Hypotensive susceptibility and antihypertensive drugs

Diana Solari
Santa Margherita Ligure, 7 aprile 2016
• Many elderly patients with recurrent syncope take one or more hypotensive drugs for associated conditions.

• It is generally believed that vasoactive drugs may have a role in causing vasodepressor reflex syncope

   but

• in literature there are very few data about the relationship between hypotensive syncope and antihypertensive drugs

   and

• current guidelines do not mention how to manage patients with recurrent hypotensive syncope who are taking vasoactive drugs.
Withdrawal of vasodilator therapy → significant decrease in the risk of falls in patients with TTT negativization

Withdrawal of psychotropic medications → significant reduction in the risk of falls

Withdrawal of vasodilator therapy → significant reduction in the magnitude of the vasodepressor reflex induced by CSM

Reduction/suspension of vasoactive therapy → reduction in the burden of syncope in pts with CSS
SPRINT: Systolic Blood Pressure Intervention Trial

9361 pts at high cardiovascular risk using antihypertensive drugs targeting a systolic BP of 120 mmHg versus 140 mmHg:

→ increased risk of syncope and hypotension

Table 3. Serious Adverse Events, Conditions of Interest, and Monitored Clinical Events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Treatment (N=4678)</th>
<th>Standard Treatment (N=4683)</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department visit or serious adverse event</td>
<td>158 (3.4)</td>
<td>93 (2.0)</td>
<td>1.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypotension</td>
<td>163 (3.5)</td>
<td>113 (2.4)</td>
<td>1.44</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Systematic review of studies evaluating the relationship between antihypertensive medications with falls and OH (15 studies):

→ contrasting and non conclusive data

“...The prescription of antihypertensive therapy among the elderly remains a long-standing controversy in geriatric medicine due to ongoing concerns about potential complications such as falls, despite conclusive evidence supporting the treatment of hypertension even among the very elderly...”
STOP-VD
Stop vasodepressor drugs in reflex syncope
A randomized controlled trial

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From the Syncope Units of:
Ospedali del Tigullio, Lavagna  
University of Firenze  
Ospedale Generale, Bolzano  
Ospedale Villa Scassi, Genova

A trial sponsored by GIMSI
AIM OF THE STUDY

Randomized, parallel, prospective, safety/efficacy study conducted from January 2014 to December 2015 in 4 general hospitals (Lavagna, Genova, Firenze, Bolzano)

→ to investigate the clinical effects of discontinuation of vasoactive drugs in patients affected by vasodepressor reflex syncope

END-POINT:
recurrence of
- syncope
- pre-syncope
- adverse events: stroke, TIA, worsening HF, AMI
PATIENTS AND METHODS

INCLUSION CRITERIA:

• ≥2 episodes of reflex syncope during the previous year
• 1 or more vasoactive drug (antihypertensive agents, nitrates, diuretics, neuroleptic antidepressants or L-dopa antagonists)

positivity of TILT TABLE TEST and/or CSM for a VD FORM

EXCLUSION CRITERIA:

• orthostatic hypotension
• severe hypertension (office BP >150/95) poorly controlled with ongoing therapies
• severe structural heart disease
• previous transient cerebral ischemic attack or stroke.
STUDY DESIGN

ENROLMENT

- History, physical examination, ECG and supine/standing BP
  - SSS-OI questionnaire
  - Tilt table test and CSM
  - 24 hours BP continuous monitoring

RANDOMIZATION

STOP/REDUCE VASOACTIVE THERAPY

CONTINUE VASOACTIVE THERAPY

THERAPY OPTIMIZATION

- Daily BP diary
- Weekly phone contact

- supine/standing BP
- SSS-OI questionnaire

1° MONTH VISIT

- supine/standing BP
- SSS-OI questionnaire

FOLLOW UP

Every 6 months until end point occurrence

Every 6 months until end point occurrence
STUDY DESIGN: SSS-OI QUESTIONNAIRE

Specific Symptom Score - Orthostatic Intolerance
→ evaluation of QoL

- Dizziness and presyncope
- Visual disturbances
- Syncope
- Hearing disturbances
- Pain in the neck, low back pain, precordial pain
- Weakness, fatigue, lethargy
- Palpitations, hyperhidrosis

Score between 0 to 10 for each item during the last month.

