Significance of hypertension
Hypertension affects about 50 million people in the US, and about 1 billion worldwide. Under age 50, diastolic BP is a major predictor of coronary artery disease but above age 60, systolic BP is more important. At least two-thirds of hypertensive patients do not have their blood pressure at the recommended target levels.

Hypertension increases oxygen demand due to increased afterload on the left ventricle, left ventricular hypertrophy and increased wall tension. At the same time, it decreases coronary blood flow because of plaque-related coronary disease. Coronary flow reserve is the difference between resting flow and the flow through a maximally dilated circulation. It is reduced in left ventricular hypertrophy or coronary artery disease.

Systolic hypertension results in thinning and fragmentation of the elastin fibers, increased collagen deposition and thus decreased compliance of the vessel. It also causes endothelial dysfunction. For every 20 mm increase in systolic blood pressure or 10 mm increase in diastolic blood pressure, the mortality from ischemic heart disease and stroke doubles.

Many of the disorders that cause hypertension may also damage target organs. Activation of the sympathetic nervous system and of the renin-angiotensin-aldosterone system, deficiencies of nitric oxide and other vasodilators, and production of inflammatory cytokines are some examples.

Evaluation of the hypertensive patient
History
In particular, the following points should be addressed:
- Duration of hypertension, previous treatment and compliance.
- Degree of blood pressure control
- What prescribed and non-prescription drugs have been used
- Cardiac and neurological history
- Comorbidities – diabetes, hyperlipidemia, renal disease, bronchospastic disease

Physical examination
Overdiagnosis of hypertension is a common problem. The emotional effect of a medical examination may temporarily elevate the blood pressure, giving a false impression of chronic hypertension (“white coat hypertension”). This can result in unnecessary lifetime therapy as well as limiting opportunities
for employment or insurability. Repeated measurements on subsequent visits may clarify the situation. Home blood pressure readings can help. Ambulatory blood pressure monitoring is usually the most definitive approach. However, white coat hypertension is not always benign. It may progress to sustained hypertension in up to 37% of patients. Follow these patients at 3-6 month intervals.\(^3\)

Suspect prehypertension if there is intermittent elevation of BP during clinic visits, or excessive rise in BP during a treadmill test. Treating prehypertension reduces the subsequent incidence of hypertension. The opposite phenomenon has also been observed: so-called \textit{masked hypertension}. This refers to patients who have normal blood pressures in the office but are hypertensive on home or ambulatory monitoring. Their prognosis is similar to that of patients with sustained hypertension.

Measure the BP after the patient has been sitting quietly for 5 minutes. He should not have smoked or had caffeine within 30 minutes. Support the arm at heart level. Use a properly sized and calibrated BP cuff. Deflate the cuff slowly (2 mm/sec). Systolic pressure is defined at the first detection of Korotkoff sounds, and diastolic pressure at their disappearance. Check both arms. Measure the BP on at least 2 or 3 occasions before declaring patient hypertensive, unless BP is over 160/100. Younger patients should have the blood pressure measured in the lower extremity as well, to rule out coarctation of the aorta.

If there is doubt as to the diagnosis, consider ambulatory blood pressure monitoring. Considered the gold standard, it consists of an automated device that is worn by the patient. The machine measures the BP every 15 minutes during the day and every 30 minutes at night. The awake and the sleep readings are each averaged. Of interest are the mean BP readings, whether the normal “dip” of 10-20% occurs during sleep, the morning surge of BP, and whether there is supine hypertension or sudden fluctuation in BP. Patients who do not exhibit a nocturnal dip in BP have a worse prognosis than those who do. Hypertension is considered if the mean daytime BP is above 135/85. Ambulatory BP monitoring permits identification of masked hypertension as well as white coat hypertension.

In most practices, the patient’s blood pressure is measured at about the same time of day. This does not take into account possible fluctuations in pressure, which confer a poor prognosis. This can be overcome by having the patient monitor his blood pressure at home. Patients should take at least 2 readings 1 minute apart before taking medications, and again before supper. Ambulatory blood pressure monitoring is a better indicator. To achieve consistent control over 24 hours, one must know the duration of action of the medications.\(^4\) Fewer than 40% of patients achieve this goal.\(^4\)

\textit{Look for evidence of target organ damage}  
- Funduscopic examination  
- Heart failure  
- Myocardial infarction  
- Stroke,  
- Renal failure  

Check for abdominal bruises. Examine fundi, peripheral pulses

**Laboratory:**  
- Blood chemistry, renal function, electrolytes, blood sugar, uric acid, lipids, TSH, CBC, urinalysis  
- ECG and echocardiogram  

Patients with diabetes or chronic kidney disease should have urinary albumin/creatinine ratio checked.
# Classification of hypertension in adults 18 years or older (2017 Guidelines)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Blood Pressure</th>
<th>Lifestyle Modification</th>
<th>Initial drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Without compelling indications</td>
</tr>
<tr>
<td>Normal</td>
<td>SBP &lt;120 and DBP &lt;80</td>
<td>Encourage</td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>SBP 120-129 and DBP &lt;80</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Stage 1</td>
<td>SBP 130-139 or DBP 80-89</td>
<td>Yes</td>
<td>Thiazides for most. May use ACEI, ARB, BB, CCB, combination</td>
</tr>
<tr>
<td>Stage 2</td>
<td>SBP ≥ 140 or DBP ≥ 90</td>
<td>Yes</td>
<td>2 drug combination usually Usually thiazide +ACEI or BB + CCB</td>
</tr>
</tbody>
</table>

