April- June 2021 Volume 7 Number 2
ISSN (p) 2454-5996
ISSN (e) 2455-4987

HYPERTENSION Journal

An Official Journal of Current Medical Concepts
Endorsed by: The Indian Society of Hypertension and
World Hypertension League (In Association with WHO)

HTNJ
Also available online at
www.htnj.in
www.incessantnature.com

Editor-in-Chief
C Venkata S Ram

Special Issue from Queen Elizabeth University Hospital and Institute of Cardiovascular and Medical Sciences, Glasgow, Scotland

Guest Editors:
Sandosh Padmanabhan, Linsay McCallum

April-June 2021 Vol-7 No-2
HYPERTENSION Journal
ISSN (p) 2454-5996

HTNJ

April-June 2021 Vol. 7 No. 2

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

Copyright © Incessant Nature Science Publishers Pvt. Ltd.

Editor-in-Chief

C Venkata S Ram, India

Editorial Coordinator

N Madhavi Latha

Editorial Board Members

Amal Banerjee Kolkata, India
Amit Khera Dallas, USA
Anuj Maheshwari Lucknow, India
Banshi Saboo Ahmedabad, India
D Prabhakaran New Delhi, India
Daniel Lackland Charleston, USA
Giuseppe Mancia Milan, Italy
Gregory YH Lip Birmingham, UK
HK Chopra New Delhi, India
Michael Weber New York, USA
Mohsin Wali New Delhi, India
Niteen V Deshpande Nagpur, India
Omkar Nath Tripathi Lucknow, India
PK Deb Kolkata, India
Rafael Castillo Manila, Philippines
Rajeev Gupta Jaipur, India
Ravi Shankar Erukulapati Telangana
Shailendra Vajpeyee New Delhi, India
Shashank R Joshi Mumbai, India
SN Narasingan Chennai, India
SS Iyengar Bengaluru, India
Sudhir R Naik Hyderabad, India
Thomas Giles New Orleans, USA
Tiny Nair Kerala, India
VV Muthusamy Madurai, India

Editorial Consultants

Addison A Taylor Houston, USA (Pharmacology and Clinical Trials)
Ambrish Mithal New Delhi, India (Endocrinology and Metabolism)
Aram V Chobanian Boston, USA (Guidelines and Preventive Cardiology)
Felix Mahfoud Homburg/Saar, Germany (Device-based Therapies and Resistant Hypertension)
John Bisognano Rochester, USA (Hypertension and Clinical Cardiology)
Ko Ko Yangon, Myanmar (Diabetes and Preventive Medicine)
Low L Ping Singapore (Clinical Cardiology Hypertension)
M Soma Sekhar Hyderabad, India (Nephrology)
Narsingh Verma Lucknow, India (Physiology and Hypertension)
Norman RC Campbell Calgary, Canada (Guidelines, Prevention and Health Policy)
Prakash Deedwania Fresno, USA (Clinical Cardiology, Metabolic Syndrome and Pharmacology)
Prashant Mathur New Delhi, India (Public Health, Medical Research and Government Policy)
Ramesh K Goyal Chennai/Ahmedabad, India (Biotechnology and Applied Pharmacology)
Sanjeev Sharma Hyderabad, India (Clinical Pharmacology)
Satyavan Sharma Mumbai, India (Cardiology)
Upendra Kaul New Delhi, India (Cardiology)
V Dayasagar Rao Hyderabad, India (Cardiology)
Vijay Kher New Delhi, India (Nephrology)
V Mohan Chennai, India (Diabetes

Section Editors

Hypertension Cases Section
VV Muthusamy
Maheshwari
Physiology and Pathophysiology Section
Narasingh Verma
Banshi Saboo
Clinical Pharmacology Section
Shailendra Vajpayee
Sanjeev Sharma
Hypertension Literature Capsule
Niteen Deshpande
SS Iyengar
Epidemiology and Population Sciences
Rajeev Gupta
Omkar Tripathi

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 2 |April - June 2021

Contents

EDITORIAL

- **Special Issue from Queen Elizabeth University Hospital and Institute of Cardiovascular and Medical Sciences, Glasgow, Scotland** 63
  Linsay McCallum, Sandosh Padmanabhan

REVIEW ARTICLES

- **Hypertension Residual Risk and Beyond – Five Decades of Insights from the Glasgow Blood Pressure Clinic** 64-70
  Stefanie Lip, Linsay McCallum, Sandosh Padmanabhan
- **The Evolution of Hypertension Guidelines: A Global and European Perspective with a Focus on Classification of Hypertension (Review)** 71-7
  Nicole Eu Chin Ng, Christian Delles
- **Hypertension and Uric Acid (Review)** 78-81
  Alexander MacDonald, Moustafa Ibrahim Mohamed Ahmed Morsy, Jesse Dawson
- **Transforming Hypertension Care through the Lens of Planetary Health** 82-7
  Clea du Toit, Linsay McCallum, Stefanie Lip, Sandosh Padmanabhan

TOPICAL COMMENTARY

- **Weight Management in Hypertension: A Scotland Perspective** 88-91
  Maggie Rostron, Linsay McCallum

CLINICAL IMAGES

- **An Unusual Cause of the Left Ventricular Hypertrophy and Heart Failure: Eosinophilic Myocarditis (Clinical Images)** 92-4
  Antonio Iaconelli, Francesca Lassandro Pepe, Lorenzo Genuardi, Mattia Galli, Domenico D'Amario, Frediano Inzani, Biagio Merlino, Tommaso Sanna, Pierpaolo Pellicori

CASE REPORTS

- **Aortic Narrowing – Takayasu or Mid-aortic Syndrome? (Case Report)** 95-8
  Peter Schulga, Rosalyn Ardill, Neil Turner, Ben C. Reynolds
- **Under Pressure (Case Report)** 99-102
  Ciaran Groome, Ailsa Doak, Catherine Stirling, Jennifer S. Lees

INDIAN SOCIETY OF HYPERTENSION
World Hypertension League
CURRENT MEDICAL CONCEPTS
HTNJ

Editorial

Special Issue from Queen Elizabeth University Hospital and Institute of Cardiovascular and Medical Sciences, Glasgow, Scotland

Linsay McCallum[1,2], Sandosh Padmanabhan[1,2]

[1]Department of Clinical Pharmacology and Therapeutics, Queen Elizabeth University Hospital, Glasgow, United Kingdom, [2]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom

Two special issues bring together a collection of up-to-date articles from Glasgow academic clinicians and their collaborators featuring a wide range of review topics and clinical cases from pediatric and adult hypertension practice.

In the first of these special issues, the flagship hypertension database from the Glasgow Blood Pressure Clinic established in 1969 features in a review by Lip *et al.*[1] describing it history and highlighting key research publications over the past 50 years that have expanded our understanding of hypertension. Chin *et al.*[2] analyze guidelines produced by the World Health Organization from 1962 to 1999 and the European Society of Hypertension/European Society of Cardiology between 2003 and 2018 to evaluate the changes in guidelines over time highlighting the limitations and inconsistencies. The association between serum uric acid concentration and blood pressure is discussed by MacDonald *et al.*[3] who evaluated the epidemiological, Mendelian randomization, and clinical trial data highlighting the need for further research in this area. A perspective from du Toit *et al.*[4] explores options on transforming hypertension care in the context of the current imperatives on climate change, social responsibility, and global health. Finally, Rostron *et al.*[5] offer a perspective on Scotland's efforts in reducing the population burden due to overweight and obesity.

This issue features three interesting and unique case reports from Schulga *et al.*,[6] Groome *et al.*,[7] and Iaconelli *et al.*[8] offering clinical learning pearls on Takayasu's arteritis, hypertensive emergency, an uncommon cause of acute left heart failure.

How to cite this article: McCallum L, Padmanabhan S. Special Issue from Queen Elizabeth University Hospital and Institute of Cardiovascular and Medical Sciences, Glasgow, Scotland. Hypertens 2021;7(2):63.

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

Address for correspondence:
Prof. Sandosh Padmanabhan, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom.
E-mail: sandosh.padmanabhan@glasgow.ac.uk

Received: 30-12-2021; Accepted: 07-01-2022
doi: 10.15713/ins.johtn.0222

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/ © McCallum L, Padmanabhan S. 2021

Innovative Nature Science Publishers

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

Review Article

Hypertension Residual Risk and Beyond – Five Decades of Insights from the Glasgow Blood Pressure Clinic

Stefanie Lip[1,2], Linsay McCallum[1,2], Sandosh Padmanabhan[1,2]

[1]Department of Clinical Pharmacology and Therapeutics, Queen Elizabeth University Hospital, University of Glasgow, Glasgow, United Kingdom, [2]Institute of Cardiovascular and Medical Sciences, Queen Elizabeth University Hospital, Glasgow and University of Glasgow, United Kingdom

Abstract

The Glasgow Blood Pressure Clinic (GBPC) based in Greater Glasgow and Clyde is the largest specialist hypertension clinic in the West of Scotland and was established in 1969 following the merger of four hospitals. The GBPC database at the same time has continuously collected data on all hypertensive patients attending the clinic in one database until 2019 when it was decommissioned. In this review, we highlight papers outlining contributions of the GBPC database on our understanding of clinical and epidemiological aspects of hypertension over a span of 50 years.

Key words: Glasgow blood pressure clinic, hypertension, Scotland

The Glasgow Blood Pressure Clinic (GBPC)

The GBPC was established in January 1969 and operates within NHS Greater Glasgow and Clyde which is the largest health board in Scotland providing health care to a population of over 1.2 million people or 21.4% of the Scottish population. At the time of founding, the four hospitals in Glasgow (Glasgow Royal Infirmary, Southern General Hospital, Stobhill General Hospital, and the Western Infirmary) which comprised seven hypertension clinics collaborated to adopt a common record database with data storage on a centralized computer that contained clinical information for all patients attending the service.[1] Initially, the database was linked to mortality data from the General Register Office for Scotland and with the West of Scotland Cancer Surveillance Unit then subsequently to morbidity and laboratory data through linkage with the NHS Information and Statistics Division in 2007 which greatly enhanced the database with a wealth of information including hospital admissions, dispensed prescriptions, and all laboratory investigations.

Patients are referred to GBPC, the largest and main specialist hypertension clinic in the West of Scotland providing a secondary/tertiary level service,[2] if they fulfilled the following criteria - BP not controlled in primary care, resistant hypertension, high cardiovascular (CV) risk, requiring investigation of secondary causes. The GBPC has been supported by specialist hypertension nurses who are trained and experienced in BP measurement, investigation, and management. Every new patient who attended the clinic had an "initial new clinic proforma" which was completed by the clinician and nurse which was added into the database. Patients who attended the clinic were advised to take their regular medications as usual. Specialist hypertension nurses collected demographic data, anthropometric data (height, weight, and body mass index [BMI]), BP measurements (seated and standing) and current list of antihypertensive and other concomitant therapy. BP measurements were performed in a standardized manner in patients rested for 5 min in a seated position prior to recording. Three BP measurements were conducted 1 min apart, with the mean of the second and third measurements recorded as the clinic BP. The clinician who reviewed the patient then completed the sections of the proforma on past medical history (CV and non-CV), smoking status, and family medical history. Blood samples were taken at baseline and at regular intervals to monitor routine hematologic and biochemical indices. Samples were sent to the

Address for correspondence:
Prof. Sandosh Padmanabhan, Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom.
E-mail: sandosh.padmanabhan@glasgow.ac.uk

Received: 21/1/22; Accepted: 24/1/22
doi: 10.15713/ins.johtn.0223

local laboratory for processing. For follow-up visits, a "follow up document" proforma was used. Each patient attended the same clinic; therefore, at each visit, their BP measurement would occur in the same 3-h window in the morning or afternoon.

This structured approach was used to collect data from all patients attending the clinic and was stored electronically in a single computerized database. Initially, all data was entered into a KDF9 computer and stored on magnetic tapes, and proformas were included in the patient case notes.[1] In 1971, there were 944 patients seen with 4,500 follow-up visits with 183 primary care referrals and 510 from other hospital clinics. The 2009 snapshot of the database contained 16,018 unique individuals with the first patient visit recorded on 06/11/1968 and 4879 deaths registered until April 2011.

This database has provided a rich research environment and afforded excellent training opportunities for clinicians. Early use of the database was by GBPC clinicians and in 2012, the West of Scotland Research Ethics committee approved the use of anonymized data for research studies greatly expanding the use of the database to answer a range of questions.

Residual Risk in Treated Hypertension

While pharmacotherapy for hypertension has been one of the major success stories of clinical medicine the earliest signal for considerable residual risk in treated hypertensive patients came from a GBPC study in 1986. This was a seminal study by the GBPC analyzing mortality data of 3,783 hypertensive patients attending the clinic between 1968 and 1983 with an average follow-up of 6.5 years compared with that in three control groups: Strathclyde general population group (15,422 subjects aged 45–64 years and screened in Renfrew and Paisley between 1972 and 1976, and a group of hypertensive patients attending a BP clinic based in general practice in Renfrew).[3] The data revealed that despite some reduction of mortality by treatment, the relative risk to men and women in the GBPC remained 2–5-times that of the general population. This was the first large-scale confirmation of the notion that despite benefits of antihypertensive treatment, even patients with well-controlled BP may not have a normal expectation of life restored. This has led to wide-ranging research efforts to explain this conundrum. Several hypotheses have been presented including that treated patients have a higher prevalence of modifiable associated risk factors such as dyslipidemia, diabetes, excess weight, other metabolic disturbances, and target organ damage prior to starting therapy, or this excess in CV risk may be related to the presence of unmodifiable factors such as family and personal history of cardiac disease, which are also more frequent in treated hypertensive subjects. During the past 10 years, we have been systematically interrogating the GBPC database to better understand the factors that have an impact on BP control and outcomes and may explain this residual risk.

Family History of Premature Cardiovascular Disease

A positive family history (an independent risk factor for coronary heart disease [CHD]) features in several CV risk prediction scores commonly used in clinical practice. A family history of premature CHD is associated with a 1.5–7 times higher risk of future CV events.[4] Although excess risk was initially thought to be due to genetic factors, substantial evidence shows that it is also due to a shared environment and similarity in behavior and belief systems within families. Furthermore, modifiable traditional risk factors jointly mediate a substantial portion of the increased risk of the disease conferred by a positive family history. We showed that despite earlier referral and active management of CV risk factors at the GBPC, patients with a positive family history of premature CVD had a higher 35-year CV mortality compared to patients without a positive family history.[4] We showed that patients with a positive family history presented earlier to the clinic had a lower BP at presentation along with lower cholesterol and lower prevalence of CKD. There was no difference in drug adherence based on dispensed prescriptions in patients with or without a positive family history. This data raises the possibility that "the presence of family history of premature CVD represents a clinically significant sustained increase in CHD and CVD risk across the lifespan, and the pathological processes determining this increased risk must start long before the traditional risk factors are identified and treated."[4]

Socioeconomic Deprivation

Deprivation is defined as "a state of observable and demonstrable disadvantage relative to the local community or a wider society or nation to which an individual, family or group belongs."[5] The burden of CVD falls disproportionately on disadvantaged populations with socioeconomic deprivation is associated with an increased risk of a variety of CVD.[6] In hypertensive individuals attending GBPC between 1991 and 2000, we found a significant association between socio-economic deprivation and an increased risk of CV death after controlling for the effects of age, sex, systolic and diastolic BP (DBP), smoking, diabetes, alcohol excess, and BMI.[7] After adjustment, residents of the most deprived areas had a hazard ratio for all-cause mortality of 1.46 (95% confidence interval 1.04–2.04).[7] The adjusted risk ratio for CVD death in the most deprived areas was 1.65 (1.04–2.60) compared to those in the most affluent areas.[7] As the National Health Service in the United Kingdom is free at the point of access, poorer economic circumstances should not in themselves be barriers to obtaining specialist care. Our data support the hypothesis that socioeconomic deprivation is an independent risk factor for CV death in hypertensive patients.

Weather

Few studies have looked at the patterns of weather fluctuations and BP. There is increasing evidence that outdoor temperature

may be associated with the seasonal variability of BP observed. The body's thermoregulatory responses are to cause blood vessel constriction, which is a protective mechanism to maintain body temperature. Aubiniere-Robb *et al.*[8] observed that there was an average decrease of 2.1–2.2% in BP for air frost, temperature, rainfall, and sunshine. There was an average increase of 2% for temperature and sunshine. Temperature-sensitive individuals have higher mortality,[8] which is in line with current data on visit-to-visit BP variability (BPV), which is associated with increased mortality. However, more work is needed to establish whether these changes are due to physiological adaptations of the body. BP response to weather (especially temperature) changes are patient-specific, and awareness of a patient's BP response to temperature can help reduce unnecessary antihypertensive treatment modification.[8]

New Onset Diabetes

Elevated BP is considered an important additive risk factor in patients with Type 2 diabetes, augmenting the already heightened risk for morbidity and mortality in these patients. However, there is ongoing controversy regarding optimal BP treatment targets, and current guidelines provide differing recommendations.[9,10] In patients with type 1 diabetes, a linear relationship has been observed between higher systolic BP (SBP) and higher risk of stroke has been observed even below the BP levels recommended in more strict guidelines.[11] The ACCORD study demonstrated a U-shaped relationship between SBP and outcomes in diabetics.[12] The study by Lip *et al.*[13] provided insights from the GBPC database. We studied over 15,000 hypertensive patients and showed that individuals with prevalent diabetes, with early new-onset diabetes (NOD) (2–10 years after HTN diagnosis) and late NOD (>10 years) exhibited different mortality risks.[13] The earlier the onset of diabetes after the first clinic visit, the higher the mortality.[13] This suggests that early NOD patients may have an "insulin resistance phenotype" while late NOD may correspond to a "hypertension-induced diabetes," where diabetes might be a consequence of extensive hypertensive organ damage.[14]

Resting Heart Rate

There is a significant amount of epidemiological data indicating that higher resting heart rate (HR) a sensitive indicator of short life expectancies and is associated with increased risk of CV and non-CV outcomes.[15-17] In the GBPC, a change in HR achieved during follow-up of hypertensive patients is a better predictor of risk than baseline or final HR.[18] After correction for rate-limiting therapy, HR remained a significant independent risk factor.[18] The highest risk of an all-cause event was associated with patients who had increased their HR by 5 bpm at the end of follow-up (1.51, 95% CI 1.03–2.20; $P = 0.035$).[18] It is well recognized that the incidence of sudden cardiac death among patients with myocardial infarction, stable coronary artery disease, or congestive heart failure (HF) is reduced by beta-blockers, widely known for their HR lowering effects.[19] A meta-analysis of trials stratified according to whether calcium antagonists increased or decreased HR showed that for dihydropyridine calcium antagonists, there was a trend toward increased mortality, while for verapamil and diltiazem, the trend was toward a small decrease in mortality.[20] Overall, compared with β-blockade, ivabradine produces a form of HR reduction that more closely resembles the physiological situation and does not affect a series of mechanisms involved in ensuring efficient myocardial performance at different beating rates. The BEAUTIFUL study randomized 10,917 patients with coronary disease and left ventricular dysfunction to receive ivabradine or a placebo to test whether reducing HR would reduce CV mortality and morbidity. A subgroup of patients with a HR >70 bpm was shown to have a 46% higher risk of myocardial infarction (MI) and a 38% increased risk of coronary revascularization.[21]

Blood Pressure Variability

BP is inherently variable in an individual and this variability (BPV) manifests as beat to beat (very short term), within 24 h (short term), day by day (midterm), between visits spaced by weeks or months, and between seasons, years, and even decades (long term). Several studies have shown that increasing values of BPV (either in the short or in the long term) were associated with hypertensive organ damage[22] and an increased CV risk, independently of average BP values and other major confounders[23] *Post hoc* analyses of interventional trials in hypertension have shown that increasing values of intraindividual visit-to-visit BPV are strong predictors of CV morbidity, in some instances superior to average BP values.[23]

A study involving 16,011 treated hypertensive patients from the GBPC[24] explored the relationship between intraindividual visit-to-visit BPV and mortality, in whom BPV was assessed over up to 9 years and who were followed up for events over a period extending up to 35 years. Long-term visit-to-visit BPV was assessed across a range of time frames - within the 1st year (Y1); between the years from 2 to 5 (Y2–5); larger time frames (ultra–long-term BPV; i.e., from years 1 to 5, from years 5 to 10 [Y5–10], and over a time window up to 9 years of follow-up [i.e., from years 2 to 10]). The main result of this study is the finding of a consistent association between increasing values of long- and ultra-long–term BPV (assessed through calculation of average real variability, coefficient of variation, and SD) and risks of all-cause, CV, and non-CV mortality. These associations remained significant even after adjustment for average BP levels and across different strata of average SBP. Even in subjects with controlled SBP, there was a linear increase in mortality with increasing long-term BPV. This study corroborated the existing evidence that increased BPV between clinic visits has a significant prognostic value also in the long run and highlighted the need for further studies to identify therapeutic strategies that may stabilize visit-to-visit BPV and their impact on outcomes.

