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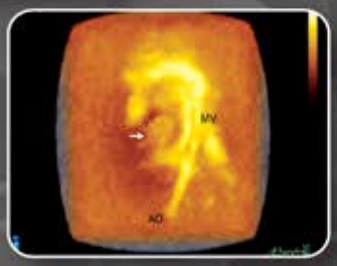

PRACTICAL CARDIOLOGY

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JAYPEE

Practical Cardiology

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CHAPTER 4

Drug Treatment for Hypertension

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INTRODUCTION

After more than 80 years of hypertension research and much talk about the newer drugs, sadly only four classes of antihypertensive agents are available to treat more than 1.2 billion individuals with hypertension: (1) diuretics, (2) beta-blockers, (3) calcium antagonists and (4) angiotensin-converting enzyme (ACE) inhibitors [angiotensin receptor blockers (ARBs)]; four drugs with numerous reduplications.

In addition, experts incorrectly advise that beta-blockers are poorly effective, should not be used in the elderly (Messerli et al. 1998) and cause diabetes (Bangalore et al. 2007), also diuretics cause diabetes. This chapter tells you otherwise.

COMMON DETRIMENTAL EFFECTS OF HYPERTENSION

- Fatal, nonfatal stroke
- Myocardial infarction (MI)
- Heart failure (HF)
- Left ventricular hypertrophy (LVH; Figs. 4.1A to D)
- Atrial fibrillation (AF)
- Renal failure
- Rupture aortic aneurysm or Berry aneurysm.

SAFETY FIRST FOR PATIENTS

Consider three key factors that allow logical choices to be made for initial therapy and drug combinations. Acknowledge that safety to patients is the most important of the three keys. Drug efficacy differs considerably in the White patients and the Black patients particularly the young (age <60 years) or elderly (age >65 years), this statement still holds. Also, patients over age of 70 years are at high risk for HF and calcium antagonists increase this risk.

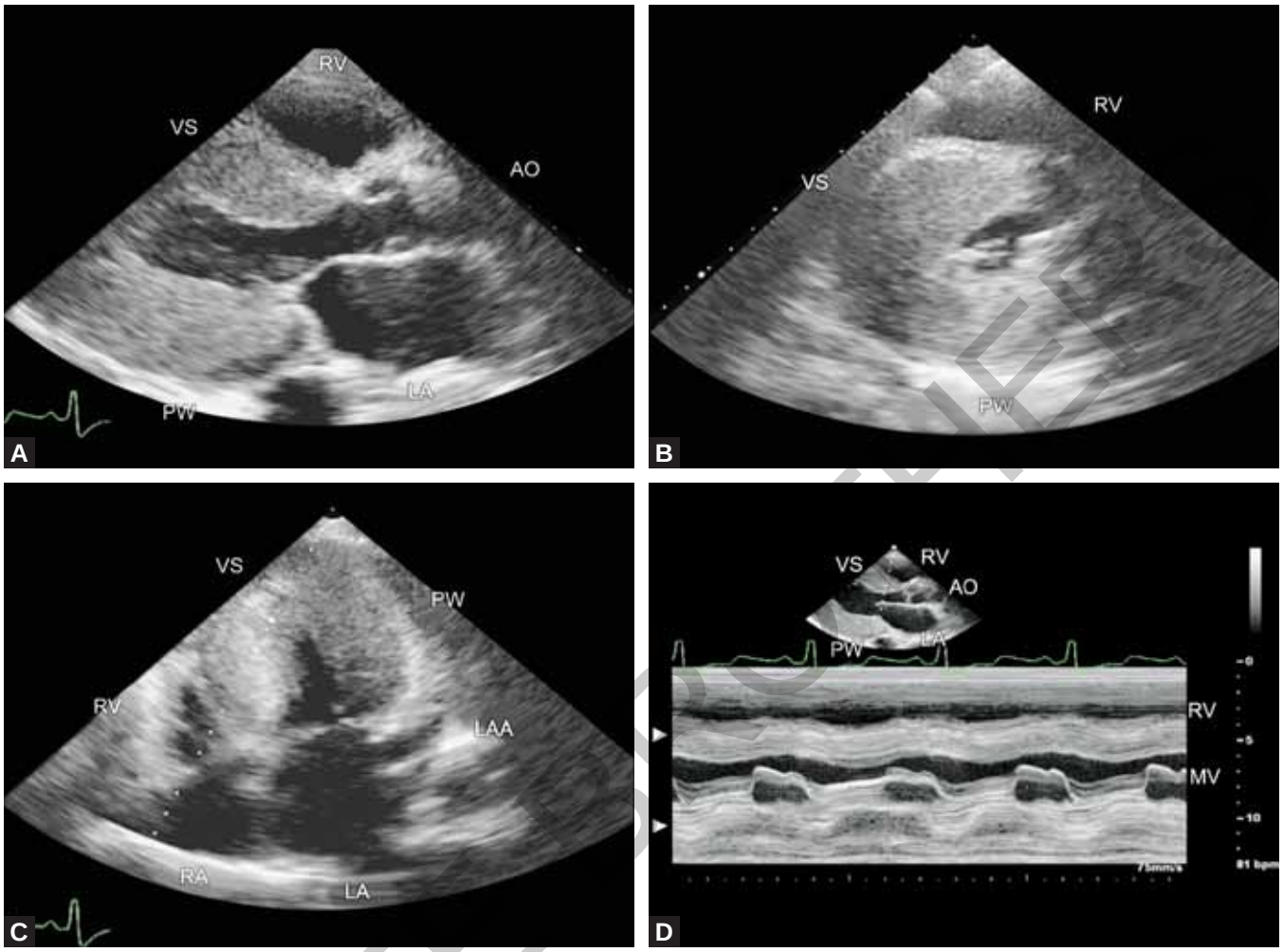
ACE inhibitors and ARBs are weak antihypertensive agents and not as effective as proclaimed by experts. A recent meta-analysis states that in diabetics ACE inhibitors and ARBs "are not superior to other antihypertensive drug classes such as thiazides, calcium channel blockers and beta-blockers at reducing the risk of hard cardiovascular and renal endpoints. These findings support the recommendations of the guidelines of the European Society of Cardiology/European Society of Hypertension" (Bangalore et al. 2016); and any class of antihypertensive agents can be used in people with diabetes.

In diabetics blood pressure (BP) lowering treatment is associated with reduced mortality and cardiovascular morbidity, if systolic blood pressure (SBP) before treatment is more than 140 mm Hg. If SBP before treatment is less than 140 mm Hg, a recent analysis found no benefit, but potential harm, with an increased risk of cardiovascular death. "Treatment reduced the risk of all-cause mortality, MI stroke and HF, if SBP was treated to 130–140 mm Hg, but was associated with a nonsignificant increase in all cause and cardiovascular mortality if SBP was lowered to less than 130 mm Hg" (Brunström and Carlberg 2016).

In addition experts who state that beta-blockers are not as effective as other agents are referring not to all beta-blockers but only to atenolol, the least effective beta-blocker that unfortunately is often used worldwide. More than 90% of hypertension drug trials done from 1984 to 2007 have used atenolol. The reasons for the drug's poor efficacy are discussed later in this chapter. Clinicians need to know that beta-blockers are not all alike (Khan 2005).

Numerous randomized clinical trials (RCTs) are analyzed and conclusions incorrectly drawn. Fuster (2015) has given an appropriate warning. Here are the results of three notable ACE inhibitor and ARB RCTs:

1. *PROGRESS (Perindopril Protection Against Recurrent Stroke Study) (2001)*: This large RCT showed that more than 55% of subjects required a diuretic added to perindopril to gain control BP less than 140 mm Hg systolic. The drug did not reduce total deaths, or fatal MI.



