Diabetes Drugs and Cardiac Disease

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Disclosures

None
Written Comments

• As I have said every time you give a talk – no reason to give anything except metformin and a sulfonylurea
• That new ACP review really messed up
• Thanks a lot - - DM meds decrease CVD, increase CVD -- what am I supposed to do now
• Too many slides

DM and Cardiovascular DX

Historically
• 75% of adults with DM have HTN
• DM
  – 2-4 x increased risk of stroke
  – 2 x increase risk for CVD death

Recently
• With all population, decreasing hospitalization for CVD
• Still 2-4 times nondiabetes (largest difference in CHF)
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.

CONCLUSIONS

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

Meta-analysis of MI and Death risk with rosiglitazone

n = 15,560 on rosiglitazone; n = 12,283 on comparator drug or placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of events/Total no. (%)</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>44/10,280 (0.43)</td>
<td>1.45 (0.88–2.39)</td>
<td>0.15</td>
</tr>
<tr>
<td>DREAM</td>
<td>15/2635 (0.57)</td>
<td>1.65 (0.74–3.68)</td>
<td>0.22</td>
</tr>
<tr>
<td>ADOPT</td>
<td>27/1456 (1.85)</td>
<td>1.33 (0.80–2.21)</td>
<td>0.27</td>
</tr>
<tr>
<td>Overall</td>
<td>86</td>
<td>1.43 (1.03–1.98)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

86/14371 (.60%)  72/11634 (0.62%)
Relative Risk = 86/72 = 1.19
Absolute Risk = -.02%
Comparison of CV risk observed in meta-analyses of RSG and PIO

Excess cases of serious CV events attributable to RSG use over the range of expected background rates in diabetic patients, 1999-2006

<table>
<thead>
<tr>
<th></th>
<th>RR=1.2</th>
<th>RR=1.4</th>
<th>RR=1.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death + nonfatal AMI</td>
<td>41K (20K-67K)</td>
<td>83K (39K-133K)</td>
<td>129K (60K-219K)</td>
</tr>
<tr>
<td>CV death + nonfatal AMI + stroke</td>
<td>66K (31K-110K)</td>
<td>131K (62K-210K)</td>
<td>205K (95K-338K)</td>
</tr>
</tbody>
</table>

1 Point estimate (± 1 SD) estimated at the median background rate
PANIC

Senate report links diabetes drug Avandia to heart attacks

February 20, 2010 4:39 p.m. EST

(CNN) -- The diabetes drug Avandia is linked with tens of thousands of heart attacks, and drugmaker GlaxoSmithKline knew of the risks for years but worked to keep them from the public, according to a Senate committee report released Saturday.

The 334-page report by the Senate Finance Committee also criticized the Food and Drug Administration, saying that the federal agency that regulates food, tobacco and medications overlooked or overrode safety concerns found...
ADVANCE: Action in Diabetes and Vascular Disease

Goal: To examine effects of reducing HgA1c to < 6.5% and routine use of fixed dose ACE-thiazide combination in >55 y/o Type 2 DM

- 11,140 Enrollees
- 60% male 40% female
- Mean age 66
- 50% macrovascular dx
- 10% microvascular

Baseline HgA1c: 7.51%
“standard”: 7.30%
Intensive: 6.53%

ADVANCE: Relative Effects of Glucose-Control Strategy on All Prespecified Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intensive Control (N=5571)</th>
<th>Standard Control (N=5569)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Relative Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary End Points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined major macrovascular and microvascular events</td>
<td>1009 (18.1)</td>
<td>1116 (20.0)</td>
<td></td>
<td>10 (4 to 18)</td>
</tr>
<tr>
<td>Major macrovascular events</td>
<td>557 (10.0)</td>
<td>590 (10.6)</td>
<td></td>
<td>6 (-6 to 16)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>153 (2.7)</td>
<td>156 (2.8)</td>
<td></td>
<td>2 (-13 to 22)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>114 (3.8)</td>
<td>209 (3.8)</td>
<td></td>
<td>-2 (-14 to 15)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>253 (4.5)</td>
<td>289 (5.2)</td>
<td></td>
<td>12 (-4 to 26)</td>
</tr>
<tr>
<td>Major microvascular events</td>
<td>526 (9.4)</td>
<td>605 (10.9)</td>
<td></td>
<td>14 (3 to 23)</td>
</tr>
<tr>
<td>New or worsening nephropathy</td>
<td>190 (4.1)</td>
<td>292 (5.2)</td>
<td></td>
<td>21 (7 to 34)</td>
</tr>
<tr>
<td>New or worsening retinopathy</td>
<td>332 (6.0)</td>
<td>349 (6.3)</td>
<td></td>
<td>5 (-10 to 18)</td>
</tr>
</tbody>
</table>

