Glucose Lowering Medications and Cardiovascular Risk Reduction: A New Era

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CONSIDERATIONS:

• Patient Centered
• Phenotype Centered
• Glucose management is complex and imperfect
• New recommendations for the ~20% DM + CVD
Disclosures

• Investigator Initiated Trial Support:
  – Merck: Sitagliptin impact on exercise capacity (T2D)
• Funding: NIH, VA
• Consultant:
  – Oramed
• Board of Directors
  – ADA
Diabetes Shortens Life Span

Men

Age of onset

Women

Age of onset

CVD CHF Tailored Therapy

Premature mortality persists in people with DM

Framingham

Intensive multifactorial treatment (STENO-2)


CVOT History: Why now? Worth it?
In light of premature CV mortality we need to get this right

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Safety concerns and response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Human proinsulin</td>
<td>Trials and development suspended&lt;br&gt;<strong>CV issues and ↑ risk of acute myocardial infarction</strong>[a]</td>
</tr>
<tr>
<td>2005</td>
<td>Muraglitazar</td>
<td>↑ Risk of death, major CV adverse events, CHF[b]</td>
</tr>
<tr>
<td>2007</td>
<td>Rosiglitazone</td>
<td>↑ CV risk; withdrawn from market in many countries[c]</td>
</tr>
<tr>
<td>2008</td>
<td>–</td>
<td>FDA issued guidance document for the evaluation of CV risk[d]&lt;br&gt;Studies are required to demonstrate that <strong>new anti-diabetic therapies do not increase CV</strong> risk in comparison with existing therapies</td>
</tr>
</tbody>
</table>

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CVOT are designed and powered to assess non-inferiority versus placebo in addition to standard of care in a high risk CVD patient population (prior CVD ± high risk patients without proven CVD).

Major endpoint composite of Major Adverse Cardiovascular Events:
- Usual is 3 point MACE – new nonfatal MI, new stroke, CV death based on careful adjudication to confirm accuracy of the events*

Key understandings:
- Powered for safety.
- Studied populations provide data on SECONDARY PROTECTION.
- Original studies not powered for subgroup analysis
- Different design does not consistently enable direct comparison of results of one study to another.
Completed and Ongoing CVOTs

- SAVOR-TIMI 53
  - n = 16,492
  - 3-P MACE

- EXAMINE
  - n = 5,380
  - 3-P MACE

- TECOS
  - n = 14,671
  - 4-P MACE

- CARAMELINA
  - n = 7,003
  - 3-P MACE

- CAROLINA
  - n = 6,072
  - 3-P MACE

2013
- EMPA-REG OUTCOME
  - n = 7,020
  - 3-P MACE

- ELIXA
  - n = 6,068
  - 4-P MACE

2015
- LEADER
  - n = 9,340
  - 3-P MACE

- SUSTAIN-6
  - n = 3,297
  - 3-P MACE

2016
- FREEDOM-CVO
  - n = 4,156
  - 3-P MACE

- CANVAS Program
  - n = 10,142
  - 3-P MACE

- PIONEER 6
  - n = 3,176
  - 3-P MACE

2017
- REWIND
  - n = 9,901
  - 3-P MACE

- HARMONY Outcomes
  - n = 9,400
  - 3-P MACE

- DEVOTE
  - n = 7,637
  - 3-P MACE

- IRIS
  - n = 3,876
  - Fatal or nonfatal stroke or MI

2018
- EXCEL
  - n = 14,752
  - 3-P MACE

- ACE
  - n = 6,522
  - 5-P MACE
  - (3-P MACE + hospitalization for HF or unstable angina)

- VERTIS CV
  - n = 8,000
  - 3-P MACE

- Dapa-HF
  - n = 4,500
  - CV death, HF hospitalization, urgent HF visit

- CREDENCE
  - n = 4,464
  - ESRD, doubling of creatinine, renal/CV death

- DECLARE-TIMI 58
  - n = 17,276
  - 3-P MACE; CV death + HF hospitalization

2019
- HARMONY Outcomes
  - n = 9,400
  - 3-P MACE

- DAPA-CKD
  - n = 4,000
  - ≥50% sustained decline in eGFR or reaching ESRD, CV death, or renal death

