CARDIOVASCULAR OUTCOMES OF TYPE 2 DIABETES DRUGS

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Figure 1  Mechanistic contribution of different tissues to hyperglycaemia. The arrows indicate the direction of change in function; site and mode of action of glucose-lowering drugs are shown in the dotted circles. HGP, hepatic glucose production; GLP-1Ra, GLP-1 receptor agonists; TZDs, thiazolidinediones; DPP4i, DPP4 inhibitors; SGLT2i, SGLT2 inhibitors; SU, sulfonylureas; AGi, α-glucosidase inhibitors.
CV Risk in T2DM

- Relationship between glucose & microvascular outcomes is much stronger (compared to macrovascular complications).

- Diabetic microvascular disease is more or less specific to diabetes; whereas atherosclerosis has many causes, many of which happen to coexist in T2DM.

- In non-diabetic individuals, the association between glucose and CVD is largely accounted for by other CV risk factors.
## Impact of Intensive Glucose-Lowering Therapy in DM

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<tr>
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<th>CVD</th>
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Tip of the iceberg

CV Risk in T2DM

- Macrovascular complications are the primary cause of mortality.
- Myocardial infarction (MI) and stroke account for 80% of all deaths in T2DM patients.
- Recurrence of major atherosclerotic events in T2DM individuals with a prior MI is very high, 6% per year.
- Mortality in T2DM patients is approximately 2X matched non-diabetic individuals.

Insulin Resistance Syndrome

- Hypertension
- Dyslipidemia (↑HDL, ↑triglycerides, small dense LDL particles)
- Obesity (especially visceral)
- Physical inactivity
- Sub-clinical inflammation
- Endothelial dysfunction

Look AHEAD

- Intensive lifestyle intervention vs. control program of diabetes support and education, among overweight or obese patients with type 2 diabetes.
- At a median follow-up of almost 10 years, there was no significant difference between the two groups in cardiovascular morbidity and mortality.
- This was despite improved biomarkers of glucose and lipid control and other health benefits.

Metformin

• **UKPDS** >> newly diagnosed T2DM patients with low CVD risk whose body weight was 120% of the ideal weight.

• Metformin significantly reduced MI, coronary deaths, and all-cause mortality by 39, 50, and 36% respectively.

• 10-year follow-up of UKPDS, metformin-treated obese T2DM patients continued to show a reduction in MI (33%) and death from any cause (33%).

Metformin

• Many retrospective analyses of large databases have concluded that metformin reduces the incidence of cardiovascular event (but sulfonylureas were the comparator).

• **SPREAD-DIMCAD** >> CAD +ve patients randomized to glipizide or metformin for a median follow-up of 5 years. The hazard ratio (0.54) for the composite endpoint (CV death, any cause mortality, MI, non-fatal stroke, and arterial revascularization) was significantly reduced in the metformin group.

Metformin: CV risk reduction mechanisms

- Improved glycemic control
- Modest weight loss (2–3 kg)
- Reduction in methylglyoxal levels
- Decrease in VLDL secretion and plasma triglyceride levels
- Reduced postprandial lipaemia
- Improved endothelial dysfunction and reduced plasminogen-activator inhibitor 1 (PAI-1) levels

Sulfonylureas

- Increased CV risk from retrospective analyses of large databases, meta-analyses and prospective cohorts
- UKPDS, ADVANCE, and ACCORD failed to demonstrate an increase in either CVD mortality or morbidity in sulfonylurea-treated T2DM patients.
- Ongoing CAROLINA study (linagliptin vs glimepiride)
Sulfonylureas

- Accelerate β-cell failure
- Promote weight gain
- Cause hypoglycemia
- Interference with myocardial ischemic preconditioning (glyburide)

If a sulfonylurea is to be used, an agent other than glyburide is preferable.
Meglitinides

- Repaglinide and nateglinide (short-acting insulin secretagogues binding to sulfonylurea receptor and a distinct site on the β-cell).
- Less hypoglycemia and weight gain compared to sulfonylureas.
- No long term data available.
- No difference in 30 day CV mortality or events among patients hospitalized due to CVD, compared to sulfonylureas.

