

Chapter 22

Management of Hypertension and Dyslipidemia for Primary Prevention of Cardiovascular Disease

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INTRODUCTION

Despite declining rates of age-standardized cardiovascular disease (CVD) mortality in high-income countries (HICs) over the past three decades, CVD remains the leading cause of death worldwide (GBD 2013 Mortality and Causes of Death Collaborators 2013). The estimated global cost of CVD in 2010 was US\$863 billion, and this cost is expected to rise to US\$1,044 billion by 2030 (World Economic Forum 2011). A large proportion of global CVD deaths (about 80 percent) occur in low- and middle-income countries (LMICs). CVD deaths are declining in HICs mainly because of a significant reduction in coronary heart disease (CHD) and in stroke mortality. This decline is largely attributable to changes in population-level risk factors and specific blood pressure (BP) and cholesterol treatments (Björck and others 2015; Davies, Smeeth, and Grundy 2007; Lewsey and others 2015). In this chapter, we discuss antihypertensive and cholesterol-lowering therapies and use of aspirin for primary prevention of CVD. Lifestyle measures such as reductions in smoking and improvements in diet and physical activity are covered in chapter 4 (Roy and others 2017), chapter 5 (Bull and others 2017), and chapter 7 (Malik and Hu 2017) in this volume. Similarly, therapies

to treat ischemic heart disease, therapies to treat chronic heart failure, and therapies to reduce risk in patients with type 1 and type 2 diabetes are described, respectively, in chapter 8 (Dugani and others 2017), chapter 10 (Huffman and others 2017), and chapter 12 (Ali and others 2017) in this volume.

This chapter highlights new findings about the global burden of high BP and lipids. It discusses changing thresholds and targets for BP- and lipid-lowering therapies in the context of newly available evidence from randomized controlled trials (RCTs) and meta-analyses of RCTs. Attention is paid to the adverse effect on blood glucose associated with statin therapy and statin-induced diabetes, the role of ezetimibe in reducing low-density lipoprotein (LDL) cholesterol, and the uncertainty about the risks of aspirin in primary prevention of CVD. We also discuss the available evidence in the context of resource-poor settings and make recommendations.

BURDEN OF HIGH BLOOD PRESSURE

Globally, the population mean BP level has decreased marginally since 1980. From 1980 to 2008, global mean

age-adjusted systolic blood pressure (SBP) declined from 130.5 millimeters of mercury (mmHg, a measure of pressure) to 128.1 mmHg in men and from 127.2 to 124.4 mmHg in women (Danaei and others 2011). Similarly, the global age-adjusted prevalence of uncontrolled hypertension decreased to 29 percent from 33 percent in men and to 25 percent from 29 percent in women. Despite these changes, high BP has gone from being the fourth-highest risk factor in 1990, as quantified by attributable disability-adjusted life years (DALYs), to the highest risk factor in 2010 (Murray and others 2013). This increase is primarily due to population growth and aging, especially in LMICs, and the consequent rise in the number of people worldwide with uncontrolled hypertension, that is, SBP \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg. For example, the number of individuals with uncontrolled hypertension increased from 605 million to 978 million between 1980 and 2008 (Danaei and others 2011). SBP declined largely in HICs, while mean SBP rose in several regions, including East Africa, Oceania, and South and South-East Asia (Danaei and others 2011). Currently, high BP is one of the five leading risk factors of morbidity and mortality in all regions of the world, with the exception of Eastern Sub-Saharan Africa, Oceania, and Western Sub-Saharan Africa (Murray and others 2013).

Furthermore, raised BP (as opposed to hypertension) is among the leading global risk factors for mortality and is responsible for 9.4 million deaths annually (Lim and others 2012). It is independently attributable for at least 45 percent of deaths from ischemic heart disease (IHD) and 51 percent of deaths from stroke. Given this high burden and population aging, hypertension remains an issue of global concern. The estimated total direct and indirect cost of high BP in 2011 was US\$46.4 billion and is expected to reach US\$274 billion by 2030 (Mozaffarian and others 2015).

BURDEN OF HYPERCHOLESTEROLEMIA

Cholesterol is required to make hormones, vitamin D, and bile acids. Cholesterol also provides cell membrane support. Two kinds of lipoproteins carry cholesterol throughout the body: LDLs (known as bad cholesterol) and high-density lipoproteins (HDLs). A high LDL level often leads to a buildup of cholesterol in the walls of arteries. Globally, hypercholesterolemia, defined as total cholesterol \geq 190 milligrams per deciliter or \geq 5.0 millimoles per liter (mmol/L), causes an estimated 2.6 million deaths (4.5 percent of total deaths) and 29.7 million DALYs (2.0 percent of total DALYs) annually (Alwan 2011). More than one-fourth

(29 percent) of DALYs from IHD can be attributed to high total cholesterol, which is the second-leading physiological risk factor for IHD after high BP (Lim and others 2012). Physiologically, LDL is critical to the generation of atherosclerosis.

Mean total serum cholesterol decreased marginally between 1980 and 2008 globally, falling less than 0.1 mmol/L per decade in men and women (Farzadfar and others 2011). The mean age-adjusted total cholesterol level decreased from 4.72 to 4.64 mmol/L (95 percent confidence interval [CI] 4.51–4.76 mmol/L) for men and from 4.83 to 4.76 mmol/L (95 percent CI 4.62–4.91 mmol/L) for women between 1980 and 2008.

