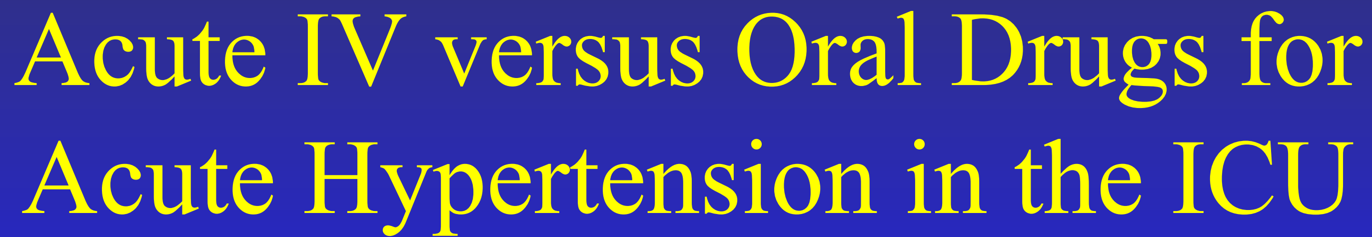

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Disclosures

- The STAT Registry was supported by an unrestricted educational grant from The Medicines Company.

- Patients who require acute blood pressure (BP) control often have a history of chronic hypertension* (HTN) and may be noncompliant or inadequately treated[1]
  - Approximately 73 million Americans have chronic HTN, of whom ~65% are uncontrolled[2]
  - It is estimated that 1 in 100 patients with chronic HTN will experience a hypertensive crisis[3]
- Acute BP management is often required in critical care
  - Postoperative patients
  - Admissions from emergency department
- Lack of recent literature regarding the prevalence and treatment of acute HTN suggests an unmet need for further research

***HTN is defined as having BP ≥140/90 mmHg, taking antihypertensive medication, or being told at least twice by a healthcare professional that one has high BP.[2]**

1. Zampaglione B, et al. *Hypertension*. 1996;27:144-147;
2. Rosamond W, et al. *Circulation*. 2008;117:e25-e146;
3. Varon J. *Drugs*. 2008;68:283-297.

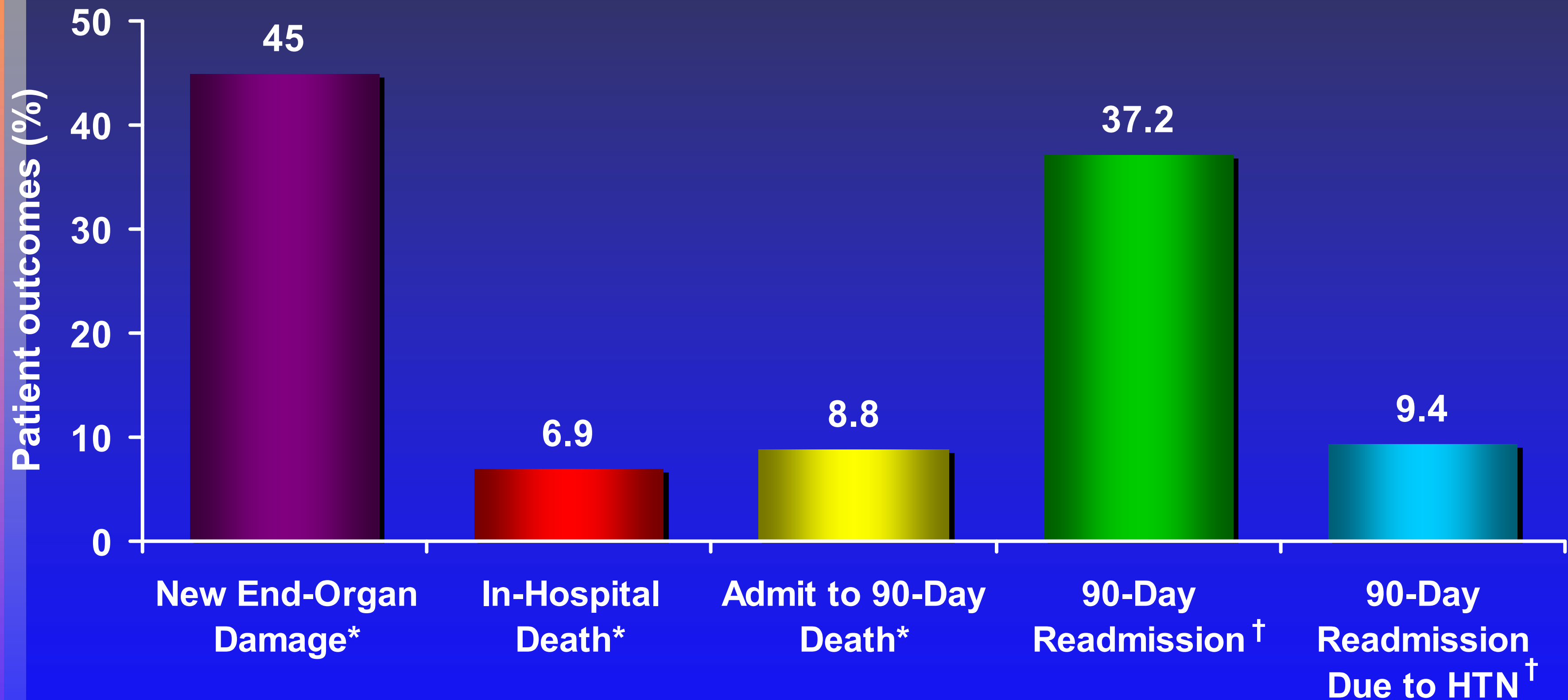
Studying the Treatment of Acute HyperTension: The STAT Registry

