Hypertension in Diabetes: Where Should the Millimeters of Mercury be?

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Objectives
1. Explain the proposed mechanism for hypertension in patients with diabetes mellitus
2. Discuss the importance of treating hypertension in patients with diabetes mellitus
3. Evaluate the evidence for intensive blood pressure control for patients with diabetes mellitus
4. Make recommendations based on current evidence for blood pressure goals in patients with diabetes mellitus
I. Epidemiology

A. United States (U.S.) Prevalence of Diagnosed and Undiagnosed Diabetes (2010)\textsuperscript{1}
   i. Any age – 25.8 million (8.3%)
   ii. Age ≥ 20 years – 25.6 million (11.3%)
   iii. Age ≥ 65 years – 10.9 million (26.9%)

![Figure 1: Estimated percentage of people aged 20 years or older with diagnosed and undiagnosed diabetes by age group (U.S., 2005-2008)](image)

B. National Trends in Diagnosed Diabetes (DM)\textsuperscript{2}
   i. Prevalence increased from 0.9% in 1958 to 6.3% in 2008
      1. In 1958, 1.6 million people had a DM diagnosis
      2. In 2008, 18.8 million people had a DM diagnosis

![Figure 2: Age-adjusted percentage of U.S. adults who had a diagnosis of diabetes](image)

C. Complications from Diabetes (DM)\textsuperscript{1}
   i. Macrovascular
      1. Two to four times higher risk for:
         a. Death from heart disease
         b. Stroke
   ii. Microvascular
      1. Leading cause of new cases of adult blindness
      2. Leading cause of kidney failure
      3. Leading cause of non-traumatic lower-limb amputations
      4. Causes mild to severe forms of nerve damage
         a. Peripheral neuropathy (e.g., impaired sensation or pain), gastroparesis and erectile dysfunction
D. Mortality from Diabetes
   i. Overall risk of death is about twice that of people of similar age without DM
   ii. Seventh leading cause of death in the U.S.
      1. Likely underreported as a cause of death
   iii. Causes of death in diabetic patients (over the age of 65 years)
      1. 68% from coronary heart disease
      2. 16% from stroke
   iv. Classified as a CV disease risk equivalent

E. Type 2 Diabetes Mellitus (T2DM)
   i. Accounts for about 90% to 95% of all diagnosed cases of DM

F. Hypertension (HTN) in Diabetes
   i. Prevalence increased among patients with either type of diabetes
      1. Most common in patients with T2DM
   ii. 67% of adults with DM have blood pressure (BP) ≥ 140/90 millimeters of mercury (mmHg) or use HTN medications (2005-2008)
   iii. Elevates the risk of cardiovascular (CV) disease associated with DM
   iv. HTN is also a risk factor for the development of:
      1. Myocardial infarction (MI)
      2. Stroke
      3. Nephropathy
      4. Retinopathy
II. Pathophysiology

A. Type 1 Diabetes Mellitus\(^1\)
   i. Auto-immune destruction of pancreatic beta cells
      1. Insulin production completely diminished
   ii. Risk factors may include:
      1. Auto-immune disorders
      2. Genetics
      3. Environment

B. Type 2 Diabetes Mellitus\(^7\)
   i. Results from two major defects
      1. Peripheral insulin resistance
         a. Contributing factors:
            i. Genetics, age, obesity, hyperglycemia
         b. Effect on muscle:
            i. Impaired glucose uptake
         c. Effect on liver:
            i. Hepatic glucose production not suppressed
               ii. Contributes to fasting hyperglycemia
         d. Effect on adipose cells:
            i. Increased lipolysis \(\rightarrow\) Increases levels of free fatty acids
               1. Impairs both beta-cell function and glucose uptake in skeletal muscles
               2. Promotes hepatic glucose release
      2. Decreased insulin secretion
         a. Insulin secretion initially increased due to insulin resistance
         b. With time, pancreatic insulin production and secretion decreases
            i. Leads to progressive hyperglycemia

   ii. Additional factors\(^7\)
      1. Adipose tissue acts as endocrine organ
         a. Secretes hormones that may regulate:
            i. Insulin sensitivity
            ii. Appetite
            iii. Inflammation
            iv. Coagulability

\[\text{Figure 4: Overview of the pathogenesis of T2DM}^{7}\]

\[\text{FFA = free fatty acid}\]
C. Hypertension in Diabetes

i. Clinical onset often precedes diagnosis of T2DM

ii. Proposed causes:
   1. Obesity
      a. Prevalence increases among T1DM, T2DM, and non-diabetic subjects as BMI increases
   2. Older age
   3. Sodium and volume
      a. Increased exchangeable sodium (correlates with age and SBP)
      b. Impaired sodium excretion
      c. Temporal increase in proximal tubular sodium reabsorption
   4. Increased vascular response to norepinephrine and angiotensin II
   5. Insulin resistance and hyperinsulinemia

![Figure 5: Associated factors in T2DM](http://assets.treesd.com/images/healthtree/articles/ht_diabetes_cholesterol_hypertension_1130.jpg)

III. Benefit of Interventions

A. Blood pressure control
   i. Reduces risk of CV disease (by 33% to 50%) and microvascular complications (by ~33%)

B. Improved glycemic control
   i. Every percent drop in hemoglobin A1c (HbA1c) reduces risk of microvascular complications (by 40%)

