Optimal Diabetes Care in Long Term Care Facilities

Jane Weinreb, MD
Acting Chief, Division of Endocrinology and Chief, Diabetes Program
VA Greater Los Angeles Healthcare System
Clinical Professor of Medicine
David Geffen School of Medicine at UCLA

Disclosures

- Speaker for Sanofi-Aventis and Novo Nordisk

- Consultant for Novartis and Novo Nordisk

Objectives

- Background:
  - Definition of diabetes
  - Diagnosis of diabetes
  - Overview of diabetes classification, pathophysiology, and epidemiology
- Glycemic goals in older patients
- Medications for diabetes management
  - How advanced age and comorbidities affect medication choices
  - Prevention of hypoglycemia
- Nonglycemic goals in older patients

Diabetes Mellitus: Definition

- Refers to a spectrum of syndromes characterized by hyperglycemia.
- Each case combines
  - absolute or relative insulin deficiency
  - peripheral resistance to insulin action… refers to diminished insulin action at the level of the tissue receptor, so that less glucose is taken up for a given amount of insulin.
    - Is increased by obesity.
    - Is increased with sedentary lifestyle.
 - increased hepatic glucose production.

Criteria for Diagnosis of Diabetes

- A1C ≥6.5% on two occasions (VA recs A1C >7%).
  - Should be performed with method certified by the National Glycohemoglobin Standardization Program and standardized to DCCT assay
  - Cannot be used in patients with increased RBC turnover
  - May identify 1/3 less pts than by BG, but missed pts may be offset by ease of screening w/ A1C.

- Fasting Plasma Glucose (FPG) >125 mg/dl on two occasions.

- 2 hour PG>200 mg/dl during 75g OGTT.

- Symptoms of DM (polys, weight loss) and a casual plasma glucose >200 mg/dl.

- Note: Impaired fasting glucose (IFG) (FPG of 100-125 mg/dl) and impaired glucose tolerance (IGT) (OGTT 2 hour value of 140-199 mg/dl) have been termed "prediabetes"; similarly an A1C of 5.7-6.4% represents similar increased risk for DM and CAD and can be included as prediabetes as well.

Standards of Medical Care in Diabetes- 2011. American Diabetes Association. Diabetes Care 34(1): S11-61, 2011.

Classification of Diabetes

- Based upon the pathogenic process that causes hyperglycemia rather than age of onset or treatment
- Age related increase in the prevalence of diabetes... 2 mg/dl/decade rise in fasting plasma glucose in "normal aging"
    - ~10% of adults have type 1 diabetes:
        - Tend to be lean
        - Need insulin therapy for life
    - most adults have type 2 diabetes

Overview of Glucose Regulation

Glucose

Defective insulin secretion

β-cell insulin secretion

Persistent Hepatic Glucose Output

Insulin action

Resistance to insulin action

Dinneen SF. *Diabetes Med*. 1997;14(suppl 3):S19-24.
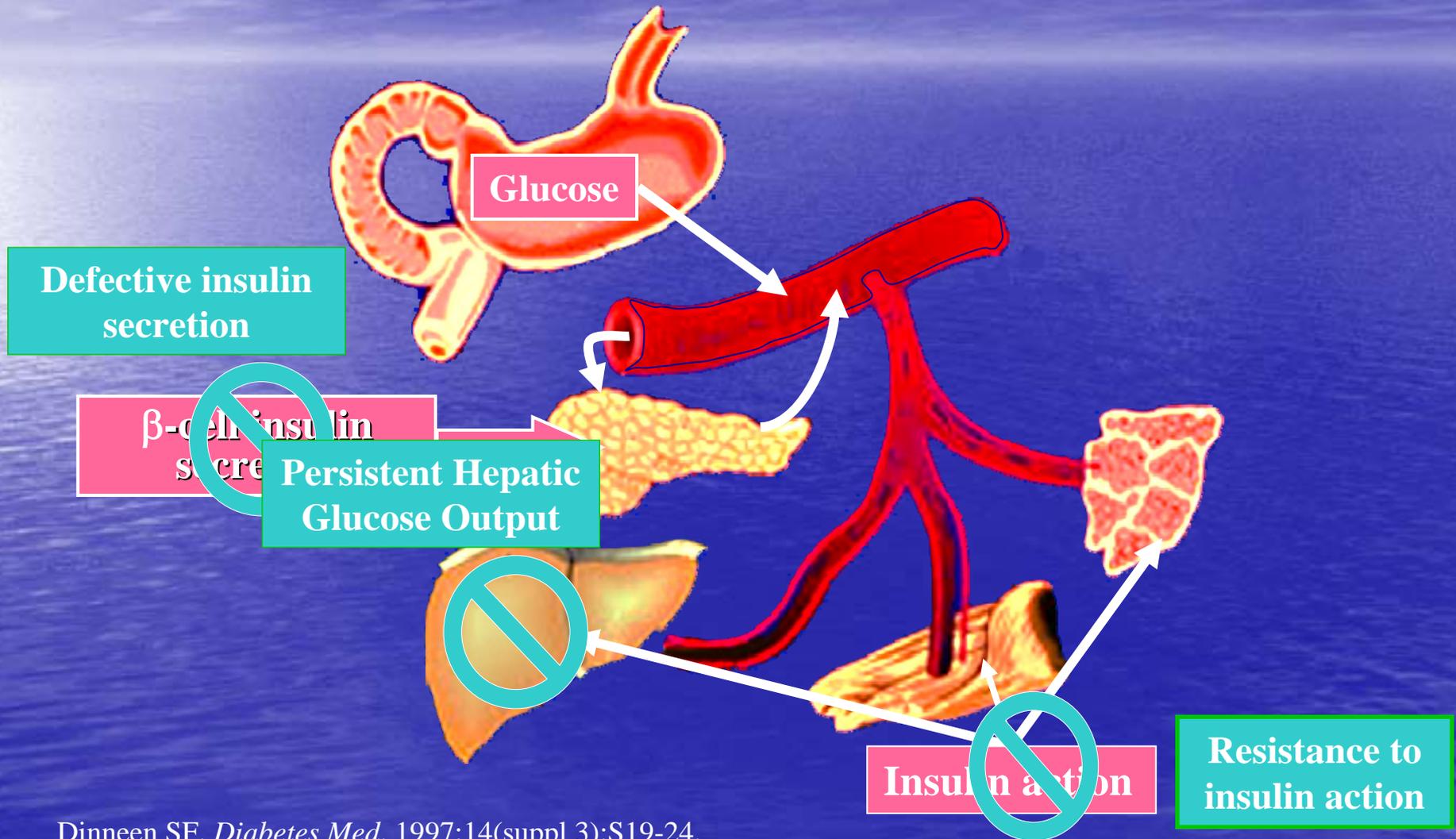
Natural History of Type 2 Diabetes

Adapted from International Diabetes Center (IDC) Minneapolis, Minnesota
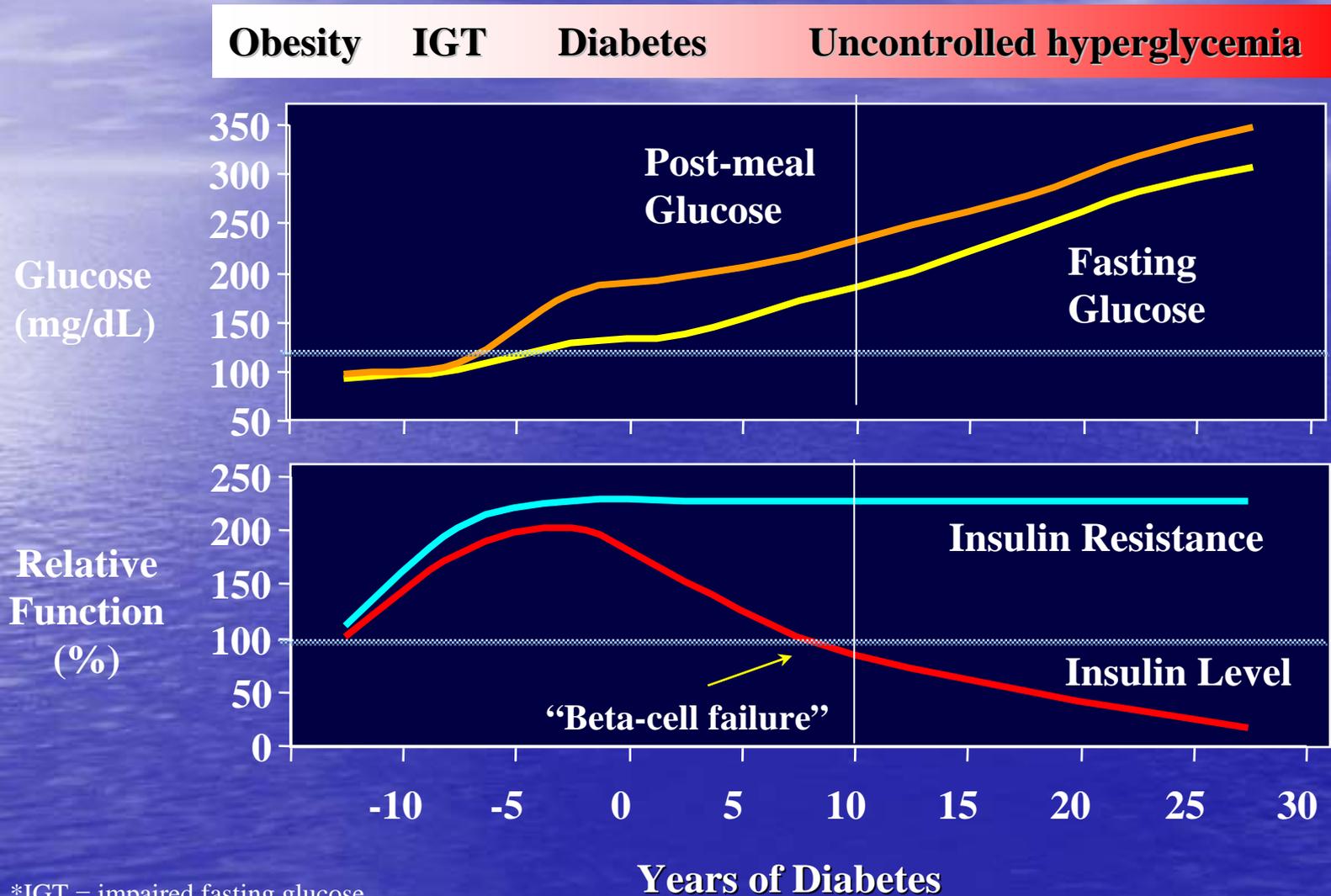
*IGT = impaired fasting glucose

Pathogenesis of Type 2 Diabetes: Summary

- Results from a progressive ß-cell defect superimposed upon background of insulin resistance.
- Develop increasing insulin deficiency with time.
- Presumed to be polygenic, and expect patients to have a strong family history.
- Obesity and high fat diet appear to contribute significantly to developing type 2 diabetes.
- Deficiency of gut peptides appears to augment post-prandial hyperglycemia.

Epidemiology of Diabetes Mellitus

- In 2007, DM was diagnosed in ~17.9 million people in the United States, but a significant number w/ DM have yet to be diagnosed (~5.7 million).
  - 10.7% of pop >20 years old
  - 23.2% of the pop >60 years old

Estimated prevalence of diagnosed and undiagnosed diabetes in people aged 20 years or older, by age group, United States, 2007

- In 2007, cost of diabetes to the U.S. medical system was $174 billion, and this figure has been increasing by 10-12% each year.

- Biggest cause of blindness, renal failure, and non-traumatic amputation in the Western world.

http://www.cdc.gov/diabetes/pubs/estimates.htm#prev
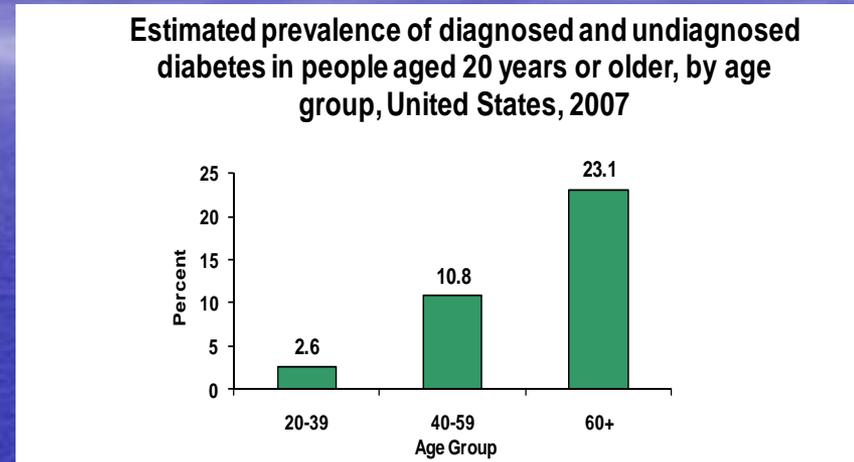
Prevalence of Diagnosed Diabetes by Age, United States, 1980–2004
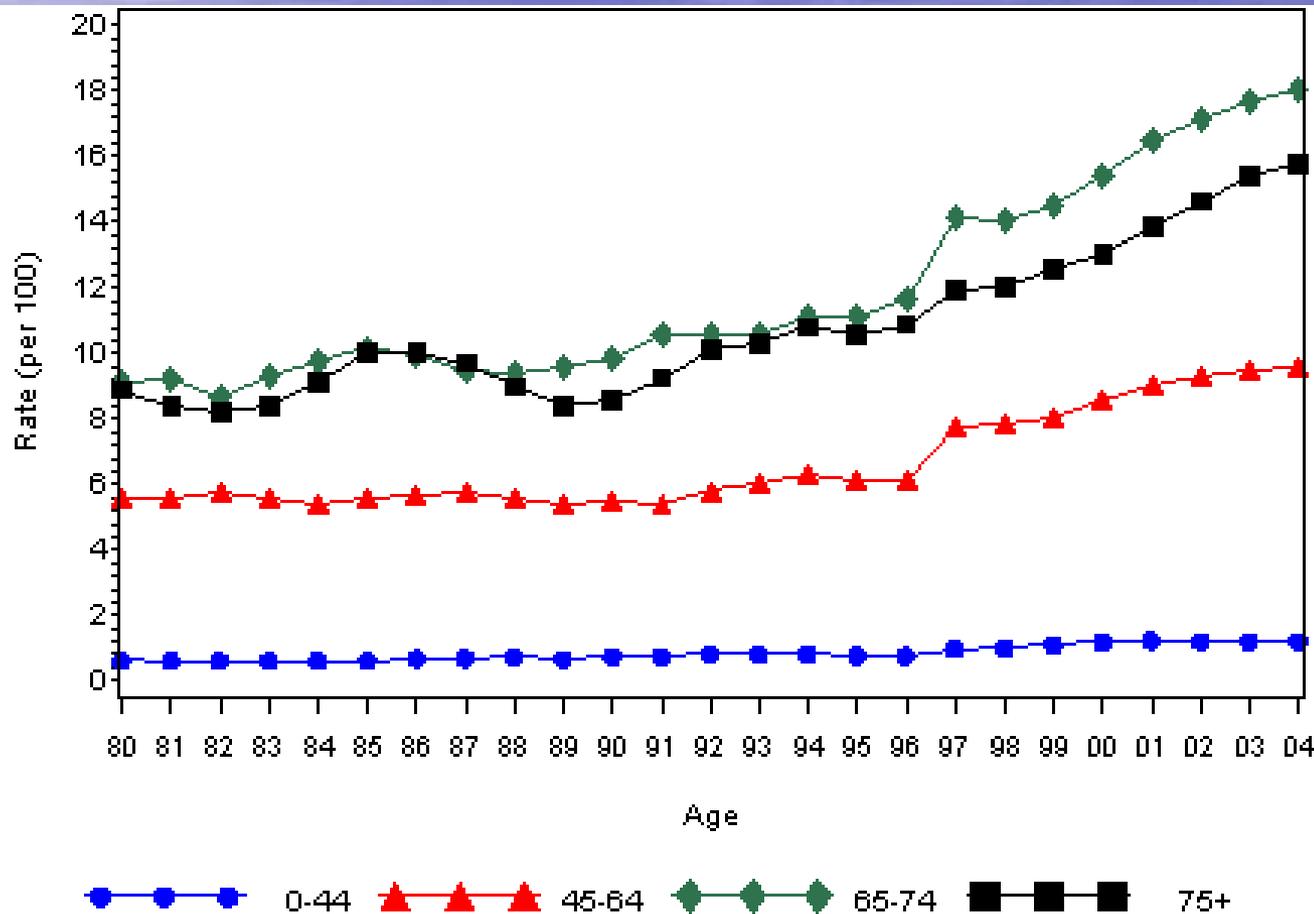
- From 1980 through 2004, the prevalence of diabetes increased in all age groups
- Those 65-74 have consistently had the highest prevalence, rising to 16.7% in 2004

