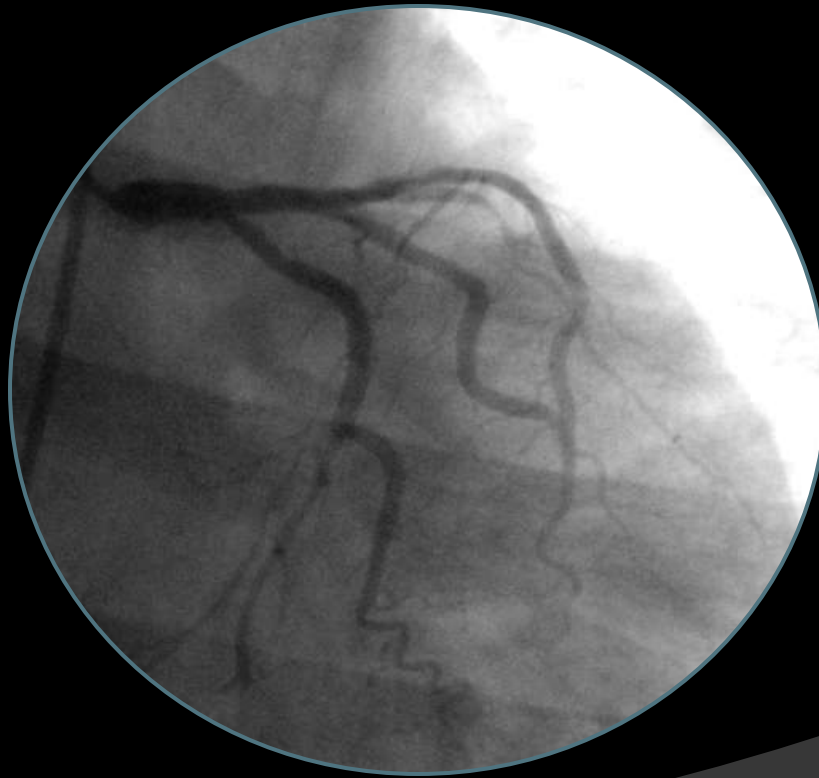
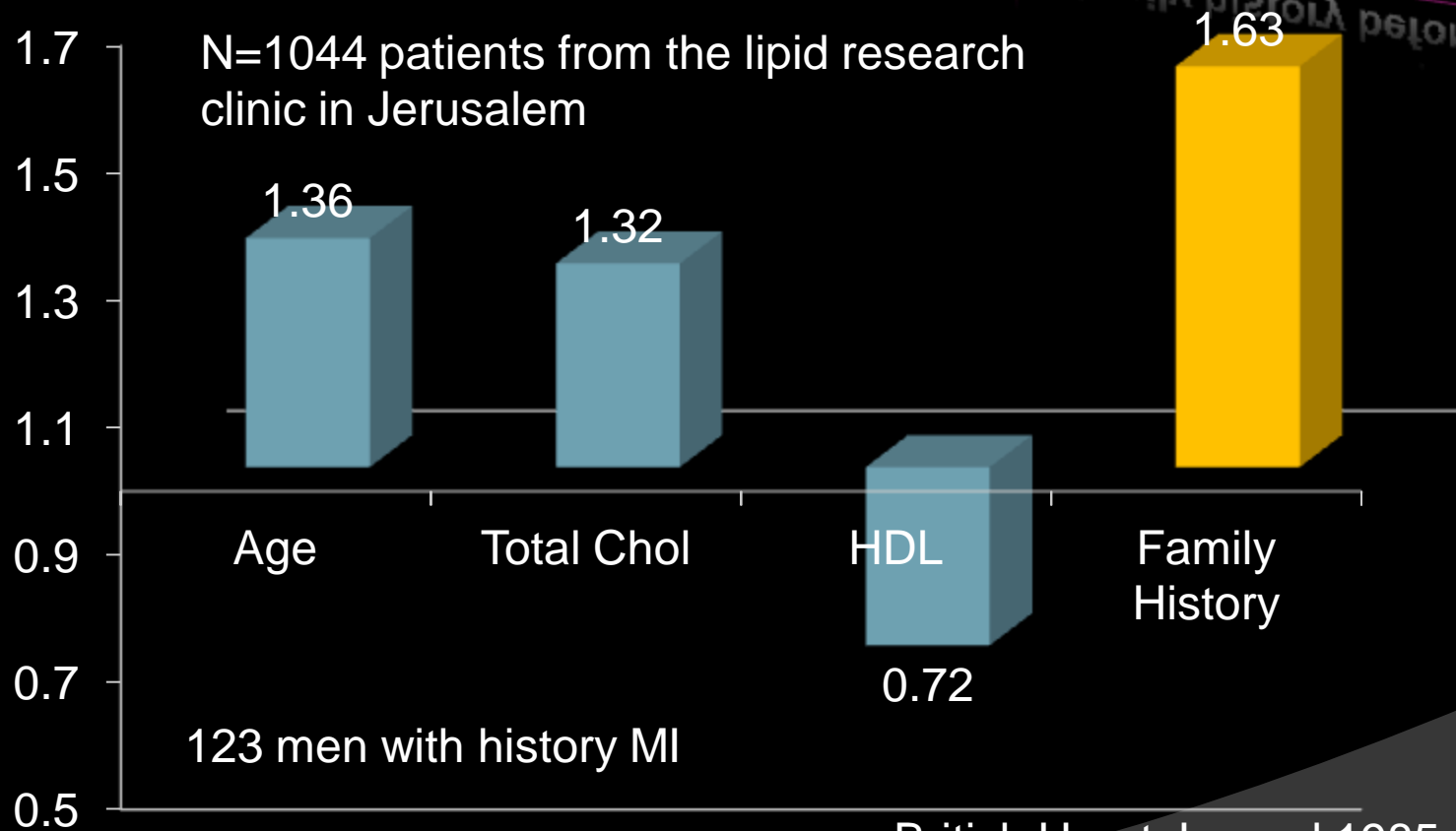


THE DIABETES SPECTRUM: PREDIABETES AND NEW TARGETS



31 y/o obese women
FBS 100 mg/dl

Family history is very important in assessment of risk for MI



British Heart Journal 1985;53:382-7



What is the clinical target ?



Preventing diabetes?

“Not just a blood glucose number”

Prevention of Cardiovascular Events

“Diabetes is a Cardiovascular Disease”



Definition by ADA

- ⦿ Impaired glucose tolerance (IGT)
 - Fasting plasma glucose (FPG) concentration <100 mg/dL
 - 2-hour plasma glucose (PG) concentration, measured by a 75-g oral glucose tolerance test (OGTT), ranging between >140 mg/dL and <200 mg/dL
- ⦿ Impaired fasting glucose (IFG)
 - 2-hour PG (measured by an OGTT) of <140 mg/dL and a FPG between >100 mg/dL and <126 mg/dL.



Obesity is a frequent front runner to CV disease

- Prospective study of more than 1 million adults in the United States

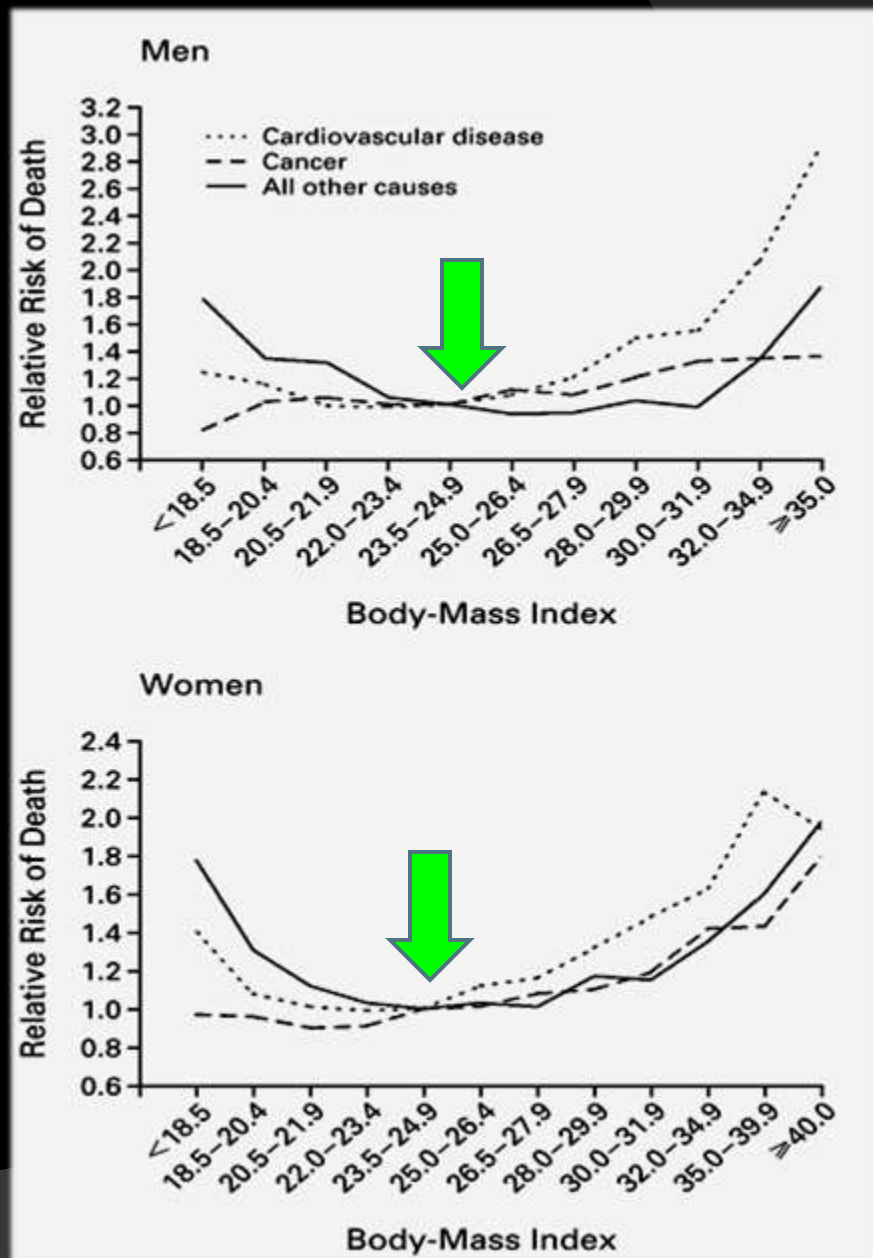
- (457,785 men and 588,369 women)

- 201,622 deaths occurred during

- 14 years of follow-up

Risk of death from all causes, cardiovascular disease increases in moderate and severe over-weight for both men and women-greater for whites

N Engl J Med 1999;341:1097-105

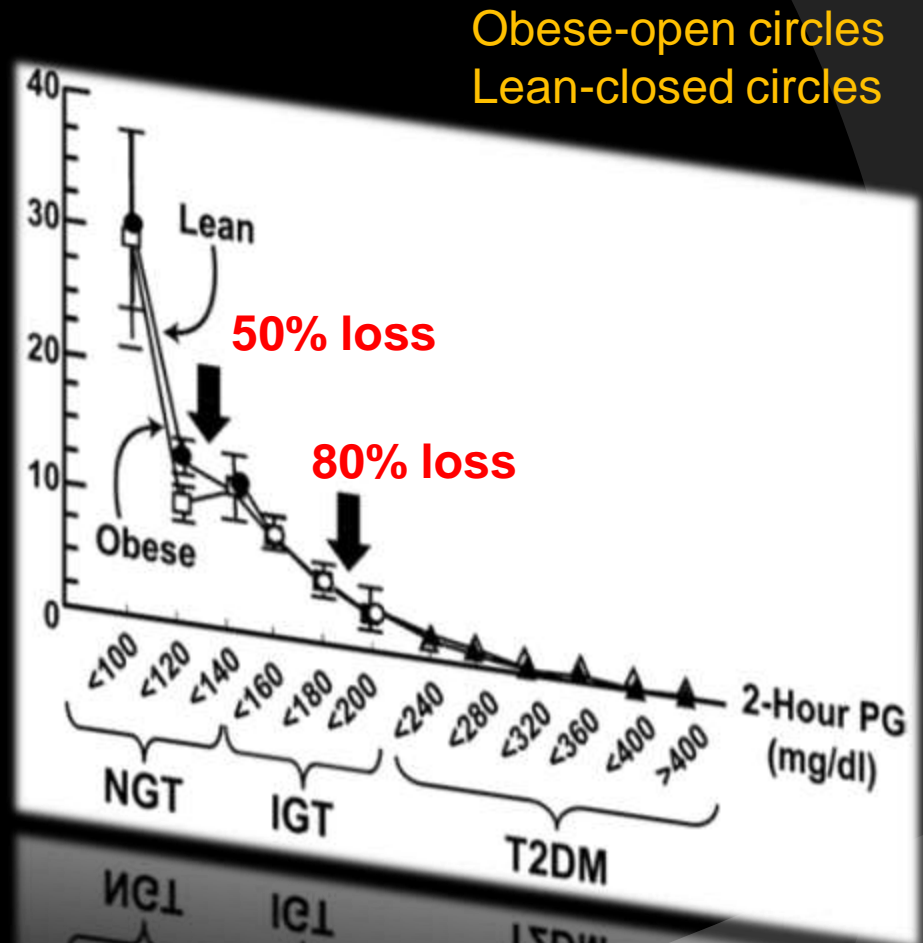


Obesity patients with pre-diabetes have lost >50% of beta cell function

- San Antonio metabolism (SAM) study
- 388 subjects in the San Antonio Metabolism (SAM)
- Patients:
 - 138 NGT, 49 IGT and 201 T2DM
- Euglycaemic insulin clamp
- 2-hour PG 120 –139 mg/dL have a loss of 50%
- Summary:
 - Plasma insulin response to oral glucose is related to glycemic stimulus & severity of insulin resistance

