Diabetes Management in CAD Patients

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Disclosure

Stuart R. Chipkin, MD, FACE

— Nothing to disclose
Case #1

64 year old man comes to see you after recent admission with heart failure. BP has been controlled (138/80) on Lisinopril (40 mg), metoprolol (50 mg bid) and furosemide (40mg). He is on atorvastatin with an LDL of 90 mg/dl. He takes ASA daily.

He has a history of T2DM with retinopathy and an a1c of 8% and has been on metformin and glipizide. His PCP just gave him samples of saxagliptin (Onglyza).

For his T2DM, he doesn’t check glucose values at home. He is not physically active (“I go up and down the stairs”). He is not “really” following a diet
Case 1: 64 y.o. man recent CHF on lisinopril, furosemide, metoprolol, metformin, glipizide and saxagliptin

EXAM: Pulse=92, BP=138/85, BMI=34 kg/m²

EYES: EOM normal

NECK: No goiter or bruits. JVD to 12 cm.

LUNGS: clear

HEART: S1 S2 with soft 2/6 systolic murmur; No S3

EXT: 1+ edema. Distal pulses intact. Monofilament OK

LABS: A1c=8.1%, BUN/creat= 30/1.2

HDL= 32, TG= 286, LDL= 90, urine ALB:CREAT= 154
Case 1: 64 y.o. man recent CHF visit on metform, glipizide, saxagliptin, lisinopril, furosemide, metoprolol with microvascular complications and edema

Do you have any concern about use of saxagliptin?

A) Not really a cardiology problem. Saxagliptin is OK
B) Suggest change to incretin (exenatide, liraglutide, dulaglutide, albiglutide)
C) Suggest pioglitazone instead of saxagliptin
D) Consider use of SGLT2 inhibitor (canagliflozin, dapagliflozin, empagliflozin)
E) No change in medications - emphasize diet and exercise
Diabetes and Cardiovascular Disease

• Diabetes and risk of death
  • Over 65% of diabetes patients die from CVD
  • 2-4 fold higher death rate from CVD
  • Higher risk for death in women than men

• Diabetes and risk of CV disease
  • HR= 2.5 for women and 2.4 for men

• Shorter lifespan for people with diabetes
  • Men live 7.4 years less
  • Women live 8.2 years less

Benefits of Treating Risk Factors in People with Diabetes

- **Blood Pressure:**
  - Lower rates of stroke and heart failure
  - Lower rates of retinopathy and nephropathy

- **Cholesterol**
  - Lower rates of MACE
    - Heart Protection Study (Primary and Secondary Prevention)
      - T1DM and T2DM
      - Even when starting LDL < 116 mg/dl
    - Reduced risk for first CVD event in T2DM (37%; p=0.001)
    - CARDS (Primary Prevention)
      - Decreased acute coronary events (36%)
      - Decreased stroke (48%)
      - Decreased coronary revascularizations (31%)

Colhoun HM et al. CARDS; Lancet 364:685-696, 2004
Estimated impact of single risk factor interventions to reduce CVD in patients with type 2 diabetes

<table>
<thead>
<tr>
<th>Relative risk reduction</th>
<th>2-yr’s event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>......</td>
</tr>
<tr>
<td>Cholesterol (down by 25 mg/dl)</td>
<td>25 %</td>
</tr>
<tr>
<td>BP (down by 5/2 mm Hg)</td>
<td>27 %</td>
</tr>
<tr>
<td>HbA1c (down by 0.9 %)</td>
<td>13 %</td>
</tr>
<tr>
<td>Aspirin</td>
<td>9 %</td>
</tr>
</tbody>
</table>

BUT: Cumulative relative risk reduction of about 57%

Turner R.C. BMJ 1998;316:823-828
He et al. JAMA 1999;282:2027-2034
Antithrombotic Trialist BMJ 2002;324:71-86
Risk Reduction in Fibrate Trials
Dyslipidemia vs. Entire Cohort

Baseline TG (mg/dL) = 176, > 200

<table>
<thead>
<tr>
<th>Trial</th>
<th># in cohort</th>
<th>Duration</th>
<th>RRR, %</th>
</tr>
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<tbody>
<tr>
<td>HHS</td>
<td>4081, 582</td>
<td>5 y</td>
<td>-34</td>
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<tr>
<td>VA-HIT</td>
<td>2531, 843</td>
<td>5 y</td>
<td>-22</td>
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<tr>
<td>BIP</td>
<td>3090, 459</td>
<td>6.2 y</td>
<td>-28</td>
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<tr>
<td>FIELD</td>
<td>9975, 341</td>
<td>6 y</td>
<td>-6.6</td>
</tr>
<tr>
<td>ACCORD</td>
<td>5518, 941</td>
<td>4.7 y</td>
<td>-41.5</td>
</tr>
</tbody>
</table>

Rosenblit PD; Curr Cardiol Rep (2012) 14:112–124
Meta-analysis of Fibrate Studies Non-Cardiac Outcomes

Diabetes and Heart Failure

- Heart failure is twice as common in diabetic men and five times as common in diabetic women (versus age-matched subjects without diabetes).
- About 12% of type 2 diabetic subjects have established heart failure.
  - Prevalence in elderly subjects with diabetes is 39%.
- Increase in HbA1c of 1% is associated with a 15% increased risk of heart failure in elderly diabetic patients.
- About 3.3% of type 2 diabetes subjects develop heart failure each year.

Bell DSH; Diabetes Care 26:2433–2441, 2003
Increased Risk of Heart Failure in Diabetes - Impact of High a1c

Bauters C et al; *Cardiovascular Diabetology* 2003; 2:1

DOI: 10.1186/1475-2840-2-1
Glucose Control Benefits
Microvascular Complications

• Benefits of Glucose Control:
  – Microvascular:
    • DCCT: 1441 people with Type 1 Diabetes
      – Decrease in Retinopathy (76%)
      – Decrease in Nephropathy (50%)
      – Decrease in Neuropathy (60%)
    • UKPDS: 5102 New/early onset type 2 diabetes
      – Decrease in microvascular disease (37%)

DCCT: Glucose Control Over Time
(Ahh...Human Nature)

**Graph Description:**
- **Y-axis:** HbA1c (%)
- **X-axis:** Year (DCCT and EDIC)
- **Lines:**
  - Orange: Intensive
  - Gray: Conventional

- The conventional group was encouraged to switch to intensive treatment after the DCCT end.

