Impact of Recent Clinical Trials on the Management of Cardiovascular Disease in Diabetes;

**Blood Pressure control**

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Combined SBP and Diabetes Increase CVD Risk

MRFIT Data: Diabetic Men With Elevated SBP at Greater Risk for CVD Than Those Without Diabetes

CVD Deaths per 10,000 Person-Years

SBP (mm Hg)

<120 120-139 140-159 160-179 180-199 200+

0 50 100 150 200 250 300

UKPDS, ADVANDE & ACCORD Trial

Adjusted incidence per 1000 person years (%)

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Updated mean systolic blood pressure (mm Hg)

UK Prospective Diabetes Study, BMJ Volume 321 12 August 2000
# 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 after Vanguard)
  - ≥ 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

# ACCORD BP Protocol

- 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
## ACCORD Key Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62 years</td>
</tr>
<tr>
<td>Women</td>
<td>38.6%</td>
</tr>
<tr>
<td>Median DM Duration</td>
<td>10 years</td>
</tr>
<tr>
<td>Previous CVD Event</td>
<td>35%</td>
</tr>
<tr>
<td>White</td>
<td>65%</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>32 kg/cm²</td>
</tr>
<tr>
<td>Mean A1C</td>
<td>8.3%</td>
</tr>
<tr>
<td>Mean SBP/DBP</td>
<td>136/75 mmHg</td>
</tr>
<tr>
<td>Mean LDL</td>
<td>105 mg/dL</td>
</tr>
</tbody>
</table>
ACCORD BP Trial – Achieved Target

**Systolic Pressures (mean ± 95% CI)**

- Mean # Meds
  - Intensive: 3.2
  - Standard: 1.9

<table>
<thead>
<tr>
<th>Years Post-Randomization</th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>140</td>
<td>130</td>
</tr>
<tr>
<td>1</td>
<td>133.5</td>
<td>119.3</td>
</tr>
<tr>
<td>2</td>
<td>132.5</td>
<td>119.3</td>
</tr>
<tr>
<td>3</td>
<td>131.5</td>
<td>118.3</td>
</tr>
<tr>
<td>4</td>
<td>130.5</td>
<td>117.3</td>
</tr>
<tr>
<td>5</td>
<td>129.5</td>
<td>116.3</td>
</tr>
<tr>
<td>6</td>
<td>128.5</td>
<td>115.3</td>
</tr>
<tr>
<td>7</td>
<td>127.5</td>
<td>114.3</td>
</tr>
<tr>
<td>8</td>
<td>126.5</td>
<td>113.3</td>
</tr>
</tbody>
</table>

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

**Medications Prescribed (12 Month Visit)**
## Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Intensive N (%)</th>
<th>Standard N (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious AE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>17 (0.7)</td>
<td>1 (0.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Syncope</td>
<td>12 (0.5)</td>
<td>5 (0.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Bradycardia or Arrhythmia</td>
<td>12 (0.5)</td>
<td>3 (0.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>9 (0.4)</td>
<td>1 (0.04)</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>5 (0.2)</td>
<td>1 (0.04)</td>
<td>0.12</td>
</tr>
<tr>
<td>eGFR ever &lt;30mL/min/1.73m²</td>
<td>99 (4.2)</td>
<td>52 (2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any Dialysis or ESRD</td>
<td>59 (2.5)</td>
<td>58 (2.4)</td>
<td>0.93</td>
</tr>
<tr>
<td>Dizziness on Standing†</td>
<td>217 (44)</td>
<td>188 (40)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

† Symptom experienced over past 30 days from HRQL sample of N=969 participants assessed at 12, 36, and 48 months post-randomization
The ACCORD BP Trial results provided no conclusive evidence that a strategy targeting normal SBP, compared with a standard SBP goal, reduces a composite of major CVD events in high-risk patients with type 2 diabetes, in the setting of good glycemic control.

- There was a higher risk of SAE in the intensive BP group, but also a 41% lower stroke rate.
- The stroke effect is consistent with other BP treatment trials.
- SBP goal <120 mm Hg may reduce strokes in patients with diabetes like those in ACCORD.
## INVEST Key Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66 years</td>
</tr>
<tr>
<td>Women</td>
<td>54%</td>
</tr>
<tr>
<td>Previous CVD Event</td>
<td>100%</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>30 kg/cm²</td>
</tr>
</tbody>
</table>
INVEST: Mortality hazard with lowest blood pressures in diabetics with CAD?

- A new retrospective analysis of the International Verapamil SR-Trandolapril (INVEST) trial
- Patients whose systolic blood pressure was lowered to 130 to 140 mm Hg had a better outcome than those with systolic pressures over 140 mm Hg. But those whose systolic blood pressure was reduced to below 130 mm Hg did not appear to receive any additional benefit and had a higher mortality rate.
INVEST: Adjusted Risk of All-Cause Mortality

Cooper-DeHoff, R. M. et al. JAMA 2010;304:61-68
Is the ‘J-Curve’ Right in Diabetic Patients?
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.4</td>
</tr>
<tr>
<td>Male (%)</td>
<td>73.3</td>
</tr>
<tr>
<td>BP at entry (mm Hg)</td>
<td>143/82</td>
</tr>
<tr>
<td>Medical history (%)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>48.7</td>
</tr>
<tr>
<td>Stable angina</td>
<td>34.8</td>
</tr>
<tr>
<td>Stroke/transient ischaemic attack</td>
<td>20.7</td>
</tr>
<tr>
<td>Peripheral Arterial Disease</td>
<td>11.8</td>
</tr>
<tr>
<td>Diabetes</td>
<td>37.3</td>
</tr>
</tbody>
</table>

The shallow nadir of the J-curve is spread over several SBP deciles and occurred around 130mmHg SBP for all outcomes except stroke.

