When Metformin is Not Enough

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I HAVE NO FINANCIAL CONFLICTS OF INTEREST
OUTLINE

• Choosing therapy
  • Newly diagnosed
  • Patient specific factors
  • Newer drugs
  • Cases
INITIATING THERAPY

• ADA made some significant changes in guidance in early 2018
Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

- A1C is less than 9%: consider Monotherapy.
- 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 500 mg/dL, or patient is symptomatic: consider Combination Injectable Therapy (See Figure 8.2)

Monotherapy

- Lifestyle Management + Metformin
- Initiate metformin therapy if no contraindications (see Table 8.1)

Dual Therapy

- Lifestyle Management + Metformin + Additional Agent
- ASCVD? Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations on p575 and Table 8.1)
- No: - Add second agent after consideration of drug-specific effects and patient factors (see Table 8.1)

- A1C at target after 3 months of dual therapy?
  - Yes: - Monitor A1C every 3-6 months
  - No: - Assess medication-taking behavior
  - Consider Triple Therapy

Triple Therapy

- Lifestyle Management + Metformin + Two Additional Agents
- Add third agent based on drug-specific effects and patient factors (see Table 8.1)

- A1C at target after 3 months of triple therapy?
  - Yes: - Monitor A1C every 3-6 months
  - No: - Assess medication-taking behavior
  - Consider Combination Injectable Therapy (See Figure 8.2)
Remember: Metformin is now approved for use down to an eGFR of 30!
UKPDS follow-up – death any cause

Hazard ratio

P = 0.01

P = 0.002

METFORMIN
PATIENT SPECIFIC FACTORS

Which medication for which person?

- Cardiovascular disease
- Obesity
- NAFLD/NASH
- Hypertriglyceridemia
- CKD
- Hypoglycemia risk
ADA GUIDELINES

A1c <9%

A1c >9%

A1c above goal after 3 months on dual therapy

A1c >10%

Combination Injectable Therapy
<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>SFU</th>
<th>TZD</th>
<th>INS</th>
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<tbody>
<tr>
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<td>high</td>
<td>high</td>
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<tr>
<td><strong>Weight</strong></td>
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<td>gain</td>
<td>gain</td>
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<tr>
<td><strong>Side effects</strong></td>
<td>GI (less with ER)</td>
<td>hypo’s</td>
<td>edema, HF, fracture</td>
<td>hypo’s</td>
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<tr>
<td><strong>Cost</strong></td>
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<td>low</td>
<td>low</td>
<td>moderate-high</td>
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<tr>
<td><strong>Benefits</strong></td>
<td>dec. mortality</td>
<td>lowers TG’s, fatty liver</td>
<td>insulin deficiency</td>
<td></td>
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<tr>
<td></td>
<td>DPP4</td>
<td>GLP1</td>
<td>SGLT2</td>
<td></td>
</tr>
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</tr>
<tr>
<td><strong>Weight</strong></td>
<td>neutral</td>
<td>loss</td>
<td>loss</td>
<td></td>
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<tr>
<td><strong>Side effects</strong></td>
<td>rare</td>
<td>GI, pancreatitis</td>
<td>GU, dehydration</td>
<td></td>
</tr>
<tr>
<td><strong>Cost</strong></td>
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<td>high</td>
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</table>
| **Benefits**     | CV, renal | CV, renal | }
DPP4 INHIBITORS

• Relatively weak effects
• Very few side effects (rare autoimmune arthralgias)
• No hypoglycemia
• Great for the frail elderly, dialysis patients
• Linagliptin does not need to be dose adjusted in kidney disease, other can be used at reduced dose
GLP-1 AGONISTS

• Provide satiety signal to the brain
• Delay gastric emptying – can cause nausea
• Suppress glucagon release from pancreas
• Increase glucose-dependent insulin release
• Do not cause hypoglycemia on their own
• Aid in weight loss
• Injectable, expensive, doesn’t facilitate weight loss in everyone
LEADER TRIAL

• High risk for CVD
• Received liraglutide or placebo
• Primary outcome: First occurrence of CV mortality, non-fatal MI, non-fatal stroke

LEADER TRIAL

GLP-1 AGONISTS

• Semiglutide and Dulaglutide showed similar CV results
• Semiglutide, dulaglutide and liraglutide showed reduced progression of CKD
  • New onset of urine albumin/creatinine ratio >300 mg/g, a doubling of the serum creatinine level and an eGFR of ≤45, the need for dialysis, or death from renal disease
• Lixisenatide and Exenatide trials: no harm, but no CV or renal benefit, enrolled some patients with A1c <7.0% in both of these trials
GLP-1 AGONISTS

- Oral semaglutide showed non-inferiority for cardiovascular outcomes and superiority for all cause mortality compared to placebo.
- FDA approved in September. Not yet available in pharmacies.
SGLT2 INHIBITORS

• Lower the renal set point for glucose reabsorption from approximately 180-200 to 140
• Associated with a couple of pounds of weight loss
SGLT2 INHIBITORS

• Lower the renal set point for glucose reabsorption from approximately 180-200 to 140
• Associated with a couple of pounds of weight loss
EMPA-REG

CREDENCE

A Primary Composite Outcome:

