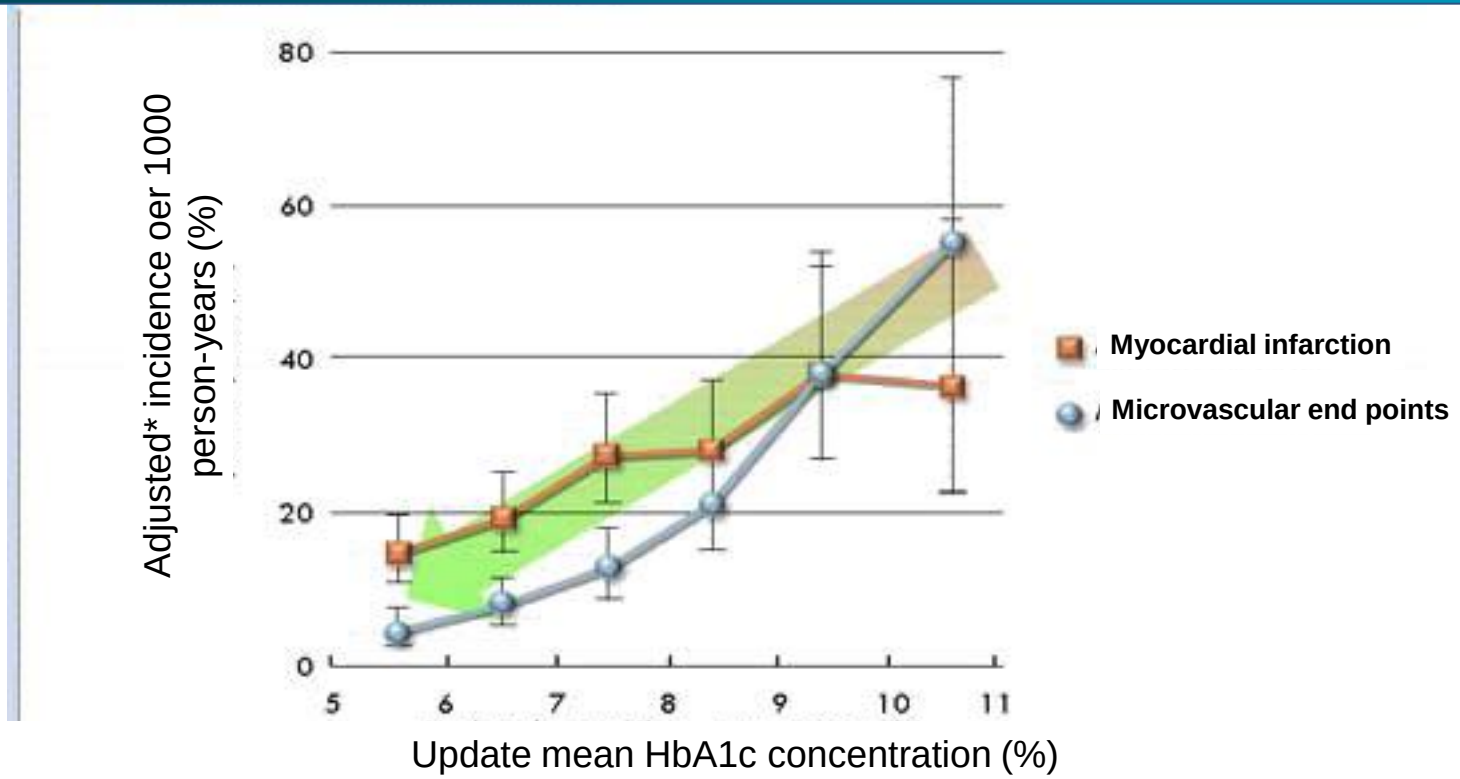
Cardiology Update 2013

Prevention, Diabetes and Renal Disease

Why is antidiabetic treatment less effective than expected?

Francesco Cosentino, MD, PhD, FESC

Myocardial infarction and microvascular endpoints incidence by mean HbA1c concentration

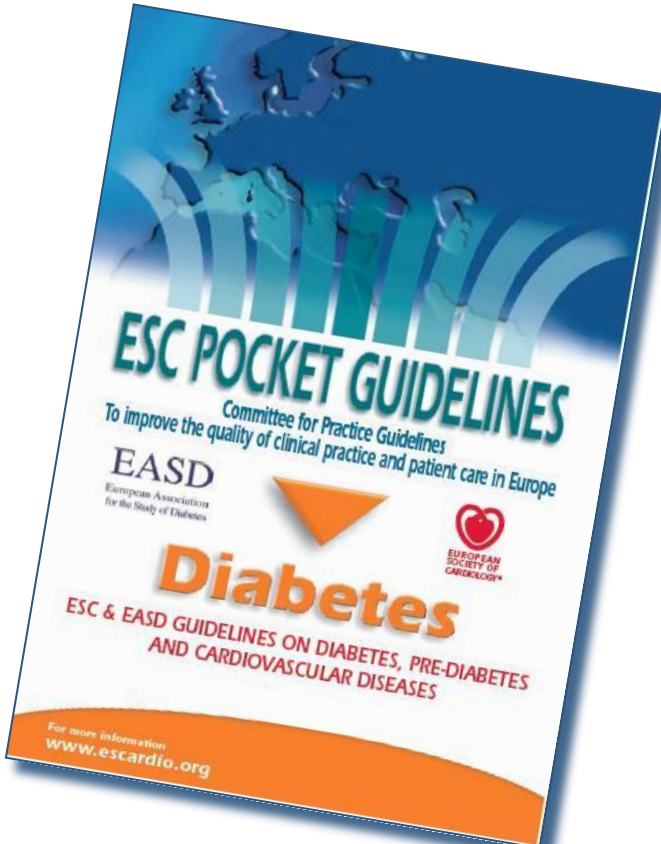


Stratton et al. BMJ 2000

Treat to Target

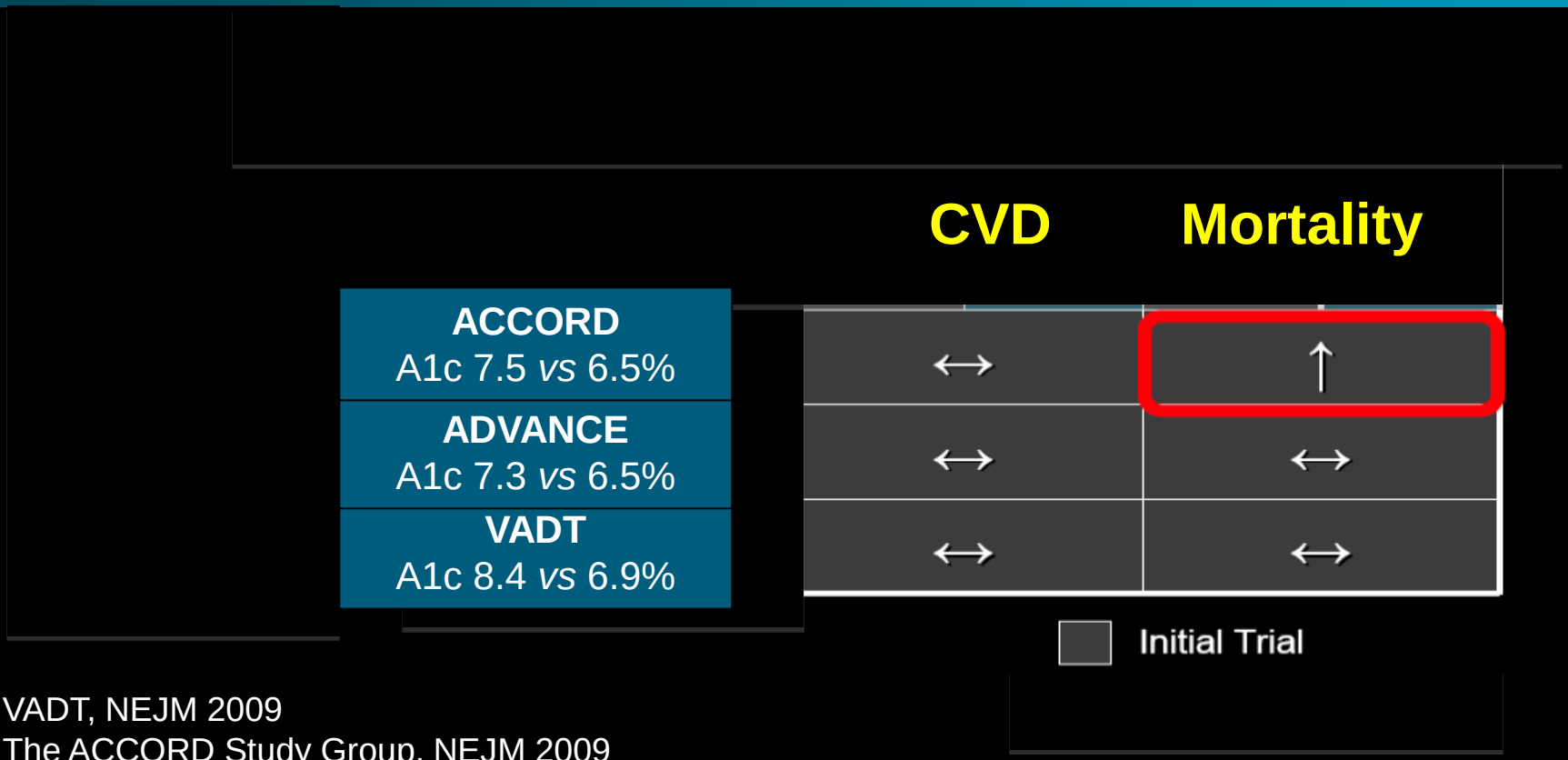
as close as possible to normal

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



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)

Lower incidence of CV events

Message:

Additional benefits by intensive glucose control difficult to achieve

Why is antidiabetic treatment less effective than expected?

