

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



Ann Bullock, MD

Division of Diabetes Treatment and Prevention

Indian Health Service

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

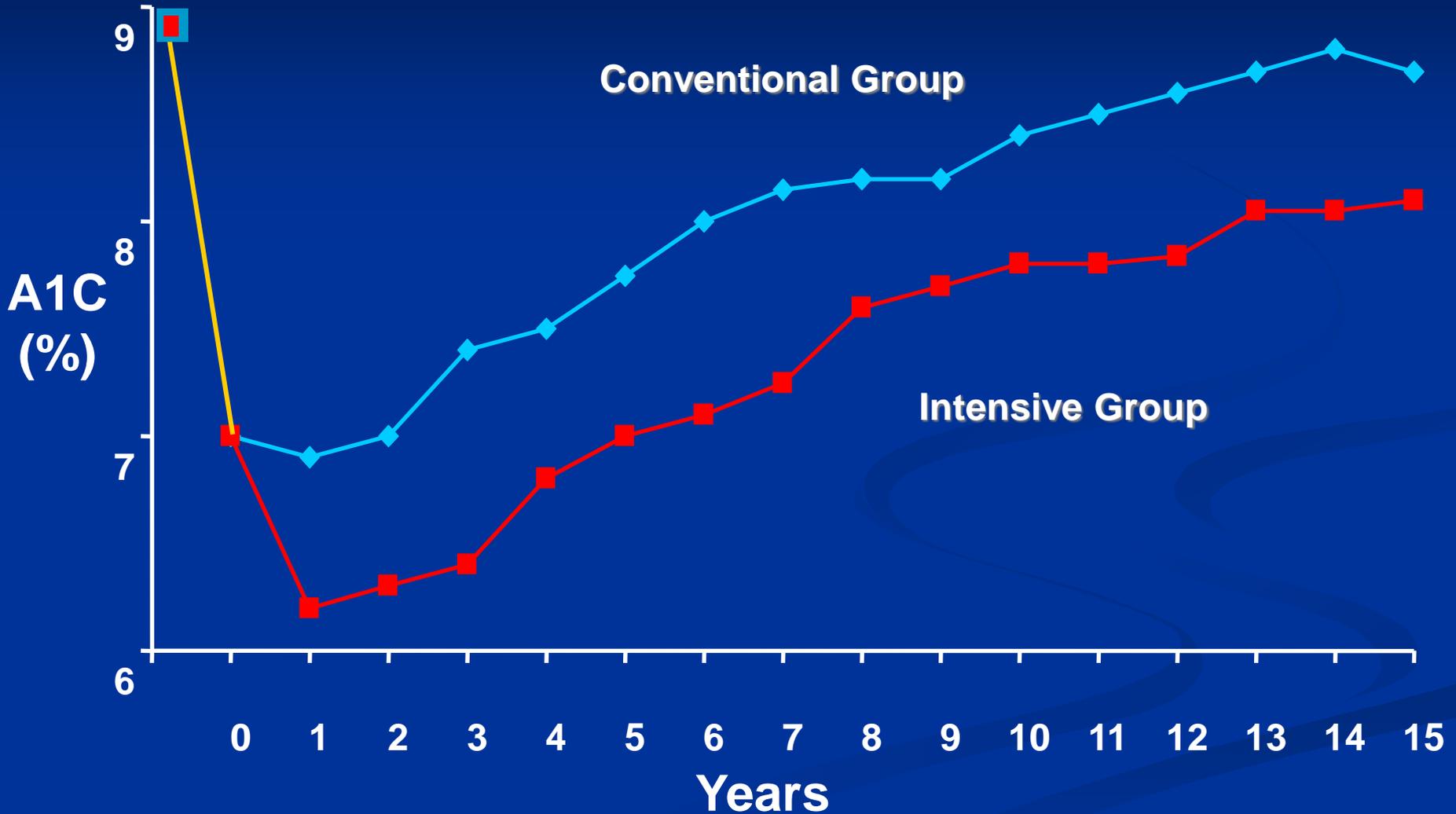
“First, do no harm”

