Vascular Dysfunction: Sequelae of Acute Hypertension
Overview

• Introduction: Scope of the problem
• Effects of acute BP elevation on the vessel wall
• Traditional parenteral antihypertensive treatment
  – Pharmacokinetic profiles and key clinical studies
  – Guidelines for use
• Clinical trial update: New paradigm in management of acute hypertension
Acute and chronic hypertension: Clinical context

Chronic hypertension

Acute vascular reactivity

Hypertensive emergencies

Courtesy of S Aronson, MD.
Sympathetic overactivation drives acute hypertension

Chronic hypertension ↔ Arteriosclerosis

Sympathetic overactivation

Acute hypertension

Important triggers include clonidine withdrawal, cocaine abuse, certain surgical settings

Components of blood pressure: New focus on pulse pressure

PRESSURE

HR x SV = CO  
BP*/CO = SVR  
CO x MAP = work  
MAP = 1/3 PP + DBP

FLOW

All in the absence of pulsations

Courtesy of S Aronson, MD.
# Perioperative ISH associated with postoperative adverse events

N = 2069 scheduled for CABG

<table>
<thead>
<tr>
<th>Event</th>
<th>Event rate (%)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure/insufficiency</td>
<td>6.7</td>
<td>8.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.3</td>
<td>10.1</td>
</tr>
<tr>
<td>LV dysfunction</td>
<td>29.1</td>
<td>34.3</td>
</tr>
<tr>
<td>Renal failure/insufficiency, stroke, LV dysfunction, death</td>
<td>33.2</td>
<td>40.9</td>
</tr>
</tbody>
</table>

ISH = isolated systolic hypertension

Proposed risk index for renal dysfunction/failure post-CABG: Importance of pulse pressure

N = 4801 scheduled for bypass

<table>
<thead>
<tr>
<th>Preoperative risk factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75 years</td>
<td>7</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>41-60</td>
<td>4</td>
</tr>
<tr>
<td>61-80</td>
<td>8</td>
</tr>
<tr>
<td>81-100</td>
<td>12</td>
</tr>
<tr>
<td>&gt;100</td>
<td>16</td>
</tr>
<tr>
<td>History</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>9</td>
</tr>
<tr>
<td>MI</td>
<td>6</td>
</tr>
<tr>
<td>Renal disease</td>
<td>13</td>
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</table>

<table>
<thead>
<tr>
<th>Intraoperative risk factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 Inotropes</td>
<td>10</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>15</td>
</tr>
<tr>
<td>Cardiopulmonary bypass ≥122 min</td>
<td>6</td>
</tr>
</tbody>
</table>


Multicenter Study of Perioperative Ischemia (McSPI)
Acute hypertension: Subgroups and settings

- Hypertensive urgency
  - Emergency department
- Hypertensive emergency
  - Intensive care unit
- Perioperative hypertension
  - Operating room
  - Postanesthesia care
### JNC 7 definitions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive emergency</td>
<td>BP &gt; 180/120 mm Hg complicated by evidence of impending or progressive end-organ damage</td>
</tr>
<tr>
<td>Hypertensive urgency</td>
<td>Severe elevation in BP without progressive end-organ damage</td>
</tr>
</tbody>
</table>

Hypertensive urgencies/emergencies: Patients and organ systems at risk

1% of hypertensives (1990 data). Contemporary prevalence may be lower

**Cardiopulmonary**
- ADHF
- ACS
- Acute pulmonary edema
- Acute aortic syndromes

**Ocular**
- Papilloedema

**Neurovascular**
- Hypertensive encephalopathy
- Stroke

**Renal**
- Acute renal dysfunction

ACS = acute coronary syndrome
ADHF = acute decompensated heart failure

Hypertensive urgencies/emergencies: Prevalence of organ system complications

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>N = 449 presenting to Emergency Department with hypertensive urgency/emergency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV</td>
<td></td>
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<tr>
<td>Pulmonary edema</td>
<td>22.5</td>
</tr>
<tr>
<td>Acute congestive heart failure</td>
<td>14.3</td>
</tr>
<tr>
<td>ACS</td>
<td>12.0</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>4.5</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>2.0</td>
</tr>
<tr>
<td>CNS</td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>24.5</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>16.3</td>
</tr>
<tr>
<td>Intracerebral/subarachnoid hemorrhage</td>
<td>4.5</td>
</tr>
</tbody>
</table>

