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## Cardiovascular & Renal

# Critical appraisal of the JNC VI, WHO/ISH and BHS guidelines for essential hypertension

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Three guidelines have been selected for this review: The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI), the 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension (WHO/ISH) and the Guidelines for management of hypertension: report of the third working party of the British Hypertension Society (BHS). The guidelines are generally in accordance on the principles of drug prescribing. There is, however, a serious divergence of opinion between JNC VI and BHS, and WHO/ISH on the levels of blood pressure chosen for defining hypertension and the level to which blood pressure should be reduced. In defining hypertension using ambulatory blood pressure measurement (ABPM), JNC VI and BHS recommendations for systolic blood pressure are 10 - 15 mmHg higher than WHO/ISH. There is even greater divergence of opinion between the guidelines on the recommended goals of treatment. Using conventional measurement WHO/ISH recommends lowering systolic blood pressure with treatment by 10 - 20/5 - 10 mmHg more than JNC VI and BHS depending on whether 'normal' or 'optimal' pressures are to be achieved. Using average daytime ABPM pressure, WHO/ISH recommends lowering the average daytime blood pressure with treatment by 10 - 30/5 - 10 mmHg more than JNC VI and BHS depending on whether 'normal' or 'optimal' blood pressures are chosen. These differing recommendations between JNC VI and BHS, and WHO/ISH cannot be reconciled and they are of such magnitude as to carry serious implications for clinical practice, not least among which is that acceptance of the WHO/ISH levels of 'normality' for blood pressure would result in some 45% of the population of all ages and nearly 60% of elderly people being classified as 'hypertensive'.

**Keywords:** antihypertensive drugs, British Hypertension Society (BHS), guidelines, International Society of Hypertension (ISH), Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI), World Health Organization (WHO)

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## 1. Introduction

The WHO/ISH [1], and the Guidelines for management of hypertension: report of the third working party of the BHS [2], were both published in 1999 and had access to more recent literature than that cited in the JNC VI

[3]. It is important to note that whereas JNC VI and the BHS guidelines both give considerable attention to characterising the evidence cited to support their conclusions, the WHO/ISH guideline does not do so.

Apart from the ever increasing number of guidelines themselves, there is an extensive critical literature on many aspects of the guideline industry, such as their content, strength, the integrity of their conclusions, their legal standing and the like, with at least two books on the methodology, ethos and implementation of guidelines - *Implementing Clinical Guidelines: A Practical Guide* [4] and *Making Use of Guidelines in Clinical Practice* [5].

## **2. Purpose of the guidelines**

Each of the guidelines is prefaced by the continuing need to improve the management of hypertension and each uses largely the same literature to make its case, albeit with differing nuance. It is recognised, for example, that in over 70% of hypertensive subjects control is imperfect in many countries, that there is evidence suggesting that the improvement in management observed in recent years is no longer evident, or may even be declining, that the rule of halves (only half of all hypertensive patients are aware that they have hypertension, only half of those aware are actually on treatment and only half of those on treatment have their blood pressure well controlled) still applies in many countries around the world and that even in the most affluent countries, the rule of halves has at best become the rule of quarters, so that in several European countries < 30% of hypertensive patients given treatment have their blood pressures restored to normal and that in the US heart disease and stroke remain the first and third leading causes of death, respectively, imposing an annual financial burden of some US\$259 billion [1-3].

All three guidelines aspire therefore to improve this poor state of affairs by providing an expert opinion to guide doctors responsible for managing and treating hypertension.

## **3. Measurement of blood pressure**

### **3.1 Clinical measurement of blood pressure**

Accurate measurement of blood pressure is the cornerstone of diagnosis and is the foundation on which management and treatment decisions are

based and ultimately judged. While it is accepted by all guidelines that any classification of hypertension is somewhat arbitrary, the necessity of formulating a classification that allows the clinician to base decisions on the actual level of blood pressure is acknowledged. Blood pressure measurement should be conducted within the context of a comprehensive clinical examination that concentrates on the cardiovascular system, at least on the first assessment.

JNC VI attributes equal significance to the role of systolic and diastolic hypertension in contributing to cardiovascular morbidity (except in the elderly in whom systolic blood pressure and perhaps, more importantly pulse pressure are of greater relevance than diastolic pressure) [3], whereas the BHS attaches more importance to systolic blood pressure than diastolic pressure [2]. Both guidelines agree that when systolic or diastolic pressures fall into different categories, the higher category should be selected.