Diastolic Blood Pressure J Curve

The therapeutic reduction of DBP and its relationship with the DBP J curve have been extensively investigated to address the hypothesis. Waller *et al.*[25] and colleagues looked at mortality data from 3,350 participants who attended the GBPC between 1968 and 1982 and found no evidence of any relationship between DBP and death from CVD. In an analysis of the 2009 snapshot of the GBPC database with 30-year follow-up data on 10,355 hypertensive patients, DBP showed a U-shaped association (nadir, 92 mm Hg) for the primary CV outcome hazard and a reverse J-shaped association with all-cause mortality (nadir, 86 mm Hg) and non-CV mortality (nadir, 92 mm Hg). The hazard ratio for the primary CV outcome after adjustment for SBP was 1.38 (95% CI 1.18–1.62) for DBP <80 compared with DBP of 80 to 89.9 mm Hg (referent), and the sub-distribution hazard ratio after accounting for competing risk was 1.33 (95% CI 1.17–1.51) compared with DBP ≥80 mmHg. The results indicate that while DBP <80 mmHg is associated with increased risk for first admissions with ischaemic heart disease (IHD), MI, and HF, it does not translate to increased CV mortality. After stratifying by age, DBP <80 mmHg is associated with increased risk of admissions with IHD and HF in both the older and younger age groups; however increased risk of stroke was evident only in the younger subgroup (<60 years). There was an increased risk of non-CV mortality with DBP <80 mmHg and competing risk analysis confirmed increased risk associated with DBP <80 mmHg for CV outcomes after accounting for the risk of non-CV mortality. These results confirm the diastolic J-curve phenomenon and indicate that the short-term adverse CV impact of intensive DBP lowering does not translate into long-term mortality risk. A possible explanation for this may be the long-term beneficial effect of the concomitant low SBP that accompanies low DBP.[26] Although hypertension treatment guidelines recommend more intensive BP reduction, this may potentially lead to unintended consequences of higher healthcare utilization because of increased CV morbidity, and this merits future prospective studies.

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) is a well-recognized marker of target organ damage in hypertension and is an independent predictor of poor outcome.[27] Dunn *et al.*[28] investigated LVH and the relation to mortality in treated hypertensive patients. They found that this was true where LVH with and without ST-T changes was the most common ECG abnormality associated with a higher mortality.[28] More recently, Guzik *et al.* followed up explored left ventricular geometry on echocardiography in 690 GBPC patients and 10 year outcomes.[29] LVH is associated with worse outcomes than eccentric hypertrophy in hypertensive subjects. However, they were unable to establish any incremental effect of cardiac geometry on outcomes beyond BP control.

Haematocrit

In prospective studies, Hct is associated with the development of CVD. The association is described as a curve "J-" or "U-" and was examined in the GBPC database to clarify whether there were sex-specific differences in risk. Hct was found to be an independent predictor of CV mortality where it showed a J-shaped association between Hct and CV in men (0.421–0.44 (quartile 2; J-shaped)), but in women, it showed a U-shaped association in non-CV mortality (0.381–0.420 [quartiles 2.3; U-shaped]).[30]

Serum Chloride

Salt (sodium chloride) is generally accepted as a major determinant of BP and by extension mortality, following evidence from the pressure natriuresis hypothesis, monogenic forms of hypertension, and reduction in dietary intake. Whilst previous literature focussed on the sodium component of salt, chloride is the major extracellular anion in the body, and there is growing interest of the role of chloride in BP regulation and its association with CV mortality. McCallum *et al.*[31] studied the association between serum chloride and mortality in 12,968 treated hypertensive patients attending the GBPC, with a follow-up period of 197,101 person years. The authors concluded that lower serum chloride (<100 mEq/L) was a predictor of all-cause mortality independent of serum sodium and diuretic use.[31] Multivariable adjusted Cox proportional hazard (PH) model showed an inverse association between serum chloride and mortality with each 1 mEq/L increase associated with a 1.5% reduction in all-cause mortality (0.985; 95% CI 0.98–0.99), CV mortality (0.985; 95% CI 0.978–0.991), and non-CV mortality (0.985; 95% CI 0.977–0.990]) after adjustment for adjusted for age, sex, BMI, prevalent CVD, smoking, alcohol use, year of first visit, SBP, DBP, serum sodium, serum potassium, and bicarbonate. This data would suggest that even within the normal laboratory reference range (95–108), lower serum chloride is a risk marker. Chloride-dependent mechanisms are key to several critical pathways underlying CVD and BP regulation though the mechanism by which low serum chloride increases mortality is unclear.[32]

Liver Enzymes

In 1977, patients who attended the GBPC were noted to have abnormal liver function tests which was associated to alcohol consumption, heavy body weight, male sex and young age, and higher DBP.[33] In 2015, McCallum *et al.* investigated the relationship between liver biochemistry and BP and its associations with long-term mortality in 12,000 patients from the GBPC.[34] In the multivariable Cox PH model, each SD increase in bilirubin and ALT was associated with an 11% (0.89, 95% CI 0.85–0.94) and 14% (0.86, 95% CI 0.81–0.95) decrease in all-cause mortality, respectively. Higher bilirubin was associated with lower longitudinal BP which may explain some of the protective effect, but bilirubin is determined by both genetic and environmental factors. The protective effect is supported by data showing that *UGT1A1* genetic variants which

underly Gilbert's syndrome are also protective.[35] Bilirubin also has antioxidant and anti-inflammatory properties which may also contribute. The mechanism for ALT is less clear. Each SD increase in GGT and alkaline phosphatase was associated with an 11% (1.11, 95% CI 1.04–1.18) and 25% (1.25, 95% CI 1.18–1.33) increase in all-cause mortality, respectively, and were consistently associated with higher longitudinal BP.[34] GGT is pro-oxidant effects due to its role in the extracellular catabolism of glutathione and high GGT is associated with incident diabetes and fatty liver.[36]

Uric Acid

The association between serum uric acid and hypertension has previously been reported in epidemiological studies and animal studies.[37-39] Dawson *et al.* found that serum uric acid level did not predict long-term BP control in a large population with treated hypertension, a higher baseline serum uric acid level is associated with a subsequent decrease in renal function, and a higher serum acid level is associated with increased all-cause CV mortality in women.[40] In a paper by Beattie *et al.*, they concluded that allopurinol initiation was associated with a fall in BP in hypertensive older adults.[41] The level of uric acid should be measured in patients with hypertension and future studies should explore whether uric acid reduction improves renal function in patients with hyperuricemia and reduces the rate of CV events in women with hyperuricemia.

Phosphate

Patel *et al.* investigated serum phosphate and calcium and their association with CV morbidity and mortality.[42] They found that serum phosphate and calcium were associated with a reduced all-cause and CV survival, and this was not associated with BP control.[42]

Microalbuminuria

Alharf *et al.* assessed the prevalence of microalbuminuria in hypertensive patients and its association with long-term mortality, where using a lower threshold of albuminuria identified 20% hypertensive subjects at increased risk of CVD.[43]

Pharmacoepidemiology

The changing patterns of antihypertensive drug use in the GBPC between 1969 and 1986 were determined from computerized data, by extracting percentages of new patients prescribed different drugs at their first clinic visit which was evaluated by Clark *et al.*[44] in 1990. In 1999, Lever *et al.*[45] observed that mortality of hypertensive patients in the GBPC was higher in the 1970s and 1980s but has fallen since then because of new antihypertensive drugs, which was the ACE inhibitor being introduced. Bevan *et al.* looked at the effects of atenolol withdrawal in patients on triple antihypertensive therapy, where they noted that there was an importance of the use of atenolol alongside standard triple antihypertensive therapy.[46] ACE inhibitors were first used in the 1980s, where there was a reduction in CV and non- CV mortality observed in patients attending the GBPC.[47,48]

Antihypertensive Therapy and Cancer

From various literature over the past 20 years, the relationship between antihypertensive therapy and cancer has always been a debate. Hole *et al.* concluded that there was no link between atenolol, calcium channel antagonists, and cancer.[49] Lever *et al.* informed that the long-term use of ACE inhibitors may be protective against cancer.[50] However, the recent metanalysis by Copland found that there is no consistent evidence that antihypertensive medication use had any effect on cancer risk.[51] Although such findings are reassuring, evidence for some comparisons was insufficient to entirely rule out excess risk, in particular for calcium channel blockers (CCB).

Antihypertensive Therapy and Depression

A bidirectional relationship between depression and CVD is thought to exist mainly because of the overlapping pathophysiological processes that underlie both conditions. Genome-wide association studies support an association of CACNA1C polymorphism with bipolar disorder and unipolar depression implicating dysfunction of L-type calcium channels (LTCCs) in neuropsychiatric disorders. LTCCs are the target of the commonly used dihydropyridines CCB. In our study of 144,066 eligible patients, we showed patients on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers had the lowest risk for mood disorder admissions.[52] Compared with ACEI/ARB group, those on β-blockers (2.11, 95% CI 1.12–3.98; $P = 0.02$) and calcium antagonists (2.28, 95% CI 1.13–4.58; $P = 0.02$) showed higher risk, whereas those on no antihypertensives (1.63, 95% CI 0.94–2.82; $P = 0.08$) and thiazide diuretics (1.56 95% CI 0.65–3.73; $P = 0.32$) showed no difference.[52] Overall, our exploratory findings suggest possible differential effects of antihypertensive medications on mood.

Service Delivery

Between January 1969 when the first of the clinics opened, and 29 November 1971, 944 new patients were seen and there have been approximately 4,500 follow-up visits.[53] Johnson *et al.* evaluated the purpose of the GBPC and the control in hypertension of antihypertensive patients in the outpatient setting. From 1969 to 1979, there were 562 patients with a reduction in systolic and DBP within 1 month of attendance and a further decrease in BP over 1 year, the average decrease in SBP was approximately 30 mmHg and DBP was 15 mmHg. These mean reductions in BP were maintained over the next 2 years. This paper in the early establishments of the GBPC showed that there is some evidence that specialist clinics can contribute to the control of BP in large numbers of patients over a period of years.

The service has developed over time with the addition of a virtual led clinic, monthly multidisciplinary team meetings, and nurse led clinic. It has adapted its practices and treatment guidelines with current hypertension guidelines (NICE/BIHS guideline/MCN hypertension guideline). In 2011, the impact of NICE/BIHS guidelines on our service was evaluated where there was a change in the profile of primary care referrals and a reduction of 17% of patients starting antihypertensive therapy.[54] Currently, patients attending the GBPC are encouraged to perform home BP measurements and bring their BP readings to the clinic to reduce the white coat effect. The effect of the COVID-19 pandemic has resulted in more telephone consultations carried out with patients who performed home BP readings, whilst the GBPC service continues to provide loaned BP monitors to patients, 24-h ambulatory BP monitoring and direct observe therapy.

Conclusion

From 1969 to 2011, the GBPC database has provided a rich database that has been systematically interrogated to understand the factors that impact BP and mortality and morbidity outcomes and highlight the value of clinical databases in expanding the understanding of disease, informing clinical practice, and improving patient outcomes.

Acknowledgments

The authors thank all patients who attended the GBPC for their contributions to advancing knowledge on hypertension and the consultants and nurses who have previously and currently part of the GBPC.

References

1. Members of the Clinic. The Glasgow blood pressure clinic. J R Coll Physicians Lond 1972;7:87-97.
2. Johnston JH, Lorimer AR, Rodger JC, Robertson WK, Thomas A, Lawrence W, *et al.* Control of hypertension in out-patients. Experience of the glasgow blood pressure clinic. Postgrad Med J 1980;56:633-7.
3. Isles CG, Walker LM, Beevers GD, Brown I, Cameron HL, Clarke J, *et al.* Mortality in patients of the Glasgow blood pressure clinic. J Hypertens 1986;4:141-56.
4. Williamson C, Jeemon P, Hastie CE, McCallum L, Muir S, Dawson J, *et al.* Family history of premature cardiovascular disease: Blood pressure control and long-term mortality outcomes in hypertensive patients. Eur Heart J 2014;35:563-70.
5. Townsend P. Deprivation. J Soc Policy 2009;16:125-46.
6. Marmot MG, Shipley MJ, Rose G. Inequalities in death--specific explanations of a general pattern? Lancet 1984;1:1003-6.
7. Stewart L, McInnes GT, Murray L, Murray L, Sloan B, Walters MR, *et al.* Risks of socioeconomic deprivation on mortality in hypertensive patients. J Hypertens 2009;27:730-5.
8. Aubiniere-Robb L, Jeemon P, Hastie CE, Patel RK, McCallum L, Morrison D, *et al.* Blood pressure response to patterns of weather fluctuations and effect on mortality. Hypertension 2013;62:190-6.
9. 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. Circulation 2018;138:e426-83.
10. 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 (ESC) and the European society of hypertension (ESH). Eur Heart J 2018;39:3021-104.
11. Hagg-Holmberg S, Dahlstrom EH, Forsblom CM, Harjutsalo V, Liebkind R, Putaala J, *et al.* The role of blood pressure in risk of ischemic and hemorrhagic stroke in Type 1 diabetes. Cardiovasc Diabetol 2019;18:88.
12. Group AS, 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.
13. Lip S, Jeemon P, McCallum L, Dominiczak AF, McInnes GT, Padmanabhan S. Contrasting mortality risks among subgroups of treated hypertensive patients developing new-onset diabetes. Eur Heart J 2016;37:968-74.
14. Bruno RM, Taddei S. New-onset diabetes in hypertensive patients and mortality: Timing is everything. Eur Heart J 2016;37:975-7.
15. Jouven X, Empana JP, Escolano S, Buyck JF, Tafflet M, Desnos M, *et al.* Relation of heart rate at rest and long-term (>20 years) death rate in initially healthy middle-aged men. Am J Cardiol 2009;103:279-83.
16. Kannel WB, Kannel C, Paffenbarger RS Jr., Cupples LA. Heart rate and cardiovascular mortality: The Framingham study. Am Heart J 1987;113:1489-94.
17. Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: A meta-analysis. CMAJ 2016;188:E53-63.
18. Paul L, Hastie CE, Li WS, Harrow C, Muir S, Connell JM, *et al.* Resting heart rate pattern during follow-up and mortality in hypertensive patients. Hypertension 2010;55:567-74.
19. Kendall MJ, Lynch KP, Hjalmarson A, Kjekshus J. Beta-blockers and sudden cardiac death. Ann Intern Med 1995;123:358-67.
20. Alderman MH, Cohen H, Roque R, Madhavan S. Effect of long-acting and short-acting calcium antagonists on cardiovascular outcomes in hypertensive patients. Lancet 1997;349:594-8.
21. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R, *et al.* Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A subgroup analysis of a randomised controlled trial. Lancet 2008;372:817-21.
22. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G. Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. J Hypertens 1987;5:93-8.
23. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, *et al.* Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010;375:895-905.
24. Hastie CE, Jeemon P, Coleman H, McCallum L, Patel R, Dawson J, *et al.* Long-term and ultra long-term blood pressure variability during follow-up and mortality in 14,522 patients with hypertension. Hypertension 2013;62:698-705.

25. Waller PC, Isles CG, Lever AF, Murray GD, McInnes GT. Does therapeutic reduction of diastolic blood pressure cause death from coronary heart disease? J Hum Hypertens 1988;2:7-10.
26. Lip S, Tan LE, Jeemon P, McCallum L, Dominiczak AF, Padmanabhan S. Diastolic blood pressure J-curve phenomenon in a tertiary-care hypertension clinic. Hypertension 2019;74:767-75.
27. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham heart study. N Engl J Med 1990;322:1561-6.
28. Dunn FG, McLenachan J, Isles CG, Brown I, Dargie HJ, Lever AF, *et al*. Left ventricular hypertrophy and mortality in hypertension: An analysis of data from the Glasgow blood pressure clinic. J Hypertens 1990;8:775-82.
29. Guzik BM, McCallum L, Zmudka K, Guzik TJ, Dominiczak AF, Padmanabhan S. Echocardiography predictors of survival in hypertensive patients with left ventricular hypertrophy. Am J Hypertens 2021;34:636-44.
30. Paul L, Jeemon P, Hewitt J, McCallum L, Higgins P, Walters M, *et al*. Hematocrit predicts long-term mortality in a nonlinear and sex-specific manner in hypertensive adults. Hypertension 2012;60:631-8.
31. McCallum L, Jeemon P, Hastie CE, Patel RK, Williamson C, Redzuan AM, *et al*. Serum chloride is an independent predictor of mortality in hypertensive patients. Hypertension 2013;62:836-43.
32. McCallum L, Lip S, Padmanabhan S. The hidden hand of chloride in hypertension. Pflugers Arch 2015;467:595-603.
33. Ramsay LE. Liver dysfunction in hypertension. Lancet 1977;2:111-4.
34. McCallum L, Panniyammakal J, Hastie CE, Hewitt J, Patel R, Jones GC, *et al*. Longitudinal blood pressure control, long-term mortality, and predictive utility of serum liver enzymes and bilirubin in hypertensive patients. Hypertension 2015;66:37-43.
35. Lin JP, O'Donnell CJ, Schwaiger JP, Cupples LA, Lingenhel A, Hunt SC, *et al*. Association between the UGT1A1*28 allele, bilirubin levels, and coronary heart disease in the Framingham Heart study. Circulation 2006;114:1476-81.
36. Fraser A, Harris R, Sattar N, Ebrahim S, Smith GD, Lawlor DA. Alanine aminotransferase, gamma-glutamyltransferase, and incident diabetes: The British women's heart and health study and meta-analysis. Diabetes Care 2009;32:741-50.
37. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, *et al*. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 2001;38:1101-6.
38. Mellen PB, Bleyer AJ, Erlinger TP, Evans GW, Nieto FJ, Wagenknecht LE, *et al*. Serum uric acid predicts incident hypertension in a biethnic cohort: The atherosclerosis risk in communities study. Hypertension 2006;48:1037-42.
39. Forman JP, Choi H, Curhan GC. Plasma uric acid level and risk for incident hypertension among men. J Am Soc Nephrol 2007;18:287-92.
40. Dawson J, Jeemon P, Hetherington L, Judd C, Hastie C, Schulz C, *et al*. Serum uric acid level, longitudinal blood pressure, renal function, and long-term mortality in treated hypertensive patients. Hypertension 2013;62:105-11.
41. Beattie CJ, Fulton RL, Higgins P, Padmanabhan S, McCallum L, Walters MR, *et al*. Allopurinol initiation and change in blood pressure in older adults with hypertension. Hypertension 2014;64:1102-7.
42. Patel RK, Jeemon P, Stevens KK, Mccallum L, Hastie CE, Schneider A, *et al*. Association between serum phosphate and calcium, long-term blood pressure, and mortality in treated hypertensive adults. J Hypertens 2015;33:2046-53.
43. Alharf AA, Cleland S, Webster J, McInnes GT, Padmanabhan S. Microalbuminuria in subjects with hypertension attending specialist blood pressure clinics. J Hum Hypertens 2016;30:527-33.
44. Clark DW, Curzio JL, Howie CA, Reid JL. First-choice antihypertensive drug use in the Glasgow blood pressure clinic. J Cardiovasc Pharmacol 1990;16 Suppl 7:S120-2.
45. Carvalho LS, Xiao R, Wassmer SJ, Langsdorf A, Zinn E, Pacouret S, *et al*. Synthetic adeno-associated viral vector efficiently targets mouse and nonhuman primate retina *in vivo*. Hum Gene Ther 2018;29:771-84.
46. Bevan EG, Pringle SD, Waller PC, Herrick AL, Findlay JG, Murray GD, *et al*. Effects of atenolol withdrawal in patients on triple antihypertensive therapy. J Hum Hypertens 1993;7:89-93.
47. McInnes GT. The differences between ACE inhibitor-treated and calcium channel blocker-treated hypertensive patients. J Clin Hypertens (Greenwich) 2003;5:337-44.
48. McInnes GT. Clinical trials and tribulations. Clin Exp Pharmacol Physiol 2002;29:951-5.
49. Hole DJ, Gillis CR, McCallum IR, McInnes GT, MacKinnon PL, Meredith PA, *et al*. Cancer risk of hypertensive patients taking calcium antagonists. J Hypertens 1998;16:119-24.
50. Lever AF, Hole DJ, Gillis CR, McCallum IR, McInnes GT, MacKinnon PL, *et al*. Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? Lancet 1998;352:179-84.
51. Copland E, Canoy D, Nazarzadeh M, Bidel Z, Ramakrishnan R, Woodward M, *et al*. Antihypertensive treatment and risk of cancer: An individual participant data meta-analysis. Lancet Oncol 2021;22:558-70.
52. Boal AH, Smith DJ, McCallum L, Muir S, Touyz RM, Dominiczak AF, *et al*. Monotherapy with major antihypertensive drug classes and risk of hospital admissions for mood disorders. Hypertension 2016;68:1132-38.
53. Anonymous. The Glasgow blood pressure clinic. J R Coll Phys London 1972;7:87-97.
54. Tan L, McCallum L, Shields S, Patel J, Boal A, Muir S, *et al*. [Pp.Lb01.07] impact of the nice/bhs guidelines on specialist hypertension clinic service. J Hypertens 2016;34 Suppl 2:e198-9.

How to cite this article: Lip S, McCallum L, Padmanabhan S. Hypertension Residual Risk and Beyond – Five Decades of Insights from the Glasgow Blood Pressure Clinic. Hypertens 2021;7(2): 64-70.

