2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension

World Health Organization, International Society of Hypertension Writing Group

Objective Hypertension is estimated to cause 4.5% of current global disease burden and is as prevalent in many developing countries, as in the developed world. Blood pressure-induced cardiovascular risk rises continuously across the whole blood pressure range. Countries vary widely in capacity for management of hypertension, but worldwide the majority of diagnosed hypertensives are inadequately controlled. This statement addresses the ascertainment of overall cardiovascular risk to establish thresholds for initiation and goals of treatment, appropriate treatment strategies for non-drug and drug therapies, and cost-effectiveness of treatment.

Conclusions Since publication of the WHO/ISH Guidelines for the Management of Hypertension in 1999, more evidence has become available to support a systolic blood pressure threshold of 140 mmHg for even 'low-risk' patients. In high-risk patients there is evidence for lower thresholds. Lifestyle modification is recommended for all individuals. There is evidence that specific agents have benefits for patients with particular compelling indications, and that monotherapy is inadequate for the majority of patients. For patients without a compelling indication for a particular drug class, on the basis of comparative trial data, availability, and cost, a low dose of diuretic should be considered for initiation of therapy. In most places a thiazide diuretic is the cheapest option and thus most cost effective, but for compelling indications where other classes provide additional benefits, even if more expensive, they may be more cost effective. In high-risk patients who attain large benefits from treatment, expensive drugs may be cost effective, but in low-risk patients treatment may not be cost-effective unless the drugs are cheap. *J Hypertens* 21:1983–1992 © 2003 Lippincott Williams & Wilkins.

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Introduction

Cardiovascular disease (CVD) is responsible for one-third of global deaths and is a leading and increasing contributor to the global disease burden [1]. Importantly, CVD is eminently preventable. In order to achieve significant reductions in the avoidable CVD burden, a combination of population-based and high-risk strategies is necessary. These strategies should target lifestyle-related risk factors such as unhealthy diet, physical inactivity and tobacco use, as well as the intermediate manifestations of these lifestyles; hypertension, glucose intolerance, and hyperlipidemia. In addition, strategies aimed at improving management of those already affected by CVD should be an integral component of a comprehensive approach for the prevention and control of CVD.

Hypertension is already a highly prevalent risk factor for CVD throughout the industrialized world. It is becoming an increasingly common health problem worldwide because of increasing longevity and prevalence of contributing factors such as obesity, physical inactivity and an unhealthy diet [2,3]. The current prevalence in many developing countries, particularly in urban societies, is already as high as those seen in developed countries [4,5]. Worldwide hypertension is estimated to cause 7.1 million premature deaths and 4.5% of the disease burden [64 million disability-adjusted life years (DALYs)]. The proportion of global disease burden attributable to hypertension is substantial [1], (Fig. 1).

Hypertension plays a major etiologic role in the development of cerebrovascular disease, ischemic heart disease, cardiac and renal failure. Treating hypertension has been associated with about a 40% reduction in the risk of stroke and about a 15% reduction in the risk of myocardial infarction [6]. Although the treatment of

Fig. 1
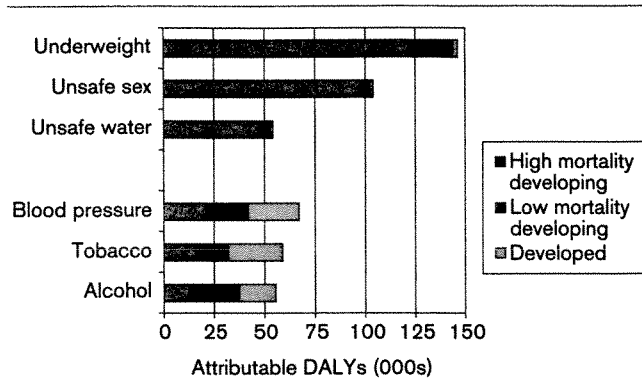
Global distribution of disease burden attributable to six major risk factors. DALYs, disability-adjusted life years (from WHO).

hypertension has been shown to prevent CVD and to extend and enhance life, hypertension remains inadequately managed everywhere [7–13]. In addition, hypertension often coexists with other cardiovascular risk factors, such as tobacco use, diabetes, hyperlipidemia and obesity, which compound the cardiovascular risk attributable to hypertension. Worldwide, these coexistent risk factors are inadequately addressed in patients with hypertension, resulting in high morbidity and mortality [7–9].

