Diabetes Medication Update
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Disclosure
- Participation as a speaker for Astra-Zeneca, Sanofi-Aventis, and Janssen Pharmaceuticals

Outline of today’s talk
- Diabetes Defined
- Clinical relevance of diabetes in the USA
- Diabetes medication review (non-insulin and insulin)
- Macrovascular outcome data (Empa Reg Outcome Trial)
- Selected strategies with different patient examples
- New medications in coming soon or in development

Current Medical Definition of Diabetes

<table>
<thead>
<tr>
<th>Table 2.1—Criteria for the diagnosis of diabetes</th>
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<tbody>
<tr>
<td>FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*</td>
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<td>OR</td>
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<tr>
<td>2 h PG ≥200 mg/dL (11.1 mmol/L), during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*</td>
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<td>A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*</td>
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In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Diabetes in the US
29.1 million Americans (9.3% of the population)
- 21.0 million diagnosed
- 8.1 million undiagnosed

Pre-diabetes
- 79 million in 2010
- 86 million in 2012

Diabetic Complications
**Cost of Diabetes**

- $245 Billion in 2013
  - $176 Billion direct medical cost
  - $69 Billion indirect cost in reduced productivity

**Diabetes Microvascular Complications:**

**Landmark Studies**

Type 1 Diabetes: Diabetes Control and Complication Trial (DCCT)
- Conventional Therapy: Hemoglobin A1c 9.1
- Intensive Therapy: Hemoglobin A1c 7.2
- 30-35% reduction in microvascular complications (eye, kidney, nerve) per every 1% drop in hemoglobin A1c

Type 2 Diabetes: United Kingdom Prospective Diabetes Study (UKPDS)
- After 10 years:
  - Conventional Therapy: Hemoglobin A1c 7.9
  - Intensive Therapy: Hemoglobin A1c 7.0
  - 25% risk reduction for every 1% drop in HgbA1c

**Diabetes and Macrovascular Complications**

Type 1 Diabetes:
- DCCT: trend towards lower risk of CVD death in the intensive control group
- EDIC (6-year post-DCCT follow-up): 57% risk reduction in non-MI, stroke or CVD death in the intensive vs. standard group

Type 2 Diabetes:
- UKPDS: 16% reduction in non-fatal MI and CVD death (p=0.052) in intensive vs. standard group
- 10-year follow up study: significant reductions in MI and all cause mortality (35% vs. 37%)

**Timeline of Non-insulin Diabetes Medications**

- Tolbutamide 1956
- Glyburide/ Glipizide 1984
- Metformin 1995
- Glimepiride 1995
- Acarbose 1995
- Repaglinide 1997
- Pioglitazone 1999
- Rosiglitazone 1999
- Exenatide 2005
- Sitagliptin 2006
- saxagliptin 2009
- Liraglutide 2010
- Canagliflozin 2013
- Linagliptin 2011
- Dulaglutide 2014
- Dulaglutide 2014

**Timeline of Insulin therapies in the US**

- 1st Human insulin 1922-23
- Lente insulin 1955
- Lispro 1996
- Aspart 2000
- NPH insulin 1955
- Detemir 2005
- Glargine U-300 2015
- Degludec 2015
- Inhaled insulin 2014
- GLP-1R agonist 2015
**Diabetes Medications: How to choose?**

**Suggested Goals for Glycemic Treatment in Patients with Type 2 Diabetes**

**ADA Strategy for Medication Management 2015**

**Non-Insulin Diabetes Medications**

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Medication names</th>
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<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
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<tr>
<td>Sulfonylureas</td>
<td>Glyburide, Glipizide, Glimepiride</td>
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<tr>
<td>Glitazones</td>
<td>Repaglinide, Nateglinide</td>
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<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone, Rosiglitazone</td>
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<tr>
<td>DPP-4 Inhibitors</td>
<td>Sitagliptin, Saxagliptin, Linagliptin</td>
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<tr>
<td>Bile acid sequestrants</td>
<td>Colesevelam HCL</td>
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<tr>
<td>Dopamin-2 agonists</td>
<td>Bromocriptine</td>
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<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Acarbose, Miglitol</td>
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<tr>
<td>SGLT-2 Inhibitors</td>
<td>Canagliflozin, Dapagliflozin, Empagliflozin</td>
</tr>
<tr>
<td>GLP-1 Receptor Agonists</td>
<td>Exenatide, Liraglutide, Exenatide LAR, Dulaglutide, Albiglutide</td>
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**Metformin (Glucophage)**

