How clinically important are the results of the large trials in hypertension?

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**DISCLOSURE**

Stéphane LAURENT, MD, PhD

**Potential conflict of interest:**
Research grant, advisory board, honorarium as speaker or chairman

<table>
<thead>
<tr>
<th>Drug companies</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASTRA-ZENECA</td>
<td>ATCOR</td>
</tr>
<tr>
<td>BAYER-SCHERING</td>
<td>ESAOTE-PIE MEDICAL</td>
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<td>BOEHRINGER-INGELHEIM</td>
<td>OMRON</td>
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<td>CHIESI</td>
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<td>DAICHII-SANKYO</td>
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<td>ESTEVE</td>
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<td>MENARINI</td>
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<td>MSD</td>
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<td>NEGMA</td>
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<td>NOVARTIS</td>
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<td>PFIZER</td>
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<td>RECORDATI</td>
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<td>SERVIER</td>
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</tbody>
</table>
How clinically important are the results of the large trials?

1. Target BP under treatment

2. Combination therapy first-line

3. Large/small artery cross talk and beta-blockers
2007 Blood pressure targets

< 140 / 90 if low and moderate CV risk

< 130 / 80 if High CV risk
  Diabetes
  Renal dysfunction
  Established CV disease
  (previous stroke or CHD)

J Hypertens 2007, 25:1105-1187
Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document

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J Hypertens 2009; 27:2121-2158

Keywords: antihypertensive treatment, cardiovascular risk, guidelines, hypertension, organ damage

Abbreviations: ACE, angiotensin-converting enzyme; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ET, endothelin; IMT, carotid intima-media thickness; JNC, Joint National Committee; LVH, left ventricular hypertrophy; LVM, left ventricular mass; PDE-5, phosphodiesterase-5; PPAR-\gamma, peroxisome proliferators-activated receptor-\gamma; PWV, pulse wave velocity; SBP, systolic blood pressure; WHO, World Health Organization

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Received 16 September 2009 Accepted 16 September 2009
BP target in patients with previous stroke
No clear evidence for < 130 mmHg SBP

BP target in patients with previous CV disease
No clear evidence for < 130 mmHg SBP

PREVENT, HOPE, EUROPA, ACTION, CAMELOT, PEACE, TRANSCE
BP target in patients with diabetes melitus
No clear evidence for < 130 mmHg SBP

HOT, SHEP, UKPDS, MICROHOPE, SYST-EUR
BP target in patients with diabetes mellitus
No clear evidence for < 130 mmHg SBP

ABCD, IDNT, RENAAL, PROGRESS, ADVANCE
The J-shape curve in clinical trials

- **ON TARGET** (Sleight et al. J Hypertens 2009)
- **VALUE** (Messerli et al. ESH Meeting, June 2009)
- **INVEST** (Cooper-DeHoff et al. JAMA 2010)
- **NDR** (Cederholm J et al. J Hypertens 2010)

![CHD events diagram]

**SBP (mmHg)**

130 mmHg
The J-shape curve in clinical trials

- **ON TARGET** (Sleight et al. J Hypertens 2009)
- **VALUE** (Messerli et al. ESH Meeting, June 2009)
- **INVEST** (Cooper-DeHoff et al. JAMA 2010)
- **NDR** (Cederholm J et al. J Hypertens 2010)

**CHD events**

- SBP → DBP
- Impaired myocardial perfusion in diastole

SBP (mmHg) vs. CHD events

130 mmHg
ONTARGET: the J-shape curve (nadir 130 mmHg)


Primary study outcome

CV mortality

Myocardial infarction

Stroke

no J-shape curve
2009 Reappraisal of European Guidelines

BP targets

< 140 / 90 if low, moderate and high CV risk
Diabetes
Renal dysfunction
Established CV disease

For all!

Mancia et al. J Hypertens 2009; 27:2121-2158
2009 Reappraisal of European Guidelines

BP targets

< 140 / 90 if low, moderate and high CV risk
Diabetes
Renal dysfunction
Established CV disease

For all!

i.e. 130-139 and 80-85 mmHg

...if possible lower range : 130-135 mmHg and 80-85 mmHg

Mancia et al. J Hypertens 2009; 27:2121-2158
How clinically important are the results of the large trials?

