Management of Metabolic Disease For Secondary Stroke Prevention

Walter N. Kernan, M.D.
Yale School of Medicine
January 11, 2010

Presenter Disclosure Information

Walter N. Kernan, M. D.

Management of Metabolic Disease for Secondary Stroke Prevention

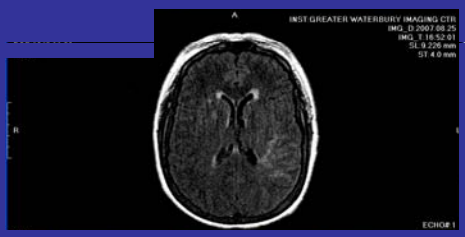
Conflict of Interest

Dr. Kernan is receiving pioglitazone and placebo from Takeda Pharmaceuticals America, Inc. for use in an NINDS-funded clinical trial.

Unlabeled Use

Pioglitazone, rosiglitazone, metformin, acarbose are not FDA-approved for diabetes or stroke prevention.

J.M. (IRIS 001-148) Three Months after Stroke

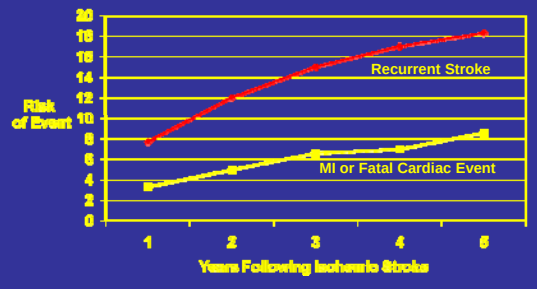


Additional Test Results For J.M. Three Months after Stroke

Analyte	Result	Normal Range
Glucose	113 mg/dL	65-99 mg/dL
HbA1c	6.6%	4.5-5.7%
Fasting insulin	24 uIU/mL	5-15 uIU/mL
HOMA*	6.7	~ <3.0
HS-CRP	6.00 mg/L	0.00-3.00 mg/L
Total Cholesterol	156 mg/dL	100-199 mg/dL
LDL Cholesterol	86 mg/dL	0-99 mg/dL
HDL Cholesterol	39 mg/dL	40-59 mg/dL
Triacylglyceride	154 mg/dL	0-149 mg/dL

*Homeostasis Model Assessment of Insulin Resistance

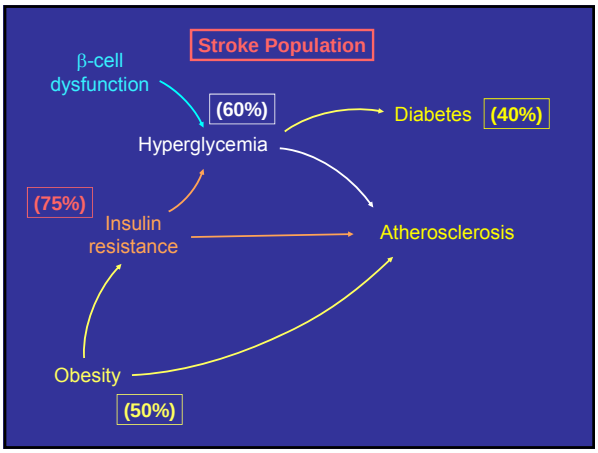
Stroke Prognosis



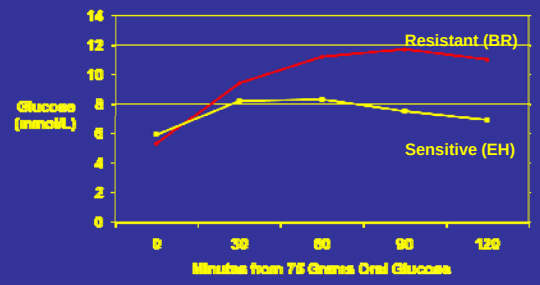
MS Dhamoon *Stroke* 2006;66:641

Outline

- Prevalence of Metabolic Disease after Stroke
- Clinical Consequences
- Biologic Pathways Metabolic Disease→Stroke
- Therapeutic Implications