Explanation

- Current glu
  balancing e
  over-insulin

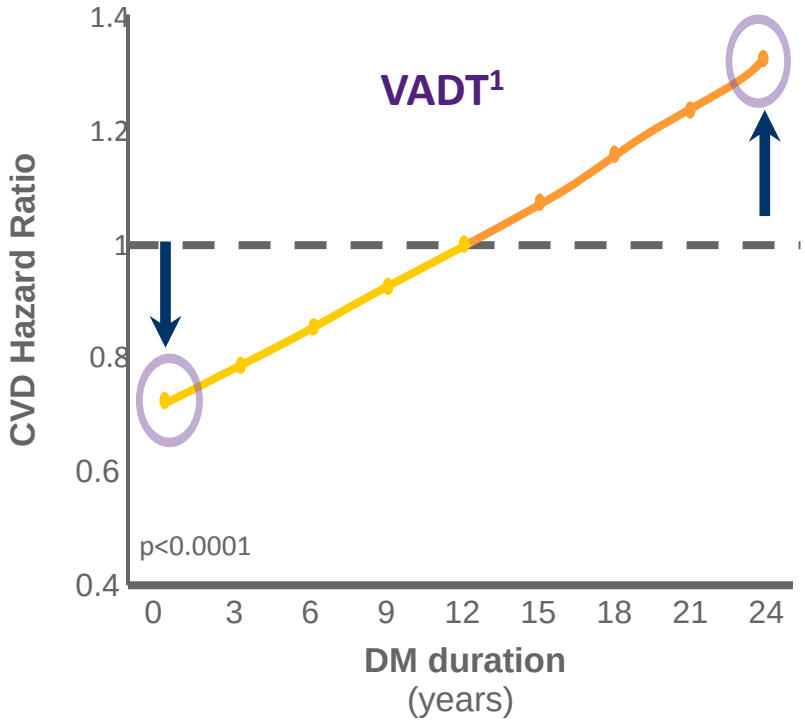
	ACCORD[1]	ADVANCE[2]	VADT[3]
Achieved median HbA1c (I vs S) %	6.4 vs 7.5	6.3 vs 7.0	6.9 vs 8.5
On insulin at study end (I vs S) %	77 vs 55	40 vs 24	88 vs 74
Weight changes, Kg - intensive arm - standard arm	 +3.5 +0.4	 -0.1 -1.0	 +7.8 +3.4
Severe hypoglycemia (≥1 episode) % - intensive arm - standard arm	 16.2 5.1	 2.7 1.5	 21.2 9.9

Why is antidiabetic treatment less effective than expected?

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_{1C} 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;

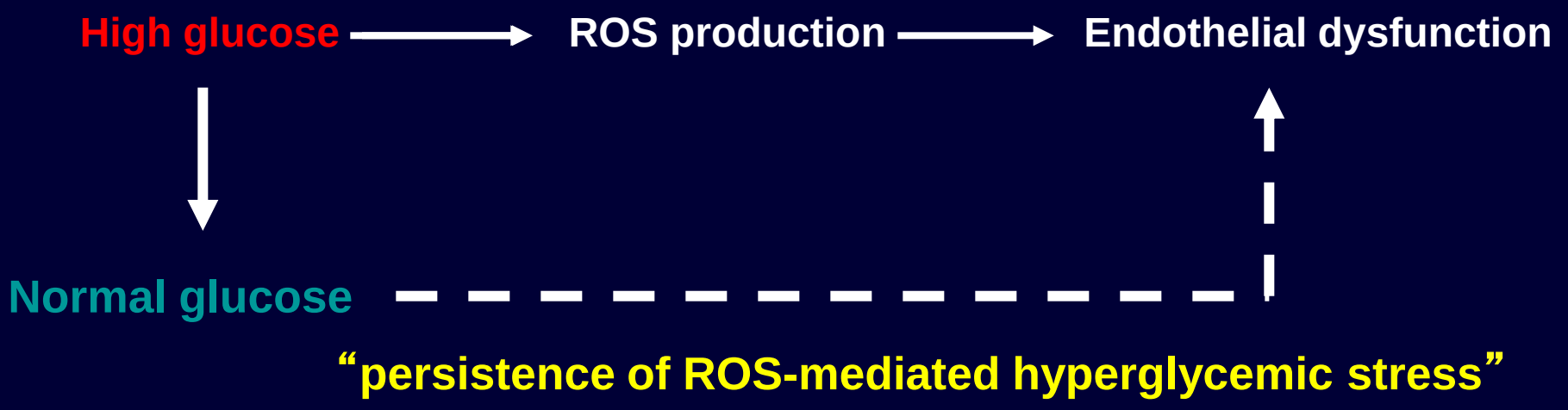
CVD and glucose control in type 2 diab

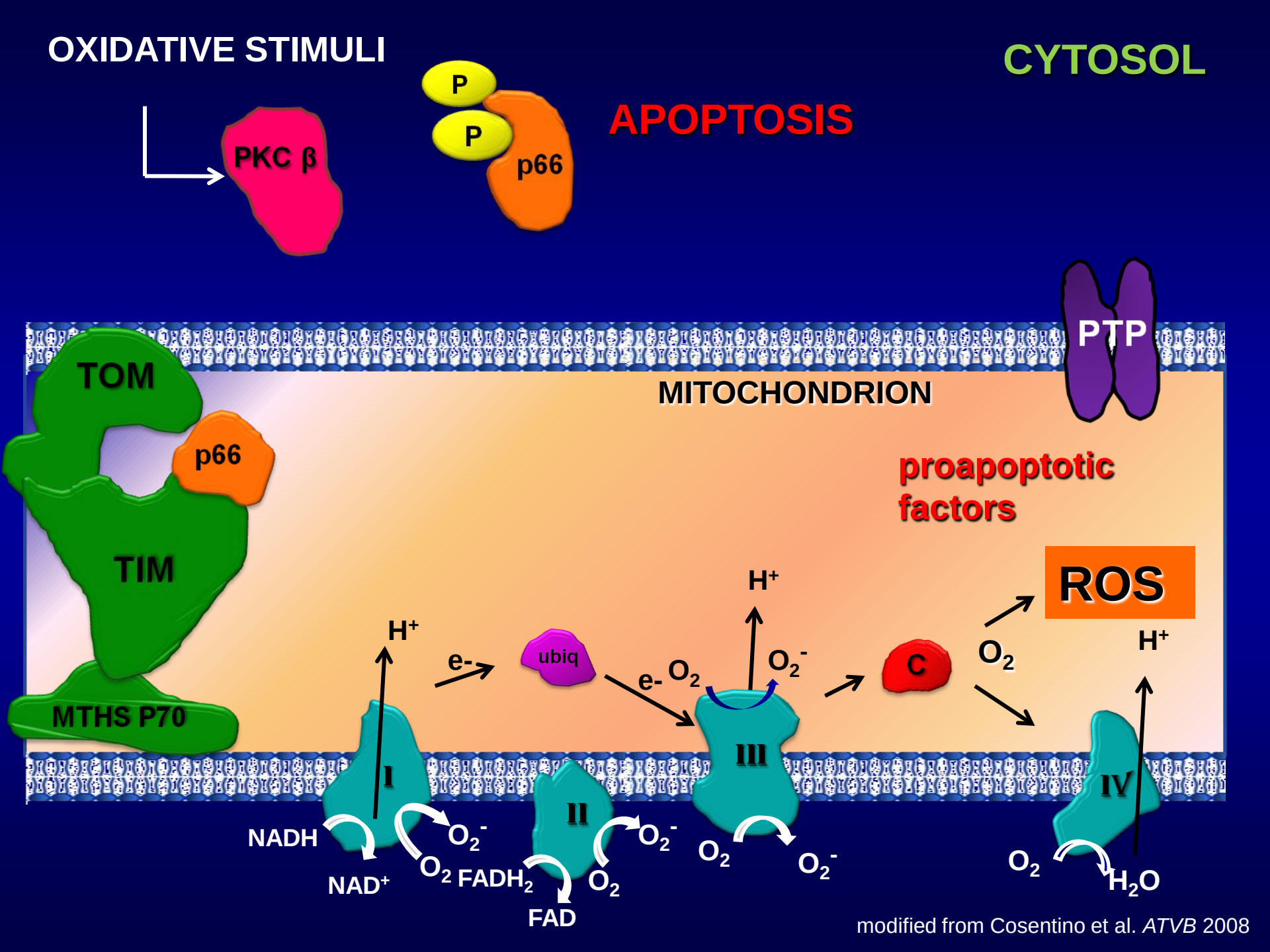
Lesson from the UKPDS:

- Glycemic control earl… of type 2 diabetes may ha… effect on later CV risk.
- Inter… results are similar to those …pe 1 diabetes (DCCT/EDIC)

Long-term detrimental impact of early sustained hyperglycaemia!

The “Hyperglycemic Memory” concept

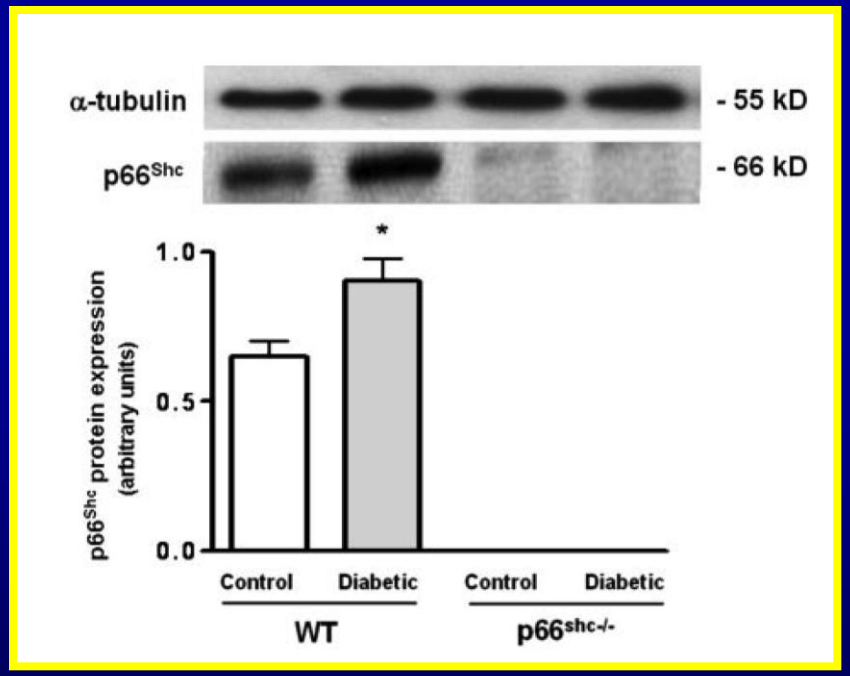




modified from Cosentino et al. *ATVB* 2008

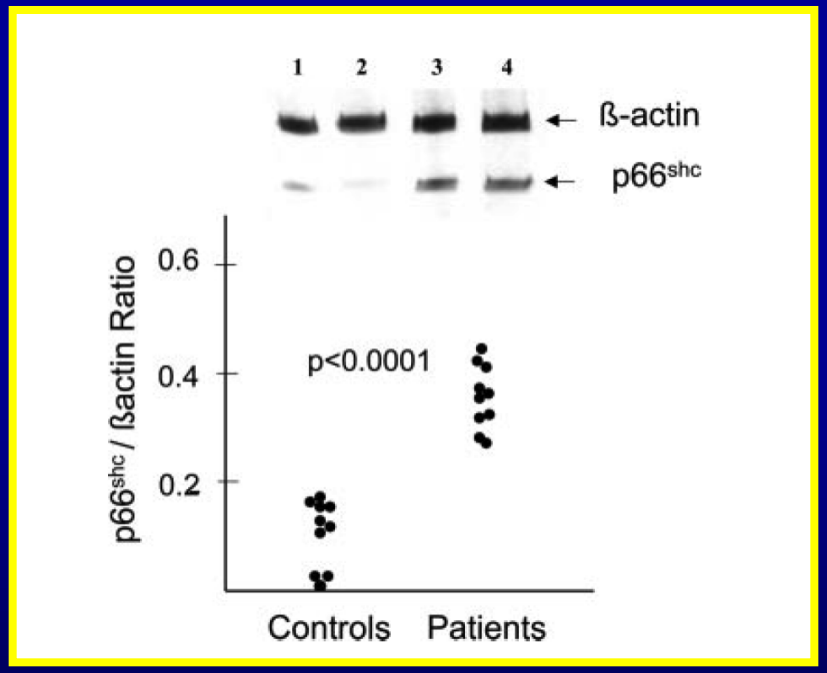
Upregulation of p66^{Shc} expression in experimental and human diabetes