http://www.cdc.gov/diabetes/statistics/prev/national/figbyage.htm

US Prevalence of Diagnosed Diabetes by Race/Ethnicity and Sex
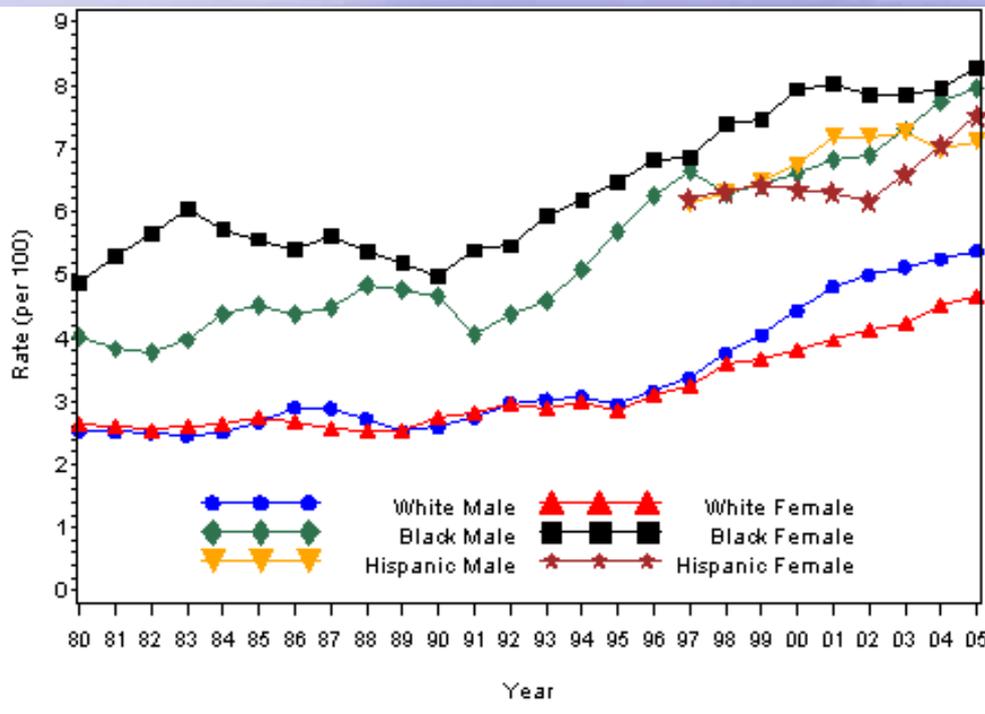
Prevalence of DM amongst adults >65 years old	
White	14%
African-American	24%
Latino	24%
Asian American	15%
Native American	30%

http://www.cdc.gov/diabetes/statistics/prev/national/figraceethsex.htm
Schoenborn et al. 2006; CDC, 2003; Gallant et al. J Cross Cult Gerontol 25:21-43, 2010

Diabetes is Common in LTC Setting

- Diabetes is an independent predictor of elderly placement in a LTC facility
- 33% prevalence in NH patients, according to 2010 MDS data
- Cost of caring for diabetics in LTC facilites was $18.5 billion in 2007
- Important to review record for evidence of diabetes
  - On diabetes medication
  - Labs with hyperglycemia
  - Diabetes complications without prior diagnosis.

Presentation of Diabetes in Older Patients

Metabolic Abnormality	Younger Patients	Older Patients
Increased Osmolality	Polydipsia	Dehydration Confusion Delerium
Glycosuria	Polyuria	Incontinence
Insulin Deficiency	Polyphagia	Anorexia Weight Loss

Goals for Glycemic Control

- The DCCT, VA Cooperative Study, and UKPDS provide convincing evidence that tight glycemic control results in delay in onset and slowed progression of microvascular complications.

- With each degree of improvement, there appears to be some benefit derived.

- Although there was a trend towards ↑'d CV events in the tight control arm of the VA Cooperative Study, this finding was not borne out in the UKPDS, in which there was a 16% ↓ in macrovasc events. In fact, the EDIC and UKPDS follow up studies reveal a ↓ in macrovasc events in diabetics with prior tight control.

- *These studies include few patients >65 yrs of age.*

- *Takes many years to derive benefit.*

DCCT, NEJM, 329:977, 1993
VA Cooperative Study, Diabetes Care, 18:1113, 1995
UKPDS, The Lancet, 352:837, 1998
Abraira et al. Diabetes Care. 21:574-9, 1998
EDIC Study. N Engl J Med 2005; 353:2643-2653, 2005.
Holman et al. N Engl J Med; 359:1-13, 2008.

Initial Goals for Type 2 DM

- Kumamoto Study revealed that in 110 T2DM, intensive control improved microvascular outcomes
- Confirmed in the UKPDS
  - Study of intensive vs conventional (A1C 7% vs 7.9%) glycemic control in ~4000 newly diagnosed type 2 diabetics
  - Intensive glycemic control resulted in 25% reduction in development of microvascular complications (~35% for each 1% decrease in A1C)
  - Also saw a 16% ↓ in combined fatal or nonfatal MI and sudden death in intensively rx'd pts
- Aggressive control of HTN significantly ↓'d strokes, diabetes related deaths, heart failure, and visual loss.

Ohkubo Y et al. *Diabetes Res Clin Pract.* 1995;28:103-117
UKPDS 33, Lancet 352:837-53, 1998.
UKPDS 34, Lancet 352:854-65, 1998.

Intensive therapy reduces retinopathy and nephropathy
Kumamoto Study – Type 2 DM

Retinopathy — Conventional therapy — Intensive therapy — Microalbuminuria

Primary prevention

-76%
P=0.039

Primary prevention

-62%
P=0.032

Cumulative percent progressing

Secondary intervention

-56%
P=0.049

Secondary intervention

-52%
P=0.044

N=110

Cumulative percent progressing

Years

Ohkubo Y et al. *Diabetes Res Clin Pract.* 1995;28:103-117
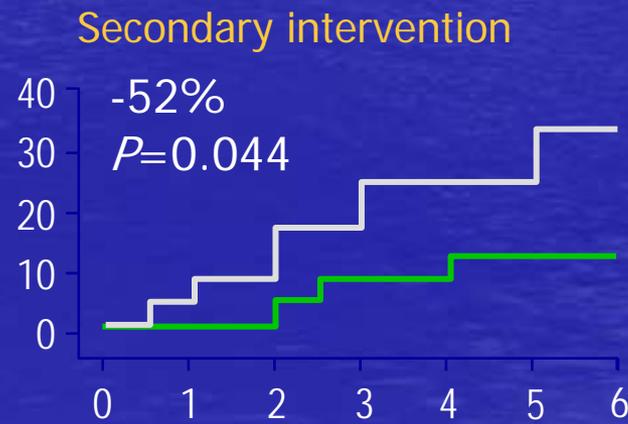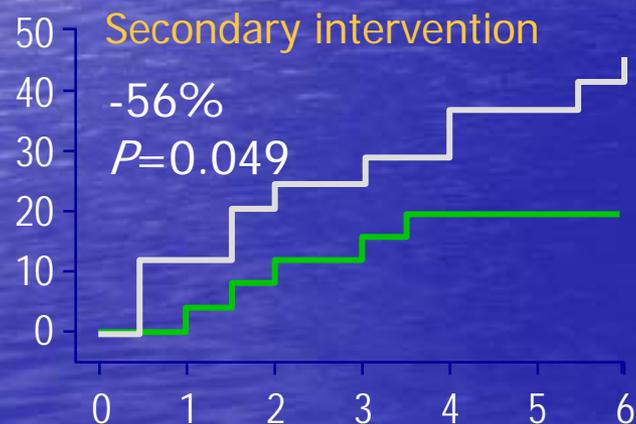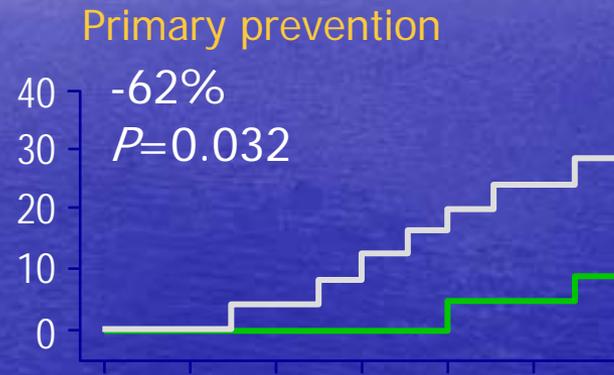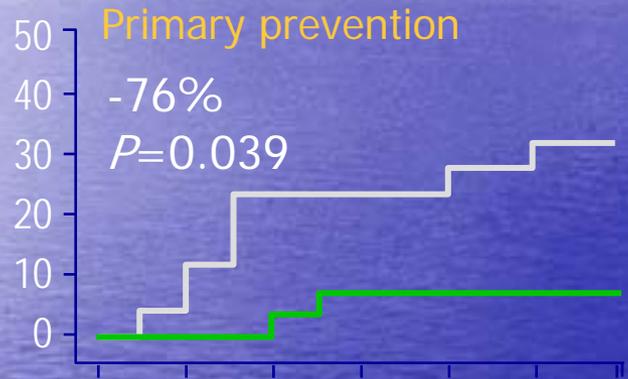
Microvascular outcomes in DM
% reduction with treatment

|	Randomized treatment	Long-term follow-up
UKPDS (mostly retinopathy)		
SU or insulin	-25% (p<0.01)	-24% (p<0.001)
Metformin	-29% (p=0.19)	-16% (p=0.31)
ADVANCE (mostly proteinuria)	-14% (0.01)	
ACCORD (retinopathy)	-33% (0.003)	
VADT (↑'d albuminuria)	not given (0.01)	
DCCT (retinopathy)	-63% (p<0.002)	-75% (0.001)

Clear benefit during treatment, and 'legacy-effect' afterwards

Effect of Tight Glycemic Control on Cardiovascular Outcomes

	DCCT	UKPDS	ADVANCE	VADT	ACCORD
Number of participants	1441	3867	11,140	1791	10,251
Age (yr)					
Duration dia					
Duration ra					
Between arm					
CV outcome					
Composite					.16)
Nonfatal M					.004)
CV mortal					.02)
Outcome ch					
Composite CV endpoint	−42% ($P = 0.02$)	---	---	|---	---
Fatal or nonfatal MI	---	−15% ($P = 0.01$)	---	---	---
All-cause mortality	---	−13% ($P = 0.007$)	---	---	---

So, tight glycemic control provides no clear cardiovascular benefit in the short term, but there is clearly a benefit in the long term.

ACCORD
Subgroup analyses for primary composite

A. Primary Outcome

Subgroup	No. of Patients	No. of Events	Hazard Ratio	P Value
Total	10,251	723		
Previous cardiovascular event				0.04
No	6,643	330		
Yes	3,608	393		
Sex				0.74
Female	3,952	212		
Male	6,299	511		
Age at baseline				0.65
<65 yr	6,779	383		
≥65 yr	3,472	340		
Glycated hemoglobin at baseline				0.03
≤8.0%	4,868	284		
>8.0%	5,360	438		
Race				0.29
Nonwhite	3,647	222		
White	6,604	501		

0.6   1.0   1.4

Intensive Therapy Better ← → Standard Therapy Better
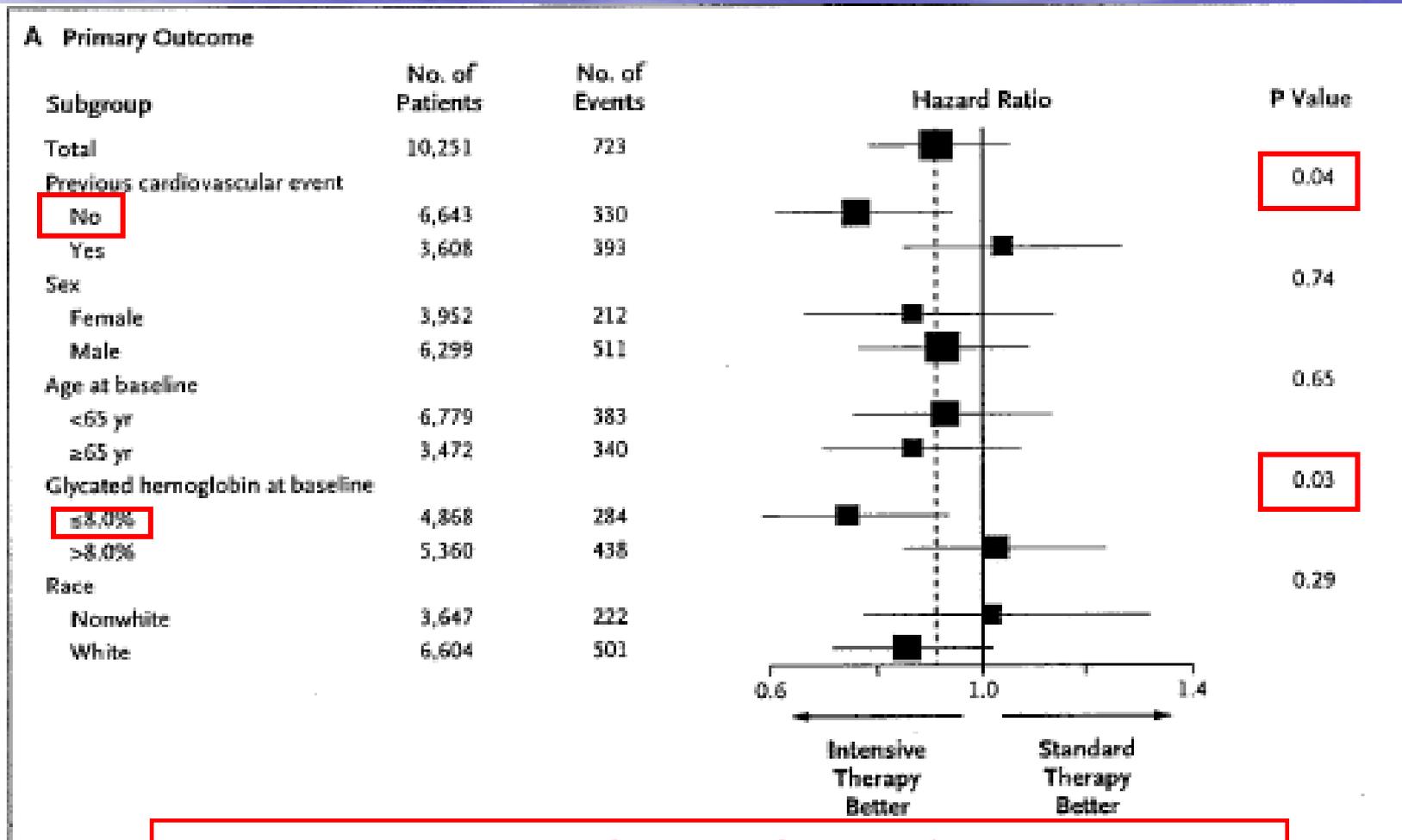
Suggestion of benefit with primary prevention and lower A1c at baseline

Data regard... level was not ava... ...d lines indicate the...