Figs. 4.1A to D: Systemic hypertension. The patient is a 37-year-old female with very severe hypertension. Two-dimensional transthoracic echocardiography. Parasternal long-axis (A), short-axis (B), and apical four-chamber views (C). Note the marked concentric hypertrophy of both the ventricular septum (VS) and the posterior wall (PW). The left atrial appendage (LAA) is clearly delineated and is free of any clot. (D) M-mode study shows left ventricular hypertrophy. (AO: Aorta; LA: Left atrium; MV: Mitral valve; RA: Right atrium; RV: Right ventricle). (Movie clips 78.23A to C).

Source: Adapted from Nanda NC. Comprehensive Textbook of Echocardiography, 1st editiion. New Delhi: Jaypee Brothers Medical Publishers; 2014, p. 1910, Figures 78.23A to D.

2. *TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease)*: Telmisartan therapy had no significant effect on the primary outcome, hospitalizations for HF (Yusuf et al. 2008).
3. *PRoFESS (The Prevention Regimen for Effectively Avoiding Second Strokes)*: Yusuf et al. (2008), the drug failed to prevent stroke in this large RCT. In a meta-analysis by Staessen and associates the authors concluded that "all antihypertensive drugs have similar long-term efficacy and safety", but in the same article indicated that new drugs significantly increased the risk of HF.

HALLMARK RANDOMIZED CLINICAL TRIALS

Systolic Blood Pressure Intervention Trial

In the Systolic Blood Pressure Intervention (SPRINT) trial (2015) BP target was less than 125 mm Hg, claimed to reduce outcomes. But patients under the age of 50 years, prior strokes and diabetics were excluded. This RCT results

were highly acclaimed by some experts. But Fuster (2015) emphasized that clinicians have to be particularly cautious when interpreting results of RCTs, including SPRINT "because the patients included in this study are only approximately 20% of our actual hypertensive patients seen in our practice. The 4.7% of the intensive-treatment group and 2.5% of the standard-treatment group had serious adverse events, which is a relative risk increase of 88%. There was an excess risk of acute renal failure in the intensive group; 4.4% versus 2.6% patients affected, which is a relative risk increase of 71%" (Fuster 2015). A disappointing result.

Action to Control Cardiovascular Risk in Diabetes

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial found that serious adverse events occurred in 3.3% of the intensive BP—lowering arm compared with 1.3% in the usual care arm. *The use of multiple antihypertensive drugs to gain tight BP control was associated with an increased incidence of serious adverse effects, including hypotension, syncope and worsening renal function.*

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (2002) a large non-drug sponsored RCT confirmed that amlodipine causes HF and older agents were as good as the newer drugs; ACE inhibitor, lisinopril, or amlodipine. The JNC-8 experts have ignored the sound findings of ALLHAT in which amlodipine and nifedipine carried a 32% and 46% risk for HF compared with diuretic therapy, and a 35% greater risk for hospitalized fatal HF than did the chlorthalidone group.

- Newer drugs certainly have more adverse effects, some are detrimental to patients.
- In ALLHAT, the primary outcome was combined fatal coronary heart disease (CHD) or nonfatal MI.
  - *Conclusion*: In older patients with hypertension and greater than or equal to 1 other CHD risk factor, amlodipine or lisinopril was no better than chlorthalidone in lowering the risk for CHD or other cardiovascular disease (CVD) events. Risks for some CVD events were greater with amlodipine or lisinopril.
- The lisinopril group had a 15% higher risk for stroke ($p = 0.02$) and a 10% higher risk of combined CVD ($p < 0.001$), with a 6-year absolute risk difference for combined CVD of 2.4%. Included in this analysis was a 19% higher risk of HF ($p < 0.001$), a 10% higher risk of hospitalized or fatal HF ($p = 0.11$), an 11% higher risk of hospitalized or treated angina ($p = 0.01$), and a 10% higher risk of coronary revascularization ($p = 0.05$).

The two older drugs diuretics and beta-blockers do not cause detrimental adverse effects. Older drugs are safer and were proven in ALLHAT (2002). Since this remarkable trial was published, only the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) trial (2008) is of note and it did not show amlodipine significantly superior to the poorly effective atenolol. Total mortality was similar.

Thus, ALLHAT results hold the key to safe drug choices as given in Flowcharts 4.1 to 4.4.

The safety of a small dose of beta-blocker is assured because we do know that the majority of elderly patients (age 70–88 years) with AF are safely controlled with a small dose of bisoprolol, 2.5–5 mg daily. The combination of small dose diuretic and very small dose of a beta-blocker is safer than the addition of an ACE inhibitor, ARB, or calcium antagonist in mild hypertension because this addition may cause too excessive lowering of BP, causing syncope, injury from falls.

My advice does not follow JNC guidelines.

Any of the two safer agents, diuretics and/or beta-blocker, are advised as initial therapy except in younger Black patients as calcium antagonist are more effective and at this age HF is rare.

Flowcharts 4.1 to 4.4 give drug choices.

Beta-blockers are effective in White patients of all ages and Black patients aged less than 65 years.

Dickerson et al. (1999) studied the four main classes of antihypertensive drugs in 40 untreated young White hypertensive patients aged less than 55 years. Success of monotherapy was achieved ($p = 0.0001$) in half the patients, BP on the best treatment was 135/85 mm Hg or less. The responses to the beta-blocker, ACE inhibitor or pair were, on average, at least 50% higher than those to the calcium antagonist or diuretic pair.

Deary et al. (2002) completed a double-blind placebo controlled crossover comparison of five antihypertensive drugs (amlodipine, doxazosin, lisinopril, bisoprolol and bendrofluazide) and placebo in 34 young non-Black hypertensives and showed that bendrofluazide performed

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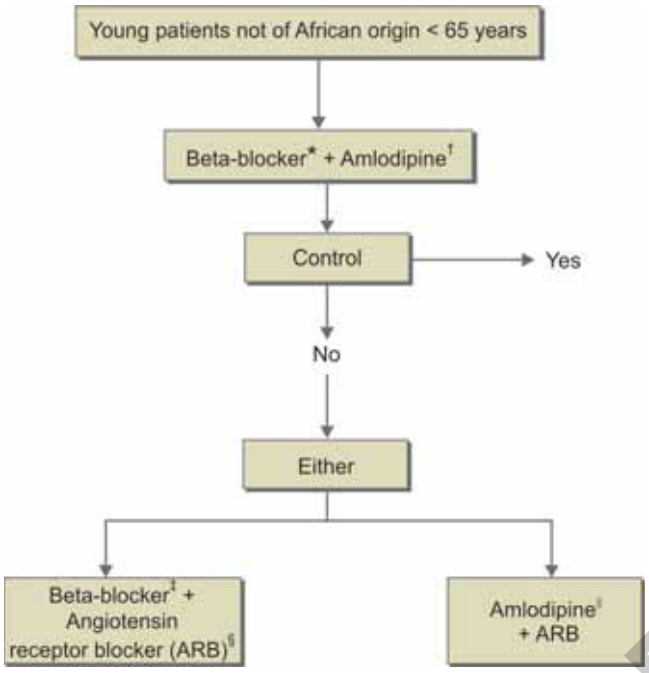
Flowchart 4.1: Suggested drug choices for hypertensive patients not of African origin with mild to moderate hypertension: systolic blood pressure = 140–180 mm Hg.



*,‡If mild hypertension, try one drug but low dose; monotherapy may succeed in approximately 45%. Then small doses of both drugs: timolol 5 mg, propranolol LA 80–240 mg; bisoprolol 5–10 mg (if cardioselective necessary) are best beta-blocker choice, propranolol and calcium antagonists only in nonsmokers. Atenolol not recommended, see text.