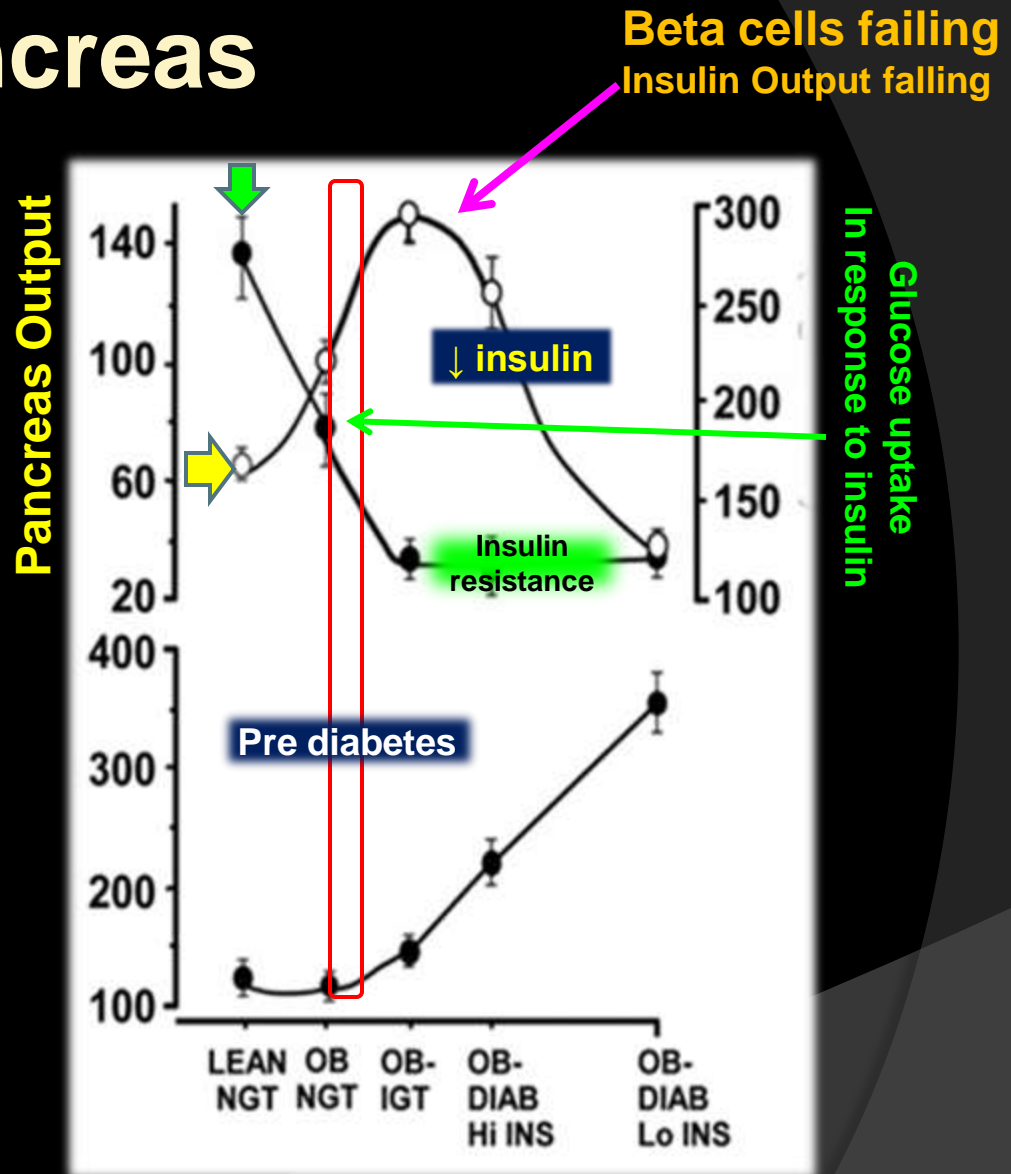
Normal

Beta cell function



Cardiologist view of Starlings curve of the pancreas

- Patients with genetics for diabetes and/or insulin resistance are destined to develop type 2 diabetes
- Beta cells respond
 - Incremental changes in glucose &
 - Modulated by IR



Introduction highlights

- Pre-diabetes patients are most all insulin resistant
- Many obese patients transition to insulin resistance and prediabetes with increased risk for CV events



Does weight loss treatment reduce the 10 yr risk for CV disease



Estimated CV events for Risk Engines

- N=3362 enrolled in contrave obesity research program
- Overweight and obese subjects with or without T2DM
- BMI 30-45 kg/m²
 - Placebo group lost 2.3% of baseline weight
 - Treatment group lost 7% (p<0.001)
- 56 weeks
- Placebo controlled
 - Naltrexone / bupropion combination

Chilton et al Presented at Obesity Society's 29th Annual Scientific Meeting, October 1-5, 2011



Overview of risk engines

Risk Engine	Population
Framingham ⁹ : 4- to 12-year risk prediction	US population of 5,573 men and women aged 30-74 years, with or without T2DM
Fremantle ¹⁸ : 5-year risk prediction	Australian population of 1,240 T2DM subjects aged 15-90 years
QRisk2 ¹⁰ : 10-year risk prediction	>2 million men and women aged 35-74 from England and Wales
Reynolds Risk Score ^{19,20} : 10-year risk prediction	24,558 US women aged 45 years and over, with or without T2DM; 10,724 US men aged 50-80 years, without T2DM; separate equations for men and women
SCORE (High and Low) ¹⁶ : 10-year risk prediction	European population of 117,098 men and 88,080 women aged 45-64 years; separate equations are used to calculate risk of death from coronary heart disease and non-coronary CV disease; baseline survival from cohorts from Belgium, Italy, and Spain were used to develop the equations for low-risk regions; baseline survival from cohorts from Denmark, Finland, and Norway were used to develop the equations for high-risk regions
UKPDS ¹⁷ : 10-year risk prediction	5,102 T2DM subjects aged 25-65 years from the UK
UKPDS ¹⁷ : 10-year risk prediction	5,102 T2DM subjects aged 25-65 years from the UK

Chilton et al Presented at Obesity Society's 29th Annual Scientific Meeting, October 1-5, 2011



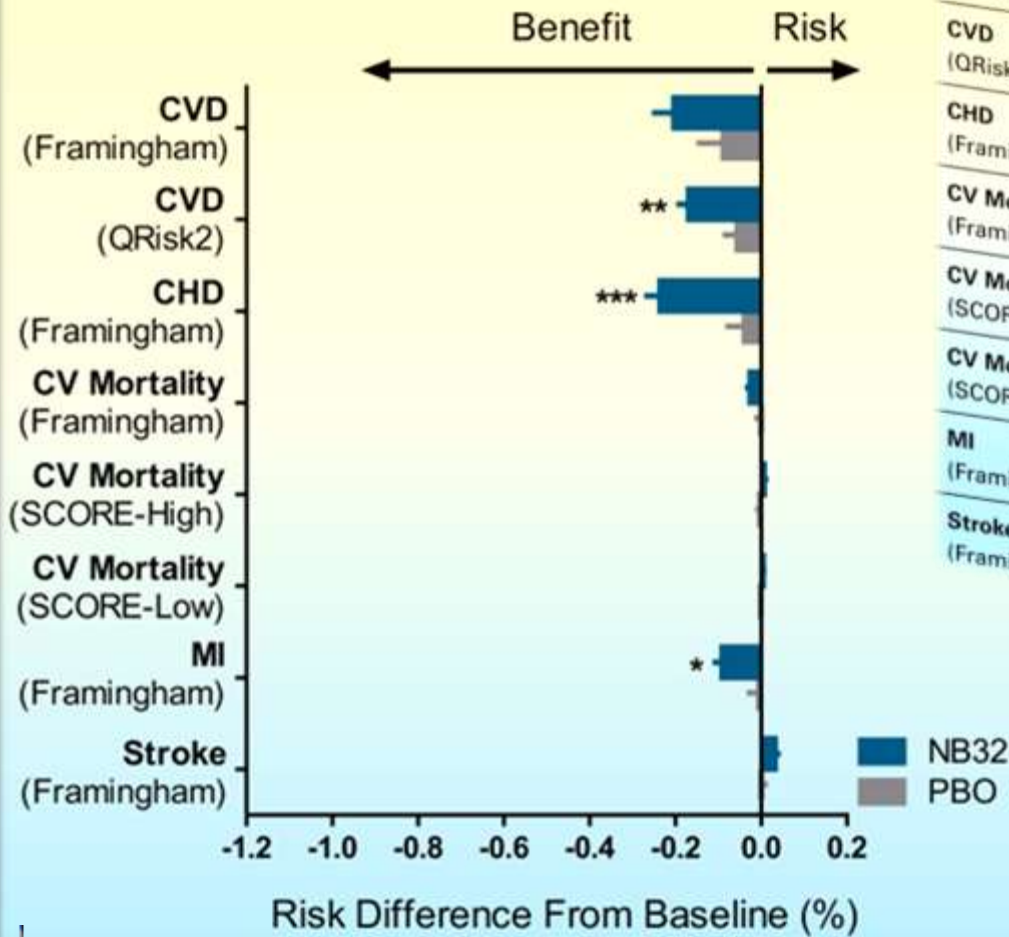
Baseline Characteristics

	Placebo N = 1319	NB32 N = 2043
Age (y, mean \pm SD)	45.5 \pm 11.5	46.1 \pm 11.1
Sex (% female)	81.6	81.0
Smoking (% yes)	8.3	8.1
BMI (kg/m ² , mean \pm SD)	36.3 \pm 4.2	36.3 \pm 4.4
T2DM (%)	12.1	13.0
Systolic Blood Pressure (mm Hg, mean \pm SD)	119.1 \pm 10.4	118.9 \pm 10.4
Total Cholesterol (mg/dL, mean \pm SD)	192.8 \pm 36.9	193.4 \pm 37.4
HDL (mg/dL, mean \pm SD)	51.7 \pm 13.2	51.7 \pm 13.4
hsCRP (mg/dL, mean \pm SD)	6.1 \pm 6.6	6.2 \pm 7.3
HbA1C (% , mean \pm SD; T2DM population; n=159-264)	8.0 \pm 0.9	8.0 \pm 0.8
Cardiovascular History ¹ (%)	1.97	1.47
Renal History ² (%)	0.30	0.49



Predicted 10 year risk of CV events

Overall population



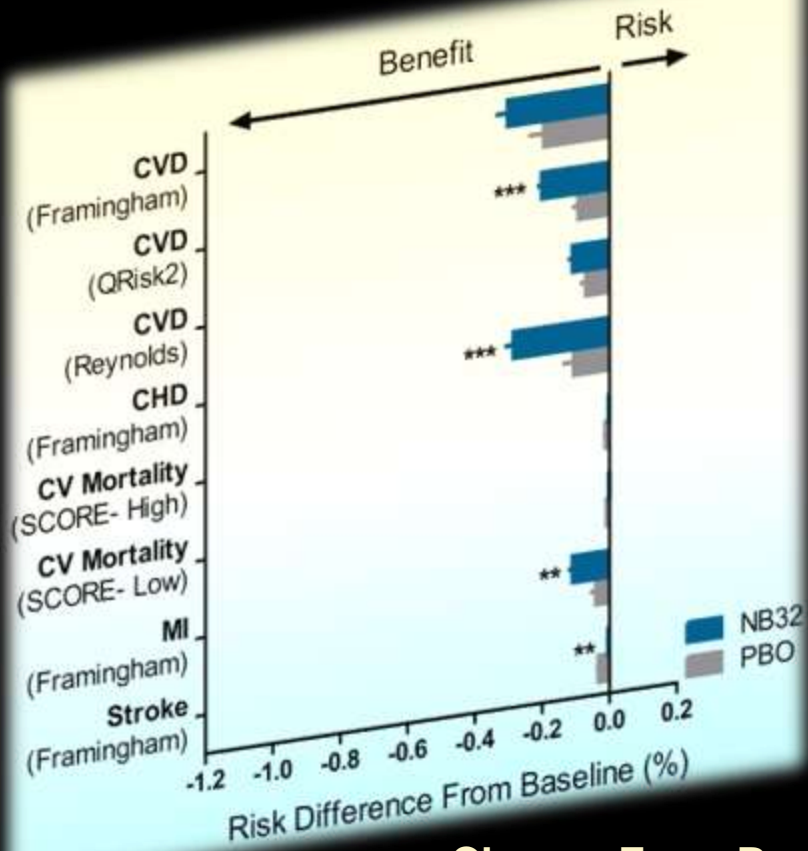
Endpoint (Risk Engine)	LS Mean Difference ± SE (%)	LS Mean Diff CI (%)	p-value
CVD (Framingham)	-0.12 ± 0.08	-0.27 to 0.04	0.134
CVD (QRisk2)	-0.11 ± 0.04	-0.20 to -0.03	0.008
CHD (Framingham)	-0.20 ± 0.06	-0.31 to -0.09	<0.001
CV Mortality (Framingham)	-0.03 ± 0.02	-0.07 to 0.01	0.197
CV Mortality (SCORE - High)	0.01 ± 0.02	-0.02 to 0.04	0.515
CV Mortality (SCORE - Low)	0.01 ± 0.01	-0.01 to 0.02	0.494
MI (Framingham)	-0.09 ± 0.04	-0.15 to -0.02	0.015
Stroke (Framingham)	0.03 ± 0.02	-0.01 to 0.07	0.093

Chilton et al Presented at Obesity Society's 29th Annual Scientific Meeting, October 1-5, 2011