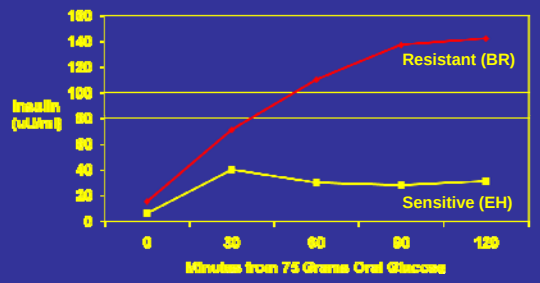


Glucose Response: 2 Non-Diabetic Patients With Ischemic Stroke



Data from WN Kernan *Neurology* 2003;60:1447

Insulin Response: 2 Non-Diabetic Patients With Ischemic Stroke



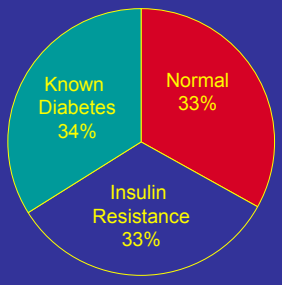
Data from WN Kernan *Neurology* 2003;60:1447

Measurements of Insulin Sensitivity

← Increasing complexity ←

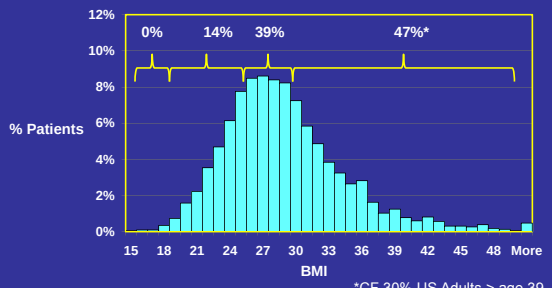
- Fasting insulin level
- Homeostasis Model Assessment (HOMA)
  - [Fasting insulin (μU/ml) x Fasting glucose (mmol/L)]/22.5
- Insulin response to oral glucose tolerance test
  - Insulin Sensitivity Index (ISI)
- Euglycemic hyperinsulinemic clamp

Prevalence of Insulin Resistance After Ischemic Stroke



Based on: Kernan *Neurology* 2003;60:1447. Matz *Diabetes Care* 2006;29:792

BMI among 2,347 Patients with Stroke/TIA (Non-Diabetic)



WN Kernan Unpublished Data IRIS Trial 9.17.08

*CF 30% US Adults > age 39

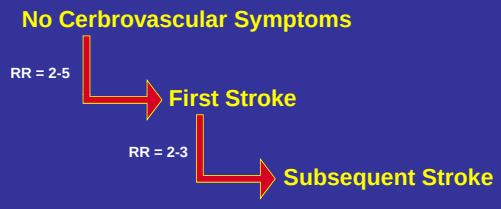
Outline

- Prevalence of Metabolic Disease after Stroke
- **Clinical Consequences**
- Biologic Pathways Metabolic Disease→Stroke
- Therapeutic Implications

Consequences
For Patients with IGT or Diabetes

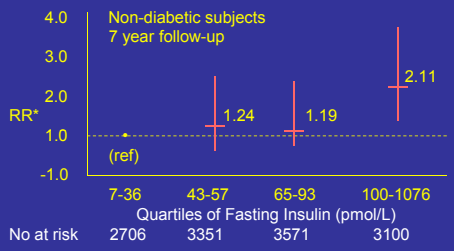
- Increased Risk of First & Recurrent Stroke
- Different Distribution of Stroke Mechanisms
- Worse Outcome
- Unique Therapeutic Options

Relative Risk for Ischemic Stroke Among Persons with DM



AR Folsom *Diabetes Care* 1999;22:1077. Kissela *Diabetes Care* 2005;28:355

Atherosclerosis Risk in Communities (ARIC) Study



*Relative risk for ischemic stroke adjusted for age, sex, race, ARIC community, smoking, education
Folsom *Diabetes Care* 1999

Diabetes and Age of Ischemic Stroke

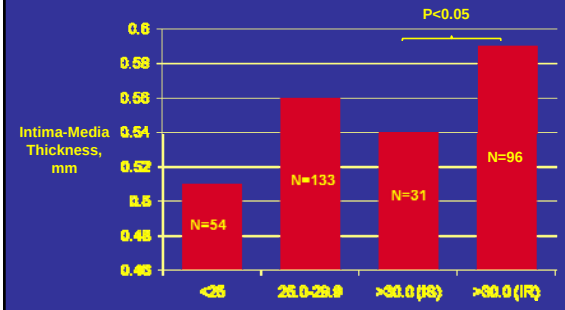
Cohort: Patients from 19 hospitals in Greater Cincinnati/Northern Kentucky.

