Type 2 Diabetes Update

04/02/14

Disclosure

GSK research support

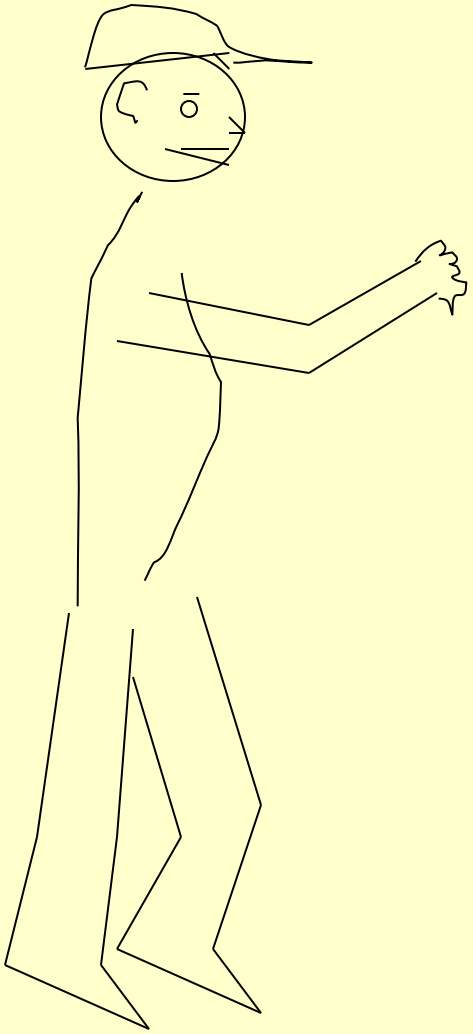
Objectives for this talk

- Brief discussion of pathogenesis of type 2 diabetes
- Treatment rationale and targets
- Updated approaches to glycemic control, BP and lipids in type 2 diabetes
- New on the horizon

What goes wrong in type 2 diabetes?

- Insulin resistance
- Impaired (not absent) ability to secrete insulin

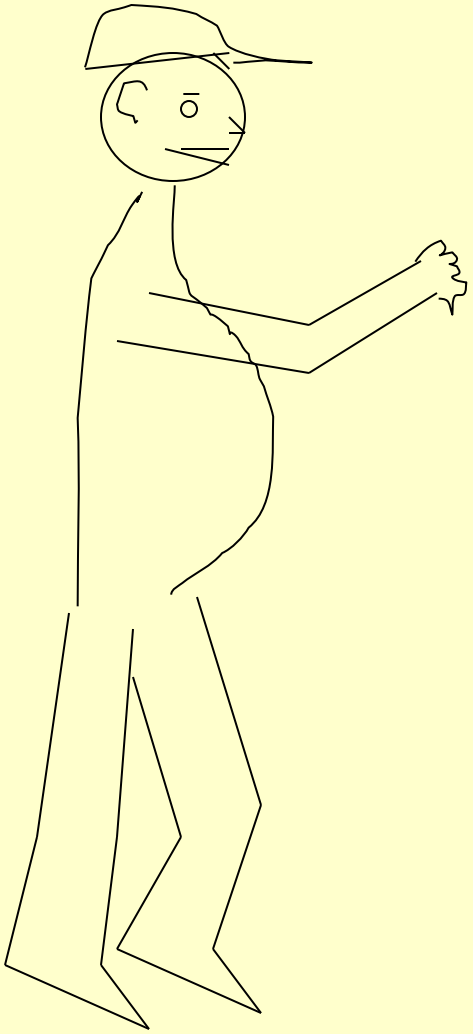
Normal



Fasting AM blood tests

Age	Insulin (U/ml)	Glucose (mg/100ml)
35	12	90

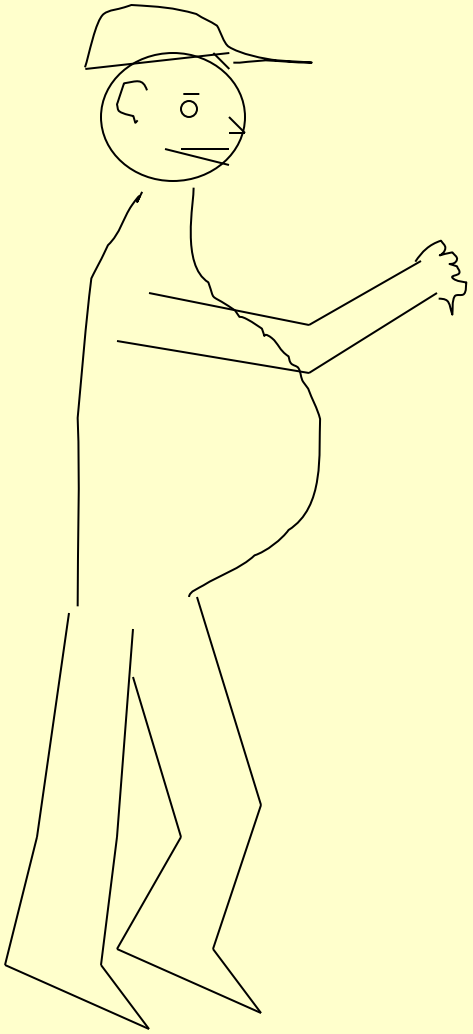
Pre-diabetes (impaired fasting glucose)



Fasting AM blood tests

Age	Insulin (U/ml)	Glucose (mg/100ml)
35	12	90
38	22	112

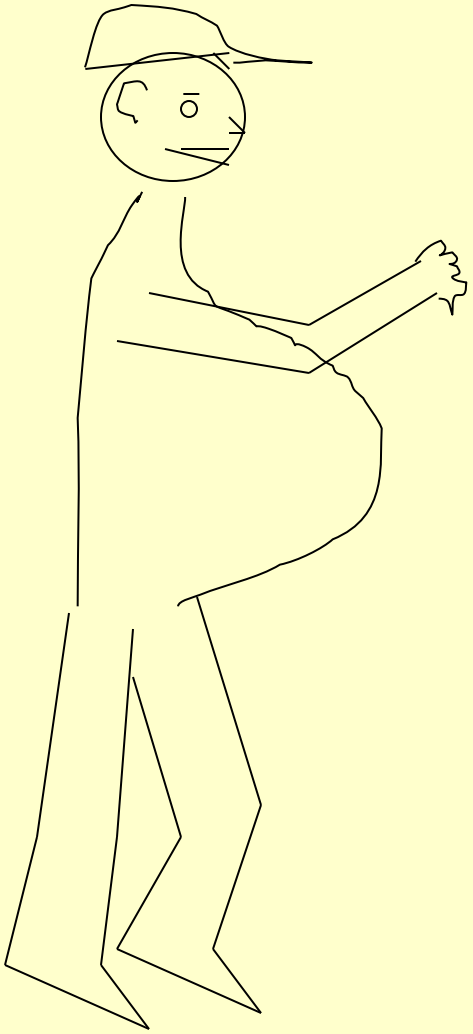
Early type 2 diabetes



Fasting AM blood tests

Age	Insulin (U/ml)	Glucose (mg/100ml)
35	12	90
38	22	112
43	29	128

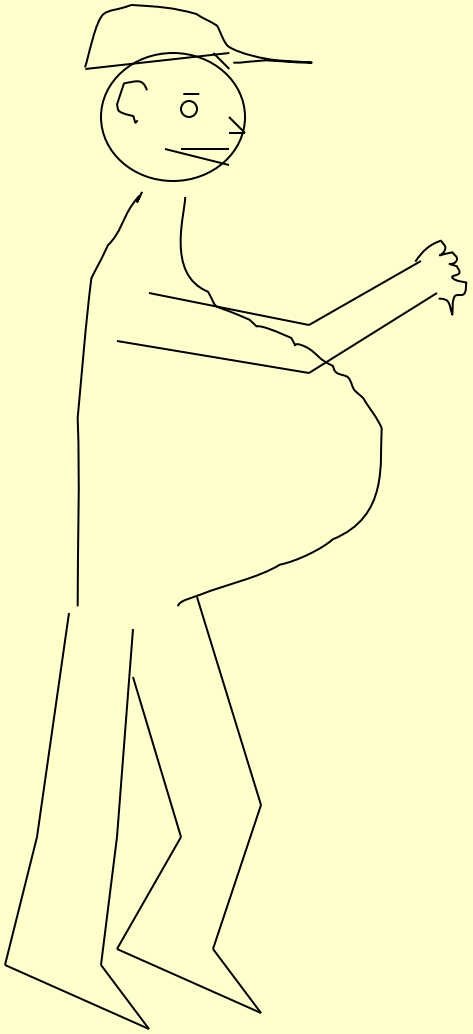
Type 2 diabetes



Fasting AM blood tests

Age	Insulin (U/ml)	Glucose (mg/100ml)
35	12	90
38	22	112
43	29	128
46	40	147

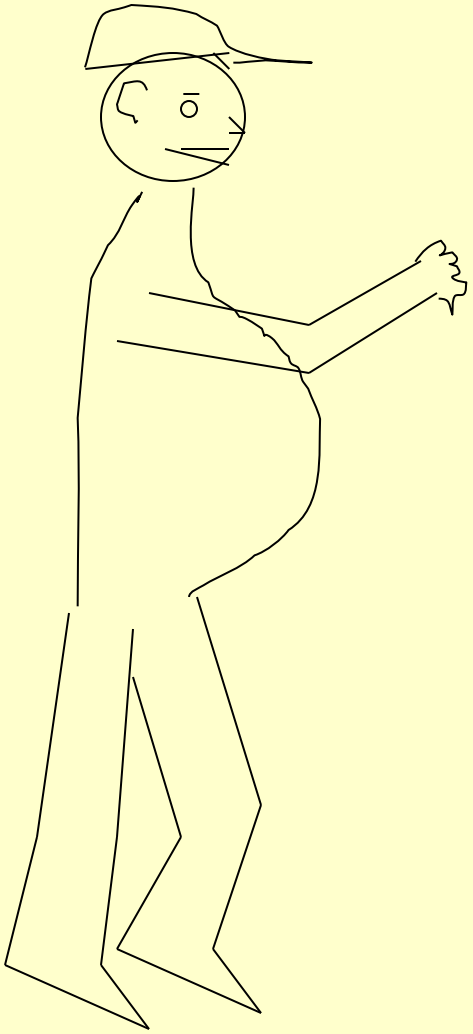
Worse type 2 diabetes



Fasting AM blood tests

Age	Insulin (U/ml)	Glucose (mg/100ml)
35	12	90
38	22	112
43	29	128
46	40	147
48	26	218

