

Insulin Management of Diabetes Mellitus
from the Generalist's Perspective

Spokane Society of Internal Medicine
Update in Internal Medicine
February 26, 2010

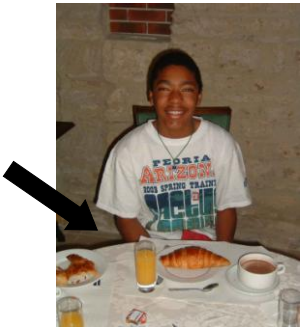
David C. Dugdale, MD
Division of General Internal Medicine
University of Washington

Disclosures

- No PHARMA or device manufacturers
- I do serve as a consultant advising about care guidelines and patient education materials for:
 - Milliman Care Guidelines
 - ADAM Corp.

Acknowledgements

- Dawn DeWitt, MD
- Irl Hirsch, MD
- Alex Dugdale
 - Carbs
 - Juice 30 grams
 - Croissant 60 grams
 - Hot choc 30 grams
 - Insulin (rapid)
 - 1 unit per 15 grams
 - 8 units



Learning Objectives

- Upon completion of this program the participants should be able to:
 - Choose and adjust an initial insulin regimen
 - Assess the adequacy of an existing insulin regimen
 - Plan and select adjustments to improve existing insulin regimens

Learning Objectives, cont'd

- Important things we are **NOT** going to cover
 - Type 1 diabetes
 - Oral agents and non-insulin injectables
 - Presumption will be that patients starting insulin are at least on metformin if they can tolerate it
 - Managing non-glucose issues
 - BP
 - Lipids
 - Aspirin
 - Screening for CAD
 - Microvascular complications

Initial Insulin Regimens

- Is there a BEST initial insulin regimen?
 - Treat to Target
 - INITIATE
 - 123 Trial
 - 4T Trial
 - Basal-prandial with insulin analogs (like in type 1)
 - Although often used for inpatients, this is overkill for most with T2DM, and unworkable for many who have been hospitalized with a new T2DM diagnosis

Diabetes Toolbox 2010

1. Trained patient!!
2. Glucometer and HBA1c
3. Metformin (1000 mg bid) +/- Sulfonylurea (SU)
4. Insulin
5. Frequent insulin adjustment by patient, based on studied algorithms

Measures of Glycemic Control

- HBA1c
- Meter readings and averages
 - Glycemic variability
 - Pre- vs. post-prandial BGs
- Continuous glucose monitoring (CGM)

Correlation of HBA1c and BG

- An HBA1c of 7% corresponds to which mean plasma glucose level:
 - A: 130
 - B: 145
 - C: 155
 - D: 170

Correlation of HBA1c and BG

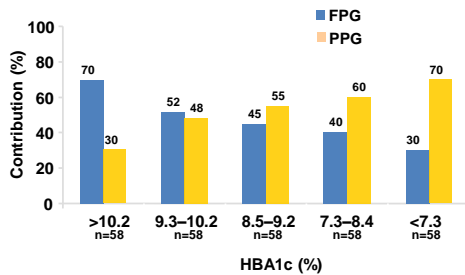
- An HBA1c of 7% corresponds to which mean plasma glucose level:
- **CLOSEST ANSWER IS:**
 - C: 155
 - It's actually 154, based on ADAG study
 - Rule of thumb: HBA1c of 6% = 126 mg/dL
 - 1% rise = 28 or 29 mg/dL rise for BG
 - This is a revision downward of mean BG for given HBA1c from previously widely quoted data
 - Available on ADA web site if you forget it

Factors that alter HBA1c

- Altered RBC turnover changes HBA1c-BG correlation
 - Affects up to 15% of patients, even after excluding those with known anemia or kidney disease
- Shorter RBC life span lowers HBA1c
 - Hemolysis
 - Hemoglobinopathy
 - Liver disease
 - Kidney disease (e.g., serum creatinine > 2 mg/dL)
 - Pregnancy
- Lowers HBA1c by inhibiting glycation: Vitamins C and E
- Raises HBA1c
 - Hypoproliferative anemia
- Total imprecision ~4% of reading (at least)
 - Therefore:
 - 7% = 6.72% - 7.28%
 - 8% = 7.68% - 8.32%

National Glycohemoglobin Standardization Program web site; JAMA 2006;295:1688-1696.