In 1990, total cholesterol was ranked fourteenth as a risk factor, as quantified by DALYs, and remained little changed in 2010, when it was ranked fifteenth (Lim and others 2012). The prevalence of elevated total cholesterol was highest in the World Health Organization (WHO) European Region (54 percent for both sexes), followed by the Americas (48 percent for both sexes); the lowest percentages were in the Africa and South-East Asia regions (23 percent and 30 percent, respectively) (Alwan 2011).

INTERVENTIONS FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

CVD encompasses a broad range of vascular conditions comprising IHD (including stable and unstable angina, nonfatal myocardial infarction, and coronary death); heart failure; cardiac arrest; ventricular arrhythmias; sudden cardiac death; rheumatic heart disease; transient ischemic attack; ischemic stroke; subarachnoid and intracerebral hemorrhage; abdominal aortic aneurysm; peripheral artery disease; and congenital heart disease. CHD accounts for the greatest proportion of CVD globally (Mozaffarian and others 2015). However, the incidence and prevalence of CHD vary greatly according to geographic region, gender, and ethnic background. After CHD, cerebrovascular disease or stroke is the second-highest cause of CVD mortality. We focus largely on these two conditions.

Over the past three to four decades, multiple longitudinal follow-up studies have provided valuable insights into the natural history and risk factors associated with the development of and prognosis for CVD (D'Agostino and others 2001; Klag and others 1993; Stamler, Stamler, and Neaton 1993; Vasan and others 2001). More recent data have updated and refined these findings (IOM 2010; Wong 2014). The results of these studies have laid a strong foundation for intervention studies and clinical trials aimed at primary prevention and have resulted in

the evolution of hypertension and cholesterol management guidelines. Primary prevention focuses mainly on the modification of risk factors through lifestyle changes, and pharmacological treatment aims to reduce the lifetime risk of developing CHD and stroke. Effective treatments are available to control most cases of hypertension and hypercholesterolemia and thereby to reduce consequent CVD. Although cost-effective interventions are available globally for reducing cardiovascular (CV) risk by addressing hypertension and hypercholesterolemia, there are major gaps in the implementation of current evidence-based interventions, particularly in resource-constrained settings. This section discusses the interventions targeting elevated BP and dyslipidemia (abnormal levels of lipids) for the primary prevention of CVD on the basis of current evidence.

Pharmacotherapy for Treatment of Hypertension

Four important risk factors of CVD—hypertension, dyslipidemia, diabetes, and smoking—are amenable to pharmacological treatment (WHO 2007). Robust RCT-based data show the benefits of lowering BP and LDL cholesterol and of controlling diabetes for preventing CVD (Antonakoudis and others 2007; Marso and others 2016; WHO 2007; Zinman and others 2015).

Meta-analyses have shown (1) that the amount of BP reduction is a more important determinant of the reduction in cardiovascular events than is the choice of drug class and (2) that a combination of at least two drugs is usually needed for long-term control, possibly making the initial choice of drug class less important (Blood Pressure Lowering Treatment Trialists' Collaboration 2000; Staessen and others 2001; Turnbull and Blood Pressure Lowering Treatment Trialists' Collaboration 2003). Currently, the BP of only about 32.5 percent of people treated for hypertension is controlled to targets; this proportion is even lower in low-income (12.7 percent) and lower-middle-income (9.9 percent) countries (Chow and others 2013). Yet lowering CVD risk in half of the people with uncontrolled hypertension, including those untreated and those inadequately treated, would avert an estimated 10 million CV events worldwide over 10 years (Angell, De Cock, and Frieden 2015).

Pharmacological Control of Blood Pressure

Several guidelines on hypertension management have been published since 2013. All current guidelines are consistent and unanimous in recommending nonpharmacological measures to lower BP (for example, weight loss, reduction in alcohol and salt intake) and to reduce CVD

risk (for example, smoking cessation), although there are some differences in the details of these recommendations (for example, reduction in caffeine consumption) (James and others 2014; NICE 2011; WHO 2013).

The thresholds for initiating therapy are largely consistent across sets of guidelines (table 22.1). The most common recommendation is a target of 140/90 mmHg with a few variations based on whether ambulatory BP measurement (ABPM) is used, the absolute estimated CV risk, and age group (James and others 2014; NICE 2011; WHO 2013). Similarly, targets are largely consistent (less than 140/90 mmHg), but again age range affects the recommended target in most guidelines. An exception is the Eighth Joint National Committee (JNC 8) recommendations, which are at odds with all other guidelines and which appear to lack sufficient support to merit compliance with them (James and others 2014).

Recent data from the SPRINT trial have given rise to the question of whether targets should fall further, but the atypical (although probably more robust) method of BP measurement used in that trial (automated unattended office blood pressure) probably exaggerates the benefits attributed to achieving SBP of less than 120 mmHg and more likely relates to SBP of less than 130 mmHg (SPRINT Research Group 2015). Meanwhile, several recent meta-analyses provide conflicting evidence on the merits of lowering BP targets (Thomopoulos, Parati, and Zanchetti 2014a, 2014b, 2014c, 2015; Weber and Lackland 2016; Zanchetti, Thomopoulos, and Parati 2015).