2020
- DECLARE-TIMI 58
  - n = 2,850
  - CV death or HF hospitalization

- EMPEROR-Reduced
  - n = 2,850
  - CV death or HF hospitalization

- EMPEROR-Preserved
  - n = 4,126
  - CV death or HF hospitalization

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Antihyperglycemic Therapy: Safety and CVD/CHF considerations

• Insulin:
  - ORIGIN trial (Glargine U-100).
  - DEVOTE trial (Degludec vs. Glargine U-100).

• Thiazolidinediones:
  - PROACTIVE trial (Pioglitazone).
  - RECORD trial (Rosiglitazone).

• DPP-4 inhibitor:
  - SAVOR TIMI (Saxagliptin).
  - EXAMINE (Alogliptin).
  - TECOS (Sitagliptin)
# DPP-4 Inhibitor CVD Outcome Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Population</th>
<th>Composite Outcome</th>
<th>Key Finding</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxagliptin</td>
<td>CVD or risk factors</td>
<td>3 point MACE</td>
<td>Safety HR 1.00</td>
<td>Increased HR 1.27</td>
</tr>
<tr>
<td>SAVOR TIMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alogliptin</td>
<td>CVD</td>
<td>3 point MACE</td>
<td>Safety HR 0.96</td>
<td>Unchanged</td>
</tr>
<tr>
<td>EXAMINE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitiglipitin</td>
<td>CVD</td>
<td>4 point MACE</td>
<td>Safety HR 0.98</td>
<td>Unchanged</td>
</tr>
<tr>
<td>TECOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Beyond Safety

SGLT2 inhibitors
GLP1 Receptor Agonists
### EMPA-REG: CV Death, MI, and Stroke

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Patients With Event/Analyzed</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>Empagliflozin: 490/4687</td>
<td>Placebo: 282/2333</td>
<td>0.86 (0.74-0.99)*</td>
</tr>
<tr>
<td>CV death</td>
<td>Empagliflozin: 172/4687</td>
<td>Placebo: 137/2333</td>
<td>0.62 (0.49-0.77)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>Empagliflozin: 213/4687</td>
<td>Placebo: 121/2333</td>
<td>0.87 (0.70-1.09)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>Empagliflozin: 150/4687</td>
<td>Placebo: 60/2333</td>
<td>1.24 (0.92-1.67)</td>
</tr>
</tbody>
</table>

Note: *95.02% CI.

**Patients With Event, %**
- 3% Favors empagliflozin
- 7% Favors placebo

EMPA-REG: CV Death


HR: 0.62
(95% CI: 0.49-0.77);
\(P < .0001\)

Patients With Event, %

Time, mo

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>4687</td>
<td>4651</td>
</tr>
<tr>
<td>2333</td>
<td>2303</td>
</tr>
<tr>
<td>4608</td>
<td>4608</td>
</tr>
<tr>
<td>2280</td>
<td>2243</td>
</tr>
<tr>
<td>4556</td>
<td>4556</td>
</tr>
<tr>
<td>2243</td>
<td>2243</td>
</tr>
<tr>
<td>4128</td>
<td>4128</td>
</tr>
<tr>
<td>2012</td>
<td>2012</td>
</tr>
<tr>
<td>3079</td>
<td>3079</td>
</tr>
<tr>
<td>1503</td>
<td>1503</td>
</tr>
<tr>
<td>2617</td>
<td>2617</td>
</tr>
<tr>
<td>1281</td>
<td>1281</td>
</tr>
<tr>
<td>1722</td>
<td>1722</td>
</tr>
<tr>
<td>825</td>
<td>825</td>
</tr>
<tr>
<td>177</td>
<td>177</td>
</tr>
</tbody>
</table>
EMPA-REG: Hospitalization for Heart Failure

Cumulative incidence function

HR: 0.65 (95% CI: 0.50-0.85);  
\( P = .002 \)