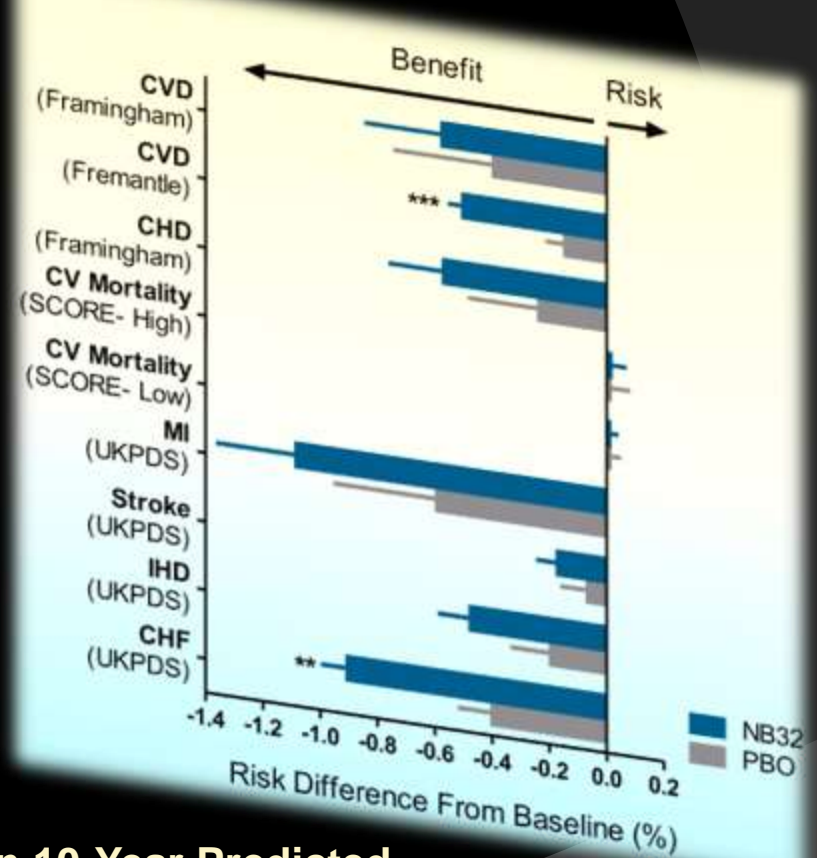


Benefits of weight loss are more significant as CV risk increases

Without T2DM



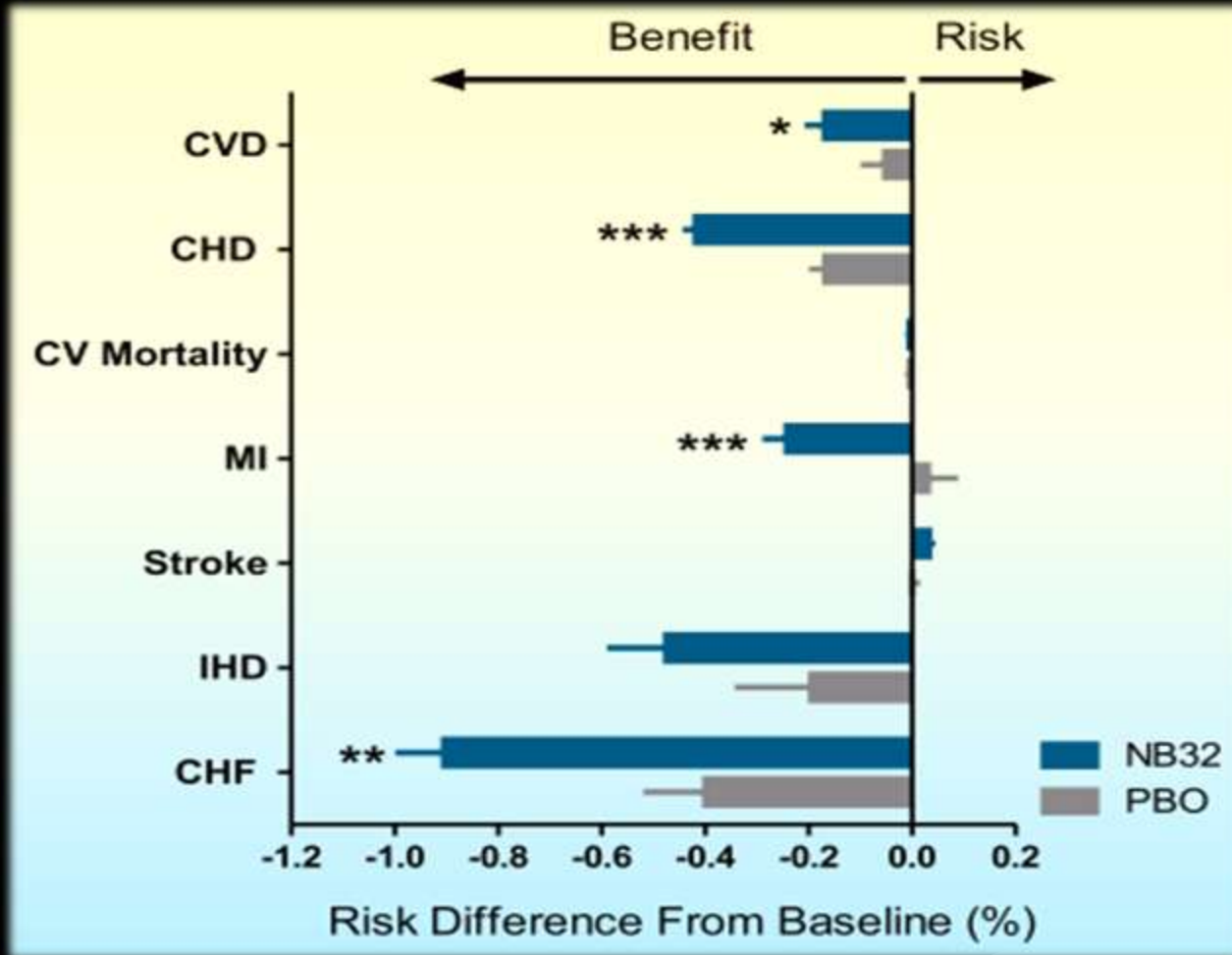
Type 2 Diabetes



Change From Baseline in 10-Year Predicted



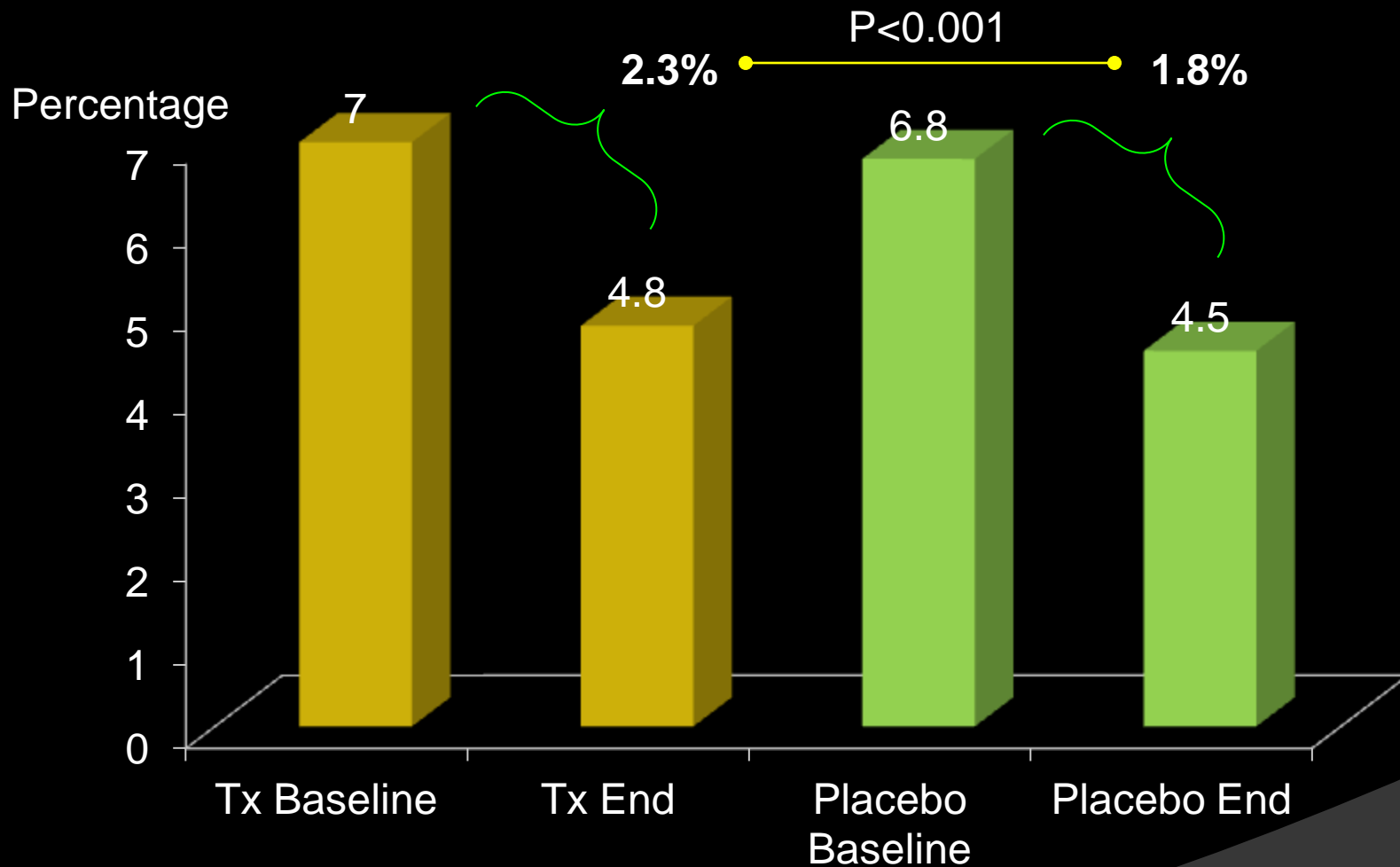
Average predicted CV risk reductions \approx 2-3X that of placebo



Chilton et al Presented at Obesity Society's
29th Annual Scientific Meeting, October 1-
5, 2011



Predicted 8 year progression to type 2 diabetes



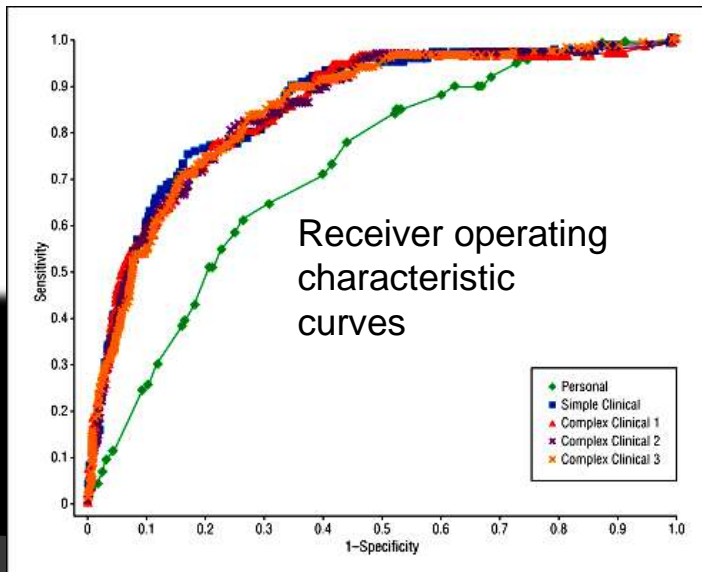
Estimating risk for type 2 diabetes- risk engine

Table 6. Algorithm to Estimate Risk for T2DM Using Simple Clinical Model*

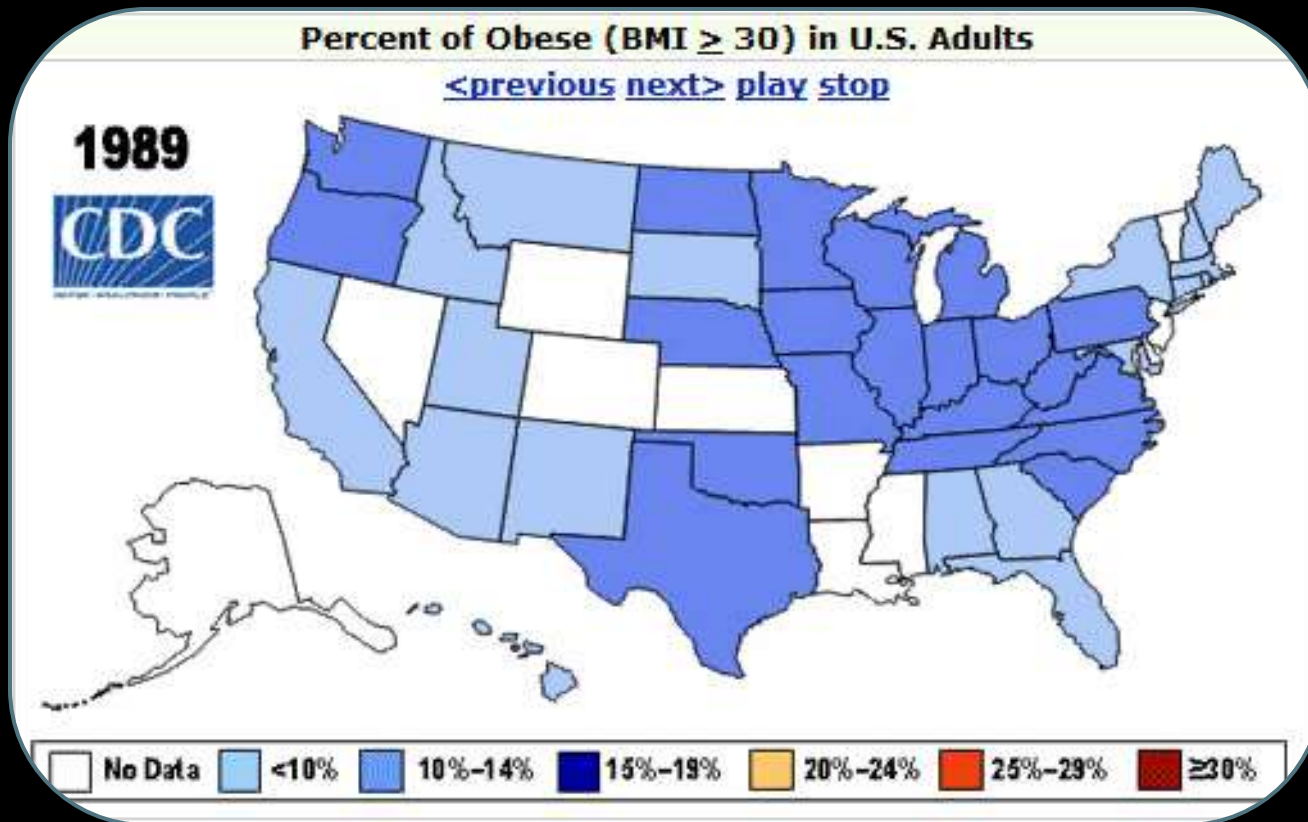
Items	Item Points	Item Point Total	8-Year Risk of T2DM, %
Fasting glucose level 100-126 mg/dL, yes/no	10	≤10	≤3
BMI 25.0-29.9, yes/no	2	11	4
BMI ≥30.0, yes/no	5	12	4
HDL-C level <40 mg/dL in men or <50 mg/dL in women, yes/no	5	13	5
Parental history of diabetes mellitus, yes/no	3	14	6
Triglyceride level ≥150 mg/dL, yes/no	3	15	7
Blood pressure ≥130/85 mm Hg or receiving treatment, yes/no	2	16	9
Item Point Total	<input type="text"/>	17	11
		18	13
		19	15
		20	18
		21	21
		22	25
		23	29
		24	33
		≥25	>35

