Primary Care Days

Update on Diabetes -2013

Answers to the 10 questions I get asked most often

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Disclosure

• I have no conflict of interest
What are the appropriate glycemic targets for those with diabetes?

**HbA1c < 7.0%** (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])

- Pre-prandial PG <130 mg/dl (7.2 mmol/l)
- Post-prandial PG <180 mg/dl (10.0 mmol/l)

- **Individualization** is key:
  - Tighter targets (6.0 - 6.5%) - younger, healthier
  - Looser targets (7.5 - 8.0%+) - older, comorbidities, hypoglycemia prone, etc.

- **Avoidance of hypoglycemia**
# Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
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<td><strong>UKPDS</strong></td>
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* in T1DM

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**Kendall DM, Bergenstal RM. © International Diabetes Center 2009**

A few lesser known facts about ACCORD

• Intensive treatment led to benefits as well as risks

• Increased mortality during intensive treatment in ACCORD has **obscured** the favorable effects reported from secondary end points and substudies

• Nonfatal MI was reduced by intensive therapy at the end of randomized treatment and after 1.5 additional years of follow-up

Riddle M et al. Diabetes Care 2012;35:2100-2107
ACCORD- Factors associated with increased mortality

• Baseline characteristics associated with increased mortality with intensive treatment:
  – A1C levels >8.5%
  – Self reported neuropathy and aspirin use

• On treatment factors associated with increased mortality
  – No reduction in A1C from baseline
  – Hypoglycemia
Figure 1 — The risk of all-cause mortality during randomized treatment in ACCORD is shown for each treatment group by spline curves over a range of average A1C from 6 to 9%. Values are adjusted for covariates by a proportional hazards model. Bold colored lines represent each treatment group and finer colored lines the 95% CI. The figure is adapted with permission from Riddle et al. (33).

Riddle M et al. Diabetes Care 2012;35:2100-2107
Figure 2—All-cause yearly mortality rates during randomized treatment in ACCORD are shown for each treatment group over a range of decreases of A1C during the first year of treatment. Covariate-adjusted values are calculated by a Poisson regression model. Bold colored lines represent each treatment group and finer colored lines the 95% CI. The figure is adapted with permission from Riddle et al. (33).

Riddle M et al. Diabetes Care 2012;35:2100-2107
Table 1—Proposed indicators of need to individualize therapeutic targets or tactics for high-risk type 2 diabetes

1. Characteristics indicating a high risk-to-benefit ratio
   - Established microvascular or CV disease
   - Short life expectancy
   - Hypoglycemia requiring medical assistance
   - A1C higher than 8.5% on prior treatment

   **Suggested action:** change target range to 7–8% A1C

2. Lack of baseline predictors, but poor response to a standard treatment algorithm
   - Failure to reduce A1C at least 0.5% from baseline in 4–12 months
   - Hypoglycemia requiring medical assistance

   **Suggested action:** change target range to 7–8% A1C

3. Inability to maintain A1C in target range over time with standard methods
   - A1C persistently >7% for lower risk individuals seeking <7%
   - A1C persistent <7% or >8% for high-risk individuals seeking between 7 and 8%

   **Suggested action:** evaluation by a diabetes specialty group to personalize treatment

Riddle M et al. Diabetes Care 2012;35:2100-2107
How to individualize glycemic targets for those with diabetes?

Patient-Centered Approach

“...providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions.”

• Gauge patient’s preferred level of involvement
• Explore, where possible, therapeutic choices
• Utilize decision aids
• Shared decision making – final decisions re: lifestyle choices ultimately lie with the patient
Approach to management of hyperglycemia:

- **Patient attitude and expected treatment efforts**
  - more stringent: highly motivated, adherent, excellent self-care capacities
  - less stringent: less motivated, non-adherent, poor self-care capacities

- **Risks potentially associated with hypoglycemia, other adverse events**
  - low
  - high

- **Disease duration**
  - newly diagnosed
  - long-standing

- **Life expectancy**
  - long
  - short

- **Important comorbidities**
  - absent
  - few/mild
  - severe

- **Established vascular complications**
  - absent
  - few/mild
  - severe

- **Resources, support system**
  - readily available
  - limited

(Adapted with permission from: Ismail-Beigi et al. Ann Intern Med 2011;154:554)
What are the cholesterol goals?