All guidelines recommend careful measurement of office or clinic blood pressure according to standard recommendations using validated devices and all accept that diagnostic decisions should only be based on repeated conventional measurements on several separate occasions and that consideration should be given to performing ABPM before making therapeutic decisions, which can have such far-reaching consequences.

### **3.2 Ambulatory blood pressure measurement**

The necessity for repeated conventional measurements inevitably leads the three guidelines to acknowledge the growing use and usefulness of ABPM in guiding treatment in hypertension. The use of self blood pressure measurement is also acknowledged, but it is accepted that evidence on the role of this technique is less extensive than for ABPM [1-3].

From the therapeutic standpoint there is agreement among all three guidelines that the main use of ABPM is to identify subjects with white coat hypertension in whom drug treatment may be deferred or avoided; the technique also permits detailed assessment of patients with resistant hypertension and those who may be experiencing hypertension due to excessive blood pressure lowering. Moreover, ABPM may give important information concerning the efficacy and duration of action of antihypertensive drugs in individual patients [1-3].

While all guidelines acknowledge that white coat hypertension is a manifestation of blood pressure variation they avoid making recommendations as to how patients with suspected white coat hypertension, or those with unusual variability of blood pressure, may be identified [1-3]. The three guidelines all subscribe to a serious misconception, namely, that average daytime blood pressures using ABPM are lower than clinic readings, whereas the reality is that though clinic blood pressures may be higher than daytime pressures in hypertensive subjects, in normotensive subjects clinic blood pressure is usually much the same as daytime blood pressure and is only greater when white coat hypertension is present [6]. There is no justification, therefore, for the BHS guideline to state that daytime blood pressure using ABPM are on average around 10 - 15 mmHg lower for systolic and 5 - 10 mmHg lower for diastolic pressure, and that daytime blood pressures can be adjusted by adding 12/7 mmHg to obtain the equivalent blood pressure measured by the conventional technique [2].

#### 4. Definitions of hypertension and goals of treatment

Given that the guidelines can satisfy the need for accurate blood pressure measurement by whatever means, their next imperative is to define three levels of blood pressure, which are crucial to therapeutic decision making:

- the levels of blood pressure at which to make the diagnosis of 'hypertension'
- the level at which intervention should be recommended
- the level to which blood pressure should be lowered by intervention

##### 4.1 Level of blood pressure for diagnosis

There is agreement among all guidelines that using conventional measurement, hypertension should be defined as a systolic blood pressure of 140 mmHg or greater and/or a diastolic blood pressure of 90 mmHg or greater in subjects who are not taking antihypertensive medication [1-3].

All guidelines also agree that when using ABPM or self-measurement of blood pressure the conventional levels must be lowered. JNC VI recommends that daytime or self-measured blood pressures above 135/85 mmHg and night-time blood pressures above

120/70 mmHg should be regarded as hypertensive [2]. BHS recommends adjusting ABPM daytime and self-measured blood pressures by 12/7 mmHg, which would give daytime or self-measured blood pressures of 128/83 as the upper limit of normal for making a diagnosis of hypertension, but the guideline goes on to introduce the concept of an 'Audit Standard' (defined as the minimum recommended level of blood pressure control), which defines hypertension as being present when the daytime or self-measured blood pressure is > 140/85 mmHg [2]. WHO/ISH regards a 24-h average or a self-measured blood pressure of 125/85 mmHg as being equivalent to a clinic blood pressure of 140/90 mmHg [1]. It needs to be emphasised that the 24-h average includes both day and night-time pressures and it is unclear how the guideline can reconcile this level with a self-measured blood pressure taken during the daytime period. In summary, the definition of hypertension using ABPM is an average daytime blood pressure > 135/85 (JNC VI [3]), 140/85 (BHS [2]) and 125/85 mmHg (WHO/ISH [1]), which in a statement means that using ABPM, the JNC VI [3] and BHS [2] recommendations for systolic blood pressure are 10 - 15 mmHg higher than WHO/ISH [1].