- Goals of the STAT registry
  - Better understand the clinical condition of acute HTN managed in a critical care setting and treated with IV antihypertensive drugs
  - Improve immediate and long-term outcomes of patients with acute severe HTN
- Design
  - Multicenter, US-based, observational, cross-sectional survey
  - Adult patients with acute severe HTN (BP >180/110 mmHg*) treated with IV antihypertensive agents in a critical care setting

***Or >140/90 mmHg plus subarachnoid hemorrhage.**
BP=blood pressure; HTN=hypertension; IV=intravenous.

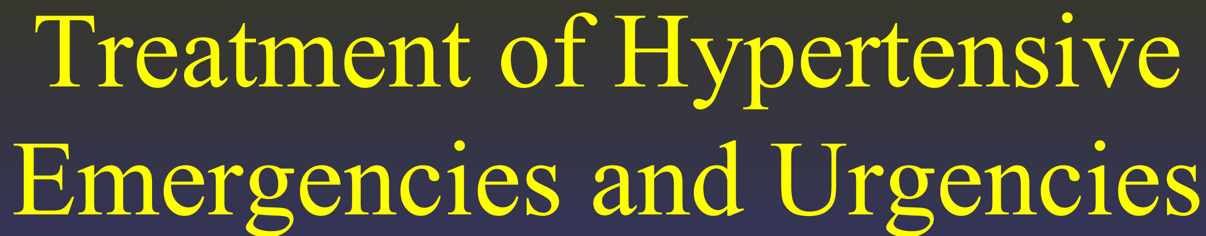
Kleinschmidt K, et al. Society for Academic Emergency Medicine 2008 Annual Meeting. Poster #140.

STAT Registry Analysis



***N=1,588 (all patients); †n=1,405 (patients alive at discharge and with 90-day follow-up). HTN=hypertension.**

Kleinschmidt K, et al. Society for Academic Emergency Medicine 2008 Annual Meeting. Poster #140.



Literature Review

- Treatment of hypertensive emergencies has never been addressed in a large clinical trial
- Cherney and Straus performed a systematic review of literature on the treatment of hypertensive emergencies and urgencies:
  - From 1966-2001 only 4 hypertensive emergency trials and 15 hypertensive urgency trials were reported
  - No data demonstrating mortality benefit were available
- Halpern et al. “Postoperative Hypertension: a multicenter, randomized comparison between IV nicardipine and nitroprusside *Crit Care Med* 1992