**Hypertensive urgencies/emergencies: Most common presenting symptoms**

<table>
<thead>
<tr>
<th>Urgencies</th>
<th>Emergencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Headache (22%)</td>
<td>• Chest pain (27%)</td>
</tr>
<tr>
<td>• Epistaxis (17%)</td>
<td>• Dyspnea (22%)</td>
</tr>
<tr>
<td>• Faintness and psychomotor agitation (10%)</td>
<td>• Neurological deficit (21%)</td>
</tr>
</tbody>
</table>

Perioperative hypertension: Scope of the problem

- Generally acknowledged to be common but little data available on exact prevalence in contemporary surgical practice

- Markers of increased risk for perioperative ↑BP include:
  - History of hypertension
  - Type of surgery
    - Cardiac
    - Carotid
    - Peripheral vascular
    - Abdominal aortic
    - Intraperitoneal/intrathoracic
    - Pheochromocytoma tumor

Perioperative antihypertensive therapy is common in cardiac surgery

N = 1660 patients, (N = 191 anesthesiologists)

Mean MAP threshold for treatment (mm Hg)
- Preoperative: 106.0
- Intraoperative: 86.3
- Postoperative: 97.1
- ICU: 109.0

Effects of Acute BP Elevation on the Vessel Wall
Pathophysiology overview

Sustained neurohormonal activation and vasoconstriction leads to
• Endothelial decompensation
• Altered vascular structure

Vicious cycle of homeostatic failure begins, leading to
• Loss of cerebral and local autoregulation
• Organ system ischemia and dysfunction
• Myocardial infarction
Pathophysiology of hypertension

INAPPROPRIATELY HIGH SYMPATHETIC OUTFLOW

Increased large arterial stiffness

Abnormal venoconstriction and high venous return

INAPPROPRIATELY HIGH RENIN RELEASE

Inappropriately high cardiac output

Increased systemic resistance

ABNORMAL RENAL SALT/WATER HANDLING

Courtesy of JL Izzo Jr, MD.
The endothelium modulates vascular tone

Endogenous vasodilators
- NO
- PGI₂

Endogenous vasoconstrictors
- Catecholamines
  - AT-II
  - TxA₂
  - ET₁
- Aldosterone
- ADH (vasopressin)

Courtesy of JJ Ferguson III, MD.
Proposed vascular pathophysiology of hypertensive urgency

Acute ↑ BP triggers ↑ cellular adhesion molecular expression

NO
Endogenous vasodilators
PGI₂

CAMs

Catecholamines
AT-II
TxA₂
ET₁
Aldosterone
ADH (vasopressin)

Endogenous vasoconstrictors

Courtesy of JJ Ferguson III, MD.
Proposed vascular pathophysiology of hypertensive emergency

- Overwhelmed control of vascular tone leads to coagulation cascade activation
- Loss of endothelial activity coupled with coagulation and platelets promotes DIC

Courtesy of JJ Ferguson III, MD.
Endothelial shear stress

ESS = endothelial shear stress

Proportional to the product of blood viscosity ($\mu$) and spatial gradient of blood velocity at the wall (dv/dy).

Endothelial mechanoreceptors sense changes in shear stress

ESS = endothelial shear stress

Shear stress rapidly activates endothelial signal transduction and gene expression

Definition and example of pulsatile, low, and oscillatory ESS

ESS = endothelial shear stress

Implications of low and high shear stress

Effects of low shear stress
- Atherosclerosis
- Plaque rupture

Effects of high shear stress
- Endothelial dysfunction
- Vascular injury
- Thrombosis
- Neurohumoral activation

Perioperative triggers of adverse physiologic states

- Surgical trauma
- Anesthesia/analgesia
- Intubation/extubation
- Pain
- Hypothermia
- Bleeding/anemia
- Fasting
- Transfusion

Physiologic state
- Inflammatory
- Hypercoagulable
- Stress
- Hypoxia

Proposed mechanisms of perioperative MI

**Inflammation**
- ↑ TNF-α
- ↑ IL-1
- ↑ IL-6
- ↑ CRP

  → Plaque fissuring

**Hypercoagulable state**
- ↑ PAI-1
- ↑ Factor VIII
- ↑ Platelet reactivity
- ↑ Antithrombin III

  → Coronary artery shear stress
  → Plaque fissuring

**Stress**
- ↑ Catecholamine and cortisol levels

  → ↑ BP
  → ↑ HR
  → ↑ FFAs
  → ↑ Relative insulin deficiency

  → ↑ Oxygen demand

**Hypoxia**
- ↓ Oxygen delivery

**Acute coronary thrombosis**
**Myocardial ischemia**

**Perioperative myocardial infarction**

Summary: The pathophysiology of acute hypertensive syndromes

- ↑BP
  - Mechanical stress on the vessel wall
  - Release of humoral vasoconstrictors