It has become increasingly evident that risks of stroke, ischemic heart disease and renal failure are not confined to a subset of the population with particularly high levels of blood pressure, but rather that risk occurs in a continuum, affecting even those with below average levels of blood pressure [14]. Globally, data indicate that about 62% of cerebrovascular disease and 49% of ischemic heart disease are attributable to

suboptimal blood pressure (systolic blood pressure > 115 mmHg) [1].

A global capacity assessment survey conducted by WHO shows that there is wide variation in the capacity for management of hypertension in various countries [15]. Of the 167 countries surveyed, national hypertension guidelines were not available in 61%, health professionals were not trained to manage hypertension in 45%, antihypertensives were not affordable in 25%, and basic equipment and drugs for the management of hypertension were not available in primary healthcare in 8 and 12% of countries, respectively.

This statement addresses the following issues: (1) the ascertainment of overall cardiovascular risk to establish both the thresholds for initiation of treatment and the goals of treatment for people with hypertension in general and for various subgroups; (2) the appropriate treatment strategies for both non-drug and drug therapies; and (3) the cost-effectiveness of drug treatment.

Assessment of risk

Decisions about the management of hypertensive patients should not only take blood pressure levels into account, but also the presence of other cardiovascular risk factors, target organ damage, and associated clinical conditions (Table 1). The risk stratification table from the 1999 WHO/ISH Guidelines [16] has been minimally amended to indicate three major risk categories with progressively increasing absolute likelihood of developing a major cardiovascular event (fatal and non-fatal stroke and myocardial infarction) within the next 10 years: (1) low risk – less than 15%; (2) medium risk – 15–20%; and (3) high risk – greater than 20% (Table 2). The simplicity of the method enables a rapid preliminary assessment of cardiovascular risk and pro-

Table 1   Factors influencing prognosis

Risk factors for cardiovascular disease	Target-organ damage (TOD)	Associated clinical conditions (ACC)

• Levels of systolic and diastolic blood pressure (grades 1–3)
• Males > 55 years
• *Females > 65 years*
• Smoking
• Total cholesterol > 6.1 mmol/l (240 mg/dl) or LDL-cholesterol > 4.0 mmol/l (160 mg/dl)*
• HDL-cholesterol M < 1.0, F < 1.2 mmol/l (< 40, < 45 mg/dl)
• History of cardiovascular disease in first-degree relatives before age 50
• Obesity, physical inactivity
	• Left ventricular hypertrophy (electrocardiogram or echocardiogram)
	• Microalbuminuria (20–300 mg/day)
	• Radiological or ultrasound evidence of extensive atherosclerotic plaque (aorta, carotid, coronary, iliac and femoral arteries)
	• Hypertensive retinopathy grade III or IV
		• Diabetes
		• Cerebrovascular disease
		  Ischemic stroke
		  Cerebral hemorrhage
		  Transient ischemic attack
		  Heart disease
		  Myocardial infarction
		  Angina
		  Coronary revascularization
		  Congestive heart failure
		• Renal disease
		  Plasma creatinine concentration: females > 1.4, males > 1.5 mg/dl (120, 133 μmol/l)
		  Albuminuria > 300 mg/day
		• Peripheral vascular disease

* Lower levels of total and low-density lipoprotein (LDL)-cholesterol are known to delineate increased risk but they were not used in the stratification table. HDL, high-density lipoprotein; M, male; F, female.

vides a flexible risk stratification system that can be customized to a range of practice settings with varying levels of resources. However, the categorical method used is less accurate than those using continuous variables, and this is a limitation of this risk stratification chart. Other techniques to assess the risk status of individual patients have been published [17–21] and may provide more accurate estimates. These risk charts use risk prediction equations derived from the Framingham heart study [19]. It should be noted that while the Framingham equations provide an acceptable prediction of risk in northern European populations, their predictive validity in other ethnic groups is less clear.

The risk charts and tables differ in the age categories used, duration of risk assessment and risk factor profiles used. The current New Zealand and Joint British charts [20,21] are similar in concept. While the former assess 5-year risk of all cardiovascular disease in eight discrete categories, the latter assess 10-year risk of coronary heart disease in three risk categories. Several recent studies have formally evaluated these charts for their comparative accuracy and patient preference [22].

