Diabetes Care Transformation
*A Change of Heart*

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Disclosures

• Boehringer Ingelheim Speakers Bureau
• Novo Nordisk Speakers Bureau
Learning Objectives

1. Appreciate the impact of diabetes on cardiovascular morbidity and mortality.
3. Understand evidence-based recommendations for optimal diabetes management.
4. Review implementation of real-world diabetes population health management strategies.
5. Recognize opportunities to leverage diabetes medications to mitigate cardiovascular risk.
The Diabetes Tidal Wave & Cardiovascular Risk
The Diabetes Tidal Wave

2015
30 million patients living with diabetes

2050
84 million patients living with diabetes

Popul Health Metr. 2010;8:29.
Pathophysiologic Links – DM & CVD
Impact of Diabetes on MI/CVA Risk

Diabetes Population

Standards of Care: Statins, ACE/ARB, ASA….

15-18xs higher risk of MI & CVA

General Population

Events per 10,000 overall adult population

Residual CV Risk Despite Advances in Care

- MI: 6.7x
- CVA: 8x

*Residual Risk*

Impact of Diabetes on CV Death

Impact of Diabetes on CV Death

Diabetes population
General population

1.4x greater incidence of CV death

Impact of Diabetes & CVD on Life Expectancy

- T2DM: -6.7 years
- T2DM s/p MI: -11.2 years
- T2DM s/p MI & s/p CVA: -15.7 years

Novel Diabetes Therapies –
A New Frontier in Cardiovascular Risk Reduction
Novel Therapy Mechanisms of Action

Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists

- Secretes GLP-1 in response to food
- Stimulates insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying

Sodium-glucose co-transporter 2 (SGLT-2) Inhibitors

-抑制SGLT2
- ~90% reabsorption in S1 segment of proximal tubule
- ~10% reabsorption in S2/S3 segment of proximal tubule

References:

*Diabetes.* 2008;57:1723-1729.
Attacking the Ominous Octet

GLP-1

GLP-1

GLP-1

GLP-1

GLP-1

SGLT-2

GLP-1

GLP-1 Receptor Agonist CV Mechanisms

Effect

Consequence

- Blood pressure reduction
- Weight loss
- Low-density lipoprotein cholesterol reduction
- Anti-inflammatory action

- Reduced myocardial work, reduced filling pressures, pre-/afterload reduction
- Improved CV disease risk profile, lower blood pressure
- Reduced atherogenesis
- Upregulated nitric oxide and suppressed NF-κB activation

SGLT-2 Inhibitor CV Mechanisms

Effect of Rosiglitazone on the Risk of Myocardial Infarction And Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Rolski, M.P.H.

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death...that had borderline significance.
Diabetes CVOTs – Timeline

Diabetes CVOTs – Timeline

SGLT-2 Cardiovascular Trial Summary

**EMPA-REG Outcome**
- **Empagliflozin**
- Dose: 10/25 mg, once daily
- Number of participants: 7020
- Mean age (years): 63.1
- Mean HbA1c at baseline (%): 8.1
- Median follow-up period (years): 3.1
- Patients with established CVD: 6964 (99%)

**CANVAS/CANVAS-R**
- Canagliflozin
- Dose: 100/300 mg, once daily
- Number of participants: 10,142
- Mean age (years): 63.3
- Mean HbA1c at baseline (%): 8.2
- Median follow-up period (years): 2.4
- Patients with established CVD: 6656 (65.6%)

**DECLARE-TIMI 58**
- Dapagliflozin
- Dose: 10 mg, once daily
- Number of participants: 17,160
- Mean age (years): 63.9
- Mean HbA1c at baseline (%): 8.3
- Median follow-up period (years): 4.2
- Patients with established CVD: 6974 (40.0%)

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**Relative Risk Reduction (RRR)**
- EMPA-REG OUTCOME
  - HHF: ↓14 p=0.04
  - HHF or CV death: ↓33 p=0.002
  - MACE: ↓34 p=0.001
- CANVAS
  - HHF: ↓14 p=0.08
  - HHF or CV death: ↓22 p=0.0015
- DECLARE-TIMI 58
  - HHF: ↓7 p=0.17
  - HHF or CV death: ↓17 p=0.005
  - MACE: ↓27 p=0.0008