Gerstein HC et al. The ACCORD Study Group. *N Engl J Med*. 2008;358:2545-2559.

Glycemic Goals for Therapy

- American Diabetes Association (ADA) recommends:
  - Fasting/ preprandial fingerstick plasma glucose of 90-130 mg/dl
  - A1C <7.0%
    - Near normal for those who are appropriate for tighter control
    - Less stringent goals may apply to those with limited life expectancy… or individuals with comorbid conditions

- American Association of Clinical Endocrinologists (AACE) recommends a goal A1C of <6.5%, with preprandial BG's <110 mg/dl and 2° postprandial BG's<140 mg/dl.

- AGS guidelines recommend as a treatment goal an A1C of <8% for selected older patients
  - Unable to achieve lower A1C goal w/o significant risk
  - Unlikely to benefit from lower A1C goal

American Diabetes Association. Diabetes Care 34(1): S11-61, 2011.
Brown et al. J Am Geriatr Soc 51:S265-80, 2003.
AACE. Endocr Pract 17:1-53, 2011

Glycemic Goals for Older Adults

- Healthy older adults: appropriate to maintain aggressive goals and intensive therapy to:
  - prevent premature mortality
  - lessen microvascular and macrovascular complications
  - minimize the effects on geriatric syndromes
  - control costs
  - improve quality of life.
- Need to **individualize** goals based upon:
  - overall health status
  - level of function- aggressive control has *not* been shown to benefit older adults with low levels of function (3 or more limitations in IADL's or ADL's)
  - personal and family desires.
- Need to take into consideration the time to expected benefit.
  - Life expectancy may be shorter than the time needed to benefit from the intervention
  - Microvascular benefits from tight glycemic control occur in ~8 years, whereas macrovascular benefit occurs in >>10 years.
  - Benefit from BP and lipid control occurs in ~2-3 years.

Olson and Norris. Geriatrics 59:18-24, 2004;   Holman et al. N Engl J Med; 359:1-13, 2008.

Additional Benefits of Glycemic Control

- Hyperglycemia has been associated with:
  - Impaired cognitive function
  - Increased pain perception
  - Nocturia, incontinence and dehydration
  - Increased risk for falls

The Limiting Factor: Hypoglycemia

- Percent of patients with one or more major hypoglycemic reaction:
    - Insulin   2.3%
    - Sulfonylureas   0.5%
    - Metformin   0%
- Percent of patients with any hypoglycemic reaction:
    - Insulin   36%
    - Sulfonylureas   14%
    - Metformin   4%

Hypoglycemia in the Elderly

- Greatest risk for hypoglycemia:
  - Frail Elderly
    - Recent hospitalization within the past 30 days
    - The "oldest of the old"
    - Use of multiple medications
    - Renal insufficiency
  - Long Duration of Diabetes (>10 years)
  - Advanced macrovascular disease.
  - Hypoglycemic unawareness
    - Counterregulatory responses are impaired in elderly diabetics, so they have reduced warning sx's.
    - Dementia is a form of hypoglycemic unawareness.
  - Limited life expectancy.
  - Severe comorbidities.
- For pts at highest risk of hypoglycemia, must closely consider agents chosen *as well as therapeutic goal.*

Prevention of nocturnal hypoglycemia

- Consider prebed snack, w/ increased carbohydrate and protein content if the BG<120 mg/dl.
- Consider switch from SU to meglitinide or from premeal regular insulin to a rapid acting analogue (aspart, lispro, or glulisine).
- Move evening NPH to bedtime or change to glargine or detemir.
- Consider measurement of 3AM blood glucose once a week.

Therapy: Medical Nutrition Therapy

- Diet and exercise remain the cornerstones of treatment, even in older patients
  - May consider wt reduction, if overweight
  - Would exercise including walking 30 mins 5x/wk and light weights
- Older patients with diabetes, especially in long term care facilities, tend to be underweight rather than overweight
  - Given the risk of undernutrition, avoid food restrictions in older individuals living in an institutionalized setting
  - Provide regular menus that are consistent in carbohydrates and served at consistent times.
- Use caution in prescribing dietary supplements, as these can be very high in carbohydrate.

Treatment Strategies Beyond Diet

- In general, try to initiate pharmacotherapy with an oral agent in newly diagnosed type 2 diabetics unless:
  - Fasting plasma glucose is >300 mg/dl with ketonemia or ketonuria
  - Markedly symptomatic
- In patients who need insulin initially, often can be switched to oral agents after 6-8 weeks when glucose toxicity resolves

Case 1

- 68 year old man with diet controlled diabetes for the last 3 years. He has limited mobility due to severe arthritis, but is otherwise generally well. He has remains mentally intact. Maintained on a consistent carbohydrate diet. Recent nocturnal urinary incontinence, but denies blurred vision, numbness.

- Meds: ASA 325 QD

- Exam reveals BMI 27, BP 122/84, otherwise normal.

- Labs reveal FPG of 254 mg/dl, A1C is 9.2%. CBC, Chem 7, and LFT's are normal.

- **What do you want to do to manage this gent?**

First Line Therapy in Type 2 DM

- **Education, Diet and Exercise** serve as the basic tenets upon which all therapeutic regimens are built. Often useful to provide education to reinforce.

- **Drug Therapy:**
  - AACE recommends that we look at efficacy and **safety**.
  - Sometimes low cost may be important as well.
  - Both ADA and AACE recommend metformin as first line therapy of T2DM in the setting of normal renal fxn

AACE/ ACE Glycemic control algorithm. Endo Practice 15:540-559, 2009
Nathan et al. Diabetes Care. 32:193-203, 2009.

Biguanides

Metformin (*Glucophage®*)

- *Mechanism:* ⬇ hepatic glucose production
  Lowers FPG more than PPG

- *Efficacy:* moderate (⬇ A1c 1-2%, FPG 60 mg/dl)

- *Advantages:* Lack of weight gain; no hypoglycemia, ? CV benefits

- *Disadvantages:* GI side effects (bloating, gas, diarrhea)
  Lactic acidosis *(rare)*

- *Contraindications* Renal disease; CHF

Bailey et al,, NEJM 334:574, 1996
DeFronzo, Ann Int Med 131:281, 1999
Inzucchi, JAMA 287:360, 2002

Biguanides – Caveats in Older Adults

- Comorbidities may limit use…
- Contraindicated with impaired renal or hepatic fxn, cardiopulmonary disease, hypoxia→lactic acidosis.
- May want to calculate creatinine clearance, esp in patients >80 years of age
  - Cleared entirely renally
  - Should be avoided if creatinine clearance is <30 ml/min, consider use of lower dose if creatinine clearance is <60 ml/min
- Start with lowest effective dose (i.e. 500 mg with dinner) and titrate slowly.
- Of benefit: no hypoglycemia when used as monotherapy

Case 1 (cont'd)

- He reviewed with his nursing home physician the goals of therapy, and discussed continued importance of dietary adherence, exercise to the degree possible.

- Metformin 500 mg added predinner.

- He initially had mild bloating which resolved.

- After a week, a second dose added prebreakfast.

- Metformin continued to be titrated up to 1000 mg BID AC (the maximum effective dose).

- **If glycemic goals are still not met once he is on max metformin, what can we do?**

"Failure" of a Single Oral Agent

- Type 2 diabetes is a progressive disease, with ↑'d loss of beta cell function over time. Confirmed by the data from the UKPDS.

- Need to progress to multi-drug therapy or add insulin in order to maintain a similar level of glycemic control.

- If glycemic goals are not met with agent in one class, we must add second agent with different mechanism of action or add insulin

- ADA concensus algorithm recommends addition of a sulfonylurea or insulin if metformin therapy is not effective in getting patients to goal A1C.[2]

Hazard ratio (95% CI)
Rosiglitazone vs. metformin, 0.68 (0.55–0.85); P<0.001
Rosiglitazone vs. glyburide, 0.37 (0.30–0.45); P<0.001

No. at Risk						
Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Monotherapy Failure at 5 Years.
Treatment was considered to have failed if a patient had a confirmed or adjudicated level of fasting plasma glucose of more than 180 mg per deciliter. Risk reduction is listed for comparisons of pairwise groups from a baseline co-variate-adjusted Cox proportional-hazards model. Gray's estimates of cumulative incidence adjusted for all deaths were smaller than Kaplan–Meier estimates of treatment failure: 10% in the rosiglitazone group, 15% in the metformin group, and 25% in the glyburide group. I bars indicate 95% CIs.

[1]Kahn et al. N Engl J Med, 355:2427, 2006

[2]Nathan et al. Diabetes Care. 32:193-203, 2009.

Algorithm for the management of T2DM

Tier 1: Well-validated core therapies

At diagnosis:
Lifestyle + Metformin

Lifestyle + Metformin + Basal insulin

Lifestyle + Metformin + Sulfonylurea[a]

Lifestyle + Metformin + Intensive insulin

STEP 1   STEP 2   STEP 3
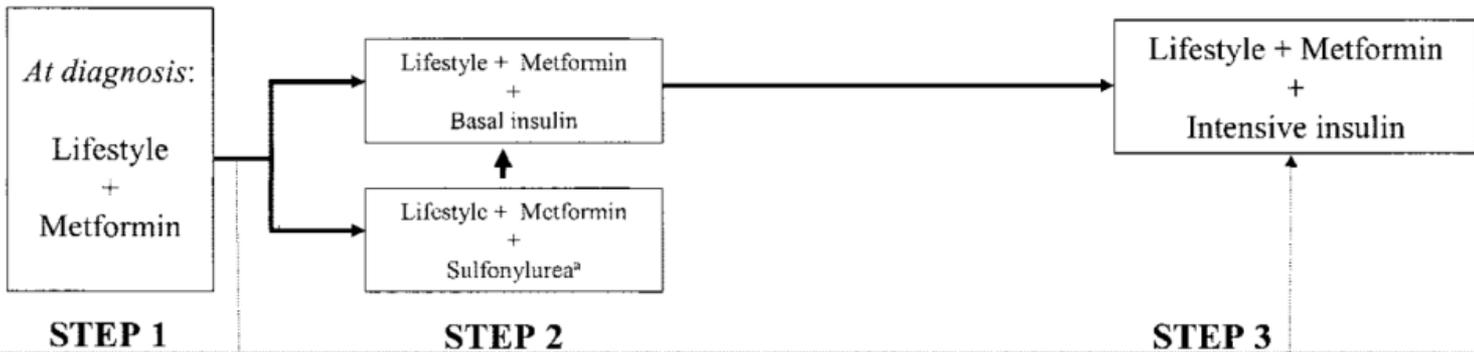
Tier 2: Less well validated therapies

Lifestyle + Metformin + Pioglitazone
No hypoglycemia
Oedema/CHF
Bone loss

Lifestyle + Metformin + GLP-1 agonist[b]
No hypoglycemia
Weight loss
Nausea/vomiting

Lifestyle + Metformin + Pioglitazone + Sulfonylurea[a]

Lifestyle + Metformin + Basal insulin
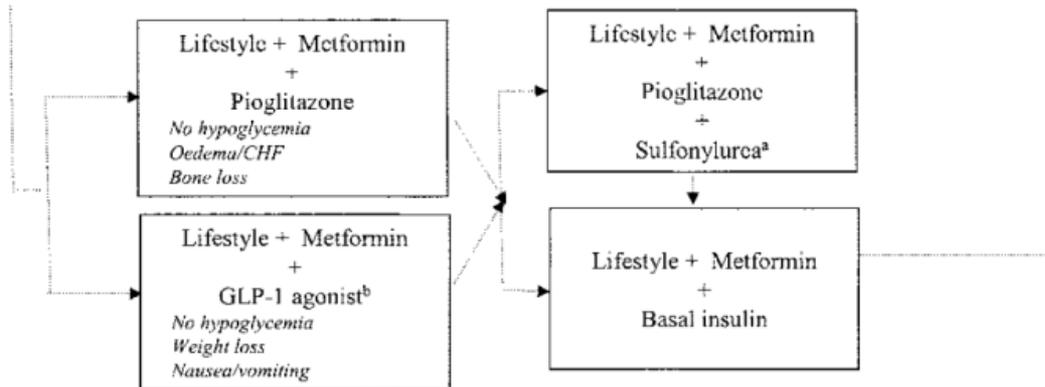
Drug choices in algorithm based mainly upon efficacy (A1C lowering)- as this is what correlates with ↓'d complications- as well as side effect profile, cost, safety.

Nathan et al. Diabetes Care. 32:193-203, 2009.

Sulfonylureas

Glyburide (*Micronase*®, *Diabeta*®, *Glynase*®)
Glipizide (*Glucotrol*®)
Glimepiride (*Amaryl*®)

- *Mechanism:*   ↑   pancreatic insulin secretion

  Lowers both FPG > PPG

- *Efficacy:*   moderate (↓   A1c 1-2%, FPG 60 mg/dl)

- *Advantages:*   inexpensive; ↓'s microvasc complications

- *Disadvantages:*   weight gain, hypoglycemia- esp in older patients or with renal impairment

- *Contraindications*:   avoid in hepatic and renal impairment

Gerich, NEJM 321:1231, 1989
DeFronzo, Ann Intern Med 131:281, 1999
Inzucchi, JAMA 2887:360, 2002

Sulfonylureas- Caveats in Use

- Chlorpropamide
  - Contraindicated in the AGS guidelines due to high risk of hypoglycemia
- Glyburide
  - longer duration of action, active hepatic metabolites, renally excreted
  - **No longer recommended in current ADA guidelines due to prolonged duration causing increased risk of lows.**
- Glipizide
  - Shorter duration of action
- Glimepiride
  - Largely excreted in bile
- All are hepatically metabolized and should be used cautiously with advanced liver disease
- Start with lowest dose and titrate slowly

Case 1 (cont'd)

- Glipizide 5 mg was added prebreakfast with the plan to titrate up to max dose of 20 mg BID AC or until glycemic goals were achieved.

- Once he was on max SU and metformin, he had some unfortunate personal events which resulted in increased eating, and decreased exercise.

- Exam revealed BMI of 32, o/w unremarkable.

- CBG's 131-184 mg/dl prebreakfast, similar predinner

- Labs revealed A1C of 7.8%

- **When do we perform capillary BG monitoring in nursing home patients?**

- **So now what do you want to do to manage this gent?**

When do we perform capillary BG monitoring in nursing home patients?

- Integral to prevention of hypoglycemia
  - May want to consider in patients on secretagogues or insulin
  - Would certainly consider in patients on such agents with hypoglycemic unawareness
- Allows rational adjustment of therapy
  - Useful during med titration
  - Useful if aiming for truly tight glycemic control
- Useful in acute illness, to help manage associated hyperglycemia
  - Prevent associated volume depletion
  - Prevent urinary dysfunction
  - Prevent cognitive decline

Additional Complementary Therapy

- If we can't get this gent to lose weight and resume activity, then we will need to deal with his increased insulin resistance.

- A thiazolidinedione is a reasonable complementary rx
  - This is what many would choose in younger patients.
  - In the older adult, need to consider comorbidities, polypharmacy, and overall drug cost, perhaps making this less palatable.

