ACCORD TRIAL- BLOOD PRESSURE

(effect of Intensive Blood Pressure Control in Type 2 Diabetes)

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Two Previous Studies Measuring Outcome and Blood Pressure

SHEP
NAVIGATOR
UKPDS
HOT
Why was ACCORD Blood Pressure Trial performed?

- Lack of evidence to support Blood pressure less than 135-140 for prevention CVD in T2DM
UKPDS Results: Tight BP Control

Risk Reduction*

- Any diabetes-related endpoint: $P=0.0046$, Reduction = 24%
- Diabetes-related death: $P=0.019$, Reduction = 32%
- Stroke: $P=0.013$, Reduction = 44%
- Microvascular endpoints: $P=0.0092$, Reduction = 37%
- Retinopathy progression: $P=0.0038$, Reduction = 34%
- Deterioration of vision: $P=0.0036$, Reduction = 47%
- Heart failure: $P=0.0043$, Reduction = 56%

*Compared with less tight control. Captopril and atenolol were equally effective in reducing risk and were equally safe in patients with diabetes.

### CVD Risk Reduction From Tight Control of BP and Glucose in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>10-Year Absolute Risk Reduction</th>
<th>NNT&lt;sub&gt;B&lt;/sub&gt; BP/Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes endpoint</td>
<td></td>
<td>8.9/31.2</td>
</tr>
<tr>
<td>Diabetes-related death</td>
<td></td>
<td>16.4/112.1</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td>23.3/125.3</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td>23.3/46.2</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>22.7/169.4</td>
</tr>
<tr>
<td>PV death or amputation</td>
<td></td>
<td>83.3/192.7</td>
</tr>
<tr>
<td>Microvascular</td>
<td></td>
<td>17.2/41.9</td>
</tr>
</tbody>
</table>

**Relative Risk With 95% Confidence Interval**

PV = peripheral vascular; NNT<sub>B</sub> = number-needed-to-treat for benefit

HOT Trial: Effect of Targeted DBP on Cardiovascular Events Over 4 Years

Events/1,000 patient-years

- ≤90: 24.4
- ≤85: 18.6
- ≤80: 11.9

51% risk reduction, P=0.005

- ≤90: 9.9
- ≤85: 10.0
- ≤80: 9.3

P=NS

Patients with diabetes (n=1,501)

All patients (n=18,790)

<table>
<thead>
<tr>
<th>Goal</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>&lt;7.0%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;130/&lt;80 mm Hg</td>
</tr>
<tr>
<td>Lipids</td>
<td>LDL-C: &lt;100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt;70 mg/dL for those with diabetes and CVD</td>
</tr>
<tr>
<td></td>
<td>For maximally tolerated, drug-treated</td>
</tr>
<tr>
<td></td>
<td>patients who do not reach target, reduction</td>
</tr>
<tr>
<td></td>
<td>in LDL-C 30%–40% from baseline is</td>
</tr>
<tr>
<td></td>
<td>alternative</td>
</tr>
</tbody>
</table>

<sup>a</sup>Referenced to a nondiabetic range of 4.0%–6.0% using a Diabetes Control and Complications Trial-based assay.

CVD=cardiovascular disease.
Inclusion criteria

- Type 2 Diabetes
- Hgb A1C ≥ 7.5%
- 40 years of age or older with CVD or 55 years of age or older with anatomical evidence of risk
- Individuals with systolic blood pressure 130-180 mm Hg taking three or fewer antihypertensive medications and a 24 protein of less than 1 gm
Exclusion Criteria

- BMI more than 45
- Serum creatinine more than 1.5 mg/dl
- Other serious illness
## ACCORD Double 2 x 2 Factorial Design

<table>
<thead>
<tr>
<th></th>
<th>Lipid</th>
<th>BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Intensive</td>
</tr>
<tr>
<td><strong>Intensive</strong></td>
<td>1383</td>
<td>1178</td>
</tr>
<tr>
<td>Glycemic Control</td>
<td>1374</td>
<td>1193</td>
</tr>
<tr>
<td><strong>Standard</strong></td>
<td>1370</td>
<td>1184</td>
</tr>
<tr>
<td>Glycemic Control</td>
<td>1391</td>
<td>1178</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2753</td>
<td>2362</td>
</tr>
<tr>
<td></td>
<td>2765</td>
<td>2371</td>
</tr>
<tr>
<td></td>
<td>5518</td>
<td>4733*</td>
</tr>
</tbody>
</table>