**NNT**
- EMPA-REG: NNT 63
- CANVAS: NNT 43
- DECLARE-TIMI 58: NNT 53

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SGLT-2 Reno-protection

**CREDENCE**

**Population**

**Inclusion Criteria**
- Age ≥30 years old with T2DM
- HbA1c 6.5–12.0% (6.5–10.5% in Germany)
- eGFR 30–89 mL/min/1.73 m²
- Urinary albumin:creatinine 300–5000 (mg/g)
- On an ACEi/ARB at the maximum labeled dose

**Exclusion Criteria**
- Type 1 diabetes
- Suspected non-diabetic kidney disease
- Dialysis
- Kidney transplantation

**Primary composite outcome**
- Doubling of serum creatinine level
- End-stage kidney disease
- Estimated GFR <15 mL/min/1.73 m²
- Dialysis initiated or kidney transplantation
- Renal death
- Cardiovascular death

**Primary Composite Outcome**
- Hazard ratio, 0.70 (95% CI, 0.59–0.82) P=0.00001
- Placebo
- Canagliflozin
- NNT 22

**Renal-Specific Composite Outcome**
- Hazard ratio, 0.66 (95% CI, 0.53–0.81) P<0.001
- Placebo
- Canagliflozin
- NNT 31

**End-Stage Kidney Disease**
- Hazard ratio, 0.68 (95% CI, 0.54–0.86) P=0.002
- Placebo
- Canagliflozin
- NNT 45

**Statistical Significance**

GLP-1 Cardiovascular Trial Summary

### LEADER
- **Drug**: Liraglutide
- **Structural basis**: Human GLP-1
- **Administration route**: Subcutaneous
- **Dose**: 1.8 mg per day
- **Diabetes duration (years)**: 12.8 (8.0)
- **HbA1c (%)**: 8.7 (1.6)
- **Established cardiovascular disease**: 7598 (81%)

**3-Point MACE**
- **Hazard ratio, 0.87 (95% CI, 0.78–0.97)**
- **P<0.001 for noninferiority**
- **P=0.01 for superiority**

**NNT 53**

### SUSTAIN-6
- **Drug**: Semaglutide
- **Structural basis**: Human GLP-1
- **Administration route**: Subcutaneous
- **Dose**: 0.5 or 1 mg per week
- **Diabetes duration (years)**: 13.9 (8.1)
- **HbA1c (%)**: 8.7 (1.5)
- **Established cardiovascular disease**: 2735 (83%)

**3-Point MACE**
- **Hazard ratio, 0.74 (95% CI, 0.58–0.95)**
- **P<0.001 for noninferiority**
- **P=0.02 for superiority**

**NNT 43**

### REWIND
- **Drug**: Dulaglutide
- **Structural basis**: Human GLP-1
- **Administration route**: Oral
- **Dose**: 1.5 mg per week
- **Diabetes duration (years)**: 14.9 (8.5)
- **HbA1c (%)**: 8.2 (1.6)
- **Established cardiovascular disease**: 2695 (85%)

**3-Point MACE**
- **Hazard ratio, 0.79 (95% CI, 0.57–1.11)**
- **Oral semaglutide, 61 events**
- **Placebo, 76 events**
- **P<0.001 for noninferiority**
- **P=0.17 for superiority**

**NNT 71**
Real-World GLP-1 & SGLT-2 Benefits – Incidence of 1st MACE

Expanding the GLP-1 Frontier - Oral Semaglutide

INDICATION: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

DOSING:

- 3mg daily for 30 days
- 7mg daily for at least 30 days
- 14mg daily

ADMINISTRATION:

- Take upon waking on an empty stomach
- Take with no more than 4oz of water
- Wait 30 minutes before first food, beverage or oral medication(s)

