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Could we simplify NICE guidance on choosing anti-hypertensive drugs?

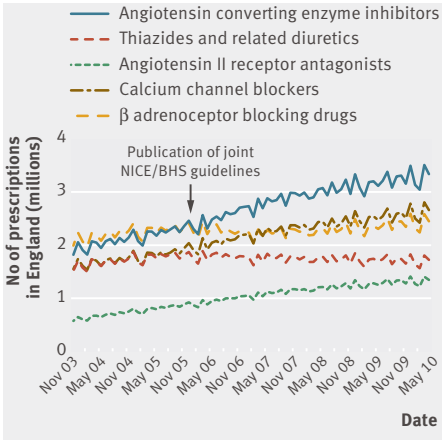
Reecha Sofat and colleagues argue that prescribing advice needs updating in the light of recent evidence that all classes of blood pressure lowering drugs are broadly equivalent

High blood pressure is the most common modifiable cause of cardiovascular morbidity and mortality worldwide,[1] and blood pressure lowering drugs from four major classes (angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers, β blockers, calcium channel blockers, and diuretics) are prescribed in large volumes. Among these, treatment would be dictated by cost or tolerability if all drugs were of similar efficacy and safety and had an additive effect when used in combination. However, guidance from the National Institute for Health and Clinical Excellence (NICE) and the British Hypertension Society emphasises differences between drug classes and combinations in blood pressure response and clinical outcomes.

NICE's recommendations are based on the view that younger patients (≤55 years) are more responsive to drugs targeting the renin-angiotensin system than older patients; that β blockers are less effective than the other drug classes for the prevention of stroke; and that β blockers and diuretics lead to a clinically important increase in the risk of type 2 diabetes. Consequently, its 2006 guidelines gave primacy to angiotensin modifying drugs and calcium channel blockers, with a substantial influence on prescribing behaviour in England and Wales (figure).[2] The updated guidelines published last August (www.nice.org.uk/CG127) maintain this view, but how strong is the evidence?

Stratification by age

Current NICE recommendations represent an evolution of the view that blood pressure is best lowered with β blockers or ACE inhibitors in patients under 55 years (in whom an activated renin-angiotensin system may be an important mechanism) and diuretics or calcium channel blockers in older patients (because sodium retention, with suppression of the renin-angiotensin system, may be more important). This was based primarily on the findings of a study (n=36) that rotated young patients through monthly treatment with each of four main classes of blood pressure lowering drugs and assessed the effect on blood pressure.[3]



Effect of 2006 NICE/British Hypertension Society guidelines on prescribing rates for all classes of antihypertensive drugs in England (data from NHS Prescriptions Service)

By 2006, NICE had relegated β blockers to third or fourth line therapy because of concerns about reduced protection from stroke,[2] and last year NICE dropped diuretics as a first line option. Renin declines with age,[4] and the major drug classes do differ in their effect on the renin-angiotensin system.[5] However, the performance of age as a proxy for stratifying blood pressure response or in comparison with measurement of renin concentrations (now possible with a rapid, cheap assay)[6] has yet to be formally evaluated. Moreover, a meta-analysis including data from 11 000 participants from 42 trials, which included people younger than 55, concluded that the "blood pressure reduction from combining drugs from these 4 classes can be predicted on the basis of additive effects."[7] This conclusion even included combinations of two drugs that both suppress or activate renin.

Efficacy of β blockers

Two sources of evidence were influential in NICE's relegation of β blockers from first line treatment: the Anglo Scandinavian Cardiovascular Outcomes Trial (ASCOT), published in 2005,[8] and three meta-analyses examining the efficacy of β blockers in the prevention of cardiovascular events, published in 2005-6.[9-11]

ASCOT was a randomised trial comparing an amlodipine based treatment regimen (with addition of perindopril and then doxazosin if required) with an atenolol based treatment regimen (with the addition of bendroflumethazide and then doxazosin if required) to achieve a blood pressure <140/90 mm Hg. The trial was terminated early on the advice of the data safety monitoring committee because of a significant treatment difference in favour of patients randomised to the amlodipine based regimen for two secondary end points (stroke and total cardiovascular events). There was no difference in the primary end point of non-fatal myocardial infarction or fatal coronary heart disease. Blood pressure was lower in the group randomised to amlodipine rather than atenolol by around 2.7/1.9 mm Hg. The trialists' analysis suggested the blood pressure difference was insufficient to explain the disparity in event rates,[12] but an accompanying commentary reached the opposite conclusion.[13]

A subsequent meta-analysis examined trials comparing β blockers with other blood pressure lowering drugs.[9] Stroke risk was 16% higher (95% confidence interval 4% to 30%) among patients randomised to β blockers than among those taking other drugs. Two other meta-analyses reached similar conclusions.[10 11] However, the inclusion and exclusion criteria of these meta-analyses were not uniform. A re-analysis shows that the pooled estimate of the comparative efficacy of β blockers for preventing stroke is sensitive to which trials were considered eligible (see supplementary analysis on bmj.com). Furthermore, they did not account for blood pressure differences between the treatment arms. The achieved blood pressure favoured the comparator drug over β blockers in all scenarios, which may bias the outcome in favour of the comparator drug. The blood pressure disparity is unlikely to be because β blockers are inherently less effective at lowering blood pressure than other drugs [14] but rather because achieving a precisely equivalent blood pressure reduction in two arms of a comparator trial is extremely challenging. Nevertheless this is essential for a fair comparison of the efficacy of two drug classes.