Further release of humoral vasoconstrictors

Fibrinoid necrosis of small blood vessels

Activation of the clotting cascade

Endothelial damage

Major physiologic derangements

Pressure natriuresis

Volume depletion

RAAS activation

Vasopressin endothelin catecholamines

Courtesy of JJ Ferguson III, MD.
Pathophysiology of acute hypertensive syndromes: A vicious cycle

Vasoconstrictor release

Tissue ischemia

Vascular injury

Courtesy of JJ Ferguson III, MD.
Traditional Parenteral Antihypertensive Treatment

Pharmacology and selected clinical trials
Profile of an ideal parenteral antihypertensive

- Treats underlying pathophysiology
- Rapid onset of action
- Predictable dose response
- Minimal dosage adjustments
- Highly selective
- No increase in intracranial pressure
- Rapidly reversible
- Low risk of overshoot hypotension or adverse reaction
- Easy conversion to oral agents
- Acceptable cost-benefit ratio

## JNC 7: Parenteral antihypertensive treatment

### Currently available

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Onset / Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium nitroprusside</td>
<td>Vasodilator</td>
<td>Faster</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β-blocker</td>
<td></td>
</tr>
<tr>
<td>Phentolamine</td>
<td>α-blocker</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Vasodilator</td>
<td></td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>D1 agonist</td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>α/β-blocker</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>CCB</td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Vasodilator</td>
<td></td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>ACEI</td>
<td>Slower</td>
</tr>
</tbody>
</table>

D1 = dopamine receptor

Sodium nitroprusside: Profile

- Arterial and venodilator
  - ↓ Preload and afterload
- Onset: Immediate
- Duration of action: 1-2 min
- Adverse effects
  - Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication, coronary steal, maldistribution of blood flow
- Light sensitive: requires special delivery system

Aggarwal M, Khan IA. Cardiol Clin. 2006;24:135-146.
Esmolol: Profile

- Blocks $\beta_1$ receptors of heart and vasculature
  - $\downarrow$ Heart rate, cardiac output, and stroke volume
- Onset: 1-2 min
- Duration of action: 10-30 minutes
- Adverse effects:
  - Hypotension, nausea, asthma, 1st degree heart block, HF

Aggarwal M, Khan IA. *Cardiol Clin*. 2006;24:135-146.
Fenoldopam: Profile

- Selective dopamine-1 receptor agonist
  - ↓Peripheral vascular resistance
  - ↑Renal blood flow, natriuresis, and diuresis

- Onset: <5 min

- Duration of action: 30 min

- Adverse effects:
  - Tachycardia, headache, nausea, flushing

Labetalol: Profile

- $\alpha_1$- and $\beta_1$-receptor blocker
  - ↓ Peripheral vascular resistance ($\alpha_1$ blockade)
  - No reflex tachycardia ($\beta_1$ blockade)
  - Maintains coronary, cerebral, and renal blood flow

- Onset: 5-15 min

- Duration of action: 4-6 hours

- Adverse effects:
  - Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension

Nicardipine: Profile

• 2nd generation dihydropyridine calcium channel blocker
  – Coronary and cerebral arterial vasodilation
  – No negative inotropic or dromotropic effects
  – ↓Systemic vascular resistance

• Onset: 5-15 min

• Duration of action: 15-30 mins

• Adverse effects:
  – Tachycardia, headache, flushing, local phlebitis

BP reduction with IV nicardipine

SBP

Target SBP

MAP

Target MAP Range

DBP

Courtesy of WF Peacock, MD
# Nicardipine vs SNP for perioperative hypertension

N = 139 following cardiac or noncardiac surgery

<table>
<thead>
<tr>
<th></th>
<th>Time to response (min)</th>
<th># Dose changes</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cardiac patients</td>
<td>Noncardiac patients</td>
<td>Adverse events</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>14.1 ± 1*</td>
<td>1.5 ± 0.2†</td>
<td>1.6 ± 0.1‡</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>(n = 51)</td>
<td>(n = 18)</td>
<td>(n = 33)</td>
<td>(5/71)</td>
</tr>
<tr>
<td>SNP</td>
<td>30.4 ± 3.5</td>
<td>5.1 ± 1.4</td>
<td>4.6 ± 0.6</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>(n = 51)</td>
<td>(n = 15)</td>
<td>(n = 36)</td>
<td>(12/68)</td>
</tr>
</tbody>
</table>

