Overview: cardiovascular outcomes and anti-diabetes agents

Dongsun Kim

Hanyang University College of Medicine
The main cause of death in type 2 diabetes is cardiovascular disease.
### Hazard Ratios for Vascular Outcomes in Diabetes

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
<th>( \hat{p} ) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease*</td>
<td>26,505</td>
<td>2.00 (1.83–2.19)</td>
<td>64 (54–71)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>11,556</td>
<td>2.31 (2.05–2.60)</td>
<td>41 (24–54)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>14,741</td>
<td>1.82 (1.64–2.03)</td>
<td>37 (19–51)</td>
</tr>
<tr>
<td><strong>Stroke subtypes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>3,799</td>
<td>2.27 (1.95–2.65)</td>
<td>1 (0–20)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1,183</td>
<td>1.56 (1.19–2.05)</td>
<td>0 (0–26)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4,973</td>
<td>1.84 (1.59–2.13)</td>
<td>33 (12–48)</td>
</tr>
<tr>
<td><strong>Other vascular deaths</strong></td>
<td>3,826</td>
<td>1.73 (1.51–1.98)</td>
<td>0 (0–26)</td>
</tr>
</tbody>
</table>
Diabetes: Cardiovascular Disease

- **Diabetes itself**
  - Insulin resistance
  - Hyperglycemia
  - Associated complications

- **Antidiabetic agents**
  - Glucose lowering
  - BP lowering
  - Weight
  - Hypoglycemia
  - Pleiotropic effects beyond the glucose-lowering effect
  - Others: lipid.....
Diabetes: Cardiovascular Disease

- Diabetes itself
  - Insulin resistance
  - Hyperglycemia
  - Associated complications

Adapted from McFarlane S, et al. J Clin Endocrinol Metab 2001; 86:713–718
Diabetes: Cardiovascular Disease

• Diabetes itself
  – Insulin resistance
  – Hyperglycemia
  – Associated complications

• Antidiabetic agents
  – Glucose lowering
  – BP lowering
  – Weight
  – Hypoglycemia
  – Pleiotropic effects beyond the glucose-lowering effect
  – Others: lipid…..

Is hyperglycemia associated with increased CV risk?
Hazard Ratios for CHD by clinically defined categories of baseline FBG concentration

<table>
<thead>
<tr>
<th>Fasting blood glucose concentration</th>
<th>Number of participants (%)</th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Known diabetes at baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥7 mmol/L</td>
<td>13 122 (4.7%)</td>
<td>1186</td>
<td>2.36 (2.02–2.76)</td>
</tr>
<tr>
<td>&lt;7 mmol/L</td>
<td>5 807 (2.1%)</td>
<td>380</td>
<td>1.61 (1.42–1.82)</td>
</tr>
<tr>
<td><strong>No known diabetes at baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥7 mmol/L</td>
<td>7 240 (2.6%)</td>
<td>452</td>
<td>1.78 (1.56–2.03)</td>
</tr>
<tr>
<td>6.1 to &lt;7 mmol/L</td>
<td>19 607 (7.0%)</td>
<td>1011</td>
<td>1.17 (1.08–1.26)</td>
</tr>
<tr>
<td>5.6 to &lt;6.1 mmol/L</td>
<td>32 008 (11.5%)</td>
<td>1631</td>
<td>1.11 (1.04–1.18)</td>
</tr>
<tr>
<td>3.9 to &lt;5.6 mmol/L*</td>
<td>185 590 (66.5%)</td>
<td>9508</td>
<td>1.00 (0.95–1.06)</td>
</tr>
<tr>
<td>&lt;3.9 mmol/L</td>
<td>15 916 (5.7%)</td>
<td>646</td>
<td>1.07 (0.97–1.18)</td>
</tr>
</tbody>
</table>
Hazard Ratios for Coronary Heart Disease:
by long-term average concentrations of FBG, cholesterol & systolic BP

Incidence of CHD by HbA1c Levels:
3.5-year follow-up study of 1,298 Finnish diabetics (65-75 yrs)

Hyperglycemia as a cardiovascular risk factor

Diabetes: Cardiovascular Disease

“Microvascular Complications”

- Diabetes itself
  - Insulin resistance
  - Hyperglycemia
  - Associated complications
    (Associated conditions)

- Antidiabetic agents
  - Glucose lowering
  - BP lowering
  - Weight
  - Hypoglycemia
  - Pleiotropic effects beyond the glucose-lowering effect
  - Others: lipid…..

75% are overweight
63% have high BP
50% have dyslipidaemia
Diabetes: Cardiovascular Disease

- Diabetes itself
  - Insulin resistance
  - Hyperglycemia
  - Associated complications

- **Antidiabetic agents**
  - Glucose lowering
  - BP lowering
  - Weight
  - Hypoglycemia
  - Pleiotropic effects beyond the glucose-lowering effect
  - Others: lipid…..
Diabetes: Cardiovascular Disease

- Diabetes itself
  - Insulin resistance
  - Hyperglycemia
  - Associated complications

- Antidiabetic agents
  - Glucose lowering
  - BP lowering
  - Weight
  - Hypoglycemia
  - Pleiotropic effects beyond the glucose-lowering effect
  - Others: lipid…..

**Intensive blood glucose control**

- Intensive blood glucose control reduces microvascular complications, but the protective effect on macrovascular disease and mortality remains disappointing

The beneficial effect of lowering blood glucose to very low levels is controversial as one of the major problems being the increase in the number of hypoglycemic events.

**The New England Journal of Medicine**

**Intensive versus Conventional Glucose Control in Critically Ill Patients**

The NICE-SUGAR Study Investigators*

**ABSTRACT**

**BACKGROUND**

The optimal target range for blood glucose in critically ill patients remains unclear.

**CONCLUSIONS**

In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter. (ClinicalTrials.gov number, NCT00220987.)

Diabetes: Cardiovascular Disease

- **Diabetes itself**
  - Insulin resistance
  - Hyperglycemia
  - Associated complications

- **Antidiabetic agents**
  - Glucose lowering
  - BP lowering
  - Weight
  - Hypoglycemia
  - Pleiotropic effects beyond the glucose-lowering effect
  - Others: lipid…..

Reducing BP to <140/90 mmHg reduces the risk of CHD, stroke and diabetic kidney disease

ADA. Diabetes Care 2015;38:S49–S57
Diabetes: Cardiovascular Disease

- Diabetes itself
  - Insulin resistance
  - Hyperglycemia
  - Associated complications

- Antidiabetic agents
  - Glucose lowering
  - BP lowering
  - Weight loss
  - Hypoglycemia
  - Pleiotropic effects beyond the glucose-lowering effect
  - Others: lipid…..

Diabetes: Cardiovascular Disease

- **Diabetes itself**
  - Insulin resistance
  - Hyperglycemia
  - Associated complications

- **Antidiabetic agents**
  - Glucose lowering
  - BP lowering
  - Weight
  - Hypoglycemia
  - Pleiotropic effects beyond the glucose-lowering effect
  - Others: lipid…..

