MEDICAL TREATMENT OF HYPERTENSION: STATE OF THE ART

Luis M Ruilope
Cardiology Update
Davos, February 14, 2011
World’s #1 killer: High blood pressure (HBP) and its consequences

Blood pressure
- Tobacco
- Cholesterol
- Underweight
- Unsafe sex
- Deficient fruit and vegetable intake
- High Body Mass Index
- Physical inactivity
- Alcohol
- Unsafe water, sanitation, and hygiene
- Indoor smoke from solid fuels
- Iron deficiency
- Urban air pollution
- Zinc deficiency
- Vitamin A deficiency
- Unsafe health care injections

Number of deaths (000s)

WHO Health Report 2002
BENEFIT OF BP CONTROL

• A fixed amount of benefit corresponds to a fixed amount of drop in BP
Facts and fallacies of blood pressure control in recent trials: implications in the management of patients with hypertension

Alberto Zanchetti\textsuperscript{a}, Giuseppe Mancia\textsuperscript{b}, Henry R. Black\textsuperscript{c}, Suzanne Oparil\textsuperscript{d}, Bernard Waeber\textsuperscript{e}, Roland E. Schmieder\textsuperscript{f}, George L. Bakris\textsuperscript{g}, Franz H. Messerli\textsuperscript{h}, Sverre E. Kjeldsen\textsuperscript{i} and Luis M. Ruilope\textsuperscript{j}

A large body of clinical trial data indicates that a given difference in blood pressure (BP), as measured in the clinic, results in a given difference in outcome. This correlation underpins current US and European guidelines for the management of hypertension. However, findings from recent comparative trials may appear inconsistent with a fixed relationship between BP lowering and outcome benefit, at least at all BP ranges, at all levels of total cardiovascular risk and with all drug combinations. We review the findings of six of these recent trials and conclude that their complex design precludes a simple interpretation, that several important questions remain unanswered and that direct evidence – particularly in support of lowering systolic BP below 140 or 130 mmHg – is urgently needed. J Hypertens 27:673–679 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CI, confidence interval; CV, cardiovascular; DBP, diabolic blood pressure; ESC, European Society of Cardiology; EJH, European Society of Hypertension; HCTZ, hydrochlorothiazide; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; RCT, randomized controlled trial; RR, relative risk; SBP, systolic blood pressure

\textsuperscript{a}Centro di Fisiologia Clinica e Ipertensione, University of Milan and Istituto Auxologico Italiano, Milan, \textsuperscript{b}Clinica Medica, University of Milano Bicocca Ospedale San Gerardo, Monza, Italy, \textsuperscript{c}New York University School of Medicine, New York, New York, \textsuperscript{d}Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA, \textsuperscript{e}Division of Hypertension, Department of Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, \textsuperscript{f}Department of Nephrology and Hypertension, University Hospital, Erlangen, Germany, \textsuperscript{g}University of Chicago, Pritzker School of Medicine, Chicago, Illinois, \textsuperscript{h}St. Luke’s–Roosevelt Hospital Center, New York, New York, USA, \textsuperscript{i}Department of Internal Medicine, Ullevaal University Hospital, Oslo, Norway and \textsuperscript{j}Hypertension Unit, Hospital 12 de Octubre, Madrid, Spain

Correspondence to Professor Alberto Zanchetti, Centro di Fisiologia Clinica e Ipertensione, University of Milan, Ospedale Maggiore, Via F. Sforza 35, 20122 Milan, Italy
New concepts even in the presence of a good BP control

• USUAL BP- True BP can not be measured with total precision.
• MEAN BP- Average of several readings (ABPM, HBPM)
• BP VARIABILITY- The variation of BP with time. Can be measured over minutes or over days, weeks or months.
• BP INSTABILITY- Transient fluctuations in BP usually in response to a specific stimulus (posture, stress, pain). Contributes to BP variability

  Peter M Rothwell, Lancet 2010, 375:938
ROADMAP: Percentage of patients reaching BP goal