## Treatment

**Goal of treatment:**

In patients without other cardiovascular risk factors, a reasonable goal is thought to be below 130/80 for patients younger than 60, regardless of comorbidities. Older patients are also targeted at < 130/80 in the absence of significant comorbidities. Otherwise, clinical judgment may determine a more appropriate goal. If the patient's blood pressure is already lower than these parameters and is doing well, the guidelines do not recommend withdrawing therapy. The initial treatment should generally include one of the classes that has been shown to reduce cardiovascular risk (ACEI, ARB, CCB and thiazides).

The 2017 guidelines take into account the ASCVD risk equation. Patients with stage 1 hypertension and a 10-year risk of <10% can be initially managed with a nonpharmacologic treatment, and should be reevaluated in 3-6 months. Those with higher risk scores should be started on drug therapy and reevaluated in 1 month. Stage 2 hypertension requires 2 drugs.

It is theoretically possible that lowering the diastolic pressure below the autoregulatory limit could actually increase the likelihood of coronary events (the so-called “J curve.”) This is still controversial, but use caution and be alert to the development of ischemic events if the diastolic pressure is reduced below 60 (particularly if the patient is over the age of 60, has coronary artery disease or is diabetic).

## Life style modification

- Diet - low sodium and rich in potassium containing foods, such as the DASH diet
- Exercise (aerobic or resistance) - 90-150 minutes per week
- Weight control
- Smoking cessation
- Moderate alcohol intake (1-2 drinks daily for men, 1 drink for women.)
Drugs
It is very important that the physician who treats the hypertensive patient know a wide variety of antihypertensive drugs very well. He should become very familiar with the doses, side effects, precautions, interactions of these drugs. Most patients require at least two drugs for adequate control. The initial treatment should usually include one of the drugs known to reduce cardiovascular risk (ACEI, ARB, CCB and thiazides). 56

Diuretics
The Joint National Committee on Hypertension originally advised a thiazide diuretic as the initial therapy for most patients. Current guidelines suggest using a drug selected based on the patient's comorbidities. Thiazides work primarily by reducing the blood volume, and thus cardiac output. Reduction in volume activates the renin system, limiting their efficacy. It is often a useful to combine them with an ACE inhibitor or an ARB.

Triamteramine and amiloride have the advantage of being potassium sparing. They must be used with caution in patients taking ACEI's, or ARB's, aliskiren, or beta-blockers.

Thiazides are used if there is no or mild renal impairment. A typical dose of hydrochlorothiazide is 12.5 – 50 mg daily. Higher doses do not provide much additional benefit, but increase the likelihood of electrolyte imbalance and can reduce HDL level and increase insulin resistance. The tendency to hypokalemia is often mitigated with coadministration of renin-angiotensin-aldosterone blocking agent. The half-life of hydrochlorothiazide is 8-15 hours. Chlorthalidone (12.5-25 mg daily) is more effective than hydrochlorothiazide for hypertension. It has a half-life of 45-60 hours. Another thiazide, indapamide is also long acting, and is less prone to cause hypokalemia than other diuretics.

There is evidence that renal cell carcinoma may develop during thiazide therapy, particularly in women, although this must be uncommon. It appears to be related to the dose and duration of therapy.14

If the creatinine clearance is under 30, use a loop diuretic

ACE inhibitors
These drugs reduce systemic vascular resistance through several mechanisms. They reduce neurohormonal activation and have a number of other cardioprotective and vascular protective properties. The dose-response curve is such that increasing the dose increases the duration of action but not the intensity of effect. Short-acting drugs (captopril, delapril, quinapril, spirapril) should be administered two or three times daily. Longer acting drugs can be given once daily. These include enalapril, ramipril, benazepril, cilazapril, fosinopril, lisinopril, perindopril, trandolapril and zofenopril.24 They are more effective than other agents in reducing albuminuria. ACE inhibitors are more likely to cause angioedema in African-American patients. Given the similar efficacy of ARBs, which also have fewer side-effects, Messeri et al recommend against using them for treatment of hypertension in all patients.
**ARBs**

These work in a similar way to ACE inhibitors and may be better tolerated by some patients. They are less likely to cause angioedema than the latter.

**Aliskiren**

This is a direct renin inhibitor. ACEI’s and ARB’s block renin, causing a reflex increase in plasma renin activity. This also happens with aliskiren, but its direct renin blocking activity opposes the adverse effects of renin increase. Aliskiren can be used in combination with diuretics and with the ARB valsartan. However, aliskiren should not be used in combination with an ACEI or an ARB in diabetic patients, due to a risk of adverse cardiovascular and renal events. Aliskiren does not appear to have any advantage over ACEI's or ARB's.