Oral Semaglutide – Glycemic Control

**PIONEER-2 (vs. SGLT-2)**
Mean baseline HbA1c: 8.1% (85 mmol/mol)

- Change in HbA1c (%)
  - Oral semaglutide 14 mg
  - Empagliflozin 25 mg

-1.4% vs. -0.9%

**PIONEER-3 (vs. DPP-4)**

-1.4% vs. -0.8%

**PIONEER-4 (vs. daily inj. GLP-1)**

-1.3% vs. -1.1%

**PIONEER-8 (insulin add-on)**

-1.3% vs. -0.1%

Oral Semaglutide – Weight Loss

**PIONEER-2 (vs. SGLT-2)**
-9.2lbs vs. -8.4lbs

**PIONEER-3 (vs. DPP-4)**
-7.3lbs vs. -1.5lbs

**PIONEER-4 (vs. daily inj. GLP-1)**
-10.3lbs vs. -7.0lbs

**PIONEER-8 (insulin add-on)**
-9.5lbs vs. +1.3lbs

Guideline Consensus Around Life-saving Therapy
FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity). If HbA₁c above target proceed as below.

**-established ASCVD or CKD**

If further intensification is required or patient is not on GLP-1 RA or SGLT2i, consider agents demonstrating CV safety:
- GLP-1 RA with proven CV benefit
- SGLT2i with proven CV benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin

If HbA₁c above target
- Avoid TZD in the setting of HF
- Consider adding the other class with proven CV benefit
- DPP-4i not saxagliptin in the setting of HF
- Basal insulin
- SU

If HbA₁c above target
- Continue with addition of other agents as outlined above

**HF or CKD predominates**

If no GLP-1 RA or SGLT2i evidence of reducing HF and/or CKD progression in CVOTs of eGFR adequate
- OR

PREFERABLY
- SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs of eGFR adequate

If HbA₁c above target
- GLP-1 RA
- SGLT2i
- TZD

If HbA₁c above target
- GLP-1 RA OR DPP-4i OR TZD

If HbA₁c above target
- GLP-1 RA OR DPP-4i OR TZD

If HbA₁c above target
- GLP-1 RA OR SGLT2i

If HbA₁c above target
- Continue with addition of other agents as outlined above

**Compelling need to minimize hypoglycemia**

- GLP-1 RA with good efficacy for weight loss

If HbA₁c above target
- SGLT2i

If HbA₁c above target
- GLP-1 RA with good efficacy for weight loss

If HbA₁c above target
- DPP-4i (if not on GLP-1 RA) based on weight neutrality

**Compelling need to minimize weight gain or promote weight loss**

- Insulin therapy basal insulin with lowest acquisition cost
- OR
- Consider DPP-4i OR SGLT2i with lowest acquisition cost

COST IS A MAJOR ISSUE

- SU
- TZD

If HbA₁c above target
- GLP-1 RA
- SGLT2i

If HbA₁c above target
- GLP-1 RA
- SGLT2i

If HbA₁c above target
- GLP-1 RA
- SGLT2i
FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity) if HbA1c above target proceed as below.

ESTABLISHED ASCVD OR CKD

NO

WOULD NOT ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

HF OR CKD PREDOMINATES

PREFERRABLY

SGLT2i with evidence of reducing HF and/or CVD progression in CVD risk if eGFR adequate

OR

If SGLT2i tolerated or contra indicated or if eGFR less than adequate add GLP-1 RA with proven CVD benefit

If HbA1c above target

If further intensification is required or patient is not able to tolerate GLP-1 RA or SGLT2i choose agents demonstrated CV safety:

- Avoid TZD in the setting of HF

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit

- DPP-4i if not on GLP-1 RA

- Basal insulin

- TZD

- SU

If HbA1c above target

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i

GLP-1 RA

SGLT2i

TZD

If HbA1c above target

SGLT2i

SGLT2i

GLP-1 RA

SGLT2i

DPP-4i

If HbA1c above target

SGLT2i

SGLT2i

GLP-1 RA

SGLT2i

DPP-4i

If HbA1c above target

GLP-1 RA

with good efficacy for weight loss

SGLT2i

with good efficacy for weight loss

DPP-4i

TZD

SULF

TZD

SU

COST IS A MAJOR ISSUE

Insulin therapy basal insulin with lowest acquisition cost

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If HbA1c above target

If HbA1c above target

If HbA1c above target

If HbA1c above target

If HbA1c above target

If HbA1c above target

Consider the addition of SU or basal insulin

- Choose GLP-1 RA with lower risk of hypoglycemia

- Consider basal insulin with lower risk of hypoglycemia
Transforming Diabetes Care at Geisinger
Taking Diabetes to Heart