---

Rate of CV events

<table>
<thead>
<tr>
<th>Condition</th>
<th>Proportion of Patients (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypoglycaemia (n=208)</td>
<td>16.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No severe hypoglycaemia (n=10,932)</td>
<td>10.2%</td>
<td></td>
</tr>
</tbody>
</table>

Glucose Lowering Agents

- Detemir
- Glargine
- Aspart
- Glinide
- Glitazone
- Lispro
- Alpha-Glucosidase inhibitors
- Human insulin
- Metformin
- Sulfonylurea
- Animal insulin
- DPP-4 inhibitors
- GLP-1 mimetics
- Insulin for inhalation
- Exenatide (USA)
- Longacting GLP1A
- SGLT2-I Degludec

Timeline:
- 1923
- 1950s
- 1982-5
- 1995 1996
- 01' 03' 05' 06' 12-16'
In addition to lowering glucose, the priority in DM management is to minimize the risks of hypoglycemia and weight gain.

The AACE preferentially recommends agents that do not increase these risks.
Adverse Effects of Antidiabetic Agents on Cardiovascular System
The Old Story of UGDP (University Group Diabetes Program)

Tolbutamide-placebo cumulative mortality

Phenformin-placebo cumulative mortality

Insulin-placebo cumulative mortality

Genell L. Knatterud. JAMA 1971;217(6):777-784
A Summary of Criticisms of the Findings and Conclusions of the University Group Diabetes Program (UGDP)

Holbrooke S. Seltzer, M.D., Dallas

The conclusion of the study that tolbutamide therapy is attended by an increased risk of cardiovascular death is rejected.
Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

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

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.
Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Rosiglitazone Group</th>
<th>Control Group</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>44/10,285 (0.43)</td>
<td>22/6106 (0.36)</td>
<td>1.45 (0.88–2.39)</td>
<td>0.15</td>
</tr>
<tr>
<td>DREAM</td>
<td>15/2,635 (0.57)</td>
<td>9/2634 (0.34)</td>
<td>1.65 (0.74–3.68)</td>
<td>0.22</td>
</tr>
<tr>
<td>ADOPT</td>
<td>27/1,456 (1.85)</td>
<td>41/2895 (1.42)</td>
<td>1.33 (0.80–2.21)</td>
<td>0.27</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.43 (1.03–1.98)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Death from cardiovascular causes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>25/6,845 (0.36)</td>
<td>7/3980 (0.18)</td>
<td>2.40 (1.17–4.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>DREAM</td>
<td>12/2,635 (0.46)</td>
<td>10/2634 (0.38)</td>
<td>1.20 (0.52–2.78)</td>
<td>0.67</td>
</tr>
<tr>
<td>ADOPT</td>
<td>2/1,456 (0.14)</td>
<td>5/2895 (0.17)</td>
<td>0.80 (0.17–3.86)</td>
<td>0.78</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.64 (0.98–2.74)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*연구 방법 ; meta-analysis
*결과; OR for MI, 1.43 (95% CI 1.03-1.98; p=0.03), OR for death from CV causes, 1.64 (95% CI 0.98-2.74; p=0.06)
Thiazolidindiones
CV Safety – Risk of MI: pioglitazone vs rosiglitazone
“Pioglitazone decreases the risk of MI”

<table>
<thead>
<tr>
<th>Decreased risk of MI with ACTOS</th>
<th>Increased risk of MI with rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROactive¹</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone meta-analysis²</td>
<td></td>
</tr>
<tr>
<td>Older patients, pioglitazone³</td>
<td></td>
</tr>
<tr>
<td>0.72</td>
<td>0.73</td>
</tr>
<tr>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>0.73</td>
<td>1.76</td>
</tr>
<tr>
<td>1.43</td>
<td></td>
</tr>
<tr>
<td>1.31</td>
<td></td>
</tr>
<tr>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td>1.33</td>
<td></td>
</tr>
<tr>
<td>1.36</td>
<td></td>
</tr>
<tr>
<td>1.42</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI)

After This.....

- **US FDA (Dec. 2008):**
  
  “The FDA guidance Diabetes Mellitus-Evaluation of Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes”

  - 당뇨병 신약을 개발한 스폰서가 신약은 받아드릴 만한 수준에서 (acceptable) 심혈관계 위험도를 가지지 않는다는 것을 입증하도록 함

- **유럽 EMA (Jan. 2010):**
  
  - 당뇨병 치료약제의 신약 임상시험 연구에 심혈관계 위험을 평가하는 항목을 요구
Metformin

- Many retrospective analyses have concluded that metformin reduces the incidence of cardiovascular events
Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)

- In newly diagnosed T2DM Pts with low CVD risk & obesity (>120% of ideal Bwt)
  -- ↓: MI (39%), coronary deaths (50%), all-cause mortality (36%)

- In the 10-year follow-up
  -- continued to show a reduction in MI (33%) and death from any cause (33%)

✓ Limitation: small number (n=342); all obese; lack of lipid lowering drugs & modern blood pressure and kidney preserving drugs
Potential Mechanisms for the Putative Protective Effect of Metformin

- Improved glycemic control
- Reduction in methylglyoxal levels
- \(\downarrow\) VLDL secretion, plasma TG level & postprandial lipemia
- Plasma LDL- & HDL-cholesterol levels are either unchanged or change minimally with metformin

- Improved endothelial dysfunction and reduced plasminogen-activator inhibitor 1 (PAI-1) levels
- Modest weight loss (~2–3 kg) \(\Rightarrow\) Neutral
  -- by the anorectic effect of the biguanide & its GI side effect profile (diarrhea, abdominal discomfort & flatulence)
Insulin ?
The biology of insulin's action on the vasculature is ambivalent (1)

- Can promote atherogenesis through several mechanisms
  - \((\uparrow)\) de novo lipogenesis & hepatic VLDL synthesis
    - via stimulation of SREBP-1c and inhibition of acetyl-CoA carboxylase
  - \((\uparrow)\) LDL-cholesterol transport, collagen synthesis, proliferation and turning on multiple genes involved in inflammation
    - in cultured arterial smooth muscle cells
  - In Rats: chronic infusion with insulin (7–10 days)
    - resistance to stimulation of glucose uptake & suppression of plasma FFA
    - hypertension
  - In humans with normal glucose tolerance: insulin infusion (3 days)
    - insulin resistance

Ferrannini E, DeFronzo RA. Eur Heart J 2015;36:2288–2296
The biology of insulin's action on the vasculature is ambivalent (2)

- **Evidence supporting anti-atherosclerotic effect:**
  - nitric oxide release, suppression of pro-apoptotic signals, and inhibition of platelet aggregation

- **Drawback**
  ✓ Cross-sectional, retrospective nature of many studies, and a strong indication bias (e.g. insulin is most often used in long-standing, complicated diabetes) → positive association between the pharmacological use of insulin and atherosclerotic CVD
  ✓ Longitudinal and trial (UKPDS and ORIGIN) evidence, if less abundant, consistently failed to show that insulin treatment per se enhances atherosclerotic CVD risk
  ✓ Factors such as background CVD risk, degree of insulin resistance, insulin dose, extent of weight gain, frequency of hypoglycemia, & even strategy of insulin administration (basal-bolus, premix formulations, etc) may impart unpredictable variability to CVD outcome
Long-Term Outcome of PCI Versus CABG in Insulin and Non-Insulin-Treated Diabetic Patients

