

Treatment of Type 2 Diabetes: Perspective From the ADA Consensus Statement on Medical Management of Hyperglycemia and Standards of Care

*Improving Health at a Local Level:
Action Today...Impact Tomorrow*

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Eastern Idaho Public Health District
Idaho Falls, Idaho

1

Objectives

- Discuss the epidemiology and natural history of type 2 diabetes.
- Identify current approaches to the management of Type 2 Diabetes including current treatment guidelines.
- Review current therapies utilized for the treatment of hyperglycemia.

2

Overview of the Diabetes Epidemic in the United States

- 23.6 million people/7.8% of the population have diabetes
- 5.7 million people are undiagnosed
- 10.7% of adults aged ≥20 years have diabetes
 - Increasing incidence of T2DM in children and adolescents in certain racial ethnic populations
- T2DM is associated with obesity, increased age, decreased physical activity, and race/ethnicity
- Total estimated cost of diabetes in 2007 was \$174 billion, including \$116 billion in excess medical expenditures

CDC. National Diabetes Fact Sheet, 2007. Atlanta, GA: US Dept of Health and Human Services, Centers for Disease Control and Prevention. http://www.cdc.gov/diabetes/pubs/pdf/nfds_2007.pdf. Accessed February 20, 2010.

3

Characteristics of T2DM

- T2DM is a chronic illness that results from a progressive insulin secretory defect on the background of insulin resistance^{1,2}
- Increased risk for serious complications^{1,2}
 - CVD
 - Retinopathy
 - Neuropathy
 - Nephropathy

CVD = cardiovascular disease.
1. ADA. *Diabetes Care*. 2010;33(suppl 1):S11-S61. 2. ADA. *Diabetes Care*. 2010;33(suppl 1):S62-S69.

4

Criteria for the Diagnosis of Diabetes: 2010 ADA Clinical Practice Recommendations

1. A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay^a

OR
2. FPG ≥126 mg/dL. Fasting is defined as no caloric intake for at least 8 hours^a

OR
3. 2-hour plasma glucose ≥200 mg/dL during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water^a

OR
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL

*In the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing on a different day.
ADA = American Diabetes Association; DCCT = Diabetes Control and Complications Trial; FPG = fasting plasma glucose; NGSP = National Glycohemoglobin Standardization Program; OGTT = oral glucose tolerance test; WHO = World Health Organization.
ADA. *Diabetes Care*. 2010;33(suppl 1):S11-S61.

5

2010 Diagnosis of Diabetes and Categories of Increased Risk for Diabetes

Test	Categories of Increased Risk	Diabetes
FPG	IFG: FPG 100-125 mg/dL	FPG ≥126 mg/dL
2-h PG on the 75-g OGTT	IGT: 2-h PG 140-199 mg/dL	2-h PG ≥200 mg
A1C	5.7%-6.4%	≥6.5%

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random PG ≥200 mg/dL is also a criterion for the diagnosis of diabetes.
FPG = fasting plasma glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test; PG = plasma glucose.
ADA. *Diabetes Care*. 2010;33(suppl 1):S11-S61.

6

Treatment Recommendations for Individuals With IFG, IGT, or Both

Population	Treatment
IFG or IGT	Lifestyle modification (ie, 5%-10% weight loss and moderate intensity physical activity ~30 min/d)

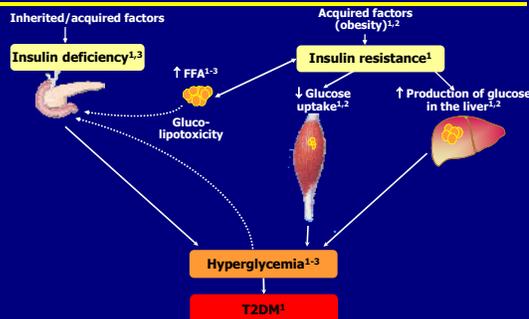
Individuals with IFG and IGT and any of the following:

- <60 years of age
- BMI ≥35 kg/m²
- Family history of diabetes in first-degree relatives
- Elevated triglycerides
- Reduced HDL cholesterol
- Hypertension
- A1C >6.0%

Lifestyle modification (as above) and/or metformin

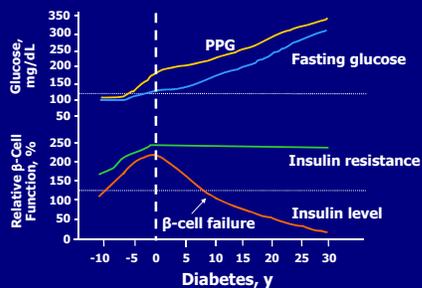
BMI = body mass index; HDL = high-density lipoprotein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance. Nathan D et al. *Diabetes Care*. 2007;30:753-759.

Pathophysiology of T2DM



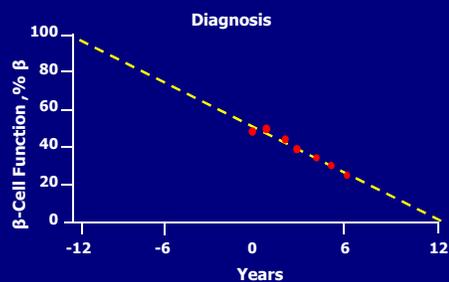
FFA = free fatty acid.
 1. Bergenstal R et al. *Endocrinology*. Philadelphia, PA: WB Saunders Co; 2001:821-835. 2. DeFronzo RA. *Diabetes*. 1988;37:667-687. 3. Pollout V et al. *Endocrinology*. 2002;143:339-342.

