Why is antidiabetic treatment less effective than expected?

Francesco Cosentino, MD, PhD, FESC
Myocardial infarction and microvascular endpoints incidence by mean HbA1c concentration

Stratton et al. BMJ 2000
Treat to Target
as close as possible to normal

Aim for good glycemic control =
HbA1c <6.5%

Eur Heart J 2007; 28: 88-136
Compare the effects of intensive vs standard glucose lowering on CV outcomes in T2DM patients.

**ACCORD**
A1c 7.5 vs 6.5%

**ADVANCE**
A1c 7.3 vs 6.5%

**VADT**
A1c 8.4 vs 6.9%

VADT, NEJM 2009
The ACCORD Study Group, NEJM 2009
The ADVANCE Collaborative Group, NEJM 2008
Why is antidiabetic treatment less effective than expected?

Explanation 1: Concomitant therapies

- Concomitant treatment of other CVD risk factors (statins, BP lowering agents, aspirin)

Message:

Additional benefits by intensive glucose control difficult to achieve
Why is antidiabetic treatment less effective than expected?

Explanation:

- Current glucose lowering strategies may have counterbalancing effects for CVD (hypoglycemia, weight gain, over-insulinitazion).

<table>
<thead>
<tr>
<th></th>
<th>ACCORD 1</th>
<th>ADVANCE 2</th>
<th>VADT 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieved median HbA1c (I vs S) %</td>
<td>6.4 vs 7.5</td>
<td>6.3 vs 7.0</td>
<td>6.9 vs 8.5</td>
</tr>
<tr>
<td>On insulin at study end (I vs S) %</td>
<td>77 vs 55</td>
<td>40 vs 24</td>
<td>88 vs 74</td>
</tr>
<tr>
<td>Weight changes, Kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- intensive arm</td>
<td>+3.5</td>
<td>-0.1</td>
<td>+7.8</td>
</tr>
<tr>
<td>- standard arm</td>
<td>+0.4</td>
<td>-1.0</td>
<td>+3.4</td>
</tr>
<tr>
<td>Severe hypoglycemia (≥1 episode) %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- intensive arm</td>
<td>16.2</td>
<td>2.7</td>
<td>21.2</td>
</tr>
<tr>
<td>- standard arm</td>
<td>5.1</td>
<td>1.5</td>
<td>9.9</td>
</tr>
</tbody>
</table>
Explanation 3:
Advanced disease at baseline

- Participants had known duration of diabetes of 8–11 years, previous CVD or multiple risk factors; established atherosclerosis
- Subset analyses suggested a significant benefit of intensive glycemic control in participants with shorter duration of diabetes, lower HbA$_1^C$ at entry, absence of known CVD

**Message:**
Long standing duration of diabetes beyond the stage where tight glycaemic control could exert any protective effect

1 Relationship of diabetes duration and HR for CVD events with intensive therapy;
Lesson from the UKPDS:

- Glycemic control early in the course of type 2 diabetes may have a beneficial effect on later CV risk.

- Interestingly, these results are similar to those observed in type 1 diabetes (DCCT/EDIC).
The “Hyperglycemic Memory” concept

High glucose → ROS production → Endothelial dysfunction

“persistence of ROS-mediated hyperglycemic stress”
OXIDATIVE STIMULI

PKC β

P

P

p66

APOPTOSIS

CYTOSOL

PROAPOPTOTIC FACTORS

MODIFIED FROM COSENTINO ET AL. ATVB 2008
Upregulation of p66$^{Shc}$ expression in experimental and human diabetes

Camici et al. PNAS 2007

Pagnin et al. JCEM 2005

Mouse

Human
It's not always the case that it's easy to forgive and forget, particularly when it comes to past memories....
Experimental Hypothesis

ROS

PKC β

p66\text{Shc}^\text{Normal Glucose}
p66^{Shc} Drives Vascular Hyperglycemic Memory

A Detrimental Vicious Cycle

Restoration of normoglycemia does not improve endothelial function in diabetic mice treated with insulin

In vivo Knockdown of p66\textsuperscript{Shc} Blunts Vascular Hyperglycemic Memory in Mice

