Type 2 Diabetes: Options after Metformin

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Disclosures

Relevant Financial Relationships
None

Off-Label/Investigational Uses
None

Other Disclosures
“These are my principles. If you don’t like them… I have others.”
- Groucho Marx
Objectives

- describe conditions where we should not move beyond metformin
- describe important adverse effects of the various anti-diabetic drugs
- compare efficacy of the various drugs
- decide on which additional antidiabetic drug to use when metformin isn’t enough
Case 1

46 y Man Type 2 DM ~1 y

- Seen ~1 y back. HbA1c 9.7%.
  - BMI 49 kg/m²; met dietitian, not nurse
- Metformin 1 g twice a day
  - Controlled ~6 months, sent back to PCP
- Simvastatin 20 mg/ d ~3 months back
- He calls PCP with high numbers
  - Convinced hyperglycemia \(\leftarrow\) simvastatin
  - PCP e-Consults us
46 y M with recent worsening of hyperglycemia on metformin. What should I recommend?

- **ADA guidelines**
  - *treatment decisions made in conjunction with the patient preferences, needs, values*

- **AACE algorithm**
  - **GLP-1 RA, DPP4-i, TZD†, SGLT-2-i†, Basal insulin†, Colesevelam, Bromocriptine QR, AG-i, SU/GLN†** (†: use with caution) (suggested hierarchy of usage)

- **ICSI glycemic control algorithm**
  - *sulfonylureas are acceptable secondary choices; relatively inexpensive*

- **Take history, examine**
46 y M with recent worsening of hyperglycemia on metformin.

What should I recommend?

1. ADA Guidelines
2. AACE Algorithm
3. ICSI glycemic control algorithm
4. Take history, examine
Case 3

39 y Woman New Type 2 DM

- F Plasma Glucose 312 mg/dL
- HbA1c 9.7%
- Inactive secretary, ex-smoker
- Obstructive Sleep Apnea
- COPD, CHF
- BMI 38 kg/m²
- AST 76 U/L; ALT 65 U/L
- Creatinine 1.3 mg/dL (N 0.6-1.1)
Can we use metformin?

1. Yes
2. No, patient has OSA
3. No, patient has COPD and CHF
4. No, patient has liver disease
5. No, patient has CKD
Before we talk about What After Metformin

- What is the cause of the worsening of glucose control?
- Do we really have to move beyond metformin at this time?
- Does this patient really need to lower HbA1c by escalating therapy?
What is the cause of worsening glucose?

- **Lifestyle:**
  - Not restricting calories
    - esp. calorie dense foods and hollow calories
  - Inactivity

- **Clinical:**
  - Infections, CV diseases, Malignancies
  - Trauma/ emotional/ depression
  - Medications, eg. Glucocorticoids

- Not using enough metformin
  - Not taking it

- Progression of the disease process
  - Decreased insulin secretion
Do we really have to move beyond metformin?

Misunderstanding:
- It is nephrotoxic
- It is unsafe in NASH
- It is unsafe in heart failure
- It causes lactic acidosis/increased lactate conc.

Unable to tolerate:
- Titrate to the best tolerated dose (≤2.5g)
- Take after full meals

Contraindicated:
- Creatinine ≥1.4 F/ ≥1.5 M
  - GFR <50 mL/min/BSA
  - Age >80 y
- End-stage liver/heart
- History of lactic acidosis

Missed Opportunity:
- Discontinued pre-op/pre-procedure
Does **this** patient really need to lower HbA1c by escalating therapy?

**No**
- HbA1c not high enough to justify intensification
  - Elderly/ limited life
  - Long standing diabetes
  - Extensive comorbidities
  - Advanced complications
- At risk for hypoglycemia & related complications

**Yes**
- Patient at risk of DM complications
  - Young/ long lifespan
  - Short duration of diabetes
  - Not at risk for hypoglycemia & complications
The first three cases

- 46 y M, recent worsening on metformin
  - Examination: axillary abscess

- 67 y M, hypoglycemia, glipizide 6 mo
  - Metformin was discontinued for CECT
    Switched back to metformin

- 39 y W, new diagnosis of DM
  w OSA, COPD, CHF, Fatty Liver, CKD
  - Metformin is safer/ better
Key Points for Therapy

- **Metformin first-line**

- **After metformin**
  - Long term studies have failed to show benefits of any particular 2nd line agent over any other
  - Combination Therapy (1–2 oral or injections)

Inzucchi et al Position Statement ADA, EASD. Diabetes Care 2012
Treatment options: then and now!

