Hinton, T. C., Adams, Z. H., Baker, R. P., Hope, K., Paton, J. F. R., Hart, E. C. J., & Nightingale, A. K. (2020). Investigation and treatment of high blood pressure in young people. Too much medicine or appropriate risk reduction. *Hypertension*, *75*(1), 16–22. https://doi.org/10.1161/HYPERTENSIONAHA.119.13820

MS ID: **HYPE201913820**

Investigation and treatment of high blood pressure in young people. Too much medicine or appropriate risk reduction?

Authors: Thomas C. Hinton BMedSci MBChB MRCP[1,3], Zoe H. Adams BSc[1], Richard Baker MBChB (Hons) MRCP[1,3], Katrina Hope BMedSci BMBS MSc FRCA[1], Julian F.R. Paton[1,2] PhD, Emma C. Hart[1] PhD and Angus K. Nightingale MB BChir MD FRCP FESC[1,3]

[1] BHI CardioNomics Research Group, Bristol Clinical Research and Imaging Centre, School of Physiology, Pharmacology & Neuroscience, University of Bristol, UK.

[2] Department of Physiology, Faculty of Medical and Health Sciences, University of Auckland, New Zealand.

[3] Department of Cardiology, Bristol Heart Institute, University Hospitals Bristol NHS Foundation Trust, Bristol, UK

Word Count of Manuscript: 5922

Word Count of Abstract: 241

Total number of figures: 4

1 online supplement (Table S1 and references)

Short title:

Management of young onset hypertension

Corresponding Author:

Dr Angus Nightingale

Consultant Cardiologist and Senior Clinical Lecturer

Department of Cardiology

Bristol Heart Institute

Marlborough Street

Bristol

BS2 8HW

Tel: +44 117 342 6691

Email: angus.nightingale@bristol.ac.uk

Abstract

Hypertension among young people is common, affecting 1 in 8 adults aged between 20 and 40 years. This number is likely to increase with lifestyle behaviors and lowering of hypertension diagnostic thresholds. Early life factors influence blood pressure (BP) although the mechanisms are unclear; BP tracks strongly within individuals from adolescence through to later life. Higher BP at a young age is associated with abnormalities on heart and brain imaging and increases the likelihood of cardiovascular events by middle age. However, diagnosis rates are lower, and treatment is often delayed in young people. This reflects the lack of high-quality evidence that lowering BP in young adults improves cardiovascular outcomes later in life.

In this review we evaluate the current evidence regarding the association between BP in young adult life and adverse cardiovascular outcomes later in life. Following this, we discuss which young people with raised BP should be investigated for secondary causes of hypertension. Third, we assess the current models to assess cardiovascular risk and show a lack of validation in the younger age group. Fourth, we evaluate the evidence for lifestyle interventions in this age group and demonstrate a lack of persistence in BP lowering once the initial intervention has been delivered. Fifth, we address the pros and cons of drug treatment for raised BP in young people. Finally, there are unique life events in young people, such as pregnancy, that require specific advice on management and treatment of BP.

Key words:

Blood pressure, hypertension, young onset, young adult, cardiovascular outcomes, risk factor

Introduction

Hypertension affects one quarter of the global population and is the leading modifiable risk factor for cardiovascular disease and mortality.[1] Previously, treatment has tended to focus upon individuals in whom the 10-year risk of cardiovascular events is greatest, with increasing age being a strong factor. However, the presence of hypertension at a young age increases risk of cardiovascular events in middle age.[2] It contributes to an earlier onset of coronary heart disease, heart failure, stroke and transient ischaemic attacks.[3] While good national guidelines exist, they do not serve low-risk, young patients with hypertension as effectively as older patients. Furthermore, risk assessment is challenging in young patients due to limited validity and a focus upon systolic blood pressure that is less well correlated with cardiovascular end-points.[2, 4]

The definition of "young" in guidelines varies as below the age of 50, 40 and 30 years.[5-7] Worldwide estimates of the prevalence of hypertension in the year 2000 amongst adults aged 20-29 were 12.7% in men and 7.4% in women rising to 18.4% and 12.6%, respectively, in 30-39 year olds.[8] The estimated prevalence of hypertension among those aged 18-39 years in the United States (2011-2012) was 7.3%.[9] Both studies defined hypertension as an average blood pressure of greater than 140/90 mmHg or use of antihypertensive medication. More recently the definition of hypertension has been expanded by the American College of Cardiology/American Heart Association (ACC/AHA) 2017 guidelines to include blood pressure above 130/80 mmHg and thus the prevalence of hypertension by this criterion is likely far greater than that reported above. Moreover, in selected populations the prevalence of hypertension may be even higher, for example African

Americans have a 2-fold higher risk of hypertension compared to whites as well as lower rates of blood pressure control.[10]

Blood pressure in adulthood may also be determined by factors occurring many years earlier.[11] Barker and colleagues proposed the Developmental Origins of Health and Disease hypothesis whereby the lifetime trajectory of BP is programmed in the perinatal period.[12] Whilst fetal growth restriction may play some role, other factors such as genetic and environmental influences are probably more significant.[13] This is supported by studies demonstrating higher BP in adolescents whose mothers had experienced hypertensive disorders of pregnancy and higher rates of anti-hypertensive prescriptions to young adults born pre-term.[14-16] Similarly, alterations in the cardiovascular system of those born prematurely or of low birth weight are well documented.[17] Risk factors for young onset hypertension have been explored through several large studies (summarized in Table S1 online supplement).

