Diabetes in Primary Care; Getting A1C to goal. Generics to novel Agents

Anna Cosyleon, MD

Internal Medicine, Colorado Permanente Medical Group

* No financial disclosures
Learning Objectives

• Maximizing use of generic cost effective agents

• When to consider new agents

• When and how to initiate/titrater insulin
Diabetes Prevalence

• 30.3 million in US affected with DM (9.4% of population)
• 84.1 million have Pre DM (33.9% of US adults)
• More than 20% of health care spending is for people diagnosed with diabetes
• Diabetes was the 7th leading cause of death in 2015 *based on death Certificates
Every 1% reduction in A1c decreases...

- Microvascular Complications by 37%
- Myocardial infarction by 14%
- Death by 21%
A1C goal

UKPDS  new Dx DM2
  • A1c drop of 1% reduced microvasc. disease by 25%

ADVANCE  known CVD or CV risk
  • No Sig. drop macrovasc. events in 2-3 yrs. Studied

ACCORD- h/o CVD or significant risk
  • 22% increase risk death in those treated to <6%
  • Significant reduction in CVD in those with no CVD and A1c < 8.0% at baseline

UK GPRD1986-2008; Currie et al.
  • Lowest all cause mortality and progression to first CV event at an A1c of 7.5%
UKPDS – post trial monitoring showed newly diagnosed with intense control vs those with standard control had:

- At 1 yr no difference in A1c
- At 10 yrs relative risk reductions were maintained for any DM related endpoint
- DCCCT/EDIC similar in DM1
<table>
<thead>
<tr>
<th>A1C &lt;7%</th>
<th>A1C 7-7.9%</th>
<th>A1C 8-8.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-64</td>
<td>Age 65-79</td>
<td>Age &gt;80,</td>
</tr>
<tr>
<td>otherwise healthy</td>
<td>comorbidities:</td>
<td>base patient-specific</td>
</tr>
<tr>
<td>patients</td>
<td>CAD/risk equivalent,</td>
<td>risk factors</td>
</tr>
<tr>
<td>short duration of</td>
<td>HF, CRF/ESRD,</td>
<td></td>
</tr>
<tr>
<td>diabetes, long life</td>
<td>dementia, blindness,</td>
<td></td>
</tr>
<tr>
<td>expectancy,</td>
<td>amputation</td>
<td></td>
</tr>
<tr>
<td>no significant CVD</td>
<td>risk for or history of severe hypoglycemia</td>
<td></td>
</tr>
</tbody>
</table>
Approach to the Management of Hyperglycemia

<table>
<thead>
<tr>
<th>Patient / Disease Features</th>
<th>More stringent</th>
<th>A1C 7%</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia and other drug adverse effects</td>
<td>low</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>newly diagnosed</td>
<td>long-standing</td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>short</td>
<td></td>
</tr>
<tr>
<td>Relevant comorbidities</td>
<td>absent</td>
<td>few / mild</td>
<td>severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>few / mild</td>
<td>severe</td>
</tr>
<tr>
<td>Patient attitude and expected treatment efforts</td>
<td>highly motivated, adherent, excellent self-care capabilities</td>
<td>less motivated, nonadherent, poor self-care capabilities</td>
<td></td>
</tr>
<tr>
<td>Resources and support system</td>
<td>readily available</td>
<td>limited</td>
<td></td>
</tr>
</tbody>
</table>

Usually not modifiable

Potentially modifiable
How Do we Get to goal?

“Achievement of Glycemic Control was significantly associated with adherence to both A1C testing and treatment modification guidelines

Lian & Liang Current Medical Research and Opinion August 2014
Barriers to Adherence

- Denial of condition
- Forgetfulness
- Cost burden
- Lack of knowledge

- Lack of trust in provider
- Inconvenience/complexity of regimen
- Fear (side effects, needles, weight gain, hypoglycemia)

Poof Control

Increased complications

Increased health care utilization/cost
Medications -
Generics to get to goal
DM Resource ADA

Start with Monotherapy unless:
- A1C is greater than or equal to 8%, consider Dual Therapy.
- A1C is greater than or equal to 10%; blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).

Monotherapy

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low risk</td>
<td>low risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>neutral/less</td>
<td>neutral/less</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>Glucose/glucose</td>
<td>Glucose/glucose</td>
</tr>
<tr>
<td>COSTS*</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not relevant for any specific preference — choice dependent on a variety of patient & disease-specific factors).