Characteristic	Diabetic* (N=856) N (%)	Non-Diabetic (N=1863) N (%)	P
Age (years)	70	72	<0.0001
History of Hypertension	676 (79)	1061 (57)	<0.0001
History of High Cholesterol	135 (16)	177 (10)	<0.0001
History of Myocardial Infarction	193 (22)	272 (15)	<0.0001
History of Atrial Fibrillation	134 (16)	266 (14)	0.4
Current Smoking	157 (18)	408 (22)	0.03

*Medical record documentation of diabetes pre-dating stroke or TIA

BM Kissela *Diabetes Care* 2005;28:355

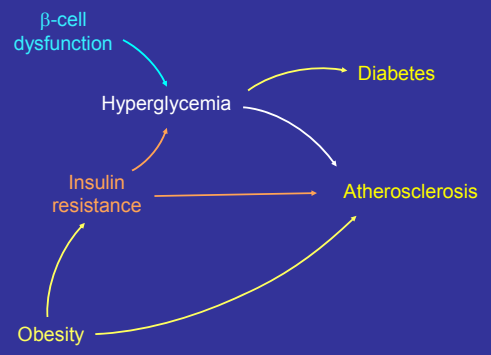
Carotid Disease in Non-Diabetic Obese Persons with Insulin Resistance

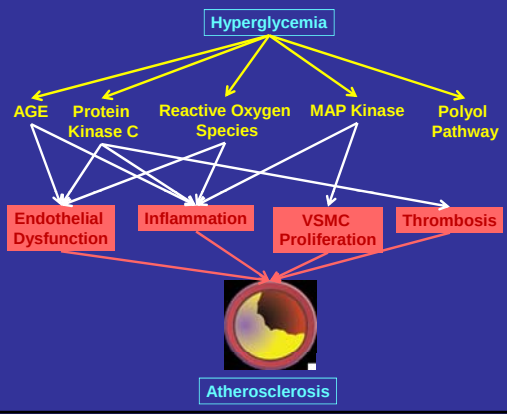


N Stefan *Arch Intern Med* 2008;168:1609

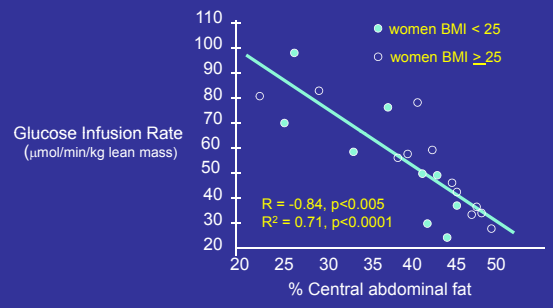
Outline

- Prevalence of Metabolic Disease after Stroke
- Consequences
- Biologic Pathways Metabolic Disease→Stroke
- Therapeutic Implications