J-Curve; A Narrow Window of Optimum BP for High-risk Individuals

- INVEST, ONTARGET, VALIANT, VALUE and TNT studies who include excessively low pressures for analysis do show a “V-,” “J-,” or “U-,” shaped curve

- Raised concern about “J-Curve” hypothesis especially in the elderly and patients with CAD
Contradicting Result from UKPDS
No J-Curve in UKPDS

Any diabetes-related endpoint
(12% ↓ per 10mm Hg ↓ in systolic BP)

Diabetes-related mortality
(17% ↓ per 10mm Hg ↓ in systolic BP)

Hazard ratio

Updated mean systolic BP (mm Hg)
(95% CI)

$P<0.001$

Adapted from Adler AI et al. BMJ. 2000;321:412-419.
## What Make This Difference?

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>INVEST</th>
<th>ONTARGET</th>
<th>UKPDS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>62</td>
<td>66</td>
<td>66.4</td>
<td>53</td>
</tr>
<tr>
<td><strong>DM duration (years)</strong></td>
<td>10</td>
<td>May be long?</td>
<td>% of DM Pts = 37.5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Prior CV event (%)</strong></td>
<td>34%</td>
<td>100%</td>
<td>MI 49%, stable angina 34.8%</td>
<td>0</td>
</tr>
</tbody>
</table>
Individualized Therapy

• (Near) normal BP is not better compared in *relatively old diabetic patients with advanced complications*

• *In case of early diabetes with relatively young age?*
Will ACCORD Change BP Target in Diabetics?
ADA Recommendation 2010

Goals

- Patients with diabetes should be treated to a systolic blood pressure < 130 mmHg. (C)
- Patients with diabetes should be treated to a diastolic blood pressure < 80 mmHg. (B)
Clinical Trials of BP Lowering in Diabetic Patients: Mean Achieved Systolic (SBP)

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Mean SBP conventional</th>
<th>Mean SBP intensive</th>
<th>CVD Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEP</td>
<td>583</td>
<td>155</td>
<td>146</td>
<td>22-56%</td>
</tr>
<tr>
<td>Syst-EUR</td>
<td>492</td>
<td>162</td>
<td>153</td>
<td>62-69%</td>
</tr>
<tr>
<td>HOT</td>
<td>1,501</td>
<td>148</td>
<td>144</td>
<td>30-67%</td>
</tr>
<tr>
<td>UKPDS</td>
<td>1,148</td>
<td>154</td>
<td>144</td>
<td>32-44%</td>
</tr>
<tr>
<td>ABCD</td>
<td>470</td>
<td>138</td>
<td>132</td>
<td>No CVD ↓</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>11,140</td>
<td>140</td>
<td>135</td>
<td>14% mortality ↓</td>
</tr>
</tbody>
</table>
• Randomized clinical trials have demonstrated the benefit (reduction of CHD events, stroke, and nephropathy) of lowering blood pressure to **140 mmHg systolic and 80 mmHg diastolic** in individuals with diabetes.

• Epidemiologic analyses show that **blood pressure 115/75 mmHg** is associated with increased cardiovascular event rates and mortality in individuals with diabetes.

• Therefore, a target blood pressure goal of **130/80 mmHg** is reasonable if it can be achieved safely.
Will ACCORD Change BP Target in Diabetics?

Probably No!

Emphasize Individualized Target!
New Recommendation 2011
- My View

• In general, no change of target goal
  - 130/80 mmHg

• Individualized approach
  – SBP <120 mm Hg to lower stroke risk, progression of proteinuria in CKD
  – Less stringent target especially in diabetics with CAD
    • Less than 140/90 mmHg or
    • Range of BP: 130<SBP<140, 80<DBP<90
**A Lesson from Unsuccessful Trial - ABC Management in ACCORD**

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1c (average)</strong></td>
<td>6.4%</td>
<td>7.5%</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- systolic (average)</td>
<td>119.3 mmHg</td>
<td>133.5 mmHg</td>
</tr>
<tr>
<td><strong>Cholesterol (at the end)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>81.1 mg/dl</td>
<td>80 mg/dl</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>122 mg/dl</td>
<td>144 mg/dl</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>41.2 mg/dl</td>
<td>40.5 mg/dl</td>
</tr>
</tbody>
</table>

*Event rate in the standard therapy group was 50% lower than the expected rate - Multifactorial intervention is important!*
What is the First-line Drug for Diabetic Hypertension?
ESH/ESC Guidelines 2007 - *Diabetic Hypertension*