Dual Therapy

<table>
<thead>
<tr>
<th>Dual Therapy</th>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY*</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low risk</td>
<td>low risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>neutral</td>
<td>less</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>hypoglycemia</td>
<td>less</td>
</tr>
<tr>
<td>COSTS*</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not relevant for any specific preference — choice dependent on a variety of patient & disease-specific factors).

Triple Therapy

<table>
<thead>
<tr>
<th>Triple Therapy</th>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY*</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low risk</td>
<td>low risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>neutral</td>
<td>less</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>hypoglycemia</td>
<td>less</td>
</tr>
<tr>
<td>COSTS*</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1RA (2) and GLP-1RA and basal insulin (3) on an optimally titrated insulin modulator, add GLP-1RA or real-time insulin. Monotherapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimen (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

http://care.diabetesjournals.org/content/diacare/suppl/2016/12/15/40.Supplement_1.DC1/DC_40_S1_final.pdf
### Therapeutic Options

<table>
<thead>
<tr>
<th>$</th>
<th>$$$-$$$$</th>
<th>Effectiveness?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Glinide</td>
<td>$\alpha$-glucosidase inhibitor$^2$</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>Glitazone</td>
<td>Pramlintide</td>
</tr>
<tr>
<td>Insulin</td>
<td>GLP-1 agonist</td>
<td>Colesevelam</td>
</tr>
<tr>
<td></td>
<td>DPP-4 inhibitor</td>
<td>Bromocriptine</td>
</tr>
<tr>
<td></td>
<td>SGLT2 inhibitor</td>
<td></td>
</tr>
</tbody>
</table>
Metformin; first choice

Start with Monotherapy unless:

- A1C is greater than or equal to 9%, consider Dual Therapy.
- A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).

Monotherapy | Metformin | Lifestyle Management

| EFFICACY* | high |  
| HYPO RISK | low risk |  
| WEIGHT | neutral/loss |  
| SIDE EFFECTS | GI/lactic acidosis |  
| COSTS* | low |  

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):
Metformin: first choice

• Targets fasting and prandial BGs

• Titrate metformin based on tolerance NOT finger stick glucose (faster to goal)

• Minimize GI upset by starting with low dose titrating slowly and taking with food.
  • Consider Metformin ER 500 mg or 750 mg if continued intolerances with IR
Metformin

• Continue indefinitely unless contraindications
  • Renal insufficiency, hypoxia, active liver disease or binge drinking

• Renal status: safe if GFR $> 30 \text{ mL/min}$

• Heart failure no longer a contraindication

• Consider Vitamin B 12 monitoring
Metformin 4 week self titration

• Week one:
  • Take ½ tablet with breakfast and evening meal (= 250 mg twice a day with food).

• If the patient is tolerating the medication and with no side effects to metformin, then move on to the next week.

• If the patient is not tolerating the medication at any point, they should contact their health care provider.
Metformin self titration

Week two:
• Take 1 tablet with breakfast and evening meal (= 500 mg twice a day with food).

Week three:
• Take 1½ tablets with breakfast and evening meal (= 750 mg twice a day with food).
Metformin self titration

Week four:
• Take 2 tablets with breakfast and evening meal (= 1000 mg twice a day with food).

3 months later:
• Have the hemoglobin A1c lab checked 3 months after patient is at their highest tolerable metformin dose.
Duel Therapy - Sulfonyluria 1\textsuperscript{st} choice

<table>
<thead>
<tr>
<th>Dual Therapy</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sulfonylurea</td>
</tr>
<tr>
<td><strong>EFFICACY</strong></td>
<td>high</td>
</tr>
<tr>
<td><strong>HYPO RISK</strong></td>
<td>moderate risk</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>gain</td>
</tr>
<tr>
<td><strong>SIDE EFFECTS</strong></td>
<td>hypoglycemia</td>
</tr>
<tr>
<td><strong>COSTS</strong></td>
<td>low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):
Sulfonylurea

• Most effective when endogenous insulin still available from pancreas

• Targets fasting and prandial BGs

• High hypoglycemic risk due to effect on insulin
  • Take with food and titrate slowly
  • Monitor finger sticks
Sulfonyolureas: require glucometer readings