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

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/ © Lip S, McCallum L, Padmanabhan S. 2021

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

Review Article

The Evolution of Hypertension Guidelines: A Global and European Perspective with a Focus on Classification of Hypertension (Review)

Nicole Eu Chin Ng, Christian Delles

Registered Dietitian, North Middlesex University Hospital, England, Professor of Cardiovascular Prevention, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, Scotland

Abstract

Hypertension guidelines play an important role in offering "balanced information" to guide clinicians in clinical decisions and have contributed to improving hypertension management over time. However, the process of guideline development is complex and subject to vulnerabilities. Consequently, key aspects of hypertension management remain highly debated. Here, we evaluate the evolution in hypertension management and identify limitations and inconsistencies in guidelines with a focus on definitions and classifications of hypertension. We analyzed guidelines from the World Health Organization (WHO) from years 1962 to 1999 and the European Society of Cardiology and European Society of Hypertension from years 2003 to 2018 to obtain a global and European perspective. Overall, it is understood that recommendations for hypertension management have and will continue to be subject to modifications with time, especially in an ever-evolving field of hypertension research with emerging evidence. Therefore, these inherent complexities and changes should be embraced, while bearing in mind that guidelines should always be based on up-to-date and robust evidence.

Key words: Blood pressure, guidelines, hypertension

Introduction

Major progress in the understanding and management of hypertension has been made over the past 50 years.[1] Hypertension guidelines have undoubtedly played a major role in improving hypertension management over the years and are developed with the aim of offering "balanced information" to guide clinicians in decision-making rather than "rigid instructions.[2]" There are several clinical practice guidelines for hypertension issued by different societies and organizations across the world, including the World Health Organization (WHO), International Society of Hypertension (ISH), and European Society of Cardiology and European Society of Hypertension (ESC/ESH).

Whilst robust clinical guidelines provide important information for the practicing clinician, the guideline development process is not without potential flaws.[3] Key aspects of hypertension management in guidelines remain highly debated and controversial despite well-established benefits of blood pressure (BP) lowering on cardiovascular outcomes.[4] Although many aspects of hypertension management across various guidelines are consistent, disparities exist and remain an issue. Some issues with guideline development include inadequate control for conflicts of interest, inconsistencies in quality, and contradictory or controversial recommendations.[3] Moreover, the generic guideline development process is subject to vested interests which could involve industries that push particular diagnostics or the government which largely considers cost implications.[3] Therefore, it is important that various vulnerabilities in guideline development are identified, especially in an evolving field of hypertension management with emerging evidence.

Tracking the evolutionary changes of guidelines through time proves pragmatic in obtaining key information that helps

Address for correspondence:
Christian Delles, Professor of Cardiovascular Prevention, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, Scotland. E-mail: Christian.Delles@glasgow.ac.uk

Received: 06-01-2022; Accepted: 12-01-2022
doi: 10.15713/ins.johtn.0224

Indexed Nature Science Publishers

identify areas for improvement. It is recognized that this is not a novel approach as a similar concept has been done in a review of the Joint National Committee guidelines[2] which provided a useful overview of the American guidelines. The main guidelines for analysis in this review include the WHO, WHO/ISH, and ESC/ESH guidelines which provide a global and European perspective. The aims and objective of this review include: (1) Evaluating the evolution in hypertension management and (2) identifying limitations and inconsistencies in guidelines by the following recommendations through time.

Methods

Original WHO, WHO/ISH, and ESC/ESH reports and guidelines were utilized. This includes the first WHO report in 1962 up to 1999 and first ESC/ESH guideline in 2003 up to 2018. Identified memoranda or prevention guidelines were excluded as they do not represent full guidelines. Additional papers were included to support arguments where relevant.

Evolution of guidelines

Hypertension guidelines: The evolution in the classification and definitions

Considering the complexity of the pathogenesis and clinical course of hypertension, it is challenging to arrive at uniform definitions and classifications of hypertension. However, these remain important considerations as cutoff BP values help simplify the diagnostic approach and facilitate treatment decisions regarding hypertension.[5] Definitions and classifications are the product of clinical trials and evidence that have determined the level of BP at which the benefits of treatment unambiguously outweigh the treatment risks.[6]

Therefore, chronologically following these definitions and classifications through time allow the identification of key modifications.

1962 WHO

The main highlight in classification in the 1962 guidelines was the adaptation of classification according to stages [Tables 1 and 2] as it was deemed more useful to consider stages of the diseases' natural history, allowing clinicians to confidently place patients in appropriate stages. This "stage" classification aimed to identify and prioritize individuals requiring regular treatment and supervision. However, despite this attempt, the lack of robust diagnostic methods and difficulty determining stages for certain presented symptoms made it challenging to clearly separate between each stage.[7]

Although there was a difficulty distinguishing between normotensive and hypertensive levels due to the absence of a clear demarcation between these levels, "accepted levels" of casual BP recordings were defined [Table 1] for screening purposes in population groups.[7] However, one limitation to note was the general lack of "accepted levels" or cutoff values recommended. Defining and classifying hypertension with the use of cutoff values continues to be important for practical use in the diagnosis and treatment of hypertension in clinical settings, although recognized as arbitrary in nature.[5-12]

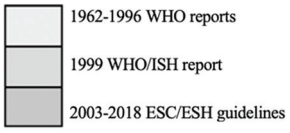
1978 WHO

For the definition of arterial hypertension, the same cutoff value was maintained from the 1962 to 1978 guidelines [Table 1]. However, the classifications had a higher level of description and new elements added. First, although not precisely defined, terms "mild," "moderate," and "severe" hypertension were introduced. Second, hypertension was no longer classified only according to stages but three distinct elements [Table 3]. This distinction between BP level and extent of organ damage was deemed particularly important as both were separate elements that each carry a hypertension risk that may present even in the absence of the other.[8] This clear classification that considered different elements aimed to assess disease severity of individuals, facilitate comparison between individuals and groups, and evaluate risks of complications or benefit of therapy.

Overall, although considerable effort was made to address the lack of detail in classification from the 1962 guideline,[7] this proposed classification still included an element of characterization according to stages [Table 3] similar to 1962 guidelines [Table 2] which did not eliminate the challenge of diagnosing and

Table 1: Overview of the definition and classification of hypertension by the WHO, WHO/ISH, and ESC/ESH reports and guidelines from 1962 to 2018

Report (year)	Hypertension classification (mmHg)
1962	≥160/95 (according to BP level stages)
1978	≥160/95 (according to BP level, organ damage, and etiology)
1984	≥160/95 (BP level, organ damage, and etiology to assess cardiovascular risk)
1996	≥140/90 (according to BP level, organ damage, and etiology)
1999	≥140/90 (according to BP level grades and total cardiovascular risk)
2003	≥140/90 (according to BP level grades and total cardiovascular risk)
2007	≥140/90 (according to BP level grades and total cardiovascular risk)
2013	≥140/90 (according to BP level grades and total cardiovascular risk)
2018	≥140/90 (according to BP level grades and total cardiovascular risk)



differentiating stages of hypertension according to organ damage previously identified. For example, individuals may vary in rate of hypertension progression and sequence of stages where not all specified stages would necessarily develop in those with elevated BP.[7] In addition, a diagnosis of arterial hypertension based on etiology, organ damage, and BP levels still required accurate clinical judgment which was especially challenging given the difficulties in obtaining an accurate reflection of disease severity.

1984 WHO

The 1984 classification similarly focused on three distinct elements of BP level, organ damage, and etiology. However, this separation into different categories was not specifically used to classify hypertension but considered part of the assessment of disease severity and overall cardiovascular risk [Table 1].

1996 WHO

The main change in the 1996 guideline was the lowered cutoff value used to diagnose and define arterial hypertension [Table 1]. With regard to classification according to BP levels, terms "mild," "moderate," and "severe" were used to indicate the extent of BP elevation and retained in this guideline due to their common use in the clinical setting.[9] However, it should be noted that these terms were not indicative of the severity of the overall clinical condition.[9] Rather, this severity of overall clinical condition and cardiovascular risk was assessed by the classification of hypertension which took into account the three distinct elements of BP level, organ damage, and etiology. This was a return of the classification style used in the 1978 guidelines [Table 3] and was deemed appropriate in this guideline as it proved a reliable risk assessment method which could help inform appropriate treatment for patients.

1999 WHO-ISH

At this point, it should be noted that the classification of hypertension remains relatively similar from the 1999 guidelines onwards, with only minor modifications. The cutoff BP values used in defining hypertension were the same as recommendations from 1996 [Table 1] with the only difference being the additional specification that diagnosed subjects should not be on any antihypertensives.[13] The terms in the classification of hypertension were amended, utilizing "grades" instead of "stages" [Table 4]. "Stages" was deemed inappropriate for use in this guideline as this would have implied a progression over time that was not applicable here.

Table 2: 1962 WHO classification of essential and all forms of arterial hypertension

Classification	Description
Stage 1	High BP without evidence of organic changes in the cardiovascular system
Stage 2	High BP with the left ventricular hypertrophy but without other evidence of organ damage.
Stage 3	High BP with evidence of organ damage attributable to the hypertensive disease.

Although classification in this guideline may appear oversimplified in comparison to previous guidelines by only including classification according to BP levels [Table 4] instead of the three distinct elements of BP levels, organ damage,

Table 3: 1978 WHO classification of arterial hypertension according to three distinct elements of (1) BP level, (2) organ damage, and (3) etiology

Classification	Description
(1) BP level	
Normal	≤140 SBP and≤90 DBP
Borderline	N/A. Defined as "BP values between the normal and hypertensive ranges as described."
Hypertension	≥160 SBP and/or≥95 DBP
(2) Organ damage	
Stage 1	No objective signs of organic changes are evident.
Stage 2	At least one of the following signs of organ involvement is present: • Left ventricular hypertrophy (on physical examination, chest X-ray, electrocardiography, and echocardiography) • Generalized and focal narrowing of the retinal arteries • Proteinuria and/or slight elevation of plasma creatinine concentration.
Stage 3	Signs and symptoms have appeared as a result of damage to various organs from hypertensive disease (includes brain and heart)
(3) Etiology	
Essential or primary hypertension	High BP without evident organic cause.
Secondary hypertension	Hypertension with identifiable cause. Possible causes classified as follows: • Hypertension due to the administration of drugs • Hypertensive disease of pregnancy • Organic disease

Table 4: 1999 WHO-ISH classification of hypertension according to BP levels

Classification	SBP (mmHg)	DBP (mmHg)
Optimal	<120	<80
Normal	<130	<85
High-normal	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Subgroup: Borderline	140–149	90–94
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90
Subgroup: Borderline	140–149	<90

When a patient's systolic and diastolic BP fall into different categories, the higher category should apply

and etiology, this was not the case. Instead, this change was made because the previous classification used to assess disease severity and overall cardiovascular risk was now replaced by a cardiovascular risk assessment method calculated from Framingham Study data.[13] Here, total cardiovascular risk was stratified into categories of "low," "medium," "high," and "very high" risk.[13] This stratification and estimation of future absolute risk of major cardiovascular events were based on several risk factors and conditions, including BP category, cardiovascular risk factors, asymptomatic organ damage, presence of diabetes, symptomatic cardiovascular disease, or chronic kidney disease.[13]

2003 ESC/ESH

The classification in this first ESC/ESH guideline was adopted from the 1999 guideline with reservations that the real thresholds for hypertension must be flexible[10] and consider individuals' total cardiovascular risk profiles. As a result, the subgroup "borderline" hypertension was not retained. An additional feature of this guideline was the addition of other measurement types used in defining hypertension [Table 5]. This was an important addition due to the recognition of the prognostic significance of home BP monitoring (HBPM) and ambulatory BP monitoring (ABPM) in hypertension diagnosis.[14]

This guideline continued using cardiovascular risk assessment to inform hypertension diagnosis and management, recognizing that these should be based on the quantification of total cardiovascular risk. The method for cardiovascular risk assessment described in the 1999 guidelines[13] was retained but extended to indicate added risk in certain groups with "normal" or "high normal" BP.[10]

2007 ESC/ESH

There were several key conditions proposed to improve the use of classification as a diagnostic tool for hypertension in clinical practice in this guideline: [11]

1) The higher category was to be applied for the quantification of total cardiovascular risk, decision about drug treatment, and estimation of treatment efficacy when a patient's systolic BP (SBP) and diastolic BP (DBP) values fell into different categories.
2) The threshold for hypertension was to be regarded as flexible, based on the level and total cardiovascular risk profile.
3) Terms "mild", "moderate," and "severe" hypertension were replaced with Grades 1, 2, and 3, respectively, to avoid confusion with quantification of total cardiovascular risk.

This guideline continued to acknowledge that patient classification should not only be in relation to hypertension grades but also consider total cardiovascular risk from coexisting risk factors, organ damage, and disease. The assessment of cardiovascular risk was also maintained from 2003[10] with only slight amendments in the description of risk factors.

Table 5: 2003 ESC/ESH definition of hypertension with different types of measurement.

Classification	Systolic BP (mmHg)	Diastolic BP (mmHg)
Office or clinic	140	90
24 h ambulatory	125	80
Home (self)	135	85

2013 ESC/ESH

Although the classification and definition of hypertension in 2013 were adopted from 2007 [Table 1], one difference was the cutoff values provided for alternative methods of measurement (i.e., out-of-office levels) in this guideline which were slightly modified from 2007. This guideline continued emphasizing the importance of cardiovascular risk assessment in hypertensive patients.[12] A similar cardiovascular risk assessment method was retained from 2003[10] and 2007 guidelines[11] with slight modifications to the description of risk factors.

2018 ESC/ESH

The recommended definition and classifications of BP levels in this guideline remained unchanged [Table 1]. This guideline continued providing cutoff values for hypertension according to different methods of measurement. These cutoff values for alternative methods became increasingly important as it was now recommended that the diagnosis of hypertension could be based on out-of-office BP measurements with ABPM and/or HBPM if logistically and economically feasible.[6] The classification of hypertension continued focusing on the assessment of cardiovascular risk as done in the previous guidelines.[10-13] One key thing to note was that this guideline began to highlight the importance of considering the impact of hypertension-mediated organ damage (HMOD), recommending that the estimation of cardiovascular risk be complemented by the assessment of HMOD.

Discussion

Hypertension management: Definitions and classification of hypertension

Classifying and defining hypertension have been identified as challenging since the first WHO report[7] to the latest ESC/ESH guideline.[6] Defining BP levels, more specifically recommending numerical cutoff values that distinguish between normotensive and hypertensive states, has recurringly been regarded as complex and arbitrary due to the continuous relationship between BP and cardiovascular or renal events, especially in the general population with a unimodal distribution of SBP and DBP values.[11,12,15] To further complicate things, arriving at a consensus from trial evidence remains a challenge for several reasons. Key evidence informing hypertension definitions mainly comprises randomized controlled trials (RCTs) measuring "direct" cardiovascular endpoints and involves hypertensive individuals demonstrating the favorable effect of BP reduction on major clinical cardiovascular outcomes.[16] Although these RCT measuring "direct" endpoints provide clinically meaningful measurements that form the basis of recommendations, there are several limitations to consider.

One limitation is that many of them involve high-risk patients (e.g., patients of old age, concomitant, or previous disease)[11,12] which could be an issue for several reasons. First, findings from this high-risk cohort may be limited in generalizability to other cohorts. Second, although considerable effort is made to control for confounders in these trials, many high-risk patients are still on other treatments or medication which may also have a confounding effect on the benefits seen in the results. Another consideration is the relatively short duration of these trials, having an average time to endpoint of 1.5–4 years due to practical reasons.[12] As a result, data are often extrapolated to obtain recommendations for life-long interventions. Thus, these recommendations are based on extrapolated data obtained over periods significantly shorter than the life expectancy of most individuals.[12] It should also be remembered that data supporting the projected continuation of measured benefits in the long term largely come from observational studies based on the Framingham Heart Study[17] which has several limitations in comparison to RCT.

There is also supportive "indirect" evidence involving measurements of albuminuria and left ventricular mass, deemed to be predictors of important clinical end points. These studies demonstrated a possible association between BP-induced regression of organ damage, such as left ventricular hypertrophy and urinary protein excretion, and reduced fatal and non-fatal outcomes.[18,19] However, this evidence was derived from *post hoc* correlative analyses of randomized data.[12] Therefore, caution must be exercised when interpreting this type of data, bearing in mind that correlations found should not immediately be interpreted as causation.

Other existing challenges in coming to consensuses stem from differences in opinion or interpretation of evidence by expert panels. A recent example was seen in the effort to redefine hypertension made by the American College of Cardiology and the American Heart Association where the threshold for hypertension diagnosis was lowered to ≥130/80 mmHg.[20] This was not in agreement with recommendations by ESC/ESH[6] and ISH[21] which both advocate a threshold for diagnosis of >140/90 mmHg. This decision sparked concerns regarding its global applicability[22] and more importantly, may have caused uncertainty and confusion in clinical practice.

Hypertension management: Cardiovascular risk assessment systems

The use of cardiovascular risk assessment systems, emerging in 1999 guidelines[13] and maintained in the European guidelines since,[6,10-12] replaced the original classification style used in guidelines before 1999.[5,7-9,13] The use of these systems came from the acknowledgment that the management of hypertension should be related to the quantification of total cardiovascular risk[10] obtained by systems that consider the combined effect of several risk factors. This is from the recognition that risk factors commonly cluster instead of occur in isolation,[6,12,23] resulting in a multiplicative effect on cardiovascular risk. Moreover, tailoring treatment strategies between individuals according to cardiovascular risk are supported by evidence showing that the level of cardiovascular risk determines the appropriate strategy required for hypertension management.[12] Thus, estimating cardiovascular risk through systems to inform management appears pragmatic given the impact of coexisting risk factors, organ damage, and disease.[11]

Types of cardiovascular risk assessment systems

The first recommended system provided in the 1999 guidelines[13] involved a method that utilized estimates calculated from data on the 10-year average risk of cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction among Framingham Study participants.[13] Thereafter, Framingham data[24] were also used to develop computerized methods to assess risk. Subsequently, the Systemic COronary Risk Evaluation (SCORE) system was formed, utilizing data from large European cohorts.[6,11] Additional resources including charts and electronic versions of the SCORE system were also made available.

Key considerations in cardiovascular risk assessment systems

It is important to recognize that each system has its own advantages and limitations. The first recommended system in the 1999 guidelines[13] lacked applicability as there was uncertainty regarding its risk predicting ability in Asian, African, or other non-Western populations. This was due to a general lack of robust evidence on how well risk factors predicted cardiovascular disease in these populations.[13] Some risk calculators also lacked applicability as Framingham data were only applicable to some European populations due to important differences in incidence of coronary and stroke events.[11] Although several risk assessment systems are available, the following discussions mainly involve the SCORE system due to the focus on European guidelines in this review.

The development of the SCORE system made available a model applicable to the European population as it was based on data from large European cohorts provided by the SCORE project.[25] Moreover, the SCORE system further improved its applicability by providing correction factors for cardiovascular risk estimates in the first-generation immigrants to Europe[6] and was recently adapted for use in patients over the age of 65 years[26] which addressed its previous limitation of only being applicable to patients aged 40–65 years. The use of the SCORE system has been recommended by European guidelines on cardiovascular disease prevention since 2003 due to its representation of the European population.[6,15] Moreover, it is relatively robust, allowing calibration of its charts for different cardiovascular risk levels across numerous European countries and has been externally validated.[27]

It is important that limitations of cardiovascular risk assessments are equally appreciated. Although classification through risk assessments have evolved and improved through the years, the rationale behind its use remains to "govern the

best use of limited resources to prevent cardiovascular disease" by creating a relatively simple method of assessment that grades preventive measures in relation to the increased risk.[11,12] However, this stratification of absolute risk through assessments is often utilized by health-care providers to form a barrier, below which treatment is discouraged.[12] Thus, there may be potential issues if decisions regarding treatment were purely based on these risk assessment systems without clinical judgment as determining risk may not always be straightforward. This can be illustrated by a few examples. First, conducting a risk assessment in hypertensive patients who do not particularly belong to defined subgroups of patients specified in the risk assessment system can be even more complex. Second, risk may be higher than indicated in the charts in certain groups of people such as those with central obesity.[12] Third, younger subjects have an even greater increased relative risk associated with overweight compared to older subjects.[12] As this group of people may require the use of different models, this implies that clinicians would not only have to factor in additional considerations but also utilize a risk assessment system lacking applicability. Although practicing clinical judgment remains a key role of every clinician, not having a robust risk assessment system in place could result in misclassification of risk in patients which could negatively impact their route of hypertension management and treatment outcomes. Therefore, this highlights the importance of refining and improving cardiovascular risk assessment systems to continually improve its predictive ability with emerging evidence that identify new aspects and risk factors for consideration.

Conclusions

Overall, it is shown that European guidelines demonstrate a willingness to "reappraise" previous recommendations, offer a flexible approach, and provide practical solutions for the use of recommendations in clinical practice. It should also be highlighted that criteria informing the classification and definition of hypertension remain a complex but key aspect in hypertension management, including treatment decisions. From this review, it is evident that guidelines have progressively recommended more rigorous criteria in both the definition and classification of hypertension with newer and more robust evidence. Therefore, with advances in hypertension research in diverse populations, newer understandings of its pathophysiology, and considerations of the interaction between BP and comorbidities, it is expected that recommendations for the management of hypertension have and will continue to be subject to modifications with time.