Natural History of T2DM



PPG = postprandial plasma glucose. Adapted with permission from Bergenstal R et al. *Endocrinology*. Philadelphia, PA: WB Saunders Co; 2001:821-835.

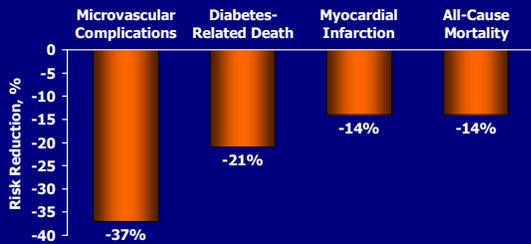
Progressive β-Cell Failure in T2DM



Based on data of UKPDS 16: conventional (diet) treatment group

UKPDS = UK Prospective Diabetes Study. UKPDS Group. *Diabetes*. 1995;44:1249-1258.

Results From the UKPDS: Correlation Between a 1.0% A1C Decrease and Reduced Risk of Complications



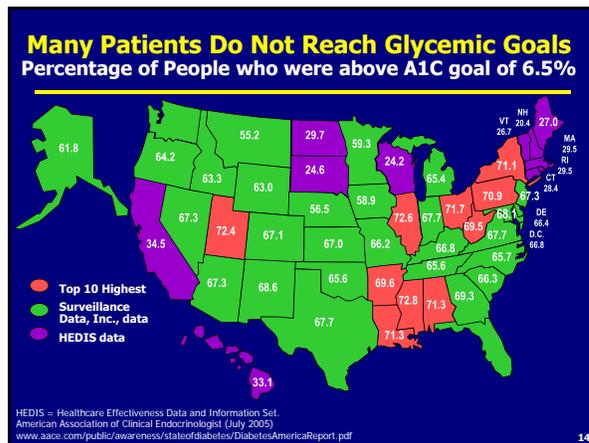
P < 0.0001 for microvascular complications, diabetes-related death, myocardial infarction, and all-cause mortality. UKPDS = UK Prospective Diabetes Study. Stratton IM et al. *BMJ*. 2000;321:405-412.

Managing T2DM

Goals of Intensive Diabetes Management

- Management of diabetes will help reduce acute complications and reduce risk of long-term complications
- Treating conditions that accompany diabetes, such as hypertension and dyslipidemia, may help improve microvascular and cardiovascular complications
- Glycemic goals (A1C <7.0%) may not be appropriate or practical for some patients
 - Clinical judgment should be based on potential benefits and risk of intensified regimens and should be individualized for the patient
 - Factors to consider include life expectancy, risk of hypoglycemia, and presence of CVD

CVD = cardiovascular disease.
ADA. *Diabetes Care*. 2010;33(suppl 1):S11-S61.



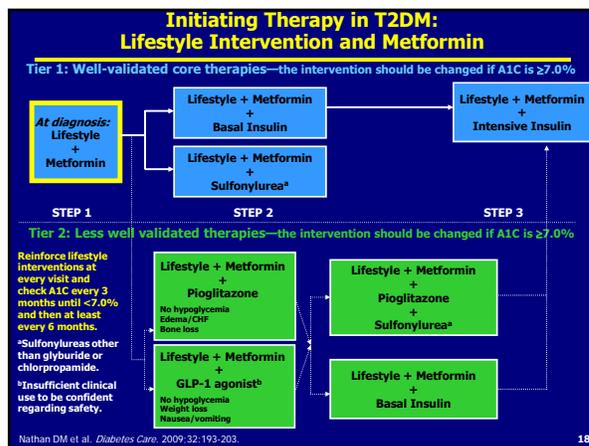
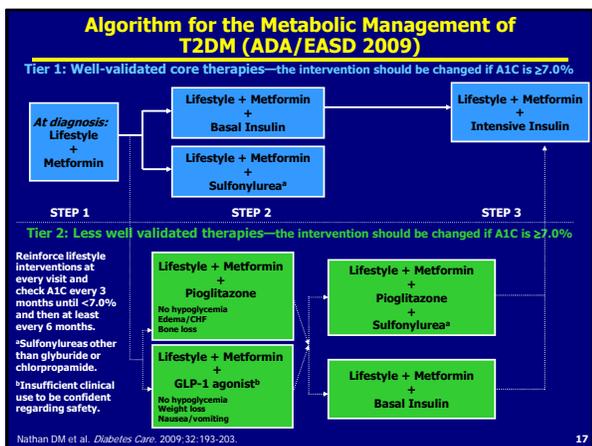
Treatment Algorithm for T2DM

ADA/EASD Guidelines

Development of the ADA/EASD Statement

- Developed based on a need to provide practitioners with a clear path to follow when managing patients with T2DM
- Consensus algorithm created to help guide health care providers in choosing the most appropriate interventions for patients with T2DM
- Based on clinical trials, clinical experience, and judgment
 - A1C ≥7.0% should serve as a call to action to initiate or change therapy with the goal of achieving A1C <7.0%

ADA = American Diabetes Association; EASD = European Association for the Study of Diabetes.
Nathan DM et al. *Diabetes Care*. 2009;32:193-203.



