Aggressive Lowering of Blood Pressure in type 2 Diabetes Mellitus:
The Diastolic Cost

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GUIDELINES FOR BLOOD PRESSURE CONTROL IN DIABETES MELLITUS

<130/85 mmHg
1993- NIH NATIONAL CONSENSUS
1997- JNC 6;

<130/80 mmHg
2000- National US consensus forum
Universally accepted
Some Blood Pressure Patterns in Type 2 Diabetes
Prevalence of Hypertension in Diabetes:
Cross sectional analysis in 2227 patients
(Kabakov et al, JCMS 2006)
Prevalence of Hypertension in Diabetes as a function of age
(Cross sectional analysis in 2227 patients)
Prevalence of Systolic & Diastolic Hypertension vs. Age: Cross sectional analysis of 2227 subjects (Kabakov et al, JCMS 2006)
BP features in Diabetic Hypertensive Subjects: Syst Eur as an example

Patients with diabetes:

⚠️ Mean **systolic blood pressure 1.7 mm Hg higher** than that in the nondiabetic patients

⚠️ Mean **diastolic blood pressure 1.1 mm Hg lower** than in nondiabetics =>

⚠️ Mean pulse pressure was 2.8 mm Hg wider in the diabetic patients
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DM (n=13101)</th>
<th>Glycemic Status IFG (n=1399)</th>
<th>NG (n=17012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>66.6 (7.4)**</td>
<td>67.0 (7.5)</td>
<td>67.1 (7.9)</td>
</tr>
<tr>
<td>Women</td>
<td>6463 (49.3)**</td>
<td>528 (37.7)**</td>
<td>5279 (45.4)</td>
</tr>
<tr>
<td>Black</td>
<td>5077 (38.8)**</td>
<td>413 (29.5)</td>
<td>5468 (32.1)</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>10.7 (4.0)**</td>
<td>11.1 (3.9)</td>
<td>11.2 (4.0)</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>1762 (13.4)**</td>
<td>329 (23.5)**</td>
<td>4714 (27.7)</td>
</tr>
<tr>
<td>Atherosclerotic CVD</td>
<td>4693 (35.8)**</td>
<td>876 (62.8)</td>
<td>10495 (61.7)</td>
</tr>
<tr>
<td>History of MI or stroke</td>
<td>2412 (18.4)**</td>
<td>288 (27.7)</td>
<td>4493 (26.4)</td>
</tr>
<tr>
<td>History of coronary revascularization</td>
<td>1403 (10.7)**</td>
<td>215 (15.4)</td>
<td>2479 (14.6)</td>
</tr>
<tr>
<td>Other atherosclerotic CVD</td>
<td>1969 (15.0)**</td>
<td>394 (28.2)</td>
<td>4994 (29.4)</td>
</tr>
<tr>
<td>Major ST depression/T-wave inversion#</td>
<td>865 (6.7)**</td>
<td>197 (14.3)</td>
<td>2104 (12.5)</td>
</tr>
<tr>
<td>History of CHD at baseline##</td>
<td>2578 (19.8)**</td>
<td>426 (30.8)</td>
<td>2951 (17.3)</td>
</tr>
<tr>
<td>History of HDL-C &lt;35 mg/dl</td>
<td>1171 (8.9)**</td>
<td>252 (18.0)**</td>
<td>2250 (13.2)</td>
</tr>
<tr>
<td>History of LVH by electrocardiogram or echocardiogram</td>
<td>1656 (15.3)**</td>
<td>322 (26.3)</td>
<td>4061 (27.1)</td>
</tr>
<tr>
<td>Taking anthihypertensive medication</td>
<td>12098 (92.3)**</td>
<td>1247 (89.1)</td>
<td>15107 (88.8)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4415 (33.7)**</td>
<td>533 (38.1)</td>
<td>6451 (37.9)</td>
</tr>
<tr>
<td>Estrogen supplements 9women only</td>
<td>914 (14.1)**</td>
<td>82 (15.5)**</td>
<td>1637 (21.2)</td>
</tr>
<tr>
<td>Medication to lower lipid levels*</td>
<td>1682 (13.0)**</td>
<td>215 (15.6)</td>
<td>2423 (14.4)</td>
</tr>
<tr>
<td>Systolic/diastolic blood pressure, mean (SD), mm Hg</td>
<td><strong>146.5 (15.4)/82.9 (10.0)</strong></td>
<td><strong>146.5 (15.7)/84.0 (9.8)</strong></td>
<td><strong>146.0 (15.8)/84.8 (10.0)</strong></td>
</tr>
<tr>
<td>Taking antihypertensives</td>
<td><strong>145.8 (15.5)/82.6 (9.9)</strong></td>
<td><strong>145.1 (15.5)/84.0 (9.8)</strong></td>
<td><strong>144.7 (15.6)/84.1 (9.9)</strong></td>
</tr>
<tr>
<td>Not taking antihypertensives</td>
<td><strong>155.2 (11.5)/87.3 (9.6)</strong></td>
<td><strong>158.4 (12.0)/89.8 (9.9)</strong></td>
<td><strong>156.4 (12.4)/90.4 (8.9)</strong></td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>31.1 (6.3)**</td>
<td>30.5 (6.0)**</td>
<td>28.7 (5.8)</td>
</tr>
</tbody>
</table>

Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CHD, coronary heart disease; CDV, cardiovascular disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose level; LVH, left ventricular hypertrophy;MI, myocardial infarction; NG, normoglycemic.

SI conversion factor: to convert HDL-C to millimoles per liter, multiply by 0.0259.

*Unless otherwise indicated, data are expressed as number (percentage) of patients. Because of missing or invalid values, some denominators varied.

**Denominators were 12957 for DM, 1381 for IFG and 16678 for NG.

*Denominators were 12991 for DM, 1376 for IFG and 16902 for NG.

#Denominators were 12977 for DM, 1376 for IFG and 16902 for NG.


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**Diastolic Blood pressure is lower in Diabetes: Baseline BP Characteristics of 31512 ALLHAT Participants by Glycemic Status***

<table>
<thead>
<tr>
<th></th>
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<th>NG (n=17012)</th>
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<td><strong>Systolic/diastolic BP, mean (SD), mm Hg</strong></td>
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<tr>
<td><strong>Taking antihypertensives</strong></td>
<td>145.8 (15.5)/82.6 (9.9)**</td>
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<td>144.7 (15.6)/84.1 (9.9)</td>
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<td><strong>Not taking antihypertensives</strong></td>
<td>155.2 (11.5)/87.3 (9.6)**</td>
<td>158.4 (12.0)/89.8 (9.9)</td>
<td>156.4 (12.4)/90.4 (8.9)</td>
</tr>
<tr>
<td>Guidelines</td>
<td>Blood Pressure</td>
<td>Year</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>NIH National Consensus</td>
<td>&lt;130/85 mmHg</td>
<td>1993</td>
<td></td>
</tr>
<tr>
<td>JNC 6</td>
<td></td>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>National US Consensus Forum</td>
<td>&lt;130/80 mmHg</td>
<td>2000</td>
<td></td>
</tr>
</tbody>
</table>
Achieved blood pressure in major studies including diabetic hypertensive subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>BP, mmHg</th>
<th>Mean Age</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOT</td>
<td>143/82</td>
<td></td>
<td>penedil</td>
</tr>
<tr>
<td>IDDNT</td>
<td>141/83</td>
<td>+58</td>
<td>irbesartan</td>
</tr>
<tr>
<td>RENAAL</td>
<td>140/74</td>
<td>+60</td>
<td>losartan</td>
</tr>
<tr>
<td>UKPDS</td>
<td>144/86</td>
<td></td>
<td>atenolol</td>
</tr>
<tr>
<td>ABCD</td>
<td>133/78</td>
<td>+58</td>
<td>enalapril</td>
</tr>
<tr>
<td>SYST-EUR</td>
<td>162/82</td>
<td>&gt;60</td>
<td>nitendip.</td>
</tr>
<tr>
<td>Micro-HOPE</td>
<td>140/77</td>
<td>+65</td>
<td>ramipril</td>
</tr>
</tbody>
</table>
Recently completed cardiovascular and renal trials in which patients received 2 or more antihypertensive agents for intensive blood pressure control.

