Cardiovascular disease prevention depends on reduction of risk factors, including hypertension. Guidelines designed to improve management of hypertension are widely available. Their purpose is to assemble the available data from basic biomedical science, epidemiology, and clinical science in an accessible form with which physicians and patients can make reasoned decisions for individual cases. However, guidelines have been neither widely accepted, nor effectively implemented. We recommend a strategy for guideline preparation designed to yield a product more user friendly, accessible, and effective. Guideline recommendations and the evidence used to make them should be based on an explicit grading system. Relevant clinical as well as nonclinical factors must be considered. Moreover, because the goal of antihypertensive therapy is to prevent cardiovascular events, and the likelihood of such events is determined by multifactor or absolute risk assessment, risk, rather than level of blood pressure (BP), should determine the need for therapy. Similarly, the benefit of therapy must be assessed by reduction in cardiovascular disease morbidity and mortality.

Although guidelines for the management of blood pressure (BP) abound, there is substantial evidence that they frequently do not achieve their objectives. Many factors impede ready utilization of hypertension guidelines. Some physicians are unfamiliar with existing guidelines, and others are unconvinced of their validity. Elements related to the construction and content of guidelines may contribute to the gap between written word and clinical practice. Our goal is to suggest criteria that may make hypertension guidelines more clinically useful.

Elevated BP is, with rare exceptions, an asymptomatic condition rather than a disease. The goal of treating high BP is to prevent the devastating complications of untreated hypertension. However, as the association between level of BP, especially systolic, and risk of a complication is broadly continuous and graded, no single BP level defines the need for antihypertensive drug therapy. Treatment based on an individual’s multifactor risk for cardiovascular disease events will identify those with the greatest potential for clinical benefit. Moreover, as the goals of antihypertensive therapy are the prevention of stroke, heart attack, and renal insufficiency, it is by these outcomes that interventions must be judged. Although a lower BP is likely to provide vascular protection, comparative clinical trial data also suggest that the way in which a lower BP is achieved matters.

Guidelines can help practitioners provide more reproducible and improved care by intelligently packaging available knowledge. Proper guidelines are the scaffolding on which individual care is constructed. To accomplish this task, they need to be user friendly, flexible, and provide an explicit evidence base for recommendations.

Methodology for Guideline Construction

Disclosures

Participants in guideline committees generally have multiple commitments with the potential for intellectual or
financial conflicts. Authors of hypertension guidelines have not traditionally disclosed these potential conflicts. Recent examples include the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI),\(^1\) the World Health Organization–International Society of Hypertension (WHO–ISH),\(^2\) and the British Hypertension Society (BHS).\(^3\) Questions about potential undisclosed support from industry for the WHO–ISH guidelines encouraged the WHO to reevaluate several key questions in the original guidelines.\(^8\) Many hypertension experts receive support from the pharmaceutical industry for lectures, consulting, or research. Choudhry and colleagues\(^9\) report that 87% of authors of clinical practice guidelines had some form of interaction with the pharmaceutical industry, and 58% had received financial support to perform research. To maintain credibility, however, complete disclosure of potential conflicts is essential. Full disclosure, a preventive effort, precludes the possibility that some potential conflict may eventually be revealed and discredit both the guidelines and the profession (see Appendix).

**Format**

Although guidelines are designed to influence general clinical practice, hypertension guidelines, with the exception of the BHS executive summary published in the *BMJ*,\(^10\) appear to be written for other hypertension experts. They are too long to be useful to busy clinicians. Guidelines need to be brief, clear, and simple. In some, the complex scheme for defining BP categories precludes a clear and simple message for patients as well. A two-sided card summarizing the full guideline is likely to be more useful and accessible for busy clinicians than an extensive document. Simple algorithms for diagnostic procedures, risk stratification, and therapeutic options are often more accessible than lengthy descriptions.

**Grading of Evidence and Recommendations**

Neither the JNC VI\(^1\) nor the WHO–ISH\(^2\) guidelines graded levels of evidence for recommendations, although their intent was a complete and unbiased review of the literature. The BHS\(^3\) used the North of England Group criteria to grade the evidence for most recommendations.\(^10\) Indeed, the BHS guidelines required, for a grade A recommendation of pharmacologic treatment, support from a randomized trial or a meta-analysis of randomized trials with major disease end points rather than surrogate end points. Therefore, a randomized trial evaluating drug therapy with BP as the primary end point was not grade A evidence for drug therapy. The BHS authors required evidence that a particular pharmacologic agent reduced the risk of coronary disease or stroke in patients with high BP. Other forms of evidence, including findings from experimental studies of the mechanisms of disease and their pathophysiology are also important components of an evidence-based approach to clinical decision making.