Lifestyle Modification—Diet and Exercise

- Major environmental factors that increase the risk of T2DM include overeating and a sedentary lifestyle¹
- Exercise and weight loss help reduce hyperglycemia and may improve coincident cardiovascular risk factors¹
- Lifestyle modification is effective at reducing the risk of developing diabetes in people with elevated fasting or postload plasma glucose concentrations²

1. ADA. *Diabetes Care*. 2010; 33(suppl 1):S11-S612. Knowler WC et al. *N Engl J Med*. 2002; 346:393-403.

Advantages of Initiating Therapy With Metformin

- Metformin is the only available OAD that acts primarily by inhibiting hepatic glucose release¹
- Targets insulin resistance and reduces plasma insulin concentrations²
- Lowers A1C by 1.0-2.0%³
- Does not cause weight gain¹

OAD = oral antidiabetic drug.
1. Seltzer SM et al. *Clin Ther*. 2003; 25:2991-3026. 2. Bailey CJ. *N Engl J Med*. 1996; 334:574-579.
3. Nathan DM et al. *Diabetes Care*. 2009; 32:193-203.

Advantages of Initiating Therapy With Metformin (cont)

- In clinical trials of patients with T2DM, metformin was found to
 - Improve glycemic control and lipid concentrations¹
 - Maintain fasting blood glucose and A1C targets over several years in obese patients with T2DM²
- Metformin is well tolerated; GI adverse events are most common but usually resolve spontaneously within a few days to weeks³
- Renal dysfunction is considered a contraindication to metformin use because of increased risk of lactic acidosis, an extremely rare but potentially fatal complication⁴

GI = gastrointestinal.
1. DeFronzo RA et al. *N Engl J Med*. 1995; 333:541-549. 2. Turner RC et al. *JAMA*. 1999; 281:2005-2012. 3. Seltzer SM et al. *Clin Ther*. 2003; 25:2991-3026. 4. ADA. *Diabetes Care*. 2010; 33(suppl 1):S11-S61.

Metformin Titration and Advancement of Therapy

- Begin with low-dose metformin (500 mg) qd or bid with meals (breakfast and/or dinner), or 850 mg qd
- Increase dose to 850 mg or 1000 mg before breakfast and dinner if no GI side effects after 5 to 7 days
- If GI side effects occur as doses are advanced, decrease to a previously lower dose and advance at later time

bid = twice daily; GI = gastrointestinal; qd = once daily.
Nathan DM et al. *Diabetes Care*. 2009; 32:193-203.

Metformin Titration and Advancement of Therapy (cont)

- Maximum effective dose can be 1000 mg bid, but is often 850 mg bid
 - Modestly greater effectiveness has been observed with 2500 mg/d
 - GI side effects may limit dose that can be used
- Based on cost considerations, generic metformin is the first choice of therapy
- If unable to meet goals or side effects limit dose, add second medication within 2 to 3 months of initiation or at any time when A1C goal is not achieved

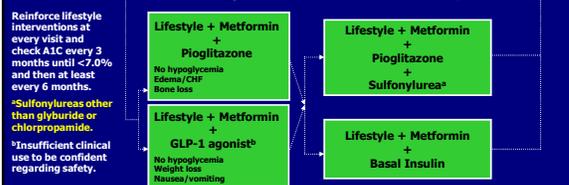
bid = twice daily; GI = gastrointestinal; qd = once daily.
Nathan DM et al. *Diabetes Care*. 2009; 32:193-203.

Advancing Therapy: Adding a Sulfonylurea

Tier 1: Well-validated core therapies—the intervention should be changed if A1C is $\geq 7.0\%$



Tier 2: Less well validated therapies—the intervention should be changed if A1C is $\geq 7.0\%$



Nathan DM et al. *Diabetes Care*. 2009; 32:193-203.

Adding a Sulfonylurea: Considerations

- Sulfonylureas reduce glycemia by enhancing insulin secretion
- Reduce A1C by ~1.5% (similar to metformin)
- Major side effect is hypoglycemia
 - Severe episodes infrequent but more common in elderly
- Weight gain (~2 kg) may be common

Nathan DM et al. *Diabetes Care*. 2009;32:193-203.

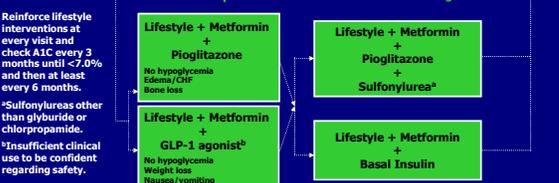
25

Advancing Therapy: Adding Basal Insulin

Tier 1: Well-validated core therapies—the intervention should be changed if A1C is $\geq 7.0\%$



Tier 2: Less well validated therapies—the intervention should be changed if A1C is $\geq 7.0\%$



Nathan DM et al. *Diabetes Care*. 2009;32:193-203.

26

Advancing Therapy: Basal Insulin

- Most patients with T2DM will ultimately require insulin therapy for effective glycemic control¹
- Insulin therapy is typically initiated with basal insulin²
 - Add basal insulin to existing OAD regimen to optimize FPG¹⁻⁴
 - Basal insulin can be initiated with patient-directed treatment algorithms⁵
 - Prandial insulin can be added later if treatment intensification is necessary²

FPG = fasting plasma glucose; OAD = oral antidiabetic drug.
 1. Dalley G et al. *Clin Ther*. 2004;26:889-901. 2. Nathan DM et al. *Diabetes Care*. 2009;32:193-203. 3. AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. *Endocr Pract*. 2007;13(suppl 1):3-68. 4. ADA. *Diabetes Care*. 2008;31(suppl 1):S12-S54. 5. Hirsch IB et al. *Clin Diabetes*. 2005;23:78-86.

27

Advancing Therapy: Basal Insulin (cont)

- Basal insulin replacement in addition to an existing oral regimen can help regain glycemic control
- Early initiation of basal insulin therapy provides rapid relief from glucotoxicity, may improve β -cell function

Dalley G et al. *Clin Ther*. 2004;26:889-901.