**Beta-blockers** (metoprolol, carvedilol and others)

These slow the heart rate and increase diastolic filling time, which helps coronary perfusion. They inhibit renin release. They are not recommended as initial therapy, unless the patient has another indication for a beta-blocker. A new beta-blocker, nebivolol, has unique vasodilator properties and appears to have greater antihypertensive effect than the others, including in African-American patients.

Several beta-blockers have intrinsic sympathetic activity (acebutolol, penbutolol, pindolol). They should generally not be used in patients with coronary artery disease.

**Calcium antagonists**

These reduce oxygen demand by decreasing peripheral vascular resistance. They also increase coronary oxygen delivery by coronary dilatation. Avoid non-dihydropyridine calcium channel blockers if there is heart failure or left ventricular diastolic dysfunction. Short-acting nifedipine should not be used because it may cause reflex sympathetic stimulation, resulting in ischemia.

In patients with coronary disease, verapamil has been found as effective as atenolol when used in combination with trandolapril. The incidence of cardiovascular complications was the same in both study groups.

Some patients are troubled by dependent edema, which often occurs when these drugs are used. The mechanism is believed to be reduction in post-capillary resistance. This may be offset by the concomitant administration of a renin-angiotensin blocker.

**Aldosterone antagonists** (spironolactone and eplerenone)

These agents counteract aldosterone, which has numerous potential deleterious effects, such as sodium and water retention, myocardial fibrosis and endothelial dysfunction. Aldosterone antagonists are often effective antihypertensives even if the patient’s aldosterone level is not elevated. They should not be used in chronic kidney disease, especially if an ACEI or ARB is being administered.

Amiloride is an indirect aldosterone antagonist. It is generally safe, but as with spironolactone, potassium must be monitored. It is contraindicated if the creatinine is above 1.5.
**Direct vasodilators** (hydralazine, minoxidil)

Hydralazine has a relatively short half-life and is administered 3-4 times a day. Side effects may include headache, nausea, vomiting, tachycardia and orthostatic hypotension. It can also cause a lupus-like syndrome.

Minoxidil is a potent vasodilator that is used mainly in severe hypertension in patients with advanced kidney disease. It has numerous side effects, including fluid retention and heart failure, exacerbation of angina, pericardial effusion, disfiguring hypertrichosis and Stevens-Johnson syndrome. It is given once daily.

**Alpha-blockers** (doxazosin and others)

These vasodilators are also effective in relieving symptoms of prostatism. They may cause orthostatic hypotension and fluid retention. They are contraindicated in the presence of left ventricular dysfunction.

**Alphamethyldopa**

This is a centrally acting vasodilator that is inexpensive but seldom used because of some of its side effects.

**Clonidine**

Clonidine is another centrally acting vasodilator. A major disadvantage is the development of severe rebound hypertension if the patient suddenly discontinues it. Rebound can also occur between doses, sometimes even if the drug is given t.i.d. It is contraindicated in heart failure.

**Guanfacine**

This is also centrally acting. It has a longer half-life than clonidine, and can be given as a single dose at bedtime. Like clonidine, it can cause rebound hypertension if it is withdrawn abruptly.

**Combination pills**

After dose titration with several drugs, it is often possible to prescribe a tablet that combines several of them. This saves money and improves compliance.

**Consideration of comorbidities and special populations**

Patients with diabetes, hyperlipidemia, renal disease, left ventricular dysfunction or heart failure should be treated with an ACEI or an ARB as first line therapy. Consider using a BB and/or aldosterone antagonist as well if there is left ventricular failure. Patients with stable coronary disease should be started on a beta-blocker.

**African Americans**

In African Americans, ACEI’s, ARB’s and BB’s are less effective in lowering BP than are diuretics or CCB’s. However, they retain their other cardiovascular benefits, and may be used to advantage in this group. Older patients with isolated systolic hypertension should usually be started on a diuretic with or without a beta-blocker, or a DHP CCB.

**The elderly**

Older patients with isolated systolic hypertension should usually be started on a diuretic with or without a beta-blocker, or a DHP CCB. Elderly patients (e.g. over 80) may tolerate some degree of
hypertension. The SPRINT trial found that blood pressure goal of less than 120 systolic was associated with fewer cardiovascular events, even in patients over 75 years of age. Some side effects were increased in the intensive control group (acute renal failure, syncope, hypotension), but the net benefit favored intensive control.\textsuperscript{50}

Certain groups were excluded from the trial:

\begin{itemize}
  \item History of stroke
  \item Diabetes
  \item Heart failure
  \item Severe chronic kidney disease
  \item Nursing home residents
  \item Significant dementia
  \item Standing BP <110 systolic
\end{itemize}

There have been a number of criticisms of that trial:\textsuperscript{51}

1. It did not include patients with diabetes or prior stroke, and may not be generalizable to those individuals.
2. Blood pressure was measured meticulously, with the subject seated for 5 minutes. 3 readings were taken each time. This is not what usually happens at a typical office visit. Thus, in attempting to reach the SPRINT goals, a physician might reduce the patient's blood pressure well below the recommended level.
3. In many of the patients in SPRINT, the target blood pressure could not be achieved.
4. With intensive treatment, there was a greater incidence of hypotension, syncope, electrolyte abnormalities and kidney injury.\textsuperscript{53}

\textit{Chronic heart failure}

Use diuretics together with either an ACE inhibitor or an ARB (but not both) and a beta-blocker. The target blood pressure is <130/80, but consider <120/80. Try not to lower the diastolic below 60. Aldosterone antagonists are indicated if there is heart failure or if the left ventricular ejection fraction is under 40%, provided there is no more than mild renal insufficiency and no hyperkalemia.

