**Hypertension in adults: diagnosis and management**

**Consultation on draft guideline – deadline for comments 5pm on 23/04/2019 email:** HypertensionInAdults@nice.nhs.uk

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| | **Please read the checklist for submitting comments at the end of this form.** We cannot accept forms that are not filled in correctly.<br>We would like to hear your views on the draft recommendations presented in the guideline, and any comments you may have on the rationale and impact sections in the guideline and the evidence presented in the evidence reviews documents. We would also welcome views on the Equality Impact Assessment.<br>In addition to your comments below on our guideline documents, we would like to hear your views on these questions:<br>1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.<br>2. Would implementation of any of the draft recommendations have significant cost implications?<br>3. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice<br>See section 3.9 of Developing NICE guidance: how to get involved for suggestions of general points to think about when commenting. |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | [**British and Irish Hypertension Society**] |
| **Disclosure**<br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | [**None**] |
| **Name of commentator person completing form:** | [**Professor Francesco P Cappuccio, President, BIHS**] |

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NICE National Institute for Health and Care Excellence

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| **Comment number** | **Document** [guideline, evidence review A, B, C etc., methods or other (please specify which)] | **Page number** Or **'general'** for comments on whole document | **Line number** Or **'general'** for comments on whole document | **Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
| 1 | Guideline | General | General | The British and Irish Hypertension Society welcomes the publication of the draft document of the revised NICE Guideline for the diagnosis and management of hypertension.<br><br>The new features are: (1) to confirm the diagnosis of Stage 1 to 2 hypertension with either Ambulatory Blood Pressure (BP) Monitoring or, when not practical, with Home BP Monitoring; (2) to systematically measure standing BP in diabetics, those with postural symptoms and patients over 80 years of age; (3) to treat Stage 1 hypertension (from 140/90 to 159/99 mmHg) earlier, even at an estimated absolute cardiovascular risk to 10%, potentially increasing the number of individuals requiring drug therapy to start with; (4) BP targets are maintained at below 140/90 mmHg for clinic blood pressure (below 150/90 mmHg over the age of 80 years), at variance with the European guidelines that – reviewing the same evidence – recommend targets below 130/80 mmHg and 140/80 mmHg, respectively; (5) a stepwise incremental use of anti-hypertensive medications to reach targets, as in 2011, considering the evidence of dual therapy as first step in most cases of hypertension, with or without co-morbidities, not supported yet by convincing evidence; (5) preferential use of thiazide-like diuretics compared to thiazides; (6) discussing adherence in case of resistant hypertension; (7) consider low-dose spironolactone as Step 4 choice in |

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| | | | | resistant hypertension, after patient's consent; (8) clarifications on the definitions and clinical management of accelerated hypertension.<br><br>The British and Irish Hypertension Society, whilst welcoming the new Guideline, notes that very little has changed since the guideline in 2011 and finds the recommendations rather conservative compared to recent international guidelines in the US and Europe, that have had the chance to review the same evidence. Critically, the differences in conclusions on some important points appear to depend on the selective approach NICE has taken in excluding pivotal evidence from their appraisal. The BIHS feels this Guideline is a limited step forward and it is a missed opportunity to improve the management of hypertension that is still poorly controlled in our country. The BIHS strongly suggests improvements in some areas to maximize the benefits to patients in light of current evidence.<br><br>The BIHS acknowledges that the scoping of the Guideline was to look at some specific aspects related to patients' diagnosis and management. However, the BIHS wishes to emphasize that primary prevention of raised blood pressure remains the pillar of a comprehensive strategy to reduce the burden of cardiovascular disease due to raised blood pressure and the healthcare costs associated with the diagnosis and management of those labelled as 'hypertensive". There is serious concern at the lack of cross-reference to Public Health Guideline PH25 (2010) that includes key aspects of primary prevention and, more importantly, at the proposal by NICE to withdraw Recommendations 1 to 12 from the PH25, that are specifically aiming at preventing the development of hypertension in healthy individuals. To date NICE has not published the results of that consultation launched in June 2018. The BIHS would recommend coherence across different guidelines and the retention of Recommendations 1 to 12 in NICE PH25 (2010) and subsequent revisions. |
| 2 | Guideline | 4 | 6-10 | 1.1.2 - It is suggested that it is just automated BP devices that do not measure blood pressure accurately in some instances, such as atrial fibrillation, but this is also true for auscultation. We know of no data that show one is necessarily more accurate than the other and the Guideline suggests automated devices may be less accurate. |

