Insulin Toxicity in Type 2 Diabetes

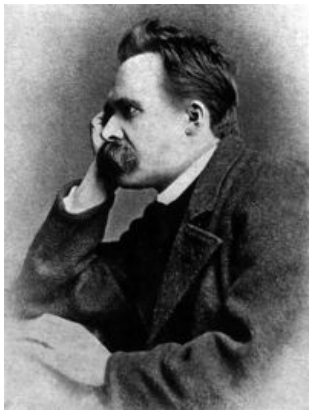
"For the greatest enemy of truth is very often not the lie – deliberate, contrived and dishonest – but the myth – persistent, persuasive, and unrealistic. Too often we hold fast to the clichés of our forebears. We subject all facts to a prefabricated set of interpretations. We enjoy the comfort of opinion without the discomfort of thought."

President John F. Kennedy

Yale University commencement address (June 11, 1962)

From: www.nusi.org

How to Cure Type 2 Diabetes

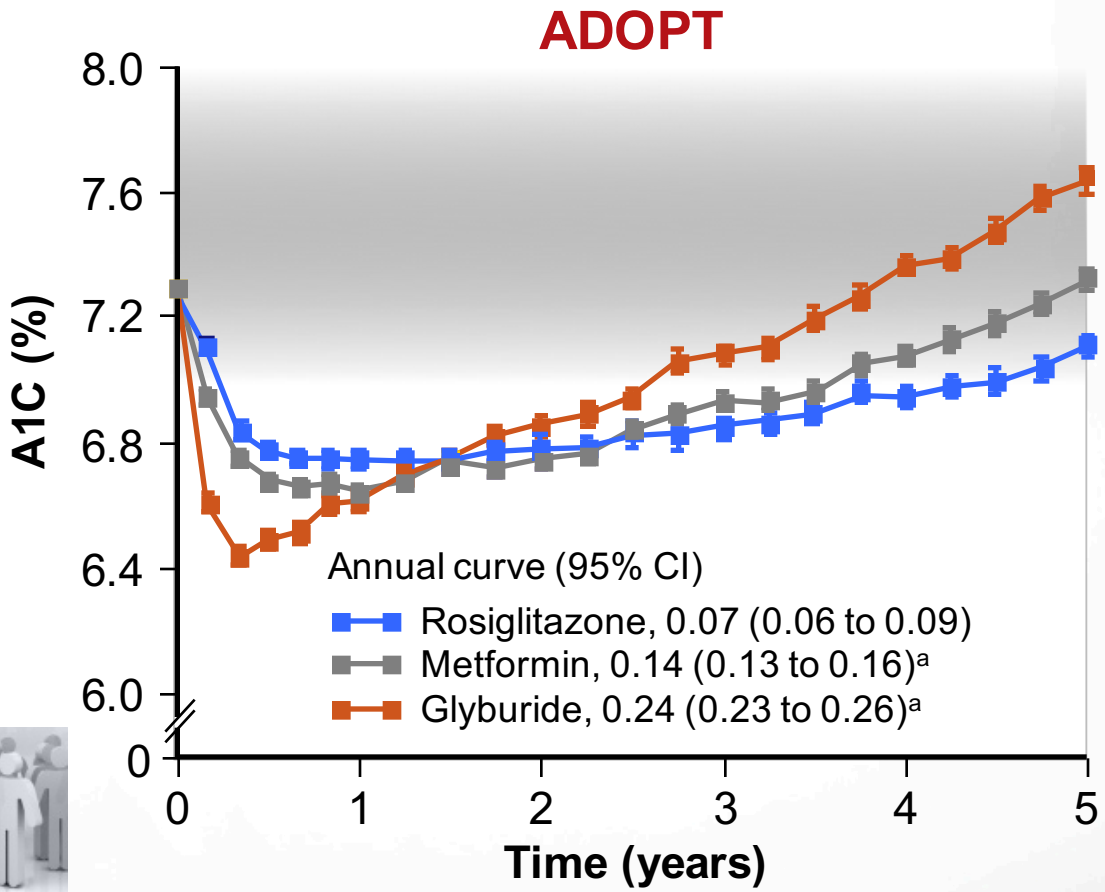


“In individuals, insanity is rare; but in groups, parties, nations and epochs, it is the rule.”

— Friedrich Nietzsche

It is Hard to Treat T2DM Adequately…

Because T2DM is a Progressive Disease



Treatment difference (95% CI)

Rosiglitazone vs. metformin,
−0.13 (−0.22 to −0.05);
$p = 0.002$

Rosiglitazone vs. glyburide,
−0.42 (−0.50 to −0.33);
$p < 0.001$

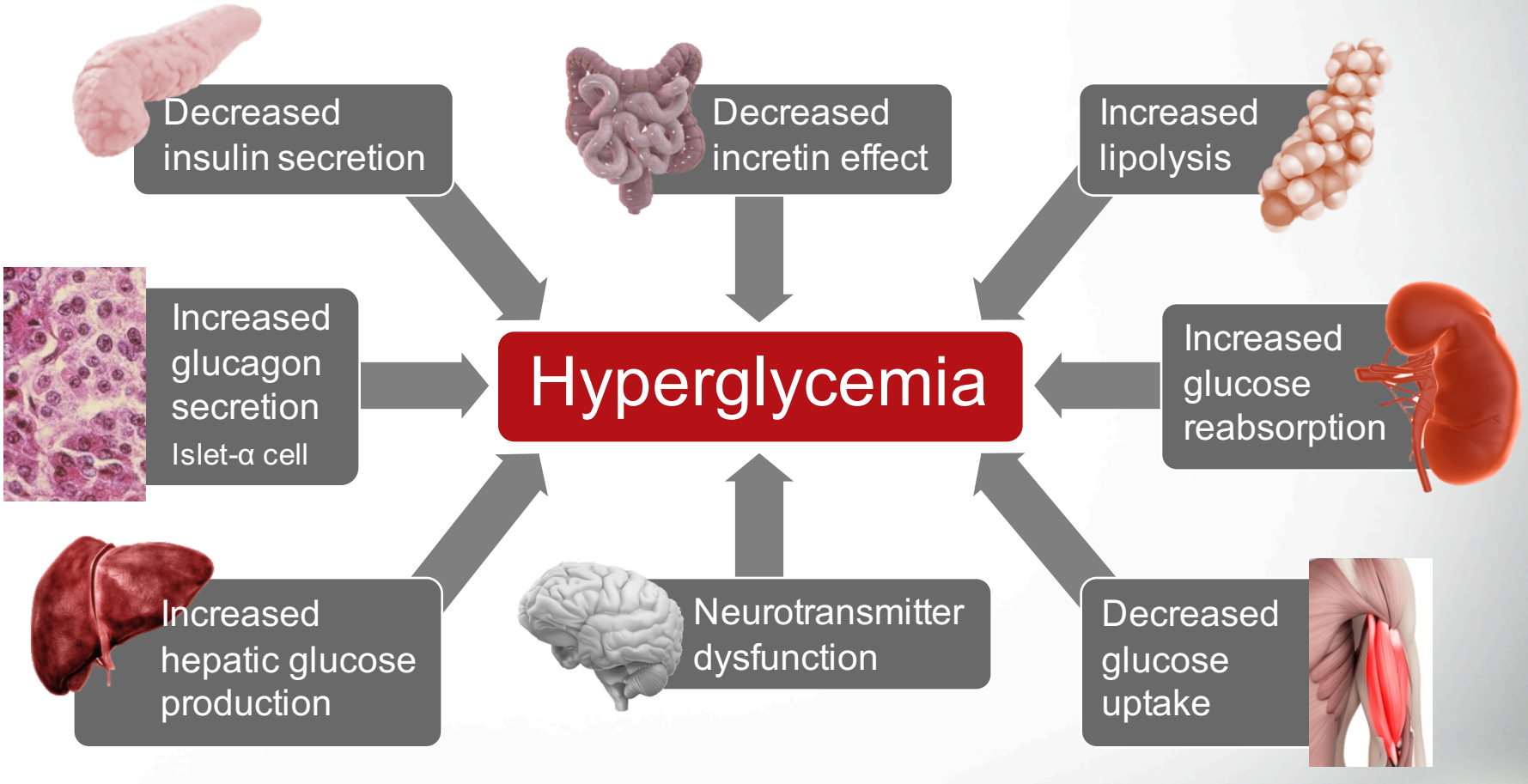
No. of patients	4012	3308	2991	2583	2197	822

[a]Rosiglitazone vs. other treatments.

Kahn SE et al. N Engl J Med 2006; 355:2427-43.

It is Hard to Treat T2DM Adequately…

Because T2DM has Multiple Pathophysiologic Abnormalities



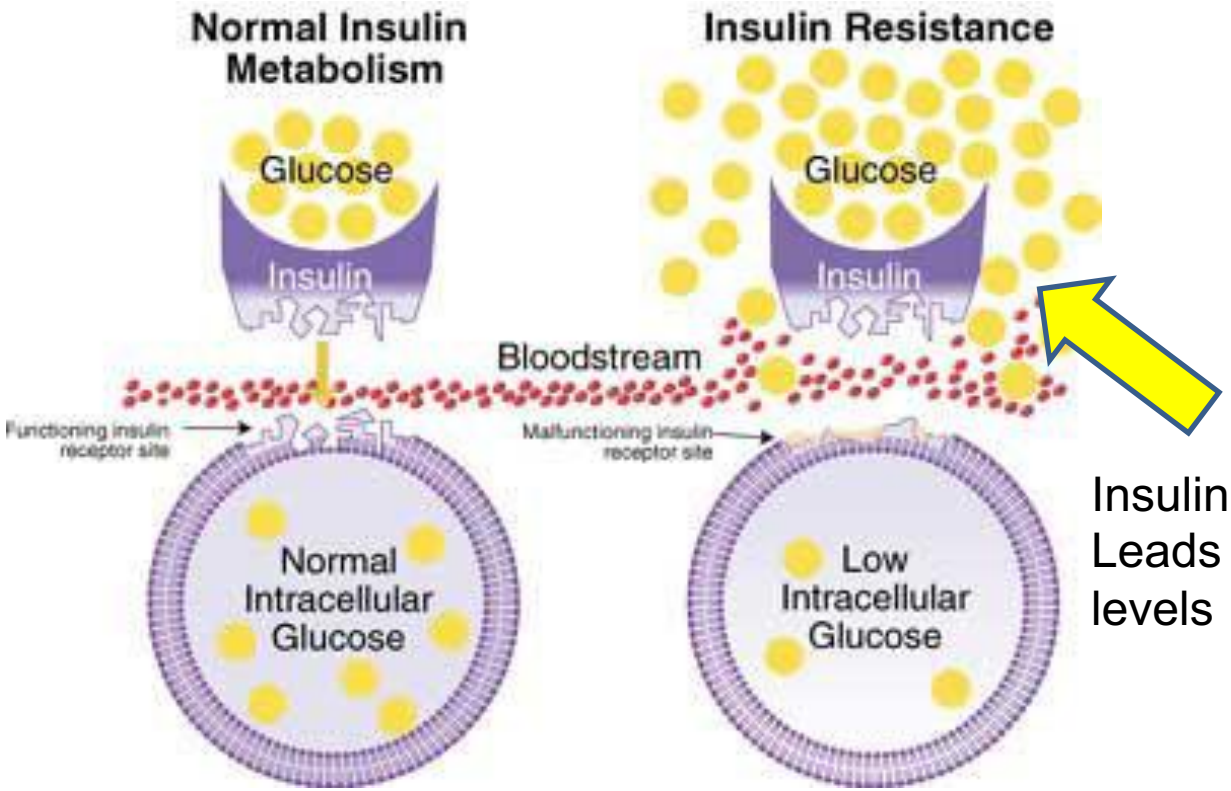
DeFronzo R. Diabetes 2009; 58:773-85.

Diabetes

Disease	Cause	Treatment	Symptom	Symptomatic Treatment
Diabetes Insulin Resistance	**????**	**?????**	High Blood Sugars	Insulin OHA
Infection	Bacteria	Antibiotic	Fever	Acetominophen

Does not alter disease process

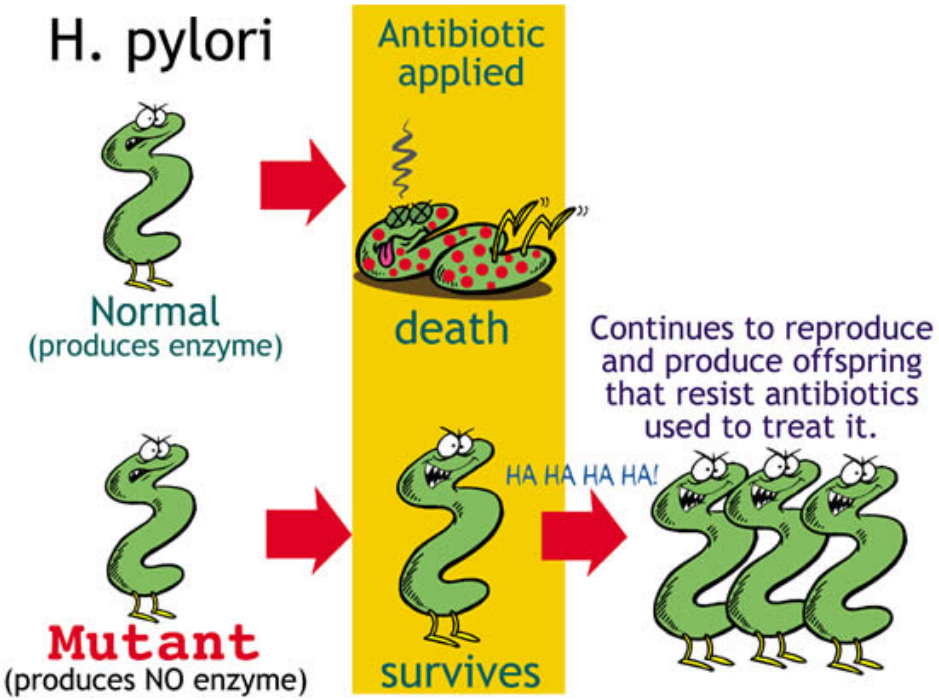
What causes Insulin Resistance?



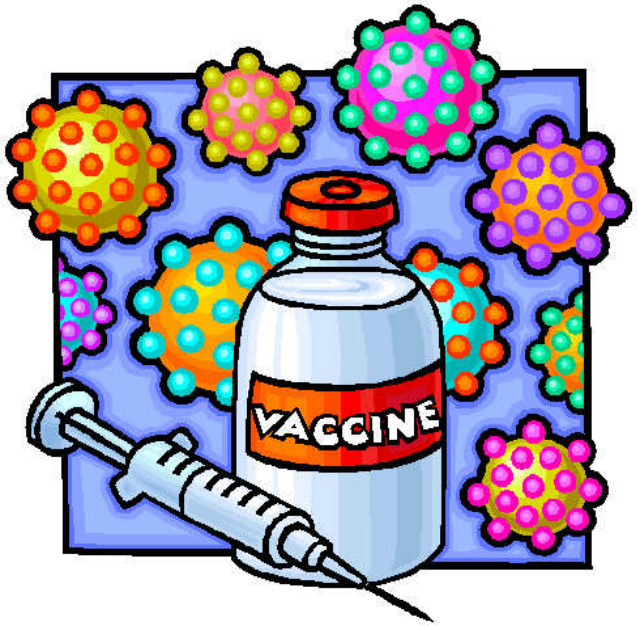
Insulin resistance
Leads to high insulin levels

How do we develop resistance in a biological system?

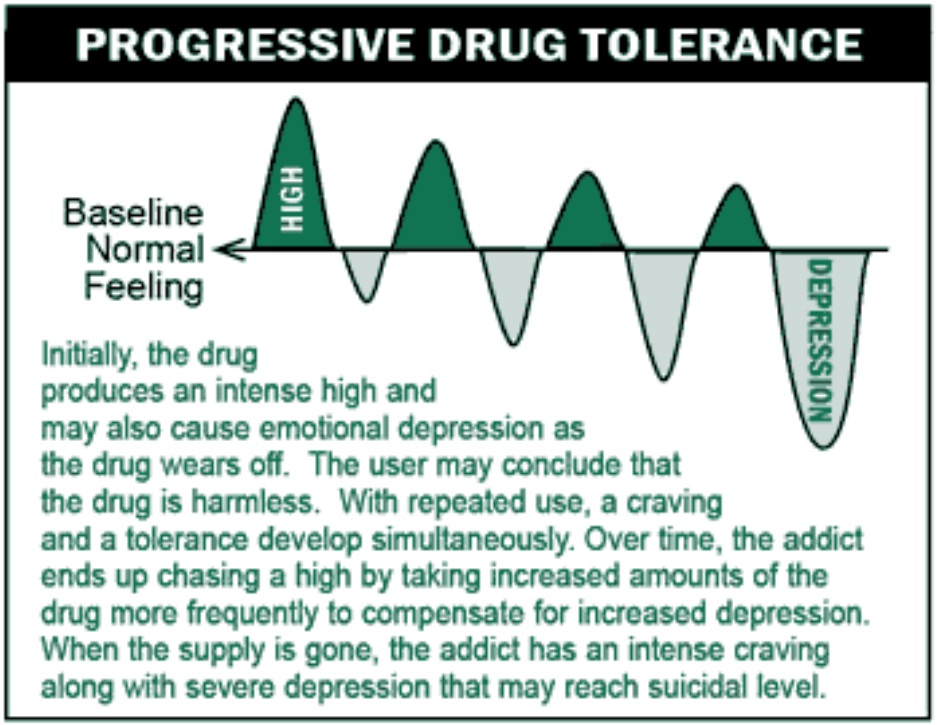
What causes resistance to antibiotics ?



What causes resistance to viruses?



What causes resistance to addictive drugs?



Nicotine
Nitroglycerin
Alcohol
Benzodiazepines
Narcotics
Cocaine
Marijuana

Down-regulation of Receptors

Ritalin (Methylphenidate)

Stimulant

Down-regulation
Of receptors

Reduced activity
In ADHD

High, persistent levels of hormone cause down-regulation of receptors

Reinforcing cycles of Resistance

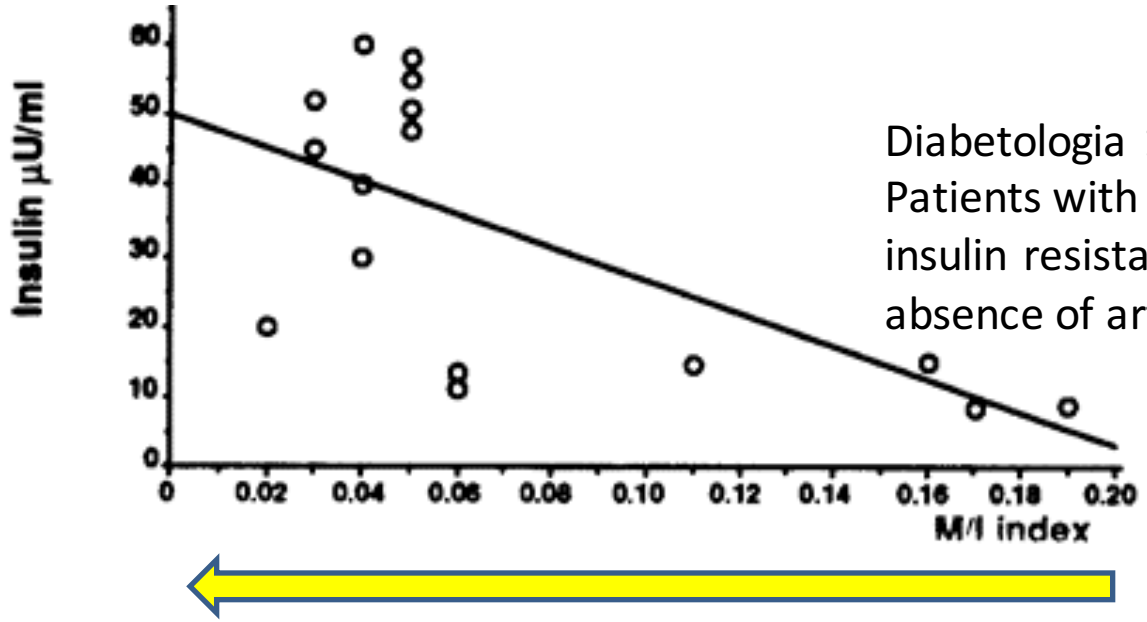
Persistent Exposure

Resistance

What causes Insulin Resistance?

Does Insulin cause Insulin Resistance?

Insulinomas



Diabetologia 1992 35:294-5
Patients with insulinoma show insulin resistance in the absence of arterial hypertension

Increasing insulin resistance

Surgical resection of adenoma reverses insulin resistance

J Endocrinol Invest 13:241–245, 1990

Insulin causes insulin resistance

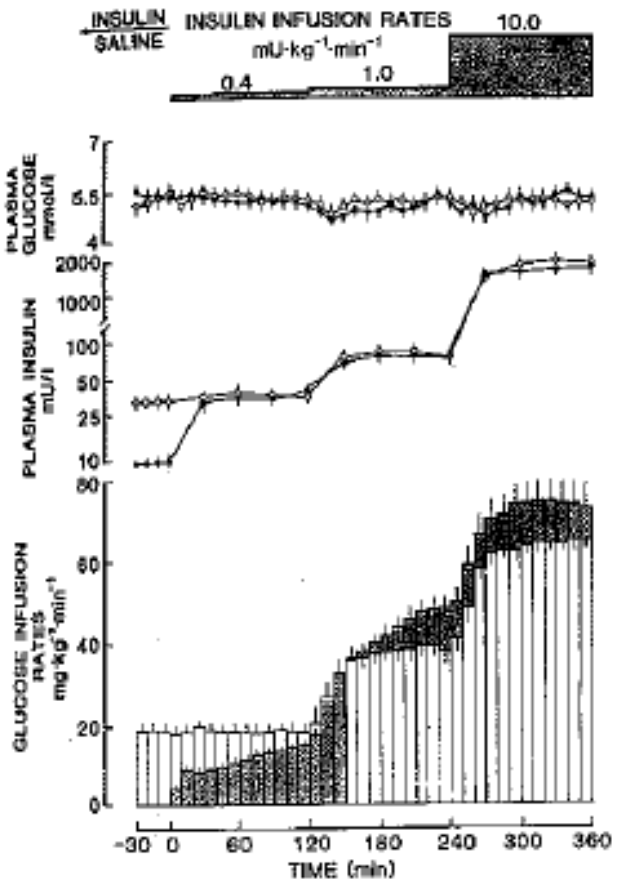


Table 1. Effect of antecedent hyperinsulinaemia on stimulation of glucose utilization and suppression of glucose production by insulin

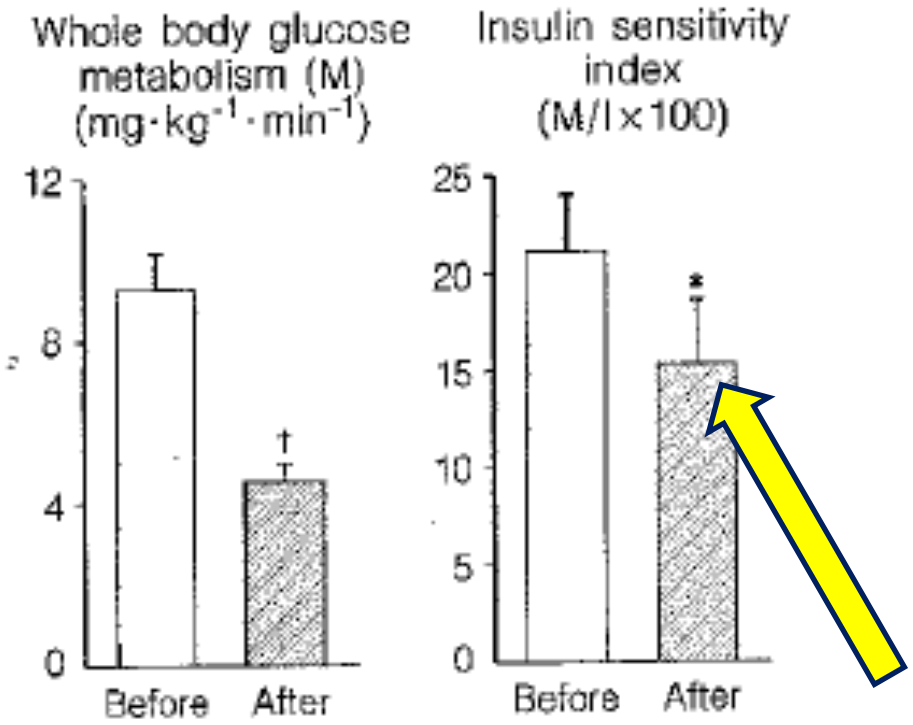
	Insulin infusion rates	
	(1 mU·kg^{-1}·min^{-1})	(10 mU·kg^{-1}·min^{-1})
Glucose utilization ($n = 7$) (mmol·kg^{-1}·min^{-1})		
Saline	44 ± 3	68 ± 5
Hyperinsulinaemia	37 ± 3	60 ± 3
	$p < 0.01$	$p < 0.05$

Insulin Resistance

Production of insulin resistance by hyperinsulinemia in man

Diabetologia 28:70 –75, 1985 Rizza RA

Insulin causes insulin resistance



P<0.001

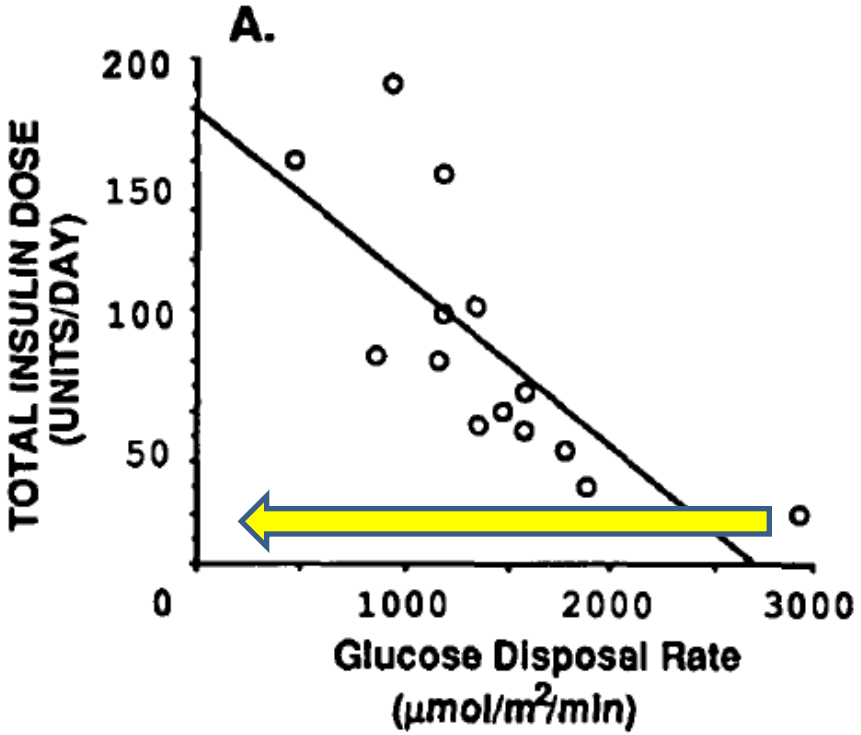
Before and after
96h constant insulin infusion

"These results demonstrate that chronic, physiologic hyperinsulinemia … leads to the development of insulin resistance"

Effect of sustained physiologic hyperinsulinemia and hyperglycemia on insulin secretion and insulin sensitivity in man

Diabetologia Oct1994, Vol37, Iss 10, 1025-1035 Del Prato S

Insulin causes insulin resistance



Intensive Conventional Insulin Therapy for Type II Diabetes

Diabetes Care 1993 16:23-31 Henry RR

Increasing insulin resistance!