Pre-DM

1 in 10 chance



***BMI ≥ 30 , or about 30 lbs. overweight for 5'4" person**



CDC 2011



Pre-diabetes obesity highlights

- Obesity is increasing in US
- Obese patients are frequently insulin resistance before pre-diabetes
- Pre-diabetes develops in combination with increasing insulin resistance and beta cell failure
- Weight loss is preferred treatment to reduce cardiovascular risk
 - Drugs are only a second best and for short term use due to off target effects (side effects)

Lifestyle intervention with caloric restriction/increased physical activity is recommended by both the ADA and the American Heart Association

Decreases the conversion rate of IGT to type 2 diabetes, reduce HbA1c levels, enhance insulin sensitivity, and improve CV risk factors

Circulation 2006;114:82–96

Diabetes Care 2003;26:24 –29



Patients with known CAD and prediabetes



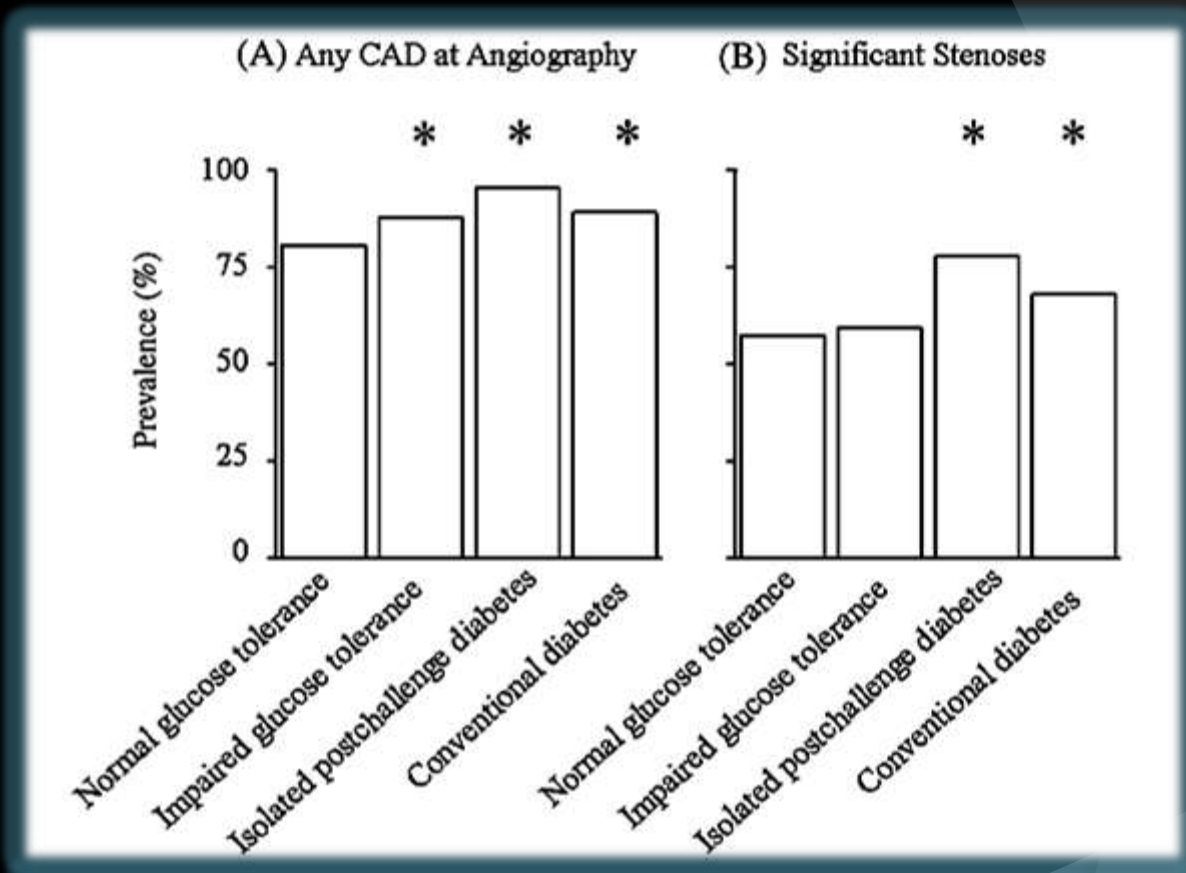
Question 2

- ◎ Patients coming to the cath lab for coronary angiography what percentage have either impaired glucose tolerance or unrecognized type 2 diabetes
 - A. 30%
 - B. 40%
 - C. 50%
 - D. 60%
 - E. 70%



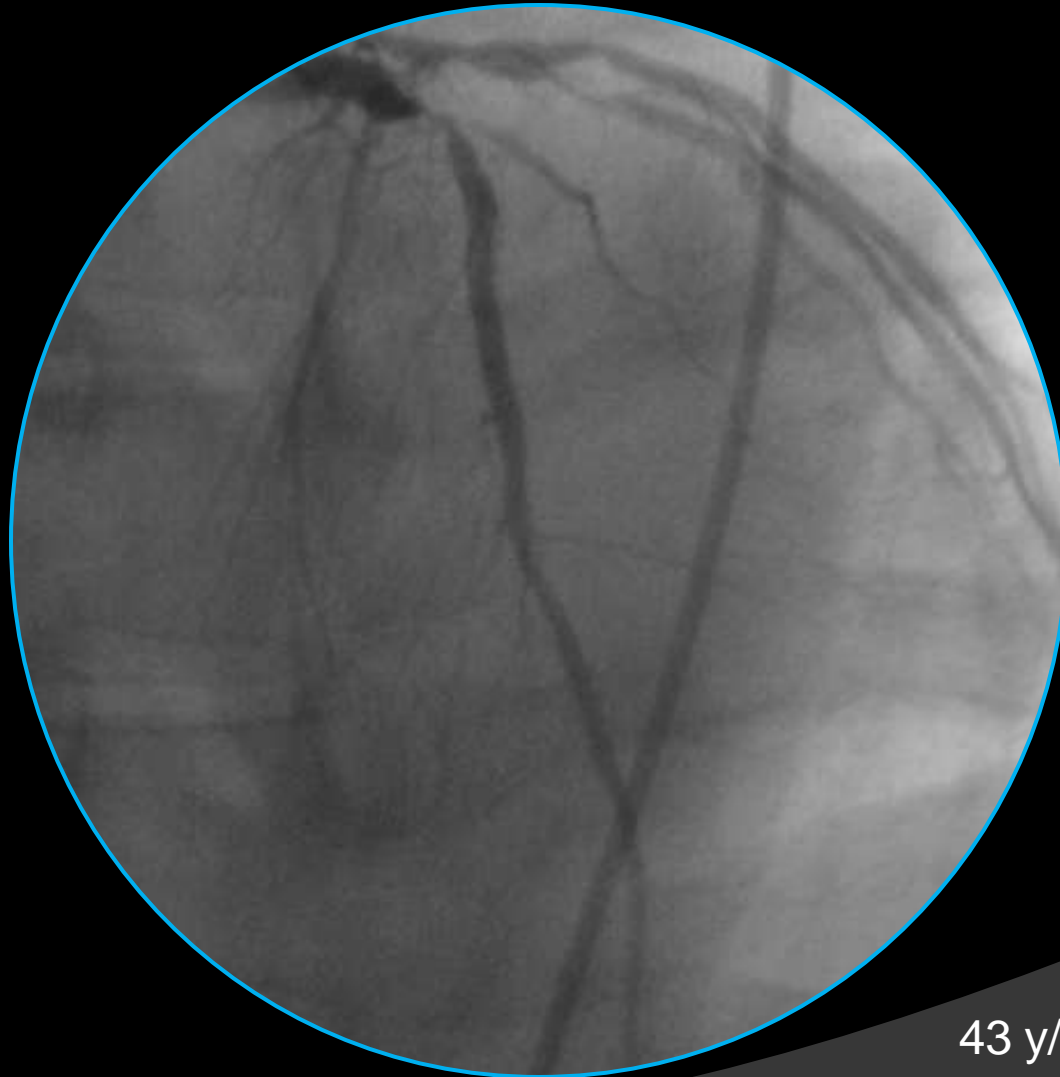
Unrecognized pre-diabetes and type 2 diabetes in patients undergoing coronary angiography exceeds 60%

- N=1040 cath patients
- Oral GTT performed without previous diagnosis of type 2 diabetes



Today's early am case in cath from San Antonio

Patient says he does not have diabetes yet... but is aware he has "pre-diabetes"



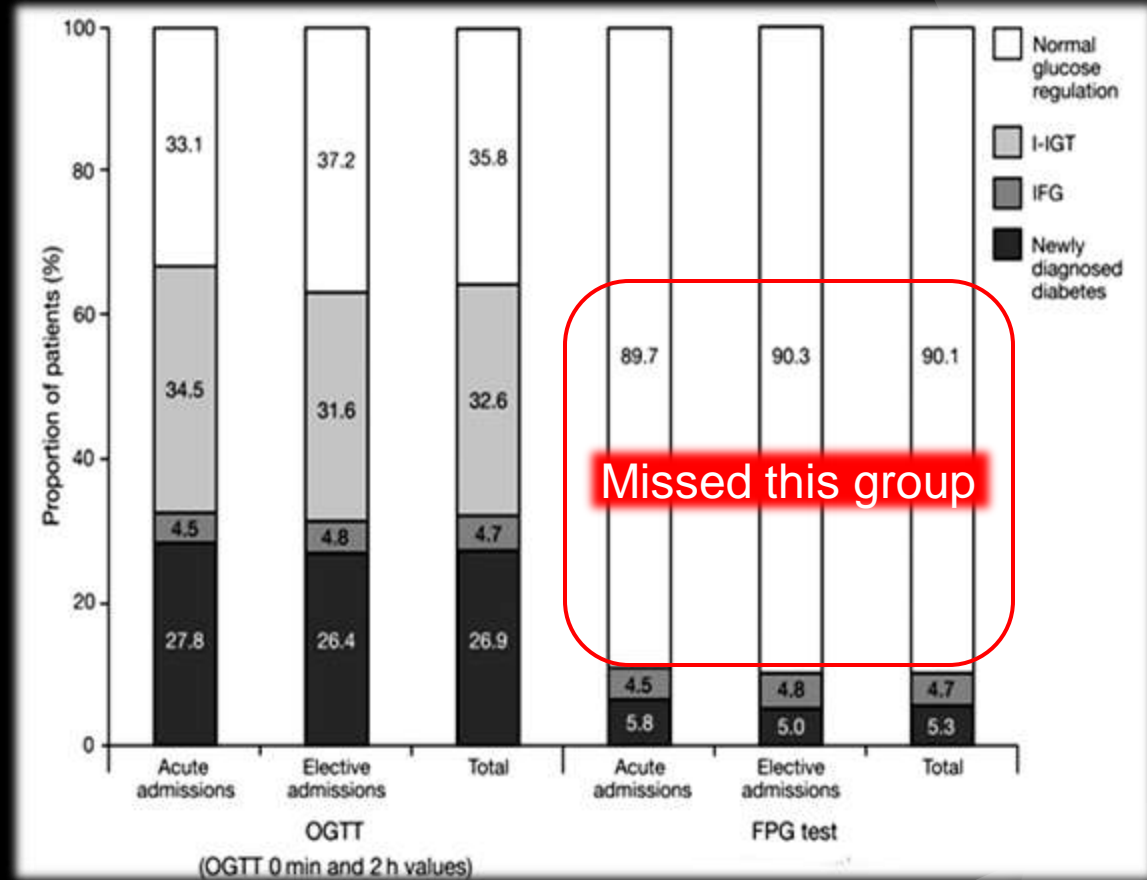
FBS 118 at cath
Mom and dad both have 2 type DM

43 y/o Hispanic male



Relationship between CAD and dysglycemia is significant

- N=3513 patients hospitalized for CAD
 - 35% acute
 - 65% elective CAD
- 2263 patients without diabetes
 - OGTTs
 - 26.9% diabetes
 - 37.3% IGT (pre-diabetes)
- Acute and elective admissions were similar in results from OGTTs



Without the post-challenge data provided by the OGTTs, most patients with acute (437/517; 84.5%) and elective (791/936; 84.5%) admission groups would have remained undiagnosed.