Hypertension can have harmful health effects even at a young age. In the short-term it is associated with higher rates of left ventricular hypertrophy[18] and alterations in brain volume and white matter hyperintensity volume, suggesting that hypertension in young adults may impact cardiovascular and brain health.[19, 20] The Strong Heart Study assessed clinical and echocardiographic features in 1940 native Americans aged 14-39. Individuals with prehypertension (blood pressure 120 to 139/80 to 89 mmHg) and hypertension (blood pressure ≥140/90 or use of antihypertensive medications) had higher rates of left ventricular hypertrophy than normotensive individuals of the same age.[18] In the long-term, multiple studies have demonstrated increased rates of cardiovascular disease and mortality

in young people with hypertension.[2, 3, 21] Furthermore, blood pressure has been shown to strongly track with age meaning that individuals with elevated blood pressure in youth are likely to have elevated blood pressure in later life.[11] Sundstrom et al. used data from 1.2 million Swedish men (mean age 18 years) conscripted into military service between 1969 and 1995 demonstrated a direct correlation between baseline blood pressure and cardiovascular mortality at follow up.[2] The Coronary Artery Risk Development in Young Adults (CARDIA) longitudinal study has been important in exploring the contribution of early life risk factors to the development of coronary heart disease in later life using a cohort of 5115 young adults in the United States aged 18-30.[3, 22] They showed that elevated systolic blood pressure at baseline was more predictive of coronary artery calcium 15 years later than risk factor profile at point of follow up.[22] Additionally a retrospective analysis of CARDIA data demonstrated a significantly higher risk of cardiovascular disease among hypertensives (defined by ACC/AHA 2017 guidelines) compared to normal blood pressure (<120/80 mmHg) in individuals below the age of 40 at baseline.[3]

This shows the impact of early life risk factors upon long term health and implies that it may not be appropriate to defer addressing cardiovascular health until middle age. This is important because hypertensive patients below the age of 40 years have lower awareness, slower diagnosis rates and poorer blood pressure control than older individuals.[9, 23, 24] A recent study identified wide-ranging barriers to good blood pressure control in young adults.[25] These included psychosocial themes (e.g. concerns regarding the projection of a "sick-identity" upon young adults) and management concerns (e.g. appropriate drug treatment of women of childbearing potential). Many respondents were concerned about the benefits and risks of treatment, fear of misdiagnosis (and potential impact on life

insurance), adherence, follow up and resource allocation. These issues have been discussed extensively, with concerns expressed by primary care physicians that new national guidelines could lead to overdiagnosis and overtreatment.[26, 27]

Defining blood pressure thresholds for hypertension in young people

The American College of Cardiology/American Heart Association (ACC/AHA) lowered the diagnostic threshold for stage 1 hypertension in the 2017 Guidelines from 140/90 to 130/80 mmHg across all age categories to some controversy, not least because it increased the prevalence of hypertension in the US population to 46%.[7, 26, 28] This change in threshold was based on a systematic review of 10 studies,[29] the largest of which was the Systolic Blood Pressure Intervention Trial (SPRINT) study.[28] The mean age of participants in the systematic review ranged from 36 to 77 years with only one small study having a mean age at entry of less than 40 years and only four recruiting any participants aged under 50 years old.[30]

Should we pay more attention to systolic or diastolic blood pressure in young people? Sundstrom et al. used data from 1.2 million Swedish men conscripted into military service between 1969 and 1995.[2] All men underwent a medical at entry and blood pressure was recorded in a standardized way; there was a clear correlation between baseline blood pressure and cardiovascular mortality at follow up. Diastolic blood pressure was more strongly correlated to all-cause mortality than systolic blood pressure, with risk rising substantially above 90 mmHg. Hazard ratios were 1.02 (0.99-1.05) and 1.35 (1.26-1.45) respectively. Furthermore, diastolic hypertension is more common among patients under the age of 50 years (62.5% compared to 42% in over 50s).[31]

Additionally, there is uncertainty regarding the significance of isolated systolic hypertension in the young (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure < 90mmHg). Less than 20% of untreated hypertensives below the age of 40 have isolated systolic hypertension, compared to 80% of over 50s.[31] Isolated systolic hypertension in young people may represent increased pulse wave amplification rather than increased aortic stiffness, meaning that in many cases young adults with high brachial systolic pressures have normal central aortic pressure.[32] However, McEniery et al. identified no difference in pulse wave amplification between isolated systolic hypertension patients and normotensives aged 17 to 27 years, but demonstrated either increased stroke volume or increased aortic pulse wave velocity suggesting isolated systolic hypertension may not be a benign state in young people.[33] More recently, Yano et al. noted among a cohort of 27,081 individuals from Chicago (mean age 33 ± SD 9 years, 39% hypertensive) that isolated systolic hypertension imparts increased risk of cardiovascular mortality compared to optimal blood pressure (<130/85 mmHg); adjusted hazard ratio for men was 1.23 (95% CI 1.03-1.46) and 1.55 for women (1.18-2.05).[21]

Finally, a recent retrospective analysis of data derived from the CARDIA study sought to identify whether young onset hypertensives defined using the 2017 ACC/AHA guidelines had increased cardiovascular events.[3] This showed a higher rate of cardiovascular events for mildly elevated blood pressure (SBP 120-129mmHg, DBP <80mmHg) and stage 1 hypertension (SBP 130-139 mmHg or DBP 80-89 mmHg). However, all-cause mortality was not significantly elevated.

What is the optimal approach to high blood pressure in young adults?