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| 3 | Guideline | 5 | 3-7, 8-13, 15-21, 22-27 | 1.1.5 - Many would suggest that in patients with symptoms at initial BP assessment it is worth recording BP both sitting and standing but it is probably preferable to measure blood pressure in both positions in all patients initially not just those with symptoms.<br>1.1.6 - The European Cardiac Society suggests in hypertensive patients a systolic fall of equal to or greater than 30 mmHg be taken as diagnostic of postural hypotension rather than a 20 mmHg fall as suggested in these guidelines.<br>1.2.1 - This procedure is made in all recommendations but having consideration to the difficulties in standardizing office BP measurement, to the time taken to perform the procedure, and to the variability of blood pressure, which can in itself account for differences between arms, this recommendation could be dropped. However, if this seems too drastic, the recommendation should contain wording acknowledging these difficulties and adding that “in ideal circumstances” (or some such wording) the above procedure should be followed.<br>1.2.2 - Some reference should be made to the substantial literature indicating that the Automated Office Blood Pressure (AOBP) measurement, either attended or unattended, should now be advocated in an effort to standardize measurement of BP in the office. |
| 4 | Guideline | 6 | 1-4, 5-7, 19-28, 29 | 1.2.3 - This recommendation is wholly dependent on the method of office BP measurement, which if not standardized could lead to overuse of ABPM.<br>1.2.4 - Although agreeing that ambulatory and home blood pressure monitoring are of great value in diagnosing hypertension there is increasing evidence that daytime ABPM and HBPM values are not exactly the same and there may be significant differences between the two with daytime ambulatory levels being lower than home blood pressure monitoring. This assumed equivalence is brought out in other sections in this Guideline and there is no suggestion that there may actually be a clinically significant difference between the two shown in some patient groups that we and others have demonstrated.<br>1.2.7 - Whilst agreeing with the protocol of taking two readings morning and evening for those recording home blood pressure levels, it would be useful to suggest the timings of these measurements in relation to any antihypertensive medication particularly if home blood pressure monitoring is being used not only for diagnosis but also for assessing the effects of treatment. Most would take morning readings before any medication. In addition, |

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| | | | | an important distinction needs to be made. The above recommendation is valid if HBPM is being used as a diagnostic substitute for ABPM to obtain a BP measurement that approximates to mean daytime BP obtained with ABPM. However, the recommendation is very onerous and precludes the use of HBPM as a useful technique to provide information on the adequacy of BP control over time. This subject has not been much addressed in the literature, but the recommendation from the ESH guideline is: "*For the long- term follow- up of patients with treated hypertension, HBPM once or twice per week or less frequently seems to be appropriate to ensure maintenance of adequate BP control*."<br>1.2.8 - It would be useful to have more information on masked and white coat hypertension in terms of their diagnosis and CV risk. |
| 5 | Guideline | 8 | 1-5 | 1.3.2 – It is perhaps confusing to take clinic blood pressure measurements to calculate cardiovascular risk where the diagnosis is based on ambulatory or home recordings. What does one do if the diagnosis is confirmed on home blood pressure monitoring but the clinic values are significantly lower though still in the hypertensive range and therefore puts the patient at a lower level of cardiovascular risk if just clinic values are just used? Moreover, this recommendation is wholly dependent on the method of office BP measurement, which if not standardized will lead to miscalculation of risk. |
| 6 | Guideline | 9 | 1-2 | 1.4.4 - What is excessive consumption of coffee? Should levels of consumption and type of coffee be mentioned or referenced somewhere at least? |
| 7 | Guideline | 10 | 17-20 | 1.4.14 - This statement is vague and should be followed by clearer qualification. Screening of all hypertensives under 40 years of age for all secondary causes of hypertension is not feasible or cost-effective.<br>*"For adults aged under 40 with hypertension…"* – Patients under 40 years of age should only be considered for specialist investigations if presenting with stage 2 hypertension. If presenting with stage 1 hypertension the criterion of young age (under 40 years) should be accompanied by at least one other criterion (for example target organ damage, clinical or biochemical features suggestive of secondary causes, clinical features suggestive of obstructive sleep apnoea, CKD, or phaeochromocytoma.(1) |