*P = 0.0029 vs SNP, †P ≤ 0.05 vs SNP
‡Significant treatment differences in 2/5 centers (P < 0.05)

Fenoldopam vs SNP in acute hypertension: Similar hemodynamic effects

N = 153 evaluable patients; acute end-organ damage not a study requirement

*P < 0.05 FNP vs SNP

Fenoldopam vs dopamine: Similar effects on perioperative renal function

N = 80 cardiac surgery patients at high risk for perioperative renal dysfunction*

*Continuous Improvement in Cardiac Surgery Program score >10

Currently available parenteral antihypertensive treatments: Summary

• Many options are available, offering vasodilation via a number of different mechanisms
• All are associated with limitations
• Short-acting formulations with improved safety profile vs sodium nitroprusside and minimal effects on heart rate, CNS, contractility, and intracranial pressure are now available
Newer Parenteral Antihypertensive Treatment

Pharmacology
# Parenteral antihypertensive treatment

<table>
<thead>
<tr>
<th>Approved</th>
<th>Class</th>
<th>Investigational</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP</td>
<td>Vasodilator</td>
<td>Nesiritide</td>
<td>B-type natriuretic peptide</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β-blocker</td>
<td>Diazoxide*</td>
<td>K⁺ channel agonist</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>α-blocker</td>
<td>Torsemide*</td>
<td>Loop diuretic</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Vasodilator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenoldopam</td>
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<td>Hydralazine</td>
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<td></td>
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</tr>
<tr>
<td>Enalaprilat</td>
<td>ACEI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clevidipine</td>
<td>CCB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Limited data only

Calcium channel blockers in acute hypertension

1st generation: Nifedipine

2nd generation: Nicardipine

3rd generation: Clevidipine

Clevidipine: Pharmacokinetic overview

- Dihydropriyridine calcium channel blocker (CCB)
- $T_{1/2} \approx 1 \text{ min}$
- Selective arteriolar dilation
  - ↓ Systemic vascular resistance
  - ↓ Afterload
  - ↑ Stroke volume
  - ↑ Cardiac output
- No venous dilation
  - No effect on cardiac filling pressure
- No effect on HR

Clevidipine: Principles of use

- Clevidipine is indicated for the reduction of blood pressure when oral therapy is not feasible or not desirable
- Linear relationship between dosage and arterial blood concentrations
  - Relationship maintained for dose rates up to 7 nmol/kg per min
- Rapid clearance following infusion discontinuation
  - BP returns to baseline within 10 min

Nesiritide: Pharmacokinetic overview

- Recombinant B-type natriuretic peptide (BNP)
- Venous and arteriolar dilation
  - ↓ Preload
  - ↓ Afterload
  - ↑ Cardiac output
- No direct inotropic effects
- Approved only for treatment of acute decompensated heart failure

Hypertensive Urgencies/Emergencies: Guidelines
Hypertensive emergencies: JNC 7 consensus recommendations*

- Admit to ICU
- Administer short-acting parenteral antihypertensive with close monitoring
  - ↓BP by ≤25% within 1 hour
  - ↓BP to 160/100-110 mm Hg over next 2-6 hours
  - ↓BP to 130/85 mm Hg over next 24-48 hours

*Expert opinion

Hypertensive urgencies: JNC 7 consensus recommendations*

- Some patients may benefit from short-acting oral antihypertensive treatments
  - However, in one recent study, resting for 60 min was associated with ↓BP of >20% in 1/3 of patients
  - In addition, no evidence that failure to ↓BP in emergency department is associated with ↑short-term risk

- Adjust or reinstitute antihypertensive regimen to gradually ↓BP over next few days

