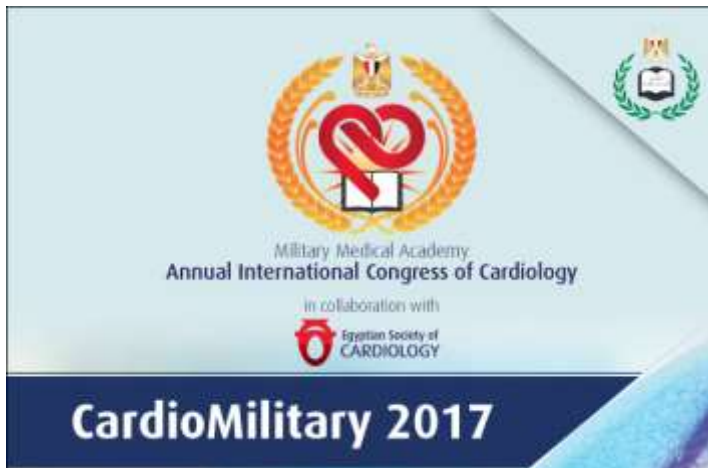


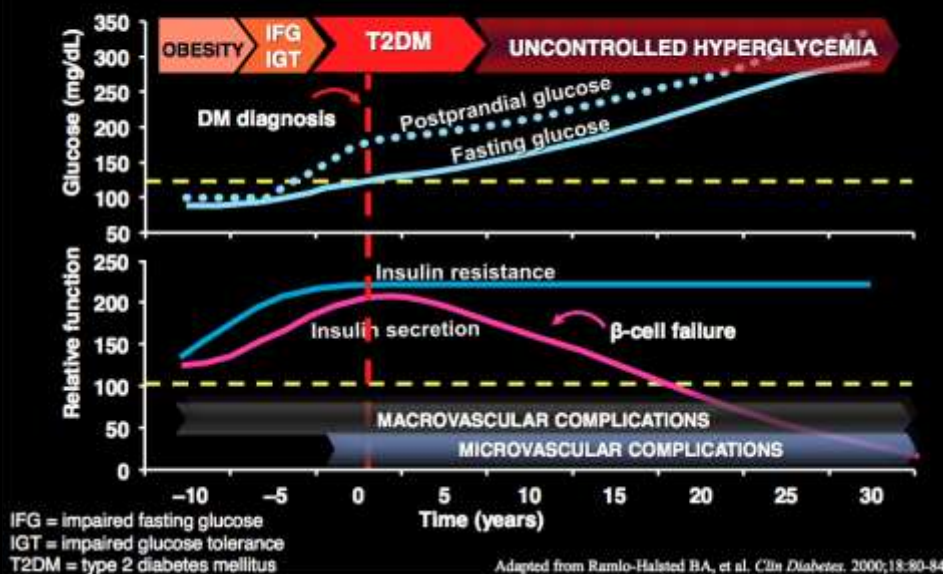
Insulin and atherosclerosis: Revisited

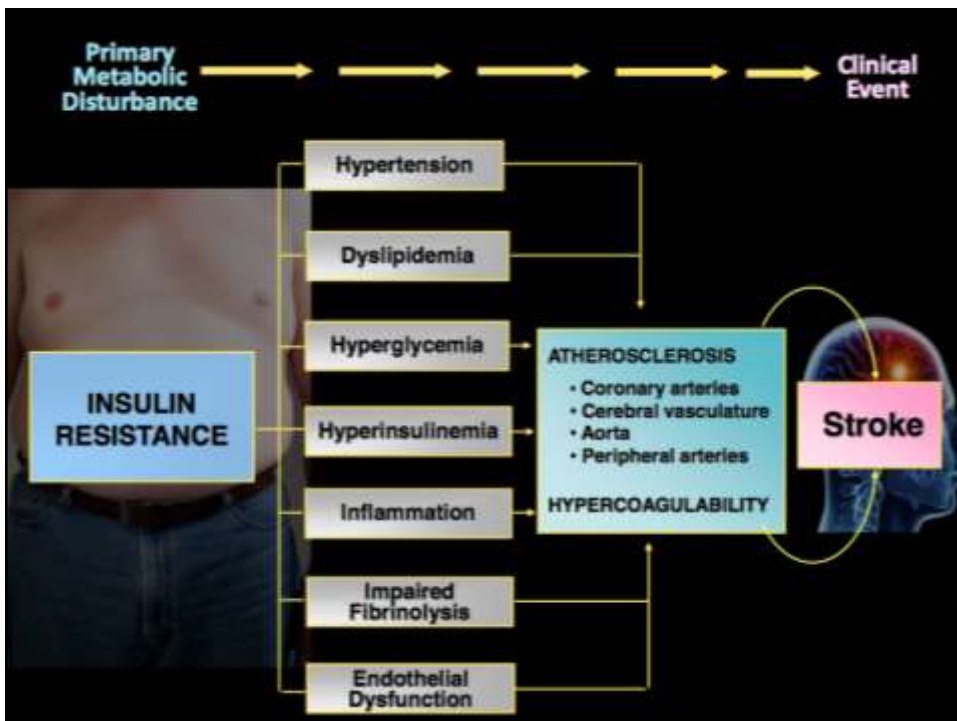
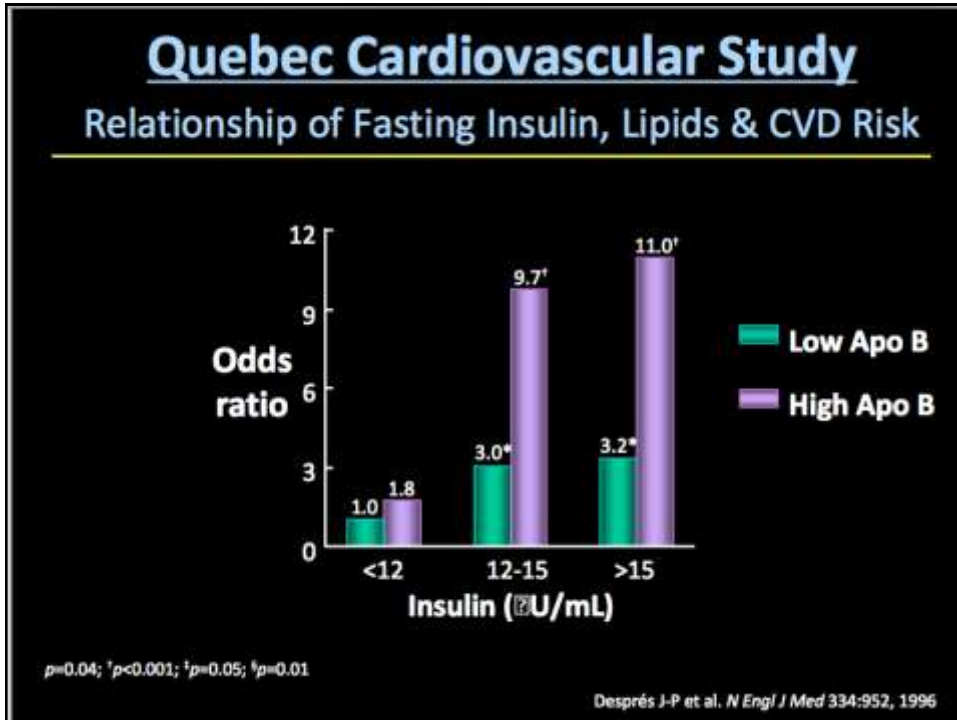


