Hypoglycemic Agents

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July 2022
Disclosures

Relationships with Commercial Interests:
– Consultant with the Foundation for Medical Education at McMaster University (non-profit org)
  • (PBSG module consultant & reviewer)
– Occasional consultant with Rxfiles (non-profit org)

Disclosure of Commercial Support: None

Potential for Conflict(s) of Interest: None
Objectives

• List the classes of oral antihyperglycemic agents and understand their place in therapy.
  – Determine the relative efficacy, toxicity, cost and convenience of these agents before choosing therapy
  – Rationalize prescribing of oral hypoglycemics

• Describe the current approach to pharmacologic management of type 2 diabetes.
## Targets

<table>
<thead>
<tr>
<th></th>
<th>A1C</th>
<th>Fasting blood glucose (sugar) (mmol/L)</th>
<th>Post-prandial glucose 2h after eating (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target for most people with diabetes</td>
<td>( \leq 7.0% )</td>
<td>4.0 - 7.0</td>
<td>4.0 - 10.0</td>
</tr>
</tbody>
</table>

Diabetes Canada. MANAGING YOUR BLOOD SUGAR  
Diabetes: complications

MACROvascular
- Stroke
- Heart disease
- Hypertension
- Peripheral vascular disease
- Foot problems

MICROvascular
- Diabetic eye disease (retinopathy & cataracts)
- Nephropathy
- Neuropathy
- Foot problems
Priorities / Goals of Care

**Lifestyle Modification / Weight Loss**

- **Quality** of evidence: All RCT / cohort data
- **Time** to benefit: All in months
- **Quantity** of benefit?

↓ Mortality via:

**Glycemic Control**

**Vascular Protection**
Finnish Diabetes Trial

- Pre-diabetics (n = 522)
- Moderate wt loss (5%) (esp. abd fat)
- Physical activity
  - ≥ 150 min/week
- **12%** ARR / **58%** RRR for DM2 at 4 years
  - 11% (95% CI 6-15%) vs.
  - 23% (95% CI 17-29%)

N.B. Drugs ~ 30% RRR

DiRECT trial

- Diabetics (n = 306)
  - Specially-formulated 800 calorie liquid diet
  - Consisted of 4 shakes that replaced all meals x 3-5 months
- 15kg wt loss at 1 yr
  - 24% vs. 0% control (p<0.0001) NNT=5
- DM2 remission at 1 yr
  - 46% vs. 4% control (p<0.0001, O.R. 19.7, 95% CI 7.8-49.8) NNT=3
  - 36% remission at 3 yrs

Bariatric surgery

(all types)
- ROUX-EN-Y GASTRIC BYPASS
- SLEEVE GASTRECTOMY
- ADJUSTABLE GASTRIC BAND
- DUODENAL SWITCH

- Bariatric surgeries in >135,000 pts found:
- Improved DM2 in **90%**
- DM2 remission in **78%**
  - American Society for Metabolic and Bariatric Surgery (ASMBS)
Diabetes

Previously,
DM2 = MI equivalent
– Automatic Rx for:
  • ASA, statin, ACEinh

Currently…
Vascular Protection & Glycemic Control

- Any ACEinh or ARB
  - Less clear benefit at lower risk
  - Very clear benefit at higher risk

- Any Statin
  - Less clear benefit at lower risk
  - Very clear benefit at higher risk

- ASA
  - NNT ~ NNH (1’ prevention)
  - Only for 2’ prevention

- Metformin
  - UKPDS-34 trial
  - Diabetes-specific mortality
    - (= Death from MI, stroke, PVD, kidney disease, hypo- or hyperglycemia, or sudden death).
    - Metformin vs. intensive:
      - 7.5 vs. 10.3 (P=0.11)
    - Metformin vs. diet:
      - 7.5 vs. 12.7 (P=0.017)
  - 2.8% - 5.2% ARR
  - All-cause mortality
    - Metformin vs. intensive:
      - 13.5 vs. 18.9 (P=0.021)
    - Metformin vs. diet:
      - 13.5 vs. 20.6 (P=0.011)
  - 5.4% - 7% ARR
Prevention of Microvascular Complications & Hgb-A1C Targets

- Intensive vs Conventional insulin therapy (n=110)
- Median A1c: 7.1% vs 9.4%

Non-Pharmacologic Tx

Mainstay of therapy!