Two new comprehensive meta-analyses now supersede these studies.[15 16] These examined the efficacy of all major blood pressure drug classes (not just β blockers) in the context of the achieved reductions in blood pressure. The Blood Pressure Treatment Trialists Collaboration, which incorporated information from 190 606 participants across 31 treatment trials, concluded that all classes of drug were broadly equivalent with respect to protection from serious cardiovascular events.[15] The analysis indicated a log-linear association between blood pressure reduction and the relative risk of events, in keeping with predictions from observational studies. A second analysis by Law and colleagues, which included information from 147 published trials among 464 000 participants, concluded the protective effect of lowering blood pressure on coronary heart disease was the same for all drug classes with two exceptions.[16]

Calcium channel blockers had a small class specific advantage in protecting from stroke over all other classes. The authors considered that this probably accounted for most of the apparent disadvantage of β blockers in stroke protection because calcium channel blockers had been the most common comparator drug in trials of β blockers

Calcium channel blockers had a small class specific advantage in protecting from stroke over all other classes. The authors considered that this probably accounted for most of the apparent disadvantage of β blockers in stroke protection because calcium channel blockers had been the most common comparator drug in trials of β blockers.

Law and colleagues also found β blockers to have a specific action over and above their blood pressure lowering effects in preventing a recurrence in the first few years after a coronary heart disease event. Because blood pressure is an important risk factor for recurrent events in patients with established cardiovascular disease, as well as those at risk of a first event, it had seemed counterintuitive that β blockers should be an unfavoured treatment before a patient has had a coronary event but a preferred option immediately afterwards. In the longer term, their benefits were consistent with the degree of blood pressure lowering and proportionally similar to that seen in individuals with no prior event.[16]

Risk of type 2 diabetes

Patients receiving β blockers or thiazides rather than other drugs such as ACE inhibitors are at higher risk of diabetes.[18] But what is the magnitude of the blood glucose increase; by how much is the risk of diabetes increased; and, importantly, how does this affect the risk of cardiovascular events?

In the ASCOT trial, diabetes risk was increased among people randomised to the atenolol-bendroflumethiazide arm (hazard ratio for the comparison of groups randomised to amlodipine rather than atenolol was 0.70, 95% confidence interval 0.63 to 0.78), yet the average absolute difference in blood glucose concentration was only 0.2 mmol/L (SD 2.08 mmol/L, P<0.0001).[8] The seemingly substantial increase in the risk of diabetes arises because an average increase in glucose of as little as 0.2 mmol/L leads to a substantial increase in the proportion of people marginally exceeding the diagnostic fasting blood glucose threshold of 7 mmol/L and therefore being classified as diabetic (fig 3 on bmj.com).

However, the evidence is not compelling that this small average increase in glucose translates into a shortfall in protection from stroke or coronary heart disease. In the Asia Pacific Cohort Studies Collaboration (a participant level meta-analysis of 237 468 people), a decrease in fasting glucose by 1 mmol/L was associated with a 21% (18% to 24%) lower incidence of stroke and a 23% (19% to 27%) lower incidence of ischaemic heart disease.[18] If the association is causal, and assuming a log-linear relation between glucose and risk of cardiovascular events, an increase in fasting glucose of 0.2 mmol/L should confer about a 5% increase in the risk of stroke, which is less than the differences reported in the recent trials. Moreover, recent overviews of prospective observational studies indicate that although the risk of coronary heart disease is linearly and modestly increased above a fasting glucose value of 5 mmol/L, the risk of stroke is substantially raised only at fasting glucose values well above 7 mmol/L (fig 4 in supplementary analysis on bmj.com). [19-21]

Furthermore in the ALLHAT trial (in which 33 357 patients were randomised to chlortalidone, amlodipine, or lisinopril) there was a difference in blood glucose of 0.16 mmol/L in the amlodipine group compared with the chlortalidone group, with an odds ratio for diabetes of 0.73 (0.58 to 0.91).[22] Yet the hazard ratio for stroke was 0.93 (0.82 to 1.06). There was only a small blood pressure disparity between the chlortalidone arm and amlodipine arm (blood pressure difference amlodipine versus chlortalidone 0.8 mm Hg systolic (P=0.03)/−0.8 mm Hg diastolic (P<0.001)). This suggests that the observed differences in risk of stroke in these trials are more likely to be explained by differences between the

The most recent evidence indicates that the four classes of drug are more similar than different in their clinical efficacy and safety

treatment arms in blood pressure rather than glucose. The relevance of the small average increase in glucose is further questioned by recent trials that indicate that tight glucose control does not necessarily lead to a reduction in cardiovascular event rates.[23]

Despite this, NICE cost effectiveness models were based on the assumption that β blockers provide less protection from stroke than all other drug classes (not just calcium channel blockers) and that any diagnosis of diabetes is associated with twice the risk of mortality and other cardiovascular disease events compared with no diabetes. It is not clear whether the known effects of β blockers in preventing recurrent coronary heart disease events were modelled in the economic analysis.

How does guidance compare internationally?

Guidance in the United States published before 2006 recommends diuretics as first line treatment, with β blockers given equal standing to the other drug classes.[24] The European Society of Hypertension and the European Society of Cardiology guideline from 2007 also recommends β blockers and thiazide diuretics as first line options in the absence of contraindications, except among those with established metabolic syndrome or a particularly high risk of diabetes.[25] However guidance in Scotland[26] and New Zealand[27] has changed in line with NICE's 2006 recommendations.

Resolving uncertainty

Network (mixed treatment) meta-analysis was used to evaluate the comparative efficacy and safety of the main blood pressure lowering drug classes in relation to cardiovascular events[28] and diabetes,[17] but these analyses preceded the recent large influential trials and meta-analyses. An updated network meta-analysis that includes efficacy and safety outcomes and which accounts for blood pressure and glucose differences between treatment arms could help reduce any remaining uncertainty.