If nonpharmacological interventions have been insufficient to lower BP below the recommended thresholds, the agents recommended for lowering BP are largely restricted to seven drug classes—angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers, alpha blockers, calcium channel blockers, diuretics, and mineralocorticoid receptor antagonists—with variably strong RCT-based evidence to support their use (table 22.2). Recent statements and guidelines differ in their recommendations for the initial pharmacological treatment of hypertension and for which combinations of two drugs from distinct classes of drugs should be used. Some guidelines suggest initiating therapy with two drugs, particularly for persons with very high initial BP or high CV risk (AAFP 2014; Mancia and others 2013). However, initiating drugs from any of three drug classes—calcium channel blockers, diuretics, or renin-angiotensin system blockers—as first-line monotherapy or low-dose combinations of two drugs is more appropriate in low-resource settings for treating hypertension in general (Bronsert and others 2013).

Table 22.1 Thresholds for Initiating Therapy
Blood pressure (mmHg), except where noted

Indicator	NICE 2011	ESH, ESC 2013	ASH, ISH 2014	AHA, ACC, CDC 2013	2014 hypertension guidelines, JNC 8
Definition of hypertension	≥ 140/90; daytime ABPM (or home BP monitoring) of ≥ 135/85	≥ 140/90	≥ 140/90	≥ 140/90	Not addressed
Drug therapy in low-risk patients after nonpharmacological treatments	≥ 160/100 or daytime ABPM ≥ 150/95	≥ 140/90	≥ 140/90	≥ 140/90	In persons < age 60 years, ≥ 140/90; in persons > age 60 years, ≥ 150/90
Beta blockers as first-line drug	No (step 4)	Yes	No (step 4)	No (step 3)	No (step 4)
Diuretics	Chlorthalidone, indapamide	Thiazides, chlorthalidone, indapamide	Thiazides, chlorthalidone, indapamide	Thiazides	Thiazides, chlorthalidone, indapamide
Initiation of drug therapy with two drugs	Not mentioned	In patients with markedly elevated BP	≥ 160/100	≥ 160/100	≥ 160/100
BP targets	< 140/90; for persons > age 80 years, < 150/90	< 140/90; in patients < age 80 years, SBP of < 140; in fit patients, SBP of < 140; in patients > age 80 years, SBP of 140–150	< 140/90; in patients > age 80 years, < 150/90	< 140/90; lower targets may be appropriate in some patients, including the elderly	In persons < age 60 years, < 140/90; in persons > age 60 years, < 150/90
BP target in patients with diabetes mellitus	Not addressed	< 140/85	< 140/90	< 140/90; lower targets may be considered	< 140/90

Note: ABPM = ambulatory blood pressure measurement; ACC = American College of Cardiology; AHA = American Heart Association; ASH = American Society of Hypertension; BP = blood pressure; CDC = Centers for Disease Control and Prevention; ESC = European Society of Cardiology; ESH = European Society of Hypertension; ISH = International Society of Hypertension; JNC 8 = Eighth Joint National Committee; mmHg = millimeters of mercury, a measure of pressure; NICE = National Institute for Health and Care Excellence; SBP = systolic blood pressure.

Table 22.2 Pharmacological Agents Available as Generics for Controlling Hypertension and Reducing Cardiovascular Risk in Many Countries

Class	Common examples (alphabetic)
Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril, perindopril, ramipril
Angiotensin receptor blockers	Candesartan, losartan, olmesartan, telmisartan, valsartan
Calcium channel blockers	Amlodipine, cilnidipine, lercanidipine, nifedipine
Diuretics (thiazides and thiazide-like)	Bendroflumethiazide, chlorthalidone, chlorothiazide, hydrochlorothiazide, indapamide
Beta blockers	Atenolol, bisoprolol, carvedilol, metoprolol, nebivolol, propranolol
Mineralocorticoid receptor antagonists	Eplerenone, spironolactone
Alpha blockers	Doxazosin, prazosin
Others	Clonidine, hydralazine, methyl dopa, minoxidil, reserpine

Note: Preferred antihypertensive drugs in women of reproductive age with intention for conception and for pregnant and breastfeeding women are methyl dopa, nifedipine, and hydralazine.

Combination Therapy for Management of Hypertension

Population and trial-based evidence shows that the majority of patients with hypertension require at least two antihypertensive agents to control BP to currently recommended targets (figure 22.1).

Limited RCT-based evidence is available with which to evaluate the best combination of two antihypertensive agents, as reflected in the inconsistent recommendations of recent hypertension guidelines (table 22.3). However, most guidelines recommend at least one of the possible combinations of three classes: renin-angiotensin system blockers, calcium channel blockers, and diuretics (Weber and others 2014).

For several logical reasons, albeit not based on definitive RCT data, several sets of guidelines (James and others 2014; Mancia and others 2013) recommend initiating therapy with two drugs. The WHO list of essential medicines for antihypertensive drugs includes calcium channel blockers (amlodipine); beta blockers (atenolol, bisoprolol, carvedilol, metoprolol); ACE inhibitors (enalapril); hydrochlorothiazide; hydralazine; and methyldopa. The Sustainable Developmental Goals of the United Nations envisage making these essential medicines available in at least 80 percent of health care facilities by 2030. Similarly, when a combination of drugs is indicated, the use of single-pill combinations of drugs (frequently and often inaccurately described as fixed-dose combinations) is usually recommended in guidelines (AAFP 2014; WHO 2007) based on largely observational data and logic.