*94% power for 20% reduction in event rate, assuming standard group rate of 4% / yr and 5.6 yrs follow-up*
ACCORD- Blood Pressure (Design)

- Randomized nonblinded trial at 77 clinical sites in United States and Canada

- Entire ACCORD trial 10,251 high-risk participants with stable type 2 diabetes mellitus (glucose control was the driver)

- Randomly assigned to targeted therapy of 120 mm Hg (intensive treatment) or 140 mm Hg (standard therapy)

- Treatment strategy study to achieve blood pressure goal rather than evaluating efficacy of a specific therapy
Primary Endpoint

- Composite of Nonfatal MI, nonfatal stroke, and CVD death
- Intensive less than 120mm Hg
- Standard less than 140mm Hg
ACCORD BP Trial Eligibility

- **Stable Type 2 Diabetes >3 months**
- **HbA1c 7.5% to 11% (or <9% if on more meds)**
- **High CVD risk = clinical or subclinical disease or ≥2 risk factors**
- **Age (limited to <80 years)**
  - ≥ 40 yrs with history of clinical CVD (secondary prevention)
  - ≥ 55 yrs otherwise
- **Systolic blood pressure**
  - 130 to 160 mm Hg (if on 0-3 meds)
  - 161 to 170 mm Hg (if on 0-2 meds)
  - 171 to 180 mm Hg (if on 0-1 meds)
- **Urine protein <1.0 gm/24 hours or equivalent**
- **Serum Creatinine ≤1.5 mg/dl**
Drug Titration

- Many drugs/combinations provided to achieve goal BP according to randomized assignment.

Intensive Intervention:

- 2-drug therapy initiated: thiazide-type diuretic + ACEI, ARB, or β-blocker.
- Drugs added and/or titrated at each visit to achieve SBP <120 mm Hg.
- At periodic “milepost” visits: addition of another drug “required” if not at goal.

Standard Intervention:

- Intensify therapy if SBP ≥160 mm Hg @ 1 visit or ≥140 mm Hg @ 2 consecutive visits
- Down-titration if SBP <130 mm Hg @ 1 visit or <135 mm Hg @ 2 consecutive visits
Medications Prescribed (12 Month Visit)

Participants (%)

ACE-Inhibitor  ARB  ACE or ARB  Diuretic  β-blocker  CCB  α-blocker  Reserpine  Other  Statin  Platelet Inhibitor

Red: Intensive  Blue: Standard
ACCORD BP: Effects of Intensive BP-Control on Type 2 Diabetes

- Evaluated effects of intensive BP control (<120 mm Hg SBP) on CVD events among high-risk subjects with type 2 diabetes
- Subjects (N=4,733)
  - SBP between 130-180 mm Hg
  - taking ≤3 antihypertensives
  - <1.0 g 24-hour protein exchange rate
  - randomized to intensive (SBP <120 mm Hg) or standard (SBP <140 mm Hg) therapy
  - BP assessment was conducted once/month for 4 months and every 2 months thereafter for intensive therapy, and at months 1 and 4 and every 4 months thereafter for standard therapy
- Primary outcome: first occurrence of major CV event, including nonfatal MI, nonfatal stroke, or death from CV causes

ACCORD=Action to Control Cardiovascular Risk in Diabetes
BP=blood pressure; CVD=cardiovascular disease; MI=myocardial infarction; SBP=systolic blood pressure

Visit schedule

- Intensive arm once monthly for 4 months
- Every 2 months thereafter

- Standard arm months 1 and 4 then 4 months thereafter

- Additional visits were scheduled on an as needed basis
- 4 month visits study outcome and adverse events were ascertained –some of which were self reported
Systolic Pressures (mean ± 95% CI)

Average after 1st year: 133.5 Standard vs. 119.3 Intensive, Delta = 14.2
What do you observe?

