Antihypertensives in stroke: Hyper-acute, acute & sub-acute (maintenance) therapies ....

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Blood pressure control and stroke ....
Context for today: Blood Pressure & Stroke....

**Cause** & **Effect**

Hypertension &/or Hypotension

Stroke 1° or 2°

worse clinical outcomes
BP in acute stroke....

Associated with ADVERSE/WORSE clinical outcomes:

- poor functional outcome
- early neurological deterioration
- recurrent stroke
- death

• extremes of BP (both very HIGH and LOW systolic BP)
  - both independently associated with ↑ early death, late death, dependency
  - HIGH BP → ↑ risk of early stroke recurrence
  - LOW BP → much less common, but also poor outcomes

• fluctuating BPs (in ALL stroke types)
Blood pressure (BP) in acute stroke:

- **variable, fluctuating, unpredictable**, especially in first 24-48 hours

  $\uparrow$ BP in $\geq 75\text{-}80\%$ of pts

  **but**

  spontaneously $\downarrow$ in $\sim 2/3$ pts within first 7 days

**Due to:**

- PRE-stroke ‘triggers’ (BP and stroke precipitants)
- POST-stroke: loss of normal cerebral auto-regulation of BP

- WITH observed $\uparrow$ in other related haemodynamic variables:
  - peak SBP
  - SBP variability
  - mean arterial pressure (MAP)
  - pulse pressure
BP in acute stroke....

BUT ......!!

• modulation of BP (decreasing or increasing BP) is controversial
• debate ongoing for both major stroke types

• significant risks in treating BP
• significant risks in NOT treating BP

AND → worsening parameters further worsen cerebral auto-regulation of BP!

<table>
<thead>
<tr>
<th>Ischaemic Stroke (IS)</th>
<th>Intracerebral Haemorrhage (ICH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ BP (HYPO-perfusion)</td>
<td>• Increased cerebral infarction</td>
</tr>
<tr>
<td></td>
<td>• Peri-haematomatal ischaemia</td>
</tr>
<tr>
<td>↑ BP (HYPER-perfusion)</td>
<td>• Cerebral oedema</td>
</tr>
<tr>
<td></td>
<td>• Haemorrhagic transformation</td>
</tr>
<tr>
<td></td>
<td>• Haematoma expansion</td>
</tr>
</tbody>
</table>
So, how do we approach BP management in acute stroke?

Discussion around use of antihypertensives in stroke:

- BP lowering across the stroke continuum
- Current Australian guideline recommendations
- Key pharmacotherapies to lower BP – options & considerations
Managing BP across the stroke continuum...
Managing BP across the stroke continuum….

<table>
<thead>
<tr>
<th>Pre-stroke</th>
<th>Stroke</th>
<th>Post-stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>3 broad phases plus sub-phases</strong></td>
<td></td>
</tr>
</tbody>
</table>

**NB/**

- each phase managed as a separate entity:
  - “hypo” and “hyper” HTN viewed differently across phases → different risks
  - different BP targets (sometimes arbitrary!)
  - level of evidence differs across each phase
  - no consistency in terms of anti-hypertensive agents used

→ lots of uncertainty
## Managing HTN across the stroke continuum

<table>
<thead>
<tr>
<th>Pre-stroke</th>
<th>Stroke</th>
<th>Post-stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic HTN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Untreated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(undiagnosed, suboptimal care, non-adherence)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Treated but high/labile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(resistant HTN, non-adherence)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Treated &amp; controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(other risk factors for stroke)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute HTN triggers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• arrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• emotional stress</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1° and 2° stroke prevention
Pre-stroke BP management....

Stringent (low) BP targets based on:
- overall CVD risk
- specific risk factors

---

**Guideline for the diagnosis and management of hypertension in adults 2016**

Recommendations for treatment strategies and treatment targets for patients with hypertension

