

Pharmacotherapy for a Hypertensive Crisis

Amanda J. Hays, Pharm.D., BCPS
Pharmacy Quality Improvement Manager
Alaska Native Medical Center
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Learning Objectives

- Define the differences in hypertension crisis terminology
- Describe the pathophysiology and related causes of hypertensive crisis
- Select pharmacologic options using a diagnosis based approach
- Discuss new pharmacologic options for a hypertensive crisis
- Review patient specific cases

Pre-assessment patient case #1

- 27 y/o M presents to the ED after a “night out” with chest pain and shortness of breath.
- VS: HR 127 BP 214/163 RR 22
- He is started on a esmolol drip at 50 mcg/kg/minute.
- Repeat VS (20 minutes after esmolol started):
 - HR 147 BP 287/204 RR 24
- What is the likely cause of his reaction to esmolol?

Epidemiology

- Hypertension affects 1 out of 3 people
 - 73 million Americans
 - 23.9% of all Alaskans have hypertension
- 1% of these patients will have a hypertensive emergency
 - Accounts for 25% all ED visits
 - 14% of these lead to hospitalization
- 1 year mortality for an untreated HTN emergency = 90%
- 5 year treated survival is 74%
- Median survival after ED visit is 144 months
- Demographics of those affected
 - AA > Caucasians
 - M > F
 - Age 40-50

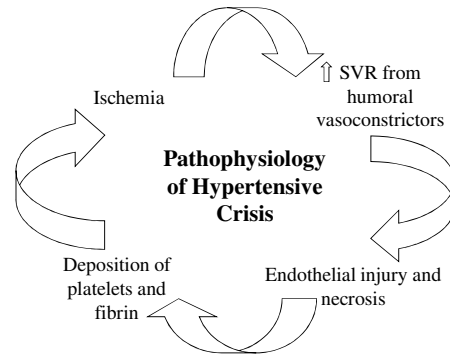
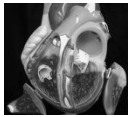
Definitions

- Hypertensive crisis:
 - SBP > 180 or DBP > 120
- Hypertensive urgency:
 - Elevated BP with DBP > 115
- Hypertensive emergency:
 - Hypertensive urgency + Target organ damage

Definitions

- Malignant hypertension:
 - Elevated BP with encephalopathy or nephropathy
- Postoperative hypertension:
 - SBP > 190 or DBP > 100
- Preeclampsia
 - SBP > 169 or DBP > 109, usually associated with HELLP syndrome

Target Organ Damage



Causes of Hypertensive Crisis

Renal disease: Scleroderma, primary disease, renovascular HTN	CNS disease: ICH, Ischemic stroke, SAH
Endocrine HTN (Pheochromocytoma)	Systemic vasculitis
Cardiac disease: Acute MI, Aortic dissection, USA	Pulmonary disease: PE, pulmonary edema
Drugs: OCs, NSAIDs, steroids, Cocaine, Decongestants, MAOIs	Severe burns
Pre-eclampsia	Med non-compliance

Initial approach- Goals

- Urgency
 - Control BP within a 24 to 48 hour period
 - Oral medications preferred
- Emergency
 - ICU setting
 - IV medication, arterial line recommended
 - MAP reduction of 20-25%
 - Timeline:
 - 5-10 minutes in aortic dissection
 - 30-60 minutes in most other patients

*** CVA patients should not have MAP reduced dramatically during the acute phase- goal MAP ~ 120

Pearls for Pharmacists

- Assess patient compliance
- Ask about OTC, CAM, and illicit drug use
- Avoid diuretics & medications with prolonged half-lives
- Refer to ED if signs of TOD

Ideal Pharmacotherapy Agent

- Readily available
- Easy to dose
- Short half-life
- Fast onset
- Short to intermediate duration
- Easy transition to oral agents
- Minimal side effects

Rapid Correction: Complications

- Prolonged hypotension
 - Decreased organ perfusion
- CNS hypoperfusion
 - Watershed stroke
 - Paraplegia
 - Permanent blindness
 - Death

Treatment

Oral Agents for Hypertensive Urgency

- Clonidine:
 - Central acting alpha-2 adrenergic receptor agonist
 - Dose: 0.1-0.3 mg po
 - Onset: 30 min to 2 hours
 - Duration: 6-8 hours
 - **Side effects: sedation, dry mouth, rebound**
- Nifedipine SL
 - **SHOULD NOT BE USED DUE TO NUMEROUS CASES OF CEREBRAL AND CARDIAC ISCHEMIA**

