Diabetes – A Cardiac Condition Manifesting as Hyperglycemia
Speaker’s Bureau:

AstraZeneca
Novo Nordisk
Janssen
AS A DOCTOR, I’D RATHER HAVE HIV THAN TYPE 2 DIABETES

Dr. Max Pemberton (UK Psychiatrist) Spectator 2014.
LIFE EXPECTANCY AND T2DM

- OVER AGE 50 T2DM
  - MEN 7.5 YRS LESS
  - WOMEN 8.2 YRS LESS

WITH ESTABLISHED CVD NO DIFFERENCE IN DIABETIC AND NON-DIABETIC SUBJECTS

Causes of Death*

*Based on US studies.
## Established Modifiable Cardiovascular Risk Factors in Type 2 Diabetes

### UKPDS 23

<table>
<thead>
<tr>
<th>Position in Model</th>
<th>Variable</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Low-density lipoprotein cholesterol</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Second</td>
<td>High-density lipoprotein cholesterol</td>
<td>0.0001</td>
</tr>
<tr>
<td>Third</td>
<td>Hemoglobin A$_1$C</td>
<td>0.0022</td>
</tr>
<tr>
<td>Fourth</td>
<td>Systolic blood pressure</td>
<td>0.0065</td>
</tr>
<tr>
<td>Fifth</td>
<td>Smoking</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Adjusted for age and sex in 2,693 white patients with T2DM with dependent variable as time to first event.

*Significant for CAD (n=280). P values are significance of risk factors after controlling for all other risk factors in model.
TOBACCO USE CAN MAKE YOU IMPOTENT

Cigarettes may cause sexual impotence due to decreased blood flow to the penis. This can prevent you from having an erection.

Health Canada
TYPE 2 DIABETES AND SMOKING

SMOKING

INFLAMATION

↑ PERITONEAL FAT

NICOTINE

↑ FFA

↑ BETA CELL APOPTOSIS

↓ INSULIN PRODUCTION

INSULIN RESISTANCE

T2DM

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURRENT</td>
<td>1.37</td>
<td>1.33-1.42</td>
</tr>
<tr>
<td>2° HAND</td>
<td>1.22</td>
<td>1.1-1.35</td>
</tr>
<tr>
<td>HEAVY</td>
<td>1.57</td>
<td>1.47-1.66</td>
</tr>
<tr>
<td>NEW QUITTERS</td>
<td>1.54</td>
<td>1.36-1.74</td>
</tr>
<tr>
<td>5-9 YEARS</td>
<td>1.18</td>
<td>1.07-1.29</td>
</tr>
<tr>
<td>LONG TERM</td>
<td>1.11</td>
<td>1.02-1.2</td>
</tr>
</tbody>
</table>

ARIC STUDY – INCREASED T2DM WITH SMOKING

42% HEAVY SMOKER

35% LIGHTER SMOKER

73% QUITTER

22% FORMER
Non–HDL-C Is Superior to LDL-C in Predicting CHD Risk

- Within non–HDL-C levels, no association was found between LDL-C and the risk for CHD.
- In contrast, a strong positive and graded association between non–HDL-C and risk for CHD occurred within every level of LDL-C.
- Non–HDL-C is a stronger predictor of CHD risk than LDL-C.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors/10-year risk</th>
<th>Treatment goals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C (mg/dL)</td>
</tr>
<tr>
<td>Extreme risk</td>
<td>– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C &lt;70 mg/dL</td>
<td>&lt;55</td>
</tr>
<tr>
<td></td>
<td>– Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– History of premature ASCVD (&lt;55 male, &lt;65 female)</td>
<td></td>
</tr>
<tr>
<td>Very high risk</td>
<td>– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk &gt;20%</td>
<td>&lt;70</td>
</tr>
<tr>
<td></td>
<td>– DM or stage 3 or 4 CKD with 1 or more risk factor(s)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>– ≥2 risk factors and 10-year risk 10%-20%</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>– DM or stage 3 or 4 CKD with no other risk factors</td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>– ≤2 risk factors and 10-year risk &lt;10%</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Low risk</td>
<td>0 risk factors</td>
<td>&lt;160</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.