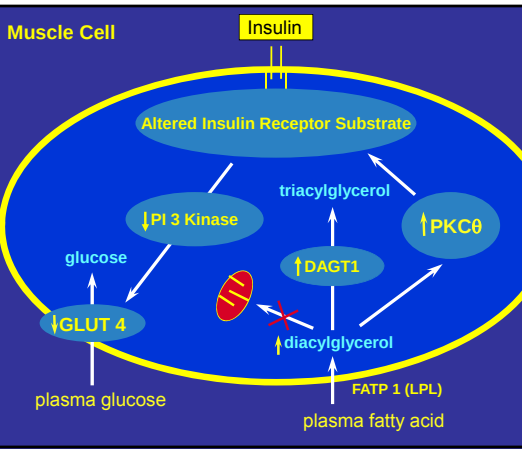




Insulin Sensitivity and Central Adiposity: 22 Healthy Women



Carey DG *et al. Diabetes* 1996;45:633



Pro-Atherosclerotic Events in Insulin Resistant States

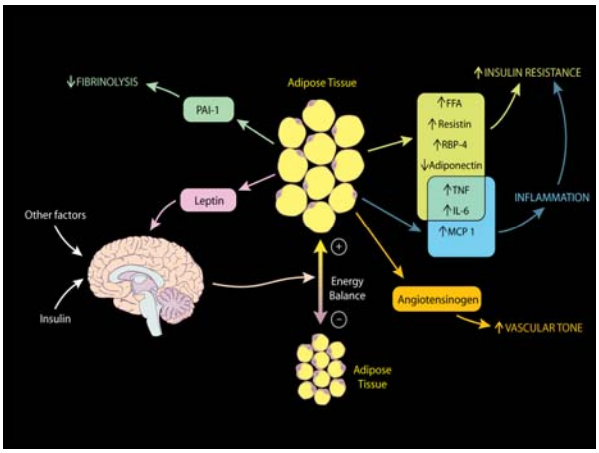
Endothelial Dysfunction

Inflammation

Dyslipidemia

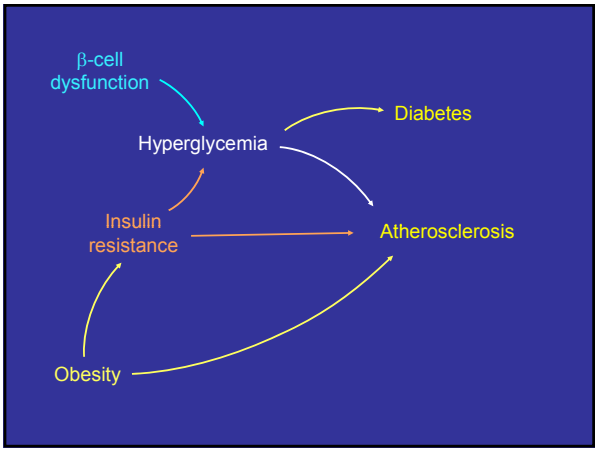
VSMC Proliferation

Thrombosis

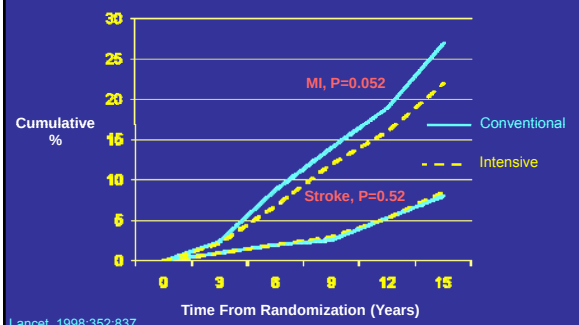


Outline

- Prevalence of Metabolic Disease after Stroke
- Causes
- Consequences
- Therapeutic Implications

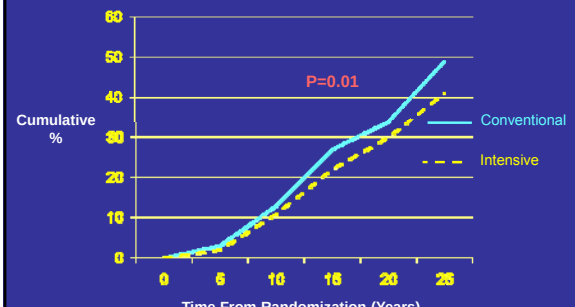


UKPDS: Main Results



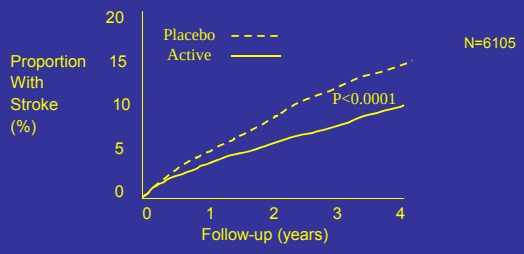
Lancet 1998:352;837

UKPDS: The Legacy Effect for MI



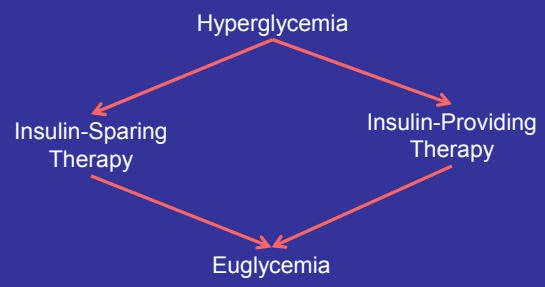
N Eng J Med 2008;359:1577

Blood Pressure Envy



Progress Collaborative Group *Lancet* 2001;358;1033

Two Strategies For Glucose Control



Metformin in Obese Persons with New-Onset Diabetes (UKPDS 34)