- Metformin, Phenformin
  - Glucophage®, Glucophage XR®, Riomet®, DBI®
- Sulfonylurea: Chlorpropamide, Tolbutamide, Glyburide
  - Orinase, Diabeta, Metformin, Precose®, Glyset®
- Meglitinide: Repaglinide, Nateglinide
  - Prandin®, Starlix®
- Thiazolidinedione (TZD): Pioglitazone, Rosiglitazone
  - Actos®, Avandia®
- α-glucosidase inhibitor: Acarbose, Miglitol
  - Precose®, Glyset®
- SGLT-2 inhibitor: Canagliflozin
  - Dapagliflozin, Empagliflozin
- GLP-1 receptor agonist: Exenatide, Liraglutide, Albiglutide, Dulaglutide
  - Byetta®, Bydureon®, Victoza®, Tanzeum®, Trulicity®
- DPP-4 inhibitor: Sitagliptin, Saxagliptin, Linagliptin, Alogliptin
  - Januvia®, Onglyza®, Tradjenta®, Nesina®
- Dopamine D2-receptor agonist: Bromocriptine QR
  - Cycloset®
- Bile acid binding resin: Colesevelam
  - Welchol®
- Insulin: NPH, R, Lente, Aspart, Glulisine, Lispro, Detemir, Glargine
  - N, R, Humalog®, Apidra®, Novolog®, Levemir®, Lantus®
- Amylin analog: Pramlintide
  - Symlin®
What After Metformin?

- Metformin
  - Glucophage®, Glucophage XR®, Riomet®

- Sulfonylurea: Glipizide, Glimepiride, Glyburide
  - Glucotrol®, Glucotrol XL®, Amaryl®, Diabeta®, Micronase®, Glynase®

- Meglitinide: Repaglinide, Nateglinide
  - Prandin®, Starlix®

- Thiazolidinedione (TZD): Pioglitalone, Rosiglitazone
  - Actos®, Avandia®

- α-glucosidase inhibitor: Acarbose, Miglitol
  - Precose®, Glyset®

- SGLT-2 inhibitor: Canagliflozin
  - Dapagliflozin, Empagliflozin
  - Invokana®, Farxiga®, Jardiance®

- GLP-1 receptor agonist: Exenatide, Liraglutide, Albiglutide, Dulaglutide
  - Byetta®, Bydureon®, Victoza®, Tanzeum®, Trulicity®

- DPP-4 inhibitor: Sitagliptin, Saxagliptin, Linagliptin, Alogliptin
  - Januvia®, Onglyza®, Tradjenta®
  - Nesina®

- Dopamine D2-receptor agonist: Bromocriptine QR
  - Cycloset®

- Bile acid binding resin: Colesevelam
  - Welchol®

- Insulin: NPH, R, Aspart, Glulisine, Lispro, Detemir, Glargine
  - N, R, Humalog®, Apidra®, Novolog®, Levevir®, Lantus®

- Amylin analog: Pramlintide
  - Symlin®
Monotherapy

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<thead>
<tr>
<th>Efficacy (↓A1c)</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Side Effects</th>
<th>Costs</th>
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<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>Low risk</td>
<td>Neutral/ Loss</td>
<td>Low</td>
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Two Drugs

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<tr>
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<td>High</td>
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<tr>
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<td>Hypoglycemia</td>
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<tr>
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<td>GL</td>
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<td>DPP-4 inhibitor</td>
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<td>Low risk</td>
<td>GI</td>
<td>High</td>
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Three Drug Combinations

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<th>GLP-1ra</th>
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More Complex Insulin Strategies

<table>
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<tr>
<th>Insulin (multiple Daily Doses)</th>
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Inzucchi et al Position Statement ADA, EASD. *Diabetes Care* 2012
Parameters to Help Decide: What After Metformin?

- Reduction in HbA1c
- Weight Changes
- Reduction in Blood Lipids
- Effects on Mortality and CV Events
- Effects on Renal Failure & Retinopathy
- Adverse Effects
- Clinical Utility: Cost, Complexity of Use
Parameters to Help Decide: What After Metformin?