STATIN-INDUCED DIABETES

- INCREASED RISK IN PREDISPOSED (IR, ELDERLY, OBESE)
- CLASS EFFECT WITH A DOSE-RELATED RELATIONSHIP (ROSUVASTATIN)
- REDUCTION IN ADIPONECTIN LEVELS (EXCEPTION PITAVASTATIN)
- SMALL RISK OF T2DM cF DECREASED CARDIAC EVENTS

Bell, DSH. Diabetes Obes Metab (2014) 16(8) 689-94.
CALCIUM SCORE AND CARDIAC EVENTS IN VADT
WARFARIN AND CORONARY ARTERY CALCIFICATION

- WARFARIN INHIBITS THE SYNTHESIS AND FUNCTION OF MATRIX G1α PROTEIN, WHICH IS DEPENDENT ON VITAMIN K LEVELS
- MATRIX G1α PROTEIN INHIBITS VASCULAR CALCIFICATION BY BLOCKING BONE MORPHOGENETIC PROTEIN SIGNALING
- POSSIBLY MORE STABLE PLAQUE
- NEW ORAL ANTICOAGULANTS WORK BETTER IN DIABETES WITHOUT HF OR AF

Zhang, YT. J Cardiovasc Pharmacol (2014) 63(1) 76-82.
Postprandial Glucose Is an Independent Risk Factor Predicting Mortality

*Adjusted for age, sex, and study center.

THE POST - PRANDIAL STATE

- HYPERGLYCEMIA AND HYPERLIPIDEMIA
- INCREASED CYTOKINES
- INSULIN RESISTANCE
- INCREASED PAI$_1$
- INFLAMATION
- ENDOTHELIAL DYSFUNCTION
- PLAQUE INSTABILITY
SUSTAINED HYPERGLYCEMIA VERSUS ACUTE FLUCTUATIONS IN OXIDATIVE STRESS

GLUCOSE FLUCTUATIONS DURING POST-PRANDIAL PERIODS AND DURING GLUCOSE SWINGS EXHIBITED A MORE SPECIFIC TRIGGERING ON OXIDATIVE STRESS THAN CHRONIC SUSTAINED HYPERGLYCEMIA

POST-PRANDIAL HYPERGLYCEMIA AND CORONARYATHEROSCLEROSIS

POST-PRANDIAL DYSMETABOLISM AND CARDIAC MORTALITY

LOW 1.5-ANHYDROGLYCITOC LEVELS ARE ASSOCIATED WITH LONG-TERM CARDIAC MORTALITY IN ACUTE CORONARY SYNDROME PATIENTS WITH HbA1c LESS THAN 7%

Ouchi, S. Cardiovascular Diabetology (2017) 16:151.
Acarbose for the prevention of type 2 diabetes: STOP-NIDDM

- Double-blind, placebo-controlled study comparing acarbose 100 mg three times daily vs placebo, in 1429 patients with impaired glucose intolerance

**Cumulative probability of remaining free of diabetes**

- Acarbose reduced risk of diabetes by 25% (HR 0.75, 95% CI 0.63–0.90, p=0.0015)
- Acarbose reduced risk of cardiovascular events by 49% (HR 0.51, 95% CI 0.28–0.95, p<0.03)

<table>
<thead>
<tr>
<th>Days after randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>Acarbose</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
</tbody>
</table>

- **p=0.0022**

**Patients at risk**

<table>
<thead>
<tr>
<th>At risk</th>
<th>Acarbose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>682</td>
<td>686</td>
</tr>
<tr>
<td>2</td>
<td>655</td>
<td>671</td>
</tr>
<tr>
<td>3</td>
<td>628</td>
<td>655</td>
</tr>
<tr>
<td>4</td>
<td>612</td>
<td>640</td>
</tr>
<tr>
<td>5</td>
<td>531</td>
<td>512</td>
</tr>
<tr>
<td>6</td>
<td>523</td>
<td>505</td>
</tr>
<tr>
<td>7</td>
<td>515</td>
<td>497</td>
</tr>
<tr>
<td>8</td>
<td>497</td>
<td>470</td>
</tr>
<tr>
<td>9</td>
<td>463</td>
<td>434</td>
</tr>
<tr>
<td>10</td>
<td>447</td>
<td>427</td>
</tr>
<tr>
<td>11</td>
<td>432</td>
<td>414</td>
</tr>
<tr>
<td>12</td>
<td>349</td>
<td>331</td>
</tr>
<tr>
<td>13</td>
<td>331</td>
<td>268</td>
</tr>
<tr>
<td>14</td>
<td>268</td>
<td>255</td>
</tr>
<tr>
<td>15</td>
<td>212</td>
<td>208</td>
</tr>
</tbody>
</table>
Acarbose-induced reduction in post-prandial glucose: Correlation with reduction in cardiovascular events (Meta-analysis of 7 studies)