<table>
<thead>
<tr>
<th>Recommendations for treatment strategies and treatment targets for patients with hypertension</th>
<th>Grade of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Lifestyle advice is recommended for all patients.</td>
<td>Strong</td>
<td></td>
</tr>
<tr>
<td>b. For patients at low absolute CVD risk (&lt;10% 5-year risk) with persistent blood pressure ≥160/100 mmHg antihypertensive therapy should be started.</td>
<td>Strong</td>
<td>I</td>
</tr>
<tr>
<td>c. For patients at moderate absolute CVD risk (10–15% 5-year risk) with persistent blood pressure ≥140 mmHg and/or ≥90 mmHg antihypertensive therapy should be started.</td>
<td>Strong</td>
<td>I</td>
</tr>
<tr>
<td>d. Once decided to treat, patients with uncomplicated hypertension should be treated to a target of &lt;140/90 mmHg or lower if tolerated.</td>
<td>Strong</td>
<td>I</td>
</tr>
<tr>
<td>e. In selected high cardiovascular risk populations where a more intense treatment can be considered, aiming to a target of &lt;120 mmHg systolic blood pressure can improve cardiovascular outcomes.</td>
<td>Strong</td>
<td>II</td>
</tr>
<tr>
<td>f. In selected high cardiovascular risk populations where a treatment is being targeted to &lt;120 mmHg systolic, close follow-up of patients is recommended to identify treatment related adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury.</td>
<td>Strong</td>
<td>II</td>
</tr>
</tbody>
</table>
Pharmacotherapy choice based on:

- evidence (lots!)
- comorbidities (including contraindications)
Managing HTN across the stroke continuum....

<table>
<thead>
<tr>
<th>Pre-stroke</th>
<th>Stroke</th>
<th>Post-stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyper-acute</strong></td>
<td><strong>Acute</strong></td>
<td><strong>Sub-acute</strong></td>
</tr>
<tr>
<td>(Time: 0 → 24hs, esp first 6hs)</td>
<td>(Time: 24hs → 7 days)</td>
<td>(Time: → to hospital discharge/30 days)</td>
</tr>
</tbody>
</table>
Managing HTN across the stroke continuum….

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<thead>
<tr>
<th>Pre-stroke</th>
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<th>Post-stroke</th>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

New HTN
- Treat to target BP
- Risk vs benefit
- Polypharmacy indicated

Chronic HTN

→ all dependent on comorbidities
Post-stroke BP management....

(Australian) Clinical Guidelines for Stroke Management 2017
Chapter 4 of 8: Secondary prevention

Long term blood pressure management

- All stroke and TIA patients, with a clinic blood pressure of >140/90mmHg should have long term blood pressure lowering therapy initiated or intensified. (SPS3 2013 [44]; Thomopoulos et al 2016 [49]; Ettehad et al 2016 [50]; Lahkan and Sapko 2009 [45])

- Blood pressure lowering therapy should be initiated or intensified before discharge for those with stroke or TIA, or soon after TIA if the patient is not admitted. (SPS3 2013 [44]; Thomopoulos et al 2016 [49]; Ettehad et al 2016 [50]; Lahkan and Sapko 2009 [45])

- Any of the following drug classes are acceptable as blood pressure lowering therapy; angiotensin-converting-enzyme inhibitor, angiotensin II receptor antagonists, calcium channel blocker, thiazide diuretics. **Beta-blockers should not be used as first-line agents unless the patient has ischaemic heart disease.** (Lakhan and Sapko 2009 [45]; Mukete et al 2015 [52])
Post-stroke BP management....

https://app.magicapp.org/app#/guideline/2437/section/29697

PRE & POST stroke approaches are similar, NOTING:

• treat all persistent ↑BP → intensification of Rx → low BP targets
• use polypharmacy where appropriate to reach target
• large choice of agents (evidence-based) .... β-blockers last line
Pre and post-stroke BP management....

..... AND support adherence to long-term therapy

6 Adherence to pharmacotherapy

**Weak recommendation**

Benefits outweigh harms for the majority, but not for everyone. The majority of patients would likely want this option.

Interventions to promote adherence with medication regimens may be provided to all stroke survivors. Such regimens may include combinations of the following:

- reminders, self-monitoring, reinforcement, counselling, motivational interviewing, family therapy, telephone follow-up, supportive care and dose administration aids (Lawrence et al 2015 [27]; Mahtani et al 2011; Nieuwlaat et al 2014 [33]; Haynes et al 2008 [32])
- development of self-management skills and modification of dysfunctional beliefs about medication (O'Carroll et al 2014 [29]; Kronish et al 2014 [28])
- information and education in hospital and in the community (Lawrence et al 2011 [35]; Nieuwlaat et al 2014 [33]).
Managing HTN across the stroke continuum....

