Is a Lower BP Better in DKD?

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Disclosure of Interests

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Board Member – National Kidney Foundation
Perspective

- The bulk of outcome data about BP levels in diabetes is based on trials in patients with high CV risk (generally >7-10 years).
- Only two prospective trials were powered to address the question of BP level and effect on CV outcome in diabetes (UKPDS and ACCORD).
- There are NO powered CKD outcome studies in people with diabetic nephropathy.
- Only one trial tried to assess early intervention on outcomes and that was very underpowered for CV or renal outcomes because of funding constraints (ABCD).
RCTs Designed to Test Glycemic Control on CVD in T2DM

- UKPDS (1998)
  United Kingdom Prospective Diabetes Study
- ACCORD (2008)
  Action to Control Cardiovascular Risk in Diabetes
- ADVANCE (2008)
  Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation
- VADT (2009)
  Veterans Affairs Diabetes Trial
### Achieved BPs in Diabetes Outcome Clinical Trials

<table>
<thead>
<tr>
<th>Clinical Outcome Trial</th>
<th>Achieved Level of Systolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD (primary)</td>
<td>119 (intensive); 133 (conventional)</td>
</tr>
<tr>
<td>UKPDS (primary)</td>
<td>144 (intensive); 154 (conventional)</td>
</tr>
<tr>
<td>ACCOMPLISH (secondary)</td>
<td>Overall mean 133</td>
</tr>
<tr>
<td>INVEST (Secondary)</td>
<td>144 (tight control); 149 (conventional)</td>
</tr>
<tr>
<td>ONTARGET (secondary)</td>
<td>Averaging around 140</td>
</tr>
<tr>
<td>VADT (secondary)</td>
<td>127 (intensive); 125 (conventional)</td>
</tr>
<tr>
<td>ADVANCE (secondary)</td>
<td>137 (in both intensive and conventional glucose control)</td>
</tr>
</tbody>
</table>
### Summary of Guideline Goal BP and Initial Therapy in Kidney Disease to Reduce CKD Progression?

<table>
<thead>
<tr>
<th>Group</th>
<th>Goal BP (mmHg)</th>
<th>Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014 Expert Panel (2014)</td>
<td>&lt;140/90</td>
<td>ACE Inhibitor/ARB</td>
</tr>
<tr>
<td>ADA (2015)</td>
<td>&lt;140/90</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>KDIGO/KDOQI (NKF) (2012)</td>
<td>&lt;140/90</td>
<td>ACE Inhibitor/ARB</td>
</tr>
<tr>
<td>ESH (2007+ 2009)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>KDOQI (NKF) (2004)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>JNC 7 (2003)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Am. Diabetes Assoc (2003)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Canadian HTN Soc. (2002)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Natl. Kidney Foundation (2000)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor*</td>
</tr>
<tr>
<td>British HTN Soc. (1999)</td>
<td>&lt;140/80</td>
<td>ACE Inhibitor</td>
</tr>
<tr>
<td>WHO/ISH (1999)</td>
<td>&lt;130/85</td>
<td>ACE Inhibitor</td>
</tr>
<tr>
<td>JNC VI (1997)</td>
<td>&lt;130/85</td>
<td>ACE Inhibitor</td>
</tr>
</tbody>
</table>
JNC 7 Goals for CKD

<130/80 mmHg

Was this defensible?
3 Randomized Trials of BP control on CKD progression In Non-Diabetic CKD

- **MDRD** (Modification of Dietary Protein in Renal Disease)
- **REIN-2** (Ramipril Efficacy in Nephropathy)
- **AASK** (African American Study of Kidney Disease)
Mean arterial pressure in each study arm of REIN-2

Proportion of patients with end-stage renal disease in each study arm REIN-2

IgA Nephropathy

Composite Clinical Events: Declining GFR Event, ESRD or Death by BP Goal

Low vs. Usual:
RR=2%, (p=0.85)

Low (Achieved: 127/77)
Usual BP ((Achieved: 140/85)

Wright JT Jr, et.al. JAMA, 2002
There are **No** randomized trials of BP goal among those with diabetic kidney disease
Data from the ADVANCE trial
Data from the ADVANCE trial (6 Year Post hoc follow-up)

- The mean between-group difference in BP during the randomized ADVANCE trial (5.6/2.2 mm Hg, P<0.001)
- No longer evident 6 months after the end of that part of the trial.
- BPs recorded at the time of the final randomized visit for the patients in the glucose-control comparison (6 months after the last visit for the BP control comparison)
- 137/74 mm Hg in the perindopril–indapamide group and 136/74 mm Hg in the placebo

Only BP Randomized Trial in Type 2 Diabetes

ACCORD-
No renal endpoints
No CV benefit overall

Event rates (per 1000 patient years) for CV outcomes in ACCOMPLISH categorized according to their achieved systolic blood pressures.

- **Primary Endpoint**
  - Achieved Systolic Blood Pressure (mmHg):
    - 110 to <120
    - 120 to <130
    - 130 to <140
    - ≥140
  - Events per 1,000 patient-years:
    - p-Values versus ≥140
    - 0.0007
    - <0.0001
    - <0.0001

- **Cardiovascular Death**
  - Achieved Systolic Blood Pressure (mmHg):
    - 110 to <120
    - 120 to <130
    - 130 to <140
    - ≥140
  - Events per 1,000 patient-years:
    - p-Values versus ≥140
    - NS
    - 0.0008
    - 0.0147

- **All-cause Mortality**
  - Achieved Systolic Blood Pressure (mmHg):
    - 110 to <120
    - 120 to <130
    - 130 to <140
    - ≥140
  - Events per 1,000 patient-years:
    - p-Values versus ≥140
    - NS
    - 0.0027
    - 0.0110

- **Total Stroke**
  - Achieved Systolic Blood Pressure (mmHg):
    - 110 to <120
    - 120 to <130
    - 130 to <140
    - ≥140
  - Events per 1,000 patient-years:
    - p-Values versus ≥140
    - 0.0002
    - 0.0069
    - 0.0002
Relationship Between Achieved BP and Decline in Kidney Function from Primary Renal Endpoint Trials

Nondiabetes
REIN. *Lancet.* 1997
AASK. *JAMA.* 2002
Parsa A et al. NEJM 2013

Diabetes
IDNT. *NEJM.* 2001
RENAAL. *NEJM.* 2001
ABCD. *Diabetes Care (Suppl).* 2000

Update from Kalaitzidis R and Bakris GL In: *Handbook of Chronic Kidney Disease* Daugirdas J (Ed.) 2011
Rates of end-stage renal disease per 1000 person-years

Data from KEEP
Mean follow-up 2.8 years
N=16,000+

Multivariable-adjusted relative hazards (hazard ratios [95% CIs]) of all-cause mortality associated with SBP and DBP relative to a hypothetical patient with the mean time-varying SBP (133 mm Hg) and DBP (71 mm Hg).
IS A LOWER BP BETTER IN DKD?

Yes—to a point below 140 mmHg and above 60 mmHg