§Angiotensin receptor blocker is as effective as ACE inhibitor and preferred to avoid angioedema, rare death (particularly in Africans and probably East Indians), ER visit or cough. Best choice is losartan, 25–50 mg, avoid valsartan, as it interacts with beta-blockers. Avoid telmisartan.

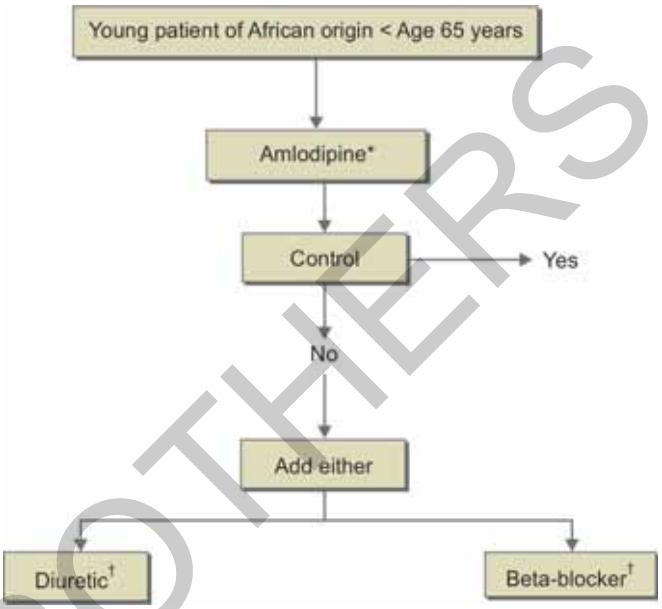
‖Calcium antagonist, amlodipine best choice, used in most large RCTs. Safest dihydropyridine calcium antagonist; avoid verapamil due to risk of HF, and bradycardia; all made worse if added to beta-blocker.

†Combinations allow smaller doses of drug; fewer side effects; Amlodipine + timolol (β1 and β2 drug strongly recommended if family history of MI or diabetic.

significantly worse (p = 0.0016) and a beta-blocker, bisoprolol, significantly better (p = 0.004). Beta-blockers have the advantage of providing some cardioprotection depending on the beta-blocker used and the presence or absence of smoking.

Calcium antagonists (*dihydropyridines,* the author chooses amlodipine and occasionally nifedipine) are effective in Blacks of all ages and older Whites but are not superior to beta-blockers or diuretics in the latter group. Cigarette smoking may inhibit salutary effects.

Flowchart 4.2: Suggested drug choices for hypertensive patients of African origin with mild to moderate systolic hypertension: blood pressure = 145–180 mm Hg.



*Good response to monotherapy expected >70%. Diltiazem long acting controlled release is also recommended. Verapamil not advisable.

†Combinations allow smaller doses of drug; fewer side effects; Amlodipine + timolol (β1 and β2 drug strongly recommended if family history of MI or diabetic; *see* Chapter 17). Timolol can prevent sudden deaths or nonfatal infarcts in smokers and nonsmokers bisoprolol 5–10 mg/day is a proven antihypertensive drug for most patients with mild hypertension and is needed if chronic obstructive pulmonary disease (COPD).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS CAUSE ANGIOEDEMA

Angiotensin-converting enzyme inhibitors cause angioedema requiring emergency room (ER) visits and deaths have been reported. Causing death, albeit rare, is not acceptable.

- Angiotensin receptor blockers can replace ACE inhibitors for the treatment of hypertension; they are as effective but can cause angioedema particularly in Black patients.
- Angiotensin-converting enzyme inhibitors and ARBs are effective in young Whites, poorly effective in older Whites, but are not predictably effective in Blacks at any age. They require the addition of small dose diuretic to attain goal BP in more than 55% of treated patients.

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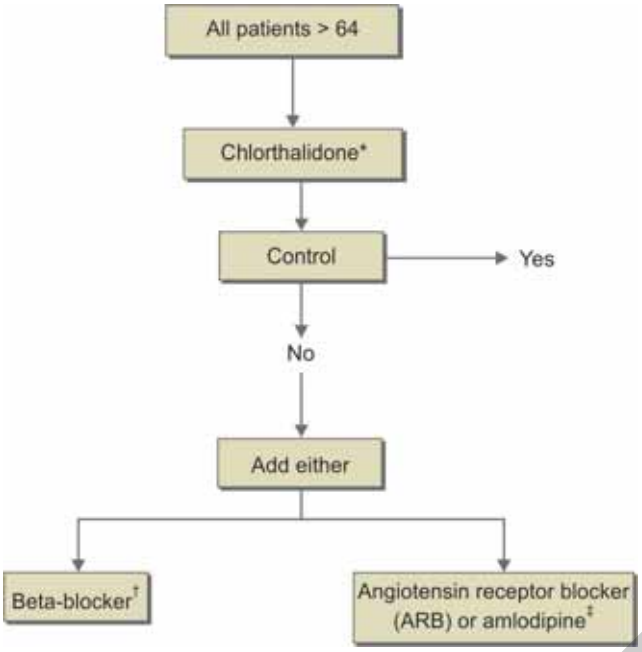
Flowchart 4.3: Suggested drug choices for hypertensive patients older than age 64, with mild to moderate hypertension; systolic blood pressure = 145–180 mm Hg any ethnicity.



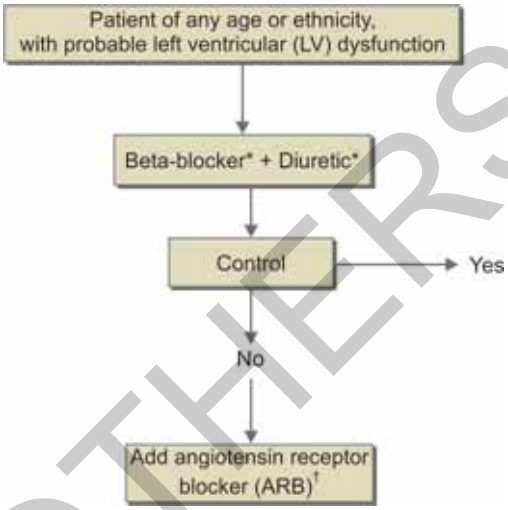
*12.5 mg/day; much more effective than other thiazides. Proven 100% the best drug in the soundly run large ALLHAT, shown to be safer and as effective as ACE inhibitor or amlodipine; but may cause significant hypokalemia. If serum potassium falls to <3.5 mmol/L, add amiloride to prevent this.

Chlorthalidone or hydrochlorothiazide 12.5 mg/day + amiloride to conserve potassium and assist thiazide diuresis; assess renal function and serum potassium.

†If not controlled replace diuretic with amlodipine.

‡ACE inhibitor not recommended as risk of angioedema particularly in individuals of African origin; ARB of choice is losartan 25–50 mg/day; avoid Telmisartan (*see* text for TRANSCEND and PRoFESS study failures). Calcium antagonist not recommended if known or probable left ventricular dysfunction as may cause heart failure. ALLHAT The amlodipine group had a 32.5% higher risk of heart failure (HF) ($p < 0.001$) with a 6-year absolute risk difference of 2.5% and a 35% higher risk of hospitalized/fatal HF ($p < 0.001$). Risk is higher for nifedipine other dihydropyridines and diltiazem and much higher for verapamil. Use amlodipine or nifedipine only if other agents fail to control BP, and in the absence of left ventricular dysfunction. Amlodipine is often necessary for severe hypertension at a dose of 5–7.5 mg/day; edema of legs can be a bothersome adverse effect.

Flowchart 4.4: Suggested drug choices for hypertensive patients with prior heart failure, or probable LV dysfunction, old MI, atrial fibrillation or other heart disease.