28

The Burden of Treatment Failure in T2DM

- Prospective population-based study using retrospective observational data from Kaiser Permanente Northwest
- The study examined 7208 complete courses of treatment with nondrug therapy, sulfonylurea monotherapy, metformin monotherapy, and combination oral therapy from 1994-2002
- The average patient accumulated
 - Nearly 5 years of excess glycemic burden with A1C $> 8.0\%$ from diagnosis until starting insulin, and
 - About 10 years of burden with A1C $> 7.0\%$ from diagnosis until starting insulin

Brown JB et al. *Diabetes Care*. 2004;27:1535-1540.

29

Delay of Insulin Addition to Oral Combination Therapy Despite Inadequate Glycemic Control

- Subsequent Kaiser Permanente Northwest study examining 3891 patients with T2DM, newly initiated on SU/MET during 1996-2000
- During 54.6-month follow-up, 41.9% of patients added insulin; 11.8% received maximum doses of both oral agents
- Over half of the SU/MET patients attained but failed to maintain A1C of 8.0%
 - Yet therapy continued for an average of nearly 3 years, sustaining a glycemic burden equivalent to nearly 32 months of A1C of 9.0%
- Another 18% of patients never attained the 8.0% goal with SU/MET, yet continued on such therapy for an average of 30 months, reaching mean A1C of 10.0%

MET = metformin; SU = sulfonylurea.
 Nichols G et al. *J Gen Intern Med*. 2007;22:453-458.

30

Short-term Insulin Therapy in Newly Diagnosed T2DM

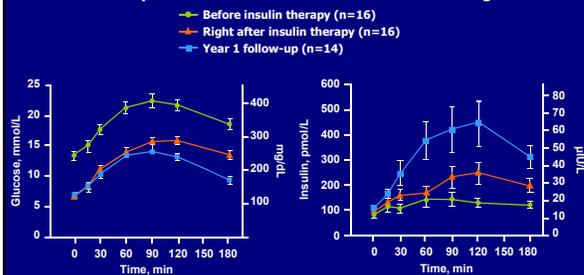
- A total of 16 subjects with newly diagnosed T2DM had a 2- to 3-week course of intensive insulin therapy that was then discontinued
 - Age 52 ± 2 years (range 36-64 years)
 - BMI 30.8 ± 1.9 kg/m²
- Fasting glucose fell from 239 to 126 mg/dL and this improvement was maintained at year 1 follow-up
- Area under the curve for posttreatment OGTT was also improved
- 7 patients maintained good glycemic control on diet therapy alone

BMI = body mass index; OGTT = oral glucose tolerance test.
 Ryan EA et al. *Diabetes Care*. 2004;27:1028-1032.

31

Short-term Insulin Therapy in Newly Diagnosed T2DM

Mean Postprandial Glucose and Insulin Levels During OGTT



OGTT = oral glucose tolerance test.
 Ryan EA et al. *Diabetes Care*. 2004;27:1028-1032.

32

Short-term Insulin Therapy in Newly Diagnosed T2DM

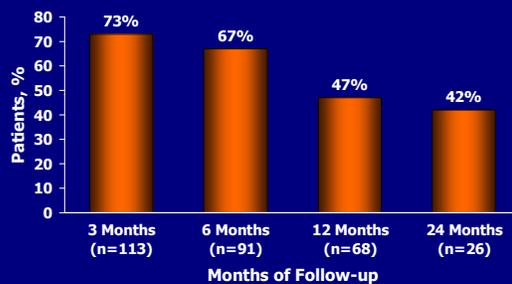
- 138 newly diagnosed T2DM patients (fasting glucose >200 mg/dL) were treated with CSII for 2 weeks
- Optimal glycemic control achieved in 126 patients
- Remission rates (% maintaining near euglycemia) were assessed at 3, 6, 12, and 24 months
- Patients who maintained glycemic control >12 months had greater recovery of β -cell function than those who did not

CSII = continuous subcutaneous insulin infusion.
 Li Y et al. *Diabetes Care*. 2004;27:2597-2602.

33

Short-term Insulin Therapy in Newly Diagnosed T2DM

Remission Rates



Li Y et al. *Diabetes Care*. 2004;27:2597-2602.

34

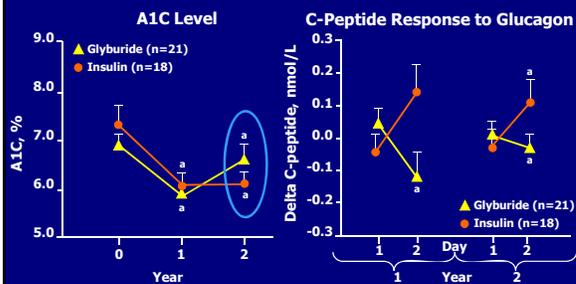
Early Insulin Replacement Improves Glycemic Control and β -Cell Function

- Swedish multicenter randomized trial monitoring 51 patients with T2DM diagnosed 0 to 2 years before inclusion
- Patients were randomized to either glyburide or 2 daily injections of premix 70/30 human insulin
- To evaluate whether treatment with insulin in recently diagnosed T2DM is advantageous compared with glyburide treatment

Alvarsson M et al. *Diabetes Care*. 2003;26:2231-2237.

35

Early Insulin Replacement Improves Glycemic Control and β -Cell Function (cont)



Average dose after year 1: glyburide 2.4 mg/d; insulin 21 IU/d; average dose after year 2: glyburide 3.0 mg/d; insulin 22 IU/d.
 *P<0.05 vs baseline.
 Alvarsson M et al. *Diabetes Care*. 2003;26:2231-2237.

