Resistant Hypertension

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DEFINITIONS

blood pressure that remains above goal in spite of concurrent use of three antihypertensive agents of different classes(ACC/AHA and ESC/ESH guideline)

Patients whose blood pressure is controlled with **four or more medications** should also be considered to have resistant hypertension.

- If tolerated, one of the three agents should be a **diuretic**

- all agents should be prescribed at **maximum recommended** (or maximally tolerated) antihypertensive doses

Refractory hypertension

resistant hypertension cannot be controlled, even with maximal medical therapy (five or more drugs including chlorthalidone and a mineralocorticoid receptor antagonist)

- approximately **3 percent** of those with resistant hypertension
- may be due to **neurologic mechanisms** (eg, sympathetic overactivity).

RISK FACTORS

1. higher baseline blood pressure (particularly systolic),
2. left ventricular hypertrophy (especially by echocardiogram),
3. older age
4. obesity
5. African-American race
6. chronic kidney disease
7. diabetes

PREVALENCE

- **not known**.

- A major problem is that not all patients with uncontrolled hypertension have resistant hypertension as defined above. Many are uncontrolled because of poor adherence or inadequate treatment regimens.

- apparent resistant hypertension is 8.9 percent

reversible factors

1. suboptimal therapy
2. lifestyle and diet
3. medications (NSAIDs except CCBs, sympathomimetics ,decongestants, amphetamine-like stimulants, glucocorticoids, estrogen-containing contraceptives, calcineurin inhibitors, and antidepressant)
4. herbal preparations

EVALUATION

1. confirm true treatment resistance
2. identify contributing factors
3. document target-organ damage including retinopathy, left ventricular hypertrophy, and kidney disease
4. Suboptimal therapy
5. Lifestyle and diet
6. Medications
7. Extracellular volume expansion

8. Secondary causes of hypertension
9. accurate measurement of the blood pressure

- **Cuff inflation hypertension**→can acutely raise the blood pressure by as much as 12/9 mmHg (dissipates within 5 to 20 seconds (average 7 seconds in one study)

Laboratory evaluation

1. serum electrolytes
2. Glucose
3. creatinine
4. urinalysis with estimation of proteinuria (eg, urine albumin-to-creatinine ratio).
5. Screening for primary aldosteronism is also warranted at the initial visit if possible

since24-hour urine collection should be obtained at the time of the blood testing on the patient's usual diet for determination of sodium excretion, creatinine clearance, and aldosterone excretion.

Treatment of resistant hypertension

- Goal blood pressure

1. nonpharmacologic
2. pharmacologic therapies

3- Identify and treat secondary hypertension

Secondary causes of resistant hypertension

Common
Obstructive sleep apnea
Renal parenchymal disease
Primary aldosteronism
Renal artery stenosis
Uncommon
Pheochromocytoma
Cushing's disease
Hyperparathyroidism
Aortic coarctation

4- Stop medications that raise the blood pressure

Agents that can interfere with blood pressure control

Non-narcotic analgesics (nonsteroidal anti-inflammatory agents, selective COX-2 inhibitors, aspirin)
Sympathomimetic agents (decongestants, diet pills, cocaine)
Stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, methamphetamine)
Alcohol
Oral contraceptives
Cyclosporine
Erythropoietin
Natural licorice
Herbal compounds (ephedra or ma huang)