<table>
<thead>
<tr>
<th>Pre-stroke</th>
<th>Stroke</th>
<th>Post-stroke</th>
</tr>
</thead>
</table>
| **Hyper-acute**
  (Time: 0 → 24hs, esp first 6hs) | **Acute**
  (Time: 24hs → 7 days) | **Sub-acute**
  (Time: → to hospital discharge/30 days) |

Most critical phase including for BP management:
- time-sensitive
- assessment, stabilisation, Tx in first hours after stroke onset
- when most BP fluctuations AND extremes of BP
  → approach different to PRE / POST stroke phases
BP in HYPER-acute stroke....

Causes / triggers of extreme and fluctuating acute BP response:

↑ BP:
- pre-existing hypertension
- activation of cortisol, natriuretic peptide, renin–angiotensin-aldosterone (RAAS) and sympathetic neuroendocrine systems
- impaired cardiac baroreceptor sensitivity
- raised intracranial pressure (Cushing’s reflex)
- stress related to hospitalisation
- infection
- pain, e.g., urinary retention

↓ BP:
- hypovolaemia
- heart failure and ischaemia
- cardiac arrhythmias
- aortic dissection
- sepsis

Multiple factors present concurrently
All affect BP regulation →
Blood pressure (BP) regulation.... physiology

Blood Pressure (BP) [mmHg] = Cardiac Output (CO) [L/min] x Peripheral (systemic vascular) resistance (R)

- Stroke Volume (SV) x Heart Rate (HR)
- ↑ Plasma (fluid) Volume

So, how to manage BP in acute stroke with so many influencing and unpredictable factors? → cautiously & conservatively! (unlike PRE/POST stroke)
Acute ISCHAEMIC STROKE (IS) ....

<table>
<thead>
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<th>Post-stroke</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hyper-acute

- BP >220/120 mmHg
  - Initiate specific Rx for BP CAUTIOUSLY

- BP >185/110 mmHg
  - IF tPA, initiate specific Rx for BP

- BP >180/110 mmHg
  - Can withhold usual BP Rx
  - Monitor BP

- BP >160/100 mmHg
  - Allow BP to stabilise
  - Treat PRN comorbidities/triggers/stroke complications

Acute

- BP >220/120 mmHg
  - Initiate PRN standard oral Rx for BP

- BP >185/110 mmHg
  - Cont. oral Rx for BP

Sub-acute

- BP >180/110 mmHg
  - Restart usual Rx for BP

- BP >160/100 mmHg
  - Initiate standard OR
  - Restart usual Rx for BP

Treat PRN comorbidities/triggers/stroke complications
Intracerebral Haemorrhage (ICH) ....

Pre-stroke | Stroke | Post-stroke

Hyper-acute | Acute | Sub-acute

Within 6 hs of onset:

SBP >150 mmHg

Initiate specific Rx for RAPID BP reduction

Cont. Rx for BP for >7 days

Initiate standard OR Restart usual Rx for BP

In ICH: SBP reduction is well tolerated and associated with attenuation of hematoma expansion

In SAH: “BP management in SAH remains woefully understudied”
No definitive BP management strategies in acute SAH, but generally:
- hypertension should likely be avoided before an aneurysm is secured
- hypotension should be avoided altogether
BP in acute stroke....

Guidelines informed by evidence to date that in:

**Hyperacute setting of both ischaemic and haemorrhagic stroke:**
Initiation of cont. IV administration of newer agents *may* achieve treatment goals

**Acute IS:**
When *thrombolysis is not an option*, acute management of BP is a balancing act between maintaining cerebral perfusion and avoiding systemic adverse events due to persistently elevated BP

Increasing trial evidence suggests BP lowering is safer than thought in IS

In the subacute setting of IS, there may not be a need to rapidly bring BP down to the targeted secondary stroke prevention range

**ICH:**
Rapidly lowering BP to <140/90 mm Hg is safe and may be associated with improved radiographic and clinical outcomes

BP lowering is recommended in acute ICH
Factors influencing response to BP Tx....

- most information for acute ischaemic stroke
- factors influencing outcomes from BP Rx:

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Treatment factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient population</td>
<td>• Time to treatment</td>
</tr>
<tr>
<td>• History of hypertension</td>
<td>• Intensity of BP lowering</td>
</tr>
<tr>
<td>• Initial BP</td>
<td>• Agents used</td>
</tr>
<tr>
<td>• Stroke severity</td>
<td>• Route of administration</td>
</tr>
</tbody>
</table>
1. Time to treatment ....

