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FEATURED EDITORIAL

Will generic hypertension guidelines reduce the proliferation of directives?

Jan A Staessen, Eoin O'Brien

"...practitioners should realise that recommendations can never replace sound clinical judgment or take precedence over the personal interaction between patient and doctor"



J Staessen



E O'Brien

The National Institute for Health and Clinical Excellence (NICE)¹ and the Joint British Societies² recently updated their recommendations for the management of hypertension. This short editorial commentary reviews some aspects of these guidelines^{1,2} against the background of other directives³⁻⁶ and identifies some areas of discrepancy that need further reflection. A detailed overview of the literature falls beyond the scope of this commentary, but references supporting our views are available in the guideline documents^{1,2,4-6} or in our previous publications.⁷⁻⁹

BLOOD PRESSURE MEASUREMENT

The management of hypertension rests on the accurate assessment of blood pressure. Compared to conventional blood pressure measurement, automated techniques of recording, especially ambulatory blood pressure monitoring (ABPM), provide a more precise estimate of a patient's usual blood pressure, exclude observer bias, minimise the white-coat effect, and refine risk stratification.¹⁰ In addition, ABPM gives information on the diurnal blood pressure pattern, the efficacy of 24 h blood pressure control, and the presence of nocturnal hypertension, which carries an adverse prognosis.¹⁰

A major difference between the British guidelines¹⁻³ on the one hand and the European⁶ and US⁵ directives on the other lies in the use of ABPM in primary care. The original NICE guideline¹ states that the appropriate use of ABPM in primary care remains an issue for future research. The guideline of the British Hypertension Society does not recommend the use of ABPM for all patients, but acknowledges its use in specific circumstances.³ On the other hand, the US⁵ and European⁶ guidelines clearly accept that ABPM has a definite place in the clinical management of hypertension. Future revisions of the British guidelines¹⁻³ will have to address this inconsistency.

There are also discrepancies between guidelines in the systolic/diastolic cut-off limits for ABPM. They are 125/80 mm Hg for the 24 h blood pressure in Europe,⁶ 135/85 mm Hg and 120/75 mm Hg for the awake and asleep blood pressure in the US,⁵ and 135/85 mm Hg and 120/70 mm Hg for the daytime and nocturnal blood pressure in Britain.² Recently, an international

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research consortium proposed diagnostic thresholds in terms of the 10 year cardiovascular risk observed in population studies.¹¹ After rounding, approximate thresholds for an optimal ambulatory blood pressure amounted to 115/75 mm Hg for the whole day, 120/80 mm Hg for the daytime, and 105/65 mm Hg for the nighttime. These outcome-driven ABPM thresholds are substantially lower than in the hypertension guidelines.^{5,6}

GLOBAL CARDIOVASCULAR RISK

The US hypertension guidelines⁵ tend to place less emphasis on the importance of global cardiovascular risk in determining the blood pressure thresholds at which antihypertensive drug treatment should be initiated. The European,⁶ British^{1,2} and New Zealand⁴ directives, on the other hand, favour a more global approach and include charts for risk stratification based on risk indicators, target organ damage, or associated conditions, such as diabetes mellitus or a history of cardiovascular or renal disease. This approach is justified on the basis that hypertension, hypercholesterolaemia and smoking account for approximately 85% of the modifiable cardiovascular risk.¹² Modern biomarkers, such as the serum levels of B-type natriuretic peptide, C reactive protein, or homocysteine, or the urinary albumin-to-creatinine ratio do not substantially improve risk stratification.¹³ Most guidelines⁴⁻⁶ agree that a blood pressure of 140 mm Hg systolic and 90 mm Hg diastolic is an indication to institute antihypertensive drug treatment. The British guidelines still propose more conservative thresholds (160/100 mm Hg) for treatment in patients with uncomplicated hypertension.^{1,2}