*Small dose either drug: timolol 2.5–5 mg twice daily or propranolol in nonsmokers 120–240 mg/day; β1 and β2 drugs more cardioprotective than cardioselective.

Bisoprolol 5–10 mg also advisable for most patients and for COPD.

†ACE inhibitor not recommended as risk of angioedema particularly in individuals of African or Indian origin.

ARB of choice is losartan 25–50 mg/day; avoid Telmisartan (*see* text for TRANSCEND and PRoFESS study failures). Calcium antagonist not recommended as may cause heart failure.

DIABETICS

Diabetics are at high risk for cardiac events and beta-blockers are recommended; choose timolol, or propranolol only in nonsmokers, as they can prevent fatal and nonfatal MI in those at high risk which includes diabetics with family history of MI (*see* Chapter 17 for prevention of hypoglycemia that should never occur with β 2 agents if fasting glucose goal is set high at 7–8 mmol/L and never < 7.0. Bisoprolol is advisable at dose 5–10 mg/day).

The safety of a small dose of beta-blocker is assured because we do know that the majority of elderly patients (aged 70–85 years) with AF are safely controlled with a small dose of bisoprolol, 2.5–5 mg daily. The combination of small dose diuretic and very small dose of a beta-blocker is safer than the addition of an ACE inhibitor, ARB or calcium antagonist in mild hypertension because this addition may cause too excessive lowering of BP and cause syncope, injury from falls.

DIURETICS

A diuretic, particularly chlorthalidone has been shown in many studies to be effective in White and Black patients aged older than 65 years (ALLHAT 2002 and HYVET 2008).

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If hypokalemia is observed with thiazides, amiloride. or spironolactone can be added; amiloride does not cause gynecomastia. Spironolactone has hormonal side effects and is not recommended by the author.

Physicians must now recognize that all thiazide diuretics are not all alike. Chlorthalidone is much more effective than hydrochlorothiazide (HCTZ) and others, but potassium loss must be prevented.

The ALLHAT (2002) a National Institutes of Health (NIH), nondrug sponsored, soundly run large RCT proved the safety and effectiveness of diuretic therapy. 33,357 hypertensive patients of mean age 67 years were randomized to receive the diuretic, chlorthalidone, 12.5–25 mg/day (n = 15,255), amlodipine, 2.5–10 mg/day (n = 9,048), or lisinopril, 10–40 mg/day (n = 9,054) with a follow-up of 4.9 years. There was good representation for women (47%) and Blacks (35%); 36% were diabetics. The primary outcome combined fatal CHD or nonfatal MI occurred in 2,956 participants, with no difference between treatments. *All-cause mortality did not differ between groups but HF was noted.*

- Risk for HF was substantial 82% versus diuretic for the alpha-blocker "doxazosin" which should not be prescribed for hypertension. Cardiac drug therapy (1988) states that "alpha-blockers are not recommended and in 2003 the 6th edition (Khan 2003) emphasized that doxazosin (all alpha-blockers) should become obsolete". Yet a recent (2015) European trial on spironolactone compares doxazosin [Williams et al. for the Prevention and Treatment of Hypertension with Algorithm-based Therapy (PATHWAY) Studies Group Lancet 2015].
  "Chlorthalidone" proved as effective in controlling BP to goal levels and outcomes were similar to calcium antagonist or ACE inhibitor therapy (ALLHAT 2002).
- Diuretics must remain the mainstay of hypertensive drug therapy to be used as first line for more than 50% of individuals with mild hypertension (systolic between 145 mm and 170 mm).

"Chlorthalidone" is a more powerful antihypertensive agent than usual thiazides, and thus causes serious potassium (K^+) loss. With this knowledge we can correct the K^+ loss.

- "Dosage 12.5–25 mg/day". The 25 mg dose should be used with caution because hypokalemia is a major concern; I advise addition of amiloride when the 25 mg is used and for most patients on 12.5 mg. The drug causes less hypokalemia in patients with mild to moderate renal failure [estimated glomerular filtration rate (eGFR) 45–60] because renal failure causes hyperkalemia. A combination with amiloride, 5 mg, is recommended for patients with normal renal function to enhance diuresis and conserve K^+.

Chlorthalidone causes better control of BP compared with HCTZ (Ernst et al. 2006). The BP difference was particularly impressive in the evening hours. The reduction in SBP during night-time hours was 13.5–1.9 mm Hg for chlorthalidone versus 6.4–1.7 mm Hg for HCTZ, and was highly significant.

The extremely long half-life of 40–60 hours for chlorthalidone differentiates it from HCTZ, which has a much shorter but wider variation in half-life, from 3.2 hours to 13.1 hours (Chen and Chiou 1992). This plasma half-life difference can be expected to correlate with a more extended effect of chlorthalidone on diuresis and possibly BP. The drug has a very large volume of distribution, because of its extensive partitioning into red blood cells. This latter feature creates a hefty depot for chlorthalidone, allowing for a slow streaming effect with subsequent gradual elimination from the plasma compartment by tubular secretion (Riess et al. 1977). A study used 24 hours ambulatory BP measurements to study the effects of 25 mg of chlorthalidone daily as compared with 50-mg HCTZ daily.

Although BP levels measured during the daytime in the clinician's office were similar, BP levels measured during the night-time and 24 hours average BPs were considerably lower with chlorthalidone than with HCTZ (Ernst et al. 2006). The author does not recommend high dose chlorthalidone (>25 mg daily) because hypokalemia commonly occurs except in patients with mild renal dysfunction in whom potassium is retained. When this drug is prescribed in patients with normal renal function I strongly advise addition of amiloride to prevent hypokalemia. Also HCTZ at 50 mg is not advisable because of hypokalemia and metabolic effects.

Caution is needed in interpreting results of small clinical trials.

Hydrochlorothiazide

Hydrochlorothiazide 12.5–25 mg daily or equivalent thiazide is recommended often with addition of amiloride to conserve potassium; 50 mg HCTZ is not recommended.

Spironolactone

- In a study of over 300 people with a SBP of 140 mm Hg or greater and a home SBP of 130 mm Hg or greater

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who were already taking three medications [(1) an ACE inhibitor or ARB, (2) a calcium-channel blocker, and (3) a diuretic], patients cycled through four treatments for 12 weeks each (spironolactone, doxazosin, bisoprolol, and placebo). Spironolactone was associated with significantly greater average reductions in home SBP than placebo (Williams et al. 2015).

I am surprised that an expert doing a recent trial would use doxazosin. This drug use has been curtailed since 2003 in the United States of America and Canada following the ALLHAT 2002 results showing that the drug causes a high incidence of HF.

Alpha-blockers are contraindicated and the advice given in CDT 2003 is "Do not use alpha-blockers" (Khan 2003, *see* Chapter 10, Drugs for the Heart).

"Spironolactone, or amiloride" is not an effective antihypertensive agent and is not superior or equivalent to a beta-blocker as the trialists seem to indicate; it is only useful for some patients with resistant hypertension to assist the thiazide to eliminate some more sodium and water.

Spironolactone without a thiazide or chlorthalidone would not be effective except in Conn's syndrome.

The authors say that the findings suggest that resistant hypertension may be caused predominantly by sodium retention; thus aldosterone antagonist should assist. Amiloride which does not cause breast problems in men is preferred in males. Spironolactone has hormonal adverse effects and use is curtailed except in exceptional circumstances; do not use if the eGFR is < 60 mL/min.

The combination pill amilzide, or other generic name, contains too large a dose of HCTZ (50 mg + only 5 mg amiloride) available in Canada, the USA and in many countries is not recommended because the dose of 50 mg HCTZ is excessive. If half a tablet is taken the dose of amiloride, 2.5 mg, is useless.

It would be most useful to have a combination of chlorthalidone 25 mg + amiloride 5 mg.

