



Hypertensives Emergency and Urgency

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Background



USA:

- Hypertension is 30% of the population age >20 years old.
- Hypertension emergency is 25% of the total hypertension cases.
- One and five year mortality of
 - 70% - 90% and 100% (not treated).
 - 25% -50% (treated).

Improper handling of hypertensive emergencies may caused by:



- Emergency vs. urgency diagnosis
- Decreased blood pressure too fast
- Late blood pressure reduction

worsening the prognosis



- JNC VII:
 - Hypertension crisis (severe hypertension / accelerated hypertension)
 - SBP > 179 mmHg or DBP >109 mmHg
- JNC VI (in 1993):
 - Hypertension crisis:
 1. Hypertension urgency
 2. Hypertension emergency



Hypertensive emergency:

- Severe hypertension (SBP >179 mmHg or DBP >109 mmHg) accompanied by acute target organ damage.

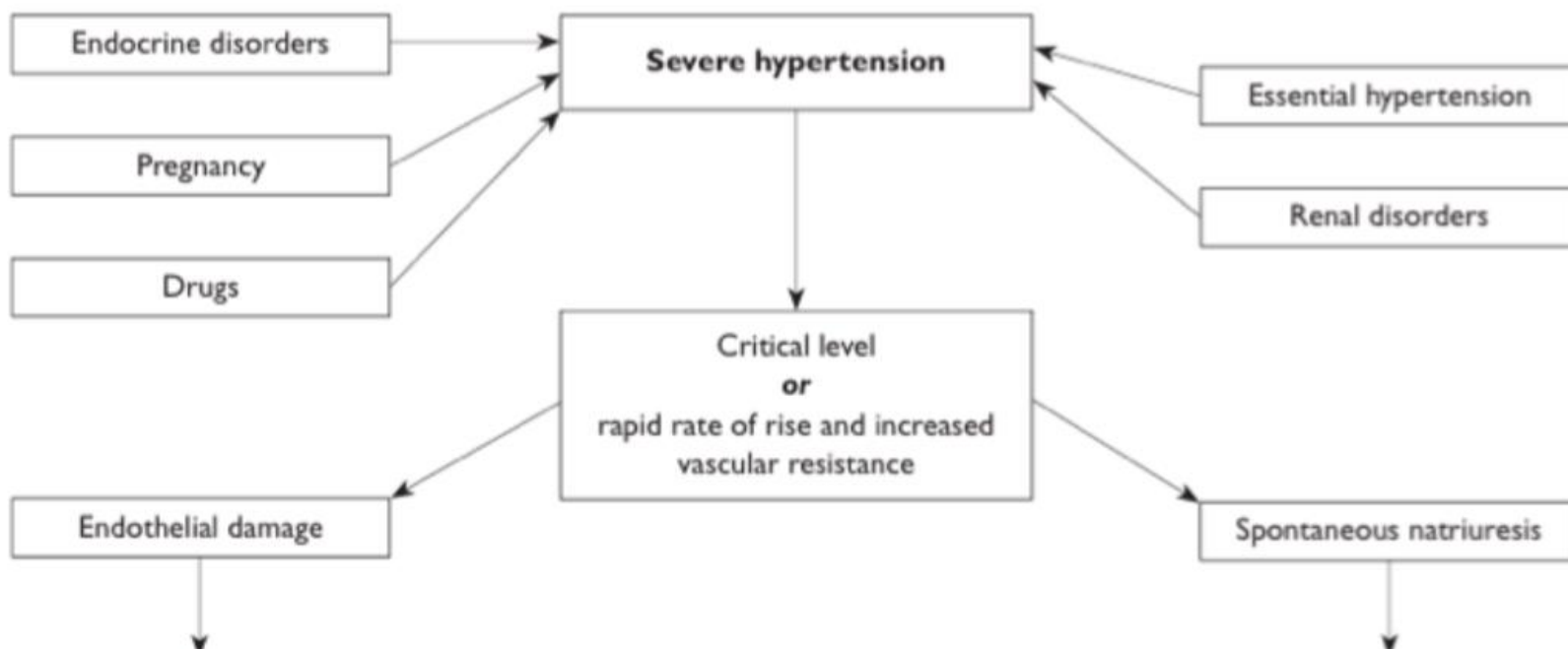
Hypertension urgency:

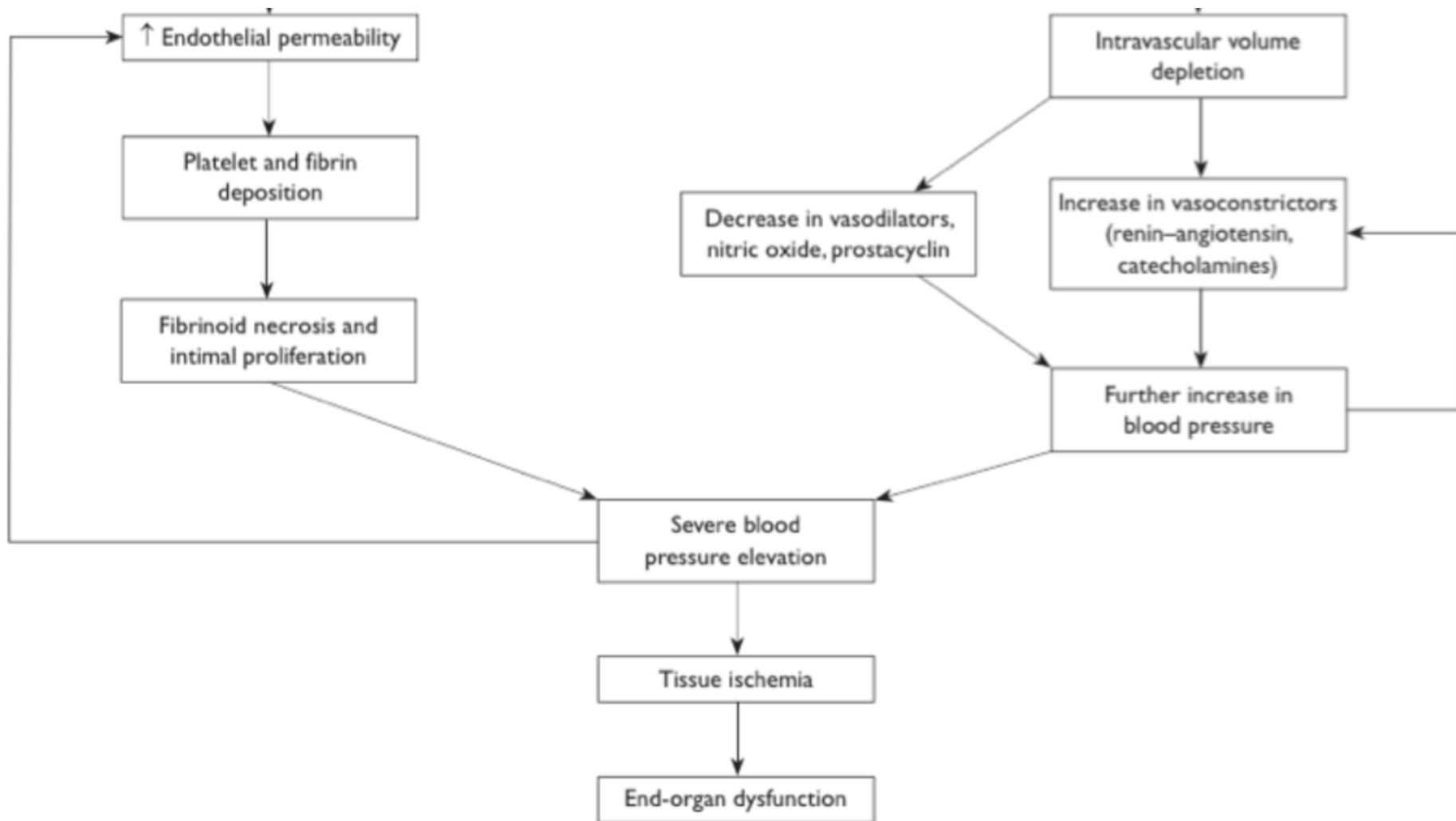
- Severe hypertension (SBP >179 mmHg or DBP >109 mmHg) without accompanied by acute target organ damage.