Relative Contributions of Fasting PG and Prandial PG to Overall Hyperglycemia Depending on HBA1c



Monnier L et al. *Diabetes Care*. 2003;26:881-885.

Blood Glucose (BG) Meter Readings

- It is easy to be overwhelmed by data
- Most meters offer some kind of averaging function
- Most meters come with software that allows a patient to download their meter to a computer and do analysis of their BGs
 - Mean BG by time of day usually most helpful
 - Standard deviation can assess glycemic variability
 - Most physician offices **DO NOT** have this capability (>90%)

BG Meters

- One Touch Ultra
 - Various types
- Freestyle Lite
- For Medicaid patients
 - Payment for meters is fixed, so pharmacies typically dispense cheaper meter (True Track)
 - Payment for strips is not fixed, so patient with more expensive meter can get strips
- For most patients, insurance plan will influence meter choice: BG strips cost about \$1 each

Case 1

- A 53 year old man presented with polyuria and fatigue for 3 months. BG was 478 mg/dL, HBA1c was 9.9%.
- PMH: MI with CHF and HTN.
- BMI 27
- Random BG 4 months previously was 133 mg/dL.

Case 1 Management

- Initial Rx: glyburide 5 mg qAM, and NPH insulin 10 units at hs.
 - Increase NPH by 2 units every 3 days if fasting BG > 120 mg/dL
- Over 2 months, fasting BGs went from the low to mid 200s to the mid to high 100s. Predinner BGs went down to the high 100s to low 200s.
- No hypoglycemic symptoms
- His NPH dose was 35 units hs
- What should we advise him now?

*Note: "hs" usually means ~ 9 PM in clinical trials; consistent timing is the most important thing

Case 1 Management, cont'd

- He was asked to increase NPH dose by 2 units every 3 days if fasting BG > 120 each time
- 2 months later
 - Fasting BGs = 100 – 120
 - One fasting BG was 78
 - His predinner BGs were 96 - 154
 - Felt fatigued once when he skipped a meal
- His NPH dose was 75 units
- HBA1c was 6.3%
 - We decided to "back off" a little to reduce hypo risk

The "Treat to Target" Trial: NPH vs. Glargine: Design

- Randomized, multi-center (U.S. and Canada) open-label trial of hs NPH vs. hs glargine x 24 weeks in 756 overweight T2DM patients with HBA1c 7.5% - 10.0% and fasting BG \geq 140 mg/dL
 - Mean HBA1c = 8.6%
- Duration of DM > 2 years
 - Mean 8.7 years
- Already on 1 or 2 oral agents

TTT Trial Protocol

- If 2 day mean fasting BG is above target, increase insulin dose weekly as follows:

> 141	increase insulin by 6-8 units
121-140	increase insulin by 4 units
100-120	increase insulin by 2 units
< 100	no change

- If fasting BG < 63 on more than one occasion decrease dose by 2 units

TTT: Results, effectiveness

- Fraction of patient with HBA1c < 7%: 58% for G; 57% for NPH
- Mean HBA1c: 6.96% (G); 6.97% (NPH)
- Mean fasting BG: 117 (G); 120 (NPH)
- Mean insulin doses at end of trial
 - 0.48 units/kg for G
 - 0.42 units/kg for NPH

TTT: Results, side effects

- Mean weight gain at end of trial
 - G: 3 kg
 - NPH: 2.8 kg
- Symptomatic hypoglycemia was 21-48% lower with G
 - For all symptomatic events, 13.9 vs. 17.7 events/pt-yr
 - For BG < 72, 9.2 vs. 12.9 events/pt-yr
 - For BG < 56, 3.0 vs. 5.1 events/pt-yr
 - For symptomatic nocturnal events, 3.1 vs. 5.5 events/pt-yr
 - "Severe hypoglycemia" per patient report: 2.5% with G, 1.8% with NPH
- "Treatment success": HBA1c < 7%, with no nocturnal hypos: 33% with G, 27% with NPH