SCREENING FLOW

INCLUSION/EXCLUSION CRITERIA

328 Assessed for Eligibility *
   - 90 Excluded: no vasoactive therapy
   - 238 on ≥1 Vasoactive Drug
      - 157 Excluded: No M or VD tilt test or VD-CSS
      - 81 M or VD Tilt Test or VD-CSS
         - 23 Excluded: refused randomization or follow-up impossible

58 Randomized

32 Assigned to Stop/reduce Vasoactive Drugs
   - 1 Lost to Follow-up (personal reason)
      - 31 Included in Analysis

26 Assigned to Continue Vasoactive Drugs
   - 2 Lost to Follow-up (personal reason)
      - 24 Included in Analysis
### BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Stop/reduce therapy (n=31)</th>
<th>Continue therapy (n=24)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>75±12</td>
<td>73±11</td>
<td>0.54</td>
</tr>
<tr>
<td>Male sex</td>
<td>18 (58%)</td>
<td>10 (42%)</td>
<td>0.28</td>
</tr>
<tr>
<td>History of arterial hypertension</td>
<td>29 (94%)</td>
<td>23 (96%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>9 (29%)</td>
<td>5 (21%)</td>
<td>0.55</td>
</tr>
<tr>
<td>- ischaemic</td>
<td>5 (16%)</td>
<td>3 (12%)</td>
<td>1.00</td>
</tr>
<tr>
<td>- non ischaemic</td>
<td>4 (13%)</td>
<td>2 (9%)</td>
<td>0.69</td>
</tr>
<tr>
<td>ECG abnormalities</td>
<td>11 (35%)</td>
<td>7 (29%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Echocardiographic abnormalities</td>
<td>6 (19%)</td>
<td>5 (21%)</td>
<td>1.00</td>
</tr>
<tr>
<td>History of atrial tachyarrhythmias</td>
<td>1 (3%)</td>
<td>2 (8%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Neurological diseases (Parkinson, encephalopathy)</td>
<td>2 (6%)</td>
<td>3 (12%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>3 (10%)</td>
<td>3 (12%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>History of syncope</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median lifetime number of syncoposes</td>
<td>3.0 (2.0 - 4.0)</td>
<td>3.0 (2.0 - 5.0)</td>
<td>0.77</td>
</tr>
<tr>
<td>Median number of syncopones in the last year</td>
<td>2.0 (1.3 - 3.0)</td>
<td>2.0 (1.8 - 3.0)</td>
<td>0.99</td>
</tr>
<tr>
<td>No. of patients with history of syncope &gt;1 year</td>
<td>15 (48%)</td>
<td>14 (58%)</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>SSS-Ol questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score (score 0-70)</td>
<td>21±11</td>
<td>25±11</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of vasoactive drugs per patient</td>
<td>2.4±1.1</td>
<td>2.5±0.9</td>
<td>0.77</td>
</tr>
</tbody>
</table>
## BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Stop/reduce therapy (n=31)</th>
<th>Continue therapy (n=24)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Office arterial blood pressure</strong>, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine SBP</td>
<td>127±16</td>
<td>122±12</td>
<td>0.19</td>
</tr>
<tr>
<td>Standing SBP</td>
<td>119±17</td>
<td>118±14</td>
<td>0.81</td>
</tr>
<tr>
<td>Median orthostatic SBP decrease per patient</td>
<td>10 (5 - 15)</td>
<td>5 (2.3 - 10)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>24-hour ambulatory blood pressure monitoring (ABPM)</strong>, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean SBP</td>
<td>120±14</td>
<td>120±11</td>
<td>1.00</td>
</tr>
<tr>
<td>day-time mean SBP</td>
<td>122±12</td>
<td>122±11</td>
<td>1.00</td>
</tr>
<tr>
<td>night-time mean SBP</td>
<td>115±14</td>
<td>117±13</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Tilt table test</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive response</td>
<td>31 (100%)</td>
<td>23 (96%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Mixed response</td>
<td>9 (29%)</td>
<td>8 (33%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Vasodepressor response</td>
<td>22 (71%)</td>
<td>15 (62%)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Carotid sinus massage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive vasodepressor response</td>
<td>2 (6%)</td>
<td>2 (8%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
1-MONTH RESULTS: OFFICE SBP (SUPINE AND STANDING)