- Reduction in HbA1c
- Weight Changes
- Reduction in Blood Lipids
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- Effects on Renal Failure & Retinopathy
- Adverse Effects
- Clinical Utility: Cost, Complexity of Use
HbA1c Changes on 2nd Agent Added to Metformin

TZDs GLP1-ra SU Insulin gliptins glinides AGi SGLT-2 Bromo- Colese-

% 0 -0.2 -0.4 -0.6 -0.8 -1 -1.2 -1.4 -1.6 -1.8

*: addition to metformin + SU

Hirst et al Diabetologia 2013
Rosenstock et al Diabetes Care 2012
Vinik et al Endocr Pract 2012
McIntosh et al Open Medicine 2011
after Phung et al JAMA 2010
Bays et al Arch Intern Med 2008
Addition of a Second Agent to Metformin

**HbA1c Reduction (~1%)**

Exceptions to the rule

Reduction by ~0.5%

- DPP-4 inhibitors (gliptins)
- Meglitinides
- Newer agents

*modified after Nathan et al. Diabetes Care 2008*
Other Issues with Sulfonylurea Use

- Stability of Blood Glucose Control on Sulfonylurea vs. other classes of antidiabetics
- Effect of Sulfonylureas on Heart differences between sulfonylureas
- Mortality on Sulfonylurea vs. other classes of antidiabetics
Stability of Glycemic Control on Sulfonylurea
Stability of Glycemic Control on Sulfonylurea

Plasma glucose (mg/dL) and HbA1c(%) over time for Non Obese and Obese individuals on different medications:

- Insulin
- Metformin
- Sulfonylurea

Graphs show a decrease in plasma glucose and HbA1c levels at 0, 1, 2, 3, 4, 5, and 6 years, with a comparison between non-obese and obese patients.

All regimens resulted in similar Life Years and Quality Adjusted Life Years

- sulfonylurea, DPP-4 inhibitor, GLP-1 receptor agonists, or insulin

Regimen with sulfonylurea:
- significantly lower cost per QALY
- resulted in the longest time to insulin dependence
Parameters to Help Decide: What After Metformin?

- Reduction in HbA1c
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- Clinical Utility: Cost, Complexity of Use
Weight Changes on 2\textsuperscript{nd} Agent Added to Metformin
Weight Changes on 2\textsuperscript{nd} Agent Added to Metformin

-4 \rightarrow -3 \rightarrow -2 \rightarrow -1 \rightarrow 0 \rightarrow 1 \rightarrow 2 \rightarrow 3 \rightarrow 4

SGLT-2 inhib. AGi GLP1-ra

DPP4-i Colese- Bromo-
velam gliptins criptine

Glinides SU TZDs Insulin

*: addition to metformin + SU

Vasilakou et al Ann Intl Med 2013
Rosenstock et al Diabetes Care 2012
Vinik et al Endocr Pract 2012
McIntosh et al Open Medicine 2011
after Phung et al JAMA 2010
Bays et al Arch Intern Med 2008
Weight Changes

**weight loss**

- **GLP-1 agonists**
  - (exenatide; liraglutide; albiglutide)
  - -2.8 kg (-3.4 to -2.3)
    - Vilsbøll et al BMJ 2012

- **α-glucosidase inhibitors**
  - (acarbose; miglitol)
  - -1.8 kg (-0.8 to -3.0)
    - Phung et al JAMA 2010

- **SGLT-2 inhibitors**
  - (canagliflozin; dapagliflozin)
  - -1.8 kg (-0.1 to -3.5)
    - Vasilakou et al Ann Int Med 2013

**weight gain**

- **Insulin**
  - 0-4.5 kg
    - Monami et al DRCP 2008

- **TZDs**
  - (Pioglitazone, Rosiglitazone)
  - 2.3 kg (1.7 to 2.9)
    - Phung et al JAMA 2010

- **Sulfonylureas**
  - (glipizide, glibenclamide, glimepiride)
  - 2.0 kg (0.9 to 3.0)
    - Phung et al JAMA 2010

**weight neutral**

- DPP-4 i (gliptins) (Januvia®, Onglyza®, Tradjenta®, Nesina®)
- Colesevelam (Welchol®)
- Bromocriptine (Cycloset®)

modified after Qaseem et al Ann Intern Med 2012
Parameters to Help Decide: What After Metformin?