However, it should always be considered that guidelines are based on consensus statements formed through critical analyses of evidence by expert panels, making it open to interpretation. Thus, inconsistencies in recommendations by different organizations will continue to exist as a product. The shortcomings in the processes of guideline development should be acknowledged[28] to ensure that recommendations are held to a high standard and based on the most robust evidence, recognizing that guidelines should provide guidance without replacing clinical judgment based on person-specific factors and the overall clinical picture.

References

1. National Institute for Health and Care Excellence (NICE) Guideline [NG136]. Hypertension in Adults: Diagnosis and Management (NG136); 2019.
2. Kotchen TA. Developing hypertension guidelines: An evolving process. Am J Hypertens 2014;27:765-72.
3. Jennings GL, Touyz RM. Hypertension guidelines: More challenges highlighted by Europe. Hypertension 2013;62:660-5.
4. 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.
5. Gross F, Pisa Z, Strasser T, Zanchetti A. Management of Arterial Hypertension: A Practical Guide for the Physician and Allied Health Workers. Geneva: World Health Organization; 1984.
6. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, *et al*. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021-104.
7. World Health Organisation. Arterial Hypertension and Ischaemic Heart Disease (Preventive Aspects): Report of a WHO Expert Committee. Geneva: World Health Organisation; 1962.
8. World Health Organisation. Arterial Hypertension: Report of a WHO Expert Committee. Geneva: World Health Organisation; 1978.
9. World Health Organisation. Hypertension Control: Report of a WHO Expert Committee. Geneva: World Health Organisation; 1996.
10. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European society of hypertension and European society of cardiology guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011-53.
11. Mancia G, de Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al*. 2007 guidelines for the management of arterial hypertension. J Hypertens 2007;25:1105-87.
12. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, *et al*. 2013 ESH/ESC guidelines for the management of arterial hypertension. J Hypertens 2013;31:1281-357.
13. Chalmers J, MacMahon S, Mancia G, Whitworth J, Beilin L, Hansson L, *et al*. 1999 World Health Organization-international society of hypertension guidelines for the management of hypertension. Clin Exp Hypertens 1999;21:1009-60.
14. Fagard RH, van den Broeke C, de Cort P. Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. J Hum Hypertens 2005;19:801-7.
15. Whitworth JA. 2003 World Health Organization (WHO)/ international society of hypertension (ISH) statement on management of hypertension. J Hypertens 2003;21:1983-92.
16. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease.

Br Med Bull 1994;50:272-98.
17. Sytkowski PA, D'Agostino RB, Belanger AJ, Kannel WB. Secular trends in long-term sustained hypertension, long-term treatment, and cardiovascular mortality. Circulation 1996;93:697-703.
18. Devereux RB. Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA 2004;292:2350-6.
19. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, *et al*. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients. Hypertension 2005;45:198-202.
20. Whelton PK, Carey RM, Aronow WS, Casey DE, 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: A report of the American college of cardiology/American heart association task force on clinical practice guidelines. Hypertension 2018;71:1269-324.
21. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, *et al*. 2020 International society of hypertension global hypertension practice guidelines. Hypertension 2020;75:1334-57.
22. Poulter NR, Castillo R, Charchar FJ, Schlaich MP, Schutte AE, Tomaszewski M, *et al*. Are the American heart association/american college of cardiology high blood pressure guidelines fit for global purpose? Thoughts from the international society of hypertension. Hypertension 2018;72:260-2.
23. Zanchetti A. The hypertensive patient with multiple risk factors is treatment really so difficult? Am J Hypertens 1997;10:223S-9.
24. D'Agostino RB, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores. JAMA 2001;286:180-7.
25. Conroy R. Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. Eur Heart J 2003;24:987-1003.
26. Cooney MT, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk. J Am Coll Cardiol 2009;54:1209-27.
27. Aktas MK. Global risk scores and exercise testing for predicting all-cause mortality in a preventive medicine program. JAMA 2004;292:1462-8.
28. Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, editors. Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011.

How to cite this article: Ng NEC, Delles C. The Evolution of Hypertension Guidelines: A Global and European Perspective with a Focus on Classification of Hypertension (Review). Hypertens 2021;7(2): 71-77.

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

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/ © Ng NEC, Delles C. 2021

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

Review Article

Hypertension and Uric Acid (Review)

Alexander MacDonald[1], Moustafa Ibrahim Mohamed Ahmed Morsy[1], Jesse Dawson[2]

[1]School of Medicine, Dentistry and Nursing, College of Medical, Veterinary and Life Sciences, University of Glasgow, UK, [2]Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, UK

Abstract

There is a strong mechanistic basis for a role of uric acid in the development of hypertension. This is supported by a number of preclinical studies which demonstrate a rise in blood pressure following induction of hyperuricemia. A number of epidemiological studies support an association between hyperuricemia and hypertension in humans. This is further supported by the largest Mendelian randomization study to date. However, what is less clear is whether this relationship can be manipulated to benefit cardiovascular outcomes and to improve blood pressure control. Clinical trials in humans strongly suggest that there is a temporary effect of urate reduction on blood pressure, particularly in younger people. However, this is less apparent in older adults and in particular, in people with treated chronic hypertension. This observation fits nicely with preclinical experimental data showing that chronic hyperuricemia ultimately causes a salt sensitive hypertension which is resistant to urate lowering. In summary, it seems likely that uric acid has a role in the pathogenesis of hypertension but there is insufficient evidence to use urate lowering for the treatment of hypertension.

Key words: Blood pressure, Uric acid, Xanthine oxidase

Uric acid is the end product of nucleic acid metabolism and is also generated during the breakdown of high-energy nucleotides such as adenosine triphosphate (ATP). It is generated in cells by the enzyme xanthine oxidoreductase and the most uric acid circulates in the body as the urate anion. Mutations during primate evolution mean humans lack the urate-degrading enzyme uricase and thus have higher levels of serum uric acid than other mammals. Further, in humans, serum urate concentrations are higher in industrialized populations because diets are typically rich in purines and fructose (both of which generate urate). Alcohol intake is also associated with higher levels. A putative association between high serum uric acid level, hypertension, and cardiovascular disease has been debated for many years but remains controversial.

The underlying mechanisms by which hyperuricemia may cause hypertension have been described in a number of well conducted preclinical experiments. It has been suggested that hyperuricemia elevates blood pressure in two phases. The initial phase is reversible with urate-lowering agents[1,2] but, with time, the hypertension becomes salt sensitive and resistant to urate lowering.[3] In rodent models, inhibition of uricase and acute hyperuricemia leads to a rise in blood pressure.[1,3] This can be prevented both by xanthine oxidase inhibitors which reduce production of serum uric acid and uricosuric drugs. This acute phase of hyperuricemia-induced hypertension is proposed to be predominantly mediated by endothelial dysfunction and is not crystal dependent. Hyperuricemia has been demonstrated to elevate juxtaglomerular renin release and inhibit nitric oxide synthase (NOS) expression in the macula densa.[1] Impaired phosphorylation of endothelial NOS through the activation of uric acid transporters is a further effect of hyperuricemia. This contributes to reduced vasodilatation and endothelial dysfunction.[4] Moreover, although urate may function as an antioxidant in the extracellular space, intracellular uric acid can induce an oxidative burst. Intracellular uptake or intracellular production of uric acid is followed by the activation of mitogen-activated protein (MAP) kinases (such as p38) and a significant NADPH oxidase-mediated increase in the production of reactive oxygen species (ROS).[5] Aldose reductase (AR) has been shown

Address for correspondence:
Prof. Jesse Dawson, Professor of Stroke Medicine and Consultant Physician, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, UK. E-mail: Jesse.Dawson@glasgow.ac.uk

Received: 06-01-2022; Accepted: 12-01-2022
doi: 10.15713/ins.johtn.0225

to contribute to this oxidative stress. Uric acid stimulates AR expression through the p38/MAP kinase pathway, resulting in endogenous fructose production, triglyceride accumulation, and enhanced ROS production in endothelial cells.[6] An additional proposed mechanism is the alteration of human endothelial mitochondria. Uric acid decreases mitochondrial mass, enoyl-CoA hydratase expression, aconitase activity, and intracellular ATP production. Such alterations characterize mitochondrial dysfunction which is considered a key feature of early endothelial dysfunction.[7]

Increased arterial stiffness combined with renal microvascular disease and inflammation likely drive the proposed chronic phase of hyperuricemia-induced hypertension. Hyperuricemia stimulates platelet-derived growth factor and cyclooxygenase-2 expression, and ERK MAP kinase phosphorylation, promoting vascular smooth muscle cell proliferation and increased collagen deposition. This may cause a progressive afferent arteriolopathy and decreased arterial luminal diameter.[3] The resulting reduced renal perfusion can cause ischemia that induces tubulointerstitial inflammation and fibrosis.[8] A subsequent salt-sensitive hypertension develops and persists independently of serum uric acid levels[3] and is resistant to urate lowering. Furthermore, through a crystal-dependent mechanism, hyperuricemia can increase arterial stiffness.[9] Phagocytosis of urate crystals induces NLRP3 inflammasome activation in macrophages, which induces interleukin-1β production. This stimulates inflammation, smooth muscle cell proliferation, endothelial dysfunction, and ultimately promotes arteriosclerosis.[9,10] However, increased arterial stiffness can additionally be induced through the previously mentioned crystal-independent mechanisms, including RAAS upregulation, reduced endothelial NO, and oxidative stress.[9] Although the two proposed phases of hyperuricemia-induced hypertension are interlinked, their distinction may have profound importance regarding the effectiveness of urate-lowering therapy for lowering blood pressure.

The Association between Uric Acid Level and Blood Pressure

A major obstacle in the identification of the association between serum uric acid levels and hypertension is the fact that hyperuricemia typically exists alongside other cardiovascular risk factors. Confounding is a significant potential source of bias. Despite this, numerous epidemiological studies suggest that hyperuricemia is independently associated with hypertension.[11-16]

A meta-analysis of 97,824 participants from 25 observational studies demonstrated that hyperuricemia was associated with a higher risk of incident hypertension. For every 1 mg/dL (60 μmol/L) increase in serum uric acid levels, the relative risk (RR) of hypertension rose by 15% (RR = 1.15, 95% confidence interval [CI] 1.06–1.26) after adjusting for confounders.[11] Such findings were consistent with a previously conducted meta-analysis[12] and a recent study found that elevated serum uric acid predicts hypertension independent of alcohol drinking status.[13] Hyperuricemia has been shown to be independently associated with altered blood pressure variability and a nocturnal non-dipping hypertensive profile. Such changes are associated with increased risk of cardiovascular, cerebrovascular, and renovascular disease, suggesting that uric acid could be involved in establishing a more pathogenic form of hypertension.[17,18] Although the risk of hypertension from hyperuricemia is well established in both sexes, a stronger association is observed in females.[12] This relationship is also apparent in pregnancy. Serum uric acid levels increase in gestational hypertensives and positively correlate with the severity of hypertension. Consequently, uric acid may act as a sensitive predictive marker for pre-eclampsia.[19]

The relationship between hyperuricemia and hypertension exists from an early age. The 1999–2006 National Health and Nutrition Examination Survey examined this association in 6036 US adolescents aged 12–17 years of age. About 34% of participants had elevated serum uric acid, defined as ≥5.5 mg/dL (≥330 μmol/L). Compared to those with a lower serum uric acid, these adolescents had a 2-fold increased risk for elevated blood pressure after adjusting for age, sex, ethnicity, and body mass index (odds ratio [OR] = 2.03, 95% CI 1.38–3.00).[14] A study of a similar population supported these results and found that adolescents who drank more fructose-containing beverages had increased serum uric acid levels and elevated blood pressure.[20] The Bogalusa Heart Study also demonstrated that childhood uric acid levels predict blood pressure in adulthood. A total of 577 participants aged 5–17 years were followed, and their childhood serum uric acid levels were strongly correlated with blood pressure in both childhood and adulthood.[15]

However, the risk is less apparent in older populations. In fact, in a meta-analysis, an inverse relationship was observed between increasing mean sample age and RR of hypertension afforded by uric acid.[12] A recent prospective study followed 808 non-hypertensive Korean adults and found a significant association between hyperuricemia and incident hypertension in those aged <55 years. In contrast, the association was not demonstrated in those aged ≥55 years.[16] Thus, the association between hyperuricemia and hypertension appears to weaken with age.

A recently performed Mendelian randomization (MR) analysis using data from UK Biobank, Million Veterans Program, and genome-wide association study consortia found a consistent relationship between genetically predicted serum uric acid and blood pressure.[21] In addition, it showed that every 1 standard deviation increase in genetically predicted serum urate was associated with an increased risk of coronary heart disease (OR 1.19, 95% CI 1.10–1.30, $P = 4 \times 10^{-5}$), peripheral artery disease (1.12, 95% CI 1.03–1.21, $P = 9 \times 10^{-3}$), and stroke (1.11, 95% CI 1.05–1.18, $P = 2 \times 10^{-4}$). The relationship between uric acid and blood pressure was also found to be an important component of this increased risk of cardiovascular disease. Network MR mediation analysis found that 29% (95% CI 9–48%) of the risk of CHD, 44% (95% CI 5–83%) of risk of PAD, and 45% (95% CI 14–76%) of risk of stroke were mediated through blood pressure.

Clinical Trials of Urate-Lowering Therapy

Allopurinol, a drug commonly prescribed for the prophylaxis of gout, inhibits the activity of xanthine oxidase, leading to reduction in both serum uric acid and oxidative stress through reduced superoxide anion production. Allopurinol has been shown to improve cerebral nitric oxide bioavailability in people with type 2 diabetes,[22] reduce markers of inflammation after ischemic stroke,[23] reduce carotid intima-media thickness progression,[24] cause regression of LVH in patients with diabetes,[25] renal impairment, and angina,[26] reduce myocardial ischemia in patients with angina,[27] and reduce augmentation index.[28]

Several studies have directly assessed the effect of urate-lowering therapy on blood pressure. First, in a randomized, placebo-controlled, double-blinded trial of adolescents with early-onset hypertension,[29] allopurinol was found to significantly reduce 24 h ambulatory systolic and diastolic blood pressure over 8 weeks. The mean change in 24 h ambulatory systolic blood pressure (SBP) was −6.3 mmHg (95% CI, −3.8–−8.9 mmHg) with allopurinol and 0.8 mmHg (95% CI, 3.4–−2.9 mmHg) with placebo ($P = 0.001$). In another study including obese adolescents with pre-hypertension,[30] both allopurinol and probenecid led to a significant reduction in blood pressure. The fact that both a xanthine oxidase inhibitor and uricosuric drug lowered blood pressure suggests the change was mediated through uric acid reduction and not secondary effects of allopurinol. This is further supported by a recent study where pegloticase, a recombinant uricase, significantly decreased blood pressure in people with chronic gout.[31]

However, not all studies have shown a reduction in blood pressure with urate-lowering drugs. In a randomized, double-blind, placebo-controlled study of African-Americans with Stage 1 hypertension,[32] 4 weeks allopurinol did not lower SBP (mean change in SBP vs. placebo [difference 4.3 mmHg (95% CI, −0.2–8.7); $P = 0.059$]). In this study, baseline blood pressure was very low (119.9 ± 13.6 in the allopurinol group and 117 ± 11.2 in the placebo group). Similarly, in a double-blind, placebo-controlled trial of 149 overweight or obese adults with hyperuricemia, 8-week urate lowering with probenecid or allopurinol did not affect RAS activity of measures of blood pressure.[33] Baseline blood pressure was also well controlled in this study. The most recently published trial is the SURPHER study.[34] This was a randomized, double-blind, crossover clinical trial. Participants were adults with hyperuricemia and a baseline systolic BP ≥120 and <160 mmHg or diastolic BP ≥80 and <100 mmHg. After 4-week allopurinol, there was no change in SBP compared to the placebo phase, although flow-mediated dilatation did increase.

A recently published systematic review and meta-analysis included data from 15 randomized controlled clinical trials which assessed the effect of urate-lowering therapy on blood pressure.[21] After exclusion of one study (of people receiving dialysis) causing significant heterogeneity with a high risk of bias, people treated with urate-lowering therapy had greater reduction in SBP than controls (mean difference in SBP −2.55, 95% CI −4.06–−1.05, $P = 1 \times 10^{-3}$, I^2 43%). However, the difference did not reach statistical significance when only studies with a low risk of bias were included (mean difference in SBP −7.40, 95% CI −15.98–1.18, $P = 0.09$). Meta-regression demonstrated that higher baseline serum urate concentration was associated with greater SBP reduction with urate-lowering therapy but did not identify an association with change in serum urate and BP. The study also found that urate-lowering therapy was associated with reduction in risk of MACE in people with a history of a previous cardiovascular event.

Conclusions

Uric acid likely does have a role in the development of hypertension in certain individuals. This may be particularly true in younger adults with obesity. This observation is supported by numerous epidemiological studies, MR studies, and results of clinical trials. However, clinical trials have not yet convincingly demonstrated a role for urate-lowering therapy in the treatment of essential hypertension. Although this remains a very promising area, further research is needed.

References

1. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, *et al*. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 2001;38:1101-6.
2. Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, *et al*. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. Hypertension 2002;40:355-60.
3. Lu J, Hou X, Yuan X, Cui L, Liu Z, Li X, *et al*. Knockout of the urate oxidase gene provides a stable mouse model of hyperuricemia associated with metabolic disorders. Kidney Int 2018;93:69-80.
4. Mishima M, Hamada T, Maharani N, Ikeda N, Onohara T, Notsu T, *et al*. Effects of uric acid on the no production of HUVECs and its restoration by urate lowering agents. Drug Res (Stuttg) 2016;66:270-4.
5. Sautin YY, Nakagawa T, Zharikov S, Johnson RJ. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. Am J Physiol Cell Physiol 2007;293:C584-96.
6. Huang Z, Hong Q, Zhang X, Xiao W, Wang L, Cui S, *et al*. Aldose reductase mediates endothelial cell dysfunction induced by high uric acid concentrations. Cell Commun Signal 2017;15:3.
7. Sanchez-Lozada LG, Lanaspa MA, Cristobal-Garcia M, Garcia-Arroyo F, Soto V, Cruz-Robles D, *et al*. Uric acid-induced endothelial dysfunction is associated with mitochondrial alterations and decreased intracellular ATP concentrations. Nephron Exp Nephrol 2012;121:e71-8.
8. Sanchez-Lozada LG, Tapia E, Santamaria J, Avila-Casado C, Soto V, Nepomuceno T, *et al*. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. Kidney Int 2005;67:237-47.
9. Kuwabara M, Kanbay M, Hisatome I. Uric acid and hypertension because of arterial stiffness. Hypertension 2018;72:582-4.
10. Jin Y, Fu J. Novel insights into the NLRP 3 inflammasome in atherosclerosis. J Am Heart Assoc 2019;8:e012219.