	Absolute Risk (events per 1000 patient-years) by Treatment Group			
Outcome	Metformin	Conventional	RRR	P
Stroke	11	18	0.61	0.01
MI	3.3	5.5	0.59	0.13

UKPDS Group. Lancet 1998:352;854

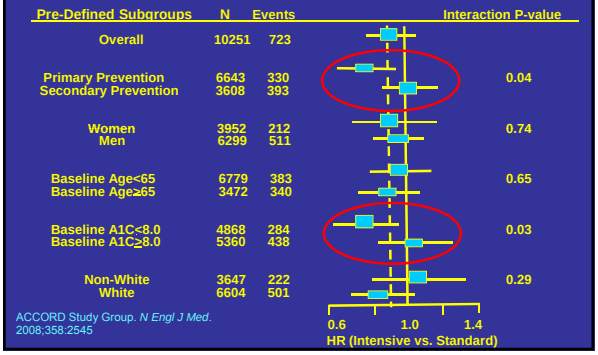
Trials of Glucose Lowering to Prevent Macrovascular Disease in Diabetes

		Mean HbA1c Achieved		Primary Outcome Rate†	
Study	N	Intensive*	Control	Intensive	Control
ACCORD	10,250	6.4%	7.5%	6.9%	7.2%
ADVANCE	11,140	6.5%	7.3%	10.0%	10.6%
VADT	1791	6.9%	8.4%	29.5%	33.5%

*Intensive Rx based on clinician's choice (ACCORD), gliclazide (ADVANCE), rosiglitazone (VADT)
†Non-fatal stroke, non-fatal MI, CV death for ACCORD & ADVANCE studies. Broader composite for VADT. P>0.05 for all comparisions.

ACCORD Study Group *N Engl J. Med* 2008:358;2545
The Advance Collaborative Group *N Engl J Med* 2008;358:2560

ACCORD HRs for 1° Outcome: Subgroup Analyses



ACCORD Study Group. *N Engl J Med*. 2008;358:2545

"It may be that glycemic control plays a greater role before macrovascular disease is well developed and minimal or no role when it is advanced."

- ADA 2010

ADA. Diabetes Care 2010;33:S22

Intensive Glycemic Control to Prevent Macrovascular Disease in Diabetes

Probably effective for some persons, not others
- Not for older patients with established vascular dz
- Maybe for recent onset diabetes, better baseline control, no known vascular disease.

More effective for preventing CHD than stroke or death

Potentially risky
- ↑ Hypoglycemia
- ↑ Mortality (ACCORD)

How glucose is lowered may be important

Benefit emerges only after years of treatment

Effective Therapies for Insulin Resistance

- Weight loss
- Diet
- Exercise

} First Line

- Drugs

Adjustable Gastric Banding for DM

Eligibility: Age 20-60 years
BMI >30 Kg/m^2 and < 40 Kg/m^2
No renal failure
Recent onset type 2 diabetes

R → Conventional DM Rx* 2 Years
R → Laparoscopic Adjustable Gastric Banding 2 Years

} Remission Of DM

*focus on weight loss and lifestyle change

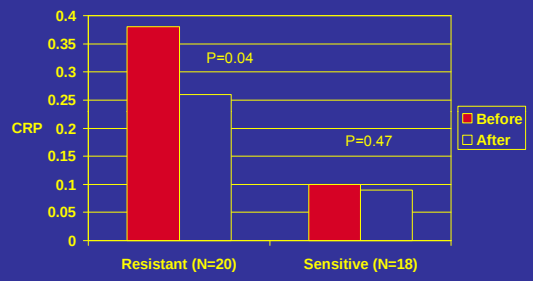
J.B. Dixon JAMA 2008;299:316-323

Results

Variable	Surgery N=30	Conventional N=30	P
Remission DM, No. (%)	22 (73)	4 (13)	<.001
Weight change, Kg	-21.1	-1.5	<.001
HbA1c change	-1.8	-0.4	<.001
Plasma glucose change, mg/dl	-51.2	-18.4	.002
Plasma insulin change, µU/ml	-12.4	1.0	<.001
HOMA change, %	-45	-3.3	<.001
Triglyceride change, mg/dl	-71.7	-2.1	.02
HDL change, mg/dl	12.6	2.6	<.001