Meanwhile, the most recent evidence indicates that the four classes of drug are more similar than different in their clinical efficacy and safety and that their effects in combination are additive, irrespective of mechanism. The initial choice of drug class and combination could thus rest on price, tolerability, and specific contraindications in individual patients. This simplification would benefit healthcare commissioners, doctors, and patients.

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Navigating the shoals in hypertension
DISCOVERY AND GUIDANCE

Despite the extensive evidence underpinning treatment of high blood pressure, important questions remain. **Morris Brown**, **Kennedy Cruickshank**, and **Thomas MacDonald** argue that assumptions in recent treatment guidelines are based on insufficient evidence

The treatment of hypertension is arguably the most evidence based and cost effective medical intervention ever.[1] Not only is there a greater choice of drug classes than for other common diseases but there are more long term data that establish their efficacy in reducing risks from strokes, heart attacks, and heart failure. Uniquely, a prospective meta-analysis was planned by the leaders of the long term trials before their completion to avoid the post-hoc selection of questions and answers that can confound meta-analyses and guidelines.[2] The drugs concerned are now off-patent and inexpensive. The benefits are evident: treating patients saves money as well as reducing morbidity and mortality.[3]

However, the population attributable risks of raised blood pressure in those not currently classified as hypertensive are large. The prize for public health is to extend the benefits of blood pressure reduction to all those who would benefit. Two such groups exist. One is people whose blood pressure is below current definitions of hypertension (which are based on proved benefit of treatment in outcome trials) but above the threshold where epidemiological studies show a log-linear increase in risk with blood pressure.[4] The other is young patients with stage 1 (mild) hypertension, who paradoxically have higher relative and lifetime risk of complications than older people but are not treated in the UK for reasons of cost effectiveness. If we wait for patients to reach a blood pressure >160/100 mm Hg, or absolute cardiovascular risk >2% a year, before starting treatment we cannot be confident that a return to "normal blood pressure" can normalise risk. In outcome trials the benefits of treatment are limited to those with a clinic blood pressure >140/90 mm Hg and to reductions in blood pressure averaging just 10/6 mm Hg.[4]

Any changes in treatment should be based on evidence. Outcome trials designed to extend the use of antihypertensive drugs will need to be large and long because the event rate in lower risk groups will be lower. Because of concerns about medicalising a healthy population, these trials should also include, by stratification or randomisation, a prospective look at identifying people at whom future treatment should be targeted. For instance, if people were entered into an outcome trial that used home or ambulatory blood pressure monitoring, the trial could test the prediction that people whose blood pressure is variable will benefit more than those whose blood pressure is steady.[5 6] Variability might reflect stiffness of the large arteries, and user friendly equipment now allows us to test whether variability or stiffness is useful in selecting patients and blood pressures for treatment.[6 7]

Box 1 | Unanswered questions in hypertension

Outcome

- Should treatment be extended to all those whose blood pressure increases their cardiovascular risk?
- Should blood pressure targets be reduced to a similar, or greater, degree than thresholds?
- Can the cost effectiveness of treating more borderline hypertension be enhanced by supporting clinic blood pressures with additional measures of risk?

Surrogate

- Does initial combination therapy prevent compensatory haemodynamic or neurohumoral responses that attenuate the efficacy or tolerability of single drugs?
- Are potassium sparing diuretics the most effective treatment for resistant hypertension, and do they counter the diabetes risk of higher dose thiazides?
- Does the cheap test for plasma renin herald an era of personalised medicine in hypertension?

Other questions remain about best treatment (box 1). In its 2006 guidelines NICE called for a comparison of the options for managing resistant hypertension, such as spironolactone and other diuretics, and of starting treatment with combinations rather than single drugs to prevent resistance.[1] It also wanted studies to predict the best treatment for individual patients.[8 9] Several of the shorter term questions are being examined in a British Hypertension Society (BHS) Research Network collaborative programme (PATHWAY) established soon after the questions were identified. The PATHWAY trials build on the ACCELERATE study, which showed that combining drugs from the outset improves blood pressure control and reduces adverse events.[10]

NICE 2011

Against this background the recent NICE guidance appeared.[3] NICE generally prides itself on a bottom-up process, moving from evidence to conclusions to advice, so guarding against selection of evidence by special pleading.[11] However, the 2011 hypertension guidance made headlines not because it answered any of the questions NICE had raised in 2006 but because of the conclusions of two cost effectiveness articles that appeared only in the week of the guidance yet seemed pivotal to its advice.[12 13] Most surprising was the conclusion that we overtreat hypertension and that we could reduce the numbers starting antihypertensive treatment by 25% if we used ambulatory blood pressure monitoring instead of clinic blood pressure to diagnose hypertension. The cost-benefit argument in favour of ambulatory monitoring concluded

The white coat effect of doctors is neither new nor benign. Head et al do not suggest the routine introduction of ambulatory monitoring. Indeed, in outcome trials such as the MRC Mild Hypertension Trial, it was the doctors' readings, not the lower readings by nurses, that were used to enter patients

that it would save £10m (€12m; $15.5m), but this was true only if the monitoring was not repeated for five years. The combination of a rise, compared to previous guidance, in the blood pressure threshold for treatment and a longer interval before repeat monitoring is not plausible, evidence based, or safe.[14]

Other recommendations in the guidelines also do not seem to be based on evidence (box 2). These are the relegation of diuretics from first choice to third choice treatment and the change in diuretic drug of choice from bendroflumethiazide to either indapamide (for which there are no data from a primary prevention trial that met its primary outcome) or chlortalidone (for which there is no suitable formulation available in the UK). There are no comparative effectiveness data to underpin this guidance.