Thiazolidinediones

Pioglitazone and rosiglitazone: peroxisome proliferator-activated receptors-γ activators

- Increase plasma HDL-cholesterol, reduce plasma triglyceride and FFA
- Convert small dense LDL-cholesterol particles into larger, more buoyant particles
- Reduce BP
- Improve endothelial dysfunction
- Ameliorate insulin resistance
- Decrease visceral fat
- Increase adiponectin and reduces PAI-1, CRP, TNF-α levels
- Improve non-alcoholic steatohepatitis
Thiazolidinediones

Rosiglitazone

• Increases plasma LDL-cholesterol and triglyceride level
• Enhance renal sodium and water reabsorption
• Can cause congestive heart failure (CHF), especially in patients with diastolic dysfunction.
Rosiglitazone

- 2010: Rosiglitazone consistently was associated with an HR of 1.0 for CVD events. GSK settled >11,000 claims.
- 2011: FDA restricted its use only to certified doctors.
- 2013: FDA re-examined the RECORD study and concluded that there was no increase in overall CV risk. FDA lifted its restriction on rosiglitazone.
- To date: Still remains unavailable in Europe.
Pioglitazone

- **PROactive**: 5238 T2DM patients with a previous CV event or multiple CVRFs. MACE ↓16%. MI ↓16%. CVA ↓47%.

- **IRIS**: 3876 non-diabetic but insulin resistant patients with recent CVA or TIA. ↓CVA (hazard ratio in the pioglitazone group, 0.76; 95% CI 0.62 to 0.93; P=0.007)

- Weight gain, edema, fracture, bladder cancer risk?

Dipeptidyl peptidase-4 inhibitors

- Retrospective analyses showed CV event reduction, but based on studies not designed to measure CV outcomes.

- **SAVOR-TIMI 53**: Saxagliptin did not increase the risk of major adverse cardiovascular events, but ↑CHF hospitalization rate (3.5% vs. 2.8% incidence of hospitalization for CHF).

- **EXAMINE**: Alogliptin did not increase the risk of major adverse cardiovascular events. No CHF signal.

- **TECOS**: Sitagliptin did not increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events.

Glucagon-like peptide-1 receptor agonists

- Small studies show improvement in LV function.
- Reduce weight (3-5 kg) with visceral and subcutaneous fat loss.
- Reduce BP, systolic (4–5 mmHg) and diastolic (1–2 mmHg) by enhancing urinary sodium excretion.
- Reduce postprandial lipemia, FFA.

- Slight increase in heart rate (2-3 bpm), likely from stimulation of GLP-1 receptors in the SA node.
Glucagon-like peptide-1 receptor agonists

- **LEADER**: 9340 patients with T2DM and high CV risk treated with liraglutide vs. placebo.
- Median followup 3.8 years. ↓ MACE (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P=0.01 for superiority). ↓ CV mortality (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). ↓ All-cause mortality (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02).
- NNT to prevent one event in 3 years was 66.
- No change in CHF hospitalization rate.

Glucagon-like peptide-1 receptor agonists

- **ELIXA**: Among type 2 diabetics with high cardiovascular risk, no change in MACE was observed despite the addition of lixisenatide.

- **SUSTAIN**: Among type 2 diabetics with high cardiovascular risk, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; P<0.001 for noninferiority).

SGLT-2 Inhibitors

- **EMPA-REG**: Type 2 diabetics with established CVD. Empagliflozin vs placebo (no other hypoglycemic agents). Median observation time 3.1 years.
- ↓ CV mortality (38% RR reduction)
- ↓ CHF hospitalizations (35% RR reduction)
- ↓ All-cause mortality (32% RR reduction)
- NNT: 39 to prevent 1 death in 3 years.

Potential pathways to CV impact of SGLT2-inhibitors

- Lower BP
- Lower arterial stiffness
- Lower SNS activity
- Lower weight
- Lower visceral adiposity
- Lower oxidative stress
- Lower albuminuria
- Lower glucose
- Lower insulin
- Lower uric acid
- Higher LDL-C
- Higher HDL-C
- Lower triglycerides
**Large CV Outcomes Trials in Diabetes (Non-Insulin)**

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<thead>
<tr>
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<th>SAVOR</th>
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At diagnosis of type 2 diabetes:

- Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

  **A1C <8.5%**
  - If not at glycemic target (2-3 mos)
    - Start / Increase metformin
  - Start metformin immediately
    - Consider initial combination with another antihyperglycemic agent
  - If not at glycemic targets

  **A1C ≥8.5%**
  - Symptomatic hyperglycemia with metabolic decompensation
  - Initiate insulin +/- metformin

Add another agent best suited to the individual by prioritizing patient characteristics:

**Patient characteristic**

- **Priority:** Clinical Cardiovascular Disease
  - SGLT2 inhibitor with demonstrated CV outcome benefit

- Degree of hyperglycemia
- Risk of hypoglycemia
- Overweight or obesity
- Cardiovascular disease or multiple risk factors
- Comorbidities (renal, CHF, hepatic)
- Preferences & access to treatment

- Consider relative A1C lowering
- Rare hypoglycemia
- Weight loss or weight neutral
- Effect on cardiovascular outcome
- See therapeutic considerations, consider eGFR
  - See cost column; consider access

See next page...
QUESTIONS

It's not that diabetes, heart disease and obesity runs in your family. It's that no one runs in your family.