8.7 kg weight gain!

Table 2—*Insulin requirement and weight gain during intensive CIT of type II diabetes patients*

	Months of insulin treatment			
Parameter	0	1	3	6
Total insulin dose (U)	—	86 ± 13	92 ± 16	100 ± 24
Body weight (kg)	93.5 ± 5.8	97.2 ± 5.9	100.5 ± 6.5*	102.2 ± 6.8*
Weight gain (kg)		3.7 ± 1.0	7.0 ± 1.5	8.7 ± 1.9
Caloric intake† (kcal/day)	2023 ± 138	1937 ± 122	1918 ± 121	1711 ± 119

High insulin secretion is primary

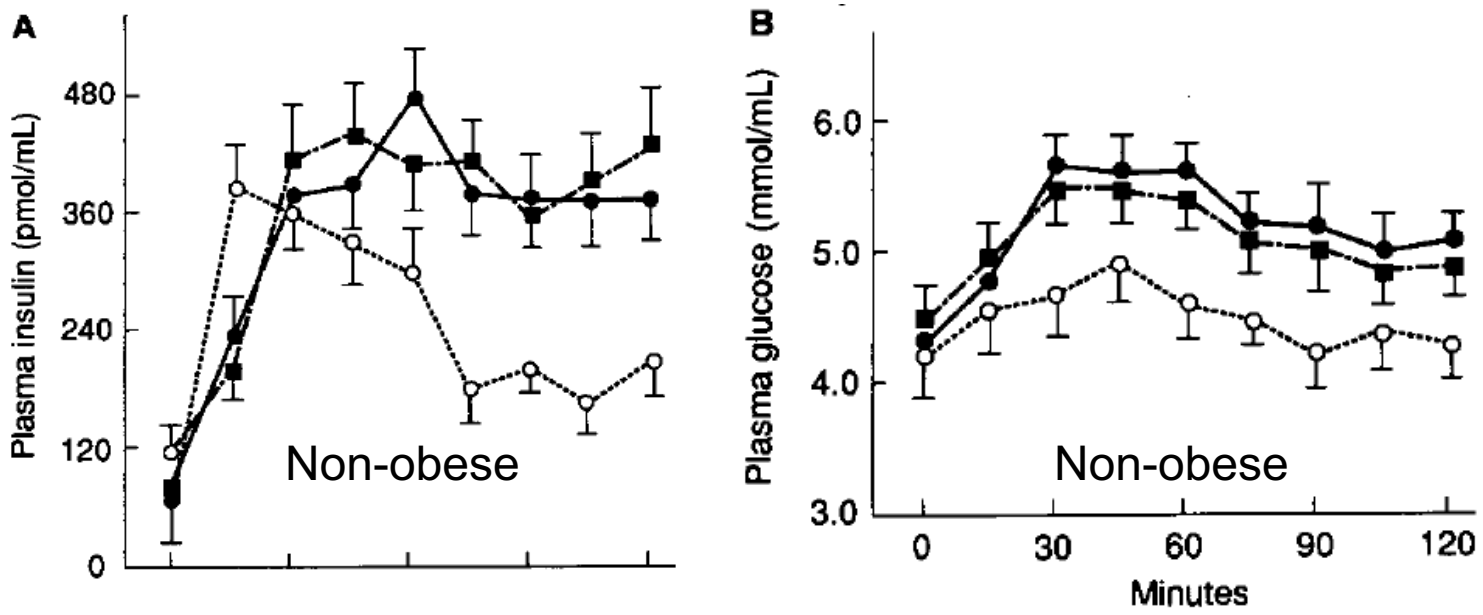


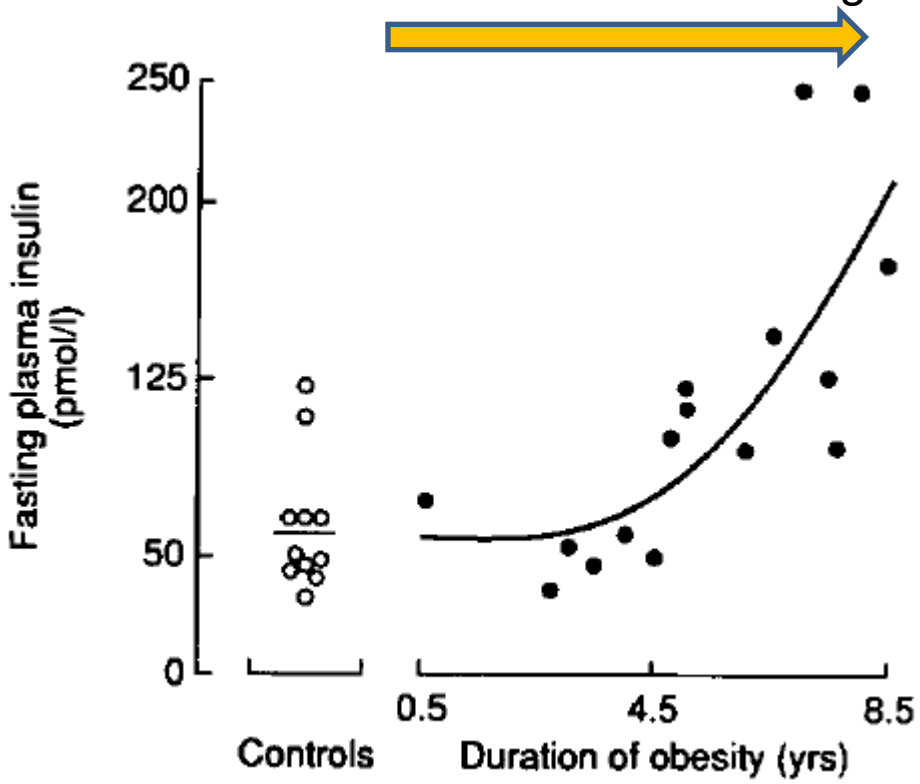
FIG. 2. Evolution of plasma insulin (*A*) and plasma glucose concentrations (*B*) during the 120 min after the ingestion of a normal isocaloric lunch in normal children (○), children with obesity of 0–4.5 years duration (■), and children with obesity of 4.5–8.5 years duration (●). The insulin and glucose curves were obtained using the group

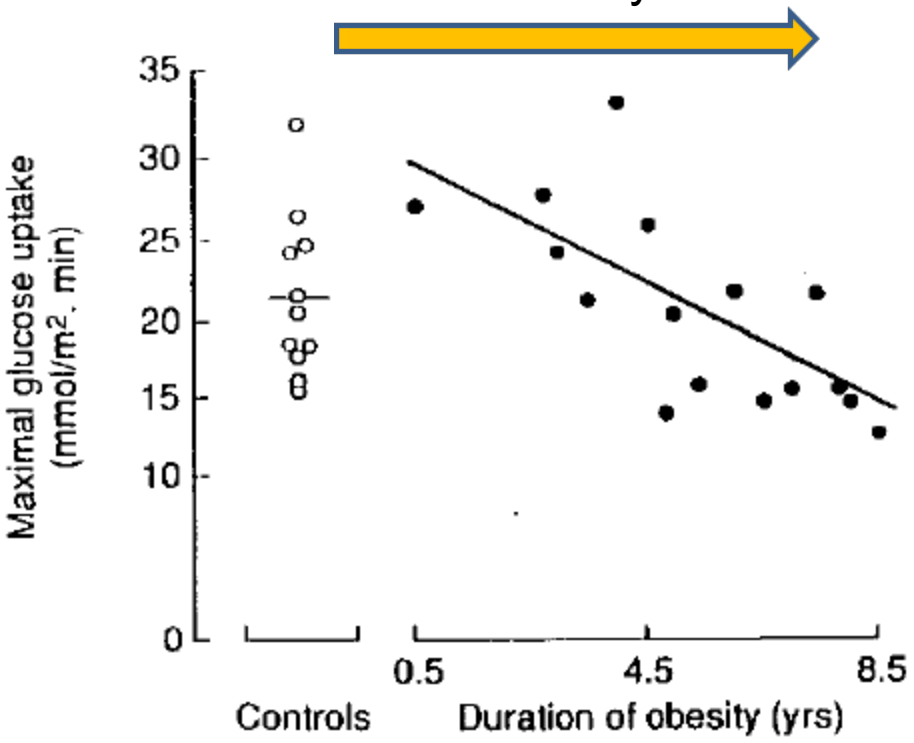
Early Changes in Postprandial Insulin Secretion, not in Insulin Sensitivity Characterize Juvenile Obesity

Diabetes 43:696-702; 1994 Le Stunff C

High insulin secretion is primary

Increasing resistance with duration of obesity





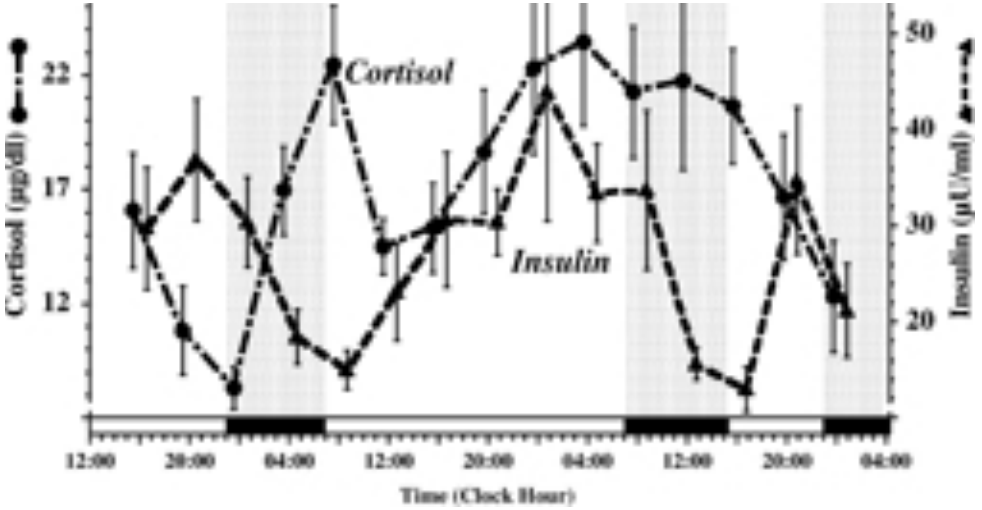
Diabetes 43:696-702; 1994 Le Stunff C

Time Sequence of Juvenile Obesity

Genetics → Increased insulin → Insulin Resistance → Obesity

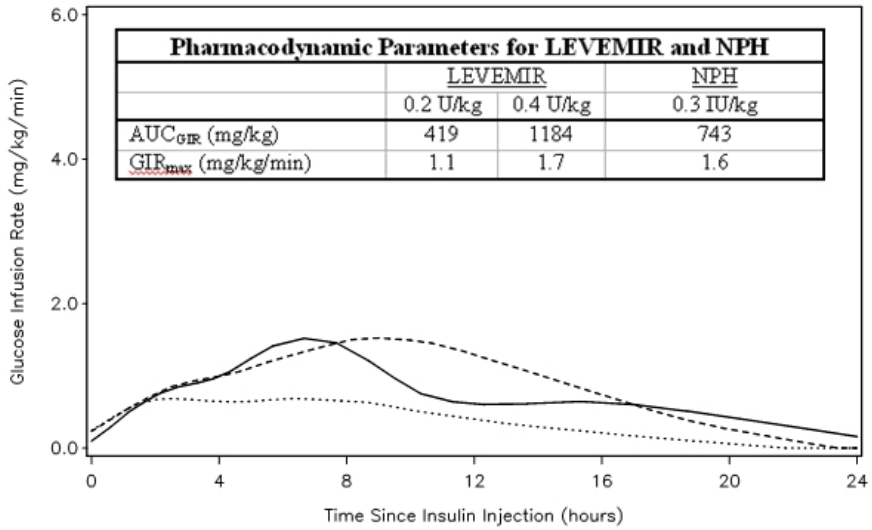
Pulsatile Release Prevents Tolerance

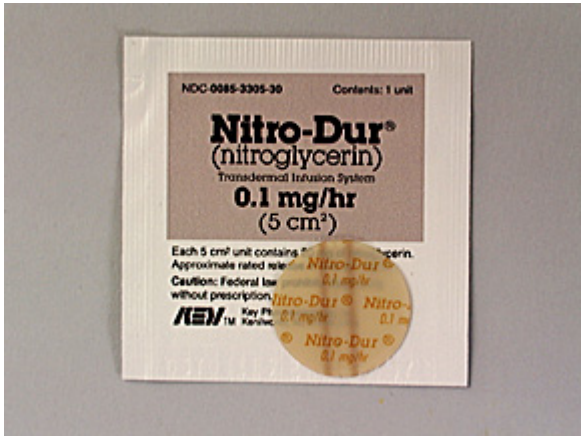
Endogenous Insulin



Pharmacodynamic Parameters for LEVEMIR and NPH

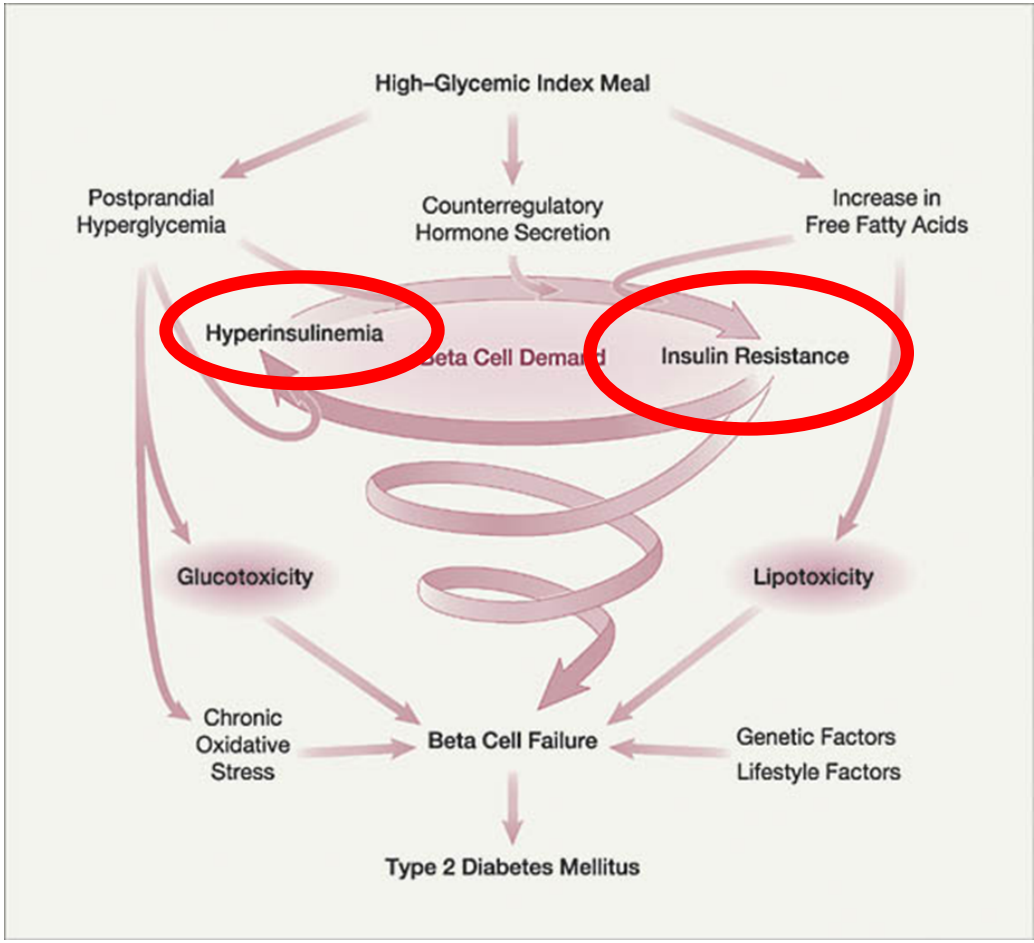
	LEVEMIR		NPH
	0.2 U/kg	0.4 U/kg	0.3 IU/kg
AUC_{GIR} (mg/kg)	419	1184	743
GIR_{max} (mg/kg/min)	1.1	1.7	1.6





Conclusions

1) Insulin causes insulin resistance
2) Insulin resistance causes hyperinsulinemia
3) Resistance requires high, *persistent* level



David Ludwig JAMA May 8, 2002 – Vol 287 No 18

Insulin causes diabetes!

Complications of Diabetes

Complications of Diabetes

Type 1 and 2 Diabetes

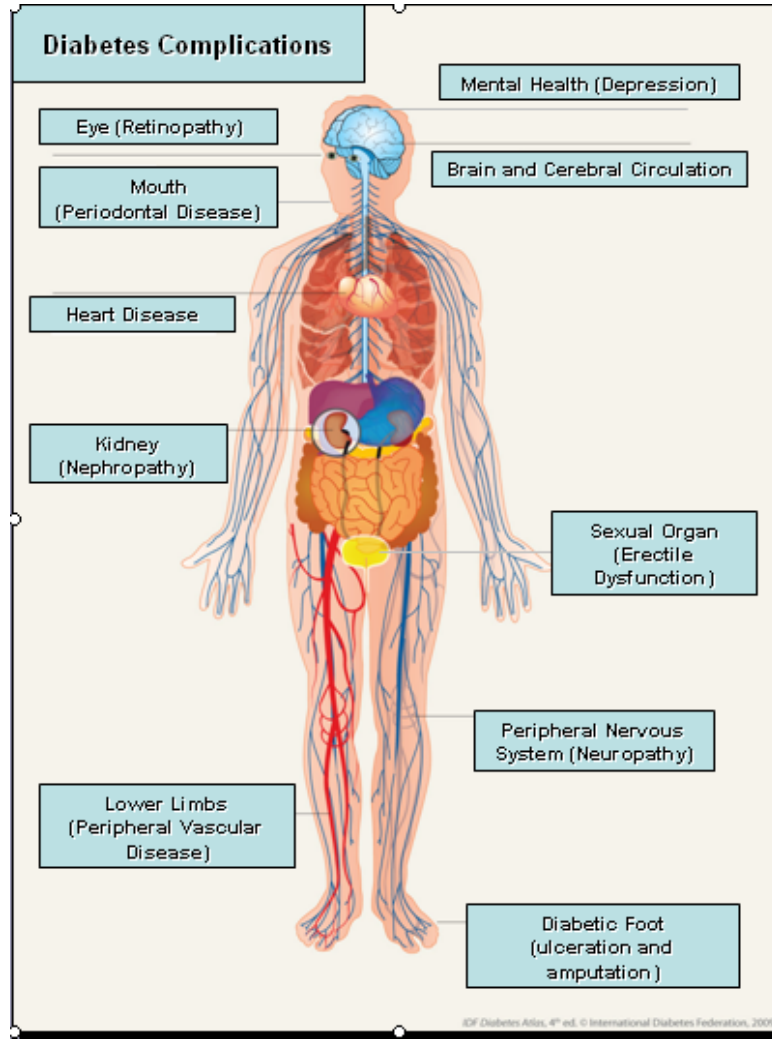
High B d Sugars

(Ox t Str s)

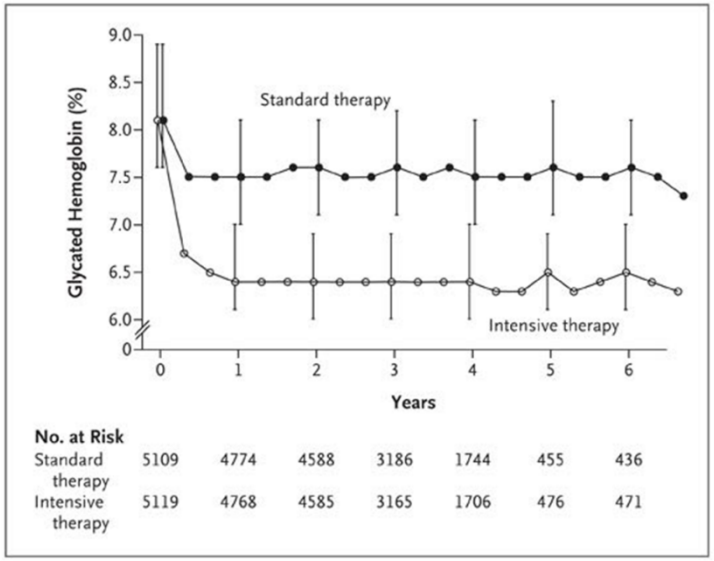
(Adv ce C tion

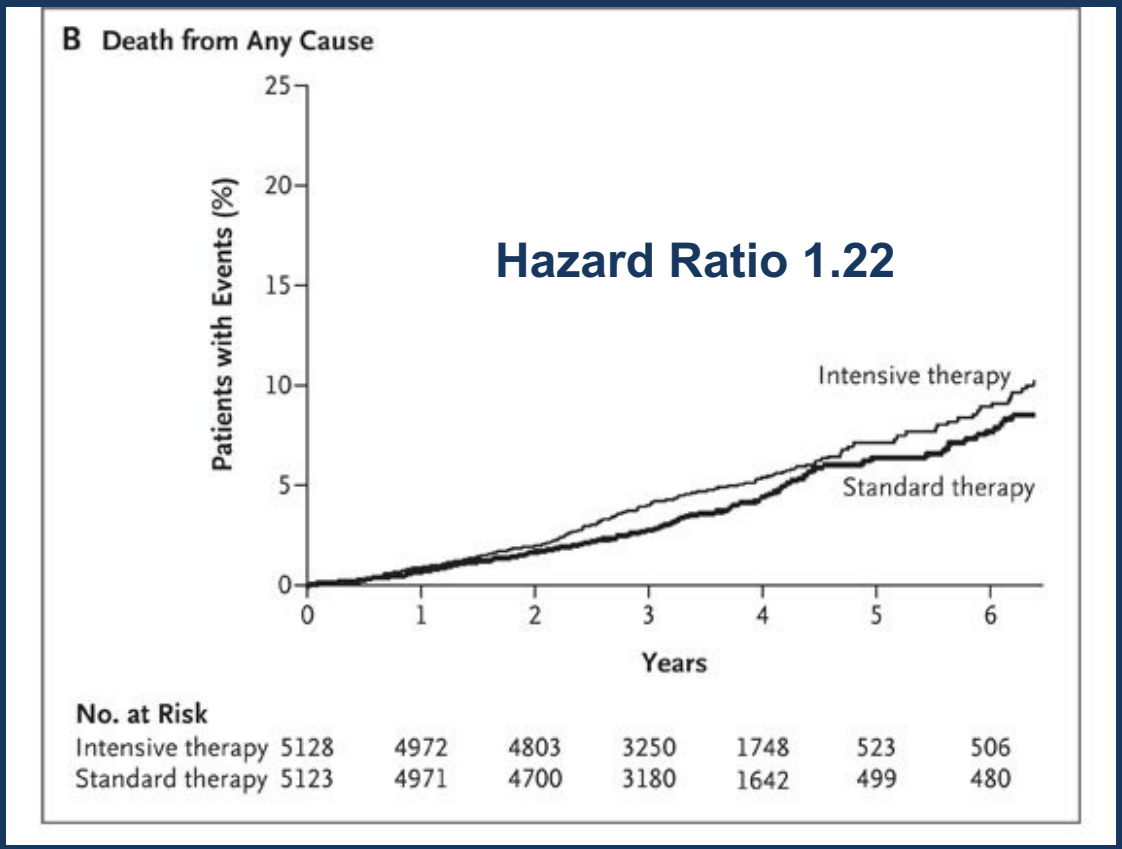
End P s)

