Understanding the Role of the Healthcare System and Quality Improvement in Supporting People with Cardiometabolic Conditions

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Recent clinical trials in diabetes and pre-diabetes

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Denver, CO
The traditional perspective:

Diabetes Drug

CV Drug
The new perspective:

Diabetes Drug  CV Drug
Consider by **class of drug**
- Biguanide (metformin)
- TZD (pioglitazone)
- SGLT2 inhibitors
- GLP1 agonists
- DPP-4 inhibitors

Consider by **category of patient**
- Type 2 diabetes
- Pre-diabetes
# Diabetes drugs as CV drugs: Evidence in type 2 diabetes

## Favorable

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Agents</th>
<th>Trials</th>
<th>CV efficacy established?</th>
<th>CV outcomes</th>
<th>Safety and tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>UKPDS (1998)</td>
<td>Many caveats</td>
<td>Death, MI, diabetes-related outcomes</td>
<td>Lactic acidosis; GI symptoms</td>
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<tr>
<td>TZDs</td>
<td>Pioglitazone</td>
<td>PROACTIVE (2005)</td>
<td>Principal secondary endpoint</td>
<td>Death, MI, stroke</td>
<td>Weight gain, edema, fractures, heart failure</td>
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<tr>
<td>SGLT2 inhibitors</td>
<td>Empagliflozin</td>
<td>EMPA-REG* (2015)</td>
<td>Yes</td>
<td>CV death, MI or stroke*†</td>
<td>Amputations†, fractures†, volume depletion, GU infections</td>
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<tr>
<td></td>
<td>Canagliflozin</td>
<td>CANVAS† (2017)</td>
<td>Yes</td>
<td>Death*</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Renal**†</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heart failure*†</td>
<td></td>
</tr>
<tr>
<td>GLP1 agonists</td>
<td>Liraglutide</td>
<td>LEADER* (2016)</td>
<td>Yes</td>
<td>CV death, MI or stroke*†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Semaglutide</td>
<td>SUSTAIN6† (2016)</td>
<td>Yes</td>
<td>Death*</td>
<td></td>
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<tr>
<td></td>
<td>Lisasenatide</td>
<td>ELIXA (2015)</td>
<td>Yes</td>
<td>Renal**†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exenatide</td>
<td>EXSCEL (2017)</td>
<td>No</td>
<td>Heart failure</td>
<td></td>
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</table>

## Neutral

<table>
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<th>CV outcomes</th>
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### No demonstrated CV efficacy:
- DPP4 inhibitors, basal insulin (glargine), other PPAR-gamma agonists, sulfonylureas
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<th>Trials</th>
<th>CV efficacy established?</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TZDs</td>
<td>Pioglitazone</td>
<td>IRIS (2016) (population defined by insulin resistance)</td>
<td>Yes</td>
<td>Fatal or non-fatal MI or stroke</td>
</tr>
<tr>
<td>Acarbose</td>
<td>Acarbose</td>
<td>ACE (2017)</td>
<td>No</td>
<td>CV death, MI, stroke, unstable angina, heart failure hosp.</td>
</tr>
</tbody>
</table>
Practical questions for the specialist, generalist, and patient: How should the evidence be applied?

1. I have a patient with well-controlled type 2 diabetes on metformin + SU. Should I change the SU to a drug with proven CV benefit?

2. I have a patient on metformin who needs additional medication. Should I choose a 2nd or 3rd medication based on likelihood of CV benefit?

3. Should I start my patient with pre-diabetes on pioglitazone or metformin?

4. How do I integrate new evidence for CV efficacy of diabetes drugs with evidence for CV efficacy of new lipid-lowering, anti-inflammatory, and anti-thrombotic drugs? How many drugs should my patient be on?
5. Who will make the treatment decisions and be responsible for monitoring and managing side effects and safety?