Oral Agents for Hypertensive Urgency

- Captopril
 - Dose: 6.25-50 mg po or SL
 - Onset: 15 min
 - Duration: 4-6 hours
 - Side effects: Rash, pruritis, proteinuria, hypotension
- Labetalol
 - Dose: 200-400 mg po q 4-6 hours
 - Onset: 30 min- 2 hours
 - Duration: 4-6 hours
 - Side effects: Orthostatic hypotension, nausea, vomiting

Other Agents

- Nitroglycerin
 - Spray, SL, or paste can all be effective in reducing BP
 - Beneficial in situations of cardiovascular disease or with evidence of pulmonary edema

IV Agents

- Nicardipine (Cardene[®])
- Labetalol (Normodyne[®])
- Esmolol (Brevibloc[®])
- Enalaprilat (Vasotec[®])
- Fenoldopam (Corlopan[®])
- Nitroprusside (Nipride[®])
- Phentolamine (Regitine[®])
- Diazoxide
- Nitroglycerin (Tridil[®])
- Hydralazine (Apressoline[®])
- Clevidipine (Cleviprex[®])

Nicardipine (Cardene[®])

- Dihydropyridine calcium-channel blocker, selective for smooth muscle, pure afterload reducer, decreases SVR
- Kinetics:
 - Onset: 5-15 minutes
 - Duration: 4-6 hours
 - 95% protein bound
 - Hepatic metabolism
- Dosing:
 - 5 mg/hr, increase by 2.5 mg/hr every 15 minutes to max of 15 mg/hr

Nicardipine (Cardene[®])

- Side effects:
 - Headache
 - Hypotension
 - Nausea/vomiting
 - Tachycardia
- Recommended by the AHA/ASA for hypertension control in acute ischemic stroke and intracerebral hemorrhage

Nitroprusside (Nipride[®])

- Peripheral (arterial and venous) vasodilator
- Dose:
 - 0.5-3 mcg/kg/minute, titrate by 0.25 mcg/kg/minute every 3-5 minutes until goal BP obtained
- Kinetics:
 - Onset: seconds
 - Duration: 5-10 minutes
 - Hepatic and renal elimination
- Side effects:
 - Reflex tachycardia
 - Increase intracranial pressure
 - V/Q mismatch
 - Coronary steal

Nitroprusside (Nipride[®])

- Side effects:
 - Cyanide/Thiocyanate toxicity
 - 44% cyanide by weight
 - Acidosis, mental status changes, dyspnea, coma, nausea
 - Levels are sent out- consider methemoglobin levels
 - Treat for toxicity if suspected
- Sodium nitroprusside combines with Hgb = 1 cyanomethemoglobin and 4 cyanide radicals
- Detoxification occurs when they react with thiosulfate to form thiocyanate (sulfate donor)
- Toxicity prevention:
 - Lowest effective dose for as short as possible
 - Monitor renal/hepatic dysfunction
 - Sodium thiosulfate infusion at a 10:1 ratio
 - Cyanokit?

Nitroglycerin (Tridil[®])

- Peripheral and coronary venous and arterial vasodilator
- Dose: 0.25-0.5 mcg/kg/min
- Kinetics:
 - Onset: 2-5 minutes
 - Duration: 5-10 minutes
- Side effects:
 - Headache: cerebral vasodilation and tachycardia resulting in reflex sympathetic activation
 - Tachycardia
- Clinical Pearl:
 - Preferred for acute decompensated CHF and myocardial infarctions
 - Doses of up to 1 mcg/kg/minute may be used for rapid vasodilation to reduce pulmonary edema
 - Tolerance is generally not seen until 48-72 hours

Labetalol (Normodyne[®])

- Selective alpha-1 and nonselective beta-adrenergic receptor blocker (alpha to beta-blocking ratio 1:7)
- Dose:
 - IVP: 20 mg over 2 minutes. May repeat q10 minutes up to 40-80 mg.
 - Continuous infusion: 2 mg/minute (after load)
 - Max 300 mg/day
- Kinetics:
 - Onset: 2-5 minutes, peak 5-15 min
 - Duration: 2-4 hrs
 - Hepatic metabolism
- Should be used until BP controlled and then changed to po therapy (lacking long term data IV)