MULTIPLE RISK FACTOR INTERVENTION

The corollary of the global cardiovascular risk is multiple risk factor intervention. This approach raises two issues. First, the number of tablets to be taken each day and a long interval between the start of antihypertensive and lipid-lowering treatment are major determinants of poor adherence.¹⁴ Single-pill combinations of antihypertensive drugs and lipid-lowering medications improve the attainment of treatment goals and probably enhance adherence to treatment.¹⁵ Regulators

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Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 1 receptor blocker; CCB, calcium-channel blocker; NICE, National Institute for Health and Clinical Excellence

and expert committees have to consider whether single-pill combinations simultaneously addressing two risk factors are cost-effective by superior prevention of cardiovascular complications compared to the treatment with their constituents in separate pills. Second, in high-risk patients, lowering normal or mildly elevated values of cholesterol substantially enhances the risk reduction of blood pressure lowering drugs. However, the parallel question of whether lowering a high normal or normal blood pressure to an optimal level would result in significant benefit in patients at high cardiovascular risk has never been formally proven.

ROLE OF BLOOD PRESSURE LOWERING

In keeping with large-scale prospective observational studies, meta-regression analyses of randomised clinical trials demonstrated that small gradients in the achieved systolic blood pressure explained most of the differences in cardiovascular outcome.^{8,9} This association was particularly strong for the prevention of stroke, the complication most directly associated with blood pressure, and weakest for heart failure. A recent meta-analysis questioned the specific renoprotective effects of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin type 1 receptor blockers (ARBs) on renal outcomes, over and beyond those attributable to blood pressure lowering per se.¹⁶ These findings once more underscore the importance of vigorous blood pressure control in the treatment of high-risk patients, regardless of the drug class prescribed. Tighter blood pressure control undoubtedly provides better protection, especially in patients with diabetes or at high-risk. However, there is presently no evidence backing blood pressure goals below 130 mm Hg systolic and 80 mm Hg diastolic. Indeed, the currently available evidence might also support a less stringent goal of 140 mm Hg systolic and 90 mm Hg diastolic, as proposed by the British guidelines.¹

CHOICE OF ANTIHYPERTENSIVE AGENTS

The overriding role of blood pressure lowering in preventing the cardiovascular complications of hypertension, at first sight, suggests a generic approach to blood pressure lowering treatment and supports the role of low-dose combinations of antihypertensive agents. Additional arguments in favour of such a depersonalised concept of treatment are that most patients require more than a single drug to be controlled and that low-dose combinations expose patients to fewer side effects and might increase compliance.⁶ Expert committees will have to consider whether the convenience of the generic approach, which has never been proven to result in fewer cardiovascular complications, outweighs the more laborious—but intellectually more attractive—strategy of starting with one drug and subsequently optimising treatment in terms of blood pressure lowering and tolerance by substitution or addition of other compounds.

Several guidelines suggest that thiazide diuretics should be used to initiate antihypertensive treatment or should at least be combined with other agents early on in the adjustment of antihypertensive treatment.^{4,5} The revised British guidelines propose the use of ACEIs below age 55 years and diuretics or calcium-channel blockers (CCBs) in older patients.¹ The European directives⁶ leave it the clinician's prerogative to choose the agent best suited for each individual patient. All guidelines¹⁻⁶ list conditions favouring the prescription of certain drug classes and compelling contraindications. Meta-regression showed that CCBs compared to ACEIs, above and beyond blood pressure, provided a benefit (~14%) in the avoidance of stroke, and that the same was true for ACEIs compared to CCBs in relation to coronary heart disease (~10%).⁹ In contrast to

ACEIs, ARBs do not produce a blood pressure independent reduction in the relative risk of coronary heart disease.¹⁷ The recommendation to use preferentially ACEIs for the prevention of recurrent stroke⁵ goes against the evidence.⁷

Recent trials support the use of newer above older antihypertensive drugs to avoid metabolic side effects, in particular treatment-induced diabetes mellitus. In a long-term prospective study unconfounded by previous treatment, new-onset diabetes compared to having diabetes already at baseline carried similar cardiovascular risk.¹⁸ Avoiding diabetes mellitus over a patient's lifespan, although not formally proven, might represent true benefit beyond blood pressure lowering.