Suggestions... >60% with CAD / MI have prediabetes / diabetes

- All patients with acute MI and new-onset angina or CAD should have a 75-g, 2-hour OGTT
- Chronic stable angina patients consider OGTT to exclude underlying prediabetes / diabetes

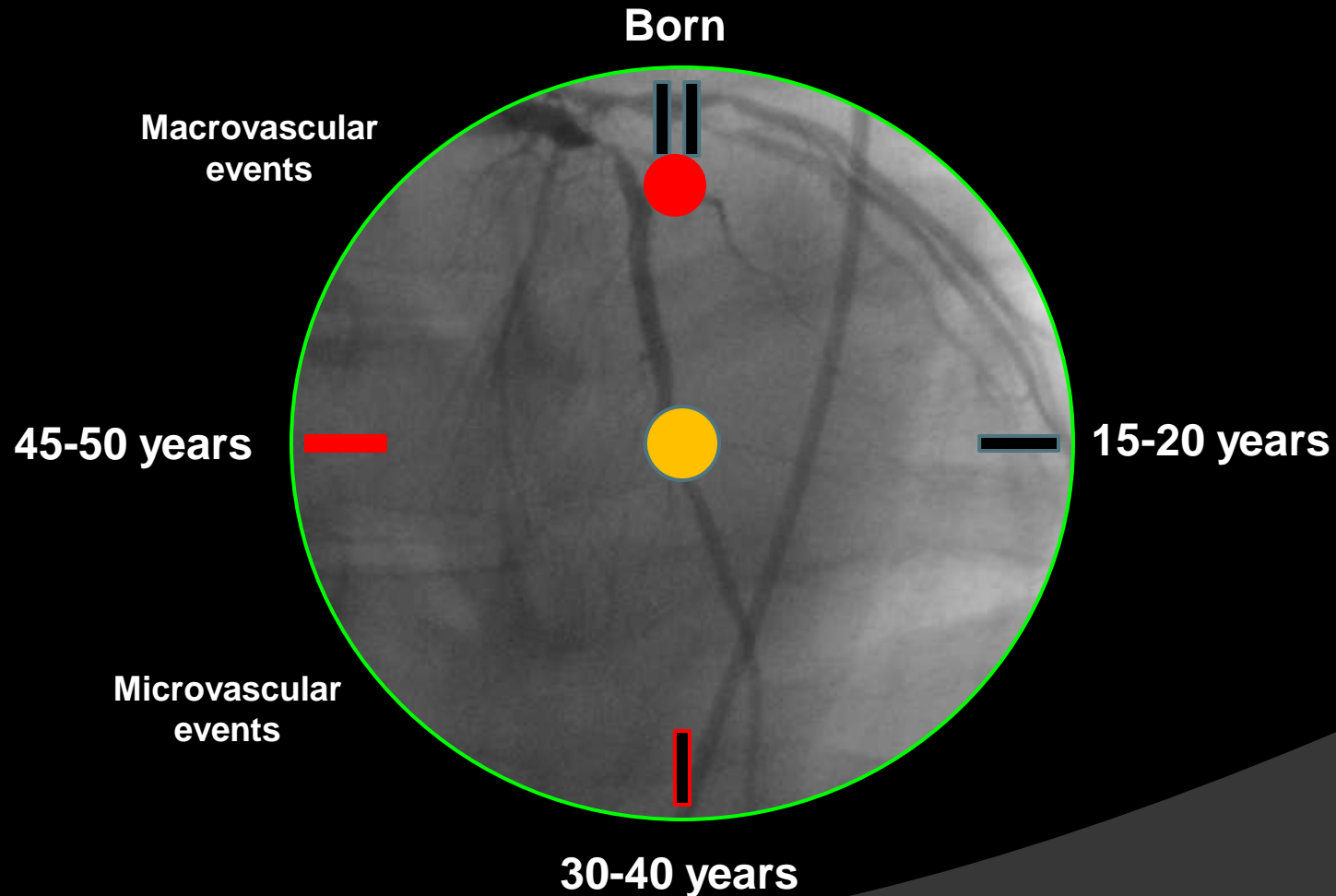
Especially high diabetes prone areas...San Antonio



Closing comments: the ticking clock

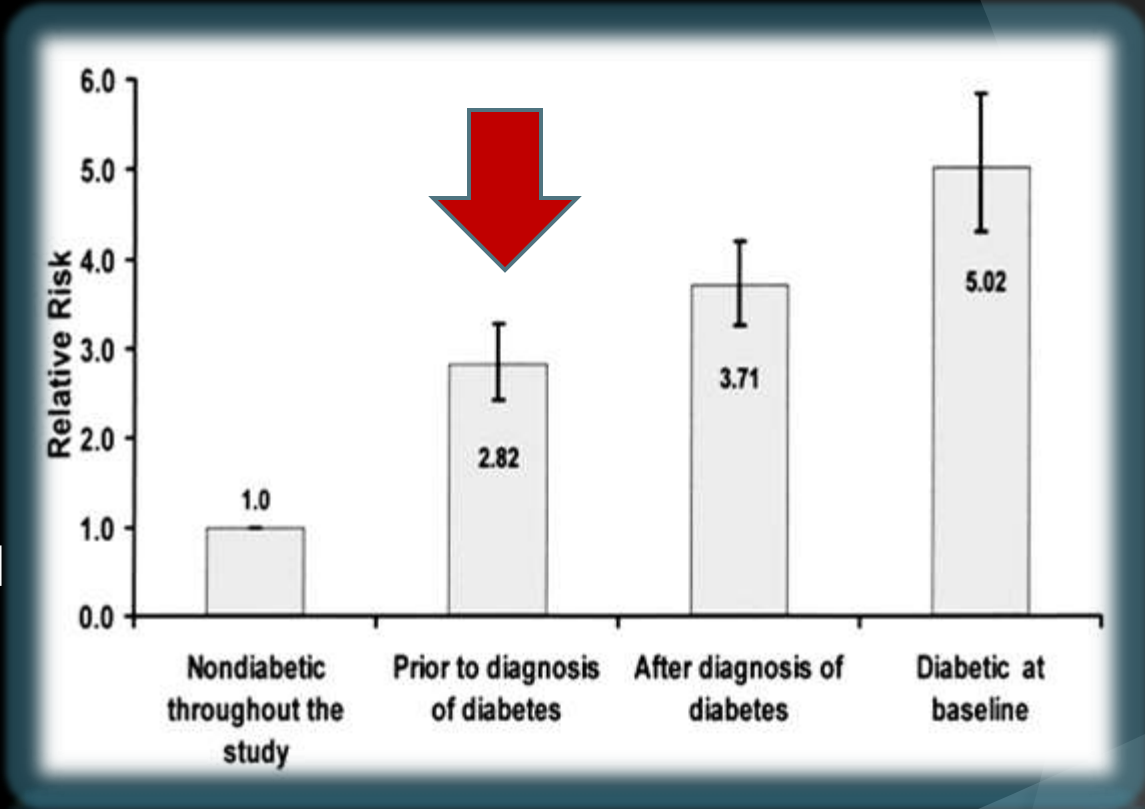


Ticking clock of insulin resistance and atherothrombosis



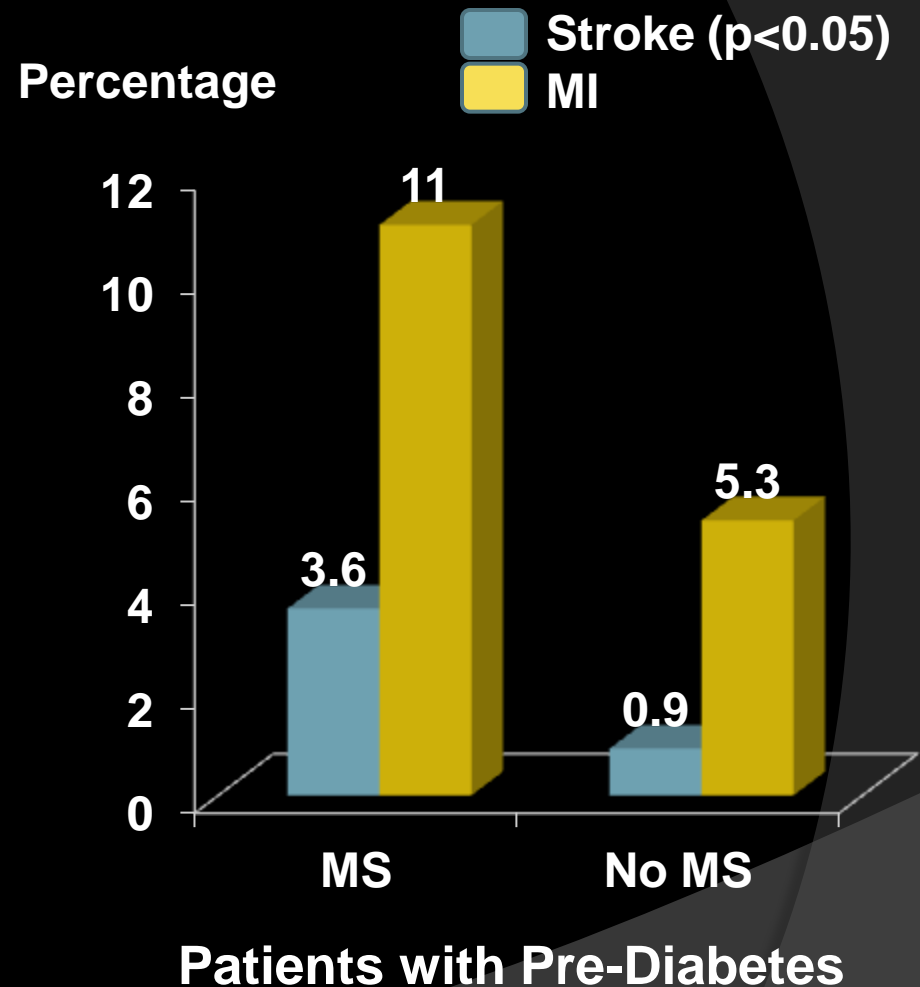
CV risk factors start before the development of overt diabetes

- Nurses Health Study
- N=110227 women
- Free of diabetes
- 20 years follow 5894 developed diabetes
 - 1556 MI
 - 1405 strokes
 - 815 died from CAD
 - 300 died from strokes
- Women who developed diabetes during follow up
 - Adjusted risk for MI 3.75 **before diagnosis**



Pre-diabetes and metabolic syndrome increases risk for CV events

- Botnia study
- N=4483 patients
 - 1697 type 2 DM (85% MS)
 - **798 IFG/IGT(42-64% MS)**
 - 1988 NGT with IR (10-15% MS)
- Metabolic syndrome definition (>2)
 - Obesity
 - HT
 - Dyslipidemia
 - Microalbuminuria
- Median follow up 6.9 years



Diabetes Care 24:683–689, 2001

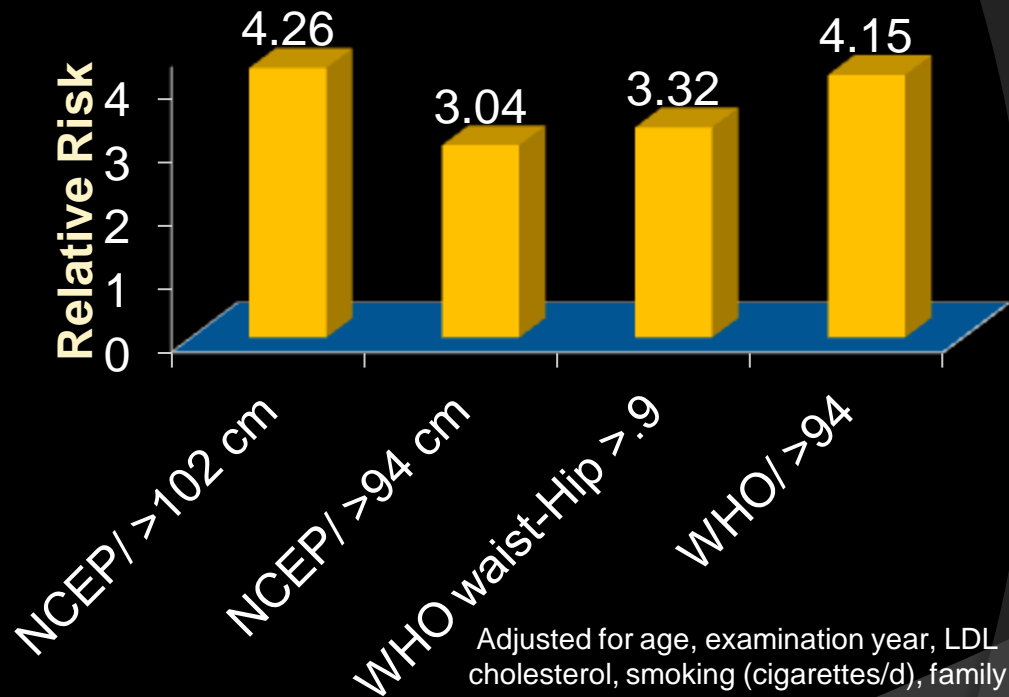


Metabolic syndrome causes increased mortality

All significant

- Kuopio Ischaemic Heart Disease Risk Factor Study, a population-based, prospective cohort study of 1209 Finnish men
- Aged 42 to 60 years at baseline (1984-1989) who were initially without CVD, cancer, or diabetes
- Follow-up continued through December 1998
- F/U 11 years

Coronary Heart Disease



Adjusted for age, examination year, LDL cholesterol, smoking (cigarettes/d), family history of CHD, fibrinogen levels, white blood cell levels, alcohol consumption (g/wk), and socioeconomic status

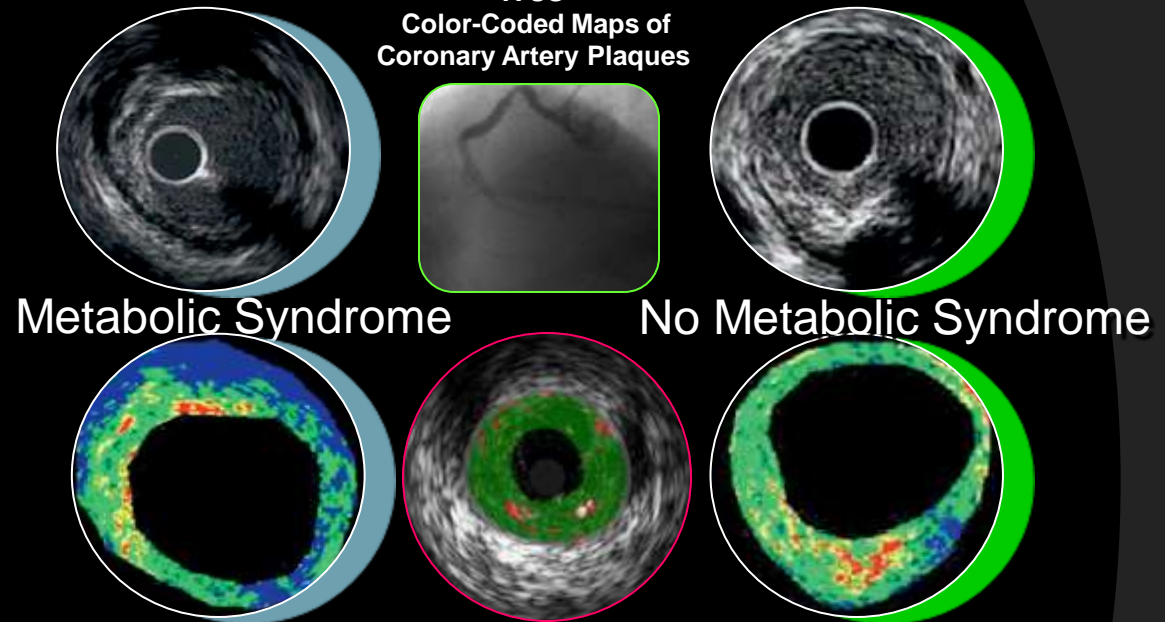


Vascular Wall Imaging & Tissue Lipotoxicity

Selected Characteristics

	MS+	MS-
N=	61	61
HT	85%	49%
DM	75%	39%
TRG	181 mg/dl	109 mg/dl
HDL	43	51
Statins	59%	61%