##### 4.2 Level of blood pressure for intervention

As to the level at which intervention should be initiated there is again consensus that this decision should be based not only on the level of blood pressure, but also on the overall risk profile of the individual patient [1-3]. As WHO/ISH describes it: 'The primary goal of treatment of the patient with high blood pressure is to achieve the maximum reduction in the total risk of cardiovascular morbidity and mortality.' [1]. Hence all guidelines agree that patients deemed to be at low or medium risk with clinic blood pressures of 140 - 179/90 - 109 mmHg with no more than two risk factors are observed for 3 - 12 months before a decision to institute antihypertensive medication is made, whereas patients deemed to be a high or very high risk because of the presence of three or more risk factors and/or diabetes mellitus and/or target organ involvement and/or other cardiovascular disease should be started on antihypertensive drugs even when their blood pressures are as low as 140/90 mmHg (WHO/ISH [1]), or 130/85 mmHg (JNC VI [3]). BHS recommends that all patients with average blood pressure of 140 - 159 or 90 - 99 mmHg should be offered antihypertensive drug treatment if complications are present, or there is evidence of target organ

**Table 1:** Recommended levels of normality for ABPM [6].

	Normal	Abnormal
Daytime	≤ 135/85	> 140/90
Night-time	≤ 120/70	> 125/75
24-h	≤ 130/80	> 135/85

The evidence supporting these demarcation levels are based on firm evidence from a number of studies: the evidence is not yet available to make recommendations for the intermediate pressure ranges between the 'normal' and 'abnormal' levels, nor for recommendations lower than those given. It must be emphasised that these levels are only a guide to 'normality' and that lower levels may taken as 'abnormal' in patients whose total risk factor profile is high and in whom there is concomitant disease, such as diabetes mellitus.

involvement, or if diabetes is present and/or the 10-year CHD risk is ≥ 15% despite institution of non-pharmacological advice [2]. There are, therefore, important differences between the guidelines as to when antihypertensive treatment should be commenced, which are that the WHO/ISH [1] and BHS [2] recommendations are 10/5 mmHg higher than JNC VI [3].

### 4.3 Goal levels of blood pressure

When it comes to deciding on the goals of treatment, there is more serious disagreement between the recommendations of BHS [2] and JNC IV [3], and WHO/ISH [1], but also between WHO/ISH and a body of international opinion [7-10].

Using conventional measurement, WHO/ISH recommends that antihypertensive treatment should restore blood pressure to 'normal' (< 130/85 mmHg), or to 'optimal' levels (< 120/80 mmHg) [1]. JNC VI recommends that systolic blood pressure should be brought and maintained below 140 mmHg and diastolic blood pressure below 90 mmHg; it adds that lower levels may be desirable, if tolerated, especially to prevent stroke, preserve renal function and to prevent heart failure [3]. BHS recommends bringing blood pressure below 140/85 mmHg for most patients and below 140/80 mmHg in diabetic patients [2]. It is evident, therefore, that there is a difference of at least 10 mmHg in the stated goal blood pressure for systolic blood pressure in non-diabetic subjects between JNC VI [3] and BHS [2], and WHO/ISH [1].

The divergence of opinion is even greater when blood pressure is measured using ABPM. WHO/ISH states that when ABPM measurements are used to evaluate

the efficacy of treatment, daytime values should be on average 10 - 15 mmHg lower for systolic and 5 - 10 mmHg lower for diastolic blood pressure [1]. It follows that if ABPM was used to measure blood pressure, 'normal' daytime blood pressure would be below 120/75 mmHg and 'optimal' blood pressure below 110/75 mmHg. The equivalent figures recommended by BHS are below 140/85 and below 130/80 mmHg, respectively [2]. JNC VI does not give 'normal' and 'optimal' levels for daytime ABPM, but recommends that normal daytime blood pressure should be below 135/85 mmHg [3]. In summary, using conventional measurement, JNC VI [3] and BHS [2] recommend levels that are 10 - 20/5 - 10 mmHg higher than WHO/ISH [1], and using average daytime pressure measured with ABPM, the JNC VI [3] and BHS recommendations [2] are 10 - 30/5 - 10 mmHg higher than WHO/ISH [1], depending on whether 'normal' or 'optimal' blood pressures are chosen.