- If elect to treat high BP, start EARLY! (hyperacute phase)
  - “the earlier the better” → better outcomes
  - rough guide:

<table>
<thead>
<tr>
<th>Better outcomes</th>
<th>No effect</th>
<th>Worse outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\downarrow) BP &lt; 12 hours</td>
<td>(\downarrow) BP 12 – 24 hours</td>
<td>(\downarrow) BP &gt; 24 hours</td>
</tr>
</tbody>
</table>

NB/
- time periods vary between agents (clinical trial data)
- time to start Rx vs time to \(\downarrow\)BP ? (lag times?)
2. Intensity of treatment....

<table>
<thead>
<tr>
<th>How fast should BP be lowered?</th>
<th>SLOW</th>
<th>GRADUAL</th>
<th>FAST/RAPID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>?</td>
<td>✓ beneficial</td>
<td>✓ beneficial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How much should be BP lowered? (within 24h period)</th>
<th>A LITTLE (5-10%) (Small decrease using low dose Rx)</th>
<th>MODERATE</th>
<th>A LOT (&gt;20%) (Large decrease using high dose Rx)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>? / ✓ beneficial</td>
<td>✓ beneficial</td>
<td>x dangerous</td>
</tr>
</tbody>
</table>

Ischaemic stroke trials:

- **moderate** reduction of BP *seems* to be safe and protective
- rapid reduction of BP does not *seem* to be dangerous as long as reduction is moderate
- **AVOID**: large and fast ↓ in BP
SO, what are the exact thresholds for treatment?

• Unclear! Targets are somewhat arbitrary (limited evidence)

Currently:

• **IS:**
  • extremes of systolic BP have a negative impact on patients outcomes BUT thresholds for treatment unclear

• **ICH:**
  • rapid and large reduction in ICH may be tolerated BUT impact on outcomes unknown

• **SAH:**
  • lowering systolic BP <160mmHg may ↓ risk of aneurysmal re-bleed
2. Intensity of treatment....

Clinical Guidelines for Stroke Management 2017
Chapter 4 of 8: Secondary prevention

Practice statement

Consensus-based recommendations
- All acute stroke patients should have their blood pressure closely monitored in the first 48 hours after stroke onset.

Weak recommendation
Pre-existing antihypertensive medication may be withheld until patients are neurologically stable and treatment can be given safely. (Bath and Krishnan 2014 [116])

11 Acute blood pressure lowering therapy

Weak recommendation AGAINST
Intensive blood pressure lowering in the acute phase of care to a target SBP of < 140 mmHg is not recommended for any patient with stroke. (Bath and Krishnan 2014 [116])

https://app.magicapp.org/app#/guideline/2437/section/29697
2. Intensity of treatment....

Clinical Guidelines for Stroke Management 2017
Chapter 4 of 8: Secondary prevention

For acute ISCHAEMIC STROKE:

- Patients with acute ischaemic stroke eligible for treatment with intravenous thrombolysis should have their blood pressure reduced to below 185/110 mmHg before treatment and in the first 24 hours after treatment.
- Patients with acute ischaemic stroke with blood pressure > 220/120 mmHg should have their blood pressure cautiously reduced (e.g. by no more than 20%) over the first 24 hours.

https://app.magicapp.org/app#/guideline/2437/section/29697
For INTRACEREBRAL HAEMORRHAGE:

Weak recommendation

In patients with intracerebral haemorrhage, blood pressure may be acutely reduced to a target systolic blood pressure of around 140 mmHg (but not substantially below) (Tsivgoulis et al. 2014 [119]; Qureshi et al. 2016 [117])
3. Agents used to lower BP....

- Which agent/s should be used?

- **no definitive answers yet!**
  
  - lack of trials
  - no direct comparisons
  - mixed findings
  - unclear findings:

  eg
  
  Nimodipine data: ORAL $+ve$ effect but IV $-ve$

  ACE drugs: lisinopril $+ve$ effect but candersartan $-ve$
Pharmacotherapeutic options .....
3. Agents used to lower BP....

Preferred pharmacological agent for lowering BP in acute stroke:

**Pharmacodynamics:**
- lower BP **without**:
  - impairing cerebral autoregulation
  - increasing ICP
  - decreasing cerebral perfusion
- acceptable safety profile

**Pharmacokinetics:**
- reliable dose-response profile (predictable effect in most patients)
- rapid-acting (fast onset) AND short-acting (fast offset)
- easy to titrate

**Pharmaceutics (formulation):**
- administered via IV infusion (easier to manipulate dosing; NBM)
RECALL:
Blood pressure (BP) regulation.... physiology