DIURETICS FOR TREATMENT OF HYPERTENSION IN THE ELDERLY

The results of the Systolic Hypertension in the Elderly Program (SHEP 1991) confirmed the effectiveness of diuretic (chlorthalidone) for individuals aged over 60 years.

A group of 4,736 patients aged 60 years or more (mean 72 years, 57% were women and 14% were Black) was randomized (2,365 to active treatment, 2,371 to placebo). SBP ranged from 160 mm Hg to 220 mm Hg, diastolic BP was less than 90 mm Hg. The average SBP was 170 mm Hg; diastolic 77 mm Hg. For step 1 of the trial, dose 1 was *chlorthalidone 12.5 mg/day*, or matching placebo; dose 2 was 25 mg/day. For step 2, dose 1 was atenolol, 25 mg/day, or matching placebo; dose 2 was 50 mg/day.

The 5-year average SBP was 155 mm Hg for the placebo group and 143 mm Hg for the active treatment group, diastolic BP was 72 mm Hg and 68 mm Hg. The 5-year incidence of total stroke was 5.2 per 100 participants for treatment and 8.2 for placebo (p = 0.0003). The relative risk was 0.64. For the secondary end point of fatal and nonfatal MI the relative risk was 0.73. All-cause mortality relative risk was 0.87. In patients with isolated systolic hypertension, antihypertensive stepped-care drug treatment with low-dose chlorthalidone as step 1 medication reduced the incidence of total stroke by 36%.

HYVET (HYpertension in the Very Elderly Trial) 2008: Diuretics are the recommended therapy for the elderly except in those with bladder problems. Their effectiveness and safety was shown in a soundly run, double-blind RCT of 3,845 hypertensive patients 80 years of age or older (Beckett et al. 2008). Stepped-care therapy began with indapamide with addition of perindopril as needed. At 2 years, the trial was halted because active treatment, as compared with placebo, was associated with a 21% reduction in the relative risk of death from any cause, a 64% reduction in the relative risk of HF, and a 30% reduction in the relative risk of stroke (Beckett et al. 2008).

BETA-BLOCKERS

These well-tried inexpensive agents that cause no major adverse effects have been dismissed by the JNC-8 (2014) and United Kingdom experts because of the results of RCTs in which the most ineffective beta-blocker, atenolol, showed poor results (*see* later discussion on atenolol and my recommendation to render the drug obsolete).

There are more than 8 beta-blockers available, but of the 10 or more hypertensive RCTs, atenolol was the choice beta-blocker in more than 90% of trials.

- Guideline providers in many countries including the US JNC-8 (2014) fail to understand that beta-blockers have subtle and important differences (Khan 2005).
- It must be emphasized that worldwide, up to the year 2006, atenolol was the most prescribed beta-blocker and was used in most RCTs. The 6th edition Cardiac Drug Therapy (Khan 2003) states that "the use of

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atenolol in clinical trials should be curtailed". Lindholm et al. (2005) from a misleading meta-analysis stated that beta-blockers should not remain the first choice in the treatment of primary hypertension.

- This statement was printed on the front cover of the Lancet; a most embarrassing happening for the Lancet.
- Bangalore et al. (2007) based on a blunderbuss meta-analysis demoted beta-blockers to third-line therapy. The JNC and the UK experts believe this nonsensical report. In the majority of studies used in the Lindholm et al. meta-analysis, unfortunately, atenolol a most ineffective beta-blocker was administered. A Lancet correspondence emphasized that "by lumping together all randomized hypertension trials involving beta-blockers, Lars Lindholm and colleagues have arrived at misleading conclusions" (Cruickshank 2006). This report made no impact; all writers proclaim the conclusions of Lindholm et al. and Bangalore et al.

Trials selected by Lindholm et al. were as follows:

- In IPPPSH (the International Prospective Primary Prevention Study in Hypertension), oxprenolol was used (1985). The drug has intrinsic sympathomimetic activity (ISA) that renders it noncardioprotective. "Agents with ISA are currently obsolete".

Berglund et al. trial (1986) and Yurenev et al. (1992), studied "only 106, and 304 patients, respectively."

- *STOP-2 (Swedish Trial in Old Patients with Hypertension-2)*: A blunderbuss prospective, randomized trial in 6,614 patients aged 70–84 years with stage 2 hypertension assigned conventional antihypertensive drugs [atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg (pindolol is an ISA beta-blocker; that must become obsolete), or HCTZ, 25 mg plus amiloride 2.5 mg daily] or newer agents.
- *The Medical Research Council (MRC) trial (1985) of mild hypertension*: This single-blind trial compared a diuretic versus propranolol in patients aged 35–64 years. The rate of all CVD events was not reduced by bendrofluazide (now bendroflumethiazide), regardless of the smoking habit, or in smokers taking propranolol. Most important CVD events were reduced in nonsmokers taking propranolol, and the difference between the two drugs in this respect was significant ($p = 0.01$). Propranolol, but not diuretics, reduced the risk of MI by 13% that increased to a significant 18% when silent infarctions were included.

In a subsequent subanalysis compared with placebo, the reduction in nonsmokers was 33%; the diuretic showed a reduction in strokes in smokers and nonsmokers. Nonsmokers given propranolol showed a significant decrease in strokes.

Thus, pure beta-blocker therapy without the addition of other agents significantly reduced stroke. This important positive result on stroke reduction obtained with propranolol has been misinterpreted or ignored by investigators and editorialists in the field. Cigarette smoking increases the rate of metabolic degradation of propranolol, and a decrease in plasma propranolol levels has been shown in smokers.

- The MRC (1992) was a *blunderbuss* RCT, the beta-blocker used was the nonlipophilic agent, atenolol
  - The MRC investigators confirmed that "over 5.5 years, about 25% of people were lost to follow-up" and more than half the patients were not taking assigned therapy by the end of the study.
  - The cumulative percentages of patients who discontinued their randomized treatment, including both those withdrawn but continuing on follow-up and those lost to follow-up, were 48% of the diuretic group, 63% of the beta-blocker group and 50% of the placebo arm.

Their erroneous conclusions of 1992 are used today by experts such as Bangalore et al. (2007) who regard beta-blockers as relatively useless for the treatment of hypertension. The results of this blunderbuss trial were as follows:

- There was no difference in total mortality between atenolol and diuretic therapy; surprisingly, however, diuretics reduced CHD events, but atenolol did not (perhaps we should use diuretics to reduce CHD events base on this spurious result).
- Diuretics do not prevent heart attacks; this is the only RCT that purports to that notion.
- The diuretic group had a modest reduced risk of stroke ($p = 0.04$). Atenolol the poorly effective but favorite beta-blocker of trialists showed no significant reduction in risks of stroke but the drug was administered once daily; atenolol is a drug that sometimes should be given twice daily because of an inconsistent 24-hour action.
- The lack of a 24-hour action and weak antihypertensive effects for atenolol have been overlooked by most trialists who selected atenolol as their favorite beta-blocker trial drug between 1980 and 2005.
- Messerli et al. (1998) included the spurious result of the MRC (1992) trial in a meta-analysis. They concluded

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that beta-blockers should not be first-line therapy for elderly hypertensives.

