Glucose Control: What's a Provider to Do?

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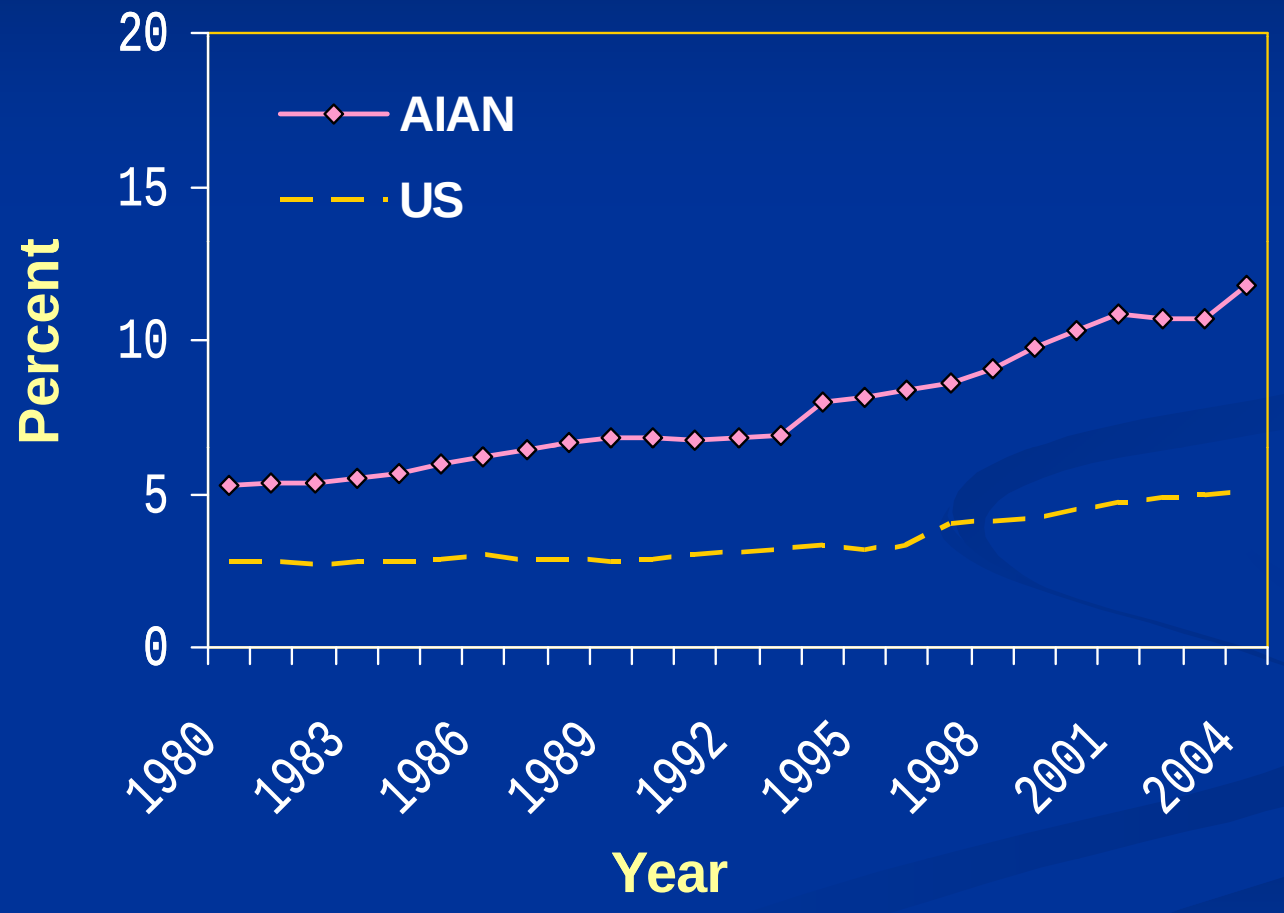
Today's Discussion

- Diabetes Data in AI/AN population
- A1c for diagnosis
- Goals for treating glucose: one size doesn't fit all
- Diabetes and Depression
- Medications: the good, the bad and the ugly

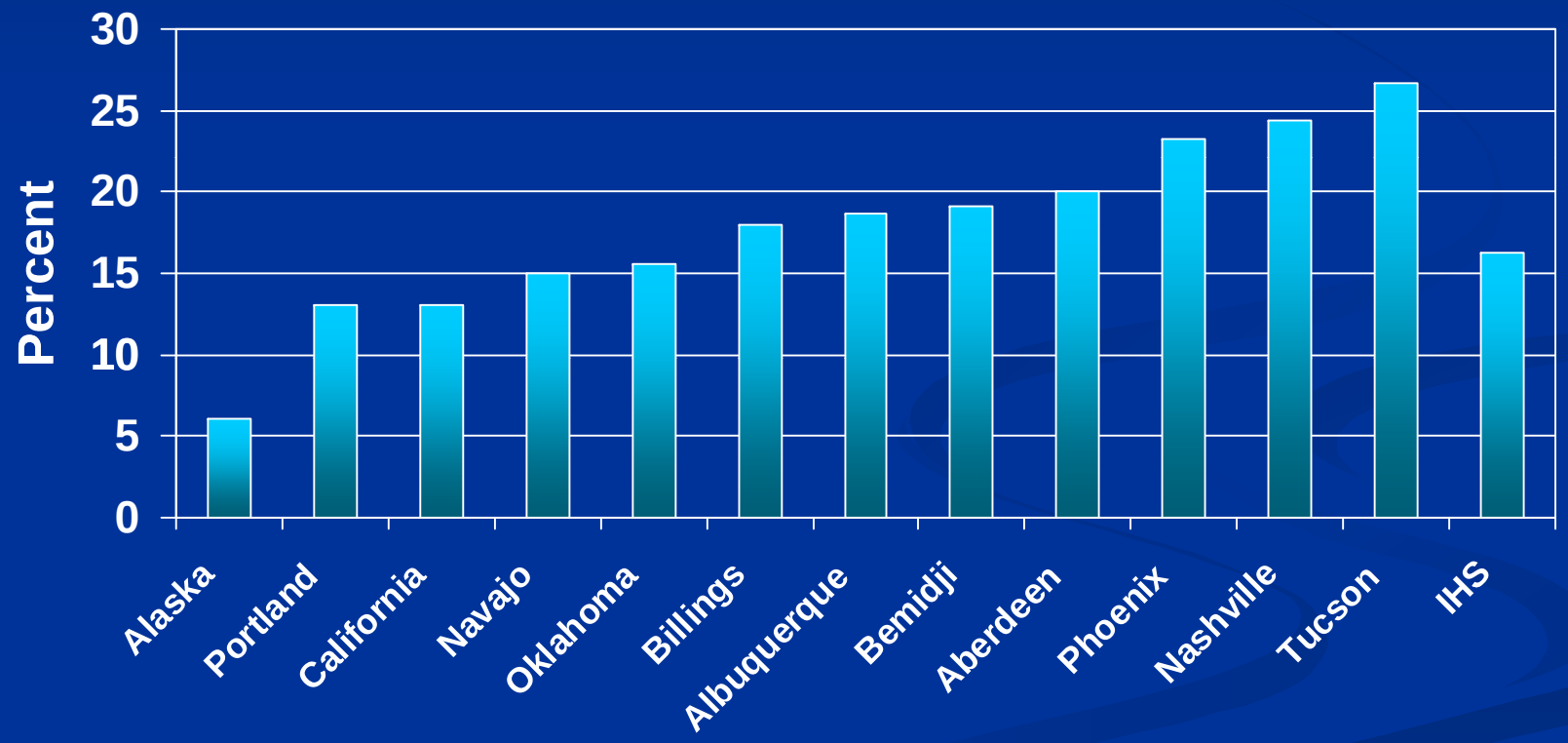
Prevalence of Diagnosed Diabetes AI/ANs
compared to U.S. population

