Endorama

5/7/15
Luke J. Laffin MD
58 year-old male with history of DM2, HTN, and CKD

Presented to us in clinic in 7/2014

- HTN since his “30s”, DM2 and CKD for >10 years
- Multiple anti-hypertensives tried in the past (no adverse reactions)
- Uses CPAP for OSA
- High salt diet

- Currently taking
  - amlodipine 10mg daily
  - carvedilol 12.5mg BID
  - clonidine 0.4mg qpm
  - furosemide 40mg daily
  - quinapril 40mg BID
  - hydrochlorothiazide 12.5mg daily
  - hydralazine 75mg TID
  - [Insulin for DM2]
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- quinapril 40mg BID
- hydrochlorothiazide 12.5mg daily
- hydralazine 75mg TID
- [Insulin for DM2]

Home and ambulatory BPs “uncontrolled” per patient
Home and Ambulatory BPs are “uncontrolled”

What is uncontrolled for him?

A. >130/80 mmHg

B. >140/90 mmHg

C. >135/85 mmHg

D. We do not have enough information to be certain about a BP treatment target
For those of you that answered D

What else do you want to know (history / labs etc.)?
Physical Exam

**BP Sitting**

191/83, HR 65

**BP Standing**

175/75, HR 68

- BMI is 51.63 kg/(m^2).
- Generally: An obese well-appearing male in no acute distress.
- Neck: No carotid bruits auscultated bilaterally. Thyroid normal size and texture.
- Respiratory: Clear to auscultation bilaterally.
- Cardiovascular: Regular rate and rhythm. No murmurs, rubs, or gallops. 2+ lower extremity edema.
- Abdomen: positive bowel sounds. Soft, nontender, nondistended
- Skin: No rash. Normal temperature and texture.
- Musculoskeletal: Normal gait and station.
- Lymphatic: No lymphadenopathy in the neck.
- Psychiatric: Alert and oriented x3. Appropriate mood/affect.
Labs

Urine microalbumin/creatinine

97.8

BMP

140/5.0/105/24/38/2.1 (GFR 33) → 100

Hgb A1c

7.2

Albumin

4.2
BP Guidelines in patients with DM

What are they now?
Guidelines in patients with DM

What are they now?

- 2014 NIH Expert Panel (JNC 8)
- ADA 2014
- ESH/ESC 2013
- ASH/ISH 2014

Table 1  Major organizational guidelines focused on diabetes mellitus *

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<tr>
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RAS renin angiotensin system blockers, i.e., ACE inhibitors or angiotensin receptor blockers, CCB calcium channel blockers, BP blood pressure

Guidelines in patients with DM

What are they now?

- **2014 NIH Expert Panel (JNC 8)**
- **ADA 2014-2015**
- **ESH/ESC 2013**
- **ASH/ISH 2014**

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ADVANCE was not considered in 2014 Expert Panel Recommendations (JNC 8), given that it was not based on targeted BP goals and there was not a pre-specified minimum baseline BP.

- It is the only major placebo-controlled randomized trial that explicitly examined the role of different antihypertensive agents in DM2 (perindopril / indapamide).

Guidelines

What are they now?

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*RAS renin angiotensin system blockers, i.e., ACE inhibitors or angiotensin receptor blockers, CCB calcium channel blockers, BP blood pressure

Most significant change from 130/80 mmHg in JNC 7 (2003), why?

“Lower SBP goal is not supported by any RCT that randomized participants into 2 or more groups in which treatment was initiated at a lower SBP threshold than 140 mm Hg (or into treatment groups in which the SBP goal was lower than 140 mmHg) and that assessed the effects of a lower SBP threshold or goal on important health outcomes.”