*Expert opinion

# JNC 7: Treatment of acute hypertension in preeclampsia

Consider if childbirth is imminent

<table>
<thead>
<tr>
<th></th>
<th>Dosing</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>5 mg IV bolus, then 10 mg q20-30 min to max 25 mg; Repeat in several hr</td>
<td></td>
</tr>
<tr>
<td>Labetalol (second-line)</td>
<td>20 mg IV bolus, then 40 mg 10 min later, 80 mg q10 min for 2 additional doses to max 220 mg</td>
<td>Precipitous ↓BP when using with MgSO₄</td>
</tr>
<tr>
<td>Nifedipine (controversial)</td>
<td>10 mg po, repeat q20 min to max 30 mg</td>
<td>Cyanide poisoning may occur if used &gt;4 hr</td>
</tr>
<tr>
<td>SNP (rarely-when others fail)</td>
<td>0.25 µg/kg per min to max 5 µg/kg per min</td>
<td></td>
</tr>
</tbody>
</table>

BP management in acute aortic syndrome

Goal: Decrease aortic wall stress by rapidly ↓BP and ↓HR

IV β-blockers and SNP or oral ACEI
IV CCBs if β-blockers contraindicated

All patients should also be evaluated to determine if surgical management is necessary

AHA/ASA guideline: BP management in acute hemorrhagic stroke

SBP >200 mm Hg or MAP >150 mm Hg
• Consider aggressive ↓BP with continuous IV infusion
  – Monitor BP q5 min

SBP >180 mm Hg or MAP >130 mm Hg; ↑ICP evident or suspected
• Monitor ICP
  Administer intermittent or continuous IV antihypertensive treatment to keep cerebral perfusion pressure 60-80 mm Hg

SBP >180 mm Hg or MAP >130 mm Hg and no ↑ICP
• Administer intermittent or continuous IV antihypertensive treatment to achieve modest ↓BP (eg, target BP 160/90 mm Hg or MAP 110 mm Hg)
  – Reexamine patient q15 min

ICP = intracranial pressure

AHA/ASA guideline: BP management in acute ischemic stroke

Candidates for rtPA or other acute reperfusion intervention

- SBP >185 mm Hg or DBP >110 mm Hg

  - Nitropaste 1-2 in

  - Nicardipine infusion 5 mg/hr and uptitrate by 2.5 mg/hr q5-10 min
  - When desired BP attained, reduce to 3 mg/hr

- If BP not controlled, consider SNP

Labetalol 10-20 mg IV over 1-2 min
May repeat once

rtPA = recombinant tissue plasminogen activator

Hypertensive urgencies/emergencies: Issues

• Lack of consensus on defining emergencies and urgencies

• Clinical trial data lacking:
  – BP target
  – BP measure (SBP, DBP, MAP?)
  – Prevalence in disease states other than chronic hypertension

• Consensus that overly rapid ↓BP may result in cerebral/coronary/renal hypoperfusion
  – Patients have rightward shift of end-organ autoregulatory curve

Perioperative Hypertension: Guidelines
Perioperative hypertension: No consensus on degree of BP control

- No formal guidelines on definitions, treatment strategies, and BP goals
- General strategy is to maintain MAP ±20% of baseline
- Treatment threshold in clinical studies varies:
  - MAP: 90-110 mm Hg
  - SBP: 110-175 mm Hg
  - DBP: 95-110 mm Hg

Management of Hypertensive Emergencies
New paradigm in treatment of acute hypertension

Acute vascular injury has chronic sequelae

SBP too high
- Cardiac overload
- Vascular damage

SBP too low
- Thrombosis?
- Organ dysfunction

Prevention of exaggerated BP variation (too high/too low) is desirable

Courtesy of JL Izzo Jr, MD.
Hypertensive urgencies/emergencies: Issues

- Lack of consensus on defining emergencies and urgencies
- Consensus that overly rapid ↓BP may result in cerebral/coronary/renal hypoperfusion
  - Patients have rightward shift of end-organ autoregulatory curve
  - Clinical trial data lacking on how rapidly to ↓BP in various disease states

**VELOCITY: Study design**

Evaluation of the Effect of Ultrashort-Acting Clevidipine in the Treatment of Patients with Severe Hypertension

| Multicenter, open-label, uncontrolled  
| SBP target range prespecified by investigators |
| N = 126 with acute severe hypertension (BP >180/115 mm Hg) |
| Clevidipine infusion started at 2 mg/hr  
| Doubling every 3 min until SBP target range achieved |