• Titrate based on blood sugars NOT A1C

• Observe post prandial effect

• Ensure no unsafe low readings
### Sulfonylurea (SFU) Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Glimepiride</th>
<th>Glipizide</th>
<th>Glyburide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tablet</strong></td>
<td>1, 2, 4 mg</td>
<td>5, 10 mg</td>
<td>1.25, 2.5, 5 mg</td>
</tr>
<tr>
<td><strong>Initial dose</strong></td>
<td>1-2 mg QD</td>
<td>2.5-5 mg BID</td>
<td>1.25-2.5 mg BID</td>
</tr>
<tr>
<td><strong>Max effective dose</strong></td>
<td>4-8 mg QD</td>
<td>10 mg BID</td>
<td>10 mg BID</td>
</tr>
</tbody>
</table>

- GDM
Glimepiride Self titration

Week one:

• Take ½ tablet with breakfast (= 1 mg once daily with food).

• If the fasting blood sugar is always less than 130, stay at that dose.

• If the fasting blood sugar is greater than 130 two or more times during week one, then move on to week two.
Glimepiride Self titration

**Weeks two and three:**

- Take 1 tablet with breakfast (= 2 mg once daily with food).

- If the fasting blood sugar is always less than 130, stay at this dose.

- If the fasting blood sugar is greater than 130 two or more times during these two week, then move on to week four.
Glimepiride Self titration

Week four:

• Take 2 tablets with breakfast (= 4 mg once daily with food).
  • If the fasting blood sugar is always less than 130, stay at this dose.
  • If the fasting blood sugar is greater than 130 two or more times during this week, then the patient should contact their health care team for instructions.

• Check hemoglobin A1C 3 months after the patient reaches their goal dose of Glimepiride.
Blood Glucose targets for A1c goal <7%

<table>
<thead>
<tr>
<th>Plasma glucose</th>
<th>Goal (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting/preprandial</td>
<td>80-130</td>
</tr>
<tr>
<td>2-hour postprandial+</td>
<td>&lt; 180</td>
</tr>
<tr>
<td>At bedtime</td>
<td>100-150</td>
</tr>
</tbody>
</table>

*Target postprandial BGs when premeal BGs at goal but A1c above goal*
Key points: Sulfonylureas

• Avoid Medical Inertia – titrate based on blood sugars to get adequate control sooner than titrating based on A1Cs every 3+ months

• Use Patient Instructions and encourage follow up at short intervals.
Duel Therapy - TZD 2nd choice

<table>
<thead>
<tr>
<th>Dual Therapy</th>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>intermediate</td>
<td>intermediate</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>intermediate</td>
<td>high</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>Insulin (basal)</td>
<td>highest</td>
<td></td>
</tr>
</tbody>
</table>

- **EFFICACY**:
  - high
  - high
  - intermediate
  - intermediate
  - high
  - highest

- **HYPO RISK**:
  - moderate risk
  - low risk
  - low risk
  - low risk
  - low risk
  - high risk

- **WEIGHT**:
  - gain
  - gain
  - neutral
  - loss
  - loss
  - gain

- **SIDE EFFECTS**:
  - hypoglycemia
  - edema, HF, fxs
  - rare
  - GU, dehydration, fxs
  - GI
  - hypoglycemia

- **COSTS**:
  - low
  - low
  - high
  - high
  - high
  - high

---

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):
Pioglitazone

- Pioglitazone dosing: Start at 15 mg qd. Titrate by 15 mg every month; Max 45 mg per day
- Targets fasting and postprandial BGs
- A1C lowering potential up to 1.5%
- Initial response in 2-4 weeks/peak response 6-12 weeks
- Check ALT at baseline and periodically if indicated
## Pioglitazone (generic)

<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low hypoglycemia</td>
<td>Edema/wt gain (1-3 kg)</td>
</tr>
<tr>
<td>No renal adjustments</td>
<td>HF exacerbation (Black Box)</td>
</tr>
<tr>
<td></td>
<td>Fracture Risk</td>
</tr>
<tr>
<td></td>
<td>? Bladder cancer</td>
</tr>
</tbody>
</table>
### Triple Therapy

<table>
<thead>
<tr>
<th>Sulfonylurea +</th>
<th>Thiazolidinedione +</th>
<th>DPP-4 inhibitor +</th>
<th>SGLT2 inhibitor +</th>
<th>GLP-1 receptor agonist +</th>
<th>Insulin (basal) +</th>
</tr>
</thead>
<tbody>
<tr>
<td>TZD</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>TZD</td>
</tr>
<tr>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td>or TZD</td>
<td>or SU</td>
<td>or TZD</td>
<td>or DPP-4-i</td>
</tr>
<tr>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or DPP-4-i</td>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
</tr>
<tr>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td>or Insulin&lt;sup&gt;®&lt;/sup&gt;</td>
<td>or GLP-1-RA</td>
<td>or Insulin&lt;sup&gt;®&lt;/sup&gt;</td>
<td>or GLP-1-RA</td>
</tr>
<tr>
<td>or Insulin&lt;sup&gt;®&lt;/sup&gt;</td>
<td>or Insulin&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).
DPP-4 Inhibitors – “gliptins”