11. Wang J, Qin T, Chen J, Li Y, Wang L, Huang H, *et al*. Hyperuricemia and risk of incident hypertension: A systematic review and meta-analysis of observational studies. PLoS One 2014;9:e114259.
12. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: A systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2011;63:102-10.
13. Tatsumi Y, Asayama K, Morimoto A, Satoh M, Sonoda N, Miyamatsu N, *et al*. Hyperuricemia predicts the risk for developing hypertension independent of alcohol drinking status in men and women: The Saku study. Hypertens Res 2020;43:442-9.
14. Loeffler LF, Navas-Acien A, Brady TM, Miller ER 3rd, Fadrowski JJ. Uric acid level and elevated blood pressure in US adolescents: National health and nutrition examination survey, 1999-2006. Hypertension 2012;59:811-7.
15. Alper AB Jr., Chen W, Yau L, Srinivasan SR, Berenson GS, Hamm LL. Childhood uric acid predicts adult blood pressure: The Bogalusa Heart Study. Hypertension 2005;45:34-8.
16. Lee SW, Kim HC, Nam C, Lee HY, Ahn SV, Oh YA, *et al*. Age-differential association between serum uric acid and incident hypertension. Hypertens Res 2019;42:428-37.
17. Cagli K, Turak O, Canpolat U, Ozcan F, Tok D, Mendi MA, *et al*. Association of serum uric acid level with blood pressure variability in newly diagnosed essential hypertension. J Clin Hypertens (Greenwich) 2015;17:929-35.
18. Turak O, Ozcan F, Tok D, Isleyen A, Sokmen E, Tasoglu I, *et al*. Serum uric acid, inflammation, and nondipping circadian pattern in essential hypertension. J Clin Hypertens (Greenwich) 2013;15:7-13.
19. Sakr HI, Khowailed AA, Al-Fakharany RS, Abdel-Fattah DS, Taha AA. Serum uric acid level as a predictive biomarker of gestational hypertension severity; a prospective observational case-control study. Rev Recent Clin Trials 2020;15:227-39.
20. Nguyen S, Choi HK, Lustig RH, Hsu CY. Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. J Pediatr 2009;154:807-13.
21. Gill D, Cameron AC, Burgess S, Li X, Doherty DJ, Karhunen V, *et al*. Urate, blood pressure, and cardiovascular disease evidence from mendelian randomisation and meta-analysis of clinical trials. Hypertension 2021;77:383-92.
22. Dawson J, Quinn T, Harrow C, Lees KR, Weir CJ, Cleland SJ, *et al*. Allopurinol and nitric oxide activity in the cerebral circulation of those with diabetes: A randomized trial. Diabetes Care 2009;32:135-7.
23. Muir SW, Harrow C, Dawson J, Lees KR, Weir CJ, Sattar N, *et al*. Allopurinol use yields potentially beneficial effects on inflammatory indices in those with recent ischemic stroke: A randomized, double-blind, placebo-controlled trial. Stroke 2008;39:3303-7.
24. Higgins P, Walters MR, Murray HM, McArthur K, McConnachie A, Lees KR, *et al*. Allopurinol reduces brachial and central blood pressure, and carotid intima-media thickness progression after ischaemic stroke and transient ischaemic attack: A randomised controlled trial. Heart 2014;100:1085-92.
25. Szwejkowski BR, Gandy SJ, Rekhraj S, Houston JG, Lang CC, Morris AD, *et al*. Allopurinol reduces left ventricular mass in patients with Type 2 diabetes and left ventricular hypertrophy. J Am Coll Cardiol 2013;62:2284-93.
26. Kao MP, Ang DS, Gandy SJ, Nadir MA, Houston JG, Lang CC, *et al*. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. J Am Soc Nephrol 2011;22:1382-9.
27. Noman A, Ang DS, Ogston S, Lang CC, Struthers AD. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: A randomised, placebo controlled crossover trial. Lancet 2010;375:2161-7.
28. George J, Carr E, Davies J, Belch JJ, Struthers A. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. Circulation 2006;114:2508-16.
29. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: A randomized trial. JAMA 2008;300:924-32.
30. Soletsky B, Feig DI. Uric acid reduction rectifies prehypertension in obese adolescents. Hypertension 2012;60:1148-56.
31. Johnson RJ, Choi H, Yeo AE, Lipsky PE. Pegloticase treatment significantly decreases blood pressure in patients with chronic gout. Hypertension 2019;74:95-101.
32. Segal MS, Srinivas TR, Mohandas R, Shuster JJ, Wen X, Whidden E, *et al*. The effect of the addition of allopurinol on blood pressure control in African Americans treated with a thiazide-like diuretic.J Am Soc Hypertens 2015;9:610-9.
33. McMullan CJ, Borgi L, Fisher N, Curhan G, Forman J. Effect of uric acid lowering on Renin-angiotensin-system activation and ambulatory BP: A randomized controlled trial. Clin J Am Soc Nephrol 2017;12:807-16.
34. Gaffo AL, Calhoun DA, Rahn EJ, Oparil S, Li P, Dudenbostel T, *et al*. Effect of serum urate lowering with allopurinol on blood pressure in young adults: A randomized, controlled, crossover trial. Arthritis Rheumatol 2021;73:1514-22.

How to cite this article: MacDonald A, Morsy MI, Dawson J. Hypertension and Uric Acid (Review). Hypertens 2021;7(2): 78-81.

Source of support: Research funding to investigate the effect of urate reduction in people with stroke from British Heart Foundation and UK Stroke Association, **Conflicts of interest:** None

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/ © MacDonald A, Morsy MI, Dawson J. 2021

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

Review Article

Transforming Hypertension Care through the Lens of Planetary Health

Clea du Toit, Linsay McCallum, Stefanie Lip, Sandosh Padmanabhan

Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK

Abstract

Hypertension is the most significant modifiable cardiovascular disease risk factor and is projected to affect 1.5 billion people worldwide by 2025. Despite being relatively easily diagnosed and treated, hypertension remains poorly managed in up to 80% of affected individuals. This implies that simply scaling up existing paradigms of hypertension screening and treatment may not translate to better and sustained hypertension control. Rather, there is a case for rethinking existing paradigms and additionally accommodating emerging priorities brought about by climate change and the COVID-19 pandemic. Indeed, the pursuit of planetary health calls for innovative solutions as set out in the UN's Sustainable Development Goals. Transforming hypertension care requires reimagining the role of the randomized controlled trial as the gold standard in a world where patients are seen as individuals rather than an average of a population. We propose n-of-1 trials (single-subject clinical trials) enabled by technology as a moonshot strategy to affect a quantum change in hypertension management with trickle-down benefits across all cardiovascular and chronic diseases.

Key words: Cardiovascular disease, climate change, hypertension, moonshot, n-of-1 trial

Introduction

Annually a third of all global deaths (>18 million people worldwide) can be attributed to cardiovascular diseases (CVD) such as coronary artery disease, cerebrovascular disease, and heart failure.[1,2] Hypertension is the major risk factor for CVD directly accounting for up to 10.5 million of these deaths annually and 7% of global disability-adjusted life years.[1-4] By 2025, hypertension is projected to affect more than 1.5 billion people globally compared to the 1 billion people affected currently.[3] There is robust evidence from randomized controlled studies that control of risk factors such as dyslipidemia, hypertension, smoking, and diabetes can reduce the burden of CVD.[5] Modeling indicates that effective control of hypertension through improving treatment rates and lifestyle could save more lives than any other clinical intervention. Despite being relatively easy to detect and treat (in most cases) using inexpensive generic drugs, hypertension is controlled to target in <1 in 5 patients.[4,6,7] Achieving adequate blood pressure (BP) control is challenging, because of the asymptomatic nature of the condition, high levels of non-adherence to treatment, and more importantly the underpinning cause of hypertension remains unclear in most patients. The current strategy is to treat only those with established hypertension,[8] which does little to end the global BP burden as the "low-risk" patients, who make up the largest share of the population at risk, are ignored. For the population at large, the greatest burden from hypertension occurs among people with only minimally elevated BP,[7] because there are so many of them - population attributable risks of raised BP in those not currently classified as hypertensive are large. The disproportionate risk for the global population from relatively mild hypertension bears strongly on the question of how to achieve the greatest reduction in the risks of hypertension. Globally, there remain major shortfalls in awareness of hypertension, uptake of hypertensive therapy, and BP control. Increased awareness of hypertension does not necessarily imply increased uptake of antihypertensive therapy, and increased uptake of antihypertensive therapy does not imply better BP control. The most recent study of trends in hypertension control in the United States showed that the

Address for correspondence:
Prof. Sandosh Padmanabhan, Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK.
E-mail: Sandosh.padmanabhan@glasgow.ac.uk

Received: 07-01-2022; Accepted: 11-01-2022
doi: 10.15713/ins.johtn.0226

estimated proportion of adults with hypertension who had controlled BP increased from 31.8% in 1999 to 2000 to 48.5% in 2007 to 2008, and then remained stable until 2013 to 2014, but significantly decreased to 43.7% in 2017 to 2018.[9] This implies that scaling up existing paradigms of hypertension screening and treatment may not translate to higher and higher levels of BP control. Furthermore, existing paradigms must be adapted to accommodate new priorities caused by climate change and the COVID-19 pandemic.

Sustainable Development Goals and Planetary Health

From greater air and water pollution to an increase in extreme weather events, our economic and development progress over the last 100 years has created unintended consequences for the natural world and increased the incidence of disease as the growing human population is more susceptible to the effects of environmental change. Carbon risk affects both patients and health services through the impact of climate change on many of the social and environmental determinants of health and on the consequent impact on healthcare service delivery.[10] For hypertension, increased pollution and socioeconomic disruption linked to climate change promote the incidence of hypertension and poorer outcomes. Concurrently, hypertension drives carbon emissions primarily from suboptimal BP control, increasing patients' travel to attending clinics and investigations often separated in space and time. Thus, there is a case for considering the wider implications of optimizing BP management beyond not only improving patient outcomes but also reducing the carbon footprint.

The adoption of the United Nations 2030 agenda for sustainable development in 2016 by the global community reflects an understanding that opportunities to improve health can be found not just in specific health interventions but more crucially through interactions of environmental protection and social justice. The wide-ranging and interconnected nature of the Sustainable Development Goals (SDGs) presents an opportunity for creative and innovative approaches. Goal 3 on health encompasses a large number of disease or condition-specific areas (maternal and child health, infectious diseases, non-communicable diseases (NCDs), injuries, substance abuse, and road traffic accidents) as well as cross-cutting or systems-related issues including universal health coverage, health financing, human resources for health and disease surveillance. The combination of targets under Goal 3 means that a narrow focus on a handful of specific health conditions and the systems needs related to them is no longer a viable health systems strengthening strategy. Instead, we need to consider how different approaches to health systems strengthening may intersect with multiple different health conditions. The United Nations Development Programme envisions a planetary health program as a means to achieve SDGs and defines it as "the health of human civilization and the state of the natural systems on which it depends."[11] To accomplish this, the concept also calls for a multidisciplinary, cross-sector, and transborder approach to change mindsets and behaviors at every level, from global to local. Many of the ecosystem threats to human health are global and will require long-term planet-wide solutions, with climate change being the most prominent of those threats. Unlike traditional public health measures such as spraying for mosquitoes, interventions inspired by planetary health often have multiple health benefits: green spaces can not only combat mosquito-borne disease and heat-related deaths but also improve water quality and provide important mental health benefits.

Impact of the COVID-19 Pandemic

COVID-19 has impacted health in several different ways and those at risk of or already living with CVD are at an especially heightened risk. Indeed, the excess mortality risk due to COVID-19 was comprised not only of the immediate consequences of the infection itself but also those related to the cardiovascular system.[12,13] The OpenSAFELY platform documented across a large database of adults in the UK that chronic cardiac disease, stroke, dementia, reduced kidney function, uncontrolled diabetes, and organ transplant considerably increase the risk of death in patients with a positive diagnosis of COVID-19.[14] While OpenSAFELY shows that hypertension itself does not necessarily increase the risk for severe disease and death from COVID-19, many CVD patients also live with multiple coexisting comorbidities, which make them even more vulnerable to COVID-19, and hypertension was observed as the most frequent comorbidity in patients who died from COVID-19. International lockdown protocols, access to regular COVID-19 reports and updates and overwhelmed healthcare services have resulted in a decline in individuals accessing healthcare services for non-COVID-related conditions.[13] Before the COVID-19 pandemic, fewer than 1 in 3 individuals globally were either aware of their BP or had their hypertension controlled on treatment. The COVID-19 pandemic-related rise of remote consultations, limited face-to-face primary-care/hospital visits and routine screening has had a negative impact on diagnosis, monitoring, and management of all NCDs including hypertension.[15,16] Predictably, the impact of COVID-19 upon circulatory health will be of a greater extent and longer duration in low-to-middle-income countries (LMICs) due to late-onset and expansion of vaccination programs.[17] The decline in non-COVID-related hospital admissions was greater in areas of resource constraints, as was the decline in BP control in ethnic minorities.[18] Furthermore, there is less information available from LMICs with only a third of publications in a recent review stemming from LMICs.[18] Access to telehealth or remote healthcare (e.g. home BP monitoring and telemedicine consultations on glycemic control for diabetes patients) is not necessarily able to alleviate these disparities because it often comes with the expense of extra personal equipment.

Transforming Hypertension Care through the Lens of Planetary Health

The global underdiagnosis and undertreatment of hypertension indicate that systematic transformation is required.[19] Broad commitments to improved cardiovascular health will no doubt lead to some improvements, but much like the cancer moonshot, they are doomed to fade into obscurity without strict timelines, milestone-driven plans, and adapting to the new priorities and responsibilities envisioned by SDGs and planetary health.

The key challenges facing hypertension diagnosis and management from a global to local perspective are summarised below and highlight the scale of the problem requiring innovative solutions that must consider the whole range of requirements from managing hypertension in a personalized and participatory manner across all levels of raised BP, global relevance and application, not overburdening healthcare systems, generating new evidence on efficacy and safety and new insights into the underlying mechanisms of disease.

Challenges

(1) Pharmacotherapy is informed by randomised controlled trials (RCTs) that are usually conducted in high-risk populations and the results are extrapolated to the largest at-risk population subgroup (young and/or with low cardiovascular risk). Current treatments of CVD are based on RCTs, the gold standard to establish the effectiveness and utility of therapy. RCTs have revolutionized healthcare, but most of the population-level improvements observed for CVD as a result of this have now plateaued suggesting new approaches are needed. RCTs offer population-level average estimates of the efficacy of a treatment that has been applied in the current 'all-comers' one-size-fits-all approach to management. This approach does not account for an individual's genetic, physiologic, demographic, and environmental characteristics. These factors are known to influence drug response at an individual level which is reflected in the high inter-individual and inter-population variability of response to most cardiovascular medications.

(2) Treatment and preventive strategies are not truly individualized. Discounting the rare monogenic forms of hypertension in which specific drugs or drug classes are indicated, the underpinning mechanism of essential hypertension is multifactorial with genetic and other biomarker tests not currently useful in determining the best antihypertensive therapy. Prescribing decisions are still based on broader factors such as age, sex, or ethnicity. For instance, individuals of African descent tend to respond better to diuretics and calcium channel blockers, while white Europeans benefit slightly more from ACE inhibitors or β-blockers.[8]

(3) The process of drug selection, dose titration, and recording of BP and adverse effects during the trial-and-error period is rarely comprehensively standardized on a national level and completely lacks international harmonization. Current management approaches are inefficient, expose patients to extensive periods of suboptimal treatment, and there is no systematic repetition of prior treatments or systematic assessment of outcomes. Consequently, both the patient and physician may be lulled into a false sense of security about the true effects of a particular prescribed therapy.

(4) Non-adherence to pharmacotherapy or preventive measures.

(5) Because of costs, even if a new drug/device shows success for hypertension, they are likely to be directed towards a relatively small fraction of the at-risk population and applied primarily in high-income countries.[20]

(6) The high prevalence of hypertension in relation to the number of primary care or specialist doctors means more and more responsibility for follow-up may need to be divested to the patient.[20]

(7) Factors specific to LMICs:
   a. Paucity of clinical trials and genetic studies in non-European populations resulting in a major gap in evidence base for non-European populations on population-specific drug response or adverse reaction rates.
   b. Lack of genomic data in these populations that essentially disenfranchises them from personalized management or precision medicine.
   c. Lack of effective systems to monitor and manage NCDs due to the recent epidemiological transition from communicable diseases to NCDs in these countries.

Importantly, the issues identified above are not specific to hypertension and are relevant to other conditions along the cardiovascular continuum. For example, in atrial fibrillation, the drug that is most efficacious, best tolerated, and results in optimum health-related quality-of-life is unknown and may differ for each individual patient;[21] there is no known effective treatment for heart failure with preserved ejection fraction resulting in an empirical approach to therapy with existing drugs;[22] a wide range of treatments are available for chronic stable angina which is prescribed on a trial-and-error basis.[23] Diabetes is another important cardiovascular risk factor and studies examining relative efficacy (on glucose levels, as well as weight and BP) of old and new diabetes drugs across ethnicity are entirely lacking, as is information on patients' experiences of different drugs.[24]

Hypertension "Moonshot"

We posit that the major barrier to achieving an exponential improvement in cardiovascular health is the set of interlinked problems listed above that are common to conditions across the cardiovascular continuum. *A paradigmatic shift in* CVD *management requires leveraging current structures, tools, and guidelines to build newer models of care that need to simultaneously generate evidence, offer better prediction, demonstrate improved outcome, catalyze new research, and change behavior*. The solution must transcend taxonomic labels and geographic

boundaries and move from an empirical, all-comers, RCT-informed strategy to a multi-omics, technology-driven, patient-empowered, precision medicine system that is inclusive of all populations. Realization of this goal requires transformative advances focussed on collecting more patient data, enabling faster research, better decision support for physicians, and better engagement of patients on a global scale. More crucially, given the scale of the problem, it is essential that any solution developed is available early to have a meaningful impact on global health.

Here, we evoke the "moonshot" metaphor despite decades of overuse and misuse of the term having given it a trite and overly simplistic flavor. However, a plan which promises to bring together players from disparate fields of science, technology, and engineering to solve a clearly defined human problem in a short timeframe is undeniably captivating, regardless of its phrasing. Hence, how about a moonshot to improve global hypertension in 5 years?

The hypertension moonshot is to develop a technology-driven healthcare platform that will address a majority of the aforementioned challenges to produce a substantial impact on the burden of hypertension within a reasonable time span, for instance, 5 years [Figure 1]. The moonshot model is essential in order to adapt and integrate clinical management, patient participation, and evidence generation into a learning technology platform that can be implemented globally. This requires clinicians, technologists, public health experts, epidemiologists, clinical triallists, behavioral scientists, and patients with global representation to engage in the development and implementation.

The underpinning concept for our proposal is n-of-1 trials, which are single-subject clinical trials that consider an individual patient as the sole unit of observation with the goal to determine the optimal intervention for the individual patient using objective data-driven criteria. Crucially, n-of-1 trials allow value to be returned to the patient immediately along with positive impacts on physician training. However, n-of-1 trials are not an off-the-shelf solution and require adaptation to fulfill the aims of this project. Conducting n-of-1 trials at scale in different countries offers a unique opportunity to level the playing field in terms of

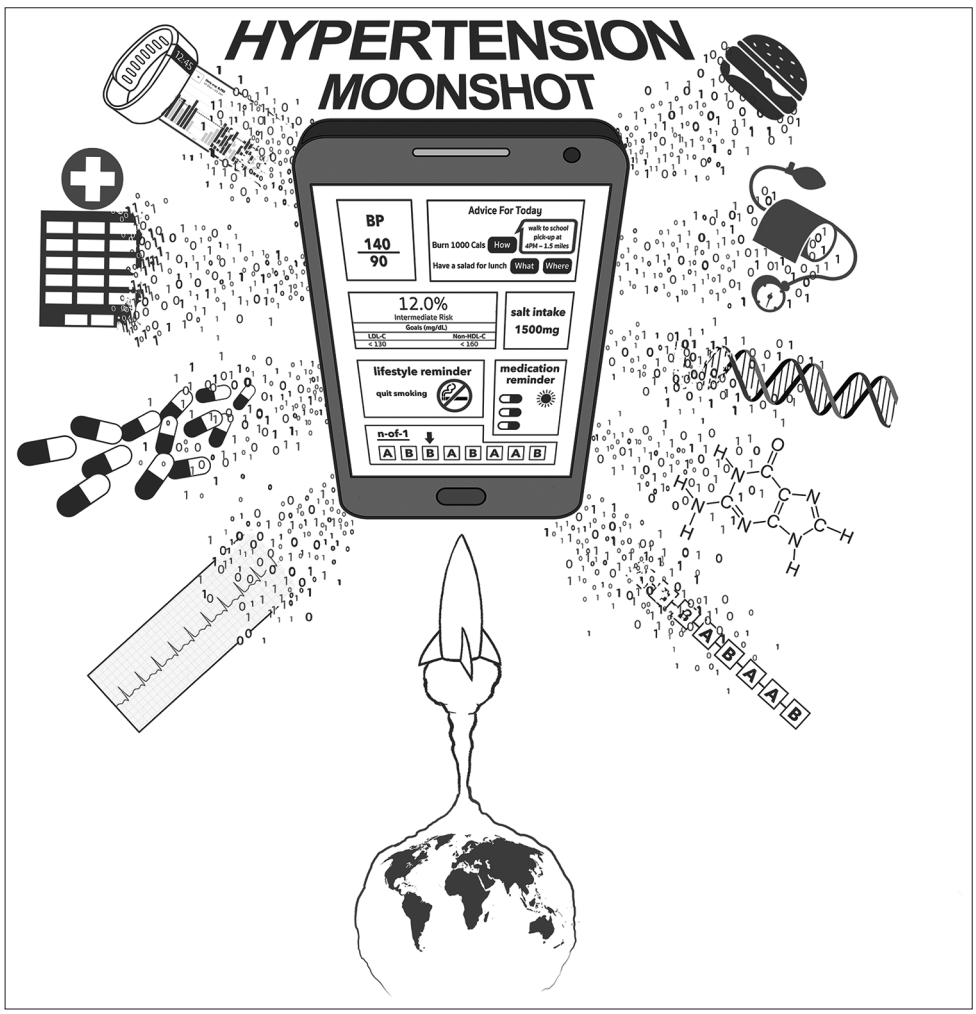


Figure 1: Hypertension moonshot

generating population-specific drug response patterns through meta-analysis of multiple n-of-1 trials. The critical enablers that make n-of-1 trial realizable are the ubiquitous use of mobile phones globally, and more recently the COVID-19 pandemic-related disruption of routine healthcare for chronic conditions. The feasibility of using n-of-1 trials to generate evidence globally is exemplified in this power calculation - for the trials of standard care vs. a systematic approach to drug selection for hypertension, assuming the standard deviation of systolic BP to be 10 mmHg, then 86 patients per group would be required to have 90% power to detect a 5 mmHg difference. Allowing for 30% loss to follow-up, a total of 224 patients randomized per country would be required.

To fully empower patients to conduct n-of-1 trials independently and safely with a collection of reliable measurements, wearable devices need to be developed for continuous data collection with minimal patient involvement and this needs to be integrated into the workflow. Increasing patient engagement in their health requires robust methods of data security and privacy. Solutions using blockchain hyperledger technology, for instance, will permit data security, integrity, and personal ownership of data and additionally may enable different methods of incentivization to improve treatment adherence or maintain healthy behavior. Establishing a technology-enabled system that will permit collection of high-quality data from controlled studies globally allows populations underrepresented in clinical trials and genomic studies to leap-frog towards opportunities in precision medicine whilst populations in advanced economies can leverage the ability to generate personal-level data at scale to drive more ambitious research for global benefit and impact.