1980- 2004



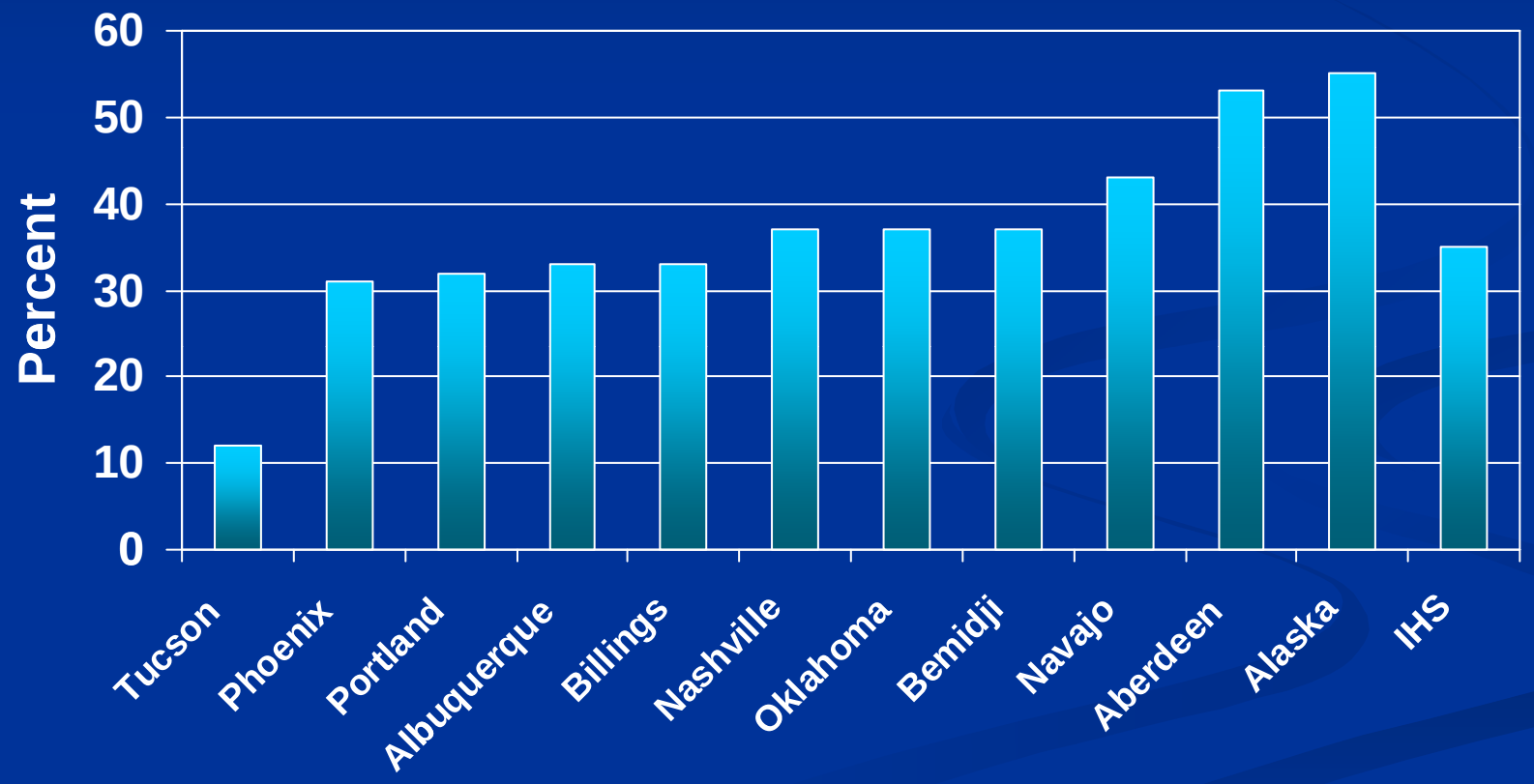
Source: IHS Program Statistics and National Diabetes Surveillance System. Age-adjusted to the 2000 US standard population with the exception of 1981–1993 data for AIAN, which was age-adjusted to the 1980 US standard population.

Age-adjusted* prevalence of diagnosed diabetes among American Indians/Alaska Natives, by Area, Indian Health Service 2004



