Individualizing Glycemic and Blood Pressure Control Targets: One Size Does Not Fit All

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This presentation:

- Give an overview of the evolution in the evidence for glucose and blood pressure targets in type 2 diabetes

- Current status of glucose and blood pressure targets: one size doesn’t fit all

- Recently updated and webpage-based “IHS Diabetes Standards of Care and Clinical Practice Recommendations” on the IHS DDTP website: www.diabetes.ihs.gov
Remember when we thought that the same diabetes targets applied to everyone?

- A1C <7%
- BP <130/80 mmHg
- LDL <100mg/dL

That is so 2007!

Universal targets sure are easier for data people

But they don’t work well for many of our patients

“First, do no harm”
Glucose targets across the lifespan

“To everything there is a season…”
United Kingdom Prospective Diabetes Study (UKPDS)

Years

A1C (%)

Conventional Group

Intensive Group

Years

UKPDS Group Lancet 1998;352:837–53
UKPDS: Post-Trial Changes in A1C

Sulfonylurea/insulin vs. Conventional

Mean (95% CI)

**UKPDS: “Legacy Effect” of Glucose Therapy**

*After median 8.8 years post-trial follow-up*

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRR:</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td><em>P</em>:</td>
<td>0.029</td>
<td>0.040</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRR:</td>
<td>25%</td>
<td>24%</td>
</tr>
<tr>
<td><em>P</em>:</td>
<td>0.009</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRR:</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td><em>P</em>:</td>
<td>0.052</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRR:</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td><em>P</em>:</td>
<td>0.44</td>
<td>0.007</td>
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</tbody>
</table>

**RRR = Relative Risk Reduction**  **P = Log Rank**

“The UKPDS showed the benefits of an intensive strategy to control blood glucose levels in patients with type 2 diabetes sustained up to 10 yrs after cessation of the randomized intervention. Benefits persisted despite the early loss of within-trial differences in A1C levels between the intensive-therapy group and conventional-therapy group – a so-called legacy effect.”

UKPDS

- Showed that glycemic control early in diabetes has lasting benefit, including for CVD risk
- However, it was interpreted as implying that everyone should have an A1C <7%--and national guidelines followed suit
  - But UKPDS included only healthy, newly-diagnosed patients <65 yrs old

*Lancet* 1998;352:837-853
And then came major studies on intensive glucose control in more “real world” diabetes populations

- **ACCORD, ADVANCE, and VADT**

- Showed little benefit to intensive glucose control other than for nephropathy (in ACCORD and ADVANCE)

- And showed increased mortality (ACCORD), weight gain, and hypoglycemia
## Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UKPDS</strong></td>
<td>↓</td>
<td>◀ ◀ ◀ ◀ ◀</td>
<td>◀ ◀ ◀ ◀ ◀</td>
</tr>
<tr>
<td><strong>DCCT / EDIC</strong>*</td>
<td>↓</td>
<td>◀ ◀ ◀ ◀ ◀</td>
<td>◀ ◀ ◀ ◀ ◀</td>
</tr>
<tr>
<td><strong>ACCORD</strong></td>
<td>↓</td>
<td>◀ ◀ ◀ ◀ ◀</td>
<td>◀ ◀ ◀ ◀ ◀</td>
</tr>
<tr>
<td><strong>ADVANCE</strong></td>
<td>↓</td>
<td>◀ ◀ ◀ ◀ ◀</td>
<td>◀ ◀ ◀ ◀ ◀</td>
</tr>
<tr>
<td><strong>VADT</strong></td>
<td>↓</td>
<td>◀ ◀ ◀ ◀ ◀</td>
<td>◀ ◀ ◀ ◀ ◀</td>
</tr>
</tbody>
</table>

* in T1DM

Kendall DM, Bergenstal RM. © International Diabetes Center 2009

May not affect CVD outcomes after macrovascular disease established—but good glucose control in the early years of DM may affect long-term risk of macrovascular disease.

Makes a difference in microvascular disease.

However, BG goal should be adjusted to the individual patient:

- In general, A1C goal: <7%
  - Lower goal if short duration DM, long life expectancy, and little co-morbidity
  - Higher goal if the converse—there are risks with aggressive control
And the discussion has continued

- Meta-analysis of 13 recent RCTs (>34,000 pts) that evaluated intensive glucose lowering:
  - *Limited* benefits on all-cause and CV mortality
  - At best, *modest* benefits for microvascular disease
    - ↓ albuminuria, a *trend* toward ↓ retinopathy, but little else
  - Severe hypoglycemic events doubled  *BMJ* 2011;343:d4243 doi:10.1136/bmj.d4243

- *Guidelines* starting to reflect recent evidence, now *Performance Measures* will need to be re-thought
  - Much more benefit to ↓ patient’s A1C from 9% to 7.1% than to ↓ it from 7.1% to 6.9%
  - Unknown effects of adding on multiple meds to achieve target  *Diabetes Care* 2011;34:1651-1659
Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)
3. ANTI-HYPERGLYCEMIC THERAPY

• Glycemic targets

- **HbA1c < 7.0%** (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])

- Pre-prandial PG <130 mg/dl (7.2 mmol/l)

- Post-prandial PG <180 mg/dl (10.0 mmol/l)

- **Individualization** is key:

  ➢ Tighter targets (6.0 - 6.5%) - younger, healthier

  ➢ Looser targets (7.5 - 8.0%+) - older, comorbidities, hypoglycemia prone, etc.