Blood Pressure (BP) [mmHg] = Cardiac Output (CO) [L/min] \times \frac{\text{Peripheral (systemic vascular) resistance (R)}}{\text{Stroke Volume (SV)} \times \text{Heart Rate (HR)}} \uparrow\text{Plasma (fluid) Volume}
Blood pressure (BP).... pharmacological targets

Blood Pressure (BP) [mmHg] = Cardiac Output (CO) [L/min] \times \text{Peripheral (systemic vascular) resistance (R)}

\text{Stroke Volume (SV)} \times \text{Heart Rate (HR)}

\text{Plasma (fluid) Volume} \rightarrow \text{Renin} \rightarrow \text{Angiotensin II} \rightarrow \text{Aldosterone}

\text{AT1 / AT2 receptors}

\text{ADRENERGIC SYSTEM}

\text{Sympathetic activation (noradrenaline)}

\beta_1 \text{ receptors} \quad \alpha_1 \text{ receptors}

\alpha_2 \text{ receptors} \quad \beta_2 \text{ receptors}

\text{Ca}^{2+} \text{ channels} \quad \text{nitrous oxide}

\text{RAAS SYSTEM}

\text{AT1 / AT2 receptors}
Selected Medications and the Blood Pressure Equation\textsuperscript{3,5}

\[ BP = CO \times SVR \]

- **BP**: Blood Pressure
- **CO**: Cardiac Output
- **SVR**: Systemic Vascular Resistance
- **SV**: Stroke Volume
- **HR**: Heart Rate

Medications:
- Esmolol\textsuperscript{6-9}
- Nicardipine
- Clevidipine\textsuperscript{10,11}
- Nitroprusside\textsuperscript{12-14}
- Labetalol\textsuperscript{16-20}
- Nitroglycerin\textsuperscript{15-17}
Beta-adrenergic antagonists (ie β-blockers)....
<table>
<thead>
<tr>
<th>Beta-blocker Class</th>
<th>Selectivity</th>
<th>Effects</th>
<th>Agents</th>
<th>ISA (intrinsic sympathetic activity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Generation</td>
<td>Non-selective ($\beta_1 &amp; \beta_2$)</td>
<td>Nadolol, Oxprenolol, Pindolol, Propranolol, Timolol, Sotalol</td>
<td>*** (lipid soluble)</td>
<td></td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Generation</td>
<td>$\beta_1$ selective</td>
<td>Acebutolol, Atenolol, Bisoprolol, Esmolol, Metoprolol</td>
<td>* (lipid soluble)</td>
<td>(lipid soluble)</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Generation</td>
<td>Non-selective ($\beta_1 &amp; \beta_2$)</td>
<td>Carteolol</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-selective ($\beta_1, \beta_2$ and $\alpha$-blockade)</td>
<td>Carvedilol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\beta_1$ selective</td>
<td>Betaxolol, Nebivolol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recall Pre/POST stroke BB recommendations re beta-blockers...
<table>
<thead>
<tr>
<th></th>
<th>Esmolol</th>
<th>Labetalol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administration</strong></td>
<td>Bolus + Continuous infusion</td>
<td>Bolus Continuous infusion</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Rapid (60 seconds)</td>
<td>Intermediate (peak 5-15 min)</td>
</tr>
<tr>
<td><strong>Offset</strong> (Duration of action)</td>
<td>Rapid (10-20 min)</td>
<td>Slower (2-4 h)</td>
</tr>
<tr>
<td><strong>Heart Rate</strong></td>
<td>Decreased</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>SVR</strong></td>
<td>0</td>
<td>Decreased</td>
</tr>
<tr>
<td><strong>Cardiac output</strong></td>
<td>Decreased</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Myocardial O₂ balance</strong></td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Sinus bradycardia Heart block &gt;1° Overt heart failure Cardiogenic shock</td>
<td>Severe bradycardia Heart block &gt;1° Overt heart failure Cardiogenic shock</td>
</tr>
</tbody>
</table>

- β<sub>1</sub> selective
- Non-selective β<sub>1</sub>, β<sub>2</sub> and α-blockade & vasodilatory
Calcium (Ca$^{2+}$) channel blockers (ie CCBs)....
- Act on vascular smooth muscle
- ↓ SVR (potent)
- ↓ inotropy
- ↓ chronotropy
- ↓ dromotropy