Glucose targets across the lifespan

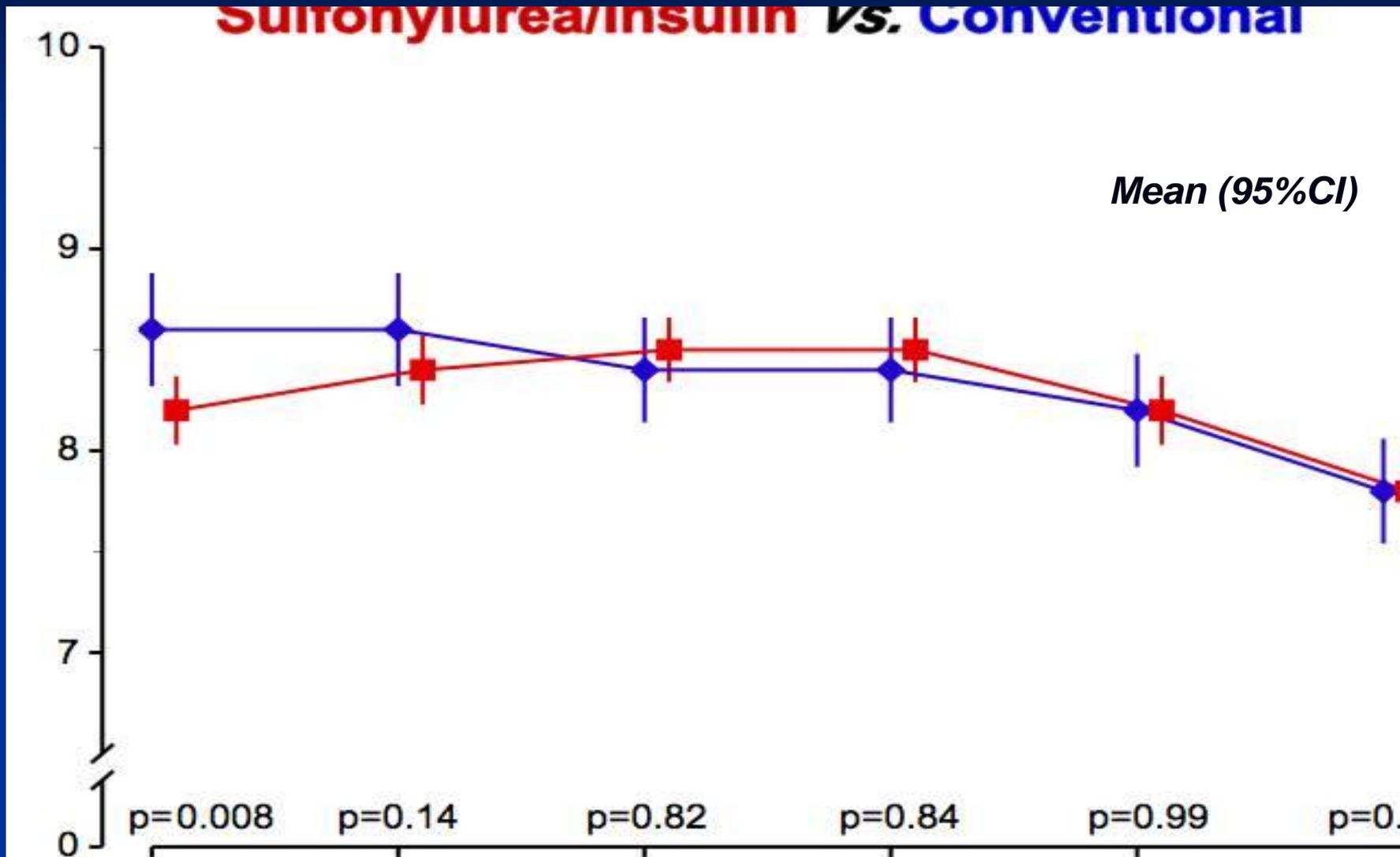
“To everything there is a season...”



United Kingdom Prospective Diabetes Study (UKPDS)



UKPDS: Post-Trial Changes in A1C



UKPDS: “Legacy Effect” of Glucose Therapy

After median 8.8 years post-trial follow-up

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

RRR = Relative Risk Reduction

P = Log Rank

The Legacy Effect: conclusions

“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*.”