TTT: Conclusions

- In moderately advanced diabetes, an escalating basal insulin program will control the majority of patients
- The target fasting BG of 100 mg/dL may have been too strict
- The clinical importance of the differences between G and NPH is not clear
- NPH is half the cost of G
- In the intervening years, multiple studies have validated this general approach to basal insulin dose titration

Case 2

- A 45 year old man presented with a 3 month history of fatigue and more recently, polyuria. BG was 688 mg/dL.
 - Last measured BG was 15 months previously and was normal.
- PMH notable for HTN, HIV, and gout.
- What else would you like to know?

Case 2

- BMI 33
- Meals are “typical” TID schedule, and consistent
- Serum creatinine 1.8 mg/dL
- HBA1c 11.5%

Case 2, Cont'd

- What would you recommend to treat this patient?:
 - A: Glipizide and metformin
 - B: Glipizide and hs glargine
 - C: Twice daily pre mixed insulin
 - D: Basal-bolus therapy with insulin analogs

Initiating Insulin: Type 2 DM

- **BEST ANSWER IS:**
 - C: Twice daily pre mixed insulin
 - D: Would also work, but probably overly complex
 - B: Might also work though quite high HBA1c makes it less likely
 - A: Metformin contraindicated due to creat = 1.8 mg/dL

Reasons to consider BID insulin

- Already on once daily insulin that is optimized, but target not reached
- Level of control is bad enough that you think basal insulin alone will not work
 - Though some of initially poor control may be magnified by glucose toxicity
- Duration of diabetes is long enough that you think basal insulin alone will not work

Case 2, cont'd

- Started on 70/30 N/R 14 units pre-BF and 10 units pre-D (about 0.25 units/kg per day)
- 1 week later, pre-BF and pre-D BGs in high 100s to low 200s

Initiating Insulin: Type 2 DM

- What would you recommend now?:
 - A: Add glipizide
 - B: Add lunch time lispro
 - C: Increase dose of pre mixed insulin
 - D: Add glargine at hs

Initiating Insulin: Type 2 DM

- **BEST ANSWER IS:**
- **C: The most logical choice**
 - A, B, D: Would all help, but not the best choice
- Insulin increased to 14 units pre-BF and 14 units pre-D

Case 2, cont'd

- 1 week after that:
 - Fasting BGs are 160-185
 - Pre-dinner BGs are more variable: 115-192 with most on the lower end.
- Insulin increased to 14 units pre-BF and 18 units pre-D

Case 2, cont'd

- 3 weeks after that:
 - Fasting BG range past 2 weeks 112-147
 - Meter means:
 - 14 day mean BG 143
 - 30 day mean BG 169

Initiating Insulin: Type 2 DM

- What would you recommend now?:
 - A: Add glipizide
 - B: Add lunch time lispro
 - C: Increase dose of pre mixed insulin
 - D: No change in regimen

Initiating Insulin: Type 2 DM

- **BEST ANSWER IS:**
 - **D: The most logical choice**
 - A, B, C: Any of these could be considered, but many patients will see further improvements at this point as they learn how to live with diabetes
 - His HBA1c will not be stable for ~3 months

Case 2, cont'd

- Insulin continued without change:
 - 3 months later, HBA1c 6.7%
 - 1 year later, HBA1c 7.3%

Starting prandial insulin with **premixed** insulin in T2DM: INITIATE trial design

- **INITIATE** trial methods
 - 28 week, multi-center RCT of T2DM patients in the U.S. with HBA1c \geq 8%, already on at least 1000 mg/day of metformin +/- other oral agents
 - Mean diabetes duration 9 years (no minimum)
 - Mean baseline HBA1c 9.7%
 - Mean fasting BG 250