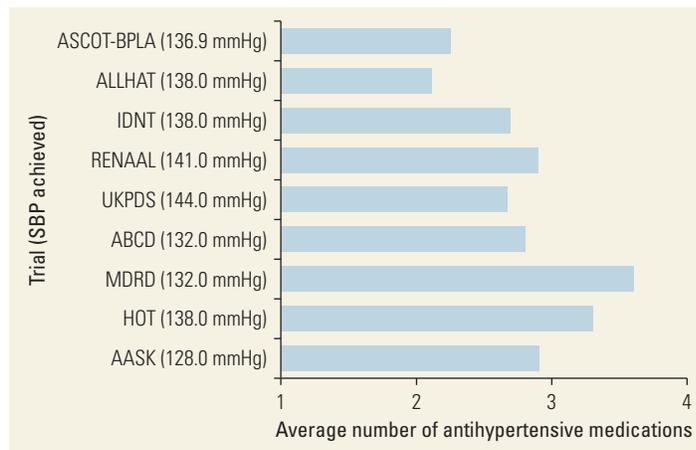
Antiplatelet Therapy

In the context of primary prevention, the RCT-based evidence regarding the level of CV risk at which aspirin (or other antiplatelet therapy) provides more good than harm remains uncertain. Trials with huge sample sizes and long-term follow-up are required to establish the evidence for aspirin in primary prevention. Halvorsen and others (2014) proposed a pragmatic step-wise approach for the use of aspirin in primary prevention. It includes assessing both short-term CV risk and bleeding risk simultaneously and then starting low-dose aspirin with caution if the CV risk is 10 percent to 20 percent. However, if there is no bleeding risk and the CV risk is more than 20 percent, aspirin should be started immediately. There is no need to start aspirin if the CV risk is less than 10 percent.

Pharmacotherapy for Lowering of Lipids

Extensive observational and experimental data have confirmed that elevated LDL cholesterol is not only an

Figure 22.1 Average Number of Antihypertensive Agents Used to Try to Reach Blood Pressure Goal in Several Hypertension Trials



Sources: Bakris 2004; Dahlöf and others 2005.

Note: AASK = African American Study of Kidney Disease and Hypertension; ABCD = Appropriate Blood Pressure Control in Diabetes trial; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-BPLA = Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm; HOT = Hypertension Optimal Treatment Study; IDNT = Irbesartan Diabetic Nephropathy Trial; MDRD = Modification of Diet in Renal Disease study; mmHg = millimeters of mercury, a unit of pressure; RENAAL = Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study; SBP = systolic blood pressure; UKPDS = U.K. Prospective Diabetes Study.

Table 22.3 Recommended Two-Drug Combinations of Antihypertensive Drugs

NICE	ESH, ESC 2013	ASH, ISH	JNC 8
A + C	A + C	African American	African American
	A + D	A + C	C + D
	C + D	A + D	
		C + D	
		Non-African American	Non-African American
		A + C	A + C
		A + D	A + D
			C + D

Note: A = ACE (angiotensin-converting enzyme) inhibitor or angiotensin receptor blocker; C = calcium channel blocker; D = diuretic (including thiazides or thiazide-like or type); ASH = American Society of Hypertension; ESC = European Society of Cardiology; ESH = European Society of Hypertension; ISH = International Society of Hypertension; JNC 8 = Eighth Joint National Committee; NICE = National Institute for Health and Care Excellence.

independent risk factor for the generation of atherosclerosis and major adverse CV events, but also the pivotal component of the atherosclerotic process (Libby 2000). Data are also compelling, but less consistent, in showing that low HDL cholesterol and high triglycerides are independent risk factors for the generation of major adverse CV events (Miller and others 2011; Toth 2005). Nevertheless, before the introduction of statin therapy

in the 1990s, the benefits of lipid-lowering therapy were controversial and the use of lipid-lowering agents was not part of routine practice, except possibly for persons with familial hypercholesterolemia. However, since publication of the results of the Scandinavian Simvastatin Survival Study trial in 1994, which confirmed the significant benefits of lowering lipids with simvastatin for all-cause mortality (Olsson and others 1994), credible doubts about the benefits of statin use have largely disappeared.

The benefits of various statins have been clearly shown in the context of secondary and primary prevention—for strokes and CHD among men and women, persons of young and old age, persons with diabetes and hypertension, and irrespective of baseline CV risk or starting lipid levels (Baigent and others 2010). High-dose statin use has been shown to reduce intravascular atherosclerotic load. Meta-analyses suggest that for every 1.0 mmol/L reduction in LDL cholesterol, there is a 22 percent reduction in CHD mortality and a 29 percent reduction in nonfatal myocardial infarction, and no level below which benefits are not apparent (Baigent and others 2010).

The following lipid-lowering agents for clinical management are currently available:

- Statins
- Ezetimibe
- Fibrates
- Cholesteryl ester transfer protein (CETP) inhibitors
- Fish oils
- Nicotinic acid
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

Statins constitute the overwhelming majority of lipid-lowering agents in use and hence are the focus of this review.

Statins

The enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is the rate-limiting enzyme for synthesizing cholesterol. HMG-CoA reductase inhibitors (statins) lower LDL cholesterol by, as their name suggests, intrahepatic inhibition of HMG-CoA reductase, which reduces cholesterol biosynthesis and leads to reduced blood levels of LDL cholesterol. Statins also induce small (about 5 percent) increases in serum HDL cholesterol levels and modest (about 20 percent) reductions in serum triglyceride levels.