Target organ damage:

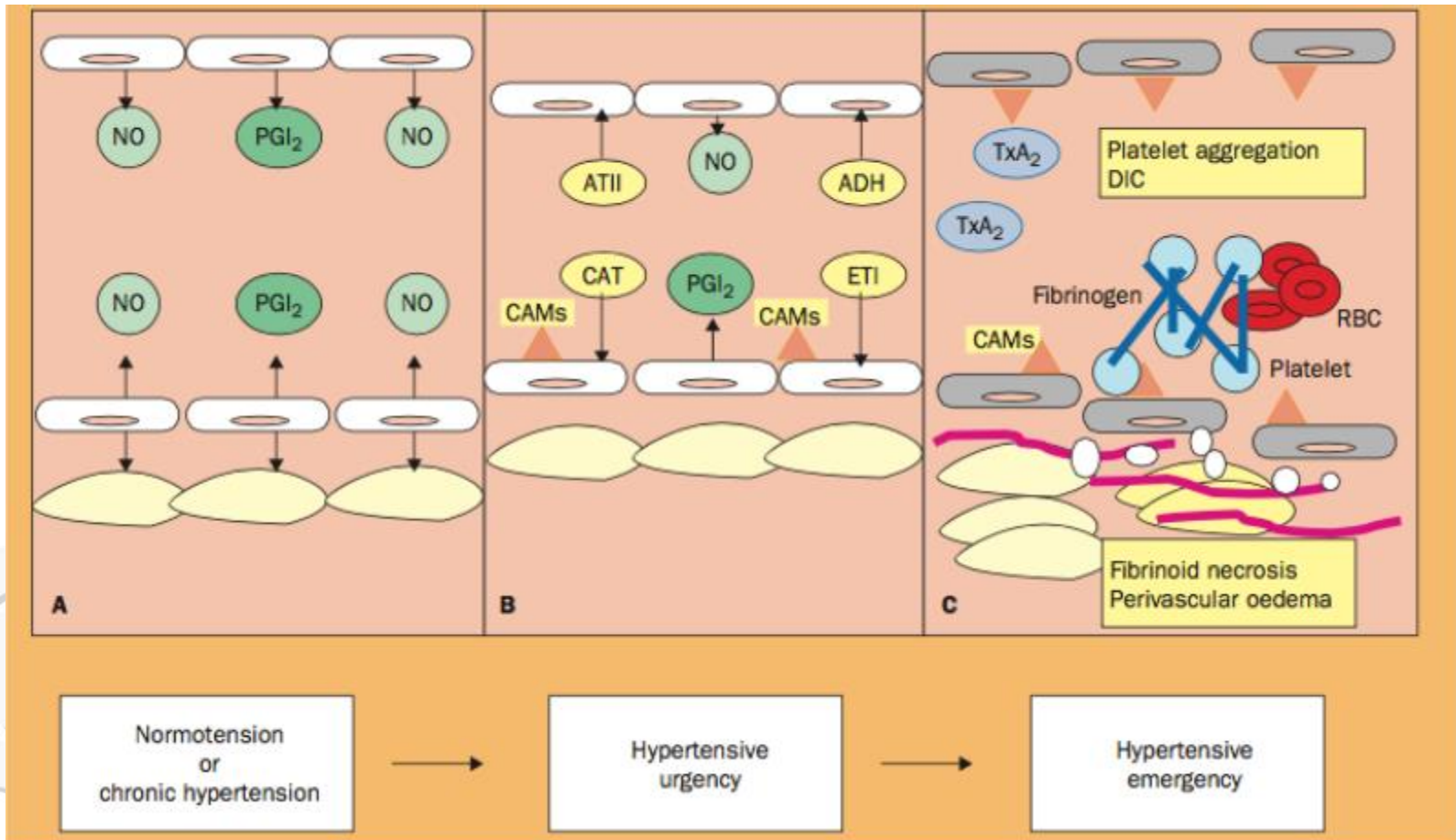
- Encephalopathy hypertension
- Aortic dissection aneurysm
- Left ventricular heart failure with pulmonary edema
- Acute coronary syndrome
- Eclampsia