- Within 4 months BP reduced to 119 mm Hg in the intensive arm verses 134 mm Hg in the standard arm
  (15 mm difference)
Primary Outcome: Nonfatal MI, Nonfatal Stroke or CVD Death

Event 15

HR = 0.88
95% CI (0.73-1.06)

Years Post-Randomization

Patients with Events (%)
Nonfatal Stroke

Total Stroke

Patients with Events (%)

Years Post-Randomization

Intensive  Standard

HR = 0.63

95% CI (0.41 - 0.96)

HR = 0.59

95% CI (0.39 - 0.89)

Patients with Events (%)

Years Post-Randomization

0 1 2 3 4 5 6 7 8

0 1 2 3 4 5 6 7 8
## Primary & Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Intensive Events (% / yr)</th>
<th>Standard Events (% / yr)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>208 (1.87)</td>
<td>237 (2.09)</td>
<td>0.88 (0.73-1.06)</td>
<td>0.20</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>150 (1.28)</td>
<td>144 (1.19)</td>
<td>1.07 (0.85-1.35)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cardiovascular Deaths</td>
<td>60 (0.52)</td>
<td>58 (0.49)</td>
<td>1.06 (0.74-1.52)</td>
<td>0.74</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>126 (1.13)</td>
<td>146 (1.28)</td>
<td>0.87 (0.68-1.10)</td>
<td>0.25</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>34 (0.30)</td>
<td>55 (0.47)</td>
<td>0.63 (0.41-0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total Stroke</td>
<td>36 (0.32)</td>
<td>62 (0.53)</td>
<td>0.59 (0.39-0.89)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>Intensive N (%)</td>
<td>Standard N (%)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------------</td>
<td>----------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Serious AE</td>
<td>77 (3.3)</td>
<td>30 (1.3)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>17 (0.7)</td>
<td>1 (0.04)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>12 (0.5)</td>
<td>5 (0.2)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Bradycardia or Arrhythmia</td>
<td>12 (0.5)</td>
<td>3 (0.1)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>9 (0.4)</td>
<td>1 (0.04)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Renal Failure</td>
<td>5 (0.2)</td>
<td>1 (0.04)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>GFR ever &lt;30 mL/min/1.73m²</td>
<td>99 (4.2)</td>
<td>52 (2.2)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Dizziness on Standing†</td>
<td>217 (44)</td>
<td>188 (40)</td>
<td>0.36</td>
<td></td>
</tr>
</tbody>
</table>
The ACCORD BP trial evaluated the effect of targeting a SBP goal of 120 mm Hg, compared to a goal of 140 mm Hg, in patients with type 2 diabetes at increased cardiovascular risk.

The results provide no conclusive evidence that the intensive BP control strategy reduces the rate of a composite of major CVD events in such patients.
Summary

- ACEI/ARB were the most commonly used medications
- There was no difference in the primary outcome composite of nonfatal MI, nonfatal stroke or CVD death
- Secondary outcome of nonfatal and fatal stroke was significantly improved in the intensively treated verses standard groups (numbers of events were small 32 Int verses 62 Std)
- Side effects of syncope and hypotension was greatest in the intensively treated group (2.6 fold)
- Hypokalemia more individuals in the intensively treated group
- Same number in both groups progressed to ESRD (systolic BP to 140 mm Hgb may be sufficient to progress to ESRD)
- End of study intensively treated group had lower GFR than standard group
- Small number of stroke events and under powdered

  94% power for 20% reduction in event rate, assuming standard group rate of 4% / yr and 5.6 yrs follow-up
Stroke Results

- Assuming that this finding was real, the number needed to treat to the lower SBP level to prevent one stroke over 5 years was 89.
<table>
<thead>
<tr>
<th>Clinical Parameters assessed at last clinic visit</th>
<th>Intensive</th>
<th>Standard</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium (mean mg/dl)</td>
<td>4.3</td>
<td>4.4</td>
<td>0.17</td>
</tr>
<tr>
<td>Serum Creatinine (mean mg/dl)</td>
<td>1.1</td>
<td>1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Estimated GFR (mean mL/min/1.73m²)</td>
<td>74.8</td>
<td>80.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urinary Alb/Cr (median mg/g)</td>
<td>12.6</td>
<td>14.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Macroalbuminuria (%)</td>
<td>6.6</td>
<td>8.7</td>
<td>0.009</td>
</tr>
</tbody>
</table>