Complic ti s o Diabetes



ACCORD

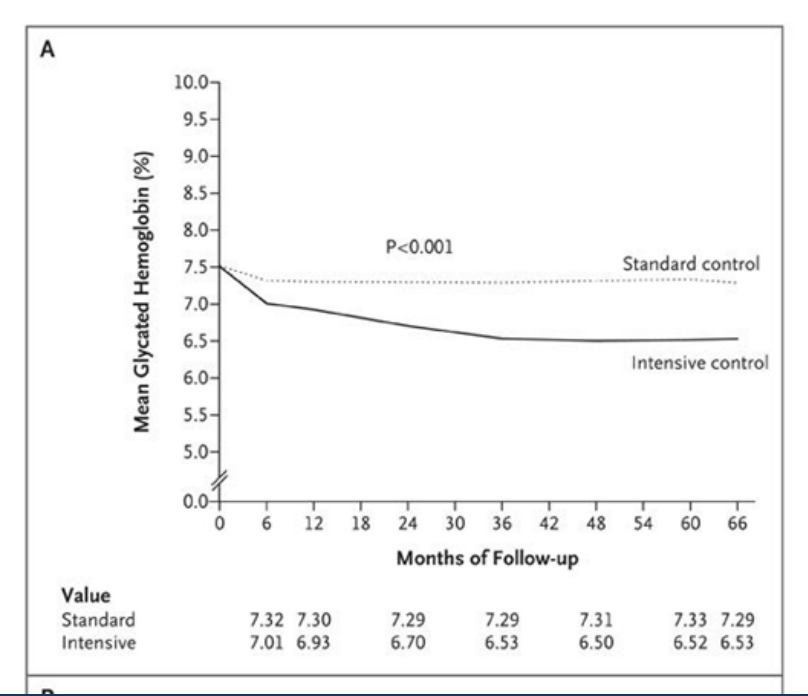


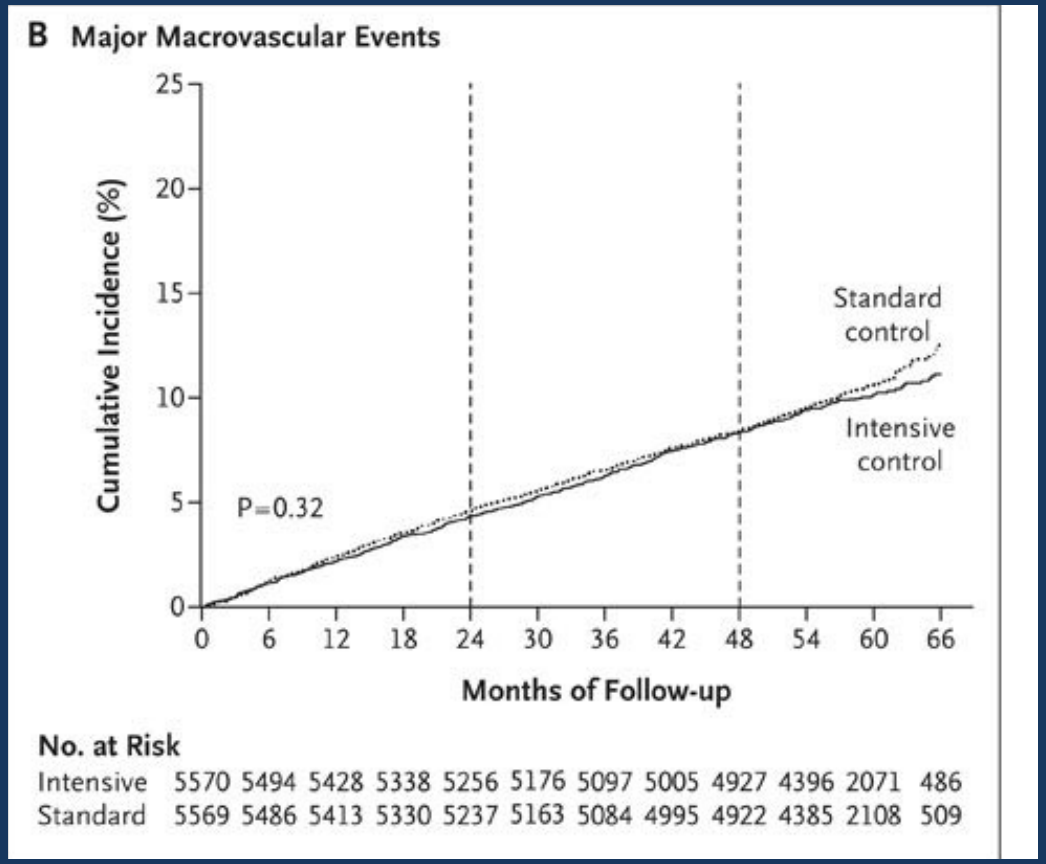


The Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med 2008;358:2545-2559

The NEW ENGLAND JOURNAL of MEDICINE

ADVANCE





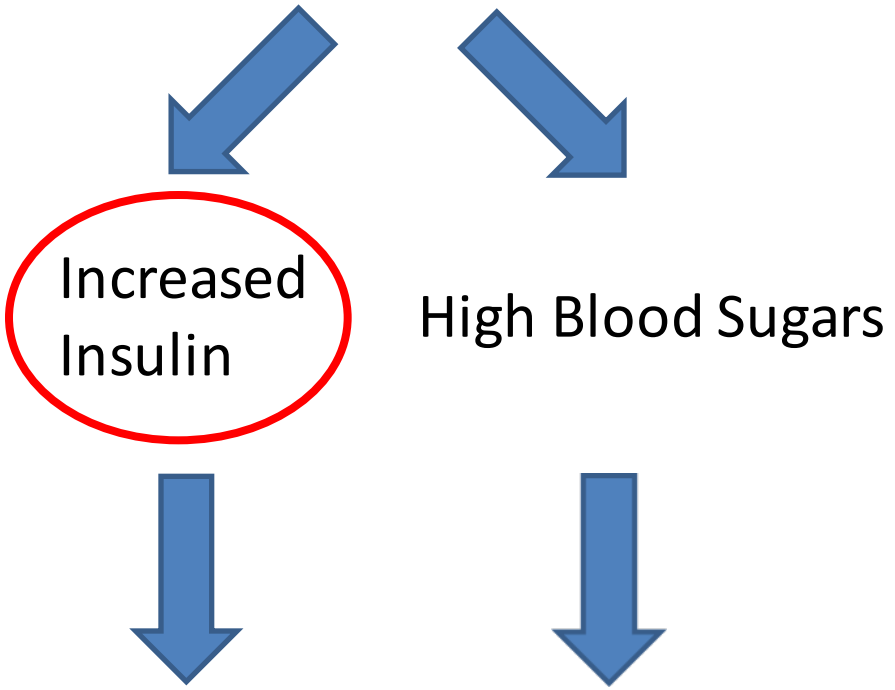
Cumulative Incidences of Events, According to Glucose-Control Strategy

The ADVANCE Collaborative Group. N Engl J Med 2008;358:2560-2572

The NEW ENGLAND JOURNAL of MEDICINE

What about hyperinsulinemia?

Type 2 Diabetes



Insulin and atherosclerosis

Insulin:

- enhances VLDL synthesis and may reduce HDL-cholesterol levels
- increases cholesterol transport into arteriolar smooth muscle cells
- is a growth factor that:
  - augments collagen synthesis
  - stimulates proliferation of arteriolar smooth muscle cells
- promotes atherogenesis in animal models (rabbit, chicken, dog)
- causes insulin resistance

Complications of Diabetes

Diabetes is disease of *insulin resistance*

Current treatment is directed at *high blood sugars*

Insulin treatment has toxicity

Insulin exposure category*	Mortality rate per 1000 person-years† (95% CI)	Unadjusted HR	95% CI	p-Value	Adjusted‡ HR	95% CI	p-Value§
No exposure (reference)	39.86 (38.28–41.50)	1.00	Reference		1.00	Reference	
Low	82.60 (58.66–116.06)	2.03	1.44–2.86	<0.001	1.75	1.24–2.47	0.002
Moderate	85.70 (72.27–102.14)	2.11	1.77–2.52	<0.001	2.18	1.82–2.60	<0.001
High	95.29 (80.86–110.79)	2.32	1.96–2.73	<0.001	2.79	2.36–3.30	<0.001

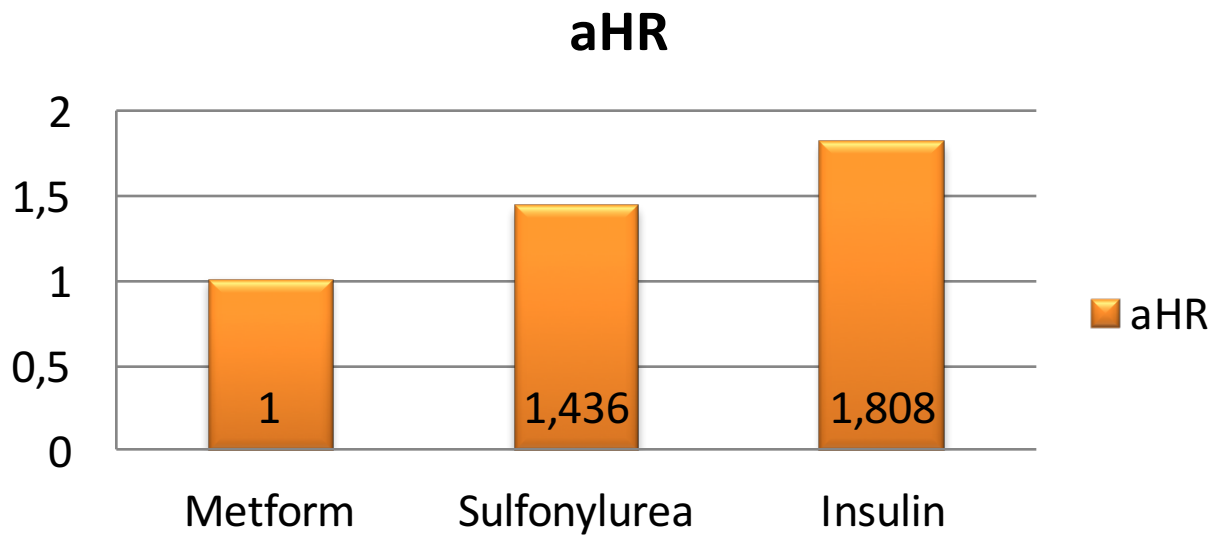
"significant and graded association between mortality risk and insulin exposure level"

12,272 new diabetics 1991-1996 Saskatchewan

Insulin use and increased risk of mortality in type 2 diabetes: a cohort study

Diabetes, Obesity and Metabolism 12: 47–53, 2010 Gamble JM

Insulin treatment has toxicity

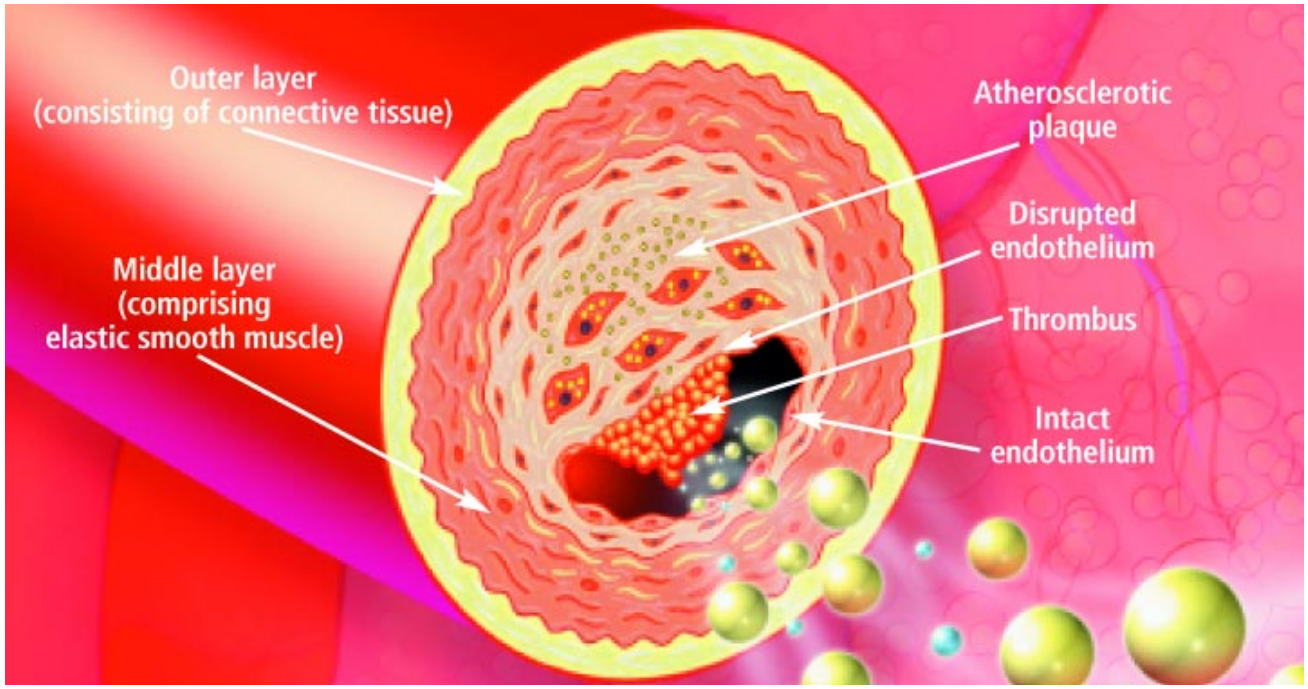


84,622 incident Type 2 DM cases

Hyperinsulinemia or insulin resistance?

Mortality and Other Important Diabetes-Related Outcomes With Insulin vs Other Antihyperglycemic Therapies in Type 2 Diabetes
J Clin Endocrinol Metab 98: 668–677, 2013 Currie CJ

Hyperinsulinemia

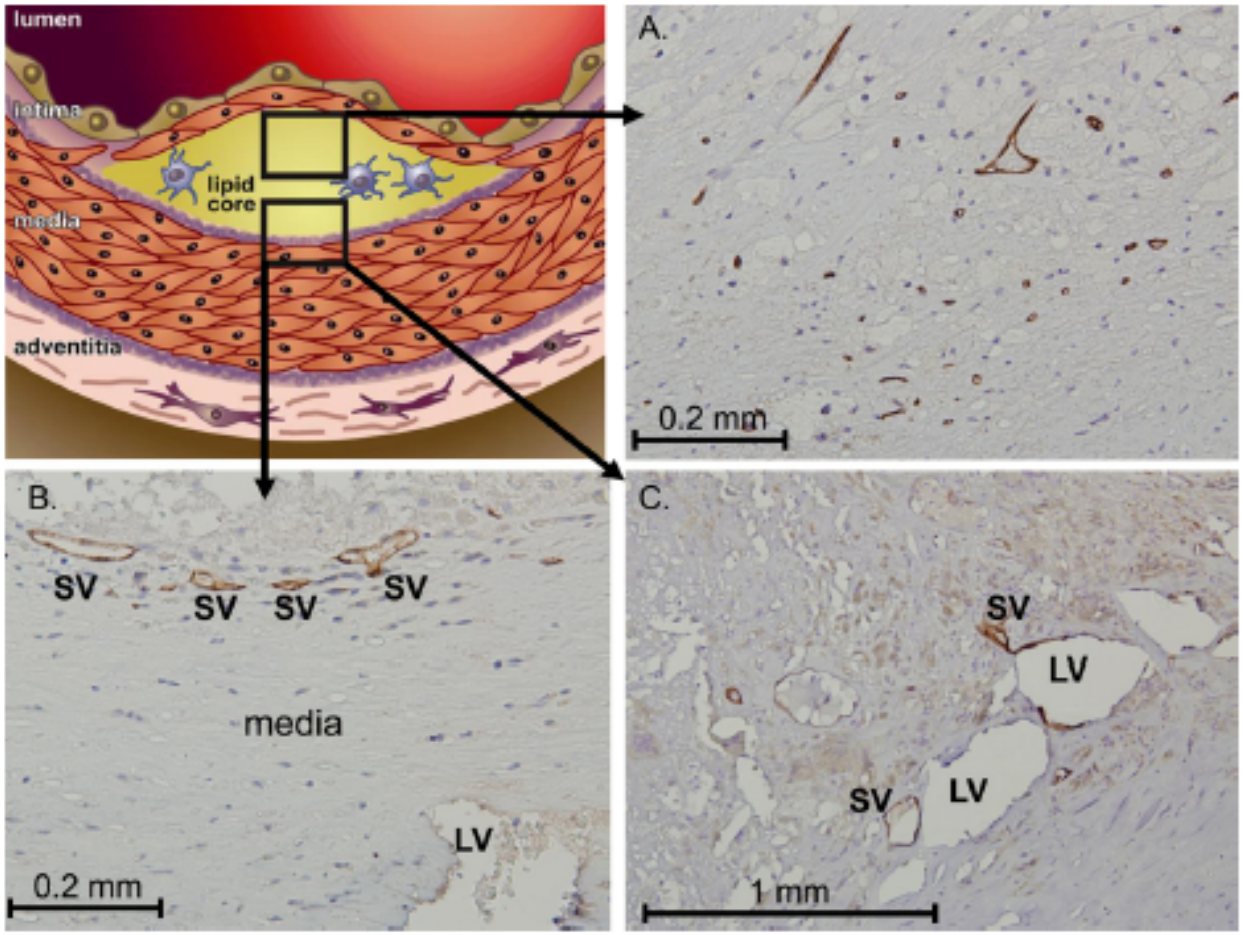


1. Increased adhesion molecule expression on endothelial cells
2. Increased trans-endothelial migration of leukocytes
3. Stimulation of smooth muscle cell proliferation
4. Pro-inflammatory effects

References

(1) Madonna R, De Caterina R. Prolonged exposure to high insulin impairs the endothelial PI3-kinase/Akt/nitric oxide signalling. Thromb Haemost 2009;101:345–50.
(2) Okouchi M, Okayama N, Imai S, et al. High insulin enhances neutrophil transendothelial migration through increasing surface expression of platelet endothelial cell adhesion molecule-1 via activation of mitogen activated protein kinase. Diabetologia 2002;45:1449–56.
(3) Pfeifle B, Ditschuneit H. Effect of insulin on growth of cultured human arterial smooth muscle cells. Diabetologia 1981;20:155–8.
(4) Stout RW, Bierman EL, Ross R. Effect of insulin on the proliferation of cultured primate arterial smooth muscle cells. Circ Res 1975;36:319–27.
(5) Iida KT, Shimano H, Kawakami Y, et al. Insulin up-regulates tumor necrosis factor-alpha production in macrophages through an extracellular-regulated kinase-dependent pathway. J Biol Chem 2001;276:32531–7.

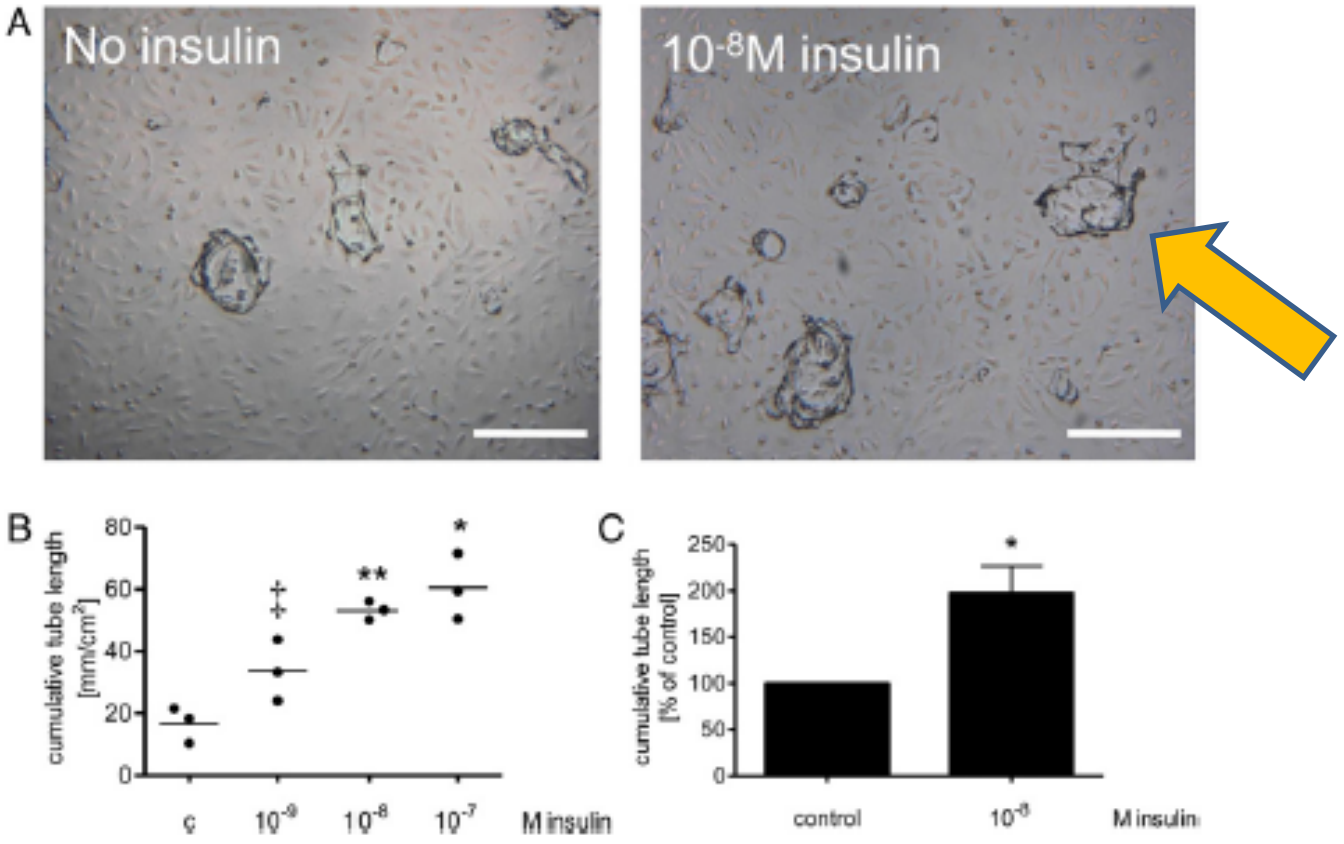
Insulin receptor staining in human plaque



Endothelial insulin receptor expression in human atherosclerotic plaques: Linking micro- and macrovascular disease in diabetes?

Atherosclerosis 222 (2012) 208– 215, Rensing KL

Insulin stimulates angiogenesis



In vitro angiogenic sprouting assay.

Endothelial insulin receptor expression in human atherosclerotic plaques: Linking micro- and macrovascular disease in diabetes?

