New Paradigm in Treatment of Type 2 Diabetes Mellitus: An Evolving Concept

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Why a New Paradigm?

• Prior to 2008, treatment of type 2 DM was glucocentric—and new drugs merely had to demonstrate efficacy with regard to glucose-lowering.

• In 2008, a sentinel publication identified unanticipated incidence of heart failure and CVD events among users of rosiglitazone (a TZD).

• Since 2008, all new antihyperglycemic drugs must demonstrate non-inferiority vs. standard of care, with regard to CVD (“MACEs”) in phase 3 clinical trials, to gain FDA approval.

• In years since 2010, drug developers engage in post-FDA approval, post-marketing Phase 4 trials, to demonstrate superiority vs. standard of care, with regard to CVD.
Overriding Strategies in T2DM Treatment

• Achieve near-euglycemia
• Prevent hypoglycemia (safety)
• Promote weight loss
• Prevent cardiovascular disease events
• Minimize cost of treatment
Earliest Stages of DM  
(Prediabetes and 1-5 years After Onset)

- Promote weight loss
- Achieve near-euglycemia ("Myagi Principle")
- Prevent hypoglycemia (safety)
- Prevent cardiovascular disease events
- Minimize cost of treatment
Diabetes Drugs Promoting Weight Loss

• SGLT2 inhibitors (SGLT2I’s)
• GLP-1 receptor antagonists (GLP-1 RA’s)
• Metformin
Bariatric Surgery Is a Game-Changer in T2DM!
STAMPEDE Study (Cleveland Clinic series)

Mid-Course of T2DM
(5 years – 15 years duration, no complications)

• Primary prevention of cardiovascular disease events
• Achieve near-euglycemia
• Promote weight loss/prevent weight gain
• Prevent hypoglycemia (safety)
• Minimize cost of treatment
T2DM Drugs Which Reduce CVD Risk

• GLP-1 RA’s
• SGLT2i’s
• Metformin
Non-Insulin Anti-hyperglycemics:
Realistic Expectations

- 1\(^{st}\) Drug in play: 1-2% ↓ in HbA\(_1\)c
- 2\(^{nd}\) Drug in play: 0.5-1% ↓ in HbA\(_1\)c
- 3\(^{rd}\) Drug & beyond: 0.5% ↓ in HbA\(_1\)c
- Diet & Exercise ALWAYS worth one drug!
Latest Stages of T2DM Treatment (Complications Present—including CVD)

• Secondary prevention of CVD
• Prevent hypoglycemia (safety)
• Promote weight loss
• Achieve near-euglycemia
• Minimize cost of treatment
DPP-4 Inhibitor CVD Trials

- SAVOR-TIMI 53
- EXAMINE
- TECOS

All neutral for MACE (no advantage vs. SOC)

Slight ↑ risk for CHF (vs. SOC)
# SGLT2i Trials: Effect on MACE and CHF

<table>
<thead>
<tr>
<th>Trial</th>
<th>RR MACE</th>
<th>RR CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG (empagliflozin)</td>
<td>0.86</td>
<td>0.65</td>
</tr>
<tr>
<td>CANVAS (canagliflozin)</td>
<td>0.86</td>
<td>0.67</td>
</tr>
<tr>
<td>DECLARE-TIMI 58 (dapagliflozin)</td>
<td>NS</td>
<td>0.73</td>
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</tbody>
</table>
Beneficial Effects of SGLTi’s

• 0.5 – 0.8% ↓ in HbA1c
• 3-5% ↓ in body weight
• 3-5 mmHg ↓ in systolic BP
• ↓ albuminuria
• ↓ rate of azotemia progression
Adverse Effects of SGLT1’s

- DKA (often with nearly-normal blood glucose)
- Hyperkalemia
- Acute renal failure
- Genitourinary infections (more often in women)
- Fournier’s gangrene
- Lower extremity amputation
- Osteopenia/fractures
GLP-1 RA Trials: Effect on MACE and CHF

<table>
<thead>
<tr>
<th>Trial</th>
<th>RR MACE</th>
<th>RR CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEADER (liraglutide)</td>
<td>0.87</td>
<td>NS</td>
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<tr>
<td>SUSTAIN-6 (semaglutide)</td>
<td>0.74</td>
<td>NS</td>
</tr>
<tr>
<td>HARMONY (albiglutide)</td>
<td>0.78</td>
<td>n/a</td>
</tr>
<tr>
<td>REWIND (dulaglutide)</td>
<td>0.88</td>
<td>NS</td>
</tr>
<tr>
<td>EXSCEL (exenatide)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
Beneficial Effects of GLP-1 RA’s

• Enhance insulin secretion and insulin action
• Induce satiety: significant weight loss
• Antithrombotic
• Anti-inflammatory (↓ CRP etc)
Adverse Effects of GLP-1 RA’s

• Nausea (including worsening gastroparesis
• Possibly, induction of pancreatitis
• C-cell hyperplasia (experimental data; not proven in humans
• Contraindications
  • Severe gastroparesis
  • h/o gastric bypass
  • h/o pancreatitis (?)
  • h/o MEN2a or MEN2b
  • ?proliferative retinopathy
Drug Therapy in T2DM and CHD
Acharya T, Deedwania P. Progress in Cardiovascular Diseases 2019; 62: 342-348

- Does the patient have DM2 and ASCVD?
  - Yes: Metformin Use as first line
  - No: Does the patient have or is a high-risk for heart failure?
    - Yes: Heart Failure present
    - No: Is the patient already on or willing to initiate an injectable medication?
      - Yes: Injectable OK
        - GLP1RA ↓ MACE
      - No: Injectable not OK
        - SGLT2i ↓ MACE, ↓ HF Hospitalization, ↓ MACE

SGLT2 inhibitors: prefer empagliflozin or canagliflozin
GLP1 receptor antagonist: prefer liraglutide, semaglutide, dulaglutide, or albiglutide
Treating T2DM in the Uninsured and Underinsured

• Minimize cost of treatment
• Prevent cardiovascular disease events
• Promote weight loss
• Prevent hypoglycemia (safety)
• Achieve near-euglycemia
Summary and Conclusions

- Priorities in T2DM treatment include DM prevention/remission (early), and prevention of CVD events (mid-late, duration of DM)
- Newer DM treatment classes, the SGLT2i’s and GLP-1 RA’s, promote durable weight loss, better glycemia, AND have been shown to reduce CVD risk
- Making effective therapy affordable is a challenge, and a moral imperative, for all of us!