Threshold for blood pressure lowering in hypertensive patients at low and medium risk

Before 1999, when the WHO/ISH Guidelines on Management of Hypertension were published [16], evidence of the benefits of initiating drug therapy to lower blood pressure at thresholds less than 160 mmHg systolic pressure was limited to observational data. While some evidence from early randomized, controlled trials (RCT) did support an intervention threshold of 90 mmHg diastolic blood pressure, almost all trials confirmed the benefits of treatment at levels of 160 mmHg systolic and 100 mmHg diastolic and above [6,23]. Both new clinical-trial evidence and observational data published since 1999 support the lowering of the systolic blood pressure threshold [24–28]. While there has been no new clinical trial evidence to support lowering thresholds to below 160 mmHg systolic and 90 mmHg diastolic in hypertensive patients at low risk,

observational data published since 1999 do support the lowering of the systolic threshold [24,25]. These observational data suggest that even low-risk patients with blood pressure ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic are likely to benefit from lower pressures. Although women are at lower absolute risk of cardiovascular disease for a given level of blood pressure, and RCT evidence includes a greater proportion of men than women, the treatment threshold should be the same in both men and women.

Absolute risk of cardiovascular disease for any given level of blood pressure rises with age, but only limited RCT evidence is currently available about the benefits of treating those over 80 years of age. For now, the treatment threshold should be unaffected by age at least up to the age of 80 years. Thereafter, judgement should be made on an individual basis and therapy should not be withdrawn from patients over 80 years of age. This is suggested by a meta-analysis of data from patients above 80 years of age in which the group on antihypertensive treatment showed a significant reduction in stroke incidence compared to the control group [29].

Thresholds for blood pressure lowering in hypertensive patients at high risk

Since 1999, several new trials in high-risk patients [26–28] have demonstrated morbidity and mortality benefits of lowering blood pressures from thresholds significantly below 160 mmHg systolic and/or 90 mmHg diastolic. These trials [26–28] support the hypothesis that additional blood pressure lowering in high-risk complicated patients, irrespective of initial blood pressure, results in a reduction in the number of cardiovascular events. Similarly other smaller trials, evaluating the effect of angiotensin II receptor blockers (ARBs) on the progression of nephropathy, also suggest that treatment for such patients should begin at lower thresholds [30–32]. As with the uncomplicated patients, this seems likely to be the case for older or female hypertensive patients.

Table 2 Stratification of risk to quantify prognosis

Other risk factors and disease history	Blood pressure (mmHg)		
	Grade 1 (SBP 140–159 or DBP 90–99)	Grade 2 (SBP 160–179 or DBP 100–109)	Grade 3 (SBP $\geq$ 180 or DBP $\geq$ 110)
I No other risk factors	Low risk	Medium risk	High risk
II 1–2 risk factors	Medium risk	Medium risk	High risk
III 3 or more risk factors, or TOD, or ACC	High risk	High risk	High risk

SBP, systolic blood pressure; DBP, diastolic blood pressure; TOD, target-organ damage; ACC, associated clinical conditions.

Targets for blood pressure lowering in hypertensives at low- and medium-risk

No new trial evidence about blood pressure targets in medium-risk hypertensive patients is available beyond that known in 1999 from the Hypertension Optimal Treatment (HOT) trial, which found optimal reduction of major cardiovascular events at about 139/83 mmHg [33]. However, HOT trial data suggested that most of the benefit was achieved by lowering the systolic blood pressure to about 150 mmHg and the diastolic blood pressure to about 90 mmHg in non-diabetic patients.

However, clinic- and population-based survey data continue to suggest that the lower the blood pressure levels achieved, the lower the cardiovascular event rate [34,35]. In those over the age of 55, the systolic level assumes greater importance [36], so the primary goal of therapy is to lower systolic blood pressure, and the pragmatic target of below140 mmHg is reaffirmed. This also has a strategic value because aiming at below 140 mmHg as a systolic blood pressure target makes it more likely that more patients will reach values at or slightly above 140 mmHg. There is no apparent reason to modify this target for women or older patients with uncomplicated hypertension.