2-D Integrated Backscatter
IVUS
Color-Coded Maps of
Coronary Artery Plaques



Metabolic syndrome

(Definition >3)

- WC > 85 cm
- HDL < 40
- TRG > 150
- BP > 130/85
- FBS > 110

Blue-lipid pool
Green yellow-fibrous lesion

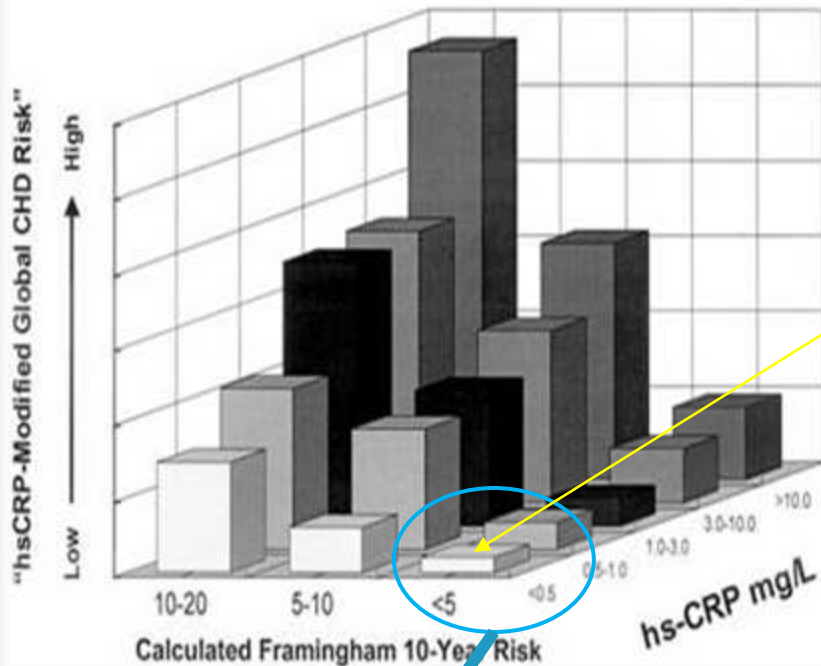
3D of Lipid Pool



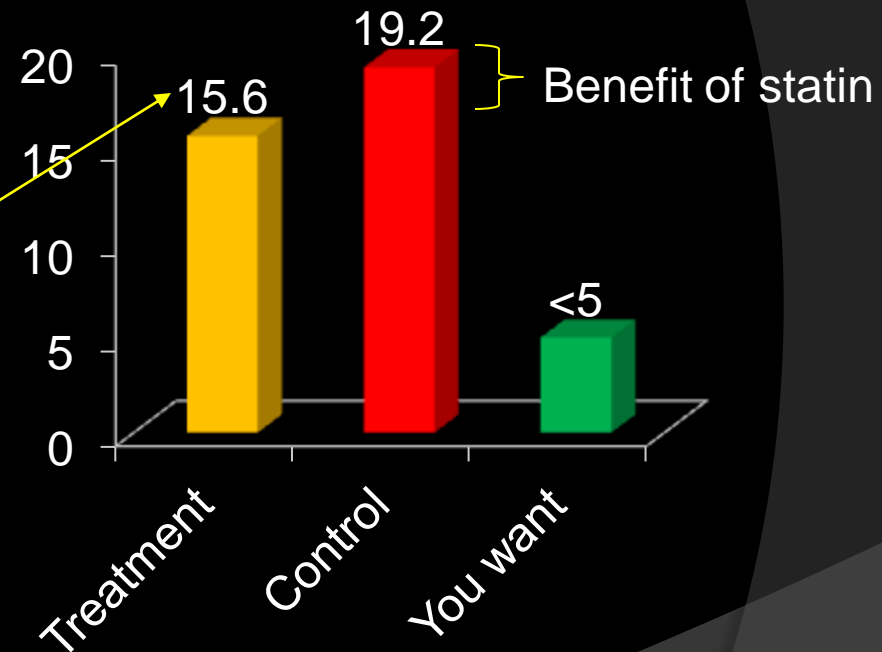
Realty check: Risk for CV events

ARR-3.6%

Lifestyle is the "real thing"



Diabetes Patients - 5 Year Major Vascular Events



This is what you want @ **10 years**

14 randomized statin trials
N=90056 prospective meta-analysis

Lancet 2005; 366: 1267-78



Pre diabetes and prothrombosis risk

Clotting

Vulnerable plaque in **insulin resistance**

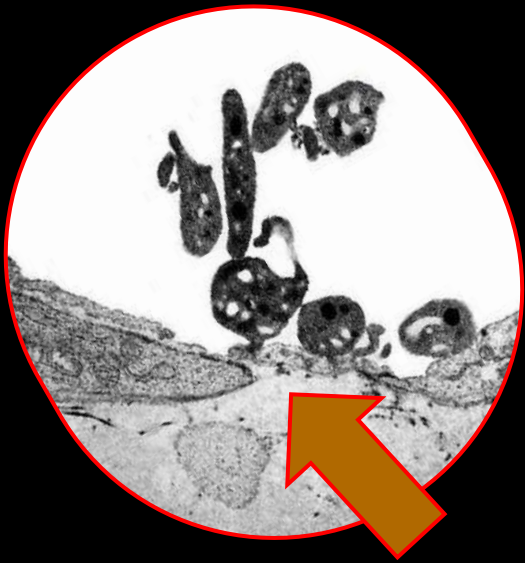
Close up look

Characteristics

Factors affecting fracture risk

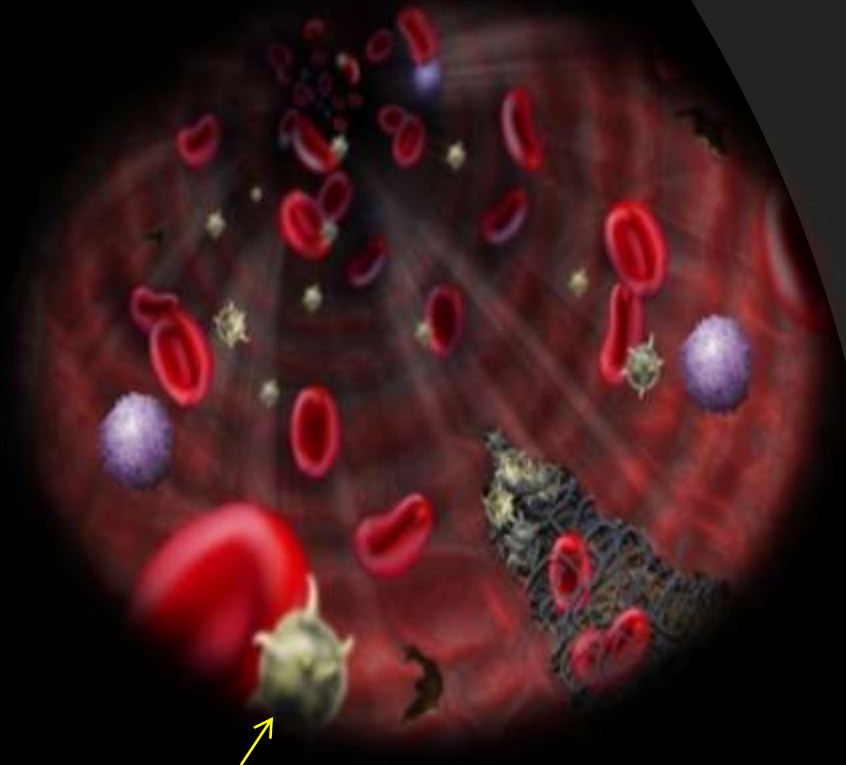
Matrix





Ruptured plaque

Necrotic lipid core
Tissue factor
Collagen
Others



Constriction of the injured blood vessel

Platelet binds to **collagen** and is activated by **thrombin**

CD40L upregulated

Proinflammatory

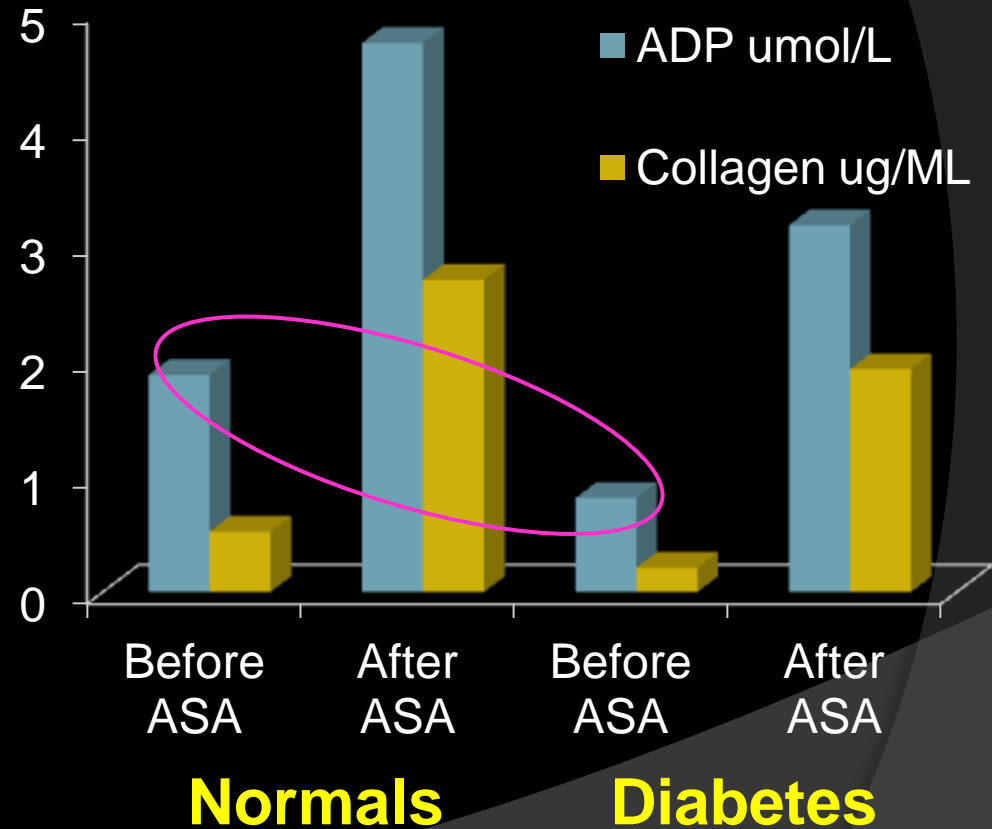
Fibrin mesh - binds to the platelet aggregate-leading to thrombus



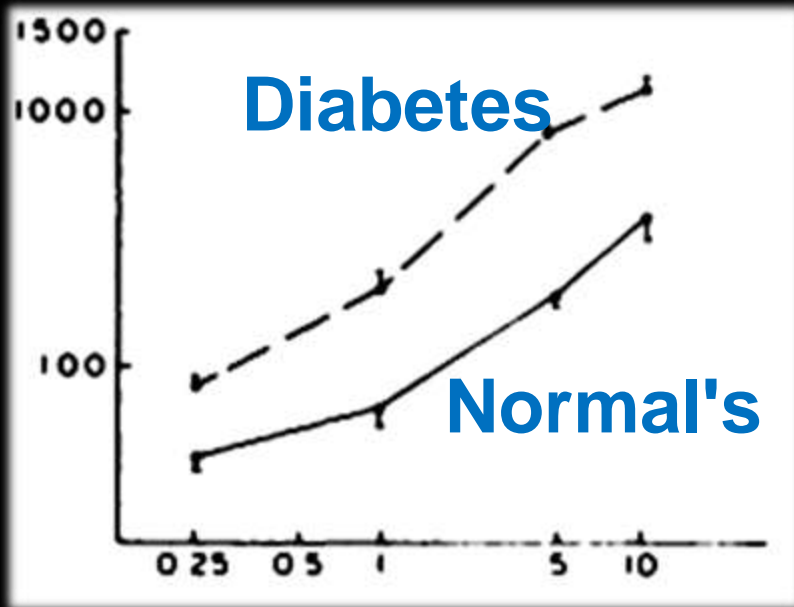
Diabetes patients have increased sensitivity to aggregation with ADP and collagen

Aggregation of Platelets

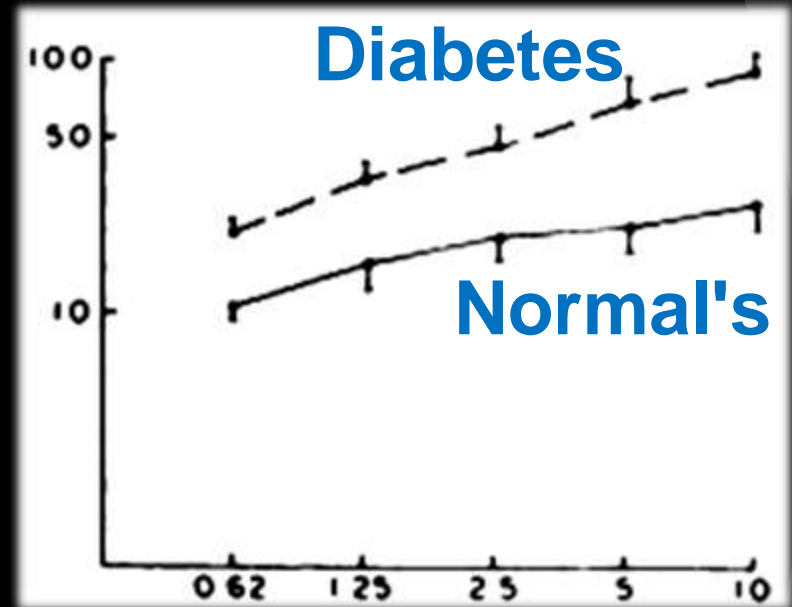
- 15 diabetes patients with 10 controls
- Platelet aggregation tests were performed



Diabetes patients have increased platelet Thromboxane B₂ response to ADP and collagen



Collagen (ug/ml)