INITIATE trial protocol

- Metformin and TZDs “optimized” to 1500 – 2550 mg/day and pio 30 mg/day (if pt was already taking a “glitazone”) over 4 weeks; other oral agents stopped
- Then, insulin added:
 - 70/30 aspart 5-6 units before BF and D or
 - Glargine 10-12 units at hs
 - Used higher of the 2 doses if fasting BG \geq 180

INITIATE trial protocol, cont'd

- Upward dose titration weekly for 12 weeks, then q 2 wk
 - For 70/30 aspart group, dose increased based on premeal BGs:
 - <80, decrease 2; 80-110, no change; 111-140, increase 2; 141-180, increase 4; >180, increase 6
 - For glargine group, dose increased based on fasting BGs:
 - <80, decrease 2; 80-110, no change; 111-140, increase 2-4; 141-180, increase 4-6; >180, increase 6-8
 - Max daily increase 10 units or 10% of current total daily dose

INITIATE trial results

	70/30 aspart	glargine
Fraction of patients with HBA1c < 7.0%	67%	41%
Mean HBA1c (%)	6.9	7.4
Mean daily insulin dose (units)	78	51
Mean weight gain (kg)	5.4	3.5
Hypos (minor), per pt-yr	3.4	0.7* (*1 major hypo)

Changing to BID aspart pre-mix (NovoLog 70/30) from
once-daily basal insulin

- If post-prandial BG is > 140 mg/dL after BF and L
 - Use same total daily dose
 - Divide doses based on biggest meal and highest sugars, e.g. if L is the biggest meal and after L sugars are highest, give more at D
 - Have patient check post-meal for several days after initiation to assess control

Changing to BID aspart pre-mix (NovoLog 70/30) from
once-daily basal insulin

- Adjust pre-mix insulin: beware hypos at mid-day and mid-night
 - If pre-D is high and no day-time hypos: increase pre-BF insulin 2 units every 5-7 days
 - If pre-BF is high and no night hypos: increase pre-D insulin 2 units every 5-7 days

Case 3

- A 70 year old man presents with a history of diabetes for 15 years
 - Current Rx: glipizide ER 10 mg BID for the past 10 years
 - HBA1c was 8.7% 2 months earlier
- PMH: alcoholic cirrhosis with history of variceal bleeding and hepatic encephalopathy
- Wt 75 kg, BMI 26
- BG testing was very intermittent

Case 3: Management

- What would you recommend to this patient?
 - A: Add metformin
 - B: Add hs glargine
 - C: Twice daily pre mixed insulin
 - D: Basal-bolus insulin
 - E: None of the above

Case 3: Management

- **BEST ANSWER IS:**
 - E: **You need more data**
 - Current general medical status
 - Current HBA1c
 - Dietary and BG records

Case 3, cont'd

- When seen 30 days later, HBA1c was 10.2%. His liver disease is stable.
- Analysis of the patient's meals showed:
 - His diet was fairly consistent
 - He generally eats BF. By his description, it is ~ 100 g of carb.
 - Lunch is ~ 60 g of carb, usually beans and some salmon or meat
 - Dinner seems less consistent, ~ 30 g of carb
 - Evening snack of a sweet bread, some nights only.
 - He does notice that his BG is high the next morning when he eats the sweet bread.
 - NOTE: it took about 10 minutes of clinic time to collect this information, and feel confident about it (via an interpreter).

Case 3: Management

- What would you recommend to this patient now?:
 - A: Add hs glargine
 - B: Pre meal rapid acting insulin
 - C: Twice daily pre mixed insulin
 - D: Basal-bolus insulin

Initiating Insulin: Type 2 DM

- **BEST ANSWER IS:**
 - D: This will best address his needs, if he can deal with the complexity. Caveats:
 - It is OK (and often desirable) to start sequentially!
 - In patients with cirrhosis, basal dose needs are usually less than expected (therefore premixed insulin would not match needs well)
 - For small doses, pen systems give greater accuracy