\textit{Prior myocardial infarction}\textsuperscript{49}

Patients with a prior myocardial infarction should receive a beta-blocker. If this is not tolerated, a nondihydropyridine calcium channel blocker may be substituted, provided there is not left ventricular dysfunction. Patients who have a reduced left ventricular ejection fraction, diabetes or chronic kidney disease benefit from an ACE inhibitor or and ARB. The latter should also be considered in post-myocardial infarction patients without these comorbidities.

\textit{Stable coronary artery disease}\textsuperscript{49}

For patients with stable coronary artery disease, a goal of <130/80 is advised. The same target has also been recommended for patients with acute coronary syndrome or those with heart failure. A beta blocker should be included in the regimen.

\textit{Acute coronary syndrome}\textsuperscript{49}

Do not lower the BP rapidly because of the risk of compromising coronary flow. In these patients, a target BP of <140/90 is advised in stable patients, and a goal of 130/80 is considered reasonable at the time of discharge.
Patients with acute coronary syndrome should also be treated with a beta-blocker (without intrinsic sympathetic activity). Esmolol is a reasonable choice if there is ongoing ischemia or severe hypertension. If the patient is hemodynamically unstable, do not give a beta-blocker until the shock or heart failure is corrected. Other contraindications include severe first degree atrioventricular block (PR > 0.24 seconds) or second or third degree block, and severe bronchospastic disease. Early intravenous use should be reserved for low-risk patients. Esmolol can be used in the acute setting.

Nitrites may also be used to lower the BP, provided there is no contraindication. Nitroglycerine lowers the blood pressure, reduces congestion and relieves symptoms. Use caution if the patient is elderly or volume-depleted, and do not use any nitrate if the patient has taken sildenafil within 24 hours or has a right ventricular infarct. Nitrate tolerance can develop within 24 hours. This can be avoided by using intermittent percutaneous, oral or sublingual forms rather than intravenous dosing, or by reducing the intravenous dose.

Aldosterone blockers are indicated if there is left ventricular dysfunction and either heart failure or diabetes. They have multiple protective effects. They should be avoided in women with a creatinine ≥ 2.0 or in men with creatinine ≥ 2.5, or in anyone if the K is ≥ 5.0. Kidney function and potassium levels should be monitored closely.

Non-dihydropyridine calcium channel blockers can be used for non-ST elevation myocardial infarction or unstable angina if beta-blockers are contraindicated and the patient has ongoing ischemia. They should be avoided if there is left ventricular dysfunction, bradycardia, moderate to severe heart failure, or if the patient is on a beta-blocker. Non-dihydropyridine calcium channel blockers are not useful in ST elevation myocardial infarctions, but long-acting dihydropyridine calcium channel blockers can be used if there is ongoing ischemia. Do not use a short-acting dihydropyridine calcium channel blocker.

Diuretics are indicated if there is increased filling pressure, pulmonary venous congestion, or heart failure.

ACE inhibitors are especially useful in the following settings:
- persistent hypertension
- left ventricular dysfunction
- a large or an anterior myocardial infarction
- heart failure
- diabetes

They can be given orally or intravenously, depending on hemodynamic stability. They reduce infarct expansion and remodeling and chamber dilatation. This helps to prevent arrhythmias, heart failure or rupture. Captopril appears to increase adverse outcomes and is not recommended. ARB’s are an alternative. However, valsartan increased adverse events without improving survival.

Coronary artery disease with heart failure

Patients with heart failure and coronary artery disease should be treated with a beta-blocker and ACE inhibitor of ARB as well as diuretics and an aldosterone antagonist, in the absence of contraindications. A target of <130/80 should be considered. Titration should be done slowly and carefully. Hydralazine and isosorbide dinitrate should be added in African American patients.
Titration and followup

Most antihypertensive drugs require one to several weeks to take full effect. This should be explained to the patient. During the initial phase of treatment, he should be seen at 2–4 week intervals to determine the efficacy of treatment and to detect side effects. Even after stabilization of the regimen, periodic re-evaluation is necessary, both to assess blood pressure control and to detect target organ damage. To this end, the following are helpful: the electrocardiogram and echocardiogram (looking for left ventricular hypertrophy), glomerular filtration rate and urinary protein excretion.

Home BP monitoring

This is a valuable adjunct to the management of hypertension and is recommended for routine use. It provides a profile of the patient’s blood pressure, rather than the “snapshots” that are obtained during office visits. In addition, patients are more relaxed at home, and the readings obtained may be more representative of the true values. It has been found to be more reliable than office readings. Follow these precautions:

- Cuff should be applied to upper arm (avoid wrist or finger devices)
- The patient should sit quietly for about 5 minutes before taking the blood pressure.
- He should not have had coffee, smoked, or exercised within 30 minutes.
- Both feet should be on the floor and the back should be supported.
- The arm should be supported so that the upper arm is at heart level
- Two to three readings should be obtained, both morning and night
- Check the device against your own measurement.
- Either use a self-inflating device, or have spouse check it.
- If there is difference in blood pressures between the arms, use the arm with the higher reading.
- At least 12 readings over a week should be obtained before making a clinical decision.