Patients With Event, %

Placebo
Empagliflozin

Time, mo

No. of patients
Empagliflozin  
4687  
4614  
4523  
4427  
3988  
2950  
2487  
1634  
395

Placebo  
2333  
2271  
2226  
2173  
1932  
1424  
1202  
775  
168

CANA VS and CANVAS-R Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin (N=5795)</th>
<th>Placebo (N=4347)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>11.6</td>
<td>12.8</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9.7</td>
<td>11.6</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7.1</td>
<td>8.4</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>11.2</td>
<td>12.6</td>
<td>0.89 (0.73–1.09)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>7.9</td>
<td>9.6</td>
<td>0.87 (0.69–1.09)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>118.7</td>
<td>131.1</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or hospitalization for heart failure</td>
<td>16.3</td>
<td>20.8</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.3</td>
<td>19.5</td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>89.4</td>
<td>128.7</td>
<td>0.73 (0.67–0.79)</td>
</tr>
<tr>
<td>40% reduction in eGFR, renal-replacement therapy, or renal death</td>
<td>5.5</td>
<td>9.0</td>
<td>0.60 (0.47–0.77)</td>
</tr>
</tbody>
</table>

CVD-REAL Study

• Real world study of 6 countries (US, Norway, Denmark, Sweden, Germany, UK) for relative rates death and hospitalization for heart failure in pts. newly started on SGLT2i or matched controls (n=154,528 in both).
  – Baseline 3% HF, 13% CVD, 27% microvascular disease.
  – Canagliflozin 53%, Dapagliflozin 42%, Empagliflozin 5%.

• Lowered relative rates in SGLT2i patients:
  – Heart failure – 0.61 (95% CI 0.51-0.73, p<0.001).
  – All cause death – 0.49 (95% CI 0.41-0.57, p<0.001).

• No significant heterogeneity by country.

Who are the people in CVOT studies?
**EMPA-REG: Baseline Characteristics T2D**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 2333)</th>
<th>Empagliflozin 10 mg (n = 2345)</th>
<th>Empagliflozin 25 mg (n = 2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c, %</strong></td>
<td>8.08 (0.84)</td>
<td>8.07 (0.86)</td>
<td>8.06 (0.84)</td>
</tr>
<tr>
<td><strong>Time since diagnosis of type 2 diabetes, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 5</td>
<td>423 (18.1)</td>
<td>406 (17.3)</td>
<td>434 (18.6)</td>
</tr>
<tr>
<td>&gt; 5 to 10</td>
<td>571 (24.5)</td>
<td>585 (24.9)</td>
<td>590 (25.2)</td>
</tr>
<tr>
<td>&gt; 10 YEARS!!</td>
<td>1339 (57.4)</td>
<td>1354 (57.7)</td>
<td>1318 (56.3)</td>
</tr>
<tr>
<td><strong>Glucose-lowering medication</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>1734 (74.3)</td>
<td>1729 (73.7)</td>
<td>1730 (73.9)</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>992 (42.5)</td>
<td>985 (42.0)</td>
<td>1029 (43.9)</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>101 (4.3)</td>
<td>96 (4.1)</td>
<td>102 (4.4)</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>1135 (48.6)</td>
<td>1132 (48.3)</td>
<td>1120 (47.8)</td>
</tr>
<tr>
<td><strong>Mean daily dose, U†</strong></td>
<td>65 (50.6)</td>
<td>65 (47.9)</td>
<td>66 (48.9)</td>
</tr>
</tbody>
</table>

*Medication taken alone or in combination
†Placebo, n = 1135; empagliflozin 10 mg, n = 1132; empagliflozin 25 mg, n = 1120
Data are n (%) or mean (SD) in patients treated with ≥ 1 dose of study drug.