**Adapted from:**
Cardiovascular complications in T1DM - DCCT
Either Any CV Endpoint or MI/CVA/CV Death

Type 1 diabetes
- Little insulin resistance
- Less hypertension and/or hyperlipidemia

# Legacy Effect ofEarlier Glucose Control

After median 8.5 years post-trial follow-up

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
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<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>RRR:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>P:</td>
<td>0.029</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>P:</td>
<td>0.0099</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>P:</td>
<td>0.052</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>P:</td>
<td>0.44</td>
</tr>
</tbody>
</table>

- Intervention started at diagnosis
- BP not controlled to current standards
- Sulfonylureas did not increase risk for CVD

RRR = Relative Risk Reduction,  
P = Log Rank

UKPDS 80, NEJM 2008 359:
## Impact of Intensive Therapy in Diabetes: Summary of Major Clinical Trials (pre-2012)

<table>
<thead>
<tr>
<th>STUDY NAME</th>
<th>MICRO: STUDY END</th>
<th>MICRO: FOLLOW-UP</th>
<th>MACRO STUDY END</th>
<th>MACRO: FOLLOW-UP</th>
<th>MORT: STUDY END</th>
<th>MORT: FOLLOW-UP</th>
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<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>↓</td>
<td>--</td>
<td>↓</td>
<td>--</td>
<td>↓</td>
</tr>
<tr>
<td>DCCT EDIC</td>
<td>↓</td>
<td>↓</td>
<td>--</td>
<td>↓</td>
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<td>--</td>
</tr>
<tr>
<td>ACCORD</td>
<td></td>
<td></td>
<td>--</td>
<td></td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td></td>
<td>--</td>
<td>--</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td></td>
<td>--</td>
<td></td>
<td></td>
<td>--</td>
</tr>
</tbody>
</table>

UKPDS = UK Prospective Diabetes Study; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease; VADT = Veterans Affairs Diabetes Trial.
Glucose Control and Macrovascular Events
Subtleties may be everything

**Possible issues**
- Duration of diabetes (UKPDS vs. ACCORD/ADVANCE/VA)
- Age of subjects (DCCT and UKPDS vs. ACCORD/ADVANCE/VA)
- Specific medications (DCCT and UKPDS vs. ACCORD/ADVANCE/VA)
- Hypoglycemia
- Prior CV history or events
- Low event rates (1/3 of original predictions)

**Other considerations**
- Microvascular benefits
- Glucose control may be more important if BP and Lipids not at goal
## Newer Classes of Diabetes Medications

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>AGENTS</th>
<th>ACTIONS</th>
<th>DOSING</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incretins (GLP-1 receptor agonist)</td>
<td>Exenatide (Byetta) Liraglutide (Victoza) Dulaglutide (Truliccy) Albiglutide (Tanzeum) Lixisenatide (Adlyxin)</td>
<td>Increases insulin action Weight loss</td>
<td>Twice daily to Once weekly</td>
<td>GI: mostly N/V Rare- pancreatitis</td>
</tr>
<tr>
<td>DPP-IV Inhibitors “Gliptins” (Inhibits breakdown of incretins)</td>
<td>Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta) Alogliptin (Nesina)</td>
<td>Increases insulin action Weight neutral</td>
<td>Daily</td>
<td>Heart failure (saxa, not sita or lina) Joint pains Fracture</td>
</tr>
<tr>
<td>SGLT2 Inhibitors (Induces glycosuria)</td>
<td>Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance)</td>
<td>Decreases glucose, blood pressure and weight</td>
<td>Daily</td>
<td>Orthostasis Genitourinary infections Increase in LDL Rare- ketoacidosis Fracture (not empa)</td>
</tr>
</tbody>
</table>
Impact of Newer Diabetes Agents: FDA Mandated Studies on CVD

• SGLT2:
  – EMPA-REG- empagliflozin

• GLP-1 (Incretin):
  – LEADER- liraglutide
  – ELIXA- lixisenatide

• DPP-4:
  – SAVOR-TIMI- saxagliptin
  – TECOS- sitagliptin
  – EXAMINE- alogliptin
Impact of DPP-IV Inhibitors on Cardiac Endpoints

• EXAMINE (alogliptin)
  – No difference in MACE (mortality, nonfatal MI, nonfatal CVA, urgent CABG, heart failure admission) for patients on alogliptin (2701) vs. placebo (2679) with recent ACS
  – Decrease in Carotid Intima Media Thickness (IMT) in Japanese subjects on medication (172) vs. placebo (169)

• SAVOR (saxagliptin)
  – Not cardio-protective but slight increase in CHF admissions (3.5% vs 2.8%; HR= 1.27)

Mita et al. Diabetes Care 2016; 39:139-148
Impact of DPP-IV Inhibitors on Cardiac Endpoints

• TECOS (sitagliptin)
  – No difference (sitagliptin vs. placebo) for CV death, nonfatal MI, nonfatal CVA or admission for unstable angina
  – No difference in heart failure admissions
  – No difference in acute pancreatitis

• Coming Attractions:
  – Linagliptin (CAROLINA and CARMELINA): to be completed in 2018

Impact of SGLT2 Inhibitors on Cardiac Endpoints

• EMPRA-REG (empagliflozin)
  – Significant reduction in death from cardiovascular causes (3.7% vs. 5.9%; 38% RRR),
  – No significant differences in risk of MI or stroke
  – Significant reduction in risk for hospitalization from heart failure (2.7% vs 4.1%; 35% RRR)

• Coming Attractions
  – Canagliflozin (CANVAS): 2018
  – Dapagliflozin (DECLARE-TIMI58): 2019

Impact of GLP-1 Agonists on Cardiac Endpoints

• ELIXA (lixisenatide)- Patients with ACS
  – No difference in CV death, MI, CVA or unstable angina
  – No difference in heart failure (either new or recurrent)

• LEADER (liraglutide)- Patients at high risk for CVD
  – Reduction in CVD (RR=0.86)
  – No difference in heart failure

• Coming up:

<table>
<thead>
<tr>
<th>DRUG</th>
<th>STUDY NAME</th>
<th>N</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulaglutide</td>
<td>REWIND</td>
<td>9000</td>
<td>2019</td>
</tr>
<tr>
<td>Exenatide (weekly)</td>
<td>EXSCEL</td>
<td>14,000</td>
<td>2017</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>SUSTAIN 6</td>
<td>3,200</td>
<td>2016</td>
</tr>
</tbody>
</table>

Return to Case: 64 y.o. man recent CHF visit on metformin, glipizide, saxagliptin, lisinopril, furosemide, metoprolol with microvascular complications and edema

Do you have any concern about saxagliptin?
A) Not really a cardiology problem. Saxagliptin is OK
B) Suggest change to incretin (exenatide, liraglutide, dulaglutide, albiglutide, lixisenatide)
C) Suggest pioglitazone instead of saxagliptin
D) Consider use of SGLT2 inhibitor (canagliflozin, dapagliflozin, empagliflozin)
E) No change in medications- emphasize diet and exercise
Slightly different case: 64 y.o. woman with CHF on metformin, glipizide, lisinopril, furosemide, metoprolol with microvascular complications. A1c=8%.