Targets for blood pressure lowering in hypertensive patients at high risk

Effective blood pressure control has considerable and immediate benefits in patients with established cardio-vascular disease, diabetes, and renal insufficiency [26–28,30–32]. While several new trials [26–28] have shown clear cardiovascular benefits associated with lowering blood pressure significantly below 160/90 mmHg, none of these trials has attempted to identify the optimal blood pressure target for such patients. However, several trials have shown that, in patients with diabetes, reduction of diastolic blood pressure to about 80 mmHg and of systolic blood pressure to about 130 mmHg was accompanied by a further reduction in cardiovascular events or diabetes-related microvascular complications, as compared to patients with less stringent blood pressure control [37,38]. Based on clinical trial evidence, and also on extrapolation from epidemiological studies, a target of < 130/< 80 mmHg seems appropriate. There is no evidence of a need to modify these target blood pressures for female or older patients with hypertension.

Feasibility and resource implications

The blood pressure thresholds for treatment discussed above will result in as many as 25% of all adults – and more than 50% of those over the age of 65 – in some populations requiring antihypertensive therapy. Further, less than half of all hypertensive patients will attain the blood pressure targets recommended above with mono-therapy [33,39,40]. Most will need at least two anti-

hypertensive drugs, and as many as 30% of patients will need three or more drugs in combination to attain target blood pressure levels. Even in healthcare systems with generous resources, control of blood pressure is often unsatisfactory. One-half of all patients may drop out of care entirely within 1 year of diagnosis [40]. Of those who continue under medical supervision, only about half tend to adhere to their prescribed medication [41] and adherence is significantly influenced by drug choice, co-morbidity, and health services' utilization [41].

Further, numerous surveys have shown that about three-quarters of all patients with hypertension do not have optimal blood pressure control [10–12]. The reasons for this are complex, but include failure to detect hypertension; failure of patients or doctors to initiate and/or continue with treatment; incomplete adherence to treatment by patients and to guidelines by doctors; and lack of adequate therapy to control blood pressure [10–12,40,41].

The high prevalence of hypertension and the difficulties in attaining and maintaining blood pressure targets outlined above pose particular problems for healthcare systems that have very limited resources. The cost of drug therapy can be kept low by using the least expensive drugs and generic formulations. Priority for drug therapy where resources are limited should be given to all hypertensive patients with high and then medium cardiovascular risk (Table 2). In those with low cardiovascular risk (Table 2), the decision to treat or monitor without treatment should be based on estimated cardiovascular risk and patients' choice. While some patients in the blood pressure range of 140–159/90–99 mmHg have 10-year cardiovascular risk > 20% (Table 2), and should be treated, many patients are at low cardiovascular risk, albeit substantially higher than those with optimal BP. Low-risk patients have a correspondingly lower chance of gaining benefits from treatment (Table 3). These patients should be given lower priority for treatment when resources are limited.

As regards blood pressure targets, where resources are limited it should be remembered that recommendations are not based on robust clinical trial data. Furthermore,

Table 3   Chance of preventing a cardiovascular event during 5 years of antihypertensive treatment (5-year Number Needed to Treat) in patients with BP 140–159/90–99 mmHg

10-year cardiovascular risk	5-year Number Needed to Treat (assuming a BP reduction of 10/5 mmHg and relative risk reduction by treatment of 25%)
30%	27
20%	40
15%	53
10%	80
5%	160
2%	400

although based on a *post-hoc* analysis, the data from the HOT trial [33] suggest little disadvantage associated with a systolic blood pressure target of < 150 mmHg. This is therefore a reasonable 'fallback' target when resources are limited or adequate treatment fails to attain target values. It is also important to remember that even partial control of blood pressure provides substantial protection against cardiovascular complications.

It must be noted that in all parts of the world, population strategies to reduce blood pressure are very cost effective [1]. Legislative action and voluntary agreements with industry to ensure reduction of salt in processed food can lead to substantial reductions in salt intake, resulting in a significant shift of the population blood pressure levels to a more optimal distribution (Fig. 2). Therefore high-risk approaches to management of hypertension should always be complemented with population-wide approaches.

Treatment strategies
Value of lifestyle modifications
A variety of lifestyle modifications have been shown, in clinical trials, to lower BP [42] and to reduce the incidence of hypertension [43]. These include weight loss in the overweight [44], physical activity [45], moderation of alcohol intake [46], a diet with increased fresh fruit and vegetables and reduced saturated fat content [47], reduction of dietary sodium intake [47–49], and increased dietary potassium intake [50].