ACCORD: Action to Control Cardiovascular Risk in Diabetes

- 10,251 Enrollees
- 60% male 40% female
- Mean age 62.2
- Baseline HgA1c 8.1%
- BMI - 32
- 30% macrovascular dx
- Duration DM: 10 years
- Majority of intensive group on 3-5 oral agents plus insulin
- Hypoglycemia 3 times greater in intensive group

Primary and Secondary Outcomes

Table 4. Primary and Secondary Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy (N=5128)</th>
<th>Standard Therapy (N=5123)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td>% per yr</td>
<td>no. of patients (%)</td>
<td>% per yr</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>352 (6.9)</td>
<td>2.11</td>
<td>371 (7.2)</td>
<td>2.29</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cause</td>
<td>257 (5.0)</td>
<td>1.41</td>
<td>203 (4.0)</td>
<td>1.14</td>
</tr>
<tr>
<td>Cardiovascular causes</td>
<td>133 (2.6)</td>
<td>0.79</td>
<td>94 (1.8)</td>
<td>0.56</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>186 (3.6)</td>
<td>1.11</td>
<td>235 (4.6)</td>
<td>1.45</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>67 (1.3)</td>
<td>0.39</td>
<td>61 (1.2)</td>
<td>0.37</td>
</tr>
<tr>
<td>Fatal or nonfatal congestive heart failure</td>
<td>152 (3.0)</td>
<td>0.90</td>
<td>124 (2.4)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* The primary outcome was the first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes. Data within categories are not mutually exclusive, and patients who were classified as having more than one possible cause of death are listed in the relevant categories. Hazard ratios are for the intensive-therapy group as compared with the standard-therapy group.

† This condition was a component of the outcome of fatal cardiovascular disease.

‡ Additional details are provided in the Supplementary Appendix.
ACCORD: Hazard Ratios for the Primary Outcome and Death from Any Cause in Prespecified Subgroups


Epidemiologic Relationships Between A1C and All-Cause Mortality During a Median 3.4-Year Follow-up of Glycemic Treatment in the ACCORD Trial

Diabetes Care May 2010 vol. 33 no. 5 983-990
VADT - Veterans Administration Diabetes Trial

- 1,742 enrollees
- 97% male
- Mean age 60.4

- BMI 31.3
- Majority had multiple CV risk factors

- 72% HTN
- 40% macrovascular dx
- 62% retinopathy
- 43% neuropathy

Table 1. Cardiovascular Risk Factor Profile during VADT

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Baseline</th>
<th>Intensive</th>
<th>Year 6</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Standard</td>
<td></td>
<td>Standard</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.4</td>
<td>9.4</td>
<td>6.9</td>
<td>8.4</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>132/76</td>
<td>132/76</td>
<td>126/69</td>
<td>126/68</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>103</td>
<td>104</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>34</td>
<td>34</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>160</td>
<td>162</td>
<td>124</td>
<td>124</td>
</tr>
<tr>
<td>Anti-platelet agent use (%)</td>
<td>76</td>
<td>76</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>57</td>
<td>59</td>
<td>83</td>
<td>86</td>
</tr>
</tbody>
</table>

- Primary Endpoint: NO DIFFERENCE IN CARDIOVASCULAR DISEASE OUTCOMES
  - Standard: 29.3% (predicted – 40%)
  - Intensive: 27.4% (predicted – 31.6%)
VADT - Veterans Administration Diabetes Trial

- **When duration of DM factored in:**
  - Intensive glycemic control showed benefit
  - Benefit declines until about 12-15 years of disease

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**Deaths Halt Part of Diabetes Study**
Scientists Fear Heart Attacks, Strokes Were Tied to Treatment

*By Rob Stein*
*Washington Post Staff Writer*
*Thursday, February 7, 2008*

Aggressively driving blood sugar levels as close to normal as possible in high-risk diabetes patients appears to increase the risk of dying from a heart attack or stroke, according to a major government study that stunned and disappointed experts.