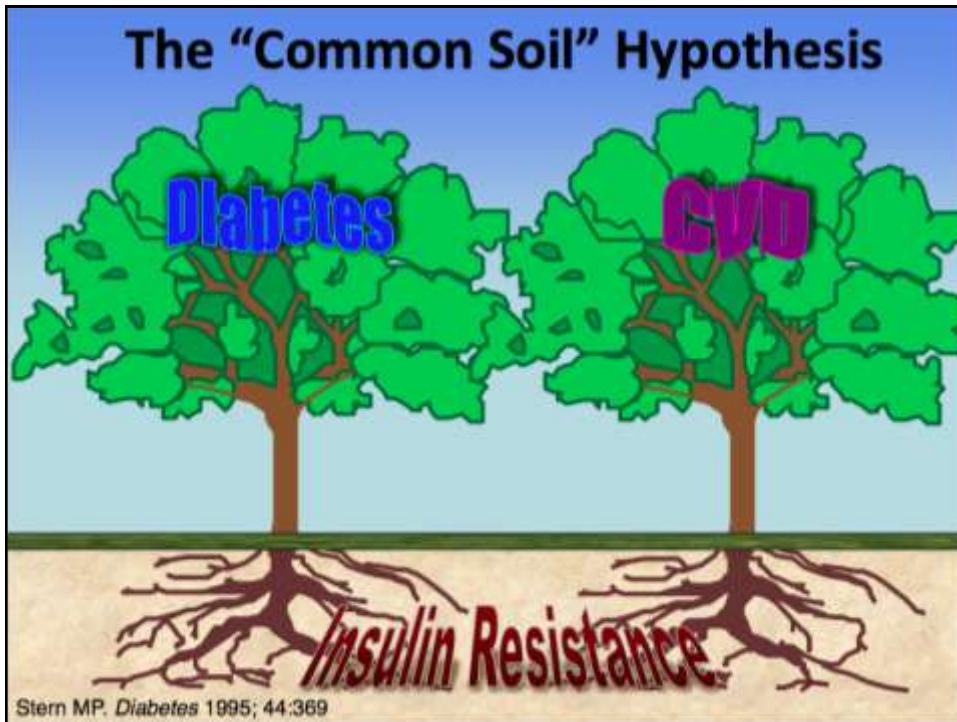
Nasser Taha, MD
Professor of Cardiology



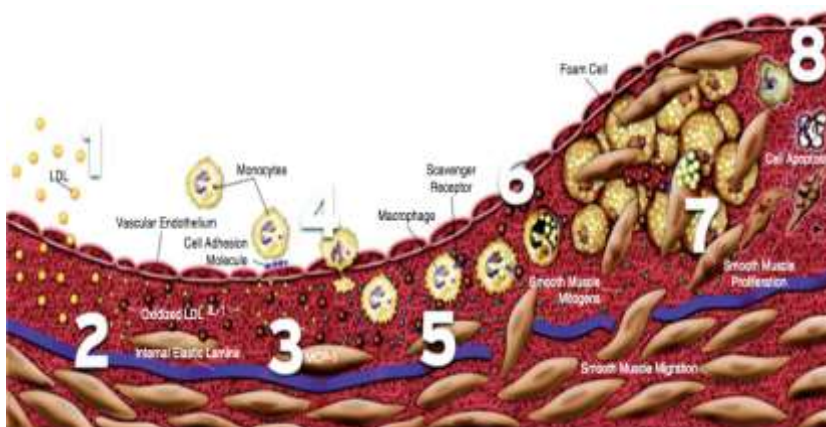
Pathophysiologic Progression of T2DM & Its Vascular Complications