• For those without overt CVD LDL goal is <100 mg/dl
• For those with overt CVD LDL goal is <70 mg/dl
  – TG<150 mg/dl and HDL>40 mg/dl in men and >50 mg/dl in women are desirable, but LDL lowering with a statin is the preferred strategy
How low is it safe to pharmacologically lower the LDL cholesterol?

Experiments of nature

• Neonates have an LDL cholesterol 30-70 mg/dl
• Hunter gatherers LDL 50-75 mg/dl
• Familial hypobetalipoproteinemia have LDL 30-40 mg/dl and life expectancy 15 years longer than their birth cohort
• Reduction of mean LDL to 79 mg/dl led to plaque regression of 0.4%, compared to plaque increase of 2.7% when mean LDL was 110 mg/dl (REVERSAL)

• 3500 pts. with baseline mean LDL 97 mg/dl had a 25% risk reduction in CV events when mean LDL reduced to 65 mg/dl (HEART PROTECTION STUDY)

• Many major studies TNT, TIMI etc. back LDL~70
Figure 3. Relationship Between Mean Low-Density Lipoprotein Cholesterol Levels and Median Change in Percent Atheroma Volume for Several Intravascular Ultrasound Trials

$\text{Median Change in Percent Atheroma Volume, } \%$

$\text{Mean Low-Density Lipoprotein Cholesterol, mg/dL}$

$\text{ASTEROID}^{13}$

$\text{Rosuvastatin}$

$\text{REVERSAL}^{12}$

$\text{Atorvastatin}$

$\text{CAMELOT}^{14}$

$\text{Placebo}$

$\text{REVERSAL}^{12}$

$\text{Pravastatin}$

$r^2 = 0.97$

$P < .001$

Steve Nissen et. al. JAMA 2006, 295:1556-1565
Greater relative benefit in those with higher baseline LDL cholesterol

Negative effect of hyperglycemia on plaque regression after lowering of plasma LDL cholesterol.

Does a positive urine microalbumin have to be rechecked yearly?

• A positive microalbumin should be reconfirmed between 3 and 6 months from the first test (2 of three specimens should be positive). A first void sample is preferred.

• A serum creatinine (eGFR) should be measured yearly.
  – Many individuals with diabetes will have a decrease in GFR in absence of albuminuria.
Cardiovascular survival according to microalbuminuría status in a population-based cohort between 50-75 years

The susceptibility to albuminuria, cardiovascular disease and renal disease cluster together in diabetes

Jager A et al: Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: Five-year follow-up of the Hoorn Study. 1999, 19:617-624
• Utility of continued measurement of yearly microalbumin after a confirmed positive test and institution of treatment is unclear
• Continued assessment after initiating treatment:
  – May be useful in monitoring response to therapy
• Insurance company quality process measures do not require MA checks once treatment is instituted
What is an appropriate blood pressure target in those with diabetes?

- The BP goal is <140/80
  - Epidemiological analysis shows that CV risk and mortality increases at BP>115/75 in diabetes
  - ESRD risk increases at BP >120 systolic

- RCT’s show benefit in reduction of CVD and nephropathy when BP is lowered to <140/80 (UKPDS, HOT)

- ACCORD did not show benefit in the intensive arm (119/64) versus standard arm (133/70)

- Most evidence of treatment benefits of HTN are based on office measurements
What are the indications for aspirin prophylaxis in those with diabetes?

- Recommended for primary prevention at a dose of 75-162 mg/day for
  - Those with increased CV risk >10% at 10 yrs
  - Men >50 years, with one additional risk factor
  - Women >60 years with one additional risk factor
  *Additional risk factors are smoking, HTN, hyperlipidemia, renal disease, microalbuminuria, family history of CVD
- In others risk of bleeding outweighs benefits
• Antithrombotic Trialists (ATT) collaboration is a meta analysis of 6 large trials with 95,000 persons of Aspirin for primary prevention
• ~4000 people with diabetes were included
• Nonfatal MI was reduced, but there was no effect on CHD death
• The number of CV events prevented in those with a CV risk of 1% per year is similar or greater than the increased risk of bleeding
• For secondary prevention use aspirin in those with diabetes and CVD history.
• In those with CVD and documented aspirin allergy clopidrogel or prasugrel should be used
• Combination of aspirin and clopidrogel is suggested for a year after acute coronary syndrome
What are the recommendations for immunization in those with diabetes?