**BP goal**: <130/80 mmHg

*Additional antihypertensive treatment except RAAS blockers at physician’s discretion, CCBs diuretics, BBs allowed to reach target BP goal*
Systolic Pressures (mean ± 95% CI)

Mean # Meds

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.2</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Average: 133.5 Standard vs. 119.3 Intensive, Delta = 14.2

Years Post-Randomization

N = 4382

0  1  2  3  4  5  6  7  8


ESH–ESC and JNC 7 Guidelines Recommend Target BP Goals of <140/90 mmHg for Uncomplicated Hypertension and <130/80 mmHg for Complicated Hypertension

<table>
<thead>
<tr>
<th>Type of hypertension</th>
<th>BP goal (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>Complicated</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>&lt;130/80*</td>
</tr>
<tr>
<td>Other high risk (stroke, myocardial infarction)</td>
<td>&lt;130/80</td>
</tr>
</tbody>
</table>

*Lower if proteinuria is >1 g/day

CCBs and ARBs are recommended as preferred combination therapy partners

Continuous lines show two-drug combinations that have been found to be well tolerated and effective.

Valsartan and Amlodipine: Cardiovascular Endpoints in High-risk Hypertension\textsuperscript{1,2}

### ASCOT BPLA\textsuperscript{1}

- Non-fatal MI (excluding silent) + fatal CHD
- Total coronary endpoint
- Total CV events and procedures
- All-cause mortality
- CV mortality
- Fatal/non-fatal stroke
- Fatal/non-fatal HF
- Development of renal impairment
- Development of diabetes

- Amlodipine-based better
- Atenolol-based better

### VALUE trial\textsuperscript{2}

- Primary cardiac composite endpoint
- Cardiac mortality
- Cardiac morbidity
- All MI
- All congestive heart failure
- All stroke
- All-cause death
- New-onset diabetes

- Favors valsartan
- Favors amlodipine

Systolic Blood Pressure Over Time

Difference of 0.7 mmHg p<0.05*

130 mmHg

129.3 mmHg

Month

0
6
12
18
24
30
36
42

Patients

5731
5387
5206
4999
4804
4285
2520
1045
5709
5377
5154
4980
4831
4286
2594
1075

*Mean values are taken at 30 months F/U visit

DBP: 71.1  DBP: 72.8

ACCUMPLISH
Kaplan Meier for Primary Endpoint

- ACEI / HCTZ
- CCB / ACEI

Time to 1st CV morbidity/mortality (days)

Cumulative event rate

- 20% Risk Reduction
- 650
- 526

p = 0.0002

HR (95% CI): 0.80 (0.72, 0.90)

INTERIM RESULTS Mar 08
A) THE EVIDENCE SUGGESTS THAT TO IMPROVE CV OUTCOMES WE REQUIRE A NEW PARADIGM THAT EMPHASIZES RAPID ACHIEVEMENT OF BP CONTROL (1).

B) BP CONTROL SHOULD BE ATTAINED PREFERABLY WITHIN 3 MONTHS OF INITIATING THERAPY (2)

1- Basile J. J Clin Hypertens 2008
2- Berlowitz DR & Franklin S. J Clin Hypertens 2010
Initiating therapy with the combination of nifedipine GITS/telmisartan reduced office SBP as early as 2 weeks

Reduction in SBP from baseline (mmHg)

A  B  C

Group A (n=164)
Group B (n=89)
Group C (n=74)

*p<0.001 vs baseline

Based on least-squared (LS) mean ± standard error of the mean (SE) data

Primary composite endpoint of the LIFE stratified by time-varying albuminuria.

