao PS. Is NO an endogenous antiatherogenic molecule? Arterioscler Thromb 1994;14:653-5.
18. Tsao PS, Lewis NP, Alpert S, Cooke JP. Exposure to shear stress alters endothelial adhesiveness: Role of nitric oxide. Circulation 1995;92:3513-9.
19. Barbee KA, Mundel T, Lal R, Davies PF. Subcellular distribution of shear stress at the surface of flow-aligned and nonaligned endothelial monolayers. Am J Physiol (Heart Circ Physiol) 1995;268:H1765-72.
20. Levesque MJ, Nerem RM. Elongation and orientation of endothelial cell shape in response to shear. J Biomech Eng 1985;107:341-7.

How to cite this article: Wali M, Ram CVS. Endothelial Function and Cardiovascular Health. Hypertens 2021;7(1):7-13.

Source of support: Nil, **Conflicts of interest:** None

INDIAN SOCIETY OF HYPERTENSION
World Hypertension League
CURRENT MEDICAL CONCEPTS
HTNJ
CrossMark

Review Article

Limited Long-Term Efficacy of Lifestyle-Mediated Weight Loss on Blood Pressure Control and the Biology of Weight Regain

Brent M. Egan[1], Susan Sutherland[1], Michael E. Hall[2]

[1]Department of Improving Health Outcomes, American Medical Association, Greenville, SC, United States, [2]Departments of Medicine and Physiology, University of Mississippi Medical Center, Jackson, MS, United States

Abstract

Hypocaloric weight reduction, with or without increased physical activity, lowers blood pressure (BP). Heart rate, sympathetic nervous system, and renin-angiotensin-aldosterone system activity also decline. However, with time, substantial weight is typically regained in most individuals who lose weight, and the beneficial effects of weight loss on BP decline or are reversed. The initial decline in BP with weight loss is likely enhanced by negative caloric balance. Thus, even with isocaloric weight loss maintenance, the magnitude of the initial BP reduction appears to decline with time. Of further concern, the complex physiological (counterregulatory) adaptations to weight loss foster weight regain as more calories are desired than required and energy expenditure falls. Sustained weight loss generally requires a substantial long-term time commitment to physical activity and a high level of vigilance. High protein, low glycemic, high fiber, and reduced energy density diets may also be beneficial in reducing hunger and increasing satiety. Individuals who are counseled to lose weight should be aware of the challenges in maintaining weight loss, receive education on the lifestyle changes required to sustain weight loss, and commit to an evidence-based plan designed to foster long-term success. Future research directed at blocking or ameliorating the disproportionately large reductions of anorexigenic hormones and decreases in energy expenditure that accompany weight loss would help sustain the beneficial effects of weight loss on BP.

Key words: Lifestyle, weight loss, weight regain, hypertension, blood pressure

In 1923, William E. Preble stated that being overweight by 15 pounds or more is an increasingly serious condition with advancing years, conducive to heart, arterial and kidney diseases, diabetes, and hypertension.[1] Preble stated that obesity and its complications reflected an eating disorder. Along that line, in 1948, Brozek, Chapman, and Keys reported that various dietary limitations were recurring themes for the cure or amelioration of hypertension.[2] They summarized a "natural experiment" on prevalent hypertension before, during, and after the German siege of Leningrad in World War II.

The siege intentionally interrupted the food supply to Leningrad from October 1941, through March 1942.[3] The combination of harsh weather, multiple theaters of warfare, long supply lines, and local resistance kept German troops from occupying Leningrad, although some residents died from starvation. The percentage of admissions for hypertension to the First Medical Institute in Leningrad declined from 10% to 15% pre-siege to 2% during the siege [Figure 1].[1] Hypertension-related admissions rose to 24.5% with refeeding of the population over the next 8 months, then peaked at 50% in 1943 before declining to 35% in early 1944. The percentage of patients with hemorrhages and/or exudates on funduscopic examination also increased from ≤25% before to 70% after the siege, suggesting more severe hypertension with refeeding. In fact, prevalent hypertension rose 2–4-fold across age groups after as compared to before the siege [Figure 2] and coincided with hospital admissions for hypertension.[2]

Keys and colleagues subsequently conducted the "Minnesota experiment" of calorie deprivation and refeeding in 34 healthy young men.[2] After consuming a diet of <1500 kcal/d for 6 months, mean body weight fell 23.9%. Mean blood pressure (BP) for the group declined ~11.8/4.3 mmHg from 106.5/69.9 to 94.7/64.5 mmHg

Address for correspondence:
Brent M. Egan, Department of Improving Health Outcomes, American Medical Association, Greenville, SC, United States.
E-mail: brent.egan@ama-assn.org

Received: 18-12-2020; Accepted: 02-01-2021
doi: 10.15713/ins.johtn.0218

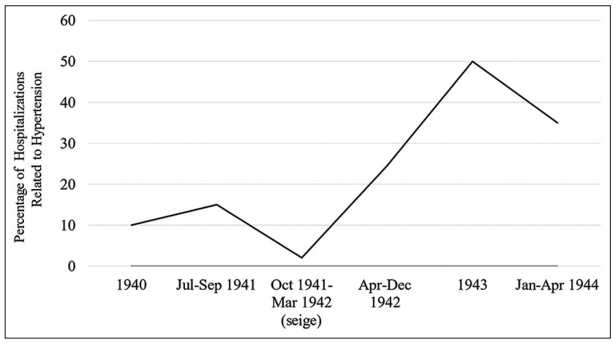


Figure 1: The percentage of hospital admissions at the First Pavlov Medical Institute was assessed at various time periods before, during, and following the German siege of Leningrad during World War II. As shown, hypertension-related hospital admission declined dramatically during the siege then rapidly increased above the pre-siege baseline with refeeding of the population post-siege

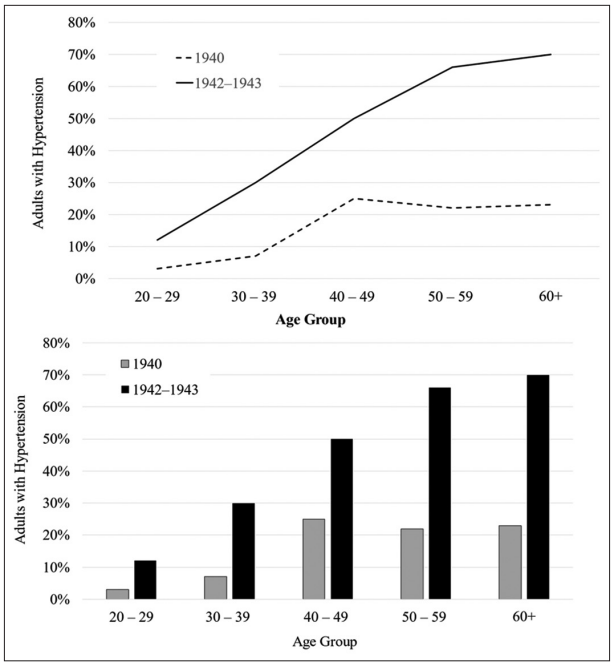


Figure 2: The prevalence of hypertension by age group in Leningrad is depicted in the calendar year before the siege (1940) and the year following the siege (1942–1943). As shown, the prevalence of hypertension was greater after than before the siege of Leningrad during World War II

as mean heart rate fell from ~56 to 37 beats/min. In a subset of 12 men, BP after 6 months of underfeeding was 92.7/63.2 mmHg and rose to 104.9/68.8 mmHg after 20 weeks of refeeding, an increase of ~12.2/4.5 mmHg. However, BP with refeeding did not exceed the original baseline of 105.3/79.1 mmHg, although mean body weight of 70.8 kg after 20 weeks refeeding was 3.1 kg higher than 67.7 kg at baseline. The fall in BP with calorie deprivation in normal volunteers was consistent with the decline in prevalent hypertension during the siege of Leningrad. The failure of BP to overshoot with refeeding in normal volunteers was inconsistent with the prominent rise in prevalence and severity of hypertension in Leningrad with refeeding after the siege.

Several subsequent studies addressed the BP effects of weight loss in response to lifestyle, primarily diet, and exercise, and BP responses to weight regain. The potential adverse health effects of weight cycling, that is, repeated episodes of weight loss and regain, and the biological mechanisms underlying recidivism after weight loss will be discussed.

Lifestyle Change, Weight Loss, and Hypertension

The medical literature

While this paper is not a systematic review or meta-analysis, this topic appears frequently in the medical literature. An Ovid Medline literature search using "weight loss and hypertension" identified 4277 original papers and 1306 review articles from 1946 to May 2020; 3441 original papers and 1074 review articles were identified since 2000. A search using "weight loss and BP" identified a moderately larger number of papers. Despite the relatively large number of papers, three systematic reviews found very few original studies of sufficient duration and quality to assess the long-term effects of weight loss on BP.[4-6]

Systematic reviews of long-term lifestyle interventions, weight loss, and BP

Horvath *et al*. identified a 6.3 mmHg reduction in mean systolic BP in two dietary interventions of limited duration, that is, one of 6 months and the other of 56 weeks [Table 1].[4] Body weight fell an average of 4.1 kg in five studies.

Aucott *et al*. included eight clinical trials and eight cohort studies of at least 2 years duration between 1990 and 2008. All studies assessed the effect of lifestyle interventions on weight loss and BP.[5] The 16 studies combined showed 2.8 kg weight loss (95% confidence interval [CI] −13.2, 7.5) and BP reduction of 2.9/1.9 mmHg (95% CI −9.2, 3.3/−9.5, 5.6). The changes of body weight and BP were not statistically significant given wide CI. In meta-regression analysis, systolic BP declined ~1 mmHg/kg weight loss for 2–3 years. BP appeared to revert to higher levels over longer time periods.

Semlitsch *et al*. conducted a systematic review of randomized dietary weight loss interventions at least 24 weeks in duration on patients with hypertension.[6] In three studies with 371 patients in the dietary intervention and 360 controls, systolic BP declined 4.5 mmHg on evidence deemed low quality. Body weight fell 4.0 kg in five studies with 435 participants assigned to the intervention and 445 to control. Weight loss data were of moderate quality. The authors concluded that weight loss diets reduced body weight and BP. The magnitude of effects was uncertain given small numbers of subjects in studies of low-to-moderate quality. The systematic reviews are consistent with the conclusion that the long-term impact of weight loss on BP in adults with hypertension is uncertain but appeared limited.[7]

A recent review of weight loss and hypertension in obese subjects included 13 interventional or observational studies

Table 1: Summary of studies and systematic reviews on studies showing limited long-term impact of weight loss on BP

Author, Ref#	Study description	Study sample	N	BP results	Weight	Notes
Systematic reviews of long-term lifestyle interventions, weight loss, and BP						
Horvath[4]	2 diet interventions 6 months, 56 wks			SBP −6.3	−4.1 kg	
Aucott[5]	8 Trials+8 Cohort ≥2 years			−2.9/−1.9	−2.8 kg	SBP −1 mmHg/1 kg loss over 2–3 years, but BP reverted over longer time
Semlitsch[6]	Randomized trials >24 wks, 3 studies	Patients with Hypertension	371 diet 360 controls	SBP −4.5		Low quality
Semlitsch[6,7]	5 studies, randomized trials	Patients with hypertension	435 diet 445 controls		−4.0 kg	Moderate quality
Fantin[8]	13 studies (2010–2019)	Obese patients				Lack of evidence on long-term BP effects with weight loss
Selected studies of weight loss, weight regain, and BP						
Brozek,Leningrad WW II[2,3]	Ecological					Rates of HTN fell markedly with starvation during siege and exceeded baseline with refeeding after siege
Keys, Minnesota Experiment[2]	<1500 kcal/d×6 months	Healthy young men	34	106.5/69.9 94.7/64.5	69.4 kg 52.9 kg	BP decreased with weight loss
Keys, Minnesota Subset[2]	Baseline/6 mo underfeeding/20 wks refeeding	Healthy young men (subset)	12	105.3/79.1 92.7/63.2 104.9/68.8	67.7 kg --- 70.8 kg	Weight gain with refeeding but BP did not rise above baseline
Stevens, TOHP II[9]	Weight loss and usual care arms	Men, Women 30–54 years. BP <140/83–89, 110–165% IBW	595 weight loss; 596 usual care	−3.7/−2.7 −1.8/−1.3 −1.3/−0.9	−4.4 kg 6 mo −2 kg 18 mo −0.2 kg 36 mo	Risk ratio for HTN weight loss versus control 0.58 (0.36–0.94) at 6 mo., 0.78 (0.62–1.00) at 18 mo., and 0.81 (0.70–0.95) at 36 mo.

wks: Weeks; SBP: Systolic BP; kg: Kilogram; HTN: Hypertension; kcal: Kilocalories; mo: Months; vs: Versus; IBW: Ideal body weight

between 2010 and 2019.[8] A positive effect of weight loss on BP was found in each study, albeit with differences in the magnitude and durability of BP reduction overtime. The authors concluded that "there is still a lack of evidence about long-term effects of weight loss on hypertension," yet recommended that weight management should be pursued in patients with obesity and hypertension.

Selected studies of weight loss and BP

Systematic reviews provide a useful overview of the extant literature, yet further insights can be gained by evaluating details of individual interventional and observational studies. The Trials of Hypertension Prevention (TOHP), Phase II, included adults 35–54 years old with untreated BP <140/83–89 mmHg and body weight 110–165% of ideal [Table 1]. One TOHP II report focused on 595 overweight and obese adults randomized to weight loss (diet change, physical activity, and lifestyle support) and 596 to usual care.[9] Mean weight changes at 6, 18, and 36 months in the intervention and control groups, respectively, were −4.4 versus 0.1 kg, −2.0 versus 0.7, and −0.2 versus 1.8. The magnitude of weight loss and the difference in weight between the intervention and control groups declined with time.

In a *post hoc* analysis of the TOHP, subjects randomized to weight loss were divided into three subgroups: (i) Weight loss ≥4.5 kg at 6 and 36 months (successful maintenance [n = 73, 12.3%]), (ii) weight loss ≥4.5 kg at 6 months but <2.5 kg at 36 months (relapse [n = 129, 21.7%]), and (iii) weight loss ≤2.5 kg at 6 and 36 months (no loss [n = 198, 33.3%]) with 195 (32.8%) who did not fit these groups. Systolic BP fell approximately 9.5 and 5.8 mmHg at 6 and 36 months, respectively, in successful maintainers, ~9 and 0 in the relapse group, and ~2.8 and +1.8 in the no loss group. Successful maintainers had ~65% lower risk for hypertension than participants randomized to the control group. Thus, ~1 in 8 (12.3%) intervention participants attained significant reductions in BP and hypertension risk with modest sustained weight loss.

Among 14,306 adult participants who were ever overweight or obese (cross-sectional representative samples of the U.S. population repeated at 2-year intervals from 1999 to 2006), 82.3% had hypertension. For the entire group, 36.6% and 17.3% had maintained weight loss of ≥5% and ≥10%, respectively, for at least a year.[10] Lower income, less education, female sex, older age, poor health status, and diabetes, and non-Hispanic White race/ethnicity were among the independent predictors of ≥10% weight loss.

A trial of sodium reduction and weight loss in older persons provided support for the success of older adults in sustaining weight loss.[10,11] The study included a subset of 585 adults 60–80 years who were overweight or obese with BP <145/<85 mmHg on a single antihypertensive medication. Overweight and obese participants were randomized to

reduced sodium intake (goal 80 mmol/d), weight loss (goal ≥4.5 kg), both, or usual care. After 90 days intervention, the protocol required attempted withdrawal of antihypertensive therapy. Participants were then followed for the primary outcome of BP ≥150/≥90 mmHg, restarting antihypertensive medication, or a cardiovascular event. BP medications were successfully withdrawn in 93% of weight loss and 87% of control participants. Adults randomized to weight loss achieved a 5 kg weight reduction at 6 and 9 months and maintained weight loss of 4 kg at 21 and 24 months, 4.4 kg at 27 months, and 4.7 kg at 30 months (median follow-up 29 months). In addition to successful long-term weight loss, older adults randomized to weight loss had a lower relative hazard ratio for the primary outcome (0.64, 95% CI 0.49–0.84, p=.002) compared to the control group.

A systematic review and meta-analysis of long-term weight loss in adults ≥60 years identified nine studies from a literature search spanning 1966 through 2008.[12] A median weight loss of 3 kg at 1 year was identified from seven studies. No significant changes were seen in the lipid profile. Only one study in the meta-analysis included sufficient data to assess BP.[11] BP fell 4.0/1.1 mmHg after 90 days of the weight loss intervention and before withdrawal of antihypertensive medication compared to 0.8/0.8 mmHg in the control arm.

Biological and Behavioral Mechanisms Contributing to Weight Regain Following Weight Loss

On balance, studies of lifestyle and weight loss in overweight and obese adults with hypertension show a recurring pattern of initial success with reduction of weight and BP. Overtime weight and BP return toward baseline. In fact, a substantial proportion of normal weight, overweight, and obese individuals has repeated cycles of weight loss followed by weight regain, that is, weight cycling.[13] In fact, some evidence suggests that the adverse health effects of weight cycling may be greater among individuals of normal than excess weight.

Not surprisingly, obese individuals maintaining weight loss report a higher burden of effort than reported by normal weight individuals maintaining weight.[14] While both groups had similar levels of energy intake, the obese weight maintenance group reported significantly higher levels of physical activity. Moreover, the obese weight maintenance group reported both more restraint and greater disinhibition of eating behaviors, while normal weight individuals relied more on internal cues. The biology of weight regain may account for the greater effort including the need for greater restraint and higher levels of physical activity by previously obese individuals sustaining weight loss than the effort of normal weight individuals maintaining weight.

In their review, "Attenuating the biologic drive for weight regain following weight loss," Melby *et al.* summarized and integrated 150 research reports on the biology of weight loss and regain.[15] They describe an "energy gap" following weight loss in which more energy is desired than required. The experience of hunger in excess of needs is associated with and likely driven at least partially by elevation of ghrelin, an orexigenic hormone, and reduction of anorexigenic hormones, for example, cholecystokinin, peptide YY, amylin, pancreatic polypeptide, and glucagon-like peptide-1. Moreover, the decline in anorexigenic hormones exceeds that expected for the magnitude of weight loss. After weight loss in obese individuals, total daily energy expenditure, thermic effect of food, resting metabolic rate, and physical activity energy expenditure all decline, that is, energy efficiency rises. The authors succinctly summarized the multiple changes in energy regulation, which serve to powerfully promote weight regain [Figure 1].

A report from the Biggest Losers weight loss competition is consistent with the aforementioned adaptive changes to weight loss that foster weight regain.[16] This group achieved a mean weight loss of 58.3 kg after 30 weeks in the competition, which was accompanied by a reduction in resting metabolic rate averaging 610 kcal/day. After 6 years follow-up, they regained a mean of 41.0 kg (70% weight regain). Of note, resting metabolic rate remained 704 kcal/day below the pre-weight loss baseline and was similar to the change at 30 weeks, despite weight regain. The fall in resting metabolic rate with weight loss is termed metabolic adaptation or adaptive thermogenesis and emerges as a major contributor to weight regain.

Applying the Biology of Weight Regain to Approaches that Sustain Weight Loss

The counterregulatory responses to weight loss promote weight regain [Figure 3, right upper half]. On a positive note, the factors that promote weight regain can help inform an intervention to mitigate recidivism after successful weight loss [Figure 3, right lower half].[15] Of the various factors shown, high-protein diets and consistent time commitment to physical activity emerge as especially important factors in sustained weight loss. On a calorie basis, the thermic effect of protein is roughly 3 times greater than that of carbohydrates and fat. Protein also produces greater satiety than comparable calories from carbohydrate or fat. High levels of physical activity increase exercise energy expenditure during exercise and for several hours after physical activity ends. The effect of physical activity to raise resting metabolic rate essentially requires daily renewal. After successful weight loss, a high level of daily exercise raises physical activity energy expenditure and total daily energy expenditure, which support a higher isocaloric ceiling than lesser exercise. The greater isocaloric ceiling maintains a higher thermic effect of food, especially when protein comprises a relatively high percentage of total calories. Under these conditions, a more favorable equilibrium is maintained between calories desired and required, resulting in better weight loss maintenance.

Among 170 subjects on a reduced calorie diet for 18 months, weight loss was not significantly different at 18 months in those

randomized to supervised exercise for 300 min/week in months 0–6 versus 7–12 (−6.9 vs. −7.9 kg, P = NS).[17] Weight loss at 6 months was greater in the group that received supervised exercise in the first 6 months (−8.7 vs. −6.9, P = 0.047). Both groups had approximately 60 min daily of moderate physical activity at baseline, which rose to ~90 min/day during supervised exercise training. During months 12–18, when neither group received supervised exercise, both groups averaged ~75 min daily of moderate physical activity. This study is consistent with other reports indicating that a significant time commitment to physical activity is a component of successful long-term weight loss.

Individuals in the National Weight Control Registry have maintained a minimum 13.6 kg weight loss for a year or more with a mean 33 kg weight loss over 5 years.[15,18] These registrants provide additional confirmation on the importance of high levels of physical activity and limited sedentary time, frequent weight monitoring, and high levels of dietary restraint. Conversely, weight regain was associated with more depression, hunger, disinhibition, and binge eating as well as higher fat consumption than in those who successfully sustained weight loss.

Adverse Health Effects of Weight Regain and Cycling: Focus on BP

Several variables may impact the assessment of BP responses to weight loss and regain. One important concept to consider is that the BP response to the initial period of weight loss with negative caloric balance may be substantially greater than longer-term effects of isocaloric sustained weight reduction. For example, in response to an 800 calorie daily diet for 9 weeks, body weight declined among 34 men and women from a mean of 101.7 to 87.3 (−14.4 kg) and 24 h ambulatory systolic BP fell from 130.1 to 122.1 (−9 mmHg).[19] Despite full maintenance of weight loss at 6 months, mean 24 h systolic BP rose to 126.5 (−3.6 mmHg from baseline [40% of initial response]). Although ~88% of initial weight loss was sustained at 1 year (−12.6 kg), systolic BP rose to 127.9 (−2.2 mmHg from baseline [~24% of initial BP response]).

In a study of 18 non-diabetic adults with the metabolic syndrome, 9% weight loss over 12 weeks reduced total body norepinephrine spillover by 23%, muscle sympathetic nerve activity (MSNA) by ~40%, and plasma renin activity ~25% (all changes statistically significant).[20] Despite excellent maintenance of weight loss at 7 months, MSNA and plasma renin activity returned to baseline levels, although norepinephrine turnover remained lower. Unlike the preceding report, BP responses at 12 weeks were largely maintained at 7 months. Yet, these data suggest that even with sustained weight loss, key neurohormonal responses to initial weight loss are not fully retained over longer time periods. In other words, the biological responses to initial weight loss with negative caloric balance are often not as robust as the longer-term responses to successful, isocaloric weight loss maintenance.

The relationship of weight cycling to incident hypertension has not been consistent across studies.[13] Among 46,224 women in the Nurses Heath Study II who had non-hypertensive BP values, weight gain was associated with incident hypertension

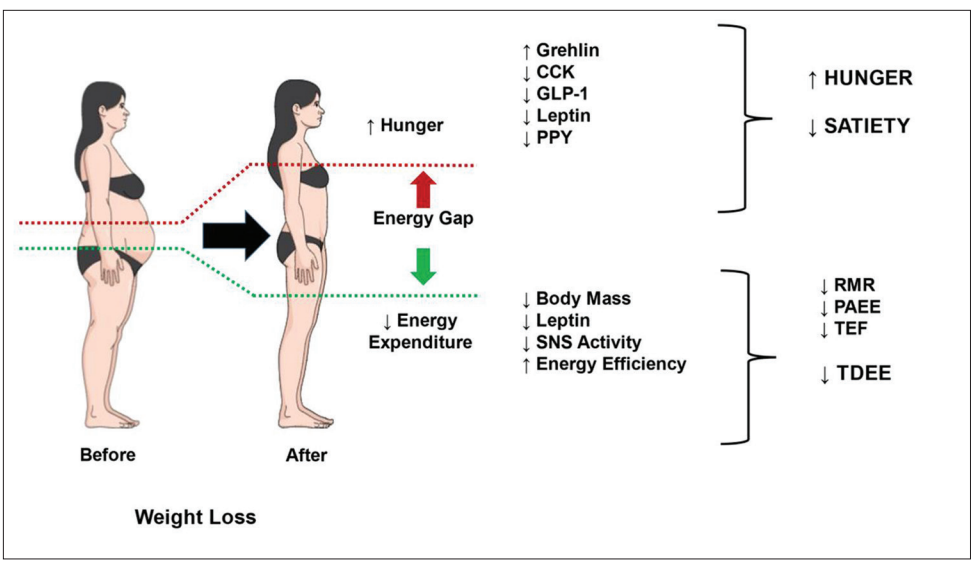


Figure 3: Successful weight loss activates pathways fostering weight regain (from reference 15). Energy intake and expenditure are balanced in weight stable obesity. Weight loss from decreased energy intake heightens hunger and lowers energy expenditure resulting in an "energy gap." The energy gap is linked to increased orexigenic and decreased anorexigenic peptides, which signal nutrient deprivation to the brain resulting in hunger, food cravings, and less satiety. Diet-induced weight loss also reduces total daily energy expenditure, physical activity energy expenditure as resting metabolic rate, and the thermic effect of food fall. Greater hunger and less energy expenditure promote weight regain

but mild or severe weight cycling was not.[21] In 12,362 middle-aged German men and women, weight cycling was positively associated with incident hypertension among individuals who were obese but not among those who were not obese.[22] Among 3965 men and women participating in a prospective primary prevention study of heart disease and cancer in France, weight fluctuations were not associated with incident hypertension after adjusting for relative weight change.[23] In a cross-sectional study of 664 Japanese men 40–49 years old, weight cycling was not significantly related to incident hypertension after adjusting for the slope of weight overtime and body mass index at the time of study and at age 20.[24] Similar findings were reported from a single clinical site in Italy that evaluated 459 obese men and women.[25] On balance, the effect of weight cycling on BP and incident hypertension appears minimal after accounting for the magnitude and rate of increase in weight and adiposity.

Summary and Clinical Implications

Hypocaloric weight reduction lowers BP, heart rate, sympathetic nervous system, and renin-angiotensin-aldosterone system activity. Yet, overtime weight is regained in most individuals who lose weight, and the beneficial effects of weight loss on BP are significantly diminished or reversed. Moreover, the initial BP responses to weight loss are likely enhanced by negative caloric balance with a diminished longer-term BP response, despite successful, isocaloric maintenance of weight loss. Moreover, the complex physiological adaptations to weight loss foster weight regain as more calories are desired than required and energy expenditure falls. Sustained weight loss generally requires a long-term commitment to physical activity and a high level of vigilance. High protein, low glycemic, high-fiber diets, reduced energy density diets may also be beneficial in reducing hunger and increasing satiety. Patients who are counseled to lose weight should be aware of the challenges in maintaining weight loss, understand the potential loss of some BP benefits with isocaloric weight maintenance or weight regain, and be committed to an evidence-based plan to foster long-term success. Future research directed at blocking or ameliorating the disproportionately large reductions of anorexigenic hormones and decreases in energy expenditure that accompany weight loss would help sustain the beneficial effects of weight loss on BP.