- Avoidance of hypoglycemia

PG = plasma glucose

*Diabetes Care, Diabetologia.* 19 April 2012 [Epub ahead of print]
Figure 1

Approach to management of hyperglycemia:

- **Patient attitude and expected treatment efforts**
  - more stringent: highly motivated, adherent, excellent self-care capacities
  - less stringent: less motivated, non-adherent, poor self-care capacities

- **Risks potentially associated with hypoglycemia, other adverse events**
  - low
  - high

- **Disease duration**
  - newly diagnosed
  - long-standing

- **Life expectancy**
  - long
  - short

- **Important comorbidities**
  - absent
  - few / mild
  - severe

- **Established vascular complications**
  - absent
  - few / mild
  - severe

- **Resources, support system**
  - readily available
  - limited
A1c Variability “Speedometer”
VA uses A1C target ranges

<table>
<thead>
<tr>
<th>Major comorbidity or physiologic age</th>
<th>Microvascular complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent or mild</td>
</tr>
<tr>
<td>Absent &gt; 10 years of life expectancy</td>
<td>&lt; 7</td>
</tr>
<tr>
<td>Present 5-10 years of life expectancy</td>
<td>&lt; 8</td>
</tr>
<tr>
<td>Marked &lt; 5 years of life expectancy</td>
<td>8-9</td>
</tr>
</tbody>
</table>

A1C Target Recommendations, VA/DoD Diabetes Practice Guidelines, 2010
“Wait a minute—what happened to all the hype about getting everyone’s A1C down to <7% or even lower??”

- Do people who have A1Cs<7%, on their own or with a little bit of medication, do better in the long-run? Yes!
  - But this is a marker of their overall systemic health

- That is *not* the same thing as having to use 3 or 4 meds to beat someone’s glucoses down to achieve a low target
  - Not known if polypharmacy is safe, effective or cost-effective
  - Hypoglycemia risk increases

- Performance measures (like GPRA) have reflected the national guidelines — and providers have felt pressured to get all their patients’ A1Cs down to <7%, no matter what it takes
  - Do what’s best for each individual patient
So, what do we do with all this?

- **Individualize** glucose targets—really!
  - Younger, healthier patients: aim for $<7\%$ (or *lower*)
    - Excellent glucose control achieved and maintained *early* in the course of diabetes has long-term benefits, including for CVD
  - Longer duration of diabetes, more co-morbidities and lots of meds already: liberalize glucose targets (ranges)
    - Think carefully about whether to add another medication (and which one) to lower glucose
    - Polypharmacy, hypoglycemia have consequences!

- Focus some efforts on patients whose A1Cs $>9.5%$

- Future EHRs: help with selecting/determining target for each patient
Absolute number of events prevented by different interventions per 1000 patient years of treatment (data taken from Cholesterol Treatment Trialists’ Collaboration and Blood Pressure Lowering Treatment Trialists’ Collaboration).

Preiss D, Ray K K BMJ 2011;343:bmj.d4243
Blood Pressure

A Similar Story
Blood Pressure Target

- As with glucose targets, UKPDS played a major role in target selection for BP in international guidelines.

- For diastolic BP target, so did the randomized Hypertension Optimal Treatment (HOT) study.
  - Study paper noted ↓ CV risk in diabetic patients with DBP <80 mm Hg.
  - Accompanying editorial noted the slight ↑ mortality in intensively treated diabetic patients with ischemic heart disease so recommended caution in lowering BP to <140/85 in this group.  

  *Lancet* 1998;351:1755-62 and 1748-1749
UKPDS

• “This paper reports that patients with hypertension and type 2 diabetes assigned to tight control of blood pressure achieved a significant reduction in risk of 24% for any end points related to diabetes, 32% for death related to diabetes, 44% for stroke, and 37% for microvascular disease. In addition there was a 56% reduction in risk of heart failure. The mean blood pressure over nine years was 144/82 mm Hg on tight control compared with a less tight control mean of 154/87 mm Hg”

  *BMJ 1998;317(7160):703-713*

• UKPDS observational study showed that “risk of diabetic complications was strongly associated with raised blood pressure. Any reduction in blood pressure is likely to reduce the risk of complications, with the lowest risk being in those with systolic blood pressure less than 120 mm Hg.”