• Renal dose adjustments needed for all but Linagliptin (Tradjenta)

• Targets prandial > fasting

• A1C lowering potential only up to 0.8% for over $300/month

• Onset same day/Peak 2-5 days

• Recommend against the use of DPP-4 inhibitors with GLP-1 Agonist – duplication in therapy
DPP-4 Inhibitors – Linagliptin, alogliptin, saxagliptin, sitagliptin

<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Neutral</td>
<td>Minimal A1C lowering</td>
</tr>
<tr>
<td>Low hypoglycemia (increased with insulin/SU)</td>
<td>Heart Failure risk – specific to alogliptin and saxagliptin</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
</tr>
</tbody>
</table>
GLP-1 Agonist – “tides”

• Do not use in eGFR <30 ml/min/1.73m²

• Targets fasting > prandial with the long acting forms

• A1C lowering potential up to 1.5%

• Initial response in 2 weeks/peak response 6-7
GLP-1 Agonist – exenatide, liraglutide, albiglutide, dulaglutide, exenatide

<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss 1-3 kg</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Low hypoglycemia (increased with insulin/SU)</td>
<td>Medullary Thyroid cancer – avoid use in personal or family history</td>
</tr>
<tr>
<td>? Cardiovascular risk reduction</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td></td>
<td>Injectable and injection site reactions</td>
</tr>
</tbody>
</table>
SGLT2 inhibitors -

- Use Empagliﬂozin (Jardiance™) ½ tab 25 mg qd
  - Avoid eGFR <45 ml/min/1.73m²
- Targets prandial and fasting
- A1C lowering potential up to 0.8%
- Onset same day/Peak 2-5 days
- Take with first meal of the day
SGLT2 inhibitors – empagliflozin, canagliflozin, dapagliflozin

<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowers BP</td>
<td>Ketoacidosis</td>
</tr>
<tr>
<td>Weight loss (1-3 kg)</td>
<td>Fracture risk</td>
</tr>
<tr>
<td>? Secondary CV risk reduction</td>
<td>? Bladder cancer</td>
</tr>
<tr>
<td>Low hypoglycemia</td>
<td>Increase LDL</td>
</tr>
<tr>
<td></td>
<td>UTI, mycotic infections</td>
</tr>
</tbody>
</table>
Stopping Therapy

• Continue **metformin** in absence of intolerance or contraindications
  • Regardless of insulin regimen
  • Stop if eGFR <30ml/min/m²

• Stop **sulfonylurea/meglitinide**
  • When on multi-dose bolus insulin, at the very latest
  • Continue during basal insulin due to meal time coverage needs
Stopping Therapy

- Stop pioglitazone
  - When beginning insulin
  - If rapid weight gain

- Stop incretin/SGLT2 based therapies
  - If no/limited response after 3-6 months
  - Initiation of insulin especially if also on a SU
### A1c Reduction and Cost Comparisons

<table>
<thead>
<tr>
<th>Drug</th>
<th>A1C Reduction with Monotherapy</th>
<th>Annual Cost per Avg % A1C Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.0% to 2.0%</td>
<td>$</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>1.0% to 1.5%</td>
<td>$</td>
</tr>
<tr>
<td>TZD e.g. Pioglitazone</td>
<td>0.5% to 1.5%</td>
<td>2 x $</td>
</tr>
<tr>
<td>NPH or Regular vials*</td>
<td>0.5% to 1.5%</td>
<td>9$</td>
</tr>
<tr>
<td>Humalog® vials*</td>
<td>1.5% to 3.5%</td>
<td>18 x $</td>
</tr>
<tr>
<td>Lantus® vials*</td>
<td>1.5% to 3.5%</td>
<td>90 x $</td>
</tr>
<tr>
<td>SGLT2 e.g. empagliflozin</td>
<td>0.5% to 1%</td>
<td>190 x $</td>
</tr>
<tr>
<td>GLP-1 e.g. Exenatide ER</td>
<td>1% to 1.5%</td>
<td>480x $</td>
</tr>
<tr>
<td>DPP-4 e.g. Linagliptin</td>
<td>0.5-1%</td>
<td>312x $</td>
</tr>
</tbody>
</table>

*Using 30 units per day  **Using 25 mg ½ qd
When is Insulin the best choice?