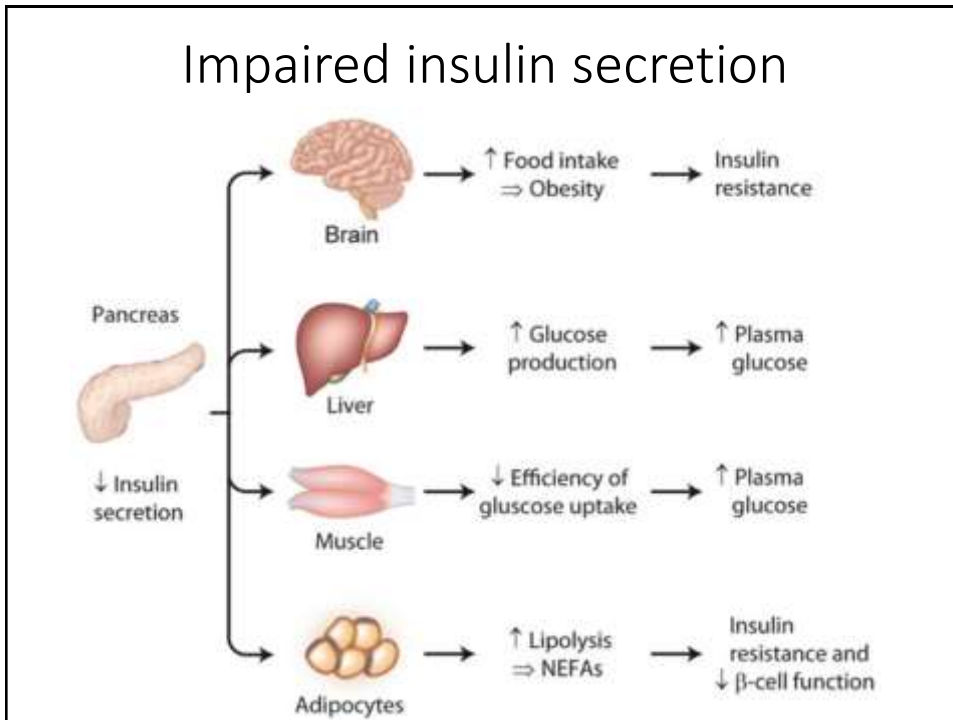




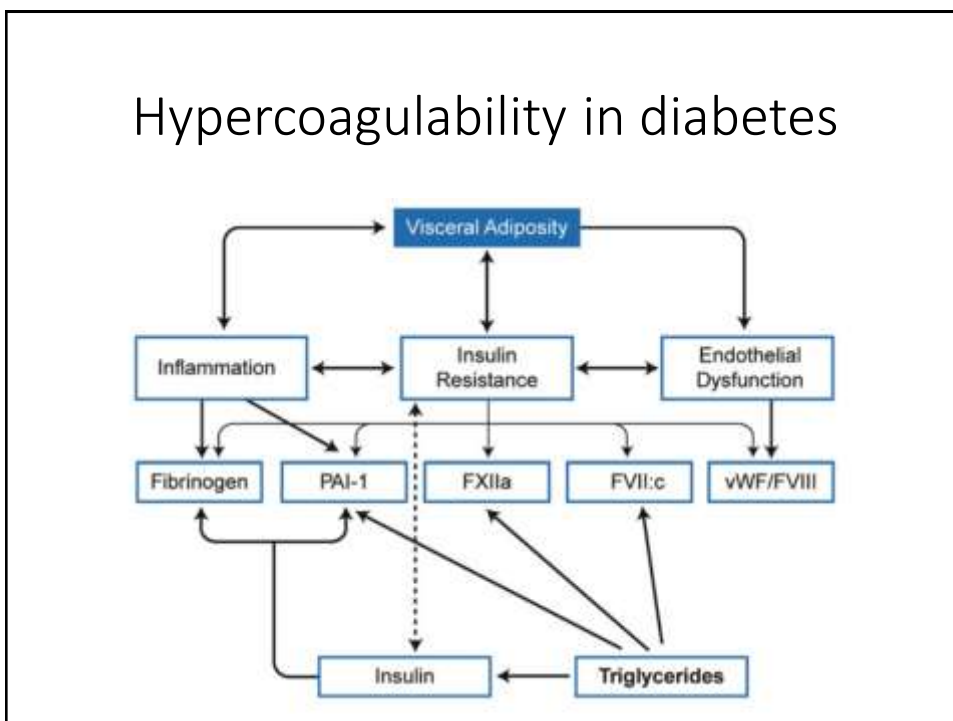