The BHS [2] and JNC VI [3] recommendations for ABPM are in accordance with the generally accepted view that daytime blood pressures > 140/90 mmHg are probably abnormal, whereas those < 135/85 mmHg are probably normal, with blood pressures in the intermediate zone being considered in the overall context of individual cardiovascular risk (Table 1) [6-10].

Indeed the goal level of blood pressure recommended by the WHO/ISH guidelines led to an open protest on the internet, (signed by more than 800 family doctors, specialists, pharmacists and scientists from nearly 60 countries) to the Director-General of WHO, because if these goals were accepted internationally the burden of hypertension would have serious clinical and health-economic implications, especially in the developing world. Scientific support for this concern has been expressed previously in noting that using the WHO/ISH criteria for daytime blood pressures some 45% of the population of all ages and nearly 60% of elderly people would be classified as 'hypertensive' [7]. The evidence is not available to support the WHO/ISH recommendation that the lower blood pressure the better and a recent statistical analysis of the Framingham data challenges the WHO/ISH recommendations by showing that the concept that lower pressures imply lower risk is not valid [11]. For these reasons the WHO/ISH recommendations for goal pressures must be rejected until the results of on-going longitudinal studies are available.

## 5. Relating blood pressure level to the risk factor profile

The three guidelines produce slightly differing schema stratifying patients by absolute level of cardiovascular risk and illustrate how management and treatment is influenced by the presence of other risk factors, which may include age, gender, ethnicity, geographic region, smoking, lipids and lipoproteins, obesity, fibrinogen, alcohol, physical activity, hormone replacement therapy, socio-economic status, other risk factors including passive smoking, blood type, LDL particle size, apolipoproteins, plasma renin activity, blood homocysteine levels, blood uric acid levels, several common genetic polymorphisms, several infective agents and several psychological factors, the presence of concomitant diseases, pre-existing cardiovascular disease, renal disease and microalbuminuria, diabetes, hyperinsulinaemia and hyperglycaemia, and the presence of target organ disease, such as left ventricular hypertrophy [1-3]. Patients are thus divided into low, medium, high and very high-risk groups for each of which the management and treatment strategy varies. There is a consensus on the importance of viewing high blood pressure within the context of the total risk factor profile and on the need for a holistic approach to cardiovascular treatment, with, for example, antiplatelet agents and statins [1-3].

## 6. Principles of treatment

There is general agreement between the guidelines on the principles governing the use of antihypertensive drugs to lower blood pressure, independent of the choice of particular drugs [1-3]. Low doses of drugs should be used to initiate therapy. Appropriate drug combinations can maximise hypertensive efficacy while minimising side effects. Combinations with additive hypotensive effects may double the blood pressure reduction that might be expected with a single drug. The Hypertension Optimal Treatment (HOT) study, in which blood pressure was lowered to below 90 mmHg in over 90% of patients, has demonstrated that combination therapy was necessary in 70% of participants [12]. It is recommended that a small dose of a second drug be added rather than increasing the dose of the original drug, thus allowing both the first and second drugs to be used in the low dose range that is more likely to be free of side effects. In this context, fixed low-dose

combinations are being increasingly produced and are recommended. Changing to a different drug class altogether is recommended if there is very little response or poor tolerability to the first drug used, before increasing the dose of the first drug or adding a second drug. The use of long-acting drugs providing 24-h efficacy on a once-daily basis is preferred because such drugs improve adherence to therapy and they may provide greater protection against the risk of major cardiovascular events and the development of target-organ damage [1-3].

## 7. Factors influencing treatment

All guidelines acknowledge that the decision to initiate pharmacological treatment requires consideration of several factors (which include the degree of blood pressure elevation, the presence of target organ damage and the presence concomitant disease) that may be beneficially or adversely affected by the antihypertensive agent chosen. Other considerations in the selection of initial therapy include demographic characteristics, quality of life, cost and use of other drugs that may lead to drug interactions. Selection of an antihypertensive agent that also treats a co-existing disease will simplify therapeutic regimens and reduce costs. The cost of therapy may be a barrier to controlling high blood pressure and should be an important consideration in selecting antihypertensive medication. Non-generic newer drugs are usually more expensive than diuretics or  $\beta$ -blockers [1-3].