Broadly the management of young onset hypertension is the same as that of older individuals, but distinctions are made regarding investigation and referral strategies. Table 1 sets out a summary of the American, European and British guidelines with respect to the management of hypertension in young adults. They differ in their classification of blood pressure and varied use of risk-based thresholds for treatment. We address 3 key questions:

1. ***How should young adults with hypertension be investigated?***

Investigation in young adults is advocated across American, European and British guidelines for the identification of secondary causes of hypertension and evidence of organ damage.[5-7] Predictors of a secondary cause for hypertension include young age (<30 years) with no other risk factors, drug resistant hypertension, severe hypertension (>180/110 mmHg), sudden deterioration in blood pressure control, non-dipping status on ambulatory blood pressure monitoring or the presence of hypertension-mediated organ damage.[34] Recognizing secondary causes of hypertension is potentially beneficial, as this might direct specific treatment strategies and potentially cure high blood pressure in young patients. This is especially important in young people where the sustained duration of high blood pressure on organs such as the brain and kidneys may produce irreversible changes. Furthermore, the identification and treatment of secondary hypertension below the age of 40 years is associated with better blood pressure control.[35]

This beneficial impact needs to be balanced against the risks such as cost, patient burden, and incidental diagnoses from imaging investigations. Both the European and British guidelines state that secondary forms of hypertension are more common among young

adults with high blood pressure and more likely to be detected,[5, 6] making a case to meet incurred costs through specific treatment gains. However, one study showed that young adults were less likely to have a recognized underlying cause than older patients, with prevalence ranging from 5.6% in the 18-29 age group, 8.1% in the 30-39 age group and 17.4% in the over 70s.[36] The most common causes of secondary hypertension among young adults were hypothyroidism (1.9%), renovascular disease (1.7%), renal insufficiency (1.5%), primary hyperaldosteronism (1.2%), Cushing's syndrome (0.5%), and pheochromocytoma (<0.3%). Renovascular disease was caused predominantly by fibromuscular dysplasia in 18-29 year olds (89%) and atherosclerosis in 30-39 year olds (61%).

An electrocardiogram (ECG) is recommended to identify evidence of left ventricular hypertrophy alongside serum creatinine and microalbuminuria to evaluate for sub-clinical renal damage.[5] However, ECG assessment has limited sensitivity for identifying left ventricular hypertrophy and therefore the European guidelines recommend an echocardiogram.[6] Cardiac magnetic resonance imaging is more sensitive and specific than echo at identifying left ventricular hypertrophy and may be used to simultaneously evaluate for secondary causes of hypertension.[37] Renal ultrasound and computerized tomography angiography are established modalities for screening for renal and renovascular disease.[34]

2. Is a risk-based approach appropriate in young adults with hypertension?

All three guidelines utilize 10-year cardiovascular models to provide thresholds for the initiation of antihypertensive therapy (Table 1). Basing treatment upon overall cardiovascular risk rather than specific blood pressure levels is supported by two meta-analyses focused on cardiovascular risk reduction in middle-aged and older individuals.[38, 39]

However other authors have pointed to reports of overestimation of risk and lack of validity for using risk scores in this way.[26, 27] Risk-based approaches can be problematic in the young because absolute 10-year cardiovascular risk is often low, irrespective of other risk factors, despite a substantially increased lifetime risk of cardiovascular events.

In this respect the ACC/AHA guidelines are helpful as they advocate treating all stage 2 hypertensives (SBP>140 and DBP>90 mmHg) regardless of 10-year cardiovascular risk.[7] When considering stage 1 hypertension (SBP 130-139 or DBP 80-89 mmHg) they advise treating those with atherosclerotic cardiovascular disease (ASCVD) estimated 10-year cardiovascular risk ≥ 10% or presence of diabetes or chronic kidney disease. However, the ASCVD risk score was validated on data derived from people aged 40-79 years so may be less applicable to younger patients.[40] The European Guidelines for Cardiovascular Disease Prevention suggest the use of relative risk tables and heart age calculation (using the Systematic Coronary Risk Evaluation (SCORE) system).[41] The validation window for SCORE is 40 to 65 years and in contrast to the ASCVD which predicts mortality, SCORE assesses the risk of a first fatal atherosclerotic event.[6]

The European guidelines highlight the lack of evidence for blood pressure lowering therapy in the young while acknowledging the epidemiological evidence of harm from higher blood pressure. Therefore, they suggest consideration of treatment to avoid more severe hypertension and the development of hypertension-mediated organ damage.[6] In the UK, NICE recommends treatment of those with systolic blood pressure 140-159 mmHg or diastolic blood pressure 90-99 mmHg with evidence of target organ damage, or in those free of cardiovascular disease with a 10-year cardiovascular event risk of greater than 10%.[5] In

the UK QRISK2® is the preferred 10-year risk assessment tool but was validated on 35-74 year olds. [42] The latest version QRISK®3 has been extended to 25 to 84 years of age and includes relative risk, heart age and lifetime risk calculation.[43]

3. How should young onset hypertension be treated?

Epidemiological data suggests that blood pressure reduction at a population level is beneficial. The close tracking of blood pressure from early adulthood to later life and the finding of cardiovascular and brain changes in young adults with hypertension support the argument that young people with high blood pressure should be treated in the same way as older adults. However, there is an absence of data assessing pharmacological intervention in this young age group. Lifestyle interventions to address the risk factors are recommended. A recent systematic review and meta-analysis of 14 exercise studies in 18 to 40-year olds showed that supervised exercise programs improve clinic blood pressure by an average of 4-5 mmHg at 3-6 month follow up, but the blood pressure lowering benefits were not sustained at 12 months.[44] Furthermore, higher intensity programmes associated with greater than 4Kg weight loss had greater benefits. Weight loss was found to have a greater impact on blood pressure compared to metoprolol treatment in young overweight patients (age less than 50 years).[45] More research is required on how to sustain the short-term benefits of exercise, weight loss and other lifestyle interventions in this young population.