<table>
<thead>
<tr>
<th>Study</th>
<th>Target Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom Prospective Diabetes Study (UKPDS)</td>
<td>&lt;85 mm Hg (Diastolic BP)</td>
</tr>
<tr>
<td>Appropriate Blood Pressure in Diabetes Trial</td>
<td>&lt;75 mm Hg (Diastolic BP)</td>
</tr>
<tr>
<td>Modification of Diet in Renal Disease Study (MIDED)</td>
<td>&lt;92 mm Hg (Mean arterial Pressure)</td>
</tr>
<tr>
<td>Hypertension Optimal Treatment Study (HOT)</td>
<td>&lt;80 mm Hg (Diastolic BP)</td>
</tr>
<tr>
<td>African-American Study of kidney Disease (AASKD)</td>
<td>&lt;92 mm Hg (mean Arterial pressure)</td>
</tr>
</tbody>
</table>

**Antihypertensive Agents, No**

<table>
<thead>
<tr>
<th>Antihypertensive Agents, No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>
Attempted Lowering of Both Systolic and Diastolic Pressure in Clinical Practice

- As of 1997 we systematically implemented JNC-VI guidelines (target < 130/85 mm Hg) for the treatment of hypertension in all type 2 diabetic hypertensive patients treated for hypertension at a university-affiliated medical center (n=257). Results of this intervention were reviewed in all subjects who had a minimal follow up period of 12 months (mean 20 months).

Osher et al, J Clin Hypert 2006
Principles of Intervention

- Individualized tailoring of medications based on a) the use of flexible drug combinations
- Gradual increments in dose or number of medications at 4-12 week intervals
- Use of ACE inhibitors whenever possible
- Use of beta blockers in individuals with documented previous coronary events
FINAL DIASTOLIC & SYSTOLIC PRESSURES DISTRIBUTION

- <130; >85 (N=4) 2%
- >=130; <85 (N=150) 58%
- >130; >85 (N=21) 8%
- <85/130 (N=82) 32%

Osher et al, J Clin Hypert 2006
FINAL DIASTOLIC PRESSURE GROUPS

- >=85 mmHg (N=25) 10%
- 71-84 mmHg (N=86) 33%
- 70 mmHg (N=93) 36%
- <70 mmHg (N=53) 21%
Final diastolic pressure (by diastolic pressure groups)

![Bar chart showing diastolic pressure by groups.

- <70 mmHg (N=57): 60±1
- 70 mmHg (N=93): 70
- 71-84 mmHg (N=86): 79
- >85 mmHg (N=25): 90±1

P=0.0001; All comparisons

Osher et al, J Clin Hypert 2006]
Initial diastolic pressure
(by final diastolic pressure groups)

- <70 mmHg (N=53): 85±2
- 70 mmHg (N=93): 89±1
- 70-84 mmHg (N=86): 89±1
- >=85 mmHg (N=25): 90±2
Decrease in diastolic pressure (by final diastolic pressure groups)

Osher et al, J Clin Hypert 2006
Initial systolic pressure (by final diastolic pressure groups)

- <70 mmHg (N=53): 166±4
- 70 mmHg (N=93): 159±3
- 70-84 mmHg (N=86): 153±2
- >=85 mmHg (N=25): 161±5

p<0.04, ANOVA
INITIAL PULSE PRESSURE
(By Final Diastolic Blood Pressure Groups)

P<0.01, ANOVA
Age by final diastolic pressure groups

- <70 mmHg (N=53): 70.3±1.3
- 70 mmHg (N=93): 67.4±1.1
- 70-84 mmHg (N=86): 61.7±1.2
- >=85 mmHg (N=25): 59.6±3

p<0.0001, ANOVA
Diabetic patients who normalized systolic & diastolic pressure vs. patients who normalized diastolic pressure only

- Diabetic patients who normalized systolic & diastolic pressure: 63 ± 1.4
- Diabetic patients who normalized diastolic pressure only: 67.5 ± 0.8

P < 0.01

Age distribution:
- <130/85 (N=82)
- <85;> ≥130 (N=150)
Patients who normalized both systolic & diastolic pressure vs. patients who normalized diastolic pressure only