There are manifold benefits if such a platform can be successfully developed and deployed. N-of-1 trials can help patients and clinicians recognize ineffective therapies, thus reducing polypharmacy, minimizing adverse effects, conserving health care resources, and fulfilling net-zero goals. Patients become more acquainted with the scientific method and in particular the value of rigorous clinical experiments. Clinicians become more connected to the process of generating clinical evidence, more engaged in clinical research, and potentially more interested in participating in clinical trials. Technological advances in data science, smartphone technology, and wearables make this the right time to make greater use of n-of-1 clinical trials in improving outcomes, increasing compliance to healthcare interventions, and healthcare cost savings.

Conclusions

Implementing a technology solution based on n-of-1 trials for hypertension management within 5 years is an ambitious ask, but one which is imperative if we are to reduce the global burden of hypertension. As with climate change, we cannot afford to delay taking transformative action while attempting to scale up existing solutions which are failing to meet the goals of planetary health. Since hypertension lies at the beginning of the cardiovascular continuum, the benefits of addressing it will have trickle-down effects across all CVD. Worldwide adoption of such a technology-enabled platform will facilitate the equitable improvement of BP control, which is all the more crucial as the effects of both climate change and hypertension continue to ravage vulnerable populations LMICs.

Acknowledgments

S. Padmanabhan is funded by the Medical Research Council (MR/M016560/1), the British Heart Foundation (PG/12/85/29925, CS/16/1/31878, and RE/18/6/34217), Health Data Research UK (HDR-5012), Chief Scientist Office, Scotland, Heart Research UK and UKRI Strength in Places Fund. CdT is funded by Health Data Research UK (HDR-5012), LM and SL acknowledge funding from Heart Research UK.

References

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: Analysis of worldwide data. Lancet 2005;365:217-23.
2. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, *et al.* A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: A systematic analysis for the global burden of disease study 2010. Lancet 2012;380:2224-60.
3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: A pooled analysis of 1479 population-based measurement studies with 19.1 million participants. Lancet 2017;389:37-55.
4. Brunstrom M, Carlberg B. Association of blood pressure lowering with mortality and cardiovascular disease across blood pressure levels: A systematic review and meta-analysis. JAMA Intern Med 2018;178:28-36.
5. Visseren FL, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, *et al.* 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227-337.
6. 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.
7. 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.
8. 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 (ESC) and the European society of hypertension (ESH). Eur Heart J 2018;39:3021-104.
9. Muntner P, Hardy ST, Fine LJ, Jaeger BC, Wozniak G, Levitan EB, *et al.* Trends in blood pressure control among US adults with hypertension, 1999-2000 to 2017-2018. JAMA 2020;324:1190-200.
10. Climate-smart Healthcare; 2017. Available from: https://www.documents1.worldbank.org/curated/en/322251495434571418/

pdf/113572-WP-PUBLIC-FINAL-WBG-Climate-smart-Healthcare-002.pdf [Last accessed on 2022 Jan 06].
11. Whitmee S, Haines A, Beyrer C, Boltz F, Capon AG, de Souza Dias BF, *et al.* Safeguarding human health in the anthropocene epoch: Report of the rockefeller foundation-lancet commission on planetary health. Lancet 2015;386:1973-2028.
12. Wu J, Mamas MA, Mohamed MO, Kwok CS, Roebuck C, Humberstone B, *et al.* Place and causes of acute cardiovascular mortality during the COVID-19 pandemic. Heart 2021;107:113-9.
13. Banerjee A, Chen S, Pasea L, Lai AG, Katsoulis M, Denaxas S, *et al.* Excess deaths in people with cardiovascular diseases during the COVID-19 pandemic. Eur J Prev Cardiol 2021;28:1599-609.
14. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, *et al.* Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430-6.
15. Alexander GC, Tajanlangit M, Heyward J, Mansour O, Qato DM, Stafford RS. Use and content of primary care office-based vs telemedicine care visits during the COVID-19 pandemic in the US. JAMA Netw Open 2020;3:e2021476.
16. Carr MJ, Wright AK, Leelarathna L, Thabit H, Milne N, Kanumilli N, *et al.* Impact of COVID-19 on diagnoses, monitoring, and mortality in people with type 2 diabetes in the UK. Lancet Diabetes Endocrinol 2021;9:413-5.
17. Choi EM. COVID-19 vaccines for low-and middle-income countries. Trans R Soc Trop Med Hyg 2021;115:447-56.
18. Bress AP, Cohen JB, Anstey DE, Conroy MB, Ferdinand KC, Fontil V, *et al.* Inequities in hypertension control in the united states exposed and exacerbated by COVID-19 and the role of home blood pressure and virtual health care during and after the COVID-19 pandemic. J Am Heart Assoc 2021;10:e020997.
19. Dzau VJ, Balatbat CA. Future of hypertension. Hypertension 2019;74:450-7.
20. Padmanabhan S, Aman A, Dominiczak AF. Recent findings in the genetics of blood pressure: How to apply in practice or is a moonshot required? Curr Hypertens Rep 2018;20:54.
21. Beaser AD, Cifu AS. Management of Patients With Atrial Fibrillation. JAMA 2019;321:1100-1.
22. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr., Colvin MM, *et al.* 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: A report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. J Am Coll Cardiol 2017;70:776-803.
23. Ford TJ, Corcoran D, Berry C. Stable coronary syndromes: Pathophysiology, diagnostic advances and therapeutic need. Heart 2018;104:284-92.
24. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, *et al.* Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427-43.

How to cite this article: du Toit C, McCallum L, Lip S, Padmanabhan S. Transforming Hypertension Care through the Lens of Planetary Health (Review). Hypertens 2021;7(2):82-87.

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

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/ © du Toit C, McCallum L, Lip S, Padmanabhan S. 2021

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

Topical Commentary

Weight Management in Hypertension: A Scotland Perspective

Maggie Rostron[1], Linsay McCallum[1,2]

[1]Department of Medicine, Queen Elizabeth University Hospital, Glasgow, United Kingdom, [2]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom

Abstract

Hypertension affects 1.2 million people in Scotland and often co-exists with other cardiovascular risk factors such as diabetes mellitus, dyslipidaemia and obesity, amplifying the morbidity and mortality risk. Obesity levels in Scotland are the highest in the United Kingdom and result in a high economic burden for the National Health Service. Scotland utilises a 4-tier framework to deliver adult weight management services ranging from behavioural and preventative interventions to bariatric surgical management. There are limitations to service delivery and lack of consistent data on service evaluation. For weight management services to be effective for patients with co-existing hypertension there needs to be integration into primary and secondary hypertension care pathways with engagement of all stakeholders, most importantly patients to move the service forward in a positive way.

Key words: Blood pressure, lifestyle changes, obesity

An estimated 1.2 million people in Scotland are living with hypertension, which is a leading cause of stroke and myocardial infarction. Less than a third of those people have their blood pressure (BP) adequately treated and controlled. The Scottish Parliament Cross Party Group Inquiry into hypertension[1] identified several areas that should be prioritized, including early detection, adherence to medication, and providing health and social care professionals with the right information and training. Hypertension is a condition which often coexists with other long-established cardiovascular (CV) risk factors including diabetes mellitus, dyslipidemia, and obesity. Obese patients are prone to arterial hypertension, require more antihypertensive medications, and have an increased risk of treatment-resistant arterial hypertension. In addition, obesity increases the risk for diseases affecting almost every organ system, including type 2 diabetes, non-alcoholic fatty liver disease, and certain types of cancer.[2] The coexistence of these risk factors further amplifies the risk of both CV and non-CV morbidity and mortality.

In Scotland data from the Scottish Health Survey[3] show that since 2018 the prevalence of overweight and obesity in adults has remained stable at around 65% with significantly higher prevalence among men compared with women (68% and 63%, respectively). The proportion of children (2–15 years old) at risk of overweight is around 12–15% with a higher prevalence among girls than boys and substantial inequalities in the risk of overweight and obesity between children living in the least and most deprived areas in Scotland - and evidence to suggest that this gap is widening.[4]

Obesity levels in Scotland are not only the highest in the UK[5,6] but also rank among the highest of the Organisation for Economic Co-operation and Development countries. The cost to the health service in Scotland of overweight and obesity combined is estimated to be between £363 and £600 million (most of these costs are incurred because of associated conditions such as CV disease and type 2 diabetes, rather than direct costs of treating or managing overweight and obesity). The latest estimate, in 2015, of the total (direct and indirect) costs of overweight and obesity in Scotland, including labor market-related costs such as lost productivity, have been put at £0.9–4.6 billion.[7]

Treating hypertension in the obese requires addressing the obesity as part of the therapeutic plan. However, obesity is a condition that has few preventive strategies that have proven effective on a population basis and require medications,

Address for correspondence:
Dr Linsay McCallum, Consultant Physician and Honorary Clinical Senior Lecturer, Queen Elizabeth University Hospital, Glasgow and University of Glasgow, UK. E-mail: linsay.mccallum@glasgow.ac.uk

Received: 10/1/22; Accepted: 11/1/22
doi: 10.15713/ins.johtn.0227

aggressive diet counseling, and behavioral techniques, and sometimes bariatric surgery.[2,8]

Weight Management in NHS Scotland

A body mass index (BMI) of 25–29.9 kg/m^2 is defined as overweight, with a BMI of ≥30 kg/m^2 classified as obese.[9] The NHS in Scotland uses a 4-tier framework to deliver adult weight management (WM) services, ranging from public health initiatives to bariatric surgery, as outlined in Table 1.[9-11]

Tier 1 focuses on public health. Rising obesity rates have largely been attributed to the availability of cheap, calorie-dense foods and increasingly sedentary lifestyles.[12] The Scottish Government produced a 2018 review aiming to tackle obesity with its "diet and healthy weight delivery plan" acknowledging the increased volume of fat and sugary snacks consumed by children, meaning the problem is starting early in the Scottish population. The 2016 Scottish Health Survey reported 29% of children were at risk of being overweight with 14% already categorized as obese and highlighted the important association with deprivation. Recommendations focussed on improving access to WM services and promotion of healthy weight and diet. This included the Soft Drinks Industry Levy to reduce sugar content in soft drinks and challenging the food industry to reduce the sugar content by 20% in foods commonly eaten by children.[13] Following government initiatives, community pharmacists are considered a useful tool for engaging the public and offering lifestyle advice and products.[5,14] Effectiveness data are sparse, and some studies have shown that although the resource has potential to be an effective tool, awareness among the Scottish population is low, and there was reluctant to engage due to perceived lack of privacy and lack of pharmacist's specialist knowledge.[5,14] Online advice is provided by NHS Inform as part of the tiered approach to WM e.g. adults with a BMI >25 kg/m^2 can access a free online self-directed 12-week WM program with telephone support.[15] Online weight loss programs have yielded modest results with positive effects on weight loss maintenance, though require online access and a degree of computer literacy.[16] Dietary and exercise advice offered by clinicians tend to recommend controlled calorie deficit, and advice to increase activity. SIGN highlights that many diets are not universal in their description and that studies into their effectiveness have been small, meaning there is insufficient evidence on which to base a recommendation.[11]

Table 1: NHS weight management 4-tier framework

Tier 1	Behavioural and preventative interventions set in pre-healthcare, primary care, and community settings. Combination of general practitioners, district nurses, pharmacists, public health interventions, and national campaigns to identify those at risk of overweight and obesity.
Tier 2	Lifestyle management services and interventions often time-limited set within community and local services. Often referral-based for dietetic-led services and exercise referrals aimed at those who are overweight or low risk (without significant comorbidities) obesity.
Tier 3	Clinic-based clinician-led MDT approach with input from bariatric surgeons/specialist-interest GPs, nurses, and psychiatric services.
Tier 4	Bariatric surgical management of obesity with pre- and post-procedure follow-up.

Tier 2 services are often time-limited, such as the NHS subsidized referral to Weight Watchers, offering 12 sessions for in person WM input. The number of sessions or weeks offered varies across health boards as well as the definition of a successful outcome. Some programs across Scotland offered free pedometers or gym membership, but this was often not individualized and offered general advice about increasing activity levels. Strategies to increase patient engagement with WM vary, with differing results. High attrition rates from referral to attendance, poor compliance from the public with services (<25% program completion), and low rate of referral from primary care are the main barriers to successful long-term weight loss success.[10] However, data are encouraging that when used, referral to community-based WM services is cost-effective for managing co-morbidities associated with obesity.[17] There is a lack of data regarding longer-term success of WM programs.

Telephone-delivered[18] and text message[19] WM services, along with services offering financial incentive,[19] have been researched as potential tools for WM support and to bridge the socioeconomic spectrum. Barriers were noted as being decision-makers awareness of the service and using the referral system.[18] In fact, the referral of patients and the confidence in decision-makers of using such services for WM and communication between primary care and WM services were repeatedly reported as the barrier to the success of WM programs within Scotland and afar.[5,14,17]

Tier 3 services ideally offer 1-2-1 input with dietetics, cognitive behavioral therapy, and pharmacotherapy however within Scotland, availability is limited. Evidence shows high success rates, especially within the first few months, however, such as tiers 1 and 2, attrition rates were high and the reasons behind this are unclear.[20]

Referral to tier 4 is stricter than previous (BMI >35 kg/m^2 with obesity-related disease present). Bariatric surgery is a cost-effective treatment option, however, access is limited nationally to this service, though there is a discrepancy in data over long-term savings made both in terms of health and cost to the NHS.[11]

Impact of COVID-19 Pandemic

As indicated above social, economic, and racial disparities in obesity and CV disease are well recognized. The disproportionate impact of the COVID-19 pandemic among ethnic minorities in the UK and in indeed in other developed countries[21] has brought sharply into focus fundamental issues how "intersections between socioeconomic status, ethnicity

and racism intensify inequalities in health for ethnic groups" on all health outcomes.[22] The Scottish Government Expert Group on COVID19 and Ethnicity has embarked on a broad approach to mitigating ethnic disparities in COVID-19 and the impact extending to CV and other health conditions where these disparities exist.[23]

We can conclude that obesity is a national problem with poor projections for health and the economy. Hypertension in Scotland is predominately delivered in primary care with complex patients referred to secondary care. Risk factor reduction is crucial to reduce the public health burden of CV disease. WM from an individual and public health perspective is problematic. Challenges are linked to lack of public awareness and engagement with the services available through to the large disparities in the provisions of WM services and rates of referral in primary care settings. The lack of data available for best practice for short and longer-term weight loss services needs addressed to improve WM from both a health and economic approach, along with a closer look at causes for high attrition rates from treatment programs, and what can be done to improve patient engagement and therefore better WM outcomes. The Scottish Tier system is a national program to help tackle obesity. To be effective, this needs to be integrated into hypertension and other relevant care pathways, consider the complex drivers of health disparities and needs to be co-developed with patients and other stakeholders, for example, primary and secondary care physicians, nurses, pharmacists, and dieticians. Evaluation and quality improvement are key to moving the service forward in a positive way for individuals and health care systems.

References

1. Available from: https://www.bhf.org.uk/bpinquiry [Last accessed on 2022 Jan 10].
2. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, *et al.* 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: A report of the American college of cardiology/American heart association task force on practice guidelines and the obesity society. Circulation 2014;129:S102-38.
3. Available from: https://www.gov.scot/publications/scottish-health-survey-2018-volume-1-main-report/pages/62 [Last accessed on 2022 Jan 10].
4. Available from: https://www.isdscotland.org/Health-Topics/Child-Health/Publications/2018-12-11/2018-12-11-P1-BMI-Statistics-Publication-Summary.pdf [Last accessed on 2022 Jan 10].
5. Weidmann AE, MacLure K, Marshall S, Gray G, Stewart D. Promoting weight management services in community pharmacy: Perspectives of the pharmacy team in Scotland. Int J Clin Pharm 2015;37:599-606.
6. World Health Organisation. Global Action Plan for the Prevention and Control of Non-communicable Diseases 2013-2020. 2013. Available from: http://www.apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf?ua=1 [Last accessed on 2021 Dec 03].
7. Available from: http://www.scottish.parliament.uk/ResearchBriefingsAndFactSheets/S4/SB_15-01_Obesity_in_Scotland.pdf [Last accessed on 2022 Jan 10].
8. Jordan J, Nilsson PM, Kotsis V, Olsen MH, Grassi G, Yumuk V, *et al.* Joint scientific statement of the European association for the study of obesity and the european society of hypertension: Obesity and early vascular ageing. J Hypertens 2015;33:425-34.
9. Logue J, Thompson L, Romanes F, Wilson DC, Thompson J, Sattar N. Management of obesity: Summary of SIGN guideline. BMJ 2010;340:c154.
10. Blane DN, McLoone P, Morrison D, Macdonald S, O'Donnell CA. Patient and practice characteristics predicting attendance and completion at a specialist weight management service in the UK: A cross-sectional study. BMJ Open 2017;7:e018286.
11. Capehorn MS, Haslam DW, Welbourn R. Obesity treatment in the UK health system. Curr Obes Rep 2016;5:320-6.
12. Tod E, Bromley C, Millard AD, Boyd A, Mackie P, McCartney G. Obesity in Scotland: A persistent inequality. Int J Equity Health 2017;16:135.
13. Childhood obesity: A plan for action. In: Part 2 of the Government's Plan for Action to Significantly Reduce Childhood Obesity by Supporting Healthier Choices. Ch. 2. United Kingdom: Department of Health and Social Care; 2018. Available from: https://www.gov.uk/government/publications/childhood-obesity-a-plan-for-action-chapter-2 [Last accessed on 2021 Dec 01].
14. Weidmann AE, Cunningham S, Gray G, Hansford D, Bermano G, Stewart D. Views of the Scottish general public on community pharmacy weight management services: International implications. Int J Clin Pharm 2012;34:389-97.
15. NHS Inform. 12 Week Weight Management Programme: Eat Well. Feel Well. Working towards a healthier weight. Available from: https://www.nhsinform.scot/healthy-living/12-week-weight-management-programme [Last accessed on 2021 Dec 01].
16. Read S, Logue J. Variations in weight management services in Scotland: A national survey of weight management provision. J Public Health (Oxf) 2016;38:e325-35.
17. Fuller NR, Carter H, Schofield D, Hauner H, Jebb SA, Colagiuri S, *et al.* Cost effectiveness of primary care referral to a commercial provider for weight loss treatment, relative to standard care: A modelled lifetime analysis. Int J Obes (Lond) 2014;38:1104-9.
18. Whelan ME, Goode AD, Hickman IJ, Eakin EG, Reeves MM. Telephone-delivered weight management services in the hospital outpatient setting: Decision-makers' perceptions of their use in routine practice. Nutr Diet 2017;74:261-7.
19. Dombrowski SU, McDonald M, van der Pol M, Grindle M, Avenell A, Carroll P, *et al.* Game of stones: Feasibility randomised controlled trial of how to engage men with obesity in text message and incentive interventions for weight loss. BMJ Open 2020;10:e032653.
20. Alkharaiji M, Anyanwagu U, Donnelly R, Idris I. Tier 3 specialist weight management service and pre-bariatric multicomponent weight management programmes for adults with obesity living in the UK: A systematic review. Endocrinol Diabetes Metab 2019;2:e00042.
21. Hooper MW, Napoles AM, Perez-Stable EJ. COVID-19 and racial/ethnic disparities. JAMA 2020;323:2466-7.
22. Mathur R, Rentsch CT, Morton CE, Hulme WJ, Schultze A, MacKenna B, *et al.* Ethnic differences in SARS-CoV-2 infection and COVID-19-related hospitalisation, intensive care unit

admission, and death in 17 million adults in England: An observational cohort study using the OpenSAFELY platform. Lancet 2021;397:1711-24.
23. Available from: https://www.gov.scot/binaries/content/documents/govscot/publications/research-and-analysis/2020/09/expert-reference-group-on-covid-19-and-ethnicity-recommendations-to-scottish-government/documents/systemic-issues-and-risk-initial-advice-and-recommendations-from-the-expert-reference-group-on-covid-19-and-ethnicity/systemic-issues-and-risk-initial-advice-and-recommendations-from-the-expert-reference-group-on-covid-19-and-ethnicity/govscot%3Adocument/Systemic%2BIssues%2Band%2BRisk%2B-%2BInitial%2BAdvice%2Band%2BRecommendations%2Bfrom%2Bthe%2BExpert%2BReference%2BGroup%2Bon%2BCOVID-19%2Band%2BEthnicity%2B%2528002%2529.pdf [Last accessed on 2022 Jan 10].

How to cite this article: Rostron M, McCallum L. Weight Management in Hypertension: A Scotland Perspective. Hypertens 2021;7(2): 88-91.