1. Fasting plasma glucose >250 mg/dL or
2. A1C >10% or
3. Random plasma glucose consistently >300 mg/dL or
4. A1C ≥ 2% from goal with oral hypoglycemic agents or
5. Oral hypoglycemic agents are contraindicated or
6. Hyperglycemia and...
   a) Ketonuria / Metabolic acidosis
   b) Symptomatic diabetes with polyuria, polydipsia, and weight loss
Cost effective 3 med combo

NPH Insulin is the 3rd line agent of choice for most DM 2 patients who need a cost effective regimini
Why not Glargine for every patient?

• NPH and glargine insulins have been shown to be equally efficacious at lowering A1c in multiple published studies.

• Investigators of a comprehensive Cochrane review and meta-analysis concluded that long-acting insulin analogues, such as glargine, provide only a minor clinical benefit over NPH in type 2 diabetes related to symptomatic and nocturnal hypoglycemia.

Why not Glargine for every patient?

• There was no clinical or statistically significant difference with the mean change for fasting blood glucose (FBG) or A1c between the NPH and glargine groups.

• There was no significant difference in confirmed or severe hypoglycemia with NPH compared to glargine. Patients on glargine were less likely to experience symptomatic or nocturnal episodes.

• Glargine is currently 2 times more expensive than NPH.

Psychological insulin resistance is common, but not all patients are resistant

Questionnaire in ~700 Type 2 DM patients not on Insulin, willingness to begin insulin therapy

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>~25% very willing</td>
<td>~25% quite willing</td>
</tr>
<tr>
<td>~25% slightly willing</td>
<td>~25% unwilling</td>
</tr>
</tbody>
</table>

Insulin Needles
Implementing Insulin Starts Psychological Insulin Resistance

**It prevents** blindness, kidney failure and leg loss

**It’s natural** it’s what your body makes

**It’s OK** to use with other drugs

**It quickly** adjusts to plan changes

**It’s reliable** and it always lowers your sugar!
How to start NPH insulin

• Start NPH. (Administration time should be consistent.)
• Set dose initiation of insulin
• NPH – 5-10 units at bedtime
  A weight based formula is more precise:
  0.2 units/kg (e.g. total weight in lbs/2.2 = kg X 0.2 units)
• Titration: Increase the dose by 1 unit every day until the morning (fasting) glucose is less then 110 mg/dl
• Do not stop the oral hypoglycemic agents at this time.
Implementing Insulin Starts

**NPH:**
Start 5-10 units once a day

**Finger Stick:**
Check finger stick each morning

- If over 120, add 1 to last dose
- If 70 to 120, no change from last dose
- If under 70, take away 1 from your last dose
Blood Sugar Targets to reach your A1c target

<table>
<thead>
<tr>
<th>When</th>
<th>Ideal</th>
<th>Acceptable</th>
<th>Take action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before meals</td>
<td>80-130</td>
<td>80-140</td>
<td>Over 140</td>
</tr>
<tr>
<td>2 hr after meals</td>
<td>&lt;160</td>
<td>&lt;180</td>
<td>Over 180</td>
</tr>
<tr>
<td>At bedtime</td>
<td>110-150</td>
<td>110-160</td>
<td>Under 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Over 160</td>
</tr>
</tbody>
</table>
Insulin action curves
## Insulin Action Profiles

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Simplified Coverage Message</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humalog®</td>
<td>Covers that meal</td>
</tr>
<tr>
<td>Regular</td>
<td>Covers up to next meal</td>
</tr>
<tr>
<td>NPH</td>
<td>Covers ½ the day</td>
</tr>
<tr>
<td>Lantus®</td>
<td>Covers all day</td>
</tr>
</tbody>
</table>
Key Point: Basal Insulin (NPH)

• Make clear it is not a sign of failure
• Emphasize simple nightly dose
• Bedtime basal insulin targets fasting BGs
• Bedtime dose allows pancreatic support overnight
• Suppresses hepatic glucose production
Key point: Basal Insulin (NPH) and other DM medications

• Continue metformin which inhibits gluconeogenesis and improves insulin sensitivity