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| | | | | *"…a more detailed assessment of the long-term balance of treatment benefit and risks".*- this statement is not very helpful in the context of clinical guidance for practicing physicians. There is no indication on 'how' benefits and risks be assessed at the time of consultation and 'how 'to balance the choice in an evidence-based manner.<br><br>(1) Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 39: 3021-104. |
| 8 | Guideline | 11 | 1-2, 5-11 | 1.4.15 - Although this comment that clinic BP should be used to assess response to lifestyle and treatment it is rather at variance with the advice given in 1.4.16 (line 3-4). In addition, if ABPM and HBPM are the preferred methods of measurement why is clinic BP measurement used to monitor the response to therapy. It is now well established that office measurement will lead to either overtreatment because of the white-coat effect or undertreatment because of masked hypertension.<br>1.4.17 - This recommendation is in conflict with the above [1.4.15] recommendation. If clinic blood pressure is normal it is unlikely from these guidelines that ambulatory or home monitoring would then take place and masked hypertension therefore be identified. We could find no advice on the treatment of masked or white-coat hypertension or if it needed treating at all. |
| 9 | Guideline | 12 | 5-10 | 1.4.21 No evidence is given for treating to the standing BP. Measurements of OH are highly variable and so problematic to use as a target. Retain the seated BP as the target and (in the absence of evidence) use longer-acting preparations of antihypertensives and split them up so that not all the antihypertensives are taken at one time. Review and reduce or stop if possible other drugs such as those with anticholinergic potential and ensure the patient is not dehydrated.<br>1.4.22 - We would draw attention to the recently published issue of the Journal of Clinical Hypertension 2018; 20(7): 1084 with 13 papers discussing in detail BP measurement issues that are relevant in the context of NICE Guideline 2019 |
| 10 | Guideline | 13 and 16 | 20-22 and 12 | We congratulate the NICE Hypertension Committee on their comprehensive review and the proposed hypertension guideline. We are delighted by the recommendation on |

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| | | | | discussion of adherence (1.4.29 and 1.4.4) and its link to NICE guideline on "Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (CG76- 2009, reviewed 2016)"<br>We would be amiss, if we did not point out the new evidence that has accumulated in the field of non-adherence in hypertension over the last five years. Unfortunately, it appears that these data have not been reviewed in either the draft of the guideline or the CG76 guideline on adherence.<br>We would urge the NICE Committee to consider a stronger emphasis on testing for non-adherence especially in patients labelled as resistant hypertension (patients with uncontrolled blood pressure despite prescription of three or more antihypertensive medications). Furthermore, we request that the Committee should consider the selection of objective methods when testing for non-adherence to antihypertensive treatment.<br>We make our case based the following:<br>• As the Committee is aware, despite the availability of potent, cheap and tolerable therapies, blood pressure targets are achieved in less than half of patients worldwide including in Europe.(1) Recent data collected in one month as part of the May Measurement Month initiative shows that of the 105 456 (46·3%) of the 227 721 individuals receiving treatment did not have controlled blood pressure. (2)<br>• Non-adherence is now clearly recognised as one of the key reasons for this apparent treatment failure and translates directly into poor cardiovascular outcomes. (3-6)<br>• Non-adherence is not assessed in 40-50% of clinic appointments (7). The subjective "suspicion" of non-adherence by the doctor or health care professional is no better than a coin toss.(8). Hence, it is our considered view that non-adherence in patients with hypertension needs to be assessed by robust methods.<br>• The incidence of resistant hypertension is thought to be around 10-20% of all cases with hypertension.(9-11) It is particularly important to address blood pressure control in this group of patients as they are difficult to treat and have worse cardiovascular outcomes. (10,12) |