36

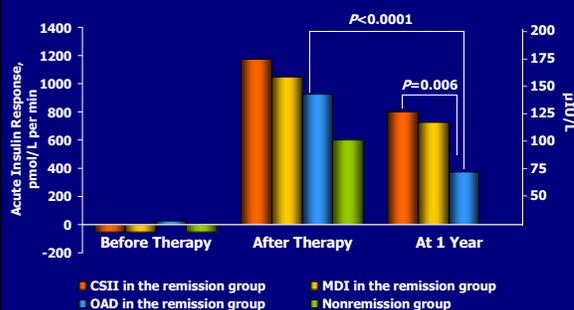
Effect of Intensive Insulin Therapy on β -Cell Function and Glycemic Control in Patients With Newly Diagnosed T2DM

- Multicenter randomized trial to compare intensive insulin therapy vs oral agents on β -cell function and diabetes remission rate
- 410 patients, aged 25 to 70 years, in 9 centers in China, Sept. 2004 to Oct. 2006
- Patients randomized to insulin therapy (CSII or MDI) or oral hypoglycemic agents for initial rapid correction of hyperglycemia
- Treatment stopped after normoglycemia was maintained for 2 weeks, and patients followed up on diet and exercise alone
- Primary endpoint was time of glycemic remission and remission rate at 1 year after short-term intensive therapy

Remission defined as patients who maintained optimum glycemic control for at least 12 months without medication; non-remission defined as those who relapsed during the 12 months of follow-up.
 CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injection.
 Weng J et al. *Lancet*. 2008;371:1753-1760.

37

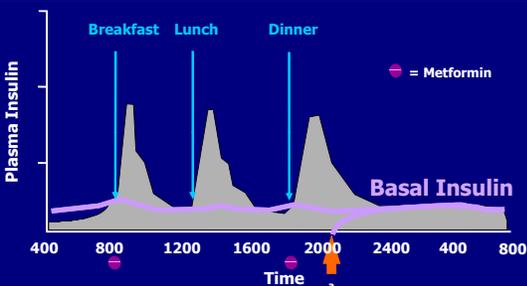
Effect of Intensive Insulin Therapy on β -Cell Function and Glycemic Control in Patients With Newly Diagnosed T2DM



CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injection; OAD = oral antidiabetic drug.
 Weng J et al. *Lancet*. 2008;371:1753-1760.

38

Adding Basal Insulin to Metformin



^aSample administration time.
 Adapted with permission from Leahy JL. *Insulin Therapy*. New York, NY: Marcel Dekker, Inc.; 2002:87-112; McCall AL. *Insulin Therapy*. New York, NY: Marcel Dekker, Inc. 2002:193-222; and Nathan DM et al. *Diabetes Care*. 2009;32:193-203.

39

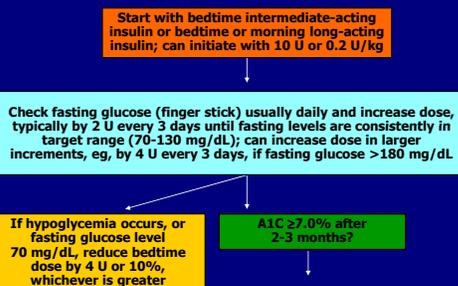
Concerns About Insulin Therapy

- Hypoglycemia in T2DM^{1,2}
 - Severe hypoglycemia is very uncommon^{1,3}
 - Incidence rates range from 0 to 73 episodes per 100 patient-years
 - This is lower than incidence rates in type 1 diabetes of 100 to 160 episodes per 100 patient-years
- Weight gain^{1,2}
 - Modest and controllable by intensification of diet and exercise⁴
 - Also, may be reduced or offset when insulin is used with metformin⁴

1. Nathan DM et al. *Diabetes Care*. 2009;32:193-203. 2. UKPDS Group. *Lancet*. 1998;352:837-853. 3. Akram K et al. *J Diabetes Complications*. 2006;20:402-408. 4. Russell-Jones D et al. *Diabetes Obes Metab*. 2007;9:799-812.

40

Initiation and Adjustment of Insulin Therapy



Adapted with permission from Nathan DM et al. *Diabetes Care*. 2009;32:193-203.

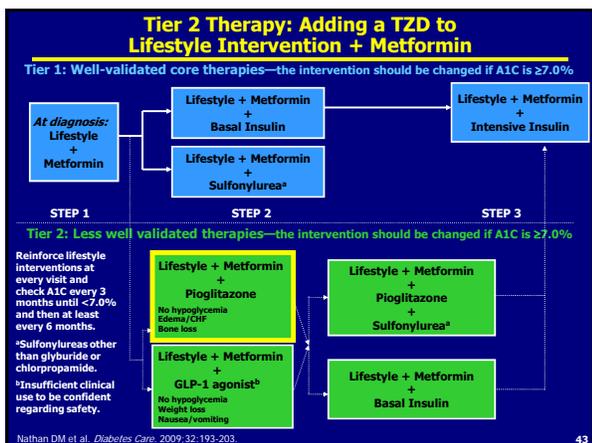
41

Initiation and Adjustment of Insulin Therapy

- Note: Premixed insulins not recommended during adjustment doses; however, they can be used conveniently, usually before breakfast and/or dinner if proportion of rapid- and intermediate-acting insulins is similar to fixed proportions available

Adapted with permission from Nathan DM et al. *Diabetes Care*. 2009;32:193-203.