**Primary efficacy measure:** % patients at SBP target range within 30 min  
**Primary safety measure:** % patients below SBP target range within 3 min

NIH. www.clinicaltrials.gov.  
VELOCITY: Clevidipine in acute hypertension

- 89% of patients reached SBP target range within 30 min
  - 10.9 min (median)

- 1.6% had SBP fall below target range within 3 min
  - Infusion continued in these patients without any adverse effects

- 91.3% successfully transitioned to oral therapy
  - Patients became eligible after 18 hours of IV therapy

PROACTION: Effects of Nesiritide on BP

Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially as Outpatients with Nesiritide, N = 237

Limited data on other parenteral antihypertensives for hypertensive emergencies

Diazoxide

• Oral formulation used to treat hyperinsulinemia-related hypoglycemia
• Mini-bolus formulation shown to be similar in efficacy to IV hydralazine; N = 124 pregnant women with acute hypertension

Torsemide

• Loop diuretic
• Similar efficacy as enalaprilat; N = 52 patients with severe hypertension + acute pulmonary edema

Follow-up care in hypertensive emergencies

- Goal: Transition to oral therapy as soon as patient can tolerate therapy
- Monitor carefully: Abrupt switch may result in ↑BP
- Most patients may be discharged on oral medication within 24-72 hours
- Clinical setting offers an opportunity to improve BP control and medication adherence

Vidt DG. In: Hypertension Primer. In press.
STAT Registry: Addressing knowledge gaps in contemporary acute hypertension

Studying the Treatment of Acute Hypertension

- Frequency
- Management with IV agents
- Patient characteristics
- Clinical outcomes
### STAT: Design

**Multicenter, US, hospital-based observational study**

- N ~ 2500 consecutive patients, BP >180/110 mm Hg* treated with IV antihypertensive agents in a critical care setting Jan-Dec 2007

**Main clinical outcomes measures:**
- In-hospital mortality, end-organ damage (stroke, encephalopathy, CHF, renal failure), 6-month survival

*or >140/90 mm Hg + subarachnoid hemorrhage
STAT: Exclusion criteria

• Severe, uncontrolled hypertension related to surgery
• Pregnant or post-partum (<1 month)
• IV antihypertensive treatment begun >24 hours following admission
• “Comfort measures only” orders
• Transfer from other hospital for reason other than acute hypertension
• IV antihypertensive treatment initiated off-site
STAT: Sources of antihypertensive management data

- **Survey** completed by pharmacy, emergency medicine, and intensive care medicine team members

- **Objectives:**
  - Characterize how IV antihypertensives are used
  - Describe variability in IV antihypertensive usage
    - 1\textsuperscript{st}/2\textsuperscript{nd} line agents
    - Dosage
    - Duration
    - Endpoints of therapy
  - Document incidence of adverse drug events

- **Case report form** will provide additional patient information on BP at specified intervals during IV administration and transition to oral therapy
ESCAPE: Design overview

Efficacy Study of Clevidipine Assessing its Pre/postoperative Antihypertensive Effect in Cardiac Surgery

ESCAPE-1
N = 105 with preoperative SBP ≥160 mm Hg

- Clevipidine*
- Placebo

ESCAPE-2
N = 110 with postoperative SBP >140 mm Hg

- Clevipidine*
- Placebo

Primary endpoint:
Incidence of bailout within 30 min

Secondary endpoints:
Time to ↓SBP ≥15%
ΔMAP from baseline
ΔHR from baseline
Incidence of bailout by causality

*0.4-8.0 µg/kg per min infusion

NIH. www.clinicaltrials.gov.
ESCAPE-1: Rapid control of preoperative SBP

Mean % change

Time (min)

## ESCAPE: Clevidipine superior to placebo

<table>
<thead>
<tr>
<th></th>
<th>ESCAPE-1</th>
<th>ESCAPE-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clevidipine</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Bailout (%)</strong></td>
<td>7.5*</td>
<td>82.7</td>
</tr>
<tr>
<td><strong>Median time to ↓SBP ≥15% (min)</strong></td>
<td>6</td>
<td>NE</td>
</tr>
<tr>
<td><strong>ΔMAP (%)</strong></td>
<td>-31.2</td>
<td>-11.2</td>
</tr>
</tbody>
</table>

*P = 0.0001 vs placebo

NE = not estimable


**ECLIPSE program: Overview**

Evaluation of Clevidipine in the Perioperative Treatment of Hypertension
Assessing Safety Events