PHARMACOLOGIC THERAPY

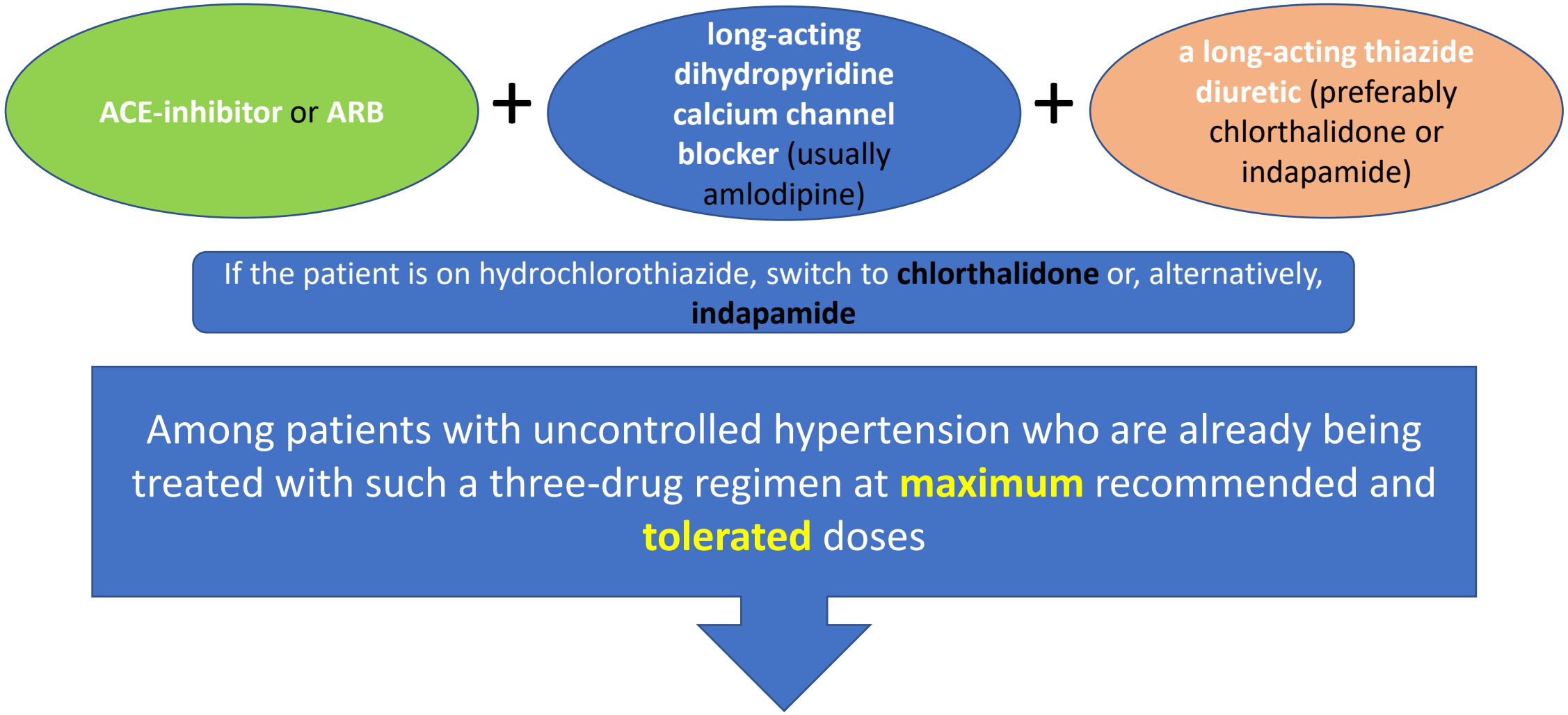
combinations of **three or more** drugs, including a **diuretic**.

- The choice of agents should be **individualized** and may depend upon consideration of prior benefit, history of adverse events, financial limitations, and the presence of concomitant disease processes such as chronic kidney disease or diabetes

CHOICE OF REGIMEN

- The following approach applies to patients with resistant hypertension who do not have a **reversible secondary** cause of hypertension and who do not have a **specific indication** for a class of drugs

sequentially combine agents with **diferent** mechanisms of action


ACE-inhibitor or ARB
+
long-acting dihydropyridine calcium channel blocker (usually amlodipine)
+
a long-acting thiazide diuretic (preferably chlorthalidone or indapamide)
If the patient is on hydrochlorothiazide, switch to chlorthalidone or, alternatively, indapamide
Among patients with uncontrolled hypertension who are already being treated with such a three-drug regimen at maximum recommended and tolerated doses