Fig. 2

Strategies aimed at diet and physical activity of the Population shifts the BP distribution of the whole population to the left
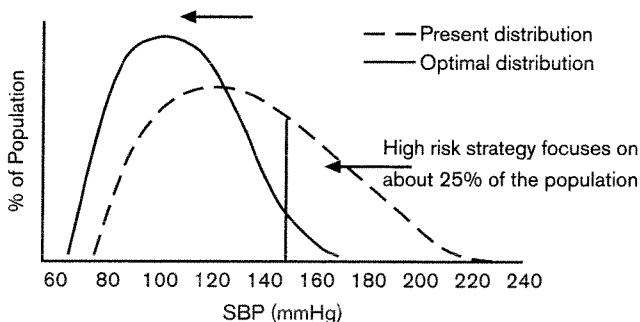
Distribution of systolic blood pressure in adults

Present and optimal systolic blood pressure distribution of the population. These smoothed curves portray the present distribution (interrupted lines) and the optimal distribution (continuous line) of systolic blood pressure in adults. A combination of population and high-risk strategies of blood pressure control is necessary to achieve the optimal blood pressure distribution. (From WHO).

Other lifestyle changes have not been found in multiple clinical trials to have a significant or lasting antihypertensive effect. These include calcium [51] and magnesium supplements [52], reduction in caffeine intake [53], and a variety of techniques designed to reduce stress [54].

The overall antihypertensive effect of effective lifestyle interventions varies with the patient's adherence to therapy. When adherence is optimal, systolic blood pressure has been reduced by more than 10 mmHg [47], but, in less-controlled clinical practice, more modest effects have been seen [42]. Trials to evaluate the effects of lifestyle interventions on levels of blood pressure have not been designed or powered to evaluate reductions in overall or cardiovascular mortality or morbidity. None the less, these lifestyle modifications are recommended for all patients with hypertension, since even small reductions in blood pressure are associated, in long-term, large-scale population studies, with a reduced risk of cardiovascular diseases [55].

In addition to their possible influence on blood pressure, observational studies have found that other lifestyle modifications, in particular cessation of smoking, reduce cardiovascular disease mortality [56]. Moreover, weight reduction, dietary manipulation and physical activity reduce the incidence of type 2 diabetes [57,58] and a low-saturated fat diet improves dyslipidemia [59].

Therefore, regardless of the level of blood pressure, all individuals should adopt appropriate lifestyle modifications. The protective effects of modifying lifestyle include a reduction in the incidence of hypertension, diabetes, and dyslipidemia, a reduction in mortality by cessation of smoking, and a lowering of blood pressure that, in itself, is likely to reduce cardiovascular morbidity and mortality. Furthermore, unlike drug therapy, which may cause adverse effects and reduce the quality of life in some patients, non-pharmacological therapy has no known harmful effects, improves the sense of well-being of the patient and is often less expensive.

Choice of initial drug therapy
Data from more than 20 RCTs have been published since 1967, comparing diuretics, β-blockers, and calcium channel blockers (CCBs) against placebo in hypertensive patients [6,23,60]. The data conclusively demonstrate reductions in both mortality and morbidity with these three drug classes. A meta-analysis of data from RCTs comparing two newer classes, i.e. angiotensin-converting enzyme inhibitors (ACEIs) and CCBs, against older classes, i.e. diuretics and β-blockers, in almost 75 000 hypertensive patients was published in 2000 [23]. For the endpoints of total cardiovascular mortality, the meta-analysis shows no significant convincing differences between drug classes or between

groups of old and new drugs. However, the available data do not exclude small to modest differences between different classes or drugs on specific fatal or non-fatal outcomes. For instance, in these comparative trials, ACEIs were associated with a lower incidence of coronary heart disease than CCBs, whereas CCBs were associated with a lower incidence of stroke than diuretic ± β-blockers [23].

Two other large trials have been published since the meta-analysis in 2000, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [61] and the Second Australian National Blood Pressure Study (ANBP2) [62]. In ALLHAT, over 42 000 hypertensives with an initial mean blood pressure of 146/84 (90% already receiving antihypertensive therapy) were randomly assigned to a diuretic (chlorthalidone), an α-blocker (doxazosin), an angiotensin-converting enzyme inhibitor (ACEI) (lisinopril), or a calcium channel blocker (CCB) (amlodipine). The alpha-blocker limb was prematurely stopped because of increased risk of the secondary endpoint of combined cardiovascular disease (to which heart failure was a major contributor), although there was no difference in coronary events or mortality [63].