- One may also consider addition of bedtime long-acting insulin.

Thiazolidinediones

Pioglitazone (*Actos*®)
Rosiglitazone (*Avandia*®)- FDA restricted use

- *Mechanism:*　　　↑ insulin sensitivity, esp at muscle and adipose tissue

- *Efficacy:*　　　moderate (↓ A1c 1-1.5%), lowers both FPG and PPG, but effect may be delayed

- *Advantages:*　　no hypoglycemia, no reliance on renal excretion.　? CV benefits (pioglitazone)

- *Disadvantages:*　　fluid retention / edema/ heart failure, weight gain, cost, slow onset of action, bone fractures

- *Contraindications:*　　Class III or IV CHF or hepatic impairment w/ ALT > 2.5 times upper normal limits

DeFronzo, Ann Int Med 131:281, 1999
Parulkar. Ann Int Med 134:61, 2001
Inzucchi, JAMA 287:360, 2002

Thiazolidinediones- Caveats in Older Adults

- Delayed onset of action- takes 8-12 weeks to achieve maximal effect
- Fluid retention correlates with higher doses and is more common when TZD's are used with insulin. Most often seen in:
  - Older patients
  - Patients with multiple medical problems
  - Patients with underlying CAD or CHF
- Does not cause hypoglycemia as monotherapy
- Cost may be an issue: 15 mg for $180/ month or 45 mg for $283/month at drugstores.com

Case 1 (conclusion)

- Pioglitazone 15mg QD was added.
- On follow up at eight weeks, blood glucoses were improved to the 116-158 mg/dl range, A1C 7.4, and he had no pretibial edema.
  - If he were older or had multiple comorbidities implying limited lifespan, I would stop here!
- Pioglitazone was then increased to 30 mg QD with glycemic goals met.

Combination Oral Agent Therapy- What Combos to Use

Alpha glucosidase inhibitors

Glucose

Defective insulin secretion

Sulfonylureas Meglitinides

β-cell insulin secretion

Persistent Hepatic Glucose Output

Incretin analogs DPP-IV Inhibitors

Metformin

Thiazolidinediones

Insulin action

Resistance to insulin action

Amended from Dinneen SF. *Diabetes Med*. 1997;14(suppl 3):S19-24.
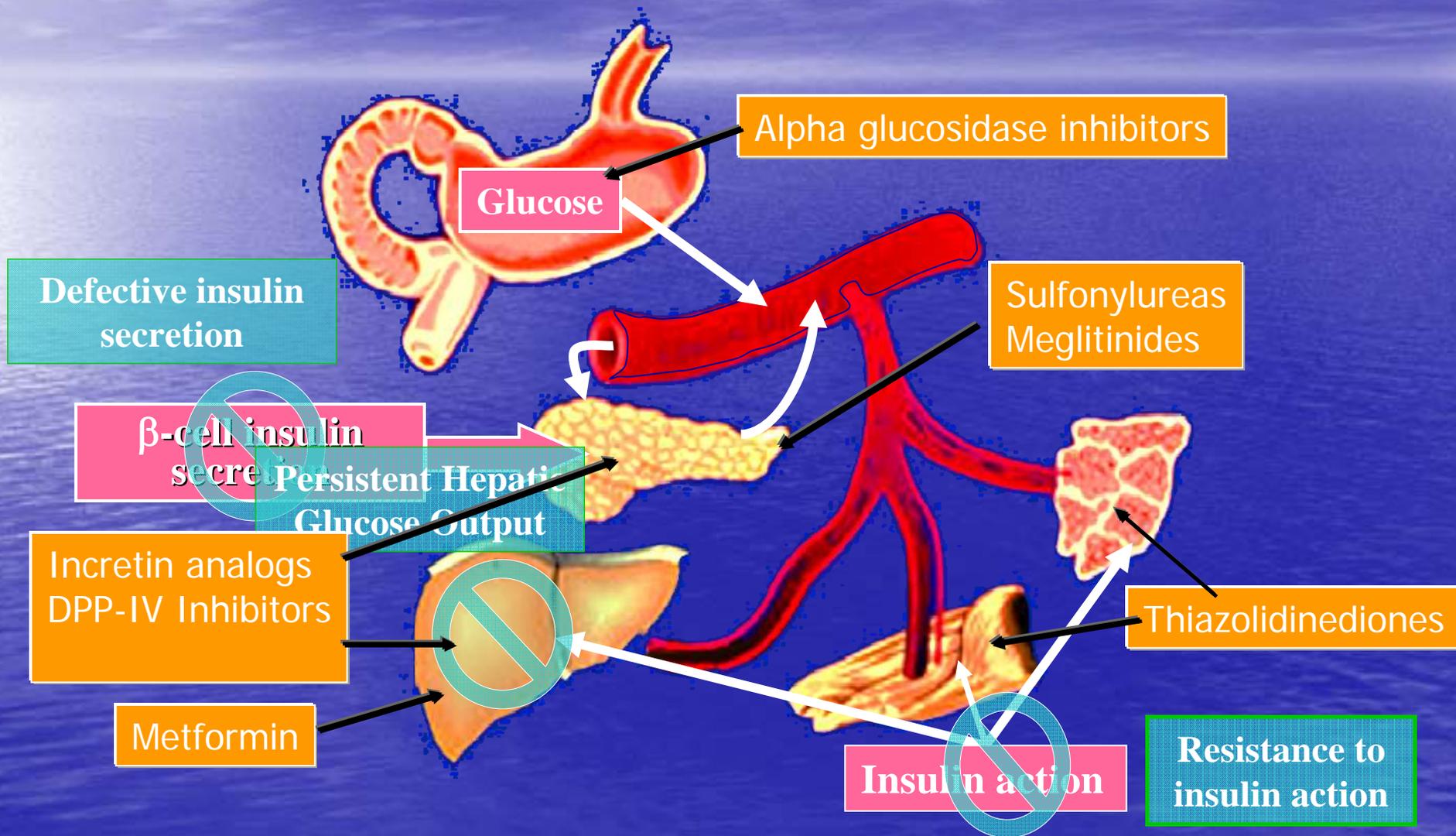
Case 2

- 75 year old man with diabetes, previously well controlled on diet and exercise, now c/o signif fatigue after meals. CBG monitoring reveals fasting values of 136-158 mg/dl; prelunch, predinner, and prebed values are 172-206 mg/dl.   Walks 30 mins 5d/wk, on consistent carbohydrate diet.

- PMH: HTN, CKD, BPH, Osteoarthritis

- Meds: Fosinopril, Metoprolol, Lasix, Tamsulosin, Tylenol, Aspirin

- Exam reveals BMI 29, BP 132/64, o/w normal

- Labs with normal CBC, Chem 7, LFT's, except for FPG of 141 mg/dl, creatinine of 1.8 (stable), A1C of 8.2%

- **What do you want to do to manage this gent?**

Monotherapy in the Diabetic Patient with Postprandial Hyperglycemia

- Sometimes older patients exhibit only mild elevation in fasting BG but have a significant rise in glucose with eating, presumably due to mismatch of timing of insulin release and glucose absorption.

- A short acting SU may be a good first line choice.
  - A meglitinide or TZD may be equally good choices.
  - An alpha glucosidase inhibitor or incretin mimetic also target the post-prandial sugar, but wouldn't get his A1C to <7%.

- May even consider nighttime long acting insulin to lower the fasting glucose.

Meglitinides-(Non-SU Secretagogues)

Repaglinide (*Prandin*®)
Nateglinide (*Starlix*®)

- *Mechanism:* ⬆ pancreatic insulin secretion. Primarily lowers PPG

- *Efficacy:* moderate (⬇ A1c 1-1.5% for repaglinide, nateglinide 0.5-0.8%)

- *Advantages:* rapid onset and offset, so fewer lows, targets PP glucose, repaglinide is hepatically excreted (use w/ renal insuff)

- *Disadvantages:* weight gain, hypoglycemia (less than with SU), frequent dosing, cost

Meglitinides- Caveats in Older Patients

- Hepatic metabolism permits use in patients with impaired renal function.

- Rapid onset permits dosing just prior to meal, skip dose if skip meal.

- Rapid offset results in ↓ in late or overnight lows.

- Many drug-drug interactions. Most concerning is gemfibrozil which increases repaglinide concentration and may result in prolonged lows.

- Cost may be an issue (0.5, 1 or 2 mg tabs: $240/month at drugstore.com)

DPP-4 Inhibitors

Sitagliptin (*Januvia*®)
Saxagliptin (*Onglyza*®)
Linagliptin (Tradjenta®)

- *Mechanism:*   Prevent breakdown of intrinsic GLP-1
  $\uparrow$ insulin secretion (BG-dependent)
  $\downarrow$ glucagon secretion
  Lowers PPG more than FPG

- *Efficacy:*   modest ($\downarrow$ A1c 0.6-0.8%)

- *Advantages:*   weight neutral, no hypoglycemia,
  ? β-cell preservation

- *Disadvantages:*   cost, rash, ? $\uparrow$'d risk of pancreatitis

DPP-4 Inhibitors- Caveats in Older Adults

- Limited side effect profile, weight neutral.
- No hypoglycemia when used as monotherapy… similarly does not cause significant lows in combo with metformin or TZD's.
- Renally adjust dose, even for use in renal failure with hemodialysis
- Cost may be an issue ($215/ month on drugstore.com)
- No long term data yet with this class of agents.

Incretin Mimetics

Exenatide (Byetta®)
Liraglutide (Victoza®)

- *Mechanism:*
  Act as incretins
  Glucose dependent ↑ insulin secretion
  Glucose dependent ↓ glucagon secretion
  Delay gastric emptying and inhibit appetite
  Lowers PPG more than FPG

- *Efficacy:*
  modest (↓ A1c 1.0-1.5%)

- *Advantages:*
  weight loss, no hypoglycemia,
  ? β-cell preservation

- *Disadvantages:*
  nausea/ vomiting/ diarrhea, injection,
  not rec w/ severe renal impairment,
  ? ↑'d risk of pancreatitis

Keating, Drugs 2005 65(12):1681-92

Alpha-Glucosidase Inhibitors

Acarbose (*Precose*®)
Miglitol (*Glyset*®)

- *Mechanism:* ↓ rate of gut polysaccharide breakdown, thereby slowing absorption

- *Efficacy:* modest (↓ A1c 0.5-1.0%), PPG lowering

- *Advantages:* weight neutral, non-systemic drug, targets post-prandial glucose, no hypoglycemia (unless used with secretagogues or insulin)

- *Disadvantages:* GI side effects (bloating, flatulence, diarrhea- ↓ w/ slow titration), frequent dosing, cost

Toeller, Eur J Clin Invest 24(3):31, 1994
DeFronzo, Ann Int Med 131:281, 1999
Inzucchi, JAMA 287:360, 2002

Management of Case 2

- He was started on repaglinide 0.5 mg prior to meals.
- After two weeks, CBG's 122-148 prebreakfast and 140's-180's predinner. Dose was increased to 1 mg TID AC.
- After two additional weeks, CBG's 110-140's prebreakfast, 130's-160's prelunch, predinner, prebed.
- Dose was increased to 2 mg with breakfast, 1 mg with lunch and dinner
- At three months follow up, A1C was 6.9%, CBG's 90's-130's without lows. No further adjustments were made at that time.

Bile Acid Sequestrants

Colesevelam (*Welchol*®)

- *Mechanism:*   Unclear

- *Efficacy:*   modest (↓ A1C 0.5%)

- *Advantages:*   ↓LDL-C, weight neutral, no hypoglycemia

- *Disadvantages:*   GI-constipation, ↑TGs, drug interactions, cost

- Contraindications: Hx of bowel obstruction, TG's>500 mg/dL; hx of hypertriglyceridemia-induced pancreatitis

Bays HE, et al. *Arch Intern Med*. 2008. 168:1975-83.
Fonseca VA, et al. *Diabetes Care*. 2008; 31: 1479-1484.
Goldberg RB, et al. *Arch Intern Med*. 2008; 168: 1531-1540.

Use of Oral Agents to Optimize Glycemic Control: Conclusions

- Choice of oral agents needs to be matched with patient characteristics (thin vs. obese) as well as concurrent medical issues (renal, hepatic, cardiopulmonary status).

- Diabetes is a progressive disease, and will require an increasing number of agents and/ or addition of insulin as the duration of diabetes increases.

- Each oral agent can only improve A1C a maximum of 2%, so if poor control persists on multiple agents, insulin is needed.

Case 3

- 72 yo woman with h/o Alzheimers dementia with recent progressive difficulty sleeping, screaming out overnight. She does better with treatment with quetiapine.

- One month later, she is noted to have progressive nocturnal incontinence and morning drowsiness.

- On exam, she is a lethargic, obese older woman w/ rapid, deep respirations, BP 120/66 with HR 105 and regular. Afebrile. No evidence of infection is found

- Labs reveal blood glucose >900 and +ketones

- So... what do you think?

Hyperglycemic Crises

Other Hyperglycemic States
Diabetes Mellitus
Non-Ketotic Hyperosmolar Coma
Impaired Glucose Tolerance
Stress Hyperglycemia

Other Ketotic States
Ketotic Hypoglycemia
Alcoholic Ketosis
Starvation Ketosis

Other Metabolic Acidotic States
Lactic Acidosis
Hyperchloremic Acidosis
Salicylism
Uremic Acidosis
Drug-Induced Acidosis
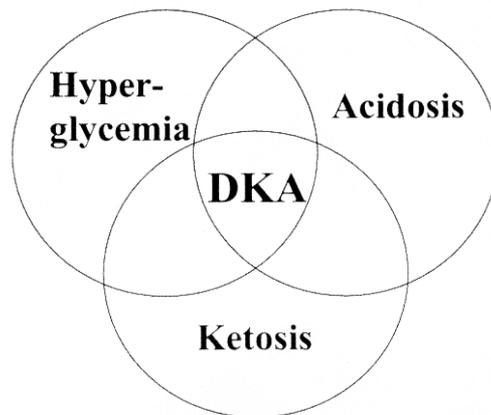
- Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State: two most serious acute metabolic complications of diabetes.
- Mortality rate in DKA ~5%, HHS ~15%.
- Prognosis in both conditions is worse at the extremes of age and in the presence of coma or hypotension.
- She was transferred to the hospital for management

Precipitating Factors

- Most common precipitant is infection.
- Insulin omission is a common cause in adolescents and the indigent.
- Others:
  - Cerebrovascular accident
  - Alcohol abuse
  - Pancreatitis
  - Myocardial Infarction
  - Trauma
  - Drugs (steroids, *second generation antipsychotics*)
  - Previously undiagnosed diabetes

Second Generation Antipsychotics and DM

- Second generation antipsychotics (SGA) assoc'd with incr'd wt gain, dyslipidemia and diabetes
  - Olanzapine and clozapine the biggest culprits
  - Risperidone and quetiapine cause problem to lesser degree
  - Aripiprazole and Ziprasidone "the best" in this regard, but both reported to cause new DM and even HHS and DKA
- Mechanism of this side effect unclear
- ADA and APA came out with guidelines for use of SGA that include evaluation and f/u of:
  - h/o DM or prediabetes   -FH of DM
  - BMI, waist circumference   -BP
  - FPG   -fasting lipids

Case 4

- 73 year old gent w/DM for 9 years. Follows consistent carb diet- tries not to cheat with snacks brought in by family. Tries to remain active.
- FBG's 170-200 mg/dl, similar predinner. No lows.
- Consistent in taking his meds. Unable to tolerate acarbose due to severe bloating.
- MEDS: Glipizide 20 BID, Metformin 1000 BID, Pioglitazone 45 mg QD, ASA 325 mg QD.
- Exam w/ BMI 27.5, o/w unremarkable.
- Labs reveal normal renal fxn and LFT's.   A1C has drifted up from 6.8→ 8.2% over the last 6 months.
- **So, what do you think?**

Next Step Therapy in Patient on All Oral Agents

- This gent sounds like he is compliant with diet, exercise and meds to the best of his capability.