- Stimulates AMP-activated protein kinase
- Reduces hepatic glucose production
- Increases insulin action
- Reduces intestinal glucose absorption
- Expect 1.0 to 2.0 % A1c reduction

**Advantages:**
- weight neutral to slight weight loss
- Hypoglycemia is rare with Metformin alone
- Inexpensive

**Disadvantages:**
- GI side effects
- Lactic acidosis (rare)
- Not recommended in renal disease (men creatinine>1.5, women creatinine>1.4)
- May cause vitamin B12 deficiency
Sulfonylureas
- Glyburide (Diabeta), Glipizide (Glucotrol), Glimepiride (Amaryl)
- Closes K<sub>ATP</sub> channels on beta cell membranes
- Stimulate insulin secretion from beta cell
- Expected A1c reduction: 1.0-1.5%
- Advantages:
  - Extensive clinical experience
  - Inexpensive
- Disadvantages:
  - Hypoglycemia
  - Less durability
  - Weight gain
  - May blunt myocardial ischemia preconditioning

Thiazolidinediones
- Pioglitazone (Actos) Rosiglitazone (Avandia)
- PPAR-γ activators: enhance insulin sensitivity in peripheral tissues and decrease hepatic glucose production
- Expected A1c reduction: 0.5-1.4%
- Advantages:
  - Hypoglycemia rare, more durable response
  - Lower TG level and raises HDL, Some evidence of CV benefit (pioglitazone)
- Disadvantages:
  - Weight gain, edema, CHF
  - Potential risk of long bone fractures, bladder cancer

Patient Case # 1
70 year old with type 2 DM, edema, and hypertension managed with Metformin 500 mg BID.
Lab work: Hemoglobin A1c 8.1, creatinine 1.9
He is concerned about medication cost
You decide to:
A. Continue Metformin and increase dose
B. Stop Metformin and start Gliburide
C. Stop Metformin and start Glipizide
D. Stop Metformin and start Pioglitazone

DPP-IV inhibitors
- Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Tradjenta), Alogliptin (Nesina)
- Dipeptidyl peptidase inhibitors, inhibit breakdown of endogenous GLP-1 and GIP
- Increases insulin secretion in glucose-dependent manner
- Reduces glucagon secretion
- Expected A1c reduction: 0.5-0.8%
- Advantages:
  - Weight neutral
  - Hypoglycemia rare
  - Side effects infrequent
- Disadvantages:
  - Less efficacy than GLP-1 receptor agonists
  - Concern for urticaria, angioedema, pancreatitis, Long-term safety unknown
  - Cost

Bile Acid Sequestrants
- Colesevelam (Welchol)
- Binds bile acids/cholesterol
- Glucose-lowering mechanism is unknown
- Expected A1c reduction: 0.5-0.6%
- Advantages:
  - No hypoglycemia
  - Lowers LDL cholesterol
- Disadvantages:
  - Constipation
  - Increases triglyceride level
  - May interfere with absorption of other medications
  - High cost

Dopamine-2 Agonists
- Bromocriptine (Cycloset)
- Activates dopaminergic receptors
- Alters hypothalamic regulation of metabolism
- Increases insulin sensitivity
- Expected A1c reduction: 0.3-0.5%
- Advantages:
  - No hypoglycemia
- Disadvantages:
  - Fairly modest A1c reduction
  - Increased nausea, dizziness, possible syncope
  - Long-term safety unknown
  - Medium cost
GLP-1 Action
- GLP-1 is a peptide hormone made in the small intestine
- GLP-1 is released in the body when food ingested
- GLP-1 acts on several organs in the body, including the pancreas
  - Induces pancreas to make more insulin and inhibit glucagon
  - The inhibition of glucagon suppresses liver breakdown of glycogen stores