Worse type 2 diabetes with symptoms



Fasting AM blood tests

Age	Insulin (U/ml)	Glucose (mg/100ml)
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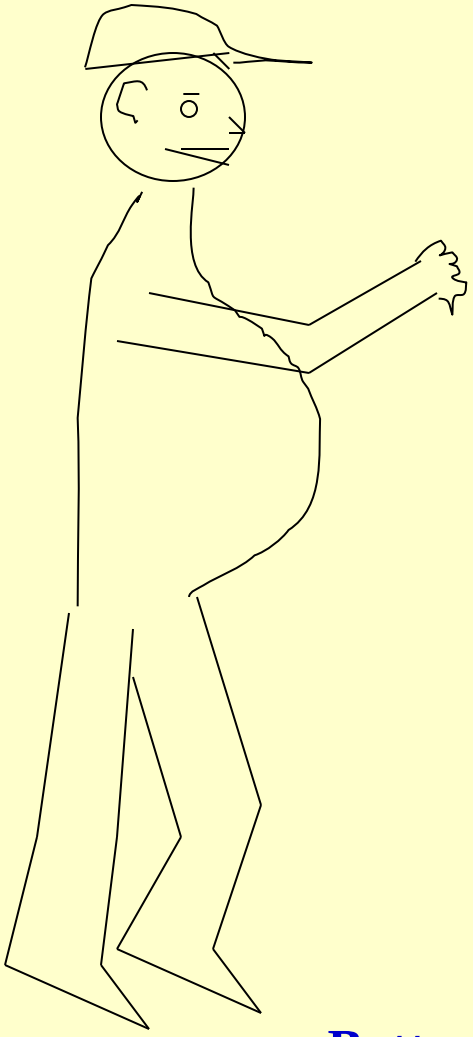
52	14	357

Worse type 2 diabetes with symptoms



Fasting AM blood tests

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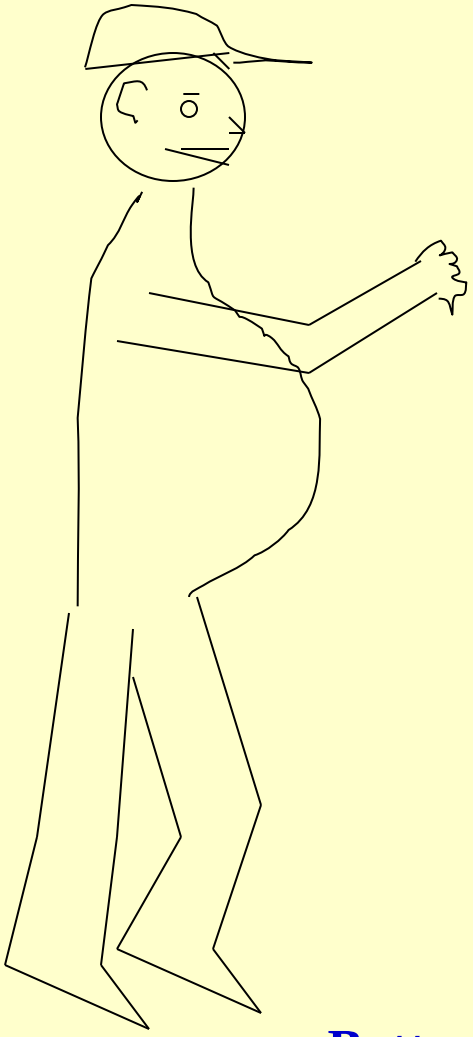
Bottom line: Type 2 diabetes is a progressive disorder

Worse type 2 diabetes with symptoms



Fasting AM blood tests

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Bottom line: Type 2 diabetes is a progressive disorder

Need to consider therapeutic implications of this.

How do we prevent diabetes or stop the progression of early type 2 diabetes?

- Patients with A1c 5.7–6.4% should be targeted to weight loss of 7% and at least moderate activity (e.g. walking) for at least 150 min/week.
  - Lifestyle change effective as long as 20 years in Da Qing study
  - 7% weigh loss based on US prevention trial (DPP2)
- Metformin therapy for prevention of type 2 diabetes may be considered in those with IGT , IFG, or an A1C 5.7–6.4%
  - Metformin may be as effective as lifestyle if BMI > 35
  - Not better than placebo in older subjects (> age 60)
- Annual monitoring for the development of diabetes
- a-glucosidase inhibitors, orlistat, thiazolidinediones (TZDs), glargine insulin have been shown to decrease incident diabetes to various degrees
- TZDs may prevent the onset of diabetes in subjects at risk and prevent worsening of early diabetes
  - But associated with worrisome adverse effects
  - Effects over long term od concern
- Incretin therapy increases islet mass in rodents
- GRADE study ongoing

Diabetes Prevention Program. NEJM 2002;346:393

DREAM Trial. Lancet 2006;368:1096–1105

STOPNIDDM trial. Lancet 2002; 359:20727

Da Qing IGT and Diabetes Study. Diabetes Care 1997;20:537

Finnish Diabetes Prevention Study. NEJM 2001;344:1343

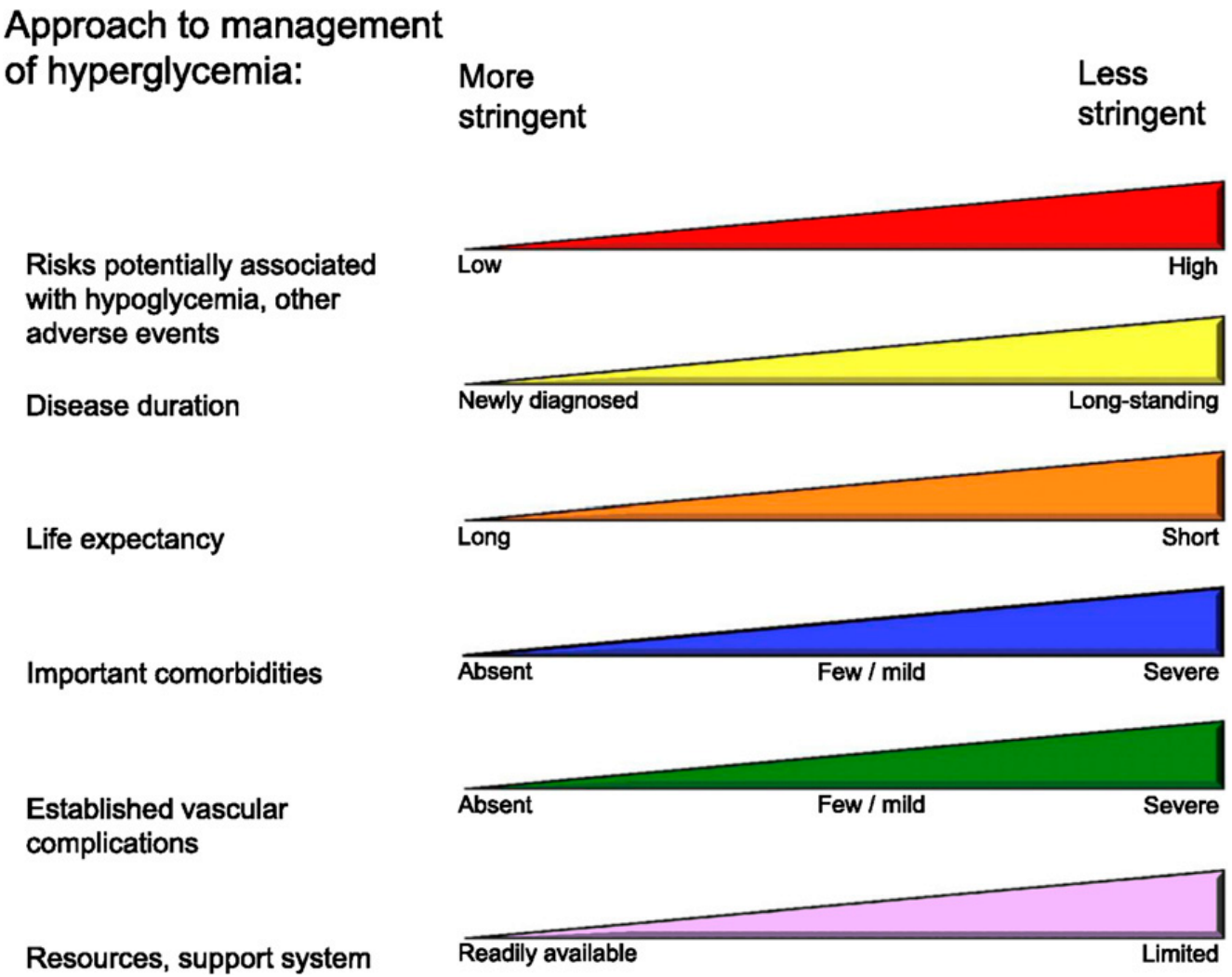
SHAI et al: NEJM 2008;359:229-41.