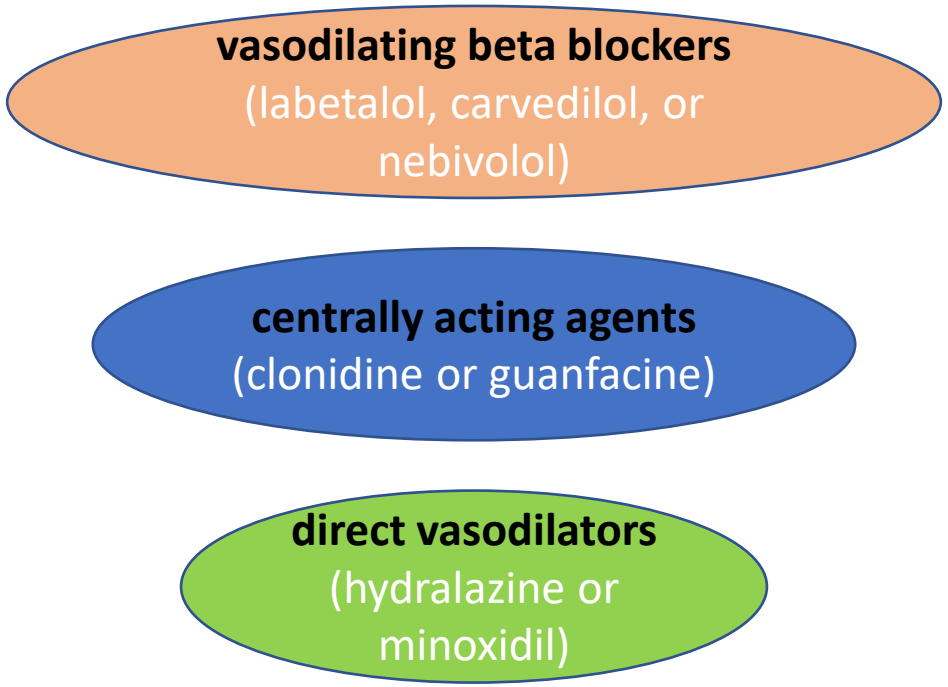
add
spironolactone

- begin spironolactone at 12.5 mg/day before titrating to 25 and, if necessary, 50 mg/day

adverse effects:
gynecomastia, breast tenderness, and erectile dysfunction

eplerenone

If the patient is still hypertensive, **additional medications** are added sequentially:



EXPERIMENTAL THERAPIES

- Stimulation of carotid sinus baroreceptors or baroreflex activation therapy (BAT)
- Central arteriovenous anastomosis

RENAL NERVE DENERVATION

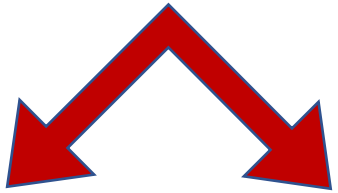
- denervation of the **renal sympathetic nerves** (also known as renal nerve denervation)

- by catheter-based radiofrequency ablation or by catheter-based ultrasound ablation

hypertensive emergencies
and
severe asymptomatic hypertension
(hypertensive urgencies)

DEFINITION

Severe hypertension in adults (often defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥120 mmHg)



hypertensive emergency

- associated with a variety of acute, life-threatening complications

1. hypertensive encephalopathy
2. retinal hemorrhages
3. papilledema
4. acute and subacute kidney injury

hypertensive urgency

- relatively asymptomatic or completely asymptomatic

1. a mild headache
2. **no** signs or symptoms of acute end-organ damage

EVALUATION

- occurs more frequently among patients who have been **nonadherent** with either their chronic antihypertensive drug regimen or their low-sodium diet.

- initial assessment of the patient with severely elevated blood pressure is to exclude acute, ongoing, target-organ damage, which would indicate a diagnosis of hypertensive emergency

Treatment of Patients With Severe Asymptomatic Hypertension

- Unclear

- **outpatient** management of patients with acute severe hypertension is **poor** and that many patients are lost to follow-up soon after evaluation

- many of these patients will return to the emergency department for recurrent uncontrolled hypertension within **three** months.

Overall approach

1. How **quickly** should the blood pressure be reduced?

2. What is the blood pressure **target** during this time period?

3. **How** should this goal be achieved?