C. Lipid control
   i. Reduces risk of CV complications (by 20% to 50%)

![Figure 6: Possible factors that elevate BP in diabetes mellitus](http://assets.treesd.com/images/healthtree/articles/ht_diabetes_cholesterol_hypertension_1130.jpg)
IV. Guideline Recommendations

A. BP goal < 130/85 mmHg (for all patients with DM)
   ii. 1997: JNC-6\(^8\)

B. BP goal < 130/80 mmHg (for all patients with DM)
   i. 2002: American Diabetes Association (ADA)\(^1\)
   ii. 2003: JNC-7\(^6\)

C. Most recent guidelines reaffirming BP goal < 130/80 mmHg (for all patients with DM)
   i. 2007: American Association of Clinical Endocrinologists (AACE)\(^1\)
   ii. 2007: European Society of Hypertension (ESH) & European Society of Cardiology (ESC)\(^1\)
   iii. 2010: ADA\(^1\)

D. Other conditions with intensive BP goals (< 130/80 mmHg)
   i. 2003: Chronic Kidney Disease (JNC-7)\(^6\)
   ii. 2007: Coronary Artery Disease (American Heart Association)\(^14\)

V. Observational Studies

A. Lewington S, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies.\(^1\)

   - Meta-analysis
     o Included prospective, observational studies with BP and mortality data
     o Combined trial populations without regard to presence of DM
     o Only used participant data with no previous vascular disease at baseline
   - Compared mortality risk across 10 mmHg intervals for both SBP and DBP at each decade of life
     o Risk of vascular mortality decreased as SBP and DBP decreased
     o No evidence of a threshold down to at least 115/75 mmHg
     o Controlling for diabetes did not alter the estimated effects of BP
   - Authors suggested:
     o The absolute benefits of a lower BP level are likely to be greatest for those at greatest absolute risk of vascular disease

\[\text{Figure 7: Ischemic heart disease (A) and stroke (B) mortality rate in each decade of age versus usual BP at the start of that decade}\]
B. Stamler J, et. al. Diabetes, Other Risk Factors, and 12-Year Cardiovascular Mortality for Men Screened in the Multiple Risk Factor Intervention Trial.\(^6\)

- Prospective, cohort study of males aged 35-57 years screened for MRFIT trial
  - 5,163 with diabetes & 342,815 without diabetes
    - Diabetes if pt reported drug tx for diabetes
    - No information on duration of diabetes, glucose control or lipid levels
  - Average follow-up: 12 years
- Compared age-adjusted CV death rates by SBP level in 20 mmHg intervals (<120 to \(\geq 200\))
  - SBP was significantly related to risk of CV death (\(p < 0.001\))
  - With higher SBP, CV mortality rates increased more steeply
- Authors suggested
  - SBP is a significant, strong, independent predictor of mortality in men
  - Risk of CV death was greater for men at every SBP interval above 120 mmHg

Table 1: Age-adjusted CVD death rates by SBP level for men with diabetes at initial screening for MRFIT

<table>
<thead>
<tr>
<th>SBP (mmHg)</th>
<th># of Men with Diabetes</th>
<th># of CVD Deaths</th>
<th>Rate per 10,000 person-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>757</td>
<td>52</td>
<td>53.61</td>
</tr>
<tr>
<td>120-139</td>
<td>2316</td>
<td>203</td>
<td>65.47</td>
</tr>
<tr>
<td>140-159</td>
<td>1421</td>
<td>206</td>
<td>108.15</td>
</tr>
<tr>
<td>160-179</td>
<td>494</td>
<td>102</td>
<td>158.71</td>
</tr>
<tr>
<td>180-199</td>
<td>131</td>
<td>27</td>
<td>155.65</td>
</tr>
<tr>
<td>(\geq 200)</td>
<td>44</td>
<td>13</td>
<td>242.61</td>
</tr>
</tbody>
</table>

C. Adler AI, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study.\(^7\)

- Prospective, observational study
  - Used patient data from UKPDS
  - Median follow-up: 10.5 years
- Comparing complication rates across SBP ranges of <120 to \(\geq 160\) mmHg
  - Each 10mmHg decrease in SBP associated with significant risk reduction for:
    - Any complications related to diabetes, deaths related to diabetes, MI, stroke, microvascular complications, and all cause mortality
  - No threshold for risk was observed for any outcome
- Authors suggested:
  - No specific target BP to aim for
  - Lower risk of complications at nearer to normal systolic blood pressure (SBP)

Figure 8: Hazard rates (95% CIs as floating absolute risks) as estimate of association between category of mean SBP and any end point related to DM and all cause mortality with log linear scales
VI. Post-Hoc Analyses of Clinical Trials

A. The International Verapamil-Trandolapril Study (INVEST)\textsuperscript{18}

- Multicenter prospective, randomized trial
- 22,576 participants (28\% with DM)
  - Age 50 years or older (mean 66 years)
  - CAD & HTN
- Intervention
  - First-line treatment with either a calcium antagonist (CCB) or beta-blocker (BB)
  - Target BP < 140/90 and < 130/85 for diabetic patients
  - Mean follow-up 2.7 years
- Outcomes
  - Primary: Composite of all secondary outcomes
  - Secondary: All-cause death, nonfatal stroke, nonfatal MI
- The strategies were equivalent in preventing all-cause death, nonfatal MI or stroke (DM or not)

i. Messerli FH, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous?\textsuperscript{19}