- Reduction in HbA1c
- Weight Changes
- Reduction in Blood Lipids
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- Effects on Renal Failure & Retinopathy
- Adverse Effects
- Clinical Utility: Cost, Complexity of Use
Changes in Blood Lipids beyond metformin

Improves LDL cholesterol only

- Colesevelam (Welchol®) (-9 to -15%; Tg: ~+8%)

Improve triglycerides and HDL cholesterol

- Pioglitazone (Actos®) (-10 to -12%; 9 to 11%)
- Insulin (~-20%; ?)

Worsen LDL cholesterol

- TZDs
  - Rosiglitazone (Avandia®) (~+15%)
  - Pioglitazone (Actos®) (+1 to +4%)
- SGLT-2 inhibitors
  - Canagliflozin (Invokana®) (+4.5 to +8%)
  - Dapagliflozin (Farxiga®) (~+ 9·5%)

References:
- Spanheimer et al. Am J Cardiol 2009
- Rosenstock et al. Diabetes Care 2012
- Spanheimer et al. Am J Cardiol 2009
Parameters to Help Decide: What After Metformin?

- Reduction in HbA1c
- Weight Changes
- Reduction in Blood Lipids
- Effects on Mortality and CV Events
- Effects on Renal Failure & Retinopathy
- Adverse Effects
- Clinical Utility: Cost, Complexity of Use
Mortality & CV Morbidity beyond metformin

Possibly reduces CV morbidity/ mortality

- **Sulfonylurea, Insulin**
  - Death: HR 0.87 (0.79 to 0.96)
  - UKPDS Holman et al *NEJM* 2008

- **TZD – pioglitazone (Actos®)**
  - Dormandy et al *Lancet* 2005

- **Bromocriptine (Cycloset®)**
  - Gaziano et al *J Am Heart Assoc* 2012

- **α-glucosidase inhibitors (Precose®)**
  - Chiasson et al *JAMA* 2003

Possibly increases CV morbidity/ mortality

- **Heart Failure: TZD –**
  - rosiglitazone (*Avandia®*)
  - pioglitazone (*Actos®*)
  - Singh et al *Diab Care* 2007

*Modified after Qaseem et al Ann Intern Med. 2012*
Renal Failure & Retinopathy

beyond metformin

UKPDS
Renal Failure, Vitreous Hemorrhage, Laser Rx

ADVANCE
Renal Failure

ADVANCE
Macular edema

ADVANCE
Retinal Hemorrhage

0.76 (0.64 to 0.89)
Holman et al NEJM 2008

0.35 (0.15 to 0.83)
Perkovic et al Kid Intl 2013

0.59 (0.34 to 1.03)
Beulens et al Diabetologia 2009

0.78 (0.61 to 1.01)
Beulens et al Diabetologia 2009

Holman et al NEJM 2008

Perkovic et al Kid Intl 2013

Beulens et al Diabetologia 2009

Beulens et al Diabetologia 2009
Renal Failure & Retinopathy
beyond metformin

Sulfonylurea and/or Insulin ± other agents reduce
- Renal failure
- Vitreous hemorrhage
- Need for retinal photocoagulation
Parameters to Help Decide: What After Metformin?

- Reduction in HbA1c
- Weight Changes
- Reduction in Blood Lipids
- Effects on Mortality and CV Events
- Effects on Renal Failure & Retinopathy
- Adverse Effects
- Clinical Utility: Cost, Complexity of Use
Hypoglycemia from Sulfonylurea & Meglitinides

- Mostly within weeks of commencing
- Longer acting > shorter acting:
  - glyburide (Glynase®) > glipizide XL (Glucotrol XL®)
  - ~ glimepiride (Amaryl®) > glipizide (Glucotrol®)
  - > repaglinide (Prandin®) ~ nateglinide (Starlix®)
- Advanced age, polypharmacy
- Comorbidities
  - Renal impairment
  - Autonomic neuropathy

modified after Inzucchi et al Position Statement ADA, EASD. Diabetes Care 2012
Other Issues with Sulfonylurea Use

- Stability of Blood Glucose Control on Sulfonylurea vs. other classes of antidiabetics
- Effect of Sulfonylureas on Heart differences between sulfonylureas
- Mortality on Sulfonylurea vs. other classes of antidiabetics
Mortality on Sulfonylurea/Insulin