• Continue sulfonylurea to cover daily food intake
Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent

Start: 10 U/day or 0.1-0.2 U/kg/day
Adjust: 10-15% or 2-4 units once or twice weekly to reach FBG target
For hypo: Determine & address cause; if no clear reason for hypo, change dose by 4 units or 10-20%

Add 1 rapid-acting insulin injection before largest meal
Start: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider basal by same amount.
Adjust: dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached.
For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

If A1C not controlled, consider combination injectable therapy

Add GLP-1 RA
If not tolerated or A1C target not reached, change to 2 injection insulin regimen
For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

Change to premixed insulin twice daily (before breakfast and supper)
Start: Divide current basal dose into ½ AM, 1/3 PM or ½ AM, ½ PM
Adjust: dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

If A1C not controlled, advance to basal bolus

Add >2 rapid-acting insulin injections before meals ("basal-bolus")
Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider basal by same amount.
Adjust: dose(s) by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

If A1C not controlled, advance to 3rd injection

Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)
Start: Add additional injection before lunch
Adjust: dose(s) by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%
Monitoring A1C is not enough

• Blood Glucose testing and analysis can help providers better manage patients with diabetes
• Blood Glucose analysis helps identify potential problems like
  o Hypoglycemia/Hyperglycemia
  o Variability
  o Adequacy of self-monitoring
  o Patterns and trends
Summary by Time of Day

Variability curves are driven by algorithms that will visually plot variable

Pattern Recognition - Saves Time

Variability Curves - Help spot areas of concern
Target Specific Blood Glucoses

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>Insulin to Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before breakfast</td>
<td>Bedtime basal</td>
</tr>
<tr>
<td>Before lunch</td>
<td>Breakfast bolus</td>
</tr>
<tr>
<td>Before dinner</td>
<td>Breakfast basal or lunch bolus</td>
</tr>
<tr>
<td>Before bedtime</td>
<td>Dinner bolus</td>
</tr>
<tr>
<td>Overnight 12-3 am</td>
<td>Bedtime basal</td>
</tr>
</tbody>
</table>
Split Insulin Total Daily Dosing (TDD)

- Split basal insulin when AM fasting is too low but day time fasting blood sugars remain above goal.

**TDD 2/3 to 1/3 split** – more NPH insulin when awake eating and less when sleeping.
  - Determine if the PM or pre 3rd meal blood glucose can support the 2/3 dose of NPH.

- Total Daily Dose of NPH split 50-50.
  - Shift workers may need to split the doses every 12 hours.
  - Patients that are close to target pre dinner (PM) blood sugars and 2/3 is too much.
Key point: Glucose pattern informs insulin dosing needs

- Instruct the patient to check fasting BG to assess the effect of the basal insulin dose.
- Instruct patient to check 2 hours after meal(s) to assess peak affect of insulin on meal and blood glucose level.
- Match peak effect of medication with peak glucose readings.
Treat Hypoglycemia: 15/15 Rule

Eat or drink something = **15 grams** of carbohydrate such as 3 glucose tablets, ½ cup juice or regular soda

Rest for **15 minutes**

Re-check blood glucose, if it is still low (below 80), repeat first step above
## Morning Hyperglycemia and NPH

<table>
<thead>
<tr>
<th></th>
<th><strong>Dawn Phenomenon</strong></th>
<th><strong>Somogyi Effect</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated FBG due to</td>
<td>Increased hepatic glucose production during sleep cycle</td>
<td>Rebound from nocturnal hypoglycemia</td>
</tr>
<tr>
<td>BG at 2-3 am</td>
<td>WNL or high</td>
<td>Low</td>
</tr>
<tr>
<td>Caused by</td>
<td>Insufficient insulin</td>
<td>Excessive insulin</td>
</tr>
<tr>
<td>Adjustment</td>
<td>↑ Bedtime basal</td>
<td>↓ Bedtime basal</td>
</tr>
</tbody>
</table>
Consider Unmet Social Needs

One third of U.S. adults with chronic illnesses cannot afford food, medicine or both

Food Insecurity is Associated with Poorer Glycemic Control

Food-insecure participants were significantly more likely to have poor glycemic control (HbA1c > 8.5%)

Food-insecure participants were more likely to report:
• difficulty affording a diabetic diet
• lower diabetes-specific self-efficacy
• higher emotional distress related to diabetes

Source: Seligman, Diabetes Care 35:233–238; 2012
ADA 2016 Standards Medical Care

Strategies for Improving Care Recommendations-
Providers should evaluate hyperglycemia and hypoglycemia in the context of food insecurity and propose solutions accordingly.
Screening for Food Insecurity

• Ask
  “Many of my patients struggle affording food. In the past 3 months, have you worried whether your food would run out before you had money to buy more?”