- Design
  - Post-hoc analysis of INVEST population
- Methods
  - Evaluated the relationship between average on-treatment BP and risk for outcomes
  - Pooled by 10–mmHg strata for SBP (from ≤ 110 to > 160) and DBP (≤ 60 to > 110)
- Results
  - Relationship between BP and all-cause death or total MI was J-shaped (particularly for DBP)
  - At a lower DBP there were substantially more MIs than strokes
- Authors suggested:
  - Risk for primary outcome, all-cause death, and MI, but not stroke, progressively increased with low DBP (below 70 to 80 mmHg)
  - Excessive reduction in DBP should be avoided in patients with CAD being treated for HTN

![Figure 9: Adjusted hazard ratios for the primary outcome by SBP and DBP strata\textsuperscript{19}](image)

![Figure 10: Incidence of total MI and total stroke by DBP strata\textsuperscript{19}](image)
- Design
  - Post-hoc subgroup analysis of diabetic population in INVEST (n=6400)
- Methods
  - Evaluated the relationship between follow-up BP and risk for the primary outcome
  - Pooled by 10 mmHg strata for SBP (from ≤ 110 to > 180) and DBP (≤ 60 to > 110)
- Results
  - BP < 140/90 mmHg was associated with reduced risk of the primary outcome
  - Reduced risk extends to BP of 110/60 mmHg
  - Risk appears to increase at levels < 110/60 mmHg (obtained by ~1% of patients)
- Authors suggested:
  - Given the small number of participants who achieved BP < 110/60 mmHg no firm statements can be made for this subgroup

![Figure 11: Incidence (percentage with 95% CI) and risk (HR) of primary outcome in the diabetes cohort by mean follow-up SBP and DBP.](image)

- Design
  - Post-hoc subgroup analysis of diabetic population in INVEST (n=6400)
- Methods
  - Compared CV outcomes and death based on average SBP achieved (among 3 groups)
    - Tight control (< 130 mmHg), usual control (130 to < 140 mmHg), uncontrolled (≥ 140 mmHg)
  - Categorized SBP of < 130 mmHg in 5 mmHg segments to compare all-cause mortality rates
- Results
  - Mean BP achieved (mmHg)
    - 121.5 (< 130)
    - 131.2 (130 to < 140)
    - 146.1 (≥ 140)
  - Comparison across the 3 groups
    - Lower BP associated with lower all-cause mortality, non-fatal MIs and stroke (P < 0.001)
  - Comparing tight vs. usual control
    - Non-fatal MI or non-fatal stroke
      - No difference (P=0.49 & P=0.38, respectively)
    - All-cause mortality
      - No difference after adjusting for baseline differences (P=0.06)
      - Increased risk in extended follow-up of U.S. cohort (P=0.04)
  - Comparing SBP range of 125-130 mmHg to lower ranges
    - SBP of < 110 had increased risk of all-cause mortality (P=0.02)
Authors suggested:
- Tight control of SBP among patients with diabetes and CAD was not associated with improved CV outcomes compared with usual control
- Decreasing SBP to < 130 mmHg in patients with DM and CAD not associated with further reduction in morbidity beyond that associated with SBP < 140 mmHg but is associated with an increased risk of all-cause mortality

Figure 12: Cumulative event rates for MI, stroke and all-cause mortality

B. Irbesartan Diabetic Nephropathy Trial (IDNT)
- Multicenter, prospective, randomized, double-blind trial
- 1715 participants (29% with history of CV disease)
  - Age 30 and 70 years
  - T2DM
  - HTN
  - Proteinuria (urinary protein excretion ≥ 900 mg per 24 hours)
  - Serum creatinine between 1 and 3 mg/dL
- Intervention
  - Treatment with irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo
  - Target BP was < 135/85 mmHg
  - 2.6 years mean duration of follow-up
- Outcomes
  - Primary: Doubling of the base-line serum creatinine concentration, the onset of end-stage renal disease, or death from any cause (composite)
  - Secondary: composite of death from CV causes, nonfatal MI, HF resulting in hospitalization, a permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle
- Results
  - Irbesartan reduced the risk of the primary outcome and the risk of doubling the serum creatinine compared to either placebo or amlodipine (P < 0.05)
  - There was no significant differences in the rates of all-cause mortality or in the CV composite end point
- Irbesartan is effective in protecting against the progression of nephropathy due to T2DM (independent of the BP reduction)