- To reach diabetic hypertension goals, combination therapy is most often required

- Evidence indicates that combinations including an ACE inhibitor in Type 1 diabetes and an ARB in Type 2 diabetes provide renoprotection benefits

- In patients with type 2 diabetes, treatment should be initiated when BP is high-normal

Type 2 Diabetes Master DecisionPath: Hypertension

At presentation

For all patients with BP above normal (SBP ≥120 mmHg)

Blood pressure targets
In-office BP <130/80 mmHg and Self-monitored BP <125/75 mmHg

Self-management
- Ensure tobacco free
- Consider self-monitored blood pressure

Nutrition and activity
- Refer for Medical Nutrition Therapy
- Lowers Systolic BP 2-20 mmHg

Emotional health
- Stress-management training
- Assess psychosocial needs including anxiety and/or depression

Add medication if not at target

Systolic BP 130-149 mmHg

Hypertension only

# BP Meds 1
ACEI / ARB or Thiazide
Titrated dose, add medication if not at target in 1-2 months

Hypertension + nephropathy

ACEI or ARB
Titrated dose, add medication if not at target in 1-2 months

Systolic BP ≥150 mmHg (Start 2 meds if SBP ≥150 mmHg)

# BP Meds 2
Add Thiazide or ACEI / ARB
Titrated dose, add medication if not at target in 1-2 months

3
Add CCB or β-blocker
Titrated dose, add medication if not at target in 1-2 months

4
Add β-blocker or CCB
Titrated dose, add medication if not at target in 1-2 months

Annual screen for microalbuminuria and eGFR (www.nephron.com)

5+
Add additional BP medication as needed
Consider: Aldosterone antagonists, reserpine, combining ACEI and ARB, α/β blocker (Carvediol), α-blocker and hydralazine

See next page for clinical considerations; key to abbreviations

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CCB: Still 3rd line Drug for the Management of Diabetic Hypertension?
ACCOMPLISH: Trial Design

Prospective, randomized, double-blind, event-driven trial

Target BP <140/90 mmHg; <130/80 mmHg in patients with diabetes or renal insufficiency

Forced titration

- Benazepril 20 mg + Amlodipine 5 mg
- Benazepril 20 mg + HCTZ 12.5 mg

Follow up at 6 months and every 6 months thereafter

11,506 patients

Free add-on*

Benazepril 40 mg + Amlodipine 10 mg
Benazepril 40 mg + Amlodipine 5 mg
Benazepril 40 mg + HCTZ 12.5 mg
Benazepril 40 mg + HCTZ 25 mg

*Beta blockers; alpha blockers; clonidine; loop diuretics; HCTZ = hydrochlorothiazide

ACCOMPLISH Trial – Diabetic subgroup

J Am Coll Cardiol 2010;56:77–85
Are Still Diuretics 2nd-line Therapy for Diabetic Hypertension?
RCT Results

- Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet.* 2007 Sep 8;370(9590):829-40


- ALLHAT findings revisited in the context of subsequent analyses, other trials, and meta-analyses. *Arch Intern Med.* 2009;169(9):832-842

- ALLHAT: still providing correct answers after 7 years. *Curr Opin Cardiol* 2010; 25:355–365
Meta-analysis


• Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;338:b1665

• Blood pressure lowering efficacy of *diuretics as second-line therapy* for primary hypertension. *Cochrane Database of Systematic Reviews* 2009, Issue 4
Treatment of Hypertension in association with Diabetes Mellitus: Summary

Threshold equal or over 130/80 mmHg and TARGET below 130/80 mmHg

Diabetes

- with Nephropathy
  - ACE Inhibitor or ARB
  - 1. ACEI Inhibitor or ARB
    - or
    - 2. Thiazide diuretic or DHP-CCB

- without Nephropathy
  - > 2-drug combinations

A combination of 2 first line drugs may be considered as initial therapy if the blood pressure is >20 mmHg systolic or >10 mmHg diastolic above target.

More than 3 drugs may be needed to reach target values for diabetic patients

If Creatinine over 150 μmol/L or creatinine clearance below 30 ml/min (0.5 ml/sec), a loop diuretic should be substituted for a thiazide diuretic if control of volume is desired.

Monitor serum potassium and creatinine carefully in patients with CKD prescribed an ACEI or ARB.

Combinations of an ACEI with an ARB are specifically not recommended in the absence of proteinuria.

CHEP 2010
ADA Recommendation 2010

• Pharmacologic therapy for patients with diabetes and hypertension should be paired with a regimen that includes either an ACE inhibitor or an angiotensin II receptor blocker (ARB)

• If needed to achieve blood pressure targets, a thiazide diuretic should be added to those with an estimated glomerular filtration rate (GFR) (see below) 30 ml min/1.73 m2 and a loop diuretic for those with an estimated GFR 30 ml min/1.73 m2 (C)
Take Home Messages

- BP target
  - In general, less than 130/80mmHg
- Individualized target
  - Early intensive,
  - Less tightly especially in patients with CAD
- BP control as one of multifactorial intervention
- First-line drug; RAS inhibitor
- Second-line drug; diuretics or CCB