Intensive vs standard BP lowering strategies on albuminuria in ACCORD-BP

## Albuminuria Groups

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Normal</td>
<td>970 (67.7)</td>
<td>862 (60.2)</td>
<td>754 (54.1)</td>
<td>766 (54.9)</td>
<td></td>
</tr>
<tr>
<td>High-Normal</td>
<td>171 (11.9)</td>
<td>213 (14.9)</td>
<td>256 (18.4)</td>
<td>223 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Micro</td>
<td>234 (16.3)</td>
<td>267 (18.6)</td>
<td>291 (20.9)</td>
<td>302 (21.6)</td>
<td></td>
</tr>
<tr>
<td>Macro</td>
<td>58 (4.0)</td>
<td>91 (6.4)</td>
<td>94 (6.7)</td>
<td>104 (7.5)</td>
<td></td>
</tr>
<tr>
<td><strong>No DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Normal</td>
<td>906 (70.0)</td>
<td>789 (63.0)</td>
<td>669 (56.1)</td>
<td>682 (58.2)</td>
<td></td>
</tr>
<tr>
<td>High-Normal</td>
<td>148 (11.4)</td>
<td>184 (14.7)</td>
<td>222 (18.6)</td>
<td>184 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Micro</td>
<td>198 (15.3)</td>
<td>217 (17.3)</td>
<td>235 (19.7)</td>
<td>238 (20.3)</td>
<td></td>
</tr>
<tr>
<td>Macro</td>
<td>43 (3.3)</td>
<td>62 (5.0)</td>
<td>67 (5.6)</td>
<td>67 (5.7)</td>
<td></td>
</tr>
<tr>
<td><strong>DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Normal</td>
<td>64 (46.4)</td>
<td>73 (40.3)</td>
<td>85 (42.1)</td>
<td>84 (37.5)</td>
<td></td>
</tr>
<tr>
<td>High-Normal</td>
<td>23 (16.7)</td>
<td>29 (16.0)</td>
<td>34 (16.8)</td>
<td>39 (17.4)</td>
<td></td>
</tr>
<tr>
<td>Micro</td>
<td>36 (26.1)</td>
<td>50 (27.6)</td>
<td>56 (27.7)</td>
<td>64 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Macro</td>
<td>15 (10.9)</td>
<td>29 (16.0)</td>
<td>27 (13.4)</td>
<td>37 (16.5)</td>
<td></td>
</tr>
</tbody>
</table>

| p DM     | <0.001 | <0.001 | <0.001 | <0.001 |       |

Development of new-onset microalbuminuria among hypertensive patients according to previous cardiovascular events

New-onset microalbuminuria was seen in 9.9% of patients without a previous event and in 17.2% \( (p=0.003) \) of those with a previous event.

CONCLUSIONS

• Albuminuria appears and progresses under RAS suppression either with ACEi or ARB.

• Renal function, severity of hypertension and glycemic control are independent factors related with the increased urinary albumin excretion.

• We need to know whether the capacity of RAS suppression is finished or can be improved in order to improve the outcome of our patients.

• New ways for RAS suppression have to be investigated in these cohort of patients (dual blockade with ACEi-ARBs plus Aliskiren, plus spironolactone).
Schematic differences between ACE/NEP inhibition (as with omapatrilat) and angiotensin receptor blockade/NEP inhibition (as with LCZ696).

ACE angiotensin-converting enzyme; Ang II angiotensin II; ARBs angiotensin receptor blockers; AT1 angiotensin II type 1; NEP neprilysin; NPs natriuretic peptides

Change in placebo-subtracted mean sitting systolic blood pressure (A) and mean sitting diastolic blood pressure (B) during the 8-week treatment period.

Patients who discontinued the study drug without a blood pressure measurement after randomisation were excluded.
Change From Baseline in 24-Hour Mean SBP at Week 6

Placebo: -0.25
TAK-491 40 mg: -13.42<sup>a,b</sup>
TAK-491 80 mg: -14.53<sup>a,b,c</sup>
Valsartan 320 mg: -10.22<sup>a</sup>
Olmesartan 40 mg: -11.99<sup>a</sup>

Baseline: 144.30-146.33 mm Hg

<sup>a</sup>P<.001 vs placebo
<sup>b</sup>P≤.001 vs valsartan 320 mg
<sup>c</sup>P=.009 vs olmesartan 40 mg
CONCLUSION

• Early BP control is desirable (increased use of combinations). Initial BP is lower than it was years ago.

• Other means of measuring BP different from office BP measurement have to be used. This could include BP variability.

• Trials with different combinations reflect different outcomes.

• Long-term RAAS suppression could not impede the development of cardiorenal damage