The startling discovery, announced yesterday, prompted federal health officials to immediately halt one part of the large trial so thousands of the Type 2 diabetes patients in the study could switch to less-intensive treatment.
Safety Studies for Diabetes Medications

• FDA change in 2008 regarding expectation of drug studies for new diabetic medications to ensure there is no unacceptable cardiovascular risk

• Prompted by
  – Recommendations of the 2008 Endocrinologic and Metabolic Drugs Advisory Committee
  – High cardiovascular risk in patients with diabetes
  – Safety issues with
    - Rosiglitazone
    - Muraglitazar
    - Intense glucose lowering in the ACCORD trial

Safety Studies for Diabetes Medications

• FDA expectations
  – Independent cardiovascular endpoints committee
  – Evaluation of
    - Cardiovascular mortality
    - Stroke
    - Myocardial infarction
  – Design studies so can be easily and clearly analyzed via a meta-analysis at study completion
  – Should include patients with high cardiovascular risk
    - Elderly
    - Renal impairment
    - Advanced cardiovascular disease
  – Pre and post-marketing trials may be required for new drugs depending upon estimated risk of pre-marketing studies
Completed and ongoing Cardiovascular Outcome Trials (CVOT)

- Most phase 4 trials
  - Required >600 primary end points
  - 3 point MACE* (CV death, nonfatal MI, nonfatal stroke)
  - 4 point MACE (added hospitalization for unstable angina)
  - 5 point MACE (hosp for angina or CHF)
- Glycemic equipoise (hence difference in overall meds and sl higher gluoses in placebo groups)

*Major Adverse Cardiac Event

William T. Cefalu et al. Dia Care 2018;41:14-31
Heart Failure

- Kaiser (older 2001 Diabetes Care study):
  - Type 2 DM <75: 3 fold higher prevalence
  - Type 2 DM 75-84: 2 fold higher prevalence

- Generally between 10-30% of patients in clinical trials.

- Associated with higher HbA1c

- In summary
  - High HbA1c levels in T2DM and HF are consistently associated with higher mortality.
  - HbA1c levels can be associated with good outcomes (at least in a clinical trial cohort), but can be associated with worse outcomes (in population-based studies and those with very advanced HF).

Heart Failure

- close relationship between DM and HF
- HF was the second most common initial presentation of CV disease, after peripheral artery disease
  - (large observational study of patients with DM)
- among patients hospitalized for HF, the prevalence of DM may exceed 40%
Metformin
Effect of Metformin-Containing Antidiabetic Regimens on All-cause Mortality in Veterans With Type 2 Diabetes Mellitus

- Decreased Hazard Ratio for all cause mortality for patients on metformin
  - vs no metformin – 0.77 (p<0.01)

- Increased Hazard Ratio for all cause mortality for patients on insulin:
  - 1.62 (p<0.001)

- Decreased Hazard Ratio for all cause mortality for patients on metformin and insulin vs insulin
  - 0.62 (p<0.04)


Metformin and CHF

- At 2 years in patients with DM and CHF

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>No Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>15.8%</td>
<td>25.5%*</td>
</tr>
<tr>
<td>Hospitalized (CHF)</td>
<td>12%</td>
<td>16%*</td>
</tr>
<tr>
<td>Hospitalized (any cause)</td>
<td>41%</td>
<td>48%*</td>
</tr>
</tbody>
</table>

*P<0.001

Circ Heart Fail. 2011 Jan 1;4(1):53-8
Cumulative incidence of heart failure hospitalization or cardiovascular death over time.

Adjusted hazard ratio and 95% CIs of subgroups.
Metformin CVD

• Meta analysis of 40 trials
  – compared with any other treatment or placebo
  – metformin was associated with a statistically significant decrease in cardiovascular mortality (OR, 0.74; 95% CI, 0.62-0.89).

Reevaluation

Another pooled data analysis-13 trials
- difficult to isolate metformin effects
- uncertainty about whether metformin reduces risk of cardiovascular disease as first line drug
- Uncertainty mainly due to absence of evidence
- it is unlikely that a definitive placebo-controlled cardiovascular endpoint trial among people with diabetes will be forthcoming

Diabetologia. 2017; 60(9): 1620–1629.