Hanefeld et al, Eur Heart J 2004; 25: 10–6

<table>
<thead>
<tr>
<th>Time (days after randomization)</th>
<th>Patients without event (%)</th>
<th>Placebo</th>
<th>Acarbose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>100</td>
<td>95</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>200</td>
<td>90</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>300</td>
<td>85</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>400</td>
<td>80</td>
<td>80</td>
<td>p=0.0057 (Log rank test)</td>
</tr>
<tr>
<td>500</td>
<td>80</td>
<td>80</td>
<td>p=0.0061 (Cox proportional model)</td>
</tr>
<tr>
<td>600</td>
<td>80</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>700</td>
<td>80</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>800</td>
<td>80</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.001, absolute change compared to placebo

2 hour PPG (mg/dL)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Baseline</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>Baseline</td>
<td>Endpoint</td>
</tr>
</tbody>
</table>

*p<0.001, absolute change compared to placebo
Central actions of dopamine

Hypothalamic neurons sense glucose and fatty acid levels

Signals modified by dopaminergic pathways

 Activation of efferent vagal nerves to adjust hepatic gluconeogenesis, glycogenolysis and hepatic glucose production

- ↓ Dopaminergic activity → Increased hepatic glucose production, increased lipolysis, and insulin resistance

Bell, Diabetes Obes Metab 2011; May 13 (Epub ahead of print)
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with bromocriptine QR or any other antidiabetic drug. Bromocriptine QR does not increase the risk of macrovascular events.

KM Curve: the separation in favor of bromocriptine QR begins 3 months and persists through the end of the study.

- Scranton et al, Diabetes 2008; 57(Suppl. 1): A95
CV EFFECTS OF HYPOGLYCEMIA

1) CATECOLAMINE RELEASE\(^1\)
2) IMPAIRED SHIFT TO MYOCARDIAL GLUCOSE UTILIZATION\(^2\)
3) PROLONGATION OF QTc INTERVAL AND CARDIAC ARRHYTHMIAS\(^3\)
4) ACTIVATION OF OXIDATIVE STRESS THROUGH GLUCOSE “SWINGS”\(^4\)
5) INCREASED RISK IN THE PRESENCE OF AUTONOMIC NEUROPATHY\(^5\)

2) Avogaro, A. Am J Cardiol (2004)93:13A-16A
Adverse Effect of Metformin-SU Combination, Intensification From Oral Monotherapy, Mortality Risk vs. A1c, n=27,965

## 4-T STUDY 3 YEAR RESULTS

<table>
<thead>
<tr>
<th>BIPHASIC</th>
<th>BASAL</th>
<th>PRANDIAL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPOGLYCEMIAS PER YEAR</td>
<td>3.0</td>
<td>1.75</td>
<td>50.001</td>
</tr>
<tr>
<td>CV MORTALITY</td>
<td>4</td>
<td>1</td>
<td>9 0.002</td>
</tr>
</tbody>
</table>

### Effect of Intensive Glucose Lowering on Macrovascular Complications of Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>VADT $^1$ (n=1700)</th>
<th>ACCORD $^2$ (n=10250)</th>
<th>ADVANCE $^3$ (n=11140)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c – Std vs. Intensive</strong></td>
<td>8.4 vs. <strong>6.9</strong></td>
<td>7.5 vs. <strong>6.5</strong></td>
<td>7.3 vs. <strong>6.5</strong></td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Non-fatal MI</td>
<td>Non-fatal MI</td>
<td>Non-fatal MI</td>
</tr>
<tr>
<td></td>
<td>Non-fatal stroke</td>
<td>Non-fatal stroke</td>
<td>Non-fatal stroke</td>
</tr>
<tr>
<td></td>
<td>CVD death</td>
<td>CVD death</td>
<td>CVD death</td>
</tr>
<tr>
<td></td>
<td>Hospitalization for CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Revascularization</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hazard Ratio for primary outcome (95% CI)</strong></td>
<td>0.87 (0.730 – 1.04)</td>
<td>0.90 (0.78 – 1.04)</td>
<td>0.94 (0.84 – 1.06)</td>
</tr>
<tr>
<td><strong>Hazard Ratio for mortality (95% CI)</strong></td>
<td>1.065 (0.801 – 1.416)</td>
<td>1.22 (1.01 – 1.46)</td>
<td>0.93 (0.83 – 1.06)</td>
</tr>
</tbody>
</table>