• Nutrition therapy
  – ↓ A1c 1-2%
  – CDA recommends counseling by a dietician for all type 2 diabetics
  – www.cvtoolbox.com diet for Type 2 diabetes
    • Continuing Medical Implementation Inc. (cvtoolbox.com)

Can J Diabetes 2003;27(2);S27
Pharmacotherapy

Comparison of antihyperglycemics
Pharmacotherapy

Drug Classes

- Sensitizers
- Secretagogues
- Other
## Drug Classes

### Sensitizers
- Metformin
- Glitazones (TZD)
  - Rosiglitazone (Avandia®)
  - Pioglitazone (Actos®)

### Secretagogues
- Sulfonylureas
  - Eg. Glyburide, Gliclazide
- Meglitinides
  - Eg Repaglinide (Gluconorm®)

### Other
- **Alpha glucosidase inhibitors** (Acarbose)
- **DPP4 inhibitors (Gliptins)**
  - Sitagliptin, Linagliptin
  - Saxagliptin, Alogliptin
- **SGLT2 inhibitors** (Cana- Dapa- Empagliflozin)
- **Incretin (GLP1) Analogues** (sc injection)
  - Liraglutide , Dulaglutide, Lixisenatide,
  - Exenatide, Semaglutide (po/sc)
Pharmacology

Sensitizers

- Metformin
- Glitazones (TZD)
  - Rosiglitazone (Avandia®)
  - Pioglitazone (Actos®)

- Reduce insulin resistance
- Increase glucose uptake & utilization in muscle and adipose tissue
- Reduce hepatic glucose output
## Drug Classes

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  - Exenatide, Semaglutide (all sc inj)
Pharmacology
Secretagogues

• ↑Basal and prandial insulin secretion
  – ↓hepatic gluconeogenesis

• Doesn’t correct impaired 1st phase insulin secretion; primarily affects 2nd phase

• Beta-cell sensitizer – primes glucose mediated insulin secretion (1st phase)

Secretagogues

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  – Eg. Glyburide, Gliclazide

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  – Eg Repaglinide (Gluconorm®)
Drug Classes

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Pharmacology: Other

- **Alpha glucosidase inhibitors** (*Acarbose*)
  - Competitive inhibitor of pancreatic α-amylase and intestinal brush border α-glucosidases, delayed hydrolysis of complex carbs & disaccharides and absorption of glucose; Dose-dependent reduction in postprandial serum insulin and glucose peaks; inhibits the metabolism of sucrose to glucose and fructose.

- **SGLT2 inhibitors** (*Canagliflozin, Dapagliflozin, Empagliflozin*)
  - Inhibits sodium-glucose cotransporter 2 (SGLT2) in the proximal renal tubules reduced reabsorption of filtered glucose from renal tubule and lowered renal threshold for glucose (RTG).
  - Results in increased urinary excretion of glucose, thereby reducing plasma glucose concentrations.

- **DPP4 inhibitors** (*Gliptins*) – (*Sitagliptin, Linagliptin, Saxagliptin, Alogliptin*)
  - Prolongs the action of endogenous incretin hormones by blocking their breakdown by the enzyme, dipeptidyl peptidase-4 (DPP-4). This leads to more insulin release after eating.

- **Incretin (GLP1) Analogues** – (*Liraglutide, Exenatide, Semaglutide, Dulaglutide*)
  - sc injection (daily or weekly) (New oral, daily semaglutide now available)
  - mimic endogenous incretin hormones:
    - “increases glucose-dependent insulin secretion, decreases inappropriate glucagon secretion, slows gastric emptying; also acts in the areas of the brain involved in regulation of appetite and caloric intake.”
So Many Options!
*How to Choose?*

- **FOUR steps to Rational Prescribing:**
  1. Benefit
  2. Harm
  3. Cost
  4. Convenience
Rational Prescribing

Prioritize:
- a) Type of benefit
- b) Quantity of benefit
- c) Quality of evidence
- d) Time to benefit

Prioritize:
- a) Type of harm
- b) Quantity of harm
- c) Quality of evidence
- d) Time to harm