NEJM 2012 Jul 26;367(4):319-28

ADA Treatment Goals for Glycemic Control

HgbA1c (%)	< 7.0% (normal 4.0 -6.0)
Selected Individuals	As close to normal as possible without significant hypoglycemia
Preprandial capillary plasma glucose	70-130 mg/100 ml
Peak postprandial plasma glucose	< 180 mg/100 ml
Severe lows, limited life expectancy, co-morbidity, children, long hx DM with minimal complications, hypoglycemic unawareness	Less stringent (e.g. HbA1c < 8.0)

American Diabetes Association: Standards of Care (*Diabetes Care* 37, Suppl. 1, Jan. 2014) Online www.diabetes.org/



Beigi et. al. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. Ann Intern Med 2011;154: 554–559

Some important diabetes treatment trials

Glycemic control and macrovascular disease in ACCORD, ADVANCE, and VADT

Large randomized trials directed at the effect of glycemic control on cardiovascular risk in type 2 diabetes in participants at **high risk for vascular events.**

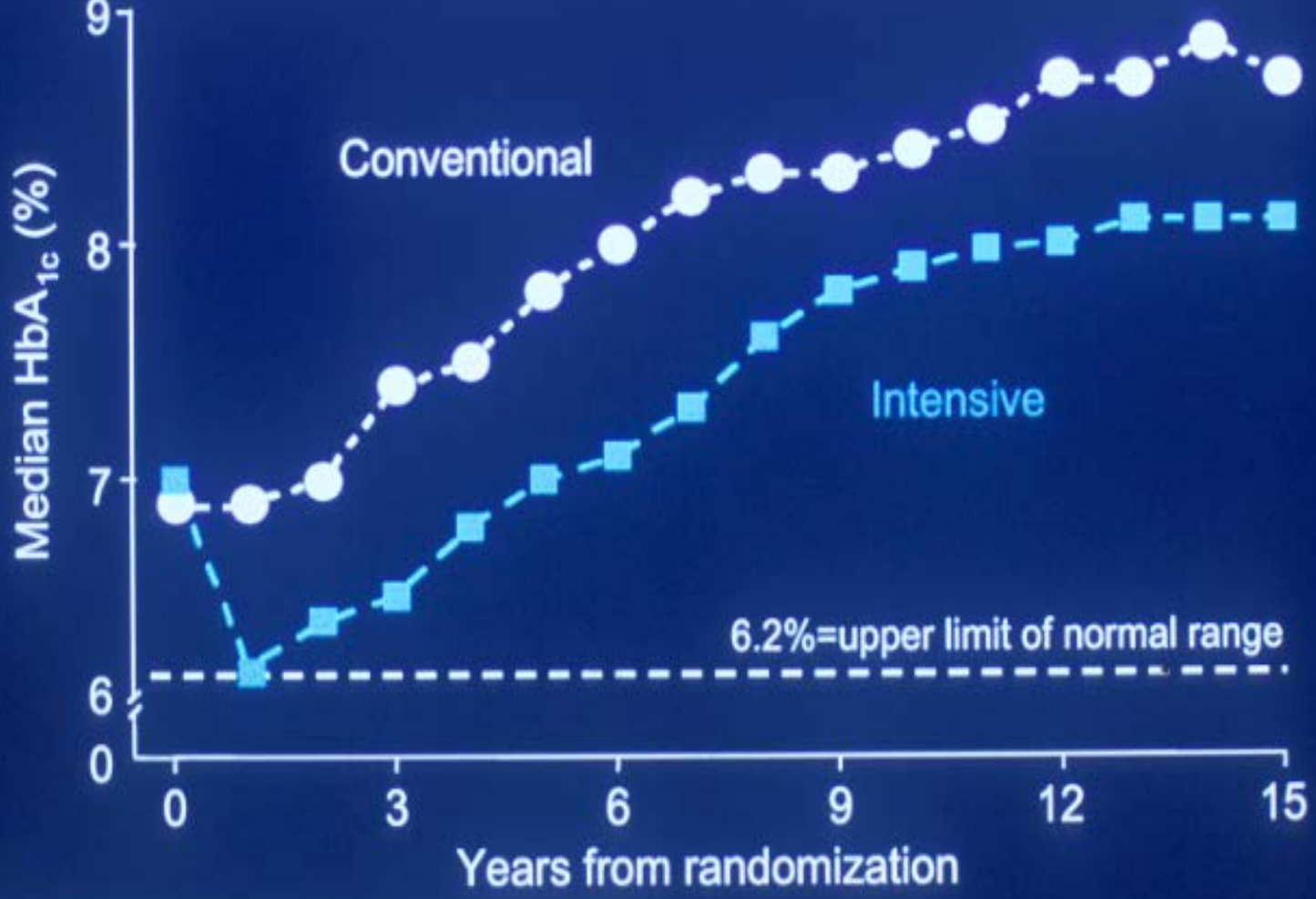
	ACCORD	ADVANCE	VADT
# subjects	10,251	11,140	1,791
Average age	62	66	60
A1c control	6.4 vs 7.5 %	6.4 vs 7.0 %	6.9 vs 8.4 %
Primary results	No decrease in cardiovascular events. Increased cardiovascular mortality with intensive Rx	No decrease in cardiovascular risk Reduced risk of nephropathy	No decrease in cardiovascular risk

Data from DCCT/EDIC and UKPDS

- DCCT
  - Nine years after DCCT, incidence of CV events was reduced 57% in former intensive patients
  - Younger age at onset (13-39) with no known CVD
- UKPDS
  - 10 years after UKPDS, follow-up showed at 15% decrease in MI in intense treatment group initially on sulfonylurea or insulin; and 33% in more obese treated initially with metformin.
  - Mortality also reduced 13 and 27% respectively

Nathan DM, et. al. *NEJM* 353:2643, 2005
Holman RR, et. al. *NEJM* 359, 1577, 2008

UKPDS: Effects of Treatment on HbA_{1c} in Glucose Control Study



UKPDS Group. *Lancet*. 1998;352:837-853.

Implications of major Rx trials

- Target of 7.0 % HbA1c still considered valid
- More aggressive treatment may need to be implemented early with cautious approach with more advanced diabetes and cardiovascular disease
- Overly persistent efforts to lower glucose in patients at risk for macrovascular events may not be warranted
- Strong evidence for microvascular benefits of glucose control
- Treat BP, lipids, smoking cessation, nutrition and lifestyle
- Type 3 DM worsens with time. Can we prevent this?

Drug therapy for type 2 diabetes

Metformin

- Near universal acceptance as initial drug therapy in absence of contraindication (e.g. renal failure, hypoxia)
- Decrease hepatic glucose release and increases muscle glucose uptake
- Beneficial effects on weight and lipids
- Lack of hypoglycemia when used alone
- Generic drug with long history of use worldwide

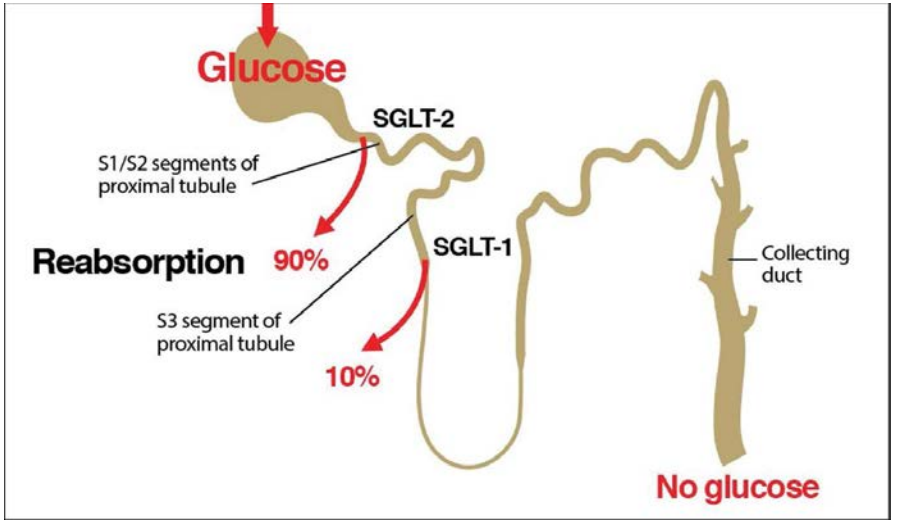
Drugs for type 2 diabetes beyond Metformin