* $P=0.04$

HYPOGLYCEMIA AND CARDIAC EVENTS

- 9,173 DIABETES SUBJECTS WITHOUT CAD IN 2006 FOLLOWED IN 1º CARE (13 PRACTICES) TO 2012

<table>
<thead>
<tr>
<th>HR</th>
<th>CAD (95% CI)</th>
<th>HIGH RISK (95% CI)</th>
<th>OVER 65 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.15(1.24-3.74)</td>
<td>3.01(1.15-7.91)</td>
<td>4.62(1.65-12.9)</td>
</tr>
</tbody>
</table>

## SEVERE HYPOGLYCEMIA IN ARIC STUDY – OVER 3 YEARS

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAD</strong></td>
<td>2.02</td>
<td>1.27-3.20</td>
</tr>
<tr>
<td><strong>MORTALITY</strong></td>
<td>1.73</td>
<td>1.38-2.17</td>
</tr>
<tr>
<td><strong>CV MORTALITY</strong></td>
<td>1.64</td>
<td>1.15-2.34</td>
</tr>
<tr>
<td><strong>CA MORTALITY</strong></td>
<td>2.49</td>
<td>1.46-4.24</td>
</tr>
<tr>
<td><strong>STROKE</strong></td>
<td>1.15</td>
<td>0.59-2.23</td>
</tr>
<tr>
<td><strong>HF</strong></td>
<td>1.37</td>
<td>0.98-1.91</td>
</tr>
<tr>
<td><strong>ATRIAL FIB</strong></td>
<td>1.05</td>
<td>0.68-1.60</td>
</tr>
</tbody>
</table>

Ischemic Preconditioning

Prolonged occlusion of an epicardial artery leads to myocardial infarction

Repeated and brief occlusion of the same vessel conditions the myocardium such that subsequent prolonged occlusion leads to a smaller infarct (ischemic preconditioning)
CLOSURE OF K⁺-ATPase CHANNELS

1) Insulin release
2) Loss of ischemic preconditioning
   - 1st hole angina
   - 2nd stress test
   - Angioplasty
   - Reperfusion injury
   - Pre-infarction angina
   - Ventricular function
   - ST-segment elevation
3) Ventromedial and arcuate nuclei of the hypothalamus
   - Lack of recognition of and blunted counterregulatory response to hypoglycemia

Bell, DSH. Canadian Medical Journal (2006)
HOT Diabetic Subgroup Reduction in Cardiovascular Events

<table>
<thead>
<tr>
<th>Target diastolic BP (mmHg)</th>
<th>Achieve d† systolic BP (mmHg)</th>
<th>Achieve d† diastolic BP (mmHg)</th>
<th># of patients with diabetess</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 90</td>
<td>143.7</td>
<td>85.2</td>
<td>501</td>
</tr>
<tr>
<td>≤ 85</td>
<td>141.4</td>
<td>83.2</td>
<td>501</td>
</tr>
<tr>
<td>≤ 80</td>
<td>139.7</td>
<td>81.1</td>
<td>499</td>
</tr>
</tbody>
</table>

† mean of all blood pressures for all study patients in BP subgroups from 6 months of follow-up to end of study

*Includes all myocardial infarction, all strokes, and all other cardiovascular deaths

P = 0.005

HOPE Study: Effect of Ramipril on Cardiovascular Events at 4.5 Years (Total Population)

Pts With Myocardial Infarction, Stroke, or CVD Death (%)

Diabetic patients*

- Placebo: 25%
- Ramipril: 19.8%

Nondiabetic patients†

- Placebo: 21%
- Ramipril: 16.5%

Risk Reduction

- Diabetic patients: 25%
- Nondiabetic patients: 21%

*\(n=3577, P=0.0004\)

†\(n=5720, P<0.001\)


From a 2024 patient study, 340 had diabetes, and 281 survived hospitalization for acute MI. Of the 127 diabetics taking β-blockers, 80% received propranolol, 20% received other β-blockers. Kjekshus J et al. Eur Heart J. 1990;11:43–50.
β-Blockers in the Diabetic Patient With CAD: Bezafibrate Infarction Prevention Study

With β-blockers event rate: 7.8%; without β-blockers event rate: 14.0%
2723 Patients with type 2 diabetes and CAD. Of those patients receiving a β-blocker, 39% received propranolol, and 61% received a cardioselective β-blocker

Coreg® (carvedilol) is indicated for hypertension, post-MI LV dysfunction, and congestive heart failure.