The efficacy of treatment may be affected by a number of conditions, which must be identified. Called 'pseudoresistance' by JNC VI [3] and 'spurious refractory hypertension' by WHO/ISH [1], this phenomenon may be due among other causes to white-coat hypertension, pseudohypertension in older patients, the use of an inappropriate cuff and non-adherence to therapy. Hypertension should be considered resistant if blood pressure cannot be reduced to below 140/90 mmHg in patients who are adhering to an adequate and appropriate triple-drug regimen that includes a diuretic, with all three drugs prescribed in near maximal doses.

JNC VI [3] and BHS [2] give separate consideration to the elderly among other special groups, such as children, women and pregnancy, whereas WHO/ISH regards the same principles of management as being applicable to the elderly as to the middle-aged and young [1]. Other factors highlighted in the guidelines

include hypertension in racial and ethnic minorities, age (children and the elderly), gender (women contemplating pregnancy, hypertension of pregnancy and the use of hormone medication either for contraception or replacement therapy), and the presence of co-existing cardiovascular and non-cardiovascular diseases [1-3].

## **8. Choice of antihypertensive drugs**

The guidelines all consider the six main drug classes used worldwide for blood pressure lowering treatment, namely diuretics,  $\beta$ -blockers, calcium antagonists, ACE inhibitors, angiotensin II antagonists and  $\alpha$ -blockers. Other less commonly prescribed drugs, such as reserpine, clonidine and methyldopa are also considered [1-3]. The differences between JNC VI and WHO/ISH in this regard have been previously reviewed [13].

All guidelines agree that there is no reliable or consistent evidence to indicate substantive differences between drug classes in their effects on blood pressure, but there are important differences in the side effect profiles of each class. The guidelines provide useful comparative tables listing the indications and complications for all classes of antihypertensive drugs as either compelling or possible [1-3].

The evidence available from randomised controlled trials on the effects of treatment on morbidity and mortality for the different classes of antihypertensive drugs is considered, but, as is emphasised in the BHS guidelines the answer to the question as to whether antihypertensive drugs that do not cause metabolic upset will be more beneficial than those that do, will have to await the results of large comparative trials, such as, the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [14] and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [15]. While there is a large body of data demonstrating the benefits of the older agents, such as, diuretics and  $\beta$ -blockers, there are fewer data available about calcium antagonists and ACE inhibitors, and less reliable data available about  $\alpha$ -blockers or the most recent classes of agents, such as, angiotensin II antagonists.

On the basis of outcome data from randomised controlled trials, all the guidelines recommend starting pharmacological therapy with diuretics and  $\beta$ -blockers for patients with uncomplicated

hypertension, but in elderly patients recent evidence suggests that diuretics and calcium antagonists should be the drugs of choice [1-3]. The trials of diuretic and  $\beta$ -blocker-based therapy in patients with hypertension provide evidence that treatment with these agents is not only effective for cardiovascular disease prevention but is also safe in terms of the overall risk of death from non-cardiovascular causes.

There is less evidence from trials in hypertensive patients about the effects of treatment on non-cardiovascular outcomes for the newer agents. However, there is no clear evidence of any excess mortality from non-cardiovascular causes with either ACE inhibitors or calcium antagonists. While there has been debate about possible adverse effects of calcium antagonists on cancer and bleeding risks, and beneficial effects of ACE inhibitors on cancer risk, these observations have been generated primarily by results from a few, potentially biased, non-randomised studies. A detailed review of the available evidence from observational studies and randomised trials does not provide clear evidence of an adverse effect of calcium antagonists on the risk of cancer or of bleeding, and these drugs have been shown to be efficient and safe in the Systolic Hypertension in Europe (SYST-EUR) trial in elderly subjects with systolic hypertension [16].

## **9. Concomitant cardiovascular drugs**

Both WHO/ISH [1] and BHS [2], which had the benefit of more recent studies than JNC VI [3], recommend using aspirin in patients with hypertension who are considered to be at risk for coronary artery disease and in whom there are no contraindications to aspirin. The BHS guideline elaborates more fully, detailing the use of aspirin for primary and secondary prevention [2].

All three guidelines recommend the concomitant prescribing of statins in hypertensive patients who have an elevated serum cholesterol, or who are considered to be at high risk for coronary heart disease [1-3]. Again the BHS guideline elaborates on the use of statins in primary and secondary prevention according to the Joint Recommendations of the British Hypertension Society, the British Cardiac Society, the British Diabetic Association and the British Hyperlipidaemia Association [2].