Cost & Convenience

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a) Mortality benefit

- **Metformin** – UKPDS-34

- **GLP1 analogs:**
  - Liraglutide – LEADER trial
  - Semaglutide
    - SUSTAIN-6 trial (sc inj)
    - PIONEER-6 trial (po tabs)
      - MACE ns; But lower all-cause death and CV death (?) odd
  - Dulaglutide – REWIND
    - Lowered MACE, (Not mortality, only non-fatal stroke, not MI)
  - Exenatide – EXSCEL - **None**
  - Lixisenatide ELIXA - **None**

- **SGLT2-inh:**
  - Empagliflozin
    - EMPA-REG trial
    - (2º prevention trial)
  - Dapagliflozin
    - DAPA-HF trial
    - DAPA-CKD trial
  - Canagliflozin
    - CREDENCE trial

- **?Insulin** – “legacy effect”
  - 1 yr tight control = reduced M&M 10 yrs later! ([UKPDS](#))
b) Morbidity benefit

(Reduction in microvascular outcomes)

- Older meds have shown a morbidity benefit (SU, etc)
- Newer meds show a reduction in HbA1c

- Metformin
- Acarbose
  - MERIA meta-analysis
  - (Driven by non-fatal MI)

- All GLP1 analogs:

- All SGLT2-inh:
  - Canagliflozin
    - CANVAS & CREEDENCE trials
  - Dapagliflozin
    - DECLARE-TIMI 58 trial
    - Renal Composite (sustained ↓eGFR ≥40% to <60mL/min, new ESRD, or death from renal/CV cause)
Cardiovascular outcome trials

### Table 2: HR and 95% CI for CV and kidney endpoints and all death for DPP4 inhibitor, GLP-1RA and SGLT2 inhibitor studies (excludes post-ACS studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Medication</th>
<th>MACE(^a)</th>
<th>MACE+(^a)</th>
<th>MI(^b)</th>
<th>Stroke(^b)</th>
<th>CV death</th>
<th>Heart failure</th>
<th>All death</th>
<th>Kidney endpoint(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4 inhibitor studies</td>
<td>SAVOR</td>
<td>1.00 (0.89, 1.12)</td>
<td>1.02 (0.94, 1.11)</td>
<td>0.95 (0.80, 1.12)</td>
<td>1.11 (0.88, 1.39)</td>
<td>1.03 (0.87, 1.22)</td>
<td>1.27 (1.07, 1.51)</td>
<td>1.11 (0.96, 1.27)</td>
<td>1.08 (0.96, 1.22)</td>
</tr>
<tr>
<td></td>
<td>TECOS</td>
<td>0.99 (0.89, 1.10)</td>
<td>0.98 (0.88, 1.09)</td>
<td>0.95 (0.81, 1.11)</td>
<td>0.97 (0.79, 1.19)</td>
<td>1.03 (0.89, 1.19)</td>
<td>1.00 (0.83, 1.20)</td>
<td>1.01 (0.90, 1.14)</td>
<td>NG</td>
</tr>
<tr>
<td></td>
<td>CARAMELINA</td>
<td>1.02 (0.89, 1.17)</td>
<td>1.00 (0.88, 1.13)</td>
<td>1.12 (0.90, 1.40)</td>
<td>0.91 (0.67, 1.23)</td>
<td>0.96 (0.81, 1.14)</td>
<td>1.00 (0.74, 1.08)</td>
<td>0.98 (0.84, 1.13)</td>
<td>1.04 (0.89, 1.22)</td>
</tr>
<tr>
<td>GLP-1RA studies</td>
<td>LEADER</td>
<td>0.78 (0.68, 0.90)</td>
<td>0.78 (0.69, 0.90)</td>
<td>0.75 (0.61, 0.90)</td>
<td>0.78 (0.66, 0.93)</td>
<td>0.87 (0.73, 1.05)</td>
<td>0.85 (0.74, 0.97)</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SUSTAIN-6</td>
<td>0.74 (0.58, 0.95)</td>
<td>0.74 (0.51, 1.08)</td>
<td>0.61 (0.38, 0.99)</td>
<td>0.98 (0.65, 1.48)</td>
<td>1.11 (0.77, 1.61)</td>
<td>1.05 (0.74, 1.50)</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EXSCEL</td>
<td>0.91 (0.83, 1.00)</td>
<td>0.97 (0.85, 1.10)</td>
<td>0.85 (0.70, 1.03)</td>
<td>0.88 (0.76, 1.02)</td>
<td>0.94 (0.78, 1.13)</td>
<td>0.86 (0.77, 0.97)</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Harmony</td>
<td>0.78 (0.68, 0.90)</td>
<td>0.78 (0.69, 0.90)</td>
<td>0.75 (0.61, 0.90)</td>
<td>0.78 (0.66, 0.93)</td>
<td>0.87 (0.73, 1.05)</td>
<td>0.85 (0.74, 0.97)</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td>SGLT2 inhibitor studies</td>
<td>EMPA-REG OUTCOME</td>
<td>0.86 (0.74, 0.99)</td>
<td>0.89 (0.78, 1.01)</td>
<td>0.87 (0.70, 1.09)</td>
<td>1.18 (0.89, 1.56)</td>
<td>0.62 (0.49, 0.77)</td>
<td>0.65 (0.50, 0.85)</td>
<td>0.68 (0.57, 0.82)</td>
<td>0.54 (0.40, 0.75)</td>
</tr>
<tr>
<td></td>
<td>CANVAS Program(^d)</td>
<td>0.86 (0.75, 0.97)</td>
<td>0.85 (0.69, 1.05)</td>
<td>0.90 (0.71, 1.15)</td>
<td>0.70 (0.52, 0.87)</td>
<td>0.67 (0.52, 0.87)</td>
<td>0.87 (0.74, 1.01)</td>
<td>0.60 (0.47, 0.77)</td>
<td>NG</td>
</tr>
<tr>
<td></td>
<td>DECLARE</td>
<td>0.93 (0.84, 1.03)</td>
<td>0.89 (0.77, 1.01)</td>
<td>1.01 (0.84, 1.21)</td>
<td>0.91 (0.82, 1.17)</td>
<td>0.73 (0.61, 0.88)</td>
<td>0.93 (0.82, 1.04)</td>
<td>0.53 (0.43, 0.66)</td>
<td></td>
</tr>
</tbody>
</table>

