Explanation for the ACCORD outcomes?

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Eli Lilly
NovoNordisk
Sanofi
Valeritas
Outline of this talk

Epidemiologic associations of A1c and FPG with CVD

Both benefits and risks in ACCORD

Why the added risk with intensive therapy?
Updated A1c correlates with myocardial infarction in T2DM

4585 participants followed for 10 Years in the UKPDS

Adjusted relative risk *

<table>
<thead>
<tr>
<th>A1c %</th>
<th>Adjusted Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>1</td>
</tr>
<tr>
<td>6 to &lt;7</td>
<td>1.3</td>
</tr>
<tr>
<td>7 to &lt;8</td>
<td>1.8</td>
</tr>
<tr>
<td>8 to &lt;9</td>
<td>1.9</td>
</tr>
<tr>
<td>9 to &lt;10</td>
<td>2.5</td>
</tr>
<tr>
<td>≥10</td>
<td>2.4</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex and duration of diabetes

Stratton IM et al. BMJ. 2000;321:405-412
High fasting glucose correlates with high risk of coronary heart disease

Meta-analysis of 102 prospective studies
~280,000 participants without prior cardiovascular disease

The Emerging Risk Factors Collaboration

Hazard ratio (95% CI) for CHD

Adjusted for age, sex, systolic BP, BMI
Plotted in reference to 5.0-5.5 mmol/L
Outline of this talk

Epidemiologic associations of A1c and FPG with CVD

Both benefits and risks in ACCORD

Why the added risk with intensive therapy?
## Characteristics of participants in ACCORD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10,251</td>
</tr>
<tr>
<td>Age (mean yr)</td>
<td>62</td>
</tr>
<tr>
<td>Female/male (%)</td>
<td>39/51</td>
</tr>
<tr>
<td>Duration of diabetes (median yr)</td>
<td>10</td>
</tr>
<tr>
<td>Body mass index (mean kg/M²)</td>
<td>32.2</td>
</tr>
<tr>
<td>Baseline A1c (median %)</td>
<td>8.1</td>
</tr>
<tr>
<td>Previous cardiovascular event (%)</td>
<td>35</td>
</tr>
<tr>
<td>Years of randomized treatment</td>
<td>3.4 (median)</td>
</tr>
</tbody>
</table>

Glycemic control in ACCORD

Median A1c at each study visit

Standard strategy - median 7.5%
Intensive strategy - median 6.4%

Δ A1c ~1.1%


N at risk
Standard 5109 4774 4588 3186 1744 455 436
Intensive 5119 4768 4585 3165 1705 476 471

Bars denote interquartile ranges
Weighing benefits vs risks

Short-term benefit vs long-term risk

Long-term benefit vs short-term risk
Physiologic or anatomic benefits in ACCORD
Relative risk-reductions with intensive therapy

18% reduction of non-fatal myocardial infarction (5 years)
The ACCORD Study Group. NEJM 2011;364:818-828

15-29% reduction of albuminuria (5 years)
Ismail-Beigi F et al. Lancet 2910;376:419-430

33% reduction of retinopathy (5 years)
The ACCORD Study Group & the Eye Study Group. NEJM 2010;363:233-243

26% reduction of decline of brain volume (3.3 years)
Launer LJ et al. Lancet Neurol 2011;10:969-977
Cardiovascular disease develops over time
Shouldn’t we expect both negative and positive effects of prior metabolic control?

Small artery arteriosclerosis

Coronary artery atherosclerosis

ACCORD Glucose Study: 3.4-year results
Increased all-cause mortality

1.41 vs 1.14% per year
Unadjusted Hazard Ratio
1.22 (1.01-1.46)
P = 0.04
<table>
<thead>
<tr>
<th>Event</th>
<th>Unadjusted HR</th>
<th>CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1.19</td>
<td>(1.03-1.38)</td>
<td>0.02</td>
</tr>
<tr>
<td>CV death, MI, stroke</td>
<td>0.91</td>
<td>(0.81-1.03)</td>
<td>0.12</td>
</tr>
<tr>
<td>CV death</td>
<td>1.29</td>
<td>(1.04-1.60)</td>
<td>0.02</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.82</td>
<td>(0.70-0.96)</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>0.87</td>
<td>(0.65-1.17)</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Epidemiologic associations of A1c and FPG with CVD

Both benefits and risks in ACCORD

Why the added risk with intensive therapy?
Short-term cardiovascular harm in ACCORD

Increased total and CV mortality with intensive regimen at 3.5 and 5 year
  ACCORD study group. NEJM 2008:358:2545-2549
  ACCORD study group. NEJM 2011:364:818-828

A few predictors of risk at baseline (High A1c, hx neuropathy, hx ASA)

Association with persisting A1c <7%
  Riddle MC et al. Diabetes Care 2010;33:983-990

Complex relationship with hypoglycemia
  Seaquist ER et al. Diabetes Care 2012;35:409-414
Why the excess mortality with the intensive strategy?

