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DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

7 – Antihypertensive therapies

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> *"On the basis of current evidence, it can be recommended that blood pressure is lowered at least below 140/90 mm Hg in all hypertensive patients and that lower values be pursued if tolerated."*
>
> *2007 Guidelines of the European Societies of Hypertension and Cardiology*[1]
>
> *"Comprehensive hypertension control strategies might address overall cardiovascular disease risk rather than an exclusive focus on blood pressure."*
>
> *Kotchen 2010*[2]

The blood pressure (BP) is the product of the cardiac output (CO) and the peripheral vascular resistance (PVR): $BP = CO \times PVR$

Hence, as shown in Fig. 7-1, all antihypertensive drugs must act either by reducing the CO (β-blockers and diuretics) or the PVR (all the others, and perhaps a late effect of diuretics and β-blockade). Diuretics act chiefly by volume depletion, thereby reducing the CO, and also as indirect vasodilators. Most of the antihypertensive drugs, including diuretics, β-blockers, α-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), and calcium channel blockers (CCBs), but excluding the centrally active agents and ganglion blockers, have other uses and are therefore also discussed elsewhere in this book. Although hypertension is easy to treat, it is often difficult to manage optimally, as most patients will require lifestyle modification plus combination therapy with two, three, or more antihypertensive drugs of different mechanisms of action (Table 7-1). Asymptomatic patients often will not stay on therapy, particularly if it makes them feel weak, sleepy, forgetful, or impotent. In this regard, the ACE inhibitors and especially the ARBs seem very well tolerated. Fortunately, with most currently used modern antihypertensive agents, the quality of life (QOL) improves rather than deteriorates and cognitive function is preserved.[3],[4] A small proportion of patients have resistant hypertension (RH) that only responds to multiple therapies after excluding poor adherence or secondary cause. It must constantly be considered that hypertension is usually multifactorial in cause, that different drugs act on different mechanisms (Fig. 7-2), and that the aim is to match the drugs to the patient. In the future such matching should be much more efficient, especially if genetic profiling ever becomes feasible.[5]

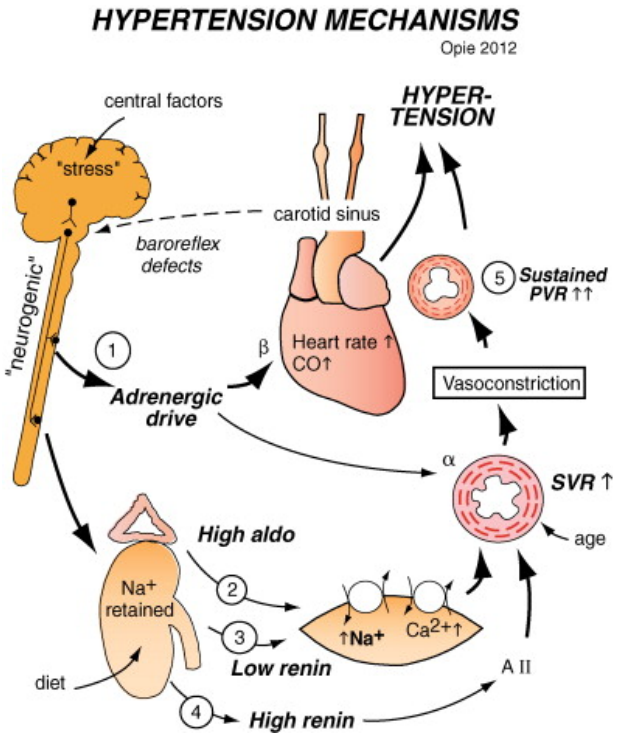

Figure 7-1 Multifactorial origin of hypertension. Note major mechanisms: **1,** Increased adrenergic drive as found especially in younger hypertensives. **2-4,** Renal-adrenal mechanisms, including (**2** and **3**) low renin hypertension as in those with inherently higher aldosterone (aldo) levels or renal sodium retention (sodium epithelial channel). **4,** High-renin hypertension, as in renal dysfunction. **5,** Increased systemic vascular resistance (SVR) or peripheral vascular resistance (PVR), the end result of all of these mechanisms. *CO,* cardiac output.
(Figure © L.H. Opie, 2012.)

Table 7-1 -- Specifics About Additional Oral Antihypertensives

Drug	Registered Trade Name (in US)	Dose Range (mg/day)	Doses/Day
α-Blockers			
Prazosin	Minipress	2-20	2
Terazosin	Hytrin	1-20	1
Doxazosin	Cardura XL	1-16	1
Direct Vasodilators			
Hydralazine	Apresoline	50-200	2-3
Minoxidil	Loniten	5-40	1
Nonreceptor Adrenergic Inhibitors			
Reserpine	Serpasil	0.05-0.25	1
Rauwolfia root	Raudixin	50-100	1
Centrally Active			
Methyldopa	Aldomet	500-1500	2
Clonidine	Catapres	0.5-1.5	2-3
Clonidine transdermal	Catapres-TTX	1 patch	(Once weekly)
Guanabenz	Wytensin	8-64	2
Guanfacine	Tenex	1-3	1
Peripheral			
Guanethidine	Ismelin	10-150	1
Guanadrel	Hylorel	10-75	2

For diuretics, see Tables 4-3 and 4-5; β-blockers, see Table 1-3; combined α- and β-blockers, see Table 1-3; angiotensin-converting enzyme inhibitors, see Table 5-4; angiotensin receptor blockers, see Table 5-12; calcium antagonists (calcium channel blockers), see Tables 3-2 and 3-5.

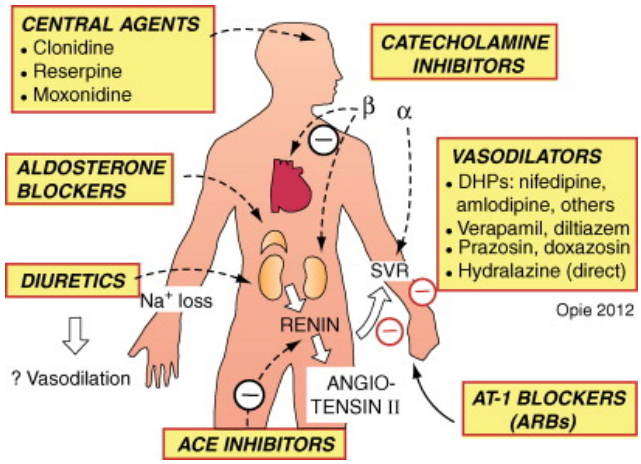

Figure 7-2 Different types of antihypertensive agents act at different sites. Because hypertension is frequently multifactorial in origin, it may be difficult to find the ideal drug for a given patient and drug combinations are often used. *ACE,* Angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *AT-1,* angiotensin II subtype 1; *DHP,* dihydropyridine; *SVR,* systemic vascular resistance.
(Figure © L.H. Opie, 2012.)

Principles of treatment

Despite the fact that hypertension remains the most common diagnosis of patients seen in practitioners' offices[6] and the most common indication for prescription drugs,[7] it remains poorly controlled in all developed nations.[8] The reasons are multiple, perhaps the most obvious being its nature as a common, incurable, persistent, but usually asymptomatic disease with a treatment that provides no obvious short-term benefit. The complications of hypertension (Fig. 7-3) will not change, but closer attention to the principles to be described could markedly improve its control. As will be noted, prevention should be our primary goal but, lacking that, effective treatment can slow if not stop its insidious damage to the heart, brain, and kidneys.

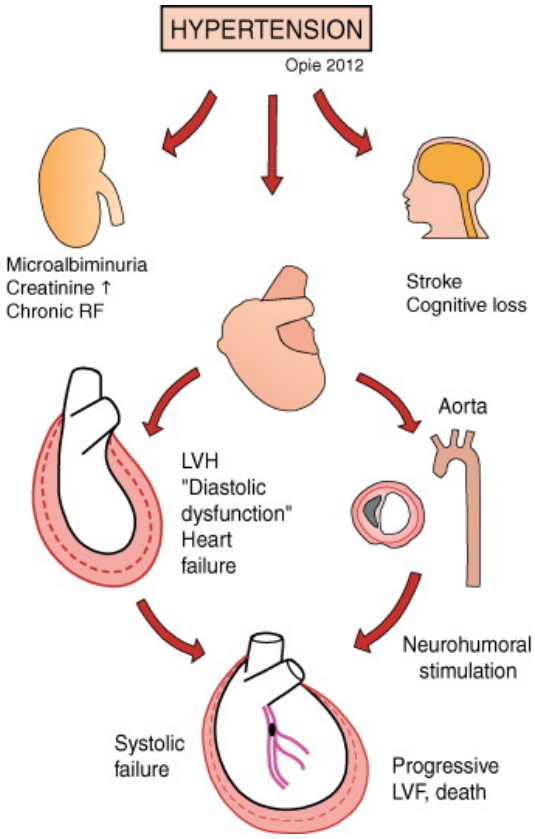

Figure 7-3 Hypertension and cardiovascular complications. Cardiac complications are the most common cause of death. Hypertension also kills by renal failure and cerebral complications such as stroke. The two major cardiovascular events are left ventricular hypertrophy (LVH) and promotion of aortic and coronary artery disease. LVH often first manifests symptoms as diastolic dysfunction, then progresses to systolic left ventricular failure (LVF) which, if allowed to progress, can lead to death. *RF,* renal failure.
(Figure © L.H. Opie, 2012.)

Ascertainment of hypertension

BP constantly changes over short and long intervals. Therefore more than a few measurements in the office are almost always needed to establish its level and range. Mean office readings are often recommended.[9] A novel proposal is that the maximum office systolic blood pressure (SBP), often ascribed to anxiety and thus ignored, is a strong predictor of cardiovascular events, independently of the mean SBP level.[10] For multiple reasons, out-of-office readings provide more accurate assessment of the future course of the disease.[11] The prognostic superiority of out-of-office readings largely reflects the larger number of readings taken, both by machine and by self-measured home readings. Despite the many different and increasingly sophisticated ways of obtaining the “true” BP, the office BP remains standard, and repeated values of *greater than* 140/90 mm Hg are taken as evidence of hypertension and major guidelines recommend lowering SBP to less than 140 mm Hg in all hypertensive patients. But how valid is this cut-off point?

There are two relevant trials. The MRC mild hypertension trial included very low-risk hypertensive patients (8.2% cardiovascular events over 10 years on placebo), and found that lowering SBP/diastolic blood pressure (DBP) to mean values of 138/86 rather than 149/91 mm Hg significantly reduced stroke and all cardiovascular events, but not coronary events or mortality.[12] Likewise in Chinese hypertensive patients treated by a daily small dose of felodipine (5 mg), a mean SBP of less than 140 mm Hg reduced major clinical events in those with a prior mean SBP of 153 mm Hg.[13] For every 100 patients treated for 3.3 years, 2.1 cardiovascular events were prevented in uncomplicated hypertension and 5.2 events in older adult hypertensive patients.

Ambulatory blood pressure monitoring.

Ambulatory blood pressure monitoring (ABPM) is the easiest and quickest way to establish the diagnosis (and to monitor its therapy). In the United Kingdom, the current recommendations are to use ABPM to confirm the diagnosis when the mean office BP is 140/90 mm Hg or higher.[14] ABPM is an excellent diagnostic procedure and, at least in the United Kingdom, is also cost effective.[15] Should we take the mean home values or pay more attention to the peak values? The peak values correlate better with the left ventricular (LV) mass index and myocardial infarction (MI) and carotid intimal-medial thickness than do the means.[16] But the failure of most health care payers in the United States and elsewhere to adequately reimburse practitioners will continue to restrict the use of ABPM.[17]

Home readings with inexpensive automatic devices, available in the United States for less than $40, provide most of the information needed for both diagnosis and monitoring of therapy.

Out-of-office ambulatory readings have a number of the vagaries of BP measurements. These include:

- *Masked hypertension* has only recently been recognized because it connotes normal office readings and elevated out-of-office readings. The diagnosis has been made in 10% to 20% of unselected patients and is associated with an eventual risk comparable to that of sustained hypertension.[11] Not surprisingly, it is characterized by a marked sympathetic overdrive.[18]

- *Morning BP* surge within the first 2 hours after awakening and ambulating is common and is associated with an increased risk for heart attack, stroke, and sudden death.[19]
- *Tachycardia,* fast heart rate frequenty found among patients with hypertension even without clinical heart disease, is not an innocent bystander.[20] Yet there are no prospective trials with drugs such as ivabradine (see Chapter 6, p. 195) that specifically reduce the heart rate. Thus the emphasis must be on lifestyle changes (aerobic exercise, no smoking, no stimulant drugs, reduced caffeine and alcohol).
- *Increased variability of BP* is now well documented to be associated with increased target organ damage[21] and cardiovascular morbidity.[22],[23] ABPM is the better way to ascertain variability[24] but monitoring in clinic or home over a longer period can provide useful information.[24] CCBs as a group are more effective than other agents in reducing blood pressure variability (BPV).[23] The X-CELLENT study compared four parallel treatment arms (placebo, candesartan, indapamide sustained release, and amlodipine).[25] The best reduction in BPV was by amlodipine, associated with decreased BP ($P < 0.006$) and reduced heart rate (HR) variability ($P < 0.02$).

J-shaped curve.

The J-shaped curve remains a tricky problem. “Alive and well,” says Norman Kaplan.[26] John Chalmers writes, “It is clear that there must be a J-curve relating blood pressure to cardiovascular risk because, at pressures below the lower limits for autoregulation, perfusion of vital organs must fail.” However, he questions whether “any such J-curve is related to the patients’ inherent risk profile or directly to blood pressure–lowering treatment.”[27] In a large prospective outcome study in patients with manifest vascular disease, with end points of cardiovascular events and all-cause mortality, there were clear J-shaped curves with the nadirs at 140-143/82-84 mm Hg.[28] The J-curve is thus an independent risk factor for recurrent events. Association is not causality, providing a strong rationale for future trials evaluating BP treatment targets.

What is the diastolic cut off point?

When the DBP drops below a certain value, perhaps at approximately 65 mm Hg (fifth Korotkoff sound), cardiovascular events increase, but what is the reason?[26] Others state that the cut off point is approximately 70-80 mm Hg, which may actually increase mortality in those with coronary artery disease.[29] Another study places the turn-around BP value at less than 60 mm Hg.[30] The European guidelines comment that a similar J-curve phenomenon occurs in placebo-treated groups of several trials.[31] Also noted is that several post hoc analyses consistently showed that the nadir of cardiovascular outcome incidence had a rather wide range, between 120 and 140 mm Hg SBP and between 70 and 80 mm Hg DBP, and that within this low BP range the differences in achieved cardiovascular protection are small (Figs.7-4 and 7-5).[32]

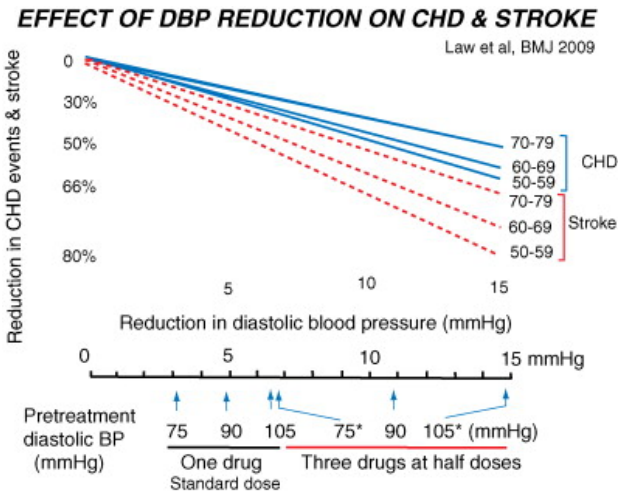

Figure 7-4 Predicted effects of reduction of diastolic blood pressure (DBP). Half-doses of three drugs could improve DBP and reduce coronary heart disease (CHD) and stroke better than standard doses of single drugs according to a meta analysis of 147 studies.
(Data from Law MR, et al. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. Br Med J 2009;338:b1665.)