Atherosclerosis

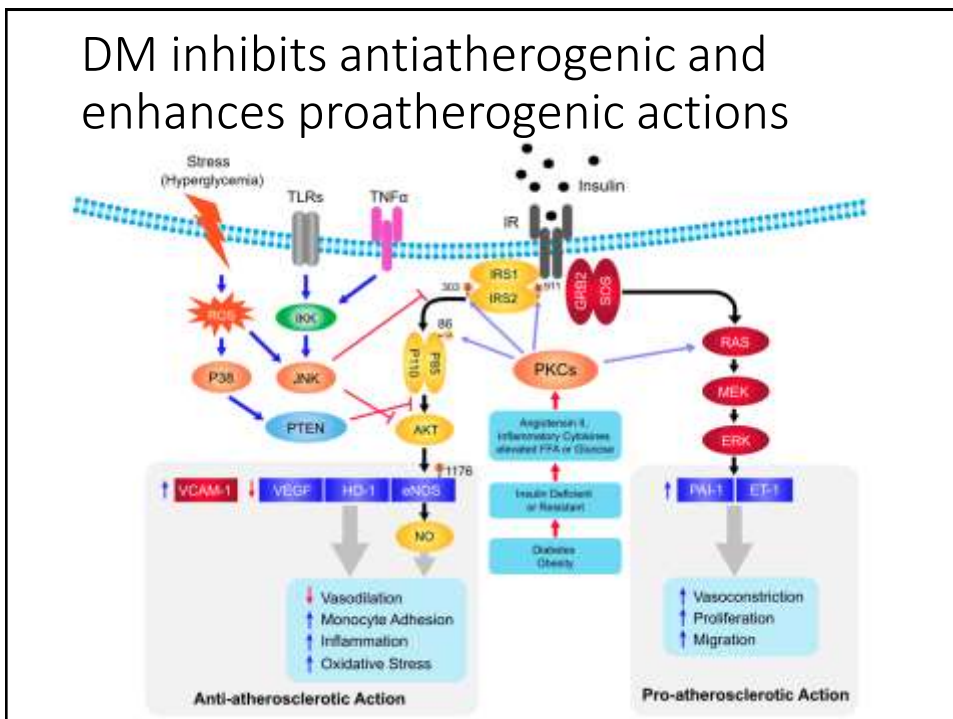
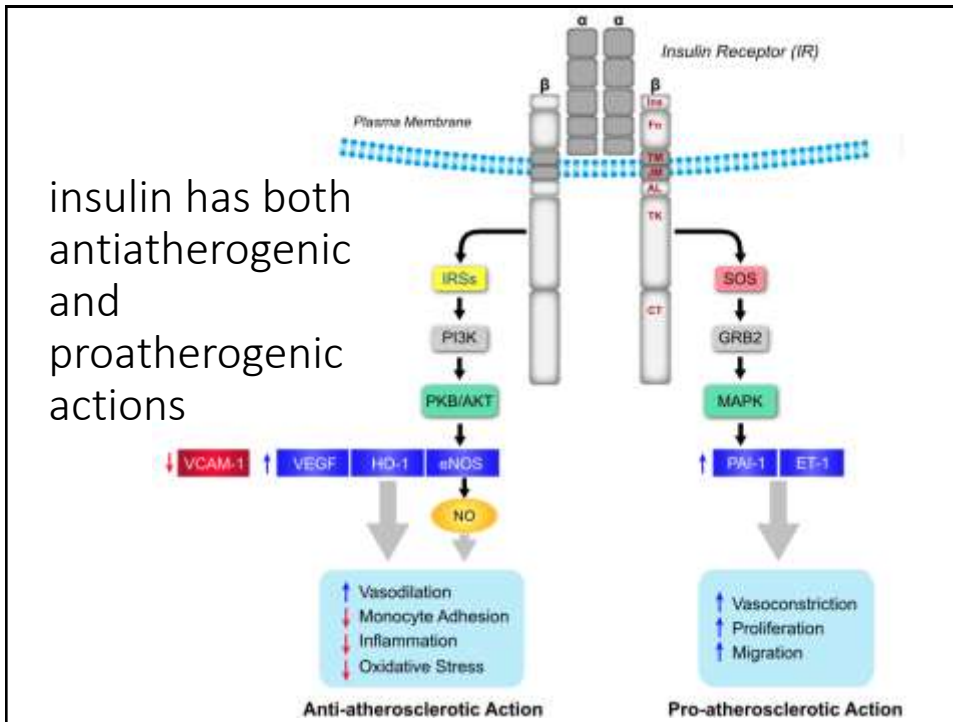