Hypotheses

- A vulnerable, high risk population
- Rapid reduction or near-normal levels of A1c
- Severe hypoglycemia
- Drugs, combinations of drugs, drug dosages
- Weight-gain
- Play-of-chance
Baseline characteristics as predictors

Subgroup analysis showing HR for death with intensive vs standard strategies

### Table of Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Standard Glycemia</th>
<th>Intensive Glycemia</th>
<th>Hazard Ratio</th>
<th>Interaction p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7.5</td>
<td>4.40% (1022)</td>
<td>4.83% (1036)</td>
<td></td>
<td>0.044</td>
</tr>
<tr>
<td>7.5-8.4</td>
<td>4.09% (2200)</td>
<td>4.18% (2226)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8.5</td>
<td>3.60% (1887)</td>
<td>6.14% (1857)</td>
<td></td>
<td>0.0008</td>
</tr>
<tr>
<td><strong>Self-report of neuropathy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4.11% (1410)</td>
<td>7.84% (1327)</td>
<td></td>
<td>0.0008</td>
</tr>
<tr>
<td>No</td>
<td>3.84% (3646)</td>
<td>4.10% (3708)</td>
<td></td>
<td>0.031</td>
</tr>
<tr>
<td><strong>Aspirin use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.83% (2771)</td>
<td>5.73% (2808)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4.12% (2352)</td>
<td>4.14% (2320)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk of death over a range of baseline A1c in ACCORD by treatment strategy

Why the excess mortality with the intensive strategy?

Hypotheses

- A vulnerable, high risk population
- Rapid reduction or near-normal levels of A1c
- Severe hypoglycemia
- Drugs, combinations of drugs, drug dosages
- Weight-gain
- Play-of-chance
Changes of A1c and mortality over time in ACCORD by treatment strategy

Riddle MC et al. Diabetes Care 2010;33:983-90
Rates of death during 3.4 years of treatment in ACCORD over a range of 1-year change of A1c

Adjusted Mortality Rates by Treatment Strategy

Excess risk with intensive strategy vs standard occurred when intensive participants failed to reduce A1c in year 1

Adjusted deaths per year

Riddle MC et al. Diabetes Care 2010;33:983-990
Risk of death over a range of average A1c in ACCORD by treatment strategy

Steady increase of risk from 6 to 9% A1c with intensive strategy

Excess risk with intensive strategy vs standard occurred above A1c 7%

Riddle MC et al. Diabetes Care 2010;33:983-990
Why the excess mortality with the intensive strategy?

Hypotheses

- A vulnerable, high risk population
- Rapid reduction or near-normal levels of A1c
- Severe hypoglycemia
- Drugs, combinations of drugs, drug dosages
- Weight-gain
- Play-of-chance
Severe hypoglycemia in ACCORD by treatment strategy

% of participants with events requiring medical assistance

- Intensive glycaemia control: 3.14% per yr
- Standard glycaemia control: 1.03% per yr

Years of followup

Miller ME et al. BMJ 2010;340:b5444
Adjudicated role of hypoglycemia in death in ACCORD by treatment strategy

Bonds DE et al. BMJ 2010;340:b4909
### Severe hypoglycemia and mortality in ACCORD
**Incidence and HR by treatment strategy**

<table>
<thead>
<tr>
<th></th>
<th>Standard Glycemia (n=175 with events)</th>
<th>Intensive Glycemia (n=528 with events)</th>
<th>HR for death (95% CI)</th>
</tr>
</thead>
</table>
| No hypoglycemia requiring medical assistance | 1.0 % / year  
180 deaths  
17,516 person years | 1.3 % / year  
220 deaths  
17,031 person years | 1.24  
(1.02-1.52) |
| At least one event  | 4.9 % / year  
17 deaths  
345 person years | 2.8 % / year  
34 deaths  
1,208 person years | 0.55  
(0.31-0.99) |
| HR for death (95% CI)| 2.87  
(1.73-4.76) | 1.28  
(0.88-1.85) |
Further complexities about hypoglycemia in ACCORD
Mortality risk and severe hypoglycemia
are both greater at higher A1c

All-cause mortality

Hypoglycemia requiring assistance

Riddle MC et al. Diabetes Care 2010;33:983-90
Bonds DE et al. BMJ 2010;340:b4909
Non-severe hypoglycemia in ACCORD

Analysis of glucose meter records
7-days of readings were sampled every 4 months

Percentage of participants reporting episodes <70 mg/dL
Intensive = 1.21 ± 1.84  (p<0.001)
Standard = 0.32 ± 0.91

HR for death among those with mild hypoglycemia compared to those with no episodes

<table>
<thead>
<tr>
<th>Prior severe hypos</th>
<th>0.68 (p&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior severe hypos</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Is there a protective effect from prior non-severe hypoglycemia? ‘hypoglycemic preconditioning’