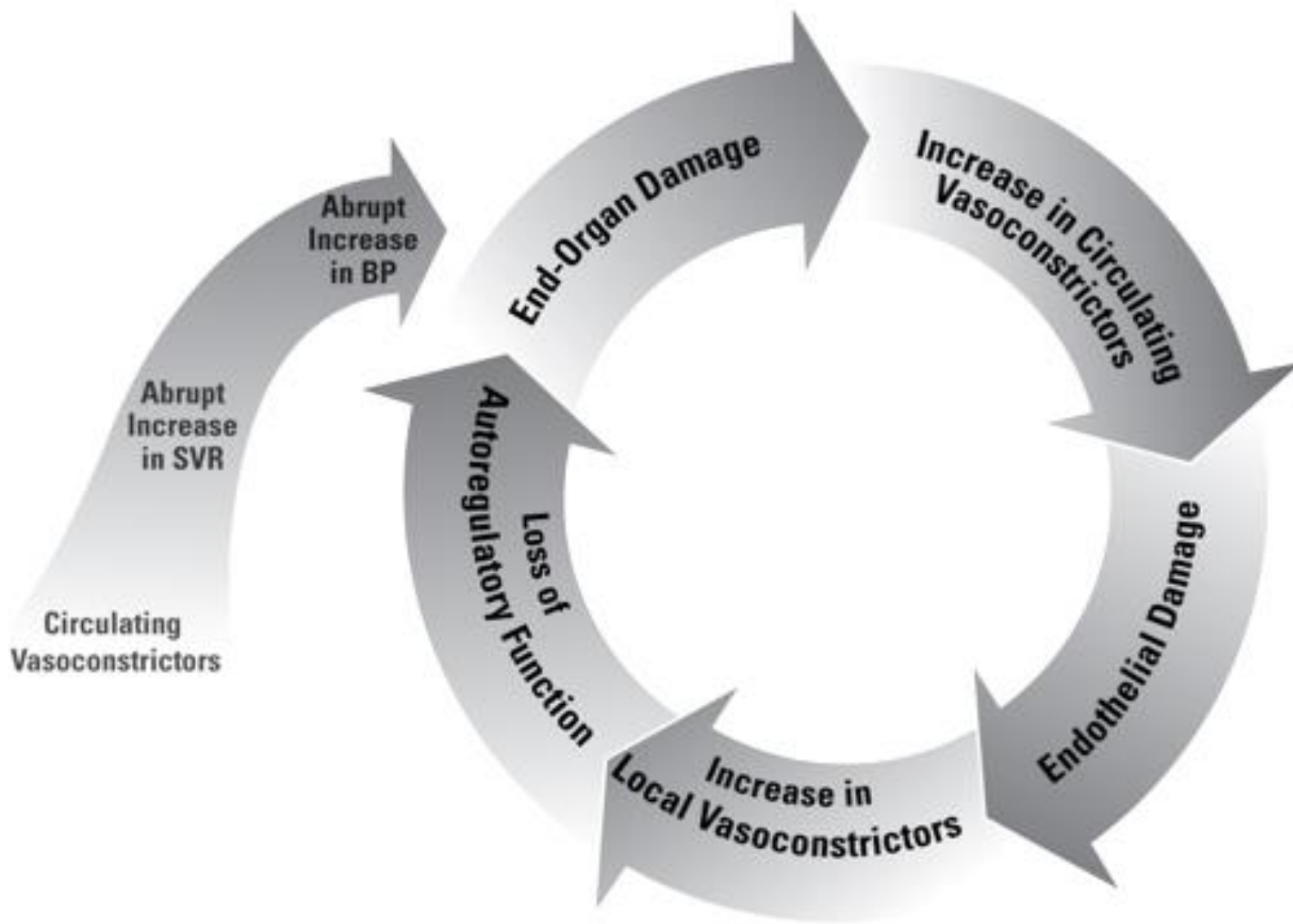






Putative vascular pathophysiology of hypertensive emergency





¹ Ault and Ellrodt. Am J Emerg Med 1985; (suppl 6):10-15.

² Varon and Marik. Chest. 2000;118:214-27.



Clinical	Anamnesis	Physical examination	Supporting investigation
Encephalopathy	Headache visual impairment loss of consciousness	Focal neurological deficits Funduscopic: bleeding, exudate, papillary edema	CT-scan
Cardiac	Sudden shortness of breath, angina	Congestion sign: cardiomegaly, basal rales	Chest x-ray ECG hs-Trop
Aortic dissection aneurysm	Chest pain	Unequal pulse	Echo CT cardiac
Acute renal failure	Oliguria/ Anuria		Proteinuria, ureum, creatinin
Eclampsia			

Types of drugs for hypertension emergency



1. Vasodilators

- Sodium nitroprusside
- Nitroglycerin
- Nicardipine
- Fenoldapam
- Hydralazine
- Enalapril

2. Adrenergic inhibitors

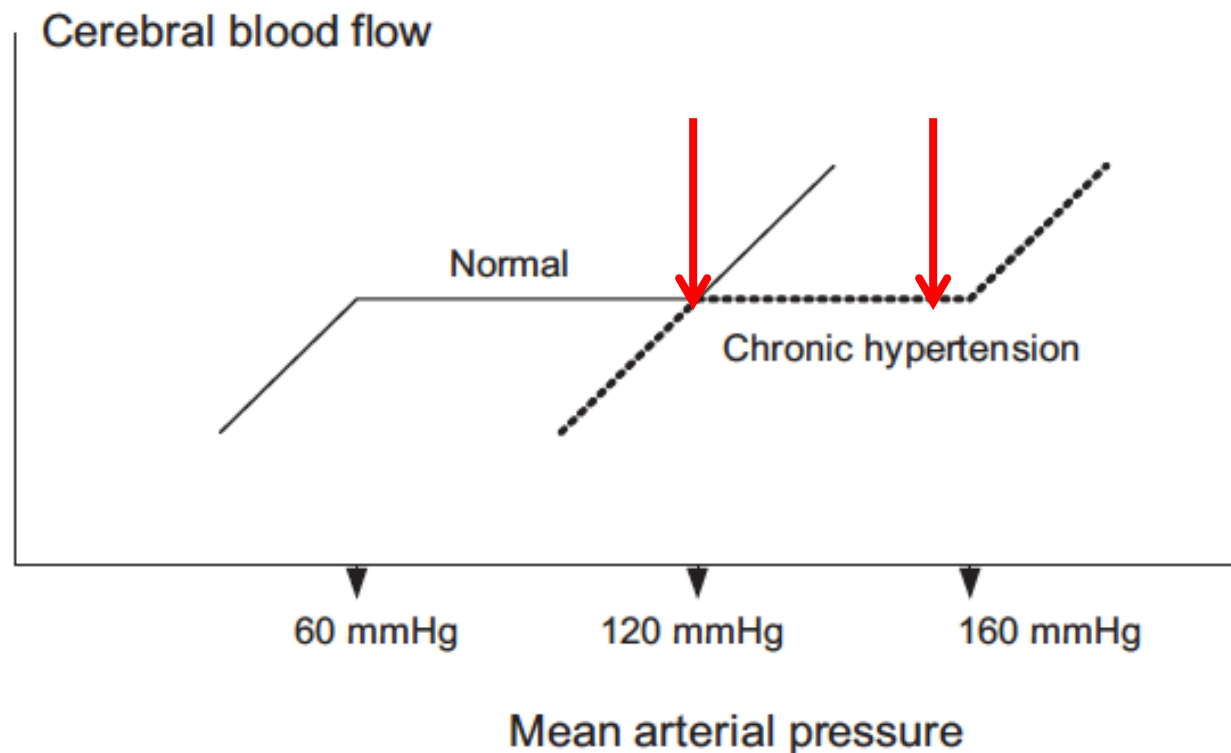
- Labetalol
- Esmolol
- Phentolamine



How Low Should You Go?