### Table 2  Key randomized trials of blood pressure control in diabetes mellitus

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<th>Trial</th>
<th>Follow-up (years)</th>
<th>#No. of subjects</th>
<th>BP goal (mmHg)</th>
<th>BP achieved (mmHg)</th>
<th>Main results</th>
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<td>UKPDS (1998)</td>
<td>8.4</td>
<td>1148</td>
<td>&lt;150/85 (tight) vs. 144/82 (tight) and</td>
<td>Tight control resulted in risk reduction in diabetes-related endpoints and strokes</td>
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<td></td>
<td></td>
<td>758 “tight”</td>
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<td>ADVANCE (2007)</td>
<td>4.3</td>
<td>2371 control</td>
<td>&lt;140 (control) none</td>
<td>134 (control) and 135/74 (intervention) and 140/76 (control)</td>
<td>Intervention reduced risk of major vascular events, including death</td>
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<td></td>
<td>11,140</td>
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<td>5569 “intervention”</td>
<td>117 (aggressive) and 129 (standard)</td>
<td>81 mmHg and 83 mmHg and 85 mmHg</td>
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<td>5571 placebo</td>
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<tr>
<td>SANDS (2008)</td>
<td>3</td>
<td>499</td>
<td>&lt;115 (aggressive) vs. 130 (standard)</td>
<td>80 mmHg and 85 mmHg</td>
<td>No difference in clinical cardiovascular events</td>
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<td>247 “standard”</td>
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<tr>
<td>HOT (1998)</td>
<td>3.8</td>
<td>18,790</td>
<td>80 mmHg</td>
<td>81 mmHg and 83 mmHg and 85 mmHg</td>
<td>No significant advantage in CV events at lower BP (1° endpoint post hoc analysis of diabetes subgroup showed reduced events in lowest BP group)</td>
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<tr>
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<td>Normotensive ABCD (2002)</td>
<td>5.3</td>
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<td>10 mmHg below baseline dia (intensive) vs. 128/75 (intensive) and 137/81 (moderate)</td>
<td>No significant improvement in composite cardiovascular events</td>
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BP blood pressure, sys systolic, dia diastolic

*a Also included low-density lipoprotein cholesterol goals

“Lower SBP goal is not supported by any RCT that randomized participants into 2 or more groups in which treatment was initiated at a lower SBP threshold than 140 mm Hg (or into treatment groups in which the SBP goal was lower than 140 mmHg) and that assessed the effects of a lower SBP threshold or goal on important health outcomes.”

“The only RCT that compared an SBP treatment goal of lower than 140mmHg with a lower SBP goal and assessed the effects on important health outcomes is ACCORD-BP, which compared a SBP treatment goal of lower than 120 mm Hg with a goal lower than 140mmHg”

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<tr>
<td></td>
<td></td>
<td>- 390 control</td>
<td>&lt;180/105 (control) and 119 sys (intensive) and 134 sys (control)</td>
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</tr>
<tr>
<td>ACCORD (2010)</td>
<td>1</td>
<td>4733</td>
<td>&lt;120 sys (intensive) vs. 135/74 (intervention) and 140/76 (control)</td>
<td>No reduction in fatal and nonfatal cardiovascular events and 117 sys (aggressive) and 129 sys (standard) and 81 mmHg and 83 mmHg and 85 mmHg</td>
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<td>2362 “intensive”</td>
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BP blood pressure, sys systolic, dia diastolic

* Also included low-density lipoprotein cholesterol goals

2010

Randomized study of 4733 subjects with DM2 (baseline BP of 139/76 mmHg)