References

1. Preble WE. Obesity: Observations on one thousand cases. Boston Med Surg J 1923;188:617-21.
2. Brozek J, Chapman CB, Keys A. Drastic food restriction: Effects on cardiovascular dynamics in normotensive and hypertensive conditions. JAMA 1948;137:1569-74.
3. Shirer WL. The rise and fall of the third Reich. In: The turn of Russia. Barbarossa: Simon and Schuster Publication; 1960. p. 793-852.
4. Horvath K, Jeitler K, Siering U, Stich AK, Skipka G, Gratzer TW, *et al*. Long-term effects of weight-reducing interventions in hypertensive patients. Arch Intern Med 2008;168:571-80.
5. Aucott L, Rothnie H, McIntyre L, Thapa, M, Waweru C, Gray D. Long-term weight loss from lifestyle intervention benefits blood pressure? A systematic review. Hypertension 2009;54:756-62.
6. Semlitsch T, Jeitler K, Berghold A, Horvath K, Posch N, Poggenburg S, *et al*. Long-term effects of weight-reducing diets in people with hypertension. Cochrane Database Syst Rev 2016;3:CD008274.
7. Mark AL. Weight reduction for treatment of obesity-associated hypertension: Nuances and challenges. Curr Hypertens Rep 2007;9:368-72.
8. Fantin F, Giani A, Zoico E, Rossi AP, Mazzali G, Zamboni M. Weight loss and hypertension in obese subjects. Nutrients 2019;11:1667.
9. Stevens VJ, Obarzanek E, Cook NR, Appel LJ, Smith D, Milas NC, *et al*. Long-term weight loss and changes in blood pressure: Results of the trials of hypertension prevention, phase II. Ann Intern Med 2001;134:1-11.
10. Kraschnewski JL, Boan J, Esposita J, Sherwood NE, Lehman EB, Kephart DK, *et al*. Long-term weight loss maintenance in the United States. Int J Obes 2010;34:1644-54.
11. Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettiner WH, Kostis JB, *et al*. Sodium reduction and weight loss in the treatment of hypertension in older persons: A randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). JAMA 1998;279:839-46.
12. Witham MD, Avenell A. Interventions to achieve long-term weight loss in obese older people: A systematic review and meta-analysis. Age Ageing 2010;39:176-84.
13. Montani JP, Schulz Y, Dulloo AG. Dieting and weight cycling as risk factors for cardiometabolic diseases: Who is really at risk? Obes Rev 2015;16 Suppl 1:7-19.
14. Kruseman M, Schmutz N, Carrard I. Long-term weight maintenance strategies are experienced as a burden by persons who have lost weight compared to persons with a lifetime of normal, stable weight. Obes Facts 2017;10:373-85.
15. Melby CL, Paris HL, Foright RM, Peth J. Attenuating the biologic drive for weight regain following weight loss: Must what goes down always go back up? Nutrients 2017;9:468.
16. Fothergill E, Guo J, Kerns JC, Knuth ND, Brychta R, Chen KY, *et al*. Persistent metabolic adaptation 6 years after "the biggest loser" competition. Obesity 2016;24:1612-9.
17. Catenacci VA, Ostendorf DM, Pan Z, Bing K, Wayland LT, Seyoum E, *et al*. The impact of timing of exercise initiation on weight loss: An 18-month randomized clinical trial. Obesity 2019;27:1828-38.
18. Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr 2005;82:222S-5.
19. Laaksonen DE, Laitinen T, Schönberg J, Rissanen A, Niskanen LK. Weight loss and weight maintenance, ambulatory blood pressure and cardiac autonomic tone in obese persons with metabolic syndrome. J Hypertension 2003;21:371-8.
20. Straznicky NE, Grima MT, Eikelis N, Nestel PJ, Dawood T, Schlaich JP, *et al*. The effect of weight loss versus weight loss maintenance on sympathetic nervous system activity and metabolic syndrome components. J Clin Endocrinol Metab 2011;96:E503-8.
21. Field AE, Byers T, Hunter DJ, Laird NM, Manson JE, Williams DF, *et al*. Weight cycling, weight gain, and risk of hypertension in women. Am J Epidemiol 1999;150:573-9.
22. Schulz M, Liese AD, Boeing H, Cunningham JE, Moore CG,

Kroke A. Associations of short-term weight changes and weight cycling with incidence of essential hypertension in the EPIC-potsdam study. J Human Hypertens 2005;19:61-7.
23. Vergnaud AC, Bertrais S, Oppert JM, Maillard-Teyssier L, Galan P, Hercberg S, *et al*. Weight fluctuations and risk for metabolic syndrome. Int J Obes 2008;32:315-21.
24. Zhang H, Tamakoshi K, Yatsuya H, Murata C, Wada K, Otsuka R, *et al*. Long-term body weight fluctuation is associated with metabolic syndrome independent of current body mass index among Japanese men. Circ J 2005;69:13-8.
25. Graci S, Izzo G, Savino S, Cattani L, Lezzi G, Berselli ME, *et al*. Weight cycling and cardiovascular risk factors in obesity. Int J Obes 2004;28:65-71.

How to cite this article: Egan BM, Sutherland S, Hall ME. Limited Long-Term Efficacy of Lifestyle-Mediated Weight Loss on Blood Pressure Control the Biology of Weight Regain. Hypertens 2021;7(1):14-20.

Source of support: Nil, **Conflicts of interest:** None

INDIAN SOCIETY OF HYPERTENSION
World Hypertension League
CURRENT MEDICAL CONCEPTS
HTNJ
CrossMark

Review Article

Validating Prediction Models for use in Clinical Practice: Concept, Steps, and Procedures Focusing on Hypertension Risk Prediction

Mohammad Z. I. Chowdhury[1], Tanvir C. Turin[1,2]

[1]Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Canada, [2]Department of Family Medicine, Cumming School of Medicine, University of Calgary, Calgary, Canada

Abstract

Prediction models are extensively used in numerous areas including clinical settings where a prediction model helps to detect or screen high-risk subjects for early interventions to prevent an adverse outcome, assist in medical decision-making to help both doctors and patients to make an informed choice regarding the treatment, and assist in health-care services with planning and quality management. There are two main components of prediction modeling: model development and model validation. Once a model is developed using an appropriate modeling strategy, its utility is assessed through model validation. Model validation provides a true test of a model's predictive ability when the model is applied on an independent dataset. A model may show outstanding predictive accuracy in a dataset that was used to develop the model, but its predictive accuracy may decline radically when applied to a different dataset. In the era of precision health where disease prevention through early detection is highly encouraged, accurate prediction of a validated model has become even more important for successful screening. Different clinical practice guidelines also recommend incorporating only those prediction models in clinical practice that has demonstrated good predictive accuracy in multiple validation studies. Our purpose is to introduce the readers with the basic concept of model validation and illustrates the fundamental steps and procedures that are necessary to implement model validation.

Key words: External validation, internal validation, model validation, Prediction model

Introduction

Prediction models also known as clinical prediction models are mathematical formula or equation that expresses the relationship between multiple variables and helps predict the future of an outcome using specific values of certain variables. Prediction models are extensively used in numerous areas including clinical settings and their application is large.[1] In clinical application, a prediction model helps to detect or screen high-risk subjects for asymptomatic disease for early interventions, predict a future disease to facilitate patient-doctor communication based on more objective information, assist in medical decision-making to help both doctors and patients to make an informed choice regarding the treatment, and assist in health-care services with planning and quality management.[1,2] For example, there exist many prediction models for calculating the risk of developing hypertension in the future.[3-5]

While specific details may vary between prediction models, the goal and process of developing prediction models are mostly similar. Conventionally, a single prediction model is built from a dataset of individuals in whom the outcomes are known and then the developed model is applied to predict outcomes for future individuals. There are two main components of prediction modeling: model development and model validation. Once a model is developed using an appropriate modeling strategy, its utility is assessed through model validation. Investigators want to see through validation how the developed model works in a dataset that was not used to develop the model to ensure that the model's performance is adequate for the intended purpose.

Address for correspondence:
Tanvir C Turin, Department of Family Medicine, Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta, T2N 4N1. Canada. Phone: +1-403-210-7199. Fax: +1-403-270-4329.
E-mail: turin.chowdhury@ucalgary.ca

Received 18-12-2020; Accepted 02-01-2021
doi: 10.15713/ins.johtn.0221

Innovative Nature Science Publishers

Model validation provides a true test of a model's predictive ability when the model is applied on an independent dataset. A model may show outstanding predictive accuracy in a dataset that was used to develop the model, but its predictive accuracy may decline radically when applied to a different dataset. In the era of precision health where disease prevention through early detection by monitoring health and disease based on an individual's risk is highly encouraged, accurate prediction in model validation has become even more important for successful screening.

There are numerous clinical prediction models available to serve different purposes, however, only a few found their application in clinical practice. One reason for that is the lack of their validation, particularly external validation. External validity establishes the generalizability of a prediction model. In general, the accuracy of a prediction model degrades from the sample in which the model was first developed to subsequent application. For a prediction model to be generalizable, the accuracy of the model needs to be both reproducible and transportable. A prediction model that cannot predict outcomes accurately in a new sample is useless. Clinicians did not find confidence and trust to use prediction models in their practice that is not well validated. Despite its importance being recognized, external validation of prediction models is not common, which has largely contributed to the failure to translate prediction models into clinical practice. Different clinical practice guidelines recommend incorporating only those prediction models in clinical practice that has demonstrated good predictive accuracy in multiple validation studies.

Model validation involves different aspects and our objective is to discuss those aspects in this paper with a particular focus on cases where hypertension prediction models were validated and to provide the readers with a basic understanding and importance of the topic. The concept of model validation is statistical. However, we tried to present a non-technical discussion of the topic in plain language. The information provided in this paper can be helpful for anyone who wishes to be better informed of model validation, have more meaningful conversations with data analysts about their project or apply the right model validation technique given that they have advanced training in statistics. We have arranged our discussion as follows. We begin the discussion with defining model validation. Then we have outlined the major steps one needs to follow in model validation. Within the model validation steps, we discussed different ways of model validation together with their strengths and limitations which we named "model validation procedures" and how to assess the performance of a validated model, which we named "model performance assessment." Within each step, we discuss cases where hypertension prediction models were validated.

Methods

The concept of model validation

Model validation is the process of demonstration that the model can reproduce its performance with reasonable accuracy to a different population or setting that was not used to develop the model. The purpose of model validation is to demonstrate that the model is accurate for the intended population (dataset) for whom the model was developed and performs well in other populations (datasets) which were not used to develop the model.

Preferably, a model should be evaluated on samples that were not used to develop the model so that a model's effectiveness can be assessed unbiasedly. However, often models are developed in one part of the sample and evaluated in the other part of the sample or the same sample is used through resampling to develop and evaluate the model. Although this kind of model evaluation belongs to model validation formally known as internal validation, this does not guarantee that the model will perform well in a different dataset from a different population. Evaluation of a model's performance in an entirely different population is formally known as external validation and is always advised to establish the generalizability of the model. Within model validation, there are different types each with its advantages and disadvantages. Once a model is validated to a different sample or population, its performance needs to be assessed. There are also different ways to assess the performance of a model. We discuss the types of model validation and how to assess the performance of a validated model within the model validation steps.

Steps of model validation

To validate a prediction model investigator need to follow a few basic steps. We broadly classify the steps of model validation into two main categories [Figure 1]:

1. Apply originally developed model into a different dataset that was not used to develop the model which we will call "model validation procedures"
2. Asses the performance of the model in the new dataset which we will call "model performance assessment"

Model validation procedures

A model can be validated either internally using the same data or data source or externally using new data from a different data source. It is important to separate these two types of validation.[6]

Internal validation

"Internal validation assesses validity for the setting where the development data originated from."[7] Internal validity is also called "reproducibility" which means the ability to produce accurate predictions among individuals not included in the development of the model but from the same population.[8] In internal validation, generally, the dataset is divided into two categories. One category is called the "training" dataset, which is used to create the model, while the other category is called the "test" or "validation" dataset, which is used to assess the model performance. Internal validation can be performed in different ways. We discuss here some of the major internal validation procedures.

Validation of clinical prediction models

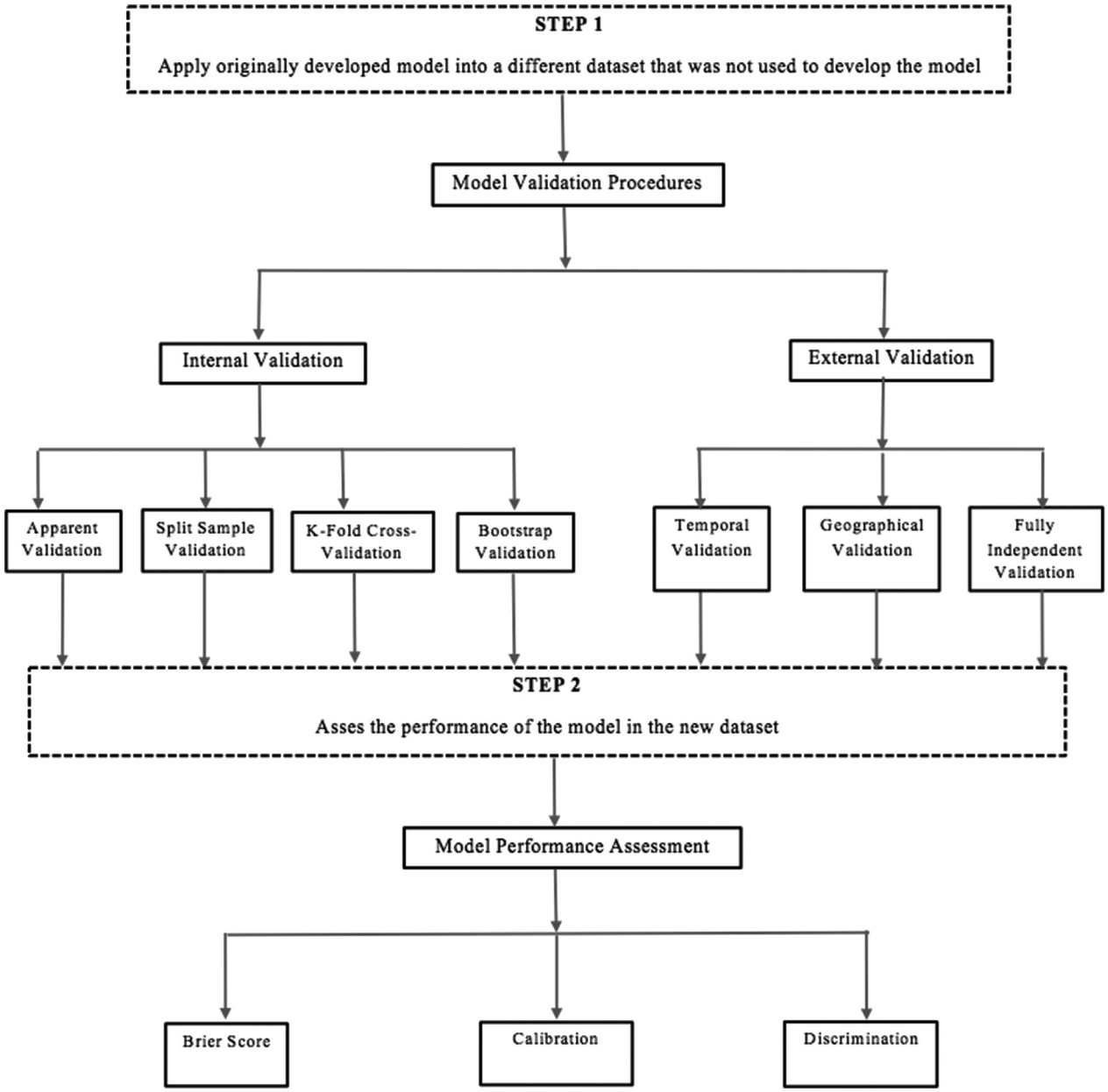


Figure 1: Model validation steps

Apparent validation

In apparent validation, the model is validated in the same sample where the model was developed; as a result, it provides an optimistic performance of the model. This leads to a biased assessment of the model's performance as the same 100% of data are used both to build the model and to test the model.[7]

Split-sample validation

Split-sample validation consists of dividing the sample into two parts, with model development in one part of the sample while assessing model performance in the other part of the sample. The splitting is done at random and typical splitting's 1/2:1/2 or 2/3:1/3. For example, if 1/2:1/2 split sample is used then the model is developed in 50% of the data and the model is evaluated in the other 50% of the data.

Split-sample is an old classical approach of model validation with several limitations.[7] As splitting is done fully at random there could be an imbalance concerning the distribution of predictors and outcome in the sample.[7] Randomly splitting the data does not guarantee that the divided data are representative of the target population. This problem is serious with small samples and a predictor with rare events.[7] One way to overcome this issue is to stratify the sampling by the outcome and relevant predictors.[7] Another issue with the

split-sample method is, it provides less stable results as only part of the data is used to model development. Besides, small validation data provide an unreliable assessment of model performance that can be even biased because we want to know the model's performance in the full dataset, but the assessment was performed only in a part.[7]

Due to its several drawbacks, split-sample validation is often treated as an inefficient approach of model validation. The performance of this procedure is reasonable when the sample size is large according to some simulation studies.[7] However, it is suggested to use other efficient model validation procedures to get reliable results.

K-fold cross-validation

"K-fold cross-validation" [Figure 2] and "bootstrapping" [Figure 3] are two popular methods that improve on the split-sample method and produce better results in terms of bias and variability. K-fold cross-validation and bootstrapping are also better in situations where the sample size is small and when external validation is not readily available.

	Original Sample				
Iteration	**1**	**2**	**3**	**4**	**5**
Iteration 1	Validate	Train	Train	Train	Train
Iteration 2	Train	Validate	Train	Train	Train
Iteration 3	Train	Train	Validate	Train	Train
Iteration 4	Train	Train	Train	Validate	Train
Iteration 5	Train	Train	Train	Train	Validate

Figure 2: 5-Fold cross-validation

Cross-validation is a resampling procedure primarily used to evaluate the performance of prediction models on unseen data set, particularly, when the dataset is small. The purpose is to see how the model performs in general when used to predict data that were not used to develop the model. K-fold cross-validation contains only one parameter "k" that refers to the number of groups (folds) that a given dataset is to be split into. If a specific value for "k" is chosen, such as k = 10, then accordingly, the procedure is called ten-fold cross-validation.

In k-fold cross-validation, each observation in the dataset is allotted to a specific subsample and remains in that subsample for the entire duration of the procedure. K-fold cross-validation starts with randomly partitioning the original sample into k roughly equal size subsamples. Then, only one subsample out of this k subsamples is kept as the validation data to test the model, and the remaining k-1 subsamples are utilized as training data to derive the model. A total of k times (the folds) this process is replicated, with each of the k subsamples used only once as the validation data. Finally, the results from the k-fold cross-validation run are summarized and a single estimate is produced by averaging (or otherwise combining) the k results from the folds.

Choosing an appropriate value for K is important to avoid misrepresentation of the performance of the model.[9] While choosing the value of k, we need to be careful that each

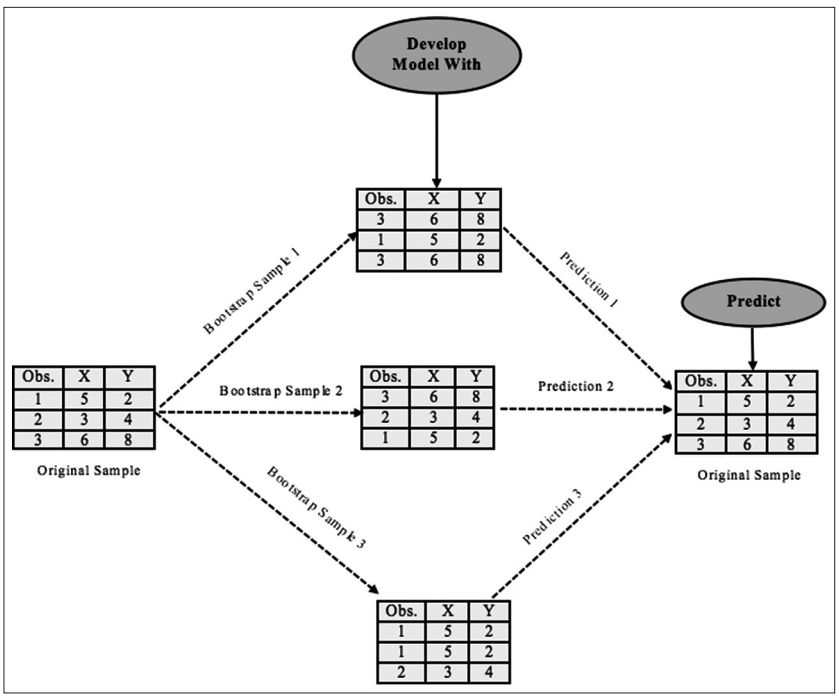


Figure 3: A graphical illustration of the bootstrap process on a hypothetical small sample containing $n = 3$ observations on two variables X and Y. Three bootstrap samples containing $n = 3$ observations drawn with replacement from the original data set. Finally, each bootstrap sample is used to obtain the prediction

Validation of clinical prediction models

subsample (particularly validation set) of data is large enough to reasonably represent the whole data set. More splits will reduce the size of the validation set and we will not have sufficient sample in the validation set to fairly and confidently evaluate model performance.[9] On the other hand, too few splits will not provide enough trained models to evaluate.[9] Furthermore, a higher k value is associated with less bias (the difference between the estimated and true values of performance) but more variability (performance of the model may change according to the data set used to fit the model) and computation. On the other hand, a lower k value is associated with more bias but less variability and computation. Although there is no formal rule, usually k is chosen between 5 or 10^4. Often K = 5 or 10 provides a good compromise for this bias-variance tradeoff.[9]

One disadvantage of k-fold cross-validation is its high variance, which makes it less attractive.[9] However, with a large training set with multiple repetitions of the whole k-fold validation-process (e.g., 50 times 10-fold cross-validation) provides true stable results that effectively increase the precision of the model estimates while still maintaining a small bias.[7] K-fold cross-validation has the big advantage that all observations are utilized for both derive and validate the model, with each observation is used only once for validation. As a result, this process has less chance to succumb to a biased division of the data.

Leave-one-out cross-validation (LOOCV)

This is another version of k-fold cross validation where k = n, the number of data points. In this method, each time, only one data-point in the original dataset is held-out for model validation while the remaining data points are used to build the model. As a result, this process runs as many times as the number of data-points in the sample. This method provides negligible bias as the almost entire dataset is used for building the model, which is its advantage. However, this method has the major disadvantage that only one data point is used for validating the model every time, resulting in a high variance in the estimates of the model's performance, particularly when multiple outliers in the dataset. In addition, this method is computationally very intensive, particularly when the dataset is large.[9]

Bootstrap validation

The bootstrap method is a resampling technique often used to estimate statistics on a population as well as validate a model by sampling a dataset with replacement. The bootstrap method allows us to use a computer to mimic the process of obtaining new datasets so that the variability of the estimates can be assessed without creating additional samples. Instead of repeatedly obtaining independent dataset from the population, which is often not realistic, in bootstrapping, distinct datasets are obtained by repeatedly doing sampling from the original dataset with replacement. The idea behind bootstrapping is the original observed data will take the place of the population of interest, and each bootstrap sample will represent a sample from that population.

Bootstrap samples are of the same size as the original sample and drawn randomly with replacement from the original sample. In a with replacement sampling, after a data point (observation) is selected for the subsample, it is still available for further selection. As a result, some observations represented multiple times in the bootstrap sample while others may not be selected at all. Because of such overlaps with original data, on average almost two-thirds of the original data points appear in each bootstrap sample.[9] The samples that are not included in a bootstrap sample are called "out-of-bag" samples. When performing the bootstrap, two things must be specified: the size of the sample and the number of repetitions of the procedure to perform. A common practice is to use a sample size that is equivalent to the original dataset and a large number of repetitions (50–200) to get a stable performance.[7,9]

In the bootstrap method, a prediction model is developed in each bootstrap sample and measures of predictive ability such as C-statistic are estimated in each bootstrap sample. Then, these models from bootstrap data are applied to the original dataset to evaluate the model and estimate the predictive measure (C-statistic) of these bootstrap models in the original data. The difference in performance in the predictive measure indicates optimism, which is estimated by averaging out all the differences in predictive measures. Finally, this estimate of optimism is subtracted from the performance of the original prediction model developed in the original data to get an optimism-adjusted measure of the predictive ability of the model.[7]

Bootstrap samples have significant overlap with the original data (roughly two-third) which causes the method to underestimate the true estimate. This is considered a disadvantage of this method. However, this issue can be solved by performing prediction on only those observations that were not selected by the bootstrap and estimating model performance. Bootstrapping is more complex to analyze and interpret due to the methods used and the amount of computation required. However, this method provides stable results (less variance) than other methods with a large number of repetitions.

It is obvious that each of the internal model validation techniques has advantages and disadvantages and no one method is uniformly better than another.[9] Researchers have a different opinion on choosing the appropriate method for internal model validation. Several factors such as sample size, finding the best indicators of a model's performance, and choosing between models were asked to consider before making the choice.[9]

The above-mentioned procedures for model validation pertain to internal validation, which does not examine the generalizability of the model. To ensure generalizability, it is necessary to use new data not used in the development process, collected from an appropriate (representative) patient population but using a different set of data. We now present how these internal model validation procedures are applied in a few existing hypertension prediction models.

Case Studies

The Framingham Hypertension Risk Score (FHRS) developed by Parikh *et al.*[3] is a hypertension risk prediction model developed using data from the US Framingham Offspring Study. The purpose of the model was to identify the persons who are at the highest risk for hypertension and to provide the probability of developing hypertension over 1–4 years. The model was developed using a sample of sizes 1717 with risk factors age, sex, systolic and diastolic blood pressure, body mass index, parental hypertension, and cigarette smoking. The model was internally validated using a bootstrap method where the same data were used in both developing and evaluating the model. Lim *et al.*[4] developed the Korean Genome and Epidemiology Study (KoGES) model for predicting hypertension incidence using Korean data. The model was internally validated using a split-sample method with a 6:4 ratio where 60% of the data were used to develop the model and the remaining 40% data were used for model validation. Chien *et al.*[5] developed a prediction model for hypertension risk in a Chinese population. Both clinical and biochemical model was derived using data from 2506 individuals. They internally validated their model using a five-fold cross-validation procedure to assess model performance.

External validation

The reliability and acceptability of a prediction model largely depend on how well it performs in a validation cohort, outside of the derivation cohort where the model was developed. Internal validation of prediction models is often not sufficient for generalizability, and external validation is necessary before implementing prediction models in clinical practice. External validation of models is often considered essential to support the general applicability of a prediction model as it addresses transportability.[6,7] Transportability requires the model to perform accurately in predicting data drawn from a different but plausibly related population or in data collected using a little different method than those used in the development sample.[8] External validation requires data collected from a similar group of patients in a different setting and aims to address the accuracy and performance of a prediction model in a different patient population. These data (sample) are fully independent of the development data and originate from different but similar patients. The generalizability of a model becomes stronger when the model is externally validated multiple times and in a more diverse setting.[7] This is the reason perhaps why the Framingham Risk Score for cardiovascular disease[10] is so widely used in the clinical setting as the model was externally validated many times with many different settings.

Most studies evaluating prediction models focus on the issue of internal validity as opposed to the important issue of external validity. Internal validation does not guarantee generalizability, and thus external validation is necessary before implementing prediction models into clinical practice.

External validation can be assessed in different ways:

1. Temporal validation (validation in more recent individuals)
2. Geographical validation (validation in other places)
3. Fully independent validation/strong external validation (by other investigators at other sites).

Temporal validation

In temporal validation, the model is typically validated in more recent individuals. The purpose of such validation is to make sure that the model maintains its accuracy when it is tested in cohorts in different periods. A model developed way back (say 20 years ago) may not work in current patients (e.g., change in risk factor distribution and availability of large dataset on many risk factors). Temporal validation can be easily achieved just splitting the data into two parts. Develop the model in one part that contains early treated patients and validate the model to assess its performance in another part that contains patients that are more recent.[7] Temporal validation can also be achieved through the prospective application of the developed model in the specifically collected cohort.[7] For example, a model can be developed in a group of patients between 2005 and 2010 and the same model can be validated in a different group of patients from the same cohort between 2012 and 2015.