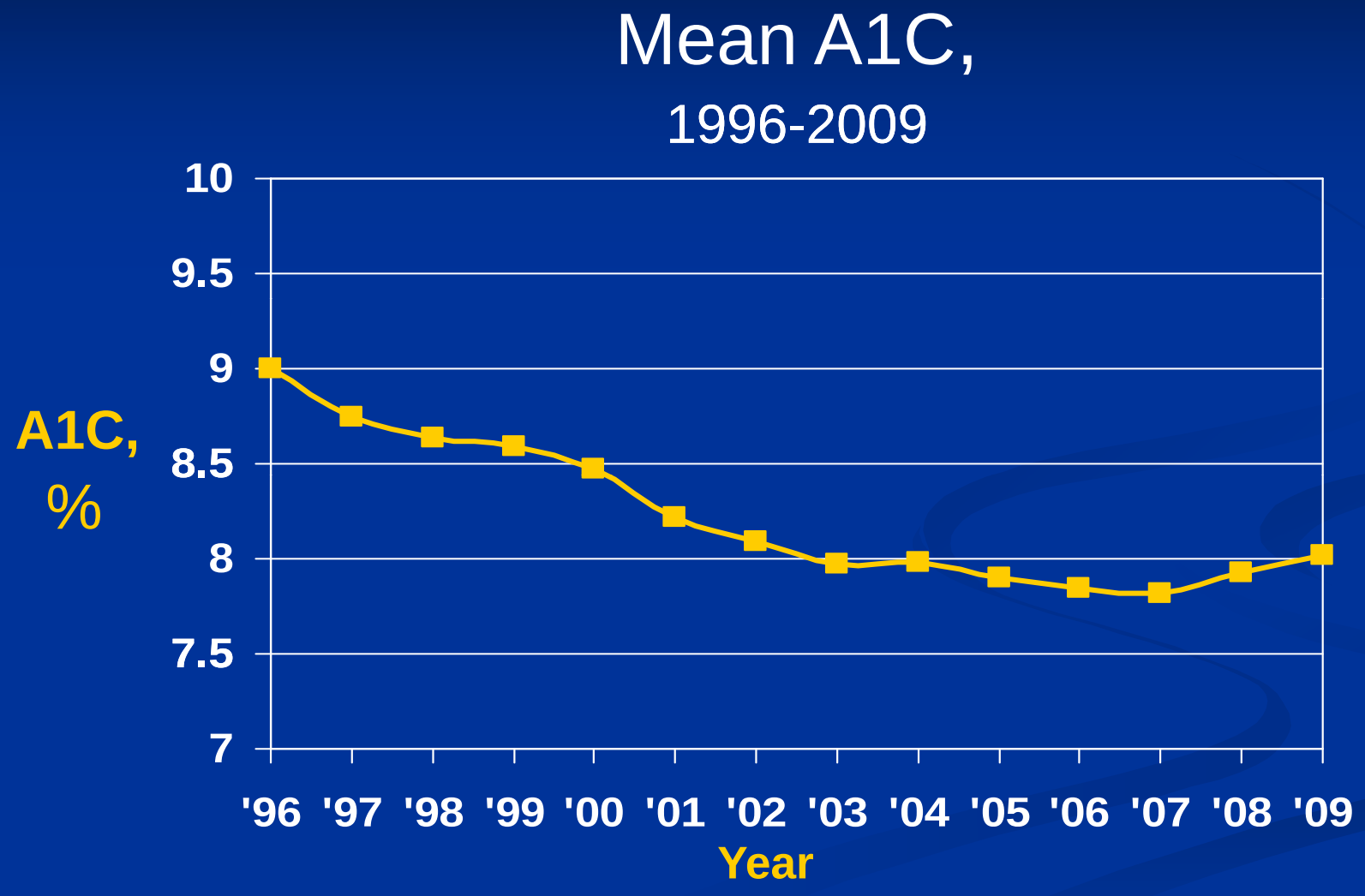
*Age-adjusted based on the 2000 U.S. population
Source: FY04 IHS APC files. Excludes data from 30 service units (4% of the IHS user population).

Increase in prevalence* of dx'ed DM among AI/AN 20 years or older, by IHS Area†, 1997 and 2004



*Age-adjusted based on the 2000 U.S. population
†Age-adjusted diabetes prevalence in California was the same in 1997 and in 2004 (13%).
Source: FY97–04 IHS APC files. Excludes data from 30 service units (4% of the IHS user population).

IHS Diabetes Care & Outcomes Audit



Source: IHS National Diabetes Program Statistics 1996-2009

*p<0.0001 comparing mean A1C levels in 1996 and 2009

A1c for Diagnosis

- Why now?
  - A1c assay standardized nationally
- Diagnostic ranges
  - Diabetes: ≥6.5% (if confirmed on different day)
  - Prediabetes: 5.7-6.4%
- Can still use FPG, OGTT, Glucose ≥ 200 mg/dl + sx
  - But use of OGTT should be *rare* outside of pregnancy
- A1c *recommended* test for general clinical purposes
  - No fasting required
  - No administration of glucose load
  - Reflects overall glycemia
  - Validated in Pima Indians
  - Recommended by Internat'l Expert Committee

Correlation of A1C with average glucose (eAG)

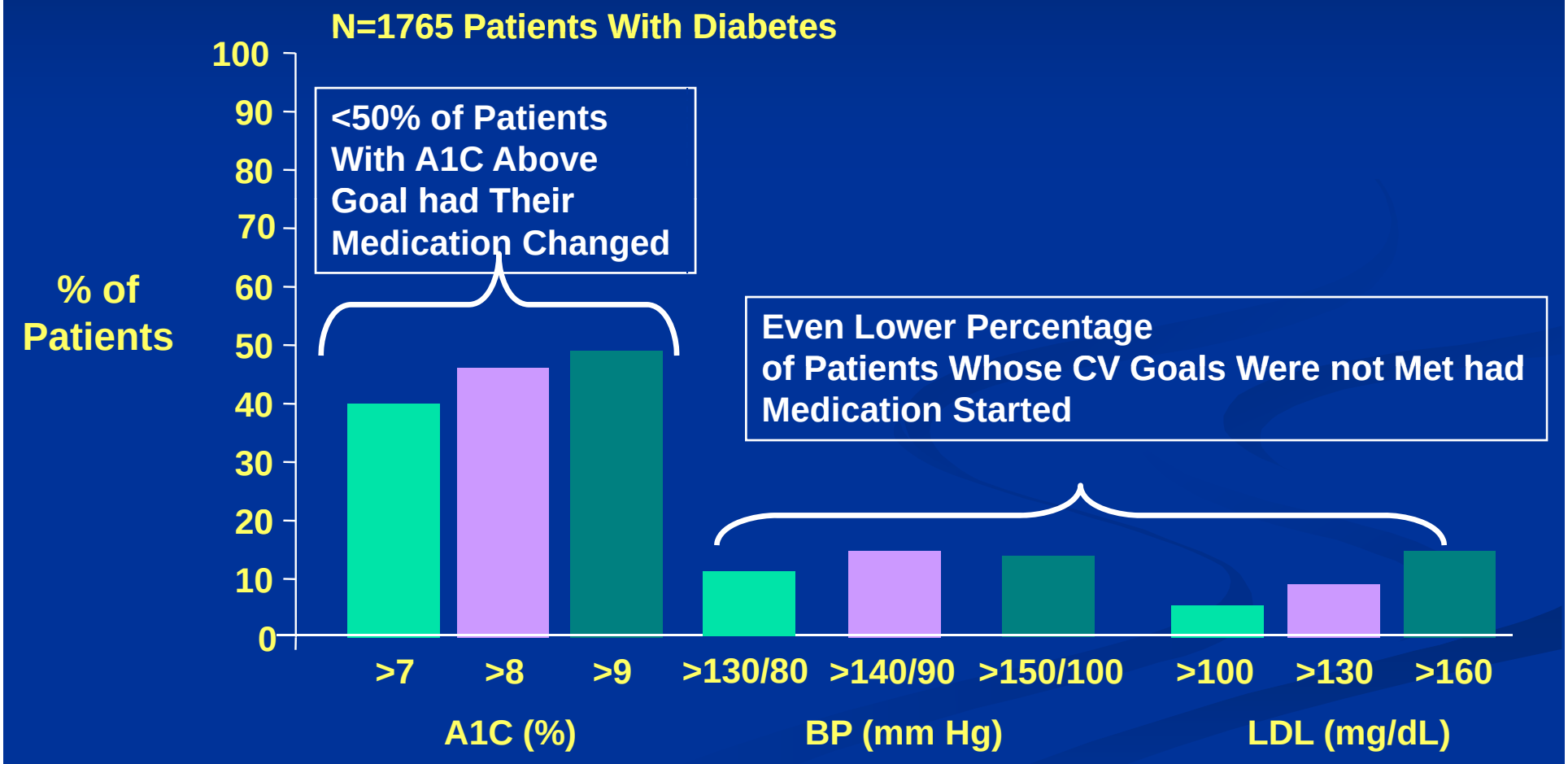
A1C (%)	Mean plasma glucose (mg/dl)
6	126
7	154
8	183
9	212
10	240
11	269
12	298