Holman, et al. *NEJM* 2008. 359: 1577-1589

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

NEJM 2008;358:245-259 and 2560-72, *NEJM* 2009;360:129-139

- 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

Study	Microvasc		CVD		Mortality	
	Initial Trial	Long Term Follow-up	Initial Trial	Long Term Follow-up	Initial Trial	Long Term Follow-up
UKPDS	↓	↓	↔	↓	↔	↓
DCCT / EDIC*	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

Kendall DM, Bergenstal RM. © International Diabetes Center 2009



Initial Trial



Long Term Follow-up

* in T1DM

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
 Holman RR et al. *N Engl J Med.* 2008;359:1577. DCCT Research Group. *N Engl J Med* 1993;329:977.
 Nathan DM et al. *N Engl J Med.* 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.
 Patel A et al. *N Engl J Med* 2008;358:2560. Duckworth W et al. *N Engl J Med* 2009;360:129. (erratum:
 Moritz T. *N Engl J Med* 2009;361:1024)

2009 ADA Statement on Glucose Control and CVD Prevention

- 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

Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials --A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association, January 2009

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

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

Approach to management of hyperglycemia:

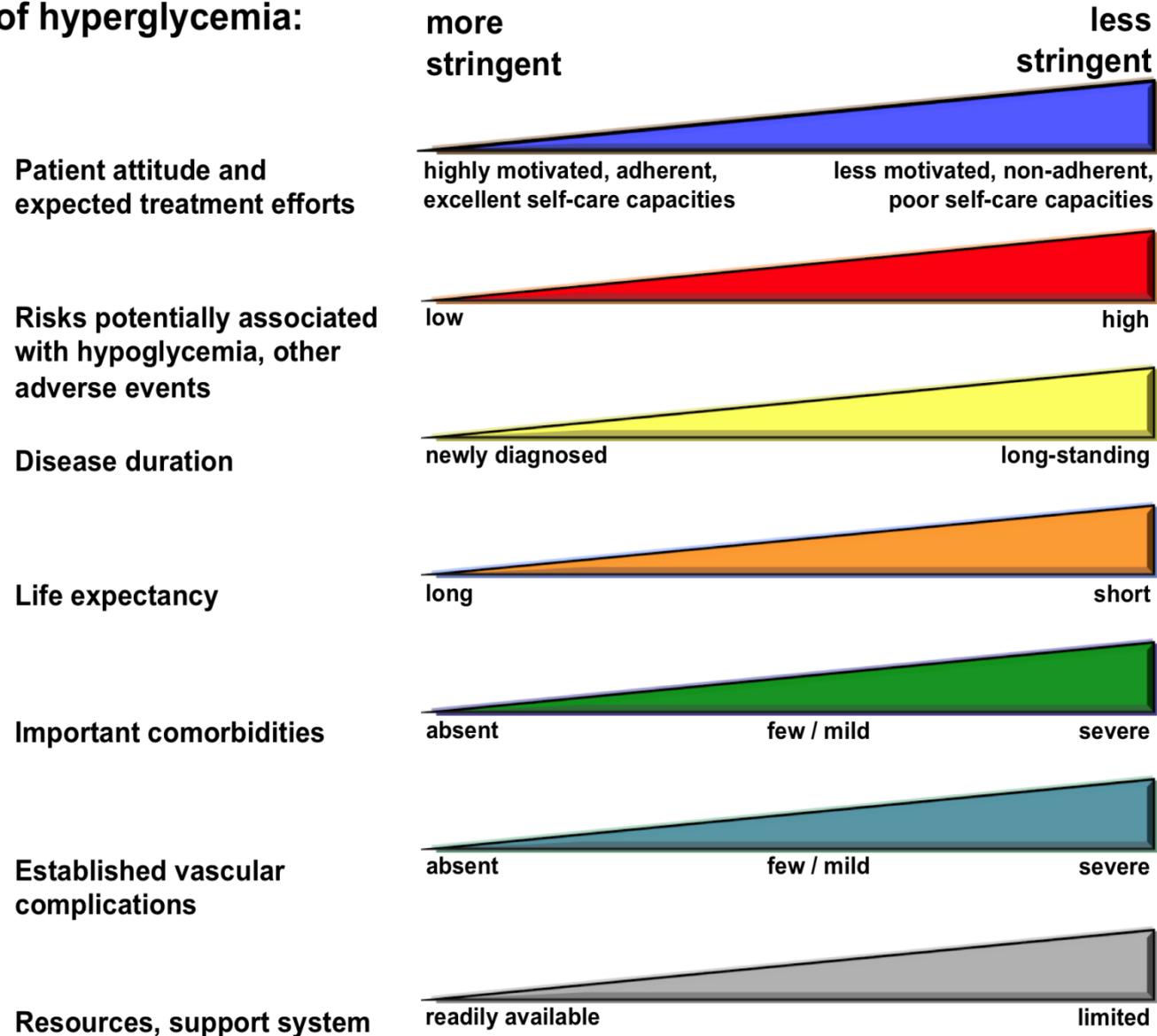
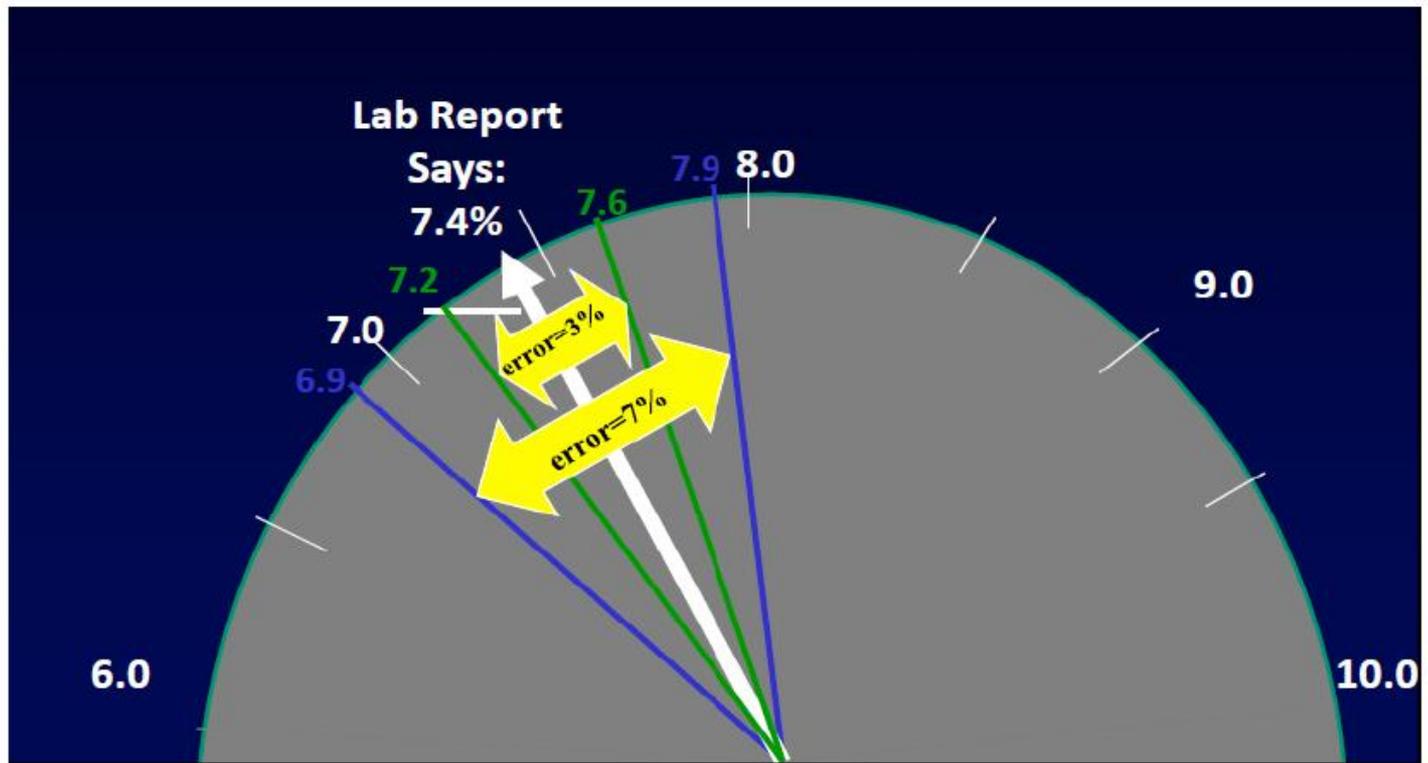


Figure 1

A1c Variability “Speedometer”



VA uses A1C target ranges

Major comorbidity or physiologic age	Microvascular complications		
	Absent or mild	Moderate	Advanced
Absent > 10 years of life expectancy	< 7	< 8	8-9
Present 5-10 years of life expectancy	< 8	< 8	8-9
Marked < 5 years of life expectancy	8-9	8-9	8-9