Results From the FREEDOM Trial

George D. Dangas, MD, PhD,* Michael E. Farkouh, MD,* Lynn A. Sleeper, ScD,† May Yang, MPH,‡ Mikkel M. Schoos, MD, PhD,* Carlos Macaya, MD, PhD,‡ Alexandre Abizaid, MD, PhD,‡ Christopher E. Bailey, MD,‡ Gerard Deol, MD, Alfredo E. Rodriguez, MD, PhD,§ Alexandra J. Lansky, MD,§ F. Sandra Saini, MPH,† Michael Domanski, MD,† Valentin Fuster, MD, PhD,* for the FREEDOM Investigators

ABSTRACT

BACKGROUND The prospective, randomized FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial found coronary artery bypass graft surgery (CABG) was associated with better clinical outcomes than percutaneous coronary intervention (PCI) in patients with diabetes and multivessel disease, managed with or without insulin.

OBJECTIVES In this subgroup analysis of the FREEDOM trial, we examined the association of long-term clinical outcomes after revascularization in patients with insulin-treated diabetes mellitus (ITDM) compared with patients not treated with insulin.

METHODS A total of 1,850 FREEDOM subjects had an index revascularization procedure performed: 956 underwent PCI with drug-eluting stents (DES), and 894 underwent CABG. A total of 602 patients (32.5%) had ITDM (PCI/DES n = 325, 34%; CABG n = 277, 31%). Subjects were classified according to ITDM versus non-ITDM, with comparison of PCI/DES versus CABG for each group. Interaction analyses were performed for treatment by diabetes mellitus (DM) status alone and for treatment by DM status by coronary lesion complexity. Analyses were performed for the primary outcome composite of death/stroke/myocardial infarction (MI) using all available follow-up data.

RESULTS The overall 5-year event rate of death/stroke/MI was significantly higher in ITDM versus non-ITDM patients (28.7% vs. 19.5%, p < 0.001), which persisted even after adjustment for multiple baseline factors, angiographic complexity, and revascularization treatment group (death/stroke/MI hazard ratio [HR]: 1.85, 95% confidence interval [CI]: 1.06 to 1.22, p = 0.041). With respect to the primary composite endpoint, CABG was superior to PCI/DES in both DM types and the magnitude of treatment effect was similar (interaction p = 0.40) for ITDM (PCI vs. CABG HR: 1.21, 95% CI: 0.87 to 1.69) and non-ITDM patients (PCI vs. CABG HR: 1.46, 95% CI: 1.10 to 1.94), even after adjusting for the angiographic SYNTAX score level. Based on 5-year event rates, the number needed to treat with CABG versus PCI to prevent 1 event is 12.7 in ITDM and 13.2 in non-ITDM.

CONCLUSIONS In patients with diabetes and multivessel coronary artery disease, the rate of major adverse cardiovascular events (death, MI, or stroke) is higher in patients treated with insulin than in those not treated with insulin. Furthermore, we did not detect a significant difference in the magnitude of PCI versus CABG treatment effect for patients treated with insulin and those not treated with insulin. (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes [FREEDOM]; NCT00086455) (J Am Coll Cardiol 2014;64:1189-97) © 2014 by the American College of Cardiology Foundation.

~ 1.5-fold increase in ITDM
Cumulative Incidence of Target Vessel Failure  
(ITDM vs non-ITDM, everolimus vs paclitaxel-eluting stents)

From TUXEDO Trial: Percutaneous Coronary Intervention in Patients With Insulin-Treated and Non–Insulin-Treated Diabetes Mellitus
Insulin Not to Blame for Heightened Risks for T2D Patients
Clinical Outcomes: ITDM vs non-ITDM

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ITDM (n = 747)</th>
<th>Non-ITDM (n = 1083)</th>
<th>P Value</th>
<th>Propensity Score, Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target vessel failure</td>
<td>42 (5.6)</td>
<td>36 (3.3)</td>
<td>.02</td>
<td>1.31 (0.78-2.20)</td>
<td>.31</td>
</tr>
<tr>
<td>Major adverse cardiac events</td>
<td>45 (6.0)</td>
<td>40 (3.7)</td>
<td>.02</td>
<td>1.28 (0.78-2.12)</td>
<td>.32</td>
</tr>
<tr>
<td>Death or myocardial infarction</td>
<td>43 (5.8)</td>
<td>35 (3.2)</td>
<td>.009</td>
<td>1.17 (0.69-2.00)</td>
<td>.55</td>
</tr>
<tr>
<td>Cardiac death or myocardial infarction</td>
<td>35 (4.7)</td>
<td>31 (2.9)</td>
<td>.04</td>
<td>1.19 (0.68-2.09)</td>
<td>.54</td>
</tr>
<tr>
<td>Cardiac death or target vessel myocardial infarction</td>
<td>31 (4.1)</td>
<td>27 (2.5)</td>
<td>.05</td>
<td>1.19 (0.65-2.16)</td>
<td>.57</td>
</tr>
</tbody>
</table>

Death
- All: 26 (3.5) vs 18 (1.7), P = .01, Adjusted Hazard Ratio 1.09 (0.52-2.29), P = .82
- Cardiac: 18 (2.4) vs 14 (1.3), P = .07, Adjusted Hazard Ratio 1.10 (0.48-2.55), P = .82
- Noncardiac: 8 (1.1) vs 4 (0.4), P = .07, Adjusted Hazard Ratio 1.05 (0.21-5.31), P = .96

Myocardial infarction
- All: 21 (2.8) vs 19 (1.8), P = .13, Adjusted Hazard Ratio 1.36 (0.60-3.08), P = .46
- Target vessel related: 17 (2.3) vs 14 (1.3), P = .11, Adjusted Hazard Ratio 1.07 (0.49-2.32), P = .86
- Non-target vessel related: 5 (0.7) vs 6 (0.6), P = .04, Adjusted Hazard Ratio 3.45 (0.60-19.83), P = .16
- Q-wave: 7 (0.9) vs 2 (0.2), P = .04, Adjusted Hazard Ratio 1.01 (0.45-2.23), P = .99
- Non-Q-wave: 15 (2.0) vs 17 (1.6), P = .48, Adjusted Hazard Ratio 1.01 (0.45-2.23), P = .99

Stent thrombosis
- All: 13 (1.7) vs 10 (0.9), P = .12, Adjusted Hazard Ratio 1.57 (0.58-4.22), P = .37
- Definite: 9 (1.2) vs 8 (0.7), P = .31, Adjusted Hazard Ratio 1.04 (0.33-3.26), P = .95
- Probable: 4 (0.5) vs 2 (0.2), P = .23, Adjusted Hazard Ratio 5.86 (0.59-58.45), P = .13