Correlation between A1C and average glucose: 0.92.
A calculator for converting A1C results into eAG, in either mg/dl or mmol/l, is available at http://professional.diabetes.org/eAG.
2010 ADA Standards of Medical Care

"I *always* make medication anges when my patients aren't at goal…"

Room for Improvement in Therapy Implementation and Change

Rates of Medical Regimen Change in 30 US Academic Medical Centers

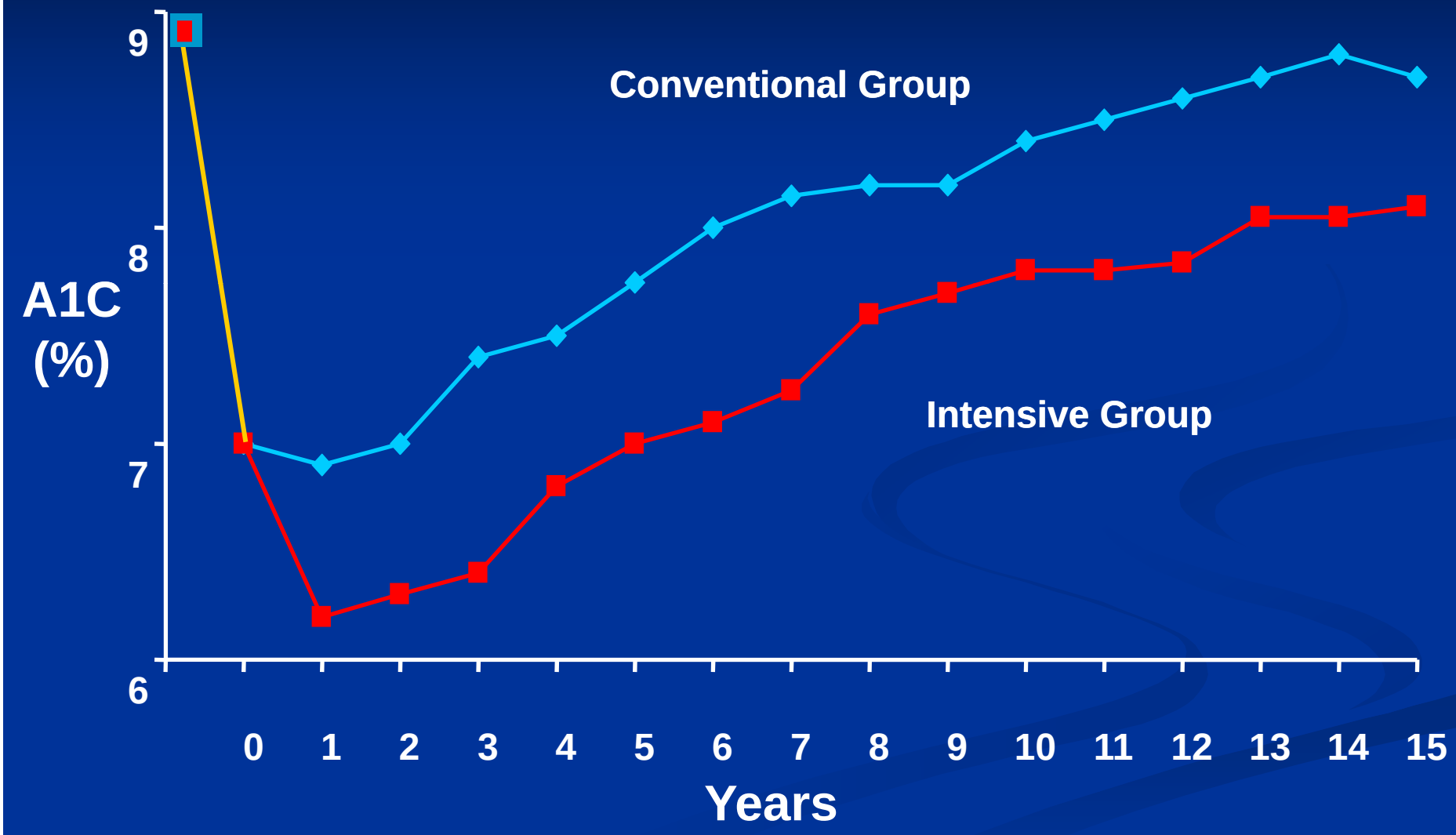


*P<.05 for A1C and LDL (P values are derived from Mantel-Haenszel test for trend).

Grant RW, et al. *Diabetes Care*. 2005;28:337-442.