HR findings are derived from intention-to-treat analyses

\(^a\) MACE: CV death, MI, stroke; MACE+: CV death, MI, stroke, acute coronary event

\(^b\) Fatal and non-fatal

\(^c\) Composite of variables, not including albuminuria

\(^d\) Composed of two studies

MR, modified release (long-acting); NG, not given

Cardiovascular outcome trials

Systematic Review of Cardiovascular Outcome Trials Using New Anti-Diabetic Agents in CKD Stratified by Estimated GFR

**Methods**
- **16 Studies found**
  - 6 GLP-1 analogues
  - 4 DPP-4 inhibitors
  - 6 SGLT-2 inhibitors
- **150,816 Total participants**
- Data stratified by study entry GFR & albuminuria
- Insufficient albuminuria data available for pooled analysis

**Relative Risk for MACE by eGFR (mL/min/1.73 m²)**

<table>
<thead>
<tr>
<th></th>
<th>&lt; 60</th>
<th>≥ 60</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.90 (0.79-1.04)</td>
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</tr>
<tr>
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<td>0.99 (0.91-1.08)</td>
<td>0.99 (0.92-1.07)</td>
</tr>
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<td>SGLT-2 inhibitors</td>
<td>0.85 (0.75-0.95)</td>
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</table>

**Conclusion**
Clear evidence for MACE prevention in diabetes patients with an eGFR <60 ml/min/1.73m² currently exists for SGLT-2 inhibitors only. However, similar GLP-1 analogue effect sizes suggest lack of sufficient power rather than lack of effect.