Resistant hypertension

Definition:

BP ≥ 140/90 (130/80 if diabetes or renal disease) despite full doses of at least three antihypertensive drugs including a diuretic.

Causes of resistant hypertension

- Noncompliance
- Medications (patient thinks he is “cured”, or ran out of pills, high cost, side effects, forgotten doses)
  - Have the patient bring in all his drugs. Compare the labeled instructions with your own list
  - Give the patient a list of instructions in plain English.
- Excessive sodium intake
- Alcohol
- High intake of natural licorice
- Obesity
- Sleep apnea
- Inadequate dosage of antihypertensive drugs
- Interfering drugs – phenylephrine, cocaine, amphetamines, anabolic steroids, NSAID’s, appetite suppressants, decongestants, COX 2 inhibitors, mineralocorticoids, glucocorticoids, oral contraceptives, steroids, antidepressants (MAO inhibitors, tricyclic and other antidepressants, especially Abilify), erythropoietin, cyclosporine. Even aspirin in excess of 150-325 mg/day may raise the blood pressure
- Acetaminophen
Other drugs – cocaine, caffeine, acute alcoholism
Herbal supplements (ephedra, ginseng, yohimbine, saw palmetto, capsicum, licorice, chewing tobacco).
Secondary causes of hypertension

Management of resistant hypertension

Confirm that the condition is present
- Be sure the BP is being taken correctly and that the patient is compliant.
- Discontinue interfering drugs.

Lifestyle changes
- Exercise
- Weight loss
- Limit alcohol intake
- Sodium restriction (read labels, avoid fast foods, restaurants)
- Encourage high fiber intake
- Encourage potassium-rich foods

Improving compliance
- Educations – explain risks, benefits, need for continuation of drugs.
- Try to use once daily drugs.
- After titration, use pills that combine several ingredients (e.g. a thiazide and an ACEI).
- Encourage home BP monitoring. Have the patient keep a diary.
- Confirm that he is taking the drugs at each visit - better yet, bring the bottles.
- Involve other family members.

Screen for secondary cause of hypertension (accounts for about 10% of cases of hypertension)

See next section.

Optimal dosing of drugs
- Titration to effective doses is essential.
- Adequate diuretic dose
- Consider adding a mineralocorticoid antagonist
- Sometimes it helps to give a drug twice daily.
- Giving at least one of the drugs at bedtime often improves control

Not all drugs in the same class are equal
- Chlorthalidone seems to work better than hydrochlorothiazide. Furosemide is weaker than thiazide diuretics.
- Carvedilol and labetalol have both alpha and beta blocking action and may be more effective than other beta blockers. However, labetalol has a half-life of only 5-8 hours Metoprolol is a relatively weak antihypertensive, and atenolol is even less effective.
- Nebivolol has more vasodilating properties than the other beta blockers.

Use drug combinations
- Victor recommends that resistant patients be started on a combination that includes a renin-angiotensin blocker, a non-dihydropyridine calcium blocker, and a diuretic. If this is inadequate, he
then adds carvedilol. His next step is to add an aldosterone-blocking drug. If necessary, he then adds a centrally acting drug, usually guanfacine.

Other combinations are sometimes used, e.g. DHP CCB + NDHP CCB.

Addition of an aldosterone blocker or doxazosin may give good results. Amiloride may be added to a thiazide, but the patient should be monitored for hyperkalemia. It should not be used if there is renal impairment or without a concomitant with a kaliuretic diuretic. For patients with renal impairment, substituting a loop diuretic for a thiazide may be beneficial.

Combining two blockers of the renin-angiotensin system (ACE, ARB, aliskirin) increases the risk of end-stage renal disease, based on several important studies.35

Rheos hypertension system
This recently approved device consists of a surgically implantable pulse generator that stimulates the carotid baroreceptors. Phase II trials have demonstrated its effectiveness and further testing is underway. The findings were presented at the 2009 annual meeting of the American College of Cardiology.35 Recent studies have not been favorable.

Renal sympathetic denervation
The renal sympathetic nerves are accessible from within the renal arteries. They can be interrupted using a radio frequency catheter-based approach. This seemed to be effective in lowering the blood pressure. Reducing the sympathetic tone increases renal blood flow, decreases norepinephrine and renin production and causes an initial natriuresis. The response rate was 84% and was durable to at least two years. The average reduction in blood pressure was 32/12. Although the procedure alone only resulted in adequate control in 39% of patients, it may prove to be an effective adjunct to drug therapy.21,35 In addition, Mahfoud et al found that renal denervation also resulted in reduced left ventricular mass when the patients were restudied at 6 months.47 In contrast, the recent SIMPLICITY 3 trial shed doubt on the efficacy of this treatment, at least with the use of the Medtronic device.40,44,45 More promising results were demonstrated in the SPYRAL HTN-OFF MED trial.55

Even if the blood pressure is controlled, it is recommended that patients with resistant hypertension be evaluated for secondary causes.43

Secondary hypertension
Look for secondary causes of hypertension in the following settings:
- No risk factors for primary hypertension (e.g. family history)
- Age of onset of hypertension before 30 or after 55
- Detection of features suggestive of a primary cause (Cushing’s, pheochromocytoma, etc)
- Abrupt onset of hypertension
- Accelerated hypertension
- Refractory hypertension
- Hypokalemia
Causes of secondary hypertension

Renal disease
Renal hypertension may be due to renal artery stenosis (atherosclerotic or fibromuscular hyperplasia), but also occurs with renal arteriovenous fistula, vasculitis, coarctation of the aorta, subcapsular hematoma of the kidney, renin-secreting tumors, or extrinsic pressure (e.g. a tumor).