### EMPA-REG: Baseline Characteristics CVD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 2333)</th>
<th>Empagliflozin 10 mg (n = 2345)</th>
<th>Empagliflozin 25 mg (n = 2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CV risk factor, no. (%)</td>
<td>2307 (98.9)</td>
<td>2333 (99.5)</td>
<td>2324 (99.2)</td>
</tr>
<tr>
<td>Coronary artery disease, no. (%)</td>
<td>1763 (75.6)</td>
<td>1782 (76.0)</td>
<td>1763 (75.3)</td>
</tr>
<tr>
<td>Multi-vessel coronary artery disease, no. (%)</td>
<td>1100 (47.1)</td>
<td>1078 (46.0)</td>
<td>1101 (47.0)</td>
</tr>
<tr>
<td>History of MI, no. (%)</td>
<td>1083 (46.4)</td>
<td>1107 (47.2)</td>
<td>1083 (46.2)</td>
</tr>
<tr>
<td>Coronary artery bypass graft, no. (%)</td>
<td>563 (24.1)</td>
<td>594 (25.3)</td>
<td>581 (24.8)</td>
</tr>
<tr>
<td>History of stroke, no. (%)</td>
<td>553 (23.7)</td>
<td>535 (22.8)</td>
<td>549 (23.4)</td>
</tr>
<tr>
<td>Peripheral artery disease, no. (%)</td>
<td>479 (20.5)</td>
<td>465 (19.8)</td>
<td>517 (22.1)</td>
</tr>
<tr>
<td>Single vessel coronary artery disease, no. (%)</td>
<td>238 (10.2)</td>
<td>258 (11.0)</td>
<td>240 (10.2)</td>
</tr>
<tr>
<td>Cardiac failure*, no. (%)</td>
<td>244 (10.5)</td>
<td>240 (10.2)</td>
<td>222 (9.5)</td>
</tr>
</tbody>
</table>

*Based on narrow standardized MedDRA query "cardiac failure."

Data are n (%) in patients treated with ≥ 1 dose of study drug.

The primary composite outcome in the time-to-event analysis was the first occurrence of CV death, nonfatal MI, or nonfatal stroke. The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses were truncated at 54 months, because <10% of the patients had an observation time beyond 54 months.

LEADER: Primary Outcome
CV Death, Nonfatal MI, or Nonfatal Stroke

Majority of LEADER patients Are High Cardiovascular Risk

- Previous CVD: 81.3%, n = 7592
- No Previous CVD: 18.7%, n = 1748

N = 9340

CV Outcomes: Semaglutide vs Placebo

N = 3,297

Median f/u: 2.1 yr

Hospitalization for HF: 3.6 vs 3.3 %
HR 1.11 (95% CI, 0.77-1.61)

Marso SP, et al. NEJM, 2016; Sept 16
# Comparison of Major Outcome Relative Rates in LEADER, SUSTAIN 6 and EXSCEL Trials

<table>
<thead>
<tr>
<th></th>
<th>LEADER</th>
<th>SUSTAIN 6</th>
<th>EXSCEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>0.87</td>
<td>0.74</td>
<td>0.91</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>0.89</td>
<td>0.61</td>
<td>0.85</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0.78</td>
<td>0.98</td>
<td>0.88</td>
</tr>
<tr>
<td>Death any cause</td>
<td>0.85</td>
<td>1.05</td>
<td>0.86</td>
</tr>
<tr>
<td>Hospital Heart Failure</td>
<td>0.87</td>
<td>1.11</td>
<td>0.94</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0.78</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>1.15</td>
<td>1.76</td>
<td></td>
</tr>
</tbody>
</table>

*Red Color* is statistically significant versus study control group.
2018 ADA Standards of Care

Note/Disclosure: ADA-EASD guidelines are in comment phase
Patient/Disease Features

- **Risk of hypoglycemia/drug adverse effects**
  - low (A1C 7%)
  - high (more stringent)
- **Disease Duration**
  - newly diagnosed (long-standing)
  - long (short)
- **Life expectancy**
  - long (short)
- **Important comorbidities**
  - absent (Few/mild, severe)
- **Established vascular complications**
  - absent (Few/mild, severe)

**Patient attitude & expected treatment efforts**

- highly motivated, adherent, excellent self-care capabilities
- less motivated, nonadherent, poor self-care capabilities

**Resources & support system**

- readily available
- limited

---

Glycemic Targets:

*Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S55-S64*
Lifestyle as Medicine

- Medical Nutrition Therapy
- Physical Activity
Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S73-S85