Camici et al. PNAS 2007



Mouse

Pagnin et al. JCEM 2005



Human

Editorial

Redox Mediating Epigenetic Changes Confer Metabolic Memories

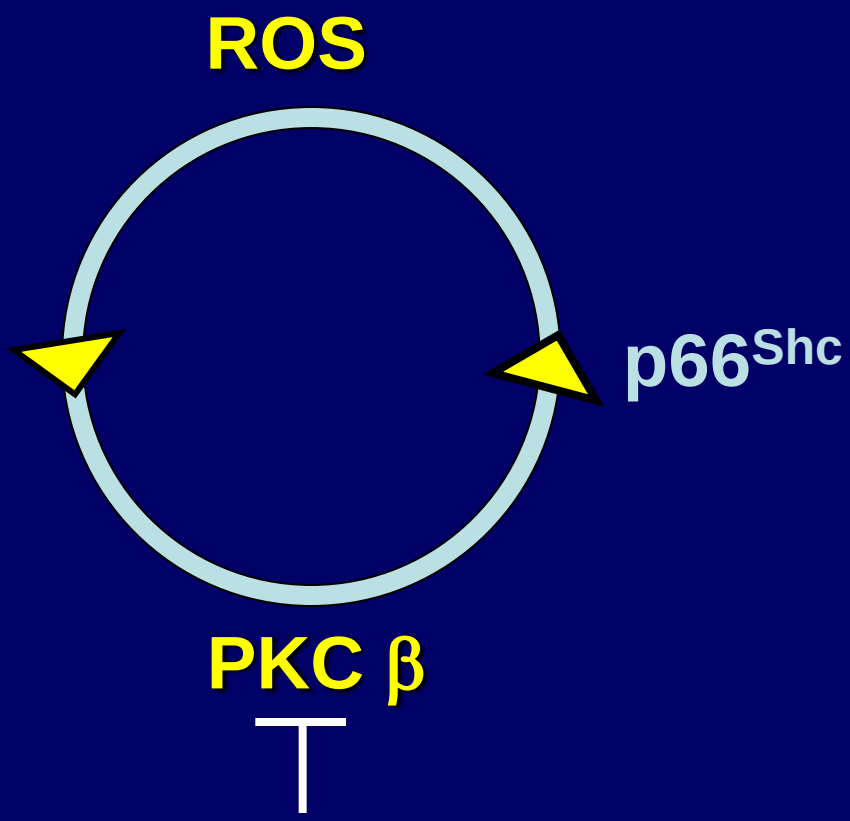
Assam El-Osta

"BAD LEGACY EFFECT" OF HYPERGLYCEMIA

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

Circ Res 2012;111:262-4

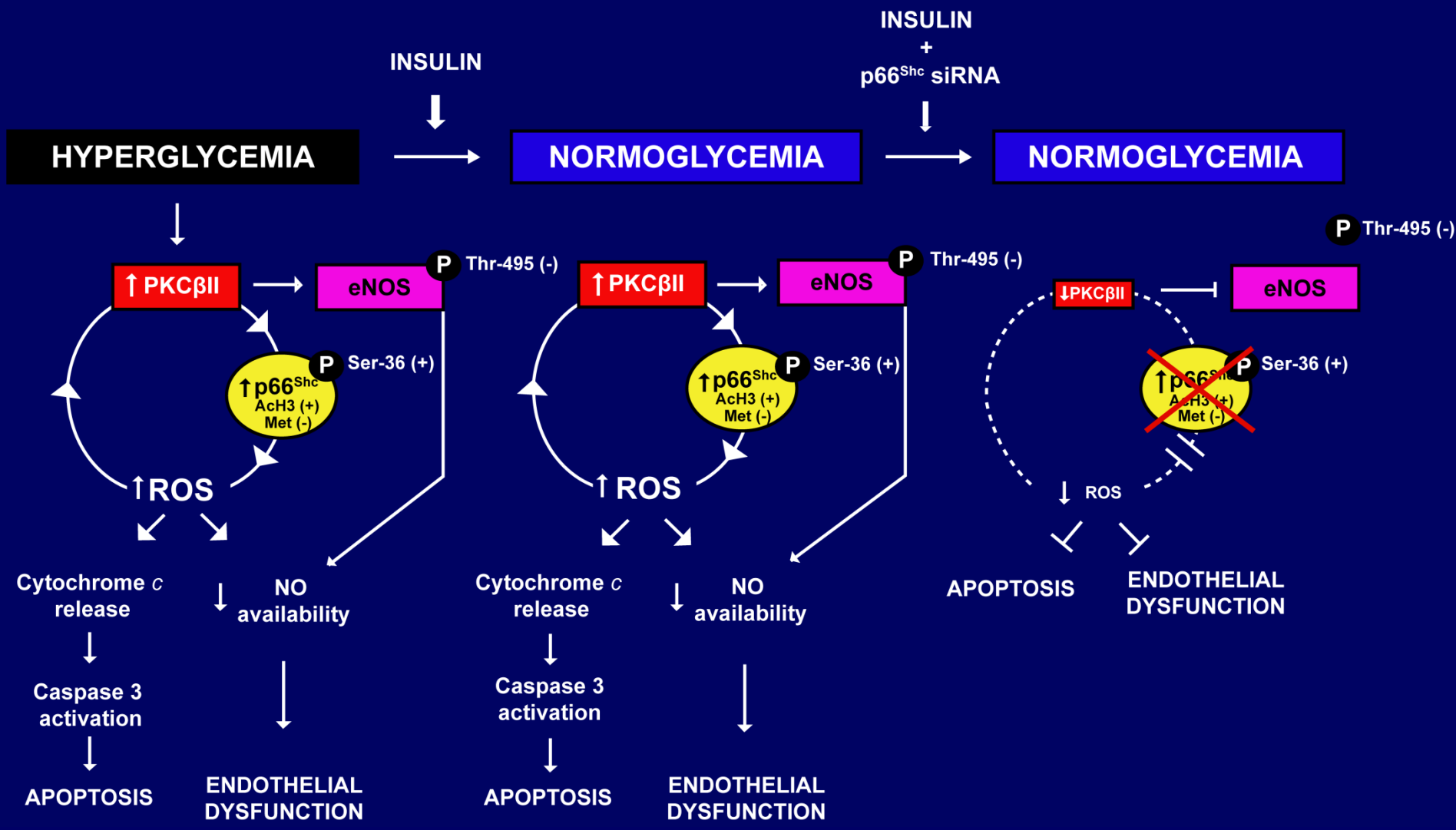
Experimental Hypothesis



Normal Glucose

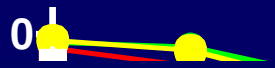
p66^{Shc} Drives Vascular Hyperglycemic Memory

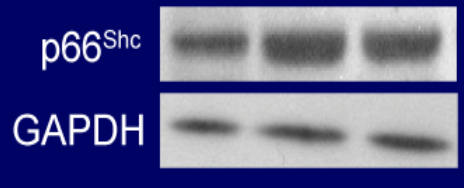
A Detrimental Vicious Cycle

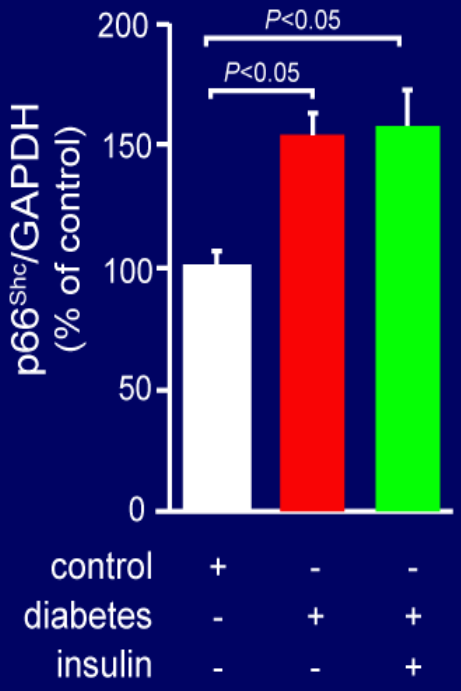


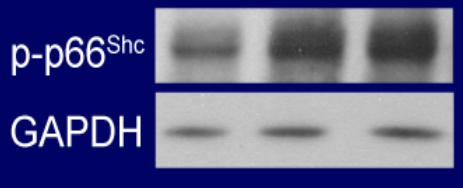
Paneni et al. *Circ Res* 2012

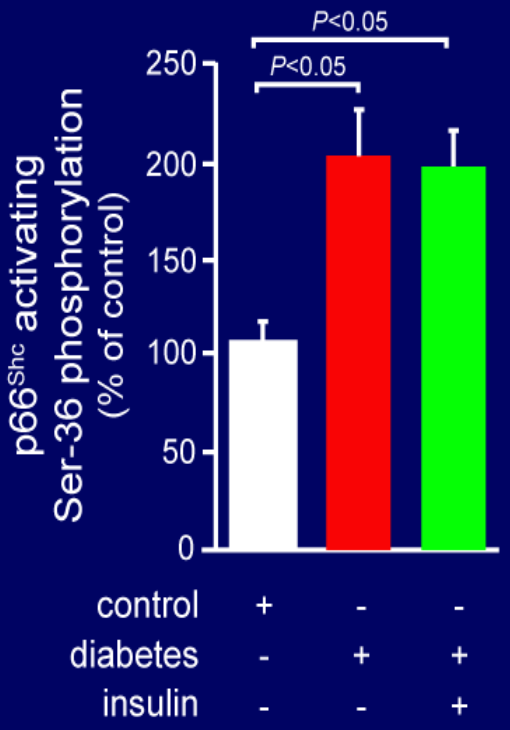
Restoration of normoglycemia does not improve endothelial function in diabetic mice treated with insulin