42



Common AEs of TZDs

- Most common AEs include dose-related weight gain and fluid retention¹
 - Weight gain likely due to combination of fluid retention and fat accumulation when used with metformin²
 - Weight gain can be attenuated when used with metformin^{2,3}
- Weight gain and fluid retention with TZDs are associated with peripheral edema and CHF⁴
 - Black box warning exists regarding potential for TZDs to cause or exacerbate CHF in some patients^{2,3}

AEs = adverse events; CHF = congestive heart failure; TZDs = thiazolidinediones.
1. Nathan DM et al. *Diabetes Care*. 2009;32:193-203. 2. Avandia [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2007. 3. Actos [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2009. 4. Nathan DM et al. *Diabetologia*. 2006;49:1711-1721.

44

Concern About Cardiovascular Safety of TZDs

- FDA added a black box warning to rosiglitazone and pioglitazone regarding potential for increased risk of heart failure¹
- Based on a meta-analysis of 42 clinical trials²
 - Significantly increased risk of MI in patients treated with rosiglitazone vs the control group (OR=1.43; 95% CI: 1.03-1.98; $P=0.03$)
 - Trend toward increased risk of cardiovascular death with rosiglitazone (OR=1.64; 95% CI: 0.98-2.74; $P=0.06$)
- Results challenged based on statistical methodology³

CI = confidence interval; FDA = US Food and Drug Administration; MI = myocardial infarction; OR = odds ratio; TZDs = thiazolidinediones.
1. Stolar MW et al. *J Manag Care Pharm*. 2008;14(5 suppl B):S2-S19. 2. Nissen SE et al. *N Engl J Med*. 2007;356:2457-2471. 3. Shuster JJ et al. *Stat Med*. 2007;26:4376-4385.

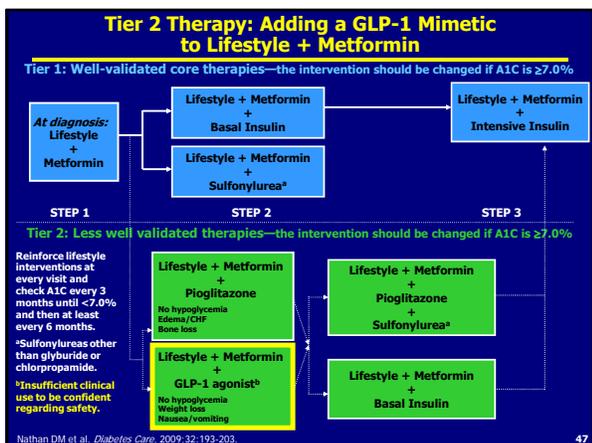
45

ADA/EASD Update Regarding TZDs

- Recent data have been mixed¹
 - 4 meta-analyses have reported an increased risk of MI in patients taking rosiglitazone
 - 1 meta-analysis found no increased risk of cardiovascular mortality due to either rosiglitazone or pioglitazone
 - 1 study found no increased risk of MI with rosiglitazone, but confirmed a risk for CHF
 - 1 meta-analysis suggests a protective effect of pioglitazone on CVD
- Previously recognized risk of fluid retention and resultant CHF with both pioglitazone and rosiglitazone¹
- Recommendation: physicians should exercise caution in using TZDs, particularly in patients at risk of or with CHF¹; the use of rosiglitazone is not recommended in patients with CV risk factors²

ADA = American Diabetes Association; EASD = European Association for the Study of Diabetes; CHF = congestive heart failure; CV = cardiovascular; CVD = cardiovascular disease; MI = myocardial infarction; TZDs = thiazolidinediones.
1. Nathan DM et al. *Diabetes Care*. 2008;31:173-175. 2. Nathan DM et al. *Diabetes Care*. 2009;32:193-203.

46



GLP-1 Modes of Action in Humans

Upon ingestion of food...

- Stimulates glucose-dependent insulin secretion^{2,3}
- Suppresses glucagon secretion^{2,3}
- Slows gastric emptying^{2,3}
- Reduces food intake^{2,3}
- Decreases blood glucose³

GLP-1 is secreted from the L-cells in the intestine¹

This in turn...

- Long-term effects demonstrated in animals...
 - Increases β -cell mass and maintains β -cell survival^{1,2}

GLP-1 = glucagon-like peptide-1.
1. Drucker DJ et al. *Lancet*. 2006;368:1696-1705. 2. Drucker DJ. *Mol Endocrinol*. 2003;17:161-171. 3. Drucker DJ. *Curr Pharm Des*. 2001;7:1399-1412.

48

GLP-1 Agonists: Exenatide

- First marketed GLP-1 analog; approved April 2005
- Potent GLP-1 receptor agonist
- Synthetic version of exendin-4, a naturally occurring peptide isolated from the venom of the Gila monster
- 2- to 4-hour half-life
- Twice-daily injection

GLP-1 = glucagon-like peptide-1.
Choukem SP et al. *Curr Diab Rep*. 2006;6:365-372.

49

GLP-1 Agonists: Liraglutide

- Long-acting GLP-1 receptor agonist approved January 2010¹
- Greater biological half-life than exenatide (~18 hours)²
- Once-daily injection not related to meals^{2,3}

GLP-1 = glucagon-like peptide-1.
1. Novo Nordisk A/S. Company Announcement. http://www.novonordisk.com/include/assets/news_attachment.pdf?AttachmentGUID=f101947-9581-4f51-838a-00c567b9f3e. 2. Choukem SP et al. *Curr Diab Rep*. 2006;6:365-372. 3. Victoza [package insert]. Bagsvaerd, Denmark: Novo Nordisk A/S, Inc.; 2010.