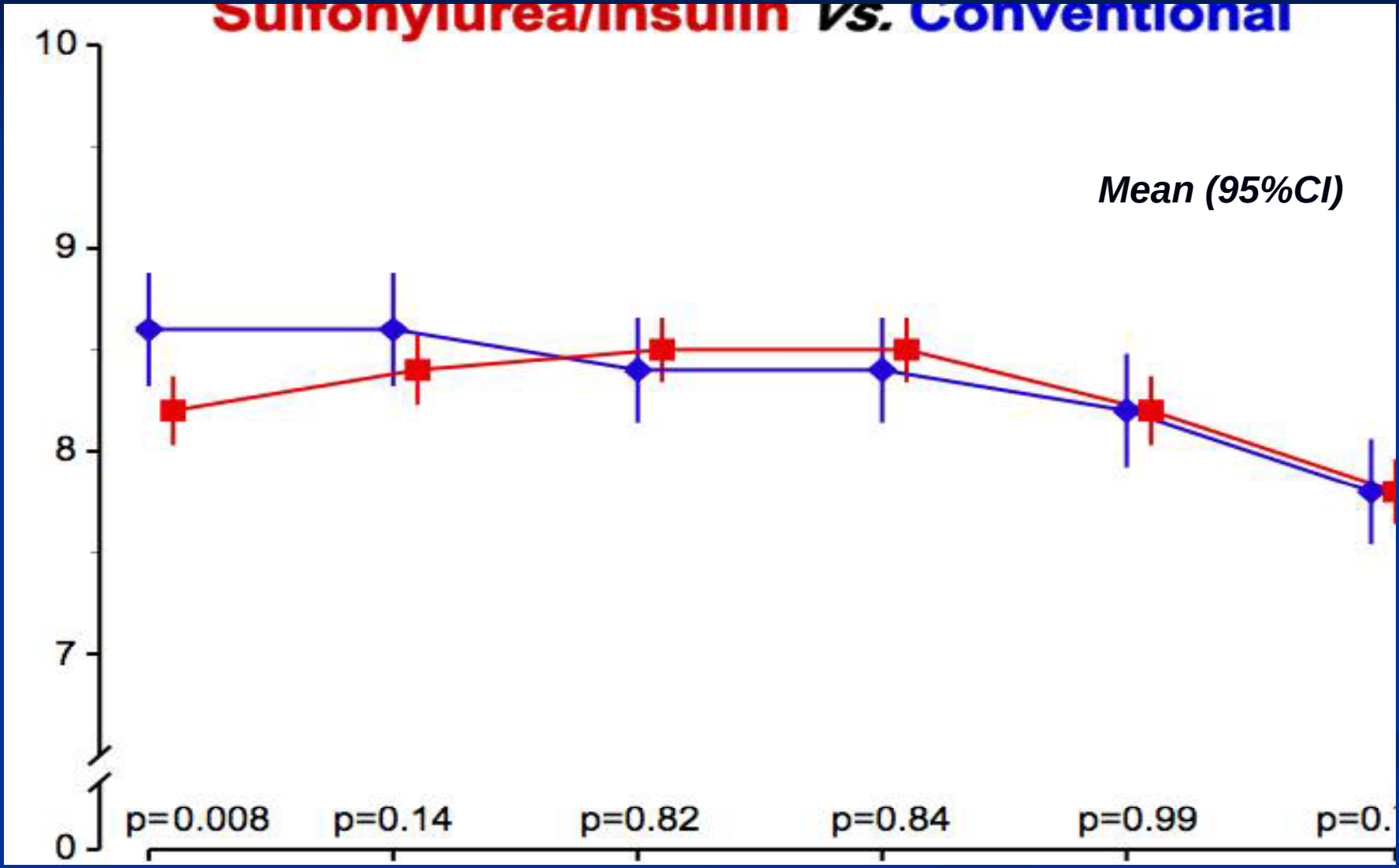
Does glucose control early in diabetes really matter?

UKPDS: A1C



UKPDS Group *Lancet* 352:837–53;1998

UKPDS: Post-Trial Changes in A1C



Holman RR, et al. *New England Journal of Medicine* 2008; 359:1577-1589

UKPDS: "Legacy Effect" of Glucose Therapy

After median 8.8 years post-trial follow-up

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

RRR = Relative Risk Reduction P = Log Rank

Holman RR, et al. *New England Journal of Medicine* 2008; 359:1577-1589

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 RH et al. NEJM 2008. 359: 1577-1589

Glucose Control

- **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 macrovasc dz**
- Does make a difference in microvascular dz
- 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

ADA Goals for Glucose

- Goals:
  - A1c <7%
  - Preprandial glucose: 70-130 mg/dl
  - Peak postprandial glucose: <180 mg/dl (1-2 hrs after start of meal)
- A1c is primary target for glycemic control
  - Postprandial glucose may be targeted if A1c goals not met despite reaching preprandial glucose goals
- Goals should be individualized based on:
  - Duration of diabetes
  - Age/life expectancy
  - Comorbid conditions
  - Known CVD or advanced microvascular complications
  - Hypoglycemic unawareness
  - Individual patient considerations

ADA 2010 Clinical Practice Recommendations

Depression Affects Glycemic Control

Diabetes and Depression: Intertwined

- **"Bidirectional association"** *JAMA* 2008;299:2751-2759
  - Diabetes doubles odds of co-morbid depression *Diabetes Care* 2001;24:1069-1078
  - Depression increases risk of Diabetes—by 23% in young adults *Diabetes Care* 2005;28:1063-1067
- **A1c levels 1.2% higher in Pimas with Diabetes who were also Depressed** *Diabetes Care* 2004;27:618-619
- **Prevalence of Depression in AI/AN pts with Diabetes**
  - BRFSS: **27.8%** --highest of all groups *Diabetes Care* 2008;31:105-107
- **Depression increases the risk of DM complications**
  - Mortality *Diabetes Care* 2005;28:1339-1345
  - **25% ↑ risk of macrovascular**
  - **36% ↑ risk of microvascular** **(independent of A1c, self-care)** *Diabetes Care* 2010;33:264-269

Medications to Achieve Glycemic Control

Classes of DM Meds

- Biguanide (metformin)
- Sulfonylureas
- Glinides (repaglinide/Prandin, nateglinide/Starlix)
- Alpha-glucosidase inhibitors (acarbose/Precose, miglitol/Glyset)
- Thiazolidinediones (pioglitazone, rosiglitazone)
- Amylin agonist (pramlintide)
- Glucagon-like peptide-1 agonists (exenatide, liraglutide)
- Dipeptidyl peptidase-4 inhibitors (sitagliptan, saxagliptin)
- Insulin

So many choices…?