Impaired insulin secretion

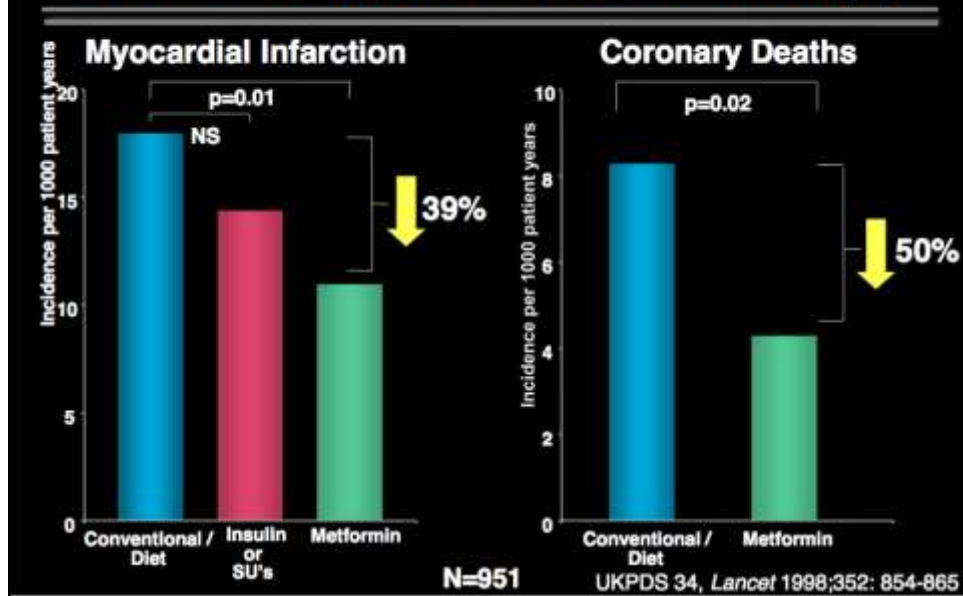


Hypercoagulability in diabetes

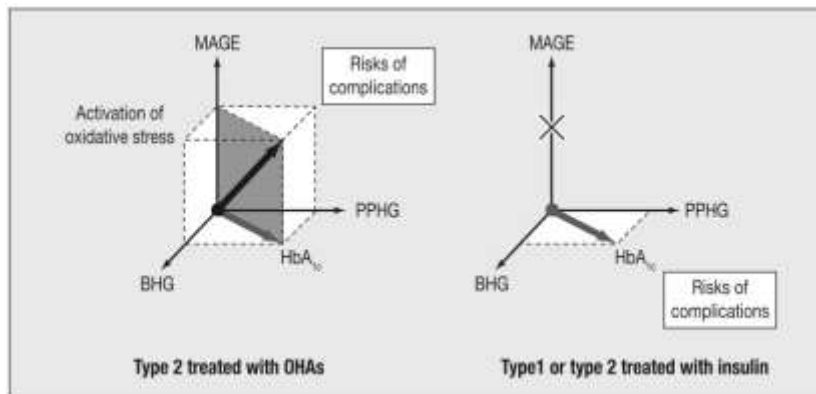




UKPDS 34 Substudy: Metformin Improves CVD Outcomes vs. Standard Therapy



Hyperglycemia and Mean amplitude of glycemic excursions (MAGE) increase complications in DM



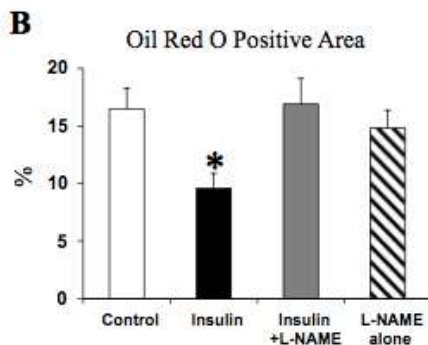
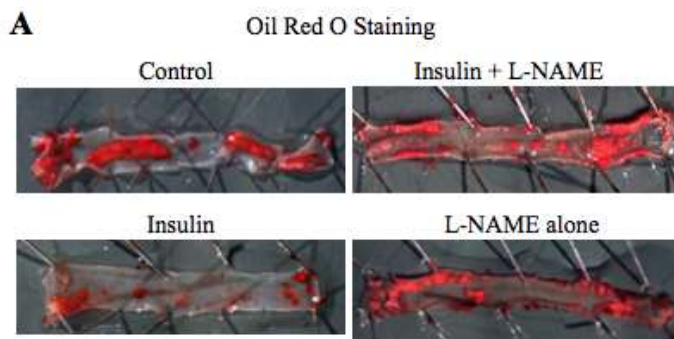
Insulin decreases atherosclerotic plaque burden and increases plaque stability via nitric oxide synthase in apolipoprotein E-null mice

Yusaku Mori,^{1,2*} Simon Chiang,^{1*} Michelle P. Bendeck,³ and Adria Giacca⁴

¹Department of Physiology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; ²Division of Diabetes, Metabolism, and Endocrinology, Showa University School of Medicine, Shinagawa, Tokyo, Japan; ³Department of Laboratory Medicine and Pathobiology, Ted Rogers Centre for Heart Research TBEP, University of Toronto, Ontario, Canada; and ⁴Department of Physiology and Medicine, Institute of Medical Science, Banting and Best Diabetes Centre, Toronto, Ontario, Canada

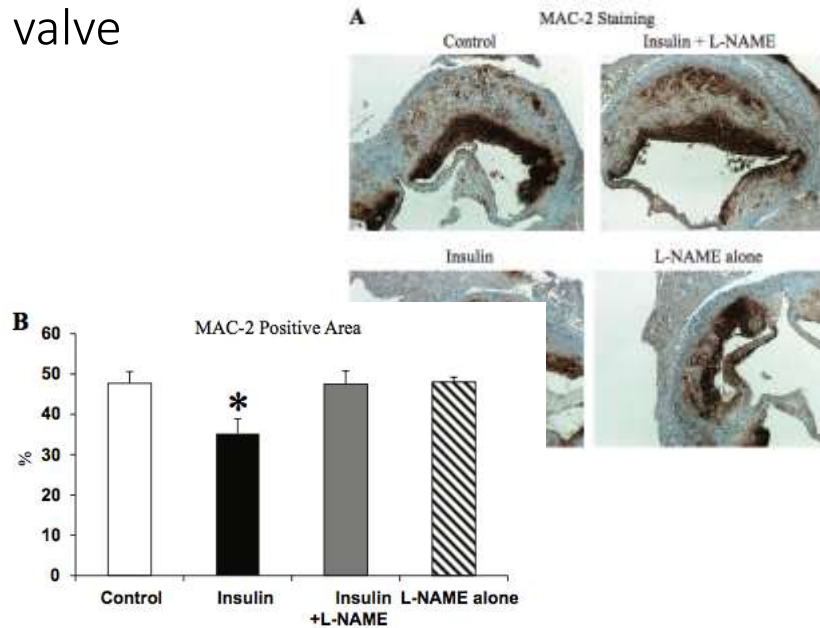
Submitted 7 July 2015; accepted in final form 19 May 2016