Bonds DE et al. BMJ 2010;340:b4909
Non-severe hypoglycemia in ACCORD

Analysis of glucose meter records
7-days of readings were sampled every 4 months

Number of episodes <70 mg/dL each prior 7 days (±SD)

Intensive = 1.06 ± 0.98
Standard = 0.29 ± 0.49

Percentage of participants reporting unrecognized hypos each visit

Intensive = 5.8%
Standard = 2.6%

Hazard ratio for all-cause mortality in models including frequency of non-severe events

Intensive = 0.93 (0.90, 0.97)  p<0.001
Standard = 0.98 (0.91-1.06)  NS

Seaquist EJ et al. BMJ 2010;340:b4909
Non-severe hypoglycemia in ACCORD

Analysis of glucose meter records
7-days of readings were sampled every 4 months

“For participants in the intensive group with a previous event requiring medical assistance, every one-unit increase in the number of hypoglycemic episodes was associated with a 17.3% reduction in mortality.”

“For participants in the intensive group without a previous event requiring medical assistance, every one-unit increase in the number of hypoglycemic episodes was associated with only a 6% reduction in mortality.”

P for interaction = 0.048

“The reason for this difference . . . is uncertain . . .”

Is there a protective effect from prior non-severe hypoglycemia? ‘hypoglycemic preconditioning’
Further insights from ORIGIN
Effect of non-severe and severe hypoglycemia on CV outcomes

Epidemiologic analysis from
12,537 participants with IGT, IFG, or early T2DM, and high CV risk
6.2 median years observation
Randomized comparison of titrated glargine vs standard oral therapy
Systematic recording of hypoglycemia every 4 months

Non-severe hypoglycemia
Symptomatic and confirmed ≤ 3.0 mmol/L (54 mg/dl)

Severe hypoglycemia
Assistance by another person and/or ≤ 2.0 mmol/L (36 mg/dL)

The ORIGIN Trial Investigators (Mellbin L et al). Eur Ht J 2013;34:3137-3144
Further insights from ORIGIN
Effect of non-severe and severe hypoglycemia on CV outcomes

Hazard ratios adjusted for baseline covariates (propensity score)

The ORIGIN Trial Investigators (Mellbin L et al). Eur Ht J 2013;34:3137-3144
Further insights from ORIGIN
Effect of non-severe and severe hypoglycemia on CV outcomes

Hazard ratios for all-cause mortality by treatment assignment adjusted for baseline covariates (propensity score)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Non-severe</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine</td>
<td>1.09 (0.94-1.26)</td>
<td>1.34 (1.00-1.79)</td>
</tr>
<tr>
<td>Standard Care</td>
<td>1.18 (0.97-1.45)</td>
<td>3.13 (2.20-4.46)</td>
</tr>
<tr>
<td>Standard vs. Glargine</td>
<td>1.10 (0.87-1.40)</td>
<td>2.31 (1.47-3.64)</td>
</tr>
</tbody>
</table>

P for interaction 0.001

The ORIGIN Trial Investigators (Mellbin L et al). Eur Ht J 2013;34:3137-3144
Comparison of ACCORD and ORIGIN findings
Risk of death associated with prior severe hypoglycemia by treatment assignment

Hazard ratios (95% CI) adjusted for baseline covariates

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ORIGIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive therapy</td>
<td>1.28 (0.88-1.85)</td>
<td>---</td>
</tr>
<tr>
<td>Standard therapy</td>
<td>2.87 (1.73-4.76)</td>
<td>---</td>
</tr>
<tr>
<td>Glargine</td>
<td>---</td>
<td>1.34 (1.00-1.79)</td>
</tr>
<tr>
<td>Standard care</td>
<td>---</td>
<td>3.13 (2.20-4.46)</td>
</tr>
</tbody>
</table>
A vulnerable, high risk population?
Yes, with high A1c and evidence of complications

Rapid reduction to near-normal levels of A1c?
No, in fact the opposite — failure to reduce A1c to targets predicts higher risk

Severe hypoglycemia?
1) Associated with risk, but this is at least partly due to concurrent risk factors
2) Risk is most prominent during intensive treatment when A1c is >7%
3) Risk of death after a severe event is especially present during standard treatment, an observation also in ORIGIN
Cardiovascular death after severe hypoglycemia

- Is associated with underlying cardiac and other disease
- Is mediated by catecholamine secretion leading to arrhythmias
- Occurs at the time of an isolated severe event, which provokes maximal response of catecholamines
- Prior non-severe hypoglycemia is protective due to blunting of catecholamine responses and/or myocardial accommodation
- People most at risk are those with intermittent adherence to treatment

Why the excess mortality with the intensive strategy?
A unifying hypothesis regarding hypoglycemia

Riddle MD & Karl DM. Diabetes Care 2012;35:2100-2107
Thanks for your attention!