Drug	Actions	Mechanism	Advantages	Disadvantages
Sulfonylureas glipizide glimepiride glyburide	↑ β-cell insulin secretion	Potassium channels	Well tolerated Low cost	Hypoglycemia Weight gain Low durability May reduce myocardial ischemic reconditioning
GLP-1 agonists exenatide liraglutide	↑ insulin secretion ↓ glucagon ↓ gastric emptying ↑ satiety	Activate GLP-1 receptors in β-cell, and nervous system	Weight loss Possible ↑β-cell mass/function Little hypoglycemia	Nausea, vomiting, diarrhea Acute pancreatitis risk ? Medullary thyroid tumors Long term safety?
DPP-4 inhibitors sitagliptin vildagliptin saxagliptin linagliptin	↑ insulin secretion ↓ glucagon	Prevent GLP-1 break-down ↑ endogenous GLP-1	Little or no hypoglycemia Weight neutral	Urticaria, angioedema Pancreatitis Long term safety?
Insulin	Well known	Well Known	Effective, “natural”	Hypoglycemia, Weight gain, may need multiple injections and large dose

Drugs for type 2 diabetes beyond Metformin (continued)

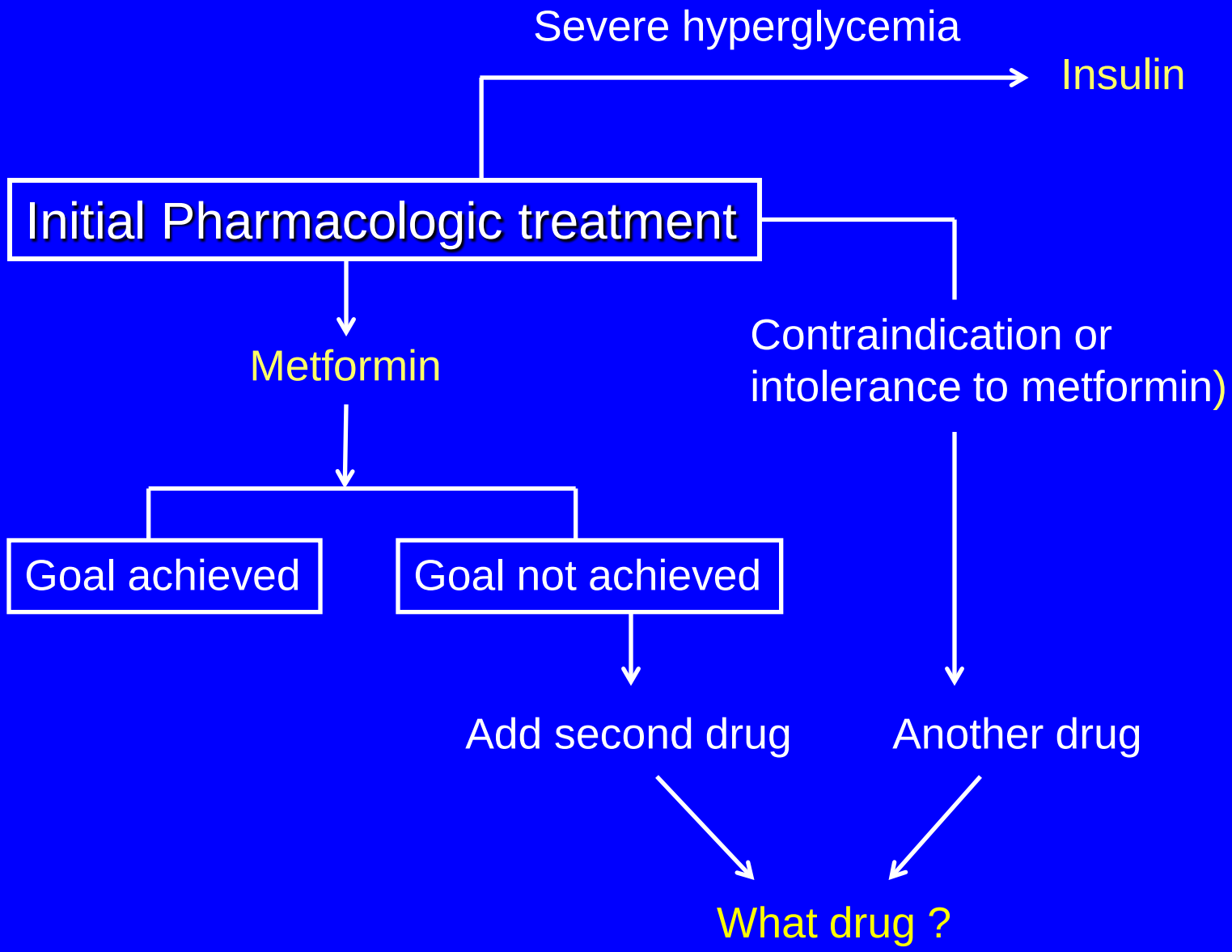
Drug	Actions	Mechanism	Advantages	Disadvantages
Canagliflozin Dapaglifloxin	Increase urine glucose excretion	Inhibits hSGLT2 (sodium/glucose cotransporter) in renal tubules	Hypoglycemia very unusual Familial renal glycosuria is a benign disease	UTIs, vulvovaginitis, balanitis: mostly mild, rarely limit therapy Osmotic diuresis Dehydration, Hypotension, Increased hepatic glucose output

Pending are postmarketing studies: a cardiovascular outcomes trial; an enhanced pharmacovigilance program to monitor for malignancies, pancreatitis, hypersensitivity reactions, photosensitivity reactions, liver abnormalities, and adverse pregnancy outcomes; a bone safety study; and two pediatric studies under the Pediatric Research Equity Act



Drugs for type 2 diabetes beyond metformin (less often used)

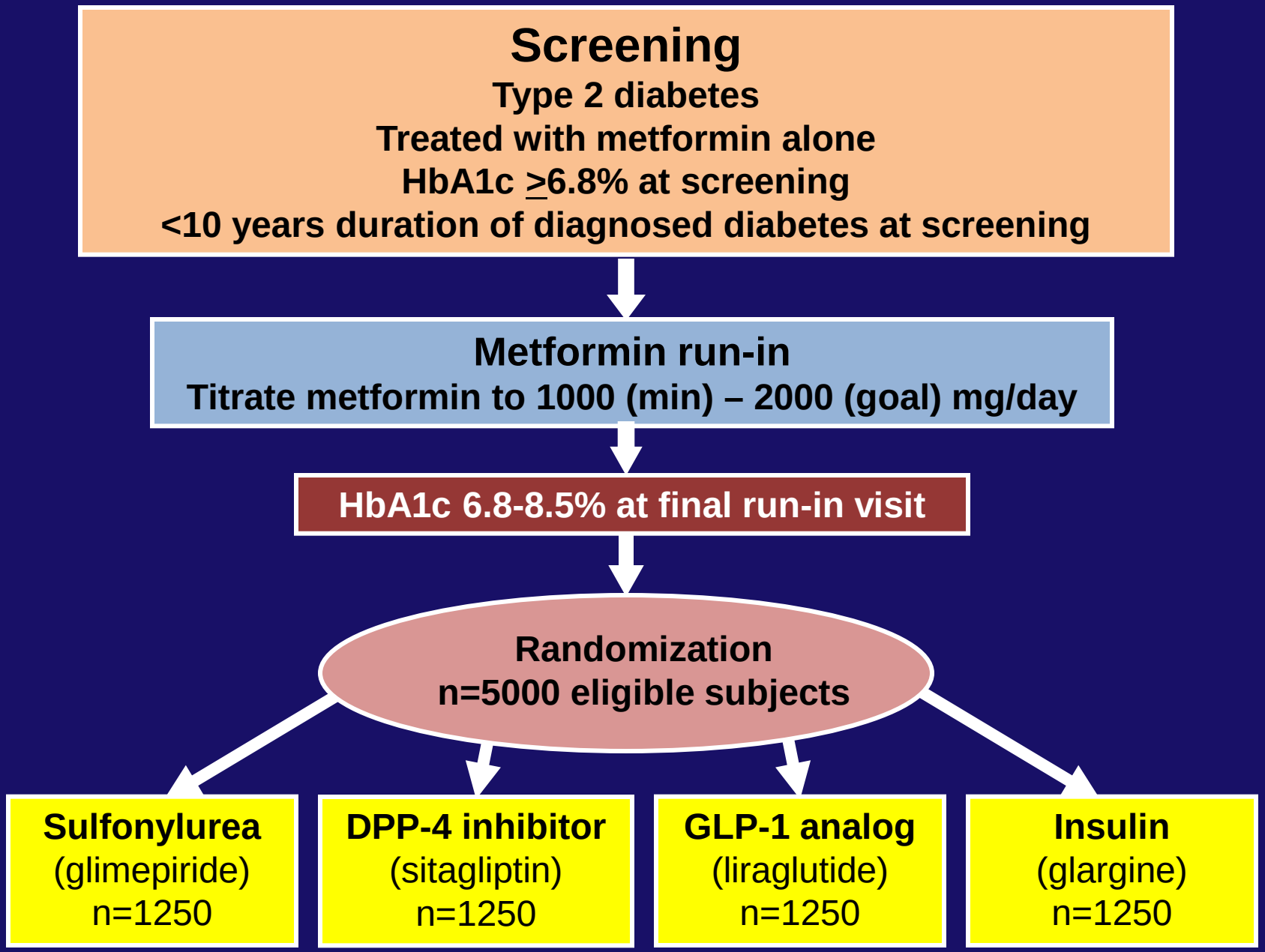
Drug	Actions	Mechanism	Advantages	Disadvantages
Meglitinides repaglinide nateglinide	↑ β-cell insulin secretion	Potassium channels	Action focused on time of food intake	Not very effective Other concerns shared with sulfonylureas
Thiazolidine-diones (TZDs) pioglitazone rosiglitazone	↑ Insulin sensitivity mainly in muscle	Activate PPAR-γ	Pioglit ↑ HDL, ↓ TG No hypoglycemia	Any use is questionable Wt gain, edema, CHF, ↑ LDL, bone fractures, bladder CA Rosiglit ↑ CV events
α-glucosidase Inhibitors acarbose miglitol	↓ intestinal glucose absorption	Inhibit α-glucosidase	Nonsystemic No hypoglycemia	Not very effective GI gas, diarrhea
colesevelam	Unclear	Bile acid sequestrant	No hypoglycemia	Constipation, ↑ TGS ↓ absorption of meds
bromocriptine	↑ Insulin sensitivity	Hypothalamic dopaminergic effect	No hypoglycemia	Dizziness, syncope, nausea, fatigue, rhinitis, Long term safety?