Simple answer:

- 25% decrease in MAP in the first 1 hour
 - Target ~ 160/100 mm Hg in 2-6 hours
- next





How Low Should You Go?

Better (see clinical conditions):

- Less aggressive in ischemic stroke
- More aggressive in hemorrhagic stroke, acute HF and aortic dissection



Acute Aortic Dissection

Chest pain or back pain with increased blood pressure:

- 3/4 patients who do not receive treatment properly will die about 2 weeks later and 1/4 only 75% can last up to 5 years.
- In aortic dissection it is recommended to reduce SBP < 140 mmHg and DBP < 110 mmHg.
- Combination of beta blockers and vasodilators



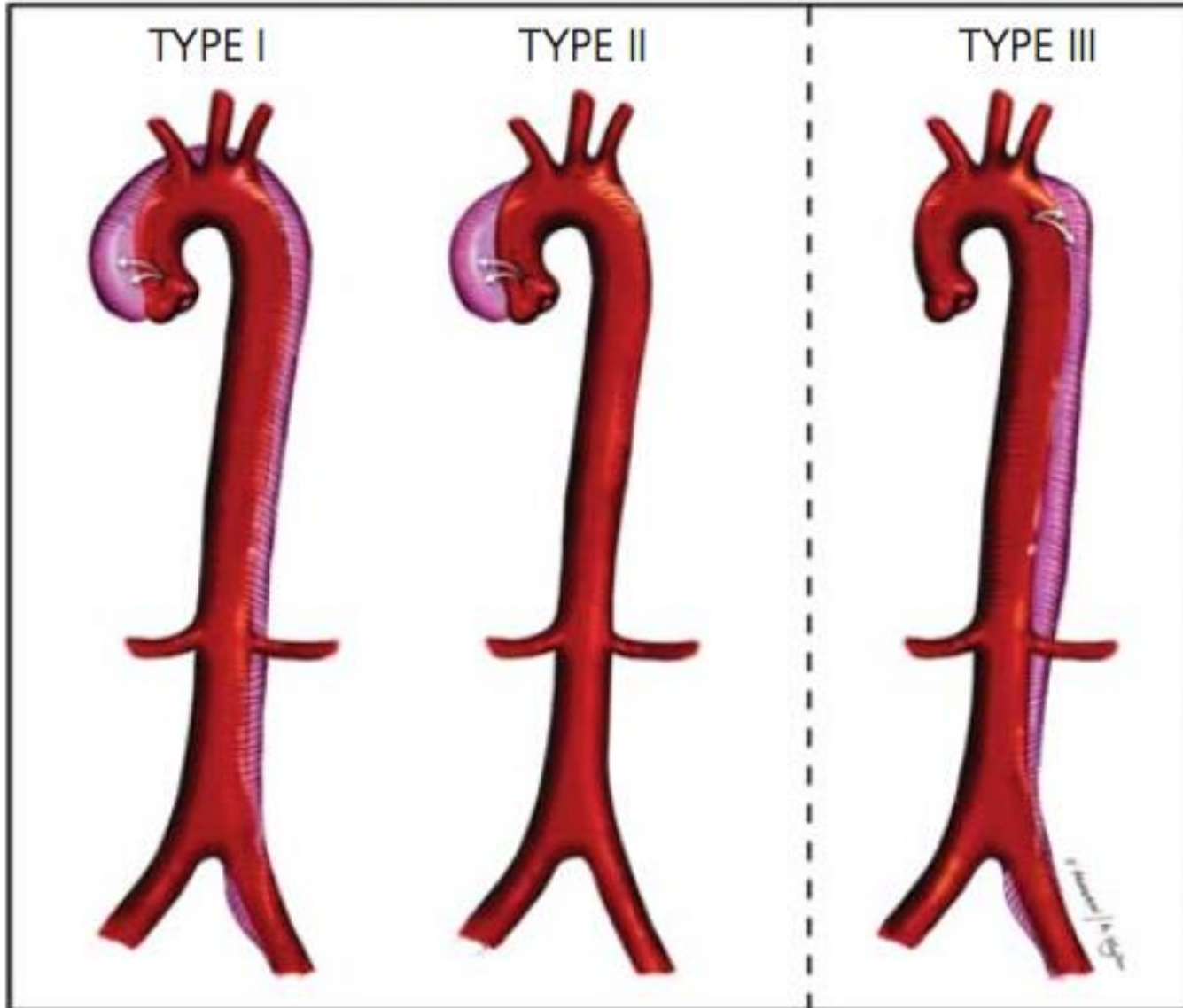
TYPE A

TYPE B

TYPE I

TYPE II

TYPE III





Hypertension in ICH

- Intracerebral hemorrhage (ICH) often causes hypertension reflexes



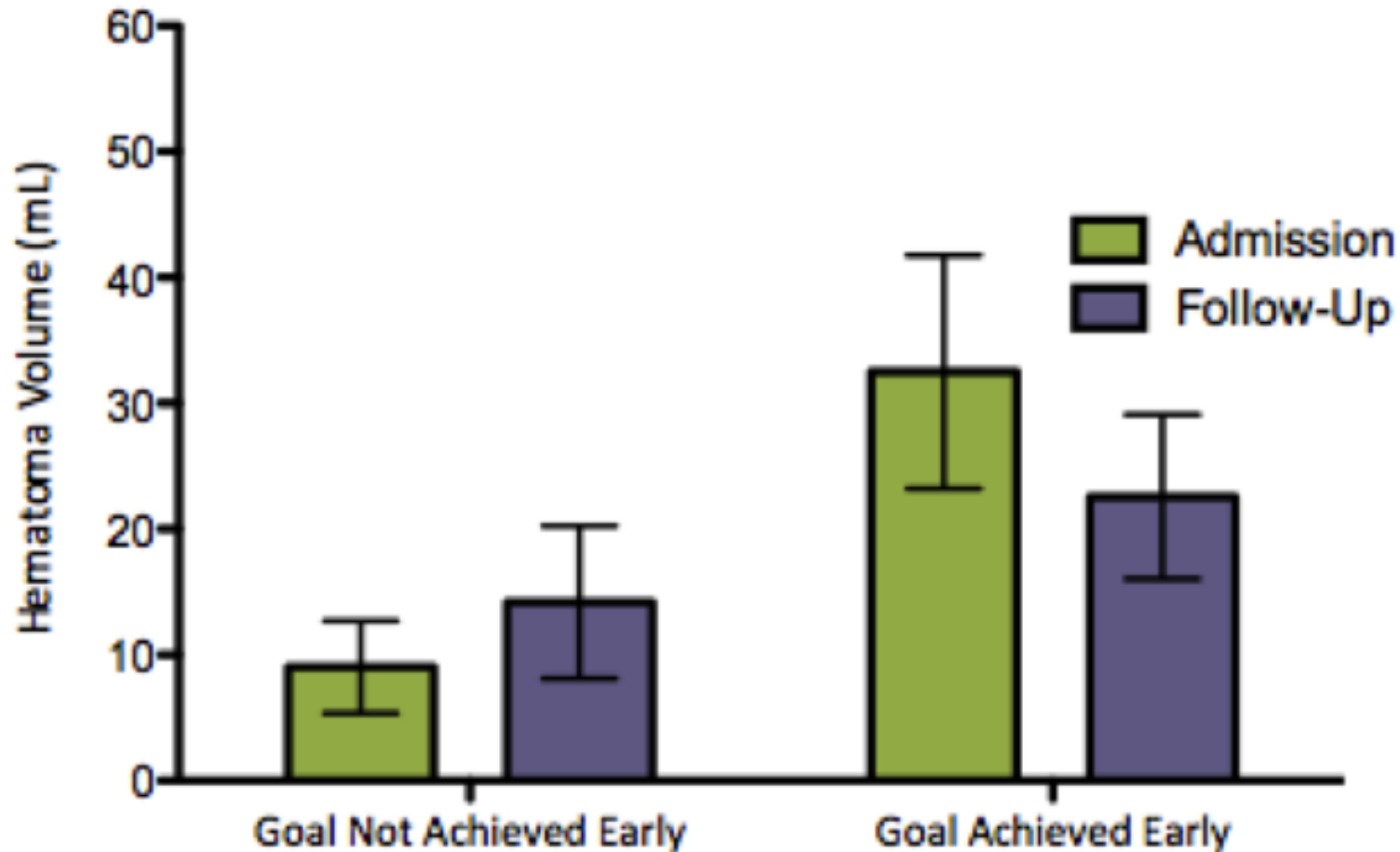


AHA / ASA recommendations on ICH management

1. If SBP is >200 mm Hg or MAP is >150 mm Hg, consider aggressive reduction of BP.
2. If SBP is >180 mm Hg or MAP is >130 mm Hg and ICP may be elevated, consider monitoring ICP and reducing BP to keep cerebral perfusion pressure between 60 and 80 mm Hg.
3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is no evidence of or suspicion of elevated ICP, consider modest BP reduction (eg, MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg).



Effect of a rapid drop in blood pressure





Hypertension in ICH

- The drug of choice in these cases is also labetalol
- The second line choice is fenoldopam



Hypertension in ischemic stroke

- Some experience an increase in blood pressure, sudden and progressive.
- It is not based on emergency conditions, but is a physiological mechanism to maintain blood perfusion pressure that supplies areas affected by ischemic stroke.