Benefit

2\textsuperscript{nd}: SURROGATE Outcomes

c) HbA1c reduction
   - Any drug that reduces Hgba1c < 7%
   - Blood glucose level reduction
   - Fasting or Prandial

d) Insulin Sparing Effects
   - Avoidance of hyperinsulinemia and associated risk factors (metabolic syndrome, atherosclerosis, elevated TGs/UA/weight/BP, etc.)
2c) **Hb-A1c reduction**

- **~ 1% to 2%**
  - Metformin (1% - 2%)
  - Sulfonylureas (1% - 2%)
  - Repaglinide (1% - 1.5%)
  - Glitazones (TZDs) (0.4% - 1.5%)
  - Canagliflozin (0.8 – 1%)
  - Liraglutide (GLP1 analogs) (1% - 2%)

- **~ 0.5% to 1%**
  - Acarbose
  - DPP4 inhibitors (‘Gliptins)
  - Dapagliflozin, Empagliflozin
  - Nateglinide


Benefit

2d) **Insulin Sparing Effect**

- Weight neutral or weight negative
- Reduction of hyperinsulinemia

- METFORMIN
- TZD’s (GLITAZONE’s)
- ACARBOSE
- DPP4 inh (‘gliptins)
- Incretin (GLP1) Analogues (Liraglutide, Semaglutide etc.)
- SGLT2 inh (Empagliflozin etc.)
Consider Harm

Ask yourself...

<table>
<thead>
<tr>
<th></th>
<th>Bothersome</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>![Checkmark]</td>
<td>Not legal</td>
</tr>
<tr>
<td>Rare</td>
<td>Who cares</td>
<td>![Checkmark]</td>
</tr>
</tbody>
</table>

- **Age?**
  - *Newer agents* = **Less** Safety Data
  - *Older agents* = **More** Safety Data
### Harm

**Serious / Rare**

- **Glitazones**
  - CHF
  - Fractures
  - M.I.
    - (rosiglitazone)
  - Bladder Cancer
    - (pioglitazone)

- **Secretatgogues**
  (Sulfonylureas & Meglitinides)
  - Severe Hypoglycemia
Harm
Serious / Rare

**SGLT2 inhibitors**
(FDA OK 2013; H.Can. OK 2015)
- Euglycemic DKA
  - Risk increased 7x in DM2
  - Estimated incidence ~ 0.1%.
  - 73 cases (2013 to 2015 in FAERS database)
- Fournier gangrene
  - 542 cases by 2020 - necrotising fasciitis in the perineum (FDA warning)
  - reported occurrence = 1.6 out of 100,000 males annually in U.S., most frequently in males 50-79 yo.
- Urosepsis
  - 19 cases (2013-2014)(FAERS database)

**Incretin (GLP1) Analogues**
(H.Can. approved in 2010)

**DPP4 inhibitors (‘gliptins)**

- ?Heart failure
  - Sitagliptin (Approved in 2008)
    - No, per 2015 TECOS trial (n = 14,671)
    - Initially, Yes, per lower quality data [2014 post hoc pooled analysis of 25 RCTs (n = 1261)]
  - Linagliptin – No (per CARMELINA trial)
  - Saxagliptin – Yes? (SAVOR-TIMI 53 trial)
  - Alogliptin - Yes? (EXAMINE trial)

- ?Pancreatitis – maybe/unlikely
  - Yes per Faillie 2014 (PMID: 2435244) & Lee 2019 (PMID: 31431452)
  - No per Chou 2014 (PMID: 24859164) & Thomsen 2015 (PMID: 25633664)
Harm
Serious / Rare

• **Metformin**

• **Risk of Lactic Acidosis**
  – 0.03 to 0.06 cases / 1000 pt-yrs
  – ~ 50% fatal
  – When implicated:
    • **Based on case reports**
      – Primarily diabetics w/ significant renal insufficiency, both intrinsic renal disease and renal hypoperfusion, w/ multiple medical/surgical problems and multiple medications.
      – Phenformin pulled from market due to L.A. in 1977
    
    • **Cohort studies and retrospective reviews:**
      – **Zero** risk of lactic acidosis with metformin
Metformin Dosing

• Dosing recommendations with renal insufficiency:
  • CrCl > 30 mL/min → full dose
    – 2.5g/day
  • CrCl = 20 – 30 mL/min → reduced dose
    – 1g/day (If NO other risk factors, else D/C)

– Take home: Assess OTHER RISK FACTORS for lactic acidosis

4) Lalau JD. Lactic acidosis induced by metformin: incidence, management and prevention. Drug Saf. 2010 Sep 1;33(9):727-40. PMID: 20701406
https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2682516 Accessed June 7, 2018
Risk Factors - Lactic Acidosis