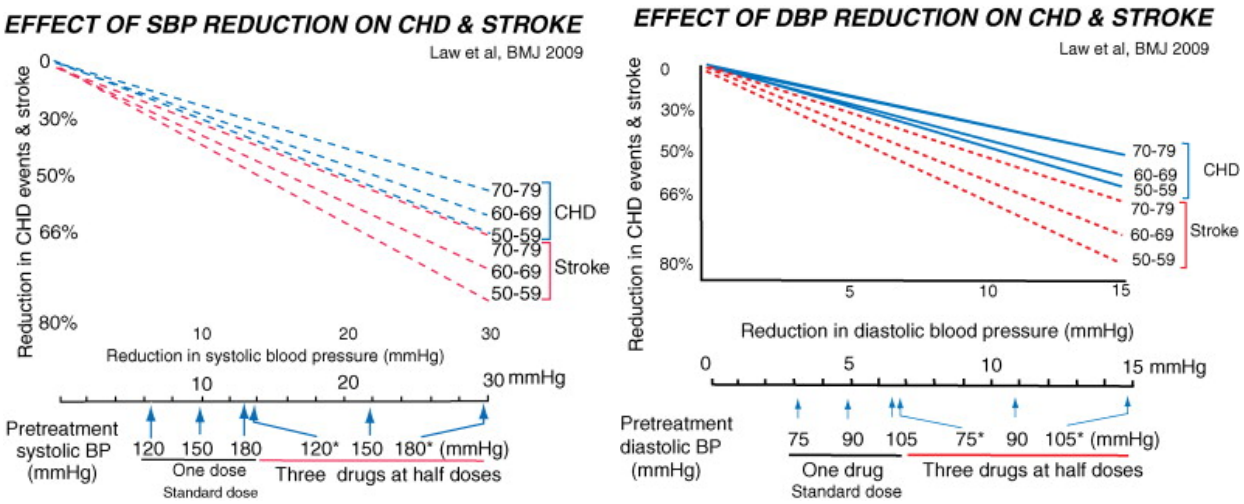

Figure 7-5 Predicted effects of reduction of systolic blood pressure (SBP). Half-doses of three drugs could improve SBP and reduce coronary heart disease (CHD) and stroke better than standard doses of single drugs according to a metaanalysis of 147 studies.
(Data from Law MR, et al. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. Br Med J 2009;338:b1665.)

What practical policy must be followed if the proposed critical DBP of 65 mm Hg is reached? Presumably but without trial data, the BP-lowering medication should be reduced when the diastolic BP drops to less than 65 mm Hg until the level rises to 65-70 mm Hg. That leaves the likely increase in systolic BP to look after itself. A few outcome studies would be helpful.

Sleep apnea hypertension.

In a consecutive series of 125 patients with RH, sleep apnea was the commonest cause (64%) (see page 258).

Central blood pressure.

Central BP obtained from carotid and radial distension waves and a validated transfer function will increasingly be used in clinical practice[24] because the central pressure is more closely related to vascular outcomes than is the brachial pressure.[33]

Aortic stiffness.

Arterial stiffness is an independent predictor of cardiovascular events and mortality in hypertensive patients, especially in older adults (see Fig. 7-11). It is calculated from the carotid-femoral wave velocity.[34] An analysis of 15 trials from one center showed that antihypertensive therapy improved arterial stiffness beyond the effect on BP.[35]

Pulse wave velocity.

Carotid-femoral pulse wave velocity is now considered the gold standard for arterial stiffness assessment in daily practice.

White-coat hypertension and prehypertension

White-coat hypertension.

White-coat hypertension (i.e., persistently elevated office readings but persistently normal out-of-office readings) is present in up to 20% of patients. Although its short-term danger is minimal, it eventually poses a hazard with the likelihood for cardiovascular events that is 68% of that seen with sustained hypertension.[11] White-coat hypertension may masquerade as RH, which is an uncontrolled office BP of 140/90 mm Hg or more, despite the use of three or more antihypertensive drugs, including a diuretic. Following this diagnosis, the use of ABPM is crucial to split up two different groups, those with true and those with white-coat RH. ABPM then classifies RH patients into two groups: true uncontrolled RH (office BP and 24-hour BP ≥130/80 mm Hg) and white-coat (controlled) RH (white-coat RH: office BP ≥140/90 mm Hg and 24-hour BP <130/80 mm Hg).[36] White-coat hypertension may account for as much as 40% of all apparently resistant patients as detected by the office BP.[11] For follow up, to avoid white-coat creeping up to sustained hypertension, ABPM is required every 6-12 months.

Prehypertension.

Does a BP of less than 140/90 mm Hg warrant drugs? A radical change in approach to modestly or even minimally elevated BP has resulted from two mega-meta-analyses on approximately 1 million adults.[32],[37] Any increase in BP to more than 115/75 mm Hg increases cardiovascular risk, which doubles with every rise of 20/10 mm Hg. The previously normal and high-normal BP ranges of 120 to 139 mm Hg systolic and 80 to 89 mm Hg diastolic are now considered *prehypertensive,* with calls for active lifestyle changes to avoid moving into the overtly hypertensive category, which remains 140/90 mm Hg or more.[38] These stricter views have led to more active antihypertensive intervention at lower BP levels, sometimes even giving drugs where there are no solid trial data as in those with BP levels less than 140/90 mm Hg in whom only lifestyle modification is presently appropriate. Contrariwise, a more radical view is that prehypertension may warrant drug therapy, as supported by the epic metaanalysis by 147 studies on nearly 1 million people (see Figs. 7-4 and 7-5).[32]

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Determination of overall cardiovascular risk

After accurate ascertainment of the usual level of BP, the other major contributors to cardiovascular risk should be assessed by history, physical examination, and routine laboratory testing, including an electrocardiogram.[39] Thereby a number of levels of risk can be calculated from Framingham or other databases. With knowledge of overall risk, appropriate therapy for hypertension and the need for additional treatments for other risk factors can be determined (Table 7-2). For some patients, testing beyond the routine (e.g., echocardiography) may be used to decide on the need to start active antihypertensive drug therapy. The presence of target organ damage generally mandates faster and more intensive therapy.

Table 7-2 -- Risk Stratification in Treatment of Hypertension

	Blood Pressure (mm Hg)				
Other Risk Factors and Disease History	**Normal SBP 120-129 or DBP 80-84**	**High Normal SBP 130-139 or DBP 85-89**	**Grade 1 SBP 140-159 or DBP 90-99**	**Grade 2 SBP 160-179 or DBP 100-109**	**Grade 3 SBP ≥ 180 or DBP ≥ 110**
No other risk factors	Average risk	Average risk	<15% 10-year risk	15%-20% 10-year risk	20%-30% 10-year risk
1-2 risk factors	<15% 10-year risk	<15% 10-year risk	15%-20% 10-year risk	15%-20% 10-year risk	>30% 10-year risk
3 or more risk factors or TOD or diabetes mellitus	15%-20% 10-year risk	20%-30% 10-year risk	20%-30% 10-year risk	20%-30% 10-year risk	>30% 10-year risk
Associated clinical conditions	20%-30% 10-year risk	>30% 10-year risk	>30% 10-year risk	>30% 10-year risk	>30% 10-year risk

Based on and modified from recommendations of European Societies of Cardiology and Hypertension.[39] 10-year risk of cardiovascular disease according to Framingham criteria.

DBP, Diastolic blood pressure; *SBP,* systolic blood pressure; *TOD,* target organ damage.

Risk factors for coronary heart disease (note slight differences from adenosine triphosphate III in Chapter 10): blood pressure as previously; cholesterol level >250 mg/dL, low-density lipoprotein >155 mg/dL, high-density lipoprotein cholesterol <40 mg/dL in men, <48 mg/dL in women; family history of premature coronary heart disease; smoking, age (men >55, women >65), abdominal obesity, C-reactive protein ≥1 mg/dL.

TOD, target organ damage: left ventricular hypertrophy; ultrasound evidence of arterial disease, increased serum creatinine up to 1.5 mg/dL (133 µmol/L) in men, slightly lower in women, microalbuminuria up to 300 mg/24 h.

Associated clinical conditions: cerebrovascular disease including transient ischemic attack, angina or myocardial infarction, congestive heart failure, renal impairment, proteinuria, peripheral vascular disease, and advanced retinopathy.

Lifetime risk versus current risk

In a very large study, 61,585 American men and women were followed from age 55 for 700,000 person-years. Life-time risk for cardiovascular disease (CVD) was 53% for men and 40% for women. Life-time risk

for CVD increased with increasing BP at index age. Individuals who maintained or decreased their BP to normal levels at index age had the lowest remaining life-time risk for CVD, 22%-41%, as compared with individuals who had or developed hypertension by the age of 55, 42%-69%. These data support a dose-response adverse effect for the length of time at high BP levels.[40]

The goals of therapy

The goal of therapy is to provide maximal protection against cardiovascular consequences with minimal bother to the patient. Currently available medications should cause little if any bother (except financial) to the patient, but there remains uncertainty regarding how to provide maximal protection.

Reduction of all-cause mortality.

As sustained reduction of BP in established hypertension lessens the overall risk of CVD, including strokes and heart failure, it is not surprising that a large US study (based on data in the Third National Health and Nutrition Examination) has linked BP control to decreased all-cause mortality.[41] Conversely, mortality risk linearly increased with SBP although not with DBP.

Lower blood pressures for higher-risk and black patients?

In patients with diabetes or renal damage 130/80 is a generally accepted goal that should be upheld[27] even though disputed.[42] For non-Hispanic black patients, the International Society for Hypertension in Blacks (ISHIB) has recently lowered the definition of uncomplicated hypertension to 135/85 mm Hg (for primary prevention), recognizing the greater rate of progression to established hypertension, and dropping the definition of complicated hypertension even lower to 130/80 mm Hg (for secondary prevention). These recommendations are based on the greater CVD risk in blacks;[43] however, these new recommendations are controversial because of limited evidence.[44]

Lifestyle modifications

Seeing that cardiovascular risk starts at only 115/75 mm Hg, and considering the shocking statistic that middle-aged American adults have a 90% lifetime risk of developing hypertension,[45] the real recommendation should be “lifestyle modification for all.” If lifestyles can be improved, BP will fall[46] and, probably, cardiovascular events prevented.[47] The problem is how to change lifetime habits in a meaningful way. Counseling of those who are overweight is of minimal value over time[48] and, for the increasing number who are markedly obese, bariatric surgery may be the only hope.[49]

Our attention should therefore turn to children and their parents to help prevent the adoption of unhealthy habits. Intermittent external counseling by itself does not seem to work to prevent weight gain[50] or to increase physical activity,[51] and perhaps only a program that integrates home, school, and community would work.

Sodium reduction.

Approximately 5% to 15% of all strokes and 10% to 20% of all heart attacks in the United States would be prevented if the food industry could be pressured to reduce the sodium content of processed food so that daily NaCl intake fell gradually over a decade from 10 g to 7; black persons would benefit the most, thus reducing racial disparity in CVD.[52]

Nondrug therapies.

Meanwhile, to optimally protect those who are hypertensive, nondrug therapies should be standard in all hypertensive patients, particularly *weight reduction* for obese patients and moderate dietary *sodium reduction* from the usual level of approximately 10 g of sodium chloride per day down to approximately 5 g or 88 mmol or 2 g sodium, which will reduce the BP by approximately 7/4 mm Hg in hypertensive patients.[46] In the DASH-sodium study, further sodium reduction to approximately 1.4 g per day (urinary sodium of 65 mmol/day),enhanced the BP-lowering benefits of the high-fruit, high-vegetable DASH diet to give a total reduction of approximately 7 mm Hg lower than the standard diet, a degree of BP fall approximately the same as seen with an effective antihypertensive agent. The *ideal diet* is low in calories, rich in fresh rather than processed foods, and high in fruits and vegetables (and hence high in potassium) besides being low in fat and sodium.[53] Better than an approach directed to an individual, a reduction in the amount of sodium added to canned and packaged foods by food processors would be more effective.[54] *Weight loss* reduces BP, improves the QOL, and specifically benefits those with left ventricular hypertrophy (LVH).[55] Multifactorial intervention with both weight loss and sodium restriction should be used before drug therapy is instituted, especially in older adults and in those with marginal BP elevations. Other measures include increased *aerobic exercise,* cessation of smoking, and moderation of alcohol. Smoking is an independent risk factor for coronary heart disease and stroke, besides increasing the risk of malignant hypertension.

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Correction of other risk factors

The efficacy of antihypertensive treatment depends not only on the control of the BP, but also on the control of co-existing risk factors, especially those for CVD, which is the major cause of mortality in hypertension (see Fig. 7-3). Whereas in low-risk groups, many hundreds of patients must be treated to prevent one stroke, in very high-risk groups, such as older adults, only 20 to 25 patients need to be treated for 1 year to prevent one cardiovascular event, including stroke. The well-known Framingham tables and several websites aid the assessment of risk factors. Explaining the exact risk over 10 years to a specific patient often helps in achieving a desirable lifestyle and reaching BP goals. The new European guidelines show color-coded tables, with the highest risk of 10-year fatality being in red and the lowest in green.[1]

In addition, risk assessment charts have been adopted for use in low-income countries.[56] The patient can readily grasp that reaching a specific BP goal means moving from a “bad” color, say orange, to a better one, say yellow, with less risk of stroke or heart attack to the best, green. Another approach is to shock the patient by calculating from the risk factor profile the age of the cardiovascular system which could be 5-20 years older that the patient’s actual age. The evidence for additional protection in hypertensive patients by improvements in blood lipids and other features of the metabolic syndrome is presented in Chapters 11 (Fig. 11-1; p. 441).

Systolic versus diastolic versus pulse pressure.

Although all recommendations for treatment in the past were based on a cut-off DBP level, there are two important new developments. First, the BP level must be seen as part of an overall risk profile. Second, systolic levels should be considered, particularly in older adults. At all ages, there are more predictive or risk values than diastolic values[57] and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) states that SBP is a “much more important” cardiovascular risk factor than the diastolic in those older than 50 years.[38] A wide pulse pressure, largely reflecting a high systolic level and increased vascular stiffness, may be the most accurate predictor of all.

Overall aims of treatment

Reducing cardiovascular risk safely is the sole aim of therapy. Some trials have suggested a *J-shaped curve* indicating an increase of coronary complications in patients whose DBP was reduced to lower than 70 mm Hg.[30] The HOT trial attempted to disprove the presence of a J-curve with treatment.[58] Despite a less than desired separation of BP in the three groups assigned to reach a diastolic of 90, 85, or 80 mm Hg, the lowest incidence of endpoints was seen at a DBP of 83 mm Hg and a small but apparent increase in cardiovascular mortality occurred when the DBP was lowered to less than 70 mm Hg. In other studies of older adults with isolated systolic hypertension, a decrease of diastolic pressure to less than 65 mm Hg increased the risk of stroke and coronary heart disease. Patients with concomitant renal disease seem particularly susceptible to systolic levels less than 130 mm Hg.[59] Patients with coronary disease are susceptible to diastolics less than 80 mm Hg.[29] Therefore caution remains advisable.

Preservation of the brain.

Preservation of the brain is now recognized as of paramount importance. Prevention of major and minor strokes by BP control starting in midlife is one imperative. Unexpectedly, factors that contribute to albuminuria may contribute to cognitive decline, suggesting that both conditions share a common microvascular pathogenesis.[60]

Guidelines: Choice of initial and subsequent drugs.