Common Hypertensive Emergencies

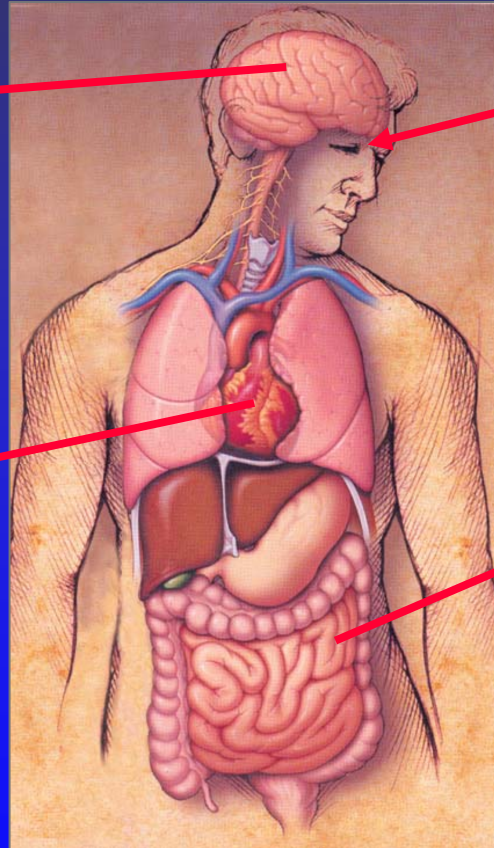
- Acute cerebrovascular syndromes
  - subarachnoid hemorrhage
  - cerebral bleeding
  - cerebral infarction
- Acute coronary syndromes, heart failure, pulmonary edema
- Aortic dissection
- Hypertensive encephalopathy and retinopathy
- Pregnancy-induced hypertension

Mansoor GA, Frishman WH. Heart Dis. 2002;4:358-371.

End-Organ Damage in Hypertensive Crises

Brain
Stroke
Hypertensive encephalopathy

Retina
Hemorrhages
Exudates
Papilledema



Cardiovascular System
Unstable angina
Acute heart failure
Acute MI
Dissecting aortic aneurysm

Kidney
Hematuria
Proteinuria
Decreasing renal function

Adapted with permission from Varon J, Marik PE. *Chest*. 2000;118:214-227.

Evaluating Patients for Hypertensive Emergencies

- BP
  - Supine and standing (if possible)
- History
  - Duration and severity of hypertension
  - Prior end-organ damage
- Symptoms of end-organ damage
  - Chest pain (myocardial infarction)
  - Back pain (aortic dissection)
  - Dyspnea (pulmonary edema, CHF)
  - Neurological symptoms, seizures, altered consciousness

Vaughan CJ, Delanty N. *Lancet*. 2000;356:411-417.

Continued

- Funduscopic exam
  - New hemorrhages
  - Papilledema
- Cardiovascular exam
  - Raised jugular venous pressure
  - Crackles, third heart sound
  - Electrocardiography and chest radiography
- Neurological exam
  - Level of consciousness
  - Signs of meningeal irritation
  - Visual fields
  - Focal signs

Vaughan CJ, Delanty N. *Lancet*. 2000;356:411-417.

Goal of Therapy in Hypertensive Crises

- Immediate and controlled BP reduction[1]
  - Reduce mean arterial pressure (MAP) by 10% to 15% (DBP ~ 110 mm Hg) within 30-60 minutes
    - Complications may result from aggressive BP reductions
    - Cerebral autoregulation considerations
  - Rapid-acting and titratable IV therapy is essential

Varon J, Marik P. Chest. 2000;118:214-227.

- Special considerations
  - Aortic dissection[1]
    - Reduce DBP 10%-15% within 5-10 minutes
  - Ischemic stroke[1]
    - HTN may be important to maintain adequate perfusion pressure
  - HTN in previously normotensive patient
  - Pre-eclampsia

Varon J, Marik P. Chest. 2000;118:214-227.

Acute BP Control in Critical Care

- The JNC 7 guidelines recommend to “reduce mean arterial BP by no more than 25% within minutes to 1 hour” for hypertensive emergencies[1]
  - The variety of patient types and clinical situations preclude more specific guidelines with regard to treatment timing or targets
- Therefore, challenges exist in individualizing treatment for each particular situation and patient[1,2]
  - The agent of choice depends on the clinical presentation and specific needs of each patient[2]

BP=blood pressure; JNC 7=Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

1. Chobanian AV, et al. *Hypertension*. 2003;42:1206-1252.
2. Varon J, Marik PE. *Vasc Health Risk Manag.* 2008;4:615-627;

- Treats underlying pathophysiology
- Rapid onset and offset of action
- Predictable dose response
- Titratable to desired BP
- Minimal adverse effects
- No increase in intracranial pressure (ICP)
- Preserves glomerular filtration and renal blood flow
- Easy conversion to oral agents
- Acceptable cost to benefit ratio
- Drug is eliminated independently of any particular end organ

Oparil S, et al. Am J Hypertens. 1999;12:653-664.
Levy JH. Anesthesiol Clin North Am. 1999;17:567-579.