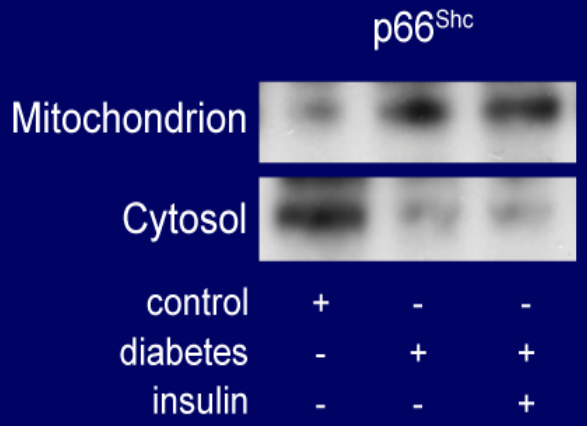






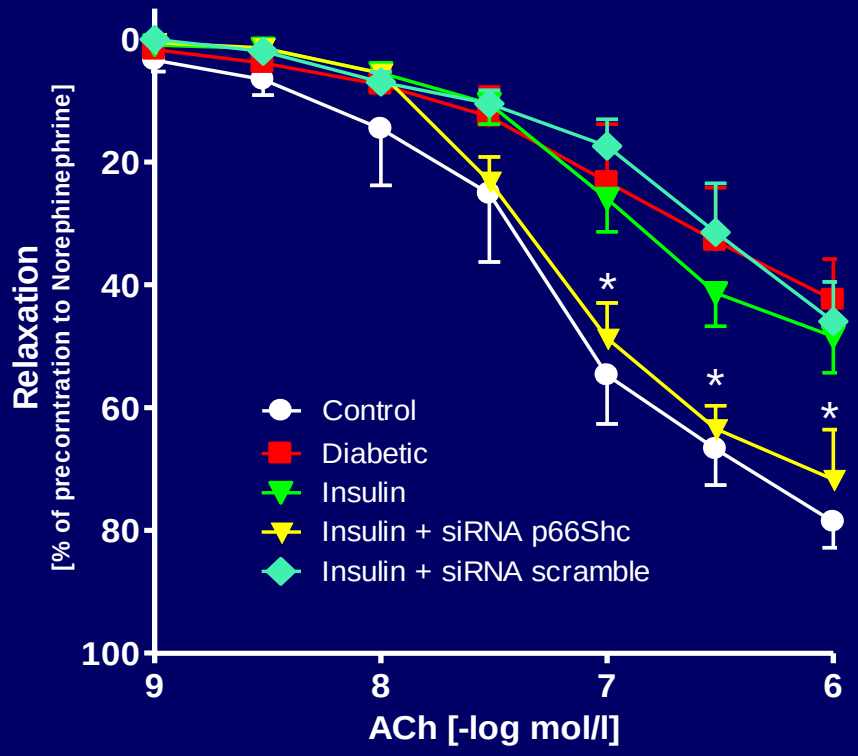


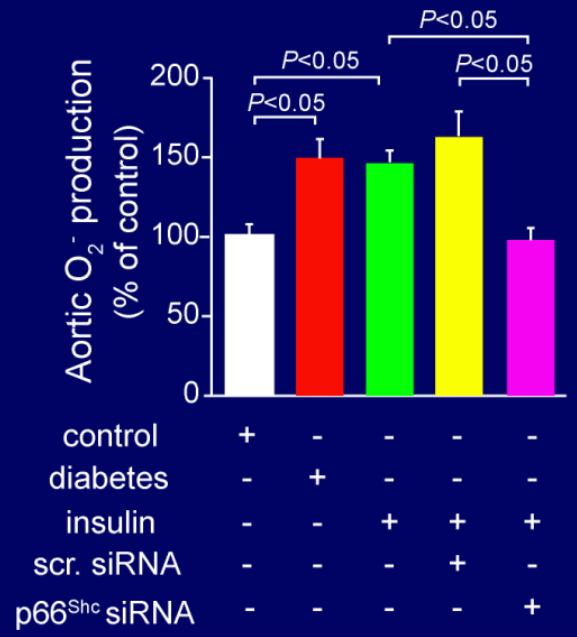


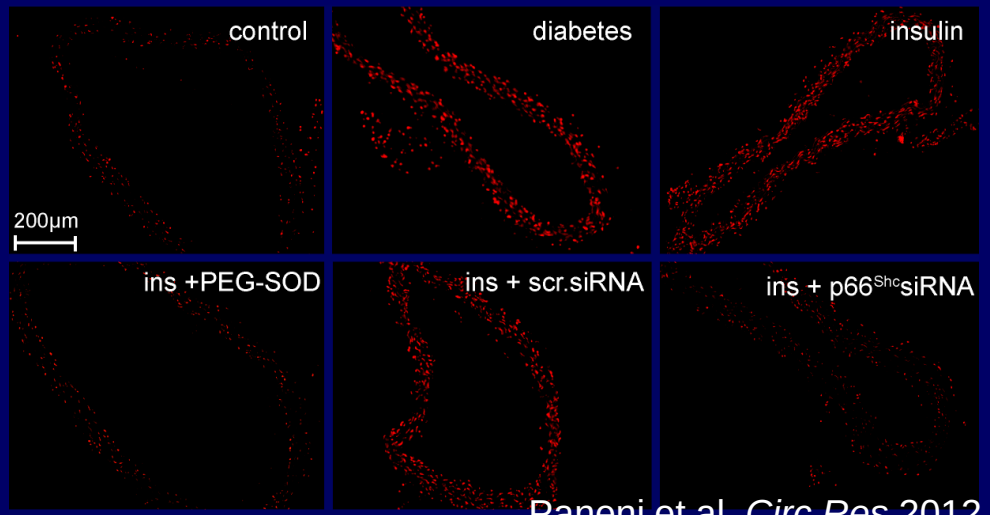


Paneni et al. *Circ Res* 2012

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

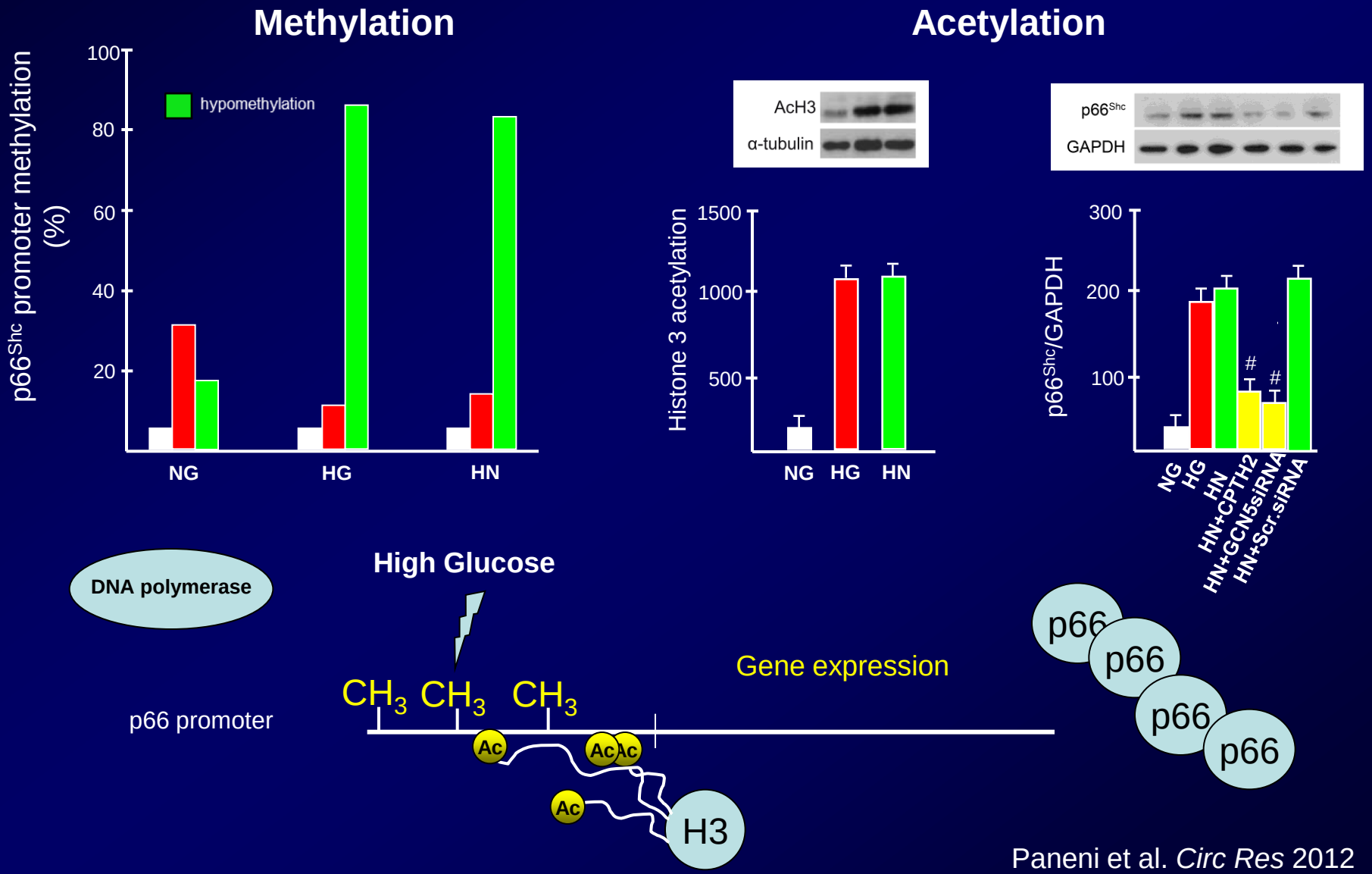




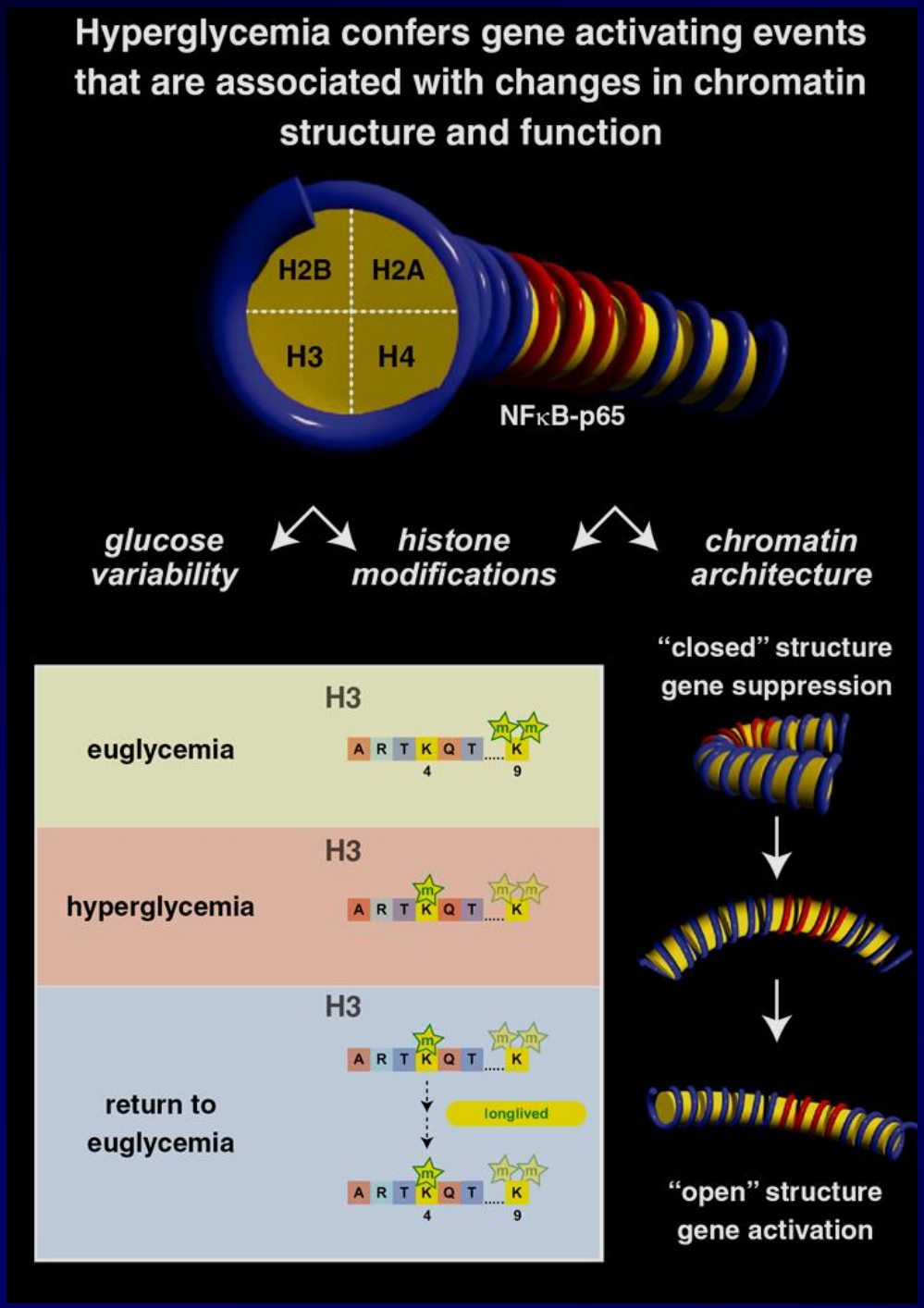