GLP-1 : Mechanism of action

GLP-1 action on glucose homeostasis

GLP-1 receptor agonists
- Five Available in US as of 2015

GLP-1 receptor agonists
- Advantages:
  - Weight loss (2 to 4 kg with use)
  - Usually not associated with hypoglycemia (except in combination with insulin or sulfonylurea)
  - Result in at least 1.0% drop in A1c
- Disadvantages:
  - GI side effects (nausea/vomiting)
  - Cost
  - Potential safety issues (pancreatitis, medullary thyroid cancer, long-term safety unknown)

Renal Glucose transport

Renal Handling of Glucose: A Potential New Drug Target?
Action of SGLT Molecules in the Kidney

Sodium-Glucose co-transporter 2 responsible for 90% of glucose re-absorption in the proximal tubule of the kidney

SGLT-2 Inhibitors

- Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance)
- Do not target the major defects of type 2 diabetes: (Insulin resistance and impaired insulin secretion)
- Do work to inhibit glucose re-absorption in the kidney
- Lead to glucosuria
- Expected A1c reduction: 0.7-2.0%

Advantages
- Low risk of hypoglycemia
- Associated with weight loss

Disadvantages
- Less effective and more risk in use with renal impairment
- Possible hypotension and dehydration in susceptible populations
- Risk of UTI, genital mycotic infections

Study Results: Canagliflozin and A1c reduction

Canagliflozin and Weight Changes

SGLT-2 Inhibitors-selected safety considerations

Cancer risk?
- In clinical studies bladder cancer noted: 0.16% Dapagliflozin vs. 0.03% placebo
- Reilly et. al. found no increase bladder cancer in vitro or in vivo with animal models and Dapagliflozin

Cardiovascular issues
- Small increases in LDL cholesterol seen in SGLT-2 inhibitor use
- -CANVAS (Canagliflozin) and DECLARE (Dapagliflozin) studies ongoing- early meta-analysis shows no increased cardiovascular risk

SGLT-2 inhibitors and cardiovascular risk the “Empa-Reg Outcome” Study

- Randomized double-blind placebo controlled trial to assess effects of Empagliflozin vs. placebo on CV events in type 2 diabetic patients at high CV risk
- 7028 patients randomly assigned Empagliflozin 10 mg vs. 25 mg vs. placebo followed over 3.1 years
- Primary endpoint: death from CV causes, nonfatal MI or nonfatal stroke
Empa-Reg Outcome Clinical study design

- Patients 18 or older with type 2 DM
- BMI of 45 kg/m² or less
- All had established CV disease
- Renal eGFR of at least 30 ml/min/1.73m² BSA
- Baseline A1c 7.0 to 9.0
- Stable background DM therapy for 12 weeks prior to randomization
- Treat other medical issues (HTN, lipids) per usual standard of care
- Study continued until at least 691 primary outcome events

Empa-Reg Outcome Clinical study Results

- Primary outcome (CV death, nonfatal stroke or MI) 490/4687 (10.5%) of pooled Empagliflozin group vs. 282/2333 (12.1%) in placebo group (p<0.0001 for non-inferiority and p=0.04 for superiority)
- No significant differences in nonfatal MI and stroke
- Significantly less CV death 3.7% vs. 5.9% (38% RR reduction)
- Significantly less heart failure hospitalization 2.7% vs. 4.0% (35% RR reduction)
- Significantly fewer deaths from any cause 5.7% vs. 8.3 % (32% RR reduction)

Empa Reg Outcome Trial results

- Effects on glycemic control and A1c reduction (not a primary endpoint of this study)
  - A1c of 7.81 in pooled Empa vs. 8.16% in placebo

Empa Reg Outcome Trial results

- No difference in CV outcomes between the 10 mg and 25 mg dose groups
- The benefits seen in the empagliflozin group was seen early in study and continued
- Increased rate of genital mycotic infections in Empagliflozin group but not other adverse events.
- Mechanism of reduced CV events might include effects on weight, visceral adiposity, blood pressure, reduction in uric acid, reduction in microalbuminuria and possibly changes in arterial stiffness, cardiac function and myocardial oxygen use.