- Clonidine
- Diazoxide
- Enalaprilat
- Esmolol
- Fenoldopam
- Hydralazine
- Labetalol
- Nicardipine
- Nifedipine
- Nitroglycerin
- Nitroprusside
- Phentolamine
- Trimethaphan
- Clevidipine

#

- Data related to selection of intravenous antihypertensive comes from 2 sources
  - Solucient ACTracker Inpatient Hospital Database
    - Patient discharge case records
    - 450 hospitals
    - ~6,284,000 raw patient discharge records
    - Numbers projected to all patients

Certain data used in this study were supplied by Solucient, a division of The Medstat Group, Inc. Any analysis, interpretation, or conclusion Based on these data is solely that of the authors, and not Solucient.

What Drugs Are Used?

	Medicine & Cardiology[1]
Enalaprilat (Vasotec IV)	15.7%
Esmolol (Brevibloc)	4.9%
Fenoldopam (Corlopam)	0.2%
Hydralazine (Apresoline)	15.3%
Labetalol (Normodyne, Trandate)	22.5%
Nicardipine (Cardene IV)	1.9%
Nitroglycerine	54.9%
Sodium nitroprusside (Nitropress)	3.4%

Source:

1. 2005 Solucient ACTracker Inpatient Hospital Database

Certain data used in this study were supplied by Solucient, a division of The Medstat Group, Inc. Any analysis, interpretation, or conclusion Based on these data is solely that of the authors, and not Solucient.

	Neurology[1]
Enalaprilat (Vasotec IV)	24.6%
Esmolol (Brevibloc)	6.2%
Fenoldopam (Corlopam)	0.3%
Hydralazine (Apresoline)	31.2%
Labetalol (Normodyne, Trandate)	59.8%
Nicardipine (Cardene IV)	13.4%
Nitroglycerine	9.5%
Sodium nitroprusside (Nitropress)	13.8%

Source:

1. 2005 Solucient ACTracker Inpatient Hospital Database

Certain data used in this study were supplied by Solucient, a division of The Medstat Group, Inc. Any analysis, interpretation, or conclusion based on these data is solely that of the authors, and not Solucient.

What Drugs Are Used?

	Cardiac & Vasc Surgery[1]
Enalaprilat (Vasotec IV)	8.0%
Esmolol (Brevibloc)	14.2%
Fenoldopam (Corlopam)	1.8%
Hydralazine (Apresoline)	20.4%
Labetalol (Normodyne, Trandate)	21.2%
Nicardipine (Cardene IV)	7.5%
Nitroglycerine	70.9%
Sodium nitroprusside (Nitropress)	39.4%

Source:

1. 2005 Solucient ACTracker Inpatient Hospital Database

Certain data used in this study were supplied by Solucient, a division of The Medstat Group, Inc. Any analysis, interpretation, or conclusion Based on these data is solely that of the authors, and not Solucient.

Nitrovasodilators

Nitroprusside vs Nitroglycerin

Drug	Nitroprusside	Nitroglycerin
Rapid onset of peak effect	++++	+++
Afterload reduction	++++	+
Preload reduction	++	++++
Coronary steal reported	+	0
Coronary dilation – large vessel	+	++++
Coronary dilation – small vessel	+/-	+/-
Tachycardia	++	++
Potential for symptomatic hypotension	++	+++
Ease of administration	++	+++
Cyanide toxicity	++++	0

Pepine CJ. Clin Ther. 1988;10:316-325.

β-Blocker vs Combined α- and β-Blocker

	Esmolol β-Blocker	Labetalol α- and β-Blocker
Administration	Bolus Continuous infusion	Bolus Continuous infusion
Onset	Rapid (60 s)[2]	Intermediate (peak 5-15 min)[2]
Offset	Rapid (10-20 min)[2]	Slower (2-4 h)[2]
HR	Decreased	+/-
SVR	0	Decreased
Cardiac output	Decreased	+/-
Myocardial O_2 balance	Positive	Positive
Contraindications	Sinus bradycardia Heart block >1° Overt heart failure Cardiogenic shock	Severe bradycardia Heart block >1° Overt heart failure Cardiogenic shock

1. Hoffman BB. In: Hardman JG, Limbird LE, eds. Goodman and Gilman's Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill; 1997:215-268
2. Varon J, Malik PE. Chest. 2000;118:214-227

JNC VII Recommendations

ACE Inhibitors

Drug	Onset of Action[1]	Duration of Action[1]	Adverse Events[1,2]	Special Considerations[1]
Enalaprilat	15-30 min	6-12 hours	Precipitous fall in pressure in high-renin states Renal dysfunction Angioedema	Acute ventricular failure Avoid in acute MI

ACE=angiotensin-converting enzyme.