For many years, a great deal of attention, energy, and money has been spent in deciding which drug is the

best choice for initial therapy and which combination is best for eventual therapy. “Drugs targeting the sympathetic nervous system are no longer considered as first-line antihypertensives. Central sympatholytics are limited by their side effects, and outcome trials have shown that α- and β-blockers are inferior in lowering the incidence of heart failure and strokes, respectively, compared with other drugs.”[61] However, this restriction may not apply to more current vasodilating β-blockers.

The most recent “ACD” guidelines come from The British Society of Hypertension acting together with the UK National Institute of Excellence (NICE). They chose three outcomes-based groups of agents that are evidenced based: A is for ACE inhibitors and ARBs, C is for CCBs, and D is for diuretics.[9] The missing “B” is for β-blockers and indicates the gap from their previous recommendations, as these agents are now downgraded (nebivolol may be an exception; see later). These authorities also distinguish between thiazide-like diuretics such as chlorthalidone and indapamide slow release and the standard thiazides such as hydrochlorothiazide (HCTZ) with preference for the thiazide-like diuretics. The major reasons are that the standard thiazides have no outcome studies in hypertension when used at the presently recommended doses, whereas the thiazide-like agents are evidence based as in ALLHAT and HYVET.

These issues are open to debate. For initial therapy JNC 7[38] advocated a low-dose thiazide diuretic for most patients. The expectation is that the eighth report due soon will support chlorthalidone as the low-dose diuretic of choice. The European Hypertension Society[39] recommends whatever class seems most appropriate for the patient, whereas the World Health Organization[29] states that any class may be used but a diuretic is preferred. Thus two out of the three major guidelines suggest a low-dose diuretic as the first choice for uncomplicated patients; this recommendation is reinforced when cost is factored into the equation. However, in most developed countries, including the United States, diuretics are used in only approximately 30% of patients.[62] The reasons include the delayed response to diuretic therapy and the possible metabolic complications. However, diuretics combine well with all other antihypertensive classes.

As to the eventual therapy needed to reach the lower goals of BP now advocated by all experts, there is agreement to add whatever is appropriate for the individual patient—in other words, a “compelling” indication or a “favored” choice—to a diuretic and to add additional drugs from other classes to reach the goal.

Although the details vary somewhat, the tabulation based on the 2007 European guidelines fits most situations very nicely (Table 7-3). All classes have their place.

Table 7-3 -- Guidelines for Selecting Drug Treatment for Hypertension

Class of Drug	Favored Indications	Possible Indications	Compelling Contraindications	Possible Contraindications
Diuretics (low-dose thiazides)	Congestive heart failure Older adults with hypertension Systolic hypertension African origin subjects	Obesity	Gout	Pregnancy Dyslipidemia Metabolic syndrome Sexually active men
Diuretics (loop)	Congestive heart failure Renal failure		Hypokalemia	
Diuretics (antialdo)	Congestive heart failure Postinfarct Aldosteronism (First or second degree)	Refractory hypertension	Hyperkalemia Renal failure	Diabetic renal disease
CCBs	Angina, effort Older adults Systolic hypertension	Peripheral vascular disease Diabetes African origin	Heart block* Clinical heart failure (possible exception: amlodipine, but needs care)	Preexisting ankle edema
ACE inhibitors	Left ventricular dysfunction or failure Postinfarct Nephropathy, type 1 diabetic	CV protection (BP already controlled) Type 2	Pregnancy Hyperkalemia Bilateral renal artery stenosis	Severe cough Severe aortic stenosis

	or nondiabetic Proteinuria	nephropathy		
Angiotensin-II Antagonists (ARBs)	ACE inhibitor cough Diabetes type 2 nephropathy including microalbuminuria LVH Heart failure	Postinfarct	Pregnancy Bilateral renal artery stenosis Hyperkalemia	Severe aortic stenosis
β-Blockers	AnginaTachyarrhythmias Post-MI Heart failure (uptitrate)	Pregnancy Diabetes	Asthma, severe COPD Heart block[†]	ObesityMetabolic syndrome Athletes and exercising patients Erectile dysfunction Peripheral vascular disease

ACE, Angiotensin-converting enzyme; *Aldo,* aldosterone; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CCB,* calcium channel blocker; *COPD,* chronic obstructive pulmonary disease; *CV,* cardiovascular; *LVH,* left ventricular hypertrophy; *MI,* myocardial infarction.

* Grade 2 or 3 atrioventricular block with verapamil or diltiazem.

† Grade 2 or 3 atrioventricular block.

If these various guidelines are followed, the use of low-dose diuretic therapy should markedly increase. On the other hand, the β-blockers will almost certainly be used less overall,[63] but more so in those patients who need them because of MI or heart failure. CCBs have been better than other classes for prevention of stroke[64] and for reduction of BP variability.[25] ACE inhibitors received good marks in black patients only when used with a diuretic[65] or when used in older adult white patients.[66] Ideally, ACE inhibitors should be combined with their natural partners, the diuretics, or with their new suitors, the CCBs (see “ACCOMPLISH” later in this chapter). ARBs, the fastest growing class, are no better than other classes in protection against stroke, heart attack, or heart failure.[64] However, in hypertension there are no good comparative head-to-head outcome studies of ARBs with their cheaper siblings, the ACE inhibitors.

Resistant hypertension and aldosterone antagonists.

“Resistant hypertension is almost always multifactorial in origin.”[67] Therapy requires strong advice on adverse lifestyles, detection and therapy of secondary causes of hypertension, and the use of effective multidrug regimens. The standard definition is the failure to control the BP on three or more agents including a diuretic at target or at least at the highest tolerated doses. In fact, most studies on RH have studied patients on four or more drugs. Thus adherence and excellent physician-patient relationships become essential, as repeated studies show that as the number of drugs that should be taken increases, the number of drugs actually taken decreases. Building on the three basic drug classes—namely a diuretic, an ACE inhibitor (or ARB), and a CCB—there is a good case to regard aldosterone blockade as the next logical step. One old drug, *spironolactone,* has been revitalized for use in heart failure[68] and RH.[69],[70] *Eplerenone* is a congener that provides more selective aldosterone blockade, and may become another major player in RH without the sexual side effects of spironolactone, although it is currently priced higher. Serum potassium levels should be measured before initiating eplerenone and then monitored regularly to avoid hyperkalemia. (Similar monitoring for hyperkalemia is required for spironolactone.) Eplerenone is considerably weaker than spironolactone, but the Food and Drug Administration (FDA) limits the maximum daily dose to 100 mg because higher doses increase the risk of hyperkalemia.

Relative efficacy.

As seen in Table 7-3, certain drugs are favored in certain patients (e.g., diuretics and CCBs in blacks and older adults and ACE inhibitors or ARBs in diabetics with nephropathy). Moreover, all drugs have certain limitations and contraindications. However, it should be noted that in the overall hypertensive population, the response rate (i.e., BP lowered to less than 140/90 mm Hg) to each of the five major groups of agents as monotherapy may be no more than 30% to 40% depending on the severity of the hypertension and the drug

chosen, so that combination therapy is usually required in addition to lifestyle modification. Finally, financial considerations may be crucial. Diuretics, reserpine, and hydralazine are inexpensive, as are generic β-blockers, ACE inhibitors, and verapamil. Of the CCBs, amlodipine is the best tested and generic in many countries. Newer agents can be much more expensive.

Compliance and adherence

There are two different yet complementary approaches, the first to target known high-risk patients, and the second to achieve better adherence of the wider population with less severe but more common hypertension levels in the community.[2] In Spain a three-pronged intervention helped to control their "high-risk" hypertensive patients: (1) counting pills during physician visits, (2) designating a family member to support adherence behavior, and (3) providing patients with an information sheet about their BP medications.[2] In Canada a hypertension education program involves pharmacists,[71] and is remarkably successful with 80% in one survey using antihypertensives, and almost all of those (89%) adhering to the prescriptions.[72] However, even in Canada many persons seen in an academic family practice were not well controlled.[73] A wide community-based approach could be the start to reach the many individuals with uncontrolled hypertension, as in approximately 50% of US blacks.[2]

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Combination therapy

An interesting concept is that combination therapy by several agents, up to three, in low doses give better control of BP than larger doses of any single agent (see Figs. 7-4 and 7-5).[32] Although impressively based on a metaanalysis of 147 studies, there is little trial data to show that substantial BP outcome benefits result from treating uncomplicated hypertension at levels less than 140/90 mm Hg, which still remains the cut-off point (Fig. 7-6). Nonetheless, this study strongly argues the case for combining several agents in half doses.

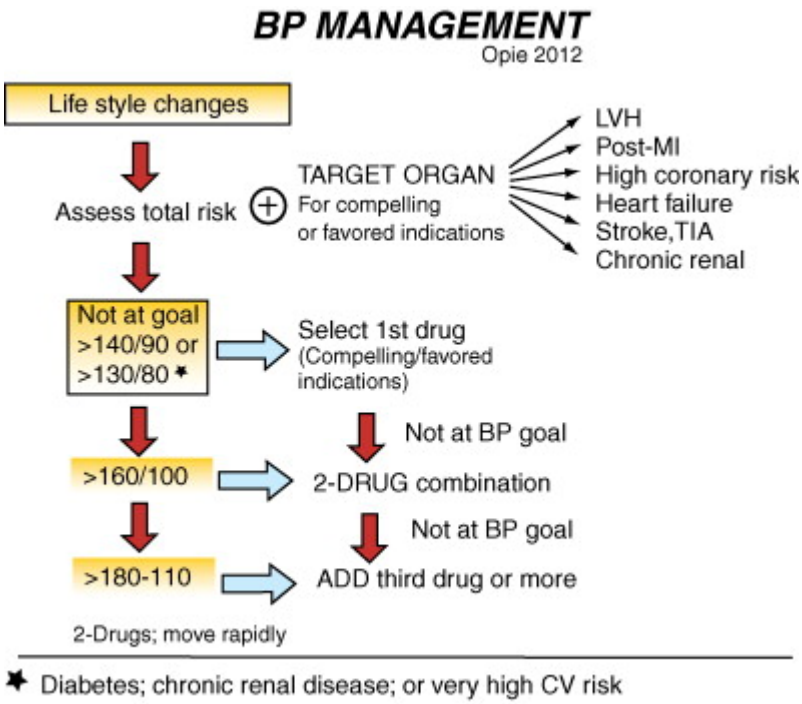

Figure 7-6 Proposed simplified treatment algorithm for hypertension therapy. *BP,* Blood pressure; *LVH,* left ventricular hypertrophy; *MI,* myocardial infarction; *TIA,* transient ischemic attack.
(Figure © L.H. Opie, 2012.)

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Diuretics for hypertension

Diuretics have been the basis of several impressive trials, many in older adult patients, in which hard endpoints have been reduced. Diuretics are widely recommended as first-line therapy (Fig. 7-7) and are among the three drug groups of first choice selected in the recent UK recommendations.[9] They are better at reducing coronary heart disease, heart failure, stroke, and cardiovascular and total mortality than placebo, and in at least one of these endpoints they are better than β-blockers, CCBs, ACE inhibitors (but equal to the ARBs), and α-blockers.[74] Diuretics are inexpensive and remain basic in the therapy of hypertension.[75] Thus it is not surprising that they are still widely used either as monotherapy (see Fig. 7-2) or in combination (Fig. 7-7). They combine particularly well with ACE inhibitors and ARBs. In contrast, the dihydropyridine (DHP) CCBs have inherent diuretic properties, making this combination less effective than expected. The vascular complications that are more directly related to the height of the BP per se (strokes and congestive heart failure) have been reduced more than that of the most common cause of disease and death among hypertensive patients, namely coronary heart disease.[74] Hypothetically, metabolic side effects from the high doses of diuretics used in earlier trials, particularly on lipids and insulin sensitivity,[76] as well as potassium and magnesium depletion, and increased uric acid levels, may in part explain why death from coronary disease has not decreased as much as it should have. For example, a serum potassium of 3.5 mmol/L or less increased cardiovascular events by approximately four times over a mean follow-up of 6.7 years.[77] Also on the debit side, impotence is a relatively frequent side effect of chlorthalidone—more so than with any other antihypertensive drug class.[78] Furthermore, the response in younger white patients (younger than 60 years) is poor.[79]

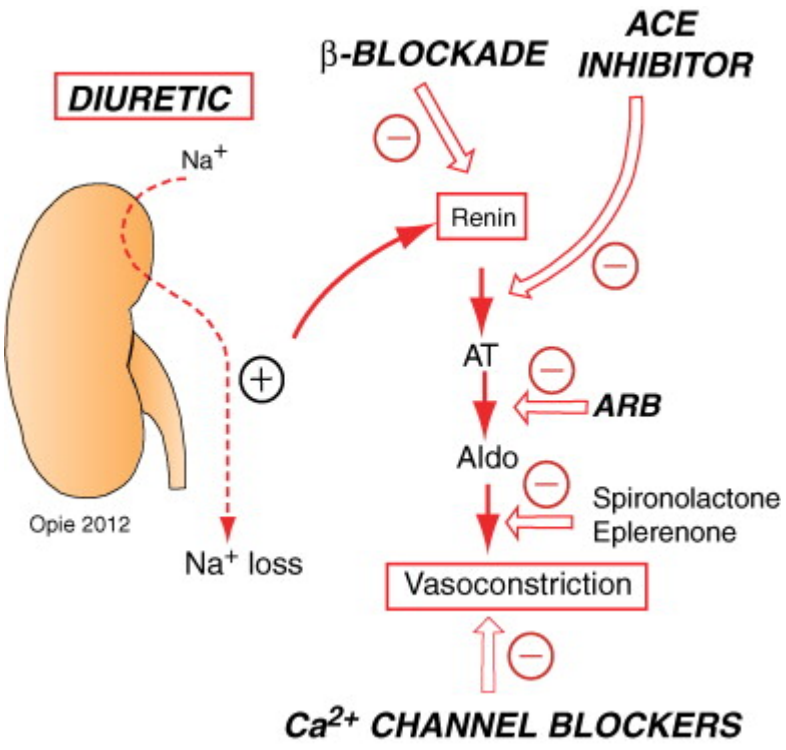

Figure 7-7 Diuretics. Diuretics, basically acting by sodium loss, cause a reactive increase in circulating renin that results in angiotensin-mediated vasoconstriction to offset the hypotensive effect. Diuretics therefore combine well with β-blockers, which inhibit the release of renin, with angiotensin-converting enzyme (ACE) inhibitors that inhibit the formation of angiotensin-II, with angiotensin receptor blockers (ARBs), and with calcium channel blockers, which directly oppose diuretic-induced vasoconstriction. Of these combinations, those of diuretic and ACE inhibitor or ARB are particularly well tested. ACE inhibitors and ARBs lessen the metabolic side effects of diuretics. *Aldo,* Aldosterone; *AT,* angiotensin.

(Figure © L.H. Opie, 2012.)

Lack of dose-finding outcome studies.

A persistent problem with the concept of low-dose diuretic therapy is that there are no good comparative studies between the different diuretics, their “low” doses, and outcomes. Strictly speaking, we do not know that the low doses of diuretics currently used really result in patient benefit except in older adults in whom low-dose chlorthalidone (12.5 mg) was chosen as initial therapy in the SHEP study.[80] Even there, in many patients the dose was doubled and a β-blocker added. Logically, the lower the dose of diuretic, the fewer the metabolic side effects, whereas (within limits) the antihypertensive potency may still be adequately expressed. However, the available evidence suggests that the following are low doses that nonetheless are effectively and safely antihypertensive in mild to moderate hypertension: HCTZ 12.5 mg, chlorthalidone 12.5 to 15 mg, and bendrofluazide 1.25 mg.[81] If chlorthalidone has a more lasting antihypertensive effect than HCTZ, as evidence suggests,[82] then these comparisons suggest an advantage for chlorthalidone.