Thrombosis
- Acute: 0 (0.0) vs 1 (0.1), P > .99
- Subacute: 8 (1.1) vs 3 (0.3), P = .03, Adjusted Hazard Ratio 3.11 (0.73-13.20), P = .12
- Late: 5 (0.7) vs 6 (0.6), P = .75, Adjusted Hazard Ratio 0.85 (0.19-3.83), P = .83
- Target lesion revascularization: 23 (3.1) vs 19 (1.8), P = .06, Adjusted Hazard Ratio 1.43 (0.71-2.88), P = .32
- Target vessel revascularization: 23 (3.1) vs 19 (1.8), P = .06, Adjusted Hazard Ratio 1.43 (0.71-2.88), P = .32

"Insulin Not to Blame for Heightened Risks for T2D Patients"
α-Glucosidase Inhibitors

- Delay CHO absorption and reduce postprandial hyperglycaemia
- Increase plasma GLP-1 levels and alter the gut microbiome
- Reduce postprandial triglycerides
- Do not significantly affect BP or body weight

STOP-NIDDM Trial in IGT

Acarbose Treatment & Risk of CV Disease

Diabetes: Cardiovascular Disease

- Diabetes itself
  - Insulin resistance
  - Hyperglycemia
  - Associated complications

- Antidiabetic agents
  - Glucose lowering
  - BP lowering
  - Weight
  - Hypoglycemia
  - Pleiotropic effects beyond the glucose-lowering effect
  - Others: lipid.....
Possible Cardiovascular Effects

Incretin/DPP-4 Inhibitor
and
SGLT2 Inhibitor
Exenatide Reduces Final Infarct Size in Patients With ST-Segment–Elevation Myocardial Infarction and Short-Duration of Ischemia

Jacob Lønborg, MD, PhD; Henning Kelbaek, MD, DMSc; Niels Vejlstrup, MD, PhD; Hans Erik Bøtker, MD, DMSc; Won Yong Kim, MD, PhD; Lene Holmvang, MD, DMSc; Erik Jørgensen, MD; Steffen Helqvist, MD, DMSc; Kari Saunamäki, MD, DMSc; Christian Juhl Terkelsen, MD, PhD; Mikkel Malby Schoos, MD; Lars Køber, MD, PhD, DMSc; Peter Clemmensen, MD, DMSc; Marek Treiman, MD, DMSc; Thomas Engstrøm, MD, PhD, DMSc

Background—Exenatide has been demonstrated to be cardioprotective as an adjunct to primary percutaneous coronary intervention in patients with ST-segment–elevation myocardial infarction (STEMI). The aim of the post hoc analysis study was to evaluate the effect of exenatide in relation to system delay, defined as time from first medical contact to first balloon.

Methods and Results—Patients with STEMI and Thrombolysis In Myocardial Infarction flow 0/1 were randomly assigned to intravenous exenatide or placebo continuous infusion. Study treatment was commenced 15 minutes before intervention and maintained for 6 hours after the procedure. The patients were stratified according to median system delay (132 minutes). Final infarct size and myocardial area at risk were measured by cardiovascular magnetic resonance. Among patients with a system delay ≤132 minutes (n=74), treatment with exenatide resulted in a smaller infarct size (9 grams [interquartile range (IQR), 4–13] versus 13 grams [IQR, 8–24], P=0.008, corresponding to 8% [IQR, 4–12] versus 11% [IQR, 7–17] of the left ventricle, P=0.015). In a regression analysis adjusting for myocardial area at risk the data points of the exenatide group lay significantly lower than for the placebo group (P=0.006). In the patients with system delay >132 minutes (n=74) no difference was observed in infarct size expressed as grams (P=0.49) or percentage (P=0.46). There was significant interaction between system delay (less than or equal to median versus greater than median) and treatment allocation in terms of infarct size (P=0.018).

Conclusions—In this post hoc analysis, exenatide treatment was associated with a 30% decrease in final infarct size in patients with short system delay, whereas no cardioprotective effect in patients with long system delay was seen. However, this finding must be confirmed in larger studies.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00835848.
Pleiotropic effects of GLP1

GLP-1 or GLP-1R AGONISTS

Insulin sensitivity

Heart
- Blood pressure
- Heart rate
- Myocardial contractility
- Cardioprotection

Kidney
- Natriuresis

Liver
- Hepatic glucose production

Pancreas
- Insulin secretion
- Glucagon secretion
- Insulin biosynthesis
- β-cell survival
- β-cell proliferation

Brain
- Appetite
- Satiety
- Energy expenditure

Adipose tissue
- Lipolysis
- FFA synthesis
- Glucose uptake

Muscle
- Glycogen synthesis
- Glucose oxidation

GIT
- Gastric emptying
- Acid secretion
- GI motility
Potential Impact of DPP-4 Inhibitor on CV System

- ↑ Endothelial function
- ↑ Nitric oxide production
- ↑ Myocardial contractility
- ↑ Systolic function in myocardial infarction
- ↑ Systolic function in cardiomyopathy
- ↓ Infarct size
- ↑ Ischemic preconditioning
- ↑ Postischemic recovery
- ↑ Myocardial glucose uptake

Decrees occurrence of hypoglycemia

<table>
<thead>
<tr>
<th>DPP - 4 inhibitors</th>
<th>Study</th>
<th>Any hypoglycemia (number)</th>
<th>investigational drug / comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>Scott, R., Loeys, T. et al. (2008)</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Goldstein, B. J., Feinglos, M. N. et al. (2007)</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Charbonnel, B., Karasik, A. et al. (2006)</td>
<td>6/5</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Rosenstock, J., Sankoh, S. et al. (2008)</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Schweizer, A., Couturier, A. et al. (2007)</td>
<td>2/1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bolli, G., Dotta, F. et al. (2008)</td>
<td>1/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bosi, E., Camisasca, R. P. et al. (2007)</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rosenstock, J., Baron, M. A. et al. (2007)</td>
<td>1/0</td>
<td></td>
</tr>
</tbody>
</table>

No weight gain compared to SU

-1.8 kg

Ferrannini E, et al. Diabetes Obes Metab.

Postprandial lipid metabolism

Schwartz et al., Atherosclerosis 2010, 212(1):217-222
GLP-1 in the Cardiovascular System

- Cardiac function:
- Vascular function: Effects on endothelial function
- Renoprotective, antihypertensive and anti-inflammatory effects
- Effects on lipids
- Gastrointestinal system and CNS effects
- Weight Reduction
- No Hypoglycemia
Risk of cardiovascular disease: The effects of diabetes and anti-diabetic drugs – A nested case–control study

Michael Gejl a,b,c,g,*, Jakob Starup-Linde c,d,1, Jan Scheel-Thomsen e, Soeren Gregersen c, Peter Vestergaard d,f

a Department of Biomedicine, Aarhus University, Aarhus, Denmark
b Centre for Advanced Imaging, The University of Queensland, Brisbane, Australia
c Department of Endocrinology and Internal Medicine (M14), Aarhus University Hospital, Aarhus, Denmark
d Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
e Department of Neurology, Aalborg University Hospital, Aalborg, Denmark
f Department of Endocrinology, Aalborg University Hospital, Aalborg, Denmark
g Department of Nuclear Medicine and PET Centre, Aarhus University Hospital, Aarhus, Denmark

ARTICLE INFO
Article history:
Received 28 August 2014
Received in revised form 24 October 2014
Accepted 10 November 2014
Available online 12 November 2014

Keywords:
Type 2 diabetes mellitus
Cardiovascular disease
Glucagon-like peptide-1
GLP-1
Liraglutide
Biguanides

ABSTRACT

Aims: Type 2 diabetes (DM) increases the risk of cardiovascular disease. We investigated the effects of antidiabetic drugs on the composite endpoint (CE) of ischemic heart disease, heart failure or stroke in DM patients.