Effect of $\beta$-Blockers on Insulin Sensitivity in Hypertensive Patients

- Propranolol
- Metoprolol
- Atenolol
- Pindolol
- Dilevalol
- Carvedilol
- Celiprolol

Between these agents, the difference on IS is ~25-45%, which is similar to the metabolic effects of the insulin-sensitizers.

Gemini

- Decrease in Insulin Resistance
- Decrease in microalbuminuria
- Decrease in HbA$_1$c
- Fewer dropouts due to Glycemic Control
- Fewer 1% increases in HbA$_1$c
- Lower non-HDL cholesterol
- Better Quality of Life

Diabetes and Risk for Thromboembolism

Hazard Ratio

No Diabetes
Diabetes

50% Increase in RR*

*95% CI, 1.1-3.5.
ASA AND DIABETES

- Meta-analysis of 140,000 patients showed a significant 22% reduction in risk of major cardiac events.
- A statistical benefit was not found in 5,000 diabetic patients.
- 7% lowering of major cardiac events.

ASA AND CARDIAC EVENTS IN TYPE 2 DIABETES

- MODEST REDUCTION IN CVEs AND MORTALITY cf NON-DIABETIC
- ONCE DAILY: ASA PLATLETS ONLY IRREVERSIBLY PARALYZED ONLY FOR A SHORT TIME
- AFTER THIS NEWLY GENERATED AGGRESSIVE PLATLETS ENTER THE CIRCULATION
- PLATLETS IN T2DM ARE MORE REACTIVE AND HAVE A MORE RAPID TURNOVER
- TWICE DAILY DOSING, HIGHER DOSE OR COMBINATION WITH OTHER ANTI-PLATLET MEDS?

Bell, DSH. Postgraduate Med(2016)128(2)180-190.
187 patients ≥40 years old from the Islington Diabetes Survey in which 1,084 subjects ≥40 were selected from a group general practice for a screening examination (75 g glucose tolerance test, blood glucose measurement and HbA1c).

MAU = urinary albumin excretion rate (AER) ≤20 mg/min; MAU += AER >20 mg/min; PVD = peripheral vascular disease.

Steno-2 Study:
Changes in Risk Factors (7.8 y)

FPG  TRG  TC  LDL  BP-sys  BP-dia

Percent Change

Intensive (n=67)  Conventional (n=63)

*p<0.001; †p=0.015; §p=0.006.
Steno-2 Study: Outcomes


50% Risk Reduction

Conventional

Intensive
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
Cardiovascular Disease Mortality Increases With Metabolic Syndrome

Cumulative Hazard (%)

Follow-up (y)

RR (95% CI), 3.55 (1.96-6.43)

INSULIN RESISTANCE

OXIDATIVE STRESS

GENETICS

INFLAMMATION

HTN T2DM DYSLIPIDEMIA LVD
TZDs: potential to impact on CVD risk biomarkers

TZDs ↓ hyperglycemia
TZDs ↑ HDL and ↓ sdLDL
TZDs ↓ PAI-1
TZDs ↓ CRP
TZDs ↓ microalbuminurinria
TZDs ↑ vascular reactivity
TZDs ↓ BP
TZDs ↓ IR
↓ Atherosclerosis, cardiovascular disease?

“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”
TZDs: effect on carotid IMT progression

IMT = intima-media thickness
Patients with clinically stable coronary artery disease without diabetes
RSG dose 4 mg/day for initial 8 weeks; 8 mg/day for remaining 40 weeks
*P = 0.03 vs. placebo

Change in mean IMT at 48 weeks (mm)

Baseline
Placebo
TZDs

Progression rate (mm/48 weeks) =

Baseline n = 41
Placebo 0.815
TZDs 0.823

Error bars = SE

IVUS Can Detect Angiographically “Silent” Atheroma

Angiogram
No evidence of disease

IVUS
Little evidence of disease
Atheroma

PERISCOPE:
Comparison to Other Trials

![Graph showing the comparison of LDL (mg/dL) to change in percent atheroma volume (%). The graph includes data points for PERISCOPE, REVERSAL, CAMELOT, ACTIVATE, ILLUSTRATE, ASTEROID, and PLATIZOSA.](image-url)
Primary Endpoint: Change in Percent Atheroma Volume (%)