Severe hyperglycemia
Insulin
Initial Pharmacologic treatment
Metformin
Contraindication or
intolerance to metformin)
Goal achieved
Goal not achieved
Add second drug
Another drug
What drug ?

Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE Study)

Overall Goal of GRADE study

To carry out an unbiased comparison of the most commonly used drugs to treat diabetes in metformin-treated patients.


Screening
Type 2 diabetes
Treated with metformin alone
HbA1c ≥6.8% at screening
<10 years duration of diagnosed diabetes at screening
Metformin run-in
Titrate metformin to 1000 (min) – 2000 (goal) mg/day
HbA1c 6.8-8.5% at final run-in visit
Randomization
n=5000 eligible subjects
Sulfonylurea
(glimepiride)
n=1250
DPP-4 inhibitor
(sitagliptin)
n=1250
GLP-1 analog
(liraglutide)
n=1250
Insulin
(glargine)
n=1250

Grade Objectives

- Comparison of the relative effects of four commonly used diabetes medications with different mechanisms of action on durability of glycemic control (i.e. prevention of worsening of the diabetic state)
  - Maintenance of metabolic control, defined as time-to-primary failure with A1c ≥7.0%, confirmed, while on maximally tolerated doses of both metformin, up to 2000 mg/d, and the assigned medication
  - Time dependent loss of insulin secretory capacity and insulin sensitivity
- CVD risk factors
- Adverse effects, tolerability and quality-of- life

Grade Problem

- Recruiting is difficult. We need your help!
- Major criteria for participation
  - On Metformin alone
  - Diabetes < 10 years
  - A1c somewhere close to range required for eligibility (6.8 to 8.5) (Can be screened even if off a bit)
- What can be done without interfering with a busy practice schedule?
  - Place brochures or poster in waiting room
  - Direct patient to brochure and/or advise to call the number listed
  - If you wish, call us yourself or have staff call
- All participants are required (per eligibility criteria) to have an ongoing relationship with a primary provider.
- We offer recognition as a research partner.

Insulin

Advantages

- Most effective
- “Natural”
- Least expensive
- Once daily for many patients
- Less weight gain than TZD
- Essentially no side effects apart from hypoglycemia

Disadvantages

- Weight gain
- Injections

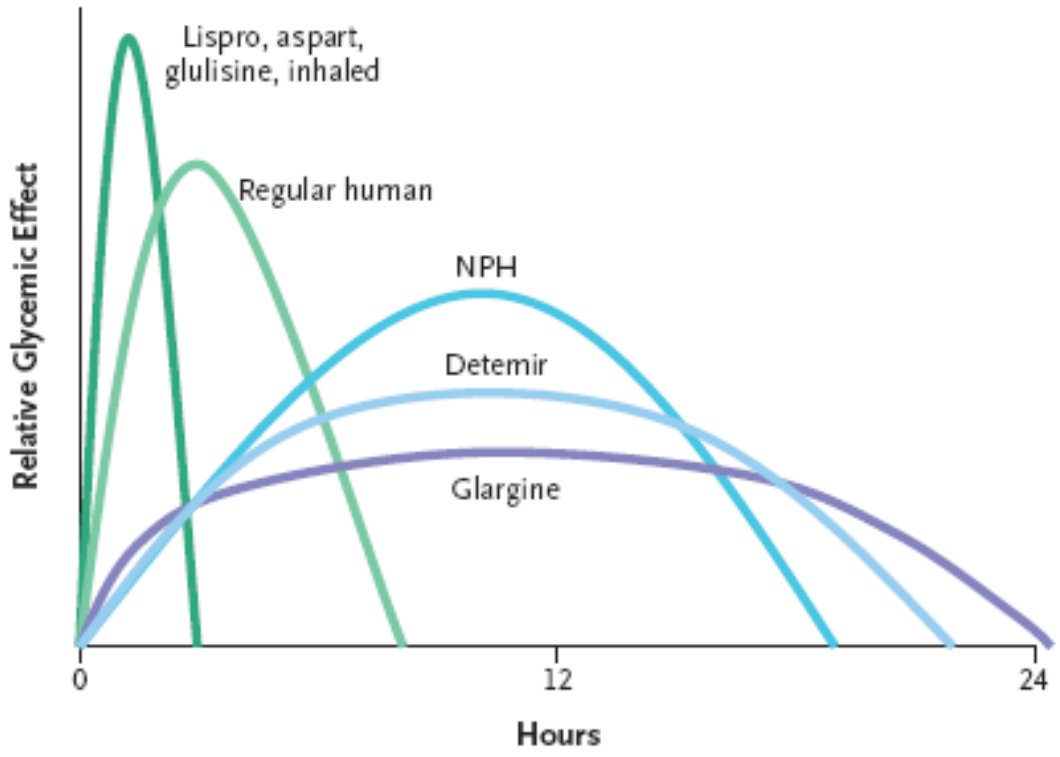


Figure 1. Schematic Time–Activity Curves for Selected Insulin Formulations.

The graph depicts time–activity profiles for selected insulin formulations. For simplicity, the known dose-dependent variability in duration of action and the wide variability in hypoglycemic effect for the selected formulations among patients are not represented. Biphasic insulin preparations are not shown.

Insulin regimens

- Simple: once or twice daily
- Complex: basal and bolus Rx using multiple doses
- Choice depends on severity of diabetes