Explicit description of evidence on which recommendations are based should be standard in hypertension guidelines. Several grading systems currently exist. The US Preventive Service Task Force,\(^11\) for instance, uses five grades for evidence (I, II-1, II-2, II-3, and III) and five for recommendations (A to E). Although the fine gradations of evidence distinguish among several types of nonrandomized trials (II-1 to II-3), the requirement for grade I evidence makes no mention of the size of the trial or the type of end points (major disease versus surrogate). The American College of Cardiology/American Heart Association (ACC/AHA; Table 1)\(^12\) grading system focuses on the importance of multiple large clinical trials. Implicitly, these grades recognize the importance of clinical rather than surrogate outcomes such as BP reduction. The grading system used for hypertension guidelines should focus not only on the quality of the study design but also on
health outcomes, such as stroke, congestive heart failure, and heart attack, that are important to patients.

Grade A evidence is the gold standard and should to the extent possible form the basis for treatment recommendations and decisions. Patients should be made aware of the supporting quality of evidence: for instance, which antihypertensive drugs have in randomized clinical trials been shown to reduce the devastating complications of hypertension and, among those, which drug has the optimal benefit–risk balance.

It should be noted that although clinical trials provide grade A evidence for therapeutics, population-based cohort studies provide grade A evidence for prognosis and are the basis for estimating absolute or multifactor risk.

**Recommendations: Who to Treat**

**Treatment Criteria** Hypertension has traditionally been defined by level of BP. Many treatment recommendations are still based mainly on BP thresholds categorized as optimal, normal, and high normal BP, or as increasing stages of hypertension. (e.g., JNC VI 1997 and WHO–ISH 1999). In contrast, randomized trials of antihypertensive therapy have shown that the relative association of BP lowering to stroke and heart attack risk reduction is consistent across a wide range of pressures. The absolute number of events prevented by BP reduction depends on the absolute or multifactor risk for cardiovascular disease (CVD) events of the study group. Absolute or multifactor risk is determined by all patient characteristics, not only level of BP, but also other risk factors including age, sex, diabetes, and dyslipidemia. The practical significance is demonstrated schematically (Fig. 1) by a sliding BP treatment threshold level, based on absolute CVD risk. As patients ascend the line of absolute CVD risk, the level of BP at which equally effective antihypertensive intervention will produce equal absolute benefit decreases.

The traditional division of guidelines into separate ones for hypertension, cholesterol, and diabetes, for instance, reflects the interests and traditions of academic, industry, and National Institutes of Health (NIH) groups. Therapies directed at specific measurable conditions quite naturally became the subject of separate guidelines. Patients, however, present with a variety of conditions. The number of treatable risk factors is now large and growing. Guidelines that define treatment thresholds on the basis of absolute or multifactor risk will best provide integrated information for practicing clinicians. The decision about whether someone should be treated will depend on the absolute level of risk; the decision about what treatments to use will depend on the presence of specific modifiable risk factors such as hypertension, hyperlipidemia, or smoking. In this model, recommended treatment thresholds will depend on BP level and absolute CVD risk. Other factors such as resources and patient preferences are also likely to be important.

**Determining Multifactor (or absolute, or total) CVD Risk in Individual Patients** To follow a risk-based strategy for BP treatment, a practical means for estimating multifactor risk is needed. High-risk patients (>15% to 20% 5-year CVD risk based on Framingham Heart Study risk equations) are those with a history of symptomatic CVD (including coronary disease, cerebrovascular disease including transient ischemic attack [TIA] and peripheral vascular disease), target organ damage (including nephropathy, significant left ventricular hypertrophy, and retinopathy), and possibly those with a definitive diagnosis.

**FIG. 1.** Blood pressure threshold for equal Rx benefit. Patient 1 – target organ disease or diabetes; Patient 2 – multiple risk factors; Patient 3 – only elevated BP.
The presence of other significant factors (e.g., family history, obesity, and activity of the renin angiotensin system) may also influence treatment decisions in borderline situations. Improved risk prediction equations may incorporate some of these in the future.