<table>
<thead>
<tr>
<th>SBP mmHg</th>
<th>Enrolment</th>
<th>Month 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>127</td>
<td>128</td>
</tr>
<tr>
<td>Standing</td>
<td>118</td>
<td>122</td>
</tr>
</tbody>
</table>

p<0.01 for Supine vs. Standing at Month 1

Stop/reduce

Continue
1-MONTH RESULTS: SSS-OI QUESTIONNAIRE

Enrolment vs Month 1

Score

Enrolment Month 1

25 NS

21 Stop/reduce

13.1 Continue

7.2 P=0.04
# MAIN RESULTS:
SYNCOPE, PRE-SYNCOPE AND ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Stop/reduce therapy (n=31)</th>
<th>Continue therapy (n=24)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary combined end-point (syncope and/or pre-syncope and/or adverse event)</td>
<td>6 (19%)</td>
<td>12 (50%)</td>
<td>0.37 (0.14-0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Recurrence of syncope and/or pre-syncope</td>
<td>6 (19%)*</td>
<td>11 (46%)</td>
<td>0.41 (0.15-1.05)</td>
<td>0.05</td>
</tr>
<tr>
<td>Recurrence of syncope</td>
<td>2 (6%)</td>
<td>9 (37%)</td>
<td>0.17 (0.05-0.55)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Mean follow-up: 9±7 months
SYNCOPE, PRE-SYNCOPE AND ADVERSE EVENTS

Combined end-point (syncope, pre-syncope, adverse events)

Freedom from events (%)

Months

Stop/reduce

Continue

p = 0.03

Number at risk

Stop/reduce vasoactive drugs
31  18  7  1

Continue vasoactive drugs
24  11  8  1
SYNCOPE

Number at risk
Stop/reduce vasoactive drugs
31  18  7  1
Continue vasoactive drugs
24  11  8  1

p = 0.007
Syncope or presyncope

Freedom from events (%)

Months

Number at risk
Stop/reduce vasoactive drugs
31  18  7  1
Continue vasoactive drugs
24  11  8  1

p = 0.05
CONCLUSIONS AND CLINICAL PERSPECTIVES

73% of old patients with reflex syncope take one or more vasoactive drug and present low/normal BP values.

- recurrence of syncope and pre-syncope can be safely prevented by discontinuation/reduction of vasoactive therapy in most old patients affected by reflex vasodepressor syncope.

- Vasoactive therapy should be discontinued or reduced as first choice treatment.

  - NO increase of the risk of cardiovascular and neurological events (adverse events: rare and balanced in both arms).

  - Strategy of accurate BP control, aimed to achieve average systolic BP values around 140 mmHg but below 150 mmHg.

\[ ‘\text{NOT TOO HIGH, NOT TOO LOW}’ \]
Gruppo Italiano Multidisciplinare per lo Studio della Sincope
## RESULTS: SSS-OI QUESTIONNAIRE

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Enrolment</th>
<th>1-month visit</th>
<th>p value</th>
<th>Enrolment</th>
<th>1-month visit</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(score during last month)</td>
<td>Stop/reduce</td>
<td>Continue</td>
<td></td>
<td>Stop/reduce</td>
<td>Continue</td>
<td></td>
</tr>
<tr>
<td>Dizziness and presyncope (score 0-10)</td>
<td>3.3±3.9</td>
<td>4.4±4.2</td>
<td>0.31</td>
<td>1.7±3.0</td>
<td>3.0±3.8</td>
<td>0.16</td>
</tr>
<tr>
<td>Visual disturbances (score 0-10)</td>
<td>1.2±2.5</td>
<td>3.3±3.8</td>
<td>0.02</td>
<td>0.5±1.6</td>
<td>1.0±2.3</td>
<td>0.42</td>
</tr>
<tr>
<td>Syncope (score 0-10)</td>
<td>7.6±3.9</td>
<td>6.3±4.0</td>
<td>0.25</td>
<td>0.8±2.7</td>
<td>1.1±2.6</td>
<td>0.76</td>
</tr>
<tr>
<td>Hearing disturbances (score 0-10)</td>
<td>1.0±2.3</td>
<td>2.7±3.7</td>
<td>0.04</td>
<td>0.2±1.0</td>
<td>1.5±2.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Pain in the neck, low back pain, precordial pain (score 0-10)</td>
<td>1.9±3.3</td>
<td>1.7±2.2</td>
<td>0.76</td>
<td>1.5±2.9</td>
<td>2.4±3.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Weakness, fatigue, lethargy (score 0-10)</td>
<td>4.9±4.0</td>
<td>3.4±3.1</td>
<td>0.16</td>
<td>2.1±3.0</td>
<td>2.6±3.1</td>
<td>0.58</td>
</tr>
<tr>
<td>Palpitations, hyperhidrosis (score 0-10)</td>
<td>1.2±2.6</td>
<td>3.2±4.0</td>
<td>0.04</td>
<td>0.3±1.8</td>
<td>1.5±2.8</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Total score (score 0-70)</strong></td>
<td>21±11</td>
<td>25±11</td>
<td>0.20</td>
<td>7.2±8.8</td>
<td>13.1±10.6</td>
<td>0.04</td>
</tr>
</tbody>
</table>
### RESULTS: VASOACTIVE DRUGS