- Lowering BP do not sudden, except for the presence of target organ damage or thrombolytic therapy will be performed, or systolic more than 220 mmHg or diastolic more than 120 mmHg.
- Thrombolytic: lower BP 185/110 mmHg to 180/105 mmHg,
- The target of decreasing blood pressure in the first 24 hours is around 15%. The choice is labetalol, nitroprusside is not recommended



Hypertensive encephalopathy

- Clinical manifestations of cerebral edema and micro-hemorrhages caused by auto dysfunction of cerebral regulation
- **Definition:**
 - acute organic syndrome or delirium in an emergency hypertensive setting

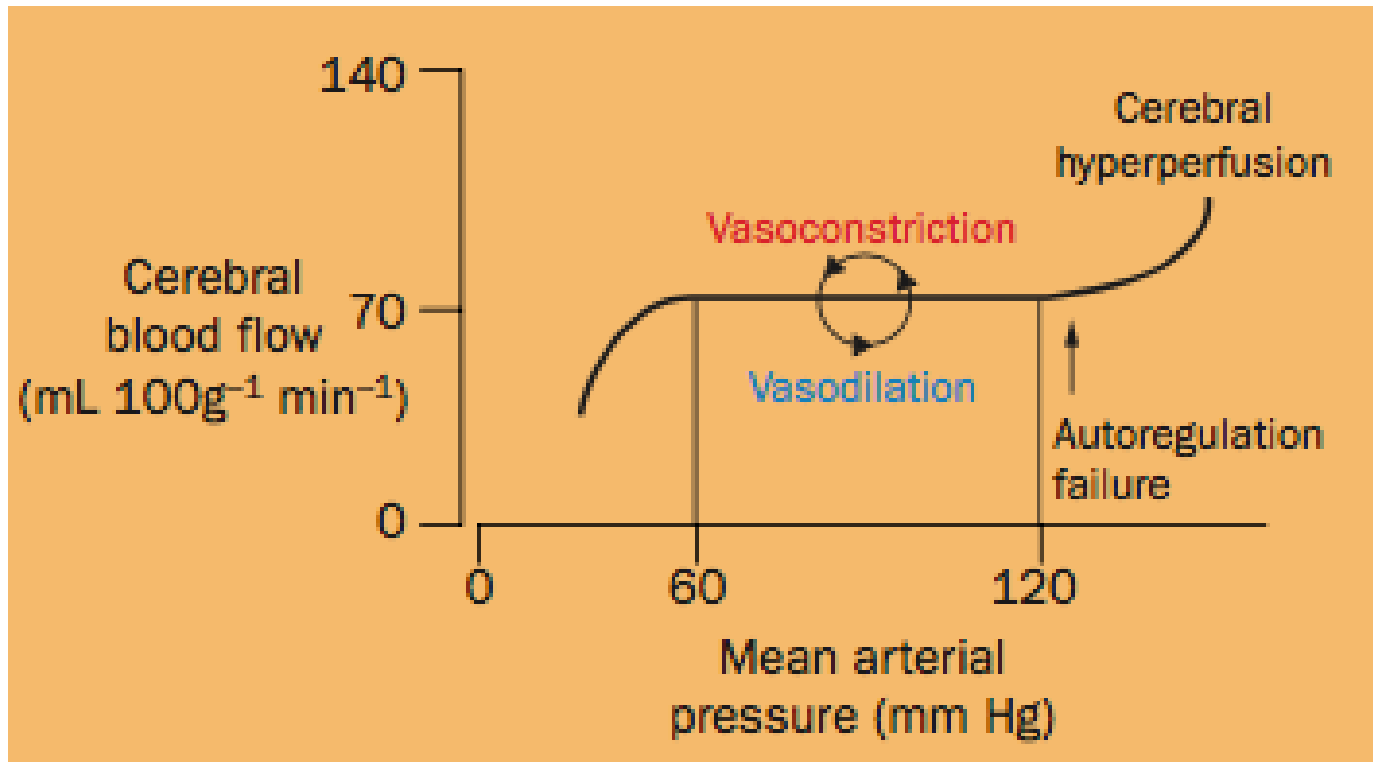


Figure 2: **Autoregulation of cerebral blood flow**

- Cerebral blood flow does not change in MAP 60-120
- If there is an increase in MAP -> auto regulation is not work -> cerebral vasodilation -> edema
- Endothelial damage -> capillary leakage -> decreased brain barrier ability -> edema



The diagnosis is through an exclusion process, namely after the possibility of cerebral hemorrhage and ischemic stroke is removed:

- Severe headaches, changes in consciousness status, seizures, and papillary edema, without the presence of neurological deficits
- The role of the overstimulation of the renin-angiotensin system as the etiology of this condition is the basis for its treatment, i.e. ACE inhibitors
- The use of diuretics and vasodilators is not recommended



Hypertension in Left Heart Failure

There are signs and symptoms of excess intravascular and interstitial volume, or secondary manifestations of tissue hypoperfusion, such as dyspnea.