- Design
  - Post-hoc analysis of IDNT population
- Methods
  - Assessing impact of achieved SBP and DBP on CV outcomes
• Results
  o Progressively lowering SBP to 120 mmHg
    ▪ Predicted a decrease in CV mortality and heart failure (HF) but not MI
  o SBP < 120 mmHg (obtained by 3.3% of pts)
    ▪ Associated with increased risk for CV deaths (P < 0.0001), HF events (P < 0.008) and all-
      cause mortality (P < 0.0001)
    ▪ Trend for increased stroke risk (non-significant)
    ▪ No increase in MI risk
  o Impact of a 10 mmHg lower mean achieved DBP (reference value of 85 mmHg with all SBP >
    120 mmHg)
    ▪ Increased risk for MI (P < 0.0001)
      • 61% increase in RR per 10 mmHg lower DBP
    ▪ Trend for increased CV deaths, HF events, all-cause mortality (all non-significant)
    ▪ Decreased risk for stroke (P < 0.005)
• Authors suggested:
  o BP < 120/85 mmHg may be associated with an increase in CV events
  o Targeting a SBP of 120 mmHg and a DBP of ~80–85 mmHg are likely to provide significant
    protection from CV events

Figure 13: Relative risk of CV mortality by level of achieved SBP

Figure 14: Relative risk of MI by level of achieved DBP
# VII. Clinical Trials Investigating Blood Pressure Goals

## United Kingdom Prospective Diabetes Study (UKPDS) 38\(^{24}\)

<table>
<thead>
<tr>
<th>Objective</th>
<th>To determine whether tight control of BP prevents macrovascular and microvascular complications in patients with type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Multi-site prospective, randomized trial</td>
</tr>
</tbody>
</table>

### Subjects

**Inclusion Criteria**
- Recruited to original UKPDS
  - New diagnosis of T2DM
  - Age 25 to 65 years
- HTN (either one)
  - SBP > 160 mmHg and/or a diastolic blood pressure (DBP) > 90 mmHg
  - Receiving antihypertensive treatment with SBP > 150 mmHg and/or a DBP > 85 mmHg

**Exclusion Criteria**
- A clinical requirement for strict BP control
  - Previous stroke, accelerated HTN, HF, or renal failure
- Beta blockade (MI in previous year or current angina)
- Severe vascular disease (> 1 major vascular episode)
- A severe concurrent illness or contraindications to BBs (asthma, intermittent claudication, foot ulcers, or amputations)

### Methods

**Intervention**
- Tight control
  - BP < 150/85 mmHg
  - Angiotensin converting enzyme inhibitor (ACEI) or BB as main tx
    - Captopril (25 to 50 mg BID)
    - Atenolol (50 to 100 mg daily)
- Less tight control
  - Was originally BP < 200/105 mmHg
    - Changed during study to < 180/105 mmHg (based on non-diabetic study results)
  - Avoided tx with ACEI or BB
  - Other agents added if BP goal not met (using suggested sequence):
    - Furosemide (20 mg daily to 40 mg BID), slow release nifedipine (10 mg to 40 mg BID), methyldopa (250 to 500 BID), prazosin (1 to 5 mg TID)

**Other Interventions**
- For blood glucose control, patients received concurrent diet treatment with or without a sulphonylurea, insulin or metformin (balanced numbers randomized to each)

### Outcomes

**Primary**
- First clinical end point related to diabetes
  - Sudden death, death from hyperglycemia or hypoglycemia, fatal or non-fatal MI, angina, HF, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye or cataract extraction
- Death related to diabetes
  - Death due to MI, sudden death, stroke, peripheral vascular disease (PVD), renal disease, hyperglycemia or hypoglycemia
- Death from all causes

**Secondary**
- MI
- Stroke
- Amputation or death from PVD
- Microvascular complications (retinopathy photocoagulation, vitreous hemorrhage, renal failure)

Used independent assessors for final arbitration
Statistics

- Intention to treat
- Log rank tests (for life table analyses)
- Cox's proportional hazards models (for hazard ratios and relative risks)
- Kaplan-Meier (for survival function estimates)
- Wilcoxon, t-test and Chi-square (for comparisons)
- Risk reductions derived from frequency tables (for surrogate end points)

Participants

- 1148 patients
  - 758 to tight control (400 ACEI, 358 BB)
  - 390 to less tight control
- Baseline characteristics
  - 55% male, ~87% white, mean age 56 years
  - ~2.6 years duration of DM (mean HbA1c 6.9%)
  - Mean BP 159/94 mmHg
- Median follow-up 8.4 years

Mean Blood Pressures Achieved

- BP significantly lower in tight control group (P < 0.0001)
  - Tight control
    - 144/82 mmHg
  - Less tight control
    - 154/87 mmHg

Results

<table>
<thead>
<tr>
<th>Outcomes (tight vs. less tight)</th>
<th>Events per 1000 patient-yrs</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related end point</td>
<td>50.9</td>
<td>67.4</td>
<td>0.76 (0.62 to 0.92)</td>
</tr>
<tr>
<td>Deaths related to diabetes</td>
<td>13.7</td>
<td>20.3</td>
<td>0.68 (0.49 to 0.94)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>22.4</td>
<td>27.2</td>
<td>0.82 (0.63 to 1.08)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>18.6</td>
<td>23.5</td>
<td>0.79 (0.59 to 1.07)</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.5</td>
<td>11.6</td>
<td>0.56 (0.35 to 0.89)</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>12.0</td>
<td>19.2</td>
<td>0.63 (0.44 to 0.89)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.4</td>
<td>2.7</td>
<td>0.51 (0.19 to 1.37)</td>
</tr>
</tbody>
</table>

Conclusions

Tight BP control in patients with HTN and T2DM achieves a clinically important reduction in the risk of death related to diabetes, complications related to diabetes, stroke and progression of diabetic retinopathy.