- This misleading information is quoted by virtually all physicians who state in peer-reviewed journals and in textbooks that beta-blockers should not be used as first-line therapy in patients over age 65 years.
- *A rebuttal was made by Kendall and Cohen*: "The systematic review by Dr Messerli and colleagues based on 10 published studies concluded that diuretics are effective antihypertensive drugs, whereas beta-blockers should no longer be considered to be appropriate first-line therapy for uncomplicated hypertension in the elderly. On the basis of the data presented, the first conclusion is quite acceptable, whereas the second is not" (Kendall and Cohen 1999). *Rebuttal letters, however, are a very small voice. Thus, virtually all textbooks and experts in the field quote this misleading study as the reason for not prescribing beta-blockers to elderly hypertensives.*

Reasons for Atenolol Poor Efficacy

Atenolol is a hydrophilic beta-blocker that attains low brain concentration. Increased brain concentration and elevation of central vagal tone confer cardiovascular protection (Pitt 1992). Lipid-soluble beta-blockers (bisoprolol, carvedilol, metoprolol, propranolol and timolol) have all been proven in large RCTs to significantly decrease cardiac deaths. These beta-blockers attain high brain concentration, block sympathetic discharge in the hypothalamus better than water-soluble agents (atenolol and sotalol) (Pitt 1992). Timolol in the Norwegian trial (1981) caused an astounding 67% reduction in sudden cardiac deaths. These agents have been shown to quell early morning catecholamine surge and control early morning and exercise-induced excessive rise in BP better compared with atenolol (Neutel et al. 1993; Kokkinos et al. 2006).

It is surprising that the experts who construct hypertensive guidelines *fail to understand the subtle but important differences that exist between the available beta-blocking agents (Khan 2005).*

Äblad et al. (1991), in a rabbit model, showed that although metoprolol (lipophilic) and atenolol (hydrophilic) caused equal beta-blockade, only metoprolol caused a reduction in sudden cardiac death. Metoprolol, but not atenolol, causes a significant increase in RR interval variation, and thus a favorable alteration in sympathetic tone.

Beta-blockers Recommended

The beta-blocking drugs have important subtle differences (Khan 2003, 2007). The following guidelines are recommended regarding which beta-blocker to choose.

Timolol

- This β-1 and β-2 agents caused a 67% reduction in sudden deaths in the Norwegian MI study (1981) and decreased total mortality and nonfatal infarction.
- Most important, only lipophilic agents with both β-1 and β-2 activity have shown these remarkable reduction in cardiac events.
- Most physicians worldwide prescribe cardioselective agents; an error made by most experts who advise the profession.
- A once daily formulation would be an advance.
- The drug unfortunately is not often used in the US perhaps because the study is lost in the archives.

Propranolol

This remarkable drug is fortunately still used because it has indications not given for other beta-blocking drugs. It reduced sudden deaths and total mortality in the BHAT (Beta-blocker Heart Attack Trial) MI RCT (1982).

- The drug is effective but not in smokers.
- This drug is advisable at doses 120–240 mg/day; do not use 320 mg. Combine it with another drug when the dose is 120 mg once daily long-acting formulation.
- In patients with chronic obstructive pulmonary disease (COPD) prescribe bisoprolol 2.5 mg, 5 mg, 10 mg once daily; or metoprolol 50 mg twice daily or long-acting 50–100 mg once daily.

Calcium Antagonists

Calcium antagonists are the most effective antihypertensive agent available when used as monotherapy depending on the age and ethnicity of the individual. Calcium antagonists are not recommended in patients with acute MI for at least 3 months post and patients with acute or compensated HF.

Caution: Use for treatment of hypertension only if there is no past history of HF, and left ventricular function is normal ejection fraction (EF) is equal to or more than 45%.

"They are especially recommended" for the following situations:

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- In older individuals of African origin or if diuretics are contraindicated or cause adverse effects
- In younger Africans if beta-blockers are contraindicated or not well tolerated
- As second-line therapy in combination with beta-blockers or other agents in patients with angina or renal dysfunction, or
- For hypertension uncontrolled with a combination of beta-blocker and diuretic.

Caution: Calcium antagonists are used with caution in the following situations:

Patients within a few months after MI.

- *Patients with hypertension and diabetes*: RCTs have shown an increase in mortality in patients treated with short-acting and extended-release calcium antagonists.
- Patients with HF, LV dysfunction, or EF less than 45%. The INSIGHT (Intervention as a Goal in Hypertension Treatment) trial (2000) showed nifedipine equivalent to diuretic in preventing stroke, but it increased the risk of HF significantly (46%).
  - In the Multicenter Diltiazem Postinfarction Trial of non-Q-wave MI (PRAISE 1988), diltiazem significantly increased the risk of HF.
  - An RCT with nisoldipine in patients with hypertension and noninsulin-dependent diabetes was terminated early because nisoldipine-treated patients had a higher risk of fatal and nonfatal acute MI than observed in the enalapril group: 25/235 vs 5/235 ($p < 0.001$).
  - *Verapamil long acting is not recommended*: It should not be used in patients with acute MI, cardiomegaly, or LV dysfunction. Also avoid in HF, conduction defects and sick sinus syndrome. Constipation and bradycardia are limiting considerations, particularly in patients aged more than 70 years. Combination with a beta-blocker is contraindicated.
  - Amlodipine 2.5–5 mg/day, maximum 7.5 mg (10 mg/day only in perfectly normal hearts). Patients aged older than 75 years start with 2.5 mg maximum 5 mg (rare 7.5 mg/day if no alternative). Leg edema may be bothersome. 10 mg may precipitate heart failure.
  - Diltiazem long acting controlled release 180 mg/day maximum 240 mg/day; avoid if EF less than 45%; do not use short acting 30 mg and 60 mg formulations.

Caution: Short-acting calcium antagonists formulations are not recommended.

ANGIOTENSIN-CONVERTING ENZYME INHIBITOR OR ANGIOTENSIN RECEPTOR BLOCKER

Note that an ACE inhibitor or ARB is not chosen as first line because these agents cause BP control in only approximately 40%; and need the addition of diuretic to achieve approximately 66% control. They are weak antihypertensive agents that are most overused. Most important they cause cough in more than 20% and angioedema occurs in approximately 0.5–1% requiring ER visits and deaths have occurred; this serious problem is more common in Blacks and probably East Indians.

Caution: ARBs do cause cough in approximately 5% cases and cause angioedema in approximately 0.2% cases; they should not be given if angioedema has occurred with an ACE inhibitor.

Angiotensin Receptor Blockers are Much Touted Antihypertensive Agents

- Telmisartan failed in two soundly run clinical trials. Although telmisartan was shown in ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial) (2008) to be as effective as ramipril, the drug failed to prevent HF in TRANSCEND (2008) and failed to prevent strokes in PRoFESS (2008). ARBs and ramipril like other ACE inhibitors are suspected and are over prescribed.
- In ONTARGET at a median follow-up of 56 months, the primary outcome was reported in 1,412 patients in the ramipril group (16.5%) and in 1,423 patients in the telmisartan group (16.7%); telmisartan was equivalent to ramipril in this study. This *is a blunderbuss study because there is no control group*. We cannot take it for granted that ramipril is a very effective drug, representing ACE inhibitors. The combination of the two drugs was associated with more adverse events with no improvement in outcomes (ONTARGET Investigators 2008).
- The HOPE (Heart Outcomes Prevention Evaluation) study is flawed because only a few patients received cardioprotective agents (statins non-enteric-coated aspirin and beta-blockers).

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The drug is useful in high risk IHD patients: In high-risk patients, ramipril 10 mg given for 4.5 years caused a 22% reduction in the primary outcome of MI, stroke, or death from cardiovascular causes.

- Total mortality for ramipril was 482 vs 569 for placebo, a modest 15.3% reduction ($p = 0.005$).
- Myocardial infarction 459 versus 570, $p < 0.001$; stroke 156 vs 226, $p < 0.001$; death from cardiovascular causes 282 vs 377, $p < 0.001$; noncardiovascular causes 200 vs 192 (HOPE investigators 2000).
- Angiotensin-converting enzyme inhibitors have a role in patients at high IHD risk and in those with CHF or ventricular dysfunction.
- There is no good reason to overprescribe them for low-risk hypertensive patients.