- His A1C is drifting upward, suggesting that he is developing beta cell failure.

- Addition of bedtime long-acting insulin is needed in order to get his glycemic control back into desirable range.

Addition of Bedtime Glargine or NPH Insulin to Oral Therapy Improves Glycemic Control
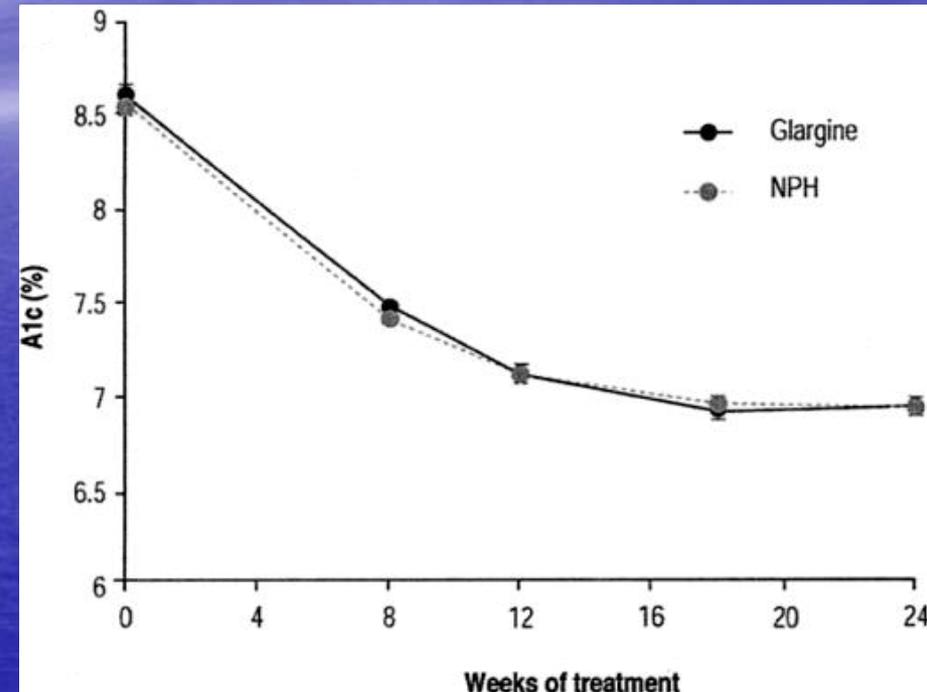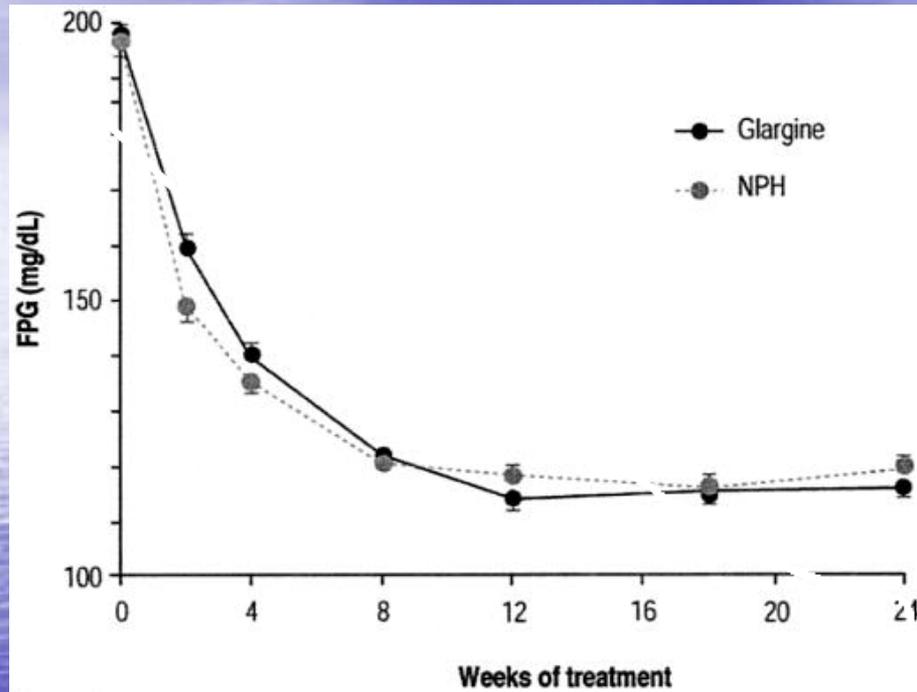
- N=756 Type 2 DM w/ mean BMI 32.5
- Mean age 55+/-10 years (30-70)
- Mean disease duration 8.5 +/- 5 years
- On SU, Metformin, or SU + Met
- Baseline A1C 7.5-10%
- Randomized to QHS NPH or glargine w/ aggressive titration of insulin to FBG<100

OUTCOME-
- Equal improvement in glycemic control, with 57-58% achieving A1C target <7%
- Fewer hypoglycemic episodes with glargine

Riddle et al. Diabetes Care. 2003; 26:3080-3086.

NPH Insulin

- Modified (cloudy) insulin which is released slowly from its subcutaneous depot with resultant delayed onset and prolonged duration.

- Onset of action is 2-4 hours, peak is ~6-8 hours, duration of action is 12-16 hours.

- Advantages:
  - "Inexpensive" ($70/vial on drugstore.com)
  - Can mix w/ regular insulin with little change in insulin kinetics.

- Disadvantages: Not truly flat, giving a peak in the afternoon when used in the AM and peak at 2-3 AM when taken predinner.

- Used for basal insulinization at bedtime, BID, TID or QID, but not truly flat.

Glargine (Lantus)

- Long acting insulin analogue which is clear.
- Onset is ~90 minutes, and it is virtually peakless.
- Duration is 20-24 hours.
- Provides ~flat basal insulinization.
- More expensive ($110/vial on drugstore.com)
- Cannot be mixed with other insulins.

Insulin Detemir (Levemir)

- Long acting analog, FDA approved 6/05
- Myristic Acid side chain strengthens self-association→ Acts to delay absorption from the subcutaneous depot
- Fatty Acid side chain binds to albumin
  - Binding to albumin does not interfere w/ receptor binding
  - Binding to albumin does not interfere w/ albumin binding to other drugs
  - Drug is dropped off smoothly and gradually in tissues
- Duration of action depends on the dose
  - $\leq$0.4 units/kg/d: divide dose BID
  - $\geq$0.6 units/kg/d: dose daily
- Cost is similar to other analog insulins, ~twice that of NPH

Detemir- Caveats in Older Patients

- Can be added at bedtime to oral agents, as can NPH or glargine
  - May or may not provide 24 hour control as single injection
  - If need to split dose, give 50% Q12hrs
- Potential benefits of using detemir as a basal insulin
  - Less Variability
  - More consistent glycemic profile
  - Fewer lows
  - Less Weight Gain

Case 4, Continued

- Bedtime NPH insulin, 10 units, was added to his prior regimen (start with 0.1-0.2 units/kg BW). Fasting BG's decreased to the 130-160 mg/dl range and NPH was gradually titrated up by 2 units every 3-5 days.

- After one month, he was taking 18 units NPH QHS with continued max glipizide, metformin and pioglitazone. AM and predinner BG's were back in the 80-130 mg/dl range, without significant lows.

- If fasting BG could be controlled but still had high predinner BG, could try switching insulin to glargine or detemir.

  – May also consider checking C-peptide to ensure residual endogenous insulin... if this is low, needs prandial insulin as well, and would stop the SU

Implications When Adding Basal Insulin

- Many providers would stop the TZD

> What if you still cannot achieve control with addition of basal insulin?

- Many providers would choose glargine or detemir as the basal insulin to help avoid nocturnal hypoglycemia, especially in the frail elderly

Normal 24 Hour Insulin Secretion Profile in Lean and Obese Subjects
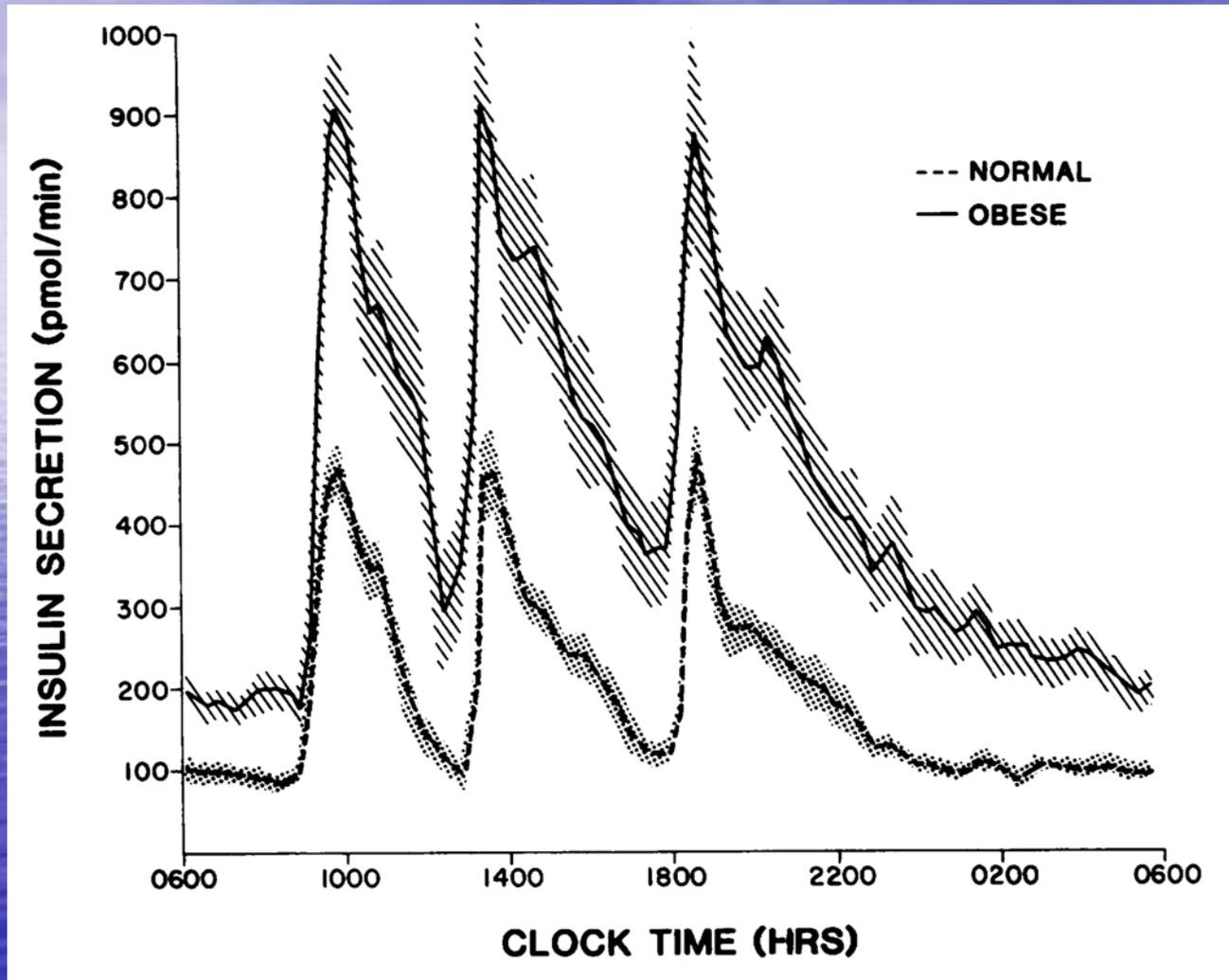
INSULIN
REPLACEMENT

~half of insulin
is basal
~half of insulin
is prandial
Can add to this a
correction dose

Polonsky et al. JCI, 1988, 81:442-8.

Why Not Just Use Sliding Scale Insulin?

- Dose is not individualized
- Insulin is reactive, rather than proactive
  - Giving insulin to cover when the BG is already high, rather than preventing the hyperglycemia

- Leads to wide fluctuations in glucose levels
- Does not provide basal insulinization (needed by insulin deficient diabetics) nor consider nutritional coverage

Leahy J. Endocr Pract 12:86-90, 2006
Queale WS et al. Arch Intern Med 157:545-552, 1997
Clement S et al. Diabetes Care 27:553-91, 2004
American Diabetes Association. Diabetes Care 32:S13-S61, 2009

Case 5

- 76 year old woman with longstanding Type 1 DM. She is maintained on 16 units of NPH and 8 units of regular insulin in the AM, 6 units NPH, 6 units of regular predinner.

- CBG reveals:
  - FBG's of 140-210 mg/dl
  - Prelunch, predinner, and prebed values of 80-135 mg/dl
  - 2-3AM rings for help… "doesn't feel well" … BG 36 mg/dl, repeat 41 mg/dl

- Exam is benign including BMI of 21.

- Labs reveal normal chem7, LFT's, and A1C 6.8%.

- **So, what do you think?**

Case 5 (cont'd)

- Glycemic control okay based upon her A1C.
- However, overnight symptoms are classic for hypoglycemia, as documented by her CBG's.
- Morning BG's are elevated, suggesting:
  - inadequate evening NPH dose
  - inappropriate timing (its effect is wearing off).
- Can try to decrease predinner NPH dose, which is peaking at 2-3AM, or may try to move dose to bedtime and decrease slightly.
- *Personal commentary: Evening NPH truly shouldn't be given predinner-- problematic when try to use 70/30 insulin as well.*

Case 5 (cont'd)

- NPH was changed to bedtime and decreased by 2 units (new regimen 16N/8R//6R//4N).

- Subsequent premeal and bedtime blood glucoses were all in the 80-140 mg/dl range on >80% of readings. Given her insulin doses 30-45 minutes prior to meals.

- A1C 7.3%.

- She notes postprandial fatigue.

- On occasion, she would not be hungry and skip lunch, with resultant severe lows (20's-40's)-- she became agitated if the staff insisted she ate.

- **So, what do you think?**

Management of Postprandial Hyperglycemia, Afternoon Lows

- Postprandial fatigue may represent high postprandial blood glucoses which come down by the time of the next meal, when CBG is being measured.

- Afternoon lows when she skips meals are problematic... as a type 1 diabetic (or in a longstanding, insulin deficient type 2), she needs insulin, but when she skips meals, she is guaranteed to be low when her morning dose of NPH is peaking.

- **So, what should we do?**

Regular Insulin

- Referred to as clear or unmodified insulin.
- Onset of action 30-60 minutes, Peak action 2-3 hours, Duration of action: 5-8 hours.
- Advantages:
  - Inexpensive (~$70/vial)
  - Long track record of safety.
- Disadvantages:
  - Need to take doses 30-45 minutes prior to eating a meal.
  - Effect is not truly rapid… it is delayed which can result in postprandial hyperglycemia, late hypoglycemia.
- Uses: Premeal SQ, IV or IM for hyperglycemic crisis.