Geographic validation

In geographic validation, the model is validated in a different location that was not used to develop the model. The purpose of geographic validation is to confirm that the model remains accurate when it is tested in data from other locations. Although it may be questioned, whether a model developed in another location will work in a new location that is completely different. Geographical validation can be achieved by applying and assessing the performance of a developed model to a different site within the same region or a different cohort from a different region. For example, a model developed in the USA for predicting hypertension can be validated in a similar Canadian cohort.

Fully independent validation

In fully independent validation, model validation is performed in data collected by independent investigators, usually at a different location. In general, the validation sample is drawn from a different time. It is important to establish that the model is equally accurate when applied by independent investigators, as they are unlikely to study identically selected patients and data collecting tools.[8] Furthermore, the definition of predictors and outcomes and study participants selection may be slightly different compared with the development setting in fully independent validation.[7]

Full independent validation often shows poor results (more unfavorable) than temporal or geographical validation. There

Validation of clinical prediction models

could be several reasons for that. Some of those reasons are related to the original model's development issues such as inadequate model development strategy, small sample size, and suboptimal statistical analysis. It also happens frequently that not all the variables used to build the original model may be available at validation data, which eventually affects the model's performance in validation data. In addition, a true difference between development and validation samples may cause poor validation results. Fully independent external validation of a model is often more difficult than anticipated. However, if a model can demonstrate adequate performance in a fully independent validation in a different setting, then the results of this model's performance are more authentic, acceptable, and generalizable.

To justify the generalizability of the prediction models external validation is inherent; however, only a few models being externally validated. We discuss below a few cases where hypertension prediction models were externally validated.

Case Studies

The FHRS of Parikh *et al*.[3] was externally validated in a European cohort by Kivimaki *et al*.,[11] in a Chinese cohort by Chien *et al*.,[5] and a Korean cohort by Lim *et al*.[4] These external validations belong to fully independent validation. Although Parikh *et al*.[3] did not perform the external validation of their FHRS model in an independent cohort, the above group of investigators did. Validation of prediction model by an independent group of investigators in an independent cohort is regarded as the strongest of all validation and FHRS showed good discrimination and calibration in those validations.[3] Lim *et al*.[4] externally validated their KoGES model in an independent large nationwide Korean sample cohort and found the good performance of their model in terms of discrimination and calibration. This type of external validation belongs to geographic validation and often used to assess a model's generalizability.

Model Performance Assessment

Once a prediction model is developed then it needs to be validated to see or quantify how good the predictions from the models are, often referred to as model performance. There are different methods and metrics to assess the performance of a prediction model. These methods and metrics depend on the type of modeling technique used in model developing which again largely depends on the outcome of interest. We will restrict our discussion of model performance assessment for binary or survival outcomes, common in health research. For binary and survival outcomes, the most commonly used measures include the Brier score to indicate overall model performance, the concordance statistic (also known as the C-statistic) for discriminative ability, and goodness-of-fit statistics for calibration.

Brier Score

The model's overall performance is quantified by considering the distance between the actual outcome and the predicted outcome with better models has smaller distances.[12] The Brier score is used to calculate the model's overall performance and is measured by calculating the squared differences between actual binary outcomes and predictions calculated by the model. The range of values that the Brier score of a model can take lies between 0 and 0.25 with 0 indicating a perfect model and 0.25 indicating a non-informative model with only a 50% incidence of the outcome.[7,12] Brier score for survival outcome is not possible to calculate directly because of censoring. However, it is possible to calculate it indirectly defining a weight function that considers the conditional probability of being uncensored during the time. One disadvantage of the Brier score is that its interpretation depends on the incidence of the outcome with lower (higher) incidence corresponds to the lower (higher) Brier score.[7]

Discrimination

The discrimination is defined as the model's ability to distinguish between participants who do or do not experience the event of interest (e.g., disease outcome such as hypertension). A good prediction model can accurately discriminate between those with and without the outcome.[12] C-statistic, which is equal to the area under the receiver operating characteristic (ROC) curve for binary outcomes, is commonly employed to assess discrimination. ROC curve plots the sensitivity against (1 – specificity) for consecutive cutoffs for the probability of an outcome. The value of C-statistic (area under ROC curve) points out to the probability that a randomly selected subject who experienced the outcome will have a higher predicted probability of having the outcome occur compared to a randomly selected subject who did not experience the event. The C-statistic can range from 0.5 to 1, with higher values indicating better predictive models. A C-statistic of 0.5 indicates that the model's performance in predicting an outcome is no better than the random chance while a C-statistics of 1 indicates the model perfectly distinguishes those who will experience a certain outcome and those who will not. In general, a model with a C-statistic ranging from 0.70 to 0.80 is considered adequate, while a range of 0.80–0.90 is considered excellent.[13]

For survival data, an extension of C-statistic called Harrell's C-statistic is suggested which indicates the proportion of all pairs of subjects who can be ordered such that the subject who survived longer will have the higher predicted survival time than the subjects who survived shorter, assuming that these subject pairs are selected at random. Although C-statistic is insensitive to outcome incidence, one disadvantage of C-statistic is, its interpretation is based on an artificial situation assumption

that we have a pair of patients, one with and one without the outcome.

Calibration

The agreement between observed outcomes and predictions made by the model is referred to as calibration.[6] Model calibration measures the validity of the predictions and determines whether the predictions based on the risk prediction model align with what is observed within the study cohort. For example, if we predict a 20% risk that a person will develop hypertension, the observed frequency of hypertension should be 20 out of 100 people with such a prediction. Calibration plot is a method that visually inspects calibration and presents plot for predicted against observed probabilities. It also uses the Hosmer-Lemeshow test to assess calibration. In a calibration plot, predictions are plotted on the X-axis and the observed outcome on the Y-axis. In the Y-axis, the plot contains only 0 and 1 values for binary outcomes. Different smoothing techniques (e.g., the loess algorithm) can be employed to estimate the observed probabilities of the outcome for the predicted probabilities. Perfect predictions should be on the 45° line suggesting that predicted risks are correct. An alternative assessment of calibration is to categorize predicted risk into groups (e.g., deciles) and assess whether the event rate corresponds to the average predicted risk in each risk group. The Hosmer-Lemeshow goodness-of-fit-test makes the plot of a graphical illustration to assess whether the observed event rates match expected event rates in subgroups of the model population.

For survival data, the calibration is usually assessed at fixed time points.[7] Within each time point, survival rates are calculated by the Kaplan–Meier method for a group of patients. Then this observed survival is compared with the mean predicted survival from the prediction model.[7]

Besides the above-mentioned major measures of model assessment, there are other measures occasionally used to assess a model. Although calibration and discrimination are considered the most important aspects to assess a model, they did not provide any assessment regarding the clinical usefulness of a model. Clinical usefulness assessment helps to understand the ability of a model to make better decisions compared to a situation when the model was not used. The measures associated with clinical usefulness are generally related to a cutoff, a decision threshold of the model, which classify peoples into low- and high-risk groups balancing the likelihood of benefit and likelihood of harm. Net benefit is one such measure that can be used to assess the clinical usefulness of a model.[14]

Case Studies

Assessing model performance is an imperative step and almost all models do so. Discrimination through C-statistic/Area under the ROC curve (AUC) and calibration through the Hosmer-Lemeshow Chi-square test are the most common measures to assess a models performance. C-statistic/AUC was 0.788 for FHRS,[3] 0.791 for KoGES,[4] and 0.732 for the model by Chien *et al*.[5] when the models were internally validated. Discrimination was good in all of these models. Hosmer-Lemeshow Chi-square statistic was 4.35 for FHRS (p-value = 0.88),[3] 4.17 ($P = 0.84$) for KoGES,[4] and 8.3 ($P = 0.40$) for model by Chien *et al*.[5] All of the models were well-calibrated during validation.

Conclusion

Validation of a prediction model is extremely important as it provides model applicability in different populations. The model's internal validation is quite common. However, to make a model generalizable and applicable in clinical practice, the model must need to be externally validated. Models that are externally validated multiple times with sufficient good performance are reliable and often recommended in clinical guidelines for implementation. Although, there are many prediction models only a few with external validations. We suggest investigators focus not only on just prediction model development but also on external validation of their developed model.

References

1. Chowdhury MZ, Turin TC. Variable selection strategies and its importance in clinical prediction modelling. Fam Med Community Health 2020;8:e000262.
2. Chowdhury MZ, Turin TC. Precision health through prediction modelling: Factors to consider before implementing a prediction model in clinical practice. J Prim Health Care 2020;12:3-9.
3. Parikh NI, Pencina MJ, Wang TJ, Benjamin EJ, Lanier KJ, Levy D, *et al*. A risk score for predicting near-term incidence of hypertension: The Framingham heart study. Ann Intern Med 2008;148:102-10.
4. Lim NK, Son KH, Lee KS, Park HY, Cho MC. Predicting the risk of incident hypertension in a Korean middle-aged population: Korean genome and epidemiology study. J Clin Hypertens 2013;15:344-9.
5. Chien KL, Hsu HC, Su TC, Chang WT, Sung FC, Chen MF, *et al*. Prediction models for the risk of new-onset hypertension in ethnic Chinese in Taiwan. J Hum Hypertens 2011;25:294-303.
6. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: Seven steps for development and an ABCD for validation. Eur Heart J 2014;35:1925-31.
7. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. Berlin, Heidelberg: Springer Science and Business Media; 2008.
8. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. Ann Intern Med 1999;130:515-24.
9. Kuhn M, Johnson K. Applied Predictive Modeling. New York: Springer; 2013.
10. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, *et al*. General cardiovascular risk profile for use in primary care. Circulation 2008;117:743-53.
11. Kivimaki M, Batty GD, Singh-Manoux A, Ferrie JE, Tabak AG, Jokela M, *et al*. Validating the Framingham hypertension risk

Validation of clinical prediction models

score: Results from the Whitehall II study. Hypertension 2009;54:496-501.
12. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, *et al*. Assessing the performance of prediction models: A framework for some traditional and novel measures. Epidemiology (Cambridge, Mass) 2010;21:128.
13. Lee YH, Bang H, Kim DJ. How to establish clinical prediction models. Endocrinol Metab 2016;31:38-44.
14. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. BMJ 2016;352:i6.

How to cite this article: Chowdhury MZI, Turin TC. Validating prediction models for use in clinical practice: concept, steps, and procedures focusing on hypertension risk prediction. Hypertens 2021;7(1):21-29.

Source of support: Nil, **Conflicts of interest:** None

INDIAN SOCIETY OF HYPERTENSION
World Hypertension League
CURRENT MEDICAL CONCEPTS
HTNJ
CrossMark

Review Article

Troponin and B-type Natriuretic Peptides Biomarkers in the Management of Hypertension

Aliza Hussain[1], Matthew Deshotels[1], Preethi V. Nambi[2], Kamna Bansal[2], Hani Jneid[1,3], Vijay Nambi[3]

[1]Department of Medicine, Baylor College of Medicine, Houston, Texas, United States, [2]Department of Family and Community Medicine, Baylor College of Medicine, Houston, Texas, United States, [3]Department of Medicine, Michael E. DeBakey VA Medical Center, Houston, Texas, United States

Abstract

The American Heart Association/American College of Cardiology (AHA/ACC) Guidelines for the management of high blood pressure (BP) recommend intensive BP goals in high-risk individuals. However, intensive BP therapy comes with a higher risk of side effects. It is, therefore, important to identify individuals with higher cardiovascular risk who will in turn derive the greatest absolute benefit from BP reduction. In line with this, both ACC/AHA and European guidelines on the management of hypertension recommend the use of risk assessment using traditional risk factors. The European guidelines also recommend complementing risk estimation using additional markers of hypertension-mediated organ damage. Cardiac biomarkers such as natriuretic peptide and high sensitivity cardiac troponins (hs-cTn) reflect structural and/or functional changes in end organs (i.e., myocardium, vasculature) and have been associated with increased cardiovascular risk. These cardiac biomarkers may supplement risk assessment of patients with elevated BP and help personalize treatment strategies. Both NT-pro B type Natriuretic Peptide (NT-proBNP) and hs-cTn have been shown to predict cardiovascular events across different systolic and diastolic BP categories. Furthermore, observational data suggest that individuals with elevated levels of NT-proBNP and/or high-sensitivity troponin have lower numbers needed to treat to prevent cardiovascular events with intensive BP therapy, with the lowest NNT seen in those with elevated levels of both. While the data related to biomarkers in hypertension are encouraging, future randomized clinical trials are needed to further characterize the clinical utility of biomarker-based evaluation and treatment strategies in patients with hypertension.

Key words: Hypertension, biomarkers, cardiovascular risk assessment, NT-pro B type natriuretic peptide, high sensitivity cardiac troponins

Introduction

Cardiovascular disease (CVD) remains a leading cause of death in the world over.[1] Hypertension is an important risk factor for CVD and its treatment can substantially reduce cardiovascular morbidity and mortality.[2,3] Large observational studies have shown a continuous association between elevated blood pressure (BP) and incident coronary heart disease (CHD), stroke, heart failure (HF), and vascular mortality, with the association noted from BPs above 115/75 mmHg.[4] Meta-analyses of randomized controlled trial (RCTs) including several hundred thousand patients have shown that a 10-mmHg reduction in systolic BP (SBP) or a 5-mmHg reduction in diastolic BP (DBP) is associated with significant reductions of ~20% for all major CV events, 10–15% for all-cause mortality, ~35% for stroke, ~20% for coronary events, and ~40% for HF.[3,5]

In clinical practice, guidelines recommend BP thresholds to simplify the diagnosis of and guide treatment decisions in the management of hypertension. The American Heart Association/American College of Cardiology (AHA/ACC) Guidelines for the Prevention, Detection, Evaluation, and Management of High BP[6] recommend cardiovascular risk assessment in the management of hypertension and advocate for intensive BP control for high-risk adults with BPs >130/80 given clinical trials have shown mixed results for intensive BP therapy. The landmark SBP Intervention Trial (SPRINT) showed that intensive BP lowering in high-risk individuals

Address for correspondence:
Vijay Nambi, Department of Medicine, Michael E. DeBakey VA Medical Center, 6655 Travis St, Ste 320, Houston, Texas 77030, United States. E-mail: vnambi@bcm.edu

Received: 12-05-2021; Accepted: 13-05-2021
doi: 10.15713/ins.johtn.0220

resulted in a significant reduction in combined primary outcomes of myocardial infarction, acute coronary syndrome, stroke, HF events, and cardiovascular mortality compared to routine management over a median follow-up of 3.26 years (5.2% vs. 6.8%, hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.64–0.89). Furthermore, there was reductions see with intensive BP control compared to routine management in the event rates of HF hospitalizations (1.3% vs. 2.1%, $P = 0.002$), cardiovascular mortality (0.8% vs. 1.4%, $P = 0.0005$), and all-cause mortality (3.3% vs. 4.5%, $P = 0.0003$).[7] However, the Heart Outcomes Prevention Evaluation 3 trial, which had individuals with lower risk compared to SPRINT, did not show similar benefit with intensive BP lowering.[8] Moreover, in both these trials, there were increased side effects from intensive therapy, including acute kidney injury, hypotension, and electrolyte abnormalities. For example, in SPRINT, among individuals without chronic kidney disease, 3.8% of participants in the intensive treatment arm versus 1.1% in placebo had a ≥30% decline in Glomerular filtration rate (GFR) to <60 ml/min ($P < 0.001$), while 2.4% versus 1.4% had hypotension ($P = 0.001$), 2.3% versus 1.7% had syncope ($P = 0.05$) and 3.8% versus 2.1% had hyponatremia ($P < 0.001$), respectively[7] [Table 1].

Physiologically, at a certain lower limit of SBP, autoregulation, and perfusion of vital organs may become impaired and result in worsening outcomes. Moreover, lowering SBP is accompanied by lowering of DBP as well which may impair myocardial perfusion which is dependent on diastolic blood flow.[9]

Hence, although there is a consistent relative risk reduction per unit decrease in SBP, the net benefit versus harm has to be considered. Individuals with higher cardiovascular risk will derive greater absolute risk reduction from BP treatment.[10] Therefore, different thresholds of cardiovascular risk have been explored where the benefit-to-harm ratio favors initiation of pharmacotherapy.[11] Hence, based on the available evidence, the 2017 ACC/AHA BP guidelines classified patients into 3 categories based on BP levels and indication for anti-hypertensive therapy. The two categories in which anti-hypertensive therapy was not recommended included: (1) Normal BP (<120/80 mm Hg); and (2) elevated BP (120–129/<80 mm Hg) or low-risk stage 1 hypertension (130–139/80–89 mmHg) (note: Appropriate lifestyle changes should be pursued in these categories). For the others, that is, the third category, anti-hypertensive medications are recommended and include patients with high-risk stage 1 hypertension (130–139/80–89 mmHg) or stage 2 hypertension (≥140/90 mm Hg) [9]. "High-risk stage 1 hypertension" was defined by the presence of any of the following: An estimated 10-year atherosclerotic CVD (ASCVD) risk ≥10% by the pooled cohort equation (PCE), diabetes mellitus, estimated GFR <60 ml/min/1.73 m^2, or age ≥65 years with SBP ≥ 130 mm Hg.

Similarly, the 2018 European Society of Cardiology/European Society of Hypertension Clinical Practice Guidelines for the Management of Arterial Hypertension[12] also recommends the use of risk assessment by the Systematic COronary Risk Evaluation (SCORE) tool which also uses traditional risk factors to evaluate the risk of fatal atherosclerotic events. However, both PCE and SCORE do not include HF among the CV outcomes predicted. Given that HF has the highest hazards among all CV outcomes resulting from HTN and given that HF is projected to becoming the most frequent CVD outcome in the coming decades, consideration of HF risk will be of immense value in the management of HTN.

The European guidelines additionally recommend complementing risk estimation by assessment of hypertension-mediated organ damage (HMOD).[12] Circulating biomarkers and imaging of HMOD including kidney disease (e.g. cystatin, microalbuminuria), arterial stiffening (e.g. carotid-femoral pulse wave velocity), left ventricular hypertrophy (LVH) by electrocardiography or echocardiography, and subclinical atherosclerosis (e.g., ankle-brachial index [ABI], coronary artery calcium score [CACs], carotid plaque/carotid intima-media thickness) may help identify individuals at higher risk and prove helpful in the individualized definition of hypertension and associated risk. However, imaging testing

Table 1: Comparison of incident adverse events among participants in three major intensive blood pressure clinical trials

Adverse event	SPRINT[7]			ACCORD[55]			HOPE-3[8]		
	Intensive therapy (%)	Standard therapy (%)	HR (*P*-value)	Intensive therapy (%)	Standard therapy (%)	p-value	Treatment (%)	Placebo (%)	*P*-value
Hypotension	2.4	1.4	1.67 (0.001)	3.3	1.27	<0.001	3.4	2.0	<0.0001
Syncope	2.3	1.7	1.33 (0.05)	0.5	0.21	0.10	0.1	0.1	0.55
AKI or ARF	4.1	2.5	1.66 (<0.001)	0.2	0.04	0.12	0	0	
Electrolyte abnormalities	3.1	2.3	1.35 (0.02)	0.4	0.04	0.01	0.5	0.3	0.13
Injurious falls	2.2	2.3	0.95 (0.71)				0.4	0.5	0.61
Bradycardia	1.9	1.6	1.19 (0.28)	0.5	0.13	0.02			

SPRINT trial: Intensive therapy: BP target <120 mm Hg. Standard therapy: BP target <140 mm Hg. ACCORD trial: Intensive therapy: BP target <120 mm Hg. Standard therapy: BP target <140 mm Hg. Electrolyte abnormalities were listed as isolated hyperkalemia in the ACCORD trial. HOPE3: Treatment group: Daily fixed-dose combination candesartan 16 mg and hydrochlorothiazide 12.5 mg. Hypotension, syncope, AKI, and electrolyte abnormalities were listed as adverse events leading to permanent discontinuation of study drugs, whereas injuries were reported as reasons for hospitalization. AKI: Acute kidney injury; ARF: Acute renal failure; HR: Hazard ratio

such as CACs, ABI, carotid ultrasound, or echocardiography has limitations when applied to a population due to cost, throughput, and in the case of CACs risk of radiation (albeit minimal). Circulating biomarkers on the other hand may be more convenient as they are in general cheaper and repeatable and hence may prove useful. In this review, we will focus on the role of select circulating biomarkers NT-pro B type natriuretic peptide (NT-proBNP) and high sensitivity cardiac troponins (hs-cTn) and explore their potential role in the management of hypertension.

Natriuretic peptide (NT-proBNP and brain natriuretic peptide [BNP]) and hs-cTn reflect neurohormonal stress, structural, and/or functional changes in end organs (i.e., myocardium, vasculature) from various causes, including hypertension. NT-proBNP and BNP are validated for use in diagnosis and prognostication of HF.[13,14] hs-cTn T and I are routinely used in the diagnosis of acute coronary syndrome.[15,16] Over the last decade, these biomarkers have been shown to have value in the prediction and stratification of risk of future CVD in populations with and without CVD.[17,18] Their role in the risk assessment of patients with elevated BP has recently been explored.[19] They are attractive markers for several reasons; first, they are not included in either SCORE or PCE; second, they have important prognostic significance irrespective of the presence of CVD risk factors and third, these are important predictors of HF, a major cardiovascular outcome of HTN which is not captured in the PCE or SCORE. Hence, the inclusion of these biomarkers in the assessment of cardiovascular risk was explored to identify high-risk patients with hypertension.[20]

High-sensitivity Troponins

The troponin complex regulates contraction in striated muscles and consists of three subunits: troponin C, troponin I, and troponin T. Cardiac troponin I (cTnI) and troponin T (cTnT) have become the standard biomarker for the detection of myocardial injury, diagnosis of acute myocardial infarction, and risk stratification of patients with acute coronary syndrome. Most of the cardiac troponin is present in the contractile apparatus within myocardial cells, with a small fraction (approximately 6-8%) found as a free cytosolic component.[21] While the majority of evidence suggests that cardiac troponin release occurs as a result of irreversible cell death, the release of cytosolic troponin has been reported to occur with ischemia.[22]

New generation hs-cTn assays measure the same protein as traditional troponin assays but allow detection of troponin at concentrations 10–100 times lower than assays currently in clinical use.[23] The term "high-sensitivity" is defined by 2 assay criteria: (1) The total imprecision at the 99th percentile value is ≤10% and (2) measurable concentrations below the 99th percentile are attainable at a concentration value above the assay's limit of detection for at least 50% of healthy individuals.[24] The development of hs-cTn assays has provided the ability to detect subclinical myocardial injury in asymptomatic patients without known ASCVD.[17,18]

Elevations in cardiac troponins have been shown to predict all-cause and cardiovascular mortality and the development of CHD, stroke, and HF in the general population without CVD.[17,18,25-27] Moreover, hs-cTnT has been shown to predict the development of hypertension and be an independent determinant of pre-hypertension.[28-30] In a study of 6516 Atherosclerosis Risk in Communities (ARIC) participants without baseline hypertension or CVD, compared to patient with hs-cTnT <5 ng/L, patients with higher categories of hs-cTnT had a higher risk of developing incident hypertension, with HR 1.16 (95% CI 1.08–1.25) for hs-cTnT 5–8 ng/L, HR 1.29 (95% CI 1.14–1.47) for hs-cTnT 9–13 ng/L, and HR 1.31 (95% CI 1.07–1.61) for hs-cTnT ≥14 ng/L (p-for-trend <0.001) after a median follow-up of 12 years.[29] hs-cTn are associated with greater cardiac structural and functional abnormalities, including LVH in patients with hypertension.[26,30,31] This suggests that elevated baseline hs-cTnT levels can identify patients who are at risk for the development of hypertension and/or LVH and in turn trigger closer monitoring and initiation of prevention strategies.

Hypertension has been shown to cause myocardial injury even in the absence of atherosclerosis.[31] Several analyses from studies, including the ARIC, Cardiovascular Health Study (CHS), and Dallas Health Study, have clearly demonstrated a diagnostic and prognostic role for hs-cTnT as a biomarker of subclinical myocardial damage in hypertensive heart disease.[26,32,33] For example, in 8571 ARIC Study participants without CVD, patients with baseline hypertension had a significant increase in hs-cTnT over a 6-year period with a linear association between increasing baseline SBP and a 6-year increase in hs-cTnT.[32] Similarly, in the CHS among 2219 adults, those with an increase in hs-cTnT over 2–3 years had a higher CVD risk despite either stable SBP (HR: 1.28 [1.04–1.57], $P = 0.02$) or decreased SBP (HR: 1.57 [1.08–2.28], $P = 0.02$) compared to those within the same SBP group but a stable hs-cTnT.[33] Moreover, in both the Jackson Heart Study and Dallas Heart Study, participants with elevations in cardiac troponin and presence of LVH had a significantly higher risk for HF compared to those with LVH but undetectable troponin levels which suggested that troponin identified a malignant phenotype of patients that showed higher risk for progression to HF and CVD death.[34,35]

Elevated hs-cTnT was also shown to be associated with increased risk of CV events across a spectrum of systolic and diastolic categories. In a study of 11,191 ARIC study participants, hs-cTnT was associated with increased adverse CV events (new-onset HF, CHD, and stroke) in each range of SBP in increments of 10 mm Hg.[36] Interestingly, patients with elevated hs-cTnT >14 nl/L and SBP 130–139 mm Hg had a higher risk of incident HF (HR 3.7, 95% CI 2.3–6.1) and CHD (HR 1.7, 95% CI 1.1–2.6) compared to patients with SBP 140–159 mm H and hs-cTnT <3 ng/L. In contrast, participants with low DBPs of 60–69 mmHg and <60 mmHg had higher odds of elevated hs-cTnT (reflecting lower coronary perfusion) and higher incidence of cardiovascular events compared to those with DBP between 80 and 89 mmHg.[37]

These data suggest that for individuals with hypertension, the risk of cardiovascular events may vary at different SBP or DBP level, and biomarkers such as hs-cTnT by identifying myocardial injury can help identify those at higher risk for subsequent cardiovascular events across a wide range of systolic and DBP who would benefit from more aggressive BP management.