The effects of the other two choices in ALLHAT compared to diuretic on the primary endpoint of fatal and non-fatal coronary disease were identical. Some differences were seen in protection against various secondary endpoints, in particular a higher risk of stroke with the ACEI in the Afro-American enrollees and a higher risk of heart failure with both ACEI and CCB. The lesser protection with the ACEI may be attributed in large part to the 3 mmHg lesser fall in systolic blood pressure provided by that agent compared to diuretic.

In the ANBP2 trial [62], a diuretic was compared to an ACEI in 6083 patients who were, in general, older but with fewer cardiovascular risk factors than the ALLHAT participants. Those assigned to an ACEI had fewer cardiovascular events, particularly the men, and, despite equal reductions of blood pressure, differences were of borderline statistical significance only when events subsequent to the first event were included.

In the LIFE trial [64], among patients with ECG-determined left ventricular hypertrophy, therapy based on an angiotensin II-receptor blocker (ARB) was more protective against a composite cardiovascular endpoint than therapy based on a β-blocker, despite very similar blood pressure reductions. In fact, the benefits were largely attributable to a protection against stroke and were particularly striking in the diabetic subgroup [65].

With the exception of ALLHAT, these trials typically included Caucasian patients in North America, Europe and Australasia, and in recent trials most participants had multiple cardiovascular risk factors. It is likely, however, that these relative risk reductions would apply to all patients with hypertension. In no trial were all enrollees maintained on the initial one drug to which they were assigned, and in most trials the majority received two or more drugs to achieve the predetermined goal of therapy. Despite these potential limitations, the available data conclusively document the value of antihypertensive therapy and suggest that the benefits are largely derived from their reduction in blood pressure.

For the majority of patients without a compelling indication for another class of drug, a low dose of a diuretic should be considered as the first choice of therapy on the basis of comparative trial data, availability and cost.

As previously noted, some patients need to have their blood pressure reduced to lower levels than previously recognized and will often require more than one drug [26,27,33,38,64]. However, pending results of trials such as the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [66], there are no comparative RCT data on mortality or morbidity to guide selection of optimal combinations. In the absence of such data, and since a diuretic should enhance the efficacy of all classes, a diuretic most often will be a component of combination therapy. A diuretic is often available in single tablets combined with other classes of drugs. Where they are no more expensive, such combined formulations may be preferable, since they have advantages in terms of compliance and BP-lowering efficacy. Other combinations of drugs with complementary actions may be appropriate for patients' needs.

Choice of drugs in different populations

Most drugs used to treat hypertension have also been evaluated for a number of specific indications. These include ACEIs, ARBs, β-blockers, CCBs, and diuretics in patients with concomitant diabetes, nephropathy, coronary and cerebrovascular disease, heart failure, and left ventricular hypertrophy. When studies have shown a greater reduction in various fatal and non-fatal major-disease endpoints with one or another type of drug class, that class is considered to have a compelling indication for its use (Table 4). The table indicates the clear and compelling indications for which certain drugs are preferred, based on greater reductions in either mortality or morbidity in large, long-term randomized trials.

In addition, comparisons have been made between the ability of different classes of drugs to regress left ventricular hypertrophy (LVH) and to slow the progres-

Table 4 Compelling indications for specific antihypertensive drugs

Compelling indications	Preferred drug	Reference for evidence	Primary endpoint
Elderly with isolated systolic hypertension	Diuretic	71	Stroke
	DHPCCB	72	Stroke
Renal disease			
Diabetic nephropathy type 1	ACEI	73	Progression of renal failure
Diabetic nephropathy type 2	ARB	30–32	Progression of renal failure
Non-diabetic nephropathy	ACEI	70	Progression of renal failure
Cardiac disease			
Post-MI	ACEI	26,74	Mortality
	β-blocker	75	Mortality
Left ventricular dysfunction	ACEI	76	Heart failure
	ACEI	76,77	Mortality
CHF (diuretics almost always included)	β-blocker	78	Mortality
	Spironolactone	79	Mortality
Left ventricular hypertrophy	ARB	64,65	CV morbidity and mortality
Cerebrovascular disease	ACEI + diuretic	27	Recurrent stroke
	Diuretic	28	Recurrent stroke

DHPCCB, dihydropyridine calcium channel-blocker; ACEI, angiotensin-converting inhibitor;
ARB, angiotensin receptor blocker; MI, myocardial infarction; CHF, congestive heart failure; CV, cardiovascular.