Diuretic dose: Hydrochlorothiazide.

Although a single morning dose of 12.5 mg of HCTZ or its equivalent will provide a 10 mm Hg fall in the BP of most patients with uncomplicated hypertension within several weeks, even that dose may be too high in combination therapies. Higher doses such as 25 mg increase the risk of diabetes.[83] Lower doses (6.25 mg HCTZ) may be equally effective when combined with β-blockade, ACE inhibition, or an ARB. Such low doses of HCTZ may require several weeks to act. Low-dose thiazides may be combined with all other classes, including the DHP CCBs,[84] which have their own mild diuretic capacity. Alternatively, sodium restriction may be the secret in making low-dose HCTZ work. The advantage of low-dose HCTZ (or its equivalent in other diuretics) is that adverse metabolic and lipid effects are minimized or completely avoided. Nevertheless, even 12.5 mg HCTZ may still induce potassium wastage and hypokalemia.[76],[85] This trend to hypokalemia can be prevented by concomitant ACE inhibitor or ARB therapy.[76]

Chlorthalidone.

A 15 mg daily dose was used in the TOMH study[86] in patients with very mild hypertension. Combined with weight loss and other measures, it was as effectively antihypertensive as other groups of agents. It gave an unexpectedly good QOL (despite the doubling of impotence) and at the end of 4 years blood cholesterol changes (elevated at 1 year) had reverted to normal.[86] Chlorthalidone 12.5 mg daily was the first-line treatment in the study on systolic hypertension in the SHEP study of older adults.[80] Thereafter the dose was doubled in about one third of patients and atenolol was added, if needed, to control BP. In SHEP, after 4.5 years, total stroke was reduced by 36%. On the debit side, the higher dose increased the risk of hypokalemia with partial loss of cardiovascular benefit.[87] In ALLHAT, chlorthalidone at a daily dose of 12.5 to 25 mg was considered the best overall drug versus the CCB amlodipine or the ACE inhibitor lisinopril, but at the cost of increased diabetes and hypokalemia.[88]

Chlorthalidone versus hydrochlorothiazide.

As fully discussed in Chapter 4 (p. 102), overall data favor cardiovascular outcomes with the longer-acting chlorthalidone over HCTZ despite more metabolic problems such as hypokolemia.[89]

Bendrofluazide.

Bendrofluazide is a standard thiazide in the United Kingdom, once given at 10 mg a day in a large trial, and is effective over 24 hours at a daily dose of only 1.25 mg.[90] Current UK guidelines favor its replacement whenever starting therapy by more widely used agents.

Amiloride.

Among diuretics, amiloride uniquely has potassium-retaining effects. In difficult-to-treat hypertension in black patients on two drugs (thiazide and CCB), amiloride was at least as effective as spironolactone and the combination with a standard thiazide was not much more effective than amiloride alone.[91]

Indapamide.

The modified thiazide *indapamide (Lozol, Natrilix SR)* may be more lipid neutral than standard thiazides and is promoted in some countries as a vasodilating diuretic. The previous standard dose of 2.5 mg once daily has been dropped by the manufacturers to 1.5 mg daily in a sustained-release formulation. Yet the potassium may fall, and the blood glucose and uric acid rise, as warned in the package insert. Indapamide induces regression of LVH and was better than enalapril 20 mg once daily.[92] A large indapamide-based antihypertensive trial in much older adults, HYVET, had to be stopped because of reduced mortality.[93]

Loop diuretics for hypertension.

Furosemide is not ideal as it is short acting and needs to be given at least twice a day to be adequately antihypertensive. Torasemide is free of metabolic and lipid side–effects, yet is antihypertensive when used in the subdiuretic dose of 2.5 mg once daily.[94] At the higher daily doses registered for hypertension in the United States, namely 5 to 10 mg, it becomes natriuretic with greater risk of metabolic changes.

Potassium-sparing combination diuretics.

Potassium-sparing combination diuretics may add a few cents to the cost but save a good deal more by the prevention of diuretic-induced hypokalemia and hypomagnesemia. The risk of torsades-related sudden death should also be reduced.[95] A small observational study suggests better retention of cognitive function in older adults.[96] To be effectively antihypertensive, the potassium-sparing agents are combined with another diuretic, generally a thiazide. Fixed-dose combinations of *triamterene (Dyazide, Maxzide)* or *amiloride (Moduretic)* with HCTZ are available. The general problem is that the thiazide dose is too high. The dose of HCTZ in one tablet of Dyazide is 25 mg, but only approximately half is absorbed. Maxzide contains 25- or 50-mg HCTZ. Standard Moduretic contains 50 mg (far too much), but in Europe, a “mini-Moduretic” *(Moduret)* with half the standard thiazide dose is now marketed to overcome this objection. However, even these doses are probably too high. *Aldactazide* combines 25-mg spironolactone with 25-mg thiazide. Note that in general, thiazides are relatively ineffective with poor renal function as compared with loop diuretics.

Combinations of diuretics with other antihypertensives.

Diuretics may add to the effect of all other types of antihypertensives. Combination with ACE inhibition or an ARB is logical and part of the ACD concept (see p. 235) but may not be as good a combination as A and C (see Chapter 5, p. 134). A number of well-designed factorial studies have varied the dose of HCTZ from 6.25 mg to 25 mg and studied the interaction with a β-blocker,[97] diltiazem,[98] or an ACE inhibitor.[99] In general, somewhat greater antihypertensive effects were obtained with 25-mg HCTZ, yet the difference between the high and the low doses of thiazide were negligible when the alternate agent was given at higher doses. Thus there is a good argument for starting combination therapy with 6.25-mg HCTZ, a dose that effectively avoids hypokalemia. A combination that has trial support in much older adults is that of indapamide with an ACE inhibitor.[93]

Diuretics: Conclusions.

Despite reservations about metabolic side effects such as new-onset diabetes at higher doses, low-dose diuretics remain among the preferred initial treatments, especially in older adults, the obese, and black patients. Compared with placebo, low-dose diuretics reduce stroke and coronary disease in older adults and achieve outcome benefit, including mortality reduction, in patients with mild to moderate hypertension.[76] Diuretics appear to work particularly well in older black patients while being much less effective in younger white patients.[64] Two large positive outcome studies with diuretics have been in older adults, with the mean age well older than 60 years even at the start of the trial.[80],[88] Of note, in these trials the diuretic dose was often uptitrated, whereas a better course would probably be to keep the diuretic dose low and to add another agent, as in HYVET, in which an ACE inhibitor was added.[93] In this trial there was an early mortality benefit, so that the trial had to be stopped.

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Calcium channel blockers

CCBs (calcium antagonists) compare well in their antihypertensive effect with other classes and are more effective than the others in protection against stroke.[100] CCBs act primarily to reduce PVR, aided by at least an initial diuretic effect, especially in the case of the short-acting DHPs. No negative inotropic effect can be detected in patients with initially normal myocardial function. Regarding the effects on plasma catecholamines, DHPs must be distinguished from non-DHPs such as verapamil and diltiazem. As a group, DHPs reflexly stimulate the adrenergic system to increase plasma catecholamines modestly,[101] with a borderline elevation of plasma renin activity caused by the counterregulatory effect (Fig. 7-8). Non-DHPs tend to decrease catecholamine levels. There are several long-term outcome studies available with CCBs in hypertension and the consistent message is that CCBs are safe and effective, particularly for prevention of stroke.[100] Amlodipine, often combined with an ACE inhibitor, provided greater antihypertensive efficacy and better protection against cardiovascular events, mortality, and the development of new diabetes than did atenolol-based therapy in the ASCOT trial.[102] CCBs are particularly effective in older adult patients and are equally effective in blacks as in nonblacks. They act independently of sodium intake. CCBs may be selected as initial monotherapy, especially if there are other indications for these agents such as angina pectoris or Raynaud phenomenon or supraventricular tachycardia (non-DHPs). Previous ungrounded fears that CCBs increased MI have now been laid to rest and replaced by data suggesting superior protection against MI by amlodipine.[100],[102]

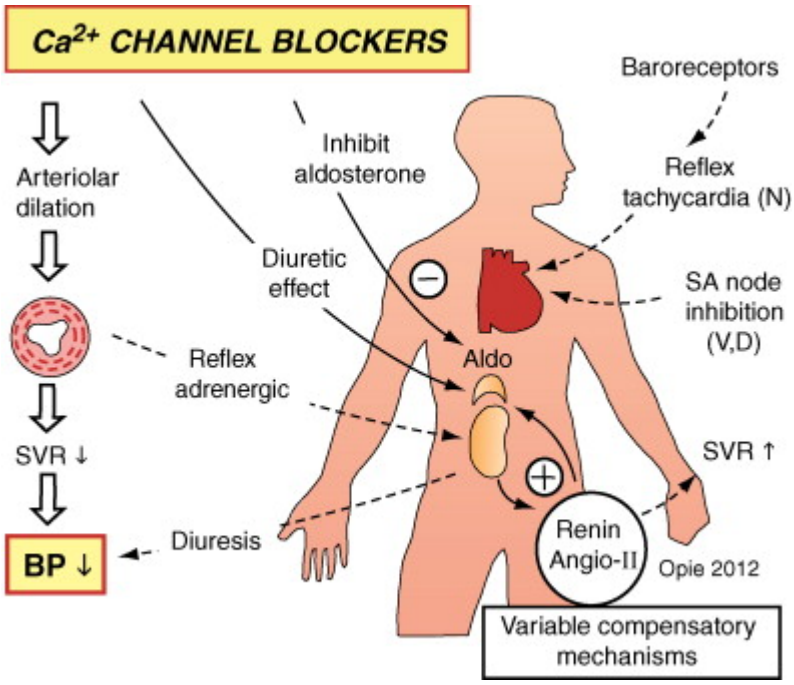

Figure 7-8 Calcium channel blockers (CCBs). CCBs act largely by peripheral arterial dilation, with a lesser diuretic effect. They also evoke counterregulatory mechanisms that depend on stimulation of renin and formation of angiotensin, as well as on reflex release of norepinephrine. Such acute adrenergic stimulation with short-acting nifedipine (N) may precipitate myocardial ischemia in the presence of coronary disease (see Fig. 3-6). Currently only long-acting CCBs are used in the treatment of hypertension. The inhibition of aldosterone release obviates overall fluid retention. *Aldo,* Aldosterone; *BP,* blood pressure; *D,* diltiazem; *SA,* sinoatrial; *SVR,* systemic vascular resistance; *V,* verapamil.
(Figure © L.H. Opie, 2012.)

CCBs compared with diuretics.

Compared with diuretics (also advocated for older adult and black patients), generic CCBs are becoming less expensive, with generic amlodipine now being widely available and being added to many $4 formularies; moreover, CCBs cause no metabolic disturbances in potassium, glucose, uric acid, or lipid metabolism. Patients on CCBs do not require intermittent blood chemistry checks. In a study on South African black patients with hypertension, a CCB regimen was better able to reduce DBP to less than 90 mm Hg than HCTZ 12.5 to 25 mg.[103] There is no evidence that CCBs cause impairment of renal function. On the contrary, in ALLHAT indices of renal function were better preserved in the CCB group.[88] Yet it still is considered prudent to have an ACE inhibitor or ARB on board before adding a DHP-CCB to achieve BP control in the hypertensive patient with chronic kidney disease;[104] the concept is to achieve balanced dilation of the afferent and efferent arterioles so as not to expose the glomerulus to excessive pressure and flow.

CCBs compared with ACE inhibitors or ARBs.

With equal antihypertensive efficacy, CCB-based therapy provides better protection against stroke than does ACE inhibitor– or ARB-based therapy,[88],[100] but is less protective against heart failure.[105] In black hypertensive patients with renal insufficiency in the AASK trial, those with microalbuminuria had an initial increase in glomerular filtration rate (GFR) on amlodipine and a subsequent equal fall in GFR as did those on ramipril or metoprolol.[106] Those with macroalbuminuria did better on the ACE inhibitor or β-blocker. In the ALLHAT trial, amlodipine and lisinopril were both equally protective compared with chlorthalidone against renal damage and heart attacks, with better protection against stroke in the black participants.[88] In INVEST, verapamil-trandolapril compared well on coronary outcomes with atenolol-HCTZ.[83]

CCBs combined with an ACE inhibitor.

ACCOMPLISH argues for the ACE inhibitor–CCB combination versus the ACE inhibitor–thiazide as the preferred initial therapy in a high-risk hypertensive population.[107] Importantly, initial antihypertensive treatment with benazepril plus amlodipine slowed progression of nephropathy to a greater extent than did benazepril plus HCTZ.[108]

Metaanalysis of outcome studies with CCBs.

Taking together the available studies in 2007, CCBs compared with placebo reduced stroke, coronary heart disease, major cardiovascular events, and cardiovascular death with, however, a trend to increased heart failure.[105] Compared with conventional therapy by diuretics and β-blockers, CCBs had the same effect on cardiovascular death and total mortality, increased heart failure, with a strong trend to decreased stroke. In addition, there was a lower rate of new diabetes with CCBs, including verapamil,[109] than with β-blocker or diuretic therapy.[88],[110]

Lacidipine, a new CCB.

Lacidipine, available in Europe, is claimed to cause less ankle edema than amlodipine. In the ELSA trial on 2334 hypertensives over 4 years, lacidipine was superior to atenolol in restraining carotid atherosclerosis and limiting development of new metabolic syndrome.[111]

Present assessment of CCBs.

The questions previously relating to the long-term safety of CCBs have been resolved in that only very high doses of short-acting agents may cause ischemic events, probably by precipitously lowering the BP, whereas long-acting CCBs are safe. CCBs may be better at cardiovascular and stroke prevention than some other choices.[100],[102] Thus CCBs are now accorded a position among the first-line choices by the NICE group.[112] ACE inhibitor plus amlodipine combinations may also be considered as first-line therapy, having performed very well in both ASCOT and ACCOMPLISH. Many pharmaceutical companies recently have branded fixed-dose combinations of amlodipine with almost every ACE inhibitor or ARB.

ACE inhibitors for hypertension

Captopril was the first ACE inhibitor, but multiple others are now available. All are antihypertensive, with few practical differences, except for duration of action (see Table 5-4). ACE inhibitors have few side effects (principally cough and rarely angioedema), are simple to use, have a flat dose-response curve, and have a virtual absence of contraindications except for bilateral renal artery stenosis and pregnancy. By preferentially relaxing the renal efferent arterioles and thereby reducing the intraglomerular pressure, they usually cause the serum creatinine to rise initially. They may precipitate hyperkalemia, especially in the presence of preexisting renal dysfunction, diabetes complicated by type 4 renal tubular acidosis, or when combined with potassium-retaining agents such as spironolactone. They readily combine with other modalities of treatment—with the exception of ACE inhibitors or the direct renin inhibitor—and are well accepted by older adults. Furthermore, a strong case has been made for their preferential use in diabetic hypertensive patients, in postinfarction follow-up, and in renal or heart failure. The HOPE study[113] emphasizes their role in cardiovascular protection in high-risk patients.

Mild to moderate hypertension.

ACE inhibitors can be used as monotherapy in patients with mild to moderate hypertension, even in low-renin patients, or in combination with other standard agents. For monotherapy, moderate dietary salt restriction is especially important.[114] Differences in sodium intake and the relative activity of the renin-angiotensin mechanism may explain why only a variable percentage of mild to moderate hypertensive patients respond to monotherapy with ACE inhibition.

Metaanalysis of outcome studies.