Regular Insulin- Caveats in Older Adults

- Long duration can be problematic
  - Can have late lows if don't tend to snack
  - Especially worrisome in elderly frail
- Theoretically should take 30-60 mins prior to meals to permit onset of action
  - This can be challenging to orchestrate
- Expect post-prandial highs

Approximate Pharmacokinetic Profiles of Human Insulins and Insulin Analogues
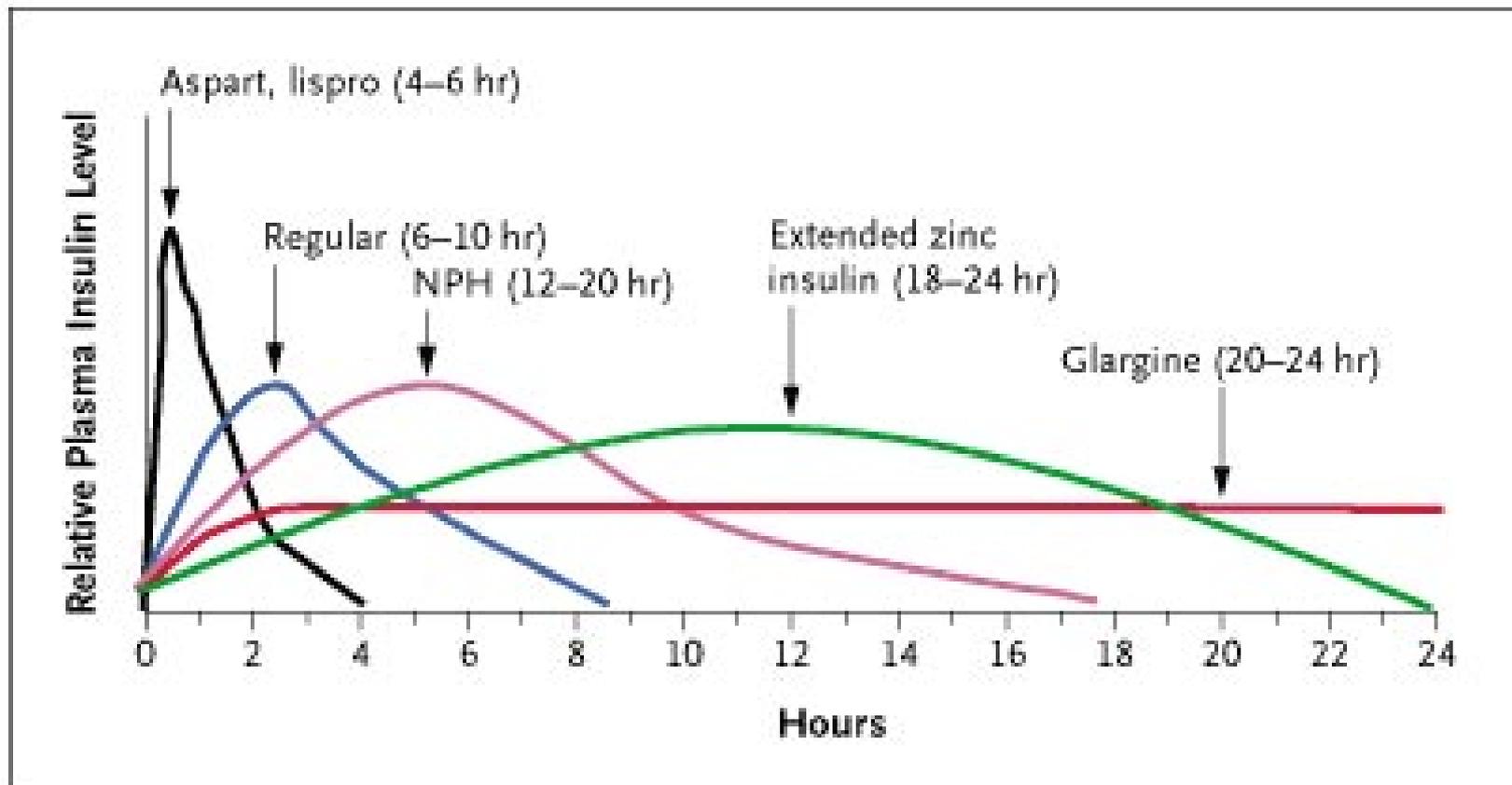
Hirsch. NEJM. 2005; 352:174-83.

Rapid Acting Insulin Analogues

- Agents in group include lispro, aspart, and glulisine.
- Remain monomeric after injection, resulting in rapid absorption, and relatively rapid onset and offset.
- Onset of action is 5-15 minutes, peak action at 60-90 minutes, and duration of ~4-5 hours.
- Advantages include:
  - increased convenience- can take just prior to meal.
  - better postprandial glycemic control.
- Disadvantages include:
  - short duration of action, so need basal insulinization.
  - more expensive than regular insulin (~$120 per vial, ~$230 for 5 pack of pens).

Holleman and Hoekstra, NEJM, 337:176-83, 1997
Hirsch, NEJM, 352:174-83, 2005

Rapid Acting Insulin Analogs- Caveats for Older Adults

- More closely match food absorption with insulin action →Expect better post-prandial control, fewer late lows

Glycemic Excursion w/ Premeal RHI versus Postmeal Glulisine
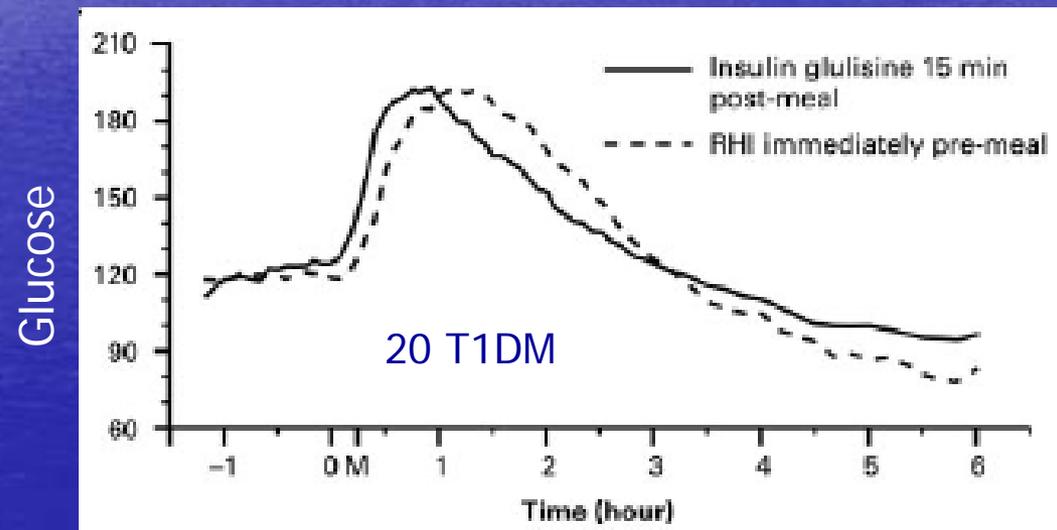
- For patients who sometimes do not eat, may consider dosing their rapid acting analog *after they eat* to prevent lows.

Rave et al. Diabetes Care 29:1812-1817, 2006

Need for long acting flat basal insulinization

- All type 1 diabetics and many long standing, insulin deficient type 2 diabetics need 24 hour basal insulinization
- Can achieve this with BID injections of NPH- far from flat
- Can achieve this with two long acting analogs
  - Glargine (Lantus)
  - Detemir (Levemir)

Amylin Analogs

Pramlintide (Symlin®)

- *Mechanism:* $\downarrow$ glucagon secretion
Slows gastric emptying
$\uparrow$ satiety
Lowers PPG more than FPG

- *Efficacy:*   modest ($\downarrow$ A1c 0.3-0.5%)

- *Advantages:*   improves PP BG

- *Disadvantages:*   cost, $\uparrow$'d risk of hypos, signif nausea

Approved as adjunct therapy for patients w/ DM who inject insulin at mealtimes and have failed to achieve adequate glycemic control.

I am presently unsure of this drug's place in management of our older diabetic patients.

Case 5 (cont'd)

- She was changed to a regimen of bedtime NPH with three postmeal injections of aspart.

- She had no further severe lows.

- However, she began to experience increased urination shortly after bedtime, with BG's of 200-350 mg/dl and trace ketonuria.

- **So, what do you think?**

Case 5 (cont'd)

- Aspart, with postmeal use, prevents lows when she does not eat.

- However, it appears that late at night, BG rises while the bedtime NPH dose has yet to begin working.

- Can provide more continuous basal insulinization with BID, TID or QID NPH, but best if could give flat QD insulin.

- So?

Case 5: Conclusion

- Bedtime NPH was switched to glargine, with mealtime aspart continued.
- She continues to be a picky eater, but has no further severe lows.
- A1C is maintained at 6.5%.

Note on Treatment

- If wanted to use analog insulins (glargine or detemir with aspart, glulisine, or lispro) as initial regimen, would use 40-50% as basal, 50-60% as prandial
- Start 0.3-0.5 units/kg BW/ day as initial total daily dose.
  - So, if choose initial TDD of 36 units/day for 90 kg man...
  - 18 units glargine QD or 9 units detemir Q12H
  - 6 units aspart, glulisine or lispro TID AC
  - Start w/ lower dose in frail or those with impaired renal fxn.
- When converting from basal NPH to analog
  - If on NPH once a day, can switch to the same dose glargine or detemir
  - If on NPH twice daily, add up doses and use ~80% of total NPH dose as glargine or detemir

Use of Insulin to Optimize Glycemic Control

- Diabetes is a progressive disease, and will require an increasing number of agents and/ or addition of insulin as the duration of diabetes increases.

- Choice of insulin regimen needs to be matched w/ pt characteristics as well as concurrent medical issues.

- Patients who require insulin include:
  - All patients with Type 1 diabetes.
  - Many pts with secondary diabetes due to pancreatic insufficiency
  - Patients with otherwise unexplained weight loss, short history with severe sx's, or moderate ketonuria.

- May also want to initiate therapy with insulin in patients with a FBG>250 mg/dl.

Medical Therapy for Optimizing Glycemic Control in Older Adults: Conclusions

- Try to think of all the agents which a given patient can tolerate, and which complement each other.

- The complexity of the regimen should be consistent with the desired goals- this should be individualized based upon life expectancy, comorbidities, and patient and family preference.

Non-Glycemic Goals: HTN

- HTN contributes to the development and progression of diabetic complications, including CVD, retinopathy, and nephropathy.
- Control of HTN has clearly been shown to ↓:
  - progression of nephropathy
  - complications of cerebrovascular and vascular disease.
- ADA Goal is BP <130/80, whereas VA goal BP is <140/80
  - Based upon pt characteristics and response to therapy, higher or lower systolic BP targets may be appropriate (new)
- If BP >130/80, repeat within one month to confirm.
- If BP>140/90, pharmacological rx should be initiated immediately along with lifestyle changes.

The ACCORD Study Group N Engl J Med 362:1575, 2010
American Diabetes Association. Diabetes Care 34(1): S11-61, 2011.

Blood pressure control and risk of macrovascular complications
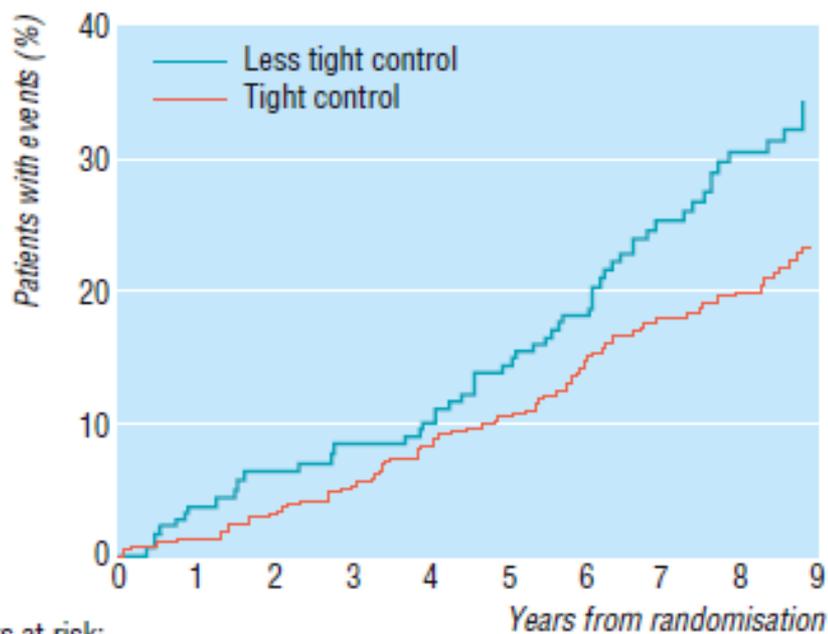
Fig 6 Kaplan-Meier plots of proportions of patients who die of disease related to diabetes (myocardial infarction, sudden death, stroke, peripheral vascular disease, and renal failure)

- Compared tight BP control, aiming for <150/85 vs usual control of 180/105 mm Hg.

- Achieved BP of 144/82 versus 154/87 mm Hg.

- Statistically significant 32% risk reduction of death related to diabetes and 44% reduction in rate of strokes.

Effects of Tight Blood Pressure Control in the UKPDS

UK Prospective Diabetes Study Group. *BMJ*. 1998;317:703-713.
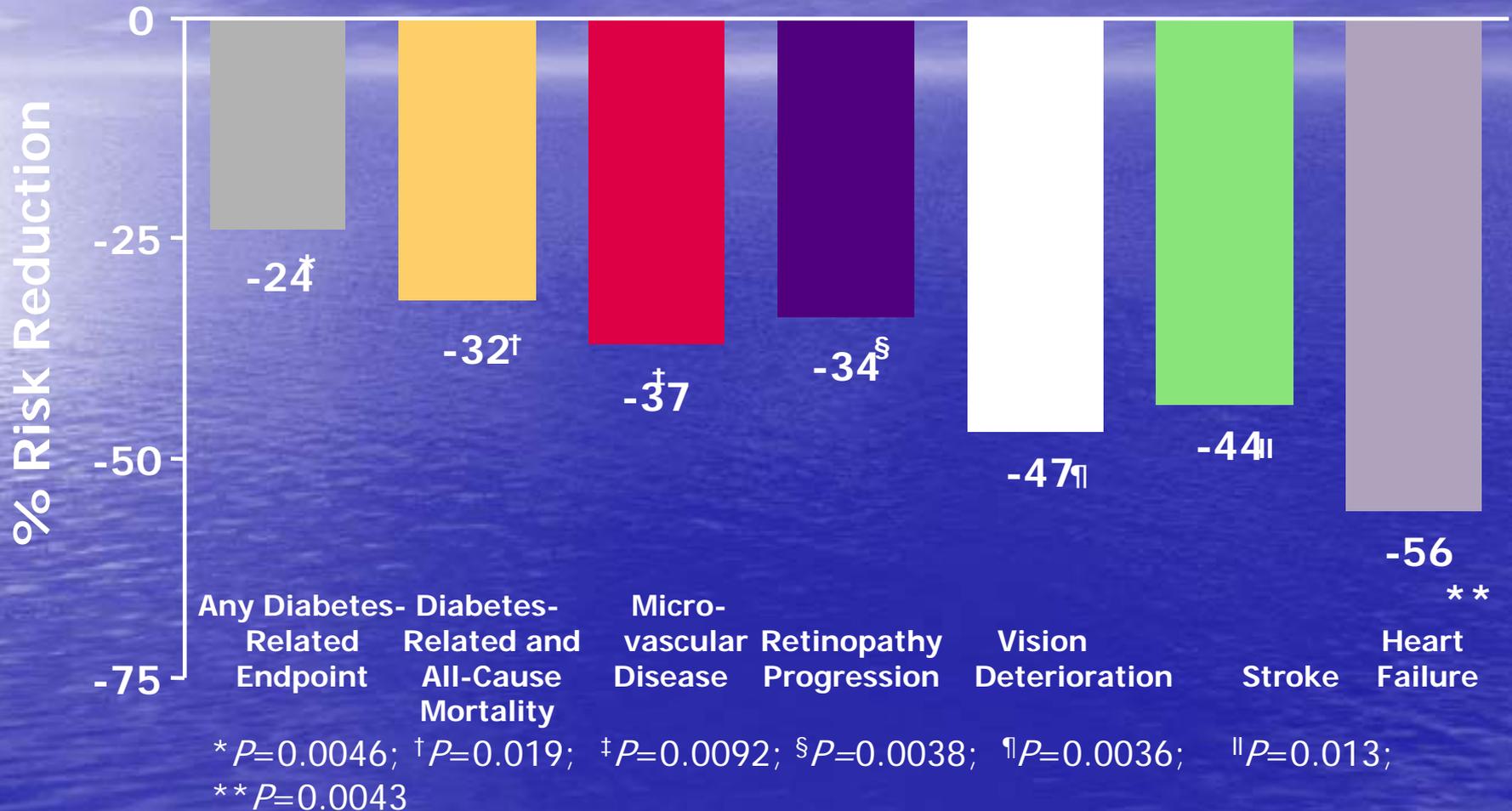
ACCORD BP Study: Kaplan Meier Analyses of Selected Outcomes

- Compared target SBP of <120 vs 130-140 mm Hg.