Sulfonylureas
Mortality and Cardiovascular Risk of Sulfonylureas in South Asian, Chinese and Other Canadians with Diabetes

- population-based cohort of adults 35 years of age or older who had diabetes and had been diagnosed between April 2004 and March 2014
- administrative databases from British Columbia
- The primary outcome was time to death from any cause or from a major cardiovascular event (MACE) with sulfonylurea treatment within each ethnicity. Propensity score modelling was applied using inverse probability of treatment weights. Results were stratified by agent and adjusted for age, sex, comorbidities, income and other medications

Mortality and MACEs were higher in other Canadian patients for whom sulfonylureas had been prescribed

- (adjusted HR (hazard ratio)= 2.0; 95% confidence interval 1.9 to 2.2; and HR = 1.9, 1.7 to 2.2).

Among Chinese and South Asian patients who had been prescribed sulfonylureas

- mortality (HR = 2.6, 2.0 to 3.5; and HR = 2.4, 1.7 to 3.4, respectively)
- MACEs (HR = 2.3; 1.4 to 4.0; and HR = 2.0, 1.2 to 3.2, respectively)

Conclusions:
Considering the widespread use of sulfonylureas, there is a significant signal for increased mortality in all patients
In particular, increased mortality and MACEs were observed in South Asian and Chinese patients.

Glibenclamide-related excess in total and cardiovascular mortality risks: Data from large Ukrainian observational cohort study

All-cause mortality among:
(1) glimepiride-treated
(2) gliclazide-treated
(3) glibenclamide-treated (glyburide)

Retrospective observational cohort studies of primary care-based diabetes register in Ukraine. ($n = 50,341$),

Diabetes Research and Clinical Practice 2009. 86:247-253
Sulfonylureas as Initial Treatment for Type 2 Diabetes and the Risk of Severe Hypoglycemia

Cardiac Effects of Sulfonylurea Related Hypoglycemia

- 30 type 2 DM patients on sulfonylureas
- Mean HbA1c 6.9
- 48 hour CGM
- Hypoglycemia (<63 mg/dl for >20 minutes) was detected in 9 of 30 subjects
- Episodes were typically nocturnal (67%) and asymptomatic (73%).
- Hypoglycemia associated QTc prolongation was seen in five of nine subjects with a large variation in individual response.
- Higher QT dynamicity, a poor prognostic factor in cardiac disease, was seen in subjects who experienced hypoglycemia compared with subjects who did not (0.193 vs. 0.159 for the nocturnal period; P = 0.01). This finding persisted after the hypoglycemic event.
- The rates of ventricular and supraventricular ectopy demonstrated a nonsignificant trend toward an increase during hypoglycemia

Diabetes Care 2017 Feb; dc161972.
Sulfonylureas and the Risks of Cardiovascular Events and Death: A Methodological Meta-Regression Analysis of the Observational Studies

- 19 studies identified
- 6 had no major design-related biases.
  - Sulfonylureas were associated with an increased risk of cardiovascular events and mortality in five of these studies (relative risks 1.16–1.55).


Sulfonylureas and the Risks of Cardiovascular Events and Death: A Methodological Meta-Regression Analysis of the Observational Studies

- Among studies with important biases, the association varied significantly with respect to the comparator, the outcome, and the type of bias.
- With the introduction of new antidiabetic drugs, the use of appropriate design and analytical tools will provide their more accurate cardiovascular safety assessment in the real-world setting.

Modern Sulfonylureas: Dangerous or Wrongly Accused?

**exposure misclassification**
- a failure to identify the time each patient is actually taking the drug in question.

**time-lag bias**
- in which the analysis does not account for the effect of studying patients at earlier versus later stages of diabetes.

**selection bias**
- exclusion of certain patients because of changes of regimen or clinical events during the period of observation.

*Diabetes Care 2017 May; 40(5): 629-631*

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**Time-lag bias introduced by comparing patients at different stages of the disease progression.**

*A* 0 years | 5 years | 8 years | 12 years
---|---|---|---
Metformin | Sulfonylurea | Combination therapy | Insulin

*Duration of disease*

*B* 0 – 5 years | 5 – 8 years | 8 – 12 years | > 12 years
---|---|---|---
Metformin | Sulfonylurea | Combination therapy | Insulin

*Comparing patients at different stages of the disease*

*Duration of follow-up*

*Laurent Azoulay, and Samy Suissa Dia Care 2017;40:706-714*
## Modern Sulfonylureas: Dangerous or Wrongly Accused?