Case 3, cont'd

- Rx NovoLog FlexPen 4 units with BF and L
- 2 weeks later, add glargine 5 units hs
- 2 weeks after that, meter downloads show that
 - Mean pre-BF was 225 with a range 126-351
 - Mean pre-L was 369 with a range 266-472
 - Mean pre-D was 422 with a range 411-435
 - Aggregate mean was 266 with a range 126-472 (total of 41 tests in the past 30 days; most consistent was pre-BF)

Case 3, cont'd

- Recommend: Increase glargine to 10 units hs
- 1 month later, BGs reviewed. Recommend: increase aspart :
 - 10 units before BF
 - 7 units before L
 - 3 units before D
- 1 more month later, BGs reviewed. Recommend: increase aspart :
 - 15 units before BF
 - 10 units before L
 - 6 units before D
 - AND increase glargine to 12 units hs

Case 3, cont'd

- 1 month later, he reports some episodes of shakiness at ~0530
- BG in clinic 299, approximately 1.5 hours post-BF
- Meter download shows
 - Pre-BF BGs in the low to mid 100s
 - Pre-L BGs in the high 100s to mid 200s
 - Pre-D BGs in the low to mid 200s

Case 3, cont'd

- Recommend:
 - Reduce glargine to 10 Units each hs
 - Change aspart to
 - 15 units before BF
 - 12 units before L
 - 6 units before D

Case 3, cont'd

- One month later he returns, still having an occasional "low" in the early AM.
- His pre-L and pre-D BGs are in the mid to high 100s. He is currently taking:
 - Glargine 10 units at hs
 - Aspart 15 units before BF, 12 units before L, 6 units before D
- Recommend:
 - Stop glipizide: not likely to be contributing much
 - Reduce glargine to 9 units at hs
 - Increase aspart to 20 units before BF, 15 units before L, 7 units before D

Case 3, cont'd

- He returns 4 months later. He has had 2 hypos, 1 in the middle of the night.
- His insulin regimen is unchanged
- HBA1c = 7.1%
- Recommend: reduce glargine to 8 units
- Follow-up HBA1cs
 - 6 months later HBA1c = 6.7%
 - 12 months later HBA1c = 6.8%

123 Trial

- Enrolled 100 pts with T2DM for 1+ yr
 - HBA1c 7.5%-10% on 2 oral drugs OR 1 oral drug plus basal insulin < 60 units per day
 - Mean HBA1c 8.6%
 - Mean duration of diabetes 12 yrs
- Open label multi-center observational study in U.S.
- Used BIAsp 30 (equal to NovoLog Mix 70/30), 1, 2, or 3 times per day to control BG

123 trial Phase 1: start pre-D insulin

- Start insulin 12 units before dinner OR transition from basal to pre-D insulin at 70-100% of previous dose
- Increase insulin dose every 3-4 days based on mean fasting BG by:
 - 3 (111-140)
 - 6 (141-180) or
 - 9 (>180) units
- Hold dose steady when fasting BG 80-110
- Check HBA1c at 16 weeks; if $\leq 6.5\%$, keep dose the same (N=21)

123 trial Phase 2: add pre-BF insulin

- Stopped oral secretagogues
- Start insulin before BF, 3 (FBG ≤ 110) or 6 (FBG > 110) units
- Increase pre-BF insulin dose every 3-4 days based on mean pre-D BG by:
 - 3 (111-140)
 - 6 (141-180) or
 - 9 (>180) units
- Hold dose steady when pre-D BG 80-110
- Check HBA1c at 16 weeks; if $\leq 6.5\%$, keep dose the same (N=31)

123 trial Phase 3: add pre-L insulin

- Start insulin 3 units before L
- Increase pre-L insulin dose every 3-4 days based on mean 2 hour post-L BG by:
 - 3 (141-180) or
 - 6 (>180) units
- Hold dose steady when 2 hour post lunch BG 100-140
- Check HBA1c at 16 weeks; an additional 8 subjects achieved HBA1c $\leq 6.5\%$