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| | | | | • It has been recently recommended that pseudo-resistant hypertension (in particular that driven by non-adherence) should be excluded before the resistant hypertension is diagnosed. (13)<br>• It has been demonstrated that non-adherence increases with increase in number of prescribed anti-hypertensives and around 30-50% of patients on 3 or more medications are non-adherent. (14)<br>• Therefore, evaluation of non-adherence has been recommended as a routine to exclude pseudo-resistant hypertension. (15)<br>• There are various measures to assess non-adherence. Objective measures such as pharmacy refill rates or prescription pick up rates, electronic medication monitoring systems and direct biochemical measures are in our view the preferred measures over subjective methods. (16)<br>• The 2014 Cochrane review on non-adherence concluded that advances in the field of non-adherence in chronic disease requires advances in objective measures.(17)<br>• In UK, the use of direct biochemical measurement of non-adherence is growing in routine clinical practice undertaken in Hypertension centres. The National Centre for Adherence Testing (NCAT) at Leicester hospitals provides a routine NHS service to 33 centres across UK and analyses around 1000 samples a year. The service has been found to be very useful across these centres.<br>• Retrospective studies have demonstrated that the objective screening test for non-adherence has improved blood pressure control on follow up. (18,19) It has been estimated by Markov modelling to be cost-effective to the NHS with a QALY saving of £495. (20)<br>• The recent ESC/ESH guidelines place a strong emphasis on exclusion of non-adherence (Level 1A recommendation). They state: "*Poor adherence to prescribed medicines is a frequent cause of pseudo-resistant hypertension, occurring in 50% of patients assessed by therapeutic drug monitoring, and is directly related to the number prescribed tablets*". (21) "*Today, the most accurate methods that can be recommended, despite their limitations, are the detection of prescribed drugs in blood or urine samples*." |

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| | | | | (1) Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol 2016;23:636-648.<br>(2) Beaney T, Schutte AE, Tomaszewski M, et al. May Measurement Month 2017: an analysis of blood pressure screening results worldwide. Lancet Glob Health 2018;6:e736-e743.<br>(3) Elliott WJ. Improving outcomes in hypertensive patients: focus on adherence and persistence with antihypertensive therapy. J Clin Hypertens 2009;11:376-382.<br>(4) Bosworth HB, Granger BB, Mendys P, et al. Medication adherence: a call for action. Am Heart J 2011;162:412-424.<br>(5) Burnier M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. Am J Hypertens 2006;19:1190-1196.<br>(6) Gosmanova EO, Kovesdy CP. Adherence to antihypertensive medications: is prescribing the right pill enough? Nephrol Dial Transplant 2015;30:1649-1656<br>(7) Clyne W, Mshelia C, McLachlan S, et al. A multinational cross-sectional survey of the management of patient medication adherence by European healthcare professionals. BMJ Open 2016;6:e009610-2015-009610.<br>(8) Meddings J, Kerr EA, Heisler M, Hofer TP. Physician assessments of medication adherence and decisions to intensify medications for patients with uncontrolled blood pressure: still no better than a coin toss. BMC Health Serv Res 2012;12:270-6963-12-270.<br>(9) Calhoun DA, Booth JN, Oparil S, et al. Refractory hypertension: determination of prevalence, risk factors, and comorbidities in a large, population-based cohort. Hypertension 2014;63:451-458.<br>(10) Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation 2012;125:1635-1642.<br>(11) de la Sierra A, Segura J, Banegas JR, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension 2011;57:898-902. |

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| | | | | (12) Muntner P, Davis BR, Cushman WC, et al. Treatment-Resistant Hypertension and the Incidence of Cardiovascular Disease and End-Stage Renal Disease: Results From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Hypertension 2014;64:1012-1021.<br>(13) Calhoun A, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008;117:e510-526.<br>(14) Gupta P, Patel P, Strauch B, et al. Risk Factors for Nonadherence to Antihypertensive Treatment. Hypertension 2017;69:1113-1120.<br>(15) Berra E, Azizi M, Capron A, et al. Evaluation of Adherence Should Become an Integral Part of Assessment of Patients With Apparently Treatment-Resistant Hypertension. Hypertension 2016;68:297-306.<br>(16) Gupta P, Patel P, Horne R, et al. How to Screen for Non-Adherence to Antihypertensive Therapy. Curr Hypertens Rep 2016;18:89-92.<br>(17) Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2014;11:CD000011.<br>(18) Jung O, Gechter JL, Wunder C, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens 2013;31:766-774.<br>(19) Gupta P, Patel P, Bransilav S. Biochemical Screening for non-adherence is associated with blood pressure reduction and improvement in non-adherence. Hypertension 2017;70:1042-1048.<br>(20) van Schoonhoven AV, van Asselt A, Tomaszewski M, et al. Cost-utility of an objective biochemical measure to improve adherence to antihypertensive treatment. Hypertension 2018;72:1117-1124.<br>(21) Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021-3104. |