Side effects (established in RCTs with more than 160,000 patients) include myopathy, rhabdomyolysis (breakdown of skeletal muscle), and increased rates of

new-onset diabetes. On the basis of observational data, statin use has also been linked with several other side effects, including myalgia, cognitive impairment, erectile dysfunction, and cataract—none of which has been confirmed in the extensive RCT database. Nevertheless, the link between statin use and side effects has had an unfavorable and inappropriate impact on the use of statins (Schaffer and others 2015). In a review of 39 statin trials, stopping the use of statins as a result of perceived side effects was associated with a significant increase in CV and cerebrovascular events and death rates (Gomez Sandoval, Braganza, and Daskalopoulou 2011).

Statins are currently recommended for all patients with primary lipid disorders, established CVD, or diabetes and, in the context of primary prevention, persons at high levels of estimated absolute risk. The definition of *high* varies across guidelines but has been altered recently in both U.S. and U.K. guidelines to 10-year risk of 7.5 percent and 10 percent, respectively (Rabar and others 2014; Stone and others 2014). All guidelines recommend healthy diets and lifestyles to improve lipid profiles and reduce CV risk. However, guidelines differ in their recommendations regarding the pivotal lipid measurement—LDL cholesterol (Stone and others 2014) or non-HDL cholesterol (Rabar and others 2014)—and whether a target lipid level is appropriate for the use of statins (Stone and others 2014).

Other Lipid-Lowering Agents

Results of individual trials or meta-analyses have undermined the use of fish oils (Kwak and others 2012), fibrates (Katsiki and others 2013; Shipman, Strange, and Ramachandran 2016), CETP inhibitors (Nicholls and others 2011), and nicotinic acid (Kones and Rumana 2015; Tuteja and Rader 2014) for the treatment of dyslipidemia to prevent major adverse CV events. Fibrates, nicotinic acid, and fish oils remain in use by lipid specialists, but on a relatively tenuous basis, for subgroups of patients in whom low HDL cholesterol and high triglycerides predominate (Dierkes, Luley, and Westphal 2007; Shearer, Savinova, and Harris 2012; Zhao and others 2004).

The significant beneficial effect of ezetimibe versus placebo when added to a statin has established this agent as the only evidence-based add-on therapy to statins that helps prevent major adverse CV events in the context of secondary prevention.

In the near future, the first PCSK9 inhibitor to be used in addition to routine high-dose statin therapy may become readily available for secondary prevention purposes (Stoekenbroek, Kastelein, and Huijgen 2015; Yang 2015). The role of these agents in primary prevention where statins are insufficient or not tolerated remains to be established.

Polypills

The most cost-effective way to prevent major adverse CV events is to acknowledge the frequent coexistence of major risk factors—which has a critical impact on absolute risk of a CV event—and therefore to target persons at highest estimated CV risk. Hence, risk assessment is a routine component of the management of risk factors such as raised BP and, particularly, lipid levels (NICE 2011; Räber and others 2015; Stone and others 2014).

Some of the major determinants of CV risk, such as age and sex, are not “treatable,” and lipid levels may not be abnormal in a person with mild hypertension. However, if the person is older (for example, 69 years) and a male with mild hypertension, the estimated risk levels may be sufficient (for example, 20 percent risk in the next 10 years) to merit intervention with a statin. Indeed, British guidance recommends using a statin for almost all persons with treated hypertension or diabetes. This routine use of two or more agents has given rise to increased interest in the use of multicomponent pills (polypills). These formulations of two or more agents have been shown to increase compliance and to thereby generate better control of individual risk factors (Castellano and others 2014).

The polypill concept first received attention in an article by Wald and Law (2003). This article proposed the idea of a population-based approach to preventing CVD by giving a single polypill that included six components to all middle-aged persons, with the expectation of preventing 80 percent of heart attacks. The proposed components were a statin, aspirin, folate, and three low doses of BP-lowering agents: a diuretic, an ACE inhibitor, and a beta blocker. Since then, several trials have yielded strong evidence that the use of polypills improves adherence (Webster and others 2013). Additionally, improved adherence was found to be directly associated with a reduction in targeted risk factors. None of these initial trials was designed to detect a difference in outcomes, and no differences in fatal or nonfatal events were demonstrated. In a nested case control analysis of 13,029 patients with IHD in the United Kingdom, however, combinations of drugs such as a statin, aspirin, and a beta blocker rather than single agents decreased mortality in patients with known CVD (Hippisley-Cox and Coupland 2005).

Screening

CVDs are characterized by the commonality and presence of a wide overlap of modifiable and nonmodifiable risk factors. This section focuses on screening for potentially modifiable CVD risk factors, subclinical disease in asymptomatic persons, and clinical disease. Novel or

emerging risk factors are not discussed. Screening approaches are guided by simplicity, wide availability, relatively low cost, applicability in resource-limited settings, noninvasiveness, and cost-effectiveness of selected tools; are supported by evidence when available; and are guided by detailed history and thorough clinical examinations whenever applicable.

Screening programs rely on several prerequisites. First, the condition being identified must be serious or lead to serious clinical outcomes; second, preclinical conditions should be common and asymptomatic; and third, early treatment of the condition detected through screening should have proven benefit (Wilson and Jungner 1968). Unfortunately, the inherent imperfection of clinical diagnostic tests introduces uncertainty into their interpretation. The magnitude of diagnostic uncertainty after any test may be quantified by information theory. However, understanding the theory of conditional probability (Bayes’s theorem) may not be necessary for applying a screening program effectively in asymptomatic individuals and in medical decision making.