2 groups: intensive (<120 mmHg SBP) vs. control (<140 mmHg)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy (N=2363)</th>
<th>Standard Therapy (N=2371)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome*</td>
<td>208</td>
<td>237</td>
<td>0.88 (0.73–1.06)</td>
<td>0.20</td>
</tr>
<tr>
<td>Prespecified secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>126</td>
<td>146</td>
<td>0.87 (0.68–1.10)</td>
<td>0.25</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>36</td>
<td>62</td>
<td>0.59 (0.39–0.89)</td>
<td>0.01</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>34</td>
<td>55</td>
<td>0.63 (0.41–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>150</td>
<td>144</td>
<td>1.07 (0.85–1.35)</td>
<td>0.55</td>
</tr>
<tr>
<td>From cardiovascular cause</td>
<td>60</td>
<td>58</td>
<td>1.06 (0.74–1.52)</td>
<td>0.74</td>
</tr>
<tr>
<td>Primary outcome plus revascularization or nonfatal heart failure</td>
<td>521</td>
<td>551</td>
<td>0.95 (0.84–1.07)</td>
<td>0.40</td>
</tr>
<tr>
<td>Major coronary disease event†</td>
<td>253</td>
<td>270</td>
<td>0.94 (0.79–1.12)</td>
<td>0.50</td>
</tr>
<tr>
<td>Fatal or nonfatal heart failure</td>
<td>83</td>
<td>90</td>
<td>0.94 (0.70–1.26)</td>
<td>0.67</td>
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* The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.
† Major coronary disease events, as defined in the protocol, included fatal coronary events, nonfatal myocardial infarction, and unstable angina.
Figure 2. Kaplan–Meier Analyses of Selected Outcomes.
Shown are the proportions of patients with events for the primary composite outcome (Panel A) and for the individual components of the primary outcome (Panels B, C, and D). The insets show close-up versions of the graphs in each panel.
Aside from ACCORD-BP, a **post-hoc analysis of RCTs** and a nationwide **register-based observational study** in Sweden, which suggest that benefits do not increase below 130mmHg.

### Treatment strategies in patients with diabetes

<table>
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<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
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<tr>
<td>While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ( \geq 160 ) mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ( \geq 140 ) mmHg</td>
<td>I</td>
<td>A</td>
<td>275, 276, 290–293</td>
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<td>A SBP goal (&lt; 140 ) mmHg is recommended in patients with diabetes.</td>
<td>I</td>
<td>A</td>
<td>270, 275, 276, 295</td>
</tr>
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<td>The DBP target in patients with diabetes is recommended to be (&lt; 85 ) mmHg.</td>
<td>I</td>
<td>A</td>
<td>290, 293</td>
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<td>All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria.</td>
<td>I</td>
<td>A</td>
<td>394, 513</td>
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<tr>
<td>It is recommended that individual drug choice takes comorbidities into account.</td>
<td>I</td>
<td>C</td>
<td>-</td>
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<tr>
<td>Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes.</td>
<td>III</td>
<td>B</td>
<td>433</td>
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**DBP**, diastolic blood pressure; **RAS**, renin–angiotensin system; **SBP**, systolic blood pressure.

- **Class** of recommendation.
- **Level** of evidence.
- **Ref.** (Reference(s)) supporting levels of evidence.

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What about attenuated CVA Risk in ACCORD-BP at lower goal?

Not new discovery...

**INVEST / ONTARGET**
- Both large international hypertension clinical trials
- >20,000 patients each,
- 37 and 28% patients with diabetes, respectively.
- SBP <130 mmHg is associated with stroke reduction in DM patients but no other CV risk reduction.
However in ACCORD-BP…

Risk of serious adverse events (hypotension, syncope, arrhythmia, hyperkalemia, angioedema, and renal failure) was associated with more aggressive BP control

3.3 % intensive vs. 1.3 % in the standard arm

Small absolute benefit in stroke reduction (1 in 89 patients at 5 years)

(all in background of) 50% lower event rate than anticipated in standard therapy arm
However in ACCORD-BP...

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Small absolute benefit in stroke reduction (1 in 89 patients at 5 years)

(all in background of) 50% lower event rate than anticipated in standard therapy arm

Younger individuals with history of stroke or at high risk - lower BP goals should be considered if well-tolerated.
Guidelines

What are they now?

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*RAS* renin angiotensin system blockers, i.e., ACE inhibitors or angiotensin receptor blockers, *CCB* calcium channel blockers, *BP* blood pressure

What about DBP goals? Why were guidelines recommending <80mmHg?
2 trials: HOT trial and UKPDS

**HOT trial**

Frequently cited to support a lower DBP

Goal of <90mmHg vs. <80mmHg or lower.