- Male apolipoprotein E-null mice (8 wk old)
- fed a high-cholesterol diet (1.25% cholesterol)
- 12-wk treatments:
 - control
 - insulin (0.05 U/day via subcutaneous pellet),
 - *N*-nitro-L-arginine methyl ester hydrochloride (L-NAME)
 - insulin plus L-NAME

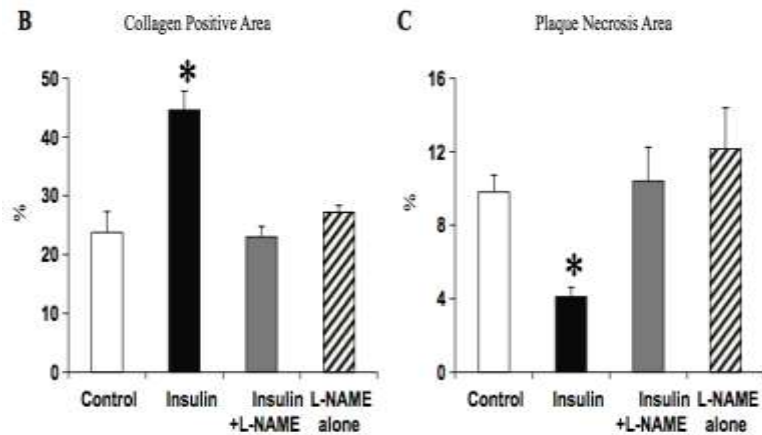


Atherosclerotic lesions in the descending aorta

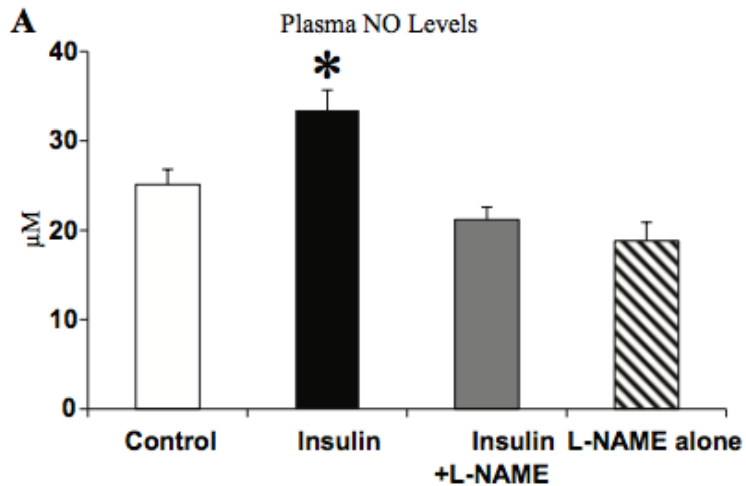
Macrophage accumulation of the Aortic valve