Table 2 provides individual examples of the 5-year risk of a cardiovascular event based on a number of clinical circumstances. In addition, both baseline multifactor risk and the impact of interventions to reduce individual risk factors are provided. The absolute benefit is then described in the final two columns, first as percent reduction in events, and as number needed to treat (NNT) to yield that benefit. Thus, for example, the greatest absolute benefit (and the lowest NNT) is realized by a smoking 60-year-old woman with low HDL and diabetes and a smoking 75-year-old man without diabetes with lower systolic BP (140 v 150 mm Hg). In contrast, the least efficient near-term (5-year) effect of risk factor intervention would be realized by a nonsmoking 45-year-old woman who has the highest level of systolic BP (160 mm Hg). The risk-based approach helps to highlight the individual components of risk and, therefore, the best strategies for reducing total coronary risk.

**Aids to Risk Classification** Several studies have indicated that physicians are unable to estimate risk accurately without assessment aids. Wide availability of computers and the Internet, however, makes individual risk assessment practicable. In fact, several risk assessment tools based on the Framingham Heart Study have been developed. These include paper-based charts†‡§ and electronic calculators. All CVD (including nonfatal myocardial infarction [MI], coronary death, new angina, fatal or nonfatal stroke or TIA, development of [congestive heart failure] or [peripheral vascular disease]) and all coronary heart disease (CHD) (including MI, CHD death, and angina—about 75% of all CVD) have been used as the predicted outcome in various risk assessment aids. The time frame for the estimated risk is typically either 5- or 10-year risk.

**Patient Preferences** Patient values and preferences need to be an integral part of evidence-based decisions. The clinician cannot presume full responsibility for determining what is in the best interest of their patients. Instead, a shared decision-making approach is advocated, in which patients are the experts on judging their own values. For this approach to work, patients first need to be properly informed about their condition, the treatment options, and the outcomes of treatments, including possible complications. Side effects that compromise functional capacity are of particular relevance. Trade-offs between short-term and long-term outcomes should be articulated. This strategy seems to work. A recent trial showed that use of a cardiovascular risk chart in patient education was associated with better BP control. Other research has suggested improved medication adherence when patients are involved in decisions regarding treatment choices. The value of various decision aids for patients has been reviewed through the Cochrane Collaboration.
Socioeconomic Factors Drug cost is a major consideration for hypertensive subjects. The choice of an antihypertensive drug should be based on its value to the patient and to society. There are marked differences in cost between classes of antihypertensive drugs and in some instances even between agents within a class. Guidelines ought to incorporate the role of cost and socioeconomic factors in making treatment decisions. If two antihypertensive agents offer a similar reduction in risk of cardiovascular complications, but they clearly differ in cost, the less expensive agent is more cost-effective and should be recommended. The unnecessary and unwarranted use of expensive agents precludes the use of these resources for other effective preventive efforts. Generic formulations of all antihypertensive medications should be recommended when they are available. Guidelines ought to acknowledge the role of socioeconomic factors in making treatment decisions.

Differences in Risk of CVD Complications Cardiovascular complications of hypertension differ in different populations. For example, stroke incidence is higher than acute MI in Asian populations, and in elderly white. Important differences exist between drug classes in their effect on the risks of stroke, acute MI, heart failure, and renal complications. Thus, population differences in types of CVD complications are other factors to consider both in the assessment of risk, and in the selection of drugs.

Clinical Recommendations: How to Treat The absolute level of risk and the other factors considered provide the basis for deciding whether and when intervention reduce BP may be indicated and, to some extent, help determine the components and objectives of that intervention.

Importance of Randomized Clinical Trials Crucial evidence to support therapeutic decisions derives from large, long-term, and properly designed clinical trials. The findings of these trials and of meta-analysis of such trials provide powerful support for the efficacy of individual treatments—at least for patients similar to those in the studied populations. The extent to which these findings can be extrapolated to other agents of the same class, or to persons not meeting eligibility criteria for the available studies is a matter of judgment.

Lifestyle Modifications Most lifestyle recommendations are based on small trials of limited duration with the outcome of BP rather than major disease end points with the result that most of these recommendations rest on grade B or C evidence.