Several meta-analyses have shown that thiazide diuretics, calcium channel antagonists, ACE inhibitors, angiotensin receptor blockers (ARB) and beta blockers are equally effective in reducing cardiovascular events in older individuals and “younger” individuals below the age

of 65 years.[46 47 48] This finding is reflected across the European and ACC/AHA hypertension guidelines that do not advocate a specific starting agent out of those drug classes. NICE, in contrast, advocates an aged-based algorithm whereby an ACE inhibitor or ARB is recommended first line for those below 55 years except for people of black African or African-Caribbean family origin in whom calcium channel antagonists are recommended.[5] The reason for this age-based approach is due to two crossover studies that pointed to individuals below the age of 55 being more responsive to ACE inhibitors and beta blockers than calcium channel antagonists and diuretics. [49 50] Where pharmacological management is indicated, clinicians should consider ethnicity, gender and comorbidity (in keeping with older individuals).

Whilst national guidelines do not recommend different treatment of men and women, it is important to consider pregnancy potential in women for several reasons. Firstly, poor control of chronic hypertension during pregnancy increases the risk of pre-eclampsia and good blood pressure control prior to pregnancy is beneficial.[51] Secondly, ACE inhibitors and ARBs in women of childbearing age should be avoided during pregnancy due to risk of adverse fetal outcomes.[6, 52] Those already taking ACE inhibitors or ARBs should be counselled of the fetal risks in pregnancy and consider switching to alternative anti-hypertensives such as labetalol, nifedipine or methyl dopa if they are planning to conceive.[52] It is also important to consider that up to 50% of pregnancies are unplanned so ACE inhibitors and ARBs should be withdrawn promptly upon awareness of pregnancy and alternative agents offered.

What are the gaps in evidence?

This review has identified a number of areas where more evidence is needed to guide clinicians who manage young people with hypertension. Whilst it is clear that high blood pressure in young adults has important detrimental consequences in later life, there is very limited evidence whether interventions can reduce the risk of cardiovascular events or adverse changes in brain structure. Randomized controlled trials of interventions are urgently needed to answer this question as the number of young adults world-wide with hypertension increases. Progress has been made to make risk scores more relevant to young adults, including the use of lifetime risk and heart age scores. Diastolic blood pressure may be important to include in risk assessment. However, a change from 10-year cardiovascular risk to lifetime risk would have implications for the number of people becoming eligible for intervention. The risks and benefits of this approach need to be explored further. How this is best communicated to improve shared decision making and increase persistence of lifestyle changes over time also warrants further investigation. As a previously untreated cohort of young adults with hypertension are offered pharmacological interventions, we are still not sure whether the drugs that are effective in older people are as efficacious in young people. Therefore, studies comparing different treatment strategies in young onset hypertension are needed.

Conclusions

Young-onset hypertension is a common condition that increases all-cause mortality and results in subclinical organ damage early in its natural history. Epidemiological studies suggest that early life factors are important and should be addressed by public health

policies to reduce cardiovascular disease later in life. Although higher blood pressure in young people tracks with blood pressure later in life and is associated with adverse short- and medium-term cardiovascular outcomes, the absence of randomized trials of blood pressure lowering in young adults means the safety and efficacy of anti-hypertensive therapy in mild grades of hypertension are unknown.

Referral of selected patients to secondary care (Table 2) is suggested as it permits more detailed assessment, evaluation of subclinical organ damage and investigation of secondary causes of hypertension (Table 3). This can allow more personalized management given the limitations of current risk-based approaches in this population. However, care needs to be taken to avoid overdiagnosis and overtreatment. Early intervention with medication in young mild hypertensives (blood pressure > 140/90 mmHg) free of cardiovascular disease could be considered following a one-year trial of lifestyle modification. Given the uncertainty in this group of patients, shared decision making is crucial, involving patients, primary care physicians and specialists.

Acknowledgments, Sources of Funding, & Disclosures

a) **Acknowledgments:**

None.

b) **Sources of Funding:**

Our group is supported by the British Heart Foundation (FS/18/18/33522, TH, FS/17/38/32935, ZA, FS/17/49/32917, KH), British Society for Heart Failure (RB), NIHR Biomedical Research Centre (AKN), James Tudor Foundation and the David Telling Charitable trust.

c) **Disclosures:**

The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

References

1. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ and Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *Lancet*. 2002;360:1347-60.

2. Sundström J, Neovius M, Tynelius P and Rasmussen F. Association of blood pressure in late adolescence with subsequent mortality: cohort study of Swedish male conscripts. *BMJ*. 2011;342:d643.

3. Yano Y, Reis JP, Colangelo LA, Shimbo D, Viera AJ, Allen NB, Gidding SS, Bress AP, Greenland P, Muntner P and Lloyd-Jones DM. Association of Blood Pressure Classification in Young Adults Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Cardiovascular Events Later in Life. *JAMA*. 2018;320:1774-1782.

4. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R and Collaboration PS. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903-13.

5. National Institute for Health and Care Excellence (2019). Hypertension in adults: Diagnosis and management. (NICE Guideline 136).