How **quickly** should the blood pressure be reduced?

- Controversial
- over a period of **several hours** to **several days**

two major concerns

The risk of **adverse events** (eg, stroke, acute kidney injury, or myocardial infarction) that may occur if the blood pressure is lowered too rapidly or to a level below the ability for autoregulation to maintain adequate tissue perfusion most often described with sublingual **nifedipine**

The potential risk of imminent **cardiovascular events** that may result from severe hypertension if the blood pressure is not quickly and suficiently reduced

- There is **no** proven benefit from rapid reduction of blood pressure in patients with severe **asymptomatic** hypertension and **most** such patients who present in the ambulatory setting can be managed as **outpatients**

- The individual patient's risk for an adverse event and the probable duration of severe hypertension must be considered when deciding how quickly to reduce the blood pressure.

- **older adult patients :**

- high risk for **cerebral** or **myocardial ischemia** if the blood pressure is lowered excessively and/or too rapidly.

the initial goal blood pressure may need to be achieved even more **slowly** (eg, **over a week or more**)

Over hours

- Patients judged to be at high risk for imminent **cardiovascular events:**
- including those with known **aortic** or **intracranial aneurysms**

should have their blood pressure lowered over a period of **hours**.

Over days

1- Previously treated hypertension:

- **in nonadherent patients**:

Reinstitution of prior medications

avoid those associated with **rebound hypertension**, eg, central alpha-2-agonists, high dose beta blockers

- **patients receive subtherapeutic doses**

Increase the dose of existing antihypertensive medications, or add another agent.

- **Addition of a diuretic**

2- Untreated hypertension :

- A calcium channel blocker (but not sublingual nifedipine),
- beta blocker,
- ACE inhibitor, ARB can be started.

- **combination** of two long-acting drugs

What is the blood pressure target during this time period?

- lowered to =**<160/=<100** mmHg

- the **mean arterial pressure** should not be lowered by **more than 25 to 30 percent** over the first **two to four hours**

(during the first several hours, may need to be above 160/100 mmHg in patients who present with very high pressures)

- In the **long-term**, the blood pressure should usually be reduced further(eg, <140/<90)

How should this goal be achieved?

- moving patients to a **quiet room** to rest can lead to a fall in systolic pressure of **10 to 20 mmHg or more**.(32%)

lowered over a period of hours

1. Short-acting drugs are most commonly used when the blood pressure must be below an arbitrary threshold before discharge:
- nifedipine, nitrates, captopril, clonidine or hydralazine

2. long-acting drugs and a follow-up primary care office visit in the next one to two days.
- eg, amlodipine, chlorthalidone

lowered over a period of days

1. in nonadherent patients: resumption of antihypertensive therapy
2. if patients are treatment naïve : initiation of antihypertensive therapy
3. in patients who are currently treated: addition of another antihypertensive drug

sublingual nifedipine is **contraindicated**
in this setting and should not be used.

the patient is observed for a **few hours** to ascertain a reduction in blood pressure of 20 to 30 mmHg.

Thereafter, a **longer-acting agent** is prescribed, and the patient is sent home to follow-up within **a few days**.

- A potentially safer alternative approach is:

initiate a **long-acting** agent (eg, amlodipine, chlorthalidone) with follow-up in clinic after **one or two days.**

may be **superior** to the strategy that includes the use of shorter-acting agents

- require admission:

1. a patient who does not have **established follow-up**
2. patients at high risk for **acute cardiovascular events** (eg, longstanding diabetes, known coronary artery disease or prior stroke) should probably be admitted

Over the subsequent **weeks** and **months**, the dose and selection of medications should be adjusted as needed to achieve the desired blood pressure goals.