Esmolol (Brevibloc[®])

- Cardioselective B-blocker
- Dose: 500 mcg/kg bolus, followed by 25-50 mcg/kg/min
- Kinetics:
 - Onset: peak 6-10 minutes
 - Duration: ~ 20 minutes
 - T_{1/2} = 8 minutes
 - Elimination: Rapid hydrolysis by red blood cell esterases
- Preferred for postoperative HTN, supraventricular dysrhythmias, myocardial infarction
- Adverse effects: bradyarrhythmias, hypotension
- Clinical pearl:
 - Often requires a vasodilator for optimal blood pressure control

Fenoldopam (Corlopan[®])

- Dopamine-1 agonist, rapid acting vasodilator (coronary, renal, mesenteric, and peripheral arteries)
- Renal artery vasodilation by activating dopamine receptors on proximal and distal tubules (10 x more than dopamine)
- Inhibits sodium reabsorption; promotes natriuresis/diuresis
- Dose: 0.1-1.6 mcg/kg/minute
- Kinetics:
 - Onset: 5 min, max response 15 min
 - Duration: 30-60 min
 - T_{1/2} = 5-10 minutes

Fenoldopam (Corlopan[®])

- Side effects:
 - EKG changes (t-wave)
 - Increases intraocular pressure
- Clinical pearl:
 - May be preferred in patients with renal dysfunction as it may increase renal blood flow
 - Doses > 0.1 mcg/kg/min may be associated with a dose related tachycardia

Enalaprilat (Vasotec[®])

- ACE-inhibitor leading to vasodilation
- Dose: 0.625-2.5 mg IV q6h prn
- Kinetics:
 - Onset: 10-15 minutes
 - Duration: 6 hours
- Side effects:
 - Hypotension
 - Renal effects
 - Hyperkalemia
 - Angioedema
- Clinical pearl:
 - Assuring the patient is not intravascularly depleted prior to administration will help you to avoid prolonged hypotension

Hydralazine (Apressoline[®])

- Direct acting arterial vasodilator
- Dose: 10-20 mg IV q4-6 hours prn
- Kinetics:
 - Onset: 5-15 minutes
 - Duration: up to 12 hours
- Caution:
 - May cause an increase in HR without an increase in epicardial blood flow (leading to cardiac ischemia)
- Clinical pearl:
 - Does not cross the utero-placental circulation and is therefore preferred for pre-eclampsia/eclampsia

Phentolamine (Regitine[®])

- Alpha adrenergic blocker
- Dose: 1-5 mg IV/IM
- Kinetics:
 - Onset: Immediate
 - Duration: 15 minutes
- Side effects:
 - Tachydysrhythmias
 - Angina
- Clinical pearls:
 - Positive chronotropic and inotropic effects occur in patients with LV dysfunction due to the release of norepinephrine
 - Preferred for cholinergic excess states and pheochromocytomas
 - Once HTN controlled- pts. should be switched to oral long-acting alpha-adrenergic antagonist (phenoxybenzamine)

Diazoxide

- Combination direct vasodilator and reflex sympathetic vasoconstriction
- Dose: 1-3 mg/kg IV bolus q 5-15 minutes
- Kinetics:
 - Onset: Immediate
 - Duration: 5-30 minutes
- Caution: Causes coronary steal syndrome
- Side effects:
 - Cardiac arrest
 - CHF
 - MI
 - Hepatotoxicity and Nephrotoxicity
- Clinical pearl: Most commonly used for malignant hypertension refractory to other therapy

New Options- Clevidipine (Clevisiprex)

- Dihydropyridine calcium channel antagonist (3rd generation)
- Reduces afterload without affecting cardiac filling pressures or causing reflex tachycardia
- May protect against organ reperfusion injury
 - Reduce infarct size?
 - Preserve renal and splanchnic blood flow?
- Indication
 - Reduction of blood pressure when oral therapy is not feasible or desirable
- FDA approved in 2008
- Marketed by the Medicines Company

Clevidipine

- Kinetics:
 - Half-life is < 1 minute
 - Metabolized by red blood cell esterases (not affected by renal/hepatic dysfunction)
 - Short off-set (5-15 minutes)
- Dosing:
 - 1-2 mg/hr
 - Double dose every 90 seconds until BP reaches target
 - Max 32mg/hr
 - Duration 72 hours