Strengths

- Prospective, randomized
- Large number of patients
- Important clinical outcomes assessed
- Compared two BP targets (in pts with T2DM)
- Independent adjudication of outcomes
- Both groups maintained similar HbA1c’s throughout the study

Limitations

- BP goals were high
- Less tight BP goal changed around study midpoint
<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>To assess the association between major cardiovascular events and specific target BPs during antihypertensive treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Multi-site, prospective, randomized, open-label with blinded endpoint evaluation</td>
</tr>
</tbody>
</table>
| **Subjects** | Inclusion Criteria  
  - HTN  
  - Age 50–80 years  
  - DBP 100 to 115 mmHg |
| **Methods**  | Intervention  
  - One of three DBP targets:  
    - ≤ 90 mmHg  
    - ≤ 85 mmHg  
    - ≤ 80 mmHg  
  Antihypertensive Treatments  
  - Initial therapy  
    - Felodipine (5 mg daily)  
  - Additional therapy and dose increments in four further steps  
    - Add either ACEI or BB  
    - Increase felodipine dose (10 mg daily)  
    - Double ACEI or BB dose  
    - Add diuretic  
  Other Intervention  
  - Patients received concurrent treatment with aspirin 75mg/day or placebo (balanced numbers randomized to each) |
| **Outcomes** | Primary  
  - Major CV events  
    - Non-fatal MI, non-fatal stroke, and CV death  
  Independent clinical event committee evaluated all events |
| **Statistics** |  
  - Cox proportional-hazards model (for relative risks)  
  - Poisson model (analyze events in relation to achieved BP) |
| **Results**  | Participants  
  - 18790 patients  
    - 6264 to DBP ≤ 90 mmHg  
    - 6264 to DBP ≤ 85 mmHg  
    - 6262 to DBP ≤ 80 mmHg  
  - Baseline characteristics  
    - 53% male, mean age 62 years  
    - 8% with diabetes  
    - 7.5% with previous MI or other CHD  
    - Mean BP 170/105 mmHg  
  - Mean follow-up was 3-8 years  
  Mean Blood Pressures Achieved  
  - Total population  
    - DBP ≤ 90 mmHg  
      - 144/85 mmHg  
    - DBP ≤ 85 mmHg  
      - 141/83 mmHg  
    - DBP ≤ 80 mmHg  
      - 140/81 mmHg  
  - Diabetes population  
    - DBP ≤ 90 mmHg  
      - 148/85 mmHg  
    - DBP ≤ 85 mmHg  
      - 146/83 mmHg  
    - DBP ≤ 80 mmHg  
      - 144/81 mmHg |
## Results (cont.)

### Outcomes
- **Entire population**
  - No significant between group differences for any outcome
- **Diabetic population**

<table>
<thead>
<tr>
<th></th>
<th>Events per 1000 patient-years</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 90 mmHg</td>
<td>≤ 80 mmHg</td>
</tr>
<tr>
<td>MI</td>
<td>7.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Stroke</td>
<td>9.1</td>
<td>6.4</td>
</tr>
<tr>
<td>CV mortality</td>
<td>11.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Major CV events</td>
<td>24.4</td>
<td>11.9</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>15.9</td>
<td>9.0</td>
</tr>
</tbody>
</table>

## Conclusions
In patients with diabetes, the rates of major CV events and of CV deaths were lower the lower the target BP.

## Strengths
- Prospective, randomized
- Large number of patients
- Important clinical outcomes assessed
- Comparing BP targets
- Independent adjudication of outcomes

## Limitations
- Subgroup analysis
- Diabetes determined by use of diabetic medication
- No mention of diabetic subgroup baseline characteristics (BP, HbA1c, duration of DM)
## The Appropriate Blood Pressure Control in Diabetes (ABCD)\(^{27-28}\)

### Objective
To determine the effect of moderate versus intensive BP control on the incidence and progression of type 2 diabetic complications

### Design
Prospective, randomized, controlled trial

### Subjects

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM</td>
<td>Average DBP &lt; 80 mmHg off antihypertensive agents</td>
</tr>
<tr>
<td>Age 40 and 74 years</td>
<td>Isolated systolic HTN (SBP &gt; 160 mmHg and DBP &lt; 90 mmHg off meds)</td>
</tr>
<tr>
<td></td>
<td>Hx MI or cerebral vascular accident (CVA) within the previous 6 months</td>
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<tr>
<td></td>
<td>Coronary artery bypass surgery within the previous 3 months</td>
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<tr>
<td></td>
<td>Unstable angina pectoris within the previous 6 months</td>
</tr>
<tr>
<td></td>
<td>Class III or IV New York Heart Association classification HF</td>
</tr>
<tr>
<td></td>
<td>Receiving hemo- or peritoneal dialysis</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine level &gt; 3 mg/dl</td>
</tr>
<tr>
<td></td>
<td>Malignant hypertension (current or within the previous 5 years)</td>
</tr>
</tbody>
</table>

### Methods

**7- to 11-week single-blind placebo run-in period**

- Taper off pre-study antihypertensive treatments & assess compliance
- Determine baseline DBP and treatment arm
  - If DBP ≥ 90 mmHg
    - Assigned to hypertensive study
  - If DBP 80-89 mmHg
    - Assigned to normotensive study