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| 11 | Guideline | 13 | 24-26 | 1.4.30 - Although perhaps understandable, no mention is made of starting with low-dose combined antihypertensive preparations which seem to be more effective than full dose monotherapy. We presume this may be because of cost implications as well as the lack of outcome studies using low-dose combinations (see later) |
| 12 | Guideline | 15 | 8-13, 19-22 | 1.4.39 – We are not convinced about the suggested combination of CCB and thiazide-like diuretic for 2nd level treatment - few large outcome studies of this.<br>1.4.41 - Surely a review of patient medication should be done at all treatment stages of hypertension not just stage III? |
| 13 | Guideline | 23 | 25-28 | The most cost-effective, achievable and practical lifestyle change to reduce blood pressure is reducing salt consumption (1-3). The lack of mention in the examples is an omission to rectify, as it is in contrast with the statement listed on page 9, line 3-4 (1.4.5). From the point of view of the patient, clinical focus should be on avoiding adding salt to food at the table and when cooking, including discouraging the use of sodium-containing salts like mono-sodium glutamate (MSG) in addition to salt in all its forms (table salt, sea salt, black salt, pink salt, Himalayan salt etc.), all containing in excess of 95% sodium chloride (NaCl) (4). Patients should be encouraged to check food labels to avoid hidden salt in processed food.<br>Cross-reference to NICE PH25 (2010) should be made to highlight the importance of reducing salt consumption in people before they develop 'hypertension'.<br><br>1. Cobiac LJ, Vos T, Veerman JL. Cost-effectiveness of interventions to reduce dietary salt intake. Heart 2010; 96: 1920-25<br>2. Collins M, Mason H, O'Flaherty M, et al. An economic evaluation of salt reduction policies to reduce coronary heart disease in England: a policy modelling study. Value in Health 2014; 17: 517-24.<br>3. Hendriksen MAH, Geleijnse JM, van Raaij JMA, et al. Identification of differences in health impact modelling of salt reduction. PLoS ONE 2017; 12(11): e0186760. |

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| | | | | 4. Infanger E, Haldimann M. Report on the composition of prevalent salt varieties. Federal Food Safety and Veterinary Office FSVO, Nutrition, Federal Department of Home Affairs, Swiss Confederation, 2016; pp. 1-53.<br>5. NHS National Institute for Health and Clinical Excellence. *Prevention of cardiovascular disease at population level*. NICE Public Health Guidance 25, June 2010 (reviewed 2016). |
| 14 | Guideline | 11<br>11<br>29-31 | 19-20<br>21-22<br>All | There is strong evidence that greater reductions in BP produce greater reductions in strokes, heart attacks and other serious cardiovascular complications. Yet the draft guidance recommends BP targets that are only slightly lower than the starting threshold for treatment. The critical question is at what level of treated blood pressure will the harm outweigh the benefit?<br><br>Since the 2011 NICE guidance, new evidence has emerged on this topic. However, the selection of eligible studies to inform the NICE Guideline on this question was extremely narrow. The BIHS feels that the NCG Committee selection to assess the potential additional health benefits of lowering systolic BP <130 mmHg has been discounted hastily.<br>• The evidence of lowering systolic BP <120 mmHg is mainly provided by the results of the SPRINT study. The more rigorous measurement methods used in SPRINT would need some adjustment of the target aimed for in standard practice, in which a nurse or doctor is commonly present throughout the measurement process, equating to perhaps aiming for <130/80 mmHg. The NCG committee had downgraded the SPRINT findings using a new criterion. If the SPRINT study had not recorded whether someone was present during the measurements, as is the case for almost every other study, there would have been no discussion of the matter as a possible source of variability. It is biased to downgrade one study's findings, but not the findings of other studies in which this detail is wholly unknown.<br>• The decision of the targets is only based on the results of the Cardio-Sis trial (2009) and all new evidence dated post-2011 has been discarded. The post-2011 evidence comes from post-hoc analyses of large outcome trials and registry data (1-3), and from two new meta-analyses of randomized clinical trials (RCTs) of BP-lowering (4-5). As |