Blood Pressure Screening

BP is a powerful, consistent, independent, and continuous risk factor for CVD and for cerebrovascular and renal diseases (Lewington and others 2002). Observational studies involving more than 1 million individuals have indicated that the number of deaths from CHD and stroke increases progressively and linearly from BP levels as low as 115 mmHg systolic and 75 mmHg diastolic upward in persons of all ages from 40 years to 89 years (Lewington and others 2002). Overall, mortality from CHD and stroke doubles for every 20 mmHg increase in systolic pressure and 10 mmHg increase in diastolic pressure (Franco, Oparil, and Carretero 2004). Correct measurement and interpretation of BP is therefore essential in the accurate diagnosis of hypertension. The use of properly calibrated and validated BP measurement devices with appropriate cuff sizes is essential.

Despite several limitations, office-based BP measurement (OBPM) is the most practical and frequently used method, but home (out-of-office) BP measurement (HBPM) and ABPM are increasingly used and are more valid measurement strategies (Breux-Shropshire and others 2005). The British National Institute for Health and Care Excellence (NICE) guidelines recommend the use of ABPM to confirm the diagnosis of hypertension if OBPM is elevated, and HBPM when ABPM is unavailable or unaffordable (Krause and others 2011). However, in low-resource settings, the feasible approach currently remains OBPM.

The difference between systolic and diastolic BP (pulse pressure) is a measure of arterial stiffness. Pulse pressure is a significant predictive factor for CVD and chronic kidney disease (Franklin and others 1999; Malone and Reddan 2010). Estimation of pulse pressure is a simple and practical determinant of CV risk, provided that BP measurements have followed standardized approaches.

Lipid Screening

Lipids are perfect targets for CV screening programs, given their central role in atherosclerotic disorders leading to CHD and ischemic stroke. Furthermore, the relationship between atherogenic lipid fractions and subfractions and CHD is continuous, graded, and powerful, with lower thresholds in persons with diabetes mellitus. However, the decision to treat lipids should be guided not by lipid levels alone, but also by the overall CV risk, which is primarily influenced by age, sex, hypertension, smoking, and family history of premature CHD (that is, first-degree male relative with CHD before age 55 years or first-degree female relative with CHD before age 65 years) (Grundy and others 2004).

The most cost-effective method for predicting CHD is measuring the ratio of total cholesterol to HDL cholesterol (Lemieux and others 2001). This test is widely available, well standardized, and comparatively inexpensive and requires no prior fasting. The ratio of total cholesterol to HDL cholesterol is also widely validated in most CHD risk scores. Non-HDL cholesterol, derived by subtracting HDL cholesterol from total cholesterol, is a better predictor than LDL cholesterol. LDL cholesterol is calculated using the Friedewald equation (LDL cholesterol = total cholesterol minus HDL minus triglycerides times 0.2), which applies only to the fasting state and is affected by

hypertriglyceridemia (Fukuyama and others 2008). Direct measurement of LDL cholesterol is technically more challenging and not sufficiently standardized. Besides, different subfractions of LDL cholesterol have different atherogenic potential but have not been shown to have sufficient incremental value to traditional risk factor assessments to merit routine adoption. It is doubtful whether the marginal improvements in CVD prediction gained by including combinations of apolipoprotein B and A1 justify the application of these tools for screening purposes (Di Angelantonio and others 2012). Triglycerides also appear to have relatively smaller predictive power once total cholesterol and HDL cholesterol have been measured and hence do not form a major component of most risk prediction models.

Various guidelines have given wide-ranging target age groups for lipid screening in men and women (NICE 2014; U.S. Preventive Services Task Force 2014). Overall, in low-resource settings, it appears rational to screen all persons for total cholesterol and HDL cholesterol in nonfasting state after age 40 years, but there is evidence to support screening of men and women who are at high risk of CHD starting at age 20 years. Repeat lipid measurements are recommended every three years in persons with atherogenic lipid profiles on prior measurement, but repeat measurement may be every five years in persons with initial lipid levels below the threshold for treatment.

Diabetes Mellitus, Prediabetes, and Gestational Diabetes Screening

Diabetes mellitus fulfills all of the requisites for screening. The methods of measuring glucose both for screening and diagnosing and for managing diabetes are identical. Blood glucose values span a continuum in any population, but there is a threshold above which the risk of potential adverse events is substantial. This threshold is discussed in chapter 12 in this volume (Ali and others 2017). Other methods of screening are listed in table 22.4.

To manage CVD in low-resource settings, the WHO has developed a cost-effective package based on expert opinion (WHO 2002). The proposed strategy starts with CV risk screening by nonphysician health care workers using hypertension as an entry point, with the additional option for using diabetes or smoking as an entry point. This pragmatic approach to managing CVD in low-resource settings reduces absolute CV risk by targeting multiple risk factors at the same time. The potential improvement in health outcomes is manifold compared with the identification and treatment of individual risk factors.