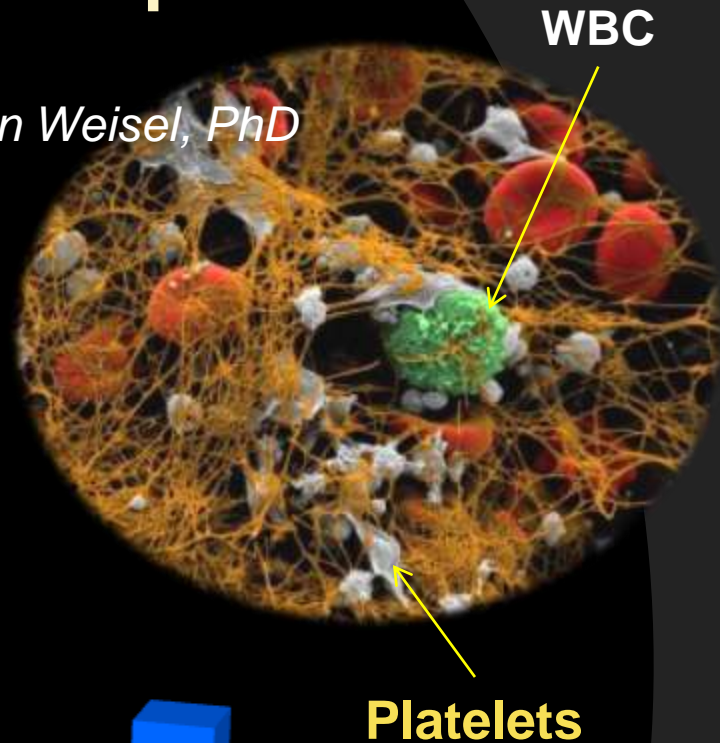
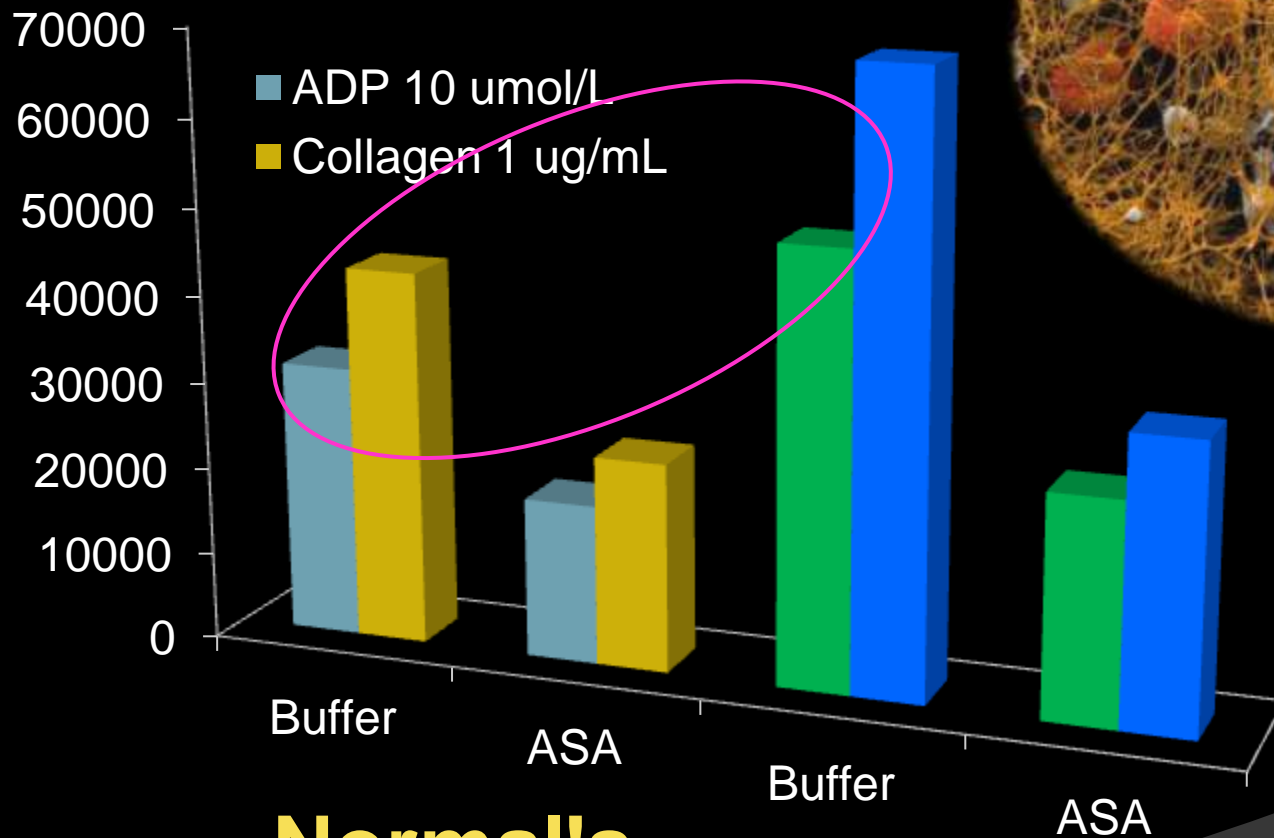
ADP (uM)



Increased binding of fibrinogen to platelets in diabetes

¹²⁵I-Fibrinogen to Platelets

John Weisel, PhD



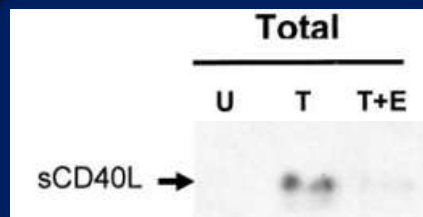
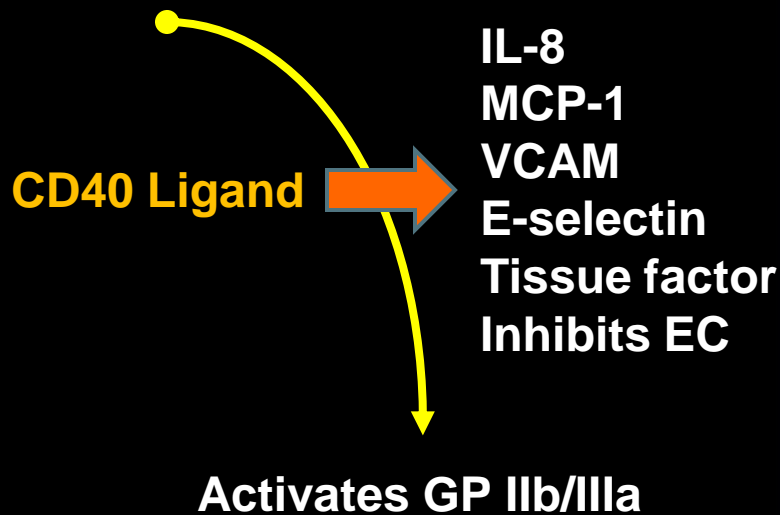
Normal's

Diabetes

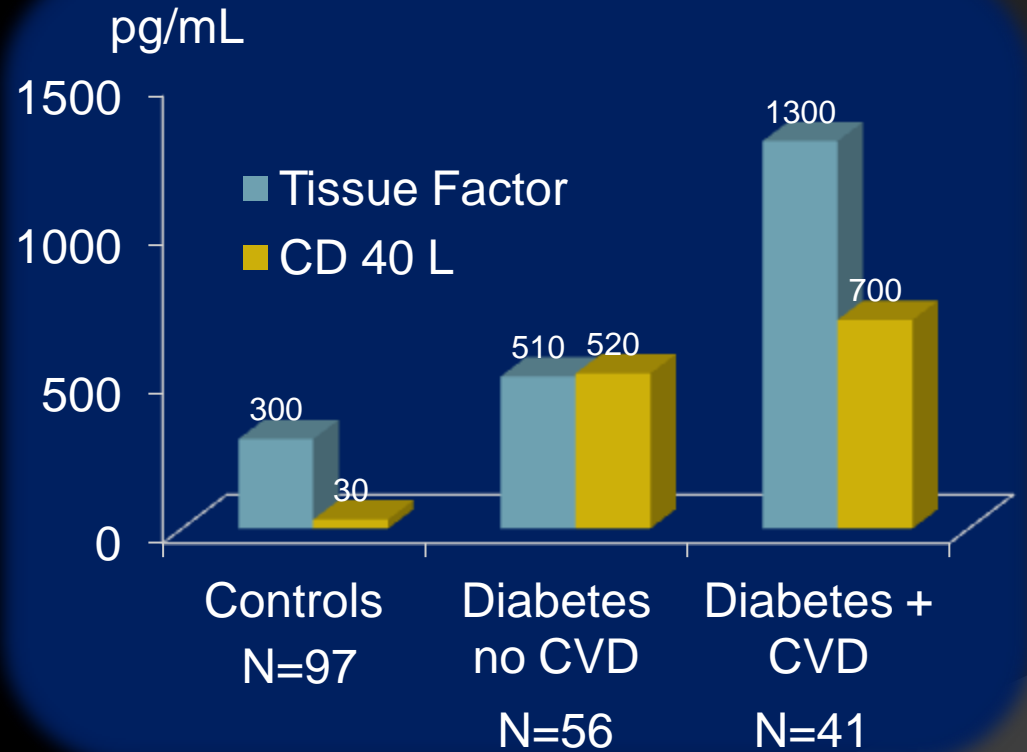


Diabetes patients have increased vulnerable blood

Platelet activation / ACS



Eptifibatide-inhibited the release of the soluble form of this protein (sCD40L) from stimulated platelets

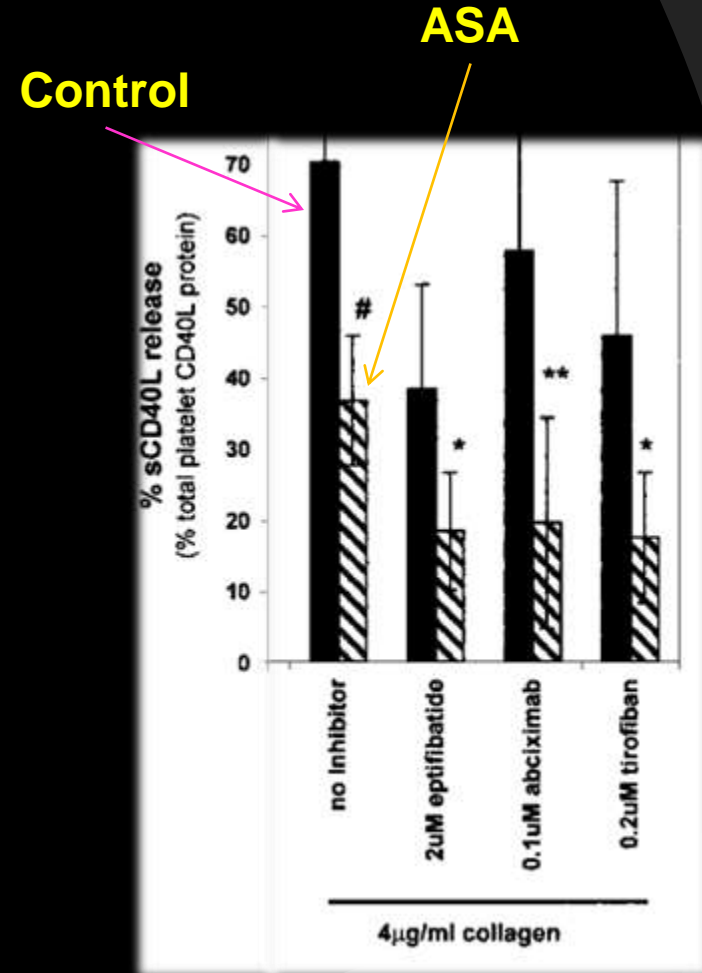


Lim et al Circ 2004, 109:2524-2528



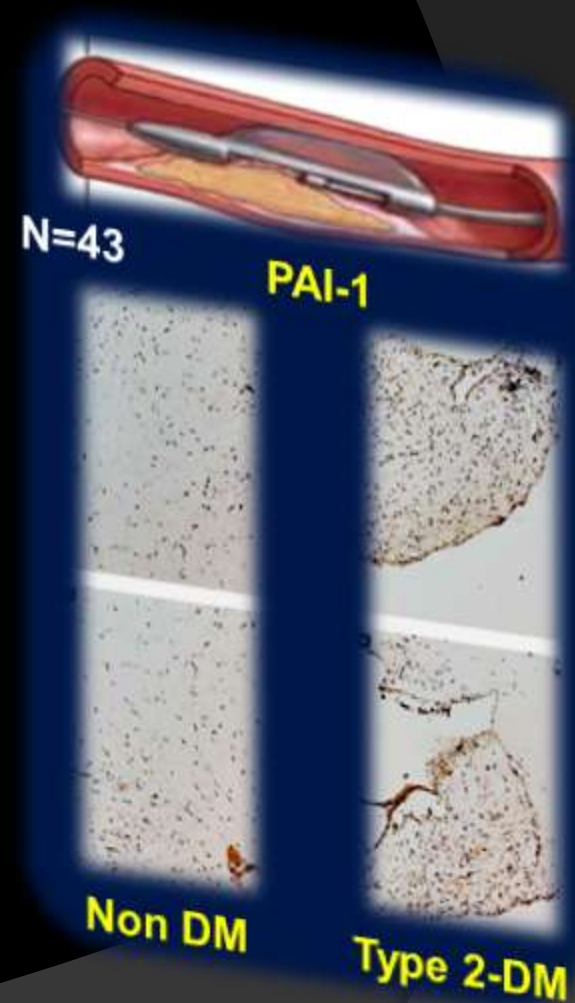
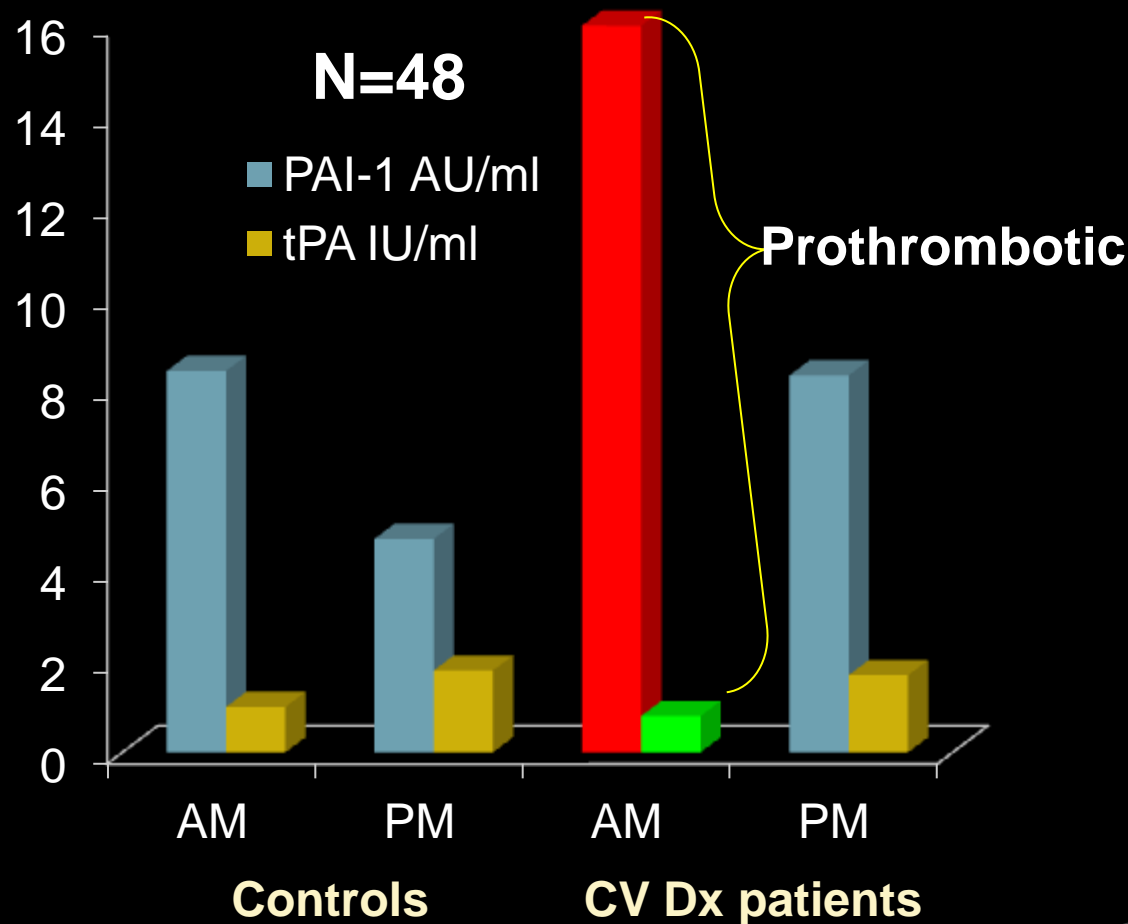
Glycoprotein IIb/ IIIa antagonists inhibit platelet aggregation