- Increased blood pressure in these conditions can be both a cause and a consequence of acute pulmonary edema.
- Treatment options:
 - Nitroglycerin or nitroprusside vasodilators accompanied by intravenous loop diuretics.
 - The use of contractility-lowering drugs such as beta blockers is avoided.



Hypertension with Acute Coronary Syndrome

ACS (Acute Coronary Syndrome) can occur in the context of severe hypertension.

Therapy goals:

- First, to reduce myocardial oxygen demand.
 - Options: intravenous nitroglycerin.
 - Nitroprusside is contraindicated because it can cause a decrease in transmural blood flow.
- Second, to block neurohumoral action.
 - Options: beta blockers such as labetalol (alpha and beta adrenergic receptor blockers) and esmolol (beta-cardioselective blockers), or intravenous enalapril.



- ACS that results from the use of cocaine
 - is characterized by the presence of adrenergic receptor stimulation, so the preferred therapy in this condition is alpha adrenergic blockers.
 - Beta blockers are formally contraindicated because they can cause alpha adrenergic storms and increase cocaine toxicity.

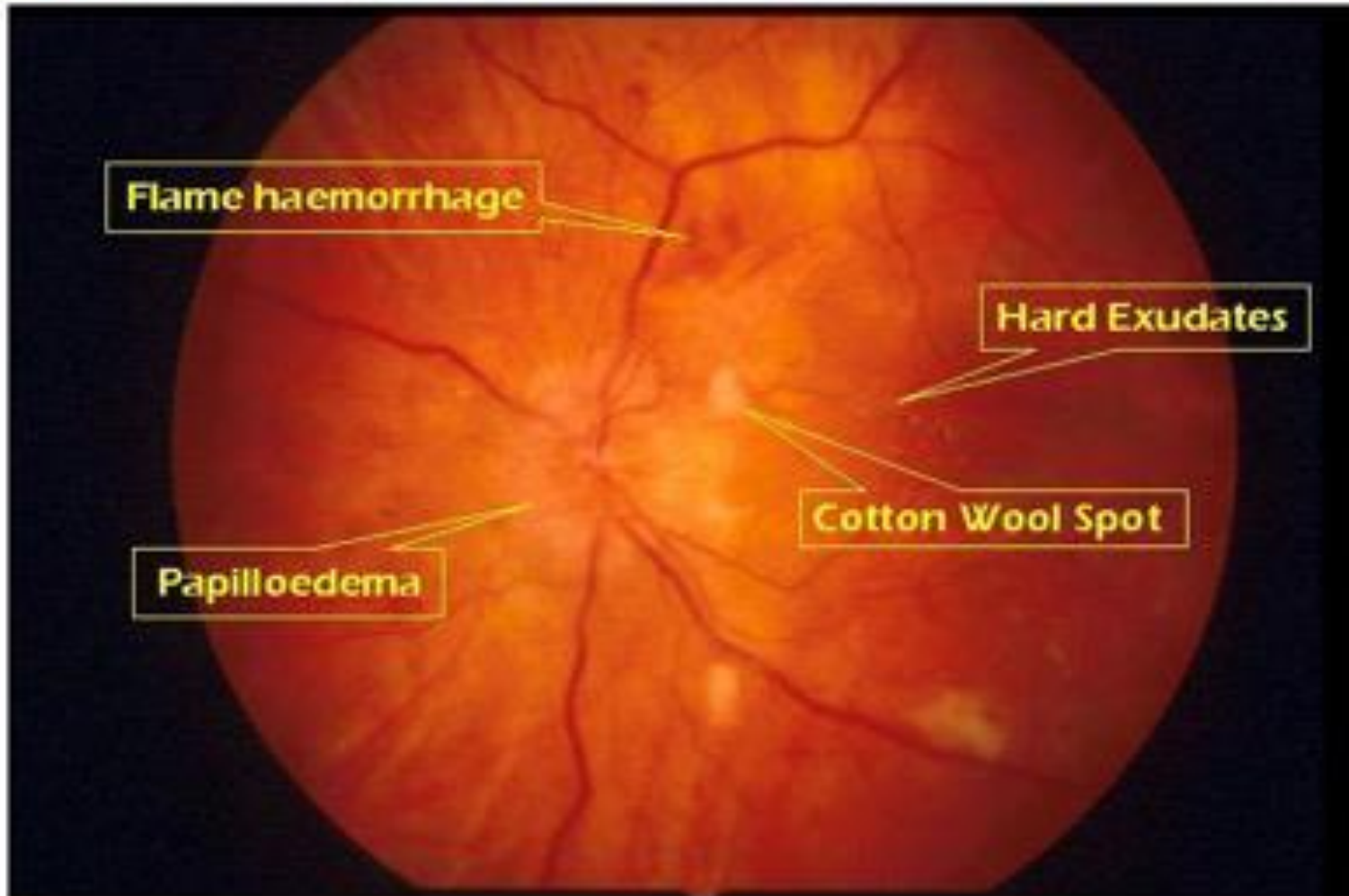


Accelerated Malignant Hypertension

- The presence of papillary edema (degree IV hypertensive retinopathy Keith Wagener) or if retinopathy is level III (with bleeding and exudate).
- Increased blood pressure is caused by over production of renin and angiotensin II in response to renal ischemia.
- Rarely appears as a new hypertension.
- Arising in the context of chronic hypertension or, more often secondary hypertension due to renovascular hypertension, scleroderma, and vasculitis.
- The goal of therapy is to reduce blood pressure by less than 25% of initial blood pressure or to reach DBP around 100-105 mmHg.
 - Options: labetalol, Fenoldopam.