**Initial systolic pressure**

- **<130/85 (N=82)**: 147±3
- **<85;>130 (N=150)**: 165±2

*P=0.0001*
Diabetic patients who normalized systolic & diastolic pressure vs. patients who normalized diastolic pressure only

Initial diastolic pressure mmHg

88±1

<130/85 (N=82)

<85;>130 (N=150)

NS
Diabetic patients who normalized systolic & diastolic pressure vs. patients who normalized diastolic pressure only

BMI

27.2±0.8

30±0.6

<130/85

<85;>130

P<0.01

*
Fraction of female gender among diabetic patients who normalized systolic & diastolic pressure vs. patients who normalized diastolic pressure only

Normalized Female/Male Ratio

F/M = 0.67

P < 0.005

F/M = 1.47

<130/85 (N=82)

<85; >130 (N=150)
Prevalence of Ischemic Heart Disease in Diabetic Hypertensive Patients by Final Diastolic Pressure (groups)

<table>
<thead>
<tr>
<th>Diastolic Pressure</th>
<th>Prevalence of IHD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70 mmHg (N=53)</td>
<td>52.8%</td>
</tr>
<tr>
<td>70 mmHg (N=93)</td>
<td>33.3%</td>
</tr>
<tr>
<td>70-84 mmHg (N=86)</td>
<td>25.6%</td>
</tr>
<tr>
<td>&gt;=85 mmHg (N=25)</td>
<td>24.0%</td>
</tr>
</tbody>
</table>

P < 0.01
Use of Nitrates in Diabetic Hypertensive Patients by Final Diastolic Pressure (groups)

<table>
<thead>
<tr>
<th>Pressure Range</th>
<th>Use of Nitrates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70 mmHg</td>
<td>34.7%</td>
</tr>
<tr>
<td>70 mmHg</td>
<td>17.5%</td>
</tr>
<tr>
<td>70-84 mmHg</td>
<td>16.7%</td>
</tr>
<tr>
<td>&gt;=85 mmHg</td>
<td>10.5%</td>
</tr>
</tbody>
</table>

P < 0.05
Excessive diastolic lowering – an inevitable outcome of aggressive BP lowering in type 2 diabetes!

- older age
- high initial systolic pressure and pulse pressure
- female gender
- presence of known coronary disease
In the treatment of hypertension in type 2 diabetes, can we avoid the diastolic cost?
In the treatment of hypertension in type 2 diabetes, can we entirely avoid the diastolic cost?

- **No BP Control** (≤130/80 mmHg)
- **No problem** (in BP control)
- **No way**
“Isolated Systolic hypertension” in the Syst-Eur Diabetic Population is defined as <95 mmHg

- ≥60 y/o
- SP: 160 to 219 mmHg (seated)
- DP: <95 mm Hg (seated)
- SP ≥ 140 mm Hg (standing)
Intensive Blood Pressure Control Reduces the Risk of Cardiovascular Events in Patients With Peripheral Arterial Disease and Type 2 Diabetes

Intensive treatment with no apparent diastolic cost (ABCD trial)

- Mean age: 59y
- Mild systolic hypertension (135-136 mmHg)
- Mild diastolic hypertension (84.4 mmHg)
- Low prevalence of known cardiovascular disease (10-11%)
The Appropriate Blood-Pressure Control in Diabetes (ABCD)

- A prospective interventional study of patients with type 2 diabetes.

- “Normotensive” patients (DP 80-89mmHg) were randomized to placebo or (moderate blood pressure control) intensive treatment with enalapril or nisoldipine.

- Moderate BP subjects had a mean blood pressure of \(137\pm0.7/81\pm0.3\) mm Hg over the last 4 years of treatment.

- Intensive treatment with enalapril or nisoldipine had a mean 4-year blood pressure of \(128\pm0.8/75\pm0.3\) mm Hg \((P<0.0001\) compared with moderate control).

- PAD, which is defined as an ankle-brachial index <0.90 at the baseline visit, was diagnosed in 53 patients.

- In patients with PAD, there were 3 cardiovascular events (13.6%) on intensive treatment Vs. 12 events (38.7%) on moderate treatment \((P=0.046)\).