***JAMA* 289:2254-2264, 2003**
***Med Clin N Am* 88, 865–895, 2004**

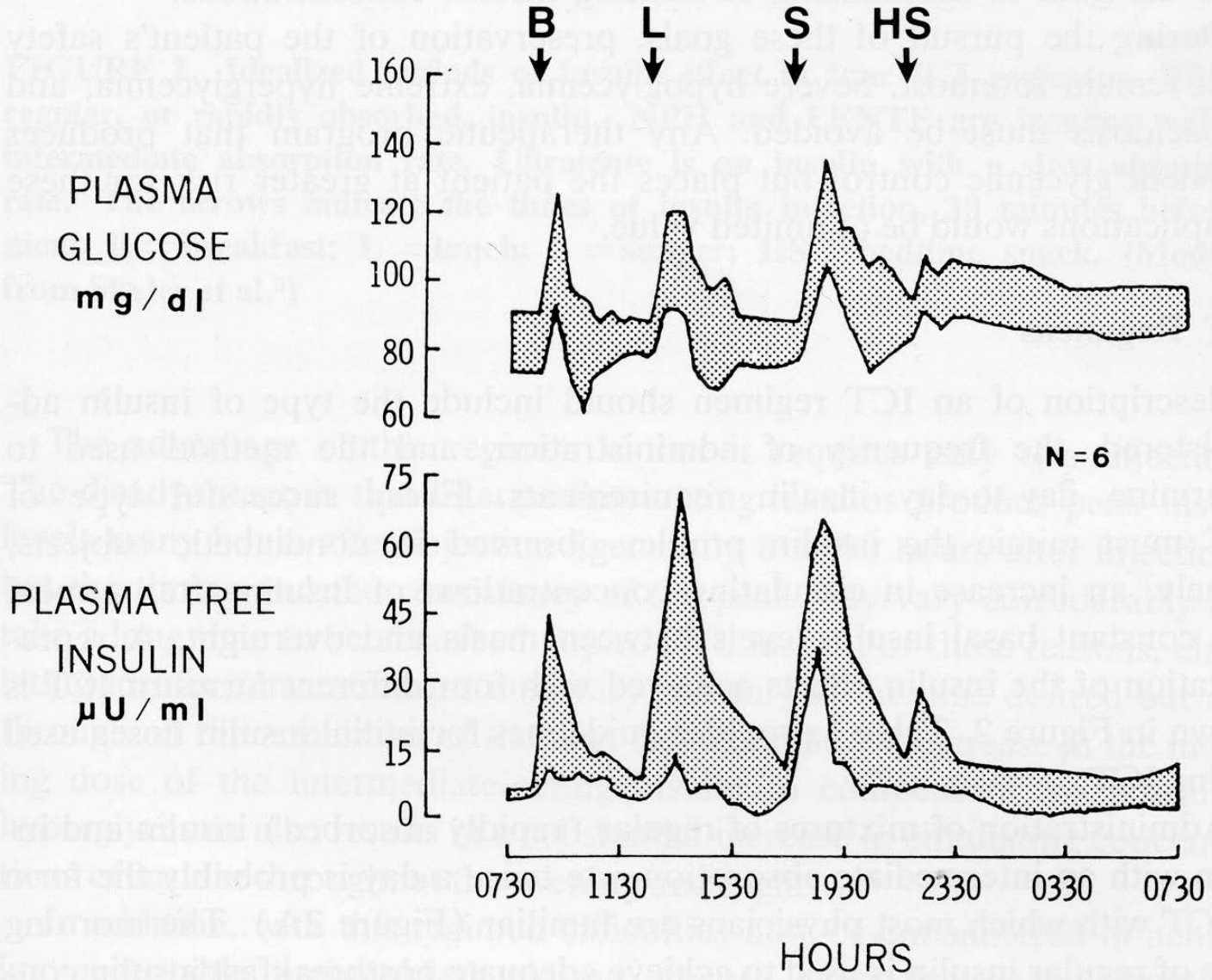
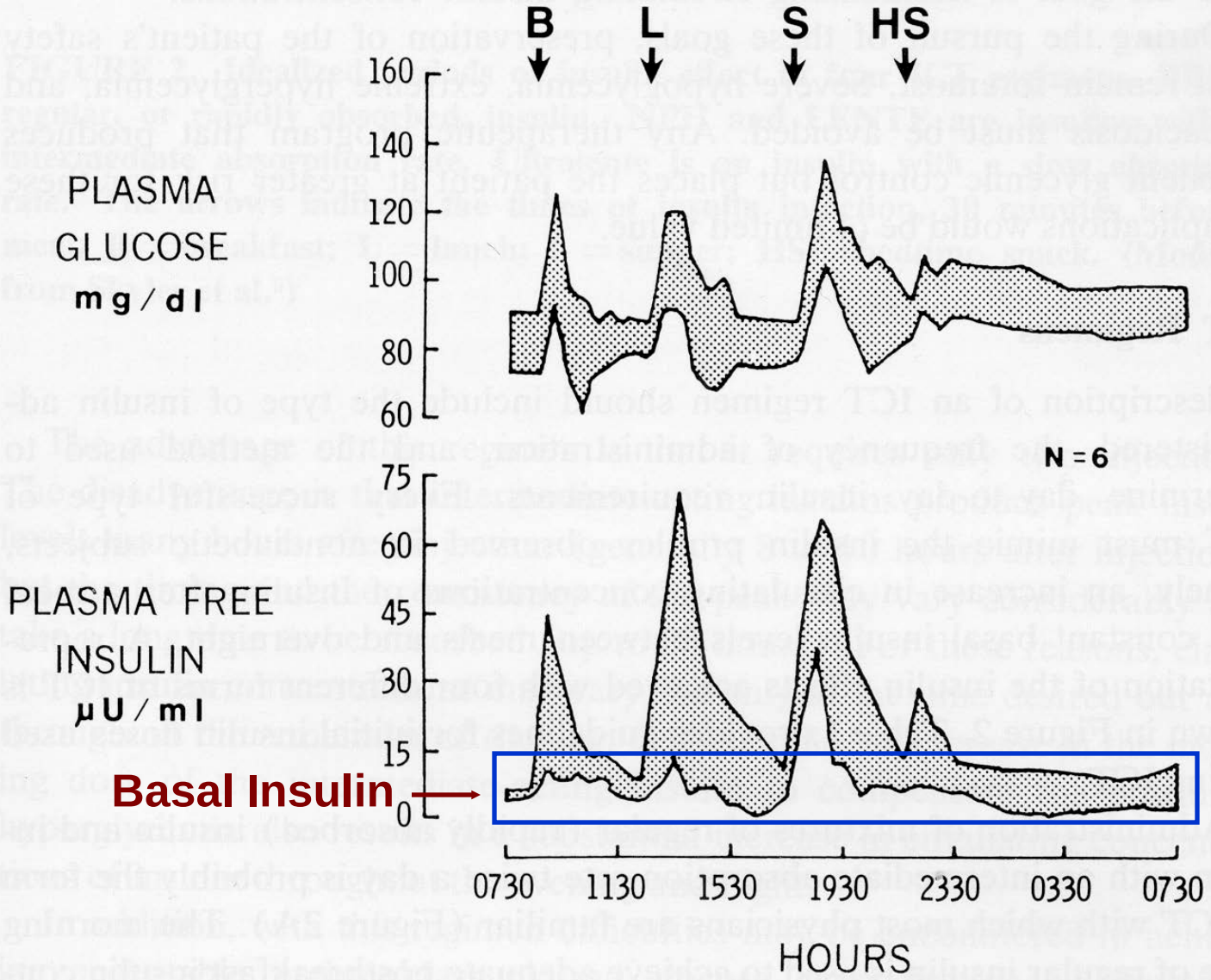


FIGURE 1. Plasma glucose and insulin concentrations in six healthy nondiabetic subjects. The shaded area represents the mean ± 1 SD. B = breakfast; L = lunch; S = supper; HS = bedtime snack. (Modified from Rizza et al.[8])



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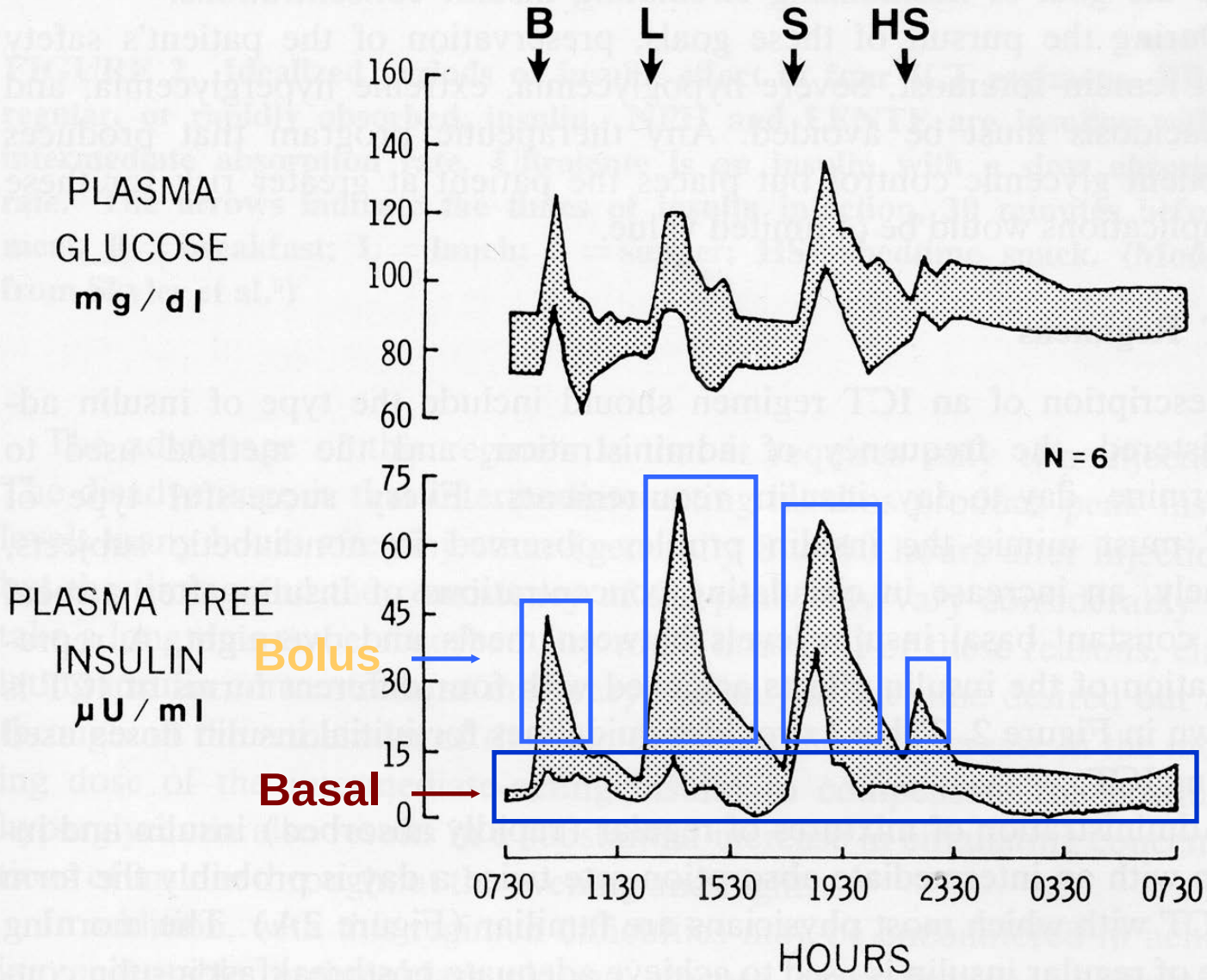
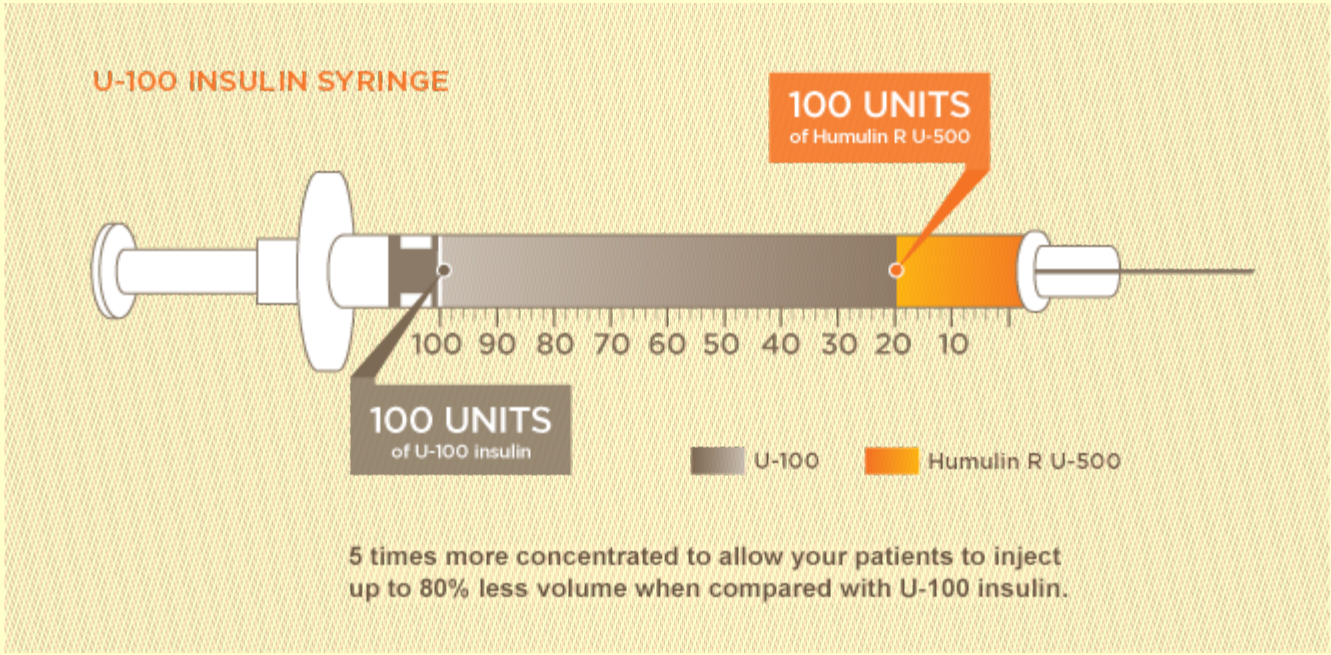