~~**HYPERTENSIVE STUDY~~**

- **Intensive**
  - DBP 75 mmHg
- **Moderate**
  - DBP 80-89 mmHg

~~**NORMOTENSIVE STUDY~~**

- **Intensive**
  - DBP 10 mmHg below baseline
- **Moderate**
  - DBP 80-89 mmHg

**Antihypertensive Treatments**

- **Intensive or moderate BP**
  - Initial therapy was either:
    - Nisoldipine (N) 10-60 mg/day plus enalapril placebo
    - Enalapril (E) 5-40 mg/day plus nisoldipine placebo
  - Additional step-wise therapy (open-label):
    - Metoprolol
    - Hydrochlorothiazide
    - Others, but not ACEI or CCB

- **If subsequent HTN (SBP ≥ 160 and/or DBP ≥ 90 mmHg)**
  - Received nisoldipine or enalapril

### Outcomes

**Primary**
- Change in 24 hour creatinine clearance

**Secondary**
- Retinopathy
- Clinical neuropathy
- Urinary albumin excretion
- CV events
  - Nonfatal MI or CVA, HF requiring hospitalization, pulmonary infarction, or death due to CV events

Independent end point committee reviewed all CV events

### Statistics
- Two-sample t test (demographics)
- Chi-square test (demographics & complications)
- General linear mixed model (to determine effects of BP control over time)
- Comparisons not made between hypertensive and normotensive groups
Results

Participants
- 950 participants
  - Hypertensive Study
    - n=470
      - 237 intensive (116 N, 121 E)
      - 233 moderate (119 N, 114 E)
  - Baseline characteristics
    - ~62% male, mean age 58 years
    - 8.7 yrs duration of DM (mean HbA1c 11.5%)
    - ~24% hx CVD
    - Mean BP (intensive and moderate)
      - 156/98 and 155/98 mmHg
  - Mean follow-up 5.3 years

Normotensive Study
- n=480
  - 237 intensive (118 N, 119 E)
  - 243 moderate (55 N, 62 E)
- Baseline characteristics
  - ~62% male, mean age 58 years
  - 8.7 yrs duration of DM (mean HbA1c 11.5%)
  - ~24% hx CVD
  - Mean BP (intensive and moderate)
    - 136/84 and 137/84 mmHg
  - Mean follow-up 5.3 years

Mean Blood Pressures Achieved
- Different by comparison (P < 0.001)
  - Intensive: 132/78
  - Moderate: 138/86

Mean Blood Pressures Achieved
- Different by comparison (P < 0.0001)
  - Intensive: 128/75
  - Moderate: 137/81 (48% had tx by end)

Outcomes
- Comparing intensive vs. moderate within each study

<table>
<thead>
<tr>
<th></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypertensive</td>
</tr>
<tr>
<td>Creatinine clearance change</td>
<td>NS</td>
</tr>
<tr>
<td>Normoalbuminuria progression</td>
<td>NS</td>
</tr>
<tr>
<td>Microalbuminuria progression</td>
<td>NS</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>0.42</td>
</tr>
<tr>
<td>Stroke</td>
<td>NS</td>
</tr>
<tr>
<td>MI</td>
<td>NS</td>
</tr>
<tr>
<td>CV mortality</td>
<td>NS</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.04</td>
</tr>
</tbody>
</table>

NS=not significant (not reported)

Conclusions
- Hypertensive study
  - The more intensive BP control decreased all-cause mortality
- Normotensive study
  - Intensive compared to moderate BP control in normotensive T2DM pts slowed progression to nephropathy, decreased progression of diabetic retinopathy and decreased occurrence of stroke
  - Lowering BP in T2DM pts should not be restricted to hypertensive patients (BP >140/90 mmHg)

Strengths
- Prospective, randomized trial with large number of patients comparing BP targets (in pts with T2DM)
- Utilized multiple arms and included “normotensive” group
- No difference in HbA1c and lipid levels throughout either study
- Independent adjudication of outcomes

Limitations
- Primary outcome was change in creatinine clearance; all-cause mortality not predefined outcome
- Relatively small number of patients
- No mention of power analysis
- Hypertensive study
  - Compared single BP target value with BP target range
  - Number on previous antihypertensive tx not reported
- Normotensive study
  - Unconventional use of specific reduction in BP to target
| **Objective** | To determine if targeting a normal SBP (i.e., < 120 mmHg) reduces major CV events in participants with type 2 diabetes at high risk for CV events |
| **Design** | Multi-site, prospective, randomized, open-label trial |

### Subjects

**Inclusion Criteria**
- T2DM
- A1C ≥ 7.5%
- SBP 130 to 180 mmHg
- Taking three or fewer antihypertensive meds
- Equivalent of a 24-hour protein excretion rate of < 1 g
- One of the following:
  - 40 – 79 y.o. with CV disease
  - 55 – 79 y.o. with anatomical evidence of a substantial amount of atherosclerosis or at least two additional risk factors for CV disease (dyslipidemia, HTN, smoking, or obesity)