Given saxagliptin- Hx of osteoporosis and recent UTI

A) Mention to PCP switching to different DPP-4
B) Mention to PCP use incretin instead of saxagliptin
C) Mention to PCP option of insulin
D) Suggest change saxagliptin to SGLT2 inhibitor
E) Emphasize diet and exercise
Class of Medications and Past History may be as Important as Degree of Control

• Type 1 diabetes- on insulin
  – Little contribution from insulin resistance (blood pressure and dyslipidemia)
    • Unless they do (because they live in America)
• Type 2 diabetes- soon after diagnosis
  – Before irreversible changes to vascular biology (metformin)
• Type 2 diabetes- with known CVD or heart failure
  – EMPA-REG patients had CVD (empagliflozin/Jardiance-SGLT2)
• Type 2 diabetes- at high risk
  – LEADER patients (liraglutide/Victoza-incretin)
• Type 2 diabetes- not at goal for other risk factors
  – How many patients do you have with BP > 140/90 mm Hg or who can’t tolerate high dose statins?
Surprise- Ranolazine in T2DM

*P = 0.0046 vs. placebo.
†P < 0.0001 vs. placebo.
‡P = 0.0004 vs. placebo.

Improvements in Diabetes-Related Complications: 1990-2010

Conclusions

- Blood pressure control is very effective for most diabetes-related complications.
- Lipid control prevents cardiac complications.
  - Lowering LDL clearly beneficial
  - Fibrates may yet have a role to be established
- Smoking cessation is a no-brainer.
- Type 1 diabetes- intensive therapy early on is helpful for most, if not all, complications
Conclusions

- Type 2 diabetes - If you *only* think about the heart, glucose is *not* the most important risk factor.

- If you *take care of whole patients*, glucose control has *multiple* benefits.
  - But, the heart may benefit the least in type 2 patients if all other risk factors controlled.

- Type 2 diabetes:
  - Early on -> metformin
  - Assist with weight loss -> incretins (liraglutide)
  - Early heart failure -> SGLT2 (empagliflozin)
  - Established heart failure -> avoid saxagliptin or pioglitazone
  - Insulin is still a very good drug (avoid “insulin resistance”)


Incidence of Diabetes-Related Complications

http://www.cdc.gov/diabetes
BARI-2D

Cumulative Incidence of the Composite Primary Outcome (according to baseline proteinuria)

P:C = Protein:Creat

<table>
<thead>
<tr>
<th>Follow-up Year</th>
<th>Standard control</th>
<th>Intensive control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>176</td>
<td>181</td>
</tr>
<tr>
<td>1</td>
<td>165</td>
<td>172</td>
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<tr>
<td>2</td>
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# Trials of New Diabetes Medications

<table>
<thead>
<tr>
<th>Name of trial</th>
<th>Drug</th>
<th>Estimated enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR TIMI-53</td>
<td>Saxagliptin (Onglyza)</td>
<td>18206</td>
</tr>
<tr>
<td>CAROLINA/ CARMELINA</td>
<td>Linagliptin (Tradjenta)</td>
<td>6000/8300</td>
</tr>
<tr>
<td>TECOS</td>
<td>Sitagliptin (Januvia)</td>
<td>14000</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>Alogliptin (Nesina)</td>
<td>5380</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Exenatide (Bydureon)</td>
<td>14000</td>
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<tr>
<td>REWIND</td>
<td>Duglaglutide (Trulicity)</td>
<td>9622</td>
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<tr>
<td>LEADER</td>
<td>Liraglutide (Victoza)</td>
<td>9340</td>
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<td>SUSTAIN</td>
<td>Semaglutide</td>
<td>3297</td>
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<tr>
<td>ELIXA</td>
<td>Lixisenatide (Lyxumia)</td>
<td>6000</td>
</tr>
<tr>
<td>DEVOTE</td>
<td>Degludec (Tresiba)</td>
<td>7500</td>
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<tr>
<td>DECLARE TIMI-58</td>
<td>Dapagliflozin (Farxiga)</td>
<td>27000</td>
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<tr>
<td>CANVAS/ CANVAS-R/CREDENCE</td>
<td>Canagliflozin (Invokana)</td>
<td>4335/5700/3627</td>
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<tr>
<td>EMPA-REG OUTCOME</td>
<td>Empagliflozin (Farxiga)</td>
<td>7000</td>
</tr>
<tr>
<td>Light Study</td>
<td>Naltrexone/bupropion (Contrave)</td>
<td>10400</td>
</tr>
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</table>
## CARDS- Primary Prevention in Diabetes

![Graph showing the number of patients with an event (%) for different cholesterol levels.](chart)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Atorvastatin</th>
<th>Hazard Ratio (95% CI)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL-cholesterol (mmol/L)</strong></td>
<td>120 mg/dl</td>
<td>54 mg/dl</td>
<td>150 mg/dl</td>
<td></td>
</tr>
<tr>
<td>≥3.1</td>
<td>66 (9.5%)</td>
<td>44 (6.1%)</td>
<td>0.62 (0.43–0.91)</td>
<td>0.63 (0.42–0.94)</td>
</tr>
<tr>
<td>&lt;3.1</td>
<td>61 (8.5%)</td>
<td>39 (5.6%)</td>
<td>0.66 (0.45–0.95)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>HDL-cholesterol (mmol/L)</strong></td>
<td>62 (8.5%)</td>
<td>36 (5.2%)</td>
<td>0.59 (0.39–0.89)</td>
<td></td>
</tr>
<tr>
<td>≥1.4</td>
<td>65 (9.6%)</td>
<td>47 (6.4%)</td>
<td>0.66 (0.45–0.95)</td>
<td>0.70</td>
</tr>
<tr>
<td>&lt;1.4</td>
<td>65 (9.6%)</td>
<td>47 (6.4%)</td>
<td>0.66 (0.45–0.95)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/L)</strong></td>
<td>67 (9.6%)</td>
<td>40 (5.5%)</td>
<td>0.56 (0.38–0.82)</td>
<td></td>
</tr>
<tr>
<td>≥1.7</td>
<td>60 (8.4%)</td>
<td>43 (6.1%)</td>
<td>0.71 (0.48–1.05)</td>
<td>0.40</td>
</tr>
<tr>
<td>&lt;1.7</td>
<td>60 (8.4%)</td>
<td>43 (6.1%)</td>
<td>0.71 (0.48–1.05)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Diabetes - Bad for the Heart and Blood Vessels

• Associated Risk Factors
  – Hypertension- decreased risk with BP control
  – Hyperlipidemia/Dyslipidemia- decreased risk with LDL control
    • HDL likely not as protective in people with diabetes
  – Hyperglycemia- “It’s complicated”
  – Smoking- QUIT (It’s NOT complicated)
Heart Failure Rates in Patients with Diabetes

Figure 1—Kaplan-Meier analysis of CHF incidence comparing the diabetic (---) and nondiabetic (—) cohorts. The cohorts are significantly different (P < 0.001).
Benefit of Glucose Control - Macrovascular

- **Macrovascular Disease:**
  - DCCT: Trial involving 1441 people with Type 1 Diabetes
    - Young population so not surprising that initial results (1993) showed no impact on CVD
  - UKPDS
    - Borderline impact on CV risk for all treatments
    - Positive impact on risk for MI in patients on metformin
    - Sulfonylureas did not increase risk for CVD
UKPDS Blood Pressure Study (Remember- done 20 years ago)

- 1,148 Type 2 patients
- BP lowered to avg. of 144 / 82 mmHg (controls: 154/87); 9 year follow-up

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Risk Reduction (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes-related endpoint</td>
<td>24</td>
<td>0.0046</td>
</tr>
<tr>
<td>Diabetes-related deaths</td>
<td>32</td>
<td>0.019</td>
</tr>
<tr>
<td>Heart failure</td>
<td>56</td>
<td>0.0043</td>
</tr>
<tr>
<td>Stroke</td>
<td>44</td>
<td>0.013</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>37</td>
<td>0.0092</td>
</tr>
</tbody>
</table>

Heart Protection Study
Mixed Primary and Secondary Prevention
Type 1 diabetes= 615; Type 2 diabetes= 5348
Even starting with LDL of < 116 mg/dl was associated with benefit from statin medication.