Atherosclerotic stenosis is commoner in elderly diabetics. Fibromuscular hyperplasia occurs in young females. A 75% reduction in renal artery diameter will activate the renin-angiotensin system, and can cause hypertension. This may also result in ischemic nephropathy.

Renal hypertension is suggested by any of the following:
- Onset before age 30 or after 55
- Abdominal bruit
- Renal failure
- Hypokalemia
- Flank trauma
- Smoking
- No family history of hypertension
- Difference in kidney size > 1 cm

Tests for renal hypertension:
- Plasma renin level can be used for screening.
- Duplex renal artery sonography
- Magnetic resonance angiography
- Computed tomographic angiography
- Arteriography (gold standard)

Treatment of renal hypertension:
- Parenchymal renal disease
  Preferred regimens are ACE or ARB with a loop diuretic; BB, CCB. Loop diuretics may be more effective if given twice daily, with the possible exception of torsemide.

Renovascular hypertension
An ACEI or an ARB with a diuretic is often effective. The creatinine may increase early in the course of treatment. A rise of serum creatinine of up to 30% over baseline and a rise in potassium up to 5.5 may be acceptable. It will usually improve over several weeks. However, in patients with bilateral renal stenosis, or unilateral stenosis with a single functioning kidney, ACEI’s and ARB’s can cause serious deterioration of renal function. In patients with fibromuscular dysplasia, angioplasty has been successful. However those with atherosclerotic renal artery disease, this does not seem to be as useful.

Angioplasty or surgical treatment has also been considered in the following situations:
- Accelerated hypertension
- Hypertensive emergency or urgency
- Resistant hypertension
- Worsening of renal function during treatment
- Flash pulmonary edema
- Very high grade stenosis (>95%)
- Dialysis dependent renal failure
- Failure of medical therapy

Currently, there is growing doubt as to the benefit of stenting for atherosclerotic renal artery stenosis and even whether it is worth imaging the renal vasculature. If stenosis is
found, at least there should be some determination of its hemodynamic significance, rather than relying solely on its angiographic appearance.

Complications of stenting:
- pseudoaneurysm
- renal artery dissection
- contrast nephropathy
- atheroembolic disease

Followup after stenting: Monitor kidney function every 1-3 months, and renal sonogram and duplex ultrasound every 6-12 months.

There is evidence that, in patients with kidney disease, bedtime dosing of at least one of components of the drug regimen reduces the risk of subsequent cardiovascular events.\textsuperscript{31}

\textit{Cushing’s syndrome}

These patients may not respond to the usual drugs. Typical features include central obesity, proximal muscle weakness, moon facies, easy bruising, pigmented striae and "buffalo hump," The diagnosis is established by the dexamethasone suppression test and elevated urinary cortisol. The treatment is surgical.

\textit{Conn’s syndrome (primary aldosteronism)}

This may account for up to 10% of cases of hypertension, and is even more common in patients with resistant hypertension. It should be suspected if there is a family history of early onset hypertension or stroke, or if hypokalemia is found. The serum potassium levels are usually not low, however.\textsuperscript{43} Screening may be done by measurement of plasma aldosterone and renin levels after correction of hypokalemia and withdrawal of aldosterone antagonists for 4-6 weeks. If the ratio is abnormal, the diagnosis is confirmed by salt loading and measuring a 24-hour urine specimen for aldosterone. The next step is to determine whether the aldosterone excess is due to unilateral or bilateral secretion. This is done by renal venous blood sampling, which should be performed in an institution that is skilled in this study.

Treatment of hyperplasia consists of aldosterone antagonists, ACE or ARB. If eplerenone is used in this setting, it should be administered twice daily, as it is short acting. Surgery is preferred for aldosterone-secreting adenomas.

\textit{Acromegaly}

Enlarging shoe, glove or hat size, headache, visual disturbances, diabetes are features of this disease. Measure serum growth hormone level. MRI of pituitary is indicated.

\textit{Obstructive sleep apnea}

\textit{Congenital adrenal hyperplasia}

Features include hypokalemia, virilization

\textit{Drug or alcohol induced}

Sodium-containing antacids, alcohol, smoking, amphetamines, NSAIDs, oral contraceptives, sympathomimetics, cyclosporins, tacrolimus, cocaine, neuropsychiatric drugs, erythropoetin, illicit
drugs. Grossman has compiled a long list of drugs and other substances that can induce hypertension.\textsuperscript{32}

**Pheochromocytoma**
Sustained hypertension is present in 50\% of these patients. In others, it is paroxysmal. Symptoms such as headache, sweating and palpitation, typically episodic, are strongly suggestive of the diagnosis. It should be suspected if the patient has neurofibromas of café au lait spots, or if there is a family history of pheochromocytoma. The best screening test is plasma free metanephrine or normetanephrine, which is 99\% sensitive and 89\% specific.\textsuperscript{43} Since some tumors are extra-adrenal, localization is critical. Surgical treatment is always indicated.