Geisinger System

Pre-Diabetes
120,000
+500/month

Diabetes
47,000

A1c >9

33%
DM + CVD

Diabetes & CVD

Leading cause of morbidity & mortality among patients with DM

- 8x higher risk of MI
- 6.7x higher risk of CVA

2 of 3 adults will die of CV cause

Aligning Stakeholders to Transform Care

Diabetes Care Transformation Committee (DCTC)

Agile framework, Disease-specific stakeholders & Common overall goal

Outcomes

Cost

Patient Experience

Clinician Experience

Endocrinology

Cardiology

Primary Care

Pharmacy

Formulary

Nursing

Nutrition

Data Analytics & Innovation

Geisinger
“An average of about [?] years is required for new knowledge generated by randomized controlled trials to be incorporated into practice, and even then application is highly uneven.”

Evidence Based Medicine – The Waiting Game

“An average of about 17 years is required for new knowledge generated by randomized controlled trials to be incorporated into practice, and even then application is highly uneven.”
Clinical Inertia – Failure of Assessment & Intensification

Repeat A1c every 3 or 6 months

Guideline directed assessment & intensification

RX Modification w/in 45 days of A1c >7%

14%

3%

18%

Clinical Inertia – Time to Intensification

Treatment Initiation Timeline (years)

- 2nd oral RX: 1.6 years
- 3rd oral RX: 6.9 years
- Basal Insulin: 6.0 years
- Bolus or Premix Insulin: 3.2 years

**17.7 years**

Deploying Tactics to Combat Clinical Inertia

“Assessment”

A1c Overdue Letters

Point-of-care A1C

“Intensification”

A1c >9 Letters

Amplified Diabetes Huddle

Pharmacist

Health Manager

Dietician

+
Ambulatory Care Sensitive Conditions (ACSC) Smartset

- ACSC DIABETES
  - Documentation Amb Care Sensitive Conditions
    - Diabetes Protocol
  - Medications
  - Labs
  - Supplies
  - Care Team Referrals
  - Diagnosis
  - Patient Instructions
  - Follow Up
  - Additional Orders
ACSC Decision Support – RX Order Set

ACSC DIABETES
- DOCUMENTATION AMB CARE SENSITIVE CONDITIONS
- MEDICATIONS
  - Metformin [1st med unless GFR <30]
  - GLP-1 [2nd med after Metformin - *if HF or CKD w/ GFR 45+, use SGLT-2 as 2nd agent*]
  - SGLT-2 [3rd med in combo w/ Metformin + GLP-1 - *if HF or CKD, use 2nd line after metformin*]
  - DPP-4 [2nd or 3rd med if GLP-1 contraindicated due to MTC/MEN-2]
- Basal Insulin
- Meal-time Insulin
- Alternative Oral Agents [for use if cost is barrier to preferred meds]
- Statins
- ACEs/ARBs
- Aspirin
- LABS
- SUPPLIES
- CARE TEAM REFERRALS
2nd-Line Prescribing by Class

8% GLP-1 or SGLT-2

54% GLP-1 or SGLT-2
Synergy of Tactics - Pottsville CMSL A1c >9

% Patients A1c >9 Non-compliant

Month


Clinical Inertia
Tactics Deployed

30.9%

23.0%

8% Improvement
Oct 2018-Oct 2019
System Quality – A1c >9

Month

% Patients A1c >9 Non-compliant

Clinical Inertia
Tactics Deployed

5% Improvement
Oct 2018-Oct 2019

25.3%
20.9%
Next Steps

Targeted Clinician Education

“Amplifying” Amp DM Huddle

GLP-1 & SGLT-2 Specific Care Gaps

“Cardio-metabolic” Pharmacists

Geisinger
According to the ADA Standards of Care, when interacting with a patient with diabetes, all clinicians should.....

1. **STOP AND EVALUATE AT EVERY VISIT**
   ....does the patient have established CVD?

2. **REDUCE RISK OF DEATH**
   ....if yes, add agent with proven CV benefits
References