50

Efficacy of Exenatide Added to a TZD (± Metformin) in Suboptimally Controlled T2DM

- 16-week, randomized, placebo-controlled, double-blind study in 233 patients with T2DM suboptimally controlled on TZD
- Compared with placebo, exenatide reduced A1C by 0.98%, serum fasting glucose by 30.4 mg/dL, and weight by 3.3 lb (all $P < 0.001$)
- Exenatide, but not placebo, lowered SMBG profiles ($P < 0.001$ vs placebo)

Effect of Exenatide on 7-Point SMBG Profiles at Baseline and Week 16^a

Time Point	Baseline (mmol/L)	Week 16 (mmol/L)
Pre-breakfast	~9.5	~8.5
Post-breakfast	~10.5	~8.5
Pre-lunch	~9.5	~8.0
Post-lunch	~10.0	~8.0
Pre-dinner	~9.0	~7.5
Post-dinner	~10.5	~7.5
Baseline	~8.5	~8.0

^a $P < 0.001$ vs baseline.
SMBG = self-monitored blood glucose; TZD = thiazolidinedione.
Reprinted with permission from Zinman B et al. *Ann Intern Med*. 2007;146:477-485.

51

GLP-1 Agonists: Safety and Tolerability of Liraglutide

- Black box information
 - Dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both sexes of rats and mice
 - It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies
 - Contraindicated in patients with a personal or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2

GLP-1 = glucagon-like peptide-1.
Victoza [package insert]. Bagsvaerd, Denmark: Novo Nordisk A/S; 2010.

52

DPP-4 Inhibitors

- Improve glycemic control by slowing the inactivation of incretin hormones¹
 - Increase insulin release and reduce circulating glucagon levels in a glucose-dependent manner¹
- Sitagliptin (Januvia—Merck): the first marketed DPP-4 inhibitor; indicated as monotherapy or in combination with metformin, insulin or TZDs in T2DM^{1,2}
- Saxagliptin (Onglyza—BMS/AZ): approved by the FDA in 2009 and now in the US market³
- Vildagliptin (Galvus—Novartis): approved in the European Union; an application has been filed with the FDA for approval in the US^{4,5}
- Alogliptin (Takeda): submitted to the FDA⁴; additional CV safety data requested⁶
- Duetogliptin (Phenomix/Chiesi PHX1149): currently in phase 3 trials⁷

AZ = AstraZeneca. BMS = Bristol-Myers Squibb. CV = cardiovascular. DPP-4 = dipeptidyl peptidase-4. FDA = US Food and Drug Administration. TZD = thiazolidinedione.
1. Januvia [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2009. 2. White JR. *Clin Diabetes*. 2008;26:53-57. 3. AstraZeneca. Press Release. <http://www.astrazeneca.com/media/press-releases/2009/onglyza-fda-approved.html>. 4. EMA. Summary of the European Public Assessment Report. http://www.ema.europa.eu/humans/cepr/EPAR/galvus/galvus_en1.pdf. 5. Bloomgarden Z et al. *Curr Drug Ther*. 2008;75:305-310. 6. Fairman KA et al. *J Managed Care Pharm*. 2009;15:696-700. 7. Phenomix Website. <http://phenomix.com/products/diabetes.asp>.

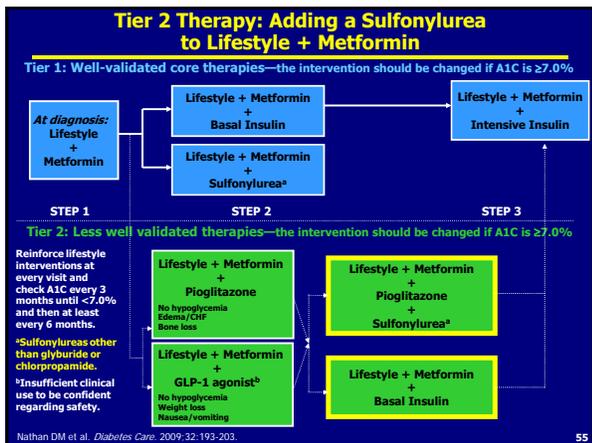
53

Incretin Therapy: Actions of GLP-1 Agonists and DPP-4 Inhibitors

Action	GLP-1 Agonists ^a	DPP-4 Inhibitors ^b
Stimulation of insulin sensitivity	Yes	Yes
Stimulation of β -cell function	Yes	Some
Stimulation of β -cell proliferation and neogenesis	Yes	Yes
Inhibition of glucagon secretion	Yes	Yes
Inhibition of gastric emptying	Yes	No
Inhibition of food intake	Yes	No
Effects on weight	Significant loss	Prevention of gain
↓ fasting glucose	Yes	Yes
↓ postprandial glucose	Yes	Yes

^aDerived from exenatide data. ^bDerived from vildagliptin data.
DPP-4 = dipeptidyl peptidase-4. GLP-1 = glucagon-like peptide-1.
Adapted from Choukem SP et al. *Curr Diab Rep*. 2006;6:365-372.

54

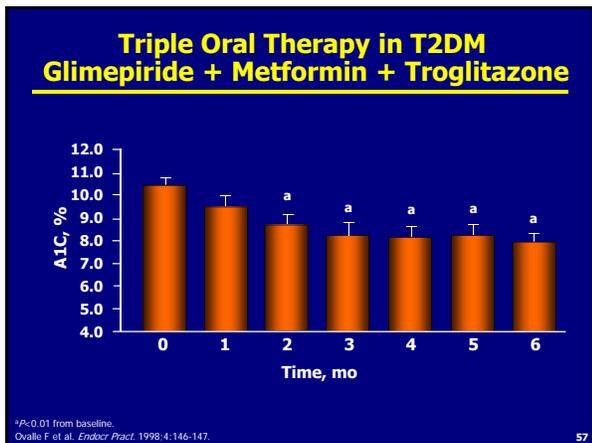


Triple Oral Therapy

- If A1C is close to goal ($< 8.0\%$) with 2 OADs, addition of a third OAD can be considered, although this approach is not preferred, as it is no more effective (and is more costly) than starting insulin¹
- OADs improve glycemic control via 3 major pathways and have synergistic mechanisms of action^{1,2}
 - Metformin (biguanides) decreases hepatic glucose output
 - Sulfonylureas enhance insulin secretion from the pancreas
 - TZDs enhance insulin action in the liver and peripheral tissues

OADs = oral antidiabetic drugs; TZDs = thiazolidinediones.