**Thyroid disease (hyper or hypo)**

**Coarctation of the aorta**
The blood pressure is higher in the upper extremities than in the legs. A continuous murmur is heard over the back and chest. CT angiogram confirms the diagnosis. Treatment is surgery or balloon angioplasty

**Sleep apnea**
CPAP, weight loss, surgery. There is also an oral appliance that is intended to keep the airway open.

**Hyperparathyroidism**

**Hypertensive urgencies**
The distinction between a hypertensive urgency and a hypertensive emergency is defined by target organ damage, and not the absolute level of the blood pressure. A hypertensive urgency refers to a severe elevation of blood pressure without target organ damage. It is not necessary to lower the blood pressure acutely in this setting. Parenteral drugs are not indicated. \textit{Do not use sublingual nifedipine}. The oral treatment should be adjusted and the patient asked to return to the clinic within a short time.

**Hypertensive emergencies**
Renal, cerebral and coronary blood flows all have autoregulatory systems. Flow is kept relatively constant over a wide range of systemic blood pressures. However, this system can be overwhelmed, resulting in acute renal ischemia, hypertensive encephalopathy or cardiac injury.

\textit{Try to identify the cause of the emergency}
Renal parenycymal and renovascular disease including systemic disorders, and acute glomerulonephritis
Endocrine – pheochromocytoma, Cushing syndrome, primary aldosteronism
Drugs – cocaine, amphetamines, cyclosporine, clonidine withdrawal, phencyclidine, diet pills, oral contraceptives
Drug interactions -- MAO inhibitors with various drugs or tyramine-containing food.
CNS trauma or cord disorders
Coarctation of aorta
Preeclampsia/eclampsia
Lead intoxication
Acute intermittent porphyria
Laboratory
CBC, urine, toxicology
Chest x-ray
Chest CT if indicated
Head CT if indicated
ECG
Echocardiogram

ACE inhibitors and hydralazine should be used with caution in acute hypertensive emergencies, as they may cause a precipitous drop in blood pressure, and they are not short acting. Do not use sublingual nifedipine.

Clevidipine (Clevieprex, The Medicines Company) is a new intravenous antihypertensive drug, which can be substituted for nitroprusside in some situations. It is a calcium channel blocker with a half-life of about 1 minute. It is contraindicated in severe aortic stenosis as well as in heart failure. Patients should not receive it if they are allergic to soy or egg products. It requires continuous blood pressure and heart rate monitoring, since it may cause tachycardia.

In patients with a compelling indication, such as dissecting aneurysm of the aorta, severe preeclampsia or eclampsia, pheochromocytoma, the BP should be lowered rapidly. In others, the SBP should be reduced by no more than 25% in the first hour, then cautiously reduced to normal in the next 24-48 hours. 54

Malignant hypertension
This is defined as severe hypertension with ischemic organ damage. The average survival rate after this diagnosis if 5 years. The organ damage can regress after treatment, which usually consists of a parenteral titratable agent, such as labetalol, nitroprusside, nitroglycerine, nicardipine or furosemide. Ultrafiltration or hemodialysis is sometimes needed. 35

Acute pulmonary edema
The left ventricle fails because it cannot overcome the high systemic vascular resistance. The result can be pulmonary edema and/or myocardial infarction. The blood pressure should be lowered promptly using one of the following:
Nitroglycerine iv
Nitroprusside iv
Furosemide iv (Caution: overdiuresis can cause hypotension)
Most patients with “flash” pulmonary edema have preserved systolic function. It often occurs in the setting of an acute coronary syndrome. Lowering the blood pressure and diuresis generally causes rapid improvement.

The initial therapy is intravenous nitroglycerine, furosemide and a short-acting or intravenous ACE inhibitor. If there is tachycardia, esmolol with intravenous nitroglycerine is usually the first choice. The blood pressure should be lowered aggressively, but be alert to evidence of ischemia or cerebrovascular insufficiency. Intravenous labetalol or nitroprusside can also be used.

Acute myocardial ischemia
Nitroglycerine iv unless contraindicated
Beta blockers iv unless contraindicated
Hypertensive encephalopathy
In normals, the range of cerebrovascular autoregulation is possible over a mean arterial pressure of 60-120, although it may be higher in the chronically hypertensive patient. If the blood pressure exceeds this limit, the system is disrupted, resulting in microhemorrhages and cerebral edema.

Symptoms may include headache, lethargy, visual disturbances, confusion, coma, seizures, nausea and vomiting. Fundoscopy typically shows hemorrhages, exudates and papilledema, but these are not always present. Transient and migratory nonfocal neurological deficits (e.g. nystagmus or weakness) can occur. With early treatment, the condition may be completely reversible. Without treatment, it may end in cerebral hemorrhage, coma and death.