Atherosclerosis 222 (2012) 208– 215, Rensing KL

INSULIN CAUSES SALT AND WATER RETENTION

“Elevation of plasma insulin concentration within the physiological range has a marked anti-natriuretic action”

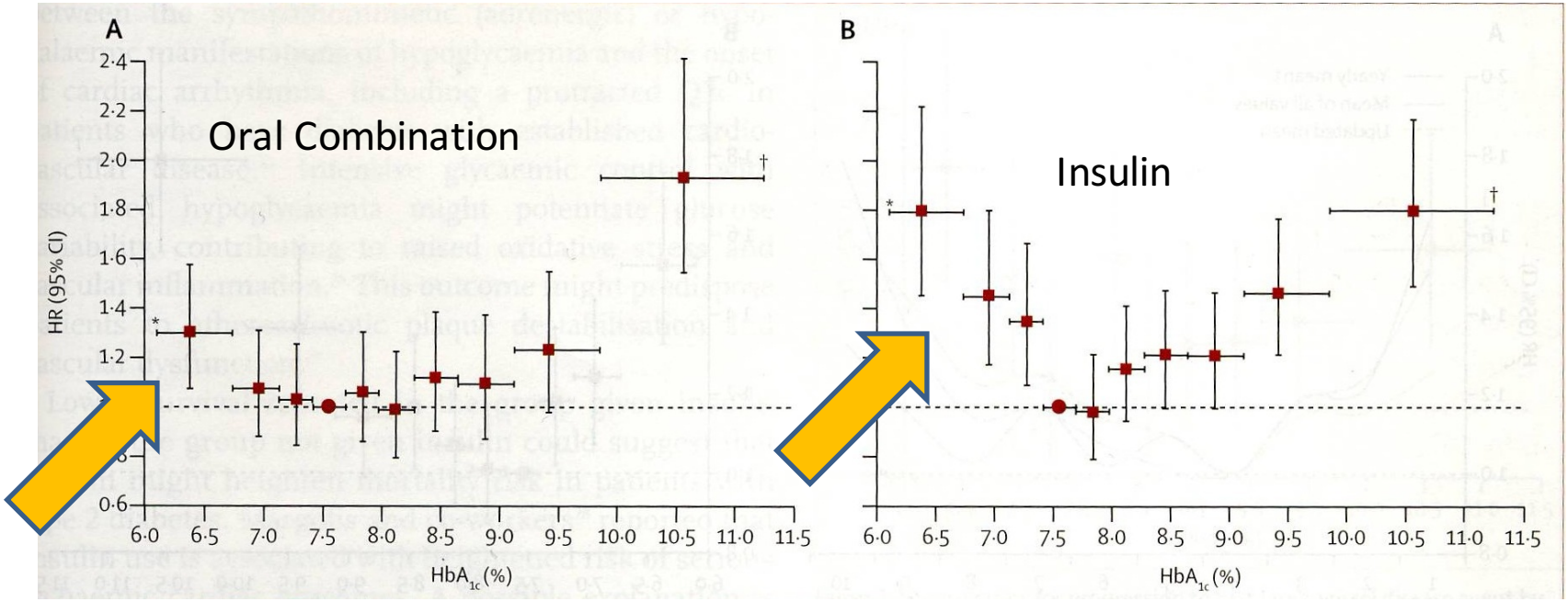
Renal effect of insulin to increase sodium retention in the kidney

Parving H DIABETOLOGIA,Volume 32, Number 9 (1989), 694-699

Insulin Toxicity in Diabetes

Basic science evidence suggests that ***insulin itself is a toxic agent***

Low A1C is **NOT** good for you



Adjusted Hazard Ratios by A1c

27,965 patients intensified from oral monotherapy to combination therapy

Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study

Lancet 2010; 375:481-89, Currie CJ

Low A1C is a risk factor

Table 2—*Conditional logistic regression model of cardiovascular events*

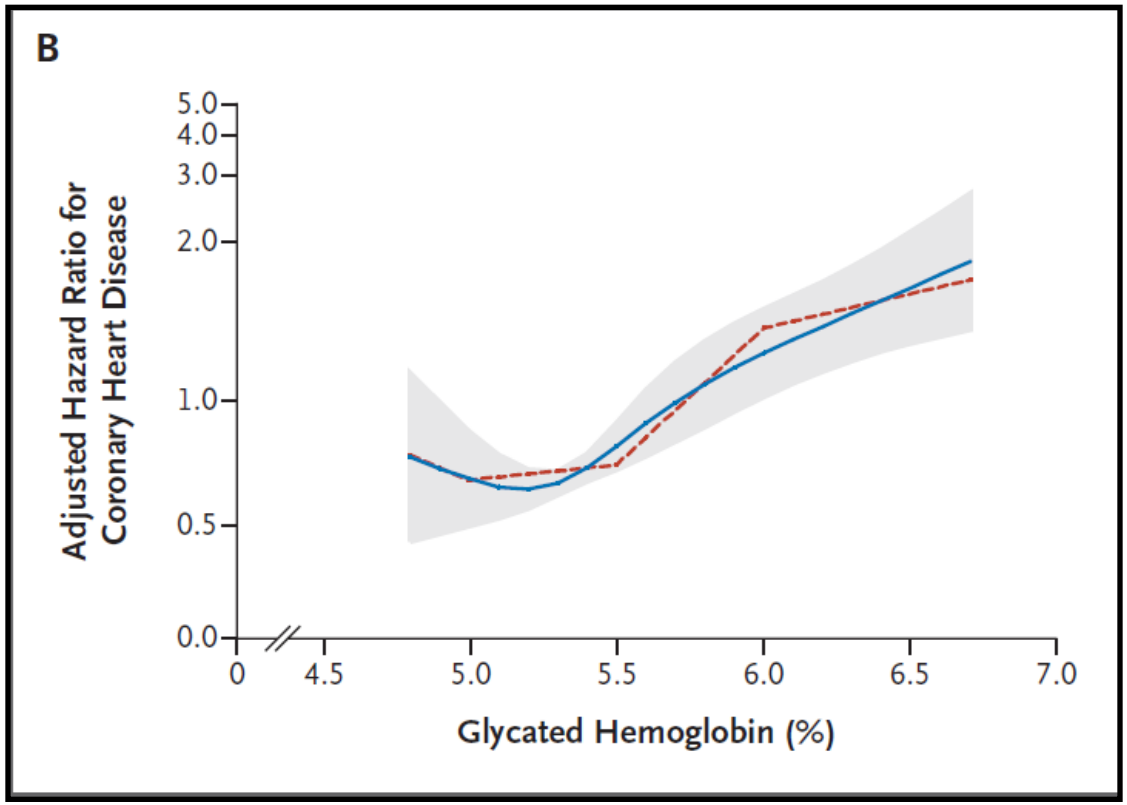
Covariate	Odds ratio (95% CI)	P
Mean A1C level (%)		
≤6.0	1.20* (1.10–1.31)	<0.001
>6.0–8.0	Reference	—
>8.0	1.16* (1.09–1.25)	<0.001
≥6 A1C tests over prior 3 years	0.84 (0.80–0.89)	<0.001
A1C range >1.0%	1.29 (1.21–1.38)	<0.001
Diabetes medications		
Insulin only	2.65 (2.31–3.05)	<0.001
Metformin only	1.06 (0.92–1.23)	0.41
Sulfonylurea only	1.55 (1.36–1.76)	<0.001
Insulin and oral medications	2.56 (2.19–3.00)	<0.001
Other oral medications/oral combination	1.55 (1.33–1.80)	<0.001
No diabetes medications	Reference	—

A1C and Cardiovascular Outcomes in Type 2 Diabetes

Diabetes Care 34:77–83, 2011, Colacayo et al

Nested case control study of 11,157 cases of DM2

Not the case in non-diabetics

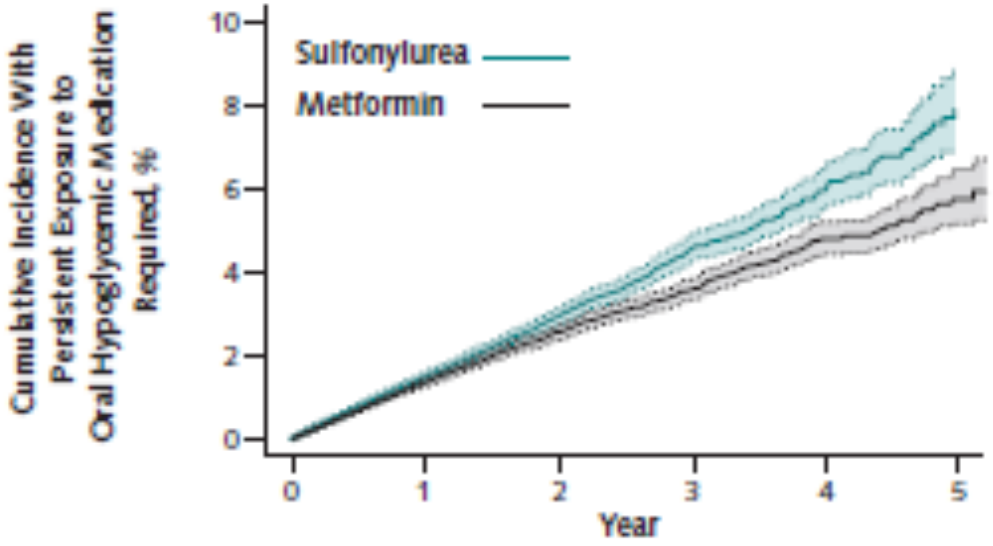


Glycated Hemoglobin, Diabetes, and Cardiovascular Risk in Nondiabetic Adults

N Engl J Med 2010;362:800-11, Selvin E

Metformin versus Sulfonylurea

Figure 2. Cumulative incidence (95% CIs) of cardiovascular disease or death.



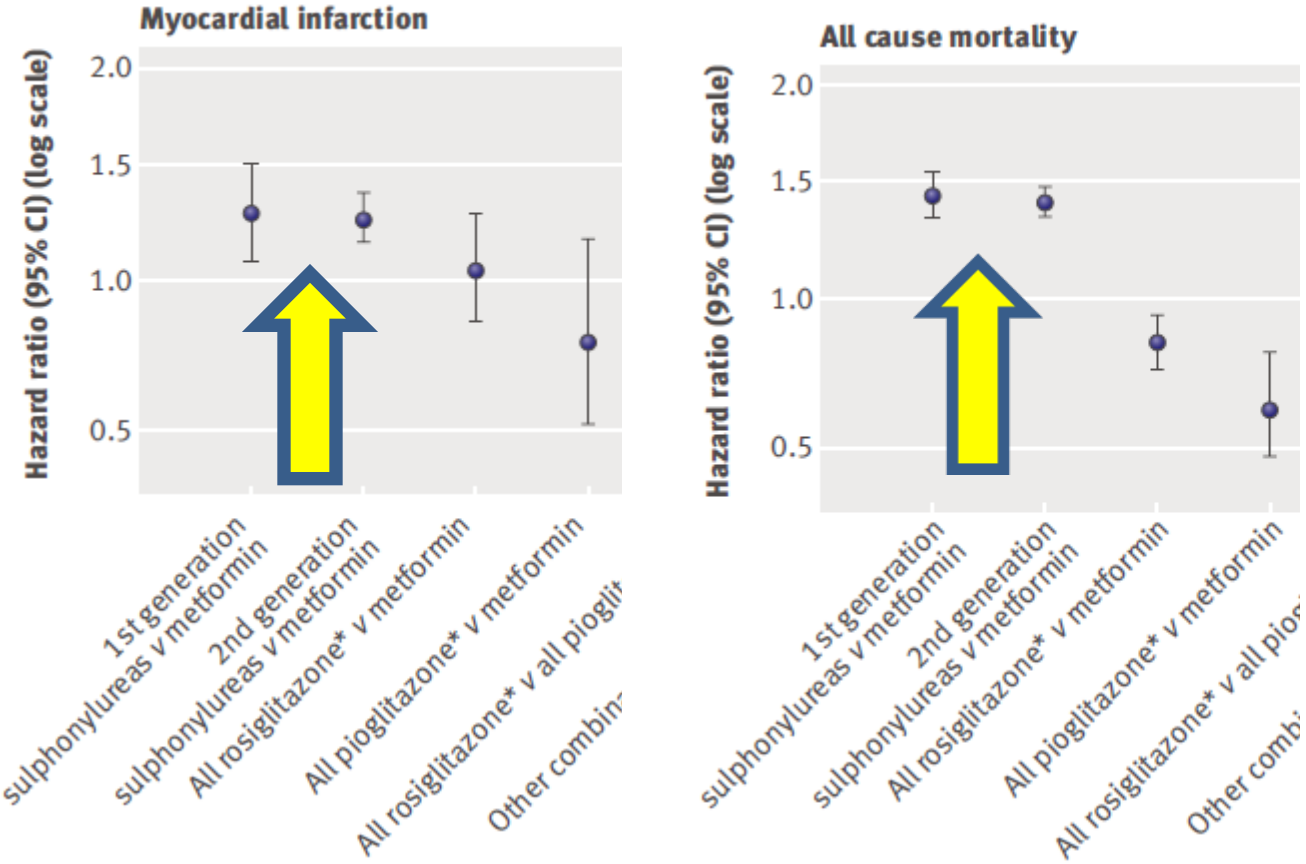
Patients receiving metformin, *n*	80 648	33 418	16 887	7976	3297	718
Patients receiving sulfonylurea, *n*	80 648	29 502	14 118	6185	2301	462

Retrospective cohort study of 253,690 patients initiating treatment

Comparative Effectiveness of Sulfonylurea and Metformin Monotherapy on Cardiovascular Events in Type 2 Diabetes Mellitus

Ann Intern Med. 2012;157:601-610 Roumie CL

Metformin versus sulphonlyurea

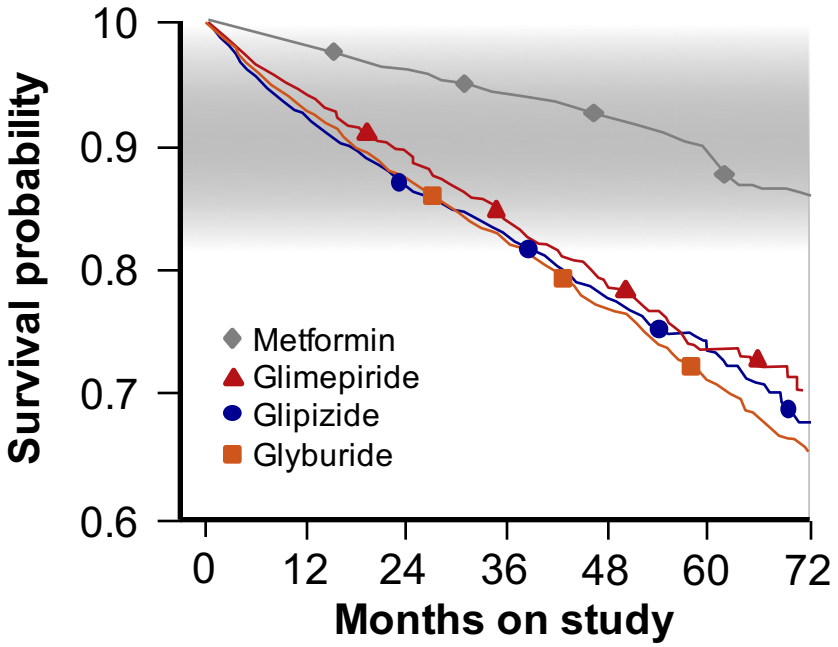


Retrospective cohort study 91,521 patients with DM

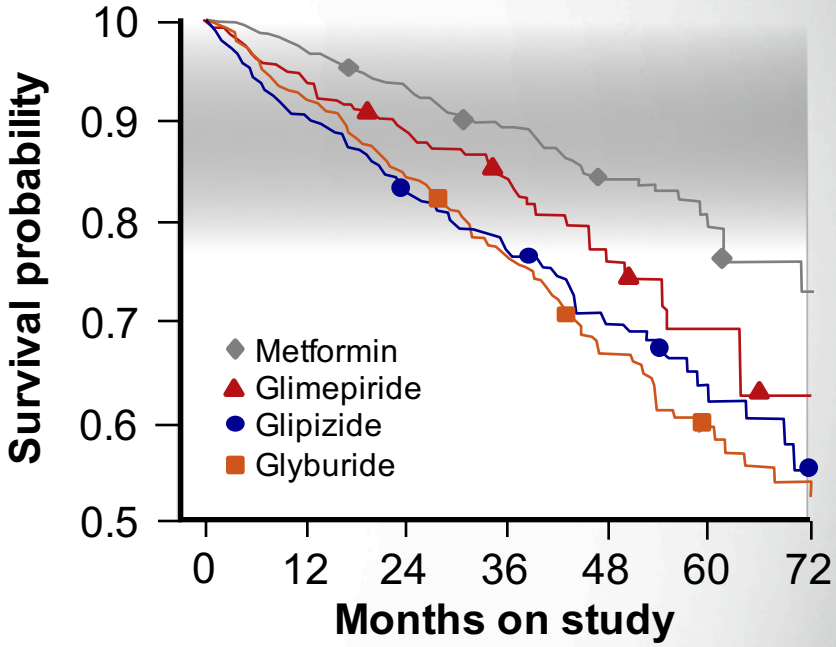
Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs
Tzoulaki I. BMJ 2009; 339:b4731

Risk of Mortality: SU vs. Metformin

A) Entire cohort



B) Subgroup w/ documented CAD



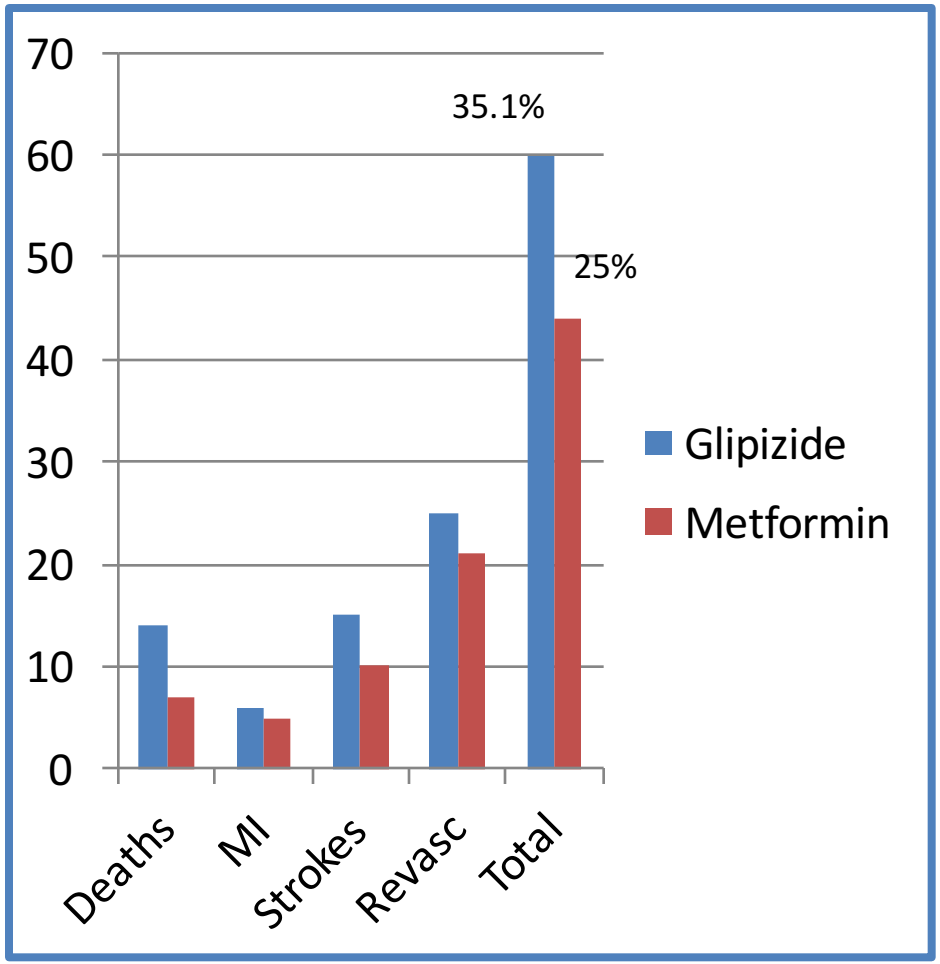
Retrospective cohort study of 23,915 DM2 patients initiated with metformin or SU

40-60% increase risk of MI/ death

Pantalone KM, et al. Diabetes Obes Metab 2012; 14(9):803-9.

Sulfonylurea versus Metformin

Multicenter, randomized, double-blind, placebo-controlled trial



Effects of Metformin Versus Glipizide on Cardiovascular Outcomes in Patients With Type 2 Diabetes and Coronary Artery Disease

Diabetes Care, epub Dec 10, 2012 Hong Jie

Insulin infusion post MI increases mortality

Table 4 The effect of insulin treatment from the time of hospital discharge for patients discharged alive (n=1073)

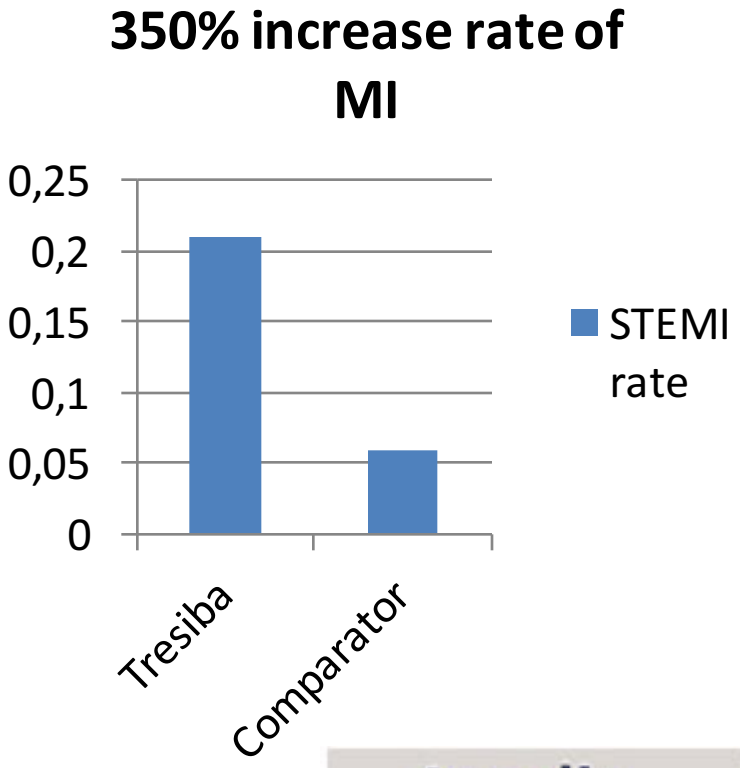
Patients on insulin	OR (95% CI)	p value
Reinfarction		
Insulin[a]	1.94 (1.34–2.81)	0.0004
New on insulin[b]	2.04 (1.29–3.21)	0.0021
Reinfarction/stroke		
Insulin[a]	1.89 (1.35–2.63)	0.0002
New on insulin[b]	2.12 (1.40–3.21)	0.0004
Death/reinfarction/stroke		
Insulin[a]	1.78 (1.32–2.38)	0.0001
New on insulin[b]	1.65 (1.14–2.40)	0.0086

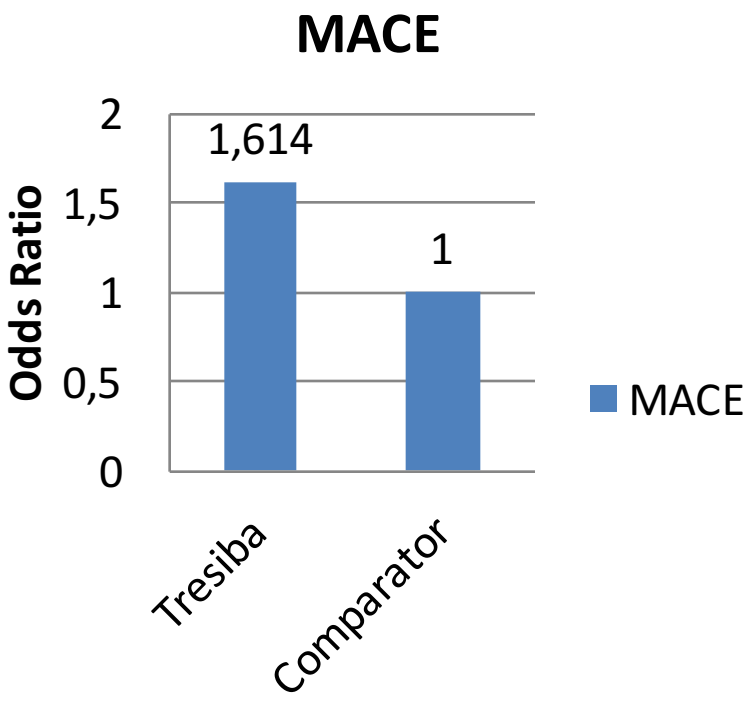
Experiences from an extended follow-up of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Study

Diabetologia. 2011 Jun;54(6):1308-17, Mellbin et al

4 – 8 year follow up, 1,145 patients

Long acting insulin increases risk





novo nordisk®

Cancer

Diabetes increases cancer risk

Table 2 Associations between diabetes (mainly type 2) and incidence cancer risk: from meta-analyses

Authors [ref.]	Cancer type	No. of cohorts/no. of case–control studies	No. of cases	Risk estimates (95% CI)
Larsson et al, 2007 [11]	Breast (all)	15/5	30,407	1.20 (1.12, 1.28)
	Premenopausal	Not stated	Not stated	0.91 (0.62, 1.34)
	Postmenopausal	Not stated	Not stated	1.16 (1.09, 1.24)
Larsson et al, 2005 [12]	Colorectal	9/6	26,306	1.30 (1.20, 1.40)
Friberg et al, 2007 [13]	Endometrial	3/13	7,596	2.10 (1.93, 3.24)
Larsson and Wolk, 2011 [14]	Kidney	9/0	8,757[a]	1.42 (1.06, 1.91)
Larsson et al, 2006 [15]	Bladder	3/7	Not stated	1.24 (1.08, 1.42)

Mechanism:

Hyperinsulinemia?
Hyperglycemia?