- Glimepiride (n=181): 
  - Change in PAV (%): 0.73
  - P = 0.002

- Pioglitazone (n=179): 
  - Change in PAV (%): -0.16
  - P = 0.44

*JAMA. 2008;299:1561-1573.*
PROactive: significant difference in principal secondary endpoint*

*Death, MI (excluding silent) or stroke
Pioglitazone vs. placebo: HR: 0.84; 95% CI: 0.72–0.98

PROactive: no significant difference in primary composite endpoint.*

*All-cause mortality, non-fatal MI (including silent MI), stroke, major leg amputation (above the ankle), acute coronary syndrome, cardiac intervention including CABG or percutaneous coronary intervention, leg revascularization. Pioglitazone vs. placebo: HR: 0.90; 95% CI: 0.80–1.02.

Baseline Medication Subgroups

<table>
<thead>
<tr>
<th>Baseline medications</th>
<th>Neither</th>
<th>Metformin</th>
<th>Sulphonylureas</th>
<th>Metformin + sulphonylureas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary Composite

Principal Secondary

0.5  1.0  1.5  2.0

Pioglitazone Better

Placebo Better

0.5  1.0  1.5  2.0

Pioglitazone Better

Placebo Better
PROACTIVE REINFARCTION STUDY

M.I. 28% REDUCTION

A.C.C. 37% REDUCTION

PIO PLACEBO

2.80% 3.80%
ProACTIVE: Fatal and nonfatal stroke with pioglitazone treatment vs placebo in patients with prior history of stroke

<table>
<thead>
<tr>
<th>End point</th>
<th>Pioglitazone, n=486</th>
<th>Placebo, n=498</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent stroke</td>
<td>27</td>
<td>51</td>
<td>0.53</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.34 – 0.94)</td>
<td></td>
</tr>
</tbody>
</table>

Wilcox RG. World Congress of Cardiology 2006; September 3, 2006; Barcelona, Spain.
GLP1- RECEPTOR AGONISTS AND CARDIAC EVENTS
<table>
<thead>
<tr>
<th>STUDY</th>
<th>GLP₁-RA</th>
<th>F/U DURATION (YRS)</th>
<th>CV EVENT RATE PLACEBO</th>
<th>CV EVENT RATE GLP₁-RA</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>LIXENATIDE</td>
<td>2.1</td>
<td>399/3034 13.2%</td>
<td>406/3034 13.4%</td>
<td>1.02</td>
<td>0.81</td>
</tr>
<tr>
<td>LEADER</td>
<td>LIRAGLUTID E</td>
<td>3.8</td>
<td>694/4672 14.9%</td>
<td>608/4668 13.0%</td>
<td>0.87</td>
<td>0.01</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>SEMAGLUTID E</td>
<td>2.1</td>
<td>146/1649 8.9%</td>
<td>108/1648 6.6%</td>
<td>0.74</td>
<td>0.02</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>EXENATIDE</td>
<td>3.2</td>
<td>905/7396 12.2%</td>
<td>839/7356 11.4%</td>
<td>0.91</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**MI AND NON-FATAL STROKE**
GLP-1 AGONISTS AND CVD

- WEIGHT LOSS
- GLP-1 RECEPTORS IN - ENDOTHELIUM
  - MONOCYTES
  - MACROPHAGES
  - LYMPHOCYTES
- INHIBIT FOAM CELL FORMATION AND ATHEROGENESIS
  - SUPRESSING INFLAMATION
  - SUPRESSING OXIDATIVE STRESS

LIRAGLUTIDE, MACROPHAGES AND ATHEROGENESIS

- Macrophages have GLP-1 receptor
- Liraglutide attenuates pro-inflammatory response and limit atherosclerosis
- Apoprotein E null mice on high fat diet atherogenesis suppressed with liraglutide

Bruen, R. Cardiovascular Diabetology(2017)16:143.
# ANTI-DIABETOGENIC CARDIAC DRUGS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>HbA1c</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOLESEVALAM</td>
<td>0.5%</td>
<td>INCREASES CCK SLOWS GASTRIC EMPYTING</td>
</tr>
<tr>
<td>RANAZOLINE</td>
<td>0.56%</td>
<td>Na CHANNEL BLOCK SUPPRESSING GLUTACAPON RELEASE</td>
</tr>
</tbody>
</table>

Diabetes – A Cardiac Condition Manifesting as Hyperglycemia
¿S? END THE