Hypertensive emergency

Definition

- ≥180/120 mmHg
- acute, life-threatening conditions
- acute, ongoing target-organ damage

- but there is **no specific threshold**

Prevalence

- Hypertensive emergencies are **uncommon**
- Incidence: **one to two** cases per million per year

EVALUATION AND DIAGNOSIS

The history and physical examination:

- Acute **head** injury or trauma
- Generalized **neurologic** symptoms, such as agitation, delirium, stupor, seizures, or visual disturbances
- Focal neurologic symptoms that could be due to an ischemic or hemorrhagic stroke
- Fresh flame **hemorrhages**, **exudates** (cotton-wool spots), or **papilledema** when direct funduscopy is performed, as these are consistent with grade III or IV hypertensive retinopathy and can rarely be associated with hypertensive encephalopathy

- **Nausea** and **vomiting**, which may be a sign of increased intracranial pressure
- **Chest discomfort** or **pain**, which may be due to myocardial ischemia or aortic dissection
- Acute, severe **back pain**, which might be due to aortic dissection
- **Dyspnea**, which may be due to pulmonary edema

- Pregnancy, as such patients with severe hypertension could have **preeclampsia** or develop **eclampsia**

- Use of drugs that can produce a hyperadrenergic state, such as **cocaine**, **amphetamine(s)**, **phencyclidine**, or monoamine oxidase inhibitors, or recent discontinuation of clonidine or, less commonly, other antihypertensive agents

tests should be performed to evaluate the presence of target-organ damage in association with targeted clinical symptoms or signs:

- Electrocardiography
- Conventional chest radiography
- Urinalysis
- Serum electrolytes and serum creatinine
- Cardiac biomarkers (if an acute coronary syndrome is suspected)
- CT or MRI of the brain (if head injury, neurologic symptoms, hypertensive retinopathy, nausea, or vomiting are present)
- Contrast-enhanced CT or MRI of the chest or transesophageal echocardiography (if aortic dissection is suspected, although rapid blood pressure lowering need not be delayed in such patients while awaiting the results of imaging)

TREATMENT

choice of agent

the blood pressure goal

✓varies according to the specific hypertensive emergency

✓It is generally unwise to lower the blood pressure too quickly or too much

approximately 10 to 20 percent in the first hour(<180/120) and by a further 5 to 15 percent over the next 23 hours(<160/110)

Choice of antihypertensive drug

- administered in an **intensive care unit**
- **parenteral** antihypertensive drug therapy
- In settings where parenteral antihypertensive drugs are unavailable, **rapidly acting oral agents** (such as sublingual captopril) may be used
- **all** are tolerated reasonably well

Thus, the drug of choice is often dictated by the type of **hypertensive emergency** and the **local hospital formulary**

Drug	Dose range	Onset of action (minutes)	Duration of action (minutes)	Adverse effects[¶]	Role[Δ]
Vasodilators					
Clevidipine	Initially 1 to 2 mg/hour as IV infusion with rapid titration. Most patients respond to 4 to 6 mg/hour and are treated with maximum doses of 16 mg/hour or less. NOTE: Delivered in lipid emulsion. 1000 mL maximum per 24 hours (equivalent to 21 mg/hour) due to lipid load.	2 to 4	5 to 15	Atrial fibrillation, nausea, lipid formulation contains potential allergens (eg, soy, egg)	Hypertensive emergencies including postoperative hypertension.
Enalaprilat	1.25 to 5 mg every six hours IV	15 to 30	approximately 6 to >12 hours	Precipitous fall in pressure in high-renin states; variable response, headache, dizziness	Acute left ventricular failure. Due to slow onset and long duration of effect, rarely used. Avoid use in AMI, renal impairment, or pregnancy.

Fenoldopam	Initially 0.1 mcg/kg per minute◊ as IV infusion titrated to a maximum of 1.6 mcg/kg per minute	5 to 10	30 to 60	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies. Use caution or avoid with glaucoma or increased intracranial pressure.
Hydralazine	10 to 20 mg IV	10 to 20 IV	1 to ≥4 hours IV	Sudden precipitous drop in blood pressure, tachycardia, flushing, headache, vomiting, aggravation of angina	In general, hydralazine should be avoided due to its prolonged and unpredictable hypotensive effect. Labetalol and nicardipine are generally preferred choices for treatment of eclampsia.
	10 to 20 mg IM (40 mg maximum per labeling)	20 to 30 IM	4 to 6 hours IM		
Nicardipine	5 to 15 mg/hour as IV infusion. Some patients may require up to 30 mg/hour.	5 to 15	approximately 1.5 to ≥4 hours	Tachycardia, headache, dizziness, nausea, flushing, local phlebitis, edema	Most hypertensive emergencies, including pregnancy induced. Avoid use in acute heart failure. Caution with coronary ischemia.