Diabetologia (2012) 55:1607–1618
Diabetes and cancer: evaluating the temporal relationship between type 2 diabetes and cancer incidence

Metformin reduces risk of cancer

Metformin use in patients with type 2 diabetes and controls in Tayside, Scotland, 1993-2001

	Unadjusted odds ratios (95% CI)	Adjusted odds ratios (95% CI)
Exposure during year before index date:		
No	1.00	1.00
Yes	0.86 (0.73 to 1.02)	0.85 (0.71 to 1.01)

Case control trial 983 cases

Metformin and reduced risk of cancer in diabetic patients

BMJ VOLUME 330 4 JUNE 2005, 1304-5

Metformin reduces risk of cancer

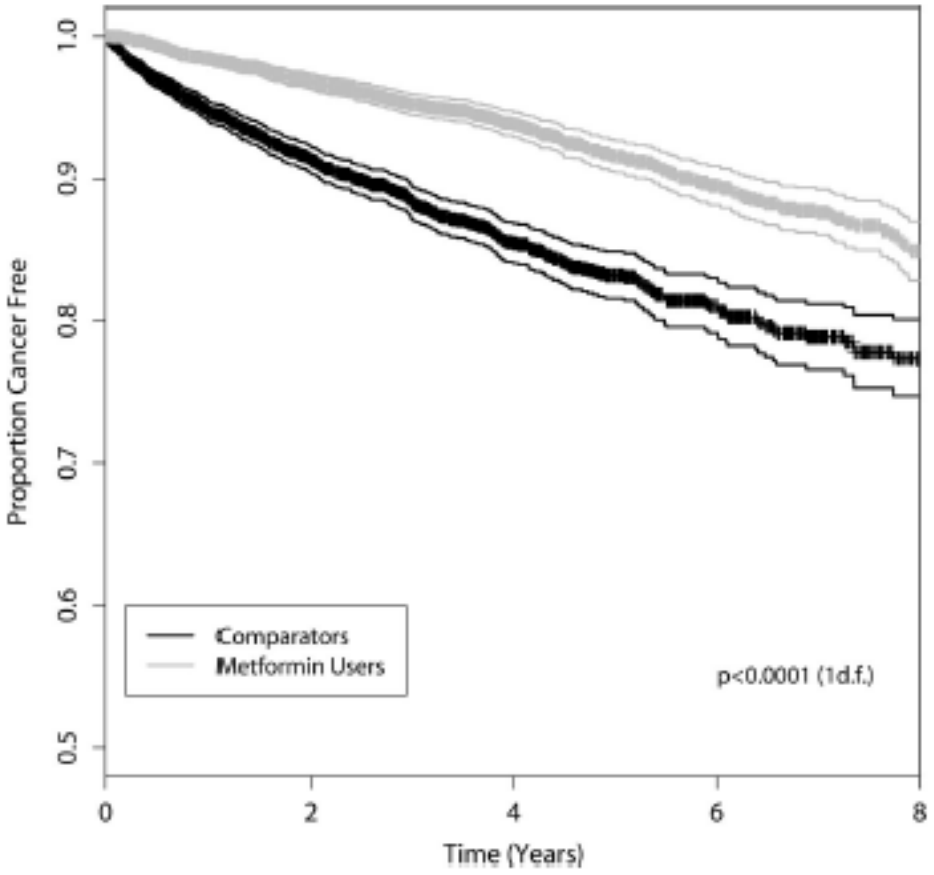


Figure 2—*Kaplan-Meier plot with 95% CIs showing time to cancer among metformin users and comparators.*

- Observational cohort study
- 4,085 patients
- Adjusted hazard ratio 0.63 (0.53-0.75)

New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes

Diabetes Care. 2009 Sep;32(9):1620-5 Libby G

Insulin increases cancer risk

Covariate	HR	95% CI for HR		*p* value
Relative risk compared to metformin mono-therapy		Lower	Upper	
Treatment[a]				
Sulfonylureas (Cohort 2)	1.36	1.19	1.54	<0.001
Metformin plus sulfonylureas (Cohort 3)	1.08	0.96	1.21	0.21
Insulin-based therapies (Cohort 4)	1.42	1.27	1.60	<0.001

Retrospective cohort of 62 809 patients newly started on diabetes medications

The influence of glucose-lowering therapies on cancer risk in type 2 diabetes
CJ Currie Diabetologia (2009) 52:1766-1777

Insulin increases cancer mortality

Table 2—*Cancer mortality and adjusted HR from multivariate Cox regression*

	Total *n*	Cancer deaths	Cancer mortality rate (per 1,000 person-years) (%)	Adjusted HR (95% CI)*
Oral antidiabetics				
Metformin	6,969	245 (3.5)	6.3	1.0†
Sulfonylurea	3,340	162 (4.9)	9.7	1.3 (1.1–1.6)
Insulin use				
No insulin use	8,866	323 (3.6)	6.8	1.0†
Insulin use	1,443	84 (5.8)	9.9	1.9 (1.5–2.4)

Population based cohort study from Saskatchewan

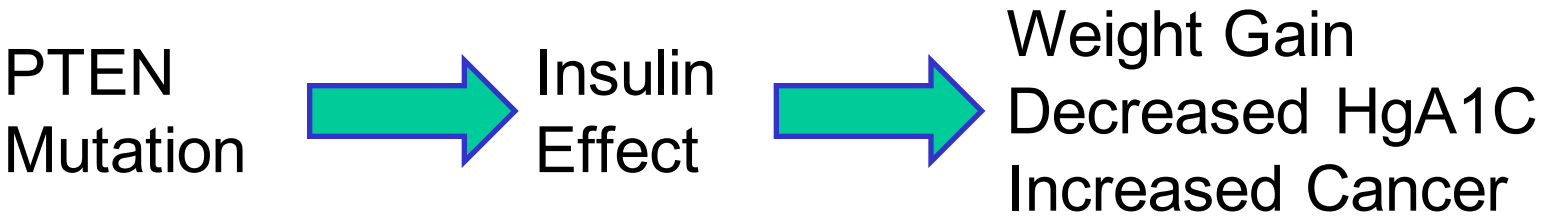
10,309 new diabetics

Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin

Diabetes Care. 2006 Feb;29(2):254-8 Bowker SL

Common pathway of insulin sensitivity, obesity and cancer risk

"persons susceptible to cancer owing to a constitutive mutation in the tumor-suppressor gene *PTEN* also have ***heightened sensitivity to insulin and are obese***"



***PTEN* Mutations as a Cause of Constitutive Insulin Sensitivity and Obesity**
N Engl J Med Volume 367(11):1002-1011 September 13, 2012

The NEW ENGLAND JOURNAL of MEDICINE

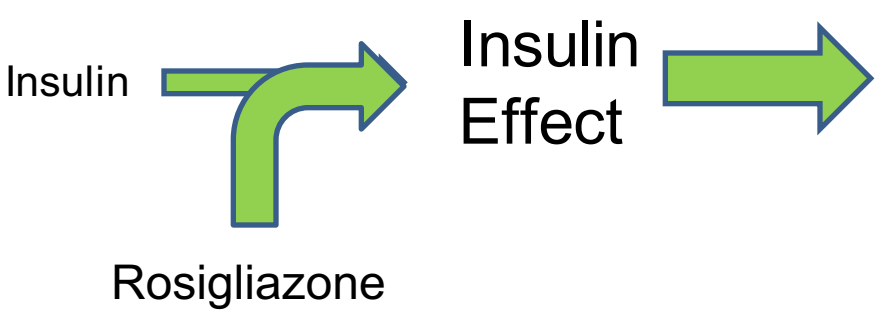
TZDs worked too well!

Table 2. Clinical and laboratory data for Responders and Non-Responders prior to rosiglitazone therapy

	Responders (n=27)	Non-Responders (n=9)
Age (years)	56±2	51±3
Male/female	14/13	5/4
Weight (kg)	85±3	85±5
Fat mass (%)	40.08±2.3	31.3±3.5*
ISIcomposite	1.89±0.14	3.55±1.34*

Predictors of improved glycaemic control with rosiglitazone therapy in type 2 diabetic patients
Br J Diab Vasc Dis Jan/Feb 2005; 5:1 28-35

"the increase in % fat mass correlated with the decrease in HbA1C during rosiglitazone treatment"



Decreased HgA1C
Weight Gain
Increased MI
Increased Cancer

Current Treatment Paradigm

Insulin Resistance (Diabetes)

Increase Insulin

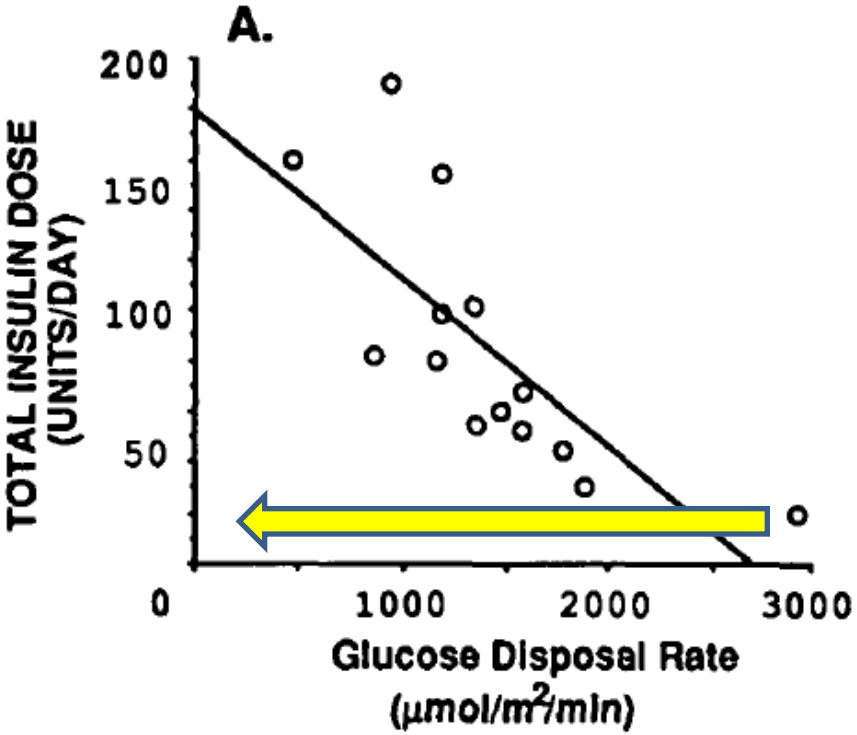
Decreased HgA1C
Weight Gain
Increased MI
Increased Cancer

Current Treatment Paradigm

Insulin cures type I diabetes

Insulin ***causes*** type II diabetes

Current Treatment Paradigm is Idiotic

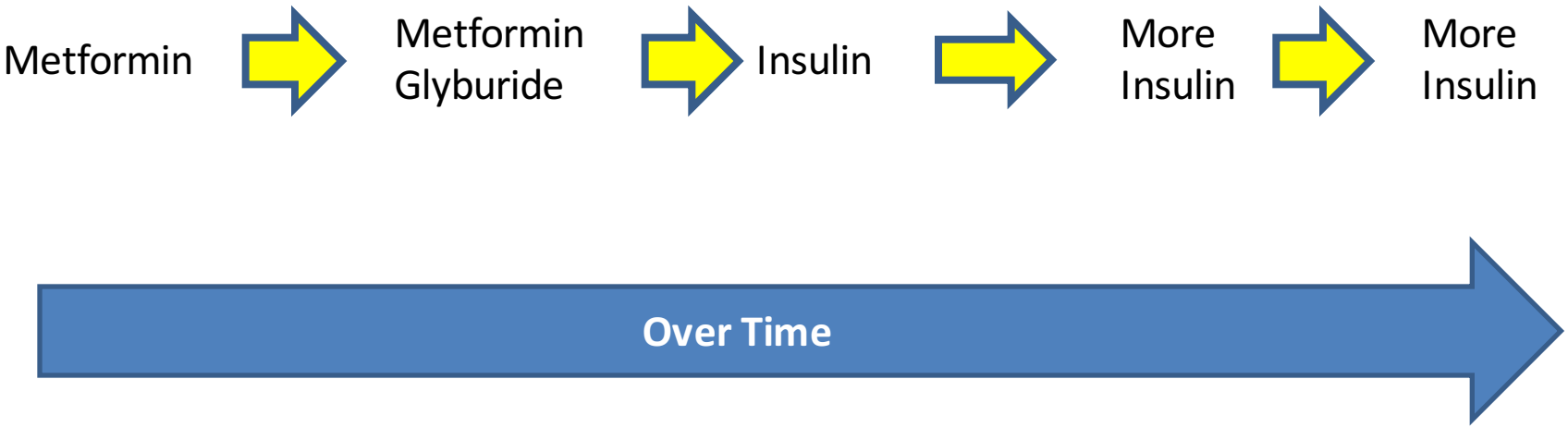


Increasing insulin resistance!

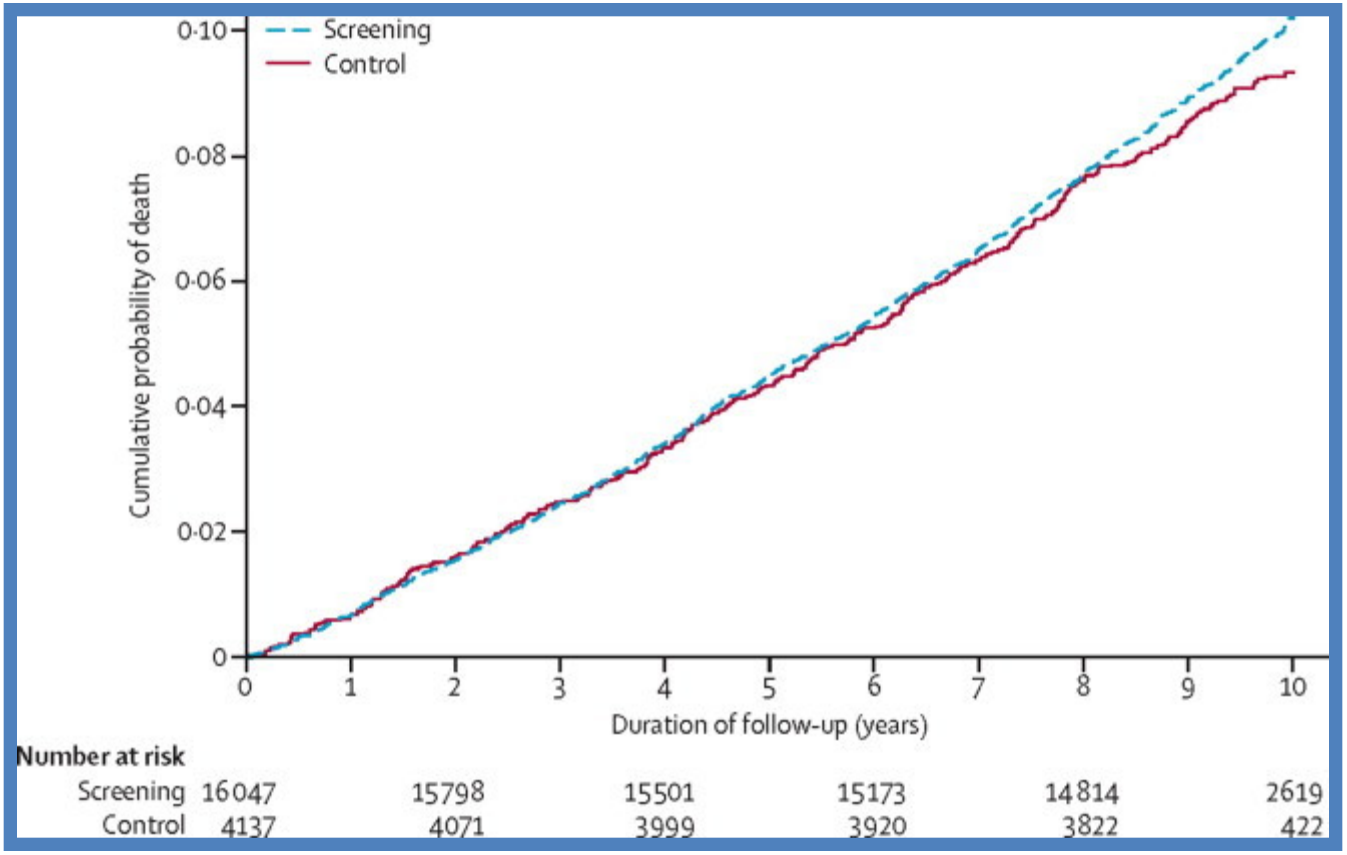
Diabetes Care 1993 16:23-31 Henry RR

You can't treat a ***hyperinsulinemic*** state with ***insulin!***

Diabetes is getting worse!



Diabetes Screening is Useless

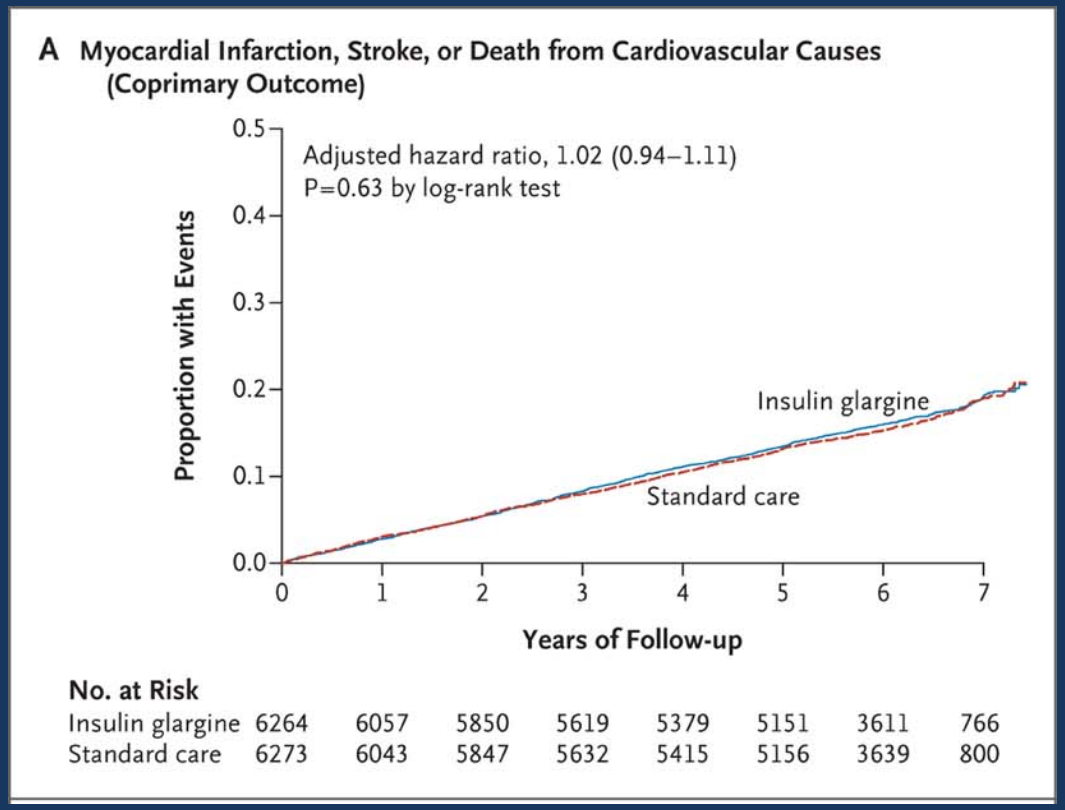


Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial

Lancet. 2012 November 17; 380(9855): 1741–1748 Simmons RK

Glucose Lowering without Hyperinsulinemia

ORIGIN



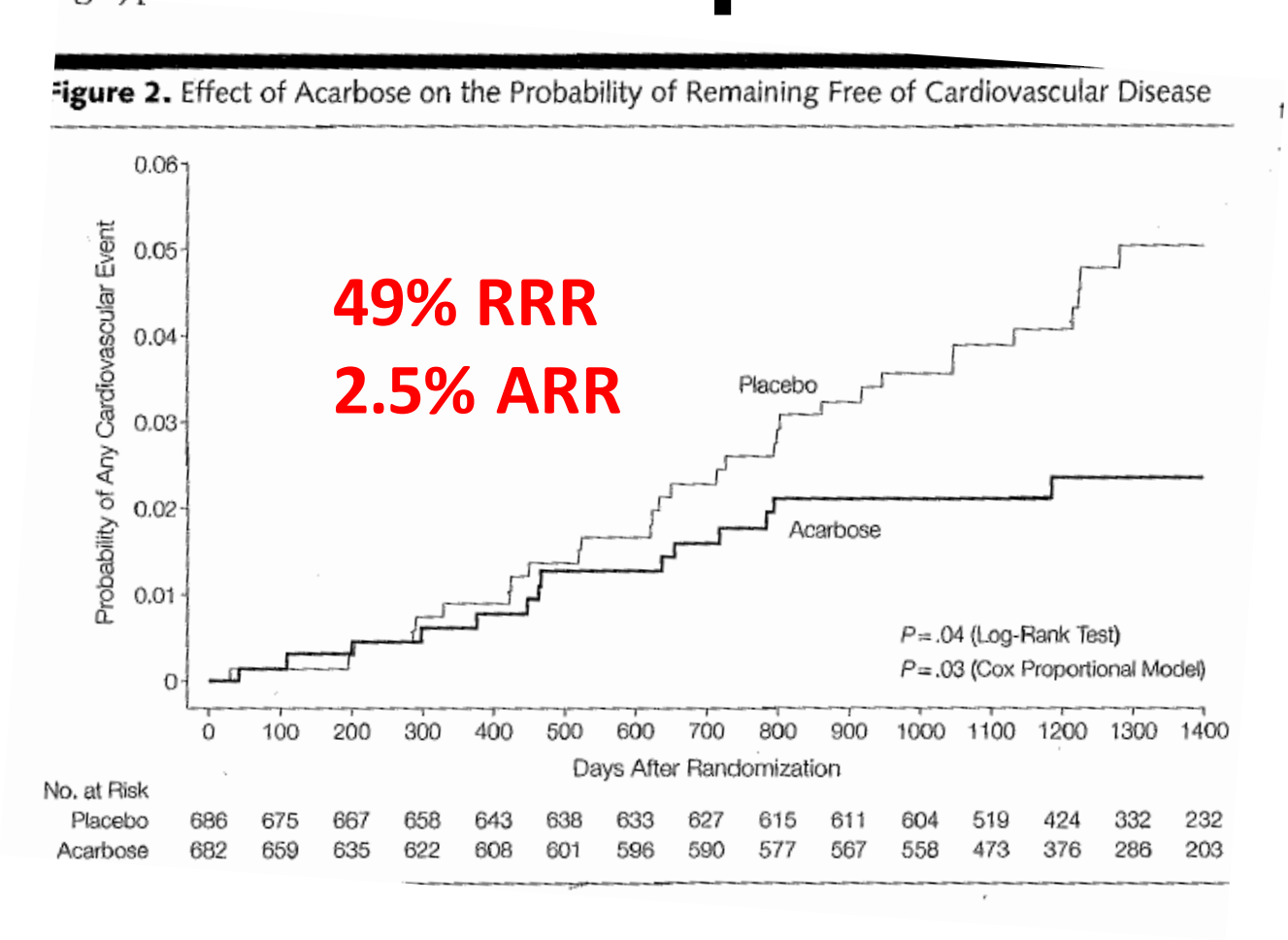
Proportion of Participants with Events over Time.