Collaborative Atorvastatin Diabetes Study (CARDS)

- Primary Prevention Trial
- Atorvastatin (10 mg) reduced the risk for first CVD events in type 2 diabetes without high LDL levels (median follow-up= 3.9 years)
- Compared with placebo, decreases observed in:
  - Total cholesterol (26%),
  - LDL (40%), and
  - Triglycerides (19%) (p<0.0001)
- First CVD events were reduced by 37% (p=0.001)
  - Acute coronary events by 36%
  - Stroke by 48%
  - Coronary revascularizations by 31%
- Trial stopped two years early

Treatment of Heart Failure in Diabetes

- Reductions in blood pressure from baseline of 150 to 140 decreased risk for cardiovascular mortality, MI, stroke and end stage renal disease (10-25%).

Brunstrom and Carlberg; : BMJ 2016; 352:i717 http://dx.doi.org/10.1136/bmj.i717
• How does heart failure relate to diabetes
  – Increased risk for heart failure in diabetes
  – Increased mortality from heart failure in diabetes

• Medications and risk of heart failure
  – Pioglitazone
  – Saxagliptin
    • Other DPP-4 agents not so much (meta-analysis?)

• Medications and possible benefit in heart failure
  – EMPA

• Briefly touch on HTN/Lipids- Glucose control may not be the priority for macrovascular disease?
Factors Affecting Outcomes

• Duration of diabetes

• Outcome measures
  – Heart failure
  – Atherosclerosis
  – Arrhythmia

• Degree of risk
  – Potential for hypoglycemia
  – Medication-specific side effects
    • Bone health
    • GU infections
Class of Medications May be as Important as Degree of Control

- **Type 1 diabetes - on insulin**
  - Little underlying contributions of insulin resistance (blood pressure and dyslipidemia)
    - Unless they do (because they live in America)

- **Type 2 diabetes - soon after diagnosis**
  - Before irreversible changes to vascular biology

- **Type 2 diabetes - with known CVD**
  - EMPA-REG patients had CVD

- **Type 2 diabetes - at high risk**
  - LEADER patients

- **Type 2 diabetes - not at goal for other risk factors**
  - How many patients do you have with LDL over 100 mg/dl, or BP > 140/80 mm Hg?
Incretin Medications

• Based on actions of GLP-1 and its analogs
  – Increase in insulin sensitivity
  – Delay in gastric emptying
  – Decrease in appetite and some weight loss

• Side effects:
  – Gastrointestinal

• Current options: Injectable
  – Exenatide (Byetta/Bydureon)- either twice daily or once weekly injections
  – Liraglutide (Victoza)- once daily injections
  – Dulaglutide (Trulicity)- weekly
  – Albiglutide (Tanzeum)- daily
Incretin Medications: Based on GLP-1

• Findings suggesting potential benefit
  – GLP-1 receptors are in cardiac myocytes, endothelial cells, macrophages, and CNS regions which regulate cardiovascular function.
  – GLP-1 enhanced cardiac function and decreased cardiomyocyte necrosis in a model of ischemia/reperfusion.

• Some of these activities may be present with DPP-IV inhibition (through direct GLP-1 receptor activity) but not if GLP-1 (9-36) is key.

• ELIXA (study with lixisenatide) showed no difference (drug vs. placebo) in patients with recent acute coronary syndrome

• Coming Attractions
  – MR Assessment of Victoza Efficacy in the Regression of CV Dysfunction In T2DM (MAGNA VICTORIA- 12/15)
  – LEADER: done in 2016

DPP-4 Inhibitors

• Raise endogenous GLP-1 levels by inhibiting enzyme which metabolizes GLP-1 to GLP-1 (9-36)
  – Increases insulin sensitivity
  – Delay in gastric emptying
  – No significant decrease in weight
  – Modest improvement in a1c (approximately 0.7%)

• Side Effects:
  – Rare but severe- pancreatitis

• Current Options: Oral
  – Sitagliptin
  – Saxagliptin
  – Linagliptin
  – Alogliptin
DPP-4 Inhibitors- Summary

• Saxagliptin (SAVOR-TIMI53):
  – Not cardio-protective but slight increase in CHF admissions (3.5% vs 2.8%; HR= 1.27)

• Alogliptin (EXAMINE)-
  – No difference in MACE (mortality, nonfatal MI, nonfatal CVA, urgent CABG, heart failure admission) for patients on alogliptin (2701) vs. placebo (2679) with recent ACS

• Sitagliptin (TECOS)-
  – No difference (sitagliptin vs. placebo) for CV death, nonfatal MI, nonfatal CVA or admission for unstable angina
  – No difference in heart failure admissions or acute pancreatitis

• Linagliptin (CAROLINA and CARMELINA): to be completed in 2018
Sodium Glucose Transport Inhibitors (SGLT2)

• **Actions**
  – Inhibit re-absorption of glucose from renal proximal tubules
  – Modest decrease in weight
  – Modest improvement in a1c

• **Side effects include:**
  – Increase risk for UTIs, yeast infections (women more than men)
  – Orthostasis
  – Increase in LDL
  – Hyperkalemia
  – Ketoacidosis (rare but severe)- reported in type 1 and type 2 patients

• **Options**
  – Canagliflozin
  – Dapagliflozin
  – Empagliflozin

• **Coming Attractions**
  – Canagliflozin (CANVAS): 2018
  – Dapagliflozin (DECLARE-TIMI58): 2019
Recent studies of patients with T2DM with or at high risk of CV disease

- **SAVOR** (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes)
- **EXAMINE** (Examination of CV Outcomes with Alogliptin in Type 2 Diabetes and Acute Coronary Syndrome)
- **TECOS** (Trial Evaluating Cardiovascular Outcomes with Sitagliptin).
- **ELIXA** (Evaluation of Lixisenatide in Acute Coronary Syndrome)

Overall, agents neither increased nor deceased major adverse CV events (CV death, nonfatal myocardial infarction, and nonfatal stroke) compared with placebo.
SAVOR- Saxagliptin and CV Outcomes in Patients with Type 2 Diabetes

Composite of CV death, MI, or ischemic CVA

Hazard ratio, 1.00 (95% CI, 0.89–1.12)
P<0.001 for noninferiority
P=0.99 for superiority

2-yr Kaplan–Meier rate:
Saxagliptin, 7.3%
Placebo, 7.2%

• **Empagliflozin (Jardiance)**

• **MACE in empagliflozin (490 of 4687 patients or 10.5%)** vs. placebo (282 of 2333 or 12.1%)