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

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/ © Rostron M, McCallum L. 2021

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

Clinical Images

An Unusual Cause of the Left Ventricular Hypertrophy and Heart Failure: Eosinophilic Myocarditis (Clinical Images)

Antonio Iaconelli[1,2], Francesca Lassandro Pepe[1], Lorenzo Genuardi[1], Mattia Galli[1], Domenico D'Amario[1], Frediano Inzani[3], Biagio Merlino[4], Tommaso Sanna[1], Pierpaolo Pellicori[2]

[1]Institute of Cardiology, Fondazione Policlinico Universitario A. Gemelli Institute of Scientific Research and Treatment, Università Cattolica del Sacro Cuore, Rome, Italy, [2]Robertson Institute of Biostatistics and Clinical Trials Unit, University of Glasgow, Glasgow, Scotland, United Kingdom, [3]Department of Anatomic Pathology, Roma ENETS Center of Excellence, Gynecological and Breast Pathology Unit, IRCCS Fondazione Policlinico Universitario A. Gemelli, Rome, Italy, [4]Department of Diagnostic Imaging, Oncological Radiotherapy, and Hematology - Diagnostic Imaging Area, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

Abstract

A 27-year-old man presented with dyspnea and chest pain; blood tests showed an elevated NT-proBNP and hyper-eosinophilia, and there was evidence of left ventricular hypertrophy and systolic dysfunction at imaging. Endomyocardial biopsy confirmed a diagnosis of eosinophilic myocarditis. Treatment with high dose corticosteroids, a beta-blocker and an angiotensin-converting enzyme inhibitor was initiated, with complete recovery of cardiac structure and function a week later. Eosinophilic myocarditis is a rare cause of heart failure: its prompt diagnosis improves management and outcome.

Key words: Eosinophilic myocarditis, corticosteroids, acute heart failure

Introduction

It is estimated that more than 900,000 people have heart failure (HF) in the UK, and 200,000 are newly diagnosed with this condition every year. Epidemiologic reports suggest that hypertension, atrial fibrillation, ischemic heart disease, and age are key drivers of the development of HF,[1] but rarer etiologies should be suspected and investigated, particularly in young patients.

Case Discussion

A 27-year-old man with no previous illness was admitted to our emergency department with chest pain and dyspnea. He was a non-smoker and had no family history of cardiomyopathy. Physical examination showed peripheral edema and inspiratory crackles at lung bases; his blood pressure was 125/70 mmHg. Serial electrocardiograms were initially normal, but blood tests revealed elevated high-sensitivity troponin-I (10.39 ng/ml, normal range (nr) <0.14 ng/ml) and amino terminal pro-brain natriuretic peptide (NT-proBNP 1056 pg/ml; nr: <125 pg/ml). C-reactive protein was 6.3 mg/L, with modest hypereosinophilia (990/μL, nr: <500). A few hours after the admission, the patient developed cardiogenic shock requiring inotropic support and diuretics. A transthoracic echocardiogram showed severe left ventricular (LV) hypertrophy with impaired systolic function (LV ejection fraction: 36%) and pericardial effusion [Figure 1; Panels a-c]: A diagnosis of acute HF was made and endomyocardial biopsy (EMB) was performed to clarify etiology further. A few days later, cardiac magnetic resonance imaging demonstrated LV systolic dysfunction with increased wall thickness and diffuse transmural edema [Figure 2; Panels a

Address for correspondence:
Dr. Antonio Iaconelli, Institute of Cardiology, Fondazione Policlinico Universitario A. Gemelli Institute of Scientific Research and Treatment, Università Cattolica del Sacro Cuore, Rome, Italy. E-mail: iaconelli.antonio88@gmail.com

Received: 07-01-2022; Accepted: 11-01-2022
doi: 10.15713/ins.johtn.0228

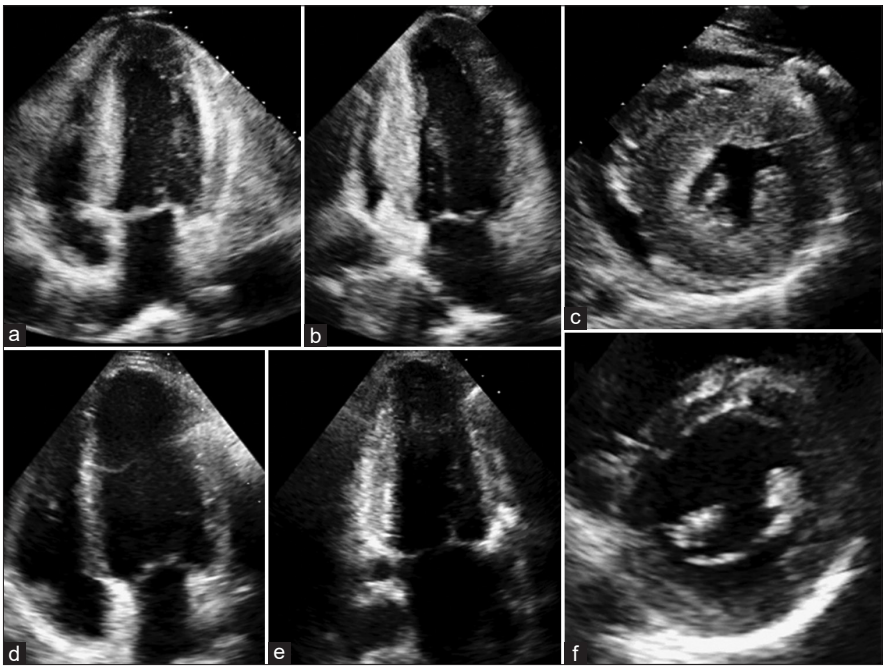


Figure 1: Transthoracic echocardiogram. At admission, apical four-chamber (Panel a), two-chamber (Panel b), and parasternal short-axis (Panel c) views showed left ventricular (LV) hypertrophy (maximal LV wall thickness 19 mm), systolic dysfunction (LV ejection fraction [LVEF] 36%), and pericardial effusion. Seven days after treatment with methylprednisolone, LV wall thickness (10 mm) and LVEF (60%) were normal, and there was resolution of pericardial effusion (Panels d-f)

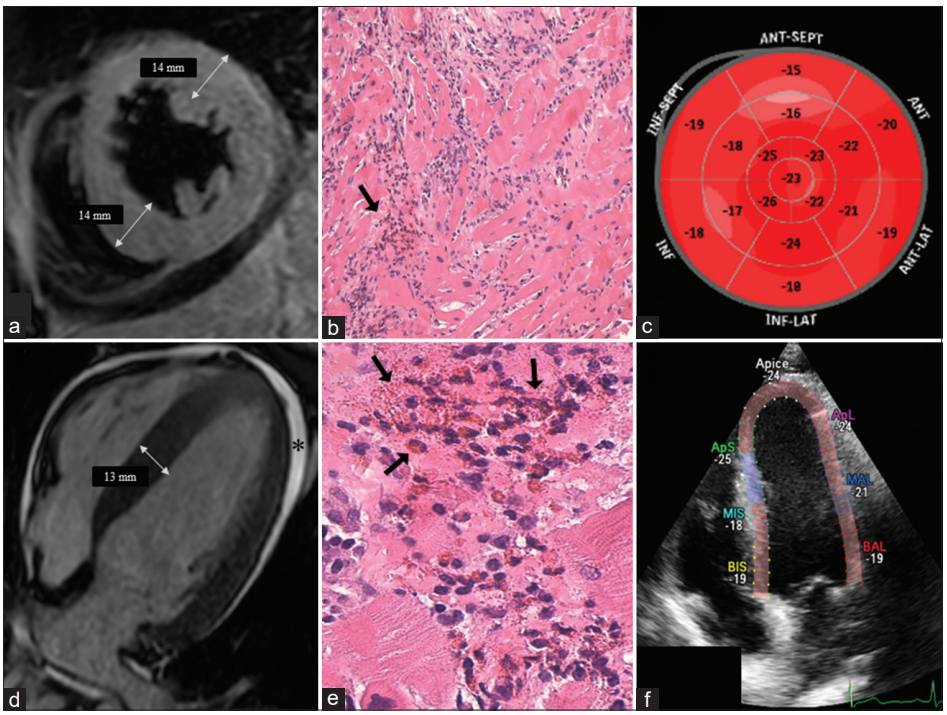


Figure 2: Magnetic resonance (MR) T2-weighted mid-ventricular short-axis image (Panel a) demonstrates a thickened left ventricular wall with transmural hyperintense signal due to edema; cine MR on the horizontal long-axis plane (Panel b) confirms LV hypertrophy and systolic dysfunction, and pericardial effusion (asterisk). Endomyocardial biopsy showed necrosis, fibrosis, and interstitial edema (Panel c, black arrow, hematoxylin and eosin [H and E] 200×) with diffuse eosinophils infiltration (Panel d, black arrows, H and E 400×). A repeated echo performed before hospital discharge and showed recovery of LV global and regional longitudinal function measured by speckle tracking (global longitudinal strain: –21%, Panels e and f)

and b]; EMB confirmed a diagnosis of eosinophilic myocarditis [Figure 2; Panels c and d]. The patient was treated with high-dose corticosteroids (methylprednisolone, 10 mg/Kg i.v. for 3 days, followed by methylprednisolone 1 mg/kg/day), a beta-blocker, and an angiotensin-converting enzyme inhibitor, with complete restoration of LV contractile function and normalization of wall thickening a week later [Figure 1 Panels d-f and Figure 2, Panels e-f].

Conclusion

Eosinophilic myocarditis is a rare cause of HF and a potential life-threatening disease, with a high in-hospital mortality.[2] Timely diagnosis and a prompt initiation of treatment are crucial to improve management of this condition.

References

1. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, *et al*. Temporal trends and patterns in heart failure incidence: A population-based study of 4 million individuals. Lancet 2018;391:572-80.
2. Brambatti M, Matassini MV, Adler ED, Klingel K, Camici PG, Ammirati E. Eosinophilic myocarditis: Characteristics, treatment, and outcomes. J Am Coll Cardiol 2017;70:2363-75.

How to cite this article: Iaconelli A, Pepe FL, Genuardi L, Galli M, D'Amario D, Inzani F, Merlino B, Sanna T, Pellicori P. An Unusual Cause of the Left Ventricular Hypertrophy and Heart Failure: Eosinophilic Myocarditis (Clinical Images). Hypertens 2021;7(2): 92-94.

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

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/ © Iaconelli A, Pepe FL, Genuardi L, Galli M, D'Amario D, Inzani F, Merlino B, Sanna T, Pellicori P. 2021

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

Case Report

Aortic Narrowing – Takayasu or Mid-aortic Syndrome? (Case Report)

Peter Schulga[1], Rosalyn Ardill[2], Neil Turner[3], Ben C. Reynolds[4]

[1]Department of Paediatric, ST7, Royal Hospital for Children, 1345, Govan Road, Glasgow, UK, [2]Department of Paediatrics, Royal Hospital for Children and Young People; 50 Little France Crescent, Edinburgh, UK, [3]Department of Nephrology, Edinburgh Medical School, University of Edinburgh, UK, [4]Department of Paediatric Nephrology, Royal Hospital for Children, 1345 Govan Road, Glasgow, UK

Abstract

Case Description: We report a 15-year-old female who presented with asymptomatic hypertension. She was overweight, with a body mass index of 27.7 kg/m^2 at presentation. Weight loss did not improve blood pressure (BP). Initial investigations demonstrating poor intrarenal vascular flows. A cross-sectional imaging identified marked aortic narrowing, consistent with either mid-aortic syndrome (MAS) or Takayasu arteritis. Multiple antihypertensive medications were ineffective, as were the placement of endovascular stents. Use of an artificial graft to replace the length of the abdominal aorta, with multiple anastomoses, was successful in establishing good renal perfusion and improved BP control. **Clinical Significance:** The challenges in diagnosing MAS and Takayasu arteritis are discussed. Reconstructive vascular surgery in pediatrics is challenging but can offer significant benefit.

Key words: Hypertension, pediatric, vascular intervention

Introduction

Pediatric hypertension (blood pressure [BP] >95th centile for age, gender, and height) affects ~4% of children globally. Although traditionally most commonly secondary to an underlying cause, particularly renovascular disease, renal parenchymal disease (i.e., dysplasia/scarring), and more rarely monogenic causes, increasingly primary hypertension is diagnosed and is the dominant pathology in adolescents.[1] Rising rates of overweight/obesity in children are a contributory cause; weight management is the initial strategy in many hypertensive patients. Further investigation in overweight adolescents has a low diagnostic yield but refractory hypertension often requires exclusion of underlying pathology. The American guidelines currently suggest no further investigation if overweight/obese, aged >6 years, normal examination, and a positive family history.

Case Report

A 15-year-old female was referred to the nephrology clinic with asymptomatic hypertension. An assessment before commencing the combined oral contraceptive pill recorded her BP as 164/92 mmHg, >99th centile, prompting referral. There was no prior medical history of note, and she reported no symptoms. Her mother was diagnosed with primary hypertension aged 26 years with no cause identified. Clinical examination was unremarkable other than overweight body habitus. Her weight was 69 kg (>95th centile), height was 157.9 cm (25th centile), giving a body mass index of 27.7 kg/m^2. She started amlodipine 10 mg once daily. Renal function, inflammatory markers, renin/aldosterone, urinary catecholamines, and urinary steroid profile were normal at presentation. Echocardiogram (ECG) demonstrated normal function with mild left ventricular hypertrophy. ECG demonstrated normal sinus rhythm with mild left ventricular hypertrophy by voltage criteria.

Ultrasound identified two normal kidneys, but Doppler flows were poorly visualized. Her BP remained unchanged despite amlodipine. Given the uncertain renal perfusion, a magnetic resonance angiogram was performed [Figure 1]. This demonstrated significant narrowing of the aortic lumen with associated thickening of the aortic wall from the level of T12 to L2. This raised congenital, that is, a mid-aortic syndrome (MAS), and inflammatory conditions such as Takayasu's arteritis (TAK)

Address for correspondence:
Dr. Peter Schulga, Royal Hospital for Children, Glasgow, UK. E-mail: peter.schulga4@nhs.scot

Received: 10-01-2022; Accepted: 12-01-2022
doi: 10.15713/ins.johtn.0229

Innovative Nature Science Publishers

as key differential diagnoses. After multicenter multispecialist consultation, Takayasu arteritis was felt the most likely pathology.

A trial of the anti-tumor necrosis factor-α (TNF-α) agent, adalimumab was commenced. Twenty-four months after beginning adalimumab, her BP remained >99th centile despite optimal dose atenolol, amlodipine, doxazosin, and clonidine and loss of weight to the 91st centile. Repeat imaging [Figure 2] demonstrated little interval change from her initial scan. Further specialist center review was performed. A repeat ECG was normal, with resolution of the previous hypertrophy. An angiogram demonstrated typical features of MAS with superior mesenteric artery stenosis, bilateral renal artery stenosis, and beading. The aorta and the renal arteries were treated with balloon angioplasty [Figure 3a and b]. BP control improved sufficiently to allow the cessation of clonidine, but she continued to require triple antihypertensive therapy. The very static appearance after 2 years of therapy was felt to favor a structural rather than inflammatory course, as there had been neither improvement nor deterioration over time, as may have been expected in Takayasu arteritis. Adalimumab was discontinued following the revised diagnosis.

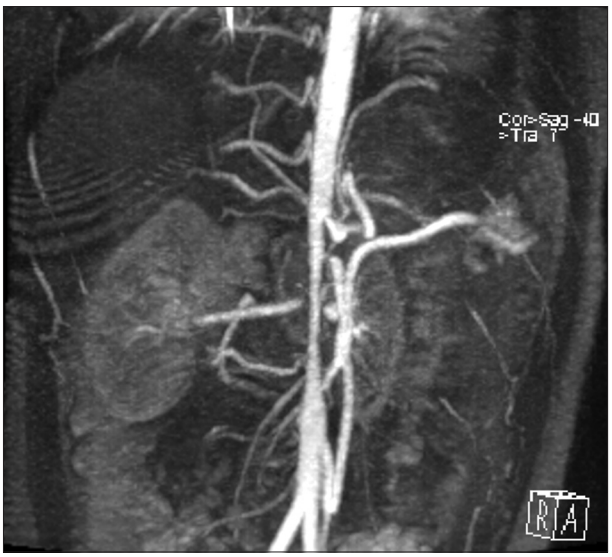


Figure 1: Initial magnetic resonance angiogram showing caliber change of the abdominal aorta from T12 to L2 with associated "pinching" of arteries arising from this region

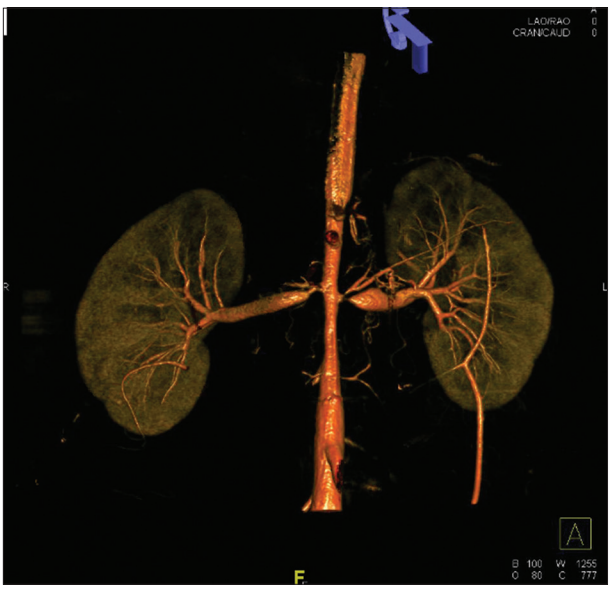


Figure 2: Rotational Angiogram, demonstrating calibre changes

The patient transitioned to adult services and had a further deterioration in BP control. Further angiography showed severe restenosis, with stenting or angioplasty not attempted. There was extensive discussion with the patient and family of the short and long-term risks and benefits of the treatment options for severe restenoses of multiple abdominal aortic branches, relatively shortly following successful angioplasty. She then underwent major vascular surgery with an insertion of an artificial aortic graft and anastomosis of all major abdominal arteries to this graft [Figure 4]. Three months post-procedure, all antihypertensive medication was discontinued, and her BP was within normal limits. She subsequently developed occlusion of the right renal anastomosis, with loss of perfusion to the right kidney [Figure 4] illustrating a long-term hazard of this approach. Flow is well maintained to the left, and renal function remains normal.

Discussion

Identification of a significant mid-aortic stenosis in an asymptomatic adolescent suggests two likely differential diagnoses. The stenosis may have been present from birth, as a structural anomaly, or may be a manifestation of an inflammatory process of more recent onset.

MAS

MAS is very rare, accounting for <2% of cases of aortic stenosis in children.[2] The hypertension is often severe. Elevated BP

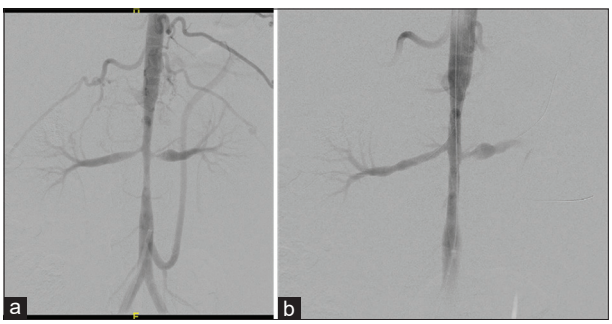


Figure 3: a – Angiography images of abdominal aorta and renal arteries before balloon angioplasty, demonstrating markedly stenotic origin of the renal arteries bilaterally. A markedly enlarged inferior mesenteric artery can be seen leaving the aorta below the narrowed segment. b – Post-balloon angioplasty with improved vessel caliber at the aortic origin and much improved aortic diameter

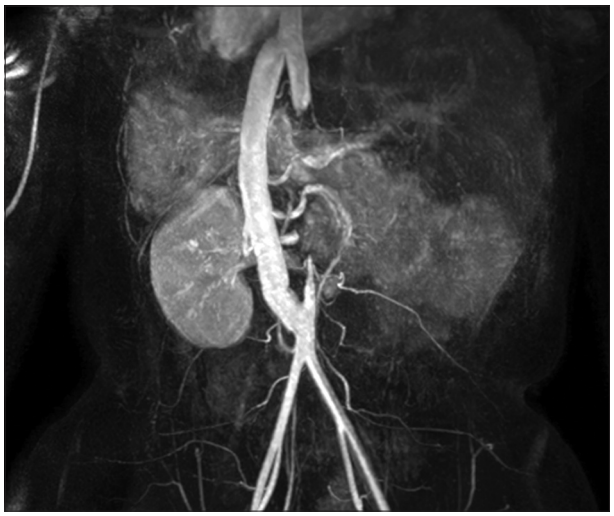


Figure 4: Angiogram demonstrating complete absence of flow through the native aorta, but widely patent graft and well-perfused left kidney

Table 1: Diagnostic criteria for Takayasu arteritis[7]

Criterion	Definition
Age at disease onset ≤40 years	Development of symptoms or findings related to Takayasu arteritis at age ≤40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremity while in use, especially the upper extremities
Decreased brachial artery pulse	Decreased pulsation of one or both brachial arteries
Blood pressure difference >10 mmHg	Difference of >10 mmHg in systolic blood pressure between arms
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not caused by arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

may be detected incidentally, or children may present with symptoms of claudication, signs of heart failure, or most severely, with hypertensive encephalopathy or retinopathy. Examination findings may include absent femoral pulses, abdominal bruits, and significant BP differences between upper and lower limbs.

Most cases appear to be sporadic, though there are associated genetic conditions including neurofibromatosis, Alagille's syndrome, and William's syndrome. Antenatal infection (especially Rubella) has also been associated with MAS.