sion of nephropathies. For regression of LVH, CCBs, ACEIs and ARBs have been found to be more effective than β-blockers and diuretics [64,67,68]. In two comparative studies, a greater reduction in proteinuria has been found with initial therapy with ACEIs or ARBs than with other classes, in particular CCBs [31,69]. Multiple placebo-controlled trials have shown significant reductions in proteinuria and a slowing of progression of renal damage in both non-diabetic and type 1 diabetic nephropathies with ACEIs [70] and in type 2 diabetic nephropathy with ARBs [30–32]. Whether ACE inhibitors and ARBs have similar benefits on progression of renal damage as each other in type 1 and type 2 diabetic nephropathy remains untested, and whether they are superior to agents other than β-blockers [64] in terms of preventing major CV events in this situation is not as yet clear.

In addition to these compelling indications, certain drugs may logically be chosen for other reasons. Thus, when used as monotherapy, a diuretic or CCB may lower blood pressure more in Afro-American and older patients than an ACEI or a β-blocker [80,81] and an α-blocker

will relieve symptoms of prostatism [82]. Central α-agonists, (e.g. clonidine), or peripheral adrenergic blockers, (e.g. reserpine), may be used as inexpensive therapies in certain settings despite the absence of outcome data.

Specific drugs are either contraindicated or should be used with caution in certain conditions (Table 5). A few of the contraindications, such as use of ACEIs and ARBs in pregnancy are absolute, but most indicate that specific drugs could aggravate various conditions. The cautions indicate the greater propensity of certain drugs to induce side-effects, but do not preclude their use if patients have strong indications for those drugs and if the patients are carefully monitored.

Cost-effectiveness

Cost-effectiveness is determined by the relationship between the benefits obtained for the expenditure. The prevalence of a condition and the total cost of treating it in a specific setting, on the other hand, determine affordability. Because of limited resources, cost-effective treatment may not be affordable. The

Table 5 Contraindications and cautions for specific antihypertensive drugs

Drug	Contraindications	Drug	Cautions
ACEIs, ARBs	Pregnancy Bilateral renal artery stenosis Hyperkalemia	α-blockers Clonidine	CHF Withdrawal syndrome
β-blockers	High degree heart block Severe bradycardia < 50/min Obstructive airways disease Raynaud's	Methyldopa Reserpine	Hepatotoxicity Depression Active peptic ulcer
		CCBs	Congestive heart failure
Diuretics	Gout		

CCBs, calcium channel blockers; CHF, congestive heart failure.

two main determinants of cost-effectiveness are the cost of drug therapy and the initial cardiovascular risk of the patient.

An overview of the totality of trial evidence suggests that the major classes of antihypertensive drugs are largely equivalent in efficacy and safety. In most places, a diuretic is the cheapest option and is, therefore, most cost-effective. However, for certain compelling indications (Table 4), other classes will provide additional benefits; even if they are more expensive, they may be more cost-effective. For equivalent blood-pressure lowering within each class, the least expensive is the most cost-effective drug.

It should be noted that in very high-risk patients, who attain large benefits from treatment, treatment with multiple drugs, even those drugs that are expensive, might be cost-effective. Conversely, the treatment of patients with low risk may not be cost-effective unless the antihypertensive drugs used are inexpensive [83].

Acknowledgements

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Appendix 1

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Appendix 2 Potential conflicts of interest of contributors (refers to the period 1997–2002)

Bo Christensen: Pfizer, MSD, Bayer – payment for teaching in accordance with the Erich Rule of the Danish Medical Association. Norman Kaplan: Astra, Bayer – has served as a consultant to most pharmaceutical companies marketing antihypertensive drugs and has received funding for research, seminars and travel. Neil Poulter: Pfizer, Servier, BMS, MSD, AstraZeneca, Aventis, Bayer, Hoescht, Solvay, Takeda – has served as a consultant to most pharmaceutical companies marketing antihypertensive drugs, and has received funding for research, seminars and travel. Bruce Psaty: Wyeth, Ayerst – Member, Events Committee, HERS trial. Karl-Heinz Rahn: AstraZeneca, Boehringer, GlaxoWellcome – Steering Committee of several clinical trials, Clinical Event Committee. Sheldon G. Sheps: Pfizer, Astra, BMS, Merck – Speaker Bureaus, short-term consultancies. Judith A Whitworth: Merck – Editorial Board of ACE Reports; Pfizer – speaker at Pfizer meeting (2002).