Methods: We conducted a nested case–control study. Cases were DM patients who subsequently suffered from CE; controls were DM patients with no history of CE after DM diagnosis. Using the Danish National Hospital Discharge Register, we included DM patients with information on date of DM diagnosis, date of CE, and comorbidities. From the Central Region of Jutland, Denmark, medication use and biochemical parameters were collected. Logistic regression analyses were conducted and mutually adjusted for comorbidities, pharmaceutical use, and biochemical parameters.

Results: 10,073 DM patients were included (65,550 person-years). 1947 suffered from a subsequent CE. CE prior to DM diagnosis (OR = 20.18, 95% CI: 16.88–24.12), neuropathy (OR = 1.39, 95% CI: 1.05–1.85) and peripheral artery disease (OR = 1.31, 95% CI: 1.02–1.69) increased the risk of CE. Biguanides (OR = 0.62 95% CI: 0.54–0.71) and liraglutide (OR = 0.48 95% CI: 0.38–0.62) significantly decreased the risk of CE as did statin treatment (OR = 0.63, 95% CI: 0.54–0.72). DPP-4 inhibitors, insulin and β-cell stimulating agents had neutral effect. When results were adjusted for biochemical risk markers (1103 patients, 7271 person-years, 189 cases), biguanides (OR = 0.54, 95% CI: 0.34–0.87) and liraglutide (OR = 0.32, 95% CI: 0.14–0.70) treatment retained a significant risk reduction. The effect of liraglutide was dose and duration dependent (p < 0.05).

Conclusion: We have shown an association between the use of biguanides and liraglutide and a reduced risk of CE in DM patients.
### Adjusted Analysis on Patients with T2D

#### Risk factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Without biochemistry</th>
<th>With biochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.025</td>
<td>1.028</td>
</tr>
<tr>
<td>Diabetes duration (per year)</td>
<td>1.087</td>
<td>1.096</td>
</tr>
<tr>
<td>CE prior to DM</td>
<td>20.175</td>
<td>15.821</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.830</td>
<td>1.337</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>1.072</td>
<td>1.131</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1.393</td>
<td>1.465</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0.643</td>
<td>0.362</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1.313</td>
<td>0.612</td>
</tr>
<tr>
<td>Male gender (vs. females)</td>
<td>1.222</td>
<td>1.332</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.959</td>
<td>0.614</td>
</tr>
</tbody>
</table>

#### Antidiabetic drugs

<table>
<thead>
<tr>
<th>Antidiabetic drugs</th>
<th>Without biochemistry</th>
<th>With biochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>0.787</td>
<td>0.653</td>
</tr>
<tr>
<td>Biguanides</td>
<td>0.623</td>
<td>0.543</td>
</tr>
<tr>
<td>β-cell stimulating</td>
<td>0.882</td>
<td>0.872</td>
</tr>
<tr>
<td>Glitazones</td>
<td>1.177</td>
<td>1.008</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.892</td>
<td>1.245</td>
</tr>
<tr>
<td>GLP-1: liraglutide</td>
<td>0.482</td>
<td>0.318</td>
</tr>
<tr>
<td>GLP-1: exenatide</td>
<td>1.722</td>
<td>2.300</td>
</tr>
</tbody>
</table>

---

*Risk of CVD*
SGLT-2 Inhibitors

A Primary Outcome

Hazard ratio, 0.86 (95% CI, 0.74–0.99)
P=0.04 for superiority

No. at Risk
Empagliflozin
Placebo
2333 2256 2194 2112 1875 1380 1161 741 166

B Death from Cardiovascular Causes

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

No. at Risk
Empagliflozin
Placebo
2333 2303 2280 2243 2012 1503 1281 825 177

C Death from Any Cause

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

No. at Risk
Empagliflozin
Placebo
2333 2303 2280 2243 2012 1503 1281 825 177

D Hospitalization for Heart Failure

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

No. at Risk
Empagliflozin
Placebo
2333 2271 2226 2173 1932 1424 1202 775 168

SGLT2 Inhibitor Decreases the Risk of CV Composite Endpoint

Dapagliflozin

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with events</th>
<th>Favors</th>
<th>CTRL</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>Dapagliflozin N=5936, CTRL N=3403</td>
<td>Dapagliflozin 0.70 (0.36, 1.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>Dapagliflozin 20/3825, CTRL 18/2200</td>
<td>Dapagliflozin 0.70 (0.36, 1.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>Dapagliflozin N=5936, CTRL N=3403</td>
<td>Dapagliflozin 0.57 (0.34, 0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>Dapagliflozin 30/5244, CTRL 33/3014</td>
<td>Dapagliflozin 0.57 (0.34, 0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>Dapagliflozin N=5936, CTRL N=3403</td>
<td>Dapagliflozin 1.00 (0.54, 1.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>Dapagliflozin 25/4227, CTRL 18/2412</td>
<td>Dapagliflozin 1.00 (0.54, 1.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>Dapagliflozin N=5936, CTRL N=3403</td>
<td>Dapagliflozin 0.87 (0.48, 1.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>Dapagliflozin 26/4592, CTRL 20/2697</td>
<td>Dapagliflozin 0.87 (0.48, 1.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unplanned coronary revascularisation</td>
<td>Dapagliflozin N=5936, CTRL N=3403</td>
<td>Dapagliflozin 0.73 (0.50, 1.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unplanned coronary revascularisation</td>
<td>Dapagliflozin 58/5525, CTRL 55/3153</td>
<td>Dapagliflozin 0.73 (0.50, 1.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>Dapagliflozin N=5936, CTRL N=3403</td>
<td>Dapagliflozin 0.36 (0.16, 0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>Dapagliflozin 10/2576, CTRL 16/1780</td>
<td>Dapagliflozin 0.36 (0.16, 0.84)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Potential Pathways Associated with CV Effects of SGLT-2 Inhibitors

Silvio E Inzucchi et al. Diabetes and Vascular Disease Research 2015
Does Glucose Lowering Prevent CVD in T2D Patients?
Preliminary Consideration: in examining the effect of currently approved glucose-lowering drugs on established CV mortality/morbidity

- The vast majority of epidemiologic studies and clinical trials is based on MACE as the outcome, which includes CV death, non-fatal MI, and non-fatal stroke (sometimes, also unstable angina requiring hospitalization, amputation, and revascularization procedures are included).

→ tip of the iceberg of a gamut of manifestations of CVD including the m/c cardiac problem in T2DM, i.e. heart failure and CKD, a potent CVD predictor

- Therefore, while MACE is a practical and well-established ‘hard’ endpoint, its ability to track the natural history of CVD is limited.