1. The 7th Report of the JNC. JAMA 2003;289:2560-2571.
2. Vasotec [package insert].

JNC VII Recommendations

Dopamine Agonist

Drug	Onset of Action	Duration of Action	Adverse Events	Special Considerations
Fenoldopam	<5 min	30 min	Tachycardia Headache Nausea Flushing	Avoid with glaucoma

The 7th Report of the JNC. JAMA 2003;289:2560-2571.

- Arterial selective
- No AV nodal depression
- Minimal myocardial depression
- Cerebral and coronary vasodilator
- Nicardipine and Clevidipine

Oates JA. Brown NJ. In: Hardman JG, Limbird LE, eds. *Goodman and Gilman's Pharmacological Basis of Therapeutics*. 10th ed. New York, NY: McGraw-Hill; 1997:645-668.

Acute Severe BP Control: VELOCITY Trial

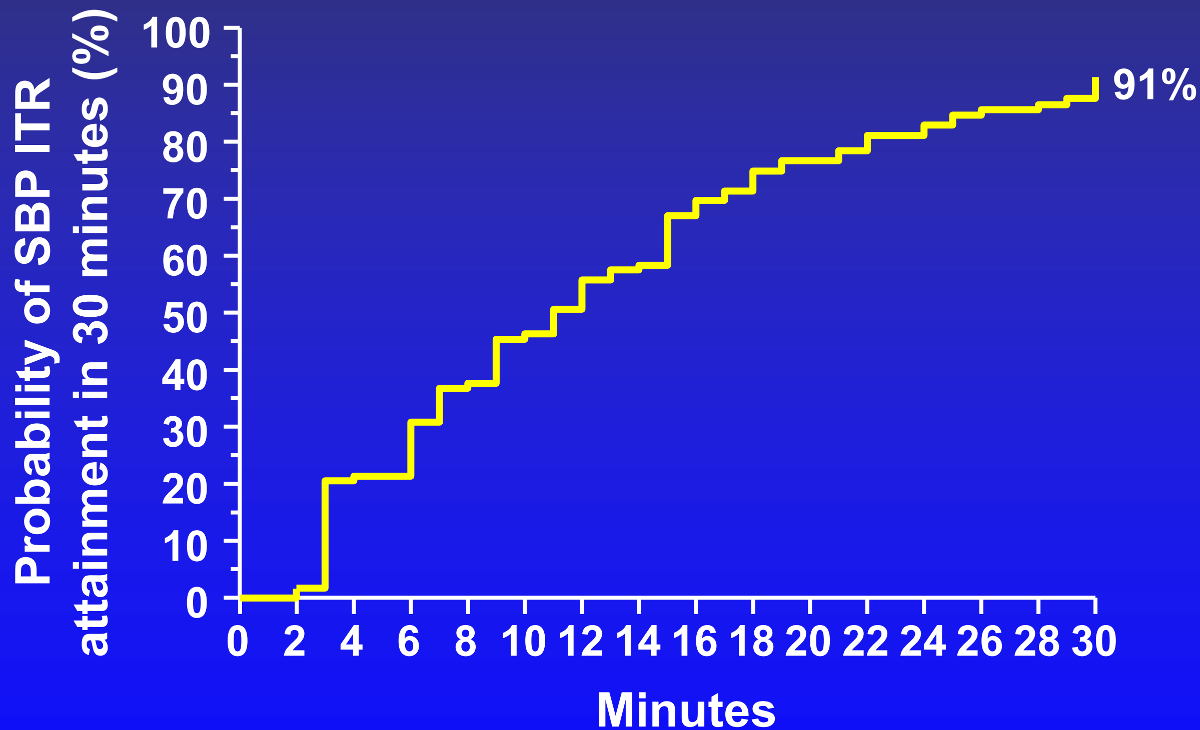
- Multicenter, phase 3, open-label, single-arm study to confirm the safety and efficacy of clevidipine butyrate using a predefined, non–weight-based dosing algorithm in 126 patients presenting in the ED or ICU with severe HTN
- Primary end points
  - Patients (%) in whom SBP fell to within the SBP ITR within 30 minutes of initiating infusion
  - Patients (%) in whom SBP fell below the lower limit of the SBP ITR within 3 minutes of initiating infusion
- Secondary end points
  - Time to achieve SBP ITR within the initial 30-minute treatment period
  - Proportion of patients successfully transitioned to oral antihypertensive therapy
  - Safety of prolonged (≥18 hours) infusion of clevidipine

ED=emergency department; HTN=hypertension; ICU=intensive care unit; ITR=initial target range; SBP=systolic blood pressure.