Drug Selection We advocate the utilization of the specific antihypertensive drugs that have been proven to be beneficial in the large outcome trials. They should be used in the full dose shown to work. Prescription of untested drugs from the same drug class adds two levels of uncertainty. The untested drug may differ from the proven one in terms of some mechanisms of action or some aspect of safety. Moreover, equipotency of the available doses of the unproven drug and the tested doses of the proven cannot be assured. The unproven drug may be less beneficial.

Thresholds and Targets The BP level at which antihypertensive therapy should be introduced, and the goal of intervention have not been adequately addressed in clinical trials. The form and intensity of treatment, and the level to be sought, should be influenced by the magnitude of risk as well as other individual clinical and nonclinical factors. Grading of recommendations and evidence for thresholds and targets should also be included.

Comorbid Conditions as Compelling Indication for Specific Drugs Previous guidelines have traditionally identified comorbid conditions as compelling indications for specific drugs. Only treatments and conditions for which there is strong evidence of health benefits on major disease end points from large long-term trials should be included in these lists. The recommendations and the evidence should be graded here as well.

Guideline Review Before publication, Guidelines should be subject to review by a sample of end users.

Guideline Maintenance Updating the guidelines whenever sufficient data become available would be useful. The Internet offers new opportunities both to support routine upgrading of guidelines as well as their wide dissemination. The National Guideline Clearinghouse offers an important avenue through which guideline quality and availability may both be improved.

Strengths and Weaknesses of Guidelines Guidelines are unnecessary when there are no therapies or when clinical practice is uniform, precise, and universally implemented. They become valuable tools with the potential to improve care and patient outcomes in situations where the science is incomplete, where multiple therapies are available, and where uncertainty exists. Guidelines are a strategy to organize and make accessible the best evidence that derives from laboratory, clinical, and epidemiologic science to support clinical decision making for and with the individual patient.

Although quantitative data from clinical trials is essential to high-quality guidelines, extrapolation from these large and rigorously defined study populations to the individual patient is often difficult and inexact. Whereas the rationale for an absolute risk-based approach to patient management is strong, even this approach involves both theoretical and practical problems. The risk equations need
to function well across a variety of populations. Moreover, without some adaptation, a purely risk-based strategy will tend to focus on high-risk individuals, generally men and older adults, to the exclusion of women and younger adults. The traditional methods of assessing progress—awareness, treatment, and control of a single risk factor such as high BP—may no longer be the appropriate or optimal measures to assess progress toward containing or reducing cardiovascular risk. Aggressive risk-driven approaches to treatment that permits, for instance, mild elevations of systolic BP in low-risk persons, may appear as loss of progress from the narrow viewpoint of a single risk factor. But if this translates into more vigorous multidimensional intervention in high-risk subjects, it may, from a community perspective, represent major progress in reducing the overall burden of cardiovascular disease. In the US, this very problem may arise from well-meaning efforts of the health plan employer data and information set. In other countries, this may no longer be the appropriate or optimal measures.

Summary

The definition of hypertension and its management remains contentious, and practice varies widely. There is no optimal BP or multifactor CVD risk level at which BP-lowering treatment should be initiated in all situations. Nor is there a single treatment regimen appropriate for all populations and every patient. Clinical guidelines for the management of hypertension should accurately reflect that uncertainty and variation. We have attempted to identify key components of clinically useful guidelines for the management of hypertension. These generic elements should be acknowledged and explicitly addressed in the preparation of future guidelines.

References


Appendix: Potential Conflict

M.H. Alderman: Speaking honoraria from Brystol-Myers Squibb, Merck, Novartis Institutional and Pfizer; research grants from Merck, Bristol-Myers Squibb, Pfizer, and Aventis.

C.D. Furberg: Lecturing fees for Merck, Merck Frosst; member of Date Safety Monitoring Committee for trials sponsored by Pharmacia Corporation, Merck, and Wyeth.

R. Jackson: Occasional honoraria for presenting at pharmaceutical company-sponsored meetings on CVD risk.

J. Kostis: Grant/research support from BMS, Pfizer, Parke-Davis; consultant for BMS, Merck, Pfizer, Parke-Davis; speaker for BMS, Merck, Pfizer.


L.R. Ruilope: A consultant to Merck, Bristol-Myers Squibb, Glaxo-SmithKline, and Novartis; received funding for studies, seminars, and travel from these pharmaceutical companies.