![CVD endpoints table]

<table>
<thead>
<tr>
<th>‘soft’</th>
<th>‘hard’</th>
<th>‘canonical’</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>Heart failure</td>
<td>Cardiac death</td>
</tr>
<tr>
<td>Stable angina</td>
<td>Unstable angina</td>
<td>Non-fatal MI</td>
</tr>
<tr>
<td>Inducible angina</td>
<td>Revase.</td>
<td>Non-fatal stroke</td>
</tr>
<tr>
<td>ECG ischaemia</td>
<td>Amputation</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrill. ↓ ABI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ferrannini E, DeFronzo RA. Eur Heart J 2015;36:2288–2296
Targeting prolyl-isomerase Pin1 prevents mitochondrial oxidative stress and vascular dysfunction: insights in patients with diabetes

Francesco Paneni¹,²,³, Sarah Costantino¹,², Lorenzo Castello⁴, Rodolfo Battista⁵, Giuliana Capretti⁴, Sergio Chiandotto⁴, Domenico D’Amario⁶, Giuseppe Scavone⁷, Angelo Villano⁶, Alessandra Rustighi⁸, Filippo Crea⁶, Dario Pitocco⁷, Gaetano Lanza⁶, Massimo Volpe³,⁴, Giannino Del Sal⁸, Thomas F. Lüscher¹, and Francesco Cosentino¹,²

¹Cardiology and Cardiovascular Research, Institute of Physiology and University Hospital, Zürich, Switzerland; ²Cardiology Unit, Department of Medicine, Karolinska University Hospital, Solna, 171 84 Stockholm, Sweden; ³RCCS Neurorad, Pozzilli, Italy; ⁴Cardiology, Department of Clinical and Molecular Medicine, University of Rome ‘Sapienza’, Rome, Italy; ⁵Internal Medicine Unit, Civil Hospital, Sora, Italy; ⁶Department of Cardiovascular Medicine, Catholic University, Rome, Italy; ⁷Diabetes Care Unit, Internal Medicine, Catholic University, Rome, Italy; and ⁸Laboratorio Nazionale CIB, AREA Science Park and Department of Life Sciences, University of Trieste, Trieste, Italy

Received 14 January 2014; revised 12 March 2014; accepted 31 March 2014; online publish-ahead-of-print 6 May 2014

This paper was handled by Stephanie Dimmeler (Prof. Johan-Wolfgang Goethe Universität, dimmeler@em.uni-frankfurt.de).

Aim
Diabetes is a major driver of cardiovascular disease, but the underlying mechanisms remain elusive. Prolyl-isomerase Pin1 recognizes specific peptide bonds and modulates function of proteins altering cellular homeostasis. The present study investigates Pin1 role in diabetes-induced vascular disease.

Methods and results
In human aortic endothelial cells (HAECs) exposed to high glucose, up-regulation of Pin1-induced mitochondrial translocation of pro-oxidant adaptor p66Shc and subsequent organelle disruption. In this setting, Pin1 recognizes Ser-116 inhibitory phosphorylation of endothelial nitric oxide synthase (eNOS) leading to eNOS– caveolin-1 interaction and reduced NO availability. Pin1 also mediates hyperglycaemia-induced nuclear translocation of NF-κB p65, triggering VCAM-1, ICAM-1, and MCP-1 expression. Indeed, gene silencing of Pin1 in HAECs suppressed p66Shc-dependent ROS production, restored NO release and blunted NF-κB p65 nuclear translocation. Consistently, diabetic Pin1−/− mice were protected against mitochondrial oxidative stress, endothelial dysfunction, and vascular inflammation. Increased expression and activity of Pin1 were also found in peripheral blood monocytes isolated from diabetic patients when compared with age-matched healthy controls. Interestingly, enough, Pin1 up-regulation was associated with impaired flow-mediated dilation, increased urinary 8-iso-prostaglandin F₂α, and plasma levels of adhesion molecules.

Conclusions
Pin1 drives diabetic vascular disease by causing mitochondrial oxidative stress, eNOS dysregulation as well as NF-κB-induced inflammation. These findings provide molecular insights for novel mechanism-based therapeutic strategies in patients with diabetes.
Hyperglycaemia-induced Pin1 up-regulation mediates mitochondrial oxidative stress in human aortic endothelial cells

Pin1 expression and activity are increased in diabetes and correlate with glycaemic markers

Pin1

- In hyperglycemia, Pin1 negatively modulates endothelial nitric oxide synthase (eNOS) activity via isomerization of the phosphorylated Ser-116 residue → inhibits endothelial nitric oxide synthase activity
- Pin1 mediates hyperglycemia-induced up-regulation of adhesion molecules
- Diabetic Pin1−/− mice are protected against endothelial dysfunction
- Diabetic mice lacking Pin1 were protected against vascular inflammation

“Cardiovascular Outcome Trials”

to gauze magnitude of vascular protection potentially afforded by glucose-lowering agents
A sustained $\sim 1\%$ decrement in HbA1c can be expected to reduce coronary risk by 10–15%
# (2) Intensive Glycemic Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UKPDS</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>↓</td>
<td>←</td>
<td>↓</td>
</tr>
<tr>
<td><strong>DCCT/EDIC</strong>&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>↓</td>
<td>←</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Action to Control Cardiovascular Risk in Diabetes (ACCORD)</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Not available</td>
<td>←</td>
<td>↑</td>
</tr>
<tr>
<td><strong>ADVANCE</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td><strong>Veterans Affairs Diabetes Trial (VADT)</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
</tbody>
</table>

4. Hypoglycaemia also occurred frequently in ORIGIN (42% in glargine vs 14% in standard therapy groups)

The possibility that high doses of insulin (>80–100 units/day) in long-standing T2DM patients may accelerate the progression of vascular damage cannot be conclusively ruled out

Ferrannini E, DeFronzo RA. Eur Heart J 2015;36:2288–2296
Antidiabetic agents: Cardiovascular Outcome

- Glucose lowering
- BP lowering
- Weight
- Hypoglycemia
- Pleiotropic effects beyond the glucose-lowering effect
- Others: lipid…..