• **No significant differences in the rates of myocardial infarction or stroke**

• **Significantly lower rates of**
  – Death from cardiovascular causes (3.7% empagliflozin vs. 5.9% in placebo; 38% RRR),
  – Hospitalization for heart failure (2.7% vs 4.1%; 35% RRR)
  – Death from any cause (5.7% and 8.3%; 32% RRR).
  – No significant difference in the key secondary outcome (P=0.08 for superiority).
  – Among patients receiving empagliflozin, there was an increased rate of genital infection
B  Death from Cardiovascular Causes

Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P<0.001

Placebo
Empagliflozin

Month
Patients with Event (%)

D  Hospitalization for Heart Failure

Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P=0.002

Placebo
Empagliflozin

No. at Risk
Empagliflozin 4687 4614 4523 4427 3988 2950 2487 1634 395
Placebo 2333 2271 2226 2173 1932 1424 1202 775 168

Zinman B et al; NEJM 9/2015
DOI: 10.1056/NEJMoa1504720
C  Death from Any Cause

Hazard ratio, 0.68 (95% CI, 0.57–0.82)  
P<0.001

No. at Risk
Empagliflozin 4687 4651 4608 4556
Placebo 2333 2303 2280 2243

A  Primary Outcome

Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)  
P=0.04 for superiority

No. at Risk
Empagliflozin 4687 4580 4455 4328 3851 2821 2359 1534 370
Placebo 2333 2256 2194 2112 1875 1380 1161 741 166
CV Benefits of Specific Diabetes Medications

SGLT2 = Na⁺ GLUT Inhibitors
Bromo = Bromocriptine
DPP-4 = Dipeptidyl peptidase-4 inhibitor
AMY = Pramlintide
GLP-1 = Glucagon-like peptide 1 receptor agonist
Glitinide = Meglitinides
TZD = thiazolidinediones
Analog = Rapid insulin
βGI = α-Glucosidase
Insulin

SU = Sulfonylureas
MET = Metformin

FDA Now Requires CV Benefit for New T2DM Treatments
### ACCORD Lipid- Overall Results

**Table 2. Prespecified Primary and Secondary Outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fenofibrate (N=2765)</th>
<th>Placebo (N=2753)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome (major fatal or nonfatal cardiovascular event)</td>
<td>no. of events rate/yr</td>
<td>no. of events rate/yr</td>
<td>0.92 (0.79–1.08)</td>
<td>0.32*</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome plus revascularization or hospitalization for congestive heart failure</td>
<td>641 5.35</td>
<td>667 5.64</td>
<td>0.94 (0.85–1.05)</td>
<td>0.30</td>
</tr>
<tr>
<td>Major coronary disease event†</td>
<td>332 2.58</td>
<td>353 2.79</td>
<td>0.92 (0.79–1.07)</td>
<td>0.26</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>173 1.32</td>
<td>186 1.44</td>
<td>0.91 (0.74–1.12)</td>
<td>0.39</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>51 0.38</td>
<td>48 0.36</td>
<td>1.05 (0.71–1.56)</td>
<td>0.80</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>47 0.35</td>
<td>40 0.30</td>
<td>1.17 (0.76–1.78)</td>
<td>0.48</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>203 1.47</td>
<td>221 1.61</td>
<td>0.91 (0.75–1.10)</td>
<td>0.33*</td>
</tr>
<tr>
<td>From cardiovascular cause</td>
<td>99 0.72</td>
<td>114 0.83</td>
<td>0.86 (0.66–1.12)</td>
<td>0.26</td>
</tr>
<tr>
<td>Fatal or nonfatal congestive heart failure</td>
<td>120 0.90</td>
<td>143 1.09</td>
<td>0.82 (0.65–1.05)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

- No significant impact of fenofibrate on outcomes

• What clinician here would add a fibrate to a patient with diabetes and TG = 160 mg/dL?

• Incidence of cardiovascular events was 70% higher in patients with high (≥ 204 mg/dL) triglycerides and low HDL-cholesterol (≤ 34 md/dl) levels vs those without this profile (17.3% vs. 12.4%, respectively).

ACCORD Lipid
Dyslipidemia vs. Entire Cohort

![Bar chart showing major fatal or nonfatal CV events in high triglycerides and low HDL groups compared to entire cohort.]

- High triglycerides (≥ 204 mg/dL) and low HDL (≤ 34 mg/dL): 17.6% (n = 941) of entire cohort
- All others in entire cohort: 82.4% (n = 4548) of entire cohort

- High TG/low HDL-C subgroup had 70% higher event rate
- 31% relative risk reduction (RRR), adjusted P = 0.057

Rosenblit PD; Curr Cardiol Rep (2012) 14:112–124
Meta-analysis of Five Studies Examining Fibrates

PROactive (Pioglitazone)

• Primary outcome was reduced by 10% (non-significant) for pioglitazone vs. placebo (36 months)
  – Primary outcome was all-cause death, non-fatal MI, stroke, ACS, leg amputation, coronary or peripheral revascularization

• Secondary outcome was reduced by 16% (P= 0.027) for pioglitazone vs. placebo
  – Composite of all-cause death, non-fatal MI, or stroke

• Ongoing concerns for all thiazolidinedione medications
  – Heart failure
  – Fracture
  – Possible increase in bladder cancer (higher doses and men)

Dormandy JA et al; Lancet 2005; 366:1279
## UPCOMING STUDIES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>STUDY NAME</th>
<th>N</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulaglutide</td>
<td>REWIND</td>
<td>900</td>
<td>2019</td>
</tr>
<tr>
<td>Exenatide (weekly)</td>
<td>EXSCEL</td>
<td>14,000</td>
<td>2017</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>SUSTAIN 6</td>
<td>3,200</td>
<td>2016</td>
</tr>
</tbody>
</table>

Canagliflozin (CANVAS): 2018  
Dapagliflozin (DECLARE-TIMI58): 2019
Major Outcomes of the HOT Trial
Diabetes Subgroup

Diastolic Target
- ≤90 mm Hg (n=501) achieved at 85.2 mm Hg
- ≤85 mm Hg (n=501) achieved at 83.2 mm Hg
- ≤80 mm Hg (n=499) achieved at 81.1 mm Hg

Events/1000 Pt-Yrs

- Major CV Events: P<0.005
- MI: P<0.045
- CV Mortality: P=0.016

Lancet 351: 1755-1762, 1998
Modifiable CVD Risk Factors

- Obesity, especially central or intra-abdominal
- Sedentary lifestyle
- Glucose intolerance
- Hypertension
- Dyslipidemia
- Cigarette smoking
- Procoagulant state
ACCORD LIPID: Results