1. Target BP under treatment

2. Combination therapy first-line

3. Large/small artery cross talk and beta-blockers
Choose between

Mild BP elevation
Low/moderate CV risk

- Single agent at low dose
- Previous agent at full dose
- Switch to different agent at low dose
- Two-to three-drug combination at full dose

If goal BP not achieved:

- Full dose monotherapy
- If goal BP not achieved
ESH 2007: Monotherapy versus combination strategies

**Mild BP elevation**
- Low/moderate CV risk
  - Single agent at low dose
    - Previous agent at full dose
    - Switch to different agent at low dose
      - If goal BP not achieved
        - 2nd line
          - Previous combination at FULL dose
            - Add a 3rd drug at low dose
        - Two-to three-drug combination at full dose
          - Full dose monotherapy
            - If goal BP not achieved

**Marked BP elevation**
- High/very CV high risk
  - Two-drug combination at LOW dose
    - If goal BP not achieved
      - Previous agent at full dose
        - Two-to three-drug combination at full dose
          - Full dose monotherapy
            - If goal BP not achieved
Clinical trials show that the majority of patients require ≥ 2 agents to achieve BP goal

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target BP (mmHg)</th>
<th>Number of antihypertensive agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>DBP &lt;85</td>
<td>1</td>
</tr>
<tr>
<td>ABCD</td>
<td>DBP &lt;75</td>
<td>2</td>
</tr>
<tr>
<td>MDRD</td>
<td>MAP &lt;92</td>
<td>3</td>
</tr>
<tr>
<td>HOT</td>
<td>DBP &lt;80</td>
<td>4</td>
</tr>
<tr>
<td>AASK</td>
<td>MAP &lt;92</td>
<td></td>
</tr>
<tr>
<td>IDNT</td>
<td>SBP &lt;135/DBP &lt;85</td>
<td></td>
</tr>
<tr>
<td>ALLHAT</td>
<td>SBP &lt;140/DBP &lt;90</td>
<td></td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure

Combining 2 drugs is 5 times more effective for SBP lowering than doubling the dose of 1 drug.

A meta-analysis of 42 trials in 10,969 hypertensives

Combining different antihypertensive agents has an additive effect


ACEI, angiotensin converting enzyme inhibitor
Combining different antihypertensive agents has an additive effect

ACEI, angiotensin converting enzyme inhibitor

Combining different antihypertensive agents has an additive effect

**Thiazide PLUS any other BP drug**

**ACEI PLUS any other BP drug**

*Actual reduction in SBP*

*Expected effect if both drugs additive*


ACEI, angiotensin converting enzyme inhibitor
Advantages of first-line combination therapy

- Pharmacodynamic synergy
  - higher BP fall and less side effects

- Less therapeutic inertia
  - Quicker BP fall
    VALUE study; Weber et al. Lancet 2004
  - Quicker regression of target organ damage
    CARDIO-SIS study; Verdecchia et al. Lancet 2009
  - Less CV events in immediate responders
    VALUE study; Weber et al. Lancet 2004

- Higher observance and persistence of treatment
  Bangalore et al. Am J Med 200
  - Better prevention against CV complications (?)
**ESH 2009: Monotherapy versus combination strategies**

Choose between:

- **Mild BP elevation**
  - Low/moderate CV risk
  - **1st line**
  - Single agent at low dose
    - Previous agent at full dose
    - Switch to different agent at low dose
      - Two-to three-drug combination at full dose
      - Full dose monotherapy

- **Marked BP elevation**
  - High/very CV high risk
  - Two-drug combination at LOW dose
    - Add a 3rd drug
  - 2 drug combination at FULL dose
Which combination?

Betablockers

Alpha blockers

Angiotensin-converting enzyme (ACE) inhibitors

Calcium channel blockers (CCBs)

Angiotensin receptor blockers (ARBs)

Diuretics

2007

ALLHAT

ASCOT LIFE

DIU

2009 Guidelines

European Society of Hypertension

www.eshonline.org
2 drug combinations: RAS blockers + CCB: highest reduction in central SBP

Favors 1st combination

- 10  - 4 mmHg  0  5 mmHg

**CAFE**
- Amlodipine + Perindopril
- Atenolol + HCTZ
- - 4.3 [-5.4 to -3.3] P<0.0001

**EXPLOR**
- Valsartan + Amlodipine
- Atenolol + Amlodipine
- - 3.9 [-7.1 to -0.8] P=0.02

**J-CORE**
- Azelnidipine + Olmesartan
- HCTZ + Olmesartan
- - 5.2 [-10.2 to -0.3] P=0.004

For a similar reduction in brachial SBP

CAFE. 6 yrs  Williams et al. Circulation 2006
EXPLOR. 6 months  Boutouyrie et al. Hypertension 2010
J-CORE 6 months  Matsui et al. Hypertension 2009
How clinically important are the results of the large trials?