**Exclusion Criteria**
- BMI > 45 kg/m²
- Serum creatinine > 1.5 mg/dL (in previous 2 months)
- CV event/procedure or hospitalization for unstable angina (within last 3 months)
- Current symptomatic HF, any hx of NYHA Class III or IV HF, or ejection fraction < 25%

### Methods

**Intervention**
- Intensive
  - Target SBP < 120 mmHg
- Standard
  - Target SBP < 140 mmHg

**Antihypertensive Treatments**
- Current treatment strategies used to lower BP
- General recommendation
  - Regimens include an ACEI, BB, CCB, or diuretic
- Recommendation for intensive group
  - Either a combination of a diuretic and either an ACEI or BB be initiated at randomization

**Other Interventions**
- For blood glucose control, patients received concurrent treatment targeting HbA1c of either < 6% or 7 to 7.9%

### Outcomes

**Primary**
- First occurrence of major CV event (composite of nonfatal MI, nonfatal stroke, or CV death)

**Secondary**
- Combination of primary outcome plus revascularization or hospitalization for HF
- Combination of a fatal coronary event, nonfatal MI, or unstable angina
- Nonfatal MI
- Fatal or nonfatal stroke
- Nonfatal stroke
- Death from any cause
- Death from CV causes
- Hospitalization or death due to HF

Utilized a centralized adjudication process for all deaths, and hospitalizations for MI and strokes (blinded)

### Statistics

- Intention-to-treat
- Chi-square test, Fisher’s exact test, Wilcoxon rank-sum test, and the two-sample t-test (for baseline characteristics and safety outcomes)
- Kaplan–Meier estimates (used to calculate proportion of participants who had an event)
- Cox proportional-hazards regression analyses (for hazard ratios and 95% CI)
### Results

#### Participants
- 4733 patients
  - 2362 intensive
  - 2371 standard

#### Baseline characteristics
- 52% male, 60% white, mean age 62 years
- 10 years duration of diabetes (mean HbA1c 8.3%)
- 34% with previous CV event
- Mean BP 139/76 mmHg
- Mean follow-up 4.7 years

#### Mean Blood Pressure Achieved (after 1 yr of treatment)
- **Intensive**
  - Mean BP 119.3/64.4 mmHg
- **Standard**
  - Mean BP 133.5/70.5 mmHg

#### Outcomes (intensive vs. standard)

<table>
<thead>
<tr>
<th></th>
<th>Percent Events per Year</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Standard</td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>1.87</td>
<td>2.09</td>
<td>0.88 (0.73–1.06)</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>1.28</td>
<td>1.19</td>
<td>1.07 (0.85–1.35)</td>
</tr>
<tr>
<td><strong>CV mortality</strong></td>
<td>0.52</td>
<td>0.49</td>
<td>1.06 (0.74–1.52)</td>
</tr>
<tr>
<td><strong>Non-fatal MI</strong></td>
<td>1.13</td>
<td>1.28</td>
<td>0.87 (0.68–1.10)</td>
</tr>
<tr>
<td><strong>Non-fatal stroke</strong></td>
<td>0.30</td>
<td>0.47</td>
<td>0.63 (0.41–0.96)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>3.3*</td>
<td>1.27**</td>
<td>not reported</td>
</tr>
</tbody>
</table>

* *majority due to hypotension, bradycardia/arrhythmia, hypokalemia; ** percent

### Conclusions
In patients with type 2 diabetes at high risk for CV events, targeting a SBP of < 120 mmHg, as compared with less than 140 mmHg, did not reduce the rate of a composite outcome of fatal and nonfatal major CV events.

### Strengths
- Prospective, randomized
- Large number of patients
- Recruited patients with high CV risk
- Important clinical outcomes assessed
- Compared two BP targets (in pts with T2DM)
- Both groups had similar HbA1c’s at baseline and study conclusion
- Independent adjudication of outcomes

### Limitations
- Under-powered
- Unconventional intensive BP target assessed
VIII. Summary of Findings

A. Observational Studies
   i. In general, risk of CV outcomes in patients with T2DM appears to decrease with lower SBP (even down to < 120 mmHg)

B. Post-hoc Analyses
   i. In T2DM patients with CAD:
      1. Lower SBP (< 110 mmHg) and DBP (< 60 mmHg) may be associated with worse outcomes
      2. SBP at level of < 130 mmHg (mean of 121 mmHg) compared to < 140 mmHg (mean of 131 mmHg) may provide no further benefit and may increase risk of all-cause mortality
   ii. In T2DM patients with macroalbuminuria & elevated creatinine:
      1. Lowering SBP to 120 mmHg may decrease CV mortality
      2. Lower SBP (< 120 mmHg) may increase risk of CV death and all-cause mortality

C. Clinical Trials (in patients with DM)
   i. Various beneficial effects seen from:
      1. BP target of < 150/85 mmHg
      2. DBP target lower than 80 mmHg
   ii. Decreased risk of stroke and increased risk of serious adverse events seen from:
      1. Targeting SBP < 120 mmHg (achieving 119 mmHg) compared to targeting < 140 mmHg (achieving ~134 mmHg)

IX. Conclusions/Recommendations

A. For patients with DM:
   i. BP goals
      1. Current evidence does not overwhelmingly favor targeting SBP levels < 130 mmHg
      2. Target BP < 140/80 mmHg (achieving SBP in low 130s mmHg)
   ii. Initiate antihypertensive therapy if:
      1. BP >140/80 mmHg
   iii. Concomitantly control other risk factors (e.g., glycemia, lipids, smoking)