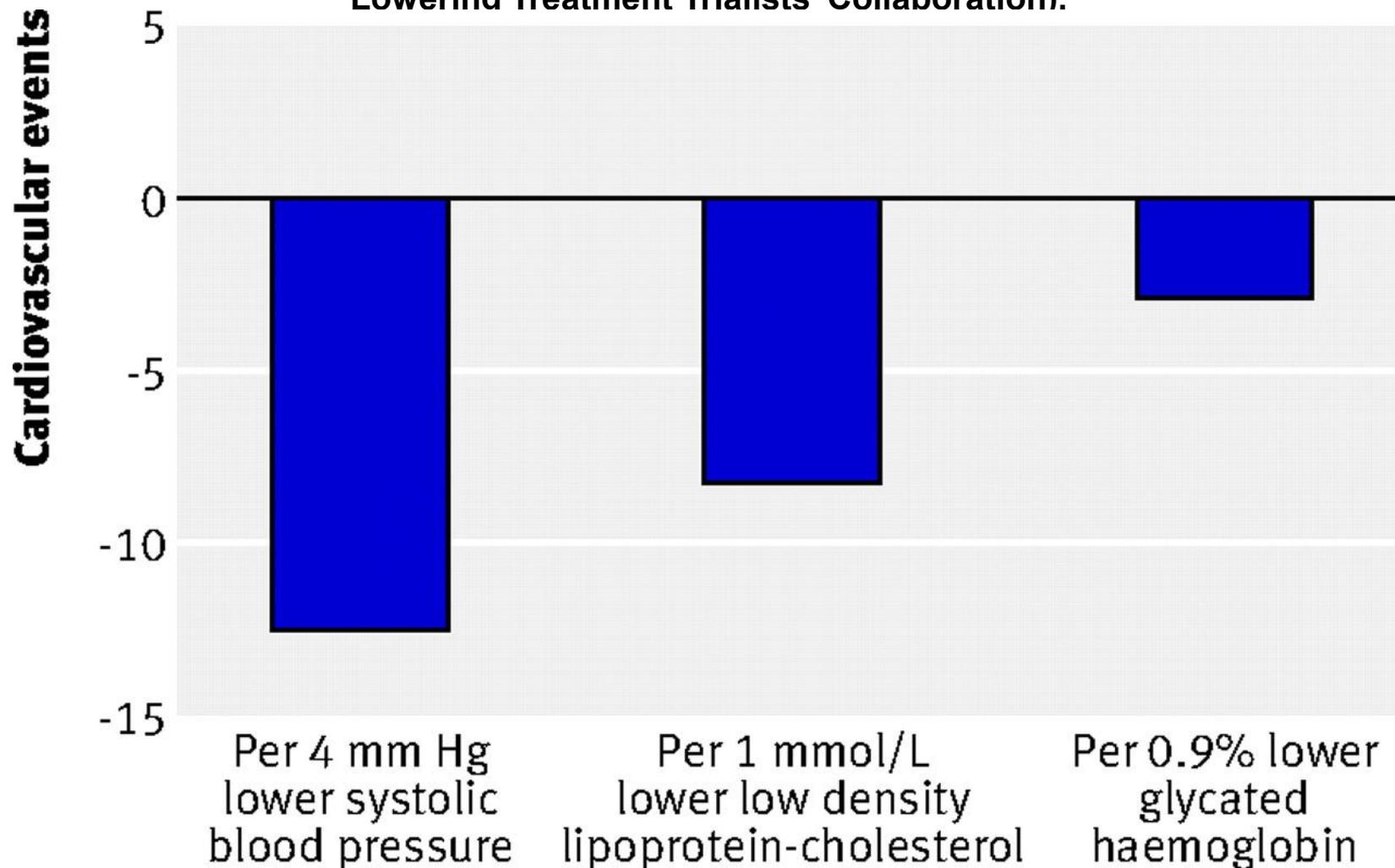
“Wait a minute—what happened to all the hype about getting everyone’s A1C down to <7% or even lower??”

- 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 144/82mm Hg on tight control compared with a less tight control mean of 154/87mm 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 $\leq 130/80$
 - But noted that “available data are somewhat sparse to justify the low target level of 130/80”

Original Article

“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



The NEW ENGLAND
JOURNAL of MEDICINE

ACCORD

- “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.”

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

J Am Coll Cardiol 2012;59:74-83

- “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.”

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

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

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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