- Primary outcome: 2.2% (fenofibrate) vs 2.4% (placebo) \( [p=0.32] \);
- Annual death rates: 1.5% (fenofibrate) vs 1.6% (placebo) \( [p=0.33] \);
- Primary outcome
  - Men: 11.2% (fenofibrate) compared with 13.3% (placebo);
  - Women: 9.1% (fenofibrate) compared with 6.6% (placebo) \( [p=0.01 \text{ for interaction}] \);
- Some heterogeneity among subjects with TG in the highest third \( (≥204 \text{ mg/dL}) \) and HDL-C in the lowest third \( (≤34 \text{ mg/dL}) \) vs all other subjects \( (P=0.057 \text{ for interaction}) \);
- Among those with high TG and low HDL-C, the primary outcome occurred in 12.4% of fenofibrate-treated subjects and 17.3% of placebo-treated subjects;
  - Was observed among 10.1% of subjects in both treatment groups for other subjects enrolled in the study

# Legacy Effect of Earlier Metformin Therapy

*After median 8.8 years post-trial follow-up*

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>RRR: 32%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>( P: ) 0.0023</td>
<td>0.013</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 29%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>( P: ) 0.19</td>
<td>0.31</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 39%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>( P: ) 0.010</td>
<td>0.005</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 36%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>( P: ) 0.011</td>
<td>0.002</td>
</tr>
</tbody>
</table>

\( RRR = \text{Relative Risk Reduction}, \ P = \text{Log Rank} \)

UKPDS 80, NEJM 2008 359:
Patient-Centered Approach to Management of Diabetes

Approach to management of hyperglycemia:

- **More stringent**
  - Highly motivated, adherent, excellent self-care capacities
- **Less stringent**
  - Less motivated, non-adherent, poor self-care capacities

<table>
<thead>
<tr>
<th>Patient attitude and expected treatment efforts</th>
<th>Highly motivated, adherent, excellent self-care capacities</th>
<th>Less motivated, non-adherent, poor self-care capacities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia, other adverse events</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Absent</td>
<td>Few/mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent</td>
<td>Few/mild</td>
</tr>
<tr>
<td>Resources, support system</td>
<td>Readily available</td>
<td>Limited</td>
</tr>
</tbody>
</table>

Diabetes Care 2012, 35:1364-1379
# ADA-EASD Consensus for Approach to Therapy

## Initial Drug Monotherapy

### Efficacy (↓ HbA₁c)
- Hypoglycemia
- Weight
- Side effects
- Costs

### Healthy eating, weight control, increased physical activity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>high</td>
<td>low</td>
<td>neutral/loss</td>
<td>low</td>
<td></td>
</tr>
</tbody>
</table>

If needed to reach individualized HbA₁c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):

## Two-Drug Combinations

### Efficacy (↓ HbA₁c)
- Hypoglycemia
- Weight
- Major side effect(s)
- Costs

### STEP 2

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin &amp; Sulfonylurea</td>
<td>high</td>
<td>moderate risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>low</td>
</tr>
<tr>
<td>Metformin &amp; Thiazolidinedione</td>
<td>high</td>
<td>low risk</td>
<td>gain</td>
<td>edema, HF, Fx's</td>
<td>high</td>
</tr>
<tr>
<td>Metformin &amp; DPP-4 Inhibitor</td>
<td>intermediate</td>
<td>low risk</td>
<td>neutral</td>
<td>rare</td>
<td>high</td>
</tr>
<tr>
<td>Metformin &amp; GLP-1 receptor agonist</td>
<td>high</td>
<td>low risk</td>
<td>loss</td>
<td>GI</td>
<td>high</td>
</tr>
<tr>
<td>Metformin &amp; Insulin (usually basal)</td>
<td>highest</td>
<td>high risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>variable</td>
</tr>
</tbody>
</table>

If needed to reach individualized HbA₁c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):
ADA-EASD Consensus for Approach to Therapy

**STEP 2**

<table>
<thead>
<tr>
<th>Two-drug combinations</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy (↓ HbA1c)</td>
<td>Sulfonylurea(^b)</td>
<td>Thiazolidinedione</td>
<td>DPP-4 Inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (usually basal)</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>Intermediate</td>
<td>High</td>
<td>High</td>
<td>Highest</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Weight</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
</tr>
<tr>
<td>Major side effect(s)</td>
<td>Hypoglycemia(^c)</td>
<td>Edema, HF, Fx's(^c)</td>
<td>Rare(^e)</td>
<td>High</td>
<td>Hypoglycemia(^c)</td>
</tr>
<tr>
<td>Costs</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Variable</td>
</tr>
</tbody>
</table>

If needed to reach individualized HbA1c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):

**STEP 3**

<table>
<thead>
<tr>
<th>Three-drug combinations</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy (↓ HbA1c)</td>
<td>Sulfonylurea(^b) +</td>
<td>Thiazolidinedione +</td>
<td>DPP-4 Inhibitor +</td>
<td>GLP-1 receptor agonist +</td>
<td>Insulin (usually basal) +</td>
</tr>
<tr>
<td>High</td>
<td>SUL(^b)</td>
<td>SU(^b)</td>
<td>SU(^b)</td>
<td>SU(^b)</td>
<td>TZD</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>DPP-4-i</td>
<td>DPP-4-i</td>
<td>DPP-4-i</td>
<td>DPP-4-i</td>
<td>DPP-4-i</td>
</tr>
<tr>
<td>Weight</td>
<td>Glipitin-RA</td>
<td>GLP-1-RA</td>
<td>GLP-1-RA</td>
<td>GLP-1-RA</td>
<td>GLP-1-RA</td>
</tr>
<tr>
<td>Major side effect(s)</td>
<td>Insulin(^d)</td>
<td>Insulin(^d)</td>
<td>Insulin(^d)</td>
<td>Insulin(^d)</td>
<td>Insulin(^d)</td>
</tr>
<tr>
<td>Costs</td>
<td>Insulin(^d)</td>
<td>Insulin(^d)</td>
<td>Insulin(^d)</td>
<td>Insulin(^d)</td>
<td>Insulin(^d)</td>
</tr>
</tbody>
</table>

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:

**STEP 4 IS MULTIPLE DAILY DOSES OF INSULIN**
### Meta-analysis of Statin Use on CV Disease in People with Diabetes

<table>
<thead>
<tr>
<th>Major vascular events</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes with vascular disease:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>755 (29.6%)</td>
<td>898 (34.9%)</td>
<td>0.82 (0.73–0.92)</td>
</tr>
<tr>
<td>Other vascular disease</td>
<td>166 (17.6%)</td>
<td>193 (21.9%)</td>
<td>0.80 (0.61–1.03)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>921 (26.3%)</td>
<td>1091 (31.6%)</td>
<td>0.80 (0.74–0.88)</td>
</tr>
<tr>
<td><strong>Diabetes without vascular disease:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>420 (10.0%)</td>
<td>499 (12.1%)</td>
<td>0.75 (0.61–0.92)</td>
</tr>
<tr>
<td>No hypertension</td>
<td>124 (7.3%)</td>
<td>192 (11.2%)</td>
<td>0.69 (0.55–0.86)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>544 (9.2%)</td>
<td>691 (11.8%)</td>
<td>0.73 (0.66–0.82)</td>
</tr>
<tr>
<td><strong>All diabetes</strong></td>
<td>1465 (15.6%)</td>
<td>1782 (19.2%)</td>
<td>0.79 (0.74–0.84)</td>
</tr>
</tbody>
</table>