FIGURE 1. Plasma glucose and insulin concentrations in six healthy non-diabetic subjects. The shaded area represents the mean ± 1 SD. B = breakfast; L = lunch; S = supper; HS = bedtime snack. (Modified from Rizza et al.[8])

U-500 insulin

- 500 units/ml (as opposed to 100 units/ml for U-100 insulin
- There are no U-500 syringes so, e.g. 25 units drawn in a U-100 syringe will deliver 125 units of insulin.
- Effect begins within 30 minutes, has peak similar to U-100 regular human insulin but has a relatively long duration of activity following a single dose (up to 24 hours) as compared with U-100 regular insulin.
- Formulated as regular insulin but duration longer than regular
- Generally used in multiple doses pre-meals and sometimes HS – but does not match well to meal glucose absorption
- Can be used in pumps

Prescribing information, Eli Lilly Co, Indianapolis, IN



PRESCRIPTION

Name _____ Age _____

Address _____ Date _____

Rx

BID Dosing (U-100 insulin syringe)

Humulin R U-500 (500 units/mL)

Dispense: 1 vial (#20 mL)

Refill: 2 vials

Administer 120 units SC 30 minutes ac-breakfast and evening meal using a U-100 syringe*

Patient instructions: Draw to 24 unit markings on a U-100 insulin syringe 2 times daily, 30 minutes before breakfast and evening meals.

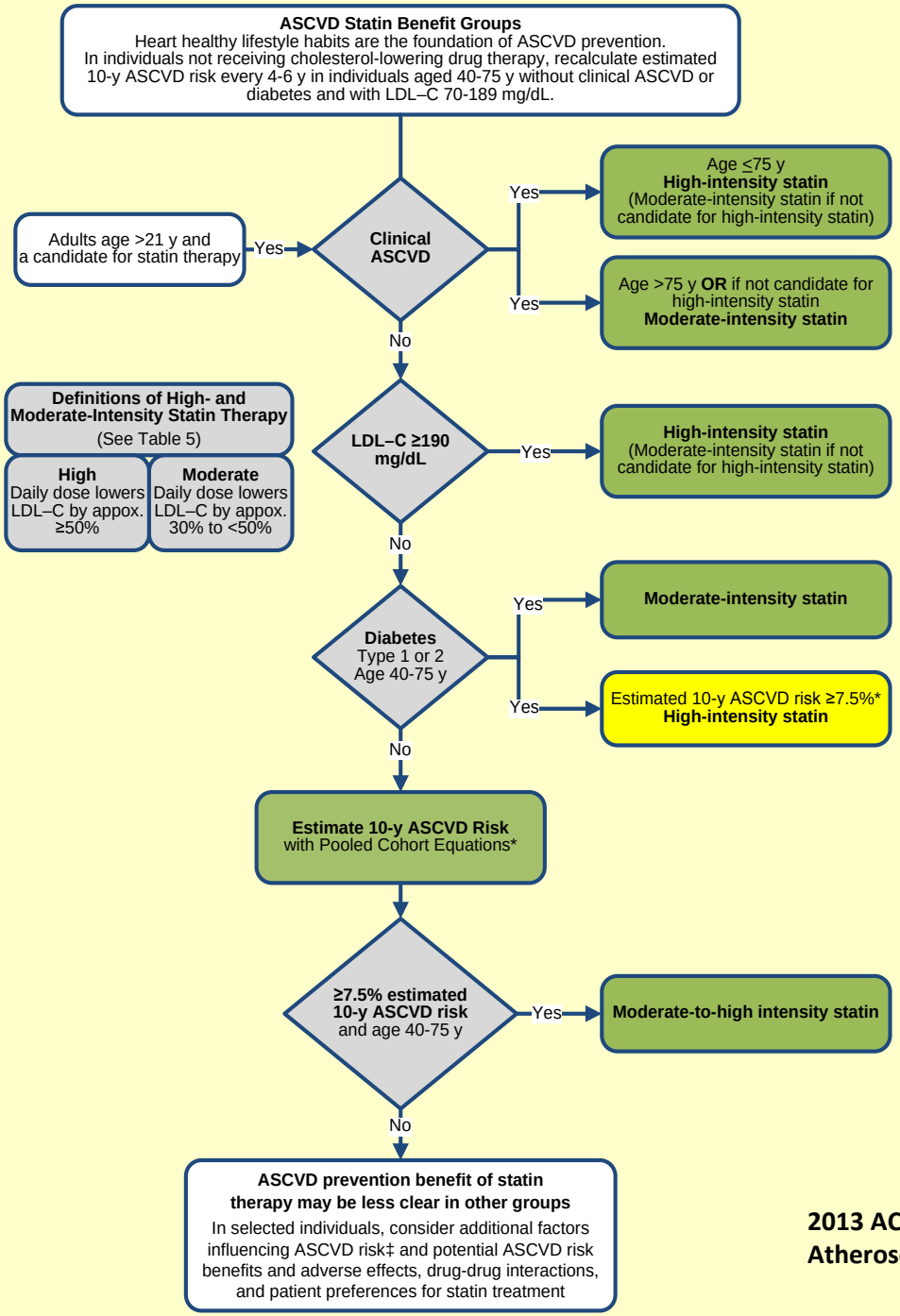
_____ M.D. Refill 1 2 3 4 5

SAMPLE

Lipid lowering therapy (American Diabetes Association)

- Lifestyle modification: reduction of saturated fat, trans fat, and cholesterol intake; increase of n-3 fatty acids, viscous fiber and plant stanols/sterols; weight loss (if indicated) and physical activity
- Statin therapy should be added to lifestyle, regardless of baseline lipid levels, for diabetic patients
  - with overt CVD
  - without CVD who are over the age of 40 years and have one or more other CVD risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).
- For lower-risk patients than the above statin therapy should be considered if
  - LDL cholesterol remains above 100 mg/dl
  - multiple CVD risk factors.
- Without overt CVD, the goal is LDL cholesterol of 100 mg/dL.
- With overt CVD, the goal is LDL cholesterol of 70 mg/dL with a high dose of a statin as an option.
- If drug-treated patients do not reach the above targets on maximum tolerated statin therapy, a reduction in LDL cholesterol of 30–40% from baseline is an alternative goal.
- Triglycerides: Goals are 50 mg/dL and HDL cholesterol 40 mg/dL in men and 50 mg/dL in women.
- LDL cholesterol–targeted statin therapy remains the preferred strategy.
- Combination therapy has been shown not to provide additional benefit above statin alone.
- Statin therapy is contraindicated in pregnancy.

American Diabetes Association: Standards of Care (*Diabetes Care* 37, Suppl. 1, Jan. 2014) Online www.diabetes.org/



Higher intensity = atorvastatin 40–80 mg
Moderate intensity = atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20–40 mg

A conservative estimate of adverse events includes excess cases of incident diabetes, myopathy, and hemorrhagic stroke.

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Circulation*, Nov. 12, 2013

BP goals (American Diabetes Association)

- People with diabetes and hypertension should be treated to a systolic blood pressure (SBP) goal of 140 mmHg.
- Lower systolic targets, such as 130 mmHg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden.
- Patients with diabetes should be treated to a diastolic blood pressure (DBP) 80 mmHg.