Box 2 | Guideline assumptions that are in need of evidence

- Hypertension is overtreated
- Hypertension should be redefined by daytime ambulatory blood pressure monitoring
- A daytime average systolic blood pressure <150 mmHg should not be treated, irrespective of clinic or other peak pressures, unless annual risk of cardiovascular morbidity exceeds 2%
- People with daytime average systolic blood pressure <135 mm Hg should not receive drug treatment but be rechecked by ambulatory monitoring every five years
- Diuretics are less effective than calcium channel blockers at reducing blood pressure variability and should therefore be third choice treatment
- Chlortalidone and indapamide are superior to bendroflumethiazide and hydrochlorothiazide

Redefinition of hypertension

NICE's relegation of clinic blood pressure measurement depends on two unstated assumptions, neither of which is supported by robust evidence. One is that the condition diagnosed by measuring blood pressure in the clinic is the same as that diagnosed by ambulatory measurement. Clinic measured hypertension has been studied in about 500 000 patients in outcome trials; these have shown that drug treatment reduces the risks of stroke, myocardial infarction, heart failure, and overall mortality.[2 15] By contrast, no trials have randomised patients to treatment on the basis of hypertension diagnosed by ambulatory monitoring. Indeed, the recent evidence cited by NICE that variability of blood pressure increases risk supports the need to treat patients whose blood pressure is higher on some occasions—that is, people with white coat hypertension.[5 16]

The second assumption is the equating of a clinic systolic blood pressure of 140 mm Hg with an ambulatory daytime systolic pressure of 135 mm Hg. It is unclear where this ambulatory monitoring threshold came from. Previous UK guidance has recommended, in round numbers, a 10/5 mm Hg difference in thresholds between ambulatory and clinic blood pressure measurements, there being a reported 12/7 mm Hg difference in measured blood pressure when these methods were compared.[14] This was based on the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study's comparison of ambulatory, home, and clinic blood pressure in 2000 participants.[17] A decade later, it reported the predictive value of each measurement on cardiovascular deaths and found no significant difference between clinic, home, or ambulatory measurements; indeed, none was individually as informative as their combined risks—that is, a blood pressure that was high only at home or in clinic was higher risk than one that was always normal but lower risk than one that was always high.[18] In PAMELA, a daytime mean ambulatory pressure of 135±14 mm Hg corresponded to a mean clinic systolic pressure of 155±22 mm Hg. Thus redefinition of hypertension as a daytime measurement of 135 mm Hg would detect many fewer "people with hypertension" than a clinic pressure of 140 mm Hg. However, half the people who died in PAMELA had a daytime ambulatory pressure below 135 mm Hg, suggesting this threshold is far too high.

Given the critical importance to NICE of equating its new ambulatory definition of hypertension with the previous clinic definition, the evidence cited is surprisingly circular. The guidance cites a *BMJ* article, which cites an "international standard" that turns out to be an unreferenced statement in the US joint national committee report from 2004.[19] The *Lancet* study on cost effectiveness of ambulatory monitoring cites both the NICE guidance and the *BMJ* article.[13] The NICE guideline does cite one primary source of data, but this article seems to undermine the call for use of ambulatory monitoring rather than support it: Head et al's 2010 retrospective comparison of doctors' and nurses' readings (both clinic and ambulatory) in 8500 Australians.[20] NICE has interpreted this study as showing that the daytime threshold of 135 mm Hg corresponded to a clinic threshold of 140 mm Hg. However, Head et al show only that 135 mm Hg was the average daytime systolic pressure for patients with stage 1 hypertension (defined as systolic 140-159 mm Hg). Their average clinic systolic pressure was 151 mm Hg if measured by a doctor (very similar to that in PAMELA) and 142 mm Hg if measured by a nurse. These figures seem inconsistent with the logic that led to the NICE guidance thresholds.

The white coat effect of doctors is neither new[21] nor benign.[18 22] Head et al do not suggest the routine introduction of ambulatory monitoring. Indeed, in outcome trials such as the MRC Mild Hypertension Trial, it was the doctors' readings not the lower readings by nurses, that were used to enter patients.[23] Of course, there is scope to supplement clinic blood pressure with other measurements, not least because the PAMELA data suggest additive risk prediction when this is done. It is common to use the same method for monitoring treatment as for making the diagnosis, and this would favour home over ambulatory measurements[24]; home measurements are also favoured on practical and cost grounds by leaders in primary care.[25]

But even if the redefinition of hypertension according to an ambulatory threshold were valid, and the headline 135 mm Hg threshold were robust, this is not the figure to be used in most patients. Previous UK guidelines already excluded most people with borderline hypertension from treatment, unless their 10 year cardiovascular risk exceeded 20%. NICE's preamble acknowledges that this absolute risk requirement has disenfranchised younger patients in the UK. NICE further concedes that lifetime risk assessment might be the more appropriate measure in younger people and would greatly increase the numbers eligible for treatment.[14]