1. Target BP under treatment

2. Combination therapy first-line

3. Large/small artery cross talk and beta-blockers
Should beta-blockers remain first choice in the treatment of primary hypertension?

Lindholm L et al. Lancet, 2005

> 104,000 hypertensives

<table>
<thead>
<tr>
<th>Stroke</th>
<th>Beta-blockers</th>
<th>Other drugs</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-BPLA</td>
<td>422/9618</td>
<td>327/9639</td>
<td>1.29 (1.12–1.49)</td>
</tr>
<tr>
<td>CONVINCE</td>
<td>118/8297</td>
<td>133/8179</td>
<td>0.87 (0.68–1.12)</td>
</tr>
<tr>
<td>ELSA</td>
<td>14/1157</td>
<td>9/1177</td>
<td>1.58 (0.96–2.33)</td>
</tr>
<tr>
<td>HAPPHY</td>
<td>32/3297</td>
<td>41/3272</td>
<td>0.77 (0.49–1.23)</td>
</tr>
<tr>
<td>INVEST</td>
<td>201/11309</td>
<td>176/11267</td>
<td>1.14 (0.93–1.39)</td>
</tr>
<tr>
<td>LIFE</td>
<td>309/4588</td>
<td>232/4605</td>
<td>1.34 (1.13–1.58)</td>
</tr>
<tr>
<td>MRC Old</td>
<td>56/1102</td>
<td>45/1081</td>
<td>1.22 (0.83–1.79)</td>
</tr>
<tr>
<td>NORDIL</td>
<td>196/5471</td>
<td>159/5410</td>
<td>1.22 (0.99–1.50)</td>
</tr>
<tr>
<td>STOP-2</td>
<td>237/2213</td>
<td>422/4401</td>
<td>1.12 (0.96–1.30)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>17/358</td>
<td>21/400</td>
<td>0.90 (0.48–1.69)</td>
</tr>
<tr>
<td>Yurenev</td>
<td>6/150</td>
<td>11/154</td>
<td>0.56 (0.21–1.48)</td>
</tr>
<tr>
<td>MRC</td>
<td>42/4403</td>
<td>18/4297</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>1650/51963</td>
<td>1594/53882</td>
<td>RR = 1.16</td>
</tr>
</tbody>
</table>

Test for heterogeneity: χ² = 22.39 (p = 0.02)

Increased risk with other drugs

Increased risk with beta-blockers
Should beta-blockers remain first choice in the treatment of primary hypertension?

> 56 000 hypertensives

**Stroke**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Atenolol</th>
<th>Other drugs</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-BPLA</td>
<td>422/9618</td>
<td>327/9639</td>
<td>1.29 (1.12-1.49)</td>
</tr>
<tr>
<td>ELSA</td>
<td>14/1157</td>
<td>9/1177</td>
<td>1.58 (0.69-3.64)</td>
</tr>
<tr>
<td>INVEST</td>
<td>201/11309</td>
<td>176/11267</td>
<td>1.14 (0.93-1.39)</td>
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<tr>
<td>LIFE</td>
<td>309/4588</td>
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<tr>
<td>UKPDS</td>
<td>17/358</td>
<td>21/400</td>
<td>0.90 (0.48-1.69)</td>
</tr>
<tr>
<td>Total events</td>
<td>1019/28132</td>
<td>810/28169</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=3.01$ (p=0.70)