American Diabetes Association: Standards of Care (*Diabetes Care* 37, Suppl. 1, Jan. 2014) Online www.diabetes.org/

HOPE study and M ICRO-HOPE substudy. Lancet 2000;355: 253–259

ADVANCE Collaborative Group. N Engl J Med 2008;358:2560–2572

BP treatment (American Diabetes Association)

- Remember lifestyle treatment
- RAS inhibitors have advantages
- Diuretics are effective and often added to ACE/ARB therapy
  - RAS inhibitors and diuretics are effective in reducing CV events in type 2 diabetes
  - RAS inhibitors protect against microvascular complications
- Often need multi-drug therapy, usually include diuretic if triple drug therapy
- If Rx not effective, consider a secondary etiology of hypertension
- Avoid ACE and ARBs and diuretics in pregnancy

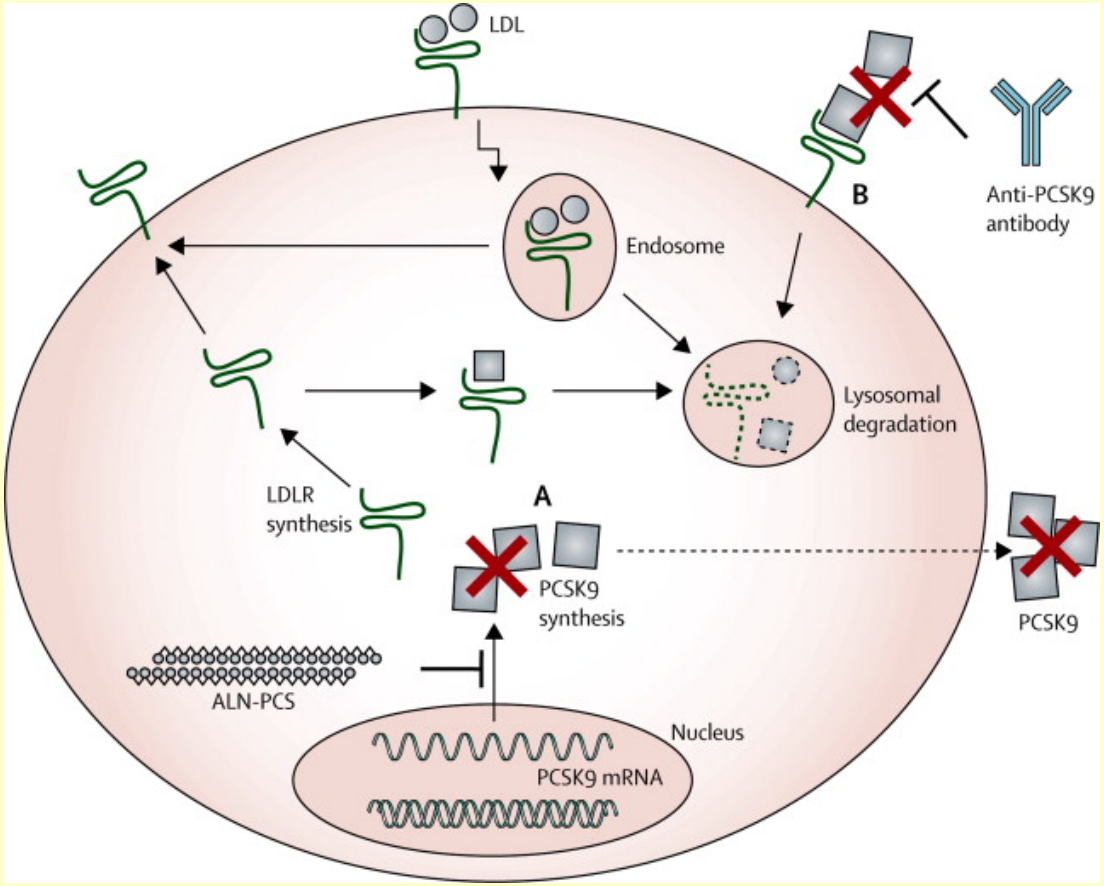
American Diabetes Association: Standards of Care (*Diabetes Care* 37, Suppl. 1, Jan. 2014) Online www.diabetes.org/

A few new ideas

Inhibition of PCSK9: A new way to lower cholesterol

- PCSK9 (proprotein convertase subtilisin/kexin type 9) binds to LDL receptors leading to their degradation.
  - Mutations resulting in lower levels of the circulating protein were associated with reduced LDL and CAD risk
  - PCSK9 is a target of LDL-lowering therapies
- Inhibit by infusion of an RNA interference drug (ALN-PCS) or by antibody administration
  - ALN-PCS is delivered using a lipid nanoparticle and inhibits synthesis of PCSK9
- Highest ALN-PCS dose resulted in average LDL reduction of 40% relative to placebo ($P<0.0001$)
- Still needs larger study – mainly proof of concept at his point

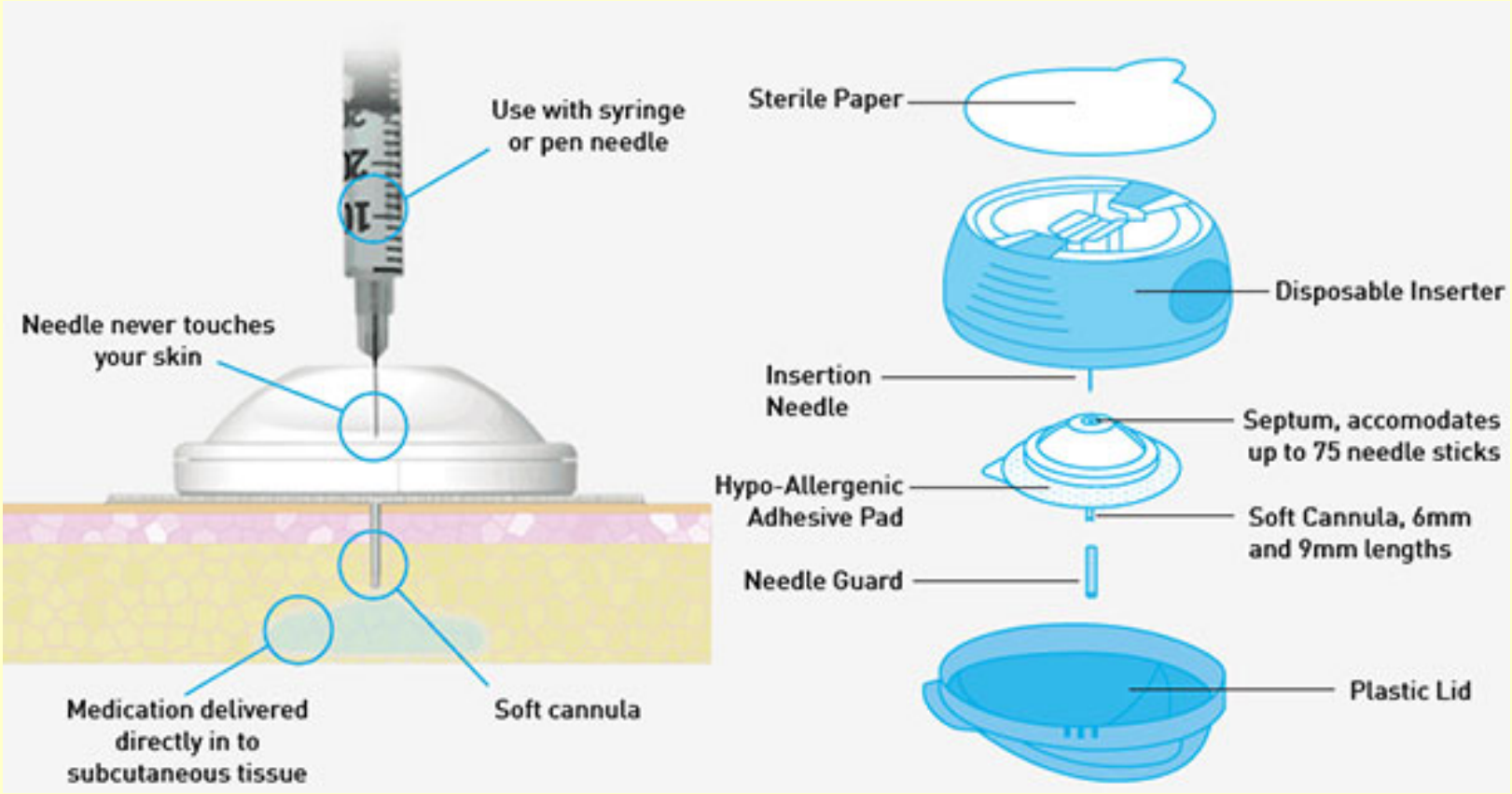
Fitzgerald et. al. Lancet 383: 60-68, 2014



PCSK9 pathway and RNA interference synthesis-inhibitor approach PCSK9 has a role in both intracellular and extracellular degradation of the LDL receptor (LDLR). PCSK9 synthesis inhibitors such as ALN-PCS inhibit PCSK9 synthesis (A) and therefore both intracellular and extracellular functions, whereas PCSK9 blockers (such as anti-PCSK9 antibodies) inhibit only extracellular function (B). mRNA=messenger RNA.

Fitzgerald et. al. Lancet 383: 60-68, 2014

Medtronic i-port



New insulins

- U-300 or U-?? Insulins. These will probably need to be administered in pen form to avoid dosing problems
- New long acting insulins
- Super short acting insulin

END

Thanks for your attention

Help us make the GRADE