Nitroglycerin (glyceryl trinitrate)	5 to 100 mcg/minute as IV infusion	2 to 5	5 to 10	Hypoxemia, tachycardia (reflex sympathetic activation), headache, vomiting, flushing, methemoglobinemia, tolerance with prolonged use	Potential adjunct to other IV antihypertensive therapy in patients with coronary ischemia (ACS) or acute pulmonary edema.
Nitroprusside	0.25 to 10 mcg/kg per minute as IV infusion. To minimize risk of cyanide toxicity, infusion duration should be as short as possible and not exceed 2 mcg/kg per minute. Patients who receive higher doses (ie, >500 mcg/kg at a rate exceeding 2 mcg/kg per minute) should receive sodium thiosulfate infusion to avoid cyanide toxicity.	0.5 to 1	1 to 10	Elevated intracranial pressure, decreased cerebral blood flow, reduced coronary blood flow in CAD, cyanide and thiocyanate toxicity, nausea, vomiting, muscle spasm, flushing, sweating	In general, nitroprusside should be avoided due to its toxicity. Nitroprusside should be avoided in patients with AMI, CAD, CVA, elevated intracranial pressure, renal impairment, or hepatic impairment.

Adrenergic inhibitors					
Esmolol	250 to 500 mcg/kg loading dose over one minute; then initiate IV infusion at 25 to 50 mcg/kg per minute; titrate incrementally up to maximum of 300 mcg/kg per minute	1 to 2	10 to 30	Nausea, flushing, bronchospasm, first-degree heart block, infusion-site pain; half-life prolonged in setting of anemia	Perioperative hypertension. Avoid use in acute decompensated heart failure.
Labetalol	Initial bolus of 20 mg IV followed by 20 to 80 mg IV bolus every 10 minutes (maximum 300 mg) **or** 0.5 to 2 mg/minute as IV loading infusion following an initial 20 mg IV bolus (maximum 300 mg)	5 to 10	2 to 4 hours	Nausea/vomiting, paresthesias (eg, scalp tingling), bronchospasm, dizziness, nausea, heart block	Most hypertensive emergencies including myocardial ischemia, hypertensive encephalopathy, pregnancy, and postoperative hypertension. Avoid use in acute decompensated heart failure. Use cautiously in obstructive or reactive airway.
Metoprolol	Initially 1.25 to 5 mg IV followed by 2.5 to 15 mg IV every three to six hours	20	5 to 8 hours	Refer to labetalol	Myocardial ischemia, perioperative hypertension. Avoid use in acute decompensated heart failure.
Phentolamine	5 to 15 mg IV bolus every 5 to 15 minutes	1 to 2	10 to 30	Tachycardia, flushing, headache, nausea/vomiting	Alternative option for catecholamine excess (eg, adrenergic crisis

- After a suitable period (often 8 to 24 hours) of blood pressure control at target in the intensive care unit

oral medications are usually given and the initial intravenous therapy is tapered and discontinued.

with the diastolic pressure being gradually reduced **to <80 mmHg** over **two to three months**

The major exceptions

- the acute phase of an ischemic stroke –
- not lowered unless it is ≥185/110 mmHg in patients who are candidates for **reperfusion therapy**

- not lowered unless it is ≥220/120 mmHg in patients who are **not** candidates for reperfusion (thrombolytic) therapy

- **Acute aortic dissection**
- The systolic blood pressure should be **rapidly** lowered to a target of 100 to 120 mmHg (to be attained in 20 minutes) to reduce aortic shearing forces

- **Intracerebral hemorrhage**
- If sBp is between 150-220 mmHg→ sBp to 140 in first hour
- If sBp>= 220 mmHg → aggressive reduction to 140-160 mmHg


Thank you.....