B. Sub-groups:
   i. Patients with T2DM and CAD:
      1. Lower SBP to ~130 mmHg (lowering SBP to ~120 mmHg may provide no further benefit)
      2. Avoid SBP < 110 mmHg & DBP < 60 mmHg
   ii. Patients with T2DM at increased risk of stroke:
      1. Target SBP < 120 mmHg (achieving ~120 mmHg) to reduce the risk of stroke if benefits are likely to outweigh increased risk of serious adverse events
   iii. Patients with T2DM and nephropathy:
      1. Target BP <130/80 mmHg

X. Additional Questions

A. Would the ACCORD have found more differences if it wasn’t under-powered?
B. Does an achieved SBP between 120-130 mmHg provide greater benefits over that of 130-140 mmHg?
C. What is the optimum target BP for patients with type 1 DM?

XI. Future Studies & Guidelines

A. Systolic Blood Pressure Intervention Trial (SPRINT)\textsuperscript{30}
   i. Will evaluate the potential benefits of maintaining SBP at < 120 mmHg for adults at risk for heart disease or kidney disease
   ii. Comparing treatment to SBP < 140 mmHg against SBP < 120 mmHg
   iii. Patients with DM are excluded

B. JNC-8
   i. Expected availability for public review and comment: Spring 2011
References


### Appendix 1: Trials Comparing More Intensive and Less Intensive Diabetic Blood Pressure Targets

<table>
<thead>
<tr>
<th>Trial</th>
<th># Participants</th>
<th>Duration</th>
<th>Patient Demographics (baseline)</th>
<th>BP Targets (mmHg)</th>
<th>Baseline BP (mmHg)</th>
<th>BP Achieved (mmHg)</th>
<th>Results (tight vs. less tight)</th>
</tr>
</thead>
</table>
| UKPDS       | 1148           | 8.4 years | T2DM, HTN, Age 25-65 yrs (mean 56) | < 150/85          | 159/94             | 144/82             | Reduced*  
  - Any clinical end point related to diabetes  
  - Deaths related to diabetes  
  - Stroke  
  - Microvascular disease |
|             |                |          | HbA1c 6.9%, 2.6 yrs DM duration | < 180/105         | 159/94             | 154/87             | No Difference  
  - All-cause mortality  
  - MI  
  - Peripheral vascular disease |
| HOT (subgroup) | 1501           | 3.8 years | DM, HTN, Age 50–80 yrs (mean 62) | DBP < 80          | 169.7/105.4**      | 139.7/81.1**       | Reduced*  
  - Major CV events  
  - CV mortality |
|             |                |          | 7.5% with previous MI or other CHD** | DBP < 85          | 169.5/105.4**      | 141.4/83.2**       | No Difference  
  - MI  
  - Stroke  
  - All-cause mortality |
| ABCD (hypertensive) | 470           | 5.3 years | T2DM, HTN, Age 40 and 74 years (mean 58) | DBP 75            | 156/98             | 132/78             | Reduced*  
  - All-cause mortality  
  - MI  
  - CVA  
  - HF  
  - Retinopathy  
  - Neuropathy  
  - Changes in CrCl or UAE |
|             |                |          | HbA1c 11.5%, 8.7 yrs DM duration, 24% hx CVD | DBP 80-89         | 155/98             | 138/86             | No Difference  
  - MI  
  - CVA  
  - HF  
  - Retinopathy  
  - Neuropathy  
  - Changes in CrCl |
| ABCD (normotensive) | 480           | 5.3 years | T2DM, DBP 80-89 mmHg, Age 40 and 74 years (mean 58) | DBP 10 below baseline | 136/84             | 128/75             | Reduced*  
  - Stroke  
  - UAE  
  - Retinopathy |
|             |                |          | HbA1c 11.5%, 8.7 yrs DM duration, 24% hx CVD | DBP 80-89         | 137/84             | 137/81             | No Difference  
  - MI  
  - HF  
  - CV mortality  
  - Neuropathy  
  - Changes in CrCl |
| ACCORD | 4733 | 4.7 years | T2DM  
|---|---|---|---|---|---|---|---|---|---|
|  |  |  | HTN  
|  |  |  | 40 – 79 yrs  
|  |  |  | (mean 62)  
|  |  |  | HbA1c 8.3%  
|  |  |  | 10 yrs DM duration  
|  |  |  | 34% with hx CV event  
|  |  |  | SBP < 120  
|  |  |  | 139/76  
|  |  |  | 119.3/64.4  
|  |  |  | Reduced *  
|  |  |  | Stroke  
|  |  |  | No Difference  
|  |  |  | All-cause mortality  
|  |  |  | CV mortality  
|  |  |  | MI  
|  |  |  | Increased*  
|  |  |  | Serious adverse events  
|  |  |  | SBP < 140  
|  |  |  | 139/76  
|  |  |  | 133.5/70.5  

*(p < 0.05); **data for entire HOT population (no baseline BPs reported for diabetic subgroup but BPs achieved were 144/81 mmHg, 146/83 mmHg, 148/85 mmHg)