Available at: www.nice.org.uk/guidance/ng136 [Accessed 18 September 2019]

6. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I and Group ESD. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021-3104.

7. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Williamson JD and Wright JT. 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:e13-e115.

8. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK and He J. Global burden of hypertension: analysis of worldwide data. *The Lancet*. 2005;365:217-223.

9. Nwankwo T, Yoon SS, Burt V and Gu Q. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011-2012. *NCHS Data Brief*. 2013:1-8.

10. Kramer H, Han C, Post W, Goff D, Diez-Roux A, Cooper R, Jinagouda S and Shea S. Racial/ethnic differences in hypertension and hypertension treatment and control in the multi-ethnic study of atherosclerosis (MESA). *Am J Hypertens*. 2004;17:963-70.

11. Chen X and Wang Y. Tracking of Blood Pressure From Childhood to Adulthood. *Circulation*. 2008;117:3171.

12. Barker DJ, Osmond C, Golding J, Kuh D and Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ*. 1989;298:564-7.

13. Alsnes IV, Vatten LJ, Fraser A, Bjørngaard JH, Rich-Edwards J, Romundstad PR and Åsvold BO. Hypertension in Pregnancy and Offspring Cardiovascular Risk in Young Adulthood: Prospective and Sibling Studies in the HUNT Study (Nord-Trøndelag Health Study) in Norway. *Hypertension*. 2017;69:591-598.

14. Fraser A, Nelson SM, Macdonald-Wallis C, Sattar N and Lawlor DA. Hypertensive disorders of pregnancy and cardiometabolic health in adolescent offspring. *Hypertension*. 2013;62:614-20.

15. Crump C, Winkleby MA, Sundquist K and Sundquist J. Risk of hypertension among young adults who were born preterm: a Swedish national study of 636,000 births. *Am J Epidemiol*. 2011;173:797-803.

16. Davis EF, Lazdam M, Lewandowski AJ, Worton SA, Kelly B, Kenworthy Y, Adwani S, Wilkinson AR, McCormick K, Sargent I, Redman C and Leeson P. Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: a systematic review. *Pediatrics*. 2012;129:e1552-61.

17. Cohen G, Vella S, Jeffery H, Lagercrantz H and Katz-Salamon M. Cardiovascular stress hyperreactivity in babies of smokers and in babies born preterm. *Circulation*. 2008;118:1848-53.

18. Drukteinis JS, Roman MJ, Fabsitz RR, Lee ET, Best LG, Russell M and Devereux RB. Cardiac and Systemic Hemodynamic Characteristics of Hypertension and Prehypertension in Adolescents and Young Adults. *Circulation*. 2007;115:221.

19. Williamson W, Lewandowski AJ, Forkert ND, Griffanti L, Okell TW, Betts J, Boardman H, Siepmann T, McKean D, Huckstep O, Francis JM, Neubauer S, Phellan R, Jenkinson M, Doherty A, Dawes H, Frangou E, Malamateniou C, Foster C and Leeson P. Association of Cardiovascular Risk Factors With MRI Indices of Cerebrovascular Structure and Function and White Matter Hyperintensities in Young Adults. *JAMA*. 2018;320:665-673.

20. Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Parker TD, Malone IB, Lu K, James S-N, Keshavan A, Murray-Smith H, Wong A, Buchanan SM, Keuss SE, Gordon E, Coath W, Barnes A, Dickson J, Modat M, Thomas D, Crutch SJ, Hardy R, Richards M, Fox NC and

Schott JM. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *The Lancet Neurology*. 2019;18:942-952.

21. Yano Y, Stamler J, Garside DB, Daviglus ML, Franklin SS, Carnethon MR, Liu K, Greenland P and Lloyd-Jones DM. Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. *J Am Coll Cardiol*. 2015;65:327-335.

22. Loria CM, Liu K, Lewis CE, Hulley SB, Sidney S, Schreiner PJ, Williams OD, Bild DE and Detrano R. Early adult risk factor levels and subsequent coronary artery calcification: the CARDIA Study. *J Am Coll Cardiol*. 2007;49:2013-20.

23. Gooding HC, McGinty S, Richmond TK, Gillman MW and Field AE. Hypertension awareness and control among young adults in the national longitudinal study of adolescent health. *J Gen Intern Med*. 2014;29:1098-104.

24. Johnson HM, Thorpe CT, Bartels CM, Schumacher JR, Palta M, Pandhi N, Sheehy AM and Smith MA. Undiagnosed hypertension among young adults with regular primary care use. *J Hypertens*. 2014;32:65-74.

25. Johnson HM, Warner RC, Bartels CM and LaMantia JN. "They're younger… it's harder." Primary providers' perspectives on hypertension management in young adults: a multicenter qualitative study. *BMC Res Notes*. 2017;10:9.

26. Miyazaki K. Overdiagnosis or not? 2017 ACC/AHA high blood pressure clinical practice guideline: Consequences of intellectual conflict of interest. *J Gen Fam Med*. 2018;19:123-126.

27. Haase CB, Gyuricza JV and Brodersen J. New hypertension guidance risks overdiagnosis and overtreatment. *BMJ*. 2019;365:l1657.

28. Wright JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT and Group SR. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015;373:2103-16.

29. Reboussin DM, Allen NB, Griswold ME, Guallar E, Hong Y, Lackland DT, Miller ER, Polonsky T, Thompson-Paul AM and Vupputuri S. Systematic Review for the 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:e116-e135.

30. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, Winklhofer FT, Brosnahan G, Czarnecki PG, Hogan MC, Miskulin DC, Rahbari-Oskoui FF, Grantham JJ, Harris PC, Flessner MF, Bae KT, Moore CG, Chapman AB and Investigators H-PT. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med*. 2014;371:2255-66.

31. Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ and Lapuerta P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension*. 2001;37:869-74.

32. O'Rourke MF and Adji A. Guidelines on guidelines: focus on isolated systolic hypertension in youth. *J Hypertens*. 2013;31:649-54.

33. McEniery CM, Yasmin, Wallace S, Maki-Petaja K, McDonnell B, Sharman JE, Retallick C, Franklin SS, Brown MJ, Lloyd RC, Cockcroft JR, Wilkinson IB and Investigators ES. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. *Hypertension*. 2005;46:221-6.

34. Rimoldi SF, Scherrer U and Messerli FH. Secondary arterial hypertension: when, who, and how to screen? *Eur Heart J*. 2014;35:1245-54.

35. Streeten DH, Anderson GH and Wagner S. Effect of age on response of secondary hypertension to specific treatment. *Am J Hypertens*. 1990;3:360-5.

36. Anderson GH, Blakeman N and Streeten DH. The effect of age on prevalence of secondary forms of hypertension in 4429 consecutively referred patients. *J Hypertens*. 1994;12:609-15.

37. Burchell AE, Rodrigues JC, Charalambos M, Ratcliffe LE, Hart EC, Paton JF, Baumbach A, Manghat NE and Nightingale AK. Comprehensive First-Line Magnetic Resonance Imaging in Hypertension: Experience From a Single-Center Tertiary Referral Clinic. *J Clin Hypertens (Greenwich)*. 2017;19:13-22.

38. Collaboration BPLTT. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet*. 2014;384:591-598.

39. Karmali KN, Lloyd-Jones DM, van der Leeuw J, Goff DC, Yusuf S, Zanchetti A, Glasziou P, Jackson R, Woodward M, Rodgers A, Neal BC, Berge E, Teo K, Davis BR, Chalmers J, Pepine C, Rahimi K, Sundström J and Collaboration BPLTT. Blood pressure-lowering treatment strategies based on cardiovascular risk versus blood pressure: A meta-analysis of individual participant data. *PLoS Med*. 2018;15:e1002538.

40. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Tomaselli GF and Guidelines ACoCAHATFoP. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of

Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S49-73.

41. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F, (EACPR) EAfCPR and (CPG) ECfPG. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012;33:1635-701.

42. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A and Brindle P. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ*. 2008;336:1475-82.

43. Hippisley-Cox J, Coupland C and Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017;357:j2099.

44. Williamson W, Foster C, Reid H, Kelly P, Lewandowski AJ, Boardman H, Roberts N, McCartney D, Huckstep O, Newton J, Dawes H, Gerry S and Leeson P. Will Exercise Advice Be Sufficient for Treatment of Young Adults With Prehypertension and Hypertension? A Systematic Review and Meta-Analysis. *Hypertension*. 2016;68:78-87.

45. MacMahon SW, Macdonald GJ, Bernstein L, Andrews G and Blacket RB. Comparison of weight reduction with metoprolol in treatment of hypertension in young overweight patients. *Lancet*. 1985;1:1233-6.

46. Tsioufis C, Thomopoulos C and Kreutz R. Treatment Thresholds and Targets in Hypertension. *Hypertension*. 2018;71:966-968.

47. Thomopoulos C, Parati G and Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs--overview and meta-analyses. *J Hypertens*. 2015;33:195-211.

48. Turnbull F, Woodward M, Neal B, Barzi F, Ninomiya T, Chalmers J, Perkovic V, Li N, MacMahon S and Collaboration BPLTT. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. *Eur Heart J*. 2008;29:2669-80.

49. Deary AJ, Schumann AL, Murfet H, Haydock SF, Foo RS and Brown MJ. Double-blind, placebo-controlled crossover comparison of five classes of antihypertensive drugs. *J Hypertens*. 2002;20:771-7.

50. Dickerson JE, Hingorani AD, Ashby MJ, Palmer CR and Brown MJ. Optimisation of antihypertensive treatment by crossover rotation of four major classes. *Lancet*. 1999;353:2008-13.

51. James PR and Nelson-Piercy C. Management of hypertension before, during, and after pregnancy. *Heart*. 2004;90:1499-504.

52. National Institute for Health and Care Excellence (2019). Hypertension in pregnancy: diagnosis and management (NICE Guideline 133).

Available at: www.nice.org.uk/guidance/ng133 [Accessed 18 September 2019]

Table 1: ACC/AHA, ESC and NICE(UK) Guidelines for the management of hypertension with special emphasis on care of young patients

Office Blood Pressure	**120-129/<80**	**SBP 130-139** or **DBP: 80-89**	**SBP ≥ 140** or **DBP ≥ 90**	**BP ≥ 160-179 /100-109**	**SBP ≥ 180** or **DBP ≥ 110**
Classification					
ACC/AHA (2017)	Elevated	Stage 1	Stage 2	Stage 2	Stage 2
ESC (2018)	-	High Normal	Grade 1	Grade 2	Grade 3
NICE NG136 (2019)	-	-	Stage 1	Stage 2	Severe
Treatment Threshold					
ACC/AHA (2017)	Lifestyle	Treat if CVD or a 10-year ASCVD[i] risk > 10%	Treat	Treat	Treat
ESC (2018)	-	Lifestyle advice but treat if high risk.	Low-mod risk: Treat if lifestyle fails. High risk: Treat	Treat	Treat
NICE NG136 (2019)	-	-	OD/CVD, diabetes or 10-year CV	Treat	Treat