### Nonglycemic Effects of Diabetes Medications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effects on Weight</th>
<th>Effects on Lipids</th>
<th>Lowered Blood Pressure</th>
<th>Improved Endothelial Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Increase</td>
<td>Mild</td>
<td>No</td>
<td>+/-</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Increase</td>
<td>Negligible</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Metformin</td>
<td>Neutral</td>
<td>Moderate</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>TZDs</td>
<td>Increase(^a)</td>
<td>Large(^b)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>(\alpha)-Glucosidase inhibitors</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Decrease</td>
<td>Large</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>Neutral</td>
<td>Moderate</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Decrease</td>
<td>Large</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
# Cardiovascular Outcome Trials in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4i</td>
<td>Saxagliptin</td>
<td>Alogliptin</td>
<td>Sitagliptin</td>
<td>Linagliptin</td>
<td>Linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Sulfonylurea</td>
<td>Placebo</td>
</tr>
<tr>
<td>Number</td>
<td>16 500</td>
<td>5400</td>
<td>14 000</td>
<td>6000</td>
<td>8300</td>
</tr>
<tr>
<td>Results</td>
<td>Ref. 213</td>
<td>Ref. 215</td>
<td>ADA 2015</td>
<td>2018</td>
<td>2018</td>
</tr>
<tr>
<td>GLP-1RA</td>
<td>Liraglutide</td>
<td>Lixisenatide</td>
<td>Semaglutide</td>
<td>Exenatide LR</td>
<td>Dulaglutide</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Number</td>
<td>8754</td>
<td>6000</td>
<td>6000</td>
<td>9500</td>
<td>9600</td>
</tr>
<tr>
<td>Results</td>
<td>2018</td>
<td>ADA 2015</td>
<td>2016</td>
<td>2018</td>
<td>2018</td>
</tr>
<tr>
<td>SGLT2i</td>
<td>Empagliflozin</td>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
<td>Ertugliflozin</td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Number</td>
<td>7300</td>
<td>7000</td>
<td>22 200</td>
<td>3900</td>
<td></td>
</tr>
</tbody>
</table>

Ferrannini E, DeFronzo RA. Eur Heart J 2015;36:2288–2296
Suggestion: Re-Assessment

- 2형 당뇨병 치료에서 혈당 조절을 개선함으로서 심근경색, 심부전 같은 심혈관질환을 예방하거나 호전시킨다는 증거는 아직 불충분하다.

- 체중증가 및 심장돌연사 등을 유발할 수 있는 저혈당의 부작용을 최소화하면서, A1c 감소를 최대화하는 최근의 새로운 약물들로, 임상 연구를 장기간 하여 심혈관질환 영향에 대한 새로운 평가를 할 필요가 있었다.
Thanks.........
Back Up
UGDP phenformin-placebo cumulative mortality

Genell L. Knatterud. JAMA 1971;217(6):777-784
UGDP insulin-placebo cumulative mortality

a) All cause mortality mortality

b) Cardiovascular


### Drug Therapies

<table>
<thead>
<tr>
<th>Drug (class)</th>
<th>N</th>
<th>Completion date</th>
<th>Patients</th>
<th>Primary endpoint</th>
<th>Results based on primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP4 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVOR (saxagliptin)</td>
<td>16,492</td>
<td>May 2013</td>
<td>History of established CVD or multiple risk factors for CVD</td>
<td>Composite of CV death, non-fatal MI or non-fatal stroke*</td>
<td>✓</td>
</tr>
<tr>
<td>EXAMINE (alogliptin)</td>
<td>5380</td>
<td>June 2013</td>
<td>History of ACS within 15–90 days of randomisation</td>
<td>Composite of CV death, non-fatal MI or non-fatal stroke</td>
<td>✓</td>
</tr>
<tr>
<td>TECOS (sitagliptin)</td>
<td>14,671</td>
<td>March 2015</td>
<td>Pre-existing CVD followed for a median of 3 years</td>
<td>Composite of CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina</td>
<td>✓</td>
</tr>
</tbody>
</table>

**GLP-1 RAs**

<table>
<thead>
<tr>
<th>Drug (class)</th>
<th>N</th>
<th>Completion date</th>
<th>Patients</th>
<th>Primary endpoint</th>
<th>Results based on primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA (lixisenatide)</td>
<td>&gt;6000</td>
<td>February 2015</td>
<td>Patients with a recent history of ACS events</td>
<td>Composite of CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina</td>
<td>✓</td>
</tr>
</tbody>
</table>

**SGLT2 inhibitors**

<table>
<thead>
<tr>
<th>Drug (class)</th>
<th>N</th>
<th>Completion date</th>
<th>Patients</th>
<th>Primary endpoint</th>
<th>Results based on primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG (empagliflozin)</td>
<td>7020</td>
<td>April 2015</td>
<td>Established CVD</td>
<td>First occurrence of CV death, non-fatal MI or non-fatal stroke</td>
<td>✓ □</td>
</tr>
</tbody>
</table>

- Other major CV outcomes trials are currently ongoing, with results due in coming years

---

* One component of the secondary composite endpoint, hospitalisation for heart failure, occurred at a greater rate in the saxagliptin group compared with the placebo group, with nominal statistical significance favouring (3.5% vs 2.8%; p=0.007).

ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; SOC, standard of care.

포시가는 CVD 질환을 가지고 있는 환자, 그렇지 않은 환자 모두에게 있어서 위약군 대비 Cardiovascular Events의 발생률을 증가시키지 않았으며 감소시키는 경향성을 보였습니다.

치료 개시 후 처음 30일 동안 CV events의 위험 증가가 없었습니다.

Kaplan-Meier estimate for primary endpoint (MACE + UA), all Phase IIb and III pool

A meta-analysis of 21 Phase IIb/III studies in which 34.4% of subjects had a history of CVD (excluding hypertension) at baseline and 67.9% had hypertension. 1 Studies that did not have at least one positively adjudicated event were excluded from analysis.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; UA, unstable angina.
require evidence of cost-effectiveness. The provision of this evidence will require data from adequately powered studies of the compound able to define the effects on cardiovascular and other important outcomes. The CANVAS trial will make an important contribution by precisely and reliably defining the effects of the compound on key biomarkers as well as documenting the safety profile in this high-risk patient group. Evidence for protection against major cardiovascular events will, however, need to be obtained from a future study.

The exploration of SGLT2 inhibitors as another strategy for the management of diabetes reflects the suboptimal control of hyperglycemia and vascular risks for many patients with diabetes. Data from multiple studies of canagliflozin and related compounds show considerable promise for inhibition of SGLT2 as a novel therapeutic strategy in this large group of patients. Not only has this approach demonstrated significant effects on HbA1c control, but it has also been shown that these drugs reduce body weight as well as lower blood pressure. The combined beneficial effects on glycemia, blood pressure, and weight could ultimately translate into reductions in the risks of macrovascular and microvascular complications.
Anti-diabetic agents impact on cardiovascular morbidity and mortality

Patients with T2DM have an inherent, elevated risk for cardiovascular disease that likely begins well in advance of a diagnosis of chronic hyperglycaemia. Data describing cardiovascular benefits with metformin are encouraging, with studies showing reductions in any diabetes-related endpoint, diabetes-related death, and all-cause mortality. Evidence for the safety of sulfonylurea therapy is still conflicting, but compared with metformin therapy, sulfonylurea use has been associated with an increased risk of developing heart failure, especially at higher doses. Meglitinide therapy with repaglinide has been shown to decrease cardiovascular markers including markers of inflammation, platelet activation, and lipid parameters, although less effectively than metformin. The TZD pioglitazone has also been shown to lower the composite of all-cause mortality, non-fatal MI, and stroke in patients with T2DM at high risk for macrovascular events. Thiazolidinediones use, primarily rosiglitazone, is contraindicated in patients with heart failure, as it has been shown to increase the risk of heart failure. Incretin-based therapies including GLP-1 agonists and DPP-4 inhibitors have potential positive effects on the cardiovascular system. The GLP-1 analogue exenatide is associated with a significantly decreased risk of CVD and CVD-related hospitalizations in patients with T2DM. Sodium glucose cotransporter 2 inhibitors are novel oral glucose-lowering agents though, the potential for cardiovascular benefits from the SGLT2 inhibitors remains to be established. There is ample evidence also to suggest that a multifactorial approach to diabetes care, which targets glycaemic control in addition to treatment of hypertension and dyslipidaemia, will significantly decrease cardiovascular risk. Cardiovascular risk reduction in diabetes, rather than focusing upon glycaemic management alone, should aim to reduce plasma glucose in addition to cholesterol and BP.
Efficacy | Lipid Profile (Add-on Study)