* Mehler et al, Circulation. 2003;107:753
Recent Evidence for Diastolic Cost in Large Clinical Trials

- LIFE
- ALLHAT
- ASCOT- BPLA
Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE)
Diabetic ALLHAT Patients: Attained
Diastolic Blood Pressure, Year 5

On – Treatment Diastolic Blood Pressure in the ASCOT-BPLA: Entire Study Population (Non-DM+DM)
Evidence for damage inflicted by (“excessive”) diastolic lowering

Examples only; evidence to the contrary not reviewed
The role of diastolic blood pressure when treating isolated systolic hypertension
Somes et al, Arch Intern Med. 159:2004-9, 1999

In the SHEP study, after adjustment for the baseline risk factors of race (black vs other), sex, use of antihypertensive medication before the study, a composite variable (diabetes, previous heart attack, or stroke), age, and smoking history (ever vs never) and adjustment for the SBP as a time-dependent variable-

decrease of 5 mm Hg in DBP in the active treatment group only increased the risk for

- **stroke** relative risk - **1.14**; 95% CI 1.05-1.22),
- **CHD** relative risk - **1.08**; 95% CI, 1.00-1.16)
- **CVD** relative risk - **1.11**; 95% CI, 1.05-1.16).
Every 10–mm Hg rise in baseline SBP increased the risk for ESRD or death by 6.7% ($P = .007$);

The same rise in DBP decreased the risk by 10.9% ($P = .01$) when adjusting for urinary albumin-creatinine ratio, serum creatinine, serum albumin, hemoglobin, and hemoglobin A$\text{l}_c$. 

Bakris et al Arch. Int Med. 2003;163:1555-1565
INVEST- post-hoc analysis

- 22576 subjects with both hypertension and coronary artery disease
- Randomized to verapamil SR- or atenolol-based protocol
- Evidence for J –curve for death, MI & stroke; nadir at 119/84 mmHg
- After multiple adjustments, J-curve persisted for diastolic pressure

Messerli F, Ann Int Med 2006
Excessive lowering of diastolic pressure is an inevitable outcome of attempts to approach target systolic pressure

- The initial excess in systolic pressure is typically much larger than in diastolic pressure (e.g., 157/86mmHg)
- There are no anti-hypertensive drugs which act exclusively on systolic pressure.
- Therefore, pushing systolic pressure all the way to < 130 mm Hg will inevitably drive diastolic pressure to low levels in some patients.
- Why has excessive diastolic lowering not been extensively addressed in diabetes? Because most clinical studies defined diastolic rather than systolic target pressure.
Is excessive lowering of diastolic pressure by anti-hypertensive agents unique to diabetes?

While it may not be unique to diabetics, it may be encountered more often in diabetes because

- It is only in diabetes that we are encouraged by guidelines to attempt forced titration of systolic pressure to less than 130 mmHg
- Low diastolic pressure per se often reflects arterial stiffening, which is increased in diabetes
- On-, as well as off-treatment diastolic pressure tends to be lower in diabetes
Correlates of excessive diastolic lowering when tight blood pressure control is attempted in diabetes

- Higher baseline systolic pressure
- Higher initial pulse pressure
- Older age
- The presence of pre-existing ischemic heart disease
- Female gender

*Initial diastolic pressure is not different!!*
Risks (?) of Diastolic Pressure Lowering Vs. Benefits of Systolic Pressure Lowering

- Because lower diastolic pressure may carry greater cardiovascular risk, particularly in patients with existing coronary disease, the problem of therapeutically induced “diastolic hypotension” in diabetes poses a real clinical challenge.

- The choice between leaving systolic pressure above the desirable range and lowering diastolic pressure to ~ 60, 50 or even 40 mmHg may not be unique for diabetics and is presently difficult to make based on real evidence. Is, for example, 136/57 worse or better than 126/48 mmHg?
Final Take-Home Questions:
In lowering BP to less than 130/80 mmHg, how far should we push and who should be exempt?

- What is the lowest acceptable on-treatment diastolic pressure?
- Is there an age limit to the “130/80 mmHg rule”?
- Should diabetic patients with hypertension and coronary artery disease be treated any differently, with respect to attained diastolic pressure, than diabetic patients with no known coronary disease?