			risk > 10%		
Specialist Referral					
ACC/AHA (2017)	Suspected secondary HTN particularly primary aldosteronism				
ESC (2018)	Suspected secondary HTN. Follow up of hypertensive emergencies. Resistant HTN. Detailed assessments of organ damage.				
NICE NG136 (2019)	Accelerated HTN (**≥** 180/110) with papilledema or retinal hemorrhages, Suspected secondary HTN				
Considerations for young patients					
ACC/AHA (2017)	Young = <30 years. Consider screening for primary aldosteronism. Optimal point of intervention is not clear.				
ESC (2018)	Refer under 40s with grade 2 HTN or greater. Treatment of uncomplicated grade I HTN "may be considered prudent". Unclear whether ISH should be treated.				
NICE NG136 (2019)	Young onset hypertension is <40. Risks are underestimated. Refer to allow detailed assessment of organ damage. ISH to be treated as per older individuals.				
SBP: Systolic Blood Pressure, **DBP:** Diastolic blood pressure, **ABPM:** Ambulatory blood pressure monitoring, **HBPM:** Home blood pressure monitoring, **CVD:** Cardiovascular disease, **ASCVD:** Atherosclerotic cardiovascular disease. **OD**: Organ Damage **ISH:** Isolated systolic hypertension. **HTN**: hypertension					

Table 2: Indications to refer young onset hypertension to secondary care

- Age < 30 years with no risk factors
- Resistant hypertension
- Sudden deterioration in BP control
- Evidence of end organ damage
- Clinical features or investigations suggesting a secondary cause of hypertension

Table 3: Summary of recommendations for young adults with hypertension

- Public health policy to optimize fetal and early life health
- Lifestyle modifications to improve risk profile including physical activity
- BP threshold to consider intervention at 140/90 mmHg
- Arrange ambulatory BP monitoring
- Assess for end organ damage and secondary causes by measuring renal function, thyroid function, microalbuminuria and ECG
- Echocardiogram if abnormal ECG or finding of LVH would alter treatment
- Refer selected patients to secondary care for further assessment (Table 2)
- If starting drug treatment in females, consider pregnancy potential

Figure legends:

Figure 1. Summary of Review of Young Onset Hypertension

Young onset hypertension

- Common (up to 18% under 40 years age)
- BP tracks strongly from youth to older age
- Cardiovascular and brain changes seen in young adults
- Associated with adverse cardiovascular events in middle age

The problem

- 10-year risk calculators not validated in this age group
- No RCTs to assess whether drug treatment is beneficial
- Lifestyle interventions don't last

Investigations

- Creatinine and microalbuminuria
- Thyroid function
- ECG
- Echo if suspect LVH
- Consider
  - Secondary causes (renal, vascular and endocrine)
  - Additional imaging (MRI, CT and US)

Treatment

- Lifestyle changes (weight loss, diet and exercise)
- Assess lifetime cardiovascular risk or heart age
- Joint decision making and personalized approach
- Consider drug treatment if BP >140/90 or evidence of organ damage or increased cardiovascular risk due to comorbidities
- ACEi or ARB or BB
- CCB if black African or African-Caribbean origin or possibility of pregnancy

Investigation and treatment of high blood pressure in young people. Too much medicine or appropriate risk reduction?

SUPPLEMENTAL MATERIAL

Authors: Thomas C. Hinton BMedSci MBChB MRCP[1,3], Zoe H. Adams BSc[1], Richard Baker MBChB (Hons) MRCP[1,3], Katrina Hope BMedSci BMBS MSc FRCA[1], Julian F.R. Paton[1,2] PhD, Emma C. Hart[1] PhD and Angus K. Nightingale MB BChir MD FRCP FESC[1,3]

[1] BHI CardioNomics Research Group, Bristol Clinical Research and Imaging Centre, School of Physiology, Pharmacology & Neuroscience, University of Bristol, UK.

[2] Department of Physiology, Faculty of Medical and Health Sciences, University of Auckland, New Zealand.

[3] Department of Cardiology, Bristol Heart Institute, University Hospitals Bristol NHS Foundation Trust, Bristol, UK

Supplemental References

1. Garrison RJ, Kannel WB, Stokes J, Castelli WP. INCIDENCE AND PRECURSORS OF HYPERTENSION IN YOUNG-ADULTS - THE FRAMINGHAM OFFSPRING STUDY. Preventive Medicine. 1987;16(2):235-51.

2. Dyer AR, Liu K, Walsh M, Kiefe C, Jacobs DR, Bild DE. Ten-year incidence of elevated blood pressure and its predictors: The CARDIA Study. Journal of Human Hypertension. 1999;13(1):13-21.

3. Chen JW, Wu SY, Pan WH. Clinical characteristics of young-onset hypertension-implications for different genders. International Journal of Cardiology. 2004;96(1):65-71.

4. Stamler J. The INTERSALT Study: background, methods, findings, and implications. (vol 65, pg 626S, 1997). American Journal of Clinical Nutrition. 1997;66(5):1297-.

5. Vollmer WM, Sacks FM, Ard J, Appel LJ, Bray GA, Simons-Aaorton DG, et al. Effects of diet and sodium intake on blood pressure: Subgroup analysis of the DASH-Sodium Trial. Annals of Internal Medicine. 2001;135(12):1019-28.