Table 22.4 Screening for Subclinical Cardiovascular Disease and Other Conditions

Method	Purpose
Echocardiography	To detect presence of left ventricular hypertrophy or valvular, myocardial, or pericardial diseases
Coronary artery calcium scanning	To quantify coronary artery calcium and thereby detect significant coronary artery disease
Intraarterial cerebral angiography, carotid duplex ultrasound, magnetic resonance angiography, computed tomography angiography	To measure carotid and coronary artery stenosis
Renal ultrasonography, duplex ultrasound	To test for renal artery stenosis

COST AND COST-EFFECTIVENESS OF INTERVENTIONS

Control of risk factors is paramount to the primary prevention of CVD and a major focus of primary health care. BP control has been a cornerstone of the reduction of stroke, IHD, and peripheral vascular disease for more than 50 years. Its cost-effectiveness is well accepted in all regions (Murray and others 2003; Rosendaal and others 2016; Rubinstein and others 2010; Wang and others 2001). Issues regarding the cost-effectiveness of such interventions have focused more recently on ways to improve the efficiency of identifying who most benefits from treatment, how to improve access to medications, how to improve adherence to medications, and how best to deliver medications. One trend has been to evaluate the overall risk of a patient compared with a single risk factor such as BP. Several studies have shown that it is more cost-effective to choose whom to treat for BP on the basis of the overall CVD risk rather than on the basis of BP or cholesterol level alone (Gaziano and others 2005; Lim and others 2007; Rosendaal and others 2016; Rubinstein and others 2010). Similar analyses have been done for cholesterol treatment, with guidelines in Europe, the United States, and the WHO moving to global risk-based assessments for recommendations regarding when to initiate statin-based medications. Work by Murray and others (2003) showed that efforts to lower cholesterol were cost-effective for persons at high cardiovascular risk (absolute risk more than 35 percent). Efforts to improve adherence to statins by writing longer prescriptions have also been shown to be cost saving and highly cost-effective in South Africa (Gaziano, Cho, and others 2015).

Another way to address the availability and affordability of medications for hypertension and dyslipidemia is to use a combination of generic CVD medications or a polypill for all adults with significant risk for CVD (Wald and Law 2003). This single intervention could reduce IHD events by as much as 50 percent. The potential advantages of a polypill for primary prevention include reduced need for dose titrations (Lonn and others 2010), improved adherence (Thom and others 2014), and availability of cheap generics in a single formulation.

Although several studies have shown reductions in risk factors such as BP and cholesterol (Yusuf and others 2009) and improvement in adherence in association with use of a polypill, no published study has shown reductions in IHD or stroke endpoints, although several studies are under way (Eguzo and Camazine 2013; Lonn and others 2010; Yusuf and others 2009). The use of combination therapy was shown to be cost-effective in LMICs for both primary and secondary prevention, with

the best cost-effectiveness ratio for secondary prevention (Gaziano and others 2005; Lim and others 2007).

Although preventive treatment is available in many LMICs, less than 10 percent of the population receives the recommended care for primary prevention (Mendis and others 2005). Major barriers to improving care include crowded primary health centers with long wait times, scarcity of professional health staff, and high costs of traditional screening programs. In a community study in Bangladesh, Guatemala, Mexico, and South Africa, shifting the responsibility for screening to community health workers (CHWs) using a simple nonlaboratory screening tool was shown to be equally effective when screening for CVD risk as using nurses or physicians (Gaziano, Abrahams-Gessel, Denman, and others 2015). CHWs using the same tool in a mobile phone application could save an estimated 15,000–110,000 lives in Guatemala, Mexico, or South Africa at very cost-effective ratios. Using CHWs to screen for CVD using a simple tool is much more cost-effective when the primary health system is prepared and equipped to treat persons identified as high risk (Gaziano, Abrahams-Gessel, Surka, and others 2015). In countries such as South Africa, where at least half of persons identified as high risk get medications, the screening intervention was cost saving. Even in settings such as Guatemala, where fewer than 5 percent of eligible patients receive statins, the intervention was still attractive at US\$565 per quality-adjusted life year (QALY). In Mexico, with initiation rates of 36 percent for hypertension medications and half that for statins, the incremental cost-effectiveness ratio for screening by CHWs was less than US\$4 per QALY.

In general, population-based interventions (such as policies to increase excise taxes on tobacco, salt, and trans-fatty acids) are highly cost-effective even in resource-constrained settings because the price elasticity is higher in such settings than in high-income regions (Gaziano and Pagidipati 2013). Multidrug regimens for secondary prevention of CVD are cost-effective even in LMICs, according to WHO standards (Gaziano and Pagidipati 2013). Application of mHealth (mobile health) strategies and involvement of CHWs in CVD screening are considered to be scalable and cost-effective in LMIC settings (Gaziano, Abrahams-Gessel, Surka, and others 2015).

RESEARCH AND DEVELOPMENT

Box 22.1 summarizes important research gaps in the area of BP management, as proposed in two recent sets of guidelines.

Box 22.1

Unresolved Issues in the Management of Hypertension Requiring Further Evidence from Randomized Controlled Trials