  *BMJ 2000;321(7258):412-419*
Blood Pressure Target: JNC 7

- 2003: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)
  - Cited studies including UKPDS, HOT
  - Agreed with ADA in recommending that pts with DM have a BP goal ≤130/80
  - But noted that “available data are somewhat sparse to justify the low target level of 130/80”

_Hypertension_ 2003;42:1206-52
“Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus”

Study Overview

• In a randomized trial, 4733 patients with type 2 diabetes mellitus who were at high risk for cardiovascular events received treatment aimed at a target systolic blood pressure of less than 120 mm Hg or less than 140 mm Hg.

• At a mean follow-up of 4.7 years, the rates of the primary end point (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) were not significantly different between the two trial groups.

The ACCORD Study Group

N Engl J Med
Volume 362(17):1575-1585
April 29, 2010
• “In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.”

• “Serious adverse events attributed to antihypertensive treatment occurred in 77 of the 2362 participants in the intensive-therapy group (3.3%) and 30 of the 2372 participants in the standard-therapy group (1/3%) (P<0.001).”

• Accompanying editorial: “…now we learn from the completed ACCORD study that flexible goals should probably be applied to the control of hyperglycemia, blood pressure, and dyslipidemia in patients with type 2 diabetes, taking into account individual clinical factors of importance.”

NEJM 2010;362:1628-1629
International Verapamil SR-Trandolapril Study (INVEST)

- Observational subgroup analysis of 6400 participants: ≥50 yrs old w/DM and CAD
  - Tight control: able to maintain SBP <130 mm Hg
  - Usual control: 130 to <140
  - Uncontrolled: ≥140

- Conclusion: “Tight control of systolic BP among patients with diabetes and CAD was not associated with improved cardiovascular outcomes compared with usual control.”

*JAMA* 2010;304:61-68
Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)

- 25,584 pts (9,603 diabetic) >55 yrs old w/↑ CVD risk
  - Randomized to ramipril +/- telmasartan
  - Observed for 4.6 yrs
  - Primary outcome: composite of CV death, nonfatal MI or stroke, hospitalized heart failure

- The higher the initial SBP, the more benefit to lowering BP
  - For initial SBPs 130-142, benefit of lowering is primarily for stroke
  - Initial SBP around or <130, anti hypertensive treatment should be implemented with caution because of possible cardiac effects

“‘Our study provides evidence that in high-CV-risk patients a BP reduction to <140/90 mm Hg is associated with CV protection. Overall CV protection, however, may not be improved by lower BP targets, as recommended for higher-risk subjects in current guidelines.’”

*J Am Coll Cardiol* 2012;59:74-83

*Circulation* 2011;124:1727-1736
HTN and Progression of CKD to End Stage Renal Disease (ESRD)

- Associations of SBP and DBP with risk of progressing to ESRD in the Kidney Early Evaluation Program (KEEP)
  - Large, diverse community-based sample
- High SBP accounted for most of the risk for progression to ESRD
  - Highest risk in those with SBP ≥150 mm Hg
  - Risk started at SBP of 140 rather than at 130

Arch Intern Med 2012;172:41-47
Current BP Targets in Diabetes

- **ADA 2012:**
  - “A goal SBP <130 mmHg is appropriate for most patients with diabetes.”
  - “Based on patient characteristics and response to therapy, higher or lower SBP targets may be appropriate.”
  - “Patients with diabetes should be treated to a DBP <80 mm Hg.”

- **VA/DoD Goal in their 2010 Guidelines:** <140/80
  - However, their performance measure....
The Way Forward: Clinical Action Measures as an Interim Step

BP Criteria Are Met:  
✓ BP < 140/90; or
✓ BP < 150/65; or
✓ SBP < 150 and on ≥ 3 mod dose BP medications

There is appropriate clinical action within 90 days:
✓ Increase in BP medication dose; or
✓ Start new BP medication; or
✓ Repeat BP < 140/90
JNC 8

- What do providers do until JNC 8 finally comes out?
  - Remember: there isn’t RCT evidence for universal <130 SBP target
    - Most benefit seen in reducing SBP to <140
  - Target selection should be individualized: “first, do no harm”
    - Use caution in setting targets: older, comorbidities, longer duration of DM, on lots of meds already, hypotensive symptoms, autonomic neuropathy
So what about GPRA?

- Current IHS GPRA targets better reflect the need to individualize A1C and BP targets
  - “Good Glycemic Control” A1C <8%
  - “Controlled Blood Pressure” <140/90

- **GPRA performance measures are not clinical practice guidelines**
  - Still need to do what’s right for each patient
    - Some patients would benefit from lower A1C target
    - And both these GPRA targets will still be too stringent for our older patients and those with multiple comorbidities
Thank You!

Questions, comments?

www.diabetes.ihs.gov