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| | | | | extensively reviewed in the recent ESC/ESH Guidelines (2018) (6) lowering systolic BP to <130 mmHg was, in general, associated with no further benefit on major CV events, except for further reductions in the risk of stroke, in post-hoc analyses of RCTs. However, new information on systolic and diastolic targets for drug treatment is provided by two large meta-analyses of RCTs of BP lowering. In the first, achieved systolic BP was stratified according to three target ranges (149–140 mmHg, 139–130 mmHg, and <130 mmHg).(4) Lowering systolic to <140 mmHg reduced the relative risk of all major CV outcomes (including all-cause mortality); similar benefits were seen when systolic BP was lowered to <130 mmHg, even when compared to 130 - 139 mmHg. Similar benefits were seen with diastolic targets. The second, which also included the SPRINT trial, showed that every 10 mmHg reduction in systolic BP reduced the rate of major CV events and all-cause mortality for baseline values >160 mmHg to values between 130 and 139 mmHg, implying benefit at achieved systolic values of <130 mmHg.(5) These benefits were consistent in patients at all levels of risk, including those with and without existing CVD, stroke, diabetes, and CKD. Whilst considering BP targets, less than 50% of patients treated for hypertension currently achieve a target office systolic BP of <140 mmHg.(7-8).<br><br>In conclusion, the BIHS believes that the evidence is sufficient to justify '*aspirational'* targets of <130/80 mmHg (but not <120 mmHg systolic using current BP measurement methodologies) in relation to optimal health gains, if applied in the right circumstances (using clinical judgment, comorbidities and frailty). However, the BIHS recognizes that since current targets are still not being met due to a variety of reasons highlighted elsewhere in the guideline, the first objective should be to lower BP to <140/90 mmHg in all patients as a '*practical*' minimum requirement when BP-lowering drugs are used. Therefore, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80mmHg or lower in most patients. In older patients (>65 years), systolic BP should be targeted to between 130 and 140 mmHg, and diastolic BP to <80 mmHg. This will result in large numbers of patients being given the opportunity to achieve the full |

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| | | | | potential benefits of treatment as a consequence of inadequate reduction in BP, whenever possible.<br><br>(1) Bohm M, Schumacher H, Teo KK, et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. Lancet 2017; 389: 2226–37.<br>(2) Kjeldsen SE, Berge E, Bangalore S, et al. No evidence for a J-shaped curve in treated hypertensive patients with increased cardiovascular risk: The VALUE trial. Blood Press 2016; 25: 83–92.<br>(3) Mancia G, Kjeldsen SE, Zappe DH, et al. Cardiovascular outcomes at different on-treatment blood pressures in the hypertensive patients of the VALUE trial. Eur Heart J 2016; 37:955–64<br>(4) Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels - updated overview and meta-analyses of randomized trials. J Hypertens 2016; 34: 613–22<br>(5) Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016; 387: 957–67<br>(6) Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 39: 3021-104<br>(7) Banegas JR, Lopez-Garcia E, et al. Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: the EURIKA study. Eur Heart J 2011; 32: 2143–52.<br>(8) Falaschetti E, Mindell J, Knott C, Poulter N. Hypertension management in England: a serial cross-sectional study from 1994 to 2011. Lancet 2014; 383: 1912–9. |
| 15 | Guideline | 14, 15, 16 | 17-20, 7 and 13, 1 | The superiority of thiazide-like diuretics vs thiazide diuretics on outcomes has never been tested in head-to-head RCTs. Chlorthalidone and indapamide have been used in a number of RCTs showing CV benefits, and these agents are more potent per milligram than |

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| | | | | hydrochlorothiazide in lowering BP, with a longer duration of action compared with hydrochlorothiazide and no evidence of a greater incidence of side effects. (1-2) Placebo-controlled studies based on thiazides, chlorthalidone, and indapamide reported similar effects on CV outcomes of the three types of diuretics. (3) Therefore, in the absence of evidence from direct comparator trials and recognizing that many of the approved single-pill combinations (SPCs) are based on hydrochlorothiazide, the BIHS would suggest a less restrictive recommendation on the type of long-acting diuretic to be used as D.<br><br>(1) Roush GC, Ernst ME, Kostis JB, et al. Head-to-head comparisons of hydrochlorothiazide with indapamide and chlorthalidone: antihypertensive and metabolic effects. Hypertension 2015; 65:1041–6.<br>(2) Olde Engberink RH, Frenkel WJ, van den Bogaard B, et al. Effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality: systematic review and meta-analysis. Hypertension 2015; 65: 1033–40.<br>(3) Thomopoulos C, Parati G, 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. |
| 16 | Guideline | 13, 14, 32 | 23-26, 4-23, 1-7 | The review of the evidence of the NICE committee on the use of 'dual therapy' in Step 1 concludes that *"in the absence of compelling new evidence on step 1 dual therapy, […] previous recommendations for step 1 treatment should be retained […], because they were based on robust clinical and cost-effectiveness evidence".*<br>• The draft guidance recommends a stepped approach to treatment that involves slowly adding drugs one at a time over an extended period until the target is reached.<br>• This is an approach that has not been updated for several decades, despite evidence showing that it does not work in practice (1-3).<br>• Most patients will require combination therapy to achieve BP targets.<br>• Initial combination therapy, even at low-dose, is invariably more effective at lowering BP than monotherapy, even at high dose (4). |