<table>
<thead>
<tr>
<th></th>
<th>For the prosecution</th>
<th>For the defense</th>
<th>Evidence yet to be presented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic pre-conditioning</td>
<td>Tolbutamide and glyburide interfere with ischemic preconditioning</td>
<td>Gliclazide, glipizide, and glimepiride do not alter ischemic preconditioning</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Hypoglycemia and weight gain occur with all sulfonylureas</td>
<td>Gliclazide, glipizide, and glimepiride cause less hypoglycemia than glyburide</td>
<td></td>
</tr>
<tr>
<td>Observational studies</td>
<td>Cardiovascular risk is higher with sulfonylureas vs. comparators in some studies</td>
<td>Cardiovascular risk is mainly higher vs. metformin, which decreases risk</td>
<td>Studies with better design to limit bias</td>
</tr>
<tr>
<td>Randomized studies</td>
<td>Short-term mortality was increased with tolbutamide in UGDP</td>
<td>Long-term mortality was decreased with glyburide, chlorpropamide, and glipizide in UKPDS</td>
<td>CAROLINA (glimepiride vs. linagliptin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GRADE (glimepiride vs. other second-line agents)</td>
</tr>
</tbody>
</table>

Diabetes Care 2017 May; 40(5): 629-631

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**Thiazolidinediones**
Positive Side to TZDs

- Reduction in glucose
- Reduces BP
- Reduces albuminuria
- Reduces CRP
- Possible DM prevention
- Reduces NASH
- Reduces LFT
- Reduces IMT
- Reduces stent failure
- Reduces death after CHF
- Increases adiponectin
- Increases HDL

Current TZD Side Effects

- Weight Gain: 5-12 lbs in 1 year
  - Blunted with metformin
  - Worse with insulin
- Edema: 4-30%
  - Unresponsive to diuretics
- BUT:
  - Increased Cardiac Index
  - Increased Stroke volume
  - Decreased systemic resistance
  - Decreased Blood Pressure
**PROactive: Reduction in primary outcome**

All-cause mortality, MI, ACS, coronary or peripheral revascularization, amputation, stroke

- **Pioglitazone**: 2488, 2373, 2302, 2218, 2146, 348
- **Placebo**: 2530, 2413, 2317, 2215, 2122, 345

10% Relative risk reduction
HR* 0.90 (0.80–1.02)
P = 0.095

**Number at risk**


**PROactive: Reduction in secondary outcome**

All-cause mortality, MI (excluding silent MI), stroke

- **Pioglitazone**: 2536, 2487, 2435, 2381, 2336, 396
- **Placebo**: 2566, 2504, 2442, 2371, 2315, 390

16% Relative risk reduction
HR* 0.84 (0.72–0.98)
P = 0.027

**Number at risk**

**PROactive: Clinical implications**

Pioglitazone added to standard antidiabetic and CV therapies showed:

- **10% RRR in primary outcome**
  - Composite all-cause mortality, nonfatal MI (including silent MI), stroke, ACS, leg amputation, coronary or leg revascularization
- **16% RRR in secondary outcome**
  - All-cause mortality, nonfatal MI (excluding silent MI) or stroke
- No difference between groups in HF mortality
- Continued divergence in survival curves
  - Greater benefit with longer treatment duration hypothesized

**PROactive results support use of PPARγ modulator in patients with diabetes at high CVD risk**
- May improve CVD outcomes and decrease need to start insulin

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**Pioglitazone and Risk of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus**

*Figure 2. Estimates of the Incidence of the Cardiovascular End Points According to Randomized Treatment Assignment to Pioglitazone or Control*

A, Kaplan-Meier curve of time to death from any cause, nonfatal myocardial infarction, or nonfatal stroke. B, Shows curve of time to serious congestive heart failure.

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

- multicenter, double-blind trial
- 3876 patients who had had a recent ischemic stroke or TIA

- No diabetes but were found to have insulin resistance on the basis of a score of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index

- received either pioglitazone (target dose, 45 mg daily) or placebo.


- Pioglitazone was associated with a greater frequency of weight gain exceeding 4.5 kg than was placebo (52.2% vs. 33.7%, P<0.001), edema (35.6% vs. 24.9%, P<0.001), and bone fracture requiring surgery or hospitalization (5.1% vs. 3.2%, P=0.003).