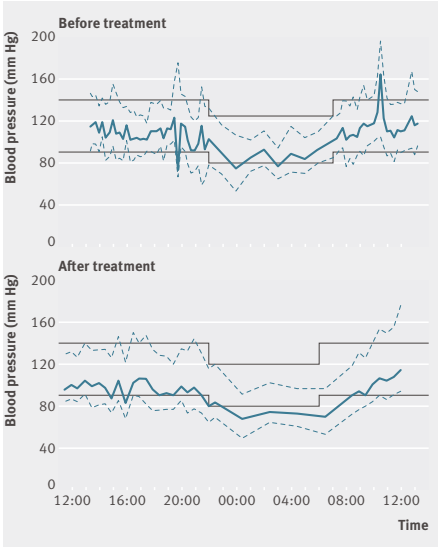
However, the new NICE guidance disqualifies even more patients than previously by raising the bars for treatment. Anomalies result. A patient might now be told one day that his clinic blood pressure predicts a 1 in 50 risk of myocardial infarction or stroke in the year ahead but discover the next day, after ambulatory monitoring, that he will not be treated for five years because his daytime systolic pressure averaged <135 mm Hg. Another patient at lower risk could have a clinic systolic pressure >180 mm Hg but remain untreated for five years if his daytime pressure averaged <150 mm Hg (figure). We are unaware of any evidence underpinning this higher threshold for "must treat" patients. Although NICE cites Head et al for using this ambulatory value instead of a clinic systolic pressure of 160 mm Hg, as we described above their figure was a mean daytime pressure not a threshold. The corresponding clinic systolic pressure for patients with stage 2 hypertension was 160-179 mm Hg.[20] In PAMELA, a daytime systolic pressure of 150 mm Hg equated to a clinic pressure >170 mm Hg.[18] Given the risks of hypertension, a threshold of 150 mm Hg seems unjustifiably high for starting treatment. On PAMELA's data, such guidance would translate into at least five avoidable deaths a year for every 1000 patients with hypertension.

Repositioning and redefinition of diuretics

For many years there has been an almost pantomime conflict between the drug industry's hope that one drug class was superior to the others and guideline writers' views that they are all equal. No one treatment is right for all patients, and most patients need a combination of drugs that reduce sodium load and vasodilate resistant arteries.[8] The original AB/CD (angiotensin converting enzyme inhibitor or β blockers/calcium channel antagonist or diuretic) algorithm offered a choice at each stage, recognising that a major hurdle in optimising treatment is the 25-30% of patients who have adverse effects from treatment. The AB/CD algorithm avoided random switching with its inevitable loss of control.[9]

The only drug class that targets a known cause of hypertension is the diuretics.[26 27] The new NICE guidance demotes diuretics from first to third choice, even though the evidence for these drugs is among the best of any drug for any indication. The guidelines now recommend chlortalidone, which is available in the UK only as a 50 mg tablet. Patients will need to use a tablet cutter and take half every other day to achieve the 12.5 mg dose used as starting dose in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and other studies.[28] Ironically, the new NICE guidelines recommend that doctors obtain informed consent before prescribing the most effective diuretic for hypertension—spironolactone—because it is not licensed for hypertension in the UK.[29 30] Finally, NICE gives the option of using indapamide, for which there are no data from any primary prevention trial that met its primary end point.

NICE's demotion of diuretics rests on the assumption that calcium channel blockers achieve a greater reduction in blood pressure variability. But variability has never been tested prospectively nor used as an entry criterion in any clinical trial of antihypertensive drugs. And the guidance seems contradictory since NICE invokes increased variability first as the indication for not treating 25% of patients with hypertension and then as the reason for treating most of the remainder with one class of drugs rather than another. In reality, the latest meta-analysis comparing calcium channel blockers with diuretics, which includes data from the international trialists' collaboration, shows no difference in their effect on variability (P M Rothwell, personal communication).[2 16] The conventional outcome data cited by NICE shows diuretics to be superior to calcium channel blockers in preventing heart failure and equivalent for other major outcomes, with no significant difference in cost effectiveness.[3] NICE selects one outcome trial in which low dose thiazide plus angiotensin converting enzyme (ACE) inhibitor was less effective than high dose calcium channel blocker plus ACE inhibitor at reducing blood pressure and preventing cardiovascular complications.[31] Since this was not a trial of first line treatment (97% were previously treated), and its results run counter to other trials comparing calcium channel blockers and diuretics, it cannot alone justify this big change.



Blood pressure of patient before and after treatment with amlodipine. Although recent evidence suggests that variable blood pressure puts this patient at greater risk of stroke than people with higher mean pressure, NICE recommends only repeat monitoring every five years

After more than 50 years of use, NICE has redefined diuretics not according to their mechanism of action (on the Na^+-Cl– cotransporter) or evidence from prospective outcome trials but according to their chemical structure. Thiazide and thiazide-like drugs are separated because they have "differential effects on carbonic anhydrase." Once again, the underlying facts are questionable, since hydrochlorothiazide, but not bendroflumethiazide, inhibits carbonic anhydrase, whereas NICE wishes to band these drugs together.

Meanwhile, NICE's (uncharacteristically) selective data review omitted the whole question of whether potassium sparing diuretics are desirable additives and, specifically, overlooked co-amilozide, which was as effective as the top dose of calcium channel blocker in one trial, and much better than placebo in another.[32-34] The 44% reduction in coronary events with co-amilozide in the MRC Older Adults trial was remarkable.[32] Co-amilozide is cheap and could replace bendroflumethiazide as first choice for diuretic.[34] However, increasing the dose of bendroflumethiazide could be just as effective. Whenever maximal, equihypotensive doses of thiazide and calcium channel blockers have been compared in morbidity and mortality trials, there is no difference in

We need to know "beyond all reasonable doubt" that we are doing the right thing—and that requires prospective clinical trials

the primary outcomes.[2 28 33] The lower efficacy of adding bendroflumethiazide to a β-blocker in reducing secondary outcomes in a trial of 18 000 patients, is more plausibly related to the submaximal (1.25-2.5 mg) dose than to the choice of diuretic.[35 36]

Conclusions

The success of antihypertensive therapy does not blunt the need for further research on a condition that remains a major global cause of serious morbidity and mortality.[37] Why NICE's consultation exercise did not forestall the criticisms raised here is unclear. Several of the points were made during stakeholder discussions, and the absence of outcome trials based on ambulatory measurements is well known.[38]

What should doctors do now? The British Hypertension Society agreed unanimously at its 2011 annual meeting that only robust research is a basis for substantive changes to practice. Let this NICE guidance be the catalyst. We need to know "beyond all reasonable doubt" that we are doing the right thing—and that requires prospective clinical trials.