- Achieved BP 119/64 vs 133/70.

- Of the prespecified secondary end points, only **stroke was significantly ↓'d by intensive blood pressure rx** (HR 0.59, NNT 89 to prevent one stroke over 5 years)

N=4733

The ACCORD Study Group. N Engl J Med 2010;362:1575-1585

Hazard Risks for SBP and DBP Categories in the VADT

Table 2 HRs for separated SBP and DBP categories relative to each reference category at baseline and On-Study

	Baseline			On-Study		
	HR	95% CI	P	HR	95% CI	P
DBP (mmHg)						
70–79	Reference			Reference		
<70	1.482	1.179–1.862	<0.001	1.491	1.206–1.844	<0.001
≥80	1.030	0.825–1.287	0.79	1.049	0.814–1.351	0.71
SBP (mmHg)						
105–129	Reference			Reference		
<105	0.974	0.591–1.603	0.92	1.364	0.977–1.904	0.07
130–139	1.004	0.786–1.283	0.97	0.938	0.733–1.201	0.61
≥140	1.508	1.203–1.890	<0.001	1.469	1.157–1.867	0.002

- BP target 105-129/70-79 in all patients.
- Primary endpoint: MI, stroke, CHF, Surgery for vascular disease, inoperable CAD, amputation for gangrene, or CVD death

Anderson et al. Diabetes Care. 34:34-8, 2011.

# Treatment of Hypertension in the Elderly: The HYVET Trial

A Fatal or Nonfatal Stroke
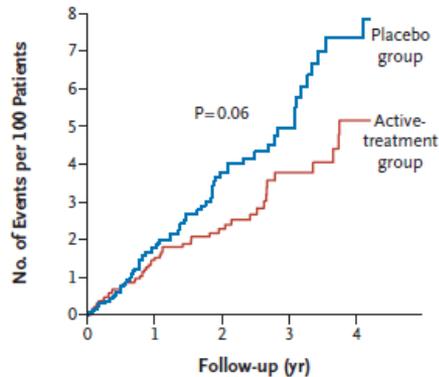
No. at Risk
Placebo group — 1912, 1484, 807, 374, 194
Active-treatment group — 1933, 1557, 873, 417, 229

B Death from Any Cause
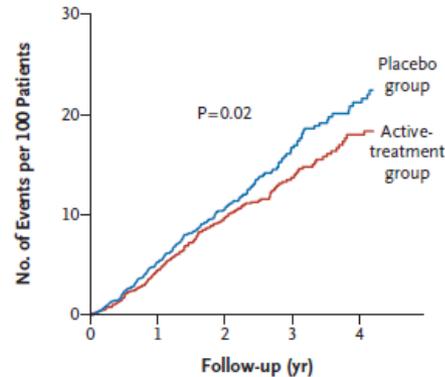
No. at Risk
Placebo group — 1912, 1492, 814, 379, 202
Active-treatment group — 1933, 1565, 877, 420, 231

Heart failure
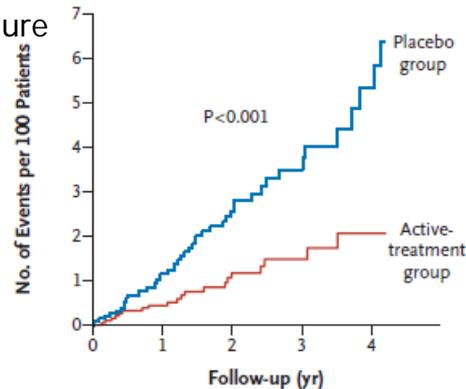
No. at Risk
Placebo group — 1912, 1480, 794, 367, 188
Active-treatment group — 1933, 1559, 872, 416, 228

Rx of HTN in pts >80 yrs old
- 3,845 >pts w/ SBP 160-199 mm Hg.
- Rx'd to standing SBP goal of 140 mm Hg.
- Started w/ Indapamide SR 1.5 mg daily, but could add Perindopril

Marked ↓ in complications:
- 30% ↓ in fatal and non-fatal CVA
- 39% ↓ in fatal CVA
- 23% ↓ in CVD death
- 64% ↓ in CHF

Recommend:
→Check BP in most upright functional position with goal SBP in 130-140 range.

→Avoid overly aggressive rx due to ↑'d risk (J-shaped curve)

Beckett NS et al. NEJM 358:1887-98, 2008

Non-Glycemic Goals: HTN

- Pts w/ SBP 130-139 or DBP 80-89 should be given lifestyle treatment for max 3 mos, then drug rx.
- Pts w/ SBP>140 or DBP>90 should be started on drug rx concurrent with lifestyle therapy.
- Initial drug rx should be w/ and ACE-I or ARB (x during pregnancy).   If these do not get the BP to goal, a diuretic (ADVANCE) or calcium channel blocker (ACCOMPLISH) should be added
  - Thiazide with normal renal fxn.
  - Lasix if eGFR <30 ml/min.
  - ASCOT Trial:
    - Black patients respond less well to atenolol and ACE-I
    - May consider different drug choices based upon ethnicity
- Multi-drug therapy is usually needed.

Once again, BP goals should be individualized.

Gupta AK, Poulter NR, Dobson J, et al. Am J Hypertens 23:1023-30, 2010

# Non-Glycemic Goals: Lipids

- Primary goal is LDL < 100 mg/dl (NCEP III$\rightarrow$ Diabetes is a CAD risk equivalent).
    - Lowering LDL is assoc'd with ↓'d cardiovascular events.
    - Rx with statin, regardless of baseline LDL, in diabetics >40 years old with one additional CVD risk factor (HPS).
        - May consider rx to Apo B goal of <90 mg/dl
    - If cannot get LDL to goal with statin rx, an alternative goal is to **reduce LDL by 30-40% from baseline** (HPS)
    - In patients with CAD and DM, may consider aiming for LDL<70 mg/dl by using high dose statin therapy.
        - May consider rx to Apo B goal of <80 mg/dl.
- Secondary goal is HDL >40 mg/dl in men, >50 mg/dl in women, and TG's<150 mg/dl.
    - Decreasing TG's and increasing HDL w/ a fibrate are assoc'd with ↓'d CV events in pts with known CAD.

Probability of Death from Coronary Heart Disease T2DM and Nondiabetic Subjects
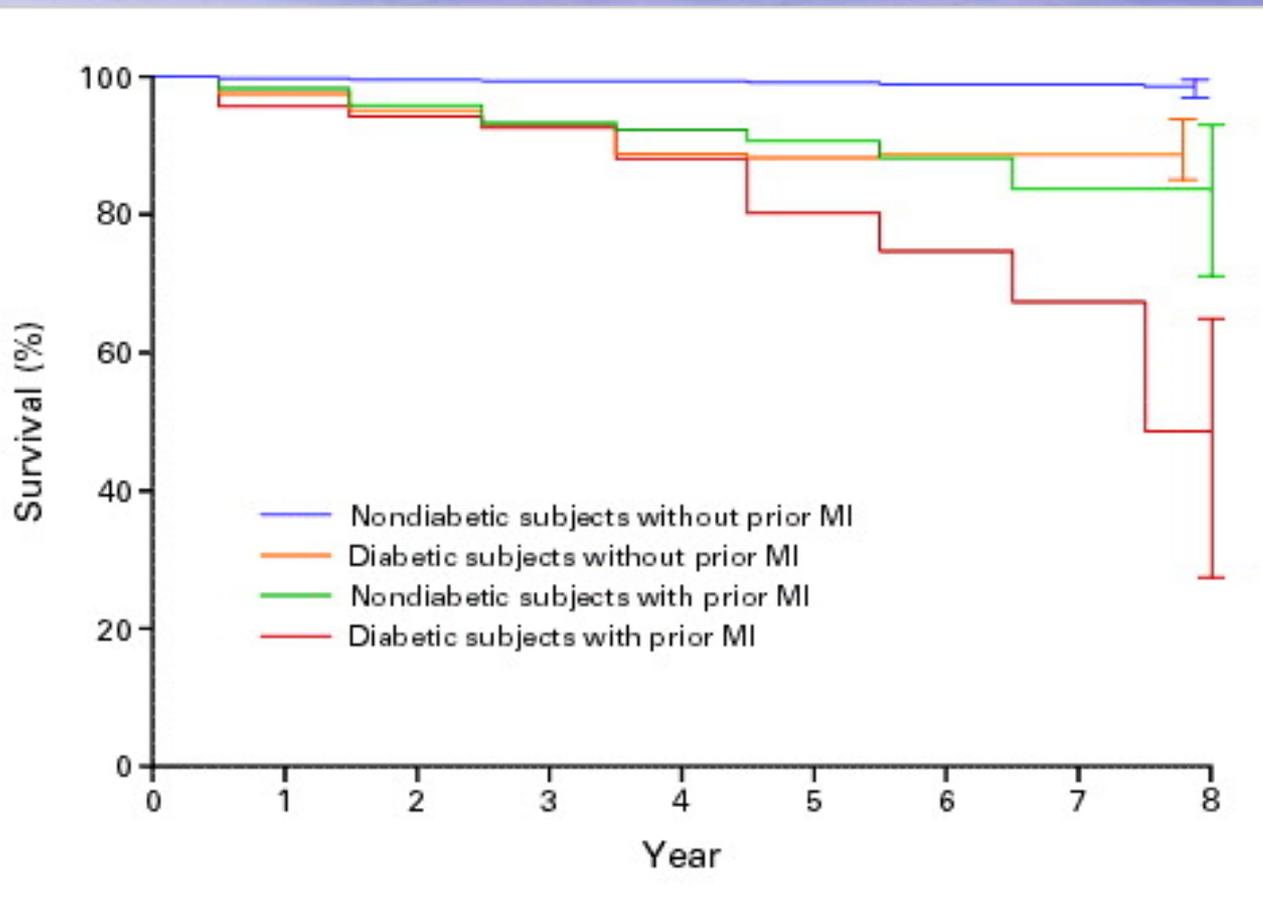
N=1371 Nondiabetics
N= 1059 Diabetics

Nondiabetic subjects without prior MI
Diabetic subjects without prior MI
Nondiabetic subjects with prior MI
Diabetic subjects with prior MI

Haffner et al. New Eng J Med 339:229-34, 1998

4S: CAD Event Reduction with Simvastatin in Subgroup of Patients With Diabetes

Pyörälä K et al. *Diabetes Care* 20:614-620, 1997.
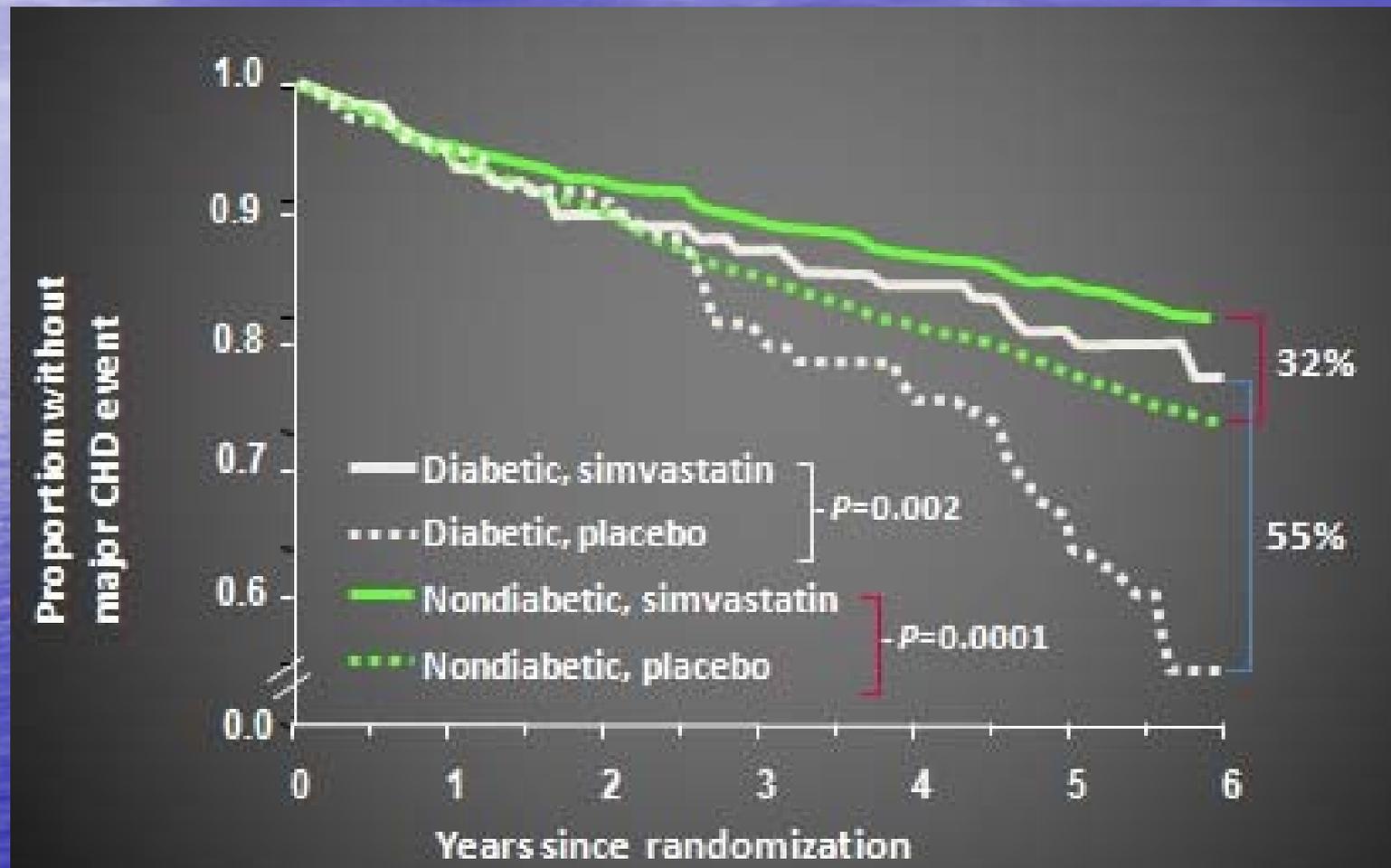
Reduction in 10-year risk of major CVD endpoints

Table 11—*Reduction in 10-year risk of major CVD endpoints (CHD death/non-fatal MI) in major statin trials, or substudies of major trials, in diabetic subjects* (n = 16,032)

Study (ref.)	CVD	Statin dose and comparator	Risk reduction (%)	Relative risk reduction (%)	Absolute risk reduction (%)	LDL cholesterol reduction (mg/dl)	LDL cholesterol reduction (%)
4S-DM (215)	2°	Simvastatin 20–40 mg vs. placebo	85.7 to 43.2	50	42.5	186 to 119	36
ASPEN 2° (220)	2°	Atorvastatin 10 mg vs. placebo	39.5 to 24.5	34	15	112 to 79	29
HPS-DM (216)	2°	Simvastatin 40 mg vs. placebo	43.8 to 36.3	17	7.5	123 to 84	31
CARE-DM (217)	2°	Pravastatin 40 mg vs. placebo	40.8 to 35.4	13	5.4	136 to 99	27
TNT-DM (218)	2°	Atorvastatin 80 mg vs. 10 mg	26.3 to 21.6	18	4.7	99 to 77	22
HPS-DM (216)	1°	Simvastatin 40 mg vs. placebo	17.5 to 11.5	34	6.0	124 to 86	31
CARDS (221)	1°	Atorvastatin 10 mg vs. placebo	11.5 to 7.5	35	4	118 to 71	40
ASPEN 1° (220)	1°	Atorvastatin 10 mg vs. placebo	9.8 to 7.9	19	1.9	114 to 80	30
ASCOT-DM (219)	1°	Atorvastatin 10 mg vs. placebo	11.1 to 10.2	8	0.9	125 to 82	34

- Reduction in hard CVD outcomes (death and nonfatal MI) are most clearly seen in diabetic subjects with high baseline CVD risk.