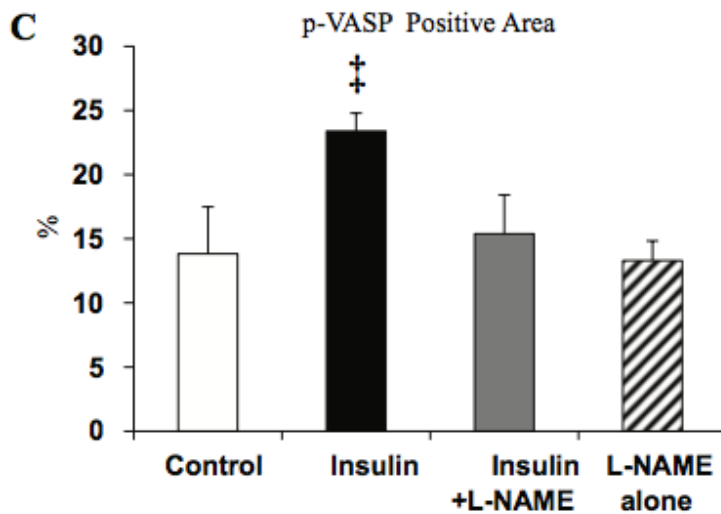
Collagen and plaque Necrosis



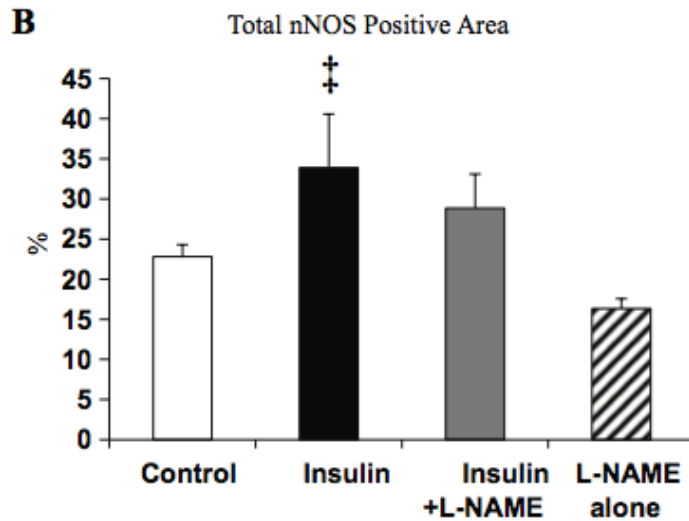
Plasma Nitric Oxide levels



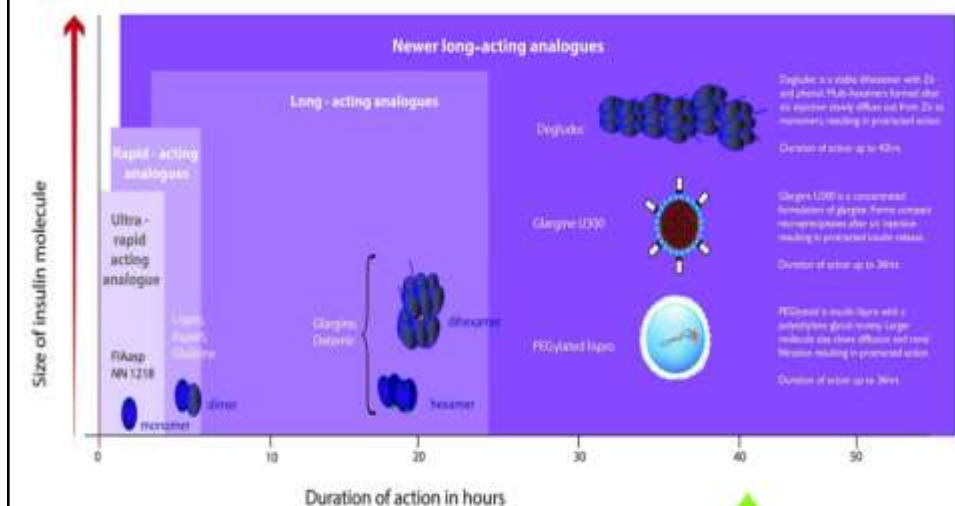
phosphorylated vasodilator-stimulated phosphoprotein (p-VASP)



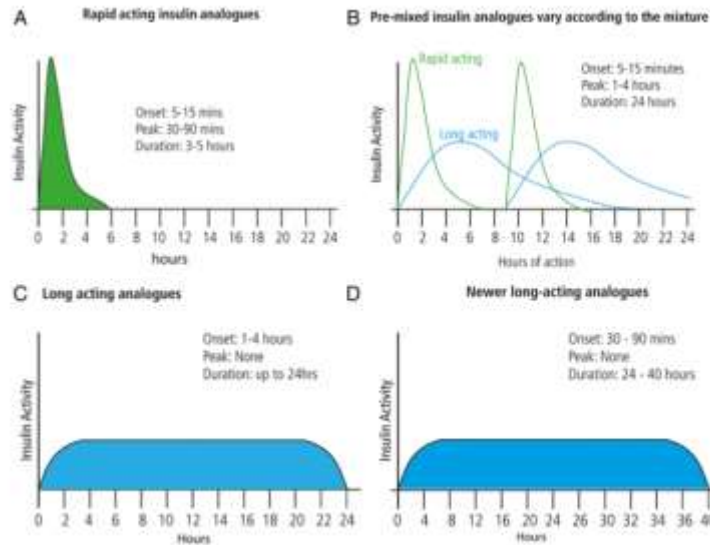
Neuronal (n)NOS expression at the aortic valve



Newer insulins



Pharmaco-kinetics of Insulins



Trials on Glargine

Diabetologia. 2014; 57(7):1325-31. doi: 10.1007/s00125-014-3258-4. Epub 2014 Apr 26.

Basal insulin glargine and microvascular outcomes in dysglycaemic individuals: results of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial.

ORIGIN trial investigators, Gilbert PG, Mann JF, Hansen M, Scirica B, Bosch J, Yusuf S, Gerstein HC

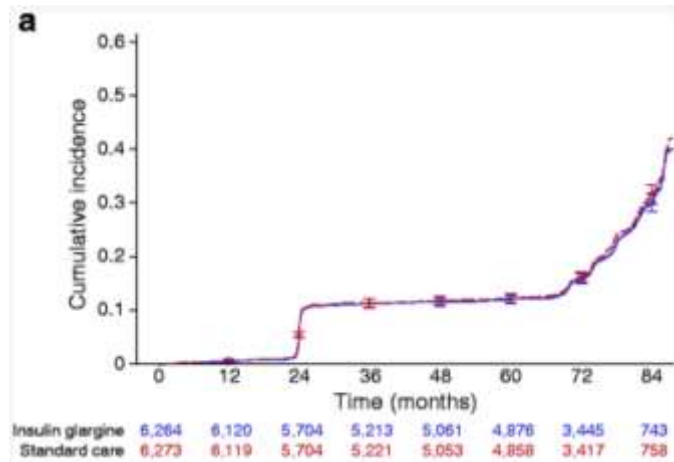
Cardiovascular and Other Outcomes Postintervention With Insulin Glargine and Omega-3 Fatty Acids (ORIGALE)

ORIGIN Trial Investigators*

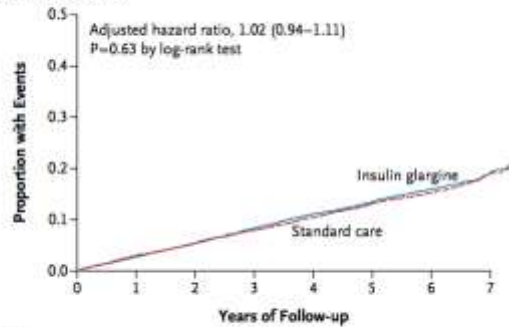
Corresponding author: Zubin Punthakee, zubin.punthakee@mcmaster.ca.