Survival (%)

Years Since Randomization

P=0.89

87.9 Sulfonylurea/Insulin

88.2 Metformin/Thiazolidinedione

The BARI 2D Study Group N Engl J Med 2009
Effects of Sulfonylureas on Heart
Myocardial Ischemic Pre-conditioning

Nondiabetics

Type 2 Diabetes

ST Segment Shift (mV)

Control

Glyburide

Glimepiride

Chest Pain

modified after Lee and Chou J Clin Endocr Metab 2003
Ischemic Preconditioning is Blocked by Glyburide

- but not glimepiride
  - Klepzig et al. *Eur Heart J* 1999
  - Lee and Chou *J Clin Endocr Metab* 2003

- but not glipizide
  - Flynn et al. *Cardiovasc Drugs Therapy* 2005
Adverse Effects

**Thiazolidinediones (TZDs)**

**Pioglitazone (Actos®) Rosiglitazone (Avandia®)**

- **Fluid retention, CHF (2-3x), worsening of HF**
  - Singh et al, *Diab Care* 2007

- **Osteoporosis – ↑ fractures (2x)**

- **Weight gain, fat gain**
  - Phung et al, *JAMA* 2010

- **Anemia (esp. with ACE-i/ ARB)**

- **¿Bladder cancer – pioglitazone 1.2 (1.1–1.4)?**
  - Ferwana et al, *Diabetic Med* 2013
Adverse Effects

**GLP-1 Based Therapies**

INJ: exenatide (Byetta®, Bydureon®); liraglutide (Victoza®); albiglutide (Tanzeum®); dulaglutide (Trulicity®)

TAB: sitagliptin (Januvia®); saxagliptin (Onglyza®); linagliptin (Tradjenta®); alogliptin (Nesina®)

- **GLP-1 receptor agonists:**
  - vomiting (~25%→10%), nausea (~50%)
  - ¿medullary thyroid cancer?
- **DPP-4 inhibitors (‘gliptins’):**
  - angioedema, infections
    - heart failure
  - [saxagliptin (Onglyza®) HR 1.27 (1.07 to 1.51);
    sitagliptin (Januvia®) HR 1.84 (1.16-2.92)]
- **Both:**
  - ¿Pancreatitis?
  - ¿Pancreatic cancer?
Adverse Effects
SGLT-2 inhibitors
canagliflozin, dapagliflozin, empagliflozin

(Invokana®, Farxiga®, Jardiance®)

- Genitourinary infections
  - Balanitis, Acquired phimosis
  - Vulvovaginitis
  - UTI
  - ? prostatitis
- Increase in LDL cholesterol
- Hypoglycemia, including severe
- Hyperkalemia
- Polyuria, Polydipsia
- Hypovolemia, hypotension, asthenia, falls, incr. Hb
- Decrease GFR
  - Not if GFR < 30 mL/min/BSA
- Abdominal pain
- Pancreatitis
- Fracture – upper extremity
- ? bladder cancer
Adverse Effects
Other Antidiabetic Medications

- **Bromocriptine QR** *(Cycloset®)*
  - Nausea, dizziness, asthenia, fatigue, rhinitis
  - Impulse Control Disorders:
    - hypersexuality (OR 5.1, p=0.03);
    - gambling (OR 1.15, NS)
    - Bancos et al *Clin Endocrinol (Oxf)* 2013

- **Colesevelam** *(Welchol®)*
  - Constipation, drug interactions

- **Acarbose** *(Precose®), miglitol* *(Glyset®)*
  - Diarrhea, gas, abdominal discomfort
**First Line**
- Metformin
  - Efficacy (↓A1c): High
  - Hypoglycemia: Low
  - Weight: Low
  - Side Effects: Neutral/Loss
  - Costs: Variable

**Second Line**
- Glipizide or Glimepiride
  - Not Glyburide
  - Use the least dose
  - Costs: $4/mo

**Metformin +**
- Best outcomes
- $8/mo

**Actos®/generic Avandia®**
- Adverse effects
- $160 or 365/mo

**Table 1**
- GLP-1ra (e.g. Januvia®, Onglyza®, Tradjenta®, Nesina®)
  - Efficacy (↓A1c): High
  - Hypoglycemia: High
  - Weight: Intermediate
  - Side Effects: Loss
  - Costs: $250/mo