Hypertensive Retinopathy - Grade 4





Sympathetic Crisis

- Sympathomimetic drugs - recreational purposes, (such as cocaine, amphetamines, or phencyclidine).
- Rarely in pheochromocytoma, sudden stopping consumption of antihypertensive drugs such as clonidine, or beta adrenergic antagonists
- Characterized by sympathetic overstimulation.
- Options:
 - Nicardipine, fenoldopam, or verapamil combined with benzodiazepines, and fentolamine is an alternative agent.
 - Use of beta adrenergic antagonists should be avoided to prevent vascular receptor antagonism.



Acute Postoperative Hypertension

Definition:

- Significant elevation in blood pressure during the initial postoperative period that can lead to serious complications in the neurological, cardiovascular and surgical scars, and therefore requires immediate (urgent) management.
- Most often associated with operative procedures in cardio thorax, vascular, head and neck, and neurosurgical.



Acute Postoperative Hypertension

- Occurs 2 hours after surgery and is typically short, with most patients requiring 6 hours of therapy.
- Postoperative complications of APH:
 - Hemorrhagic stroke, cerebral ischemia, encephalopathy, myocardial ischemia, myocardial infarction, cardiac arrhythmias, congestive heart failure with pulmonary edema, failure of vascular anastomosis, and bleeding in surgical wounds.
- Management:
 - There is no consensus, in cardiac surgery patients, therapy is recommended for blood pressure $> 140/90$ or at a minimum MAP of 105 mmHg.
 - Options: labetalol, esmolol, nicardipine, and clevidipin



Preeclampsia and Eclampsia

- Clinical appearance of patients with pregnancy-induced hypertension can vary from a mild to life-threatening disease process.
- Initial therapy for preeclampsia includes:
 - Magnesium sulfate for seizure prophylaxis,
 - MgSo₄: loading 4-6 g / 100 ml for 15-20 minutes, continued infusion of MgSo₄ 1-2 g / hour,
 - Control of blood pressure.
 - Treatment options: labetalol or nicardipin,
 - Second line: hidralazine,
 - Avoid: oral or sublingual nifedipine
- Childbirth is the definitive therapy for preeclampsia and eclampsia.



American College of Obstetricians and Gynecologists:

- SBP target between 140-160 mmHg; DBP between 90-105 mmHg.
- Initiation of therapy if SBP is between 155-160 mmHg in severe preeclampsia or eclampsia



Prognosis

- Remain developed chronic as well as moderate to severe acute vascular damage, and continuously at risk for suffering from coronary, cerebrovascular disease and kidney disease.
- Without therapy, survival for 1 year only reaches 10-20%
- With therapy, 5-year survival reaches more than 70%
- Patients with chronic kidney disease tend to have a lower survival rate

**Table 5.** Therapeutic considerations depending on the type of hypertensive emergency

Affected organ	Complications	Therapeutic considerations	Contraindicated
Aorta	Dissection	Labetalol/Esmolol + Fenoldopam/Nitroprusside	
Brain	Ischemic stroke	Labetalol/Fenoldopam	Nitroprusside
Brain	Intraparenchymal hemorrhage	Labetalol/Fenoldopam	Nitroprusside
Brain	Hypertensive encephalopathy	ACEI and/or labetalol	Nitroprusside
Heart	Acute coronary syndrome	Nitroglycerin + labetalol/esmolol/ACEI	Nitroprusside
Heart	Heart failure/pulmonary edema	Nitroglycerin/nitroprusside + loop diuretic	Labetalol
Placenta	Eclampsia/preeclampsia	Magnesium sulfate + Labetalol/Nicardipine	ACEI/Nitroprusside
Kidney	Acute renal failure/hematuria/proteinuria	ACEI ^a /Boluses Labetalol/fenoldopam perfusion	ACEI ^a /Nitroprusside

ACEI: angiotensin converting enzyme inhibitor.

Comorbidity	Preferred Agent(s)
Acute aortic dissection	Esmolol ^b
Acute congestive heart failure	Nesiritide, ^c nitroglycerin, nitroprusside
Acute intracerebral hemorrhage	Labetalol, nicardipine
Acute ischemic stroke	Labetalol, nicardipine
Acute myocardial infarction	Clevidipine, ^d esmolol, labetalol, nicardipine, ^d nitroglycerin
Acute pulmonary edema	Nesiritide, ^c nitroglycerin, nitroprusside
Acute renal failure	Clevidipine, fenoldopam, nicardipine
Eclampsia or preeclampsia	Hydralazine, labetalol, nicardipine
Perioperative hypertension	Clevidipine, esmolol, nicardipine, nitroglycerin, nitroprusside
Sympathetic crisis or catecholamine toxicity	Clevidipine, fenoldopam, nicardipine, phentolamine

^aAgents listed in alphabetical order, not in order of preference.

^bMay be used in combination with a vasodilatorlike dihydropyridine calcium-channel blocker or nitroprusside; however, β -blockade must precede administration of these agents.

^cUse is controversial.