Clevidipine

- Contraindications:
 - Allergies to soy, soy products, eggs, egg products
 - Defective lipid metabolism including pathologic hyperlipidemia, lipid nephrosis, or acute pancreatitis with hyperlipidemia
 - Severe aortic stenosis
- Adverse Reactions (< 2%)
 - Headache, Nausea, Vomiting

Clevidipine

- Negative inotropic effects
 - Can lead to adverse events in patients with decompensated heart failure
- Other concerns:
 - Maintain strict aseptic technique
 - Lipid based
 - Supports microbial growth
 - Change vial and discard within 4 hours
 - Include in caloric counts if continuous infusion, daily limit 1000 mL

Clinical Trials with Clevidipine

Trial	Type of BP Control
ESCAPE-1	Preoperative
ESCAPE-2	Postoperative
ECLIPSE (NTG as active comparator)	Perioperative
ECLIPSE (SNP as active comparator)	Perioperative
ECLIPSE (NIC as active comparator)	Postoperative
VELOCITY	Acute severe

Comparative Trials

A Comparison of Nicardipine and Labetalol for Acute Hypertension Management Following Stroke

- Retrospective, non-randomized study of 90 patients who received either IV labetalol or nicardipine
- 64 received labetalol, 26 received nicardipine
- Baseline stroke type, APACHE II and GCS scores were similar between groups
- Nicardipine group had less BP variability ($p = 0.003$), fewer dose adjustments ($p < 0.001$), and fewer additional agents required ($p = 0.013$)
- 60 minute BP goal was achieved in 33% of nicardipine pts. Vs. 6% of labetalol treated patients
- Similar side effects

Liu-Deryke X., Janisse J., et al.
Neurocrit Care. 2008

Comparison of the Effects of Nicardipine and Sodium Nitroprusside for Control of Increased Blood Pressure after Coronary Artery Bypass Graft Surgery

- Prospective randomized trial of 47 patients undergoing CABG to receive either Nicardipine or Sodium Nitroprusside.
- 26 Nicardipine, 21 Nitroprusside
- No difference at baseline characteristics
- Shorter duration of treatment with Nicardipine and less titration required.
- Few cardiovascular/hemodynamic effects were seen with Nicardipine

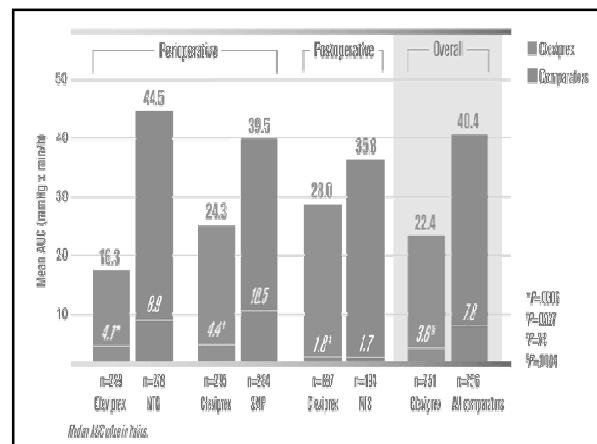
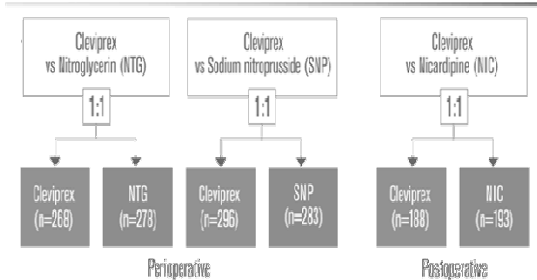
Kwak YL, Oh YJ, Bang SO, et al.
J Inter Med Res. 2004

Short-term Treatment of Severe Hypertension of Pregnancy: Prospective Comparison of Nicardipine and Labetalol

- Prospective randomized trial of 60 pre-eclamptic patients either to receive 1 hour of Labetalol or Nicardipine for a goal of 20% BP reduction
- 63% of Labetalol and 70% of Nicardipine treated patients achieved the 20% BP reduction goal.
- Nicardipine achieved a statistically significant greater reduction in BP
- No hypotensive episodes or severe adverse effects were seen in either group
- Authors concluded that either agent is safe/effective for severe hypertension of pregnancy

Elatrou S., Nouria S., et al. Intens Care Med. 2002.