- Severe renal impairment
  - (caution if CrCl ≤ 30ml/min)

- Hepatic disease
- Alcoholism
- CHF
- COPD
- CRF
- Pneumonia
- Ongoing acidosis
  - Lactic, keto etc.
1) METFORMIN

- GI upset / diarrhea – **Start low, go slow!**
  - Initial dose 250mg QDaily to BID
- B12 / folate deficiency / anemia (6 - 8/100)
  - Reduced absorption – so, **supplement**
- Anorexia – usually **transient**
2) Sulfonylureas:
   – Sulfa skin reactions
     • Rash / photosensitivity ~1%
   – Weight gain (2-3kg)
   – Mild Hypoglycemia:
     • Most with glyburide. Least w/ glimepiride & gliclazide
     • Requires consistent food intake
     • Major episodes 1-2% (esp. in elderly)
3) Glitazones:
   – Edema

4) Meglitinides:
   – Hypoglycemia

5) Acarbose:
   – GI upset / diarrhea / bloating

6) Gliptins:
   – Generally well tolerated
     • GI upset, edema, ?infection

7) Incretin (GLP1) analogues
   – N/V/D

8) SGLT2 inhibitors
   – HyperK+, AKI
   – UTI (includes bacteriuria [asymptomatic], cystitis: 9%; females: 4%-18%; males: 4%),
     – Genitourinary fungal infection (4%; females: 5% to 11% [includes bacterial vaginosis, cervicitis, vulvitis, vulvovaginal candidiasis, vulvovaginal infection, vulvovaginitis];
     – males: 2% to 3% [includes balanitis, balanoposthitis, genitourinary fungal infection, penile infection, scrotal abscess])
Cost

- Patient cost vs Societal cost
- Rx cost?
- ODB coverage?
- Covered under other plans?
### Cost

- From Rxfiles Nov 2019
- \( \text{Cost}($) / 100 \text{ days} \) (in Sask.)

  - N.B. Not true pt costs
  - Only comparative costs
### Cost

**ODB e-formulary comparative costs**

To roughly estimate pt costs: (add ~10% x No. days) + ~$10 dispensing fee

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**ODB e-formulary** [https://www.formulary.health.gov.on.ca/formulary/](https://www.formulary.health.gov.on.ca/formulary/)  Accessed Aug 9, 2018
Convenience

• PO vs IV?
• QD vs QID?
• Lab monitoring?
Convenience

- Gliptin’s - QD
- Glitazones - QD
- SGLT2 inh - QD
- DPP-4 inhibitors - QD
- GLP-1 analogs - QD sc inj
- Sulfonylureas – QD to BID
- Metformin - QD to TID
- Meglitinides – QD to TID
- Acarbose – QD to TID

with meals
Summary

1st line – **Metformin**
CV benefit, renal benefit, very safe, cheap, simple

If obesity or CVD:
- GLP1 analog
- **Semaglutide (Ozempic®)**
  - CV & renal benefit, wt loss, ODB covered, weekly sc inj

If CHF or CKD:
- Any SGLT2 inh
- **Dapagliflozin (Forxiga®)**
  - CV benefit, renal benefit, CHF specific benefit, ODB covered, combo pill with Metformin (Xigduo®)
  - But, closely monitor SCr, K+, UTI sx etc

If no CKD/MI/CVA/CHF:
**Anything else**
- (except TZDs) (never ever)

• Alternative for lower eGFR: **Canagliflozin** 100mg (low dose)
Review of Basic Concepts

1. Reduce mortality
   - BP control w/ ACEi/ARB
   - Plaque stabilization with statin
   - ASA in 2’ prevn
   - Glycemic control with Metformin
     • + GLP1 analogs
     • + SGLT2inh
     • + ?Acarbose

2. Reduce morbidity
   - Glycemic control to prevent microvascular complications
     • A1c < 7%
Summary

• Pathophysiology of disease underscores the key targets for modification
  – Insulin resistance / hyperinsulinemia
• Pharmacology of agents underscores ideal vs. suboptimal combinations of agents
• Rational Prescribing principles underscore priorities for investment in benefit/risk ratios
Questions?

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