All-cause death, nonfatal MI, or CVA

Primary composite endpoint*

10% RRR
HR 0.90 (0.80-1.02)
P = 0.095

Placebo
(572 events)

Pioglitazone
(514 events)

Main secondary endpoint†

All-cause death, nonfatal MI, or CVA

16% RRR
HR 0.84 (0.07-0.98)
P = 0.027

Placebo
(358 events)

Pioglitazone
(301 events)

*All-cause mortality, nonfatal MI (including silent MI), ACS, stroke, coronary/peripheral revascularization, leg amputation; †All-cause mortality, nonfatal MI, stroke
PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events
PIOGLITAZONE AND BLADDER CANCER

• No overall increased risk of bladder cancer with pioglitazone but
  – Increased risk of bladder cancer among patients with
    • Longest exposure; and
    • Highest cumulative dose

• European study has reported increased risk
  – France has suspended the use of pioglitazone
  – Germany has recommended not to start pioglitazone in new patients

PIOGLITAZONE AND DIABETES RECOMMENDATIONS

- FDA recommends that healthcare professionals should:
  - Not use pioglitazone in patients with active bladder cancer.
- Use pioglitazone with caution with prior history of bladder cancer.

Newer Studies- Impact of Lowering A1c on Cardiovascular Risk

- **Proactive- Pioglitazone versus Placebo**
  - Macrovascular Events

- **Accord (n=10,251)**
  - Cardiovascular events in those with existing CVD or risk factors
  - A1c goal of <6%
  - Other arms: blood pressure and lipid control

- **Advance (n= 11,140)**
  - Cardiovascular events in those at high risk for CV events
  - A1c goal of < 6.5%
  - Other arms: blood pressure

- **VA**
  - Cardiovascular events
  - A1c goal of < 6%
**ACCORD & ADVANCE: A1C Results**

\[ N = 10,251 \text{ with T2DM and existing CVD or additional CV risk factors (ACCORD)} \]
\[ N = 11,140 \text{ with T2DM and high risk for CV events (ADVANCE)} \]

<table>
<thead>
<tr>
<th></th>
<th>A1C intensive-treatment goal (achieved(^{†}))</th>
<th>A1C standard-treatment goal (achieved(^{†}))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACCORD</strong></td>
<td>&lt;6% (6.4%)</td>
<td>7.0%-7.9% (7.5%)</td>
</tr>
<tr>
<td><strong>ADVANCE</strong></td>
<td>(\leq 6.5% (6.5%)</td>
<td>(\leq 6.5% (7.3%)</td>
</tr>
</tbody>
</table>

\(^{†}\)Median (ACCORD), mean (ADVANCE)

ACCORD = Action to Control Cardiovascular Risk in Diabetes
ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation

ACCORD & ADVANCE: Treatment Effect on Nonfatal MI, Stroke, CV Death

**ACCORD**
- Standard
- Intensive
- HR 0.90 (0.78-1.04)
- P = 0.16

**ADVANCE**
- Standard
- Intensive
- HR 0.94 (0.84-1.06)
- P = 0.32

ACCORD: Treatment effect on all-cause mortality

Patients with events (%) vs. Time (years)

- Intensive therapy: HR 1.22 (1.01-1.46), P = 0.04
- Standard therapy

ADVANCE: Treatment effect on primary microvascular outcome

New/worsening nephropathy, retinopathy

**Cumulative incidence (%)**

**Follow-up (months)**

**Intensive control**

**Standard control**

**HR 0.86 (0.77-0.97)**

**P = 0.01**

Comparing ADVANCE, ACCORD and VADT

<table>
<thead>
<tr>
<th></th>
<th>ADVANCE</th>
<th>ACCORD</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>11,140</td>
<td>10,251</td>
<td>1,791</td>
</tr>
<tr>
<td><strong>Age/BMI</strong></td>
<td>~55 yrs 28 kg/m²</td>
<td>62 yrs 32 kg/m²</td>
<td>60</td>
</tr>
<tr>
<td><strong>Baseline A1c</strong></td>
<td>7.5% 6.5% 6.5% vs. 7.3%</td>
<td>8.3% 6% 6.4% vs. 7.5%</td>
<td>9.5% &lt;6% 6.9% vs. 8.4%</td>
</tr>
<tr>
<td><strong>Goal A1c Achieved</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>2.7% vs. 1.5%</td>
<td>3.1% vs. 1.0%</td>
<td>0.12 vs. 0.04 pts/yr</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>5 years</td>
<td>1 year</td>
<td>6 years</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Death/MI/CVA</td>
<td>CV death/MI/CVA</td>
<td>CV event/amputations</td>
</tr>
<tr>
<td></td>
<td>10% vs. 10.1%</td>
<td>6.9% vs. 7.2%</td>
<td>CAD/PVD interventions</td>
</tr>
<tr>
<td><strong>(lower than expected)</strong></td>
<td>Microvascular endpoints</td>
<td>Stopped early</td>
<td>Increased risk with</td>
</tr>
<tr>
<td></td>
<td>9.4% vs. 10.9%</td>
<td>-correlation between</td>
<td>-Longer duration DM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypoglycemia and mortality (but not by group)</td>
<td>-Higher A1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Increased age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Severe hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Lower HDL</td>
</tr>
</tbody>
</table>
Glucose Control and Macrovascular Events
Subtleties may be everything

**Possible issues**
- Duration of diabetes (UKPDS vs. ACCORD/ADVANCE/VA)
- Age of subjects (DCCT and UKPDS vs. ACCORD/ADVANCE/VA)
- Specific medications (DCCT and UKPDS vs. ACCORD/ADVANCE/VA)
- Hypoglycemia
- Prior CV history or events
- Low event rates (1/3 of original predictions)

**Other considerations**
- Microvascular benefits
- Glucose control may be more important if BP and Lipids not at goal
Macrovascular Complications are Not the Same as Microvascular Complications

- Concept of “Ticking Clock”
- For microvascular complications
  - Clock starts ticking with onset of hyperglycemia
- For macrovascular complications
  - Clock starts ticking before onset of hyperglycemia

Based on: Haffner SM et al; JAMA 263:2893-29898
Summary

Glucose Control and Macrovascular Events

• Surrogate CV risk factors improve
  – Carotid intimal media thickness
  – High sensitivity-CRP (hs-CRP)
  – Endothelial function (nitric oxide)
  – Insulin resistance

• Initial studies showed promise
  – PERISCOPE- intravascular ultrasound
  – PROactive- small benefit on secondary endpoint
  – UKPDS- initially borderline significance for MI (p=0.052)
  – STOP-NIDDM- small number but statistically significant

• Some studies show risk
  – UGDP study showed increased risk from sulfonylureas (not UKPDS)
  – Increased heart failure with TZD’s
  – Increased fracture with TZD’s (Also potential risk for bladder tumors)
  – Increased risk of death in ACCORD after 1-2 years
Summary
Glucose Control and Macrovascular Events