No measureable difference in outcomes

The ORIGIN Trial Investigators. N Engl J Med 2012;367:319-328

The NEW ENGLAND JOURNAL of MEDICINE

Lowering glucose *without raising insulin* improves outcomes



Randomized 1,429 patients

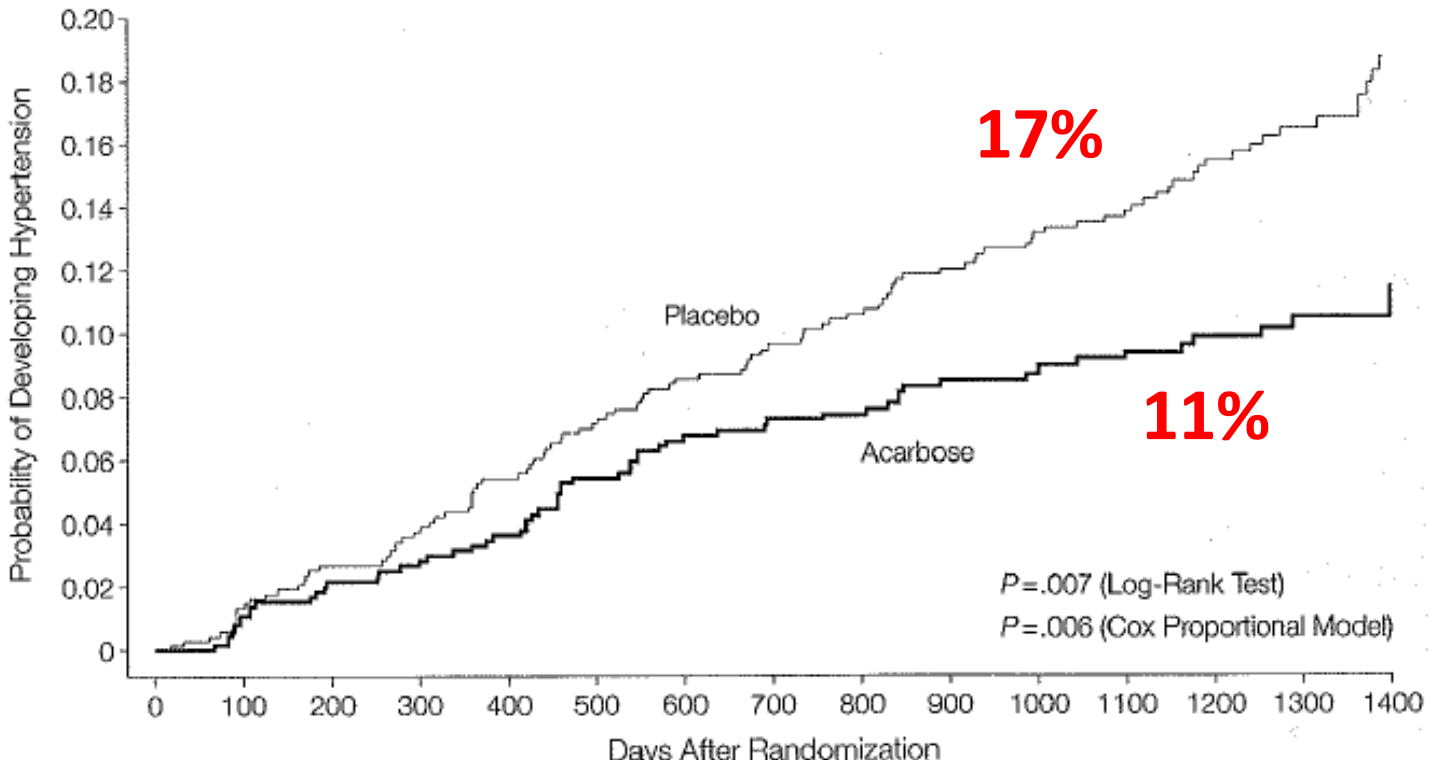
3.3 year follow up

Acarbose Treatment and the Risk of Cardiovascular Disease and Hypertension in Patients with Impaired Glucose Tolerance

JAMA 2003; 290: 486-494

Hypertension

Figure 4. Effect of Acarbose on the Probability of Remaining Free of Hypertension



HR 0.66 P= 0.006

Treatment considerations

1. Insulin causes diabetes
2. Insulin increases cancer and CV events
3. ****Decreasing insulin**** reduces diabetes, CV events, and cancer
4. How to decrease insulin without raised blood sugars?

Insulin is the *problem*, not the solution

Diabetes – Medical treatment

Good

1. Metformin
2. Onglyza
3. Acarbose

Bad

1. Insulin
2. Sulphonylureas
3. TZDs

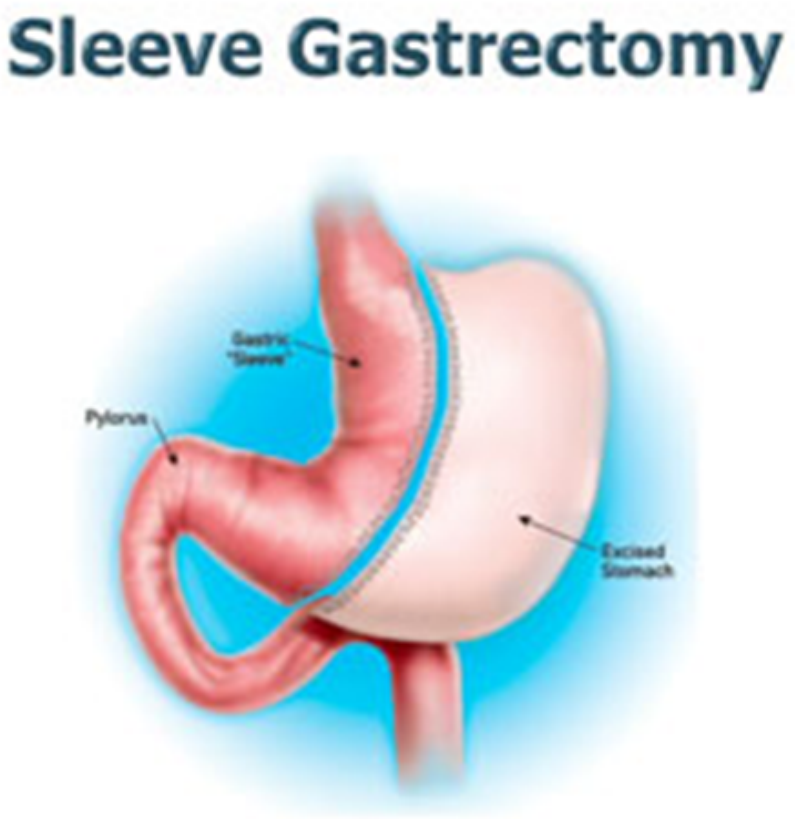
Surgical Options

Roux-En-Y Gastric Bypass

Sleeve Gastrectomy

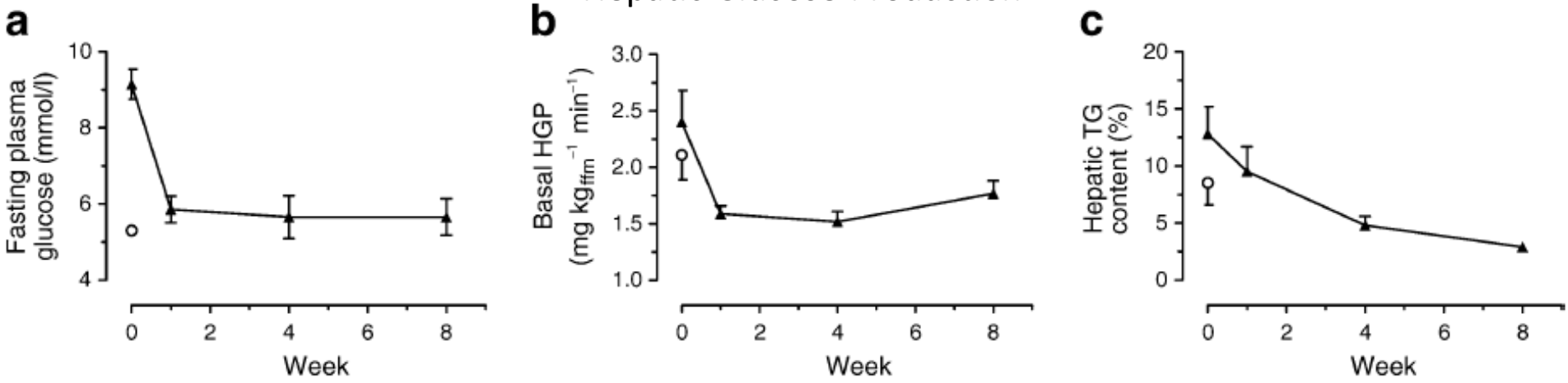
Laparoscopic banding

>90% cure rates for diabetes



Diabetes is a Reversible Disease!

Hepatic Glucose Production

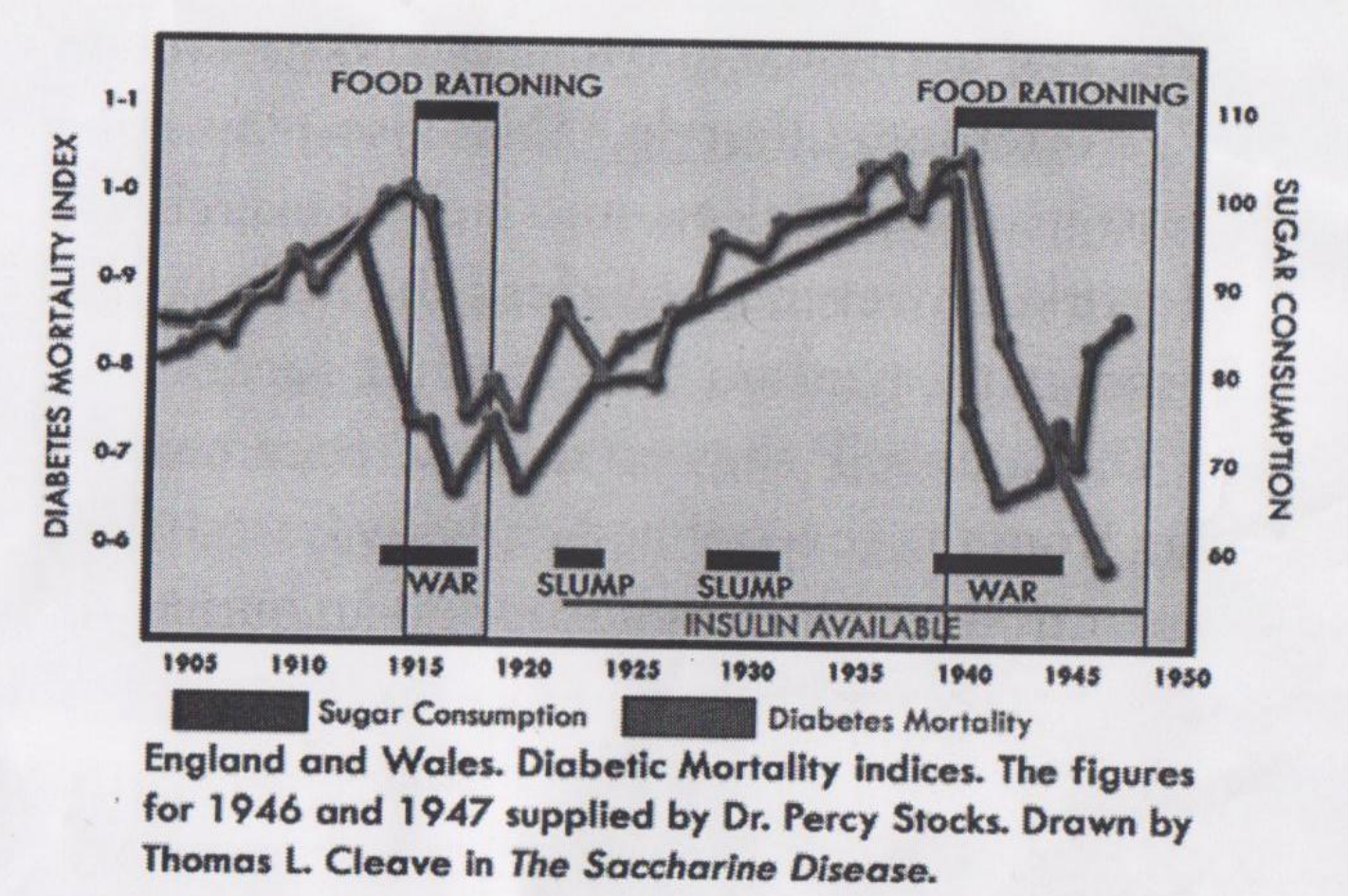


Changes of insulin sensitivity and beta cell function are reversible

Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol

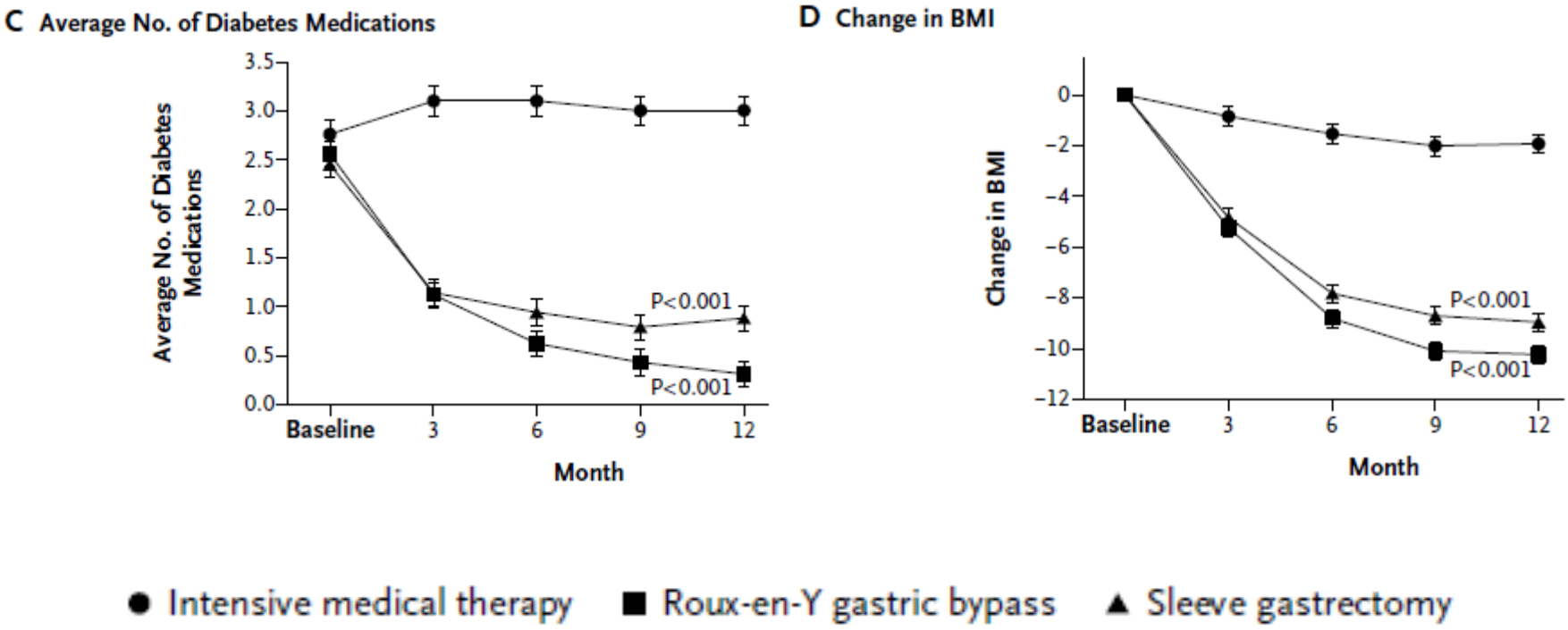
Diabetologia 2011 Oct;54(10):2506-14, Lim EL

Food Rationing decreases Diabetes



England and Wales. Diabetic Mortality indices. The figures for 1946 and 1947 supplied by Dr. Percy Stocks. Drawn by Thomas L. Cleave in *The Saccharine Disease.*

Surgery cures diabetes

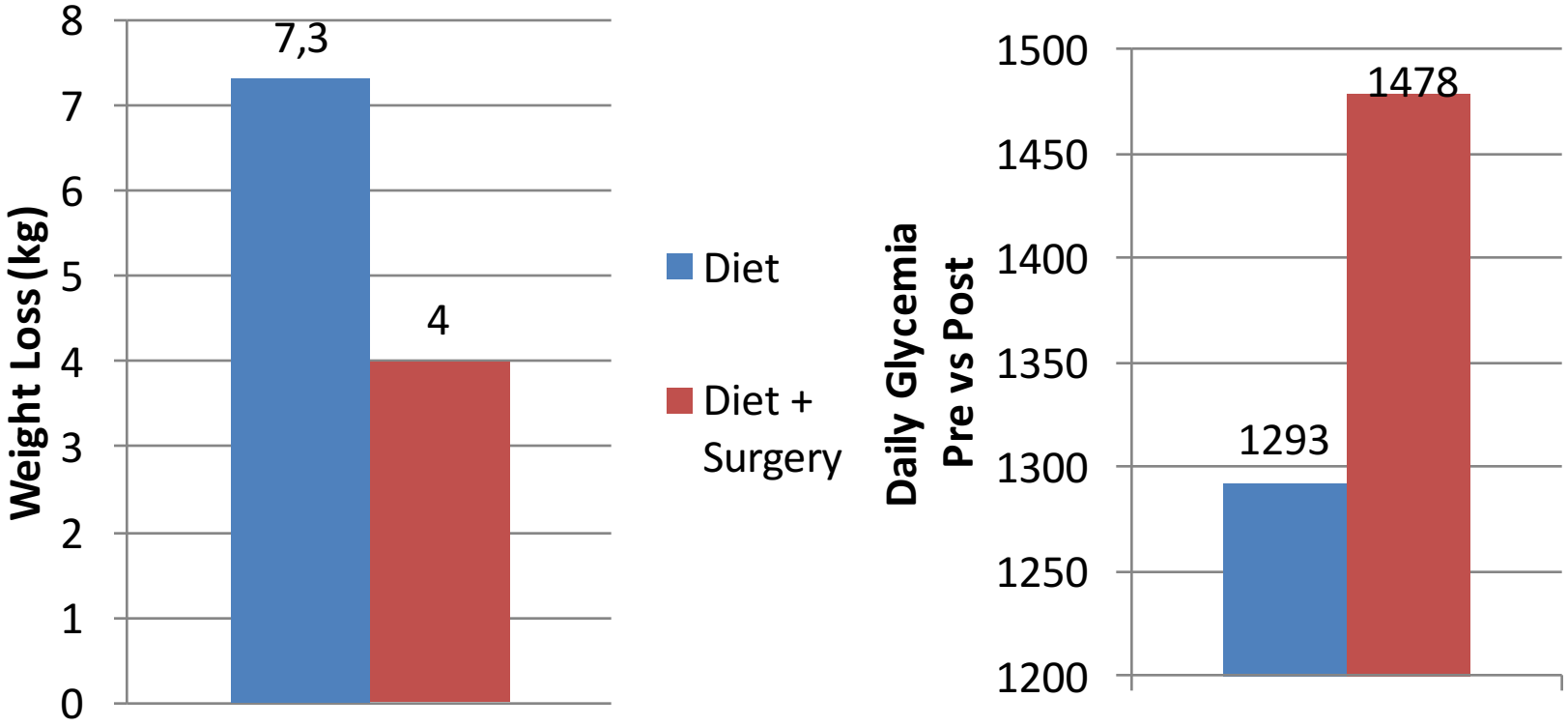


Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

N Engl J Med 2012;366:1567-76 Schauer PR

Basically surgically enforced fasting regimens

Fasting vs. Bariatric Surgery



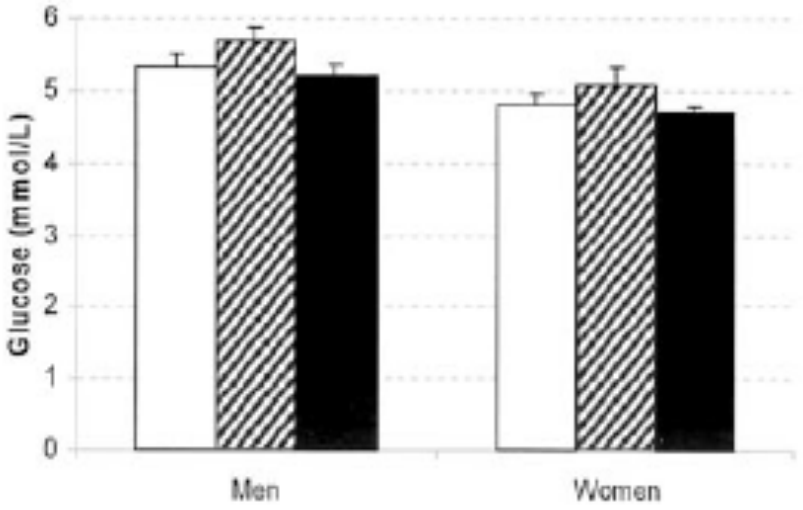
Rapid Improvement of Diabetes After Gastric Bypass Surgery: Is It the Diet or Surgery? Diabetes Care. 2013 Mar 25, Lingvay I
http://www.ncbi.nlm.nih.gov/pubmed/23530013

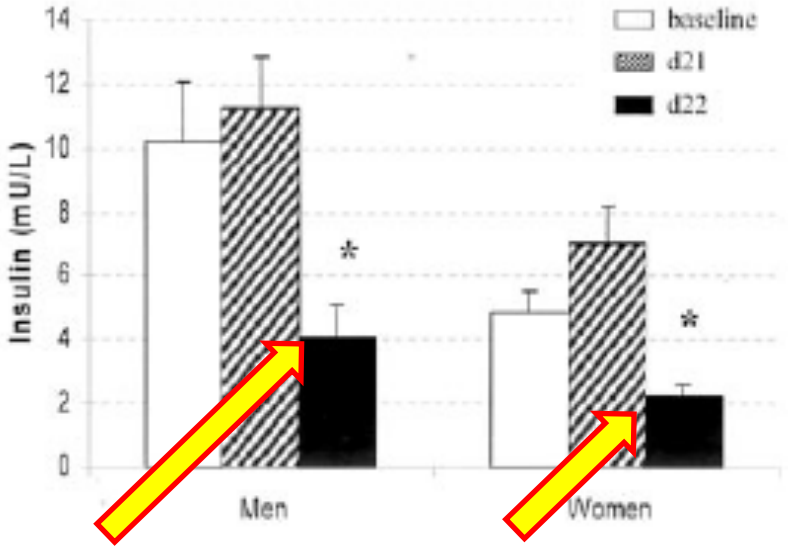
Fasting – a time tested treatment

"Our food should be our medicine. Our medicine should be our food. But to eat when you are sick is to feed your sickness."