Paneni et al. *Circ Res* 2012

Persistent p66^{Shc} upregulation due to *de novo* transcription induced by epigenetic changes of promoter



Paneni et al. *Circ Res* 2012



HYPERGLYCEMIA

ROS

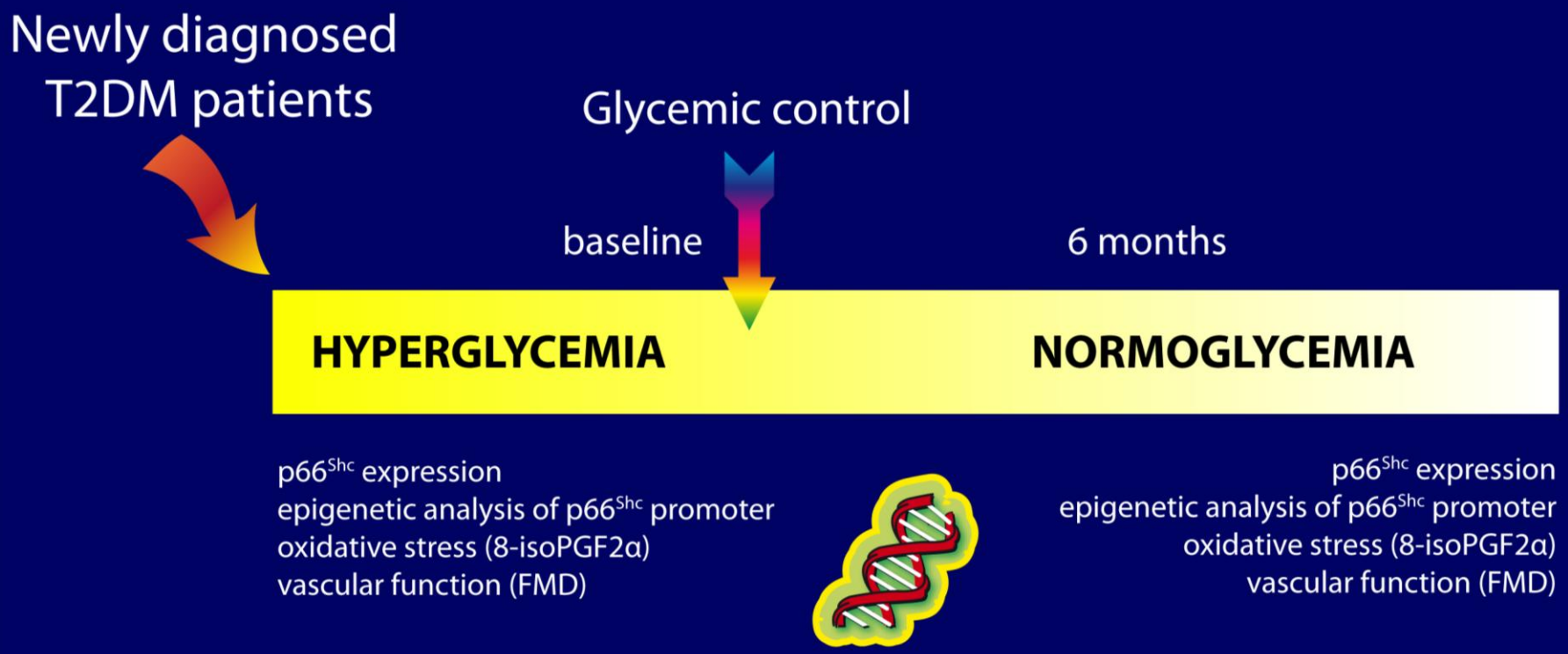
EPIGENETIC CHANGES

TRANSCRIPTION

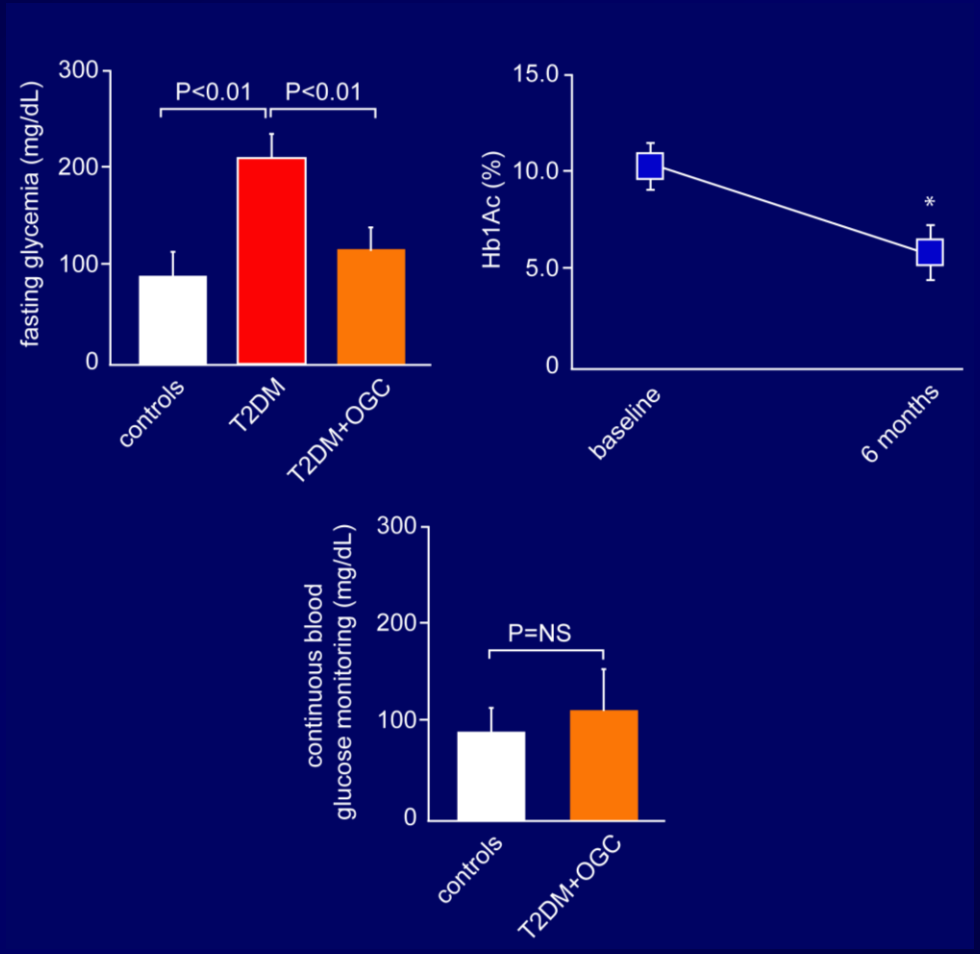
"MEMORY EFFECT"