<table>
<thead>
<tr>
<th>Vasoactive drugs</th>
<th>Enrolment</th>
<th>1-month visit</th>
<th>Last FU visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stop/reduce</td>
<td>Continue</td>
<td>p value</td>
</tr>
<tr>
<td><strong>ACE inhibitor or IRB</strong></td>
<td>27 (87%)</td>
<td>23 (96%)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Alpha antagonist</strong></td>
<td>5 (16%)</td>
<td>5 (21%)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Beta-blocker</strong></td>
<td>7 (23%)</td>
<td>5 (21%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Diuretic</strong></td>
<td>12 (39%)</td>
<td>11 (46%)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Calcium blocker</strong></td>
<td>12 (39%)</td>
<td>6 (25%)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Neuroleptic antidepressant</strong></td>
<td>5 (16%)</td>
<td>5 (21%)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>L-dopa antagonist</strong></td>
<td>2 (6%)</td>
<td>1 (4%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>2 (6%)</td>
<td>2 (8%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Total number of vasoactive drugs</strong></td>
<td>75</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td><strong>Mean number of vasoactive drugs per patients</strong></td>
<td>2.4±1.1</td>
<td>2.5±0.9</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Number of patients with unchanged (type and dosage) therapy</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
less syncope and better quality of life at the risk of a slight increase in major cardiovascular events.

The main objective of the SPRINT trial were mortality and major cardiovascular events: it was a primary prevention trial of hard clinical end-points in which syncope and hypotension were unwanted adverse events which occurred in <2% of the population.

Stop vd is a secondary prevention trial in which patients were referred specifically for vasodepressor un-tolerated recurrent syncopes that altered quality of life.

Our population cannot be defined as at “high cardiovascular risk” as was the population of the SPRINT trial.

Reducing systolic BP to less than 130 mmHg by means of antihypertensive therapy in frail elderly patients is associated with worse cognitive performance and increased mortality.

The severity of symptoms will finally guide the therapeutic strategy.
FLOWCHART FOR THE MANAGEMENT OF HYPERTENSION IN THE ELDERLY

Hypertensive patient (≥ 60 years)

Non-pharmacological recommendation & lifestyle improvement (continue throughout management)

Set blood pressure goal & consider blood pressure lowering medication based on age and chronic kidney disease (CKD)

- Same for diabetic and stroke patient

Previous falls

BP ≥ 160/90 mmHg

Treatment goal is to lower BP < 150/90 mmHg

Medication review—consider dose adjustment or withdrawal if BP ≤ 140/90 mmHg. Goal—BP ≤ 150/90 mmHg

No previous falls

BP ≤ 160/90 mmHg

Medication review—consider dose adjustment or withdrawal if BP ≤ 140/90 mmHg. Goal—BP ≤ 150/90 mmHg

Age ≤ 80 years

Treatment goal—BP ≤ 140/90 mmHg if the treatment is well tolerated

Age ≥ 80 years

Treatment goal—BP ≤ 150/90 mmHg (no cardiovascular out improvement evidence in lowering below this point while it may lead to falls)

Reassessment

Preferred drug classes for older patients (either as monotherapy or combination therapy)

- Angiotensin receptor blockers
- Angiotensin converting enzyme-inhibitors
- Calcium channel blockers
- Thiazide diuretics
- β-blockers

Don't use ARB and ACE-I receptor in combination therapy

Select a drug treatment titration strategy

- Maximize first medication before adding second or
- Add second medication before reaching maximum dose of first medication
- Start with two medication classes separately or as fixed-dose combination

Monitor the patients closely for orthostatic hypotension and falls for 1–3 weeks of start/change of blood pressure lowering therapy