Management of MAS focuses on controlling BP to prevent long-term hypertensive complications and end-organ damage. Medical management may be challenging, requires multiple antihypertensives, and often fails if there is a significant renal artery involvement. Surgical treatment is frequently required.[3] Less invasive endovascular procedures include angioplasty with stenting, with variable success rates. More invasive techniques include aorto-aortic bypass grafting, patch angioplasty, renal auto-transplantation, and vascular grafting.[4] Surgical management is additionally complicated in younger children who have not completed growth, and repeat interventions may be needed.[2]

TAK

TAK is a rare idiopathic large-vessel vasculitis of the aorta and proximal branches, 80–90% of patients are female, and more common in Asian ethnicity.[5] The initial "pre-pulseless" phase has non-specific constitutional symptoms such as fever, weight loss, night sweats, fatigue, and arthralgia – diagnosis is challenging and often missed. TAK is a chronic disease, with a relapsing-remitting course characterized by granulomatous inflammation of the arterial walls, and later permanent arterial damage resulting in occlusion, stenosis, dilatation, or aneurysm formation. Active disease may present with acute stroke, aneurysmal events, claudication, or incidentally identified hypertension. Inflammatory markers are typically normal outside of an acute exacerbation.[6] Vascular biopsy is rarely practical, given the vessels involved. The American College of Rheumatology has produced diagnostic criteria [Table 1], requiring ≥3 features to make the diagnosis, though these have limited clinical utility.[7] Diagnosis is often delayed, when significant arterial damage has already occurred.

If the diagnosis of TAK is made during acute disease, immunosuppression using glucocorticoids and steroid-sparing agents is recommended. Some patients with resistant or severe cases may benefit from anti-TNF agents and other biologic agents.[6] Vascular surgical interventions should be considered where arterial damage is remediable, but deferred until an acute phase has settled.

Both TAK and MAS are very rare diseases. This limits the opportunity to establish an evidence based for the treatment, with a necessary reliance on reports and case series. MAS is more typically in younger children, TAK in those aged 10–40 years, but there is overlap. Distinction is important, particularly given the chronic relapsing nature of TAK and potential for multiple vessel involvement. In this case, both diagnoses were plausible, but MAS felt more likely given the stable nature of lesions over prolonged follow-up

Summary

Distinguishing between MAS and TAK is challenging. Diagnosis in this case was aided by an unsuccessful trial on disease-modifying therapy, serial imaging, and regular multidisciplinary discussion involving multiple specialist centers. Surgical intervention allowed discontinuation of antihypertensive medications.

Acknowledgments

Our thanks to the patient and her family for allowing us to share their story, and to Dr. Premal Patel and Dr. Jelena Stojanovic, Great Ormond Street Hospital for Children for provision of angiographic images.

References

1. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, *et al*. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017;140:e20171904.
2. Rumman RK, Nickel C, Matsuda-Abedini M, Lorenzo AJ, Langlois V, Radhakrishnan S, *et al*. Disease beyond the arch: A systematic review of middle aortic syndrome in childhood. Am J Hypertens 2015;28:833-46.
3. Kim SM, Jung IM, Han A, Min SI, Lee T, Ha J, *et al*. Surgical treatment of middle aortic syndrome with Takayasu arteritis or midaortic dysplastic syndrome. Eur J Vasc Endovasc Surg 2015;50:206-12.
4. Delis KT, Gloviczki P. Middle aortic syndrome: From presentation to contemporary open surgical and endovascular treatment. Perspect Vasc Surg Endovasc Ther 2005;17:187-203.
5. Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: A review. J Clin Pathol 2002;55:481-6.
6. Dua AB, Kalot MA, Husainat NM, Byram K, Springer JM, James KE, *et al*. Takayasu arteritis: A systematic review and meta-analysis of test accuracy and benefits and harms of common treatments. ACR Open Rheumatol 2021;3:80-90.
7. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, *et al*. The American college of rheumatology 1990 criteria for the classification of takayasu arteritis. Arthritis Rheum 1990;33:1129-34.

How to cite this article: Schulga P, Ardill R, Turner N, Reynolds BC. Aortic Narrowing – Takayasu or Mid-aortic Syndrome? (Case Report). Hypertens 2021;7(2): 95-98.

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

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/ © Schulga P, Ardill R, Turner N, Reynolds BC. 2021

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

Case Report

Under Pressure (Case Report)

Ciaran Groome[1], Ailsa Doak[2], Catherine Stirling[3], Jennifer S. Lees[4]

[1]Specialty Registrar, Renal and General Internal Medicine, Glasgow Renal and Transplant Unit, Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde, Scotland, UK, [2]Specialty Registrar, Renal and General Internal Medicine, Forth Valley Royal Hospital, NHS Forth Valley, Scotland, UK, [3]Consultant Nephrologist. Glasgow Renal and Transplant Unit, Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde, Scotland, UK, [4]Clinical Lecturer in Renal Medicine, Honorary Specialist Trainee Renal Medicine and Internal Medicine, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Scotland, UK

Abstract

Case Description: A 55-year-old woman presents unwell to her local emergency department. She is diagnosed with a hypertensive emergency with end-organ damage. This requires admission to critical care with parenteral blood pressure (BP) control and hemofiltration for an acute kidney injury. After stabilization, she is transferred to the regional nephrology service for ongoing care with a persisting need for hemodialysis and oral BP control. Her background is notable for resistant and difficult to manage hypertension, having underwent multiple investigations in the outpatient setting across the past decade. Follow-up has not been consistent over the last few years which may have contributed to this presentation. **Conclusion and Clinical Significance**: National Institute for Health and Care Excellence recommends that those with a hypertensive emergency are reviewed in a hospital setting for controlled BP reduction and monitoring. Such emergencies are associated with reduced 5-year survival. Furthermore, a small but significant proportion of patients require acute hemodialysis and many never regain kidney function. Self-monitoring of BP has demonstrated improved outcomes – this was not part of her management.

Key words: Acute kidney injury, blood pressure, hypertension

Introduction

In this article, we submit the case of an adult woman who presents with Stage III acute kidney injury secondary to a hypertensive emergency requiring hemodialysis. She was initially managed within a critical care environment, before transferring to a tertiary renal center. We trace her medical history through to the present illness, investigated whether there were clues that could have prevented such a fulminant presentation and discuss the relationship between hypertension and kidney disease.

Case Report

A 55-year-old woman presented to the emergency department at a district general hospital feeling generally unwell, reporting 3 days of nausea, vomiting, and dizziness.

Her past medical history was notable for hypertension (diagnosed circa 2004); peripheral vascular disease – necessitating multiple angioplasties; obstructive sleep apnea – requiring overnight continuous positive airway pressure; chronic obstructive pulmonary disease; and epilepsy. Her drug history is outlined in Table 1.

Her family history included type 2 diabetes mellitus. She lived with her husband and adult son. She is an ex-smoker of 20 cigarettes/day (stopped in 2016).

In the emergency department, she was alert but noted to be confused. Non-invasive blood pressure (BP) was 270/120 mmHg. An electrocardiogram demonstrated a sinus tachycardia (rate 108 beats/min) with a pattern consistent with the left ventricular hypertrophy. Peripheral oxygen saturations were 96% (inspired oxygen concentration 28%) with bibasal crepitations on auscultation. A chest radiograph displayed

Address for correspondence:
Dr. Ciaran Groome, Glasgow Renal and Transplant Unit, Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde, Scotland, UK. E-mail: ciaran.groome@nhs.scot

Received: 10-01-2022; Accepted: 11-01-2022
doi: 10.15713/ins.johtn.0230

Increasent Nature Science Publishers

Table 1: Admission medication*

Drug name	Dose	Administration times
Amlodipine	10 mg	Once/day
Atenolol	100 mg	Once/day
Bendroflumethiazide	2.5 mg	Once/day
Irbesartan	300 mg	Once/day
Spironolactone	12.5 mg	Once/day
Methocarbamol	750 mg	Three times/day
Tolterodine	2 mg	Twice/day
Aspirin	75 mg	Once/day
Atorvastatin	80 mg	Once/day
Salbutamol inhaler	Two puffs of metered dosing	As required
Symbicort turbohaler	One spray (400/12 mg)	Twice/day
Omeprazole	20 mg	Once/day
Epilim Chrono MR	500 mg	Twice/day

*N.B. Doxazosin 1 mg was prescribed 1 day before admission

Table 2: Admission blood results

Variable	On admission	Reference range, adult
Hemoglobin (g/L)	114	120–150
White blood cells ($\times 10^9$/L)	16.3	4.0–10.0
Platelets ($\times 10^9$/L)	107	150–410
MCV (fl)	84.1	83.0–101.0
Neutrophils ($\times 10^9$/L)	14.4	2.0–7.0
Lymphocytes ($\times 10^9$/L)	0.9	1.0–3.0
Monocytes ($\times 10^9$/L)	1.0	0.2–1.0
Eosinophils ($\times 10^9$/L)	0.0	0.02–0.51
Basophils ($\times 10^9$/L)	0.1	0.02–0.1
HbA1c (mmol/mol)	45	20–41
PT (s)	16.0	12.8–15.2
APTT (s)	31.8	27.5–33.7
C fibrinogen (g/L)	6.1	2.35–4.2
Potassium (mmol/L)	Hemolyzed	3.5–5.3
Sodium (mmol/L)	131	133–146
Chloride (mmol/L)	88	95–108
Urea (mmol/L)	56.9	2.5–7.8
Creatinine (μmol/L)	1041	40–130
eGFR (ml/min/1.73 m^2)	3	>59
Bilirubin (μmol/L)	12	0–21
Alkaline phosphatase (U/L)	42	30–130
Alanine transaminase (IU/L)	18	0–55
Aspartate transaminase (IU/L)	26	0–45
Total protein (g/L)	57	60–80
Albumin (g/L)	28	35–50
Lactate dehydrogenase (U/L)	308	80–240
Calcium (mmol/L)	2.1	2.2–2.6
Corrected calcium (mmol/L)	2.31	2.2–2.6
Phosphate (mmol/L)	2.88	0.88–1.50
Magnesium (mmol/L)	0.94	0.7–1.0
C-reactive protein (mg/L)	94	0–5

MCV: Mean cell volume; PT: Prothrombin time; APTT: Partial thromboplastin time; eGFR: Estimated glomerular filtration rate

patchy bilateral upper zone pulmonary venous congestion and patchy consolidation. Computed tomography (CT) of the head was negative for pathology as was a CT urinary tract (non-contrast), with normal unenhanced appearances of the kidneys and no hydronephrosis. There were bilateral pleural effusions noted within the thorax.

Her admission blood work is listed in Table 2. H+ concentration was 44 nmol/L, with serum bicarbonate 20 mmol/L, lactate 1.5 mmol/L, and a K+ 5.0 mmol/L from a venous blood gas. Her biochemistry demonstrated a Stage III acute kidney injury (serum creatinine 1041 μmol/L; baseline creatinine 94 μmol/L 4 years prior) with anemia and thrombocytopenia. Blood films did not demonstrate evidence of hemolysis. This, combined with her BP, was the evidence of hypertensive emergency with multi-end-organ damage.

She was commenced on intravenous labetalol and glyceryl trinitrate (the latter was quickly stopped). She was discussed with on-call nephrology and deemed metabolically and physiologically unstable for transfer and taken to intensive care. A left arterial line and a right internal jugular non-tunneled vascular catheter were placed and continuous veno-venous hemofiltration (CVVH) was initiated for fluid overload and uremia. The intensive care team in conjunction with nephrology aimed for a systolic BP between 160 and 180 mmHg. There was persisting oligoanuria (urine output of 0–5 ml/h).

Peripheral blood cultures and SARS-CoV-2 testing were both negative.

Hemolysis and glomerulonephritis screens, renin and aldosterone measurements were taken (Table 3 for additional diagnostic tests) and she remained dependent on CVVH due to oligoanuria. During her 3rd day of admission, she was reviewed by a visiting nephrologist and accepted for transition of care when stable. Intravenous labetalol was weaned and oral agents were reintroduced on day 5 of the admission. She recovered a normal platelet count at this time (nadir of 84×10^9/L). She was transferred to nephrology on day 6. Urine protein to creatinine ratio was 313 mg/mmol.

Transthoracic echocardiogram revealed mild concentric left ventricular hypertrophy, with a modified apical 4-chamber biplane ejection fraction of 50%. There was mild right ventricular hypertrophy and mild mitral regurgitation.

Within the renal department, she remained dependent on hemodialysis. She was discharged on day 17 on regular hemodialysis thrice weekly and remains dialysis dependent.

Table 3: Additional blood investigations

Variable	Result	Reference range, adult
NT-pro-BNP (pg/ml)	136,821	0–400
Ferritin (μg/L)	857	15–200
Folate (μg/L)	3.4	3.0–20.0
Vitamin B12 (ng/L)	329	187–883
ASO (IU/ml)	86	<200
Haptoglobin (g/L)	1.20	0.30–2.00
Reticulocytes ($\times 10^9$/L)	80	50–100
Glomerulonephritis screen		
C3 (g/L)	1.17	0.83–1.93
C4 (g/L)	0.21	0.15–0.57
Anti-GBM ab by ELISA (U/ml)	<0.8	0.0–7.0
MPO ab (IU/ml)	<0.2	<3.5
PR3 ab (IU/ml)	<0.2	<2.0
Serum electrophoresis	No paraprotein detected	
IgG (g/L)	10.3	6.0–16
IgM (g/L)	0.26	0.40–2.40
IgA (g/L)	2.36	0.8–4.00
Urine immunofixation	No Bence-Jones protein detected	
TSH (mU/L)	1.53	0.35–5.00
Renin (mIU/L)	16.0	0–52
Aldosterone (pmol/L)	275	130–400
HIV antibody/antigen	Not detected	
HCV antibody	Not detected	
HBsAg	Not detected	

NT-pro-BNP: N-terminal pro B-type natriuretic peptide; ASO: Antistreptolysin O; C3: Complement 3; C4: Complement 4; anti-GBM ab: Antiglomerular basement membrane antibody; MPO ab: Myeloperoxidase antibody; PR3 ab: Proteinase 3 antibody; TSH: Thyroid-stimulating hormone; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; HBsAg: Hepatitis B virus surface antigen

Her BP on discharge was 120–140/60–70 mmHg on atenolol monotherapy.

Diagnostic clues

Two days before admission, she presented to a high street optician due to subjective reduction in her visual acuity. One day before admission, she was reviewed by an ophthalmologist. BP at the time of ophthalmology review was 220/180 mmHg with evidence of bilateral hypertensive retinopathy, cotton wool spots, focal retinal arteriolar narrowing, and sub- and intra-retinal edema, consistent with accelerated systemic hypertension. Her visual acuity (right and left) was 6/95 (previously 6/6 in September 2020).

The assessing ophthalmologist referred her to medical receiving for admission. However, she was not admitted to hospital and was advised to attend her general practitioner (GP) where she was reviewed the next day: BP was 230/180 mmHg, she described acute symptoms listed above, and she was advised to attend her local emergency department.

Review of medical records revealed that she had been extensively investigated and managed for hypertension. In 2006, she was seen in the cardiology clinic for "resistant hypertension" on four oral agents. Ambulatory BP monitoring gave readings in the range of 189/108 mmHg. Investigations including urinary catecholamines and a dexamethasone suppression test at this time were normal. She was referred to a specialist hypertension clinic in 2008 and a magnetic resonance angiogram of her renal vasculature was arranged. This demonstrated focal moderate stenosis of the right renal artery. Stenting was considered impossible due to challenging anatomy. Of note, her adrenal glands were "normal" on the report.

Discussion

This case highlights several learning points including the importance of outpatient monitoring of hypertension and the early recognition and management of hypertensive emergency. In this case, hypertensive emergency led to possible permanent end-organ damage and an ongoing need for hemodialysis.

Definitions

Hypertensive emergency with this patient was not immediately recognized by the receiving medical team. "Hypertensive emergency" is used to describe a BP reading of >180/120 mmHg in the setting of evidence of end-organ damage. It is thought to affect around 1–2 people per 100,000 population/year.[1] Untreated, hypertensive emergency has a mortality of around 80% at 2 years, but survival of patients with hypertensive emergency has improved over the past few decades with advances in pharmacological management, and is now up to 90% 5-year survival in some studies.[2] National Institute for Health and Care Excellence (NICE) guidelines recommend that patients with a BP of >180/120 mmHg and with signs of retinal hemorrhage or papilledema, or "life-threatening symptoms such as new-onset confusion, chest pain, signs of heart failure, or acute kidney injury," are referred for specialist same day assessment.[3] These recommendations are based on consensus opinion given the lack of large studies in the area. Due to the blurring of the right optic disc, this patient met the criteria for same day assessment and management, but did not receive this, and further initial investigations for evidence of other end-organ damage. "Hypertensive urgency" is defined as a BP reading of >180/120 mmHg in the absence of end-organ damage and does not usually necessitate hospital admission. This will not be discussed further here.

Prognosis and renal function

Identification of end-organ damage and need for hemodialysis was delayed by the deferral to the GP. Renal involvement in hypertensive emergency is common, is an independent predictor of poorer outcomes, and is the most common cause of death in patients with hypertensive emergency.[4,5] One single-center retrospective analysis of 197 patients admitted to hospital with hypertensive emergency showed that 63% had an acute kidney injury on admission, and 6.6% required hemodialysis during the admission. Of patients requiring hemodialysis, 13% of recovered sufficient renal function to allow them to come off hemodialysis.[4] There is insufficient evidence to assess whether the patient may have avoided the need for hemodialysis or had earlier recovery of renal function if hypertensive emergency had been recognized and treated 24 h earlier.

BP monitoring

There was an apparent lack of outpatient BP monitoring in a patient with resistant hypertension, on multiple antihypertensive agents, leading up to this emergency presentation. Hypertensive emergency is more common in patients with an existing diagnosis of hypertension, in older patients, and in people of Afro-Caribbean origin.[6] The most common precipitating factor for hypertensive emergency is non-adherence with prescribed antihypertensive medication.[7,8] This patient had known resistant hypertension on multiple antihypertensive agents for many years, and there was suggestion of variable adherence with treatment in clinic letters, although she states that she was adherent with medications. It is difficult to know exactly how long this patient's BP had been significantly elevated in the community. NICE recommends annual review of patients with known hypertension, but the last recorded BP on the referral letter was 133/90 mmHg in 2017.[3] She had attended in early 2020 for monitoring but further follow-up was interrupted due to the COVID-19 pandemic. Measures such as self-monitoring of BP in conjunction with patient education and medication titration have been shown to improve BP control, and a multicenter randomized controlled trial showed that BP and cardiovascular risk are lowered by ingesting antihypertensive medication at bedtime rather than in the morning.[9,10] These strategies were not employed here.

Conclusion and Clinical Significance

This case highlights important learning opportunities in the recognition of hypertensive emergencies, the importance of looking for evidence of end-organ damage, and the role of long-term monitoring in patients with established hypertension. Given the lack of clinical evidence, it is difficult to know if more frequent monitoring or hospital admission 24 h earlier would have changed the overall outcome, but the evidence of end-organ damage should be actively sought.

References

1. Lip GY, Beevers M, Beevers DG. The failure of malignant hypertension to decline: A survey of 24 years' experience. J Hypertens 1994;12:1297-305.
2. Shantsila A, Shantsila E, Beevers DG, Lip GY. Predictors of 5-year outcomes in malignant phase hypertension: The West Birmingham Malignant Hypertension Registry. J Hypertens 2017;35:2310-4.
3. National Institute for Health and Care Excellence. Hypertension in Adults: Diagnosis and Management. London: NICE; 2019. Available from: https://www.nice.org.uk/guidance/ng136 [Last accessed on 2021 Nov 10].
4. Gonzalez R, Morales E, Segura J, Ruilope LM, Praga M. Long-term renal survival in malignant hypertension. Nephrol Dial Transplant 2010;25:3272-7.
5. Szczech LA, Granger CB, Dasta JF, Amin A, Peacock WF, McCullough PA, *et al*. Acute kidney injury and cardiovascular outcomes in acute severe hypertension. Circulation 2010;121:2183-91.
6. Peixoto AJ. Acute severe hypertension. N Engl J Med 2019;381:1843-52.
7. Patel KK, Young L, Howell EH, Hu B, Rutecki G, Thomas G, *et al*. Characteristics and outcomes of patients presenting with hypertensive urgency in the office setting. JAMA Intern Med 2016;176:981-8.
8. Zampaglione B, Pascale C, Marchisio M, Cavallo-Perin P. Hypertensive urgencies and emergencies: Prevalence and clinical presentation. Hypertension 1996;27:144-7.
9. Tucker KL, Shappard JP, Stevens R, Bosworth HB, Bove A, Bray EP, *et al*. Self-monitoring of blood pressure in hypertension: A systematic review and individual patient data meta-analysis. PLoS Med 2017;14:e1002389.
10. Hermida RC, Crespo JJ, Dominguez-Sardina M, Otero A, Moyá A, Ríos MT, *et al*. Bedtime hypertension treatment improves cardiovascular risk reduction: The Hygia Chronotherapy trial. Eur Heart J 2020;41:4565-76.

How to cite this article: Groome C, Doak A, Stirling C, Lees JS. Under Pressure (Case Report). Hypertens 2021;7(2): 99-102.

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

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/ © Groome C, Doak A, Stirling C, Lees JS. 2021