Natriuretic Peptides

Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are hormones/peptides secreted by organs including the heart that have a positive physiological role in natriuresis, vasodilation, suppression of hypertrophy and fibrosis, and inhibition of the renin-angiotensin-aldosterone system.[38,39] Their respective precursor prohormones proANP and proBNP are released from the heart in response to myocardial stretch and other hemodynamic stimuli. These prohormones are then processed to their biologically active forms ANP and BNP, and biologically inactive NT-proBNP. BNP and NT-proBNP have shown sufficient value to be recommended for use by the guidelines for the diagnosis, prognostication, and management of HF.[40,41] As natriuretic peptides reflect vascular re-modeling and volume homeostasis, they may also prove clinically useful in the assessment of an even wider range of CVD outcomes than HF. Correspondingly, NTproBNP has been shown to be strongly associated with increased risk of CHD, stroke, and atrial fibrillation outcomes.[42-44] In a large systematic review and meta-analysis involving 40 studies and 87,474 participants, those in the highest tertile of natriuretic peptides levels (either BNP or NT-proBNP) had a higher risk for CVD (hazard's ratio [HR]: 2.82; 95% CI: 2.4–3.33); CHD (HR: 2.03; 95% CI: 1.54–2.66); stroke (HR: 1.53; 95% CI: 1.58–2.37); and HF (HR 3.45, 95% CI 2.66–4.46) compared to the lowest tertile.[44] Moreover, NT-proBNP has been shown to strongly improve risk prediction of multiple cardiovascular outcomes, including cardiovascular mortality, suggestive that in diverse patient populations with and without CVD, NT-proBNP could be integrated into the risk assessment of CVD in primary prevention.[45-47]

NT-proBNP has been investigated as a biomarker to augment risk prediction in the general population and those with hypertension. In a large study of 70-year-old men ($n = 907$), free of baseline disease, measurement of NT-proBNP, high-sensitivity C-reactive protein, and cystatin C, over a median of 10 years significantly improved the net reclassification (18.7–19.9%; $P < 0.01$) of incident ASCVD events (defined as fatal or nonfatal myocardial infarction or fatal or nonfatal stroke) when added to traditional risk factors which included ambulatory BP.[48] Moreover, NT-proBNP was a strong predictor of mortality in patients with hypertension, independent of and superior to ECG marker of LVH (the Sokolow index and the RaVL amplitude).[49]

In clinical practice, elevated levels of NT-proBNP may be used to identify patients with the greatest risk for CVD, who would, in turn, derive the highest absolute risk reduction from therapies targeting modifiable cardiac risk factors. For example, in the PONTIAC (NT-proBNP Prevention of Cardiac Events in a Population of Diabetic Patients without a History of Cardiac Disease) trial, NT-proBNP levels were used to identify diabetic patients for aggressive up-titration of neurohumoral therapy (renin-angiotensin system-antagonists, ACE-Is or ARBs, and beta-blockers) in 268 patients with diabetes. After 2 years, randomization to the biomarker-guided "intensified" group was associated with a 65% reduction in risk of the primary endpoint (hospitalization or death due to cardiac disease) without major side effects requiring hospitalization.[50] Similarly, in the STOP-HF (St Vincent's Screening to Prevent HF Study) trial of 1374 at-risk patients with cardiovascular risk factors, randomization to BNP screening, and collaborative care (involving echocardiography and specialist cardiovascular service) reduced the combined rates of asymptomatic LV systolic and/or diastolic dysfunction with or without newly diagnosed HF, compared to usual care (odds ratio [OR], 0.55; 95% CI, 0.37–0.82; $P = 0.003$) over a mean follow-up 4.2 years. The intervention group underwent significantly more cardiovascular investigations and received more renin-angiotensin-aldosterone system-modification therapy at follow-up.[51]

NT-proBNP may also have value in individualizing intensification of BP therapy by identifying higher-risk individuals, although this will still need to be tested in RCTs as was done in STOP HF[50] and PONTIAC[51] studies. In a study of 9,309 participants without CVD from the ARIC study, patients with NT-proBNP in 100 to 300 pg/ml, and >300 pg/ml categories, compared to <100 pg/ml, demonstrated a graded increase in the risk of CVD, HF, CV, and all-cause mortality across increasing categories of systolic blood, diastolic blood, and pulse pressure categories over a median follow-up of 16.3 years. Importantly, patients with stage 1 hypertension (SBP 130–149 mmHg) but elevated NT-proBNP (≥100 pg/mL) had a higher risk for CVD events, CV mortality, and all-cause mortality compared to those with stage 2 hypertension (SBP 140–159 mmHg) and NT-proBNP levels <100 pg/mL.[52]

The number needed to treat (NNT) to prevent 1 CVD event over 10 years with BP treatment initiation or intensification (to SBP goal of 120 mm Hg) was calculated for combined SBP and NT-proBNP category and sub-stratified by PCE risk (<10% and ≥10%). Participants with increasing levels of NT-proBNP demonstrated lower NNT across SBP groups and PCE risk. For example, among subjects with SBP 120–139 mmHg and PCE risk <10%, NNT for those with NT-proBNP ≥300 pg/ml versus <100 pg/mL was 21 versus 82 [Table 2]. The results of this study provide more evidence of the interplay between NPs and BP in the prediction of CVD and highlight the importance of measuring NP in addition to BP and pulse pressure ranges in cardiovascular risk assessment in ambulatory patients without CVD.[52]

Table 2: Comparison of incident hazard ratios of cardiovascular events and number needed to treat to prevent 1 cardiovascular event over 10 years (NNT10) across systolic blood pressure ranges and cardiac biomarker levels

Hazard ratios					Number needed to treat				
SBP, mm Hg	hs-cTnT (ng/L)		NT-proBNP (pg/mL)		SBP, mm Hg	NT-proBNP (pg/mL)		hs-cTnT ≥6 (ng/L) and/or NT-proBNP ≥100 (pg/mL)	
	<3	≥14	<100	≥300		<100	>300	no	yes
CVD									
<120			(ref)	3.01	120–139	82	21	85	36
120–129			1.08	2.59	140–159	21	10	49	26
140–149			1.22	3.35					
Heart failure hospitalization									
<120	(ref)	5.4	(ref)	4.89	120–139			300	58
120–129	1.4	5.8	1.12	3.63	140–159			123	44
140–149	1.2	4.3	1.20	5.53					
CHD									
<120	(ref)	1.8	(ref)	2.08					
120–129	1.1	2.5	1.04	1.65					
140–149	1.2	2.1	1.16	2.67					
Stroke									
<120	(ref)	1.1	(ref)	3.90					
120–129	1.2	1.4	1.52	2.84					
140–149	1.0	3.0	1.79	4.55					

Hazard ratio data for both hs-cTnT and NTproBNP and number needed to treat (NNT_{10}) for NT-proBNP alone obtained from ARIC studies.[35,51] NT10 data for the combined biomarkers (Hs-cTnT and/or NT-proBNP) were obtained from the pooled cohort study involving the ARIC study, Dallas Heart Study, and Multiethnic Study of Atherosclerosis.[52] Hazard ratios of each SBP and biomarker category are in comparison to participants with SBP<120 mm Hg and Hs-cTnT <3 ng/L or NT-proBNP<100 pg/ml. NNT_{10} is the number needed to treat to prevent one CVD event when blood pressure is lowered to target systolic blood pressure <120 mmHg where CVD includes CHD, stroke, and heart failure hospitalization. Bolded values are statistically significant (P<0.05). N CHD: Coronary heart disease; CHF: Congestive heart failure; CVD: Cardiovascular disease (composite of CHF, CHD, and stroke)

Combination of Biomarkers

Following the incorporation of ASCVD risk estimation into the ACC/AHA guidelines for the management of hypertension, Pandey *et al*. analyzed the role of cardiac biomarkers (hs-cTnT and NT-proBNP) in association with the BP categories in assessing CV risk.[53] In this cohort study that pooled 12,987 low-risk participants without prevalent CVD from the ARIC study, Dallas Heart Study, and the Multiethnic Study of Atherosclerosis, elevated hs-cTnT and NT-proBNP was observed in 32.3% of participants with elevated BP or stage 1 hypertension (i.e., not recommended for anti-hypertensive medications). Over a follow-up of 10 years, patients with elevated hs-cTnT or NT-proBNP had a substantially higher risk of CV events (nonfatal myocardial infarction, nonfatal stroke, or CV death) compared to those with undetectable hs-cTnT or NT-proBNP (11.0% vs. 4.6%, respectively). Incident HF was also higher among patients with elevated biomarkers compared to those with undetectable levels (4.3% vs. 0.9%). A similar trend of markedly higher CV events and incident HF was seen in patients with high-risk stage 1 hypertension or stage 2 hypertension (excluding those with BP ≥160/100 mm Hg) with elevated biomarkers compared to patients with undetectable levels. These data provide additional key evidence that these biomarkers are able to risk-stratify patients across a spectrum of BP ranges.

In a secondary analysis of the SPRINT, among 9361 patients enrolled, 8828 (94.3%) and 8836 (94.4%) patients had measures of hs-cTnT and NTproBNP at baseline, respectively. Abnormal baseline values of hs-cTnT defined as[3] 14 pg/L and NT-proBNP[3] 125 pg/mL were each associated with a greater risk of death, the composite of death and HF, and the SPRINT primary composite outcome (myocardial infarction, acute coronary syndrome, stroke, congestive HF, or cardiovascular death), with the highest risk seen among those with abnormal levels of both biomarkers. Furthermore, those with the elevated biomarkers achieved the highest absolute risk reduction and corresponding lower NNT with intensive BP therapy for individual HF and mortality outcomes.[54] Hence, a biomarker-based approach using biomarkers such as BNP and troponin may represent an effective strategy to guide intensive BP therapies to lower cardiovascular risk. However, future randomized clinical trials are needed to further characterize the utility of such strategies in selecting patients with hypertension for intensive BP control.

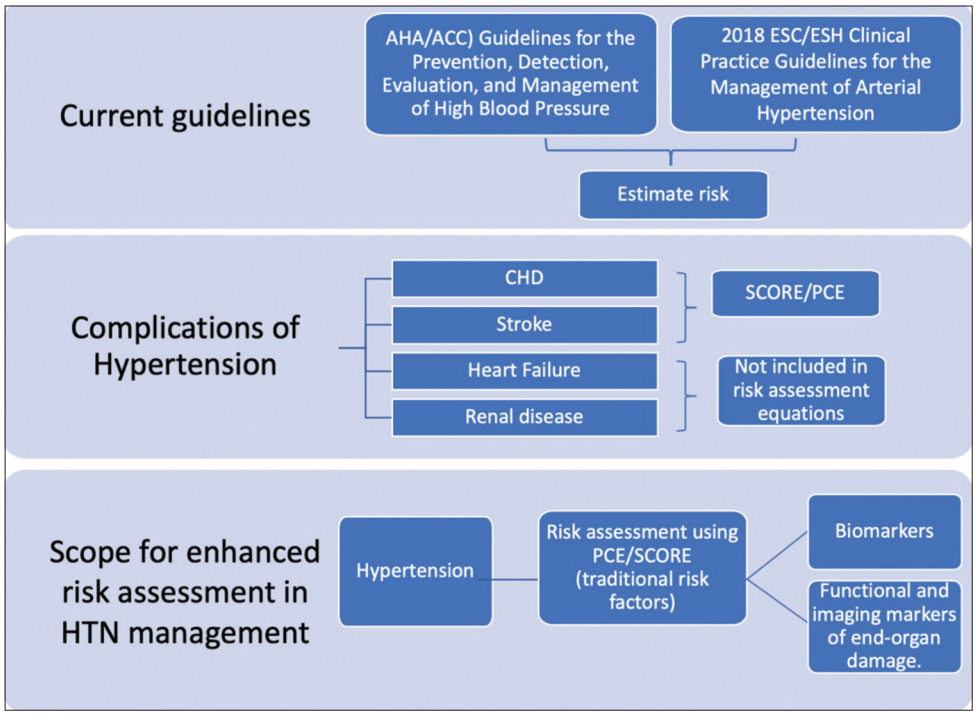


Figure 1: Proposed algorithm for use of cardiac biomarkers NT-pro B type Natriuretic Peptide and high sensitivity cardiac troponins in management of hypertension. The American College of Cardiology/American Heart Association and European guidelines on the management of hypertension recommend the use of risk assessment using pooled cohort equation and Systematic COronary Risk Evaluation based on traditional risk factors. The currently used risk scores do not include the prediction of HF and renal disease which are major end-organ complications of hypertension. Natriuretic peptide and high sensitivity cardiac troponins reflect structural and/or functional changes in end organs (i.e., myocardium, vasculature) and have been associated with increased cardiovascular risk. These cardiac biomarkers may play a complementary role in the risk assessment of patients along with other markers of end-organ damage (e.g., coronary calcium score, ankle-brachial index, echocardiographic or electrocardiogram evidence of left ventricular hypertrophy)

Conclusion

Hypertension remains a major risk factor for CVDs. There is a disconnect between epidemiological levels of BP at which CVD risk increases and BP treatment targets due to several issues, including the risk of intensive treatment. Hence, reserving intensive treatment for individuals at the highest risk has been proposed. However, the currently used risk scores do not include the prediction of HF, a major CVD event. A growing body of evidence has demonstrated that elevated hs-cTnT and NT-proBNP levels are associated with an increased risk for adverse CV events (including HF) across all BP levels and additionally identify lower-risk individuals at higher BP levels as well [Table 2]. While the data related to biomarkers in hypertension are encouraging, the majority of reports are based on observational studies. Future randomized clinical trials are needed to further characterize the clinical utility of biomarker-based evaluation and treatment strategies in patients with hypertension [Figure 1].

References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, *et al.* American heart association council on epidemiology and prevention statistics committee and stroke statistics subcommittee. Heart disease and stroke statistics-2020 update: A report from the American heart association. Circulation 2020;141:e139-596.
2. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, *et al.* Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. Lancet 2016;387:957-67.
3. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, *et al.* Blood pressure and incidence of twelve cardiovascular diseases: Lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. Lancet 2014;383:1899-911.
4. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, *et al.* Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. JAMA 2017;317:165-82.
5. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: A Meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-13.
6. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., 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: Executive summary: A report of the American college of cardiology/American heart association task force on clinical practice guidelines. Hypertension 2018;71:1269-324.
7. SPRINT Research Group, Wright JT Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103-16.
8. Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, *et al*. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2009-20.
9. Messerli FH, Panjrath GS. The J-curve between blood pressure and coronary artery disease or essential hypertension: Exactly how essential? J Am Coll Cardiol 2009;54:1827-34.
10. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: A meta-analysis of individual patient data. Lancet 2014;384:591-8.
11. Phillips RA, Xu J, Peterson LE, Arnold RM, Diamond JA, Schussheim AE. Impact of cardiovascular risk on the relative benefit and harm of intensive treatment of hypertension. J Am Coll Cardiol 2018;71:1601-10.
12. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, *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 and the European society of hypertension. J Hypertens 2018;36:1953-2041.
13. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: Systematic review. BMJ 2005;330:625.
14. Chow SL, Maisel AS, Anand I, Bozkurt B, de Boer RA, Felker GM, *et al*. Role of biomarkers for the prevention, assessment, and management of heart failure: A scientific statement from the American heart association. Circulation 2017;135:e1054-91.
15. Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, *et al*. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: A cohort study. Lancet 2015;386:2481-8.
16. Hsieh BP, Rogers AM, Na B, Wu AH, Schiller NB, Whooley MA. Prevalence and prognostic significance of incidental cardiac troponin T elevation in ambulatory patients with stable coronary artery disease: Data from the Heart and Soul study. Am Heart J 2009;158:673-9.
17. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, *et al*. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the atherosclerosis risk in communities study. Circulation 2011;123:1367-76.
18. Jia X, Sun W, Hoogeveen RC, Nambi V, Matsushita K, Folsom AR, *et al*. High-sensitivity Troponin I and incident coronary events, stroke, heart failure hospitalization, and mortality in the ARIC study. Circulation 2019;139:2642-53.
19. Pedersen F, Raymond I, Kistorp C, Sandgaard N, Jacobsen P, Hildebrandt P. N-terminal pro-brain natriuretic peptide in arterial hypertension: A valuable prognostic marker of cardiovascular events. J Card Fail 2005;11 Suppl 5:S70-5.
20. Sehestedt T, Jeppesen J, Hansen TW, Wachtell K, Ibsen H, Torp-Pedersen C, *et al*. Risk prediction is improved by adding markers of subclinical organ damage to SCORE. Eur Heart J 2010;31:883-91.
21. Voss EM, Sharkey SW, Gernert AE, Murakami MM, Johnston RB, Hsieh CC, *et al*. Human and canine cardiac troponin T and creatine kinase-MB distribution in normal and diseased myocardium. Infarct sizing using serum profiles. Arch Pathol Lab Med 1995;119:799-806.
22. White HD. Pathobiology of troponin elevations: do elevations occur with myocardial ischemia as well as necrosis? J Am Coll Cardiol 2011;57:2406-8.
23. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56:254-61.
24. Apple FS, Collinson PO; IFCC Task Force on Clinical Applications of Cardiac Biomarkers. Analytical characteristics of high-sensitivity cardiac troponin assays. Clin Chem 2012;58:54-61.
25. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, *et al*. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;304:2494-502.
26. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, *et al*. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010;304:2503-12.
27. Willeit P, Welsh P, Evans JD, Tschiderer L, Boachie C, Jukema JW, *et al*. High-sensitivity cardiac troponin concentration and risk of first-ever cardiovascular outcomes in 154,052 participants. J Am Coll Cardiol 2017;70:558-68.
28. Askin L, Tasolar H, Aksu U, Cetin M, Uslu A, Tanboga HI, *et al*. Discerning the relationship between left ventricular geometry, high-sensitivity troponin T, and nondipper hypertension. Blood Press Monit 2018;23:12-8.
29. Askin L, Yesiltepe Y. High-sensitivity cardiac troponin T levels in prehypertensive patients. Clin Exp Hypertens 2018;40:332-6.
30. McEvoy JW, Chen Y, Nambi V, Ballantyne CM, Sharrett AR, Appel LJ, *et al*. High-sensitivity cardiac troponin T and risk of hypertension. Circulation 2015;132:825-33.
31. Sato Y, Yamamoto E, Sawa T, Toda K, Hara T, Iwasaki T, *et al*. High-sensitivity cardiac troponin T in essential hypertension. J Cardiol 2011;58:226-31.
32. McEvoy JW, Lazo M, Chen Y, Shen L, Nambi V, Hoogeveen RC, *et al*. Patterns and determinants of temporal change in high-sensitivity cardiac troponin-T: The atherosclerosis risk in communities cohort study. Int J Cardiol 2015;187:651-7.
33. Tehrani DM, Fan W, Nambi V, Gardin J, Hirsch CH, Amsterdam E, *et al*. Trends in blood pressure and high-sensitivity cardiac troponin-T with cardiovascular disease: The cardiovascular health study. Am J Hypertens 2019;32:1013-20.
34. Neeland IJ, Drazner MH, Berry JD, Ayers CR, de Filippi C, Seliger SL, *et al* Biomarkers of chronic cardiac injury and hemodynamic stress identify a malignant phenotype of left ventricular hypertrophy in the general population. J Am Coll Cardiol 2013;61:187-95.
35. Pandey A, Keshvani N, Ayers C, Correa A, Drazner MH, Lewis A, *et al*. Association of cardiac injury and malignant left ventricular hypertrophy with risk of heart failure in African Americans: The Jackson heart study. JAMA Cardiol 2019;4:51-8.
36. Pokharel Y, Sun W, de Lemos JA, Taffet GE, Virani SS, Ndumele CE, *et al*. High-sensitivity troponin T and cardiovascular events in systolic blood pressure categories: Atherosclerosis risk in communities study. Hypertension

2015;65:78-84.
37. McEvoy JW, Chen Y, Rawlings A, Hoogeveen RC, Ballantyne CM, Blumenthal RS, *et al*. Diastolic blood pressure, subclinical myocardial damage, and cardiac events: Implications for blood pressure control. J Am Coll Cardiol 2016;68:1713-22.
38. Rocca HP, Kaye DM, Woods RL, Hastings J, Esler MD. Effects of intravenous brain natriuretic peptide on regional sympathetic activity in patients with chronic heart failure as compared with healthy control subjects. J Am Coll Cardiol 2001;37:1221-7.
39. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998;339:321-8.
40. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, *et al*. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European society of cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.
41. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr., Drazner MH, *et al*. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American college of cardiology foundation/American heart association task force on practice guidelines. J Am Coll Cardiol 2013;62:e147-239.
42. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, *et al*. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655-63.
43. Di Angelantonio E, Chowdhury R, Sarwar N, Ray KK, Gobin R, Saleheen D, *et al*. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. Circulation 2009;120:2177-87.
44. Natriuretic Peptides Studies Collaboration, Willeit P, Kaptoge S, Welsh P, Butterworth AS, Chowdhury R, *et al*. Natriuretic peptides and integrated risk assessment for cardiovascular disease: An individual-participant-data meta-analysis. Lancet Diabetes Endocrinol 2016;4:840-9.
45. Kistorp C, Raymond I, Pedersen F, Sandgaard N, Jacobsen P, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. JAMA 2005;293:1609-16.
46. Ndrepepa G, Braun S, Niemöller K, Mehilli J, von Beckerath N, von Beckerath O, *et al*. Prognostic value of N-terminal pro-brain natriuretic peptide in patients with chronic stable angina. Circulation 2005;112:2102-7.
47. Rudolf H, Mugge A, Trampisch HJ, Scharnagl H, Marz W, Kara K. NT-proBNP for risk prediction of cardiovascular events and all-cause mortality: The get ABI-study. Int J Cardiol Heart Vasc 2020;29:100553.
48. Skoglund PH, Höijer J, Ärnlöv J, Zethelius B, Svensson P. Amino-terminal pro-B-type natriuretic peptide improves discrimination for incident atherosclerotic cardiovascular disease beyond ambulatory blood pressure in elderly men. Hypertension 2015;66:681-6.
49. Paget V, Legedz L, Gaudebout N, Girerd N, Bricca G, Milon H, *et al*. N-terminal pro-brain natriuretic peptide: A powerful predictor of mortality in hypertension. Hypertension 2011;57:702-9.
50. Huelsmann M, Neuhold S, Resl M, Strunk G, Brath H, Francesconi C, *et al*. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): A prospective randomized controlled trial. J Am Coll Cardiol 2013;62:1365-72.
51. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, *et al*. Natriuretic peptide-based screening and collaborative care for heart failure: The STOP-HF randomized trial. JAMA 2013;310:66-74.
52. Hussain A, Sun W, Deswal A, de Lemos JA, McEvoy JW, Hoogeveen RC, *et al*. Association of NT-ProBNP, blood pressure, and cardiovascular events: The ARIC study. J Am Coll Cardiol 2021;77:559-71.
53. Pandey A, Patel KV, Vongpatanasin W, Ayers C, Berry JD, Mentz RJ, *et al*. Incorporation of biomarkers into risk assessment for allocation of antihypertensive medication according to the 2017 ACC/AHA high blood pressure guideline: A pooled cohort analysis. Circulation 2019;140:2076-88.
54. Berry JD, Nambi V, Ambrosius WT, Chen H, Killeen A, Taylor A, *et al*. Biomarkers of myocardial injury and neurohormonal stress and intensive blood pressure lowering: Insights from SPRINT. Circulation 2020;142:e470-500.
55. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr., Grimm RH Jr., *et al*. Effects of intensive blood-pressure control in Type 2 diabetes mellitus. N Engl J Med 2010;362:1575-85.

How to cite this article: Hussain A, Deshotels M, Nambi PV, Bansal K, Jneid H, Nambi V. Troponin and B-type Natriuretic Peptides Biomarkers in the Management of Hypertension. Hypertens 2021;7(1):30-37.

Source of support: Nil, **Conflicts of interest:** None, **My disclosures:** Supported by a VA Merit grant. Co-investigator on provisional patent along with Roche, Baylor College of Medicine on the use of biomarkers in prediction of heart failure. Site PI for study sponsored by Amgen.

INDIAN SOCIETY OF HYPERTENSION
World Hypertension League
CURRENT MEDICAL CONCEPTS
HTNJ
CrossMark

Review Article

Sodium-glucose Co-transporter 2 Inhibitors and Blood Pressure Reduction among Patients with Diabetes, Cardiovascular Disease, Chronic Kidney Disease

Jefferson L. Triozzi[1], Sankar D. Navaneethan[2], L. Parker Gregg[2], Addison A. Taylor[1]

[1]Department of Medicine, Baylor College of Medicine, Houston, Texas, United States. [2]Department of Nephrology, Baylor College of Medicine, Houston, Texas, United States

Abstract

The remarkable reductions in cardiovascular events and the blunting of the decline in kidney function observed in clinical trials of patients with diabetes, cardiovascular disease, and/or chronic kidney disease treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors are accompanied by a modest reduction in systolic (2–5 mm Hg) and diastolic (0.5–2.5 mm Hg) blood pressure. Blood pressure reduction occurs across a spectrum of blood pressure elevations, possibly including those with resistant hypertension, many of whom are already taking a variety of antihypertensive drugs. SGLT2 inhibitors appear to lower blood pressure to a greater extent in hypertensive Black and Asian individuals than White individuals. Mechanisms by which SGLT2 inhibitors likely contribute to blood pressure reduction and other cardiovascular and kidney benefits involve a variety of neuroendocrine, kidney, and hemodynamic systems. Some of these components include osmotic diuresis and natriuresis with a consequent decline in both interstitial and intravascular volume, weight reduction, a reduction in arterial stiffness, cardiac ventricular remodeling, loss of salt sensitivity, a decrease in uric acid concentrations, and a complicated interaction with the renin-angiotensin-aldosterone and sympathetic nervous systems. This review will provide an update on mechanisms purported to contribute to blood pressure reduction and the cardiovascular and kidney benefits observed with this the class of agents.

Key words: Blood pressure, cardiovascular disease, chronic kidney disease, diabetes, SGLT2 inhibitors

Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are primarily indicated as antihyperglycemic agents for patients with diabetes mellitus, with substantial data supporting cardiovascular and kidney benefits.[1] SGLT2 inhibitors also reduce blood pressure regardless of the presence of diabetes. Hypertension is an established risk factor cardiovascular disease, kidney disease, and death.[2] There are numerous mechanisms by which SGLT2 inhibitors affect blood pressure, but their potential use as antihypertensive agents is unclear.[3] In this review, we summarize pharmacological and clinical data that inform the role of SGLT2 inhibitors in blood pressure reduction among patients with and without diabetes.