• Positive outcomes
  – Ten year follow-up of UKPDS
    • Subjects started as close to diagnosis as possible
    • Standards for HTN and cholesterol not the same
  – Twelve year follow-up of DCCT
    • Little influence from insulin resistance- a purer “glucose” disease
  – VA trial trend towards reduced risk for decreased CV events (but not death)

• Possible issues
  – Duration of diabetes
  – Age of subjects
  – Specific medications
  – Hypoglycemia
  – Prior CV history or events
  – Low event rates (1/3 of original predictions)

• Other considerations
  – Microvascular benefits
  – Glucose control may be more important if BP and Lipids not at goal
Summary
Glucose Control and Macrovascular Events

- Surrogate CV risk factors improve
- Initial studies showed promise
  - Intravascular ultrasound
  - Secondary endpoints (16% RR in all cause death, MI, CVA)
  - UKPDS (initial p=0.052)
  - STOP-NIDDM (small number but p<0.05)
- Recent studies show no benefit or risk
  - TZDs- heart failure, fracture, possible bladder CA
  - Increased risk of death (ACCORD)
- Few studies suggest benefit
  - UKPDS (10 year follow-up)
  - DCCT (12 year follow-up)
- Possible Issues
  - Age of subjects and/or duration of diabetes
  - Specific medications and/or hypoglycemia
  - Prior CV events and underlying prevalence
FREEDOM: CABG vs. PCI in Patients with Diabetes

Absolute difference = 8% (26.6 vs. 18.7)

Farkouh ME; N Engl J Med 2012;367:2375-84
FREEDOM: CABG vs. PCI in Patients with Diabetes

P = 0.049 by log-rank test
5-Yr event rate: 16.3% vs. 10.9%

No. at Risk
PCI  953  897  845  685  466  243
CABG 947  855  806  655  449  238
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RR</th>
<th>p</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>1.10</td>
<td>0.43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes related deaths</td>
<td>1.27</td>
<td>0.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause mortality</td>
<td>1.14</td>
<td>0.44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.20</td>
<td>0.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.12</td>
<td>0.74</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microvascular</td>
<td>1.29</td>
<td>0.30</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative Risk & 95% CI

- Favours ACE inhibitor
- Favours Beta blocker

# Reasons for non-compliance

<table>
<thead>
<tr>
<th></th>
<th>Captopril (n=400)</th>
<th>Atenolol (n=358)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-compliant</td>
<td>88 (22%)</td>
<td>125 (35%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>cough</td>
<td>16 (4%)</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>increased creatinine</td>
<td>5 (1%)</td>
<td>0</td>
<td>0.064</td>
</tr>
<tr>
<td>claudication, cold</td>
<td>0</td>
<td>15 (4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>fingers or toes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bronchospasm</td>
<td>0</td>
<td>22 (6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>impotence</td>
<td>1 (0%)</td>
<td>6 (2%)</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Sudden cardiac death during follow-up of 1195 patients with diabetes and LVH treated with atenolol or losartan

Average age= 73

Kaplan–Meier curves for the composite renal outcome (dialysis or doubling of serum creatinine).

5927 subjects with CVD or DM without macroalbuminuria or heart failure (intolerant to ACE-I)

Rates of Survival and Freedom from Major Cardiovascular Events.

**β-Blocker Treatment Improves Survival of Patients With Diabetes: The BIP* Study**

Survival

With β-blockers

Without β-blockers

*Bezafibrate Infarction Prevention Study

UKPDS: Post-Trial Changes in HbA$_{1c}$
## Progression of Coronary Atherosclerosis in T2DM: PERISCOPE IVUS Results

*N = 360 with T2DM and coronary disease*

<table>
<thead>
<tr>
<th></th>
<th>Glimepiride</th>
<th>Pioglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS mean (95% CI)</td>
<td>P (Δ from baseline)</td>
</tr>
<tr>
<td>Percent atheroma volume (%)</td>
<td>0.73 (0.33, 1.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum atheroma thickness (mm)</td>
<td>0.011 (-0.0002, 0.022)</td>
<td>0.054</td>
</tr>
<tr>
<td>Normalized total atheroma volume (mm³)</td>
<td>-1.5 (-4.5, 1.54)</td>
<td>0.34</td>
</tr>
<tr>
<td>Atheroma volume in 10-mm most diseased segment (mm³)</td>
<td>-2.1 (-3.33, -0.84)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

PERISCOPE = Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation

UKPDS Findings

Risk reduction with 1% decline in annual mean A1C

- Microvascular Disease: 37% reduction (P < .0001)
- PVD: 43% reduction (P = .035)
- MI: 14% reduction (P = .021)
- Stroke: 12% reduction (P = .0001)
- Heart Failure: 16% reduction (P = .0001)
- Cataract Extraction: 19% reduction

EDIC Findings: Cardiovascular Events

Cumulative Incidence of First of Any Event

Risk reduction 42%
95% CI: 9% to 63%
P = 0.02

Conventional
Intensive

EDIC Findings: Cardiovascular Events

Non-Fatal MI, Stroke, or CVD Death

Risk reduction 57%
95% CI: 12% to 79%
P = 0.02

Conventional
Intensive

Meta-analysis of DPP-4 inhibitors and CV events

<table>
<thead>
<tr>
<th></th>
<th># trials</th>
<th># trials with events</th>
<th># events</th>
<th># events (DPP4i) (Comparator)</th>
<th>MH-OR [95%, CI]</th>
<th>p</th>
<th>Kendall’s tau</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>63</td>
<td>263</td>
<td>232</td>
<td>0.71 [0.59;0.86]</td>
<td>&lt;0.001</td>
<td>0.04</td>
<td>0.64</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>27</td>
<td>24</td>
<td>77</td>
<td>67</td>
<td>0.86 [0.60;1.24]</td>
<td>0.430</td>
<td>0.04</td>
<td>0.80</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>16</td>
<td>15</td>
<td>75</td>
<td>74</td>
<td>0.61 [0.43;0.86]</td>
<td>0.005</td>
<td>0.03</td>
<td>0.89</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>13</td>
<td>12</td>
<td>62</td>
<td>46</td>
<td>0.67 [0.45;0.99]</td>
<td>0.047</td>
<td>0.36</td>
<td>0.10</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>9</td>
<td>8</td>
<td>37</td>
<td>41</td>
<td>0.72 [0.45;1.16]</td>
<td>0.18</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>5</td>
<td>4</td>
<td>12</td>
<td>4</td>
<td>0.86 [0.25;2.93]</td>
<td>0.81</td>
<td>0.30</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>30</td>
<td>50</td>
<td>51</td>
<td>0.60 [0.41;0.88]</td>
<td>0.008</td>
<td>0.13</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>CV Mortality</strong></td>
<td>48</td>
<td>20</td>
<td>26</td>
<td>26</td>
<td>0.67 [0.39;1.14]</td>
<td>0.140</td>
<td>0.05</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Monami M et al; *Diabetes, Obesity and Metabolism* 15: 112–120, 2013