- Annual influenza vaccine to all individuals with diabetes ≥6 months of age
- Pneumococcal (PPSV23) vaccine ≥ 2 years of age. One time revaccination after age 65 if they were vaccinated at <65 and the vaccination was given >5 years ago.
- Repeat vaccination at 5 years: nephrotic syndrome, after transplantation, advanced renal disease, immunocompromised state
• Hepatitis B vaccine to individuals with diabetes 19 years or older. Most benefit in 19-59 years
  – 29 outbreaks of HBV have been reported in long-term facilities and hospitals involving individuals with diabetes receiving assisted blood glucose monitoring
• Presumed spread via lancing device, blood glucose meter even in the absence of visible blood, or insulin pen reservoirs
• HBV infection risk is twofold in adults with diabetes (CDC)
What is the best drug to use after metformin?
Fig. 2. T2DM Antihyperglycemic Therapy: General Recommendations

Initial drug monotherapy

- Efficacy (↓ HbA1c)
- Hypoglycemia
- Weight
- Side effects
- Costs

Healthy eating, weight control, increased physical activity

Metformin

- Efficacy (↓ HbA1c): high
- Hypoglycemia: low risk
- Weight: neutral/loss
- Side effects: GI / lactic acidosis
- Costs: low

*Diabetes Care* 2012;35:1364–1379
*Diabetologia* 2012;55:1577–1596
Healthy eating, weight control, increased physical activity

Initial drug monotherapy
- Efficacy (↓ HbA1c)
- Hypoglycemia
- Weight
- Side effects
- Costs

Two drug combinations
- Efficacy (↓ HbA1c)
- Hypoglycemia
- Weight
- Major side effect(s)
- Costs

Metformin
- high
- low risk
- neutral/loss
- GI / lactic acidosis
- low

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Metformin +</th>
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Fig. 2. T2DM Antihyperglycemic Therapy: General Recommendations
Fig. 2. T2DM Antihyperglycemic Therapy: General Recommendations

Healthy eating, weight control, increased physical activity

Metformin
- high efficacy (↓ HbA1c)
- low risk of hypoglycemia
- neutral to weight loss
- GI / lactic acidosis
- low side effects

Initial drug monotherapy
- Efficacy (↓ HbA1c)
- Hypoglycemia
- Weight
- Side effects
- Costs

Two drug combinations
- Efficacy (↓ HbA1c)
- Hypoglycemia
- Weight
- Major side effect(s)
- Costs

Three drug combinations
- Insulin (usually basal)

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

Metformin + Sulfonylurea
- high efficacy
- moderate risk of hypoglycemia
- gain in weight
- hypoglycemia
- low

Metformin + Thiazolidinedione
- high efficacy
- low risk of hypoglycemia
- gain in weight
- edema, HF, fx’s
- high

Metformin + DPP-4 Inhibitor
- intermediate efficacy
- low risk of hypoglycemia
- neutral
- GI
- high

Metformin + GLP-1 receptor agonist
- high efficacy
- low risk of hypoglycemia
- loss in weight
- GI
- high

Metformin + Insulin (usually basal)
- highest efficacy
- high risk of hypoglycemia
- gain in weight
- hypoglycemia
- variable

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

Metformin + Sulfonylurea + TZD
- high efficacy
- moderate risk of hypoglycemia
- gain in weight
- edema, HF, fx’s
- high

Metformin + Thiazolidinedione + DPP-4-i
- high efficacy
- low risk of hypoglycemia
- gain in weight
- GI
- high

Metformin + DPP-4 Inhibitor + GLP-1-RA
- intermediate efficacy
- low risk of hypoglycemia
- weight loss
- GI
- variable

Metformin + GLP-1 receptor agonist + Insulin
- high efficacy
- low risk of hypoglycemia
- weight loss
- GI
- variable

Metformin + Insulin (usually basal) + GLP-1-RA
- highest efficacy
- high risk of hypoglycemia
- weight gain
- hypoglycemia
- variable