Study Design

p66^{Shc} and vascular hyperglycemic memory in T2DM patients

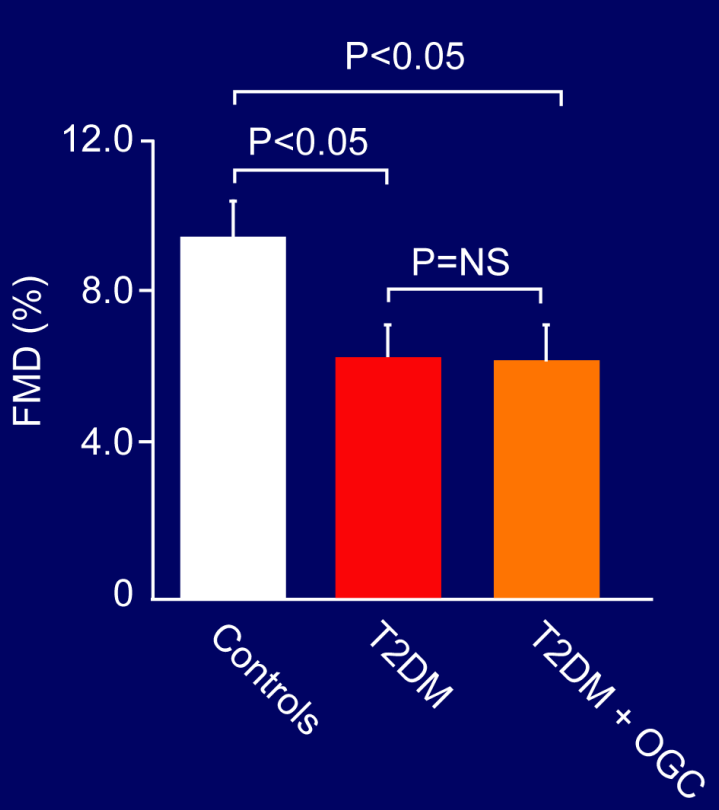


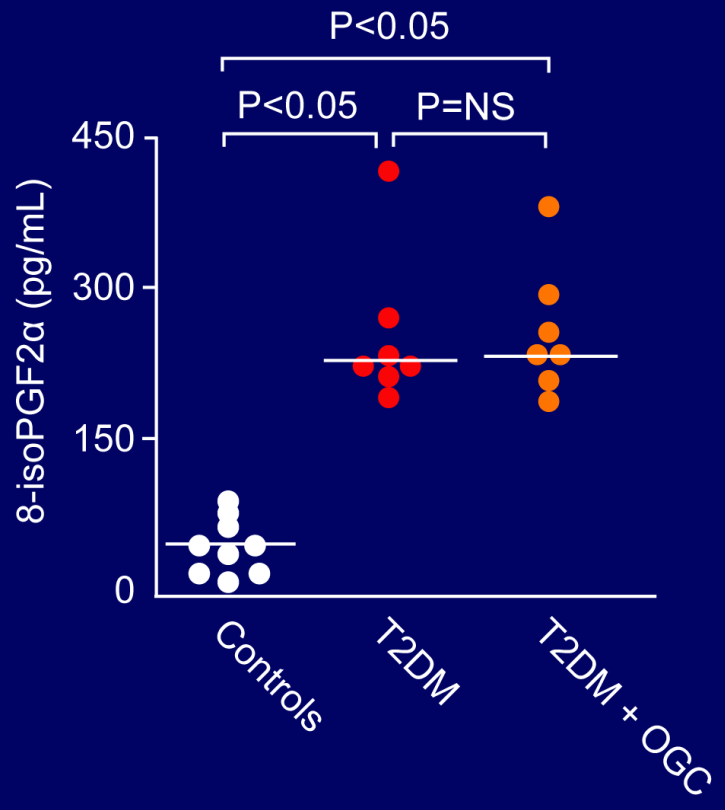
Achievement of optimal glycemic control in newly diagnosed T2DM patients



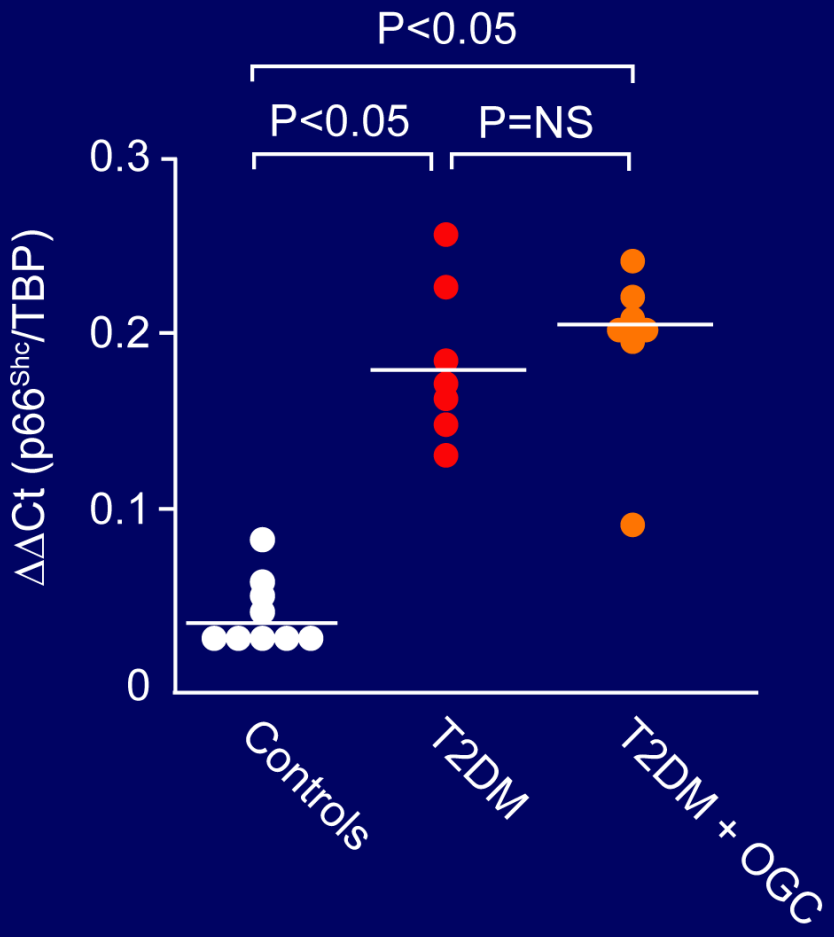
Cosentino et al. unpublished

Persistent endothelial dysfunction and oxidative stress in T2DM with optimal glycemic control (OGC)