- Effective, well-validated and cost-effective

  Welcome back to 1995!
  - Metformin
  - Sulfonylureas
  - Insulin

Figure 2

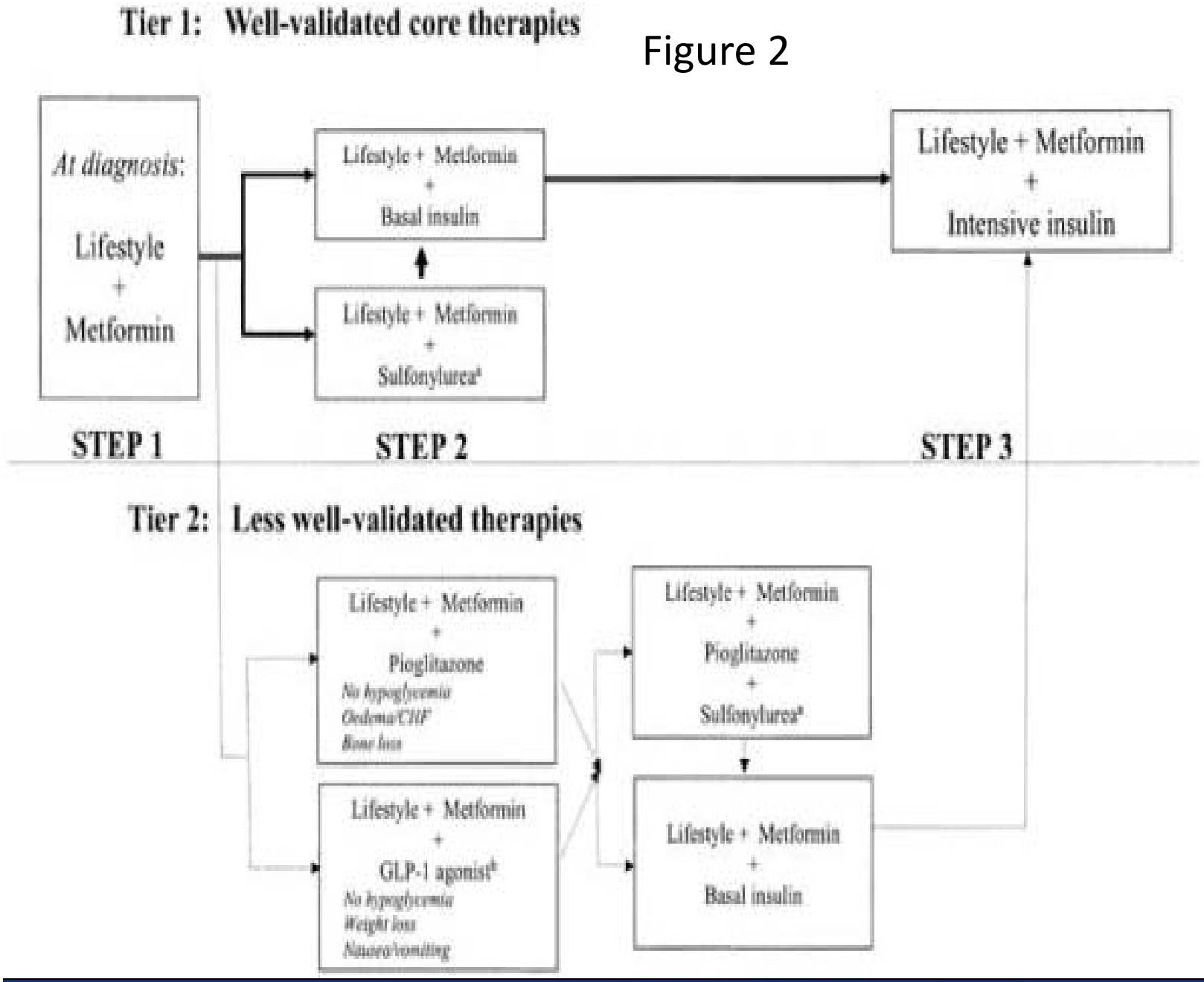


Figure 2 Algorithm for the metabolic management of type 2 diabetes; Reinforce lifestyle interventions at every visit and check A1C every 3 months until A1C is =7%. aSulfonylureas other than glybenclamide (glyburide) or chlorpropamide. bInsufficient clinical use to be confident regarding safety.

Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes.
NATHAN, DAVID; BUSE, JOHN; MD, PHD; DAVIDSON, MAYER; FERRANNINI, ELE; HOLMAN, RURY; SHERWIN, ROBERT; ZINMAN, BERNARD

Diabetes Care. 32(1):193-203, January 2009.

Table 1

Table 1—*Summary of glucose-lowering interventions*

Intervention	Expected decrease in A1C with monotherapy (%)	Advantages	Disadvantages
Tier 1: well-validated core			
Step 1: initial therapy			
Lifestyle to decrease weight and increase activity	1.0–2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0–2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: additional therapy			
Insulin	1.5–3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Sulfonylurea	1.0–2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
Tier 2: less well validated			
TZDs	0.5–1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5–1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established, expensive
Other therapy			
α-Glucosidase inhibitor	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5–1.5[a]	Rapidly effective	Weight gain, three times/day dosing, hypoglycemia, expensive
Pramlintide	0.5–1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
DPP-4 inhibitor	0.5–0.8	Weight neutral	Long-term safety not established, expensive

[a]Repaglinide more effective in lowering A1C than nateglinide. CHF, congestive heart failure; GI, gastrointestinal; MI, myocardial infarction.

Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes.

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What happened to TZDs?

- PPAR-gamma receptor modulators
  - ↑ insulin sensitivity in muscle, fat, liver
  - Pioglitazone (Actos) and rosiglitazone (Avandia)
  - Remember troglitazone (Rezulin)?—removed from market in 2000
- Common adverse effects of both
  - Weight gain
  - Fluid retention
    - Peripheral edema
    - Heart Failure risk ↑ x 2
  - Bone loss and fractures in women, ? men
- Pio vs. Rosi
  - Lipids: Pio +, Rosi neutral
  - CVD risk: Rosi--possible ↑
  - ADA Consensus Statement: advise against using rosiglitazone
  - Actos
    - Patent will expire January 2011—so should get cheaper
    - Need to select patients for use
    - Removed from IHS Core Formulary at Feb 2010 meeting

What about the newer meds?

- Amylin agonist: pramlintide (Symlin)
  - Beta cells produce amylin: ↓ gastric emptying, ↓ glucagon
  - Role in type 2 DM unclear
    - ↓A1c 0.5-0.7%, ↓ wt 1-1/2 kg
    - Injected before meals along with rapid/short-acting insulin (separate shot)
    - Expensive, frequent GI side effects
- GLP-1-based drugs
  - GLP-1 agonists: exenatide (Byetta), liraglutide (Victoza)
  - DPP-4 inhibitors: sitagliptan (Januvia), saxagliptan (Onglyza)
- Glucagon-like peptide-1 (GLP-1)
  - Produced by small intestine: ↑'s glucose-stimulated insulin secretion, ↓'s glucagon secretion, slows gastric motility
  - Synthetic mimetics have longer half-life
  - Dipeptidyl peptidase-4: enzyme that breaks down GLP-1

GLP-1 based drugs

- GLP-1 agonists
  - Benefits: ↓ A1c 0.5-1%, ↓ weight 2-3 kg
  - Side effects: GI common
- DPP-4 inhibitors
  - Benefits: ↓ A1c 0.6-0.9%
  - Side effects: possible effect on immune function
- Issues with both classes
  - Cost
  - Efficacy
  - Safety?