Detailed attention is given by all guidelines to the management of hypertension in diabetic patients, in

whom every effort must be made to achieve optimal glycaemic and blood pressure control [1-3].

## 10. Conclusions

The production of a guideline is a daunting task. Individual experts or groups of experts initiate the guideline process by expressing their view of the best use of a clinical process, be it a procedure or therapeutic intervention. These efforts are often rewarded with strident criticism. For example, a review of five guidelines - the earlier versions of JNC (JNC V), WHO/ISH and BHS guidelines and the Canadian and New Zealand guidelines - concluded that the same literature resulted in different conclusions from eminent experts, who were sometimes party to more than one set of conflicting guidelines and that if the New Zealand guidelines were taken as a standard, half of the patients with uncontrolled hypertension according to JNC V would be treated unnecessarily and more than 30% of those classified as having controlled hypertension by the Canadian guidelines would be denied beneficial treatment [17]. Indeed, the overall quality of practice guidelines developed by speciality societies has been found to be unsatisfactory [18].

In this review, we have confined ourselves to three guidelines (comprising some 80,000 words - equivalent to about 100 journal pages), from the many available across the world. An interesting feature of the review has been our difficulty in interpreting where there is harmony or divergence of opinion, not least because the design of each guideline is unique and none follows the flow of content, or theme of analysis of the other. The guidelines rarely acknowledge the existence of one another, let alone acknowledge the soundness or otherwise of their recommendations. A notable exception is the acceptance by WHO/ISH [1] of the JNC VI [3] classification of hypertension 'in order to reduce confusion and provide more consistent advice to clinicians around the world'. There are occasions when it is evident that one guideline has 'borrowed' from another without acknowledgement, an example being the use of compelling indications and contraindications for drug therapy, a concept introduced by JNC VI, [3] and elaborated by both WHO/ISH [1] and BHS [2]. In other instances a change in terminology may merely disguise an issue already covered in another guideline, an example being the use of the term 'spurious refractory hypertension' in WHO/ISH

[1] to list exactly the conditions originally described as 'pseudoresistance' in JNC VI [3]. In other words each guideline is making much the same point but has to appear original in doing so.

There is, therefore, a need for international harmony on guidelines. The guidelines reviewed have a common goal - to provide the best recommendations for managing hypertension - and though each refers to the potential for national and ethnic differences, the reality is that where these differences exist, they could easily be reconciled within a common guideline. Electronic communication should allow national bodies to come together to produce one international guideline that would provide those responsible for the management of hypertension with recommendations, which would be founded on the best evidence available and which could be applied globally. We would disagree, therefore, with a stated aspiration of WHO/ISH that 'it is hoped that national and regional experts will use them (the guidelines) as a basis for drawing up recommendations that are specifically designed for the management of patients in their own region.' [1].

The need for harmony is evident in the serious divergence of opinion between the guidelines in the level of blood pressure chosen for defining hypertension and the level to which blood pressure should be lowered by drugs. Firstly, for the definition of hypertension using ABPM the JNC VI [3] and BHS [2] recommendations for systolic blood pressure are 10 - 15 mmHg higher than WHO/ISH [1]. The greatest divergence of opinion between the guidelines concerns the levels to which blood pressure should be lowered; using conventional measurement JNC VI [3] and BHS [2] recommend levels that are 10 - 20/5 - 10 mmHg higher than WHO/ISH [1] depending on whether 'normal' or 'optimal' blood pressures are chosen, and using average daytime pressure measured with ABPM, the JNC VI [3] and BHS [2] recommendations are 10 - 30/5 - 10 mmHg higher than WHO/ISH [1] depending on whether 'normal' or 'optimal' blood pressures are chosen.

It is not for us to say which of the guidelines will be proved correct in time. We can say, however, that the evidence presently available does not support the low levels of blood pressure recommended by WHO/ISH [1]. Moreover, acceptance of these recommendations carries such serious and far-reaching clinical and financial consequences for medicine, that WHO/ISH must re-examine the evidence on which their

recommendations are based and if such a reappraisal shows the criticisms made in this review to be valid, the guideline should be withdrawn and revised.

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