- SGLT2 Inhibitors (e.g. Farxiga®, Invokana®, Jardiance®)
  - Efficacy (↓A1c): Low
  - Hypoglycemia: Low
  - Weight: Loss
  - Side Effects: N/V
  - Costs: $300/mo

- Insulin
  - Efficacy (↓A1c): Highest
  - Hypoglycemia: High
  - Weight: Highest
  - Side Effects: N/V
  - Costs: $160 or 365/mo

**Adverse effects**
- Heart failure
- Hypertension
- Vomiting
- ¿Medullary Thyroid Ca?
- ¿Pancreatitis?

**Byetta®, Bydureon®, Victoza®, Tanzeum®, Trulicity®**
- Injection
  - Efficacy (↓A1c): High
  - Hypoglycemia: High
  - Weight: Moderate
  - Side Effects: Neutral
  - Costs: 375-600/mo

**GLP-1ra**
- Tablet
  - Januvia®, Onglyza®, Tradjenta®, Nesina®
  - Hypoglycemia: High
  - Weight: Moderate
  - Side Effects: N/V
  - Costs: $100/mo

**SGLT2 Inhibitors**
- Tablet
  - Farxiga®, Invokana®, Jardiance®
  - Hypoglycemia: Low
  - Weight: Low
  - Side Effects: N/V
  - Costs: $250/mo

**Insulin**
- Injection
  - Actos®, generic Actos®
  - Hypoglycemia: High
  - Weight: Highest
  - Side Effects: N/V
  - Costs: $250/mo
Thank you!

Shah.Pankaj@mayo.edu
**Case**

56 yr M, DM 2, 7 yr; metformin + glimepiride

HbA1c: 8.7%, Fasting glucose: 224 mg/dL.

He weighs 88 kg. You want to start insulin.

What would you start?

<table>
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<tr>
<th>Date</th>
<th>Medication Dose</th>
<th>Blood Glucose Test Results</th>
<th>Comments</th>
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<td>Before Breakfast Meal</td>
<td>Before Noon Meal</td>
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<td>6/7</td>
<td></td>
<td>240</td>
<td></td>
</tr>
</tbody>
</table>
Plasma Glucose and Insulin in Type 2 Diabetes Mellitus

Plasma glucose

Plasma insulin

0600 1000 1400 1800 2200 0200 0600

meal meal meal
Question

56 yr M, DM 2, 7 yr; metformin + glimepiride
HbA1c: 8.7%, Fasting glucose: 224 mg/dL.
He weighs 88 kg. You want to start insulin.

What would you start?

A. detemir (Levemir®) or glargine (Lantus®) 16 units once a day
B. NPH (Novolin N®) 16 units once a day
C. glargine (Lantus®) 24 + aspart (Novolog®) 8x3 meals; Stop glimepiride
D. Sliding scale aspart (Novolog®) insulin
Basal NPH alone plan

Basal NPH only

meal

meal

meal

NPH16

0 25 50 75 100 125 150 175 200

0600 1000 1400 1800 2200 0200 0600
Basal insulin-alone plan

Detemir/glargine once/twice a day

Plasma insulin

0600 1000 1400 1800 2200 0200 0600 meal meal meal

glargine 16
Summary

Basal Insulin as Supplement to Patient’s Own Insulin Secretion

NPH (Novolin N/ Humulin N) or glargine (Lantus®) or detemir (Levemir®) once a day (usually bedtime)

- Start at 0.1-0.2 units/kg daily
56 yr M, DM 2, 7 yr; metformin + glimepiride
HbA1c: 8.7%, Fasting glucose: 224 mg/dL.
He weighs 88 kg. You want to start insulin.
What would you start?