<table>
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<th>No. at Risk</th>
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<th>Canagliflozin</th>
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<td>2132</td>
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<tr>
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</tbody>
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Hazard ratio, 0.70 (95% CI, 0.59 - 0.82)

B Renal-Specific Composite Outcome:

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Hazard ratio, 0.66 (95% CI, 0.53 - 0.81)

C End-Stage Kidney Disease:

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<tbody>
<tr>
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<td>2182</td>
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<tr>
<td>2202</td>
<td>2184</td>
<td>2146</td>
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Hazard ratio, 0.68 (95% CI, 0.54 - 0.86)

D Dialysis, Kidney Transplantation, or Renal Death:

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Hazard ratio, 0.72 (95% CI, 0.54 - 0.97)
SGLT2 INHIBITORS

• Empa, cana, ertu and dapagliflozin all showed improvement in CKD outcomes, larger than GLP-1 benefit despite some reversible worsening of eGFR with use of SGLT2-Inhibitors

• E-LIFT Trial- empagliflozin may decrease liver fat, transaminases in NAFLD
SGLT2 INHIBITORS

• Patients will have urine dip-stick positive for glucose
• Common side effects: polyuria, orthostatic symptoms, genital yeast infection
• Concerns for increased amputation rates, Fournier’s gangrene of the scrotum or perineum
• Normoglycemic DKA
• UTI does not appear to be increased in real world use BUT most of us aren’t using these drugs in high risk patients
Monthly cash price at a major retailer (max. dose)

- **MET**: $4, regular or ER
- **SFU**: $4
- **TZD**: $9
- **DPP4**: ~$380-540
- **SGLT2**: ~$475-600
- **GLP1**: ~$800-1000+
CASE 1

- 36 yo male presented to the ED with chest pain
- Dx with NSTEMI and new diabetes dx
- HbA1c 15%
- Insulin initiated and d/c for outpatient management of CAD and DM
- He and his wife cut out sweet tea/soda, buy lots of veggies, etc.
CASE 1

- Seen in Endo clinic 1 week later with heart failure sx
- Has emergent CABG
- In the hospital insulin needs are quite low despite post-op stress and BMI of 36
- Metformin and glipizide started and all insulin held
- Goal- lose weight and stop glipizide
CASE 1

• What other options did we have to manage this patient?

  • Metformin plus insulin
  • Metformin plus SGLT-2 inhibitor
  • Metformin plus GLP-1 receptor agonist
CASE 1

• How might you manage a newly diagnosed, glucotoxic patient as an outpatient?
  • Metformin and 1 month supply of basal insulin
  • Follow up in 1-2 weeks to add another oral agent/GLP1
    • If BG’s mostly <200 also reduce insulin
  • Follow up in another 1-2 weeks
    • Do we need to continue insulin?
    • Should we add a third agent?
CASE 1

• Why the focus on stopping insulin?
  • It tends to promote weight gain
  • Expensive
  • Quickly can progress to complex regimens
CASE 2

• 74 yo male with hx of Type 2 diabetes and CAD s/p LAD stent

• HgbA1c 4 months earlier was 7.2% on
  • Metformin 500 mg BID
  • Pioglitizone 30 mg
  • Liraglutide 1.8 mcg
  • Glargine 15-20 u QAM
CASE 2

• The month before we met he had a witnessed VTach arrest, received CPR.

• EF reduced to 25-30%.

• BiV-ICD placed and then discharged home on increased beta-blocker and amiodarone.

• Pioglitazone and metformin were stopped.

• 4 days later went into V-tach storm, ICD fired, hospitalized for several more days. Amiodarone and beta-blocker increased further.
CASE 2

• 2 weeks later comes to endocrine clinic taking Liraglutide 0.6 mcg daily, glargine 7-13 units daily
• Weight is down about 15 pounds, poor appetite
• Will be starting cardiac rehab soon
• BG getting down to about 70 every other day since discharge
• He has been having memory problems since the resuscitation
CASE 2

- Memory issues
- Poor appetite
- Huge doses of beta-blockers
- About to restart exercise

So what is our goal for this patient?
CASE 2

Avoid hypoglycemia!

• Stop insulin
• Restart metformin
• Increase GLP-1
• If needed, later add SGLT-2 inhibitor
CASE 3

Reevaluating your patients on insulin

• 61yo male with BMI of 40, SOB with rest, A1c 8.2%
  • Metformin 2000 mg
  • Glimepiride 4 mg
  • Liraglutide 0.6 mg plus 4 clicks (nausea with more)
  • U500 230u am, 230u bedtime
  • Lispro 40u with dinner
CASE 3

• Stop liraglutide
• Stop glimepiride
• Start empagliflozin 10 mg
• A1c decreased to 7.9%, weight down 5 pounds
• Started using continuous glucose monitoring
CASE 3

• CGM allowed for more aggressive and frequent decreasing of insulin
• For the first 2 weeks of use also had him keep a food diary- make some easy diet changes that kick-started the insulin reduction
• “gamification” of blood sugars
CASE 3

• 18 months later, BMI 33.6, A1c 6.8%, not short of breath
  • Metformin 2000 mg
  • Empagliflozin 10 mg
  • Glargine 50 units!
THANKS

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