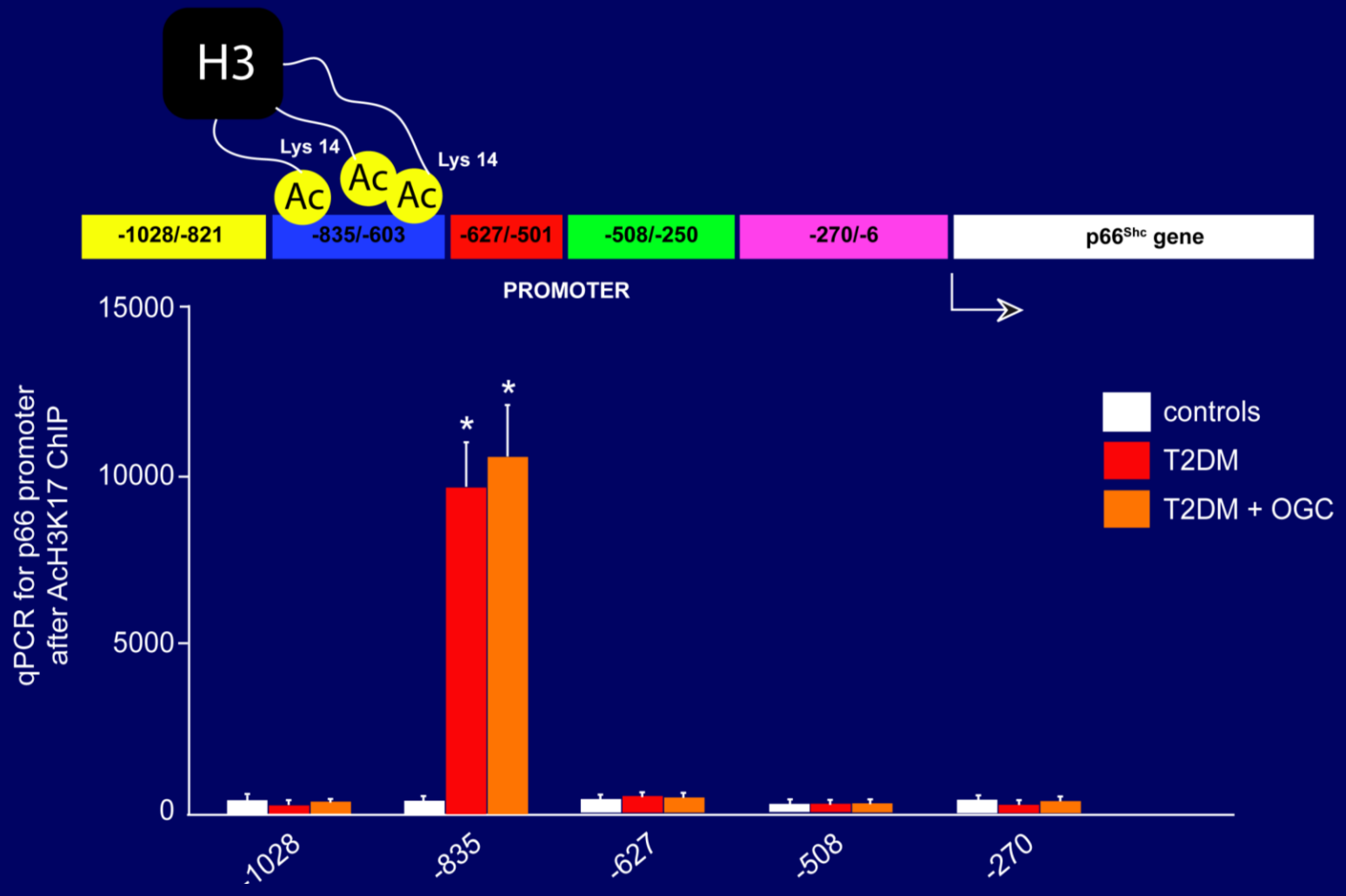


Glycemic control does not revert p66^{Shc} upregulation in patients with T2DM

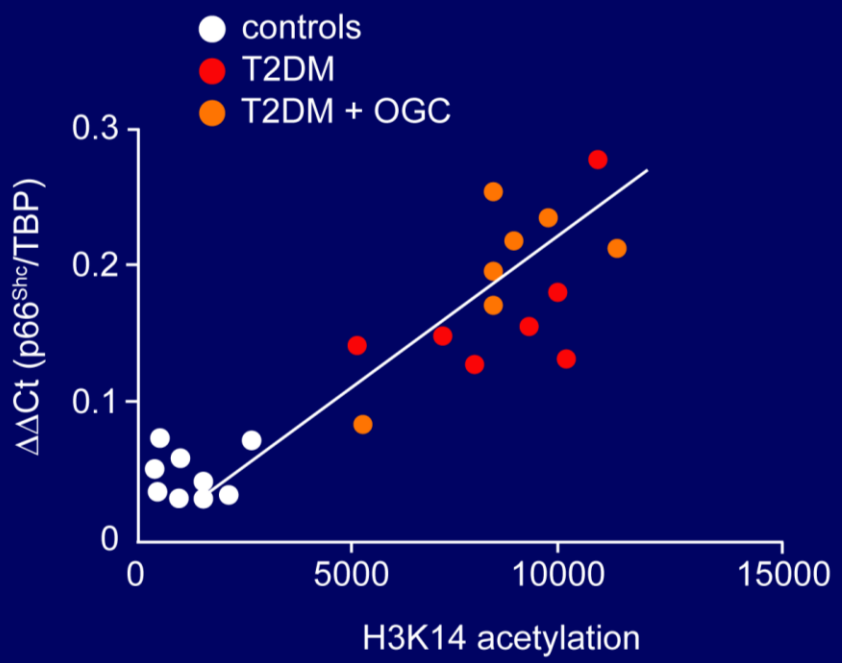


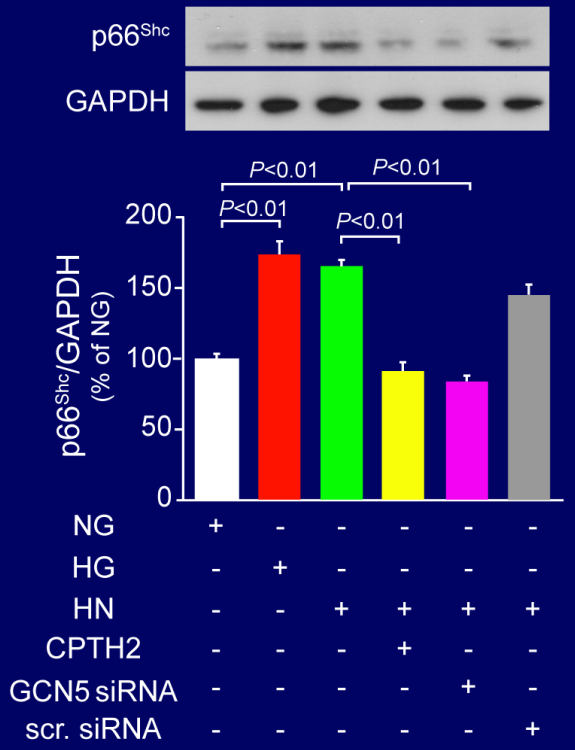
Epigenetic analysis of p66^{Shc} promoter in controls and T2DM

Histone 3 acetylation persists despite optimal glycemic control in T2DM



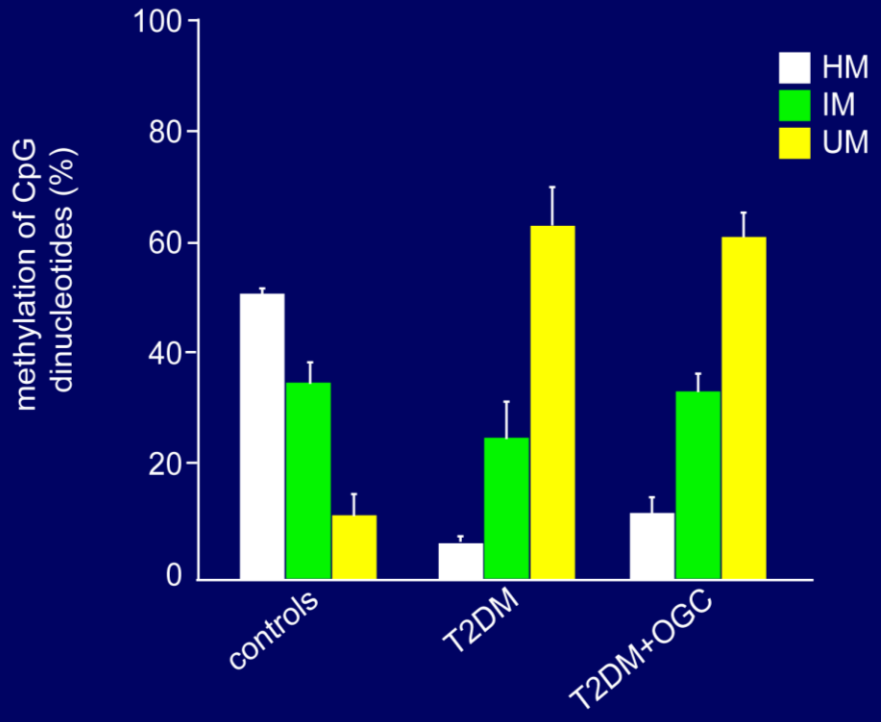
H3K14 acetylation favours sustained p66^{Shc} overexpression during subsequent normoglycemia