6. What are the implications for health care costs?
Barriers to Clinical Management of Diabetes (Type 1 and 2) Along the Lifespan

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Professor of Medicine
Division of Endocrinology, Metabolism and Diabetes
Division of Cardiology
Charles A. Boettcher II Chair in Atherosclerosis
University of Colorado Denver Anschutz Medical Campus
Barriers to Clinical Management of Diabetes (T1DM) Along the Lifespan

- Diagnosis can be confusing – 50% now occur after age 30
- Individualization of glycemic control avoiding severe hypoglycemia and DKA
- An endocrinologist/diabetologist (+ CDE) almost always needs to be involved
  - Nutrition, physical activity, alcohol
  - Insulin management – multiple daily injections vs. insulin infusion pump
  - Continuous glucose monitoring systems
  - Closed loop systems
  - β-cell replacement therapy
  - Psychosocial issues
  - Pregnancy
  - Complications – assessment and management
- Evidence from RCTs lacking for CVD prevention
  - Lipids – statins, goals, when?
  - BP – meds, goals, when?
  - Aspirin
- Cost!
Barriers to Clinical Management of Diabetes (T2DM) Along the Lifespan

- Diagnostic criteria vary.
  - Fasting glucose, OGTT, HbA1c

- When does the relationship between the metabolic syndrome and/or impaired glucose metabolism and its CVD risk begin?

- Weight loss is so often needed and effective treatment needs much time, expertise and to be individualized.

- The management of T2DM is complex, and RCTs using newer therapies have CVD benefits.
  - ADA, AACE
Barriers to Clinical Management of Diabetes (T2DM) Along the Lifespan

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- Is metformin always the first drug?

- What about sulfonylureas, cheap but hypoglycemia and increased CVD risk?

- In more difficult patients newer therapies are expensive and may require more expertise and experience than is present in the usual PCP practice.
Diabetes Prevention, Diagnosis, and Treatment Using a Simple POPULATION System

R. James Dudl, MD

Diabetes Lead
Care Management Institute & Community Benefit
Kaiser Permanente
Principles: Use a Simple System for Population Care

1. Set few, simple, measurable treatment targets, and do continual surveillance.

2. Consider “treatment intensification” of every patient at every opportunity
   1. Fix provider & TEAM accountability
   2. Develop a single treatment algorithm that is OK with providers for 80% patients (all type 1 pts are exceptions)
      1. Add “personalization” as branches that fit onto your system

3. Action: treatment intensification: Titration, Initiation Adherence (TIA)
   1. Assure with a metric

3. Measure, feedback, & correct until target
Diabetes: Prevent CVD

- **Fix Physician accountability** to use an algorithm with statin, ASA, & HTN drugs

- **Use a simple Treatment target algorithm:**
  - If over 40yo start a statin. Use L for lipid lowering (L)
    - Consider adding ASA if over 10% CVD risk. A for aspirin: (AL)
  - If CVD add Lisinopril (L) or alternative ACE/ARB: (ALL)
  - If hypertension, add a combination of BP meds, like Thiazide/Lisinopril (TALL)

- **Insure Treatment Intensification TIA**: rechecks monthly till target
  - **Adherence**: pharmacy refills till =>80% or Drug Reconciliation 6-7 days/wk
  - **Titration**: HTN: consider ½ to 1 to 2 pills/dose standard
  - **Initiation**: if both adherent @=>6 days/wk, and max titration, add the next medication.
    - Lipid lowering: ezetimibe, SGLT2 inhibitors, GLP1 agonists when the main path is insufficient to get to outcomes. PCSK9 are infrequently indicated using GRADE implementation criteria*).

- **Measure, feedback & correct system** till target.