ACE inhibitor–based therapy was better than placebo against stroke, coronary heart disease, heart failure, major cardiovascular events, cardiovascular death, and total mortality.[115] When compared to a diuretic with or without β-blocker–based therapy, ACE inhibitor therapy was exactly equal, although there was a trend toward lesser benefit in stroke. When compared with CCB-based therapy, ACE inhibitor therapy was equivalent for coronary heart disease, cardiovascular death, and total mortality; clearly better for prevention of heart failure; and marginally worse for prevention of stroke.

Coronary disease and ACE inhibitors.

In the HOPE trial of patients at high risk of coronary heart disease, the addition of ramipril provided substantial cardioprotection.[113] However, uncertainty exists as to whether this was related to the extra antihypertensive effect provided by the ACE inhibitor, especially throughout the night, because the ramipril was given as 10 mg at night with substantial BP differences in the ABPM substudy.[116] In the EUROPA study, perindopril given in a high dose of 8 mg to patients with established coronary disease but with other otherwise relatively low risk, gave substantial cardiovascular protection especially by reducing MI.[117] Here, too, there was substantial BP reduction. In addition, a large body of experimental evidence supports the notion that there are direct vascular protective effects and in three trials of heart failure, an additional BP-independent effect of ACE inhibitors has been shown.[115]

Combination therapy.

In ACCOMPLISH, the ACE inhibitor benazepril plus amlodipine gave better reduction in morbidity and mortality than did amlodipine plus HCTZ. This superiority was only found when the estimated glomerular filtration rate (eGFR) was more than 60 mL/min.[108]

Renal disease and ACE inhibitors

In *renovascular hypertension,* in which circulating renin is high and a critical part of the hypertensive

mechanism, ACE inhibition is logical first-line therapy. Because the hypotensive response may be dramatic, a low test dose is essential. With standard doses of ACE inhibitors, the GFR falls acutely to largely recover in cases of unilateral, but not bilateral, disease. However, blood flow to the stenotic kidney may remain depressed after removal of the angiotensin-II support, and progressive ischemic atrophy is possible. Careful follow-up of renal blood flow and function is required. Angioplasty or surgery is preferable to chronic medical therapy, but only now is a comparison between medical therapy versus angioplasty being performed in patients with unilateral disease.

In *acute severe hypertension,* sublingual (chewed) captopril rapidly brings down the BP, but it is not clear how bilateral renal artery stenosis can be excluded quickly enough to make the speed of action of captopril an important benefit. Furthermore, the safety of such sudden falls of BP in the presence of possible renal impairment (always a risk in severe hypertension) has not been evaluated. But we know the risk of leaving the BP so high. Thus the best option is slow reduction of BP in hospital.

In *diabetic hypertensive patients* with nephropathy and proteinuria, ACE inhibitors and ARBs provide preferential dilation of the renal efferent arterioles, immediately reducing intraglomerular pressure and thereby protecting against progressive glomerulosclerosis.[118] Although the use of ACE inhibitors and ARBs in both diabetic and nondiabetic nephropathy has become routine, two disquieting reports question their efficacy. First, Kent et al.[118] found no benefit in nondiabetic nephropathy in those with less than 500 mg/day proteinuria. Second, in a nested case-control analysis of the long-term outcome of 6102 hypertensive diabetic patients, the use of ACE inhibitors was protective of progression to renal failure up to 3 years, but the risk increased to 4.2-fold greater after 3 years.[119]

Although in the past ACE inhibitors and ARBs have often been used together for extra renal protection in proteinuric patients, ONTARGET[120] showed that combining ACE inhibitor plus ARB therapy in patients at high cardiovascular risk, including diabetics, increased serious renal outcomes and hyperkalemia when compared with monotherapy with either agent. Similar risks are seen when an ACE inhibitor or ARB is combined with the direct-renin inhibitor,[121],[122] causing the FDA to issue a black-box warning and to take the fixed-dose combination off the market. Moreover, the COOPERATE trial, which had provided the earlier evidence supporting the practice of “dual renin-angiotensin system (RAS) blockade,” has been retracted by the editors of Lancet on the basis of scientific misconduct.[123]

Special groups of patients

Older adults.

In those younger than 80 years old, the aim still remains to maintain BP at less than 140/90 mm Hg.[124] In *older adults with hypertension,* the BP aim should be 150/80 mm Hg.[93] Large outcome studies have documented the efficacy and outcome benefit of therapy based on diuretic therapy,[93] ACE inhibition in white patients,[66] with good evidence for responsiveness to ARBs.[125] The aortic pressure is markedly abbreviated and peaked, in keeping with the clinical findings of increasing systolic and decreasing diastolic pressure with age. The likelihood of multisystem disease means that older adults need more time for a careful history, clinical examination, and basic investigations, although, on the other hand, it is easy to over investigate.

Older black hypertensive men.

In older black men with hypertension captopril was no better than placebo,[64] perhaps because there were two factors (ethnic group and age) both predisposing to a low-renin state. Similarly, in the ALLHAT trial lisinopril afforded less stroke protection than chlorthalidone or amlodipine for *black patients,*[88] probably because the trial design did not allow combination with either a diuretic or a DHP CCB.

Hypertension with heart failure.

In patients who have hypertension with heart failure ACE inhibitors with diuretics have been automatic first-line therapy with equivalent results from the ARBs such as telmisartan.[126]

Pregnancy hypertension.

ACE inhibitors are totally contraindicated for pregnant patients with hypertension because fetal growth is

impaired.

Combinations with ACE inhibitors

ACE inhibitors are often combined with *thiazide diuretics* to enhance hypotensive effects (see Fig. 7-7) and to lessen metabolic side effects. This combination is logical because diuretics increase renin, the effects of which are antagonized by ACE inhibitors. The addition of a thiazide is better from the BP point of view than increasing the dose of the ACE inhibitor. When combined with potassium-retaining thiazide diuretics *(Dyazide, Moduretic, Maxzide)*, and especially spironolactone, there is a *risk of hyperkalemia* because ACE inhibitors decrease aldosterone secretion and hence retain potassium (Fig. 7-9). Nonetheless, in the RALES heart failure study, low-dose spironolactone was added to ACE inhibition and diuretic with little hyperkalemia, yet these patients were carefully monitored and the dose of ACE inhibitor reduced if necessary.[68] *ACE-inhibition plus β-blockade* is theoretically not a combination of choice except in heart failure. *ACE inhibitors plus CCBs* are now increasingly used in the therapy of hypertension.[102],[127] This combination attacks both the RAS and the increased PVR. The ACE inhibitor reduces the ankle edema of the DHPs and both types of agents are free of metabolic and central nervous system side effects. In the ASCOT trial,[102] wherein the initial CCB arm was supplemented with an ACE inhibitor in 60% of patients, BP was lowered modestly more with the CCB–ACE inhibitor combination, which might have contributed to the better outcomes. As mentioned later (see page 253), in ACCOMPLISH this combination was superior to an ACE inhibitor–diuretic in reducing major events.

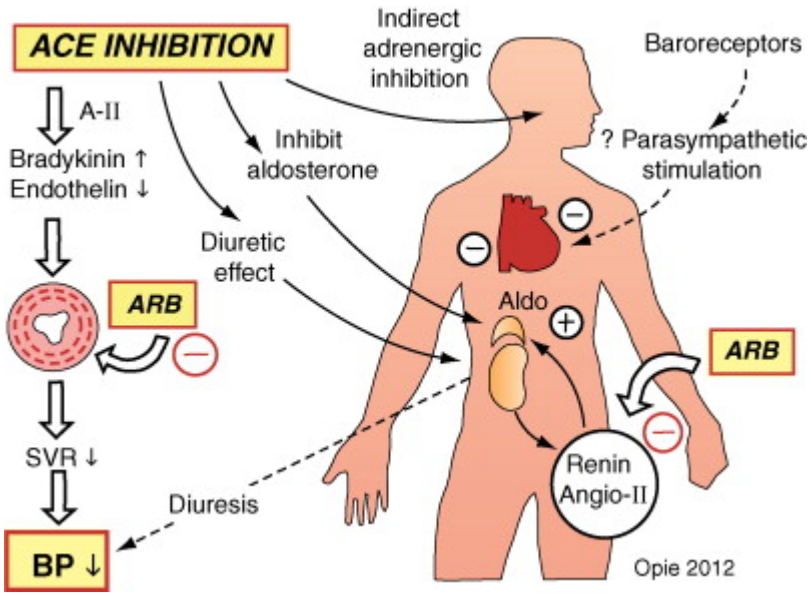

Figure 7-9 Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Proposed mechanisms whereby these agents may have their antihypertensive effects. Note that the major effect is on the peripheral arterioles causing vasodilation and a fall in the systemic vascular resistance (SVR), also called the *peripheral vascular resistance.* Indirect inhibition of adrenergic activity also promotes arteriolar dilation. Several ancillary mechanisms are at work, including renal and indirect adrenal effects, as well as possible central inhibition. Parasympathetic activity may also be stimulated. *AII & Angio-I,* angiotensin II; *Aldo,* aldosterone; *BP,* blood pressure.
(Figure © L.H. Opie, 2012.)

ACE inhibitors: Summary

In addition to BP lowering, the overall evidence is that these agents also confer some added vascular protection, especially in diabetics and in renal disease. ACE inhibitors combine well with diuretics and CCBs, and have relatively infrequent side effects. The practice of combining ACE inhibitors with ARBs (“dual RAS blockade”) should be stopped.

Angiotensin-II type 1 receptor blockers

Angiotensin-II subtype 1 receptor blockers act on the specific receptor for angiotensin-II that has highly adverse roles in promoting cardiovascular pathologic conditions (see Table 5-1; Fig. 7-9). The prototype, losartan, has now been joined by many others (see Table 5-11). ARBs are being used more and more for hypertension and for heart failure and they are, by far, the fastest growing class of antihypertensive drugs in the United States and Europe[100] because they are virtually free of side effects, in particular the cough that occurs in approximately 10% of patients given an ACE inhibitor and because they are so heavily marketed since they all remain patent-protected. There is increasing evidence of their capacity to reduce hard endpoints.[128] ARBs are superior to β-blockade in patients with LVH[128] and to alternate therapies in type 2 diabetics with nephropathy,[129] but are not better than ACE inhibitors in heart failure in postinfarct patients.[115]

ARBs were thought to be better than ACE inhibitors in protection against stroke.[130] This contention is strengthened by experimental and clinical evidence that agents that reduce circulating angiotensin-II (e.g., ACE inhibitors) are less effective in protecting the cerebral circulation than are agents that increase circulating A-II levels by blocking the AT_1 receptor (e.g., ARBs). The argument is based on increased activation of the AT_2-receptor when the AT_1 receptor is blocked, which "would facilitate the recruitment of collateral vessels or increase neuronal resistance to anoxia."[131] However, the large ONTARGET study on more than 25,000 persons at high cardiovascular risk shows that the ACE inhibitor ramipril and the ARB telmisartan are equally good in reducing cardiovascular outcomes, including stroke.[132]

Current and future role of ARBs in hypertension.

ARBs block the same RAS as the ACE inhibitors, with much the same effects but presently at greater cost. Thus an ACE inhibitor remains the more cost-effective solution, with an ARB substituted only if ACE inhibitor side effects, chiefly cough, develop. Another view is that ARBs have an excellent record in comparative studies showing better or similar cardiovascular outcome benefit,[88],[132] virtually without the major side effects of ACE inhibitors, and provide relatively symptom-free control of hypertension. ARBs are better tolerated than ACE inhibitors and all other antihypertensive drug classes, and thus promote adherence.[133]

Direct renin inhibitor

As the only new antihypertensive class introduced in more than a decade, the first direct renin inhibitor, aliskiren, was heavily promoted at first, although enthusiasm may be starting to wane. It clearly lowers BP as well as other RAS blockers[134] and according to one 24-hour ABPM study, it adds to the antihypertensive effect of a full dose of an ARB.[135] It provides dose-dependent and sustained 24-hour efficacy, which is enhanced by concomitant diuretic.[136] The possible downside is production of excess potentially pathogenic renin,[137] which might help to explain the adverse effects noted in the ALTITUDE study (see Chapter 5, p. 162).

ACCELERATE was a small study in which hypertensive persons were given either aliskiren (150-300 mg) or amlodipine (5-10 mg) or the combination, with approximately equal BP reduction in both arms and a larger drop when combined.[138] In the future aliskiren might be promoted as part of a polypill (see Chapter 5, p. 163).

Aldosterone blockers

Spironolactone and eplerenone.

There is a special argument for spironolactone and eplerenone in primary aldosteronism but also in those subjects with RH.[69],[70] Based on ASPIRANT[70] and the ASCOT-BPLA[69] studies, spironolactone is an attractive fourth-line agent. The ASPIRANT study was the first proper randomized controlled trial with spironolactone, when spironolactone 25 mg or placebo was given to patients with RH. In this small, 8-week trial on 111 patients with RH, 75% or more were taking four agents (ACE inhibitor, β-blocker, CCB, including a diuretic [100%]).The ABP nighttime systolic, 24-hour systolic, and the office systolic BP values all fell with spironolactone (difference of –8.6, –9.8, and –6.5 mm Hg; P = 0.011, 0.004, and 0.011), but the diastolic changes were not significant. Maybe higher doses would have dropped the diastolic values further. Based on the RALES trial (see Chapter 5, p. 159), spironolactone is finding wider use in hypertensive patients with congestive heart failure, provided that serum K is carefully monitored.

Eplerenone.

Eplerenone (Inspra) is a more specific congener with much less risk of gynecomastia. Unlike spironolactone, eplerenone does not have an active metabolite. It has a half-life of 3.5 to 5 hours and is excreted in urine (66%) and in feces. Because eplerenone metabolism is predominantly by hepatic CYP3A4, eplerenone must not be used with drugs that are strong inhibitors of CYP3A4 (such as ketoconazole, clarithromycin, nefazodone, ritonavir and nelfinavir). The starting dose of eplerenone is 50 mg daily, increased if needed to 50 mg twice daily. The full antihypertensive effect may need 4 weeks.

Besides improving survival in post-MI heart failure in EPHESUS,[139] eplerenone is now used for hypertension, either alone or in combination with other agents. The antihypertensive effect of eplerenone 50 mg daily was equal in black and white patients and was superior to losartan 50 mg daily in black patients.[140] Mechanistically, eplerenone improves the impaired endothelial function in hypertensive persons, which losartan does not.[141] Eplerenone may apparently be used instead of spironolactone in RH (see preceding paragraph). Nonetheless, there are no formal outcome trials on eplerenone for RH. There are strict FDA warnings about contraindications that include hyperkalemia of more than 5.5 mEq/L, a reduced creatinine clearance of 30 mL/min or less, type 2 diabetics with early renal involvement, and the use of other K-retaining agents or K-supplements.

The future.

An aldosterone synthase inhibitor is undergoing early testing.[142]

Decreased sympathetic activity.

In a small but provocative study, aldosterone blockers as first-line agents (in patients of mean age 68 years) unexpectedly reduced sympathetic activity as measured by serum norepinephrine (NE) levels, whereas the diuretic did not, thus giving an additional mechanism of action.[143] Furthermore, the BP levels fell more with the aldosterone blocker. In another small study, skeletal muscle sympathetic nerve activity as measured directly with intraneural microelectrodes increased and glucose tolerance worsened when antihypertensive therapy was initiated with chlorthalidone, but both sympathetic activity and glucose tolerance were unchanged when therapy was initiated with spironolactone.[144]

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β-blockers for hypertension

β-blockers act by multiple mechanisms (Fig. 7-10). As first recognized by Messerli et al. in 1998,[145] proven by Carlberg et al. in 2004,[146] and amply confirmed since,[63],[147] β-blockers do not protect against heart attack better than other classes and are associated with a 14% increase in the risk of stroke. β-blockers are no longer recommended for primary prevention and are now often relegated to specific concomitant conditions for secondary prevention (see Table 7-3). Their relative ineffectiveness for primary prevention can be attributed to multiple adverse effects: loss of insulin sensitivity with resultant increased risk of diabetes; increase in plasma triglyceride and lowering of high-density lipoprotein (HDL) cholesterol; increase in body weight; easy fatigability, which reduces the ability to perform physical activity; as noted in a substudy of the ASCOT trial, a lesser reduction in central as opposed to peripheral BP[148]; and finally an increase in BP variability.[148A] Furthermore, β-blockers differ from other standard antihypertensive agents in reducing aortic pressure less for a given fall in brachial pressure.[149] Their reservations may apply less or not at all to the vasodilating β-blockers, especially not to nitric oxide (NO)–generating nebivolol. At the same time, there is another strong point of view, based on an analysis of more than 200,000 persons with more than 20,000 outcome events in the BP Trialists' Collaboration, that there were no differences in the proportionate risk reductions achieved with different BP-reducing regimens.[150] In other words, the basic message remains, "Get the BP down."