• Refer
  Community Resources Hunger Free Co to outreach members to connect to all food resources.
Offer Mom’s Meals
Home delivered Medically Tailored Meals
Transportation or Food Preparation Barriers

- Fresh-prepared, home delivered, refrigerated meals
- $5.98/meal (shipping included)
- Order phone 888-860-9424 or www.MomsMealsNC.com
Additional information
DM2 Medication Treatment Algorithm
FIGURE 1: Type 2 Diabetes Medication Treatment Algorithm

Metformin → HbA1c > 2% above goal → Yes → Metformin + Basal insulin

No → Risk of Severe Hypoglycemia*

Yes → Consider factors such as comorbidities, patient preferences, adherence, and drug characteristics (such as weight gain and hypoglycemia risk) in selection of 2nd- or 3rd-line agent.

No → Metformin + Sulfonylurea
Most people with type 1 diabetes should be treated with multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion. A

Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. A

Consider educating individuals with type 1 diabetes on matching prandial insulin doses to carbohydrate intake, premeal blood glucose levels, and anticipated physical activity. E

Individuals with type 1 diabetes who have been successfully using continuous subcutaneous insulin infusion should have continued access to this therapy after they turn 65 years of age. E
Good Diabetes care is more than blood sugar management

ACE-I/ARB and Statin
Lisinopril: ACE-I

• Provides both cardioprotection and renoprotection in DM population
• ARBs are alternative in ACEI-intolerant
• Benefits cannot be fully attributed to BP lowering

HOPE. Lancet 2000
Lisinopril Strategy

- Recommend ACEI/ARB in DM if:
  - Age ≥ 18 with HTN, or
  - Age ≥ 18 with albuminuria, or
  - Age ≥ 55 with CVD or CVD risk factor

- Monitor Cr and K within 1-2 weeks then annually
- Caution in Women of Childbearing age

ADA. Diabetes Care 2009;32(suppl 1)
Evidence for Statin Use
Heart Protection Study Results

• 27% reduction in major coronary events
• 24% reduction stroke
• 22% reduction vascular events
• 17% reduction revascularization
CARDS Results

- 37% reduction major CV events
- 36% reduction acute coronary events
- 31% reduction revascularization
- 48% reduction stroke
- 27% reduction all cause mortality
- No significant adverse events atorvastatin
Cholesterol Levels as a trigger for Statin are not relevant

- If a patient falls within the four groups most likely to benefit from statin therapy, he/she should be prescribed a statin
- Titration is no longer necessary
- Monitoring LDL levels religiously may not be necessary
Rx Recommendation:

Statin strength of Atorvastatin 20mg advised if patient > 40 y.o

*but*

If Cardiovascular Risk or Stroke > 7.5 % *or*

If HIGH Risk + Risk Factors (Hypertension or protinuria)

Then, Rx = Atorvastatin 40 mg
Lipid-lowering Strategy: Conclusion

• If 40-75yo start at least simva 40 or atorva 20 but if over 7.5% cvd risk use atorva 40-80
  • If HTN, albuminuria
• No need to titrate for LDL cholesterol
  • Not appropriate to use LDL goals for metrics
  • Testing LDL only for adherence and initial variability
• The rise in glucose is minimal and less than benefit from statins
Who needs Aspirin 81mg?

Aspirin Therapy at 81 mg Orally Daily for Adults without ASCVD

• Initiate aspirin in adults aged 50-59 years with a ≥ 10% 10-year ASCVD risk. *(Strong recommendation)*

• Consider initiating aspirin in adults with Diabetes aged 40-75 years with a ≥ 10% 10-year ASCVD risk. *(KPCO recommendation)*
Risk Reduction with A-L-L

Aspirin

Lipid Lowering= Statin

ACE/ARB

22%_{MI}

33%_{CVA}

25%
Screening for Microvascular Complications

Retinopathy, Nephropathya and neuropathy
Screening for Retinopathy

• A retinal or dilated eye exam by an eye care professional (optometrist or ophthalmologist) in the measurement year.