In addition to the other causes of hypertensive emergencies, the etiology may be head trauma, encephalitis, or meningitis. The MRI characteristically shows a posterior leukoencephalopathy.

The patient should be monitored in an intensive care unit. Do not try to lower the blood pressure to normal levels. The mean arterial pressure should be reduced by no more than 20-25% in the first hour. If the patient remains stable, it should then be lowered to 160/100-110 in the next 2 to 6 hours.

Drugs:
- Nitroprusside iv
- Labetalol iv
- Fenoldopam iv
Centrally acting agents (e.g. clonidine) should be avoided.

Patients with a recent ischemic stroke and a systolic blood pressure > 220 or a diastolic BP > 120-140 can undergo cautious reduction of blood pressure by about 10-15% with iv nitroprusside or iv labetalol. However, they should be carefully monitored for neurological deterioration.

Acute intracranial hemorrhage
If the SBP is > 220, it is reasonable to administer an intravenous agent, with close BP monitoring. However rapid reduction to <140 is not recommended.54

Acute ischemic stroke
If thrombolytic therapy is planned, the BP should be slowly lowered to <185/110 prior to its administration. It should be maintained at <180/105 for at least 24 hours after has been given.

In neurologically stable patients, antihypertensive therapy may be given if the BP is >140/90. If the BP is 220/120 or higher without comorbidities, the benefit of treatment is uncertain. It is believed that lowering the BP by 15% in the first 24 hours is reasonable. If the BP is < 220/120, there does not appear to be a benefit of treatment within the first 48-72 hours.54

Patients who experience a transient ischemic attack or a stroke and are stable should be started on treatment after at least 72 hours with a target SBP of 130.54
Dissecting aneurysm

Acute dissection that includes the ascending aorta (type A) carries a mortality of about 1-2% per hour. Emergent surgery is indicated. If dissection is limited to the descending aorta (type B), medical treatment is usually the first choice.

Etiologies and risk factors include hypertension, Marfan’s syndrome, Ehlers-Danlos syndrome, familial aortic dissection, coarctation of the aorta, bicuspid aortic valve, arteritides, deceleration trauma, and invasive medical procedures involving the aorta.

Symptoms usually begin with sudden onset of chest or back pain or both. Classically, the pain begins at peak intensity, unlike that of acute coronary syndrome. The pain may radiate widely (jaw, either or both arms, the back, abdomen) and may migrate as the dissection proceeds. Uncommonly, the dissection is painless. In such cases, the patient may present later with a “healed dissection” manifested, for example, by aortic valvular insufficiency.

Side branch occlusion can occur during dissection. This may result in myocardial infarction, stroke, or limb or visceral ischemia. Pulse deficits should be sought. The aneurysm may rupture into the pericardium, chest or retroperitoneal space. Disruption of the aortic valve can occur, resulting in acute aortic regurgitation.

A routine chest x-ray is abnormal in 60-90% but is usually not highly specific. Definitive studies include CT scan, MRI or trans-esophageal echocardiogram. It may be necessary to perform more than one test to establish a diagnosis.

It is very important to initiate beta blockade early, in order to reduce the dP/dT (target heart rate ≤ 60). Preferred drugs include the following:

- Labetalol iv
- Nitroprusside iv with a beta blocker iv (e.g. esmolol)

The BP should be lowered rapidly to < 120 systolic.

Acute renal failure

- Fenoldopam iv
- Nicardipine iv
- Beta blockers iv

Pheochromocytoma

- Phentolamine iv
- Labetalol iv

Once stabilized, localization and resection of the tumor is essential

MAO interactions

- Phentolamine iv

Hypertension in pregnancy

The details of management of these conditions are beyond the scope of this paper. The original articles should be consulted. There are four categories:
**Gestational hypertension**
Definition: New onset of hypertension after 20 weeks (SBP > 140 or DBP > 90 with previously normal BP). Proteinuria and seizures are absent. The BP returns to normal by the 6-week postpartum visit.

**Preeclampsia**
Definition: New onset of hypertension after 20 weeks, accompanied by proteinuria.

Treatment
- Magnesium sulfate
- Methyldopa
- Hydralazine
- Labetalol
- Extended release nifedipine
- Nicardipine
- Nitroprusside

Diuretics are usually contraindicated unless the patient has already been receiving them.

Usually resolves after delivery. Vaginal delivery is preferred.

**Eclampsia**
New onset of hypertension after 20 weeks with proteinuria and seizures.

**Chronic hypertension**
Treatment choices include the following:
- Labetalol
- Aldomet
- CCB’s (usually nifedipine)
- Diuretics sometimes used
- ACEI and ARBs are contraindicated in pregnancy

**Preeclampsia superimposed on chronic hypertension**

**Postoperative hypertension**

**Causes:**
- Pain
- Bladder distention
- Fluid overload
- Hypercarbia
- Hypoxia
- Pheochromocytoma
- Withdrawal of clonidine or beta-blocker

**Treatment:**
- Sedation and pain control
- Catheterize if necessary
- Drugs
  - Labetol iv
  - Nicardipine iv
Nitroprusside iv
Nitroglycerine iv

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