Persistent p66\textsuperscript{Shc} upregulation due to \textit{de novo} transcription induced by epigenetic changes of promoter

\begin{itemize}
  \item Methylation
  \begin{itemize}
    \item NG
    \item HG
    \item HN
    \item Hypomethylation
  \end{itemize}

  \begin{itemize}
    \item DNA polymerase
    \item p66 promoter
    \item CH\textsubscript{3} CH\textsubscript{3} CH\textsubscript{3}
  \end{itemize}

  \begin{itemize}
    \item Gene expression
    \item p66, p66, p66, p66
  \end{itemize}

  \begin{itemize}
    \item High Glucose
    \item AcH3
    \item α-tubulin
    \item Histone 3 acetylation
    \item p66\textsuperscript{Shc}, GAPDH
  \end{itemize}

\end{itemize}
Hyperglycemia confers gene activating events that are associated with changes in chromatin structure and function.

- **glucose variability**
- **histone modifications**
- **chromatin architecture**

**EPIGENETIC CHANGES**

1. **HYPERGLYCEMIA**
2. **ROS**
3. **TRANSCRIPTION**
4. **“MEMORY EFFECT”**

**H3**
- **euglycemia**
  - ARTKQTK
- **hyperglycemia**
  - ARTKQT
- **return to euglycemia**
  - ARTKQT

“closed” structure gene suppression

“open” structure gene activation
Study Design

*p66\textsuperscript{Shc} and vascular hyperglycemic memory in T2DM patients*

Newly diagnosed T2DM patients

Glycemic control

baseline

6 months

**HYPERGLYCEMIA**

- p66\textsuperscript{Shc} expression
- Epigenetic analysis of p66\textsuperscript{Shc} promoter
- Oxidative stress (8-isoPGF2α)
- Vascular function (FMD)

**NORMOGLYCEMIA**

- p66\textsuperscript{Shc} expression
- Epigenetic analysis of p66\textsuperscript{Shc} promoter
- Oxidative stress (8-isoPGF2α)
- Vascular function (FMD)
Achievement of optimal glycemic control in newly diagnosed T2DM patients.

Cosentino et al. unpublished
Persistent endothelial dysfunction and oxidative stress in T2DM with optimal glycemic control (OGC)
Glycemic control does not revert p66\textsuperscript{Shc} upregulation in patients with T2DM
Epigenetic analysis of $p66^{Shc}$ promoter in controls and T2DM

Histone 3 acetylation persists despite optimal glycemic control in T2DM
H3K14 acetylation favours sustained p66$_{\text{Shc}}$ overexpression during subsequent normoglycemia

T2DM induces irreversible p66Shc promoter demethylation

- Methylation of CpG dinucleotides (%)
- ΔΔCt (p66Shc/TBP)

Controls, T2DM, T2DM+OGC
Adverse epigenetic remodeling of p66$^{Shc}$ promoter correlates with persistent vascular dysfunction
Adverse epigenetic remodeling of p66$^{\text{Shc}}$ promoter correlates with persistent oxidative stress.
Take home message

- Cardiovascular risk burden is not eradicated by intensive glycemic control and new mechanism-based therapeutic strategies are needed.

- Epigenetic regulation of p66Shc gene may contribute to the residual burden in T2DM patients with OGC.

- Plastic alterations of the chromatin may be amenable to pharmacological intervention (targeted approaches to reprogram these modifications).
Mechanism-based approach for the treatment of diabetic vascular disease

Paneni et al. Diabetes 2013, pending revision
Why focusing on “hyperglycemic memory”?  

Probability of all-cause mortality with intensive glucose-lowering vs standard treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Events</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>3071/1549</td>
<td>160/78</td>
<td>5.2%</td>
<td>0.91 (0.51-1.61)</td>
</tr>
<tr>
<td>PROactive*</td>
<td>2605/2633</td>
<td>86/107</td>
<td>20.5%</td>
<td>0.81 (0.60-1.08)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>5571/5569</td>
<td>238/246</td>
<td>51.4%</td>
<td>0.97 (0.81-1.16)</td>
</tr>
<tr>
<td>VADT</td>
<td>892/899</td>
<td>28/36</td>
<td>6.8%</td>
<td>0.78 (0.47-1.28)</td>
</tr>
<tr>
<td>ACCORD</td>
<td>5128/5123</td>
<td>76/72</td>
<td>16.2%</td>
<td>1.05 (0.76-1.46)</td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773</td>
<td>588/539</td>
<td>100%</td>
<td>0.93 (0.81-1.06)</td>
</tr>
</tbody>
</table>

Ray KK et al. Lancet 2009