• A *negative* retinal or dilated exam (negative for retinopathy) by an eye care professional (optometrist or ophthalmologist) in the year prior to the measurement year.
Screening for Nephropathy
(Medical Attention for nephropathy)

Must satisfy **ONE** of these criteria within the calendar year:

• Urine Microalbumin annually
• ACE/ARB therapy
• CKD Stage 4
• ESRD
• Hx kidney transplant
• A visit with nephrologist
Screening for Diabetic neuropathy

• Annual foot exam document and code procedure. Include:
  • general inspection
  • 10 point monofilament
  • either vibration or reflexes (patella or ankle)
• For those with a sensory deficit or who have a high-risk foot refer for DM foot care
  • Be mindful of your local resources and refer only with true need
• Re-refer annually
• VNA Foot care for elders without neuropathy (303) 698-6496
Legacy effect in type 2 diabetes: Impact of duration and intensity of control on future complications

Neda Laiteerapong, MD, MS; Yue Gao, MPH; Jennifer Liu, MPH; Howard Moffet, MPH; Sandra Ham, MPH; Elbert Huang, MD, MPH, Andrew Karter PhD

Midwest SGIM - September 22, 2016
DCCT and EDIC A1C <7% vs 8-9%

DM Type 1 patients

• Every 1% decrease in A1c associated with 35% decreased risk MVD
• Decreased CV/PVD by 41%
• “Legacy Effect” 10 yr study
• Delay progression retinopathy, renal damage, neuropathy
UK Prospective Diabetes Study (newer DM2)

• Intense treatment = A1C 7% Vs 7.9%
• Same significant benefit of glycemic control in microvascular disease as DM1
• A1c reduction of 1% reduced microvascular disease by 25%
  • No Threshold for benefits seen (linear)
• Decrease composite end points*

*mainly due to reduced 25% reduction in microvascular complications
UKPDS: additional learnings

• Sulfonylurea as safe as insulin
• Metformin reduced CV disease (was used in obese patients only)
• Using current treatment at the time it was impossible to maintain glucose control on a single agent over time
ADVANCE <6.5% Vs local guideline (Ave7.0)

Had to have a CV risk factor to be included:
• Significant reduction in Microvascular events (micro albuminuria) of 14%
• No significant reduction in Macrovascular events over 2-3 yrs. of study
• Baseline median a1c 7.2%
• Non significant weight gain
ACCORD A1C goal <6% Vs <8%

- **Hx CAD 40-79 or Significant CVD risk & 50-79y/o**
- Stopped at 3.5 years
- 22% increase risk death in Intensive
- Non-significant reduction risk MI in Intensive

- Significant reduction in CVD in those with no CVD and A1c < 8.0% at baseline
Retrospective Cohort 48,000 patients

• Lowest all cause mortality and progression to first CV event at an A1c of 7.5%

  • UK General Practice Research Database 1986-2008; Currie et al.
  • Mortality adjusted for age, sex, smoking status, cholesterol, CV risk and general morbidity
Metformin

• UKPDS in 1998 reported the survival benefit and cardiovascular protection of metformin compared with other conventional treatments for DM2.

• A Diabetes Outcome Progression Trial (ADOPT), the vascular benefits of metformin have been further confirmed in a meta-analysis.

• Reduction of Atherothrombosis for Continued Health (REACH) Registry (REACH) study, metformin was found to be advantageous even in patients with renal insufficiency or heart failure.
Evidence for ACE Use

• HOPE and MICRO-HOPE
  • Multicenter RCT ramipril vs. placebo
  • 3,577 ≥ 55 with DM and CVD or DM plus ≥ 1 CV risk factor
  • Significant reduction primary endpoints
HOPE. Lancet 2000;

- Ramipril was beneficial for cardiovascular events and overt nephropathy in people with diabetes.

- The cardiovascular benefit was greater than that attributable to the decrease in blood pressure.

- After adjustment for the changes in systolic (2·4 mm Hg) and diastolic (1·0 mm Hg) blood pressures, ramipril still lowered the risk of the combined primary outcome by 25% (12–36, p=0·0004).
Evidence for Statin Use

• Heart Protection Study
  • DM subgroup 5963
    • Age 40 to 80
    • Total cholesterol ≥ 135
  • Randomized simvastatin vs. placebo
Evidence for Statin Use

• CARDS Study
  • Primary Prevention CVD DM2 (n=2838)
    • Age 40-75
    • LDL ≤ 160mg
    • ≥1: retinopathy, albuminuria, smoker, HTN
  • Randomized atorvastatin 10mg vs. placebo