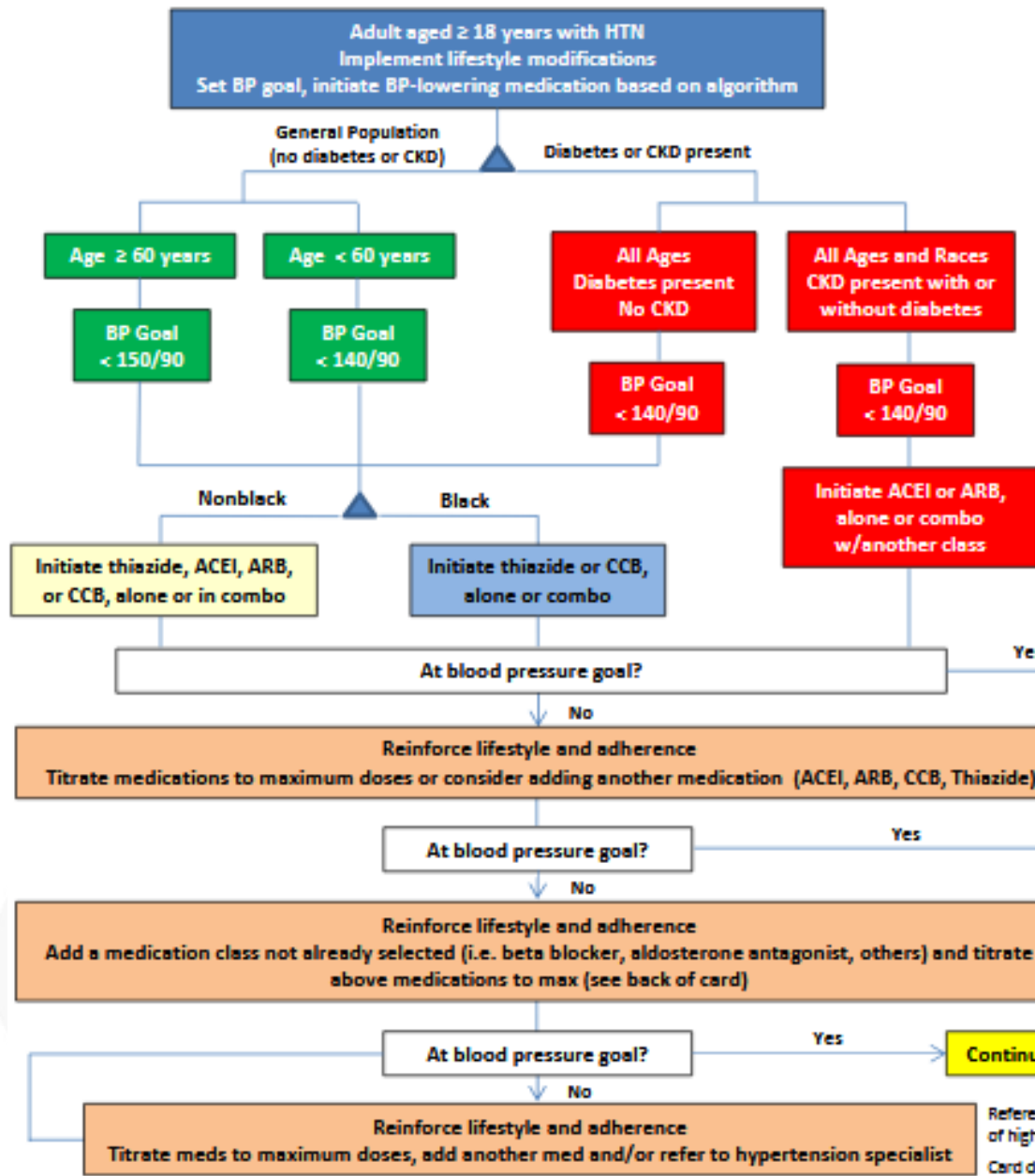
^dMay be used in patients with heart rate of <70 beats/min.



Conclusion

- Hypertensive emergencies are defined as severe hypertension associated with acute end-organ damage.
- Rapid but cautious blood pressure reduction is indicated in hypertensive emergencies.
- The choice of parenteral drugs includes nitroprusside, nitroglycerin, calcium channel blockers, fenoldopam, labetalol, esmolol, hidralazine, enalaprilat, and phentolamine, given according to the conditions of the target hypertensive organ.

JNC 8 Hypertension Guideline Algorithm



Initial Drugs of Choice for Hypertension

- ACE inhibitor (ACEI)
- Angiotensin receptor blocker (ARB)
- Thiazide diuretic
- Calcium channel blocker (CCB)

Strategy	Description
A	Start one drug, titrate to maximum dose, and then add a second drug.
B	Start one drug, then add a second drug before achieving max dose of first
C	Begin 2 drugs at same time, as separate pills or combination pill. Initial combination therapy is recommended if BP is greater than 20/10mm Hg above goal

Lifestyle changes:

- Smoking Cessation
- Control blood glucose and lipids
- Diet
 - ✓ Eat healthy (i.e., DASH diet)
 - ✓ Moderate alcohol consumption
 - ✓ Reduce sodium intake to no more than 2,400 mg/day
- Physical activity
 - ✓ Moderate-to-vigorous activity 3-4 days a week averaging 40 min per session.

Reference: James PA, Ortiz E, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: (JNC8). JAMA. 2014 Feb 3;311(5):507-20

Card developed by Cole Glenn, Pharm.D. & James L Taylor, Pharm.D.

Hypertension Treatment

Beta-1 Selective Beta-blockers – possibly safer in patients with COPD, asthma, diabetes, and peripheral vascular disease:

- metoprolol
- bisoprolol
- betaxolol
- acebutolol

Compelling Indications	
Indication	Treatment Choice
Heart Failure	ACEI/ARB + BB + diuretic + spironolactone
Post –MI/Clinical CAD	ACEI/ARB AND BB
CAD	ACEI, BB, diuretic, CCB
Diabetes	ACEI/ARB, CCB, diuretic
CKD	ACEI/ARB
Recurrent stroke prevention	ACEI, diuretic
Pregnancy	labetolol (first line), nifedipine, methyldopa

Drug Class	Agents of Choice	Comments
Diuretics	HCTZ 12.5-50mg, chlorthalidone 12.5-25mg, indapamide 1.25-2.5mg triamterene 100mg <i>K⁺ sparing</i> – spironolactone 25-50mg, amiloride 5-10mg, triamterene 100mg furosemide 20-80mg twice daily, torsemide 10-40mg	Monitor for hypokalemia Most SE are metabolic in nature Most effective when combined w/ ACEI Stronger clinical evidence w/chlorthalidone Spironolactone - gynecomastia and hyperkalemia Loop diuretics may be needed when GFR <40mL/min
ACEI/ARB	<i>ACEI</i> : lisinopril, benazapril, fosinopril and quinapril 10-40mg, ramipril 5-10mg, trandolapril 2-8mg <i>ARB</i> : candesartan 8-32mg, valsartan 80-320mg, losartan 50-100mg, olmesartan 20-40mg, telmisartan 20-80mg	SE: Cough (ACEI only), angioedema (more with ACEI), hyperkalemia Losartan lowers uric acid levels; candesartan may prevent migraine headaches
Beta-Blockers	metoprolol succinate 50-100mg and tartrate 50-100mg twice daily, nebivolol 5-10mg, propranolol 40-120mg twice daily, carvedilol 6.25-25mg twice daily, bisoprolol 5-10mg, labetalol 100-300mg twice daily,	Not first line agents – reserve for post-MI/CHF Cause fatigue and decreased heart rate Adversely affect glucose; mask hypoglycemic awareness
Calcium channel blockers	<i>Dihydropyridines</i> : amlodipine 5-10mg, nifedipine ER 30-90mg, <i>Non-dihydropyridines</i> : diltiazem ER 180-360 mg, verapamil 80-120mg 3 times daily or ER 240-480mg	Cause edema; dihydropyridines may be safely combined w/ B-blocker Non-dihydropyridines reduce heart rate and proteinuria
Vasodilators	hydralazine 25-100mg twice daily, minoxidil 5-10mg terazosin 1-5mg, doxazosin 1-4mg given at bedtime	Hydralazine and minoxidil may cause reflex tachycardia and fluid retention – usually require diuretic + B-blocker Alpha-blockers may cause orthostatic hypotension
Centrally-acting Agents	clonidine 0.1-0.2mg twice daily, methyldopa 250-500mg twice daily guanfacine 1-3mg	Clonidine available in weekly patch formulation for resistant hypertension