Patient Case # 2

- 52 year old female with Type 2 DM, hypertension, pure hyperlipidemia, tobacco use. On maximum dose Glipizide, Linagliptin
- Intolerant to: statin drugs, Pioglitazone
- Recent labs: A1c 7.5
  - Creatinine 1.9 eGFR 38
  - total cholesterol 210
  - LDL 124
  - triglycerides 140

You want to add which diabetes medication?

- A. Metformin
- B. Colesevelam
- C. Empagliflozin
- D. NPH insulin
Patient Case # 3
44 year male old with recent DM diagnosis currently on Metformin
Family history: thyroid problems, rheumatoid arthritis
BMI: 22 kg/m² A1c is 9.0. FBS 220

You recommend next:
A. Adding Exenatide LAR
B. Adding Glimepiride
C. Adding Canagliflozin
D. Adding insulin and testing c-peptide and GAD antibody levels

Insulin Therapies-selected review and update
- Review of general insulin dosing principles
- Newer basal insulins:
  - Insulin Glargine U300 (Toujeo)
  - Insulin Degludec (Tresiba)
- U500 regular insulin
- Inhaled Insulin (Afrezza)
- Newer insulin products

Insulin Therapy
Two components:
- Basal insulin: daily insulin needs even when fasting
- Bolus insulin: insulin needs to cover meals and high sugars

Initiating Insulin therapy
- Type 2 Diabetic patients:
  - use intermediate (NPH) or long acting insulin (Glargine, Detemir, Glargine U-300, Degludec) initially as a single bedtime dose
  - Initially start at 0.1 to 0.2 u/kg (may start at higher 0.5 u/kg if markedly hyperglycemic)
- Type 1 Diabetic patients:
  - start with basal/bolus from the start
  - calculate total daily dose (TDD) as 0.5 u/kg/day
  - basal: TDD x 0.5 = QD (Glargine, Detemir, Glargine U-300, Degludec)
  - bolus: TDD x0.5 ÷ 3= TID (Lispro, Aspart or Glulisine)

Insulin Therapy-Bolus Correction Factor
- Calculating Sliding scale (Correction Factor)
  - “The 1600 rule”
    - 1600 ÷ TDD= Glucose amount (mg/dl) blood sugar reduction per 1 unit of rapid acting insulin
    - eg. Total daily insulin dose = 40 units 1600 ÷ 40= 40 mg/dl
    - to bring glucose from 140 mg/dl to target of 100 mg/dl, need 1 unit extra insulin

Insulin Therapy-Bolus Mealtime Dosing
- Calculating Mealtime (carb ratio)
  - “The 500 rule” For rapid-acting insulins (Lispro, aspart, glulisine)
  - “The 450 rule” For short-acting insulin (Human R)
    - 500 ÷ TDD= Carb amount per 1 unit of insulin
    - eg. Total daily insulin dose = 40 units 500 ÷ 40= 12.5
    - Plan to consume 60 gram carbs 60 ÷ 12.5≈ 4.8 or roughly 5 units of rapid acting insulin needed
Insulin therapy in the very insulin resistant