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| | | | | • No RCT has compared major CV outcomes between initial combination therapy and monotherapy. However, observational evidence suggests that the time taken to achieve BP control is an important determinant of clinical outcomes (5), in line with the evidence that it is the level of achieved BP that predicts the CV benefits.<br>• Two-drug combination as initial therapy is safe and well tolerated (4) even in patients with stage 1 hypertension (6).<br>• Many patients remain on a single antihypertensive drug long-term despite inadequate BP control, even by the conservative standard proposed by the new guidance.<br>• Reducing the number of pills taken, in consideration of likely co-morbidities and polypharmacy, will contribute to improving adherence, the main cause of pseudo-resistance (1-3).<br>• The UK lags behind other European countries in the broad and accessible availability of single-pill combinations with the use of generic compounds, and the few options available are under patent and expensive. This would change if UK adopted the treatment strategies that result in better control of BP in other parts of the world.<br>• The UK is unique in denying convenient access to single pill combination therapy, now widely available and cheap generics, and now recommended by the U.S. and European guidelines in an effort to improve treatment compliance and the speed and efficiency of BP control. There are large amounts of data showing that single pill combination therapy, as initial therapy, results in better and faster BP control. Perhaps the lack of emphasis in the guideline in developing strategies to improve adherence and BP control is reflected in the complacency in addressing this key issue in treatment of hypertension.<br>• It appears that to fulfill the cost-effectiveness requirement, NICE will accept market-driven guidelines. On the other hand an increased demand for generic single-pill combinations may drive the market to reducing the costs in face of greater competition.<br>• The adoption of dual therapy in single-pill would also help patients of low socio-economic groups to reduce their prescription charges but perhaps not the profits made by pharmacies for dispensing multiple pills when one could suffice. |

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| | | | | The BIHS believes that dual-therapy should be used right from the start, to have a major effect on the speed and quality of BP control, and for the patients to achieve the largest reduction in the risks of strokes, heart attacks and other major cardiovascular complications.<br><br>(1) Calhoun A, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008; 117: e510-526.<br>(2) Gupta P, Patel P, Strauch B, et al. Risk Factors for Nonadherence to Antihypertensive Treatment. Hypertension 2017; 69: 1113-20.<br>(3) Berra E, Azizi M, Capron A, et al. Evaluation of Adherence Should Become an Integral Part of Assessment of Patients with Apparently Treatment-Resistant Hypertension. Hypertension 2016; 68: 297-306.<br>(4) Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 2009; 122: 290–300<br>(5) Xu W, Goldberg SI, Shubina M, Turchin A. Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: population based retrospective cohort study. BMJ 2015; 350: h158<br>(6) Yusuf S, Lonn E, Pais Pet al, HOPE-3 Investigators. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. N Engl J Med 2016; 374: 2032–2043. |
| 17 | Guideline | General | General | In current clinical practice for the management of hypertension there is still poor implementation of NICE Guideline and evidence-based criteria. The publication of the new NICE Guideline is an opportunity to re-emphasise what should NOT be considered when treating a hypertensive patient. A list of drugs now obsolete should be listed as not suitable.<br>• Hydralazine may reduce BP in patients with hypertension, but the evidence is only based on pre-post studies, not RCTs (1). There is no evidence on mortality and |