The lower goal was associated with a reduction in a composite CVD outcome

But was a post hoc analysis of a small subgroup (8%) of the study population that was not pre-specified.

Evidence is low quality.

**UKPDS**

<150/85 mm Hg vs. <180/105 mm

Significantly lower rate of stroke, heart failure, diabetes-related endpoints, and deaths related to diabetes.

**Not possible to determine whether treatment to a DBP goal of lower than 85 mm Hg improves outcomes compared with treatment to a DBP goal of lower than 90 mm Hg.**

In addition, UKPDS was a mixed systolic and diastolic BP goal study (combined SBP and DBP goals), so it cannot be determined if the benefits were due to lowering SBP, DBP, or both.
Forty trials judged to be of low risk of bias (100,354 participants)

Although proportional associations of BP lowering treatment for most outcomes studied were attenuated below a systolic BP level of 140mmHg, data indicate that further reduction (<130mmHg) is associated with a lower risk of stroke, retinopathy, and albuminuria, potentially leading to net benefits for many individuals at high risk for those outcomes.

Not necessarily surprising, but could not assess for rate of serious events
# Choice of Antihypertensive in DM

## #1

The degree of BP reduction is the major determinant of cardiovascular risk reduction in all patients with hypertension, including those with diabetes. The choice of antihypertensive medication is significantly **less important**.

## #2

However, if given the opportunity to select antihypertensive therapy, one would ideally consider the most effective medications to reduce the patient’s risk of mortality and adverse cardiovascular events and prevent progression of renal disease if present.
Role of beta-blockers in HTN and DM

- Use of beta-blockers if a compelling indication exists such as CAD

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- What beta-blocker to select?

Role of beta-blockers in HTN and DM

- **Carvedilol and nebivolol**
  - GEMINI trial* randomized 1235 diabetic hypertensive patients (already taking an ACE inhibitor or ARB) to **carvedilol** or **metoprolol**
  - Carvedilol did not increase hemoglobin A1C, whereas metoprolol did,
  - Carvedilol demonstrated an increase in a patient’s insulin sensitivity, whereas metoprolol did not.

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Figure 2. Glycosylated Hemoglobin (HbA1c) at Baseline and Each Maintenance Month by Treatment in the Modified Intention-to-Treat Population

The change from baseline to maintenance month 5 (primary outcome) was significant (mean difference [SD], 0.13% [0.05%]; 95% confidence interval, −0.22% to −0.04%; $P = .004$). Error bars indicate SD from mean.
What about the patient with diabetic nephropathy?

What if our patient had severely increased albuminuria (i.e. proteinuria)?

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**Urine microalbumin / creatinine ratio of 5178**

Diabetic nephropathy and overt proteinuria (at least 500 mg/day) may be the one subset of diabetic patients where evidence, although still not of high quality, reasonably suggests a lower BP goal (<130/80 mmHg.)

Data from nondiabetic proteinuric CKD suggest that lower SBP slows progressive renal disease in patients with a spot urine total protein-to-creatinine ratio ≥1000 mg/g and probably extends to those with diabetic nephropathy.
Follow-up (seen in clinic 4/15)

Current home BPs are 120-130s / 60s with HR in the 60-70s.

His medication regimen is:

- Quinapril 40mg daily
- Carvedilol 25m BID
- Spironolactone 25mg daily
- Nifedipine- XL 120mg daily
- Torsemide 20mg dialy
- Minoxidil 2.5mg BID
- Guanfacine 2mg qhs
Take home points

Why is this important?

- No significant randomized clinical trial of glucose-lowering therapy demonstrates a significant decrease in major adverse cardiovascular events.
- Although glucose lowering therapy significantly decreases microvascular events such as nephropathy and retinopathy.

Guidelines are meant to be a guide, clinical judgement must play a role.