Monotherapy

Lifestyle Management - Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

Dual Therapy

Metformin +

Lifestyle Management

ASCVD? Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and Table 8.1)

Triple Therapy

Lifestyle Management + Metformin + Two Additional Agents

Combination Injectable Therapy

(See Figure 8.2)
CENTRAL ILLUSTRATION: Healthy Lifestyle and Cardiovascular Disease (CVD) Events Among Diabetic Patients

<table>
<thead>
<tr>
<th></th>
<th>Intensive Lifestyle</th>
<th>Diabetes Support/Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1yr Weight</td>
<td>8.6%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Year 1yr Fitness</td>
<td>20.4%</td>
<td>5%</td>
</tr>
<tr>
<td>HR recovery</td>
<td>P&lt;0.001</td>
<td>--</td>
</tr>
<tr>
<td>A1c &lt;7%</td>
<td>46-73%</td>
<td>45-50%</td>
</tr>
<tr>
<td>Glucose/BP/Cholesterol</td>
<td>10.8-23.6%</td>
<td>9.5-16%</td>
</tr>
<tr>
<td>CAD outcome</td>
<td>153 SNP-prediction unchanged</td>
<td>153 SNP-prediction unchanged</td>
</tr>
<tr>
<td>CKD</td>
<td>0.63 per 100 person-years</td>
<td>0.91 cases per 100 per/yr</td>
</tr>
<tr>
<td>Physical Function Decline</td>
<td>Slowed progression*</td>
<td></td>
</tr>
<tr>
<td>Cognitive Function</td>
<td>Favor ILI</td>
<td></td>
</tr>
<tr>
<td>Fitness</td>
<td>Favor ILI</td>
<td></td>
</tr>
<tr>
<td>Preserve physical HRQoL</td>
<td>Favor ILI</td>
<td></td>
</tr>
<tr>
<td>Clinically significant depression</td>
<td>Favor ILI</td>
<td></td>
</tr>
</tbody>
</table>

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

**Dual Therapy**
- Metformin +

**Lifestyle Management**
- Sulfonylurea
- Thiazolidinedione
- DPP-4 inhibitor
- SGLT2 inhibitor
- GLP-1 receptor agonist
- Insulin (basal)

**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)

**Combination Injectable Therapy** (See Figure 8.2)
Summary and Points for Discussion

- Traditional CVD risk factor modification remains the top priority for CVD prevention.
- The primary goal for antihyperglycemic agents is to improve glucose control; combination therapy is often needed.
- Polypharmacy, cost, durability, adherence and cost effectiveness must be considered.*
- Studies demonstrating dual efficacy of antihyperglycemic agents on glucose and CVD/CHF change the landscape **ONLY** in people with high CHD risk or established CHD.
- No data on the person with T2D and CHD on metformin with glucose at goal.
Where are the gaps?

- **Underlying biology:**
  - The mechanisms for the interaction between GLP-1RA and SGLT2I and decreased CVD and CHF risk need clarification

- **Diabetes is a progressive disease:**
  - The timing and physiological context in which these drugs are administered needs to be tested (TZDs/Estrogen)
  - No data demonstrating a role for these agents in primary prevention despite theoretical benefit whereas lifestyle change confers consistent benefits for primary prevention

- **Health care delivery:**
  - Chronic disease with social stigma
  - Glucose management is difficult in short patient visit
  - PCPs and people with DM need support when starting GLP1 RA and SGLT2 inhibitors
  - Reallocation of the $327 Billion / 1 in 4 US Health Care dollars
Consensus and Harmonization

ADA-EASD Clinical Practice Guidelines

ADA, AACE, Endocrine Society, AAFP scheduling discussion about Glycemic Targets

ACC Expert Consensus Decision Pathways on Novel Pathways for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes

DCV Collaboration Areas
1. Advocacy
2. Community & Consumer Activation
3. Corporate Development (Funding)
4. Evaluation
5. Patient Support & Education
6. Professional Education
7. QI for Inpatient & Outpatient
8. Science

Diabetes Cardiovascular (DCV) Initiative