6. Steffen LM, Kroenke CH, Yu XH, Pereira MA, Slattery ML, Van Horn L, et al. Associations of plant food, dairy product, and meat intakes with 15-y incidence of elevated blood pressure in young black and white adults: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. American Journal of Clinical Nutrition. 2005;82(6):1169-77.

7. Halanych JH, Safford MM, Kertesz SG, Pletcher MJ, Kim YI, Person SD, et al. Alcohol Consumption in Young Adults and Incident Hypertension: 20-Year Follow-up From the Coronary Artery Risk Development in Young Adults Study. American Journal of Epidemiology. 2010;171(5):532-9.

8. Hozawa A, Jacobs DR, Steffes MW, Gross MD, Steffen LM, Lee DH. Circulating carotenoid concentrations and incident hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Journal of Hypertension. 2009;27(2):237-42.

9. Xun P, Liu K, Loria CM, Bujnowski D, Shikany JM, Schreiner PJ, et al. Folate intake and incidence of hypertension among American young adults: a 20-y follow-up study. American Journal of Clinical Nutrition. 2012;95(5):1023-30.

10. Xun PC, Liu K, Cao WH, Sidney S, Williams OD, He K. Fasting Insulin Level Is Positively Associated With Incidence of Hypertension Among American Young Adults A 20-year follow-up study. Diabetes Care. 2012;35(7):1532-7.

11. Gaffo AL, Jacobs DR, Sijtsma F, Lewis CE, Mikuls TR, Saag KG. Serum urate association with hypertension in young adults: analysis from the Coronary Artery Risk Development in Young Adults cohort. Annals of the Rheumatic Diseases. 2013;72(8):1321-7.

12. Lakoski SG, Herrington DM, Siscovick DM, Hulley SB. C-reactive protein concentration and incident hypertension in young adults - The CARDIA study. Archives of Internal Medicine. 2006;166(3):345-9.

13. Parker ED, Schmitz KH, Jacobs DR, Dengel DR, Schreiner PJ. Physical activity in young adults and incident hypertension over 15 years of follow-up: The CARDIA study. American Journal of Public Health. 2007;97(4):703-9.

14. Davidson K, Jonas BS, Dixon KE, Markovitz JH. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA study? Archives of Internal Medicine. 2000;160(10):1495-500.

15. Yan LJL, Liu K, Matthews KA, Daviglus ML, Ferguson TF, Kiefe CI. Psychosocial factors and risk of hypertension - The Coronary Artery Risk Development in Young Adults (CARDIA) study. Jama-Journal of the American Medical Association. 2003;290(16):2138-48.

16. Matthews KA, Kiefe CI, Lewis CE, Liu K, Sidney S, Yunis C. Socioeconomic trajectories and incident hypertension in a biracial cohort of young adults. Hypertension. 2002;39(3):772-6.

Supplemental Table S1: Association between risk factors and outcome in young onset hypertension

Risk factor	Association between risk factor and outcome	Ref
Greater subscapular skin fold	↑incidence of BP ≥165/90 mmHg or anti-HTN treatment over 8 year FU (aged 20-49 years)	1
Greater waist circumference	↑incidence of BP ≥138/85 mmHg or anti-HTN treatment over 10 year FU	2
BMI	↑BMI in young-onset HTN (BP ≥140/90mmHg before 40 years) versus NTN men	3
Greater 24-hour sodium excretion	↑ SBP in 20-59-year-old men and women (NTN and HTN)	4
Low sodium diet	↓SBP at 30 day follow up (aged ≤ 45 years)	5
Greater meat consumption	↑incidence of BP ≥135/85 mmHg or anti-HTN treatment over 15 year FU	6
Greater plant food consumption	↓incidence of BP ≥135/85 mmHg or anti-HTN treatment over 15 year FU	6
Greater alcohol consumption	Alcohol consumption not associated with incidence of BP ≥140/90 mmHg or anti-HTN treatment over 20 year follow up. In European American women, there was reduced HTN risk in current but not former drinkers	7
Greater serum carotenoid concentration	↓incidence of BP ≥140/90 mmHg or anti-HTN treatment over 20 year FU	8
Greater folate consumption	↓incidence of BP ≥140/90 mmHg or anti-HTN treatment over 20 year FU	9

Greater serum triglycerides	↑serum triglycerides in young-onset HTN (BP ≥140/90mmHg before 40 years) versus NTN	3
Greater fasting insulin	↑incidence of BP ≥140/90 mmHg or anti-HTN treatment over 20 year FU	10
Greater serum urate	↑incidence of BP ≥140/90 mmHg or anti-HTN treatment over 20 year FU	11
Greater C-reactive protein	↑incidence of BP ≥140/90 mmHg, history of HTN, or anti-HTN medication over 8 year follow up but not significant when BMI accounted for	12
Increased level of physical activity	↓incidence of BP ≥140/90 mmHg or anti-HTN medication over 15 years	13
Greater depression score	↑incidence of BP ≥160/95 mmHg or anti-HTN treatment over 5 years, significant in black but not white participants when analysis conducted separately	14
Personality traits (greater hostility and impatience)	↑incidence of BP ≥140/90 mmHg or anti-HTN treatment over 15 years, but not significant in all sex-race groups when analysis conducted separately	15
Lower socioeconomic status	↑incidence of BP ≥140/90 mmHg or anti-HTN treatment over 10 years	16

BP: Blood Pressure**, NTN:** Normotension**, HTN:** Hypertension**, BMI:** Body Mass Index**, SBP:** Systolic BP, **FU**: Follow Up. Study populations were NTN and aged 18-30 years at baseline, and included both men and women, unless stated otherwise.