- Defined as those patients needing >200 units of insulin/day

Syndromic Forms of Insulin resistance

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>PATIENTS</th>
<th>DOSE RANGE</th>
<th>WEIGHT</th>
<th>REFERENCE</th>
</tr>
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<tbody>
<tr>
<td>T2DM</td>
<td>5</td>
<td>6-1000</td>
<td>58.0</td>
<td>16.21</td>
</tr>
</tbody>
</table>
| Pancreatic 
Autodestruct | 3       | 30-400     | 26.5   | 15.18     |
| Type II   | 14       | 3.3-46     | 70.6   | 15.18     |
| Syndrome  | 9        | 16.9-25    | 87.6   | 16.9(20)  |
| SIVR      | 2        | 1.6-8.4    | 125.1  | 646(5.8-18) |

Algorithm for U-500 Insulin Dosing

- Less than 200U of insulin prescribed per day
- U-500 insulin therapy (NPH, regular, Novo,hardware, glucagon, resist, resistance)

Dosing recommendations for U-500 Insulin

- Human Insulin R U-500
  - January 2016 FDA approved Humulin R U-500 Kwik Pen
  - Pen contains 1,500 units of insulin
  - Doses dial in 5 unit increments
  - Reduces risk of dosing errors of tuberculin syringes/U-100 syringes
  - Opened pen stable at room temperature for 28 days

Insulin Glargine U-300 (Toujeo)

- Same insulin ingredient as Insulin Glargine (Lantus) but in a concentrated 300 U/ml dosing
- Pharmacologically different than Glargine U-100 (Lantus)
- FDA approved for use in US in April 2015 for adults
- Delivered in a pre-filled SoloStar Pen containing 450 units of insulin per pen
- Recommended to be dosed once daily at same time of day
- Maximum dose per injection is 80 units
- Opened pen can be stored at room temperature for 42 days

Insulin Glargine U-300

- Molecular structure
- Pharmacokinetic profile
Insulin Glargine U-300

- Clinical Efficacy – Edition Trials
  - 4 open-label, controlled non-inferiority trials comparing once daily Glargine U-300 vs. Glargine U-100 (800 patient, 3 type 2 DM and 1 type 1 DM)
  - All studies showed non-inferiority in FBG and A1c reduction after 26 weeks
  - 2 of the 3 type 2 DM studies showed statistically significant drop decrease in percentage with at least 1 nocturnal hypoglycemia episode with G-300 vs. G-100
    - Edition 1 (basal + bolus +/- orals) 36% G-300 vs. 46% G-100
    - Edition 2 (basal added to orals) 22.6% G-300 vs. 27.9% G-100

- Dosing conversion
  - From BID NPH to once daily G-300 (Toujeo)
    - reduce TDD by 20%
  - From G-100 (Lantus) to G-300 (Toujeo)
    - 1:1 dosing conversion
  - Titrate up Glargine U-300 (Toujeo) dose every 3-4 days as needed

- Edition 1 (basal + bolus +/- orals) 36% G-300 vs. 46% G-100
- Edition 2 (basal added to orals) 22.6% G-300 vs. 27.9% G-100

Advantages
- Reduced insulin volume vs. Glargine-100 (Lantus SoloStar) -pen holds 450 units vs. 300 units
- More prolonged insulin release
- Possibly reduced incidence of nocturnal hypoglycemia

Disadvantages
- Temporary rise in FBS after dosage conversion/initiation
  - need for increased TDD compared with Glargine 100 (Lantus)
  - maximum is 80 units per injection
  - Cost/insurance coverage issues

Insulin Degludec

- Insulin Degludec (Tresiba) is a novel basal insulin molecule, long acting up to 42 hours
- FDA rejected for use in 2013, then approved for use in USA in September 2015 for adults
- Delivered in a pre-filled Flex Touch Pen in U-100 and U-200 pens.
- Maximum dose per injection is 160 units (using the U-200 pen)
- Opened pen can be stored at room temperature for 56 days

Insulin Degludec Clinical Trials
- Open Label studies with Degludec (Tresiba) vs. Glargine U-100 (Lantus) as basal insulin and assessing non-inferiority in A1c reduction