- Pioglitazone can help prevent recurrence of stroke and progression into diabetes in those patients with insulin resistance and recent cardiovascular events.

- Bone mineral density should be closely monitored in patients taking pioglitazone due to high rates of bone fracture, hospitalizations, and surgeries.
Thiazolidinediones and Risk of Repeat Target Vessel Revascularization Following Percutaneous Coronary Intervention

Diabetes Care 30:384-388, 2007

RECORD: Kaplan-Meier Plots of time to the Primary Endpoint (Cardiovascular Death or Cardiovascular Hospitalization)

Lancet. 2009 Jun 5. [Epub ahead of print]
FDA Drug Safety Communication: FDA eliminates the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing diabetes medicines

This is an update to the FDA Drug Safety Communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines issued on November 25, 2013.

[ 12-16-2015 ]

Safety Announcement

The U.S. Food and Drug Administration (FDA) is eliminating the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing type 2 diabetes medicines, which are approved as Avandia, Avandamet, Avandaryl, and generics. The REMS is no longer necessary to ensure that the benefits of rosiglitazone medicines outweigh their risks.

Alpha glucosidase inhibitors
Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial

Patients with IGT were randomized to receive either placebo (n = 715) or 100 mg of acarbose 3 times a day


Alpha glucosidase inhibitors

- Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis.

no evidence for an effect on mortality or morbidity.

Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial.

In Chinese patients with coronary heart disease and impaired glucose tolerance:

• acarbose did not reduce the risk of major adverse cardiovascular events


Incretins
## Safety trials for DPP4 Inhibitors

<table>
<thead>
<tr>
<th>Study Name</th>
<th># of patients</th>
<th>Study drug vs placebo</th>
<th>A1C Range (%)</th>
<th>Primary Outcome (DPP4 vs placebo)</th>
<th>Hospitalization due to heart failure (DPP4 vs placebo)</th>
<th>P value</th>
<th>Comments/other results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI 53</td>
<td>16,492</td>
<td>Saxagliptin</td>
<td>6.5 - 12</td>
<td>Non-inferior</td>
<td>289 (3.5%) vs 223 (2.8%)</td>
<td>0.007</td>
<td>Higher risk HF in history of HF, renal impairment (hazard ratio, 1.27; 95% CI, 1.07 to 1.51)</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>5,380</td>
<td>Alogliptin</td>
<td>6.5 - 11</td>
<td>Non-inferior</td>
<td>106 (3.9%) vs 89 (3.3%)</td>
<td>0.22</td>
<td>Significant higher risk of hospitalization due to heart failure in patients without previous history of HF (P = 0.026) overall – NS (hazard ratio, 1.19; 95% CI, 0.90 to 1.58)</td>
</tr>
<tr>
<td>TECOS</td>
<td>14,671</td>
<td>Sitagliptin</td>
<td>6.5 - 8</td>
<td>Non-inferior</td>
<td>228 (3.1%) vs 229 (3.1%)</td>
<td>0.98</td>
<td>rates of hospitalization for heart failure was no different from placebo</td>
</tr>
</tbody>
</table>

**Retrospective (Diabetes Care 2016):**
In patients with type 2 diabetes, there was no association between HF, or other selected cardiovascular outcomes, and treatment with a DPP-4i relative to SU or treatment with saxagliptin relative to sitagliptin.

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### What About Linagliptin?

- Two large trials ongoing, results not out yet
  - CARMELINA—cardiovascular
  - CAROLINA—cardiovascular and renal outcomes
A Multicenter Observational Study of Incretin-based Drugs and Heart Failure

The rate of hospitalization for heart failure did not increase with the use of incretin-based drugs as compared with oral antidiabetic-drug combinations among patients with a history of heart failure (hazard ratio, 0.86; 95% confidence interval [CI], 0.62 to 1.19) or among those without a history of heart failure (hazard ratio, 0.82; 95% CI, 0.67 to 1.00).