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If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

- Insulin (multiple daily doses)

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OTHER CONSIDERATIONS

• Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

➢ Metformin: CVD benefit (UKPDS)
➢ Avoid hypoglycemia
➢ ? SUs & ischemic preconditioning
➢ ? Pioglitazone & ↓ CVD events
➢ ? Effects of incretin-based therapies
OTHER CONSIDERATIONS

• Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

➤ Metformin: May use unless condition is unstable or severe
➤ Avoid TZDs
➤ ? Effects of incretin-based therapies
OTHER CONSIDERATIONS

• Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

- Increased risk of hypoglycemia
- Metformin & lactic acidosis
  - US: stop @SCr ≥ 1.5 (1.4 women)
  - UK: half-dose @GFR < 45 & stop @GFR < 30
- Caution with SUs (esp. glyburide)
- DPP-4-i’s – dose adjust for most
- Avoid exenatide if GFR < 30
OTHER CONSIDERATIONS

• Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

  ➢ Most drugs not tested in advanced liver disease
  ➢ Pioglitazone may help steatosis
  ➢ Insulin best option if disease severe
OTHER CONSIDERATIONS

• Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

- Emerging concerns regarding association with increased morbidity / mortality
- Proper drug selection is key in the hypoglycemia prone
Is it better to prescribe insulin in pens as they do not need refrigeration?

• Levemir
  – Flexpen 42 days at room temp, **should not be refrigerated once opened**
  – Vials 42 days at room temp or refrigerated

• Lantus
  – Solostar 28 days at room temp, **do not refrigerate**
  – Vials 28 days at room temperature or refrigerated
• Novolog and Humalog
  – Flexpen and Kwikpen 28 days at room temp. **Do not refrigerate**
  – Vials 28 days at room temp, may be refrigerated

• Why can used pens not be refrigerated, unlike vials?
  – After refrigeration, Lilly pens may develop air bubbles in the barrel
  – Other pens develop similar problems due to repeated expansion and contraction of the liquid and mechanical components in the pen
What are the newer diabetes drugs for 2013?

• SGLT1 and SGLT2 are sodium glucose cotransporters in the proximal tubule
  – SGLT1 is high affinity low capacity
  – SGLT2 is low affinity high capacity and accounts for majority of glucose reabsorption by the kidney
  – SGLT2 mutations cause renal glycosuria
• Renal glucose reabsorption increases with chronic hyperglycemia
• SGL2 inhibitor based treatments work independently of beta cell action or insulin secretion.
• They do not cause hypoglycemia
• They can work at any stage of disease progression of diabetes
• They can be combined with other agents with different mechanisms of actions
• They promote weight loss
• These drugs are not as effective in moderate to severe renal impairment (eGFR<60)

• Increase in rates of urinary and genital infections
  – Dapgliflozin had slight increase in breast and bladder cancer rates in phase 3 trials

• Canagliflozin (300 mg/day) reduces A1C ~1%. Works well in combination with SU’s, metformin and insulin
Canagliflozin (Invokana™) approved by FDA on March 29, 2013

- FDA listed 5 postmarketing studies for Canagliflozin that Jansen Pharmaceuticals must conduct as a condition for the drug's approval:
  - A cardiovascular outcomes trial (CANVAS)
  - An enhanced pharmacovigilance program to monitor for malignancies, serious cases of pancreatitis, and other adverse events
  - A bone safety study
  - A pediatric pharmacokinetic and pharmacodynamics study
  - A pediatric safety and efficacy study
What to do when the A1C is not consistent with the blood glucose readings?

• Factors that lower A1C relative to fingerstick glucose
  – Hemoglobinopathies
  – Anemia, Blood loss, Blood transfusion, erythropoietin treatment
  – Chronic liver disease
  – Pregnancy
  – HIV medications
• Factors that increase A1C relative to fingerstick blood glucose
  – Very few- iron deficiency, blacks have higher A1C, older people have higher A1C, hemoglobin F
• In most individuals, the higher readings are being “missed” as the fingertick glucose is not being checked when the sugars are high
52 year old with average glucose of 148 mg and A1c of 8%

CGMS Ave=182 mg