Change in Fasting Lipid Parameters from Baseline at 24wk (FAS)

- **Fasting total cholesterol (mg/dL)**
- **Fasting TG (mg/dL)**
- **Fasting LDL (mg/dL)**

- **Gemigliptin 50 mg qd + Metformin (N=122)**
- **Sitagliptin 100 mg qd + Metformin (N=117)**

* P < 0.05 vs. baseline
** P = 0.0004 vs. baseline
*** P < 0.0001 vs. baseline
AACE/ACE guideline recommendations for dual therapy:¹*†

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>ADA/EASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 inhibitor</td>
<td>AACE/ACE</td>
</tr>
<tr>
<td>DPP4 inhibitor</td>
<td>Preference should be given to drugs that:¹,²</td>
</tr>
<tr>
<td>TZD</td>
<td>• Minimise side effects, especially hypoglycaemia</td>
</tr>
<tr>
<td>Basal insulin</td>
<td>• Are associated with weight loss or weight neutrality</td>
</tr>
<tr>
<td>SU</td>
<td>Drug choice should take into account patient preferences</td>
</tr>
</tbody>
</table>

¹As add on to metformin therapy; ¹Order of medications listed represents a suggested hierarchy of usage. AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; DPP4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose co-transporter-2; SU, sulphonylurea; TZD, thiazolidinedione.

## Weight & BP Issues

<table>
<thead>
<tr>
<th></th>
<th>HbA₁c</th>
<th>Weight</th>
<th>BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>↓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Insulin</td>
<td>↓</td>
<td>↑</td>
<td>—</td>
</tr>
<tr>
<td>SUs</td>
<td>↓</td>
<td>↑</td>
<td>—</td>
</tr>
<tr>
<td>TZDs</td>
<td>↓</td>
<td>↑</td>
<td>—</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>↓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

# Nonglycemic Effects of Diabetes Medications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effects on Weight</th>
<th>Effects on Lipids</th>
<th>Lowered Blood Pressure</th>
<th>Improved Endothelial Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Increase</td>
<td>Mild</td>
<td>No</td>
<td>+/-</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Increase</td>
<td>Negligible</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Metformin</td>
<td>Neutral</td>
<td>Moderate</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>TZDs</td>
<td>Increase</td>
<td>Large</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Decrease</td>
<td>Large</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>Neutral</td>
<td>Moderate</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Decrease</td>
<td>Large</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Silvio E Inzucchi et al. Diabetes and Vascular Disease Research 2015
Mayo Clinic/Endocrinology News Vol.6, No.4, 2011
Elevated risk of cardiovascular disease before clinical diagnosis of type 2 diabetes

Hyperglycemia as a cardiovascular risk factor

Incidence of IGT & new-onset diabetes in pts with AMI who previously were not known to have diabetes

IGT increases the risk of CHD mortality: Paris Prospective Study 10-year follow-up
Intensive blood glucose control

- Intensive blood glucose control reduces microvascular complications, but the protective effect on macrovascular disease and mortality remains disappointing.

- The beneficial effect of lowering blood glucose to very low levels is controversial as one of the major problems being the increase in the number of hypoglycemic events.

Acarbose Treatment and the Risk of CV Disease in Patients With IGT: The STOP-NIDDM Trial

✓ Limitation: the total number of events (n = 47) was small and the study was not powered to draw any conclusion about CVD protection.

Reduction of HbA$_1$c (1%)

All-cause mortality  Death due to diabetes  Any endpoint related to diabetes  Fatal and non-fatal MI  Heart failure  Fatal and non-fatal stroke  Microvascular endpoints

<table>
<thead>
<tr>
<th>Risk reduction (%) over 10 years</th>
<th>0</th>
<th>−5</th>
<th>−10</th>
<th>−15</th>
<th>−20</th>
<th>−25</th>
<th>−30</th>
<th>−35</th>
<th>−40</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>−14 (95% CI −9 to −19)</td>
<td>−21 (95% CI −15 to −27)</td>
<td>−21 (95% CI −17 to −24)</td>
<td>−14 (95% CI −9 to −19)</td>
<td>−16 (95% CI −1 to −26)</td>
<td>−12 (95% CI −1 to −21)</td>
<td>−37 (95% CI −33 to −41)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Incidence (per 1,000) of Major Diabetes Complications, by age

2009

Jeffrey B. Halter et al. Diabetes 2014;63:2578-2589
## Occurrence of Hypoglycemia during DPP-4i Tx

<table>
<thead>
<tr>
<th>DPP - 4 inhibitors</th>
<th>Study</th>
<th>Any hypoglycemia (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>investigational drug / comparator</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Scott, R., Loeys, T. et al. (2008)</td>
<td>1 / 1</td>
</tr>
<tr>
<td></td>
<td>Goldstein, B. J., Feinglos, M. N. et al. (2007)</td>
<td>1 / 1</td>
</tr>
<tr>
<td></td>
<td>Charbonnel, B., Karasik, A. et al. (2006)</td>
<td>6 / 5</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Rosenstock, J., Sankoh, S. et al. (2008)</td>
<td>0 / 0</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Schweizer, A., Couturier, A. et al. (2007)</td>
<td>2 / 1</td>
</tr>
<tr>
<td></td>
<td>Bolli, G., Dotta, F. et al. (2008)</td>
<td>1 / 0</td>
</tr>
<tr>
<td></td>
<td>Bosi, E., Camisasca, R. P. et al. (2007)</td>
<td>1 / 1</td>
</tr>
<tr>
<td></td>
<td>Rosenstock, J., Baron, M. A. et al. (2007)</td>
<td>1 / 0</td>
</tr>
</tbody>
</table>
**Effect on postprandial lipid metabolism**

Incretin therapies

Schwartz et al., Atherosclerosis 2010, 212(1):217-222
Insulin Resistance

Genetic & Environmental factors

**Insulin resistance**

- Hyperglycemia/IGT
- Dyslipidemia
- Hypertension
- Endothelial dysfunction/Microalbuminuria
- Hypofibrinolysis
- Inflammation

Atherosclerosis

Adapted from McFarlane S, *et al*. *J Clin Endocrinol Metab* 2001; 86:713–718
Incidence of Coronary Heart Disease by HbA1c Levels

3.5-year follow-up study of 1,298 Finnish diabetics (65-75 yrs)

Hyperglycemia as a cardiovascular risk factor
Hazard Ratios for Coronary Heart Disease:
by long-term average concentrations of FBG, cholesterol & systolic BP