Table 3. Association between Treatment with Incretin-based Drugs versus Oral Antidiabetic-Drug Combinations and Hospitalization for Heart Failure among Patients with a History of Heart Failure.2

<table>
<thead>
<tr>
<th>Treatment†</th>
<th>Hospitalization for Heart Failure</th>
<th>Adjusted Hazard Ratio (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case Patients (N=6336)</td>
<td>Controls (N=100,480)</td>
</tr>
<tr>
<td></td>
<td>no. (%)</td>
<td>no. (%)</td>
</tr>
<tr>
<td>Two or more oral antidiabetic drugs</td>
<td>684 (10.5)</td>
<td>10,608 (10.6)</td>
</tr>
<tr>
<td>Incretin-based drugs</td>
<td>940 (14.4)</td>
<td>12,394 (12.3)</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>905 (13.8)</td>
<td>11,651 (11.6)</td>
</tr>
<tr>
<td>GLP-1 analogues</td>
<td>35 (0.5)</td>
<td>743 (0.7)</td>
</tr>
<tr>
<td>Duration of treatment with incretin-based drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;365 days</td>
<td>664 (10.2)</td>
<td>9,061 (9.0)</td>
</tr>
<tr>
<td>365–729 days</td>
<td>172 (2.6)</td>
<td>2,012 (2.0)</td>
</tr>
<tr>
<td>≥730 days</td>
<td>103 (1.6)</td>
<td>1,312 (1.3)</td>
</tr>
</tbody>
</table>

Incretins (GLP-1): CVD

- neutral effect on heart failure and other cardiovascular problems

- rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo
Incretins (GLP-1): CVD

**Semaglutide** *(N Engl J Med 2016; 375:1834-1844)*
- rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo.

- No harm
- No benefit

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**SGLT2 Inhibitors**
Empagliflozin and CV Protection

- 12/2/2016
- Empagliflozin gains new FDA approval
  - To reduce cardiac death in patients with type 2 DM
- Approval based on EMPA-REG study
  - Significant improvement in various cardiovascular endpoints
    - Composite cardiovascular outcome
      - Death from cardiovascular causes
      - Non-fatal MI
      - Non-fatal stroke
    - Death from any cause
    - Hospitalization from heart failure

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Primary outcome: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

EMPA-REG Study Results

Moving Forward with Empagliflozin

- CV benefit impressive
  - Prevents death in 1 in 45 patients over 3 years
  - Prevents overall mortality in 1 in 39 patients
- Points to keep in mind
  - Benefit was shown in patients:
    - with cardiovascular disease
    - In addition to optimal treatment
  - Patients without cardiovascular disease were not a part of the study
  - No significant reduction in stroke or heart attack
  - Empagliflozin expensive
  - Side effects
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Primary outcome: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

Canagliflozin and Cardiovascular Events in Type 2 Diabetes

A Hospitalization for Heart Failure

Hazard ratio, 0.67 (95% CI, 0.52–0.87)

N Engl J Med June 12, 2017
Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs

- Data were collected via medical claims, primary care/hospital records, and national registries from the United States, Norway, Denmark, Sweden, Germany, and the United Kingdom. Propensity score for SGLT-2i initiation was used to match treatment groups. Hazard ratios for HHF, death, and their combination were estimated by country and pooled to determine weighted effect size. Death data were not available for Germany.

- After propensity matching, there were 309,056 patients newly initiated on either SGLT-2i or other glucose-lowering drugs (154,528 patients in each treatment group). Canagliflozin, dapagliflozin, and empagliflozin accounted for 53%, 42%, and 5% of the total exposure time in the SGLT-2i class, respectively.

- Initiation of SGLT-2i versus oGLDs was associated with a 39% lower incidence of HHF.

- Importantly, initiation of SGLT-2i versus oGLDs was also associated with a 51% lower rate of all-cause death, and a 46% lower rate of the combined end point of HHF or all-cause death.

Circulation. 2017;136:249-259

Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis

The Lancet Diabetes & Endocrinology 2017 5:709-717
Possible mechanisms that could contribute to the reduction of CV mortality by empagliflozin in the EMPA-REG OUTCOME study