- Overall the benefits of statin therapy in people with diabetes at moderate or high risk for CVD are convincing.

ADA. Diabetes Care. 34:S11-S61, 2011.

ACCORD Lipid Study: Kaplan Meier Analyses of Selected Outcomes

N=5518

No benefit of addition of fenofibrate to statin

ACCORD Lipid Trial: Hazard Ratios for 1º Outcome in Prespecified Subgroups
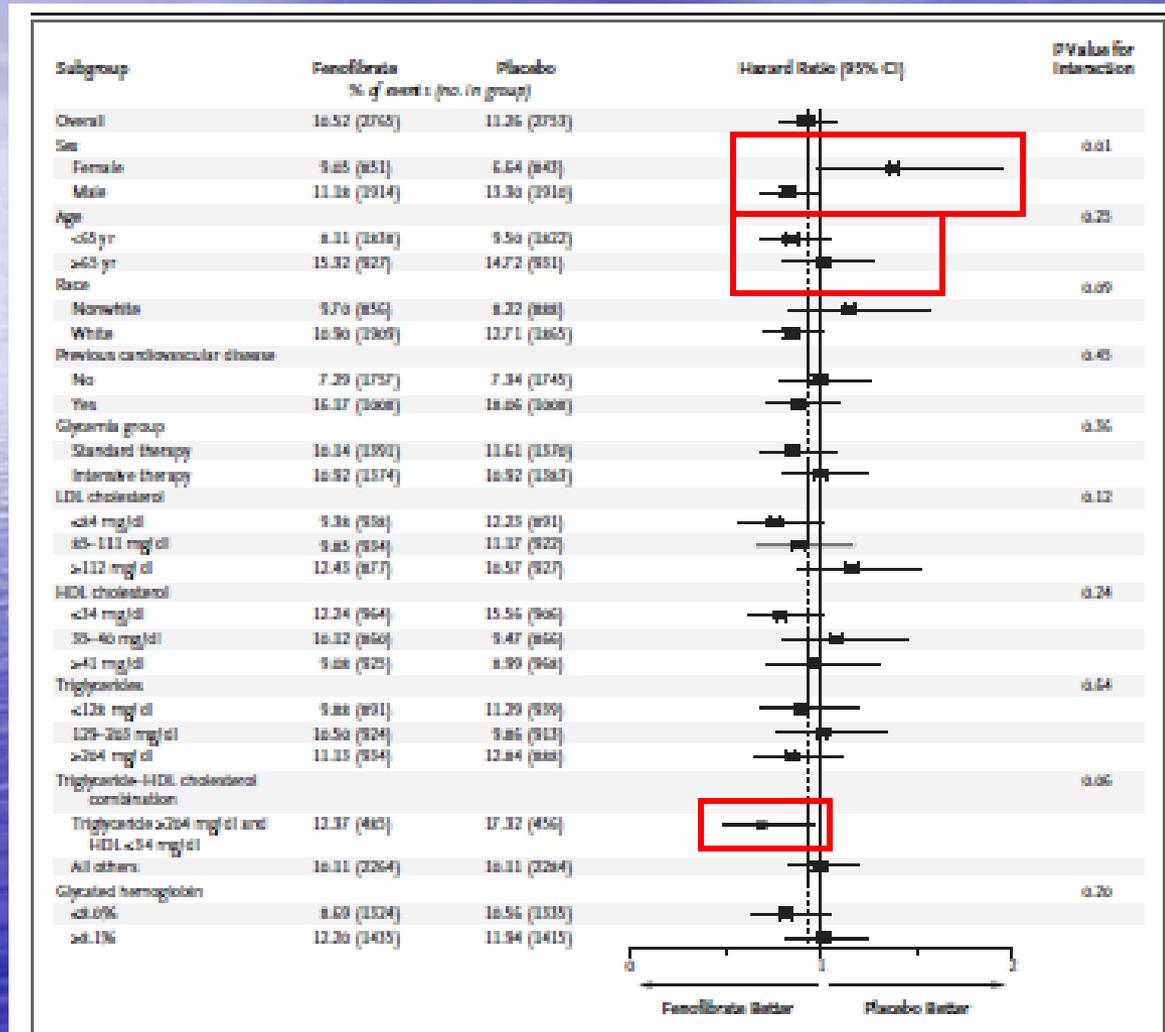
- Subgroup analysis suggests that there is:

1. A trend towards benefit w/add'n of fenofibrate in men, but ↑'d risk in women

2. A trend towards benefit if TG> 204 & HDL<34

3. No difference if young or old

The ACCORD Study Group. N Engl J Med 2010; 362:1563-1574

Non-Glycemic Goals: Lipids

- Treatment includes:
  - Diet (+/- weight loss)/ Exercise
  - Medication:
    - Statins are first line rx for LDL lowering.
    - Therapy w/ gemfibrozil in pts w/ low HDL decreases CVD rates.
    - Combo rx w/ statins and fibrates (or niacin) requires care to minimize myositis.
    - ACCORD trial did not show benefit of combo therapy of statin plus fenofibrate except in those with highest TG's (>204 mg/dl) and lowest HDL (<34 mg/dl)

The ACCORD Study Group N Engl J Med 362:1563, 2010

Non-Glycemic Targets: Aspirin Use

- Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous myocardial infarction or stroke (secondary prevention).

- Its use in primary prevention among patients with no history of cardiovascular events is more controversial.

- Main adverse risk of GI bleeding.

- 2 recent RCT addressing primary prevention in patients with diabetes.

JPAD

Figure 2. Total Percentage of Atherosclerotic Events According to Treatment Group

Log-rank P = .16
HR, 0.80 (95% CI, 0.58-1.10)

Legend: Nonaspirin, Aspirin

No. at risk						
Nonaspirin	1277	1220	1165	1117	813	135
Aspirin	1262	1210	1159	1095	806	140
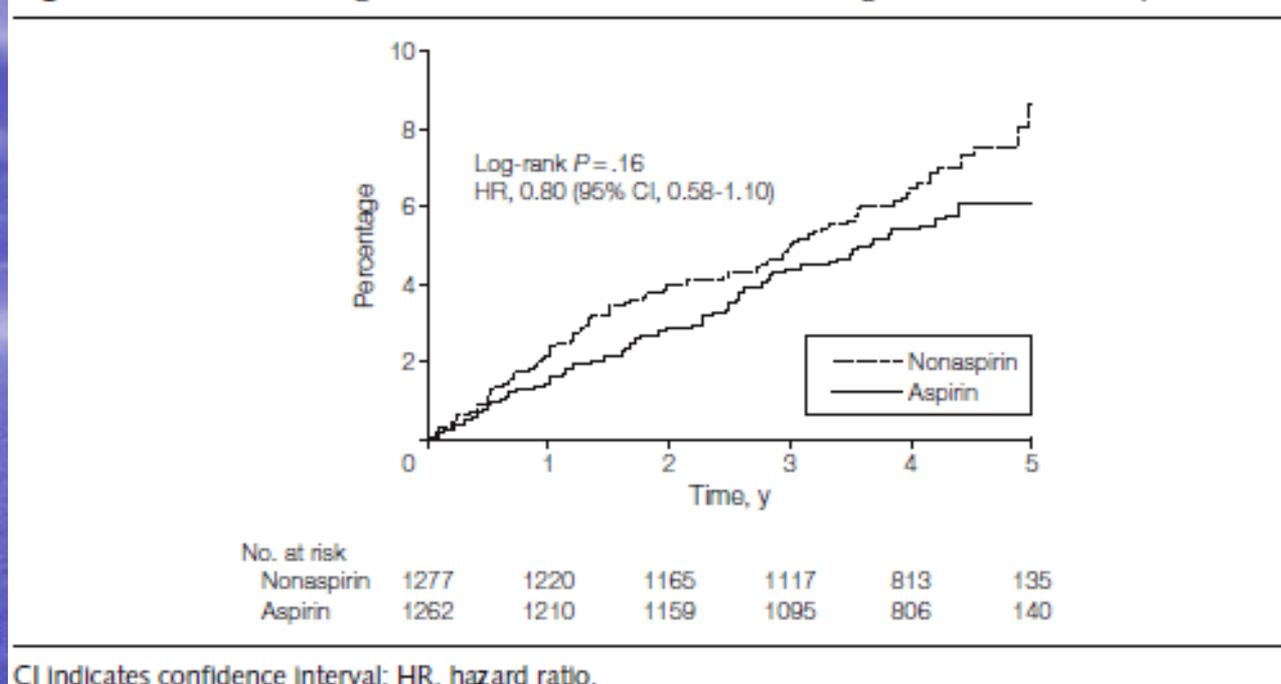
CI indicates confidence interval; HR, hazard ratio.

- RCT to evaluate effects of low dose aspirin on primary prevention of CV events in pts with t2DM (mean age at onset of study 65).

- Primary end points were fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease.

- 68 /154 events occurred in aspirin group vs 86 /154 in non aspirin group. HR 0.80; 95% CI 0.58-1.10.

- Concluded that low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.

Ogawa. JAMA. 2300:2134-2141, 2008.

The prevention of progression of arterial disease and diabetes (POPADAD) trial

RCT in pts with DM and asymptomatic PVD.

Randomized to:
  ASA100mg + antioxidant
  ASA + placebo
  Placebo + antioxidant
  Placebo + placebo

Primary outcome: 1) death from CHD or stroke, non-fatal MI or stroke, or amputation above the ankle for critical limb ischemia; and 2) death from CHD or stroke.

No signif ↓ in CVD end points were found with aspirin in primary prevention.

43 deaths from CHD or stroke in the aspirin group compared with 35 in the no aspirin group (RR 1.23 [95% CI 0.79-1.93]).

Mean age 60 at start of trial, w/ 6+ yrs f/u

Numbers at risk for composite end point

Aspirin	638	599	543	399	48
No aspirin	638	590	534	381	48

Belch. BMJ 337:a1840, 2008.
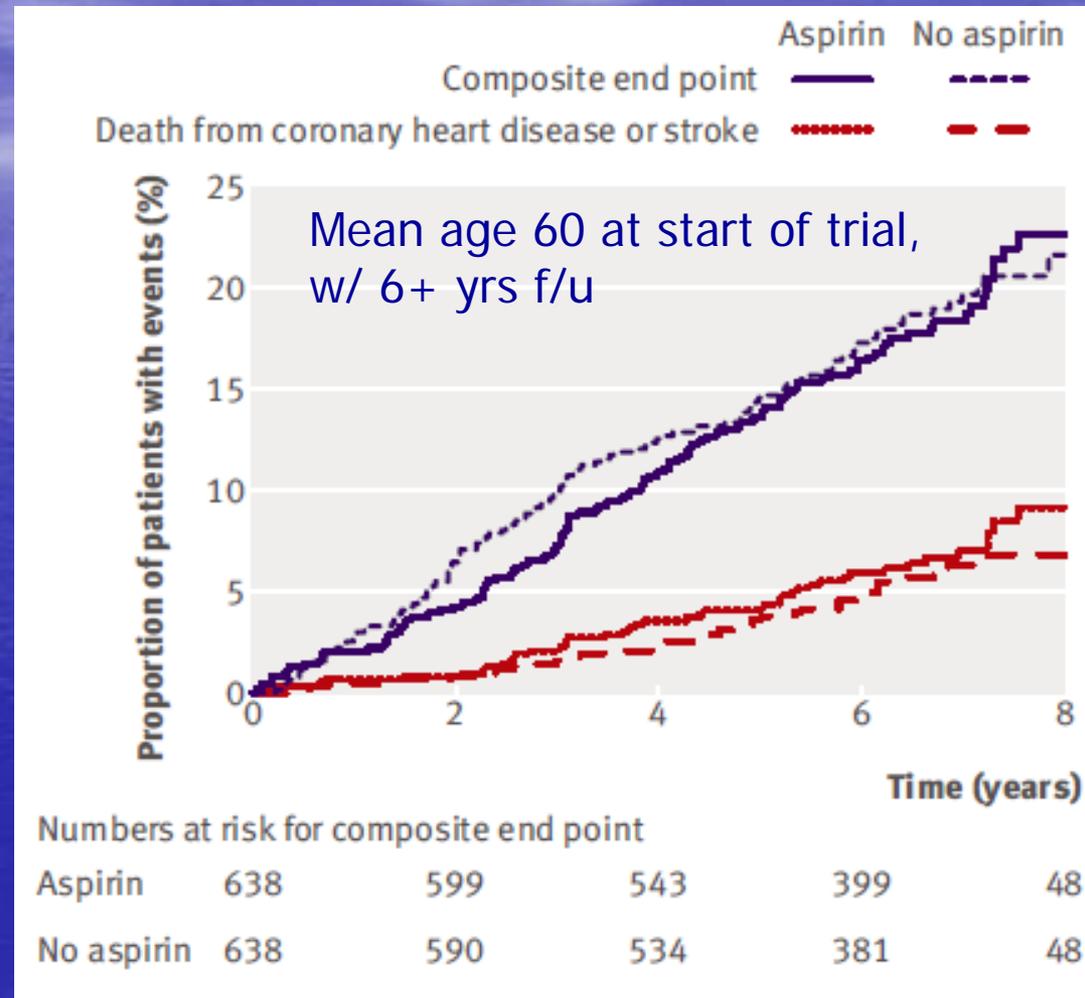
Non-Glycemic Goals: Aspirin use

- Use aspirin therapy (75-162 mg/d) in all diabetics w/ macrovascular disease
  - May consider clopidigrel as alternative in ASA intolerant pts
  - May consider combo ASA + clopidigrel rx for one year after acute coronary syndrome

- Consider ASA rx for 1° prevention of CAD in diabetics with increased CVD risk (10 year risk >10%) (new 2010)
  - Men >50 or women >60 with one additional CVD risk factor

Conclusions

- The standards of care dictate:
  - A1C <7%
  - BP<130/80
  - Cholesterol with LDL <100 (consider <70)

- In our high risk, frail, or oldest patients, perhaps we should aim for a modified A1C goal (<7.5 or 8%).

- Similarly, if we cannot get the SBP to <130 mm Hg without lowering the DBP to <70 mm Hg, perhaps we need to modify our SBP goal to <140 mm Hg.

- Should benefit from LDL control, smoking cessation and ASA rx, always balancing rx with risks