Evaluation of Clevidipine In the Perioperative Treatment of Hypertension, Assessing Safety Events



Evaluation of Clevidipine In the Perioperative Treatment of Hypertension, Assessing Safety Events

- No difference in primary endpoints (myocardial infarction, stroke, renal dysfunction)
- Higher mortality for nitroprusside treated patients (p=0.04)
- CLV was more effective compared with NTG (P=0.0006) or SNP (P=0.003) in maintaining BP within the prespecified BP range.
- CLV was equivalent to NIC in keeping patients within a prespecified BP range; however, when BP range was narrowed, CLV was associated with fewer BP excursions beyond these BP limits compared with NIC.

Ongoing Studies

- An Open-Label Prospective Study to Evaluate the Safety and Efficacy of Double or Triple Concentrated Intravenous Nicardipine for Treatment of Hypertension in Patients with Ischemic Stroke, Intracerebral Hemorrhage or Subarachnoid Hemorrhage.
- Observational Study Looking at the Diagnosis, Pathophysiology, and Molecular Biology of Pheochromocytoma.

www.clinicaltrials.gov

Treatment of Special Situations

Acute Aortic Dissection

- Presentation: Chest pain, hypertensive emergency
- Ascending aortic mortality- 75% mortality if untreated in 2 weeks
- Treatment:
 - Do not give a vasodilator alone- promote reflex tachycardia, increases aortic ejection velocity, and promotes dissection propagation
 - Surgery is treatment of choice for an ascending dissection
 - Ideal therapy:
 - B-blocker (Esmolol or Metoprolol) + Vasodilator (Nitroprusside, Nicardipine, Fenoldopam)

Stroke

- Elevated BP is common in most patients irregardless of type of infarction
- Elevated BP is a physiologic protection to maintain cerebral perfusion pressure
- ASA and ESI recommend withholding antihypertensive therapy unless planned thrombolysis
- AHA guidelines
 - Labetalol or Nicardipine for SBP > 200 or DBP > 140
 - Nitroprusside if DBP > 140
- Induced hypertension
 - Triple H therapy- Hypertension, Hypervolemia, Hemodilution
 - 20-40% mortality reduction
 - Goal BP: SBP > 160 or MAP 20% increase

Preeclampsia and Eclampsia

- Incidence: 12% of pregnancies and leads to 18% of maternal deaths
- Goal therapy choices:
 - Magnesium sulfate (seizure prophylaxis and BP control)
 - Load: 4-6 grams over 15-20 minutes
 - Continuous infusion: 1-2 grams/hr
 - Volume expansion
 - Hydralazine- historical DOC
 - Labetalol or Nicardipine
- **Contraindicated:**
 - Nitroprusside
 - ACE -inhibitors

Sympathetic Crises

- Commonly due to recreational drug use
- Characterized by sympathetic overstimulation
 - Avoid β -adrenergic antagonists to avoid unopposed α -adrenergic activity (potential increase BP and worsen tachycardia)
- Labetalol
 - No clinical data to support its use
 - May be an ideal agent due to combination α/β blockade
- Therapy of choice:
 - Nicardipine, Fenoldopam, Verapamil
 - Phentolamine

Acute Postoperative Hypertension

- Appears to be due to the activation of the sympathetic nervous system
 - elevated plasma catecholamines have been seen
- Short acting agents
- Therapy of choice
 - Labetalol
 - Esmolol
 - Nicardipine
 - Clevidipine

Acute Coronary Syndromes and Heart Failure

- Prolonged hypertension may worsen or provoke ischemia
- Goal: BP goals per JNC-7 recommendations
- If evidence of pulmonary edema
 - Nitroglycerin
 - Nitroprusside

Clinical Situation	Recommended	Avoid
Hypertensive encephalopathy	Nitroprusside, Labetalol, Nicardipine	Clonidine, B-blockers, hydralazine
Malignant hypertension	Nitroprusside, Labetalol, Diazoxide, CCB, Enalaprilat	Diuretics, Clonidine
Cerebral infarction	Nitroprusside, Labetalol, Nicardipine	Hydralazine, Diazoxide
Intracerebral hemorrhage	Nitroprusside, Labetalol, Nicardipine	Hydralazine, Diazoxide
Subarachnoid hemorrhage	Nimodipine, Nitroprusside, Nicardipine	Hydralazine, Diazoxide
Aortic dissection	Nitroprusside + B-blocker, Labetalol	Hydralazine, Diazoxide