Pollack CV, et al. *Ann Emerg Med.* 2008; Jun 6. [Epub ahead of print].

Clevidipine butyrate Rapidly Lowered BP to Target in ~90% of Patients

Primary end point results: Kaplan-Meier curve demonstrating probability of attaining SBP ITR within 30 minutes (mITT population*, n=117)



***Patients whose SBP was above their prespecified ITR at the time of Clevidipine initiation.**

BP=blood pressure; ITR=initial target range; mITT=modified intent-to-treat; SBP=systolic blood pressure.

Pollack CV, et al. *Ann Emerg Med*. 2008; Jun 6. [Epub ahead of print].

Transition to Oral Antihypertensives

- 97.5% (115/118 eligible patients) transitioned successfully to oral antihypertensive therapy within
6 hours

Successful transition to oral therapy was defined as transition with systolic blood pressure remaining within the applicable (last identified) target range at 6 hours after stopping Cleviprex™ (clevidipine butyrate).

Pollack CV, et al. *Ann Emerg Med.* 2008; Jun 6. [Epub ahead of print].

Is it safe to use oral antihypertensive drug for an emergency?

- Clonidine: Loading with oral clonidine until a dose of 0.7 mg has been given achieved control in 93% of patients *Arch Int Med* 1986
- Sublingual nifedipine and sublingual captopril: Both nifedipine and captopril given sub-lingually and both produced a lowering of blood pressure within 5 minutes that persisted for 4 hours *Jpn J Pharmacol* 1990
- Oral carvedilol versus captopril: Both produced a reduction in SBP and in DBP at 45 minutes; both also produced reduced SBP and DBP in 180 minutes; carvedilol produced a longer and more stable effect *Ter Arkh* 2006

General Principles

- Maintenance of cerebral blood flow is key goal
- Acute neurological conditions may cause loss or dysfunction of cerebral autoregulation
  - Stroke, intracerebral hemorrhage, SAH
  - Carotid endarterectomy
- Therapy must consider the baseline physiology of each patient
  - cardiac history and risks
  - pulmonary and renal function
- Consideration of current medications

Practical Considerations

- Need for frequent BP monitoring
- Availability of an arterial line
- Patients with significant cardiac conditions should have a Swan-Ganz catheter in place