However, one should interpret very carefully the recommendation to avoid β -blockers as first line treatment of essential hypertension.^{1,2} The meta-analyses contributing to this change in policy did not account for the differences in blood pressure between randomised groups or the efficacy of β -blockade based on differences in heart rate. In some β -blocker trials, investigators withdrew a substantial number of patients because of bradycardia, a sign of effective β -blockade. One cannot dismiss the large body of evidence available from the secondary prevention trials of myocardial infarction, published more than two decades ago. If not for stroke, β -blockers should remain within the first-line therapeutic arsenal for the prevention of myocardial infarction and sudden death in patients with a history of coronary heart disease. Remarkably, in a secondary prevention trial in patients with coronary heart disease, perindopril offered protection against myocardial infarction, but only in patients already on β -blockers.¹⁹ The NICE guideline assumed a drug class effect based on the evidence against atenolol, but also recognises that substantial data on other β -blockers are lacking. While accepting that the conclusion in relation to atenolol may not apply to the newer β -blockers, the onus of proof is placed on the proponents of alternative forms of β -blockade, which is much easier said than done in the costly business of conducting randomised clinical trials. More importantly, it is disingenuous to apply evidence on the one hand to excuse lack of it on the other.

CONCLUSIONS

This commentary strengthens the plea for harmonising guidelines. The international opinion leaders know each other and should be able to come together to produce an international consensus guideline on hypertension, which would relieve practitioners from the burden of identifying the differences in policies between the guidelines. Realistically, we know that international consensus is unlikely, but surely European agreement should be possible, which begs the question as to why there have to be British guidelines within the context of the European Union?

On the positive side, current hypertension guidelines are becoming more generic because they emphasise the management of global cardiovascular and multiple risk factor intervention, and because they recognise that lowering blood pressure is more important than drug class. However, in moving towards unified guidelines, expert committees might reconsider the position of single-pill combinations within and across risk factor categories, first-line treatment options, certain compelling indications for antihypertensive drugs, and the role of ABPM in risk stratification. Generic hypertension guidelines might offer the opportunity to reduce the number of published directives, which would favour their implementation by doctors and understanding by patients. While waiting for more unified guidance, practitioners should realise that recommendations can never replace sound clinical judgment or take precedence over the personal interaction between patient and doctor.

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IMAGES IN CARDIOLOGY

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Wegener's granulomatosis with progressive conduction disturbances and atrial fibrillation

A 61-year-old man presented with a history of right-sided facial palsy and haemoptysis over the previous two months. Upon admission, chest radiography showed ill defined patchy infiltrates in both lung fields. An initial ECG revealed third degree atrioventricular (AV) block and escape beats (35 beats/min) with right bundle

branch block (RBBB, panel A). On the third day, the patient complained of increasing dyspnoea, and an ECG showed atrial fibrillation (AF) with complete AV block (panel B). At that time, the QRS morphology of the escape beats (32 beats/min) changed to a left bundle branch block pattern. Brain computed tomography (CT) revealed thickening of the mucosa in the left ethmoid sinus without any pathologic findings in the brain itself. A test for cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) of anti-proteinase-3 was positive (panel D). A nasal mucosal biopsy revealed necrotising granulomatous vasculitis (panel E), leading to the diagnosis of Wegener's granulomatosis.

After establishing the diagnosis, pulse therapy with intravenous methylprednisone and cyclophosphamide, followed

by high-dose oral prednisolone, was begun. Subsequently, the patient's condition improved remarkably, and he recovered from the heart block and AF over the next five days. However, the first-degree AV block (PR interval 320 ms) with RBBB remained (panel C) when seen one month after initiation of treatment.

When a patient presents with progressive cardiac conduction system disturbances combined with systemic symptoms, small vessel vasculitis including Wegener's granulomatosis should be considered in the differential diagnosis. Correct and early diagnosis may prove to be life saving, and it may obviate the need for pacemaker insertion.

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