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HYPERTENSION GUIDELINES 2011
NICE authors respond

Richard McManus, **Mark Caulfield**, and **Bryan Williams** respond to criticisms of the 2011 NICE guidelines, arguing that it reflects the reduced costs of generic drugs and new evidence on cardiovascular risk reduction

The two articles criticising some of the recommendations in the recent National Institute for Health and Clinical Excellence (NICE) hypertension guidelines[1 2] come from different, and sometimes contradictory, standpoints.[3 4] We discuss the process undertaken in developing the recommendations and respond to the points raised.

NICE guideline development process

NICE guidelines are developed through a standardised, rigorous, and transparent method. It starts with the development of a series of questions (the "scope" of the guideline) and setting up a guideline development group with representatives from key stakeholders (typically patient and carer representatives, experts, nurses, general practitioners and a chair or clinical lead, all of whom are appointed after public advertisement), a project manager, and a technical team, with representatives from NICE and other experts sitting in as necessary. There is then a detailed search for efficacy and cost effectiveness literature; where required, technical staff do new meta-analyses and economic modelling.[5] The process is open with minutes of all group meetings freely available (http://guidance.nice.org.uk/CG/Wave2/14/Development/GDGMinutes for Hypertension), and there is an extensive and exhaustive process of external consultation for each guideline. This includes detailed consideration of the scope and publication of a draft guideline before the guideline emerges in its final form.[5] All responses to the consultation are collated and responded to individually, and an audit process ensures that difficult questions are not ignored. Groups such as specialist societies, commercial organisations, research groups with a particular interest, and hospital trusts can register as stakeholders and provide detailed comments.

In the case of hypertension, the update was partial, which meant that the scope was limited to areas where it was considered that the evidence had moved on since the last guideline in 2006. The underlying model for the guideline remained the detection and treatment of individuals with uncomplicated primary hypertension, whose blood pressure remains persistently raised above internationally recognised blood pressure thresholds.[2]

Diagnosis of hypertension

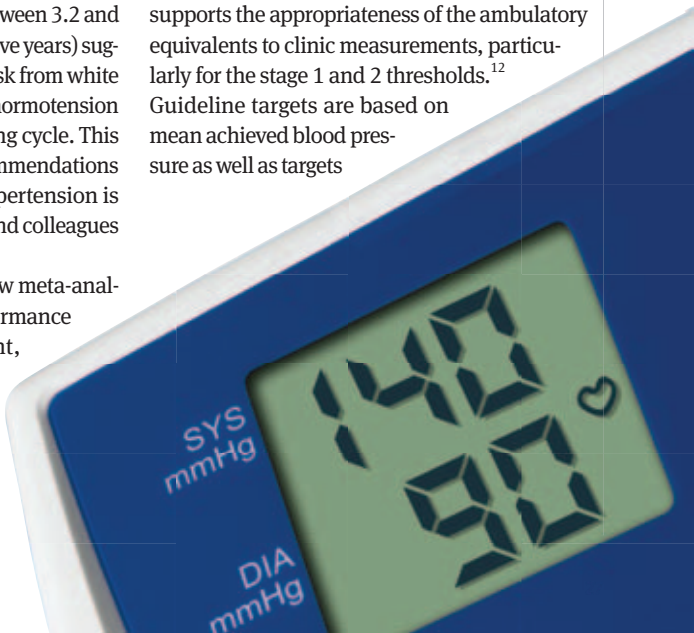
The 2011 guideline continued the risk based approach to diagnosis and starting treatment first proposed by the New Zealand guidelines in 1993 and included in subsequent British Hypertension Society and NICE guidelines since 1999.[6 7] The method for diagnosing hypertension was refined after review of evidence from 19 studies considering the relative prognostic ability of ambulatory or home blood pressure monitoring (ABPM and HBPM respectively) compared with clinic monitoring in determining outcome on the basis of baseline blood pressure. These studies showed that "out of office measures" are better than clinic measurement at predicting subsequent risk of cardiovascular events and many, including the PAMELA study, were included in Fagard and Cornelissen's 2007 meta-analysis.[8] This showed a hazard ratio for cardiovascular events of 1.12 (95% confidence interval 0.84 to 1.50) for "normal" ambulatory blood pressure with "raised" clinic measurements (white coat hypertension) compared with "normal" ambulatory and clinic pressures (definitively normotension).[8] Included studies had follow-up periods of between 3.2 and 10.9 years (only one was less than five years) suggesting no evidence of increased risk from white coat hypertension over and above normotension over a standard five yearly screening cycle. This provided the rationale for the recommendations on diagnosis, not a belief that hypertension is currently "over treated" as Brown and colleagues claim.[3]

These data, combined with a new meta-analysis showing the relative test performance of clinic and home measurement, triggered the development of an economic model.[9] This showed that ambulatory monitoring was the dominant strategy for the diagnosis of hypertension for both men and women in all age groups from 40 to 75 years and that this conclusion was robust to a wide variety of sensitivity analyses.