Clinical Situation	Recommended	Avoid
Adrenergic crisis	Phentolamine, Nitroprusside + B-blocker, Labetalol, Clevidipine	Monotherapy with B-blocker
Antihypertensive withdrawal	Phentolamine, Nitroprusside, Labetalol	
Acute pulmonary edema	Nitroprusside, Nitroglycerin	B-blockers, Verapamil, Diltiazem, Labetalol
Acute MI	Nitroglycerin + B-blocker, Nitroprusside, Labetalol, Clevidipine	Hydralazine, Diazoxide
Eclampsia	Labetalol, Methyldopa, Hydralazine	ACE inhibitors, Nitroprusside

Conclusion

- If end organ damage is present, it is a medical emergency and the patient should be treated with IV therapy
- ICU is the best clinical setting
- Choose pharmacologic options based on disease states and ability to easily titrate
- Avoid rapid reduction of blood pressure

References

- Hays A., Wilkerson T. Management of Hypertensive Emergencies- A Drug Therapy Perspective for Nurses. *AACN Advanced Critical Care* 2010; 21: 5-14.
- Haas A., Marik P. Current Diagnosis and Management of Hypertensive Emergency. *Sem Dial*; 2006; 19: 502-12.
- Feldstein C. Management of Hypertensive Crises. *Am J Ther* 2007; 14: 135-37.
- Marik P., Varon J. Hypertensive Crises: Challenges and Management. *Chest*. 2007; 131: 1949-62.
- Varon J., Marik P. The Diagnosis and Management of Hypertensive Crises. *Chest* 2000; 118:214-227.
- Mansoor A., von Hagel Keefer L. The Dangers of Immediate-Release Nifedipine for Hypertensive Crises. *P&T* 2002; 27, 7: 362-65.
- Haas C., LeBlanc J. Acute Postoperative Hypertension: A Review of Therapeutic Options. *Am J Health-Syst Pharm*. 2004; 61: 1661-73.

References

- Aronson S., Dyke C., Stierer K. The ECLIPSE trials (abbv). *Anesth Analg* 2008; 107 (4): 1110-21.
- www.cleviprex.com. Accessed 2/17/2010
- www.Clinicaltrials.gov Accessed 2/17/2010
- Kwak YL, Oh YJ, Bang SO., et al. Comparison of the Effects of Nicardipine and Sodium Nitroprusside for Control of Increased Blood Pressure after Coronary Artery Bypass Graft Surgery. *J Inter Med Res*. 2004; 32: 342-50.
- Liu-Deryke X., Janisse J., Coplin WM, et al. A Comparison of Nicardipine and Labetalol for Acute Hypertension Management Following Stroke. *Neuro Crit Care*. 2008
- Elatrous S., Nouira S., Ouanes Besbes L., et al. Short-term Treatment of Severe Hypertension of Pregnancy: Prospective Comparison of Nicardipine and Labetalol. *Intens Care Med*. 2002; 28: 1281-86.

Pre-assessment patient case

- 27 y/o M presents to the ED after a “night out” with chest pain and shortness of breath.
- VS: HR 127 BP 214/163 RR 22
- He is started on a esmolol drip at 50 mcg/kg/minute.
- Repeat VS (20 minutes after esmolol started):
 - HR 147 BP 287/204 RR 24
- What is the likely cause of his reaction to esmolol?

Learning Assessment # 1

- 50 yo F that missed dialysis and has not taken home BP meds (which included clonidine, nifedipine, and vasotec) due to a family crisis, presents with HA, SOB, and early signs of CHF.
- BP 248/170
Identify the drug of choice for this patient

Learning Assessment #2

- You are the pharmacist on call and receive a call about a patient who has a HR 105 and BP of 198/105. The patient is 18 hours s/p ex-lap, SBR.

Compare and contrast therapeutic options for this patient

Learning Assessment #3

- 51 yo M admitted to CCU service with new onset CHF.
- Initial VS: 178/122 P 78

Discuss therapeutic options and potential complications of these therapies