1. Nathan DM et al. *Diabetes Care*. 2009;32:193-203. 2. Fonseca V. *The CADRE Handbook of Diabetes Management*. New York, NY: Medical Information Press; 2004. 56



Sulfonylurea and Metformin + Troglitazone

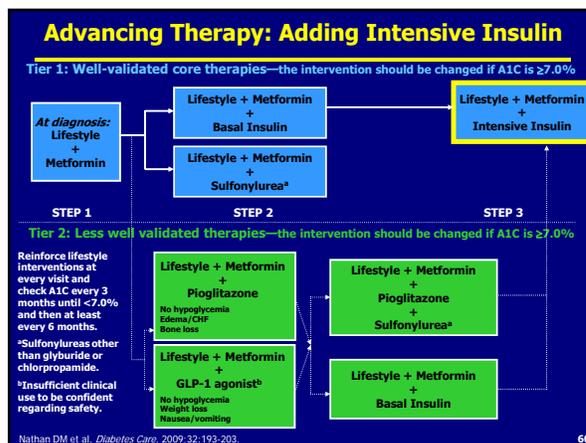
- 16 clinics in Canada
 - 200 insulin-naïve patients with A1C $> 8.5\%$ on maximum tolerated doses of sulfonylurea and metformin for at least 8 weeks
 - Placebo vs 400-mg troglitazone for 24 weeks
- Baseline A1C: 9.7%
- A1C reduction from baseline: -1.3%
- Reached target A1C $< 8.0\%$: 43%
- Reached target A1C $< 7.0\%$: 14%

Yalc JF et al. *Ann Intern Med*. 2001;134:737-745. 58

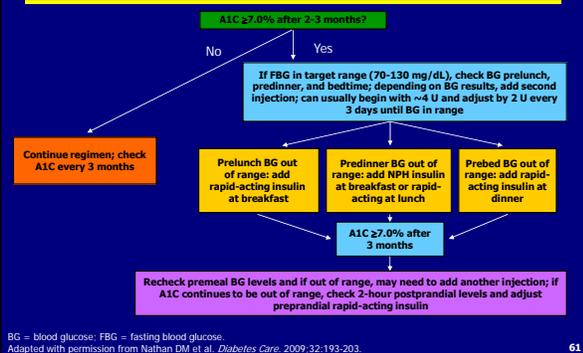
Other Agents

- Pramlintide, α -glucosidase inhibitors, and the glinides are not included in the American Diabetes Association algorithm approved for treatment of T2DM

Nathan DM et al. *Diabetes Care*. 2009;32:193-203. 59



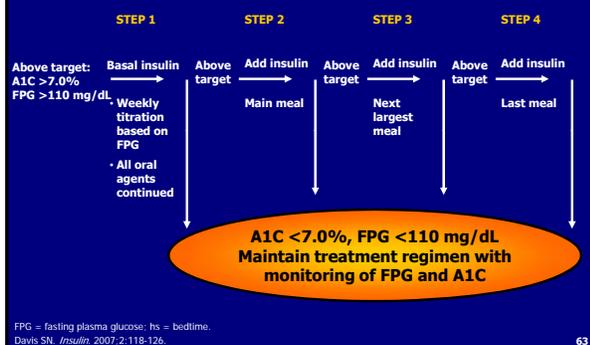
Intensification of Insulin Therapy



Basal to "Basal Plus"

- A strategy of adding bolus insulin to an existing basal insulin regimen in a stepwise manner
 - Add a single daily bolus injection with the largest meal of the day
 - Add further bolus injections at additional meal(s) if necessary
- 62
- Rosenstock J et al. *The CADRE Handbook of Diabetes Management*. New York, NY: Medical Information Press; 2004:145-168.

Steps in Transition From Basal to Basal-Bolus Insulin Therapy in T2DM



Overall Conclusions

- The increasing incidence and prevalence of T2DM in the United States represents a growing burden
 - Intensive glycemic control may help reduce the risk of microvascular complications in patients with T2DM
 - The ADA/EASD has developed a consensus algorithm to help guide health care providers in choosing the most appropriate interventions for patients with T2DM
 - Lifestyle intervention and metformin are recommended as initial therapy for most patients with T2DM
 - When lifestyle intervention and metformin are not sufficient to achieve and sustain glycemic goals, options include the addition of basal insulin or sulfonylurea (tier 1) or pioglitazone or exenatide (tier 2)
- 64
- ADA = American Diabetes Association; EASD = European Association for the Study of Diabetes.

Overall Conclusions (cont)

- Most patients ultimately require insulin because of the progressive nature of T2DM
 - Earlier initiation of insulin is recommended to reduce prolonged exposure to hyperglycemia
 - When A1C targets are not achieved with basal insulin, adding rapid-acting insulin at meals with the greatest BG excursions is an effective approach to treatment intensification for patients with T2DM
 - The ADA offers and continually updates clinical practice recommendations and standards of medical care for many aspects of treatment for the patient with T2DM
- 65
- ADA = American Diabetes Association; BG = blood glucose.