Study A: 52 week study of adult type 2 DM inadequately controlled on Metformin randomized to once daily Degludec (n=773) vs. Glargine U-100 (n=257)
Study B: 52 week study of adult type 2 DM uncontrolled on insulin +/- OADs randomized to once daily Degludec (n=795) vs. Glargine U-100 (n=257)

Molecular structure

Pharmacokinetic profile
Insulin Degludec

- Advantages
  - Longest acting basal insulin (42 hours) allowing for flexible dosing
  - Some evidence of reduced nocturnal hypoglycemia in open-label studies compared to Glargine U-100 (Lantus)
  - 3 ml U-200 pen contains 600 units of insulin and single dose to 160 units

- Disadvantages
  - Long-term safety of this newer insulin analog molecule is unknown
  - Advantage for nocturnal hypoglycemia not in US FDA label
  - Cost/insurance coverage issues

Insulin Inhaled (Afrezza)

- Afrezza (human insulin) inhalation powder
- Rapid acting insulin indicated in adults with diabetes
- Must be used in combination with long acting insulin in type 1 diabetes
- Not recommended for treating DKA
- Safety for use in smokers not established
- Risk of acute bronchospasm in patients with COPD or asthma—it is contraindicated in these patients
- Spirometry recommended in all patients before initiating Afrezza

Inhaled insulin: Dosing

- Blue cartridge: 4 units
- Green cartridge: 8 units

Inhaled Human insulin vs. Lispro

- Figure 2. Baseline-Corrected Glucose Infusion Rate (A) and Baseline-Corrected Serum Insulin Concentration (B) after Administration of AFREZZA or Subcutaneous Insulin Lispro in Type 1 Diabetes Patients

- Table 1. Comparison of Baseline Characteristics

- Table 2. Comparison of Baseline Insulin Use
Inhaled Insulin and Pulmonary Function

Inhaled Insulin

Advantages
- No need for needles in the “needle phobic” patient
- Improves diabetes control when added to oral therapy or basal insulin
- Small and portable device

Disadvantages
- Long-term safety is unknown
- Require spirometry
- Faster pharmacokinetics do not translate into superior efficacy over injectable rapid acting insulin analogs
- Cost/insurance coverage issues

New Insulin Therapies Coming soon

Basal Insulin: GLP-1 Receptor Agonist combination

Insulin Degludec-Liraglutide (Xultophy)
- Approved in Europe 2014
- US approval pending

Fixed dose of Degludec (1 unit) per Liraglutide (0.036 mg)

Maximum injection is 50 "dose steps" = 50 units Degludec/1.8 mg Liraglutide

Buse J. et al. IDegLira vs. Glargine alone
- 26 week open label study (n=557) study
- 1.8% A1c reduction IDegLira vs. 1.1% Glargine U-100
- 72% vs. 47% A1c goal <7 IDegLira vs. Glargine U-100
- 39% vs. 12% reached A1c goal with low BS IDegLira vs. Glargine

New Insulin Therapies Coming soon

Basal insulin:
- Basaglar (Eli Lilly) bio-similar insulin glargine U-100 (FDA Approved December 2015)
- Peglispro (Eli Lilly) Ceased development 12/15 due to increased fatty liver seen in phase 3 studies

Bolus/prandial insulin:
- FIAsp NN-1218 (Novo Nordisk)
  - faster acting insulin aspart (10-15 minutes onset)
  - Phase III studies (Onset®Trials 1-4)
  - Type 1 patients significant reductions in A1c and 1-hour PPG readings vs. insulin Aspart
  - Demonstrates good compatibility for insulin pump

Summary

- Diabetes is a growing problem in the US and associated with many complications and cost
- Treatment of the diabetic patient requires an individualized approach with factors including:
  - Cost of medications
  - Ability for patient to care for self/manage diabetes
  - Medical co-morbidities
  - Goals based on life expectancy
- There are many good existing and new medications available to the care provider to help in managing diabetes and emerging data that some medications may reduced macrovascular complications as well

Thank You and Happy Spring!