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| | | | | morbidity, and there are some serious adverse events reported including hemolytic anemia, vasculitis, glomerulonephritis and lupus-like syndrome (1).<br>• Direct renin inhibitors (e.g. aliskiren) reduce BP compared to placebo in short-term studies (8 weeks) with effect similar to other classes. However, little evidence in the longer-term and on CV outcomes (2). Aliskiren in combination therapy with ACEs/ARBs could control BP effectively, but is associated with increasing risks of hyperkalaemia and kidney injury and have no benefit in preventing of major cardiovascular events (3), and it may even be harmful in patients with hypertension and diabetes (4).<br>• Centrally acting drugs (e.g. moxonidine) have a higher risk of adverse effects and no endpoint evidence.<br><br>(1) Kandler MR, Mah GT, Tejani AM et al. Hydralazine for essential hypertension. Cochrane Systematic Reviews 2011; 11: CD004934<br>(2) Musini VM, Lawrence KAK, Fortin PM et al. Blood pressure lowering efficacy of renin inhibitors for primary hypertension. Cochrane Systematic Reviews 2017; 4: CD007066<br>(3) Fu S, Wen X, Han F et al. Aliskiren therapy in hypertension and cardiovascular disease: a systematic review and a meta-analysis. Oncotarget 2017; 8(51): 89364-74<br>(4) Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012; 367: 2204–13. |
| 18 | Evidence reviews | General | General | Whilst the broad questions are framed by the NCG committee, the search criteria are applied by the NGC technical team. We wonder if the two are one and the same. If they get no results, as frequently happened, they do seem to have a mechanism for relaxing their search criteria until they do find studies. They could then give guidance, but with caveats. For example, in Evidence Review G they look for CV endpoint studies in which patients are on one stage 4 treatment for a year. Not surprisingly they find no evidence. They cannot therefore consider the Pathway 2 study as shorter-term reduction in BP is well outside their criteria, yet this is the best evidence in the area and until something better comes along, should inform practice. The guidance does mention using spironolactone as an aside, but the guidance should, in our view, have been more proscriptive. |

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| | | | | Diabetes is taken as a special case in this guideline and searches dichotomized, perhaps in response to the ACCORD trial and perhaps as there are many studies recruiting only diabetics, but some thought could have gone into handling other disease states in the same way. For example, the guideline (P13 line 24 and especially 1.4.31 page 14 line 4) suggests ACE inhibitors and for patients over 55yrs calcium channel blockers. The PATS study unequivocally showed the benefit of indapamide after stroke (1), PROGRESS showed that the combination of indapamide and perindopril were beneficial (2). Multiple studies conducted of calcium channel blockers after stroke have shown no benefit or in some possible harm, even when confined to those studies using oral, once-daily CCBs sometime after stroke in metanalyses. Stroke should have been handled separately.<br><br>(1) PATS Collaborating Group. Post-stroke antihypertensive treatment study. A preliminary result. Chinese Med. J. 1995; 108: 710-717.<br>(2) PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. The Lancet 2001; 358: 1033 – 1041.<br>(3) Horn J, Limburg M. Calcium Antagonists for Ischemic Stroke. A Systematic Review. Stroke. 2001;32:570-576. |
| 19 | Research recommendations | General | General | We should consider adding the need to show that the daytime ABPM and HBPM levels are the same. |
| 20 | Table 2 wording change | 41 | 2-3 | Change from 1.1.5 to 1.1.4 omits reference to validation list from the BIHS – this ought to be reinstated as the BIHS is the only organisation in the world to provide such an update list. The list is used globally and referenced widely (also by ESC/ESH and AHA/ACC). |
| 21 | Appendix 3 | General | General | The flowchart suggests that a patient under the age of 40 years with Stage 1 hypertension without diabetes or TOD or with a CVD risk <10% should be considered for special referral. Given the rapid increase in prevalence of hypertension due to obesity and other unfavourable life-styles, these cases will be unlikely to have any secondary cause of hypertension. Tertiary referral will be overburdened with inappropriate referrals. The BIHS |

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| | | | | would suggest adding to young age any other sign or symptom suggestive of secondary cause (for instance, target organ damage, signs suggestive of secondary hypertension, like hypokalaemia, symptoms consistent with phaeochromocytoma, resistance to Step 3 management, other CV complications or multi-morbidity). |
| 22 | Appendix 4 | General | General | • The management algorithm is a direct evolution of the management algorithm of NICE Guideline 2011 (and revised version) which was co-badged from the British Hypertension Society algorithm developed in 2004 (1). It is to the BIHS' surprise that – as presented in the draft – no reference or acknowledgment is made to the original.<br>• As highlighted earlier, the BIHS believes there is little evidence to support the combination in Step 2 of a C + D.<br><br>(1) Williams B, Poulter NR, Brown MJ et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004—BHS IV. J Hum Hypertens 2004; 18: 139-85 |

Insert extra rows as needed

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