Diabetes Care 2016 May; 39(5): 709-716. <https://doi.org/10.2337/dc15-1676>

1ry outcome



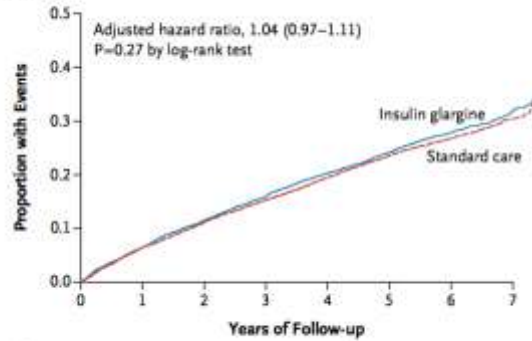
A Myocardial Infarction, Stroke, or Death from Cardiovascular Causes (Coprimary Outcome)



No. at Risk

	0	1	2	3	4	5	6	7
Insulin glargine	6264	6057	5850	5619	5379	5151	3611	766
Standard care	6273	6043	5847	5632	5415	5156	3639	800

B Coprimary Outcome plus Revascularization or Hospitalization for Congestive Heart Failure

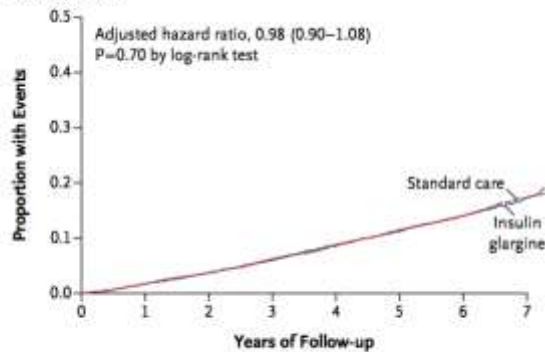


No. at Risk

Insulin glargine	6264	5827	5474	5153	4835	4523	3076	631
Standard care	6273	5833	5493	5186	4880	4555	3142	663

All cause death

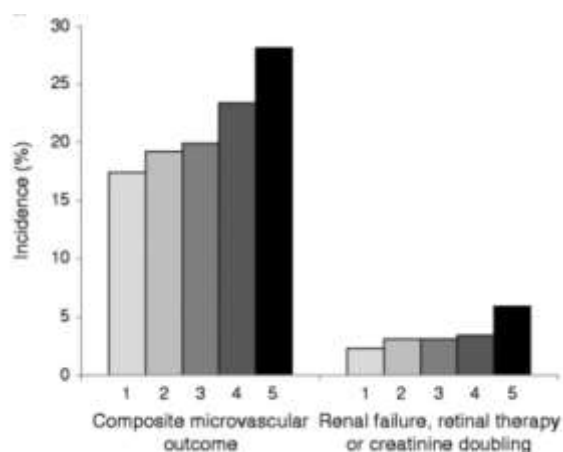
C Death from Any Cause



No. at Risk

Insulin glargine	6264	6150	6024	5857	5687	5508	3906	847
Standard care	6273	6159	6029	5878	5710	5501	3931	878

Outcome per HA1c Quintiles



Safety Outcome

Table 3. Incidence of a First Episode of Severe Hypoglycemia.

Variable	Insulin Glargine (N=6264)	Standard Care (N=6273)	P Value
Severe hypoglycemia*			
Participants with ≥ 1 episode — no. (no./100 person-yr)	359 (1.00)	113 (0.31)	<0.001
Total episodes during follow-up — no.	457	134	
Confirmed nonsevere symptomatic hypoglycemia†			
Participants with ≥ 1 episode — no. (no./100 person-yr)	2614 (9.83)	904 (2.68)	<0.001
Episodes/yr in participants with ≥ 1 episode — median (interquartile range)	0.5 (0.2–1.4)	0.3 (0.2–0.8)	<0.001
Participants with no confirmed episodes during follow-up — no. (%)	3650 (58.3)	5369 (85.6)	<0.001
Any nonsevere symptomatic hypoglycemia			
Participants with ≥ 1 episode — no. (no./100 person-yr)	3575 (16.72)	1580 (5.16)	<0.001
Episodes/yr in participants with ≥ 1 episode — median (interquartile range)	1.1 (0.4–3.1)	0.5 (0.2–1.3)	<0.001
Participants with no episodes during follow-up — no. (%)	2689 (42.9)	4693 (74.8)	<0.001

Devote Trial

DEVOTE was designed to investigate the CV safety of Tresiba® versus insulin glargine U100 in type 2 diabetes



DEVOTE®: Top-line results

CV safety:

- **9% less** Major Adverse Cardiovascular events (MACE) in favour of Tresiba® relative to insulin glargine U100, with no statistically significant difference

Hypoglycaemia:

- **40%** significant reduction in the **rate** of adjudicated **severe hypoglycaemia**
- **27%** significant reduction in the **incidence** of adjudicated **severe hypoglycaemia**
- **54%** significant reduction in the **rate** of adjudicated **nocturnal severe hypoglycaemia**

Points to remember

- Diabetes induces atherosclerosis
- Hyperglycemia and insulin resistance cause atherosclerosis through blocking the NO-dependent anti-atherogenic properties of insulin and activating the pro-thrombotic pathways
- Animal trials have proven the anti-atherogenic properties of insulin

Points to remember

- Clinical trials have proven the efficacy of treating insulin resistance in reduction of the cardiovascular adverse outcomes of diabetes
- Newer insulins have failed to demonstrate better CV outcomes than conventional guideline treatment
- Newer insulins achieved marked reduction of hypoglycemic episodes versus guideline recommended treatment
- Degludec insulin caused 40% reduction of hypoglycemic attacks with 9% reduction of CV outcomes versus glargine insulin



THANK YOU