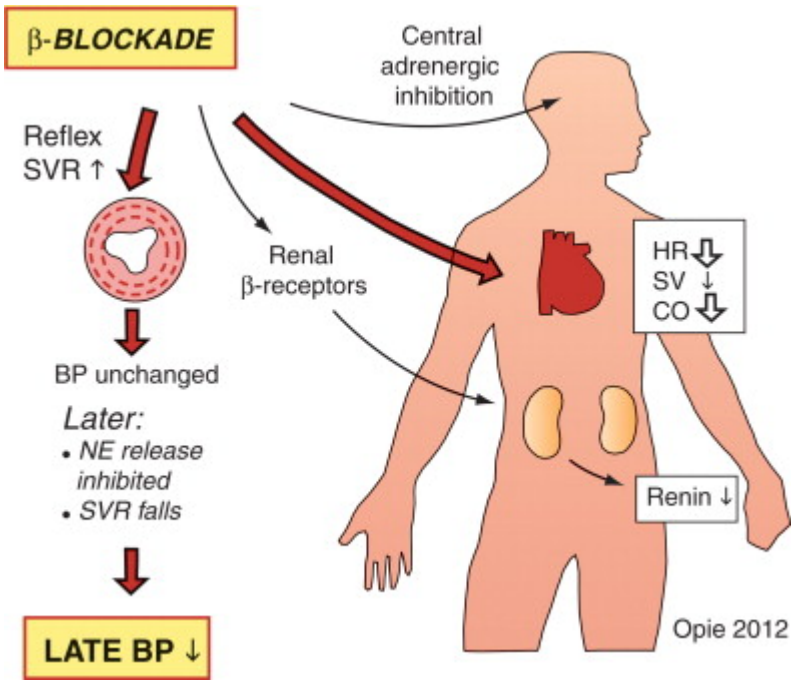

Figure 7-10 Proposed antihypertensive mechanisms of β-blockade. An early fall in heart rate (HR), stroke volume (SV), and cardiac output (CO) does not lead to a corresponding fall in blood pressure (BP) because of baroreflex-mediated increased peripheral α-adrenergic vasoconstriction, with a rise in systemic vascular resistance (SVR). Within a few days β-blockade of prejunctional receptors on the terminal neuron, with consequent inhibition of release of norepinephrine (NE), may explain why the SVR reverts to normal. The BP now falls. In the case of vasodilatory β-blockers (see Fig. 1-10) there is an early decrease in SVR and a more rapid fall in BP.
(Figure © L.H. Opie, 2012.)

Vasodilating β-blockers.

Labetalol, carvedilol,[151] and nebivolol (in SENIORS for HF), cause less metabolic mischief and logically should be used in place of metoprolol or atenolol, although there are no good outcome data for their use as antihypertensives. Nebivolol has NO-producing properties. Are these specifically protective? One claim is that nebivolol reduced central aortic pressure and LVH better than metoprolol.[152] However, in relation to the wider use of nebivolol on this basis, the caution is that "the real paradigm shift will only come if and when studies demonstrate that selective reduction in central pressure reduces cardiovascular events."[149] A strong proposal is that nebivolol is superior to metoprolol in effects on insulin sensitivity and fibrinolytic balance. At doses that were equipotent with respect to reductions in BP, heart rate, and renin activity, metoprolol treatment decreased insulin sensitivity, increased plasminogen activator inhibitor–1 antigen concentrations, and increased oxidative stress, whereas nebivolol treatment did not.[153] The real question is whether expensive nebivolol offers any real advantage over generic carvedilol, which now is included on standard formularies. In the GEMINI study, carvedilol was superior to metoprolol in limiting insulin resistance.[154]

Pharmacokinetics of β-blockers.

Dose adjustment is more likely to be required with more lipid-soluble (lipophilic) agents, which have a high "first-pass" liver metabolism that may result in active metabolites: the rate of formation depends on liver blood flow and function. The ideal β-blocker for hypertension is long acting, cardioselective (see Fig. 1-9), metabolically favorable (see previous comments on nebivolol), and usually effective in a standard dose. Simple pharmacokinetics may be an added advantage (no liver metabolism, little protein binding, no lipid solubility, and no active metabolites). Sometimes added vasodilation should be an advantage, as in older adults or in black patients. The ideal drug would also be "lipid neutral," as is claimed for some agents (see Table 10-5) and glucose neutral. In practice, once-a-day therapy is satisfactory with many β-blockers, but it is important to check early morning predrug BP to ensure 24-hour coverage (as with all agents). Combinations of β-blockers with one or another agent from all other classes have been successful in the therapy of hypertension. Nonetheless, combination with another drug suppressing the RAS, such as an ACE inhibitor or an ARB, is not logical, nor did it work well in ALLHAT.[88]

Diuretics plus β-blockers.

Diuretics plus β-blockers in combination should ideally contain no more than 12.5 mg HCTZ, 1.25 mg bendrofluazide, or preferably a similar low dose of chlorthalidone. Diuretic–β-blocker combinations should be avoided whenever diabetes risk is a consideration.

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α-adrenergic blockers

Of the α_1-receptor blockers, *prazosin (Minipress), terazosin (Hytrin)*, and *doxazosin (Cardura)* are available in the United States. Their advantages are freedom from metabolic or lipid side effects, but some patients develop other troublesome side effects: drowsiness, diarrhea, postural hypotension, and occasional tachycardia. Tolerance, related to fluid retention, may develop during chronic therapy with α_1-blockers, requiring increased doses or added diuretics. Fluid retention may explain why the doxazosin arm of the ALLHAT study was terminated because of an excess of heart failure, compared with reference diuretic.[155] Thus these agents now have a lesser place in initial monotherapy. Nonetheless, in the TOMH study on mild hypertension,[86] doxazosin 2 mg/day given over 4 years and combined with lifestyle changes reduced the BP as much as agents from other groups. The QOL improved as much as with placebo, although not quite as much as with acebutolol; blood cholesterol fell; and the incidence of impotence was lowest in the doxazosin group.[78]

Thus despite the disappointing ALLHAT result, α-blockers may still be chosen especially in those with features of the metabolic syndrome or in the many men with benign prostatic hypertrophy in whom α-blockers provide symptomatic relief.[156] α-blockers combine well with other drugs and doxazosin, and when used as the third line of therapy in the ASCOT trial, provided an impressive lowering of BP by 12/7 mm Hg in those patients who had not responded to full doses of their initial two drugs.[157] Phenoxybenzamine and phentolamine are combined α_1 and α_2-blockers used only for *pheochromocytoma.* Labetalol and carvedilol have limited α-blocking activity.

Direct vasodilators

Hydralazine used to be a standard third-line drug, its benefits enhanced and side effects lessened by concomitant use of a diuretic and an adrenergic inhibitor. Being inexpensive, hydralazine is still widely used in the developing world. Elsewhere fear of lupus (especially with continued doses of more than 200 mg daily) and lack of evidence for regression of LVH has led to its replacement by the CCBs. Nonetheless, hydralazine has undergone a facelift for use in heart failure, combined with isosorbide dinitrate (BiDil, see Chapter 2, p. 50), particularly for black patients. *Minoxidil* is a potent long-acting vasodilator acting on the potassium channel. In addition to inciting intense renal sodium retention that requires large doses of loop diuretics to overcome, it often causes profuse hirsutism, so its use is usually limited to men with severe RH or renal insufficiency (it dilates renal arterioles). Occasionally minoxidil causes pericarditis. In one series, LV mass increased by 30%.

Central adrenergic inhibitors

Of the centrally acting agents, *reserpine* is easiest to use in a low dose of 0.05 mg/day, which provides almost all of its antihypertensive action with fewer side effects than higher doses. Onset and offset of action are slow and measured in weeks. When cost is crucial, reserpine and diuretics are the cheapest combination. *Methyldopa,* still used despite adverse central symptoms and potentially serious hepatic and blood side effects, acts like clonidine on central α_2-receptors, usually without slowing the heart rate. *Clonidine, guanabenz,* and *guanafacine* provide all of the benefits of methyldopa with none of the rare but serious autoimmune reactions (as with methyldopa, sedation is frequent). In the VA study,[64] clonidine 0.2 to 0.6 mg/day was among the more effective of the agents tested. It worked equally well in younger and older age groups and in black and white patients. The major disadvantage in that trial was the highest incidence of drug intolerance. A particular problem is clonidine rebound. A *transdermal form of clonidine* (Catapres-TTS) provides once-a-week therapy, likely minimizing the risks of clonidine rebound. *Guanabenz* resembles clonidine but may cause less fluid retention and reduces serum cholesterol by 5% to 10%. *Guanfacine* is a similar agent that can be given once daily (at bedtime for less daytime somnolence), with less risk of rebound hypertension if abruptly discontinued. *Imidazole receptor blockers* (e.g., moxonidine, rilmenidine) are available in Europe, but not in the United States.

Combination therapy

Background.

In general, guidelines suggest that therapy for mild hypertension (BP <160/100 mm Hg) should start with one drug, with combinations of drugs for more severe hypertension. Guidelines also recommend initial drug combinations as first-step treatment strategy in high-risk hypertension. However, the hard evidence that this policy is associated with cardiovascular benefits compared with initial monotherapy is limited. Does a combination of antihypertensive drugs provide a greater cardiovascular protection in daily clinical antihypertensive monotherapy?

Initial combination therapy.

In a population-based, nested case-control study involving 209,650 patients from Lombardy, Italy, and using logistic regression to model the cardiovascular risk associated with starting on or continuing with combination therapy, those started on combination therapy had an 11% cardiovascular risk reduction with respect to those starting on monotherapy.[158] Compared with patients who maintained monotherapy also during follow-up, those who started on combination therapy and kept it all along had 26% reduction of cardiovascular risk (95% confidence interval [CI]: 15% to 35%). Thus the authors argue that indications for using combinations of BP drugs should be broadened. However, as pointed out in the accompanying editorial,[159] the study remains observational as the patients were not randomized. To correctly assess initial combination versus initial monotherapy would require much larger randomized trials. In the meantime, we note that the concept of low doses of two drugs being better than high doses of one receives support from the Law metaanalysis of 147 trials (see Figs. 7-4 and 7-5): addition of the starting dose of a second drug causes a fivefold greater reduction in BP than doubling the dose of the first drug.[32] In addition, low-dose combination therapy reduces the risk of dose-dependent side effects.

CCB–ace inhibitor combination.

CCB–ACE inhibitor combination therapy had a resounding success in ASCOT,[102] which paved the way for ACCOMPLISH. The amlodipine-perindopril–based combination regimen was much better than the atenolol-diuretic regimen. After a mean of 5.5 years of follow-up, major decreases were in total cardiovascular events (HR 0.84; $p < 0.0001$), stroke (HR 0.77; $p = 0.0003$), all-cause mortality (HR 0.89: $p = 0.025$) and new diabetes (HR 0.70; $p < 0.0001$).

Accomplish.

The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial showed that initial antihypertensive therapy with benazepril plus amlodipine was superior to benazepril plus HCTZ in reducing cardiovascular morbidity and mortality in high-risk hypertensive patients.[160] Benazepril is a prodrug that is rapidly converted to an active metabolite, benazeprilat, with an elimination half-life of 22 hours. In ACCOMPLISH benazepril was used once daily and was successfully combined with the long-acting DHP-CCB amlodipine in the double-blind, randomized trial on 11,506 patients with hypertension at high risk for cardiovascular events. Doses were benazepril (20 mg) plus amlodipine (5 mg) or benazepril (20 mg) plus HCTZ (12.5 mg), orally once daily. Both primary outcome events ($P < 0.001$) and secondary endpoints (death from cardiovascular causes, nonfatal MI, and nonfatal stroke [$P = 0.002$]) were reduced by approximately 20% more in the benazepril-amlodipine group.[160] ACCOMPLISH argues for the ACE inhibitor–CCB combination versus the ACE inhibitor–thiazide combination as the preferred initial therapy in a high-risk hypertensive population. Of note is the longer half-life of amlodipine versus HCTZ. Nonetheless, with exactly similar rates of 24-hour BP control,[107] there must be explanations other than better BP reduction for the superior results in the ACE inhibitor–CCB group.

Renal effects.

Progression of chronic kidney disease, a prespecified endpoint in ACCOMPLISH,[108] was defined as doubling of serum creatinine concentration or end-stage renal disease (eGFR <15 mL/min/1.73 m[2]) or need for dialysis. Events of renal progression in the benazepril-amlodipine group equalled 2% compared with 3.7% in the benazepril-HCTZ group (HR 0.52; CI: 0.41-0.65, p < 0.0001). Thus initial antihypertensive treatment with benazepril-amlodipine should be considered in preference to benazepril-HCTZ because it slows progression of nephropathy to a greater extent. Extrapolation to the broader picture is that slower ACE inhibitor plus CCB therapy should be considered as first line for patients with high-risk hypertension rather than the usual ACE inhibitor plus thiazide.

Polypill.

The polypill concept is gaining ground,[161-163] in support of the Law and Wald[32] concept that several drugs at low doses are better able to drop BP than high doses of single drugs (see Figs. 7-4 and 7-5).

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Patient profiling: The elderly

As lifespan now extends, more and more patients are falling into the older adult category. The algorithm provided in the current guidelines of the British Hypertension Society[9] is rational in giving preferential benefit of C (CCB) drugs. In much older adults, therapy is diuretic based as in HYVET.[93] Note the resounding success of CCB–ACE inhibitor combination in ASCOT[102] and in ACCOMPLISH.[160] As most patients require two or more drugs to achieve adequate BP control, the issue as to which should be chosen for initial therapy has almost become moot. Nonetheless, as noted in Table 7-3, certain choices are more appropriate for many concomitant conditions.

Changes with aging.