* BMJ 2004;328:1490–4
KP Implemented “ALL” in 70,000 DM>55 or CVD pts, after 2 yrs c/w no Rx in 170,000 pts:

- A decline of MI’s or Strokes 15/1000 low adherence [>60% decline] 23/1000 high adherence*

Decline in all MI’s in Northern Cal Kaiser over 10 yrs: >30% Non STEMI & 60% Stemi MI’s**

Hypertension control <140/90 in No Cal Kaiser >80% in 10 yrs***

- 5 Principles of population medicine

*** JAMA. 2013;310(7):699-705
Diabetes: Achieve **Glycemic Control**

Fix provider **TEAM accountability** to use an **algorithm** of lifestyle & starting with **metformin**, **add glipizide**, & **add NPH insulin** if needed

**Treatment target** of an **A1C** & **Measure** self-monitored blood glucose **[SMBG]** and consider telecommunications for results and **f/u optimally every 1-2 wks**

- **Insure Treatment Intensification (TIA):**
  - **Adherence:** insure >=6 days/wk
  - **Titration:** ½ to 1 to 2 pills/dose standard or **Insulin increase 1u/d**
  - **Initiation:** if both adherence is >=6 days/wk, and max titration, **add** next medication
    - **Pioglitazone**, SGLT2 inhibitors, GLP1 agonists, etc. are options to be used when indicated, consider if hypoglycemia is a concern.

- **Remeasure, feedback &/or correct system** till target.

**Results:** **HEDIS No Cal Kaiser > 95%ile moderate or poor A1C control**, (appendix)

*Arch Intern Med. 2011 September 26; 171(17):*
Prediabetes: Kaiser Permanente's Diabetes Impact to Surge Over Time

KP Members at risk for diabetes in 2016¹
1,514,820

29% develop diabetes over 3 years²

NEW cases of diabetes by 2019
439,298

KP members with type 2 DM through Q3 2015³
550,291

52% develop diabetes over 10 years²

NEW cases of diabetes by 2026: 787,706

1 – Preliminary data; CMI Analysis April 2017.
2 – Diabetes Prevention Research Group; Diabetes Prevention Program
3 – Preliminary data; CMI Analysis, as of Apr 2016. CORE KP HEDIS Diabetes cohort, minus expected 10% of Type 1 diabetes per CDC national prevalence
Could Screening for DM starting 45yo Every 3 Yrs save lives, MI’s and micro-vascular complications?

- **MI’s Saved**
  - 45yo Q3Y

- **Micro Vasc Saved**
  - 45yo Q3Y

- **$/QALY**
  - 45yo Q3Y

Lancet 2010; 375: 1365–74
Lifestyle Programs Can Be Successfully Implemented in the Community.

Systematic Review
All Qualifying 50 Programs
To Prevent DM
Decreased It 41%  P<.001
And Be **Cost Effective** for Preventing **Diabetes**

Systematic Review all programs for diet/exercise if increased risk for DM

Delivery method
- Individual-based: $15,846 (IQI, 7,980 to 72,723)
- **Group-based**: $1,819 (IQI, −5027 to 16,443)

Kaiser’s Prediabetes Program

Fix provider **accountability** to use an **algorithm** which includes using **lifestyle** or **metformin**

**Treatment target** is A1c< 6.5%:
- **Initiate**: consider lifestyle first, a **CDC approved lifestyle program** for 1 yr
  - If that is not done or is ineffective, consider **Metformin** initiation [encouraged recently]

- **Insure Treatment Intensification**:
  - **Adherence**: if metformin, confirmed => 6d/wk or refill data, then
  - **Titration**: consider ½ to 1 to 2 pills twice a day if max dose,
  - **Initiate**: If patient develops DM go to DM algorithm

- Remeasure, feedback &/or **correct system** till target.
  - Repeat screening test at least annually

- **Screen for CVD** risk factors; see DM protocol for CVD prevention

**Results**: **Lifestyle for 10,000 members** (80% virtual, 20% in-person) 5% wt loss achieved by 50% (appx)
Panel 1 - Breakout Session

Understanding the role of the healthcare system and quality improvement in supporting people with cardiometabolic conditions

- What are the 3 short-term solutions that could have the largest impact?
- What are the 3 long-term solutions that could come out of the summit?