1. Do the use of home, ambulatory, and office blood pressure (BP) monitoring and BP variability add incremental value to routine clinic BP monitoring for optimizing hypertension management? If so, what levels of each of these measures should be used as thresholds and targets?
2. At what BP levels (BP thresholds) should antihypertensive agents be initiated (if at all) for various subgroups of patients, including young persons (younger than age 40 years), elderly persons (older than age 65 years), persons with white-coat hypertension (high only in medical settings), and persons at relatively low CV risk? The latter subgroup has recently been investigated in the HOPE-3 trial (Lonn and others 2016).
3. How far should BP be lowered (targets) in the general management of hypertension and in specific subgroups? The SPRINT trial (Wright and others 2015) has addressed this question in high-risk hypertensive patients, but the measurement techniques used in the trial make direct translation of results into clinical practice difficult. Meanwhile, meta-analyses of this question have generated conflicting results (Brunström and Carlberg 2016; Ettehad and others 2016; Xie and others 2016).
4. What are the best two-, three-, and four-drug combinations for optimizing BP management for particular ethnic groups? The PATHWAY-2 study (Williams and others 2015) has provided robust evidence that spironolactone is the best fourth-line agent for resistant hypertension (after a renin-angiotensin-system blocker, a calcium channel blocker, and a diuretic have been shown to be inadequate). No data are available to support the best combinations of antihypertensives in each of the major ethnic groups.
5. Beyond the use of spironolactone as a fourth-line agent—for which an alpha blocker and a beta blocker are recommended add-on drugs (NICE 2011)—various devices and interventions, including renal denervation, are undergoing investigation, but no such interventions are currently established.
6. How is BP best measured for patients with atrial fibrillation?
7. How is CV risk best assessed for patients with elevated BP?
8. Can target organ damage be used reliably as a surrogate outcome in trials of hypertension management?
9. Is it possible or reasonable to evaluate lifestyle interventions to lower BP and thereby reduce major adverse CV events in randomized controlled trials?

Source: Based on a summary of recent U.K. and European guidelines (Mancia and others 2013; NICE 2011).

In the area of lipids, given the outstanding benefits associated with the use of statins, future research and development should focus on what can be done for persons who are intolerant of statins and who require additional therapy when statins are inadequate to provide optimal control of dyslipidemia. While modest, albeit significant, benefits have been associated with the addition of ezetimibe to statin therapy (Cannon and others 2015), the results of trials of PCSK9 inhibitors are keenly awaited in this regard because of their large beneficial impact on LDL reduction.

RECOMMENDATIONS FOR RESOURCE-POOR SETTINGS

The World Heart Federation has outlined key strategies for controlling hypertension (Adler and others 2015). A key challenge in the management of hypertension and dyslipidemia is that both conditions are largely asymptomatic for a prolonged period leading up to a cardiovascular event. Therefore, to prevent primary CVD events, an effective screening program is crucial, although screening should be undertaken only when treatment is possible.

Screening for hypertension is simple and costs relatively little. At a minimum, patients attending clinics for any reason should be screened at least once a year (opportunistic screening); screening can also be undertaken opportunistically as part of antenatal care, in the workplace, or in mobile units specifically set up for the purpose. To avoid false positives, screening should ideally involve 24-hour or home-based methods, but in many low-resource settings these methods are not feasible. In low-resource settings, the minimum screening should be serial paired BP readings. In these cases, if the first measurement is normal, a second reading is unnecessary. If the difference between the two readings is greater than 10 mmHg, a third reading should be made and the mean of the last two used. In cases in which the average is greater than 160 mmHg, the patient should be treated immediately (Adler and others 2015). If the patient presents with other extreme conditions (for example, pain), caution should be used in interpreting high BP.

Cholesterol screening is more difficult because it requires the drawing of a blood sample for biochemical evaluation. Given the escalation of CV risk factors, especially after age 35 in men and age 45 in women, screening for lipid disorders is recommended in these groups. However, young men and women should be screened if they are at increased risk of CHD. In low-resource settings, screening should follow a cost-effective, benefit-based, tailored treatment strategy of lowering total cardiovascular risk.

Another long-term barrier to optimizing CVD prevention, given the asymptomatic nature of hypertension and dyslipidemia, is medication adherence. Health care professionals and patients need to understand that BP and cholesterol medications are nearly always required for life and generally should be continued even after achieving target BP and cholesterol levels. Health care professionals and patients need to be educated on nonpharmacological (including heart-healthy diet, weight control, moderate alcohol use, and physical activity) and locally appropriate pharmacological BP control methods. Health care professionals need to be educated on guidelines and, where appropriate, be trained in decision support systems (Anchala and others 2012).

CONCLUSIONS

Elevated BP and total cholesterol levels are leading physiological risk factors for IHD and stroke. Although proven, cost-effective, and acceptable medical and lifestyle interventions exist to prevent and treat hypertension and dyslipidemia, uptake is still unacceptably low in all

countries, particularly in resource-poor settings. Guidelines for BP control recommend nonpharmacological measures to lower BP (including salt reduction and weight loss) and to reduce overall CVD risk (including smoking cessation and cholesterol lowering).

The pharmacological interventions recommended for lowering BP include seven drug classes—ACE inhibitors, angiotensin-receptor blockers, alpha blockers, beta blockers, calcium channel blockers, diuretics, and mineralocorticoid receptor antagonists. Although different guidelines make varying recommendations, lowering BP is most important; the means by which this is accomplished are secondary. Many guidelines suggest initiating therapy with two drugs, particularly for persons with high initial BP or high overall risk; this guideline is of particular importance in low-resource settings where it may be difficult to get patients to return for follow-up appointments.

Initiating pharmacological interventions in lipid management should be based not only on the absolute level of lipids but also on the level of total CV risk. It is important to adopt a more cost-effective, benefit-based treatment strategy of lowering total CV risk that is tailored to the individual. Pharmacological interventions recommended for high cholesterol include statins that are off patent, available in generic forms, effective, and safe (Macedo and others 2014).

NOTES

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World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US\$1,045 or less
- Middle-income countries (MICs) are subdivided:
 - (a) lower-middle-income = US\$1,046 to US\$4,125
 - (b) upper-middle-income (UMICs) = US\$4,126 to US\$12,745
- High-income countries (HICs) = US\$12,746 or more.

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