Weinsaft (2000) offered appropriate criticisms "unfortunately in HOPE, the population studied was one in which a considerable number of high-risk patients were being treated with suboptimal ACE inhibitors or ARBs medication regimens, according to current treatment guidelines." Of the total treatment population, 65.4% had hyperlipidemia, but only 28.4% were taking lipid-lowering agents. In addition, "whereas 51.9% had a documented MI and 54.8% had a history of stable angina and 25% had an unstable angina, only 39.2% were taking beta-blockers"; only 75% received aspirin (Weinsaft 2000). Enteric-coated aspirin was administered. An error made by many when prescribing aspirin. Soft chew must be used and enteric-coated should become obsolete (Khan 2007); this formulation is not as effective as soft noncoated aspirin.

In the LIFE (Losartan Intervention for Endpoint reduction in hypertension) study, 204 losartan and 234 atenolol patients died from CVD ($p = 0.206$); a nonsignificant change in cardiovascular death. MI (nonfatal and fatal) occurred in 198 and 188, respectively ($p = 0.491$), a nonsignificant finding (Dahlöf et al. 2002) in the large Captopril Prevention Project (CAPP 1999) study of captopril versus diuretic and beta-blocker, "fatal and nonfatal stroke was increased in the captopril group" ($p = 0.044$), with no significant differences in other events.

Cancer Risk with Angiotensin-receptor Blockers

Angiotensin-receptor blockers are associated with a modestly increased risk for cancer, according to a meta-analysis published in the Lancet Oncology. Researchers, examining data from five randomized trials comprising nearly 62,000 patients, found that those taking ARBs (85% were using telmisartan) had a significantly greater risk for new cancer than did controls (7.2% vs 6%). When cancer type was analyzed, only lung cancer risk was significantly increased. The authors estimate that 143 patients would need to be treated for roughly 4 years for one excess cancer to occur (Sipahi et al. 2010). In an accompanying commentary, Nissen (2010) states that until we have more data, clinicians "should use ARBs, particularly telmisartan, with greater caution". He recommends reserving the drugs for patients who cannot tolerate ACE inhibitors. *Olmesartan caused more deaths than placebo in two large RCTs (Imai et al. 2011).*

Caution: ACE inhibitors used to treat other cardiac disorders are also fraught with danger and this information relates to hypotension and increase mortality and morbidity.

Angiotensin-converting enzyme inhibitors prior to coronary bypass surgery: In a retrospective, observational, cohort study of prospectively collected data on 10,023 consecutive patients undergoing coronary artery bypass grafting (CABG), 3,052 patients receiving preoperative ACE inhibitors were matched to a control group by propensity score analysis. Rate of mortality was 1% (Miceli et al. 2009). Preoperative ACE inhibitor therapy was associated with a doubling in the risk of death (1.3% vs 0.7%; $p = 0.013$). There was a significant difference between the ACE inhibitor group and control group in the risk of postoperative renal dysfunction (PRD) (7.1% vs 5.4%; $p = 0.006$), AF (25% vs 20%; $p < 0.0001$), and increased use of inotropic support (45.9% vs 41.1%; $p < 0.0001$). In a multivariate analysis, preoperative ACE inhibitor treatment was an independent predictor of mortality ($p = 0.04$), PRD ($p = 0.0002$), use of inotropic drugs ($p < 0.0001$) and AF ($p < 0.0001$).

Caution: Preoperative treatment with ACE inhibitor is associated with an increased risk of mortality, use of inotropic support, PRD and new onset of postoperative AF (Miceli et al. 2009). Bach (2009) makes the following points: suspending ACE inhibitor therapy before CABG and restarting it postoperatively might improve early surgical outcomes, while retaining the long-term cardioprotective effects of therapy. This study, however, comes in the context of several others suggesting similar conclusions regarding long-term ACE inhibitor therapy. Bach (2009) emphasized that the EUROPA (European Trial on Reduction of Cardiac events with Perindopril in Stable. Coronary Artery Disease) study found that 50 patients

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would need to be treated for 4 years to prevent one major cardiac adverse event (the EUROPA study 2003).

- The ACE inhibitor Myocardial Infarction Collaborative Group found that only five lives would be saved per 1,000 patients treated with ACE inhibitor therapy and that therapy was associated with a twofold incidence of both persistent hypotension and renal dysfunction (ACE inhibitor Myocardial Infarction Collaborative Group 1998).
- Enalapril, 10–15 mg twice daily lisinopril 5, 10–30 mg once/day
- "Angiotensin receptor blockers appear to be somewhat less effective than ACE inhibitors"
- Candesartan 8–16 mg/day; maximum 32 mg
- Losartan 25–50 mg daily; maximum 100 mg
- Irbesartan 150–300 mg/day.

ALPHA-BLOCKERS

Alpha-blockers (Doxazosin and similar) "are not recommended agents" because they cause HF (ALLHAT 2000).

SEVERE SYSTOLIC HYPERTENSION

Severe systolic hypertension more than 190 *most of the time*; three drug combination necessary:

- Amlodipine 5–7.5 mg titrate to 10 mg (if EF > 45%) + diuretic, preferably chlorthalidone with amiloride to retain potassium + ARB; if not controlled add bisoprolol 5–10 mg/day.
- Many will need amlodipine + bisoprolol (or ACE inhibitor/ARB + diuretic + amiloride or spironolactone with serum K^+ monitoring to be less than 5 mmol/L).

RESISTANT HYPERTENSION

Causes

Drugs: Corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), decongestants, anorectics, amphetamines, cyclosporine, tacrolimus, cocaine and illicit drugs, oral contraceptive hormones, and erythropoietin. Substances include excess alcohol, herbal supplements such as ginseng, yohimbine, ma huang, bitter orange and licorice stimulate mineralocorticoid production.

- Renal artery stenosis (although rare) can cause accelerated resistant hypertension (Calhoun et al. 2008)
- Increased salt intake
- Poor drug compliance or inappropriate drug
- Patients treated with triple therapy—ACE inhibitor, calcium antagonist, and beta-blocker—without a diuretic.

A diuretic, particularly chlorthalidone and either spironolactone or amiloride is needed. Chlorthalidone should be considered as one of the initial agents (Vongpatanasin 2014). An American Heart Association (AHA) scientific statement (Calhoun et al. 2008) and a review article cover this topic in depth (Sarafidis and Bakris 2008).

- Spironolactone was associated with significantly greater average reductions in home SBP than placebo (8.7 mm Hg), doxazosin (4.0) and bisoprolol (4.5) (Williams et al. 2015) (*see* earlier discussion and criticisms of the study under diuretics). Caution: hyperkalemia is a dangerous condition; do not use the drug if eGFR is <50 mL/min.
- Glomerular filtration rate is 40–50 mL/min, chlorthalidone is more effective than HCTZ.

HYPERTENSIVE CRISIS

Hypertensive emergency is defined as a severe sudden elevation in BP, generally diastolic more than 120–130 mm Hg and/or systolic more than 220 mm Hg. The systolic pressures should reflect a knowledge of previous BPs, such as a rise within days from 160–170 to more than 220 mm Hg systolic; the rate of rise of BP in relation to previous BP is more important than the absolute BP. The sudden excessive elevation in BP should be associated with acute organ damage or dysfunction, which confers an immediate threat to the integrity of the cardiovascular system and to life. In aortic dissection or acute pulmonary edema, a BP of 200/110 mm Hg must be reduced.

Conditions associated with emergencies:

- Accelerated malignant hypertension
- Acute coronary insufficiency
- Acute pulmonary edema [left ventricular failure (LVF)]
- Acute renal dysfunction
- Aortic dissection
- Catecholamine crisis
- Eclampsia
- Hypertensive encephalopathy
- Subarachnoid hemorrhage
- Perioperative hypertension.