Exenatide use in Cherokee

- Costs had exceeded $25,000/month
- Evaluated 71 pts on exenatide from 3/08-3/09
  - Avg change in A1C of -0.26 (range +4.8 to -3.9)
  - Avg change in weight of -5lbs (range +11 to - 35.5)
- Reviewed literature
  - Exenatide not cost effective c/w insulin glargine

Cardiovascular Diabetology 2008;7:24

- Changed to non-formulary with strict criteria
- Costs dropped to $10,000/month

Incretin-based Therapies: Beyond Cost & Efficacy: Safety?

- "…the available evidence supports the use of incretin-based therapies for patients requiring effective control of glycemia and body weight while minimizing the risk of hypoglycemia."

  Diabetes Care 2010;33:428-433

- "…we believe it is premature to conclude that the GLP-1 class of drugs has been established as having a good safety profile… There are grounds for concern that the GLP-1 class of drugs may induce asymptomatic pancreatitis and, over time in some individuals, induce pancreatic cancer. …the implications of the data are sufficiently serious that continuing to promote this class of drugs without establishing clear experimental evidence to permit the concern to be rejected is irresponsible."

  Diabetes Care 2010;33:453-455

Type 2 Diabetes - Glucose Control

Type 2 Diabetes - Glucose Control

DM DX – confirm with second test

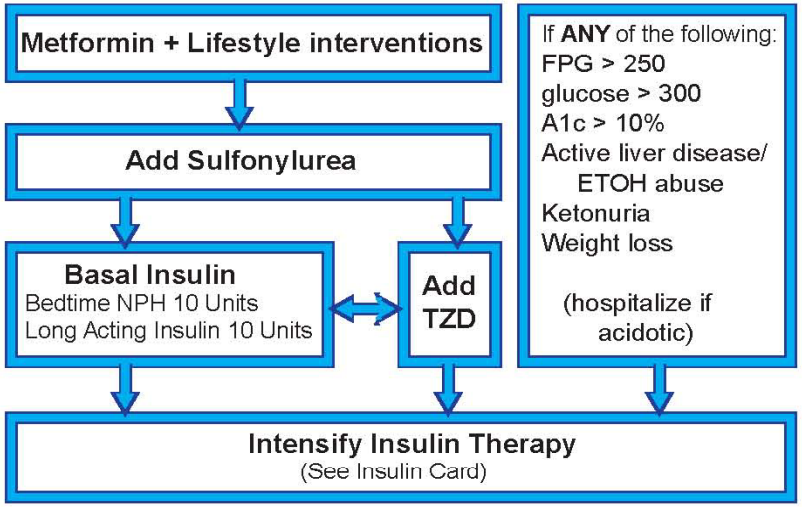
1. A1c ≥ 6.5% (preferred method)
2. FPG ≥ 126
3. 2° (OGTT) ≥ 200
4. Non-fasting lab glucose ≥ 200 with sx

Prediabetes is defined as A1c 5.7-6.4%, FPG 100-125, or 2 ° (OGTT) 140-199

DM BG Targets

Premeal: < 70-130
2° PP: < 160-180
A1c: < 7%

Individualize targets based on patient condition



Immunizations

Pneumovax—At Dx & again at age 65 (if ≥5 yrs. since 1st shot)
Flu shots yearly
Td /Tdap (routine)
PPD once after Dx of DM (Pos is ≥10mm)

Don't Forget

Glucose toxicity— Insulin production↓'s if prolonged hyperglycemia; insulin shots short-term reverse this.
Pancreatic Exhaustion— Almost all Type 2 diabetics will eventually require insulin.

Monitoring of DM

- A1c every 3-6 months
- Creatinine and eGFR yearly
- UACR yearly
- Lipid Panel yearly
- LFTs yearly
- ECG every 2-5 years
- Complete Foot Exam yearly
  - Foot inspection each visit
- Retinopathy exam yearly
- Paps, Mammograms, and Contraception
- Evaluate sexual function
- Depression, Tobacco, ETOH, and DV screening yearly

Estimated Average Glucose (eAG)

A1c %	6	7	8	9	10	11	12
Mean plasma gluc	126	154	183	212	240	269	298mg/dL

Biguanides: Metformin & Metformin XR (Glucophage,)
Start 500 mg daily with meals and increase no faster than 500 mg each week. If GI sx occur may increase more slowly.
Max. dose: 2000mg daily or divided with XR tablets. Do not split XR tablets.
2500 mg divided BID-TID with regular release tablets.
Can decrease weight. Pt. must have normal creatinine (males <1.5, females <1.4), Do not use if liver disease (check ALT) or significant ETOH use. Discontinue before surgery or IV contrast dye administration.

Sulfonylureas: Glyburide (Micronase,) and Glipizide (Glucotrol®)
Start 2.5-5mg daily – Max 10 mg BID
Can increase weight and cause hypoglycemia

Thiazolidinediones (TZD): *Pioglitazone (Actos®)*
Start 15mg daily; may increase to 30mg daily (little benefit dosing over 30mg)
Max A1c changes may take up to 12 weeks to occur
Check ALT at baseline & periodically. No underlying liver dz or significant ETOH use. Warning: heart failure and fracture risk. May use in renal insufficiency. Can cause weight gain.