123 trial: Results Summary

- 60% of subjects reached $HbA1c \leq 6.5\%$ at end of 48 weeks
- 77% of subjects reached $HbA1c \leq 7.0\%$ at end of 48 weeks
- Insulin doses:
 - For those with $HbA1c \leq 6.5\%$ in phase 1: 0.60 units/kg at dinner
 - For those with $HbA1c \leq 6.5\%$ in phase 2: 0.51 and 0.64 units/kg for pre-breakfast and pre-dinner, respectively
 - For those with $HbA1c \leq 6.5\%$ in phase : 0.58, 0.25 and 0.70 units/kg for pre-breakfast, pre-lunch, and pre-dinner, respectively
- Hypoglycemic events occurred in 85% of patients, range 12-22 events per pt-yr

Progressing from once-daily insulin glargine to basal-prandial insulin

- Be aware that patients who are dose escalated on glargine based on fasting BGs will have an incorrectly high glargine dose to compensate for a suboptimal (or non-existent) dinnertime insulin regimen
 - Clue to this is relatively low pre-D BG
- Nutritional assessment a must for this evolution
 - Need to decide whether to use carb counting or “empirical” approach (like case 3)
 - Either way, a good patient understanding of carbs will help significantly
- BG meter and skills/willingness to use it also a must
 - However, complex correction scales are optional

Progressing to basal-prandial insulin: prandial dose selection options

- Lag time: delay of eating after insulin dose
 - Analogs: 15-30 minutes unless premeal BG is low
 - Regular: 30-60 minutes unless premeal BG is low
- Carb counting
 - 1 unit insulin per 10 grams carb (“500 rule”: 500 divided by daily insulin dose = grams of carb offset by 1 unit of insulin)
- “Empirical”
 - Add pre-meal rapid insulin (e.g. 2-4 units per meal) as needed to keep post-prandial (90-120 minutes post meal under 140)
 - Duration of rapid acting insulin action is 5+ hours: ~15% insulin on board at 5 hours, so it's easy to overdose insulin if aiming at controlling prandial BG spike
- Correction dose strategies, if used
 - 1 unit of insulin per 50 above 120-140 (“1800 rule”: 1800 divided by daily insulin dose = BG drop that 1 unit of insulin will cause)

Changing from BID pre-mix to
basal-prandial insulin (glargine + rapid)

- Add up 24 hour insulin dose
- Give half as glargine
 - Once-daily at bedtime (or morning)
- Divide the other half as pre-meal rapid insulin (with each meal);
 - Divide according to meal size (especially carbohydrate, e.g. bread, potato, pasta, rice so that more would be given for high carb BF vs. tuna salad at L)

Putting it all together: the 4T Trial

- What is the best initial insulin regimen?
- Multi-center open label RCT in United Kingdom and Ireland
- Reports at 1 and 3 years, the latter in October, 2009

4T Trial: Methods

- Patients with T2DM for at least 1 year
 - Median duration 9 years
- Baseline HBA1c 7% - 10%
 - Mean HBA1c 8.5%
 - Mean fasting BG 171 mg/dL
- On maximal doses of metformin AND SU for at least 4 months

4T Trial: Methods, cont'd

- Three treatment arms, ~235 subjects in each:
 - Twice daily, pre-prandial NovoLog Mix 70/30
 - Premeal aspart only
 - Basal insulin only: daily (bedtime) or BID detemir

4T Trial: Methods, cont'd

- Insulin dosing
 - Initial dose selection based on fasting BG, weight, height and gender
 - Adjustment algorithm targeted premeal BG 72-99 and 2 hour post meal BG 90-126
 - AM basal dose added if fasting BG at target but predinner BG was not
- At 24+ weeks, if HBA1c > 10% or > 8% twice in a row, SU stopped and additional insulin dose added:
 - Luncheon aspart to biphasic (4-6 units)
 - Bedtime detemir to prandial (10 units)
 - TID premeal aspart to basal arms (4-6 units)

4T Trial: Results at 1 year

	Biphasic	Prandial	Basal
Mean HBA1c (%)	7.3	7.2	7.6
% with HBA1c ≤ 7%	42	49	28
Median daily starting insulin dose, units	16	18	16