<table>
<thead>
<tr>
<th>Effect</th>
<th>Likelihood</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic actions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowered plasma glucose concentration</td>
<td>Unlikely</td>
<td>Hyperglycemia is a weak CV risk factor; benefit of HbA1c reduction on CV death takes 10 years to observe</td>
</tr>
<tr>
<td>Increased fex oxidation</td>
<td>Unlikely</td>
<td>Increased oxygen demand per ATP generated</td>
</tr>
<tr>
<td>Increased plasma ketone concentration</td>
<td>Unlikely</td>
<td>Increased oxygen demand per ATP generated</td>
</tr>
<tr>
<td>Increased plasma uric acid concentration</td>
<td>Unlikely</td>
<td>Causal association with CV death not established</td>
</tr>
<tr>
<td>Increased plasma glucagon concentration</td>
<td>Unlikely</td>
<td>Physiological increase in glucagon has no effect on CV death</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Unlikely</td>
<td>Weight loss is modest but may contribute to long-term reduction in blood pressure</td>
</tr>
<tr>
<td>Change in plasma electrolyte concentration</td>
<td>Unlikely</td>
<td>No consistent changes observed</td>
</tr>
<tr>
<td>Hemodynamic actions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in blood pressure</td>
<td>Likely</td>
<td>Rapid reduction in blood pressure correlates with early CV benefit; proven CV protection in prior studies</td>
</tr>
<tr>
<td>Diuretic effect and decrease in extracellular fluid volume</td>
<td>Likely</td>
<td>Rapid reduction in extracellular fluid volume correlates with early CV benefit; proven protection against CHF in prior studies</td>
</tr>
<tr>
<td>Impaired arterial elasticity</td>
<td>Possible</td>
<td>Arterial stiffness is a CV risk factor; empagliflozin reduces arterial stiffness</td>
</tr>
<tr>
<td>Direct effect on the myocardium</td>
<td>Unlikely</td>
<td>No evidence</td>
</tr>
<tr>
<td>Decreased sympathetic tone</td>
<td>Possible</td>
<td>No increase in heart rate despite decrease in blood pressure and extracellular fluid volume</td>
</tr>
</tbody>
</table>

How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial

- **OVERALL**: About 50% of decrease in mortality due to glucose effect; So 50% from something else

- **Changes in hematocrit and hemoglobin mediated 51.8% and 48.9%**, respectively, of the effect of empagliflozin versus placebo on the risk of CV death on the basis of changes from baseline, with similar results in analyses on the basis of updated means. Smaller mediation effects (maximum 29.3%) were observed for uric acid, fasting plasma glucose, and HbA1c. In multivariable models, which incorporated effects of empagliflozin on hematocrit, fasting glucose, uric acid, and urine albumin:creatinine ratio, the combined changes from baseline provided 85.2% mediation, whereas updated mean analyses provided 94.6% mediation of the effect of empagliflozin on CV death.

- **CONCLUSIONS** In this exploratory analysis from the EMPA-REG OUTCOME trial, changes in markers of plasma volume were the most important mediators of the reduction in risk of CV death with empagliflozin versus placebo.

Hematocrit over time in patients treated with empagliflozin 10 mg, empagliflozin 25 mg, and placebo.

Insulin
Origin Glargine Trial

Two coprimary composite CV outcomes: CV death, nonfatal MI, or nonfatal stroke

HR, 1.02
(95% CI, 0.94-1.11);
P=0.63

Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes

CHF: Long Term Benefit

- Even recently completed large CV outcome trials of novel glucose-lowering agents lack sufficient details to fully appraise treatment effects on a HF endpoint or relative safety in patients with prevalent HF.
Future CVOT

Studies completed to date and those now under way are providing evidence for CV benefit for several drugs and reassurance about the lack of CV risk for many others.

The information on improved CV outcomes for specific antidiabetes drugs should be considered in revised clinical treatment recommendations, given that cardioprotection is an added benefit.

Future studies need to focus on populations more typical of those seen in routine care, with longer duration of follow-up, greater consistency in the ascertainment of outcomes, and improved statistical methods for analysis.

DM meds for treatment of CHF

SGLT-2
- no studies completed
- 3 large RCT started

GLP-1 agonists- liraglutide
- LIVE Trial
  - increased HR
- FIGHT Trial
  - no change
Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

Kaplan-Meier Estimates of the Risk of Death from Any Cause and from Cardiovascular Causes and the Number of Cardiovascular Events, According to Treatment Group


Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial

At 21.2 years of follow-up of 7.8 years of intensified, multifactorial, target-driven treatment of type 2 diabetes with microalbuminuria:
- a median of 7.9 years of gain of life.
- Median time before first cardiovascular event after randomization was 8.1 yr
- The increase in lifespan is matched by time free from incident cardiovascular disease.

Efficacy

Cardiovascular safety/benefit

Hypoglycemia

Patient Acceptance

Adverse Effects

Weight gain

Cost/Insurance Coverage