- ASA does not reduce release of sCD40L from platelets (ADP stimulated)
- ASA does reduce sCD 40L (50%) when collagen induced platelets aggregation
 - Thromboxane A2 is blocked by ASA

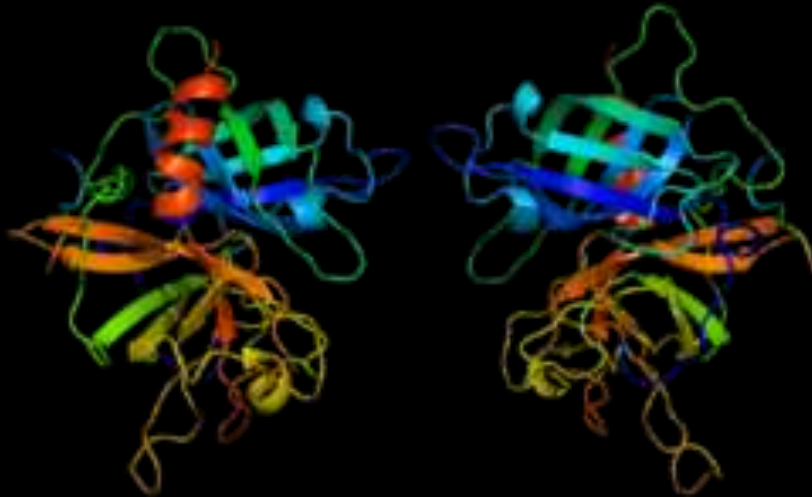


Patients with **insulin resistance** have more PAI-1 in human coronary tissue

Diurnal variation of PAI-1 and tPA



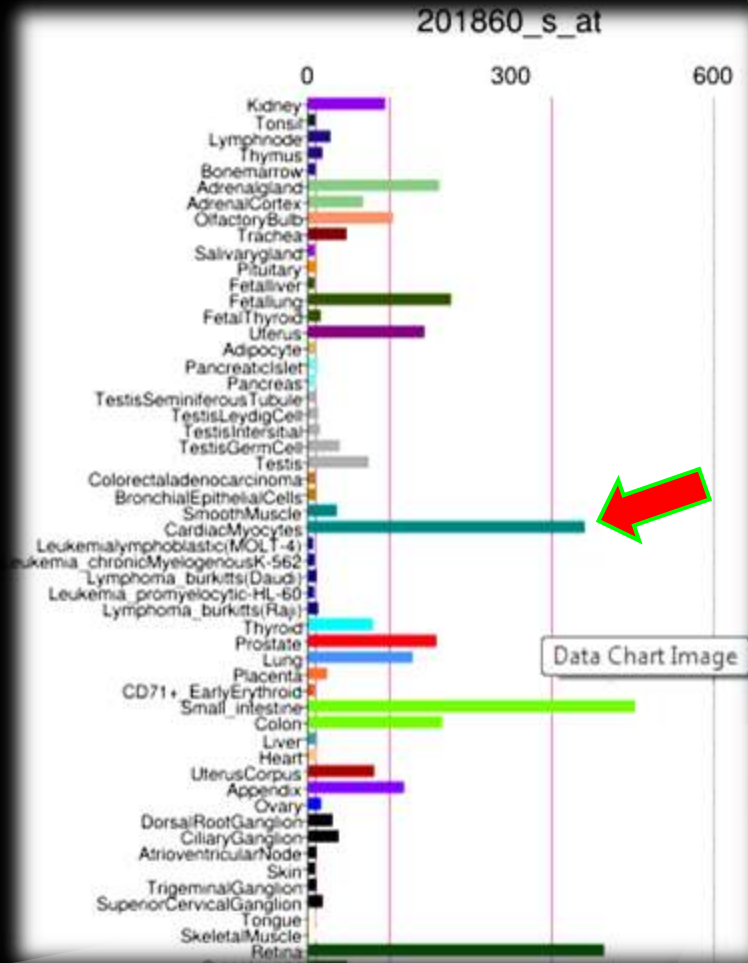
Tissue plasminogen activator is a protein encoded by the *PLAT* gene, which is located on chromosome 8



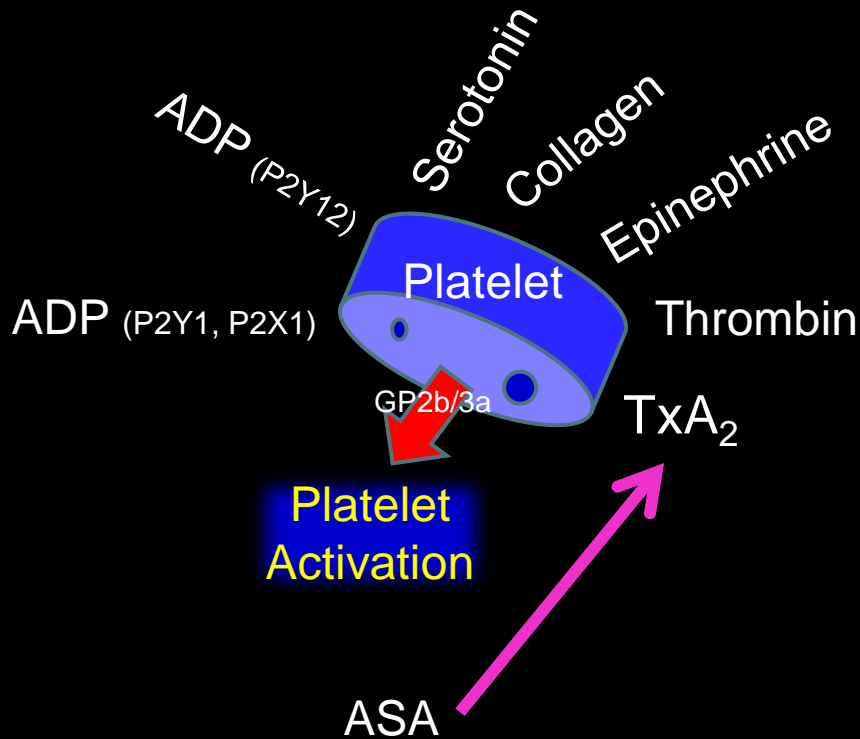
Produced from many locations:
endothelial cells and others

Angiotensin $\xrightarrow{\hspace{2cm}}$ tPA
 PAI-1

Circ 96:442
 JACC 38:49

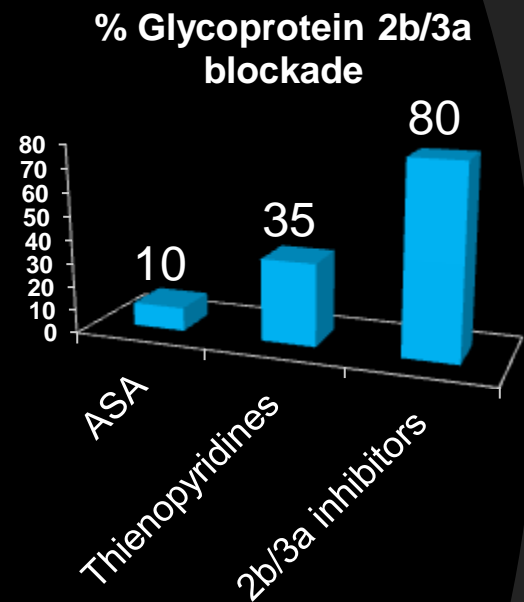


Relative potency of anti-platelet compounds



Blocks platelet activation-(8 to 10 days)
Prevents conversion of arachidonic acid to prostaglandin H₂

Thromboxane A₂



Mehta et al JACC 2003;41:79s

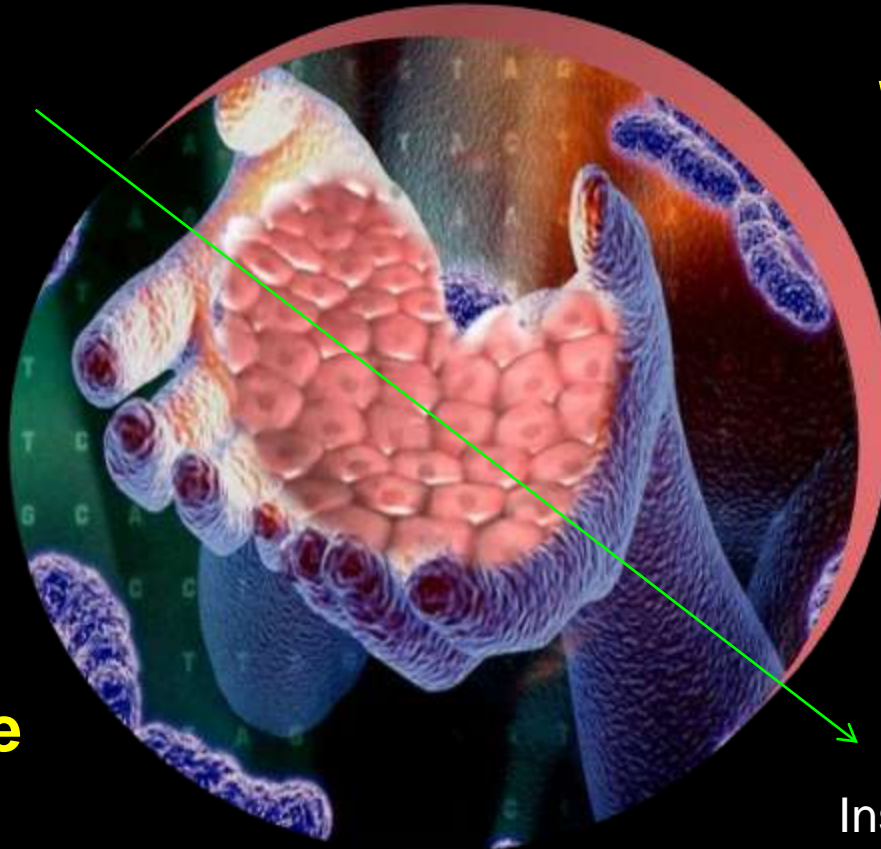
Platelets are unable to generate (no nucleus) new cyclooxygenase enzyme
 Endothelial cells also blocked but recovery quickly cyclooxygenase



Endothelial cell health.....best choice for preventing atherosclerosis

Pre-diabetes

Weight loss

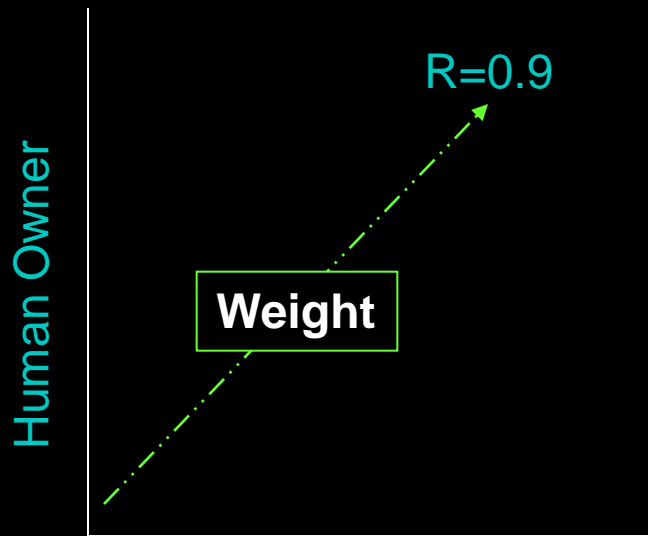


Exercise

Insulin resistant
Lost \approx 60% beta cell function
Prothrombotic
Increased risk for CV events



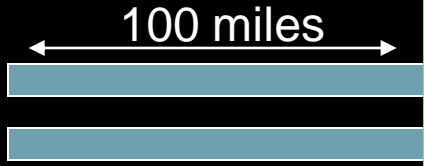
Closing Comment: weight loss works...but extremely hard to maintain



Animal



Current best medications



Magic Pill

5%

Thank you