4T Trial: Results at 1 year, cont'd

	Biphasic	Prandial	Basal
Median daily ending insulin dose (units/kg)	0.5	0.6	0.45
Fraction of patients adding insulin dose (%)	9	4	18
Mean hypo events per pt-yr	5.7	12.0	2.3
Weight gain, kg	4.7	5.7	1.9

4T Trial: Results at 3 years

	Biphasic	Prandial	Basal
Median HBA1c (%)	7.1	6.8	6.9
% with HBA1c ≤ 7%	49	67	63
% pts taking 2 types of insulin	68	74	82

4T Trial: Results at 3 years, cont'd

	Biphasic	Prandial	Basal
Median daily ending insulin dose (units/kg)	0.78	0.94	1.03
% of pts with grade 2 or 3 hypo	8	8	8
Median hypo events per pt-yr	3.8	5.7	2.7
Weight gain, kg	5.7	6.4	3.6

Conclusions: What is the best initial insulin regimen?

- For most patients, if HBA1c < 10%-11% (maybe even 12%), it is very reasonable to start with basal insulin only
 - Clinical trials show no better results with more complex regimen if HBA1c \leq 8.5%
 - Follow up dose adjustment is critical
 - Stability of BGs will take months or more to achieve

Conclusions: What is the best initial insulin regimen?

- Under some circumstances, it will make more sense to start with BID biphasic insulin or TID pre-prandial rapid acting insulin.
- Reserve true basal-prandial regimens and complex regimens (carb counting, correction algorithms) for special situations.

References: Reviews

- Hirsch, IB, et al. A real world approach to insulin therapy in primary care practice. *Clin Diabetes* 2005;23(2):77-86.
- Mooradian AD, et al. Narrative review: A rational approach to starting insulin therapy. *Ann Intern Med* 2006;145(2):125-134.
- Nathan DM, et al. Medical management of T2DM: A consensus algorithm from the ADA and AACE. *Diabetes Care* 2009;32:193-203.
- Lasserson DS, et al. Optimal insulin regimens in T2DM: Metaanalysis and systematic review. *Diabetologia* 2009;52:1990-2000.
- ADA 2010 Clinical Practice Recommendations. *Diabetes Care* January, 2010 (available at ADA web site).

References: Trials

- Treat to Target: Riddle MC, et al. Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26:3080-3086.
- INITIATE: Raskin P, et al. Initiating therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 2005;28:260-265.
- 123: Garber AJ, et al. Attainment of glycemic goals in type 2 diabetes with once, twice, or thrice daily dosing with biphasic insulin aspart 70/30. *Diabetes, Obesity, and Metab* 2006;8:58-66.
- 4T (1 year report): Holman RR, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *NEJM* 2007;357:1716-1730.
- 4T (3 year report): Holman RR, et al. Three year efficacy of complex insulin regimens in type 2 diabetes. *NEJM* 2009;361:1736-1747.

Blood Glucose Meters

- Desirable features:
 - Rapid processing (5 seconds)
 - Small sample size
 - Averages
 - Logbook function
 - Memory
 - Pre- and post-prandial flagging

Insulin pen devices

- Portable “pen” style insulin administration devices
 - Increase compliance
 - More accurate dosing (esp. at low doses)
 - May decrease wastage (dose dependent)
 - 300 units per use vs. 1000 units per use
 - Improved ease of use vs. syringes + vial
 - More discreet for use in public
 - An option for visually or manually impaired patients

Proper insulin pen use

- Secure a needle tip to pen
 - Any size is fine though large people may need longer needle
- “Prime” the pen by wasting 2 units
 - Needs to be done before EACH injection
- Dial up dose and inject SC
- Leave needle under skin for 5 seconds then remove

Insulin pen “tips” for use

- Change needle tip for each injection, or at least once daily
- Injection can be done through clothing if needed, though not ideal
- Disposable pens are easier to use than cartridges
- When calculating days supply for insurance purposes, add 6-10 extra units per day
- Refrigerate pens not in use; do not need to refrigerate pen in use