Severe elevation of BP with papilledema and/or microangiopathic hemolytic anemia, encephalopathy, or renal dysfunction require reduction in BP within minutes by intravenous (IV) therapy.

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The goal is to produce an immediate but modest reduction in BP to achieve no greater than a 20% reduction from baseline of the mean arterial pressure or to reduce the diastolic BP to 110 mm Hg and no less than 100 mm Hg over a period of several minutes to several hours.

Blood pressure is maintained at this level for a further 12–24 hours; then oral therapy should start and a decision made as to the necessity for further lowering of BP.

But with aortic dissection, BP must be reduced to a much lower level along with the use of a beta-blocking agent to decrease the rate of rise of aortic pressure.

Caution: Nitroprusside and labetalol have caused precipitous reductions in BP, resulting in cerebral and myocardial ischemia and/or MI.

Hypertensive Urgencies

Situations in which markedly elevated BP is controlled within a day or two, rather than within minutes using oral drug:

- BP systolic more than 220 mm Hg, diastolic more than 120 mm Hg; decrease to 180/100 mm Hg
- Presence of papilledema but without acute deterioration of specific organ systems
- Progressive but not acute target organ damage, as outlined earlier for hypertensive emergencies
- Rebound hypertension, e.g. after withdrawal of methyldopa, clonidine, or DHPs. If stroke, decrease only to 180/105 mm Hg.
- *Refractory hypertension*: Diastolic BP more than 120 mm Hg, no acute complications; try first on oral antihypertensive therapy and sedation plus furosemide 40–80 mg IV; this is necessary if the history suggests that volume expansion is present; with renal failure, volume overload is usually present.

Sodium Nitroprusside

Give IV administration by infusion pump only, avoiding extravasation. Wrap the infusion bottle in aluminum foil or opaque material to protect it from light.

Prepared solution must be used within 4 hours. One vial (50 mg) sodium nitroprusside in 500 mL 5% dextrose = 100 µg/mL.

Start the infusion at the lower dose range (0.5–1 µg/kg/min) and adjust in increments of 0.2 µg/kg/min, usually every 5 minutes until the desired BP reduction is obtained.

- The average dose is 3 µg/kg/min (range = 0.5–8 µg/kg/min)
- Oral antihypertensive agents should be started immediately so that the patient can be weaned from nitroprusside as quickly as possible.

Nitroprusside is a potent, rapidly acting, IV antihypertensive agent. The hypotensive effects are caused by peripheral vasodilation and reduction in peripheral resistance partly through nitric oxide. Variable reflex tachycardia occurs. The drug's effect is immediate (within 0.5–2 minutes) and usually ends when the IV infusion has stopped. The brief duration of drug action is the result of its rapid biotransformation to thiocyanate.

Contraindications

- *Hepatic failure*: Compensatory hypertension, such as arteriovenous shunt or coarctation of the aorta, corrected hypovolemia or severe anemia.
- *Abnormalities of cyanide metabolism*: Leber's optic atrophy and tobacco amblyopia
- Malnutrition, vitamin B_{12} deficiency and hypothyroidism
- Severe renal failure and inadequate cerebral circulation; caution is necessary in pregnancy.
- Raised intracranial pressure.

Fatalities have resulted from cyanide poisoning. In the presence of liver disease, cyanide levels increase with evidence of metabolic acidosis, so it is necessary to measure cyanide levels. If kidney disease exists, thiocyanate levels must be monitored, especially if treatment is to be extended for more than 2 days. Acceleration of infusion from an accident or faulty equipment and failure to monitor the BP accurately have all been associated with hypotension and shock. Retrosternal chest pain and palpitations may also be experienced. Methemoglobinemia has been reported. Hydroxocobalamin decreases cyanide levels and may be useful to increase the margin of safety. Rebound hypertension can be a problem.

Management of adverse effects: Amyl nitrite inhalations and IV sodium thiosulfate are used to treat acute cyanide poisoning. Nitrites form methemoglobin, which combines with cyanide ions to form relatively nontoxic cyanmethemoglobin.

Labetalol

Dosage: A 20–80 mg bolus dose over at least 1 minute, repeat after 5 minutes, then every 10–15 minutes if needed to maximum 200 mg.

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IV infusion of 20–160 mg/hour (2 mg/min) under close and continuous supervision is given slowly to obtain the desired BP reduction. The onset of action is 5–10 minutes, and the duration is 3–6 hours. The patient must be recumbent throughout the infusion and for at least 4 hours afterward. The hypotensive effect may last 1–8 hours after cessation of the infusion. Thus, labetalol is not as predictable as nitroprusside. Alternatively, bolus injections are used, starting with a 20-mg dose and gradually increasing the dosage every 10 minutes to a maximum of 80 mg bolus. Excessive bradycardia can be managed with IV atropine sulfate 0.6–2.4 mg in divided doses of 600 µg.

Hypertensive crisis of pregnancy: Labetalol 20 mg/hour, doubled every 30 minutes; usual maximum 160 mg/hour.

Hypertension complicating MI: Labetalol 15 mg/hour, gradually increased to maximum 120 mg/hour labetalol is a very useful drug for the management of hypertensive emergencies. The drug is especially useful for crises associated with dissecting aneurysm, renal failure, hypertensive encephalopathy, eclampsia and clonidine withdrawal, as well as in malignant hypertension and in some patients with pheochromocytoma.

Perioperatively and postoperatively, such as during neurosurgery for clipping aneurysms and in ear surgery

Adverse effects include bronchospasm, nausea, vomiting, orthostatic hypotension and rarely hepatic necrosis.

Hydralazine

Dosage: 10–20 mg. Hydralazine intramuscularly, but preferably by IV infusion, is indicated for hypertensive emergencies, particularly if the condition is associated with renal failure or pre-eclampsia.

- Test dose is 10 mg followed in 30 minutes by an IV infusion of 10–20 mg/hour, depending on the response
- Maintenance dose of 5–10 mg/hour is recommended with continuous monitoring of heart rate and BP
- Oral hydralazine is commenced within 24 hours, 100–200 mg daily
- If there is no contraindication to beta-blockers, propranolol is given IV 1–4 mg and then orally 120–240 mg daily in addition (or the equivalent dose of another beta-blocker).
- Furosemide 40 mg IV followed by oral HCTZ or furosemide greatly improves the control of BP. Hydralazine is contraindicated in patients with IHD and aneurysms, in particular dissecting aneurysm, because the drug increases cardiac ejection velocity and the rate of rise of aortic pressure can cause aneurysm rupture.

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- One million diabetics die annually in India and 1.5 million in China. The author has recently shown that diabetics have high blood sitosterol and advises on therapy for diabetic sitosterolemia.
- The chapters on ECG Interpretation Made Easy, Arrhythmias Diagnosis and Treatment are packed with practical steps.
- The chapter on Chest X-ray Interpretation is a surprise; the heart and lung move in concert.
- Bulleted statements allow rapid retrieval.

M Gabriel Khan MD FRCP (London) FACC FRCP C, graduated MB BCh, with First Class Honours at Queen's Belfast. His recent research culminated in a novel discovery that should save the lives of many diabetics who die because of heart and stroke. He emphasized that sitosterol causes atheromatous blockage of arteries, and is the first investigator to show that diabetics have high blood sitosterol. He has advised therapy for diabetic sitosterolemia. He is an Associate Professor, Department of Medicine and Division of Cardiology, University of Ottawa, Cardiologist, the Ottawa Hospital, Ottawa, Ontario, Canada. "He has become, an internationally acclaimed cardiologist through his writings": Cardiac Drug Therapy, Rapid ECG Interpretation, Heart Disease Diagnosis and Therapy, On Call Cardiology, Encyclopedia of Heart Diseases.

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