With aging, there is inevitable aortic stiffening (Fig. 7-11),[164] which explains the inevitable rise of systolic BP with age. The resulting carotid-femoral delay can be measured noninvasively.[34] Multiple trials have documented even better protection against stroke and other outcome measures by treatment of older adults than reported in the middle aged.[165] Thus an equivalent BP reduction will produce a greater benefit in older adults than in younger patients,[32] especially if there are other risk factors such as diabetes mellitus. Dementia is delayed or prevented.[166] In older adults, evidence for the benefit of β-blockers has "not been convincing," whereas CCBs match the needs of the older adult patient typically with "increasing arterial stiffness and diastolic dysfunction secondary to decreased atrial and ventricular compliance."[167] For combination therapy, this massive American College of Cardiology–American Heart Association review notes that in ACCOMPLISH (mean age 67 years), amlodipine plus the ACE inhibitor benazepril gave better reduction in morbidity and mortality than did amlodipine plus HCTZ 12-25 mg daily. Note that this superiority was only found when the eGFR was more than 60 mL/min.[108]

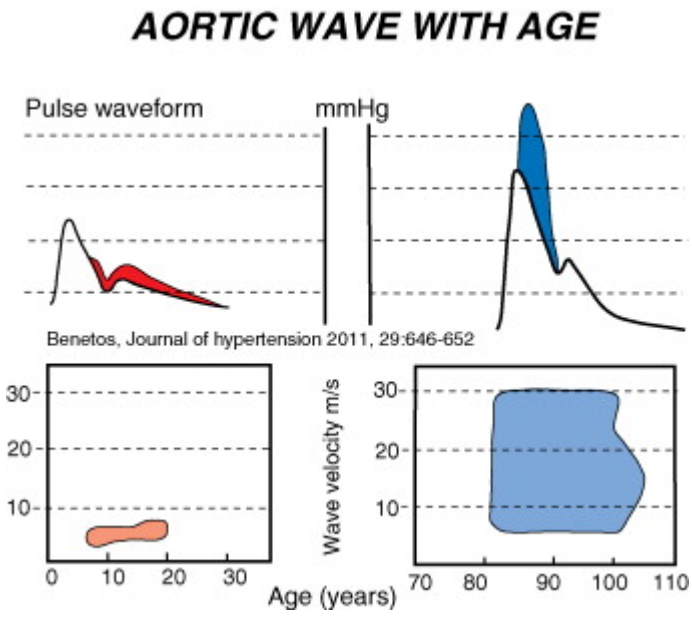

Figure 7-11 Changes in aortic pressure wave in older adults. Note abrupt rise and fall in older adults (*upper panel, right side*) and marked differences in wave velocity patterns (older adults *right lower panel*). These are direct invasive arterial measurements.[164] The associated carotid-femoral delay can be measured noninvasively.[34] *m/s*, meters/seconds.

Treating patients older than 80.

Patients older than 80 should be treated, with care, and with a BP target of 150/80 mm Hg.[93]

Blood pressure limits.

There is compelling evidence to suggest that sustained SBP elevations of more than 160 mm Hg require treatment,[93],[165] and that the systolic rather than the diastolic pressure is of greater importance in this age group. Therefore *isolated systolic hypertension* (with DBP of less than 90) should be actively treated. In the presence of end-organ damage, including abnormalities of the thoracic or abdominal aorta, or diabetes, BP values of more than 140 mm Hg should be taken as reason for active therapy. Less commonly, there is *isolated diastolic hypertension* with sustained DBP values of 90 mm Hg and systolic values that are not elevated. These levels should be treated as in younger patients.

Lifestyle changes.

Again, whenever possible, treatment includes nonpharmacological measures, including exercise training. Even walking sharpens cognitive skills in older adult patients.[168] Older women are especially sodium-sensitive. Besides sodium restriction, increased dietary potassium may be protective.[169] The combination of sodium restriction, loss of weight, and walking is especially desirable.

How low to go.

In the decisive HYVET trial in much older adults, the aim was 150/80 mm Hg.[93] The *J-shaped curve* (see "J-shaped curve" earlier in chapter) is of particular significance in hypertensive patients with myocardial ischemia or LVH, or in older adults with an increased pulse pressure and low diastolic BP to start with. Is the damage caused by excessively dropping the diastolic BP mitigated or exceeded by the benefit of dropping the systolic BP? Here there are no prospective trial data.

Drugs for older adult hypertensive patients.

Low-dose diuretics remain the first-line drug choice for older adults because they were used in the SHEP study[82] and several other major trials, including HYVET,[93] and perhaps, equally important, because they help to lessen osteoporosis (see Chapter 4, p. 105) and dementia,[166] conditions that are often disabling in older adults.

Calcium channel blockers.

CCBs are able to reduce morbidity and mortality in older adults, the agents used being nitrendipine in the Syst-Eur and Syst-China trials, and nifedipine in older adult Chinese patients with hypertension, all being long-acting DHPs. Amlodipine was equal to a diuretic or an ACE inhibitor in coronary protection in the ALLHAT trial.[88]

β-blockers.

β-blockers are at a disadvantage compared with diuretics in older adults, but may be indicated for secondary prevention of MI or for heart failure. Risks of β-blockade in older adults include excess sinus or atrioventricular node inhibition and a decreased CO, which in the senescent heart could more readily precipitate failure.

ACE inhibitors and ARBs.

ACE inhibitors and ARBs are also often used in older adults. The STOP-2 trial provides evidence that they are as good as conventional treatment and perhaps better than CCBs[170] and in the men in the Australian trial, better than a diuretic.[90] Logically, ACE inhibitors and ARBs are more effective with dietary sodium restriction, or low-dose diuretics, or both. ACE inhibitors improve insulin sensitivity in older adults, which may help protect from adverse metabolic effects of concurrent diuretics. So far SCOPE has been the only study with an ARB in older adults.[171]

Combination treatment.

Combination treatment is often required, as was the case in nearly two thirds of older adult patients with hypertension in ALLHAT.[88] ACE inhibitor or ARB plus diuretics, and CCBs plus ACE inhibitors or ARBs all

seem to work equally well, using mortality and cardiovascular events as outcome measures.

Two cautions are needed for treating older adults: they may experience cardiac or cerebral ischemia if the diastolic pressure is lowered to less than 70 mm Hg[30] and they often have orthostatic hypotension (and postprandial hypotension), which may be worsened by addition of antihypertensive therapy.[172]

Patient profiling: Other special groups

Angina and hypertension.

The only antianginal antihypertensive agents are β-blockers and CCBs. A direct comparison between atenolol and verapamil showed equality of major outcomes with some other advantages for verapamil such as fewer anginal attacks and less new diabetes.[83] Despite this trial result, verapamil is little used, mainly because constipation is a particularly limiting side effect. Diuretics, α-blockers, ACE inhibitors, and ARBs do not have direct antianginal effects, although indirect improvements in the myocardial oxygen balance by regression of LVH and reduction of BP have been shown by use of an ACE inhibitor in the HOPE trial[113] and an ARB in the LIFE trial.[128]

Black patients.

In ALLHAT, the risk for stroke was greater with the ACE inhibitor lisinopril, but the control of BP also was poorer, probably because of the trial design, which prohibited the combination of the ACE inhibitor with a thiazide or with amlodipine.[88] Of note, angioedema in black patients was much more common with lisinopril (0.7%) than seen in usual practice. Black patients respond better to monotherapy with a diuretic or to a CCB than to monotherapy with an ACE inhibitor or ARB or β-blocker. The common denominator might be the low renin status of older black patients taken as a group. Overall evidence suggests that combination with diuretic increases sensitivity to a β-blocker or an ACE inhibitor or an ARB likely because the diuretic increases renin. In a direct comparison, CCB therapy was more effective than a low-dose diuretic as first-line therapy in South African black patients,[103] perhaps because sodium intake was not controlled.

Diabetic hypertensive patients.

Based largely on expert opinion only, previous guidelines have recommended that antihypertensive therapy should be started in diabetics at a BP of more than 130/80 mm Hg and the goal of therapy is to lower systolic pressure to less than 130 mm Hg.[38] In the recent ACCORD trial, further BP reduction reduced strokes, but did not afford further protection against heart attack or other cardiovascular complications and caused more adverse drug reactions[173]; however, the benefit of more intense BP lowering may have been underestimated as the diabetic study cohort had a surprisingly low CVD event rate.

Diabetics with nephropathy.

In type 1 diabetic nephropathy, ACE inhibitors have repeatedly been shown to reduce proteinuria and protect against progressive glomerular sclerosis and loss of renal function.[174] In type 2 diabetic nephropathy, trials with ARBs have shown similar renal protection.[175] In those with type 2 diabetes the relative resistance of the renal renin response to RAS blockade supports the concept of an activated RAS in diabetes, and implies that diabetic patients might require higher doses of RAS blockers to fully suppress RAS.[176]

Evidence for specific renoprotection is stronger for ACE inhibitors for type I and ARBs for type 2 diabetic renal disease. Using the combined data of the RENAAL and IDNT trials, a progressively lower cardiovascular risk was observed with a lower albuminuria level particularly evident in those reaching the SBP target of 130 mm Hg or less. Because the SBP and albuminuria responses to ARB therapy are variable and discordant, there should be a dual target of reducing both BP and albuminuria.[177] Nonetheless, in practice ACE inhibitors may be used whenever ARBs cannot be afforded.[178]

Dyslipidemias.

For patients with established dyslipidemias, a statin will be needed, particularly in view of the impressive coronary and stroke protection with 10 mg atorvastatin in the ASCOT-LLA trial where the mean cholesterol

level was only modestly elevated (see Chapter 10, p. 420). Although the higher doses of *diuretics* previously used increased plasma cholesterol, with modern low-dose treatment the problem is less. Regarding *β-blockade,* many had assumed that the protection β-blockers provide against recurrent heart attacks may serve to prevent initial coronary events in hypertensive patients, but the evidence shows poor comparison and no benefit compared with other drugs.[179] Because earlier generation β-blockers raise serum triglycerides, lower HDL cholesterol levels, impair insulin sensitivity, and may precipitate type 2 diabetes while providing less protection against stroke, they are no longer recommended for primary prevention. The *α-blockers* clearly improve the blood lipid profile, whereas the ACE inhibitors, ARBs, and CCBs are "lipid neutral" in most studies. All of these agents also allow a better exercise performance than β-blockers.

Exercising hypertensive patients.

Low- to moderate-intensity aerobic exercise training lowers the resting BP, so that increased exercise is part of lifestyle modification in the treatment of hypertension. Lack of exercise is an independent risk factor for coronary heart disease. When, besides lifestyle modification and exercise, drug treatment is required, then the best category of drug might be that which leaves the increased CO of exercise unchanged while blunting the simultaneous BP rise. This goal is best attained by the ACE inhibitors or ARBs or by DHP-CCBs. β-blockade, in contrast, limits the CO by decreasing the heart rate, even in the case of vasodilatory β-blockers.

Metabolic syndrome.

Hypertension is present in 50% of type 1 diabetes, mostly secondary to renal damage; in type 2 diabetes, hypertension is present in 80%, often as a component of the *metabolic syndrome* (see Chapter 11, Fig. 11-1). Among treated hypertensive patients, diabetes developed over 25 years in 20.4%, related both to weight gain and use of β-blockers.[180] In diabetes, the BP aims have been stricter than in nondiabetics. JNC 7 recommended a goal BP of 130/80 mm Hg. In the ADVANCE study[181] the BP in high-risk diabetic patients already treated to mean BP levels of 140/77 mm Hg was further reduced by the addition of an ACE inhibitor, perindopril, together with a diuretic, indapamide. Mean BP reductions were 5.6/2.2 mm Hg. All-cause mortality fell by 14% ($p = 0.03$). In diabetics with isolated systolic hypertension, the systolic BP should drop to approximately 140 mm Hg. Again, treatment starts with lifestyle modification including control of hyperglycemia. It makes sense to avoid high-dose diuretics and β-blockers as initial therapy in those prone to diabetes because of a personal or family history or by the metabolic syndrome.[110] Rather, there are arguments for initial ACE inhibitors or ARBs. CCBs generally leave diabetic control unaltered and in the Syst-Eur trial the long-acting DHP nitrendipine protected the diabetics better than did the diuretic in SHEP.[182] A logical sequence (although not trial based) would be an ACE inhibitor or ARB, a CCB as the second drug, and either a metabolically neutral vasodilating β-blocker or a very low-dose thiazide as the third drug. α-blockers may also be appropriate.

Obese hypertensive patients.

The characteristics of obesity hypertension are an increased plasma volume, a high CO (explicable by Starling's law), and a low PVR. The basic mechanisms are complex but include an increased tubular reabsorption of sodium and increased sympathetic outflow. Weight reduction is not easy to achieve and even harder to maintain, but even small degrees of weight loss, if maintained, help keep BP down. For every 1 kg of weight loss, there is a BP reduction of approximately 1 mm Hg.[183] Because of the association between insulin resistance and obesity, and the potential adverse effects of high doses of diuretics on insulin, the dose of diuretic should be kept low. LVH is a particular hazard, which obesity and insulin resistance promote independently of the BP. Regarding further drug choice, in the absence of good trial data, a logical selection is an agent that is metabolically beneficial and known to combine well with a diuretic such as an ACE inhibitor or an ARB. An ACE inhibitor–DHP–CCB combination avoids the diabetogenic potential of a thiazide. In general, β-blockers should be avoided.[184]

Postinfarct hypertensive patients.

In patients with hypertension, acute myocardial infarction (AMI) often drops the BP, which may then creep back in the postinfarct months. There has been no adequate prospective study to determine the best treatment of postinfarct hypertension, but β-blockers and ACE inhibitors (or ARBs) are in any case indicated post-MI and should also handle the hypertension.

Smokers.

It is *imperative* that the patient stops smoking. Smoking, besides being an independent risk factor for coronary artery disease and for stroke, also interacts adversely with hypertension. First, smoking helps to promote renovascular and malignant hypertension. Second, smoking damages the vascular endothelium, the integrity of which is now thought to be important in maintaining a normal BP and erectile function. Third, heavy smoking results in a sustained rise in BP or intense swings to high systolic values, as revealed by ambulatory measurements.[185] Normal casual office BP values while the patient is not smoking mask the adverse effects of smoking on the BP.

Pregnancy hypertension.

The best tested drug is methyldopa (Category B; see Table 12-10). ACE inhibitors and ARBs are totally contraindicated.

Sleep apnea in hypertensive patients.

In a consecutive series of 125 patients with RH, sleep apnea was the commonest cause (64%). Age older than 50 years, large neck circumference measurement, and snoring were good predictors of obstructive sleep apnea.[186] Catheter-based renal sympathetic denervation lowered BP and decreased indices of sleep apnea in patients with refractory hypertension and obstructive sleep apnea. Interestingly, there are also accompanying improvements in glucose tolerance.[187]

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Specific aims of antihypertensive therapy

Regression of left ventricular hypertrophy.

Preferably diagnosed by echocardiography rather than electrocardiogram, LVH is increasingly seen as an important complication of hypertension. Apart from being an independent cardiovascular risk factor, LVH is associated with abnormalities of diastolic function, which can result in dyspnea or even overt LV failure. An important point is that reduction of the BP does not rapidly result in decreased LVH so that prolonged therapy, up to 3 years, may be needed to achieve full regression. Several important retrospective analyses support the concept that the most effective agents in achieving LV regression are those that interrupt the growth pathways that make myocytes hypertrophy such as the ACE inhibitors, ARBs, or CCBs.[39] The LIFE study gave a decisive advantage to the ARB losartan versus a β-blocker, atenolol.[128] In the LIFE study, both protection against sudden death[188] and the incidence of new diabetes were related to the regression of LVH.[189] Of interest is the concept that it is not only the daytime BP that governs LVH, but also the absence of a normal nocturnal BP fall. A novel aim is reduction of central aortic pressure. The hypertrophic response to catecholamines is mediated by α-adrenoreceptors, not β-adrenoreceptors. Vasodilating β-blockers should theoretically be better than standard β-blockers. Thus nebivolol reduced LVH better than metoprolol.[152]

Atrial fibrillation.

LVH caused by hypertension predisposes to left atrial enlargement and thus to atrial fibrillation (see Fig. 8-11). Control of ventricular rate is one viable strategy, as achieved by a number of antihypertensive drugs: verapamil, diltiazem, and β-blockers. Going further back, LVH itself must be tackled by strict control of the BP. A recent editorial reviews the evidence in favor of choosing ARBs as class 1 level A agents in the prevention of atrial fibrillation in hypertension, on the basis of the prespecified secondary analyses from two large trials with double-blind design (valsartan in VALUE; telmisartan in ONTARGET/TRANSCEND).[190] ACE inhibitors, although without such solid data, are likely to have much the same effects.