Increased risk with other drugs

Increased risk with atenolol

Lindholm L et al. Lancet, 2005
## Meta-analysis, 46 comparisons

**STROKE, Betablockers vs other: 10 trials, 2004 events**

<table>
<thead>
<tr>
<th>Blood pressure difference (mm Hg)</th>
<th>No of trials</th>
<th>No of events</th>
<th>Relative risk (95% CI)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazides vs any other</td>
<td>-1.4</td>
<td>0.2</td>
<td>15</td>
<td>2255</td>
</tr>
<tr>
<td>β blockers vs any other</td>
<td>1.4</td>
<td>0.6</td>
<td>13</td>
<td>2004</td>
</tr>
<tr>
<td>Angiotensin converting enzyme</td>
<td>0.9</td>
<td>0.4</td>
<td>17</td>
<td>2951</td>
</tr>
<tr>
<td>inhibitors vs any other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>-0.4</td>
<td>0.1</td>
<td>7</td>
<td>1643</td>
</tr>
<tr>
<td>vs any other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers vs any</td>
<td>-0.4</td>
<td>-0.9</td>
<td>25</td>
<td>4981</td>
</tr>
<tr>
<td>other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**+18%**
Reduction of media to lumen ratio of small arteries

Agabiti Rosei et al. J Hypertens 2009

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Reduction of media to lumen ratio (% of basal value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Diuretics</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Beta blockers</td>
<td><img src="image" alt="Graph" /></td>
</tr>
</tbody>
</table>

- **n = 79**
- **n = 42**
- **n = 45**
- **n = 33**
- **n = 96**

* vs betablockers

P < 0.05
## Comparative effect of antihypertensive drugs on aortic stiffness, wave reflection and central PP

Laurent et al. Eur Heart J 2006

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Aortic pulse wave velocity</th>
<th>Augmentation index Central PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors (ACEI)</td>
<td>↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Angiotensin receptor blockers (ARB)</td>
<td>↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Calcium channel blockers (CCB)</td>
<td>↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Thiazide diuretics (DIU)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>VD β-blockers</td>
<td>↓ (↑)</td>
<td>↓</td>
</tr>
<tr>
<td>NON VD β-blockers</td>
<td>+/− (↑)</td>
<td>↑</td>
</tr>
</tbody>
</table>

*↑* indicates increase, *↓* indicates decrease, *+/−* indicates mixed effect.
Regression of Left Ventricle Hypertrophy (LVH)
Meta-analysis of clinical trials


Diuretics  Beta-blockers  Calcium Antagonists  ACE Inhibitors  Angiotensin II Receptor Antagonists

atenolol
ASCOT study: fatal and non fatal stroke
(secondary end-point)

Dahlof B et al., Lancet 2005

- atenolol / thiazide
- amlodipine / perindopril

HR = 0.77 (0.66-0.90)
p = 0.0007
CAFE study

Williams B et al. Circulation 2006

Atenolol ± thiazide

Amlodipine ± perindopril

Atenolol ± thiazide

Amlodipine ± perindopril
Peripheral vs central BP

Brachial SBP (mmHg):
Mean difference at W24: -1.14
[-4.28 to 1.99] mm Hg, NS

Central SBP (mmHg):
Mean difference at W24: -3.95
[-7.08 to -0.83] mm Hg, P=0.02

Brachial PP (mmHg):
Mean difference at W24: -1.36
[-3.33 to 0.60] mm Hg, NS

Central PP:
Mean difference at W28: -3.74
[-5.33 to -2.15] mm Hg, p<0.001

Boutouyrie P et al. Hypertension 2010
Within visit and visit-to-visit variabilities are higher after atenolol-based regimen

Rothwell P et al. Lancet Neurology 2010

Within visit variability in SBP

Visit-to-visit variability in SBP
ASCOT and CAFE: the higher efficacy of VD than atenolol on the reduction of CV events, may have occurred through an effect on the large/small artery cross talk.

Laurent et al. Hypertension 2009
AGAINST beta-blockers
as first and second line treatments in hypertension
(except compelling indication)

1. Meta-analyses
   • More strokes  

2. Less regression of TOD than other pharmacological classes
   • LVH
   • carotid IMT
   • aortic stiffness (fibrosis)
   • small artery W/L ratio

3. Less reduction in central BP and BP variability than other pharmacological classes

4. Adverse effects
   • sexual dysfunction
   • new onset of diabetes
Conclusions

1. Target BP under treatment: <140 and <90 mmHg for all
   i.e. between 130 and 139 mmHg for SBP
   80 and 85 mmHg for DBP

2. Combination therapy for initiation of TT in patients with high BP or high added CV risk
   Choice among DIU, CCB, ARB and ACEI

3. Beta-blockers: not as first and second line
   except compelling indication
   (CHD, CHF, continuous AF, …)
Thank you!