Exceptions to this were if normotensive people were assumed to benefit from blood pressure reduction or if the test performance of all three monitoring methods was considered equal. An absence of trials of the "polypill" approach as well as evidence from the systematic review of test performance in diagnosis meant that these analyses were not considered sufficient to overturn the main results.[10 11] If re-testing of all screened individuals took place annually rather than five yearly, ambulatory monitoring was cost effective for people older than 60 but not younger.[9] This scenario was deemed extreme as only people around the diagnostic threshold are likely to need frequent retesting, hence ambulatory monitoring retained its dominance. The guideline therefore recommended at least five yearly screening but annually for those close to the threshold.[2]

Ambulatory blood pressure thresholds

The thresholds for normal ambulatory blood pressure, unchanged from NICE guidelines since 2004, were not based on a single study but were supported by the results of the prognostic meta-analysis[8] and are consistent with international recommendations.[11] Head and colleagues' paper supports the appropriateness of the ambulatory equivalents to clinic measurements, particularly for the stage 1 and 2 thresholds.[12] Guideline targets are based on mean achieved blood pressure as well as targets



in trials, hence mean blood pressure comparisons are relevant.[12]

General considerations for choice of drugs

The general argument put forward by Sofat and colleagues that choice of antihypertensive drug should rest on cost, tolerability, and specific contraindications, ignores efficacy at preventing morbid and mortal cardiovascular events, which the guidelines considered to be most important.[4] Cost is now much less relevant as the main classes are available as generic drugs at broadly equivalent prices.[2] The 2011 guidance aimed to recommend the most cost effective drugs, taking into account tolerability and most conceivable specific indications.[2]

First line treatment

The other major area where changes were implemented in the 2011 guidelines was in treatment choice.[1] Here again, the guideline development process was dictated by cost effectiveness.[5] The 2006 model critiqued by Sofat and colleagues was updated to take account of the reduced costs of drugs as all are now available as generics. Importantly, the model showed that treating hypertension is cost saving versus no treatment.[2] As in 2006, calcium channel blockers emerged as the most cost effective option but now more so because of their availability as generic formulations. This was the principal driver for recommending calcium channel blockers as the preferred initial therapy for most people over the age of 55 years, the exception being people with evidence of heart failure or at higher risk of heart failure, for whom the sensitivity analysis suggested a thiazide-like diuretic should be preferred as initial therapy.[2] That calcium channel blockers are also less likely to cause impaired glucose tolerance, electrolyte disturbances, and gout and have been reported to be particularly effective at reducing blood pressure variability (which has recently been suggested as an independent predictor of risk, especially for stroke) further strengthened the rationale for this recommendation.[2 13] Another consideration was that the only trial to directly evaluate two drug combinations of treatments with a renin-angiotensin receptor system blocker, consistent with step two of the NICE treatment algorithm, also showed that combination with a calcium channel blocker was better than with a thiazide diuretic for preventing cardiovascular outcomes.[14]

The differentiation of drug choice for initial treatment according to age was maintained because sensitivity analyses showed that even small advantages in efficacy for drugs blocking the renin-angiotensin system over other classes made angiotensin converting enzyme inhibitors and low cost angiotensin receptor blockers very cost effective in younger people.[2] Diabetes, like hypertension, relies on an arbitrary cut-off for diagnosis, but why would somebody want to develop diabetes if it could be avoided? The hazard ratio in the ASCOT trial for development of diabetes was 0.70 (95% CI 0.63 to 0.78) for calcium channel blocker plus angiotensin converting enzyme inhibitor arm compared with β blocker plus thiazide.[15] Sarwar and colleagues' outcome data show that diabetes is associated with increased hazard ratios for coronary heart disease of 2.00 (95% confidence interval 1.83 to 2.19) and 2.27 (1.95 to 2.65) for ischaemic stroke.[16] The NICE model assumed a doubling of cardiovascular risk with diabetes in the base case, but at all levels of risk from diabetes calcium channel blockers remained the most cost effective option, even if the relative risk of cardiovascular events with diabetes was set to 1 (that is, no increase in risk of events).[2]

Choice of diuretic

Another question in the scope related to the choice of diuretic. The United Kingdom is unique in the world in its almost exclusive use of lower dose bendroflumethiazide (usually 2.5 mg once daily) to treat hypertension. The evidence review found no data evaluating and supporting effectiveness of this treatment in preventing cardiovascular events.[2 17] It was therefore difficult to continue to recommend it. More contemporary studies had used thiazide-like diuretics (chlortalidone and indapamide). The evidence for these drugs at modern doses was substantial, including several large primary prevention trials such as SHEP, ALLHAT, and HYVET.[18-20] Both are also available as low cost generic formulations and the decision, based on best available evidence, was that these should be the preferred diuretics. Although chlortalidone is available in the UK only in higher doses (50 mg), it should not stretch the organisational capability of the NHS to respond because the recommended doses are widely available elsewhere.

β blockers

In the updated meta-analysis for this guideline, as in previously published independent meta-analyses, β blockers were the least cost effective treatment for hypertension and notably less effective than the recommended first line drugs.[2 21] Law and colleagues' meta-analysis also found them to be significantly worse at preventing stroke than other drugs (relative risk 1.18 (1.03 to 1.36)). This may be a function of β blockers inferiority to calcium channel blockers or of less effective blood pressure reduction, but whatever the cause it is difficult to ignore when making recommendations for treating hypertension.[22]

Fourth line treatment for resistant hypertension

The evidence for fourth line treatment options in hypertension is currently suboptimal. However, people with treatment resistant hypertension are a high risk group and the evidence, albeit primarily from six observational studies, suggested that low dose spironolactone can be very effective at further reducing blood pressure.[2] This strategy is common practice in specialist hypertension clinics. Consequently, the 2011 guideline gave a "steer" towards the use of low dose spironolactone, while making clear in the research recommendations that more definitive evidence is needed. The ongoing PATHWAY studies will hopefully provide clarity in this area.