J.B. Dixon JAMA 2008;299:316-323

CRP Before and After Weight Loss in Healthy, Obese Women



McLaughlin *Circulation* 2002

Effect of Mediterranean Diet on Weight, Insulin, and Insulin Resistance

Group	N	Wt	Insulin	HOMA	CRP
Olive Oil Diet*	257	-0.19 kg	-9.7pmol/L	-0.53	-0.60mg/L
Tree Nut Diet*	258	-0.26 kg	-9.7pmol/L	-0.54	0.10mg/L
Control†	256	-0.24 kg	6.5pmol/L	0.32	-0.05mg/L

*Both diet groups followed a Mediterranean diet. Olive oil group received 1L oil/week. Nut group received nuts (walnuts, hazelnuts, almonds).
†Typical low fat diet.

R. Estruch *Ann Intern Med* 2006;145:1

Exercise Training: Patients with Mild-Moderate Hemiparetic Gait after Ischemic Stroke

Progressive Treadmill Exercise Training 3x a week →

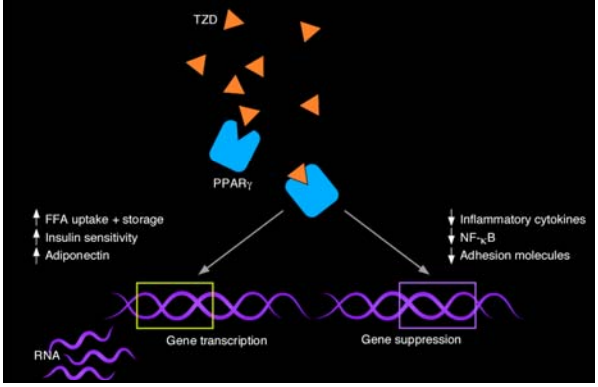
- 25% increase in insulin sensitivity
- 22% decline in fasting insulin
- No change in fasting glucose

FM Ivey *Stroke* 2007;38:2752

Drugs

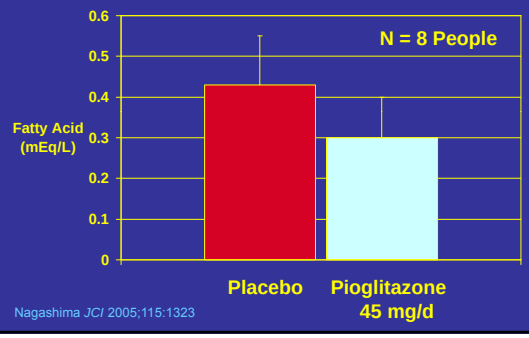
- Biguanides
  - Metformin
- Thiazolidinediones
  - Pioglitazone
  - Rosiglitazone
- Weight loss Drugs
  - Orlistat
  - Subitramine
  - Rimonabant

Thiazolidinediones (TZD): Nuclear Transcription Factors



Pioglitazone Lowers Plasma FA in Diabetes

Results of a Controlled Crossover Study



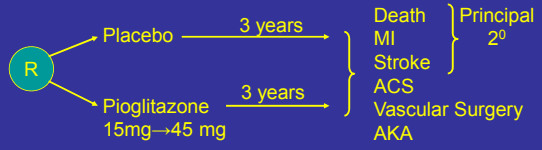
Nagashima *JCI* 2005;115:1323

Clinical Effects of Pioglitazone: Results of Major Trials

- ↓ in-stent restenosis
- ↓ carotid intimal-medial thickness (IMT)
- ↓ coronary atherosclerosis (IVUS)
- ↓ stroke, MI, vascular death (diabetic patients)

PROactive Study Design

Eligibility:
- Type 2 DM
- Age 35-75
- HgbA1c >6.5%
- Macrovascular disease
- No NYHA class >1 CHF