A Review of Clinical Trials

Blood pressure reduction appears to be a class effect of SGLT2 inhibitors [Table 1].[4] A meta-analysis of SGLT2 inhibitor trials based on seated clinic blood pressure measurements demonstrated a mean systolic and diastolic blood pressure reduction of 3.8 mg Hg and 1.6 mm Hg, respectively.[5] Similarly, a meta-analysis of SGLT2 inhibitor trials based on 24-h ambulatory blood pressure monitoring demonstrated a mean systolic and diastolic blood pressure reduction of 3.8 mm Hg and 1.8 mm Hg, respectively.[6] In initial cardiovascular outcome trials, SGLT2 inhibitors improved cardiovascular outcomes and reduced blood pressure among patients with diabetes. In subsequent dedicated chronic kidney disease and heart failure

Address for correspondence:
Addison A. Taylor, Department of Medicine, Baylor College of Medicine, Houston, Taxes, United States.
E-mail: ataylor@bcm.edu

Received: 30-04-2021; Accepted: 04-05-2021
doi: 10.15713/ins.johtn.0219

Table 1: Selected randomized controlled trials of SGLT2 inhibitors among patients with diabetes, cardiovascular disease, and chronic kidney disease

Trial	Intervention	*n*=	Baseline DM (%)	Baseline blood pressure (mean±SD mm Hg)	Baseline antihypertensive agents reported (%)	Blood pressure observations
EMPA-REG OUTCOME	empagliflozin	7,020	100	SBP 135.3±16.9, DBP 76.6±9.7	RAAS inhibitor 81.0, BB 65.2, MRA 6.5, diuretic 43.7, CCB 32.6, renin inhibitor 0.6, Other 8.2	Mean SBP/DBP at the end of study was 131.3/75.1 mm Hg. There was no significant effect on the primary outcome/death from CV causes among subgroups with SBP ≥140 versus <140 mmHg or DBP ≥90 versus <90 mm Hg
CANVAS	canagliflozin	10,142	100	SBP 136.6±15.8, DBP 77.7±9.7	RAAS inhibitor 80, BB 53.5, diuretic 44.3	Significant reduction in blood pressure versus placebo of SBP 3.93 mm Hg (4.30–3.56) and DBP 1.39 mm Hg (1.61–1.17), *P*<0.001 (mean difference [95% CI]). There was no significant effect on the primary outcome among subgroups with SBP ≥140 versus <140 mmHg or DBP ≥90 versus <90 mm Hg
DECLARE-TIMI 58	dapagliflozin	17,160	100	SBP 135.1±15.3	RAAS inhibitor 81.3, BB 52.4, diuretic 40.6	Significant reduction in blood pressure versus placebo of SBP 2.7 mm Hg (2.4–3.0) and DBP 0.7 mm Hg (0.6–0.9) (least squared mean difference [95% CI])
DAPA-HF	dapagliflozin	4,744	41.8	SBP 122.0±16.3	RAAS inhibitor 84.5, ARB + neprolysin inhibitor 10.5, BB 96, MRA 71.5, diuretic 93.4	Significant reduction in blood pressure versus placebo from baseline to 2 weeks of SBP 2.54 mm Hg (3.33–1.76), *P*<0.001 (placebo-corrected reduction [95% CI])
EMPEROR-REDUCED	empagliflozin	3,730	49.8	SBP 122.6±15.9	RAAS inhibitor 70.5, ARB + neprolysin inhibitor 18.3, BB 94.7, MRA 70.1	Non-significant reduction in blood pressure versus placebo of SBP 0.7 mm Hg (1.8–0.4) [absolute reduction (95% CI)].
CREDENCE	canagliflozin	4,401	100	SBP 140.0±15.6, DBP 78.3±9.4	RAAS inhibitor 99.9, BB 40.2, diuretic 46.7	Significant reduction in blood pressure versus placebo of SBP 3.30 mm Hg (2.73–3.87) and DBP 0.95 mm Hg (0.61–1.28) (mean difference [95% CI])
DAPA-CKD	dapagliflozin	4,304	67.5	SBP 136.7±17.5, DBP 77.5±10.7	RAAS inhibitor 98.4, diuretic 43.1	The primary outcome was statistically significant among both subgroups with SBP ≤130 mm Hg 0.44 (0.31–0.63) and >130 mm Hg 0.68 (0.56–0.84) (hazard ratio [95% CI])

DM: Diabetes mellitus, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation, CI: Confidence interval, RAAS: Renin-angiotensin-aldosterone system, ARB: Angiotensin receptor blockers, BB: Beta-blocker, CCB: Calcium channel blocker, MRA: Mineralocorticoid receptor antagonist

trials, SGLT2 inhibitors improved outcomes and reduced blood pressure among patients with and without diabetes. The extent to which blood pressure reduction accounts for cardiovascular and kidney benefits is unclear. A large meta-analysis of 40 clinical trials was statistically underpowered to identify an association between blood pressure reduction and cardiovascular outcomes.[7]

Cardiovascular outcome trials

Cardiovascular outcome trials enrolled patients with Type 2 diabetes and varying baseline cardiovascular disease, kidney disease, and hypertension. EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) demonstrated a reduction of the primary composite cardiovascular outcome of cardiovascular death, non-fatal myocardial infarction, or nonfatal stroke among patients with established atherosclerotic cardiovascular disease.[8] Approximately 95% of patients enrolled in EMPA-REG OUTCOME received baseline antihypertensive therapy. Although EMPA-REG OUTCOME did not include a pre-specified blood pressure endpoint, a post-trail analysis demonstrated an decrease of systolic blood pressure by approximately 3–5 mm Hg regardless of baseline systolic blood pressure or the presence of heart failure.[9] CANVAS (Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes) and DECLARE-TIMI 58 (Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes) enrolled patients with type 2 diabetes and either established atherosclerotic cardiovascular disease or high cardiovascular risk, including hypertension.[10,11] CANVAS demonstrated a reduction in the primary composite cardiovascular outcome and a mean reduction in systolic and diastolic blood pressure versus placebo of 3.93 mm Hg and 1.39 mm Hg, respectively. DECLARE-TIMI

58 demonstrated cardiovascular safety without a reduction in the primary composite cardiovascular outcome (although a significant reduction in hospitalization for heart failure was observed) and a mean reduction in systolic and diastolic blood pressure versus placebo was 2.7 and 0.7 mm Hg, respectively.

Heart failure

The primary composite cardiovascular outcomes in the cardiovascular outcome trials were driven by reduced heart failure events. In the subsequent heart failure trials, a marginal blood pressure reduction was observed. EMPEROR-REDUCED (Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure) similarly demonstrated a reduction in cardiovascular death or hospitalization for heart failure regardless of baseline diabetes.[12] EMPEROR-REDUCED reported a 0.7 mm Hg difference in systolic blood pressure reduction versus placebo that was not statistically significant. DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) enrolled patients with and without diabetes and there was a significant reduction in systolic blood pressure versus placebo at 2 weeks in a secondary analysis.[13] Blood pressure reduction is associated with reduced risk of acute decompensated heart failure but low blood pressure is associated with increased mortality among patients with heart failure.[14] Both trials excluded patients with baseline hypotension. SGLT2 inhibitor-mediated blood pressure reduction may reflect broader hemodynamic changes related to improved heart failure outcomes.

Chronic kidney disease

Promising secondary microvascular outcomes in the cardiovascular outcome trials prompted dedicated SGLT2 inhibitor clinical trials among patients with chronic kidney disease. It was expected that pharmacological effects of SGLT2 inhibitors would attenuate with reduced kidney function given their target of action in the proximal tubule.[15] However, SGLT2 inhibitors improved clinically meaningful kidney outcomes and reduced blood pressure among patients with advanced kidney disease. CREDENCE (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy), a seminal kidney outcomes study, enrolled patients with type 2 diabetes, an estimated glomerular filtration rate (eGFR) 30–90 mL/min/1.73 m^2, and urine albumin to creatinine ratio >300–5000 mg/g.[16] In CREDENCE, canagliflozin reduced the primary composite kidney outcome by 33% and decreased the rate of diabetic kidney disease progression by 2.74 mL/min/1.73 m^2/year among a cohort receiving maximally titrated angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy. Mean reduction of systolic and diastolic blood pressure versus placebo was 3.30 mm Hg and 0.95 mm Hg, respectively. Similarly, DAPA-CKD (Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease) investigated a primary composite kidney outcome among patients with chronic kidney disease, including one-third without diabetes. Dapagliflozin yielded a clinically and statistically significant reduction of the primary composite kidney outcome. A reduction in blood pressure was also observed, with a similar effect on patients with or without diabetes. A pooled analysis of five empagliflozin trials also demonstrated systolic blood pressure reduction with SGLT2 inhibitors in patients with advanced chronic kidney disease.[17] It was suggested that increased salt-sensitivity in patients with chronic kidney disease allows for a persistent antihypertensive effect despite reduced kidney function.[18]

Pharmacology of SGLT2 Inhibitors

The SGLT2 reabsorbs 90% of freely filtered glucose in the proximal tubule of the nephron. Glucose reabsorption in the kidney is an active process in using sodium gradients generated by the Na^+-K^+-ATPase. Thus, inhibition of sodium and glucose reabsorption in the proximal tubule produces natriuresis and glucosuria. It is speculated that SGLT2 inhibitors lead to other systemic anti-inflammatory, metabolic, and hemodynamic changes.[19] The effect of SGLT2 inhibition on blood pressure is multifactorial, but most likely involves extracellular fluid volume reduction, interaction with the renin-angiotensin-aldosterone system (RAAS), interaction with the sympathetic nervous system, and changes in vascular compliance.

Extracellular fluid volume reduction

SGLT2 inhibitors cause osmotic diuresis and reduce circulating blood volume. Natriuresis is related to direct inhibition of the sodium-glucose cotransporter and partially by inhibition of the Na^+-H^+ exchanger 3 (NHE3).[20] A pre-specified analysis of the EMPA-HEART trial (Effect of Empagliflozin on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease) measured extracellular fluid volume by cardiac magnetic resonance among patients with Type 2 diabetes mellitus and coronary artery disease. This analysis indeed demonstrated a reduction in extracellular fluid volume over 24-week follow-up suggesting that SGLT2 inhibitors are effective diuretics.[21] It is unlikely that extracellular fluid volume reduction accounts entirely for blood pressure reduction. Whereas glucosuria persists throughout SGLT2 inhibitor therapy, natriuresis may attenuate over time. A placebo-controlled randomized clinical of canagliflozin measured changes in plasma volume among patients with type 2 diabetes. A modest initial increase in urine volume approximately 160 mL per 24 h decreased to approximately 50 mL per 24 h by week 12.[22] This suggests compensatory changes in the distal nephron adapt to increase sodium reabsorption following SGLT2 inhibition.

Interaction with RAAS

RAAS activation is a primary mediator of hypertension, chronic inflammation, and oxidative stress. The interaction between SGLT2 inhibition and RAAS is complex. In mice models, SGLT2 inhibition is effective for angiotensin II-mediated hypertension. Angiotensin II is a primary RAAS end-product causing vasoconstriction,

increased secretion of antidiuretic hormone and aldosterone, and intraglomerular hypertension. In addition, observational data suggest that the uricosuric effect of SGLT2 inhibition mitigates RAAS activation and improves cardiovascular and kidney events.[23] On the other hand, SGLT2 inhibition may initially activate the RAAS as a response to osmotic diuresis and changes in extracellular fluid volume. Some studies have demonstrated increased markers of RAAS related to SGLT2 inhibition. In a preclinical model, SGLT2 inhibitor increased intrarenal and systemic plasma renin activity in mice with and without diabetes, although no changes in renal angiotensin II were observed.[24]

Interaction with the sympathetic nervous system

Sympathetic nervous system activation both contributes to hypertension and exacerbates endothelial dysfunction and the progression of cardiovascular and kidney disease.[25] SGLT2 inhibition may exert cardiovascular events and blood pressure reduction through inhibition of sympathetic nervous activity.[24] Sympathetic nervous system activation both contributes to hypertension and exacerbates endothelial dysfunction and the progression of cardiovascular and kidney disease.[25] There are interactions between sympathetic nervous system activity and SGLT2 expression in the kidney. A sympatholytic effect of SGLT2 inhibitors may explain the phenomenon of blood pressure reduction without a change in pulse rate. In a preclinical model, norepinephrine increased SGLT2 expression in the proximal tubule *in vitro*. Treatment with dapagliflozin reduced markers of sympathetic nervous system activation in both the heart and the kidney.[26] In a follow-up study of hypertensive mice, the authors suggest "cross-talk" between SGLT2 inhibitor expression and renal innervation.[27]

Arterial stiffness

SGLT2 inhibitors may increase vascular compliance. Arterial stiffness may contribute to afterload and cardiac workload. Renal vascular stiffness may also be related to kidney injury. In a small randomized controlled trial among patients with Type 1 diabetes and normal blood pressure, empagliflozin was associated with reduced indices of arterial stiffness. The authors reported no difference in heart rate variability or sympathetic nervous activity measured through adrenergic biomarkers.[28] A smaller *post hoc* analysis including two cohorts from five empagliflozin trials assessed markers of arterial stiffness and vascular resistance in addition to blood pressure.[29] A separate study found no change in arterial stiffness using cardio-ankle vascular index.[30] It is unclear how indices of arterial stiffness used in these studies are themselves influenced by blood pressure.

Interpreting the Role of SGLT2 Inhibitors in Blood Pressure Reduction

SGLT2 inhibitor-mediated blood pressure reduction is observed across clinical trials, irrespective of baseline hemoglobin A1c, kidney function, or cardiovascular disease. The role of SGLT2 inhibitors in blood pressure reduction will also depend on baseline blood pressure, circadian blood pressure patterns, race, and combination with other antihypertensive agents.

Baseline blood pressure

Patients with higher baseline blood pressure have a greater response to antihypertensive agents and greater cardiovascular disease risk reduction. Thus far, SGLT2 inhibitor-mediated blood pressure reduction data are derived from patients with well-controlled baseline blood pressure. In large cardiovascular and kidney trials, for example, baseline systolic blood pressure averages around 135 mm Hg. More studies of patients with difficult-to-control or resistant hypertension are needed to clarify the role of SGLT2 inhibitors as antihypertensive agents and whether there are differences in the effect of individual SGLT2 inhibitors on blood pressure. Based on their potential mechanisms of action, SGLT2 inhibitors may be useful in resistant hypertension, which is often characterized by RAAS activation, sodium and fluid retention, and impaired renal-pressure natriuresis.[31] A *post hoc* analysis of EMPA-REG OUTCOME identified 22% of enrolled patients taking three or more antihypertensive agents at baseline, which the authors labeled presumed resistant hypertension. In this study, empagliflozin demonstrated significant reduction in blood pressure throughout the follow-up period regardless of presence or absence of apparent resistant hypertension.[32]

Circadian patterns

Although SGLT2 inhibitors demonstrate a greater absolute blood pressure reduction during the day than at night, their efficacy in treating nocturnal hypertension may reduce cardiovascular disease risk. Nocturnal hypertension and non-dipper nocturnal blood pressure patterns are associated with increased cardiovascular risk.[32] In pre-clinical models, SGLT2 inhibition restored rats with nocturnal hypertension to a more physiologic dipper profile.[34] The SACRA Study (24 h Blood Pressure–Lowering Effect of a Sodium-Glucose Cotransporter 2 Inhibitor in Patients With Diabetes and Uncontrolled Nocturnal Hypertension) similarly reported nighttime blood pressure reduction among patients taking empagliflozin with adequate glycemic control but poorly controlled nocturnal hypertension.[35] In the EMPA-HEART trial, empagliflozin demonstrated a significant reduction in ambulatory blood pressure both during the day and night. In addition to blood pressure reduction, empagliflozin was associated with reduced left ventricular mass, a predictor of adverse cardiovascular events and heart failure.[36]

Race

Race is thought to be an important factor in hypertension pathogenesis, response to antihypertensive agents, and clinical outcomes. Pooled ambulatory blood pressure monitoring data suggest a greater antihypertensive response to SGLT2 inhibitors among Black and Asian than White individuals.[37] Thus far, the

reasons behind these differences are largely speculative and based on information we have gleaned from other antihypertensive agents. A salt-sensitive, low-renin hypertension phenotype is prevalent in Asian and Black populations. Consequently, these patients may have greater sensitivity to antihypertensive agents that reduce both sodium and volume, like SGLT2 inhibitors. Racial predispositions toward nocturnal hypertension may also affect blood pressure response to SGLT2 inhibitors. Morning hypertension is more common in non-Western populations, and SGLT2 inhibitor studies among Asian patients with nocturnal hypertension are promising. Notably, Black patients were largely underrepresented in seminal SGLT2 inhibitor clinical trials. In a smaller study with 166 participants, Ferdinand *et al*. investigated the efficacy of empagliflozin compared to placebo among Black patients with Type 2 diabetes and hypertension.[38] The study included a primary glycemic control endpoint and multiple secondary blood pressure endpoints but no cardiovascular outcomes were reported. Mean ambulatory systolic blood pressure was 146 mm Hg and one-third was receiving three or more antihypertensive medications. Empagliflozin significantly reduced 24-h ambulatory systolic blood pressure versus placebo at 12 and 24 weeks by 8.39 mm Hg and 5.21 mm Hg, respectively. Enrolling diverse study populations in future clinical trials are imperative to better understand the role of SGLT2 inhibition in blood pressure reduction.

Combination with other antihypertensive agents

SGLT2 inhibitor study populations have prevalent use of other antihypertensive agents, particularly RAAS blockade. SGLT2 inhibition may have synergism with RAAS blockade, a cornerstone of management for patients with diabetes, chronic kidney disease, or heart failure. On the single-nephron level, SGLT2 inhibitors and RAAS inhibitors have complementary effects on glomerular hypertension. SGLT2 inhibitors primarily decrease glomerular pressures through afferent arteriolar vasoconstriction, and RAAS blockers decrease glomerular pressures through efferent arteriolar vasodilation. Both agents cause anticipated hemodynamically mediated drops in eGFR in addition to reduced blood pressure. Whereas a 30% change in eGFR is permitted after initiating ACE inhibitors or ARBs, it is uncertain what degree of eGFR is tolerable with SGLT2 inhibitors in combination with RAAS blockade. A meta-analysis of eight randomized controlled trials, specific analysis of SGLT2 inhibition and RAAS inhibition in combination was not associated with increased adverse events related to kidney function when compared to either placebo or RAAS inhibition.[39] SGLT2 inhibitors may have similar antihypertensive efficacy as thiazide diuretics.[40] However, SGLT2 inhibitors may demonstrate less blood pressure reduction when used in combination with diuretics. Weber *et al*. reported that the antihypertensive effect was greater among patients receiving beta-blockade or calcium channel-blockade at baseline than those receiving a thiazide diuretic.[41] In this trial, patients were already receiving RAAS inhibitors in addition to at least one other agent.

Safety

The most common adverse events associated with SGLT2 inhibitors are genital mycotic infections. Euglycemic ketoacidosis, acute kidney injury, fracture, and amputation are less common.[42] Risks associated with blood pressure reduction are rare. SGLT2 inhibitors did not increase the risk of orthostatic hypotension in an analysis of 19 randomized clinical trials.[5] In the EMPA-REG BP study (Empagliflozin Reduces Blood Pressure in Patients With Type 2 Diabetes and Hypertension), a Phase 3 study that preceded EMPA-REG OUTCOME, only one out of 825 patients experienced a drug-related hypotension complication.[43] This is surprising given the high base rate of autonomic dysfunction and predilection for orthostatic hypotension among patients with diabetes. We also note a lack of increase in heart rate with SGLT2 inhibitor-mediated blood pressure reduction, a phenomenon associated with orthostatic hypotension. Some speculate that blood pressure reduction, dehydration, and falls could increase the risk of fractures and amputations.[44] An increased risk of fracture and amputation in the CANVAS trial was ultimately not seen in follow-up studies or meta-analyses.[45] Although elderly patients may be at higher risk, a *post hoc* analysis of elderly patients from the SARCA study did not identify hypotension or other adverse events in patients ≥75 years.[46] Finally, the reduction of blood pressure and fall in extracellular fluid volume raised concern for kidney injury among susceptible patients. In general, the drop in eGFR after initiation of SGLT2 inhibitors is associated with decreased acute kidney injury, implicating a hemodynamic phenomenon rather than glomerular, or tubular injury.[47]

Conclusion

SGLT2 inhibitors modestly lower blood pressure in patients with and without diabetes, but at this time, there is insubstantial evidence to support the use of SGLT2 inhibitors as an antihypertensive agent *per se*. Blood pressure reduction alone cannot account for the multiple cardiovascular and kidney benefits observed in SGLT2 inhibitor trials. SGLT2 inhibitors likely have multiple systemic mechanisms of action, including impact on extracellular volume, RAAS, the sympathetic nervous system, and arterial stiffness, which may all contribute to antihypertensive effect. Regardless of specific antihypertensive mechanisms or the degree of the antihypertensive effect, clinical data supporting substantial reductions in cardiovascular disease, kidney disease, and death among patients with and without diabetes strongly supports the use of SGLT2 inhibitors for many patients.

References

1. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, *et al*. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in Type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-9.

2. Messerli FH, Williams B, Ritz E. Essential hypertension. Lancet 2007;370:591-603.
3. Verma S, McMurray JJ. SGLT2 inhibitors and mechanisms of cardiovascular benefit: A state-of-the-art review. Diabetologia 2018;61:2108-17.
4. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in Type 2 diabetes mellitus: Systematic review and network meta-analysis. Diabetes Obes Metab 2016;18:783-94.
5. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: A systematic review and meta-analysis. J Am Soc Hypertens 2014;8:262-75.e9.
6. Baker WL, Buckley LF, Kelly MS, Bucheit JD, Parod ED, Brown R, *et al*. Effects of sodium-glucose cotransporter 2 inhibitors on 24-hour ambulatory blood pressure: A systematic review and meta-analysis. J Am Heart Assoc 2017;6:005686.
7. Benham JL, Booth JE, Sigal RJ, Daskalopoulou SS, Leung AA, Rabi DM. Systematic review and meta-analysis: SGLT2 inhibitors, blood pressure and cardiovascular outcomes. IJC Hear Vasc 2021;33:100725.
8. Steiner S. Empagliflozin, cardiovascular outcomes, and mortality in Type 2 diabetes. Zeitschrift Fur Gefassmedizin 2016;13:17-8.
9. Böhm M, Fitchett D, Ofstad AP, Brueckmann M, Kaspers S, George JT, *et al*. Heart failure and renal outcomes according to baseline and achieved blood pressure in patients with Type 2 diabetes: Results from EMPA-REG OUTCOME. J Hypertens 2020;38:1829-40.
10. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, *et al*. Canagliflozin and cardiovascular and renal events in Type 2 diabetes. N Engl J Med 2017;377:644-57.
11. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, *et al*. Dapagliflozin and cardiovascular outcomes in Type 2 diabetes. N Engl J Med 2019;380:347-57.
12. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al*. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413-24.
13. Serenelli M, Böhm M, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al*. Effect of dapagliflozin according to baseline systolic blood pressure in the dapagliflozin and prevention of adverse outcomes in heart failure trial (DAPA-HF). Eur Heart J 2020;41:3402-18.
14. Upadhya B, Rocco M, Lewis CE, Oparil S, Lovato LC, Cushman WC, *et al*. Effect of intensive blood pressure treatment on heart failure events in the systolic blood pressure reduction intervention trial. Circ Heart Fail 2017;10:e003613.
15. Wilcox CS. Antihypertensive and renal mechanisms of SGLT2 (sodium-glucose linked transporter 2) inhibitors. Hypertension 2020;75:894-901.
16. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, *et al*. Canagliflozin and renal outcomes in Type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-306.
17. Cherney DZ, Cooper ME, Tikkanen I, Pfarr E, Johansen OE, Woerle HJ, *et al*. Pooled analysis of Phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. Kidney Int 2018;93:231-44.
18. Meng L, Fu B, Zhang T, Han Z, Yang M. Salt sensitivity of blood pressure in non-dialysis patients with chronic kidney disease. Ren Fail 2014;36:345-50.
19. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: Cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016;134:752-72.
20. Onishi A, Fu Y, Patel R, Darshi M, Crespo-Masip M, Huang W, *et al*. A role for tubular Na+/H+ exchanger NHE3 in the natriuretic effect of the SGLT2 inhibitor empagliflozin. Am J Physiol 2020;319:F712-28.
21. Mason T, Coelho-Filho OR, Verma S, Chowdhury B, Zuo F, Quan A, *et al*. Empagliflozin reduces myocardial extracellular volume in patients with Type 2 diabetes and coronary artery disease. JACC Cardiovasc Imaging 2021;S1936-878X(20)30939-6.
22. Sha S, Polidori D, Heise T, Natarajan J, Farrell K, Wang SS, *et al*. Effect of the sodium glucose co-transporter 2 inhibitor canagliflozin on plasma volume in patients with Type 2 diabetes mellitus. Diabetes Obes Metab 2014;16:1087-95.
23. Lytvyn Y, Škrtić M, Yang GK, Yip PM, Perkins BA, Cherney DZ. Glycosuria-mediated urinary uric acid excretion in patients with uncomplicated Type 1 diabetes mellitus. Am J Physiol 2015;308:F77-83.
24. Scheen AJ. Effect of SGLT2 inhibitors on the sympathetic nervous system and blood pressure. Curr Cardiol Rep 2019;21:1-10.
25. Gamboa A, Figueroa R, Paranjape SY, Farley G, Diedrich A, Biaggioni I. Autonomic blockade reverses endothelial dysfunction in obesity-associated hypertension. Hypertension 2016;68:1004-10.
26. Matthews VB, Elliot RH, Rudnicka C, Hricova J, Herat L, Schlaich MP. Role of the sympathetic nervous system in regulation of the sodium glucose cotransporter 2. J Hypertens 2017;35:2059-68.
27. Herat LY, Magno AL, Rudnicka C, Hricova J, Carnagarin R, Ward NC, *et al*. SGLT2 inhibitor-induced sympathoinhibition: A novel mechanism for cardiorenal protection. JACC Basic Transl Sci 2020;5:169-79.
28. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, *et al*. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated Type 1 diabetes mellitus. Cardiovasc Diabetol 2014;13:28.
29. Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, *et al*. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with Type 2 diabetes. Diabetes Obes Metab 2015;17:1180-93.
30. Kario K, Okada K, Murata M, Suzuki D, Yamagiwa K, Abe Y, *et al*. Effects of luseogliflozin on arterial properties in patients with Type 2 diabetes mellitus: The multicenter, exploratory LUSCAR study. J Clin Hypertens 2020;22:1585-93.
31. Hwang AY, Dietrich E, Pepine CJ, Smith SM. Resistant hypertension: Mechanisms and treatment. Curr Hypertens Rep 2017;19:1-11.
32. Ferreira JP, Fitchett D, Ofstad AP, Kraus BJ, Wanner C, Zwiener I, *et al*. Empagliflozin for patients with presumed resistant hypertension: A post hoc analysis of the EMPA-REG OUTCOME trial. Am J Hypertens 2020;33:1092-101.
33. Kario K. Hypertension: Benefits of strict blood-pressure lowering in hypertension. Nat Rev Cardiol 2016;13:125-6.
34. Takeshige Y, Fujisawa Y, Rahman A, Kittikulsuth W, Nakano D, Mori H, *et al*. A sodium-glucose co-transporter 2 inhibitor empagliflozin prevents abnormality of circadian rhythm of blood pressure in salt-treated obese rats. Hypertens Res 2016;39:415-22.

35. Kario K, Okada K, Kato M, Nishizawa M, Yoshida T, Asano T, *et al*. Twenty-four-hour blood pressure-lowering effect of a sodium-glucose cotransporter 2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: Results from the randomized, placebo-controlled SACRA study. Circulation 2019;139:2089-97.
36. Verma S, Mazer CD, Yan AT, Mason T, Garg V, Teoh H, *et al*. Effect of empagliflozin on left ventricular mass in patients with Type 2 diabetes mellitus and coronary artery disease: The EMPA-HEART cardiolink-6 randomized clinical trial. Circulation 2019;140:1693-702.
37. Kario K, Ferdinand KC, O'Keefe JH. Control of 24-hour blood pressure with SGLT2 inhibitors to prevent cardiovascular disease. Prog Cardiovasc Dis 2020;63:249-62.
38. Ferdinand KC, Izzo JL, Lee J, Meng L, George J, Salsali A, *et al*. Antihyperglycemic and blood pressure effects of empagliflozin in black patients with Type 2 diabetes mellitus and hypertension. Circulation 2019;139:2098-109.
39. Cai Y, Shi W, Xu G. The efficacy and safety of SGLT2 inhibitors combined with ACEI/ARBs in the treatment of Type 2 diabetes mellitus: A meta-analysis of randomized controlled studies. Expert Opin Drug Saf 2020;19:1497-504.
40. Georgianos PI, Agarwal R. Ambulatory blood pressure reduction with SGLT-2 inhibitors: Dose-response meta-analysis and comparative evaluation with low-dose hydrochlorothiazide. Diabetes Care 2019;42:693-700.
41. Weber MA, Mansfield TA, Cain VA, Iqbal N, Parikh S, Ptaszynska A. Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with Type 2 diabetes on combination antihypertensive therapy: A randomised, double-blind, placebo-controlled, phase 3 study. Lancet Diabetes Endocrinol 2016;4:211-20.
42. Lupsa BC, Inzucchi SE. Use of SGLT2 inhibitors in Type 2 diabetes: Weighing the risks and benefits. Diabetologia 2018;61:2118-25.
43. Tikkanen I, Narko K, Zeller C, Green A, Salsali A, Broedl UC, *et al*. Empagliflozin reduces blood pressure in patients with Type 2 diabetes and hypertension. Diabetes Care 2015;38:420-8.
44. Cheng L, Li YY, Hu W, Bai F, Hao HR, Yu WN, *et al*. Risk of bone fracture associated with sodium-glucose cotransporter-2 inhibitor treatment: A meta-analysis of randomized controlled trials. Diabetes Metab 2019;45:436-45.
45. Inzucchi SE, Iliev H, Pfarr E, Zinman B. Empagliflozin and assessment of lower-limb amputations in the EMPA-REG OUTCOME trial. Diabetes Care 2018;41:e4-5.
46. Okada K, Hoshide S, Kato M, Kanegae H, Ishibashi S, Kario K. Safety and efficacy of empagliflozin in elderly Japanese patients with Type 2 diabetes mellitus: A post hoc analysis of data from the SACRA study. J Clin Hypertens 2021;23:860-9.
47. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ, *et al*. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with Type 2 diabetes and chronic kidney disease: A randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2014;2:369-84.