DPP-4 Inhibitors: May reduce weight, mild to mod A1c lowering
Sitagliptan (Januvia®) - Dose: 100mg PO daily; Reduce dose if ≥ Stage 3 CKD
Saxagliptan (Onglyza®) - Dose: 2.5-5mg PO daily
Dose 2.5mg if strong P450 3A/4 inhibitors or mod-sev renal impairment

GLP-1 Mimetics: Can decrease weight, mild to mod A1c lowering
May be associated with pancreatitis – seek medical care if persistent severe abdominal pain with or without vomiting
Exenatide (Byetta®) Start 5 mcg/dose BID SC inj in thigh, abdomen, or upper arm
May increase to 10 mcg/dose BID after 1 month of treatment
Administer within 60 minutes before meals Do not use if ≥ Stage 4 CKD
Liraglutide (Victoza®) - Start 0.6mg daily SC inj in thigh, abdomen, or upper arm
Inc to 1.2mg daily in 1 week. May increase to 1.8mg daily

Pramlintide (Symlin®) - Amylin mimetic
Mild A1c lowering, small decrease in weight
Start 60 mcg daily subcutaneously immediately before a major meal
(Reduce preprandial (short acting) insulin by 50% as appropriate)
Start with lower doses in type 1 diabetes
May increase to 120 mcg after significant nausea is gone x 3-7 days

Drug names in italics are not on the IHS National Core Formulary

Ref: ADA Clinical Practice Recommendations 2010 Diabetes Care 2010;33
Ref: Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy Diabetes Care 2009;32(1):193-203

Insulin

- Most powerful medication for reducing glucose
- Use early in diabetes
  - Reduce glucose toxic effects on beta cells
- Many different insulin varieties
  - None "better"
  - Adaptable to patients' lives
- Consider using U-500 when > 200 units/day
  - Smaller fluid bolus: ↑ absorption and ↓ pain
  - Less expensive on a *per unit* basis, fewer syringes
  - Nice summary article: *Diabetes Spectrum* 2009;22(2):116-122

Type 2 DM – Insulin

STEP 1: Target Fasting Plasma Glucose with **Basal insulin**
Fasting Plasma Glucose (FPG) Target = 70-130mg/dl

HS NPH or Long Acting insulin – start 10 units or 0.2 units/kg

↓

Increase dose 2 units every 3 days until FPG is 70 - 130mg/dl

May increase by 4 units every 3 days if FPG is > 180mg/dl

STEP 2: Target Pre-Meal Glucose (target one at a time)
Premeal Glucose Target = 70-130mg/dl

If Pre-lunch glucose > 130mg/dl
Start 4 units Bolus Insulin before breakfast

If Pre-supper glucose > 130mg/dl
Start 4 units Bolus Insulin before lunch
OR Add/Increase morning NPH

If Bedtime glucose > 140mg/dl
Start 4 units Bolus Insulin before supper OR Increase evening NPH

→ Increase Bolus Insulin by 2 units every 3 days

As insulin doses get larger, (over 10 units), begin to change insulin dose by 10-20%

STEP 3: If A1c not at goal: Target Post-Prandial Glucose with **Bolus** premeal insulin
2 Hour Post-Prandial Glucose Target <160-180mg/dl

Ref: Nathan, Buse, Davidson, et al. Management of Hyperglycemia in Type 2 Diabetes.: a Consensus Algorithm for the Initiation and Adjustment of Therapy. (2006). Diabetes Care 28, 1963-1972

Type 2 DM – Insulin

Basal Insulin – intermediate and longer acting insulin

Type of Basal Insulin	Onset	Peak	Duration
Intermediate Acting			
NPH (Humulin N ®, Novolin N ®)	1-3 hours	6-10 hours	12-20 hours
Long Acting			
Glargine (Lantus ®)	1 hour	None	24 hours
Levemir (Detemir ®)	1 hour	None	12-24 hours

Bolus Insulin – rapid and shorter acting insulin

Type of Insulin	Onset	Peak	Duration
Lispro (Humalog ®) *Aspart (Novolog ®)* *Glulisine (Apidra ®)*	15-30 min	30-90 min	3-5 hours
Regular (Humulin R ®, Novolin R ®)	30-60 min	1-2 hours	5-8 hours

Premixed Insulin – longer and shorter acting insulin

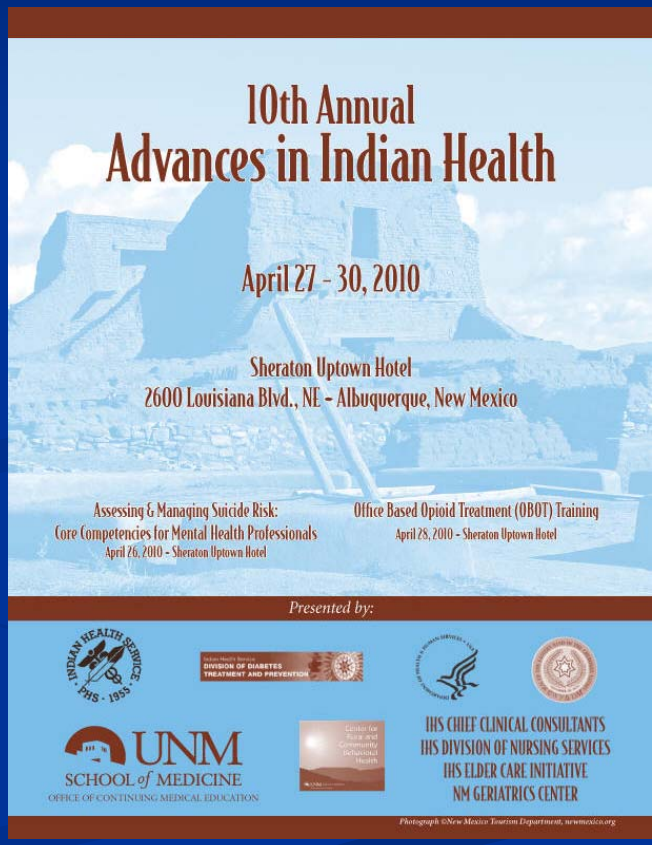
Use **ONLY** if the patient cannot mix insulin

Type of Insulin	Onset	Peak	Duration
Humulin, Novolin, Novolog 70/30	30 min	2-4 hours	14-24 hours
Humulin 50/50	30 min	2-5 hours	18-24 hours
Humalog 75/25	15 min	½-2½ hrs	16-20 hours

Drugs names in italics are not on the National Core Formulary

Tools on IHS Diabetes Website

- Algorithms:
  - Glucose Control, Insulin
  - HTN, Lipid control
  - Urine albumin testing, CKD
  - Foot Care
- Best practices: 19 of them—clinical and community
- IHS Standards of Care for Adults with Type 2 Diabetes—updated 2009
- www.ihs.gov/MedicalPrograms/Diabetes/

Advances in Indian Health Conference

- **IHS' primary care conference**
  - **Chief Clinical Consultants, Nursing, DDTP, Elder Care**
- April 27-30, Albuquerque
- 28 hours of CME/CE on AI/AN health
  - Diabetes and its complications: CKD, CVD, neuropathy
  - Mental Health, Trauma, Historical Trauma, ACEs
  - Substance Abuse, including OBOT training
  - Women's Health, Geriatrics, Pediatrics, EHR