Randomized Open-label
N = 1964 scheduled for cardiac surgery

- ECLIPSE-NTG
  - Nitroglycerin
  - Clevidipine*
- ECLIPSE-SNP
  - SNP
  - Clevidipine*
- ECLIPSE-NIC
  - Nicardipine

*2-16 mg/hr infusion

Primary efficacy endpoint: BP control within defined SBP ranges

Primary safety endpoints: All-cause death, MI, stroke, renal dysfunction

NIH. www.clinicaltrials.gov.
Aronson S. Presented at ACC. 2007.
ECLIPSE: Comparison of primary safety endpoints by treatment

<table>
<thead>
<tr>
<th>Event rate (%)</th>
<th>ECLIPSE-NTG</th>
<th>ECLIPSE-SNP</th>
<th>ECLIPSE-NIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clevidipine</td>
<td>SNP</td>
<td>Clevidipine</td>
</tr>
<tr>
<td>Death</td>
<td>2.8</td>
<td>3.4</td>
<td>1.7</td>
</tr>
<tr>
<td>MI</td>
<td>3.3</td>
<td>3.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.6</td>
<td>2.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>6.9</td>
<td>8.1</td>
<td>8.5</td>
</tr>
</tbody>
</table>

ECLIPSE: Combined effects on primary safety endpoints

Event rate (%)

- **Death**
  - Clevidipine: 3%
  - Comparators: 4%

- **MI**
  - Clevidipine: 2%
  - Comparators: 2%

- **Stroke**
  - Clevidipine: 1%
  - Comparators: 2%

- **Renal dysfunction**
  - Clevidipine: 8%
  - Comparators: 7%

BP control assessed via AUC analysis

Cumulative AUC calculated for excursions outside prespecified range.
Lower AUC = tighter BP control.

AUC = area under the curve

Time (hours)

ECLIPSE: Clevidipine vs comparators for perioperative BP control

AUC* (mm Hg x min/hr)

- NTG
- SNP
- NIC

Clevidipine
Comparator

P < 0.05

*Excursions outside SBP 85-145 mm Hg pre/postoperatively or 75-135 mm Hg intraoperatively

ECLIPSE: Relation of perioperative BP control to 30-day mortality

Odds ratios calculated for BP excursions of 1-5 mm Hg sustained for 60 min post hoc analysis

SBP above/below range* (x 60 min)

- 1 mm Hg
- 2 mm Hg
- 3 mm Hg
- 4 mm Hg
- 5 mm Hg

Unadjusted odds ratio (95% CI)

*SBP 85-145 mm Hg pre/postoperatively or 75-135 mm Hg intraoperatively

**ECLIPSE: Predictors of postoperative renal dysfunction**

N = 1512 undergoing cardiac surgery

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio (95% CI)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop serum Cr ≥1.2 mg/dL</td>
<td>4.71 (3.067-7.235)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race (African American)</td>
<td>2.166 (1.19-3.943)</td>
<td>0.0114</td>
</tr>
<tr>
<td>Primary CABG + valve</td>
<td>1.957 (1.158-3.307)</td>
<td>0.0122</td>
</tr>
<tr>
<td>BP (4th quartile AUC*)</td>
<td>1.725 (1.111-2.68)</td>
<td>0.0152</td>
</tr>
<tr>
<td>Surgery duration (hours)</td>
<td>1.263 (1.054-1.515)</td>
<td>0.0116</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.037 (1.013-1.062)</td>
<td>0.0023</td>
</tr>
<tr>
<td>BMI</td>
<td>1.05 (1.016-1.086)</td>
<td>0.0042</td>
</tr>
</tbody>
</table>

‡ Unadjusted

*Excursions outside SBP 85-145 mm Hg pre/postoperatively or 75-135 mm Hg intraoperatively

ECLIPSE: Overview of perioperative BP control

- Excursions outside a targeted BP range are correlated with 30-day mortality
- Relationship is direct and proportionate to the magnitude of excursions
- Data suggest that great attention should be given to precise perioperative BP control
- Future analysis of this finding is warranted

Summary: Acute hypertension

Nonsurgical patients

• Little studied in past decade

• Multiple knowledge gaps
  – Patient characteristics
  – Treatment patterns
  – Outcomes

Perioperative patients

• Frequent finding

• Emerging data demonstrate importance of tighter BP control than currently recommended