How to cite this article: Triozzi JL, Navaneethan SD, Gregg LP, Taylor AA. Sodium-glucose Co-transporter 2 Inhibitors and Blood Pressure Reduction among Patients with Diabetes, Cardiovascular Disease, Chronic Kidney Disease. Hypertens 2021;7(1): 38-44.

Source of support: S.D.N. is supported by research funding from the Department of Veterans Affairs Health Services Research & Development (1I01HX002917-01A1) and a grant from the National Institutes of Health (NIDDK-R01DK101500). This work was also supported in part by the Center for Innovations grant (CIN 13-413), Michael E. DeBakey VA Medical Center, Houston, TX. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or Veterans Administration, **Conflicts of interest:** S.D.N., L.P.G., and A.A.T. are employees of the US Department of Veterans Affairs. The interpretation and reporting of these data are the responsibility of the authors and in no way should be viewed as official policy or interpretation of the Department of Veterans Affairs or the US government. S.D.N. reports personal fees from Bayer, personal fees from Boehringer-Ingelheim, personal fees from REATA, personal fees from Tricida, and grants from Keryx, outside the submitted work. All remaining authors have nothing to disclose.

INDIAN SOCIETY OF HYPERTENSION
World Hypertension League
CURRENT MEDICAL CONCEPTS
HTNJ
CrossMark

Review Article

Hypertension in end-stage kidney disease

Christopher Farmakis, Roberto Collazo-Maldonado

Department of Nephrology, 1441 N Beckley Ave, Methodist Dallas Medical Center, Dallas, Texas, 75203, United States

Abstract

Hypertension remains a leading etiology of end-stage kidney disease. The disease has a complex pathophysiology and contributes to a wide array of morbidities and mortality for patients across the globe. Due to the lack of published data on the subject, diagnosing and monitoring hypertension in the dialysis population poses a great challenge, as currently there are no published blood pressure target goals and in-center monitoring is often not reliable. Moreover, the management of this condition involves conservative approaches for both adjusting dialysis prescriptions and limiting dietary fluid and sodium intake. Therapy is often escalated with pharmacologic agents, of which emerging data suggest that it may be useful to use certain drug classes initially. However, professional guidelines do not provide specific drug therapy recommendations at this time.

Key words: Dialysis, End-stage kidney disease, Hypertension, Management, Pathophysiology

Introduction

Hypertension remains prevalent among end-stage kidney disease (ESKD) patients. Not only does it significantly impact the overall well-being of patients but it also remains a challenging portion of patient care for nephrologists. To date, the topic of hypertension in ESKD remains controversial. Thus, the purpose of this review is to highlight and summarize the current data and its clinical implications in the treatment of this complex patient population. Beyond discussing the prevalence and pathophysiology of hypertension among ESKD patients, we will also highlight the data on recent blood pressure (BP) goals and monitoring. Finally, we will explore the current literature as it relates to both non-pharmacologic and pharmacologic treatments for hypertension in ESKD patients.

Prevalence

Although commonly observed, the exact prevalence of hypertension among patients undergoing renal replacement therapy varies widely from center to center around the world; data overall is lacking for exact prevalence values in several countries. Data from the United States show up to 70%–88% of all ESKD patients experience some form of hypertension.[1] One 2011 study showed that only 38% of a patient population on hemodialysis (HD) had BP controlled with pharmacologic therapy.[2] Another 2003 study showed that 86% of a patient population on HD had systolic BPs more than 150 mmHg or diastolic BPs more than 85 mmHg.[3] Studies from the early 1990s initially suggested that patients on peritoneal dialysis (PD) had better BP control when compared to patients on HD. However, more recent studies have shown a high burden of hypertension affecting up to 93% of patients at time of PD initiation and up to 79% of those PD patients already being treated with pharmacotherapies.[4]

Pathophysiology

The pathophysiology of hypertensive changes among patients with ESKD is complex and involves several mechanisms of intrinsic vascular control, volume status, and sodium loading [Figure 1]. One of the primary mechanisms responsible for hypertension in ESKD patients is volume overload beyond

Address for correspondence:
Dr. Christopher Farmakis, Department of Nephrology, 1441 N Beckley Ave, Methodist Dallas Medical Center, Dallas, Texas, 75203, United States. E-mail: ChristopherFarmakis@mhd.com

Received: 29-04-2021; Accepted: 08-05-2021
doi: 10.15713/ins.johtn.0215

Innovative Nature Science Publishers

- **Volume Overload Above Dry Weight**
- **Impaired Sodium and Water Excretion**
- **Sodium Accumulation**
- **Overactive Sympathetic Activity**
- **Elevated Plasma Renin Levels**
- **Arterial Stiffness Due to Calcium/Phosphorus Deposition**
- **Impaired Vasodilatory Response**
- **Intradialytic Hypertension**

Figure 1: Pathophysiology of hypertension in dialysis patients

one's clinically defined dry weight. Although clinically difficult to measure exactly due to the inability to reliably measure one's extracellular volume status, a patient's dry weight can be defined clinically as the weight at which there are no signs of hypervolemia or hypovolemia. Dry weight is closely related clinically with BP.[4] Among ESKD patients, the impaired ability to properly renally excrete water and sodium results in an increase in extracellular volume, cardiac output, and subsequently systemic BP.[5] The percentage of interdialytic weight gain above one's dry weight is linked to increased pre-HD systolic BP and greater reduction in systolic BP from pre- to post-HD in younger non-diabetic patients. Greater increases in interdialytic weight gain have also been linked to increased mortality.[5] Sodium load also plays a significant role in hypertension in ESKD patients. It is known that sodium accumulation contributes to greater extracellular fluid volume and hypertension. However, it has also been postulated that sodium triggers endothelial-mediated vasoconstriction further leading to hypertension.[5] In addition, it has been shown that ESKD patients have high BP sensitivity to sodium.[6] This can be especially seen when examining the effect of dialysate sodium concentration on BP. As traditionally seen through the concept of sodium modeling, higher dialysate concentrations of sodium traditionally used to combat intradialytic hypotension often contribute to increased thirst and further interdialytic weight gain.[5] Other factors involved in the pathogenesis of hypertension among ESKD patients include overactivity of plasma renin; inability to properly metabolize catecholamines; premature arterial stiffness due to impaired calcium and phosphate handling; and endothelial dysfunction due to dampened responses to inherent vasodilators such as nitric oxide.[7] Furthermore, although BP typically declines from the start to the end of each dialysis session, intradialytic hypertension occurs in 5–15% of cases.[8] Such a phenomenon involves an increase in systolic BP by more than 10 mmHg from pre- to post-dialysis and has been attributed to sodium exposure and endothelial dysfunction mediated by vasoconstrictors.[9]

BP Goals and Monitoring

Kidney Disease Outcomes Quality Initiative guidelines in 2005 initially recommended a pre-dialysis BP goal of <140/90 mmHg or a post-dialysis goal of <130/80 mmHg for ESKD patients.[10] However, observational studies found that pre- and post-dialysis BP values had either no correlation or a U- or J-shaped correlation with mortality. Further, such BP readings have been deemed imprecise.[11] Therefore, updated guidelines and data have stepped away from such recommendations, not giving any concrete targets for BP among ESKD patients. As per 2020 Kidney Disease Improving Global Outcomes (KDIGO) recommendations, extrapolating BP targets from the general population to ESKD patients may be reasonable.[8] Such recommendations include a BP target of ≤130/80 mmHg as per 2017 American College of Cardiology guidelines. With regard to monitoring BP, the gold standard remains ambulatory BP monitoring.[12] However, this method may not be universally available secondary to financial limitations and patient adherence. Thus, an acceptable alternative may be checking BP at home twice daily on interdialytic days for 1–2 weeks.[13]

Non-pharmacologic Management

Sodium intake and volume control remain cornerstone elements of non-pharmacologic BP management for patients requiring renal replacement therapy. As mentioned above, sodium plays a pivotal and complex role in the pathophysiology in ESKD patients. Overall, it is recommended to limit dietary sodium intake to <2 g daily. Doing so helps to limit interdialytic weight gain, thirst, and allows clinicians to more easily achieve patients' dry weights.[14] As introduced above, achieving dry weight is imperative to BP control. A dry weight reduction of 0.9 kg over an 8-week period resulted in a 6.6/3.3 mmHg interdialytic BP reduction according to the Dry Weight Reduction in Hypertensive HD Patients Trial.[15] Optimizing ultrafiltration during dialysis also helps to achieve adequate BP control. However, such tight control must be balanced by the risks of intradialytic hypotension, arteriovenous fistula clotting, and complications requiring hospitalization.[1] Furthermore, ultrafiltration rates exceeding 12.4 ml/kg/hr have been shown to be associated with increased mortality.[16] Among HD patients, utilizing longer dialysis times have beneficial outcomes for BP control. Several randomized trials have illustrated that longer dialysis sessions of 8 h 3 times a week or more frequent dialysis sessions up to 6 times a week led to lower overall BP and patients required less anti-hypertensive medications.[1] Among PD patients, adapting the PD prescription to a patient's membrane characteristics is useful for limiting hypertension. Observational studies illustrate that high transporters carry overall higher risks of uncontrolled BP as well as higher overall mortality. This may be secondary to sodium and water reabsorption when high transporters have been prescribed longer dwell times with glucose-containing solutions. It may thus be considered to switch such high-transport patients to automated PD to maximize ultrafiltration.[17] For low transport patients, clinicians should also be aware of shorter dwell times leading to sodium sieving and thus limiting net diffusive sodium removal.[17] The type of dialysate also plays a role in BP control in PD. The beneficial effects of icodextrin on BP control have been illustrated in several randomized studies. A double-blind trial with 50 hypertensive PD patients randomized to icodextrin or 2.27% glucose solutions during the long dwell for 6 months

resulted in overall fewer anti-hypertensive medications to achieve BP control in the icodextrin group.[18] Moreover, the use of icodextrin avoided the risks of peritoneal membrane damage and adverse metabolic effects caused by hypertonic glucose PD solutions.[19]

Pharmacologic Management

BP control using medications should be implemented for patients on dialysis if conservative measures fail [Figure 2]. Highlighting the need for medication use in such cases, a meta-analysis of five randomized control trials showed a 31% reduced risk of cardiovascular mortality when anti-hypertensive medications were used.[20] Among all medication classes, clinicians must often consider a drug's half-life, dialyzable properties, cardiovascular benefits, and side effects when choosing anti-hypertensive therapy for ESKD patients. The choice of such medications often is individualized as per the patient's HD needs, extent of pill burden, and intra-/inter-dialytic BP readings.

Various pharmacologic classes have shown beneficial roles in treating hypertension in ESKD patients. The Fosinopril in Dialysis Trial (FOSIDIAL) enrolled 397 HD patients with left ventricular hypertrophy. The results showed significant lowering of pre-dialysis BP with fosinopril, but no significant difference was found between fosinopril and placebo in preventing adverse cardiovascular events.[21] Similarly, the Olmesartan Clinical Trial in Okinawa Patients Under Okinawa Dialysis Study trial showed no significant benefit of olmesartan use in 469 HD patients in relation to all-cause mortality or adverse cardiovascular events.[22]

Overall, renin-angiotensin-aldosterone (RAAS) blockade in HD patients does not appear to confer the same benefits as such therapies do in the general population. In contrast to HD patients, the effects of RAAS blockers in PD patients have been more beneficial. A prospective cohort study of 306 PD patients showed a 62% lower risk of overall cardiovascular mortality when treated with RAAS blocking drugs.[23] A further meta-analysis showed a slower rate of residual kidney function decline in PD patients taking RAAS-blocking medications.[24]

With respect to dihydropyridine calcium channel blockers, amlodipine reduced all-cause mortality and fatal myocardial infarction by 47% in HD patients.[25] Such effect may be enhanced by the drug's poor dialyzability.

Mineralocorticoid receptor antagonists (MRAs) have shown concrete clinical benefit in HD patients. The Dialysis Outcomes Heart Failure Aldactone Study found a reduced risk of cardiovascular mortality or cardiovascular hospitalization with spironolactone use in 309 oligoanuric HD patients, with drug discontinuation due to hyperkalemia at 1.9%.[26] Similar benefits were observed in a study that showed reduced cardio-cerebral mortality in 253 patients on HD and PD when MRAs add-on therapy was used.[27]

Beta-blockers have recently emerged as promising treatments for hypertension in ESKD patients. In the Hypertension in HD Patients Treated with Atenolol or Lisinopril (HDPAL) trial, 200 HD patients with hypertension and left ventricular hypertrophy were randomized to receive lisinopril or atenolol over 12 months. Trial results showed no significant difference in ambulatory BP readings. However, the study showed more potent BP lowering in the atenolol group with a 2.3-fold higher risk of adverse cardiovascular events in the lisinopril group. The results were attributed to better intradialytic arrhythmia control among dialysis patients taking beta-blockers.[28] Furthermore, the beta-blocker carvedilol has been associated with reduced incidence of intradialytic hypertension.[29] More recently, a large multicenter Taiwanese study of 101,222 HD patients compared dialyzable beta-blockers (atenolol, metoprolol, and bisoprolol) with non-dialyzable beta-blockers (carvedilol and propranolol) on outcomes of all-cause mortality and major adverse cardiac events over 7 years of treatment.[30] Contrary to prior school of thought, the use of dialyzable beta-blockers was associated with a significantly lower risk of both all-cause mortality and major adverse cardiac events, suggesting that properties other than

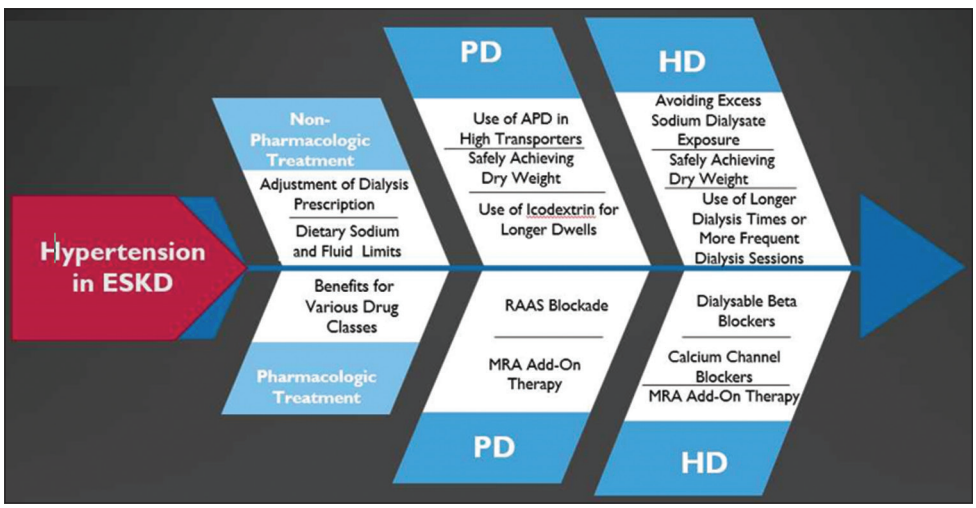


Figure 2: Summary of treatment options for hypertension in end-stage kidney disease patients

the drug's dialyzability contributed to their observed clinical benefits.

With regard to other medication classes, observational studies have shown that continuation of loop diuretics in patients with residual renal function can play a role in limited interdialytic weight gain.[31] Other medication classes such as alpha-agonists, alpha-blockers, and vasodilators have been used in ESKD as add-on therapies, individualizing such therapies to patient tolerance and side effects. Overall, recent clinical evidence suggests that beta-blockers followed by calcium channel blockers can be considered as first-line anti-hypertensive therapy for HD patients; the current evidence suggests benefits for RAAS blockade among PD patients. MRA agents have shown benefit in both HD and PD. Despite this, recent KDIGO guidelines do not specify a preferred first-line anti-hypertensive regimen in dialysis patients.[8]

Conclusion

The treatment of hypertension in ESKD patients remains a clinically challenging task for clinicians around the world [Figure 2]. The high prevalence of this disease continues to motivate nephrologists to diagnose and treat it. However, its pathophysiology remains complex, and understanding it can continue to drive our therapeutic options. The current literature does not provide clear guidance for target BP goals; however, BP goals may be able to be extrapolated from the general population to guide therapy. Monitoring BP may be best in the ambulatory setting and encouraging patients to be attentive of their home BP recordings appears best. A variety of non-pharmacologic options have been proposed for hypertension treatment, including an array of dialysis prescription alterations as well as individual restrictions on fluid and sodium intake. If pharmacologic options are required, beta-blockers and calcium channel blockers, among other agents, may be best in HD, although some data do suggest benefit from the use of RAAS blockade in PD patients. Overall, other guidelines still do not suggest preferred first- and second-line anti-hypertensive agents in the ESKD population, and further data are needed to make more concrete recommendations.

References

1. Sarafidis PA, Persu A, Agarwal R, Burnier M, de Leeuw P, Ferro C, *et al*. Hypertension in dialysis patients: A consensus document by the European renal and cardiovascular medicine (EURECA-m) working group of the European renal association-European dialysis and transplant association (ERA-EDTA) and the hypertension and the kidney working group of the European society of hypertension (ESH). J Hypertens 2017;35:657-76.
2. Agarwal R. Epidemiology of interdialytic ambulatory hypertension and the role of volume excess. Am J Nephrol 2011;34:381-90.
3. Agarwal R, Nissenson AR, Batlle D, Coyne DW, Trout JR, Warnock DG. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. Am J Med 2003;115:291-7.
4. Vaios V, Georgianos PI, Liakopoulos V, Agarwal R. Assessment and management of hypertension among patients on peritoneal dialysis. Clin J Am Soc Nephrol 2019;14:297-305.
5. Van Buren PN, Inrig JK. Hypertension and hemodialysis: Pathophysiology and outcomes in adult and pediatric populations. Pediatr Nephrol 2012;27:339-50.
6. Hall JE. The renin-angiotensin system: renal actions and blood pressure regulation. Compr Ther 1991;17:8-17.
7. Vallance P, Leone A, Calver A, Collier J, Moncada S. Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. Lancet 1992;339:572-5.
8. Flythe JE, Chang TI, Gallagher MP, Lindley E, Madero M, Sarafidis PA, *et al*. Blood pressure and volume management in dialysis: Conclusions from a kidney disease: Improving global outcomes (KDIGO) controversies conference. Kidney Int 2020;97:861-76.
9. Van Buren PN, Inrig J. Mechanisms and treatment of intradialytic hypertension. Blood Purif 2016;41:188-93.
10. KDOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 2005;45:S1-153.
11. Sarafidis PA, Mallamaci F, Loutradis C, Ekart R, Torino C, Karpetas A, *et al*. Prevalence and control of hypertension by 48-h ambulatory blood pressure monitoring in haemodialysis patients: A study by the European cardiovascular and renal medicine (EURECA-m) working group of the ERA-EDTA. Nephrol Dial Transplant 2018;33:1872.
12. Parati G, Ochoa JE, Bilo G, Agarwal R, Covic A, Dekker FW, *et al*. Hypertension in chronic kidney disease part 1: Out-of-office blood pressure monitoring: Methods, thresholds, and patterns. Hypertension 2016;67:1093-101.
13. Agarwal R, Light RP. Chronobiology of arterial hypertension in hemodialysis patients: Implications for home blood pressure monitoring. Am J Kidney Dis 2009;54:693-701.
14. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, *et al*. Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med 2010;362:590-9.
15. Georgianos PI, Agarwal R. Blood pressure control in conventional hemodialysis. Semin Dial 2018;31:557-62.
16. Movilli E, Gaggia P, Zubani R, Camerini C, Vizzardi V, Parrinello G, *et al*. Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. Nephrol Dial Transplant 2007;22:3547-52.
17. Kim YL, Biesen WV. Fluid overload in peritoneal dialysis patients. Semin Nephrol 2017;37:43-53.
18. Davies SJ, Woodrow G, Donovan K, Plum J, Williams P, Johansson AC, *et al*. Icodextrin improves the fluid status of peritoneal dialysis patients: Results of a double-blind randomized controlled trial. J Am Soc Nephrol 2003;14:2338-44.
19. Davies SJ, Phillips L, Naish PF, Russell GI. Peritoneal glucose exposure and changes in membrane solute transport with time on peritoneal dialysis. J Am Soc Nephrol 2001;12:1046-51.
20. Agarwal R, Sinha AD. Cardiovascular protection with antihypertensive drugs in dialysis patients: Systematic review and meta-analysis. Hypertension 2009;53:860-6.
21. Zannad F, Kessler M, Lehert P, Grünfeld JP, Thuilliez C, Leizorovicz A, *et al*. Prevention of cardiovascular events in end-stage renal disease: Results of a randomized trial of fosinopril

and implications for future studies. Kidney Int 2006;70:1318-24.
22. Iseki K, Arima H, Kohagura K, Komiya I, Ueda S, Tokuyama K, *et al*. Effects of angiotensin receptor blockade (ARB) on mortality and cardiovascular outcomes in patients with long-term haemodialysis: A randomized controlled trial. Nephrol Dial Transplant 2013;28:1579-89.
23. Fang W, Oreopoulos DG, Bargman JM. Use of ACE inhibitors or angiotensin receptor blockers and survival in patients on peritoneal dialysis. Nephrol Dial Transplant 2008;23:3704-10.
24. Zhang L, Zeng X, Fu P, Wu HM. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for preserving residual kidney function in peritoneal dialysis patients. Cochrane Database Syst Rev 2014;6:CD009120.
25. Tepel M, Hopfenmueller W, Scholze A, Maier A, Zidek W. Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients. Nephrol Dial Transplant 2008;23:3605-12.
26. Matsumoto Y, Mori Y, Kageyama S, Arihara K, Sugiyama T, Ohmura H, *et al*. Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. J Am Coll Cardiol 2014;63:528-53.
27. Lin C, Zhang Q, Zhang H, Lin A. Long-term effects of low-dose spironolactone on chronic dialysis patients: A randomized placebo-controlled study. J Clin Hypertens (Greenwich) 2015;18:121-8.
28. Agarwal R, Sinha AD, Pappas MK, Abraham TN, Tegegne GG. Hypertension in hemodialysis patients treated with atenolol or lisinopril: A randomized controlled trial. Nephrol Dial Transplant 2014;29:672-81.
29. Inrig JK, Van BP, Kim C, Vongpatanasin W, Povsic TJ, Toto R. Probing the mechanisms of intradialytic hypertension: A pilot study targeting endothelial cell dysfunction. Clin J Am Soc Nephrol 2012;7:1300-9.
30. Wu PH, Lin YT, Kuo MC, Liu JS, Tsai YC, Chiu YW, *et al*. β-blocker dialyzability and the risk of mortality and cardiovascular events in patients undergoing hemodialysis. Nephrol Dial Transplant 2020;35:1959-65.
31. Sibbel S, Walker AG, Colson C, Tentori F, Brunelli SM, Flythe J. Association of continuation of loop diuretics at hemodialysis initiation with clinical outcomes. Clin J Am Soc Nephrol 2019;14:95-102.

How to cite this article: Farmakis C, Collazo-Maldonado R. Hypertension in end-stage kidney disease. Hypertens 2021;7(1): 45-49.

Source of support: Nil, **Conflicts of interest:** None

INDIAN SOCIETY OF HYPERTENSION
World Hypertension League
CURRENT MEDICAL CONCEPTS
HTNJ
CrossMark

Review Article

Kidney disease in the coronavirus disease-2019 pandemic

Stephen Regina, Roberto Collazo-Maldonado

Department of Internal Medicine, 1441 N Beckley Ave, Methodist Dallas Medical Center, Dallas, Texas, 75203, United States

Abstract

While Coronavirus disease-2019 (COVID-19) is primarily a respiratory tract infection in most cases of mild to moderate disease, severe disease can involve multi-organ failure including acute kidney injury (AKI). COVID-19-associated AKI may require renal replacement therapy (RRT) in the acute setting or chronically after hospital discharge. The COVID-19 pandemic presented considerable difficulties to the nephrology community, requiring epidemiologic, clinical, and pathologic studies of AKI associated with the acute phase of infection. In this review article, AKI studies, pathologic entities, and specific adaptations to RRT will be discussed.

Key words: Acute kidney injury, Collapsing glomerulopathy, Coronavirus disease-2019, Renal replacement therapy

Introduction

"Coronavirus disease-2019" (COVID-19) emerged as an infectious disease in late 2019 that began as an outbreak in Wuhan, China. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogenic viral strain causing COVID-19, a clinical syndrome of primary pneumonia and respiratory failure with a secondary hyperinflammatory syndrome, cytokine dysregulation, and other effects. COVID-19 has a 1–2 week asymptomatic incubation period with a low likelihood of a positive diagnostic assay.[1] After respiratory symptom onset, the virus can be isolated from samples obtained from nasopharyngeal swab and detected by polymerase chain reaction (PCR) assay up to 3–4 weeks post-infection. Bronchoalveolar lavage PCR and stool PCR remain positive for SARS-CoV-2 up to 4 and after 6 weeks post-infection, respectively. IgM is detectable by serologic testing from 10 days to 6 weeks post-infection, and IgG is durably detectable post-infection.

As of April 2021, there have been over 148 million COVID-19 cases worldwide and over 3.1 million deaths. Within the United States there have been 32.1 million cases with over 572,000 deaths. One meta-analysis of 2486 patients from five countries found that among hospitalized patients with COVID-19 pneumonia, 33% developed acute respiratory distress syndrome (ARDS), 26% required intensive care unit (ICU) care, and 16% required ventilator support.[2] Among ICU patients, 63% required ventilator support, 75% developed ARDS, and there was a 45% mortality rate. ARDS was 90% prevalent among the fatalities as determined by postmortem lung examination revealing diffuse alveolar damage.

Extrapulmonary Targets of Infection

While primary SARS-CoV-2 infection follows droplet and airborne transmission through the respiratory route, patients with COVID-19 pneumonia and secondary hyperinflammatory syndrome have been reported to have extrapulmonary complications. Symptoms and findings include neurological (headaches, encephalopathy, Guillain-Barre syndrome, and stroke), cardiac (acute cardiomyopathy, myocarditis, arrhythmias, and acute cor pulmonale), renal (acute kidney injury [AKI], proteinuria, and hematuria), hepatic (elevated transaminases and bilirubin), gastrointestinal (nausea, vomiting, abdominal pain, and diarrhea), hematologic (deep venous thrombosis, pulmonary embolism, and intravascular catheter-associated thrombosis), and dermatologic (livedo reticularis, urticaria, vesicles, and lupus pernio-like lesions).[3,4] Furthermore,

Address for correspondence:
Dr. Stephen Regina, Department of Internal Medicine, 1441 N Beckley Ave, Methodist Dallas Medical Center, Dallas, Texas, 75203, United States. E-mail: stephenregina@mhd.com

Received: 24-04-2021; Accepted: 01-05-2021
doi: 10.15713/ins.johtn.0217

thrombotic disorders have been described in multiple organ systems, including cerebral venous sinus thrombosis, renal infarction, portal venous thrombosis, and mesenteric vessel thrombosis.[5,6] These events have been linked to anti-phospholipid antibodies in observational studies.[7,8]

AKI Prevalence

Early international reports from China, Europe, and the United Kingdom showed wide-ranging AKI prevalence from 0.5% to 46%. Furthermore, Chinese studies did not report prevalence of chronic kidney disease (CKD), a major AKI risk factor, among those with incident AKI.[9] Later European and US reports indicated a greater burden of comorbid conditions than early reports, with higher rates of AKI.

