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**

<table>
<thead>
<tr>
<th>Age</th>
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<tr>
<td>35</td>
<td>12</td>
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- 35 years old with normal fasting AM blood tests.
Pre-diabetes (impaired fasting glucose)

Fasting AM blood tests

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Early type 2 diabetes

Fasting AM blood tests

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Type 2 diabetes

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Worse type 2 diabetes

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Worse type 2 diabetes with symptoms

Fasting AM blood tests

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Worse type 2 diabetes with symptoms

Bottom line: Type 2 diabetes is a progressive disorder

### Fasting AM blood tests

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Worse type 2 diabetes with symptoms

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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
- α-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

References:
- 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
- NEJM 2012 Jul 26;367(4):319-28
# ADA Treatment Goals for Glycemic Control

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

Approach to management of hyperglycemia:

<table>
<thead>
<tr>
<th>More stringent</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risks potentially associated with hypoglycemia, other adverse events</td>
<td>High</td>
</tr>
<tr>
<td>Newly diagnosed Disease duration</td>
<td>Long-standing</td>
</tr>
<tr>
<td>Long Life expectancy</td>
<td>Short</td>
</tr>
<tr>
<td>Absent Important comorbidities</td>
<td>Few/mild Severe</td>
</tr>
<tr>
<td>Absent Established vascular complications</td>
<td>Few/mild Severe</td>
</tr>
<tr>
<td>Readily available Resources, support system</td>
<td>Limited</td>
</tr>
</tbody>
</table>

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.**

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

Conventional

Intensive

6.2% = upper limit of normal range

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
<table>
<thead>
<tr>
<th>Drug</th>
<th>Actions</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>↑ β-cell insulin secretion</td>
<td>Potassium channels</td>
<td>Well tolerated, Low cost</td>
<td>Hypoglycemia, Weight gain, Low durability, May reduce myocardial ischemic reconditioning</td>
</tr>
<tr>
<td>glipizide</td>
<td></td>
<td></td>
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<tr>
<td>glimepiride</td>
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<tr>
<td>glyburide</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GLP-1 agonists</td>
<td>↑ insulin secretion, ↓ glucagon, ↓ gastric emptying, ↑ satiety</td>
<td>Activate GLP-1 receptors in β-cell, and nervous system</td>
<td>Weight loss, Possible ↑β-cell mass/function, Little hypoglycemia</td>
<td>Nausea, vomiting, diarrhea, Acute pancreatitis risk, ? Medullary thyroid tumors, Long term safety?</td>
</tr>
<tr>
<td>exenatide</td>
<td></td>
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<tr>
<td>liraglutide</td>
<td></td>
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</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>↑ insulin secretion, ↓ glucagon</td>
<td>Prevent GLP-1 break-down, ↑ endogenous GLP-1</td>
<td>Little or no hypoglycemia, Weight neutral</td>
<td>Urticaria, angioedema, Pancreatitis, Long term safety?</td>
</tr>
<tr>
<td>sitagliptin</td>
<td></td>
<td></td>
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<tr>
<td>vildagliptin</td>
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<tr>
<td>saxagliptin</td>
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<tr>
<td>linagliptin</td>
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</tr>
<tr>
<td>Insulin</td>
<td>Well known</td>
<td>Well Known</td>
<td>Effective, “natural”</td>
<td>Hypoglycemia, Weight gain, may need multiple injections and large dose</td>
</tr>
<tr>
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### Drugs for type 2 diabetes beyond Metformin (continued)

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<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Canagliflozin</td>
<td>Increase urine glucose excretion</td>
<td>Inhibits hSGLT2 (sodium/glucose cotransporter) in renal tubules</td>
<td>Hypoglycemia very unusual</td>
<td>UTIs, vulvovaginitis, balanitis: mostly mild, rarely limit therapy</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td></td>
<td></td>
<td>Familial renal glycosuria is a benign disease</td>
<td>Osmotic diuresis, Dehydration, Hypotension, Increased hepatic glucose output</td>
</tr>
</tbody>
</table>

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

- Metformin
  - Goal achieved
  - Goal not achieved
    - Add second drug
    - Another drug
      - Contraindication or intolerance to metformin
  - Severe hyperglycemia
    - Insulin
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 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.)
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.3)
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.)
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
U-100 INSULIN SYRINGE

100 UNITS
of Humulin R U-500

100 UNITS
of U-100 insulin

5 times more concentrated to allow your patients to inject up to 80% less volume when compared with U-100 insulin.

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 12.0 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

Lilly USA, LLC 2014
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/
ASCVD Statin Benefit Groups
Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL–C 70-189 mg/dL.

Definitions of High- and Moderate-Intensity Statin Therapy
(See Table 5)
- High: Daily dose lowers LDL–C by approx. ≥50%
- Moderate: Daily dose lowers LDL–C by approx. 30% to <50%

High-intensity statin
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.

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 MICRO-HOPE substudy. Lancet 2000;355: 253–259
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 this point

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.

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
Thanks for your attention

Help us make the GRADE