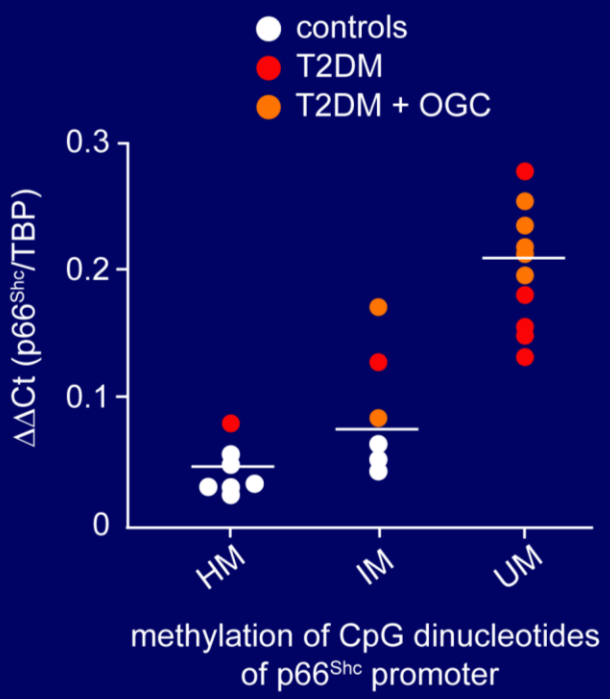




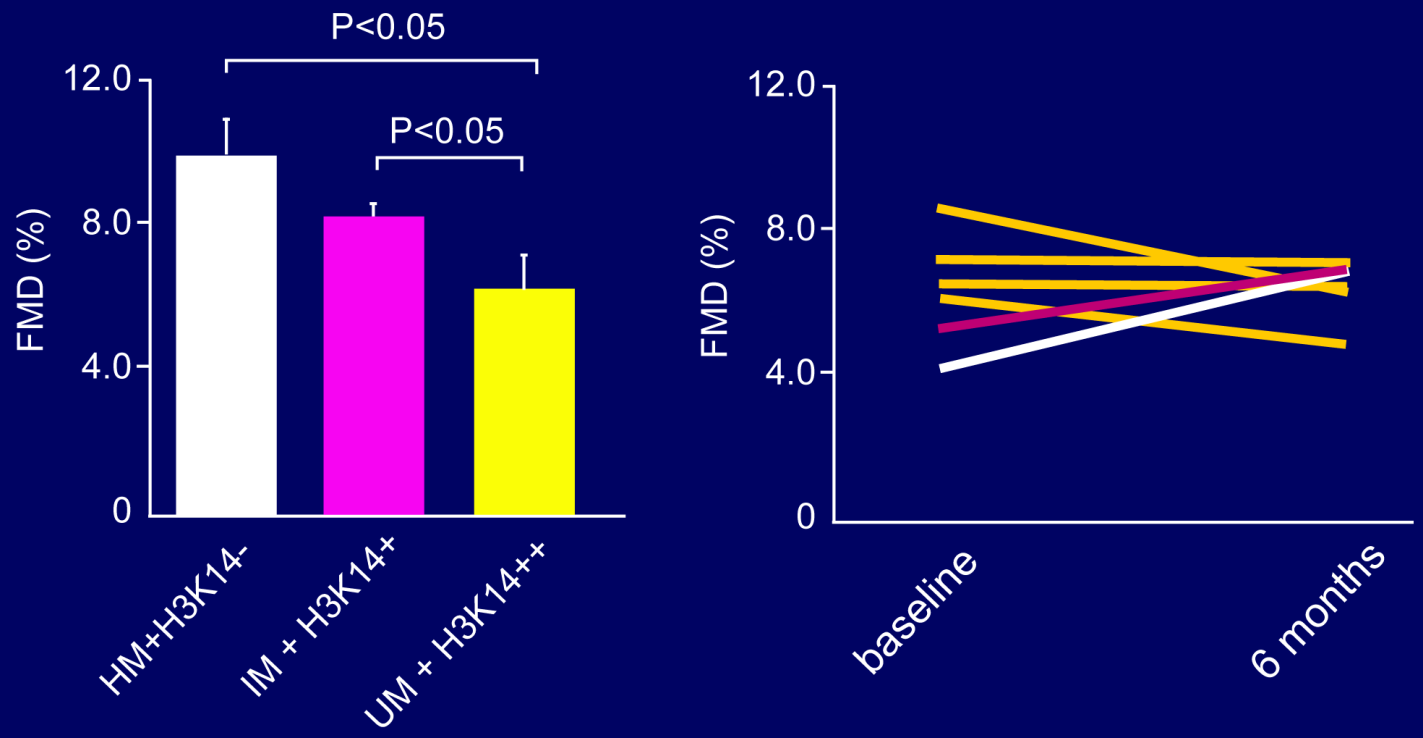
Paneni et al. Circ Res 2012

T2DM induces irreversible p66^{Shc} promoter demethylation

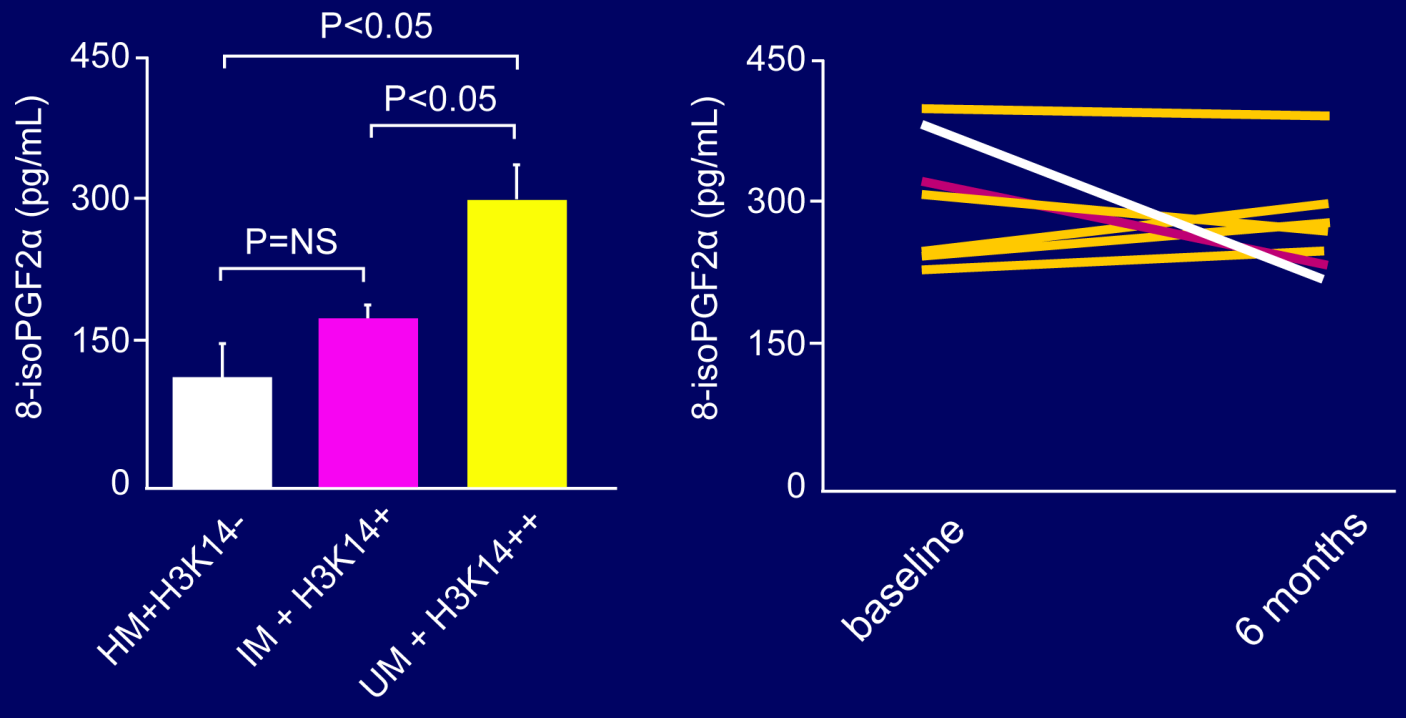




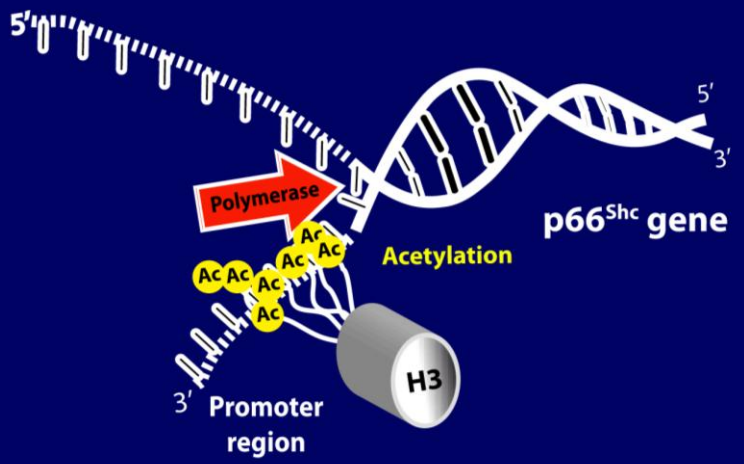
Adverse epigenetic remodeling of p66^{Shc} promoter correlates with persistent vascular dysfunction



Adverse epigenetic remodeling of p66^{Shc} promoter correlates with persistent oxidative stress

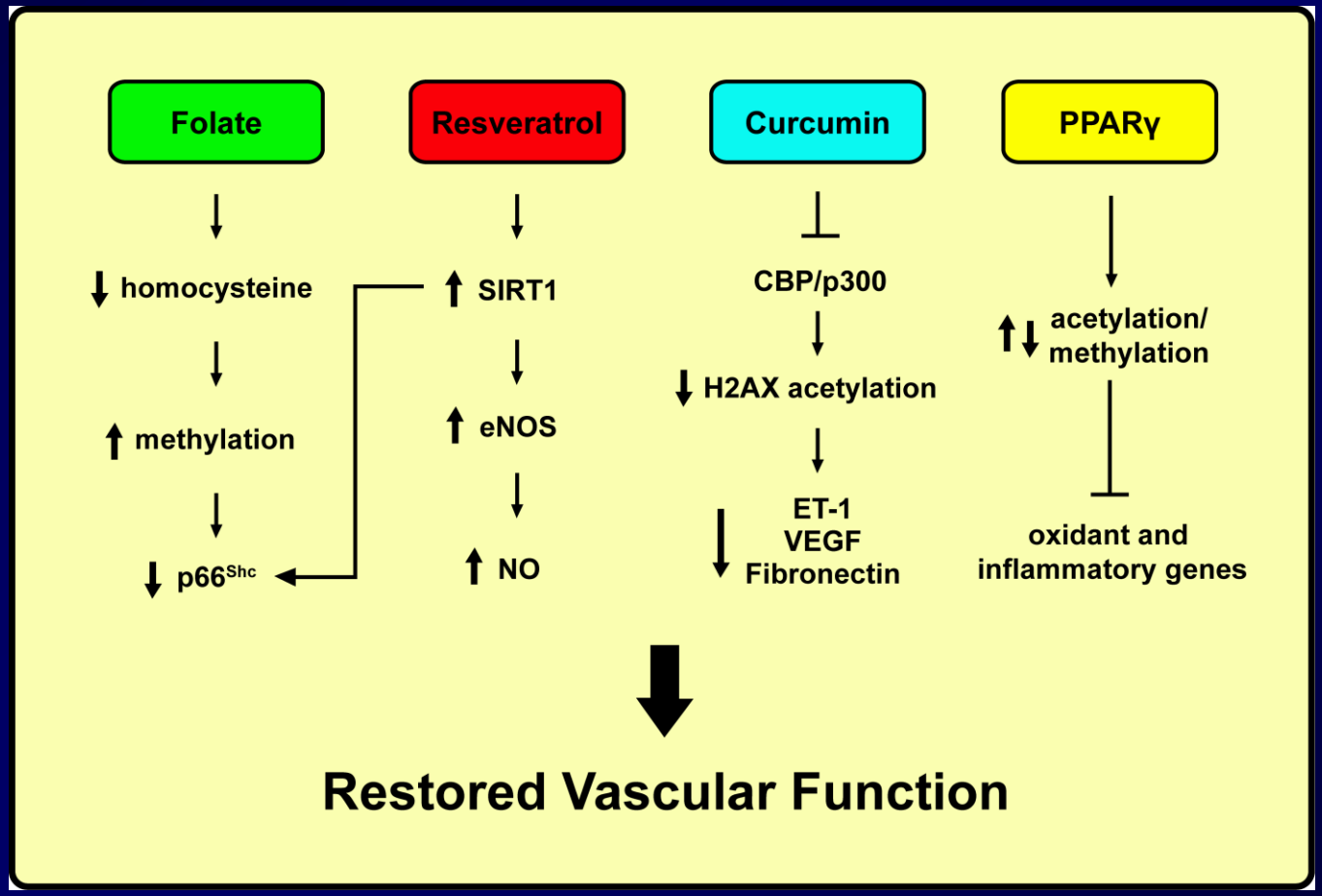


Take home message



- Cardiovascular risk burden is not eradicated by intensive glycemic control and new mechanism-based therapeutic strategies are needed
- Epigenetic regulation of $p66^{Shc}$ 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).

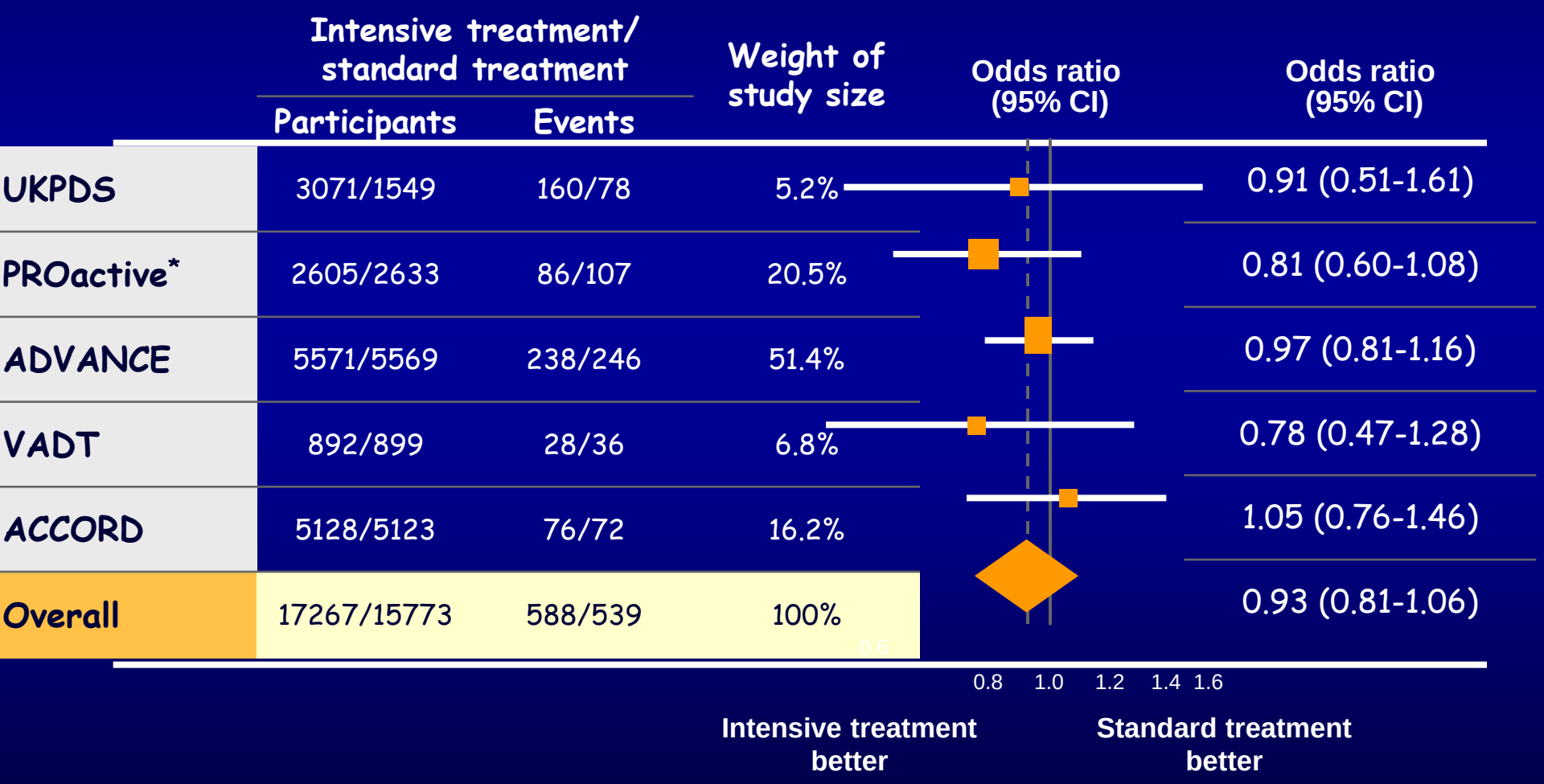
Mechanism-based approach for the treatment of diabetic vascular disease



Paneni et al. Diabetes 2013, *pending revision*

Why focusing on "hyperglycemic memory"?

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



Ray KK et al. *Lancet* 2009