One cooperative study of populations of New Orleans and three New York systems specifically assessed AKI and outcomes at 5–7 weeks post-infection.[9] AKI risk factors of male sex, African American race, and age over 50 years were identified. CKD and hyperkalemia were independent predictors of KDIGO Stage III AKI. There were higher rates of AKI and requirement of renal replacement therapy (RRT) in patients with COVID-19 versus matched historical control patients within the same hospitals. Patients with AKI were more likely to require ICU admission, require ventilator support, and vasopressors. Furthermore, 90% of ventilated COVID-19 patients versus 22% of non-ventilated COVID-19 patients exhibited AKI. COVID-19 patients with AKI also had significantly higher levels of inflammatory markers ferritin, d-dimer, C-reactive protein, lactate dehydrogenase, and procalcitonin. COVID-19 patients with AKI exhibited increased in-hospital mortality compared to COVID-19 patients without AKI (45% vs. 7%). In the ICU, 52% of COVID-19 patients with AKI had in-hospital mortality compared to 9% of patients without. AKI was associated with significant risk for in-hospital mortality, with 37.5 deaths per 1000 patient-days among AKI patients versus 10.8 deaths per 1000 patient-days among non-AKI patients. Forty-three percent of patients with AKI had abnormal kidney function at time of hospital discharge.

The STOP-COVID group of investigators in the United States began a multi-center collaborative study in March 2020 that enrolled over 5000 patients with COVID-19 admitted to ICUs at 68 centers. Descriptive and laboratory data were entered into an online database for statistical analysis. An initial study identified a 28-day mortality rate of 35.4% among 2215 critically ill patients.[10] Mortality risk factors included male sex, age, obesity, coronary disease, acute organ dysfunction, and admission to a hospital with fewer than 50 ICU beds, which carried over three-fold increase in mortality risk. There was a 30% lower risk of mortality in a subgroup of 384 (11%) patients treated with tocilizumab versus those receiving protocolized care (n = 3491). In a subgroup analysis done according to the presence of CKD (n = 521) and patients receiving chronic dialysis (n = 143) before hospital admission for COVID-19, compared to control patients without kidney disease, mortality rates were found to be 50% (HR 1.41), 51% (HR 1.25), and 35%, respectively. Chronic dialysis patients were found to exhibit more rapid progression of symptoms requiring ICU admission relative to control group patients, and they were more likely to present with metabolic encephalopathy at the time of admission. In a later analysis, investigators performed logistic regression to identify risk factors for AKI-RRT.[11] The determined risk factors were baseline CKD, male sex, non-white race, obesity, severe ARDS, and higher d-dimer level. Among the study population (n = 3099), 21% of patients developed AKI-RRT, 63% of AKI-RRT patients died in the hospital, and 34% of survivors of the index hospital admission remained dialysis-dependent on hospital discharge. About one in six patients were still dialysis-dependent 60 days after ICU admission.

AKI Mechanisms

The etiology of AKI during acute illness with COVID-19 is multifactorial. There is proven parenchymal viral infection of the kidney, which can manifest as rare primary glomerular disease, such as collapsing glomerulopathy, thrombotic microangiopathy (TMA), minimal change disease, profound proximal tubular injury, and necrosis. Superimposed on direct cytopathic effects are systemic factors due to critical illness, including sepsis, hypotension, hyperperfusion, arrhythmias, hypoxia, viral myositis, and rhabdomyolysis as well as nephrotoxic exposures such as intravenous contrast, vancomycin, and other antimicrobial agents [Figure 1].[12]

Direct viral entry of SARS-COV-2 into renal parenchymal cells is mediated by viral S-protein binding the angiotensin-converting enzyme 2 (ACE-2) receptor.[13] In renal tissue, ACE-2 expression is greatest in the proximal convoluted tubule. The viral S-protein is cleaved by host cellular transmembrane proteases (e.g., TMPRSS2 in the distal convoluted tubule) which permit ACE-2 recognition. There are postulated to be other proteases in the proximal convoluted tubule where viral mediated injury is more pronounced.[13]

This viral pathway of cell entry fostered two hypotheses of how renin-angiotensin-aldosterone system (RAAS) inhibition may have a role in the propagation of viral cytopathic injury to renal cells.[14] In the first hypothesis, RAAS inhibitor use increases ACE-2 abundance on the renocyte surface, enhances viral entry, and has a harmful effect. In the second hypothesis, reduced concentrations of angiotensin II and reduced angiotensin II type 1 receptor activation enhances Mas receptor activation, leading to attenuation of inflammation and fibrosis in tissues expressing ACE-2. These hypotheses were examined in the BRACE CORONA trial, which enrolled patients (n = 659) at 29 sites in Brazil with a mean age of 56 years.[15] Investigators found no difference in outcomes in patients who were maintained on RAAS inhibitors (n = 334) versus patients stopping RAAS inhibitor use (n = 325) for 30 days following a COVID-19 diagnosis. There was no significant difference in the primary endpoint of patient life-days and hospitalization-free days.

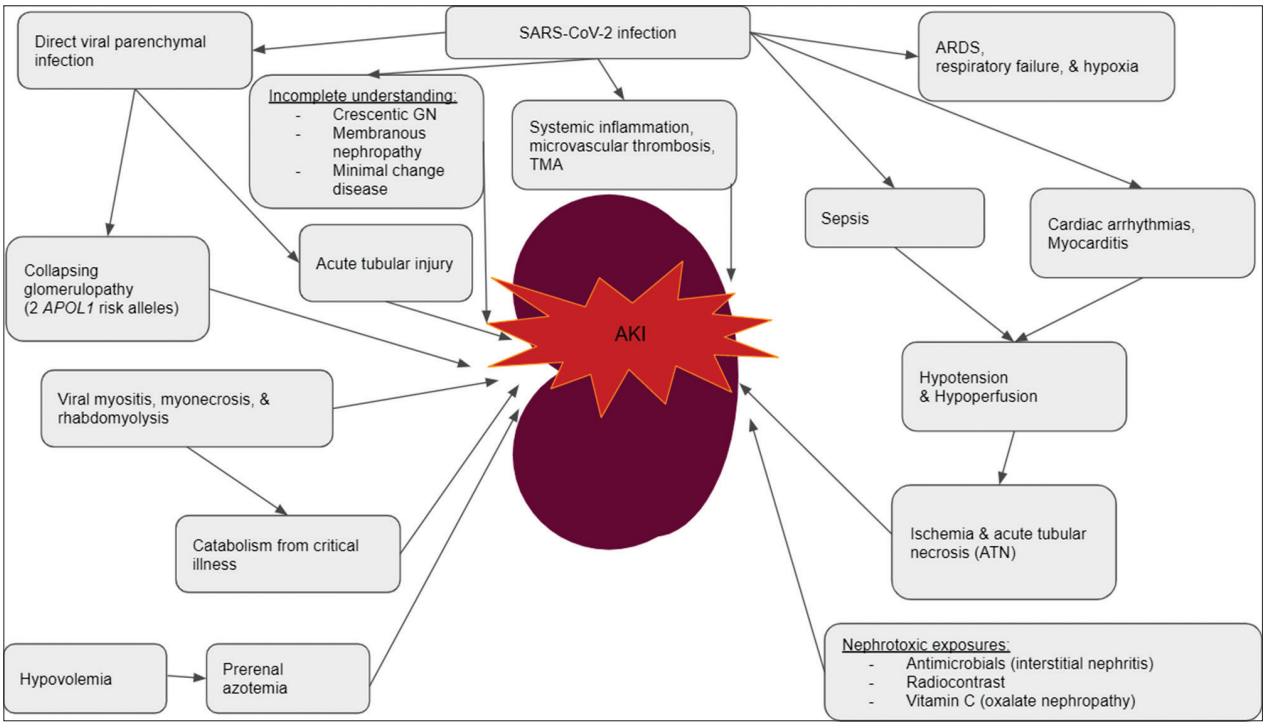


Figure 1: Direct (virally mediated) and indirect mechanisms of AKI in COVID-19

Secondary endpoints including all-cause mortality difference at 30 days, rates of myocardial infarction, stroke, and disease progression were also not significantly different between groups. A potential limitation of the study was the relatively young study population and the short period of study.

Pathologic Reports

Pathological reports provided insight into the COVID-19-associated AKI and urinary abnormalities. One of the largest series of postmortem examinations of Wuhan patients who died of COVID-19 included 26 patients.[16] In this study, the average age of deceased patients was 69 years. The patients died of respiratory failure and multi-organ failure. Nine patients (34%) had laboratory testing showing clinical kidney injury, including elevated serum creatinine, and urinalysis showing hematuria, proteinuria, and pyuria in varying severity. All patients were confirmed COVID-19-positive by nucleic acid amplification tests and had typical lung imaging. Eleven patients had past histories of hypertension, diabetes, or both. Light microscopy showed tubular necrosis with loss of the brush border, vacuolar degeneration, necrotic epithelia, and inflammatory infiltrates in the tubules and arterioles. Some biopsies also showed erythrocyte aggregation and obstruction in capillary loops without distinct TMA or fibrin thrombi. Electron microscopy showed purported viral particles in the cytoplasm of tubular cells and podocytes, but this was disputed in letters with other authors demonstrating that they were more consistent with clathrin-coated vesicles, an endogenous structure, and cellular transport mechanism.[17] One patient with historical IgA nephropathy had electron microscopic evidence of relapsing disease. A common finding among many of the biopsies was erythrocyte aggregation and varying degrees of endothelial injury. Two-thirds of patients had characteristic changes associated with diabetic nephropathy on electron microscopy. Immunohistochemistry staining showed nonspecific scarring with lymphocytic infiltrates and occasional macrophages. CD235a-positive staining was used to positively demonstrate erythrocyte obstruction. Immunofluorescence demonstrated altered ACE-2 patterns with enhanced prominence in the proximal tubules relative to control biopsies, particularly those with severe tubular injury. Indirect immunofluorescence for SARS-CoV-2 nucleoprotein showed tubular inclusions, with three out of six cases showing a granular pattern of staining in the nucleus or cytoplasmic distribution in the tubular epithelia.

Several independent case reports established the occurrence of collapsing glomerulopathy in patients with COVID-19.[18-21] These patients reportedly had severe AKI with heavy proteinuria, with later onset than the pulmonary and systemic disease course. Biopsies revealed severe collapsing glomerulopathy, prominent tubular injury, diffuse podocyte effacement, and the presence of endothelial tubuloreticular inclusions.[21] One patient had renal recovery after respiratory recovery, and two patients remained dialysis-dependent at time of hospital discharge. The occurrence of primary glomerulopathy was ascertained to be a direct viral effect in one patient and be a cytokine effect in two patients.

All patients were of Sub-Saharan African descent and two patients tested carried renal risk alleles for *APOL1*. A pathogenic explanation for collapsing glomerulopathy is that SARS-CoV-2 infection may be a "second hit" in individuals harboring *APOL1* risk alleles, leading to podocyte dysregulation and injury.[22]

Challenges and Adaptations to RRT

RRT in the inpatient setting faced challenges during the COVID-19 pandemic. As COVID-19 patients developed the secondary hyperinflammatory phase of the disease, clotting of the dialysis filter became a problematic and often recurrent issue.[23] Centers developed and reported their own protocols for monitoring the severity of coagulopathy and thrombotic diathesis with d-dimer and anti-Xa levels.[24] Full-dose therapeutic intravenous heparin emerged as the ideal anticoagulant for patients with COVID-19-associated coagulopathy.[25]

Concerning continuous RRT (CRRT) in particular, the proprietary AN69 filter Baxter Oxiris received an FDA Emergency Use Authorization (EUA). The terms of the EUA permit the filter to be selected for use for COVID-19 patients who have early acute lung injury or clinical ARDS and concomitant life-threatening disease, including septic shock, multiple organ dysfunction, and/or organ failure.[26] The filter has a novel three-layer membrane structure with a heparin-grafted membrane to reduce thrombogenicity, a polyethyleneimine surface treatment for endotoxin adsorption, and an enhanced AN69 membrane for cytokine adsorption. Available data suggest that the Oxiris filter may reduce the number of filter-related complications in patients with COVID-19.[27]

In addition to disease-related challenges, staffing and technical challenges surrounding CRRT in the ICU also emerged. Due to supply deficits in personal protective equipment (PPE), strategies to conserve PPE became essential. Some centers implemented dialysis extension tubing to locate the dialysis machine outside of the patient's room so that machine alarms and adjustments could be addressed by the staff or technician without them donning PPE. This also reduced some of the burden of machine disinfection between treatments on different patients. Many centers also adopted styles or implemented policies on selection of RRT modality and time use for treatments.[28] Examples include running CRRT for 12 h per patient per day if appropriate according to the individual goal for fluid balance and delivered clearance, and selection of prolonged intermittent RRT as the modality for patients with intermediate hemodynamic (in)stability.

Acute peritoneal dialysis (PD) for end-stage renal disease (ESRD) and AKI patients with COVID-19 was protocolized at some epidemic centers where medical need was above capacity.[29] Recipients were ESRD-PD patients or AKI patients initiated on acute PD as salvage therapy after CRRT clotting, or as the primary modality of RRT due to limited capacity. Acute PD is not the ideal modality in patients with active abdominal pathology, recent abdominal surgery, severe hyperkalemia, or increased intra-abdominal pressure. Acute PD requires the placement of a peritoneal catheter either at the bedside or laparoscopically. Patients intended to begin acute PD as the modality for RRT are recommended to be initiated strategically before the development of metabolic or fluid-related emergencies.

Conclusion

COVID-19 has been recognized not only as a respiratory disease, but also for its extrapulmonary effects. COVID-19 patients can present with severe AKI that requires intermittent dialysis or CRRT. The prevalent AKI phenotype in COVID-19 patients is ischemic tubular injury, although more rare primary glomerular presentations, including collapsing glomerulopathy, have been reported. Renal injury is linked to direct SARS-CoV-2 infection of the kidney parenchyma via the ACE-2 receptor. However, adverse outcomes were comparable among patients continuing or suspending use of RAAS inhibitors during hospital admission for acute COVID-19, indicating that blockade of the ACE-2 inhibitor in the kidney is not related to more severe forms of COVID-19. Nephrologists have faced several inpatient RRT challenges during the COVID-19 pandemic. These challenges require consultants and centers to rapidly adapt RRT protocols as well as to adeptly solve staffing and technical issues related to caring for COVID-19 patients with AKI.

References

1. Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. JAMA 2020;323:2249-51.
2. Tzotzos SJ, Fischer B, Fischer H, Zeitlinger M. Incidence of ARDS and outcomes in hospitalized patients with COVID-19: A global literature survey. Crit Care 2020;24:516.
3. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, *et al*. Extrapulmonary manifestations of COVID-19. Nat Med 2020;26:1017-32.
4. Wald R, Bagshaw SM. COVID-19-associated acute kidney injury: Learning from the first wave. J Am Soc Nephrol 2021;32:4-6.
5. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalized patients with COVID-19 in a New York City health system. JAMA 2020;324:799-801.
6. Post A, den Deurwaarder ES, Bakker SJ, de Haas RJ, van Meurs M, Gansevoort RT, *et al*. Kidney infarction in patients with COVID-19. Am J Kidney Dis 2020;76:431-5.
7. Tung ML, Tan B, Cherian R, Chandra B. Anti-phospholipid syndrome and COVID-19 thrombosis: Connecting the dots. Rheumatol Adv Pract 2021;5:rkaa081.
8. Kallapur AS, Yen EY, Singh RR. Vascular thrombosis in COVID-19: A potential association with antiphospholipid antibodies. medRxiv 2020;2020:20224642.
9. Kant S, Menez SP, Hanouneh M, Fine DM, Crews DC, Brennan DC, *et al*. The COVID-19 nephrology compendium: AKI, CKD, ESKD and transplantation. BMC Nephrol 2020;21:449.
10. Flythe JE, Assimon MM, Tugman MJ, Chang EH, Gupta S, Shah J,

et al. Characteristics and outcomes of individuals with pre-existing kidney disease and COVID-19 admitted to intensive care units in the United States. Am J Kidney Dis 2021;77:190-203.
11. Gupta S, Coca SG, Chan L, Melamed ML, Brenner SK, Hayek SS, *et al*. AKI treated with renal replacement therapy in critically ill patients with COVID-19. J Am Soc Nephrol 2021;32:161-76.
12. Kellum JA, van Till JW, Mulligan G. Targeting acute kidney injury in COVID-19. Nephrol Dial Transplant 2020;35:1652-62.
13. Batlle D, Soler MJ, Sparks MA, Hiremath S, South AM, Welling PA, *et al*. Acute kidney injury in COVID-19: Emerging evidence of a distinct pathophysiology. J Am Soc Nephrol 2020;31:1380-3.
14. South AM, Tomlinson L, Edmonston D, Hiremath S, Sparks MA. Controversies of renin-angiotensin system inhibition during the COVID 19 pandemic. Nat Rev Nephrol 2020;16:305-7.
15. Lopes RD, Macedo AV, Silva PG, Moll-Bernardes RJ, Feldman A, Arruda GD, *et al*. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: Impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome SARS-CoV-2--The BRACE CORONA trial. Am Heart J 2020;226:49-59.
16. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, *et al*. Renal histopathologic analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020;98:219-27.
17. Farkash EA, Wilson AM, Jentzen JM. Ultrastructural evidence for direct renal infection with SARS-CoV-2. J Am Soc Nephrol 2020;31:1683-7.
18. Larsen CP, Bourne TD, Wilson JD, Saqqa O, Sharshir MA. Collapsing glomerulopathy in a patient with COVID-19. Kidney Int Rep 2020;5:935-9.
19. Kissling S, Rotman S, Gerber C, Halfon M, Lamoth F, Comte D, *et al*. Collapsing glomerulopathy in a COVID-19 patient. Kidney Int 2020;98:228-31.
20. Kudose S, Batal I, Santoriello D, Xu K, Barasch J, Peleg Y, *et al*. Kidney biopsy findings in patients with COVID-19. J Am Soc Nephrol 2020;31:1959-68.
21. Nasr SH, Kopp JB. COVID-19-associated collapsing glomerulopathy: An emerging entity. Kidney Int Rep 2020;5:759-61.
22. Velez JC, Caza T, Larsen CP. COVAN is the new HIVAN: The re-emergence of collapsing glomerulopathy with COVID-19. Nat Rev Nephrol 2020;16:565-7.
23. Endres P, Rosovsky R, Zhao S, Krinsky S, Percy S, Kamal O, *et al*. Filter clotting with continuous renal replacement therapy in COVID-19. J Thromb Thrombolysis 2020;7:1-5.
24. Hardy M, Lecompte T, Douxfils J, Lessire S, Dogné JM, Chatelain B, *et al*. Management of the thrombotic risk associated with COVID-19: Guidance for the hemostasis laboratory. Thromb J 2020;18:17.
25. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094-9.
26. Baxter International. Oxiris for Critical Care; 2020. Available from: https://www.baxter.com/oxiris-critical-care. [Last accessed on 2020 Oct 29].
27. Zhang H, Zhu G, Yan L, Lu Y, Fang Q, Shao F. The absorbing filter Oxiris in severe coronavirus disease 2019 patients: A case series. Artif Organs 2020;44:1296-302.
28. Neyra JA, Connor MJ Jr., Tolwani A. Preparedness of kidney replacement therapy in the critically ill during COVID-19 surge. Kidney Int Rep 2020;5:961-4.
29. Shimonov D, Srivatana V. Peritoneal dialysis for acute kidney injury during the COVID-19 pandemic. Clin J Am Soc Nephrol 2020;15:1829-31.

How to cite this article: Regina S, Collazo-Maldonado R. Kidney disease in the coronavirus disease-2019 pandemic. Hypertens 2021;7(1): 50-54.

Source of support: Nil, **Conflicts of interest:** None

INDIAN SOCIETY OF HYPERTENSION
World Hypertension League
CURRENT MEDICAL CONCEPTS
HTNJ
CrossMark

Review Article

Implementation of a Resistant Hypertension Control Program in a Low-income Primary Care Setting in a High-Income Country: Lessons Learned and Global Applicability

Elizabeth W. Edwards[1], Gabrielle Rhinehart[2], Emily Ridley[2], Cheryl W. Chandler[2], Cynthia Garrick[2], Donald J. DiPette[1]

[1]Department of Internal Medicine, University of South Carolina and University of South Carolina School of Medicine, Columbia, South Carolina, United States, [2]Prisma Health-Midlands, Columbia, South Carolina, United States

Abstract

Hypertension is one of the leading causes of cardiovascular disease-related morbidity and mortality globally. Over the last several decades, there has been a broad shift in the management and pharmacologic treatment, specifically of hypertension, from a step-care approach to an individualized approach, and now to a population-based approach to increase the control rate of hypertension with the overall goal of decreasing major cardiovascular events related to poor control of hypertension. The Global HEARTS initiative of the World Health Organization and the HEARTS in the Americas Program of the Pan American Health Organization, in addition to the efforts of other organizations, serve as a blueprint for the implementation of a standardized, population-based approach to treating hypertension in the primary health-care setting. We have implemented components of such a program in our primary care clinic and resistant hypertension clinic here in Columbia, South Carolina, U.S. While the U.S. is a high-income country, the demographics of our clinic is one of low income and health literacy and our population is primarily black and Hispanic, female, and of an older age. Our clinic has successfully applied population-based treatment principles on an individualized basis to improve hypertension control rates and cardiovascular disease in our local community.

Key words: Hypertension, Hypertension clinic, Population-based care, Resistant hypertension

Introduction

Despite advances in the detection, treatment, and control of hypertension and its related target organ damage, hypertension remains one of the leading causes of cardiovascular disease-related morbidity and mortality worldwide. Globally, roughly one-third of all adults have hypertension, but two-thirds of these adults live in low- and middle-income countries.[1] Unfortunately, globally only approximately 14% of individuals with hypertension are controlled to a systolic blood pressure <140 mm Hg and a diastolic <90 mm Hg.[2] Controlling hypertension and reducing cardiovascular morbidity and mortality have been a major goal of the World Health Organization and other prominent organizations and stakeholders. In general while higher than in low-income countries, hypertension control rates in high-income countries such as the United States are dismal and are approximately 50–60%.[2] More ominous is the recent observation that in the U.S., hypertension control rates have suddenly started decreasing to currently approximately 44% from a high of 54% within the last decade.[2] This decrease has been accompanied by an increase in major cardiovascular events including stroke. It is important to recognize that even in high-income countries, heterogenous local communities with lower socioeconomic levels exist and the population of such communities faces many of the same challenges low-income countries face. The local population in Columbia, the capital of the state of South Carolina, located in the southeastern region of the U.S., mirrors that of the majority of the world. Approximately one-third of South Carolinians have been diagnosed with hypertension, but less than one-fifth is controlled – sobering data given that those

Address for correspondence:
Donald J. DiPette, Department of Internal Medicine, University of South Carolina and University of South Carolina School of Medicine, Columbia, South Carolina, United States. Office: 803-434-8090. Fax: 803-933-3042. E-mail: donald.dipette@uscmed.sc.edu

Received: 17-04-2021; Accepted: 24-04-2021
doi: 10.15713/ins.johtn.0216

Innovative Nature Science Publishers

with uncontrolled hypertension are 3 times as likely to die of heart disease.[3,4] Although a high-income state, we serve a low-income community and our patients face some of the same issues as their global counterparts such as disjointed healthcare, lack of health insurance, difficulty with transportation, socioeconomic struggles, and low education level, among others. We recognized the need to address these struggles and treat hypertension aggressively to improve the overall cardiovascular health of those that we medically serve. In addition to controlling hypertension, we strive to address these issues at the local and individual level. At the same time, we educate our learners – medical students, resident physicians, pharmacy residents, and pharmacy students – about the complexities of hypertension management and control. Although we are a resistant hypertension clinic, because of the population that we serve, a significant number of our patients battle poor adherence to lifestyle and pharmacologic anti-hypertensive management. One of our most important goals and challenges is to identify the reason for non-adherence and address the reason(s) on an individual basis. Importantly, the concepts that have been implemented in our hypertension clinic are generalizable to treating individuals with hypertension in the primary care setting. Based on the positive results we have seen over a short period of time, we have expanded the program to include another specialty clinic focused solely on diabetes mellitus, again embedded in the primary care setting.

Implementing a Team-based Hypertension Clinic in a Low-income Primary Care Setting

The leadership of the internal medicine residency training program at the University of South Carolina School of Medicine and our health-care system partner, Prisma Health, in Columbia, SC, recognized the need to address these critical local issues. In 2015, we responded to these needs by implementing a resistant hypertension clinic whose overarching goal was to increase the hypertension control rates of our primary care health clinic by counseling on healthy lifestyles; investigating barriers to the use of simple, evidence-based treatment regimens/protocols/algorithms; and providing in-depth education on hypertension using an interdisciplinary team of pharmacist, social worker, nurse, physicians, and learners. We strive to address the issues common to all individuals struggling with controlling hypertension and its comorbidities, as well as the issues unique to our specific population. Where appropriate, the clinic implemented interventions that are currently recommended in the WHO HEARTS technical package including standardized blood pressure measurements; a small anti-hypertensive pharmacologic formulary; a simple, standardized pharmacologic treatment algorithm; and clinical training on hypertension. Our internal medicine residents now have a structure for in-depth learning about hypertension. A large part of our model also includes intense counseling and close, frequent follow-up.

The HEARTS technical package, part of the broader World Health Organization and the Centers for Disease Control Global Hearts Initiative that includes two other packages that address prevention of cardiovascular disease, contains six modules that model an approach to the management of cardiovascular disease including hypertension. The HEARTS modules are:

- Healthy-lifestyle counseling
- Evidence-based treatment protocols
- Access to essential medicines and technology
- Risk based cardiovascular disease management
- Team-based care
- Systems for monitoring[5]
- The structure and activities of our resistant hypertension clinic align with most of the content of these modules.

Healthy lifestyle

The healthy-lifestyle module identifies four main behavioral risk factors for cardiovascular disease and describes techniques to encourage changing these risk factors. The four risk factors – unhealthy diet, tobacco use, physical inactivity, and harmful use of alcohol – plague our population in the resistant hypertension clinic. A diet low in fruits and vegetables and high in salt, fats, and sugars is a common diet of many of our patients. The typical diet of our patient population is high in sodium, as much as 8–10 g per day, and unfortunately low in potassium as well. Nineteen percent of our patients smoke. Most are inactive and the COVID-19 pandemic has worsened already limited access to gyms and pools; many of the neighborhoods in which our patients live are dangerous, preventing local outdoor exercise. We do not presently have data on alcohol use, but plan to obtain this information in the future. We provide a great deal of counseling on a healthy diet to address hypertension, including a variety of foods and at least 400 g of vegetables and fruits per day. We spend time identifying how much sodium each individual patient consumes and counseling on ways to reduce that consumption yet maintains appetizing meals. Many patients receive our handout on salt substitutes [Figure 1]. Given the key role that adequate dietary intake of potassium plays in lowering blood pressure and maintaining cardiovascular health, we have begun to provide dietary counseling on foods rich in potassium as well. We emphasize regular physical activity, focus on reducing tobacco use, and provide pharmacologic and non-pharmacologic approaches to smoking cessation. Because we intentionally limit the number of patients on our schedule, we have the necessary time to spend on intense counseling that many primary care clinics simply cannot afford.