Hippocrates

Fasting reduces plasma insulin

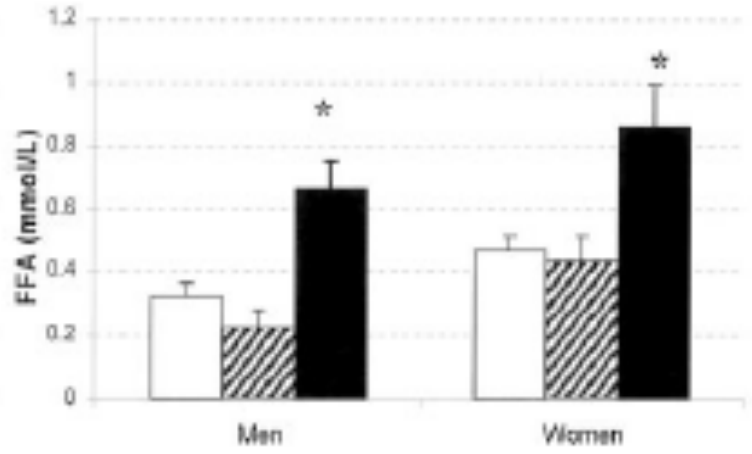




Stable blood sugars

Alternate-day fasting in nonobese subjects: effects on body weight, body composition, and energy metabolism

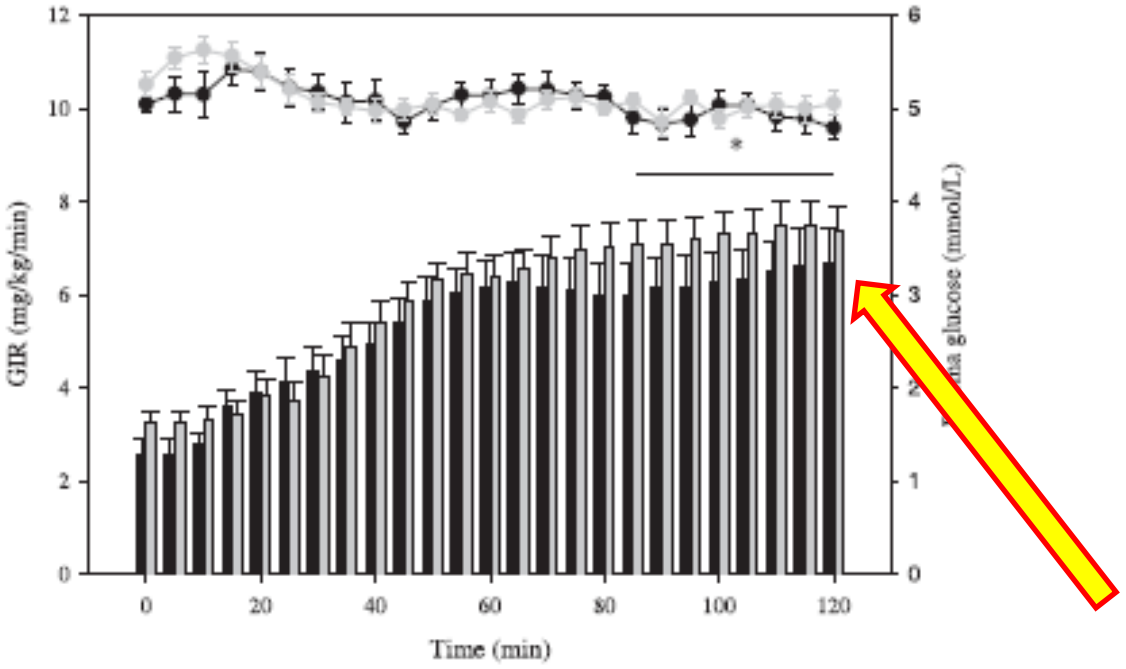
Am J Clin Nutr 2005;81:69 –73 Heilbronn LK



Fasting improves insulin sensitivity

Euglycemic clamp

Glucose Infusion rate



"Insulin-mediated whole body glucose uptake rates increased from 6.3 to 7.3 mgkg/min (*P* 0.03)"

Effect of intermittent fasting and refeeding on insulin action in healthy men

J Appl Physiol 99: 2128–2136, 2005 Halberg N

Fasting increases norephinphrine

	Day 1	Day 2	Day 3	Day 4
REE (kJ/min)	3.97 ± 0.9	4.37 ± 0.9[2]	4.53 ± 0.9[2]	4.43 ± 0.9[2]
Nonprotein RQ	0.83 ± 0.06	0.73 ± 0.04[2]	0.70 ± 0.04[2]	0.70 ± 0.04[2]
Weight (kg)	64.2 ± 13.5	63.5 ± 13.3[2]	62.6 ± 13.2[2,3]	61.5 ± 13.2[2,3,4]

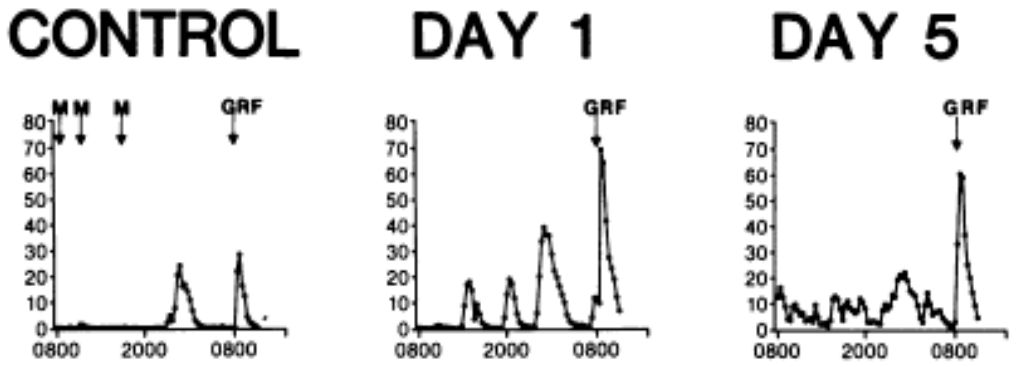
TABLE 3
Biochemical values[1]

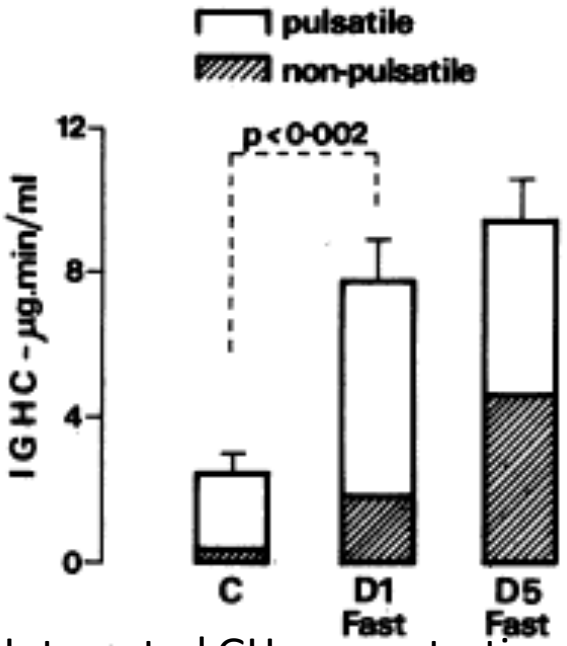
	Day 1	Day 2	Day 3	Day 4
Norepinephrine (pmol/L)	1716 ± 574	2134 ± 1079	3409 ± 1349[2,3]	3728 ± 1636[2,3]
Epinephrine (pmol/L)	425 ± 180	311 ± 152	395 ± 158	398 ± 257
Insulin (pmol/L)	71 ± 21	71 ± 41	58 ± 19	59 ± 23
Glucose (mmol/L)	4.9 ± 0.5	3.9 ± 0.5[2]	3.6 ± 0.5[2,3]	3.5 ± 0.5[2,3]
Fatty acids (μmol/L)	240 ± 191	616 ± 225[2]	957 ± 443[2,3]	1135 ± 575[2,3]

Resting energy expenditure in short-term starvation is increased as a result of an increase in serum norepinephrine

Am J Clin Nutr 2000;71:1511–5 Zauner C

Fasting increases Growth Hormone





Integrated GH concentration

Growth Hormone:

- Increases availability and utilization of fats for fuel
- Preserves muscle mass

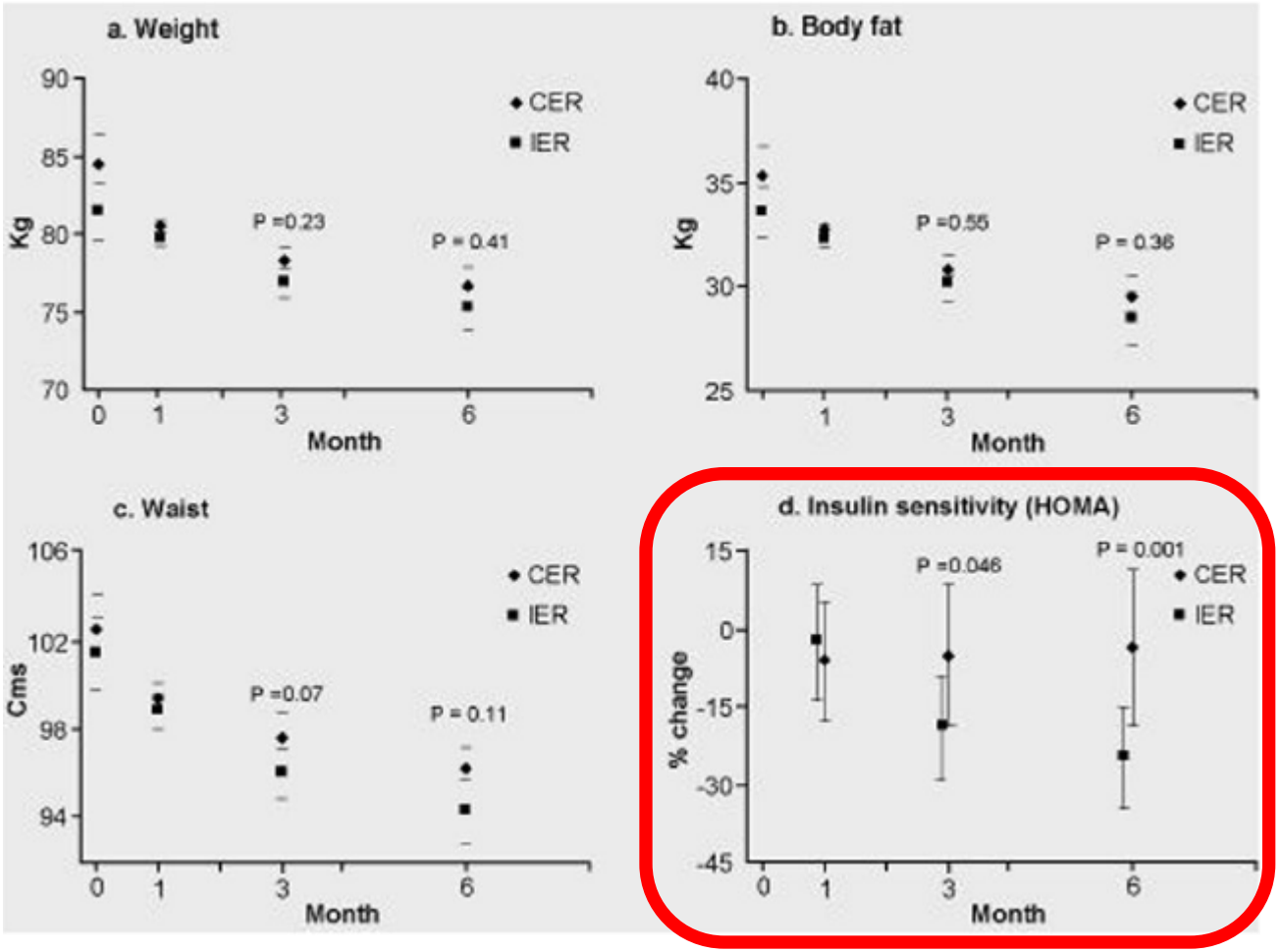
Fasting enhances growth hormone secretion and amplifies the complex rhythms of growth hormone secretion in man

J Clin Invest. 1988 April; 81(4): 968–975 Ho KY

Intermittent caloric restriction is better than continuous

Randomized trial

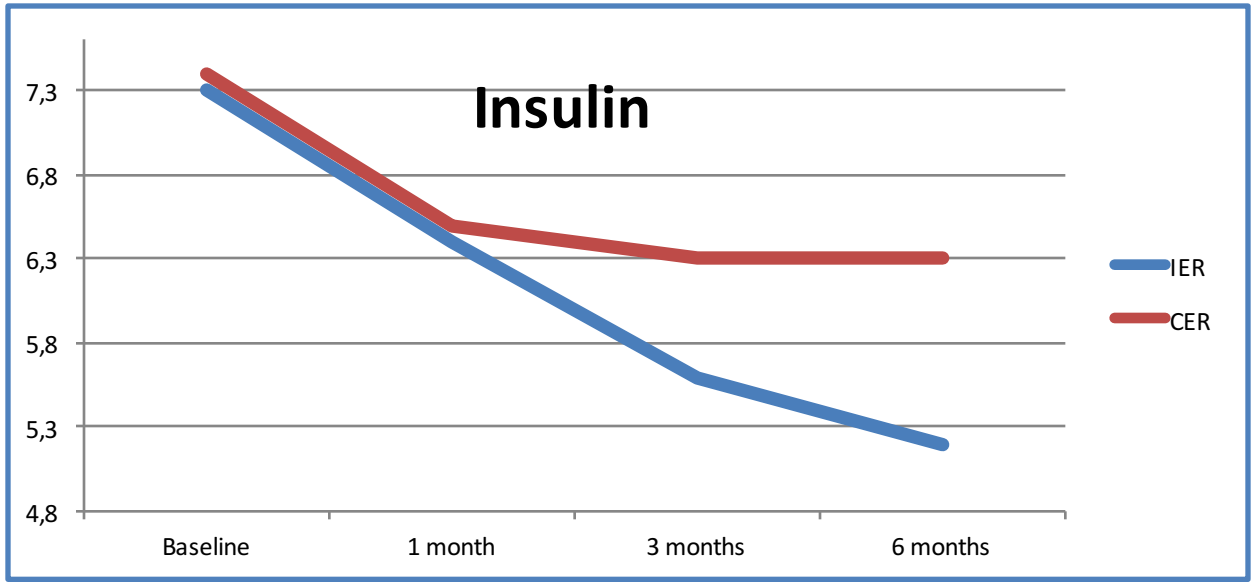
25% caloric reduction



The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomised trial in young overweight women
Int J Obes (Lond). 2011 May ; 35(5): 714–727 Harvie MN

Intermittent caloric restriction is better than continuous

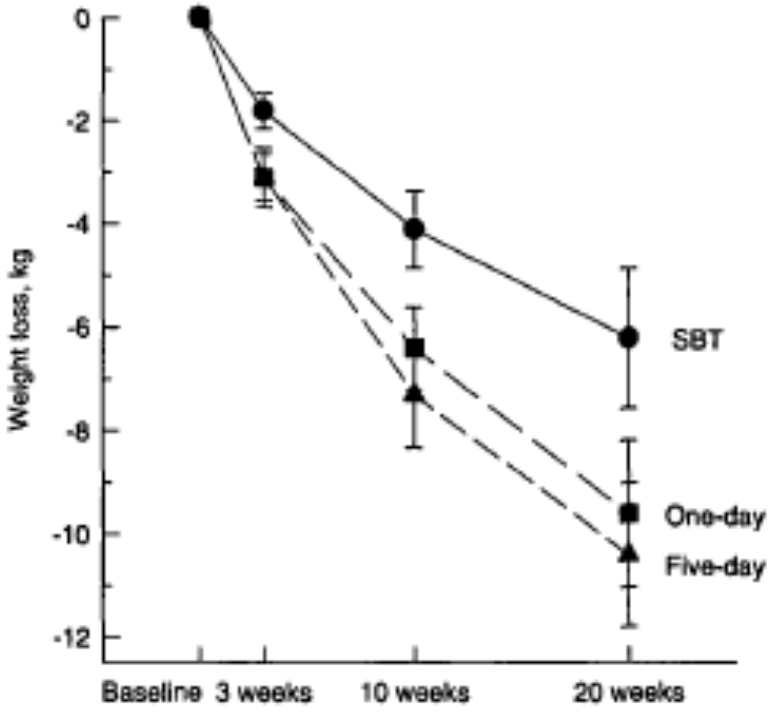
Parameter		Baseline	1 Month	3 Month	6 Month	P value[4]
Insulin (μU/ml)[2]	IER	7.3 (6.3 to 8.4)	6.4 (5.7 to 7.3)	5.6 (4.7 to 6.5)	5.2[3] (4.5 to 6.0)	0.04
	CER	7.4 (6.4 to 8.6)	6.5 (5.7 to 7.5)	6.3 (5.4 to 7.3)	6.3[3] (5.4 to 7.4)	
HOMA (μU/mmol/L)[2]	IER	1.5 (1.3 to 1.8)	1.4 (1.2 to 1.6)	1.1 (1.0 to 1.4)	1.1[3] (0.9 to 1.3)	0.04
	CER	1.6 (1.3 to 1.8)	1.3 (1.2 to 1.6)	1.3 (1.1 to 1.5)	1.3[3] (1.1 to 1.6)	

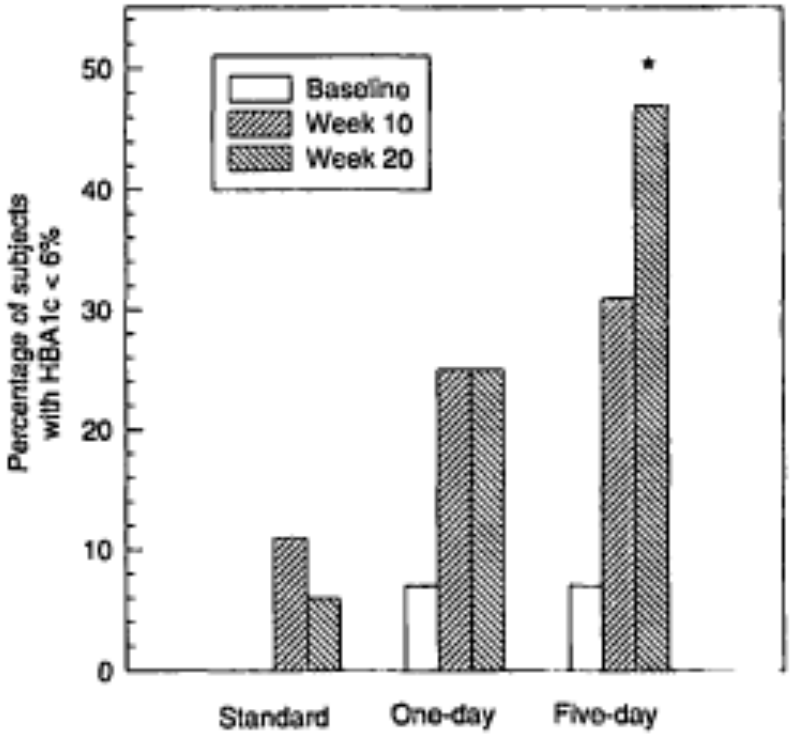


Int J Obes (Lond). 2011 May ; 35(5): 714–727 Harvie MN

Clinical Effects

Fasting reduces diabetes





P<0.05

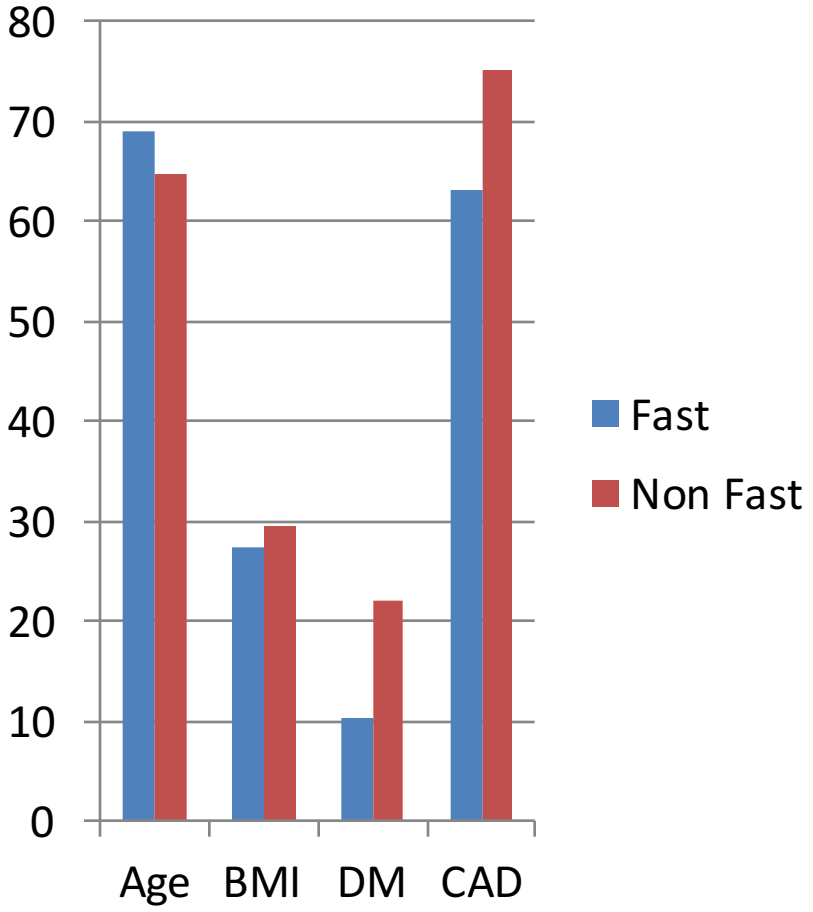
Obese DM2 patients randomized to standard calorie restriction or 5 day periodic fast or 1 day week fasting

The Effect of Short Periods of Caloric Restriction on Weight Loss and Glycemic Control in Type 2 Diabetes

Diabetes Care. 1998 Jan;21(1):2-8 Williams KV

Fasting associated with less DM and CAD

Prospective study 200 patients going for angiography



Relation of routine, periodic fasting to risk of diabetes mellitus, and coronary artery disease in patients undergoing coronary angiography

Am J Cardiol. 2012 Jun 1;109(11):1558-62 Horne BD

How to Treat Type 2 Diabetes

Insulin *causes* diabetes

Diabetes is a *curable* disease

****Lower insulin levels****

Bariatric surgery without the surgery – Fasting!

Effects of Fasting

- Decrease blood glucose (good)
- Increase FFA and cholesterol (good)
- Decrease insulin (good)
- ***Restores insulin sensitivity*** (good)
- Increase norepinephrine (good)
- Increase growth hormone (good)
- Fat loss (good)
- Preserved muscle mass (good)

How to Cure Type 2 Diabetes

Diabetes is a *curable* disease

Insulin *causes* diabetes

****Lower insulin levels****

Bariatric surgery without the surgery – Fasting!

Can We Cure Type 2 Diabetes?

No Diabetes – no diabetic nephropathy, no diabetic foot ulcers, diabetic retinopathy, reduced stroke, MI, cancers

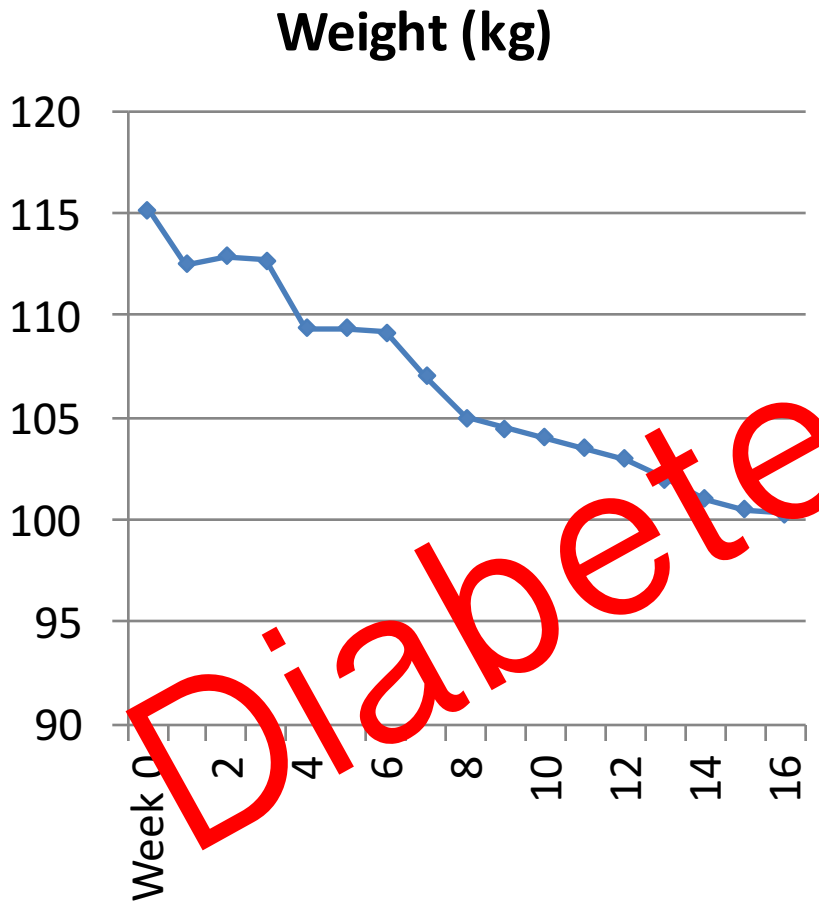
No Drugs, no surgery, no cost to patients, no long term side effects

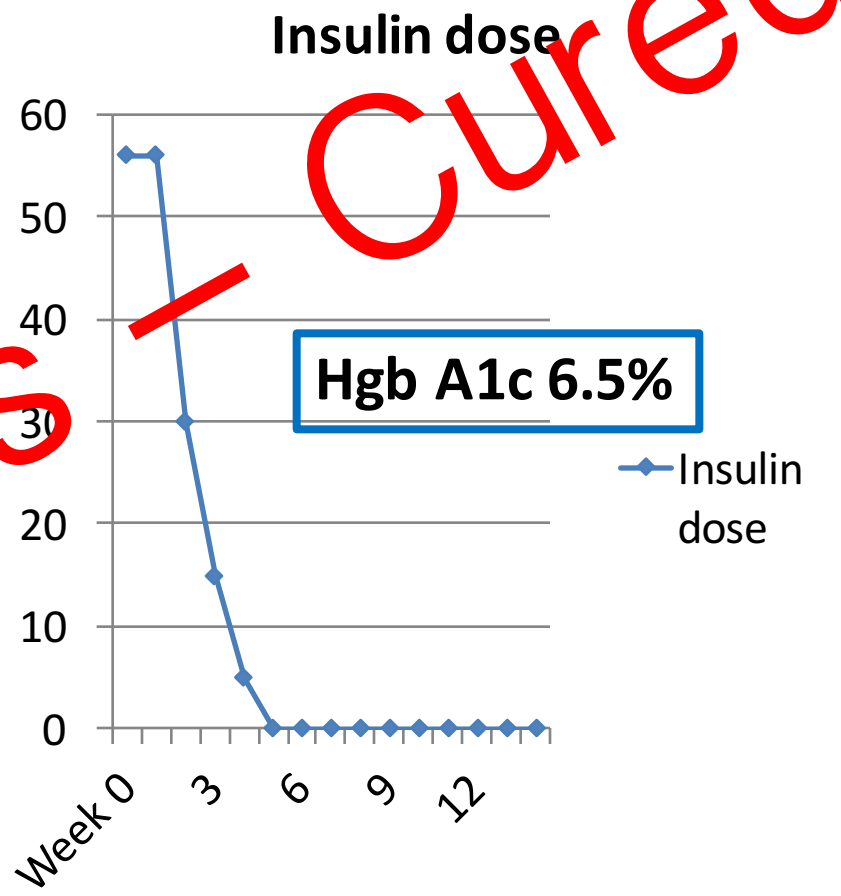
12 month intensive fasting regime to cure diabetes