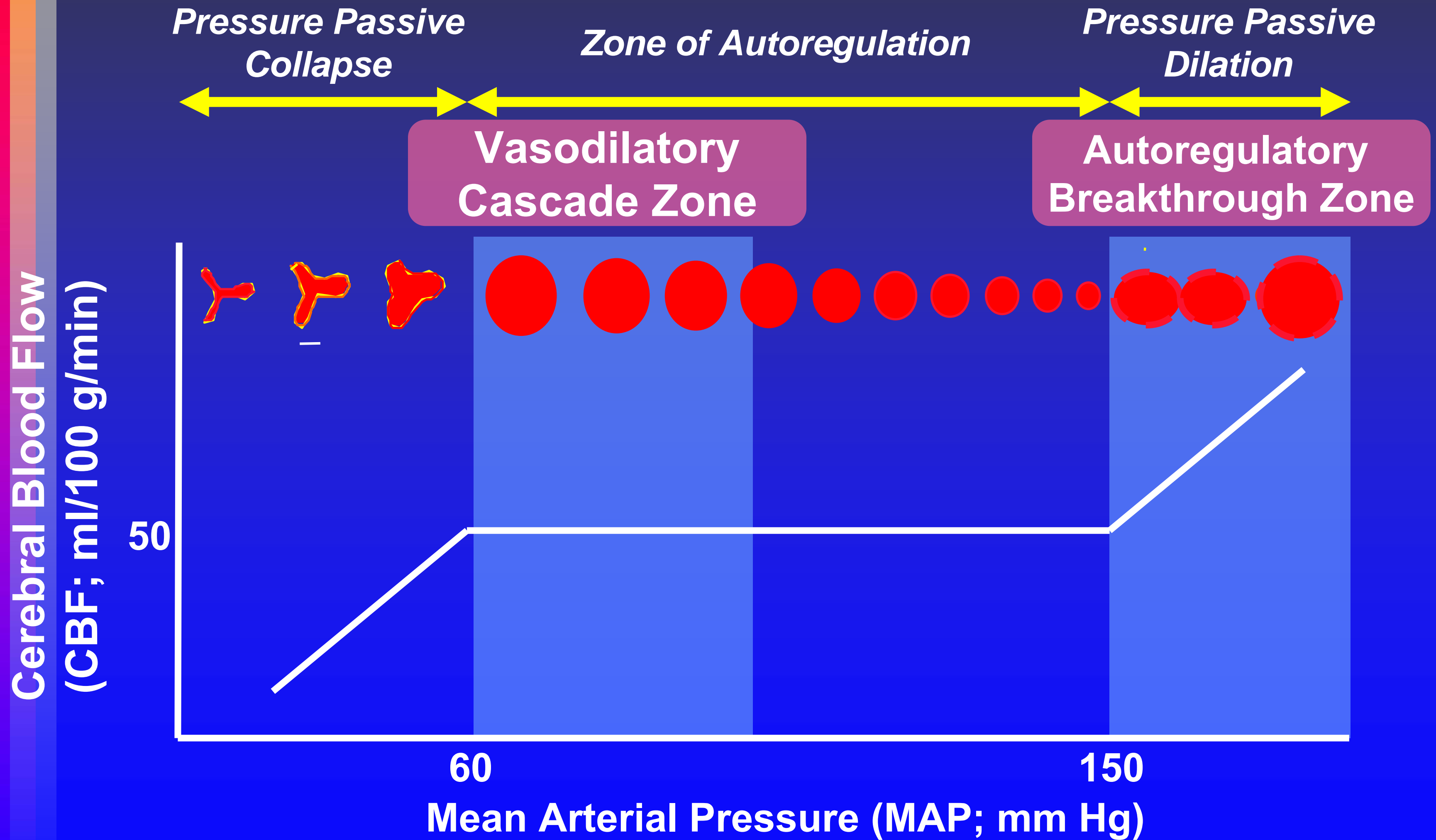
Hypertension and Stroke Epidemiology

Stroke

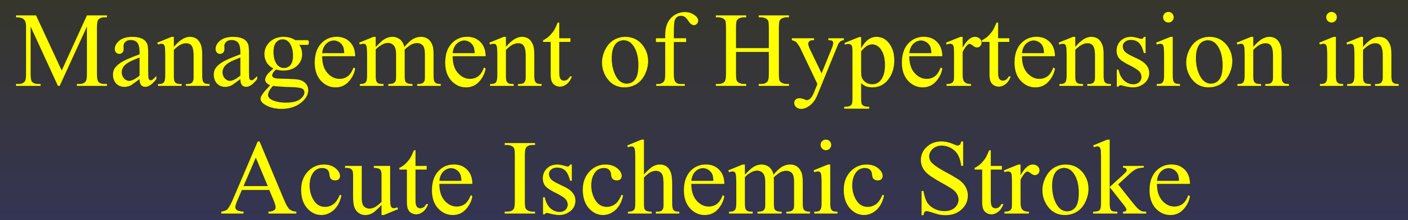
- **Ischemic Stroke** 80-85%
- **Hemorrhagic Stroke** 15-20%
  - **Intercerebral Hemorrhage** 70%
  - **Subarachnoid Hemorrhage** 28%
  - **Intraventricular Hemorrhage** 2%

Marx: Rosen's Emergency Medicine: Concepts and Clinical Practice, 5th ed 2002 Mosby, Inc.

Cerebral Autoregulation



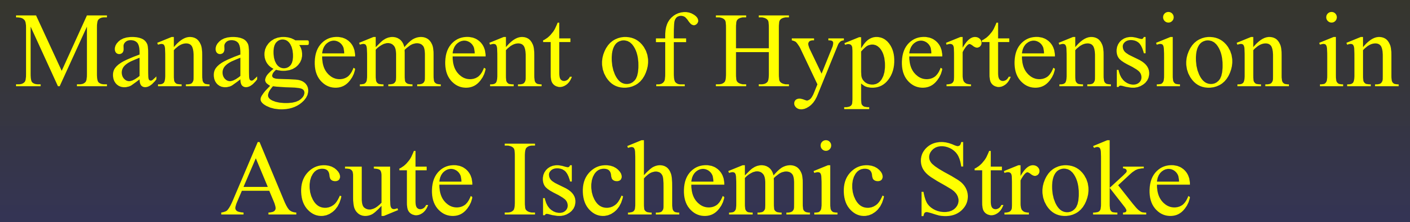
Adapted from Lang EW, et al. J Neurol Neurosurg Psychiatry. 2003;74:1053-1059.