Evidence-based Protocols

The evidence-based protocols module includes how to measure blood pressure and provides sample hypertension treatment protocols. In our clinic, we follow a precise guideline for measuring blood pressure. Our nursing staff is responsible for the correct and accurate measurement of blood pressure and follows the method for measuring blood pressure outlined in the SPRINT protocol.[6] Nursing ensures the use the appropriate cuff size and

Mrs. Dash Original Salt Free Blend (http://www.mrsdash.com/products/seasoning-blends/original-blend)
Ingredients: Onion, spices (black pepper, parsley, celery seed, basil, bay marjoram, oregano, savory, thyme, cayenne pepper, coriander, cumin, mustard, and rosemary), garlic, carrot, orange peel, tomato, lemon juice powder, citric acid, and oil of lemon.
Sodium chloride content: 0mg
Potassium content: 10mg per 1/4 tsp. serving
Mrs. Dash Onion and Herb Seasoning Blend (http://www.mrsdash.com/products/seasoning-blends/onion-herb-seasoning-blend)
Ingredients: Onion, garlic, spices (black pepper, sweet chili pepper, parsley, celery seed, basil, bay, marjoram, oregano, savory, thyme, cayenne pepper, coriander, cumin, mustard, and rosemary), orange peel, and natural flavor.
Sodium chloride content: 0 mg
Potassium content: 10 mg per 1/4 tsp. serving
Mrs. Dash Garlic and Herb Seasoning Blend (http://www.mrsdash.com/products/seasoning-blends/garlic-herb-seasoning-blend)
Ingredients: Garlic, onion, spices (black pepper, parsley, fennel, basil, bay, marjoram, oregano, savory, thyme, cayenne pepper, coriander, cumin, mustard, rosemary, and celery seed), carrot, orange peel, and spice extractives.
Sodium chloride content: 0 mg
Potassium content: 10 mg per 1/4 tsp. serving
Mrs. Dash Lemon Pepper Seasoning Blend (http://www.mrsdash.com/products/seasoning-blends/lemon-pepper-seasoning-blend)
Ingredients: Onion, spices (black pepper, basil, oregano, celery seed, bay, savory, thyme, cayenne pepper, coriander, cumin, mustard, rosemary, and marjoram), garlic, lemon juice powder, carrot, citric acid, lemon peel, turmeric color, and chili pepper.
Sodium chloride content: 0 mg
Potassium content: 10 mg per 1/4 tsp. serving
Lawry's Salt Free 17 Seasoning (http://www.mccormick.com/Lawrys/Flavors/Spice-Blends/Salt-Free-17)
Ingredients: Spices (black pepper, basil, oregano, celery seed, dill weed, sage, bay leaves, and turmeric), garlic, carrots, ground onion, minced onion, citric acid, toasted sesame seeds, red bell peppers, orange peel, corn starch, parsley flakes, and lemon peel.
Sodium chloride content: 0 mg
Potassium content: 0 mg
Nu-Salt Salt Substitute (http://www.nusalt.com/faq/)
Ingredients: Potassium chloride, potassium bitartrate, silicon dioxide, and natural flavor derived from citrus fruits and honey.
Sodium chloride content: 0 mg
Potassium content: 530 mg per 1/6 tsp. serving
Morton Lite Salt Mixture (http://www.mortonsalt.com/for-your-home/culinary-salts/food-salts/3/morton-lite-salt-mixture/)
Sodium chloride content: 290 mg per 1/4 tsp. serving
Potassium content: 350 mg per 1/4 tsp. serving
Morton Salt Substitute (http://www.mortonsalt.com/for-your-home/culinary-salts/food-salts/5/morton-salt-substitute/)
Sodium chloride content: 0 mg
Potassium content: 610 mg per 1/4 tsp. serving
Lo Salt (http://www.losalt.com/us/product/introducing-losalt/)
Sodium chloride content: 170 mg per 1/4 tsp. serving
Potassium content: 450 mg per 1/4 tsp. serving
MySALT original Salt Substitute (https://mysaltsub.com/collections/featured-products/products/my-salt-substitute)
Ingredients: Potassium chloride, L-lysine mono-hydrochloride, and calcium stearate
Sodium chloride content: 0 mg
Potassium content: 356 mg per 1/4 tsp. serving
MySALT garlic Salt Substitute (https://mysaltsub.com/collections/featured-products/products/my-salt-substitute-garlic)
Ingredients: Potassium chloride, L-lysine mono-hydrochloride, garlic, and calcium stearate
Sodium chloride content: 0 mg
Potassium content: 300mg per 1/4 tsp. serving
Diamond Crystal Salt Sense (https://diamondcrystalsaltstore.com/media/catalog/product/s/a/salt_sense_plain_product_sell_sheet.pdf)
Ingredients: Salt, silicon dioxide, tricalcium phosphate, sodium bicarbonate, dextrose, and potassium iodide (0.006%)
Sodium chloride content: 390 mg per 1/4 tsp. serving
Potassium content: 0 mg
NoSalt Original Sodium-free Salt Alternative
Ingredients: Potassium chloride, potassium bitartrate, adipic acid, silicon dioxide, mineral oil, and fumaric acid
Sodium chloride content: 0 mg
Potassium content: 650 mg

Figure 1: Sodium content of common salt substitutes

patient position and uses a validated, oscillometric, automated electronic device to measure the blood pressure at least 3 times in a quiet room without an observer. This method minimizes the chance for observer biases and manual collection errors. The goal blood pressure is <140/90 mm Hg in most patients and <130/80 mm Hg for those with cardiovascular disease, diabetes, chronic kidney disease, or high cardiovascular risk. We have recognized that standardized protocols, tailored for our specific environment, are successful in achieving blood pressure control. The clinic uses two protocols in the treatment of the patient with newly diagnosed hypertension – one initiating a single medication and the other initiating two medications [Figure 2]. Both protocols use the angiotensin-converting enzyme inhibitor lisinopril and the calcium channel blocker amlodipine in the initial steps. The angiotensin-converting enzyme inhibitor was chosen instead of an angiotensin receptor blocker solely due to its availability and low cost, even free. The starting dose of each is the half-maximal effective dose, which allows for only one titration step for blood pressure control if needed. Although these two protocols exist, we strongly recommend starting with two medications as the initial treatment. This dual antihypertensive approach as initial treatment is particularly appropriate for our clinic because these medications are free at one of the national supermarket pharmacy chains in our location; therefore, they are available to the majority of our patients who live or work near one of those pharmacies. It is extremely important given that approximately 500,000 South Carolinians (of a total state population of 5 million) lack health insurance. Furthermore, both of these two medications are available through a local medication assistance program that provides free prescription medications to uninsured South Carolina residents with income constraints. There is no charge to join the non-profit program and, once approved, patients are enrolled for up to 1 year. They usually have combination antihypertensives as well, such as lisinopril/hydrochlorothiazide, losartan/hydrochlorothiazide, and valsartan/hydrochlorothiazide. Because of the protocol-based approach we can mitigate clinical/therapeutic inertia which would otherwise prolong the duration of patients' uncontrolled hypertension, putting them at increased risk of hypertension-related complications.

Access to Essential Medications

The access to essential medicines and technology module provides information on supply chain management of cardiovascular medications, including procurement, distribution, management, and handling supplies. Since supply chain management is not typically at the clinic level and we do not dispense medications on site, our clinic is not actively or primarily involved with ensuring a steady supply of medications. However, we do try to confirm that our patients receive medications appropriate to their clinical needs, and we make every effort to encourage adherence. The fragmented health-care system in the U.S. means our patients often receive healthcare at multiple locations; therefore, health-care providers frequently do not have access to records outside of their own organizations. This situation leads to duplicate medications, unknown medications or doses, and health-care providers delivering conflicting care. This fragmentation is a constant struggle for our staff, and we simply do the best we can in requesting records and contacting outside health-care providers individually. Furthermore, many different healthcare insurance plans with varying cost coverage and medication formularies can complicate selecting medications that patients can afford. If access to medications hampers adherence, then the pharmacist's knowledge of different insurance plan formularies aids the resistant hypertension team in choosing medications which our patients can obtain and afford. Our pharmacist assesses patient adherence to medication at every visit by checking refill history, admittedly an imperfect assessment since many patients regularly may receive their meds through mail order or automated pharmacy fills, yet they may not take them.

Risk-based Cardiovascular Disease Management

The risk-based cardiovascular disease management module describes using a risk-based approach to assess and manage cardiovascular disease. Poor control of risk factors often stems from a result of a lack of awareness and our pharmacist, nurses, social worker, and physicians make every effort to tie adherence to reduced risk of heart attacks and strokes. We do not routinely measure cardiovascular risk unless it factors into the treatment decision of a given diagnosis or would enhance the educational value of the individual discussion regarding non-pharmacologic and pharmacologic therapy.

Team-based Care

The team-based care module explains the advantages of using an interdisciplinary team. Our particular interdisciplinary team consists of a pharmacist, often with a pharmacy resident or pharmacy students; a nurse specifically trained in cardiovascular disease; a social worker; two physicians; an internal medicine resident physician; and often medical students. The entire team plays an integral role in providing patient care centered around evidenced-based protocols. Our team collaborates extensively before each patient visit to develop a tentative plan for each patient and spends time teaching hypertension concepts. We have termed this group discussion "the huddle." Having an expanded team improves patient access to care in that at least one team member is almost always available to talk further to the patient before or after the visit. We use the diversity of our team members to try different approaches to counseling the patient, earning the patient's trust, and encouraging adherence to the treatment plan. We have been extremely fortunate in that we have had no staff turnover since the clinic's inception and believe it is, at least in part, because team members are valued, engaged, and feel important. Our patients know and like our team, and we have built a great deal of trust and fostered open communication. We are aware, however, that staff turnover, including physicians,

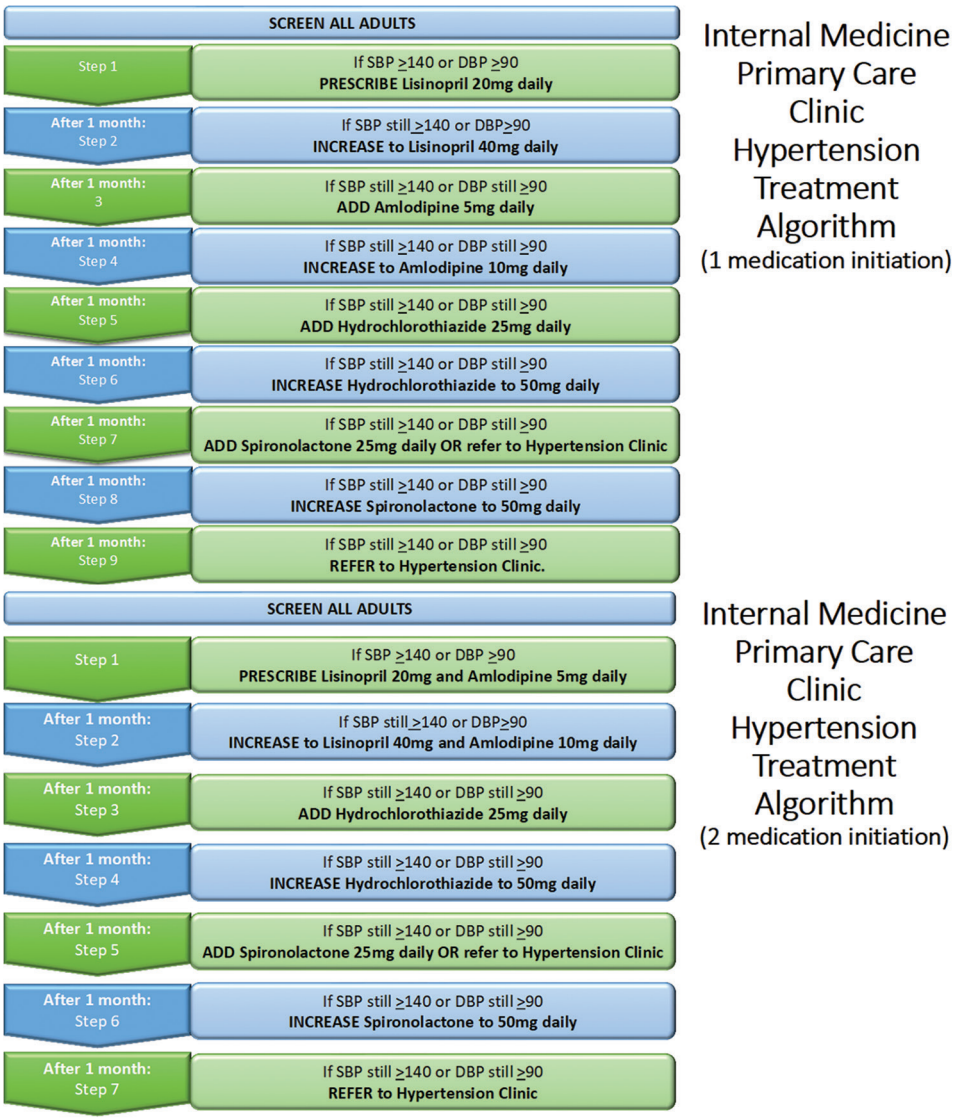


Figure 2: Hypertension Algorithms for 1- and 2-drug Initiation

is a major problem and barrier to success in other clinic settings, especially in low- to middle-income countries.

Systems for Monitoring

The module systems for monitoring contain information on monitoring and reporting on hypertension prevalence, awareness, treatment, and control. In our clinic, we use a very simple approach. Each patient has a running document that the resident updates after each visit. The document describes what was found on the initial visit of the patient (history, physical exam, average blood pressure, and laboratory results if obtained), what our team did and why, and any learning points. In the future, we would like to implement a treatment card, recording clinic blood pressures, to serve as a reminder to the patient of the importance of adhering to medications to control blood pressure, and to reduce cardiovascular risk.

Discussion

Hypertension is responsible for more deaths than any other single non-communicable disease risk factor. Thus, improved hypertension control at the population and individual level could have a substantial positive impact. Given the prevalence, human and economic consequences, and dismal control rates of hypertension, there is an urgency to change the approach to detecting and treating hypertension. Global control rates are estimated to be approximately 14%.[2] Even in high-income countries, recent data show declining control rates. According to NHANES surveys in the U.S., hypertension control rates have decreased from 53.8% in the 2013–2014 survey to 43.7% in the 2017–2018 survey.[7] If we use the blood pressure goal from the American College of Cardiology/America Heart Association of <130/80 mm Hg, the recent hypertension control rate in the U.S. is only 21%.[7] This decrease in control rates parallels

the increase in cardiovascular disease-related morbidity and mortality. Clearly, the present approach to the detection and especially management and treatment of hypertension is less than optimal. The U.S. Surgeon General's recent call to action to control hypertension highlights the fact that nearly half of adults in the U.S. have hypertension (using the criterion of ≥130/80 mm Hg for the diagnosis of hypertension). However, as mentioned above, only about 1 in 4 of those individuals are controlled,[8] which increases the risk for heart disease and stroke for millions of Americans. The U.S. Surgeon General's call to action identifies specific hypertension control goals and evidence-based interventions that can be implemented, adapted, and expanded in multiple settings across the U.S. and echoes a significant amount of the content in the Global HEARTS Initiative.

Given this background, there is an urgent need for a paradigm shift and a different way in approaching the detection, management, and treatment of hypertension. It is important to recognize that not very long ago there were no treatment recommendations and no effective pharmacologic agents for hypertension. However, when evidence clearly demonstrated that pharmacologic treatment of hypertension significantly decreased morbidity and mortality and safe, effective, and well tolerated pharmacologic agents became available, the health-care community adopted the step-care approach to treat hypertension. The step-care approach involved using a diuretic as first-step therapy and maximizing the dose if needed. If the blood pressure was still uncontrolled the next step was to add another agent and maximize the dose if needed. If the individual remained hypertensive, adding an additional agent was the third step, and so on. During this time, it was demonstrated that there were demographic differences in the blood pressure response to different antihypertensive classes. For instance, low-renin, salt sensitive individuals responded to a greater extent to diuretics and calcium channel blockers while high-renin, salt resistant individuals responded to a greater extent to beta blockers and renin angiotensin aldosterone inhibitors. Given this data, a more individualized approach to the pharmacologic treatment of hypertension gained favor. This individualized approach allowed for the use of any of the four primary antihypertensive classes as initial treatment, depending on race, gender, ethnicity, age, and comorbid conditions. The individualized approach initially included beta-blockers as a choice for initial treatment. However, given the concern that the use of beta-blockers may not reduce the incidence of stroke as much as the other classes of agents, most hypertension guidelines now recommend the use of any of the three present classes (diuretics, calcium-channel blockers, and renin angiotensin aldosterone inhibitors) as initial therapy in the newly diagnosed individual with hypertension. Although these efforts and programs were initially successful, they only have taken the control rates of hypertension so far. The step-care approach and the individualized approach both take time to control blood pressure and largely fail to address adequately the important barrier of clinical inertia, now recognized as a major obstacle to blood pressure control. These past efforts have led to a paradigm shift in the approach to hypertension that being a population-based approach to treatment. We obviously always treat one patient at a time, considering individual differences, but the overarching concept is to move to a population-based approach that is straightforward, simple, and importantly, primary care and health-system based [Figure 3].

Interestingly, earlier healthcare models have successfully addressed control of chronic medical conditions including hypertension. One such model is Kaiser Permanente. Established in 1945, Kaiser Permanente is one of the largest health-care systems in the U.S., with approximately 12 million members.[9] Kaiser Permanente uses evidence-based protocols embedded in an electronic medical record with access to essential medications, team-based care, robust progress monitoring, and timely clinician feedback. The Kaiser Permanente hypertension program rapidly exceeded national blood pressure control rates with control rates of up to 90%.[10] The improved population control of hypertension was associated with reductions in cardiovascular events.[11] The pharmacologic treatment protocol improved blood pressure control by initiating two anti-hypertensive agents in the initial treatment of the newly diagnosed individuals with hypertension, as well as detailing the use of additional anti-hypertensive agents if needed to achieve blood pressure control. In addition, medication titration intervals were clarified and the types of staff that could assist in timely patient follow-up was expanded (i.e. team-based care). The Kaiser Permanente model – with its dramatic improvements in hypertension control rates and reductions in major adverse cardiovascular events – serves as a prototype for the change required to decrease the burden of cardiovascular disease.

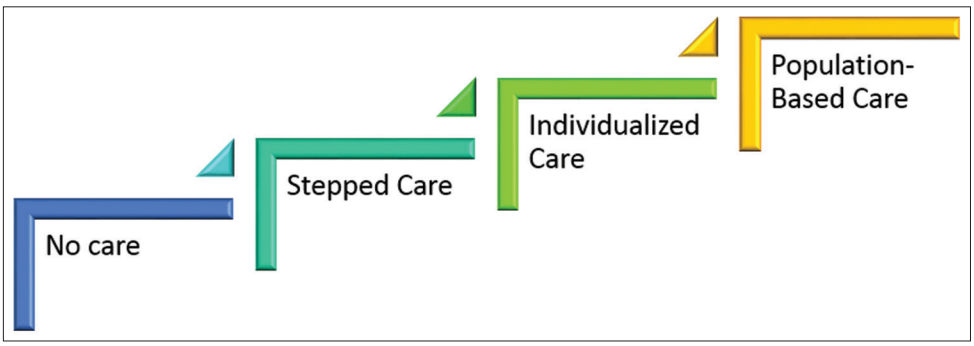


Figure 3: Approaches to care in the treatment of hypertension

If the paradigm shift to population-based hypertension care is to succeed, the system needs a blueprint for change. Patel *et al*. describe an approach the Centers for Disease Control and the Pan American Health Organization launched in 2013 to improve cardiovascular disease prevention and management using the treatment of hypertension as the entry point.[12] The project, initially known as the Standardized Hypertension Treatment and Prevention Project, builds on lessons learned from treating communicable diseases, such as HIV and tuberculosis, and advocates for standardized hypertension management protocols using a core set of available and affordable medications. In addition to guideline-based standardized treatment protocols and widely available medications, the project includes a registry to monitor and evaluate all patients within the system, promoting efficient management of populations of patients with hypertension and collecting data to track outcomes. Additional elements of the program are patient empowerment by involving patients in the decisions related to their treatment and a multidisciplinary team-based care approach. Finally, the project promotes increased awareness of hypertension as a public health priority. The Standardized Hypertension Treatment and Prevention Project has now been assimilated into the Global HEARTS Initiative and the HEARTS in the Americas Program.

Recently, the progress of the HEARTS in the Americas Initiative as a model of cardiovascular risk management, particularly hypertension, in the Caribbean and Latin America has been detailed.[13] The program is designed to be planned and implemented at the primary health-care level. The four founding countries (Barbados, Colombia, Chile, and Cuba) implemented the HEARTS program and demonstrated the model can rapidly and markedly improve hypertension control rates. At present, 12 countries have voluntarily implemented the initiative, with more to follow. Specifically, González *et al.* describe the implementation and success of HEARTS in Cuba.[14] With the assistance of the Pan American Health Organization, the Cuban Ministry of Public Health implemented HEARTS initially in a 26,000-patient clinical setting in Matanzas, Cuba, in 2016. The interventions of the Matanzas project included:

1. Standardized training on the management of hypertension
2. Education regarding lifestyle modifications
3. A simple hypertension management algorithm that included assessment of cardiovascular risk
4. A registry
5. A framework for monitoring and evaluation
6. Funding.

Like Kaiser Permanente's model, as well as newer hypertension guidelines from North America and Europe, the Matanzas algorithm started initial pharmacologic treatment with two antihypertensive agents from complementary classes. Almost 90% of those in the hypertension registry received antihypertensive medications. The hypertension control program markedly and rapidly improved blood pressure control over approximately 1 year. The control rate for the population increased from approximately 30–58%. The Matanzas project validated the potential of this model in a middle-income country.

One of the most important steps in a population-based hypertension control program is the development of a small yet comprehensive medication formulary and a simple, straightforward treatment algorithm. The key component of the treatment algorithm is the use of two medications either as two single pills or better yet in a fixed-dose combination, also termed single pill combination. All 12 countries presently in the HEARTS in the Americas Program use dual medication therapy in the initial treatment step. DiPette *et al*. highlight the importance of incorporating this strategy of initial pharmacologic combination treatment to improve hypertension control rates and outcomes.[15] For instance, it is well known that at least two or more pharmacologic agents are often required to control blood pressure.[16] In many studies (UKPDS, HOT, ALLHAT, ACCORD, HOPE-3, and SPRINT) participants often required two or more drugs – and some required as many as four – to achieve the goal blood pressure.[17-22] Therefore, the use of initial combination treatment especially in a fixed-dose, single-pill combination makes sense and can be advantageous in the management of hypertension by decreasing pill burden, medication side effects, and clinical inertia while improving adherence. Meta-analysis has demonstrated adding a drug is 5 times more effective than titrating a drug to its full dose.[23] Incorporating wider use of combination treatment is a practical and effective strategy to improve hypertension control rates and benefits the patient, provider, and health-care system.

Conclusion

It is important to acknowledge that planning and implementing the use of evidenced-based protocols in the treatment of hypertension exemplifies a paradigm shift into population-based hypertension care. The HEARTS program and the Kaiser Permanente experience facilitated the incorporation of a population-based framework while also allowing for individualization of care based on the demographics of our local community. Our clinic provides evidence and encouragement that change on a global level can begin by medically serving these local communities that mirror the demographics of the world. Not only does this clinic directly benefit our current patients but also we hope it will continue to benefit coming generations of patients and providers. As the learners who rotate through the clinic continue to accumulate lessons learned from this resistant hypertension clinic, they take with them the potential to practice medicine, specifically hypertension management, using a population-based approach. While hypertension management will inevitably continue to change and improve over the coming years, having an already existing specialty clinic positions us on the forefront of evidence-based medicine. A recently published paper describing implementation of the HEARTS initiative in 12 countries highlights that the initiative can be integrated into already existing health-care delivery systems.[24] This concept mirrors how our existing interdisciplinary team was able to apply similar principles

in an existing low-income primary care clinic setting. We hope the success of our model will offer a prototype for population-based treatment of other non-communicable diseases worldwide.

Acknowledgment

Donald J. DiPette is a Distinguished Health Sciences Professor, University of South Carolina and University of South Carolina School of Medicine, Columbia, South Carolina, U.S.A.

References

1. Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension. [Last accessed on 2021 Mar 13].
2. 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;134:441-50.
3. S.C. Department of Health and Environmental Control. SCDHEC. Heart Disease, Stroke. Available from: https://www.scdhec.gov/health/diseases-conditions/heart-disease-stroke. [Last accessed on 2021 Mar 14].
4. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. Arch Intern Med 1993;153:598-615.
5. Available from: https://www.paho.org/en/hearts-americas/hearts-americas-technical-package. [Last accessed on 2021 Mar 13].
6. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;198:50-50.
7. Rana J, Oldroyd J, Islam MM, Tarazona-Meza CE, Islam RM. Prevalence of hypertension and controlled hypertension among United States adults: Evidence from NHANES 2017-18 survey. Int J Cardiol Hypertens 2020;7:100061.
8. Available from: https://www.cdc.gov/bloodpressure/CTA.htm. [Last accessed on 2021 Mar 13].
9. Available from: https://www.about.kaiserpermanente.org/our-story/our-history. [Last accessed on 2021 Mar 13].
10. Available from: https://www.permanente.org/kaiser-permanente-nations-best-at-controlling-high-blood-pressure. [Last accessed on 2021 Mar 13].
11. Jaffe M, Young J. The kaiser permanente northern California story: Improving hypertension control from 44% to 90% in 13 years (2000 to 2013). J Clin Hypertens 2016;18:260-1.
12. Patel P, Ordunez P, DiPette D, Escobar MC, Hassell T, Wyss F, *et al*. Improved blood pressure control to reduce cardiovascular disease morbidity and mortality: The standardized hypertension treatment and prevention project. J Clin Hypertens (Greenwich) 2016;18:1284-94.
13. DiPette DJ, Goughnour K, Zuniga E, Skeete J, Ridley E, Angell S, *et al*. Standardized treatment to improve hypertension control in primary health care: The HEARTS in the Americas initiative. J Clin Hypertens (Greenwich) 2020;22:2285-95.
14. González YV, Campbell NR, Barrera EP, Martínez MC, Carrera AP, Rigau JM, *et al*. Implementation of a community-based hypertension control program in Matanzas, Cuba. J Clin Hypertens (Greenwich) 2020;22:142-9.
15. DiPette DJ, Skeete J, Ridley E, Campbell NR, Lopez-Jaramillo P, Kishore SP, *et al*. Fixed-dose combination pharmacologic therapy to improve hypertension control worldwide: Clinical perspective and policy implications. J Clin Hypertens (Greenwich) 2019;21:4-15.
16. Sica DA. Rationale for fixed-dose combinations in the treatment of hypertension: The cycle repeats. Drugs 2002;62:443-62.
17. Turner R, Matthews D, Neil A, Mcelroy H. Tight blood pressure control and risk of macrovascular and microvascular complications in Type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13.
18. Cruickshank JM. Hypertension optimal treatment (HOT) trial. Lancet 1998;352:573-4.
19. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). JAMA 2002;288:2981-97.
20. Mancia G. Effects of intensive blood pressure control in the management of patients with Type 2 diabetes mellitus in the action to control cardiovascular risk in diabetes (ACCORD) trial. Circulation 2010;122:847-9.
21. Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, *et al*. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2009-20.
22. SPRINT Research Group, Wright JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, *et al*. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103-16.
23. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 2009;122:290-300.
24. Giraldo GP, Joseph KT, Angell SY, Campbell NR, Connell K, DiPette DJ, *et al*. Mapping stages, barriers and facilitators to the implementation of HEARTS in the Americas initiative in 12 countries: A qualitative study. J Clin Hypertens (Greenwich) 2021;23:755-65.

How to cite this article: Edwards EW, Rhinehart G, Ridley E, Chandler CW, Garrick C, DiPette DJ. Implementation of a Resistant Hypertension Control Program in a Low-income Primary Care Setting in a High-Income Country: Lessons Learned and Global Applicability. Hypertens 2021;7(1): 55-62.

Source of support: Nil, **Conflicts of interest:** None