A. detemir (Levemir®) or glargine (Lantus®)
   16 units once a day  ... usually bedtime

B. NPH (Novolin N®)
   16 units once a day  ... usually bedtime

C. glargine (Lantus ®) 24 + aspart (Novolog®) 8x3 meals; Stop glimepiride

D. Sliding scale aspart (Novolog®) insulin
Type 2 Diabetes Mellitus

Show introduction
### Daily Routine

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>24 OR</td>
</tr>
<tr>
<td>Insulin</td>
<td>24 OR AM/PM</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>24</td>
</tr>
<tr>
<td>Liraglutide/Exenatide</td>
<td>24 OR WEEKLY / AM/PM  Take in the hour before meals.</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>24 OR Glipizide, Glimperidine, Glyburide</td>
</tr>
<tr>
<td>Gliptins</td>
<td>24</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>24</td>
</tr>
</tbody>
</table>

### Daily Sugar Testing (Monitoring)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>S M T W T F S No monitoring necessary.</td>
</tr>
<tr>
<td>Insulin</td>
<td>S M T W T F S Monitor once or twice daily, less often once stable.</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>S M T W T F S No monitoring necessary.</td>
</tr>
<tr>
<td>Liraglutide/Exenatide</td>
<td>S M T W T F S  Monitor twice daily after meals when used with Sulfonylureas. Otherwise not needed.</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>S M T W T F S Monitor 2 - 5 times weekly, less often once stable.</td>
</tr>
<tr>
<td>Gliptins</td>
<td>S M T W T F S No monitoring necessary.</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>S M T W T F S No monitoring necessary.</td>
</tr>
</tbody>
</table>

### Cost

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>$0.10 per day, $10 / 3 months (Generic available)</td>
</tr>
<tr>
<td>Insulin</td>
<td>$10 per 100 units: $10 Pen, per 100 units: $43 (No generic available - price varies by dose)</td>
</tr>
<tr>
<td>Liraglutide/Exenatide</td>
<td>$10.00 per day $900 / 3 months (No generic available)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>$11.00 per day $1,000 / 3 months (Generic available)</td>
</tr>
<tr>
<td>Gliptins</td>
<td>$10.10 per day $10 / 3 months ( Generic available)</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>$8.00 per day $750 / 3 months (No generic available)</td>
</tr>
</tbody>
</table>

### Considerations

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>In the first few weeks after starting Metformin, patients may have some nausea, indigestion or diarrhea.</td>
</tr>
<tr>
<td>Insulin</td>
<td>There are no other side effects associated with Insulin.</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Over time, 10 in 100 people may have fluid retention (edema) while taking the drug. For some it may be as little as ankle swelling. For others, fluid may build up in the lungs making it difficult to breathe. This may resolve after you stop taking the drug. 10 in 100 people at risk of bone fractures who use this drug will have a bone fracture in the next 10 years. There appears to be a slight increase in the risk of bladder cancer with this drug.</td>
</tr>
<tr>
<td>Liraglutide/Exenatide</td>
<td>Some patients may have nausea or diarrhea. In some cases, the nausea may be severe enough that a patient has to stop taking the drug. There are reports of pain in the abdomen that may be caused by inflammation of the pancreas with these agents.</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Some patients get nausea, rash and/or diarrhea when they first start taking Sulfonylureas. This type of reaction may force them to stop taking the drug.</td>
</tr>
<tr>
<td>Gliptins</td>
<td>A few patients may get nose and sinus congestion, headaches, and perhaps be at risk of problems with their pancreas.</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>Urinary tract infections and yeast infections are more common among patients taking this medication.</td>
</tr>
</tbody>
</table>
### Relative Risk Reduction from Glucose Control

<table>
<thead>
<tr>
<th>Event</th>
<th>Metformin</th>
<th>Sulfonylurea – insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitr. hemorrhage retinal coagulation or renal failure</td>
<td>7.4% vs. 8.0%</td>
<td>7.0% vs. 7.9%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.67 (0.51 to 0.89)</td>
<td>0.85 (0.74 to 0.97)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.73 (0.59 to 0.89)</td>
<td>0.87 (0.79 to 0.96)</td>
</tr>
</tbody>
</table>
UKPDS: HbA1c and Microvascular Complications

- Retinopathy requiring photocoagulation
- Vitreous hemorrhage
- Fatal or non-fatal renal failure

Stratton et al. BMJ 2000
Morbidity from diabetes over the last 2 decades

A Population with Diabetes

- Acute myocardial infarction
- Stroke
- Amputation
- ESRD
- Death from hyperglycemic crisis

B Population with or without Diabetes

- Acute myocardial infarction
- Stroke
- Amputation
- ESRD
- Death from hyperglycemic crisis

Gregg et al NEJM 2014