Conclusions

Finally, although we welcome healthy academic debate about the finer detail of the guideline, the key to its success is buy-in from clinicians. To date this has been high, at least in part because of the continued support of the British Hypertension Society, which has made a series of videos covering key aspects of the guidance (www.bhsoc.org/stream/BHS_Annual_Scientific_Meeting_NICE_Hypertension_Guidelines.html). These, along with the NICE implementation materials (http://www.nice.org.uk/CG127), will help facilitate dissemination and implementation of this evidence based evolution of the NICE hypertension guidelines.

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Contributors and sources: All authors contributed to the article and approved the final draft. Much of the evidence quoted was retrieved as a result of the evidence search in the 2011 guideline, supplemented by personal knowledge area. RJM leads a team investigating the management of hypertension and cardiovascular disease in primary care. MC has research interests in the genetic basis of hypertension and trials of novel therapies for cardiovascular disease. BW has research interests in experimental medicine related to hypertension, in particular the non-invasive assessment of aortic pressure and haemodynamics. BW is guarantor for the paper.

Competing interests: A full conflict of interest statement in relation to the NICE hypertension guideline is available in appendix B (http://guidance.nice.org.uk/CG127/Guidance/Appendices/B-E/pdf/English). In summary, RM, MC, and BW were all members of the guideline development group for the updated NICE hypertension guideline, and BW was the clinical lead and chair. BW (2001-3) and MC (2009-2011) were past presidents of the British Hypertension Society, and RM chairs the blood pressure monitoring working party. RM is a member of the NICE expert panel for the Quality and Outcomes Framework for hypertension and holds an NIHR career development fellowship. MC is a member of the European Society of Hypertension Council and holds a clinical directorship paid by London Genetics 2009-2010. His clinical trials unit conducted the Accelerate Trial—sponsored by Novartis. BW has received travel expenses and speaker honorariums for invited lectures, workshops, and small group meetings on hypertension at international conferences. BW's university and hospital trust has received investigator initiated research grants from drug companies, for participation as a member of the scientific steering committee of large scale clinical trials in hypertension and NIHR adopted studies. In the past year, these have been from Boehringer Ingelheim and Novartis. BW is a member of the European and international hypertension societies. He is a founding trustee (pro-bono) of the Blood Pressure Association and an NIHR senior investigator.

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ANSWERS TO ENDGAMES, p 50 For long answers go to the Education channel on bmj.com

PICTURE QUIZ Helsinki –20°C

1 The likely diagnosis is frostbite. This occurs when the temperature of the skin drops to about –0.5°C and tissue freezes, resulting in the formation of intracellular ice crystals and microvascular occlusion.
2 Risk factors include environmental factors; substance misuse, especially alcohol; psychiatric illness; peripheral vascular disease; drugs (prescribed and illicit); and trauma. It is most commonly seen in adult men.
3 Diagnosis is essentially clinical, being based on history and examination. However, scintigraphy using pertechnetate labelled with technetium-99 and magnetic resonance angiography can help assess tissue viability.
4 Prioritise any other life threatening conditions. Discuss all cases with a specialist unit that routinely performs peripheral thrombolysis. Immediate treatment includes rapid rewarming, analgesia, ibuprofen (used for its selective antiprostaglandin activity), oral antibiotics, and tetanus prophylaxis. Debride blisters containing clear fluid and apply topical aloe vera to the wound. Prohibit smoking and raise the limb. Consider adjuvant therapy.
5 Surgery is not usually indicated in the acute phase and should be delayed until the frostbitten area is thoroughly demarcated. However fasciotomy may be indicated in cases of compartment syndrome and early amputation in cases of sepsis.

CASE REPORT
A woman with rapidly progressive weakness and sensory loss

1 Guillain-Barré syndrome (GBS) is the most likely diagnosis. Other possible causes include myelitis; neuropathy caused by vasculitis, porphyria, toxins, or diphtheria; neuromuscular junction blockade by myasthenia gravis or botulism; acute myopathy secondary to inflammation or electrolyte imbalance; and rarely a brainstem disorder such as encephalitis or infarction.
2 The diagnosis is based on history and examination; other investigations are supportive. Cerebrospinal fluid analysis shows high protein and a normal or slightly raised white cell count (albuminocytological dissociation). Neurophysiology confirms an acute demyelinating (or less commonly axonal) neuropathy.
3 GBS is a post-infectious disorder, with two thirds of patients having an infection—most commonly *Campylobacter jejuni* or cytomegalovirus—two to three weeks before symptom onset. Swine flu 10 days before admission may have been the antecedent infection in this case.
4 GBS has no cure and treatment is supportive. Once a clinical diagnosis has been made, begin treatment as soon as possible with intravenous immunoglobulin or plasmapheresis because earlier treatment (in the first two weeks for immunoglobulin and the first week for plasmapheresis) shortens time to recovery in severe cases. Cerebrospinal fluid and neurophysiological confirmation are not needed before starting treatment.

STATISTICAL QUESTION
Multiple significance tests: the Bonferroni correction

The Bonferroni correction reduces the probability of making a type I error (answer *a*) but not a type II error (answer *b*).