Case 1- Richard

- 55 year old white male
- Diabetes since 2002
  - Retinopathy
  - Neuropathy
  - Nephropathy
- Started in IDM program June 2013

Richard



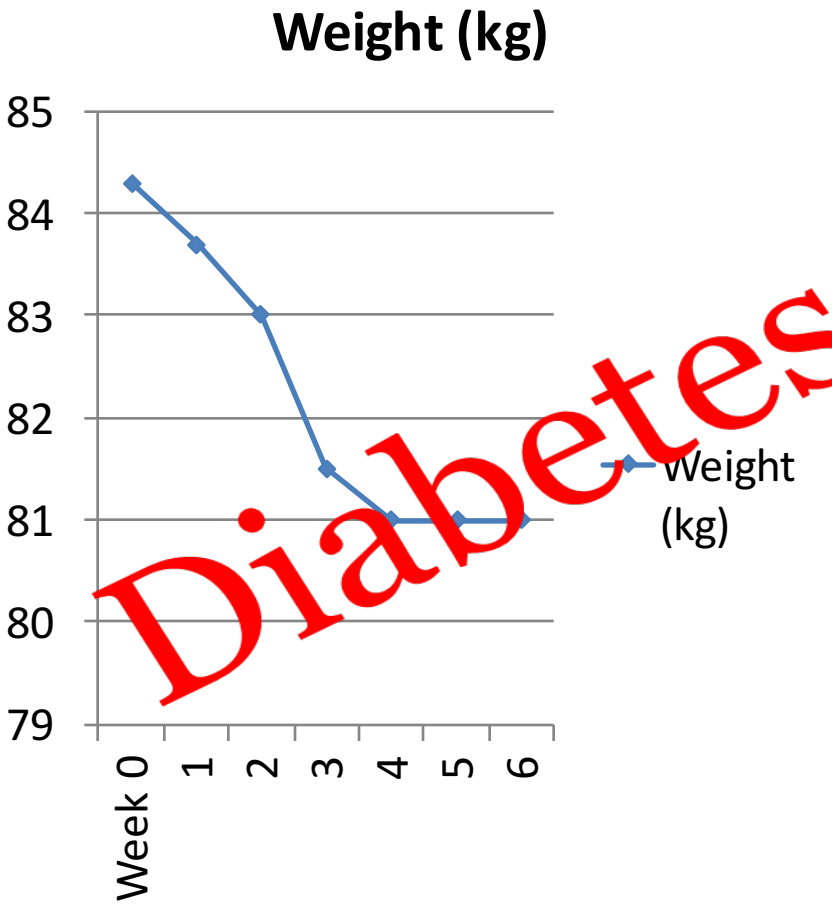


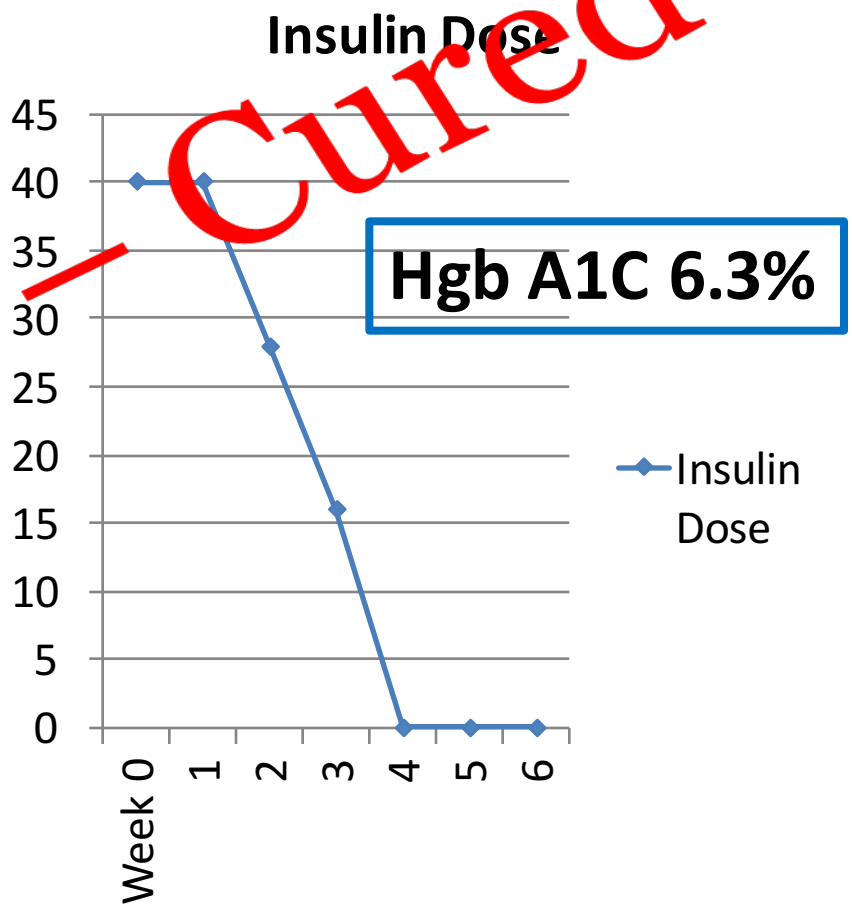
Diabetes I Cured

Case 2 - Balraj

- 45 yo Sri Lankan man
- Diabetes diagnosed 2003
  - Nephropathy
  - Retinopathy
- ITP
- Started IDM program Aug 27, 2013

Balraj





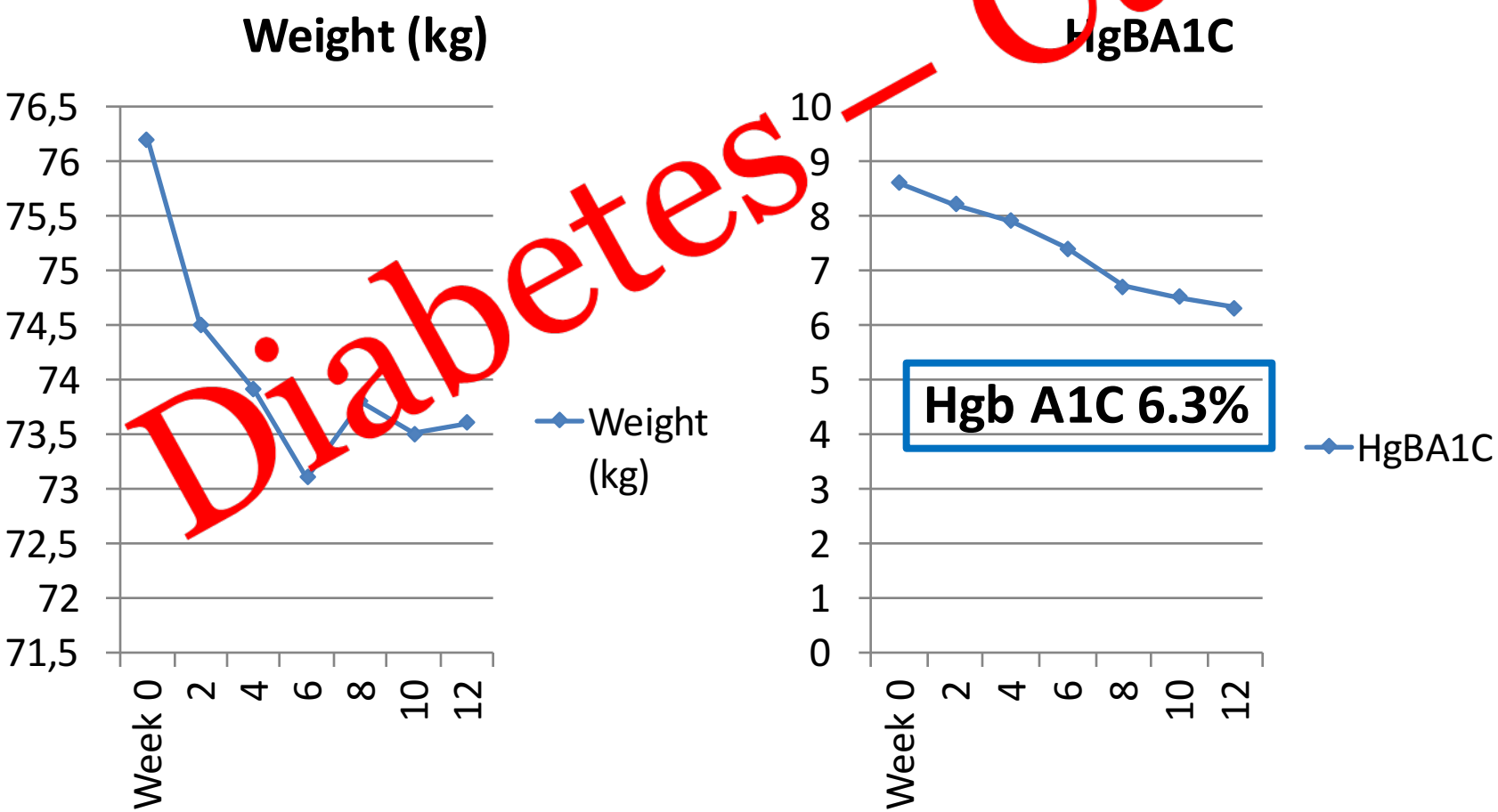
Diabetes – Cured

Hgb A1C 6.3%

Case 3 - Armando

- 45 year old Philippine patient
- Newly diagnosed with diabetes – not currently on medications and does not want to take medication
- Starting HgB A1C 8.7% and rising over 6 months
- Started IDM program June 2013

Armando

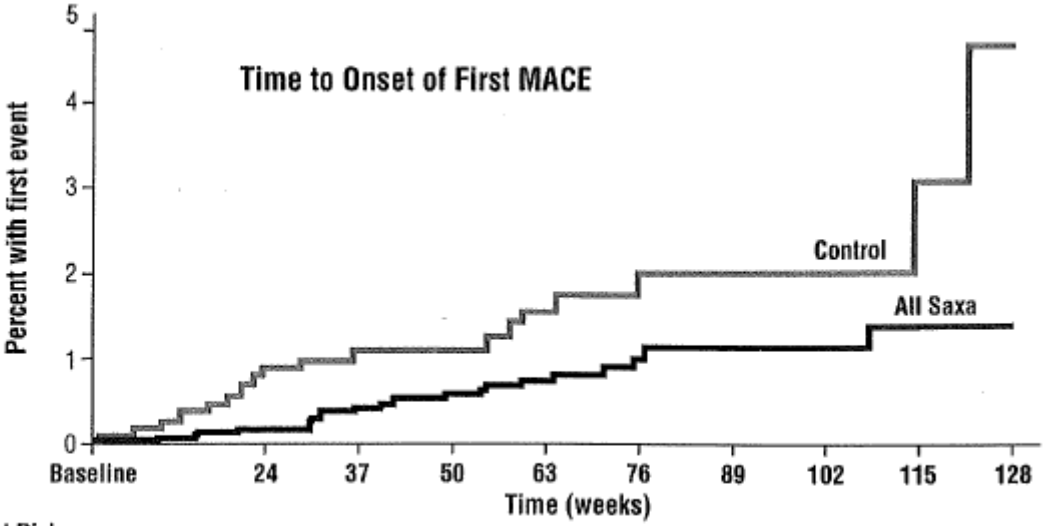


Diabetes – Cured

Time to get started…

Jason Fung's Intensive Diabetes Dietary Management (IDDM) Clinic
http://kidneylifescience.ca/drjasonfung

DPP-4 Inhibitors may reduce cardiovascular events



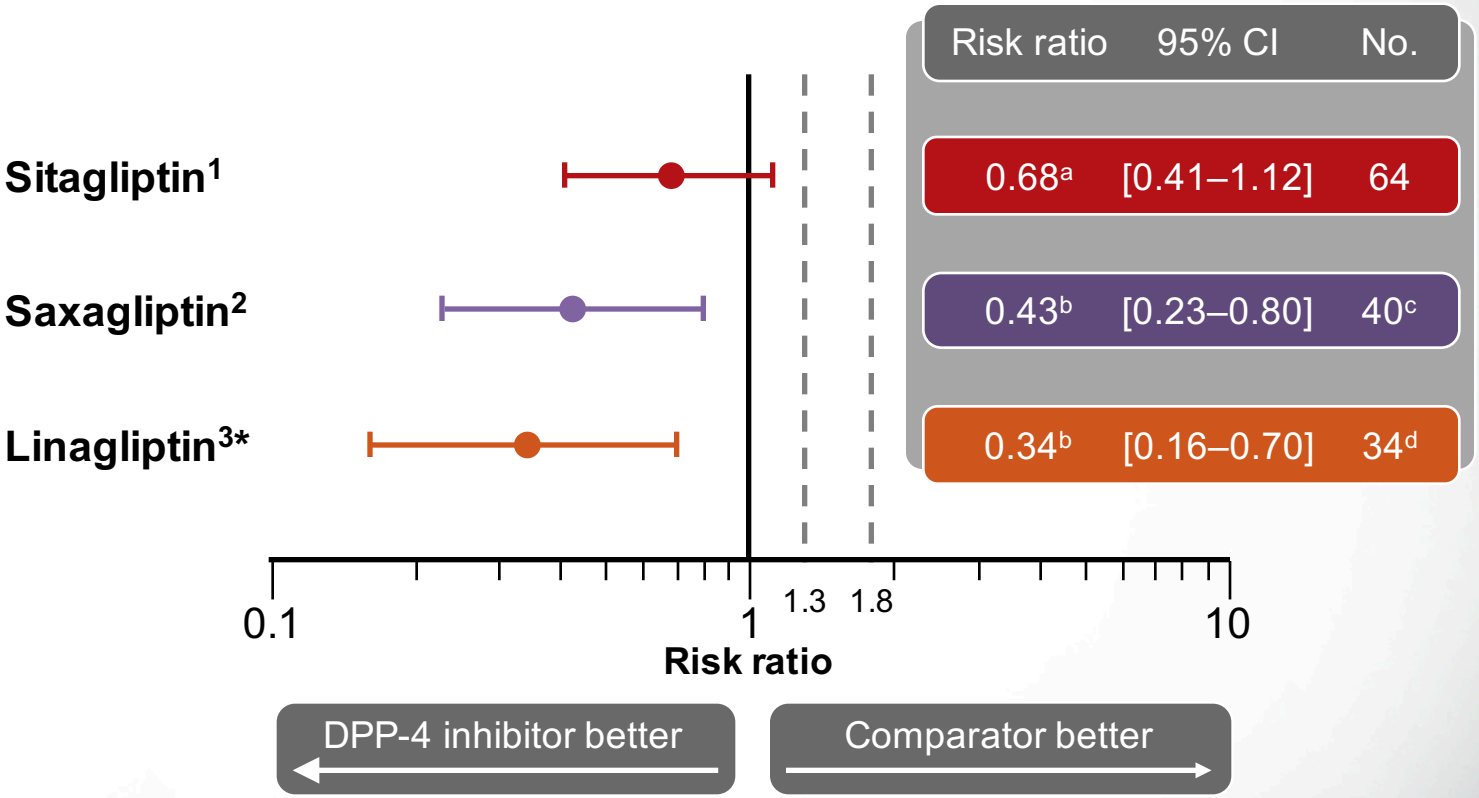
Patients at Risk										
Control	1251	935	860	774	545	288	144	123	102	57
All Saxa	3356	2615	2419	2209	1638	994	498	436	373	197

4,607 patients randomized

A Systematic Assessment of Cardiovascular Outcomes in the Saxagliptin Drug Development Program for type 2 Diabetes

Postgrad Med 2010 Vol122; 3: 16-27 Frederich

Stratified Analyses of CV Events: Pooled Data from Registration Trials (DPP-4 Inhibitors)



**The main contributor to the overall differences in the primary endpoint was the events in the head-to-head study of linagliptin vs. glimepiride. Comparisons with placebo were not statistically significant (Johansen et al 2012; Trajenta Canadian Product Monograph July 2011).*

[a]Calculated using exact procedures for the Poisson processes; [b]Cox hazard ratio; [c]Patients with events: n = 22, saxagliptin; n = 18, control; [d]Patients with events: n = 11, linagliptin; n = 23, comparator.

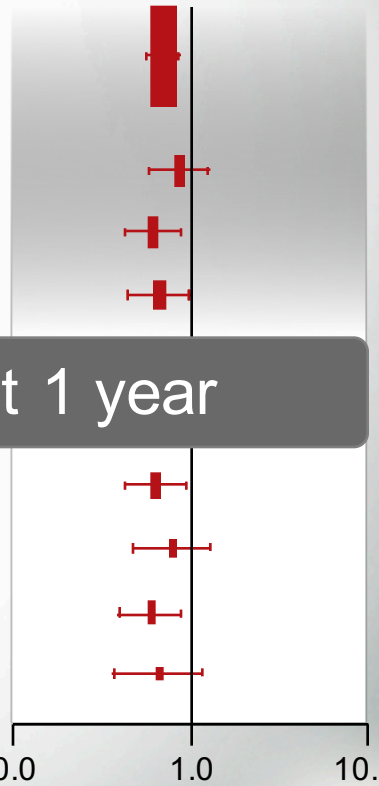
1. Williams-Herman D, et al. BMC Endocr Disord 2010; 10:7. 2. Frederich R, et al. Postgrad Med 2010; 122:16-27.
3. Johansen O-E, et al. Cardiovasc Diabetol 2012; 11:3.

Treatment with DPP-4 Inhibitors is Associated with Significant Reduction in MACE & Mortality in T2DM

Meta-analysis: 70 trials; 41,959 patients; mean follow-up of 44.1 weeks

	# trials	# trials w/ events	# events *(DPP-4)*	# events *(Comparator)*	MH-OR [95%, CI]	*p*
MACE	70	63	263	232	0.71 [0.59;0.86]	<0.001
Sitagliptin	27	24	77	67	0.86 [0.60;1.24]	0.43
Vildagliptin	16	15	75	74	0.61 [0.43;0.86]	0.005
Saxagliptin	13	12	62	46	0.67 [0.45;0.99]	0.047
AMI	62	41	61	59	0.64 [0.44;0.94]	0.023
Stroke	63	29	41	33	0.77 [0.48;1.24]	0.29
Mortality	53	30	50	51	0.60 [0.41;0.88]	0.008
CV Mortality	48	20	26	26	0.67 [0.39;1.14]	0.14

Mean duration of these trials was only about 1 year

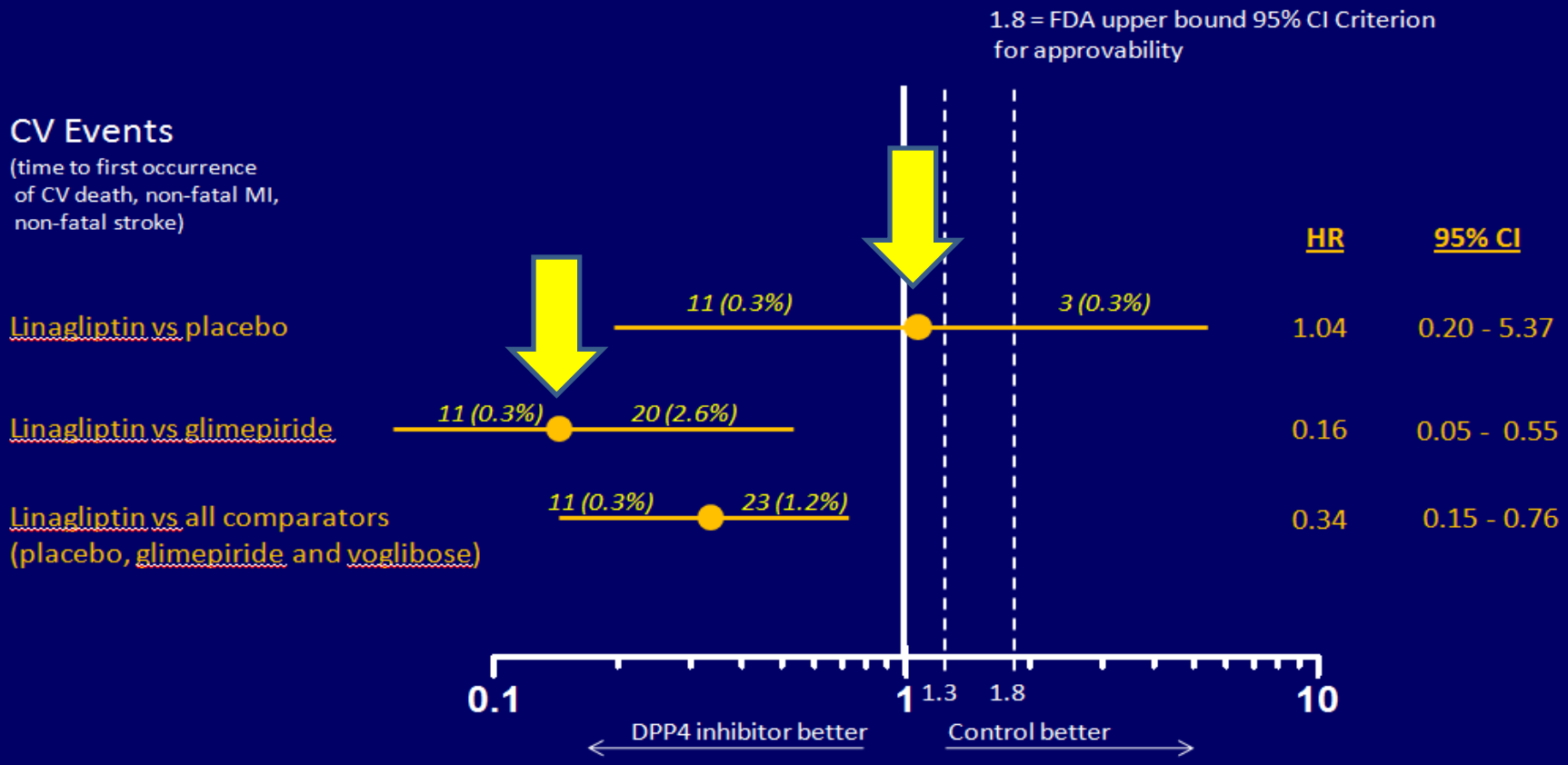


MH-OR: Mantel–Haenzel odds ratio

Monami M, et al. Diabetes, Obesity and Metabolism 2012; Aug 23 [epub ahead of print].

LINAGLIPTIN: Stratified Analysis of CV Events

Pooled Phase 3 trials (5077 patients, 3319 on Lina)



Adapted from Johansen et al., 2012 and Linagliptin Canadian product monograph (July 26, 2011)

Johansen et al., 2012. Cardiovascular Diabetology 11:3.

Ongoing CV Outcome Trials: DPP-4 Inhibitors

Trial	Therapies	#	Population	Primary endpoint	End Date
CAROLINA	Linagliptin/ Glimepiride	6000	CVD or ≥ 2 RF	***Non-inferiority:*** time to first occurrence of any component of MACE composite outcome	Sept 2018
EXAMINE	Alogliptin/ Placebo	5400	ACS 15-90 days before	***Non-inferiority:*** time to occurrence of MACE	Dec 2014
SAVOR-TIMI 53	Saxagliptin/ Placebo	16,500	CVD or ≥ 2 RF	***Superiority*** efficacy, ***non-inferiority*** safety: composite CV death, NF MI, NF stroke	July 2013
TECOS	Sitagliptin/ Placebo	14,000	Established CVD	***Non-inferiority:*** time to first occurrence of composite CV outcome	Dec 2014

CVD = cardiovascular.

Adapted from:
1. Golden SH. Am J Cardiol 2011; 108(Suppl):59B-67B.
2. Fonseca V. Am J Cardiol 2011; 108(Supp):52B–58B.
3. *www.clinicaltrials.gov*

Yes, we can

45 years old

Diabetes for 20 years

On 100 units/ day of insulin

After 2 months – off all insulin

CURED of diabetes