Clevidipine

- Act on heart muscle
- ↓ SVR (modest)
- ↓ inotropy
- ↓ chronotropy
- ↓ dromotropy
<table>
<thead>
<tr>
<th>CCBs</th>
<th>Nicardipine</th>
<th>Clevidipine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dihydropyridine CCB (2(^{\text{nd}}) gen)</td>
<td>Dihydropyridine CCB (4(^{\text{th}}) gen)</td>
</tr>
<tr>
<td>Potent cerebral &amp; coronary vasodilation: ↓BP with ↑cerebral perfusion pressure</td>
<td>Direct / selective arterial vasodilation (↓SVR) but with no venous dilation (no impact on cardiac filling pressure, no effect on HR); ↑SV &amp; ↑CO</td>
<td></td>
</tr>
<tr>
<td>Onset of action</td>
<td>5 - 10 minutes (slow onset)</td>
<td>&lt; 5 minutes</td>
</tr>
<tr>
<td>Half-life (t(\frac{1}{2}))</td>
<td>&gt;2 hours (slow offset)</td>
<td>1 minute (ultra-short)</td>
</tr>
<tr>
<td>Administered</td>
<td>IV Initiate: 5mg/hour Titrate: by 2.5mg/hour every 5-15 minutes (max 15mg/hour)</td>
<td>IV Initiate: 1-2 mg/hour (titrated every 60-90 seconds to about 4-6mg/hour)</td>
</tr>
</tbody>
</table>
Nitro-vasodilators ......
<table>
<thead>
<tr>
<th>Direct vasodilators</th>
<th>Glyceryl Trinitrate (GTN) (aka ‘nitroglycerin’)</th>
<th>Sodium Nitroprusside (SNP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of dilatation</strong></td>
<td>“venodilators”</td>
<td>“mixed dilators”</td>
</tr>
<tr>
<td>venous dilation → may ↓CO</td>
<td>arterial &amp; venous dilatation</td>
<td></td>
</tr>
<tr>
<td><strong>Effect on CBF/ICP unclear</strong></td>
<td>May ↑ICP</td>
<td></td>
</tr>
<tr>
<td>NB/ tolerance (tachyphylaxis) may develop with prolonged use</td>
<td>NB/ cyanide (thiocyanate) toxicity after 48 hours</td>
<td></td>
</tr>
<tr>
<td>Titration required but easier</td>
<td>Titration extremely difficult</td>
<td></td>
</tr>
<tr>
<td>“coronary steal” (non-selective coronary vasodilation)</td>
<td></td>
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</tbody>
</table>

NB/ Direct arteriolar or venous vasodilators:
→ vasodilation can ↑cerebral blood volume, ↑ICP
→ systemic salt and water retention due to peripheral vasodilatation → ↑cerebral oedema

**1-Arterio-dilators:** e.g. nifedipine, hydralazine, minoxidil, diazoxide.
Currently preferred agents ....

**AVOID if possible:**
- Nitroprusside
- GTN/nitroglycerin
- standard Ca blockers
- Hydralazine
- standard α & β-blockers
- ACE Inhibitors

  Direct acting cerebral vasodilators → impair auto-regulation, increase ICP, decrease CBF

  Have little effect on resting blood flow and shift the autoregulatory curve downward

**PREFERRED agents:**
- Labetalol
- Esmolol

  Do not act directly on cerebral blood vessels, do not adversely affect cerebral autoregulation nor do they increase ICP

- Clevidipine
- Nicardipine

  May have neuroprotective effect.

  NB/ CCB are direct acting vasodilators and may ↑ CBF and ICP
Key messages....

- BP control in acute stroke is challenging (vs PRE/POST stroke care)

- *Some guidance* regarding a relatively cautious approach:
  - thresholds for initiating acute Rx
  - intensity of acute Rx

- **Specific agents indicated for acute Rx**

- Much more evidence needed to inform practice

- Individualised approach

**Hypertensive Emergency Treatment**

*Disease-specific Recommendations*

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Preferred Agent</th>
<th>Goal</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ischemic stroke</td>
<td>Nicardipine, labetalol</td>
<td>Treat when &gt; 220/120 except w/thrombolitics &gt; 185/110</td>
<td>Excessive BP decrease may worsen ischemia</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>Nicardipine, labetalol, esmolol</td>
<td>Treat to target l</td>
<td>Precipitous BP fall may increase mortality</td>
</tr>
<tr>
<td>SAH</td>
<td>Nicardipine, labetalol, esmolol</td>
<td>SBP &lt; 160</td>
<td>Keep SBP &gt; 120 to maintain CPP</td>
</tr>
</tbody>
</table>
Thankyou ..... 

Any questions? 

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