Early morning blood pressure rise.

The highest BP found in the early morning hours soon after rising is strongly associated with sudden death, AMI, and stroke. Logically, there has been a drive for the use of ultra–long acting agents to blunt this early morning rise. In reality, the optimal management of early morning hypertension is still not clear and only one comparative prospective trial addressed this point. The drug used was time-released verapamil *(Covera HS)*, which showed no benefit of the CCB over β-blocker-based therapy.[191] However, this trial was prematurely terminated. Presently, the ideal policy, especially in those at risk of cardiac complications, is to achieve a normal BP in the morning, as measured at home, either by the patient or by ambulatory monitoring.

Ventricular arrhythmias.

Often associated with LVH, ventricular ectopic activity can be relatively harmless or can be indicative of underlying systolic dysfunction, the latter being due to hypertensive heart disease alone or in combination with coronary disease. β-blockade is often successful in suppression of harmless but irritating arrhythmias. Persistent and significant ventricular tachycardia may reflect accompanying coronary artery disease. Severe life-threatening arrhythmias in high-risk hypertensive patients may require class III agents, such as the β-blocker sotalol or amiodarone (see Chapter 8, p. 288), taking care to avoid diuretic-induced hypokalemia with risk of torsades.

Sildenafil to treat erectile dysfunction and hypertension.

Sexual dysfunction, especially in men, has been reported with almost every antihypertensive drug, probably

a consequence of reduction of blood flow through genital vessels already having endothelial damage from the ravages of smoking, hypercholesterolemia, and diabetes. In addition, erectile dysfunction can reflect early systemic vascular disease even in the absence of CVD. One study found an ARB to be better in maintenance of male sexual function when compared with β-blockade.[192] In the TOMH study, the incidence of impotence was lowest in those receiving the α-blocker doxasozin.[78] When needed, sildenafil or one of its successors can be used in hypertensive patients without angina and therefore not taking nitrates. It is important to note that sildenafil mainly promotes formation of vascular cyclic guansine monophosphate but also cyclic adenosome monophosphate to decrease peripheral BP, which accounts both for the well-known adverse interaction with nitrates (Fig. 2-6) and significant fall in BP.[193]

Optimal intellectual activity.

In general, antihypertensives, with the exception of centrally active agents such as clonidine and methyldopa, should be free of central side effects. Nevertheless, β-blockers may have subtle effects on the intellect. Although propranolol is the major culprit, even the lipid-insoluble agent atenolol is not blameless. To be totally sure of unimpaired intellectual activity, CCBs, ACE inhibitors, or ARBs seem to be the agents of choice. With control of hypertension, dementia may be delayed or prevented.[166]

Overall quality of life.

In general, all categories of antihypertensive agents improve the QOL except for propranolol and methyldopa, and probably other centrally active agents such as clonidine. Caution is advised in the interpretation of QOL studies because patients who drop out as a result of adverse effects are often not included. Nonetheless, impaired exercise capacity or lessened sexual performance, both occurring with β-blockers, clearly are bad news for the active male hypertensive patient. Conversely, a sufferer from anxiety-driven hypertension and tachycardia can achieve dramatic subjective relief from a β-blocker.

Cost effectiveness in the developing world.

Worldwide, expensive drugs often are a luxury, and the principles of choice are governed by economic necessity. True trial outcome data are lacking.[194] Much can be said for low-dose thiazide diuretics as initial therapy, or a CCB depending on costs. A diuretic-based therapy is logical in black patients, and when combined with enalapril and a CCB, controlled the BP in 78% of black South African hypertensive patients. With LVH as endpoint, the CCB was much more effective than the diuretic. The price of generic CCBs in a country like India is very low.

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Acute severe hypertension

First, it is important to consider whether the patient is suffering from a hypertensive urgency (BP very high, must come down but not necessarily rapidly) or emergency (complicated by acute heart failure papilledema or hypertensive encephalopathy) before choosing any of the drugs listed in Table 7-4. For urgency, careful use of rapidly acting oral agents such as furosemide and captopril is appropriate for imitation, with other agents added under tight supervision. For a true emergency, hospitalization is essential with careful administration of one of several agents (see Table 7-4). However, a rapid reduction of hypertension may have adverse end organ effects on brain and heart. *Thus it is prudent to consider whether rapid pressure reduction is really desirable in the presence of cerebral symptoms or symptoms of MI.* Therefore carefully titrated *intravenous nitroprusside, nicardipine,* or *labetalol* is preferable. Intravenous fenoldopam, a dopamine DA_1-selective agent, has the advantage of improving renal blood flow and the disadvantage of causing a reflex tachycardia. For acute LV failure, enalaprilat or sublingual captopril is first choice (see Table 7-4), together with a loop diuretic. For acute coronary syndromes, intravenous nitroglycerin is first choice, often with esmolol.

Table 7-4 -- Drugs Used in Hypertensive Urgencies and Emergencies

Clinical Requirement	Mechanism of Antihypertensive Effect	Drug Choice	Dose
Urgent reduction of severe acute hypertension	NO donor	Sodium nitroprusside infusion (care: cyanide toxicity)	0.3-2 mcg/kg/min (careful monitoring)
Hypertension plus ischemia (± poor LV)	NO donor	Infusion of nitroglycerin 20-200 mcg/min or isosorbide dinitrate 1-10 mg/h	Titrate against BP
Hypertension plus ischemia plus tachycardia	β-blocker (especially if good LV)	Esmolol bolus or infusion	50-250 mcg/kg/min
Hypertension plus ischemia plus tachycardia	α-β-blocker	Labetalol bolus or infusion	2-10 mg2.5-30 mcg/kg/min
Hypertension plus heart failure	ACE inhibitor (avoid negative inotropic rugs)	Enalaprilat (IV)Captopril (sl)	0.5-5 mg bolus12.5-25 mg sl
Hypertension without cardiac complications	Vasodilators, including those that increase heart rate	HydralazineNifedipine (see text)* Nicardipine : bolus : infusion	5-10 mg boluses1-4 mg boluses 5-10 mg sl (care) 5-10 mcg/kg/min 1-3 mcg/kg/min
Severe or malignant hypertension, also with poor renal function	Dopamine(DA-1) agonist; avoid with β-blockers	Fenoldopam[†]	0.2-0.5 mcg/kg/min
Hypertension plus pheochromocytoma	α-β-or combined α-β-blocker (avoid pure β-blocker)	PhentolamineLabetalol : bolus : infusion	1-4 mg boluses2-10 mg 2.5-30 mcg/kg/min

Modified from Foex, et al. Cardiovascular drugs in the perioperative period. New York: Authors' Publishing House; 1999, with permission. Nitrate doses from Table 6, Niemenen MS, et al. Eur Heart J 2005;266:384.

ACE, Angiotensin-converting enzyme; *BP,* blood pressure; *IV,* intravenous; *LV,* left ventricular; *NO,* nitric

oxide; *sl,* sublingual.

* Not licensed in the United States; oral nifedipine capsules contraindicated.

† Licensed as *Corlopam* for use in severe or malignant hypertension in the United States; for detailed infusion rates, see package insert. Note tachycardia as side effect must not be treated by β-blockade (package insert).

Nitroprusside.

Nitroprusside is still used extensively, but requires careful monitoring to avoid overshoot. Nitroprusside reduces preload and afterload. The package insert warns against continuing a high-dose infusion for more than 10 minutes if the BP dose not drop, because of the danger of cyanide toxicity (see Chapter 6, p. 186). *Labetalol* does not cause tachycardia and gives a smooth dose-related fall in BP; the side effects of β-blockade, such as bronchospasm, may be countered by the added α-blockade of labetalol. Hydralazine and dihydralazine may cause tachycardia and are also best avoided, especially in angina, unless there is concomitant therapy with a β-blocker or in preeclampsia for which it is the only approved parenteral agent in pregnancy.

Acute stroke with hypertension.

In acute stroke with hypertension, the benefits of BP reduction remain conjectural, and most neurologists would only reduce the BP if the diastolic level exceeds 120 mm Hg.

Maximal drug therapy

When confronted with the occasional patient who appears to be refractory to all known forms of therapy, the following points are worth considering: (1) Is the patient really adherent with the therapy? (2) Exclude white-coat hypertension. Are the BP values taken in the doctor's office really representative of those with which the patient lives? There can be striking differences. (3) Has the patient developed some complications such as atherosclerotic renal artery stenosis or renal failure? (4) Has the patient increased sodium or alcohol intake, or taken sympathomimetic agents or nonsteroidal antiinflammatory agents? (5) Are there temporary psychological stresses? (6) Could a cause of secondary hypertension be inapparent? For example, a high plasma aldosterone and low plasma rennin may be a clue to inapparent hyperaldosteronism that requires either replacing the thiazide by an aldosterone antagonist, or a combination of the two. Resistance may be overcome by aldosterone blockers even in the absence of hyperaldosteronism.[195] Then, finally, is the therapy really maximal, particularly regarding the diuretic dose? Overfilling of dilated vasculature by reactive sodium retention may also preclude a fall in the peripheral resistance. (Note that the concept of low-dose diuretic therapy must be abandoned at this stage).

Drugs for truly resistant hypertension.

RH is still an understudied clinical condition with a high cardiovascular morbidity and mortality, in which ABPM is established to guide diagnosis, therapy, and prognosis.[36] This means that the PVR or the CO or both has failed to fall. Generally, the emphasis should be on vasodilator therapy, acting on every conceivable mechanism: CCB, α-blockade, ACE inhibition, angiotensin receptor blockade, K^+ channel-induced vasodilation by *minoxidil,* high-dose diuretics, and aldosterone blockers. Severe hypertension often has a volume-dependent component and reactive sodium retention often accompanies the fall in BP induced by vasodilatory drugs and especially minoxidil; therefore the addition of more diuretics, particularly the loop agents, is an important component of maximal therapy. Of the loop diuretics, torsemide is registered for once-daily use in hypertension. Of the others, metolazone is equally effective as torsemide and even more certain to provide 24-hour efficacy. The *ganglion blockers* (guanethidine and guanadrel), now decidedly out of fashion because of frequent orthostatic hypotension and interference with sexual activity, should therefore be reserved for the last resort. The present trend is to emphasize the three basic drugs, namely a CCB like amlodipine, an ACE inhibitor–ARB, and a diuretic, and then to add two more, spironolactone and α-blockade, and only then to aim for renal artery denervation if available.

Renal artery denervation for hypertension

Catheter-based renal artery denervation is under intense investigation for the treatment of drug-resistant hypertension.[196] The US pivotal trial, Simplicity HTN-3, is recently underway. In an uncontrolled initial study of 153 patients with RH (mean: 176/98 ± 17/15 mm Hg on a mean of 5 BP agents) catheter-based renal sympathetic denervation gave a substantial reduction in BP of approximately 25/12 mm Hg sustained to 2 years or more of follow-up, without significant adverse events.[197] In SIMPLICITY HTN-2, in which patients were randomized to continued five-drug therapy alone or to continued five-drug therapy plus renal artery denervation, the 6-month data are quite promising[198] but need to be confirmed independently in the newly started SIMPLICITY HTN-3 trial that has a larger sample, a sham denervation arm, and mandatory 24-hour ABPM.

Renal artery denervation destroys both renal sympathetic (efferent) nerves, which stimulate renal vasoconstriction and renin release while blocking natriuresis, and afferent renal nerves (i.e., nerve trafficking to brain from kidney), which can trigger generalized reflex sympathetic overactivity and thus contribute to hypertension,[199] and raises the possibility that renal denervation (RDN) may exert systemic effects beyond just lowering of BP. Specifically, RDN has in early phase studies improved in measures of insulin sensitivity in diabetics with hypertension[200] and parameters of sleep apnea.[187] But an editorial in *Hypertension*[61] asks whether these patients really have drug-resistant hypertension, stating that there was almost no treatment with central sympatholytics or with α-blockers and few were treated by aldosterone antagonists. The counterargument is that many patients would prefer a one-time intervention to continuing with complex multiple medications.

Baroreflex activation therapy for hypertension

Implantation of a carotid baroreceptor pacemaker is another device-based approach being investigated for RH. Prolonged baroreflex activation by sustained electrical stimulation of the carotid sinus nerves in dogs lead to sustained reductions in arterial pressure, heart rate, and plasma NE concentrations.[201] The first US pivotal trial randomized patients with RH to an experimental condition of bilateral carotid baroreflex activation for 12 months or to a comparison condition of sham activation for the first 6 months followed by actual carotid baroreflex activation for the next 6 months; the results showed benefit for some but not all efficacy endpoints and too many adverse events (facial nerve palsy) related to the surgical procedure.[202] A second-generation device using a much smaller unilateral stimulating electrode (Barostim Neo, CVRx Inc) is currently being tested in Europe.

Summary

1. ***Major advances*** in the recent past include the following. The BP goals have become lower, but strongly related to the degree of risk. Therefore risk factor stratification is now an important part of the evaluation of hypertension. Blood lipid profiles should always be obtained and a statin given if indicated. Clinical examination should establish target organ damage prior to multifactorial lifestyle intervention.
2. ***Older adults and diabetics*** have emerged as two major high-risk groups. In older adults, treatment of systolic hypertension reduces stroke, cardiovascular events, and all-cause mortality. In diabetic patients, BP should ideally be reduced to 130/80 mm Hg in addition to statin therapy.
3. ***As agents of first choice,*** several national guidelines including those of the Joint National Committee in the United States recommend low-dose diuretics for uncomplicated hypertension in patients lacking specific indications for other agents because diuretics reduce a variety of important endpoints, including all-cause mortality. The British Society of Hypertension recommends one of three first-line choices: CCBs, ACE inhibitors–ARBs, or diuretics (chlorthalidone or indapamide). By contrast, the European Society of Hypertension proposes that any of five categories of drugs should be suitable, namely low-dose diuretics, β-blockers, CCBs, ACE inhibitors, or ARBs. The recent appreciation of a lesser protection against stroke by β-blockers has largely relegated them to secondary protection.
4. ***In diabetics,*** ACE inhibitors or ARBs are almost always the first choice. Diuretics, CCBs, and β-blockers may all be needed to bring down the BP to the low levels required.
5. ***In older adults,*** agents that have been primarily used in trials are low-dose diuretics and long-acting DPE calcium blockers. CCBs are logical therapy to counter impaired vasodilation in the aging arteries. In much older adults, the HYVET trial using initial diuretic therapy by indapamide was stopped because of a mortality reduction. The BP aim was 150/100 mm Hg. Caution is needed in further lowering already low diastolic pressure in those with isolated systolic hypertension, with data suggesting that the drop should not be less than 65-70 mm Hg.
6. ***In coronary disease*** in hypertensive patients, optimal management should control both BP and blood lipids, thereby potentially helping to reduce coronary mortality. No particular group of antihypertensive agents seems particularly effective in reducing coronary mortality. By contrast, statins are achieving increasing success.
7. ***In severe emergency hypertension,*** selection should be made from the available intravenous agents according to the characteristics of the patient. For those with severe hypertension but no acute target organ damage, fast-acting oral agents such as furosemide and captopril should be used.
8. ***In refractory hypertension,*** it is important to ensure compliance; to exclude a secondary cause, including aldosteronism; to think of white-coat hypertension; to check the 24-hour BP pattern; and only then to increase the medication.
9. ***In drug-refractory hypertension,*** renal artery sympathetic denervation is increasingly regarded as an option, although further data are needed for mechanical baroreceptor activation therapy.
10. ***As a general approach,*** we recommend a patient-guided approach together with a consideration of the major outcome trials and guidelines as the most appropriate way to treat hypertension. Improved control of hypertension is responsible for approximately 20% of the decline in coronary mortality noted in the United States from 1980 to 2000.[203] Even better effects can be achieved with more adequate control of BP.

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