Dormandy *Lancet* 2005:366;1279

PROactive Results

Group	N	Outcome	Hazard Ratio	P
All pts.*	5238	Primary	0.90	0.095
		Secondary	0.84	0.027
Prior MI†	2445	MI	0.72	0.045
Prior Stroke‡	984	Stroke	0.53	0.009
		Stroke, MI, CV death	0.72	0.047

*Dormandy, *Lancet* 2005:366;1279
†E Erdmann *JACC* 2007;49;1772
‡R Wilcox *Stroke* 2007:38;865

IRIS

Insulin Resistance Intervention after Stroke Trial

IRIS Design

Eligibility: Recent TIA or Ischemic Stroke
Non-diabetic
Insulin resistant
No serious congestive heart failure

R N=3136*

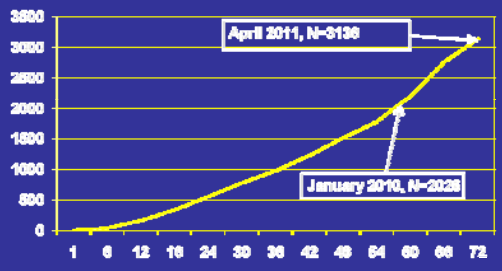
Placebo → 4 years

Pioglitazone 15mg→45 mg → 4 years

Stroke MI

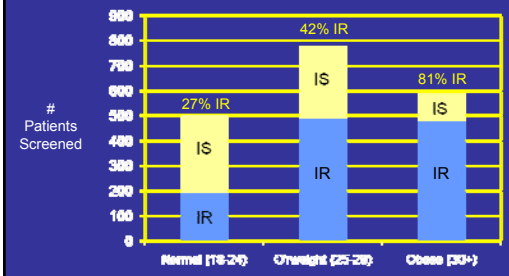
*90% power to detect a reduction from 27% in the placebo group to 22% in the pioglitazone group at an alpha level of 0.05

Enrollment

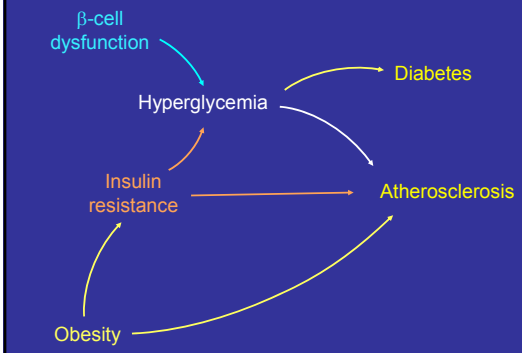


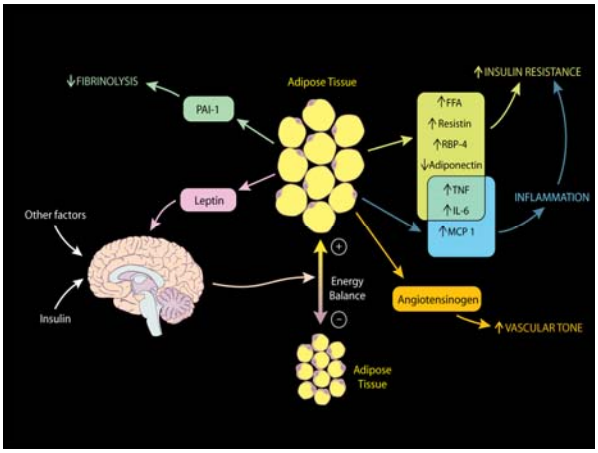
86

Prevalence of IR According to BMI



Data as of 4.29.08





Recognize:
Her Met Dxs

Counsel:
1. Vascular effects of IFG , IR, obesity
2. ↑ Risk for DM

Recommend:
1. Diet
2. Exercise
3. Weight loss

Consider:
1. Nutrition consult
2. Metformin
3. IRIS Trial

For Diabetic Patients After Stroke or TIA

- BP < 130/80
  - ACEI for all who can tolerate (especially if microalbuminuria)
- LDL < 100 or <70 mg/dl (SPARCL Trial, others)
- Glucose Control
  - HbA1c <7% for most
    - Older patients with established vascular disease may not benefit from tighter control
  - Emphasize life style interventions
  - Metformin as first agent

P. Gaede. N Engl J Med 2003;348:383

END

Thank you