Patients Ineligible for Thrombolytic Therapy

- SBP <220 or DBP <120
  - No antihypertensive therapy
- SBP >220 or DBP=121-140
  - Labetalol or nicardipine to 10%-15% reduction
- DBP >140
  - Nitroprusside to 10%-15% reduction

Adams HP, et al. Stroke. 2003;34:1056-1083.



Patients Eligible for Thrombolytic Therapy

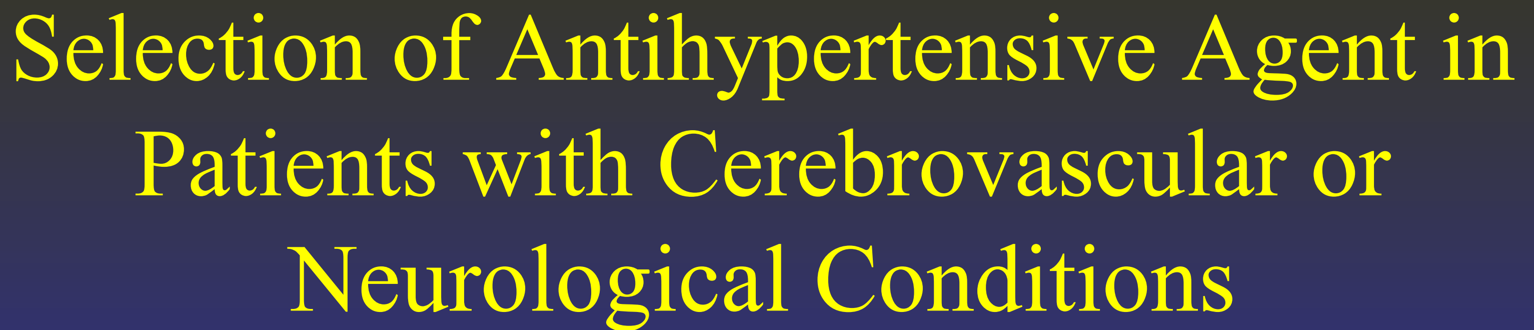
- BP Goal: SBP=180, DBP=110, MAP=130
- Prior to initiating treatment with TPA
  - SBP >185 or DBP >110
    - Labetalol or nitropaste
- During and after treatment with TPA
  - DBP >140 mm Hg
    - Nitroprusside
  - SBP >230 mm Hg or DBP=121-140 mm Hg
    - Labetalol or nicardipine
  - SBP=180-230 mm Hg or DBP=105-120 mm Hg
    - Labetalol

Adams HP, et al. Stroke. 2003;34:1056-1083

Hypertension in Acute ICH

- 90% of patients presenting with ICH are hypertensive
- Most have pre-existing hypertension
- Some have recently stopped their meds
- Intracranial hematoma also increases BP via Cushing response
- Fear, anxiety, pain also contribute to hypertension

BP=blood pressure; ICH=intracranial hemorrhage



Selection of Antihypertensive Agent in Patients with Cerebrovascular or Neurological Conditions

- Oral agents
  - Not option for many neurologic patients
  - Variable absorption and onset
- Single dose IV agents
  - Need access
  - Short acting agents protect against overtreatment
- Continuous IV infusion
  - Easier to control and titrate to proper response

Recommendations

1. If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 minutes.
2. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is evidence of or suspicion of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications to keep cerebral perfusion pressure >60 to 80 mm Hg.
3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is not evidence of or suspicion of elevated ICP, then consider a modest reduction of blood pressure (e.g., MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg) using intermittent or continuous intravenous medications to control blood pressure, and clinically reexamine the patient every 15 minutes.

ICP=intracranial pressure; MAP=mean arterial pressure.

Circulation. 2007;116:e391-e413

- Acute BP management in the ICU is a very challenging problem to the Critical Care Physician in 2009
- Quite a few options exist for treatments
- IV medication should remain the first line of therapy
- Not much in the way of evidence-based medicine is available for the clinician as of 2009