

# Type 2 Diabetes – New Therapies

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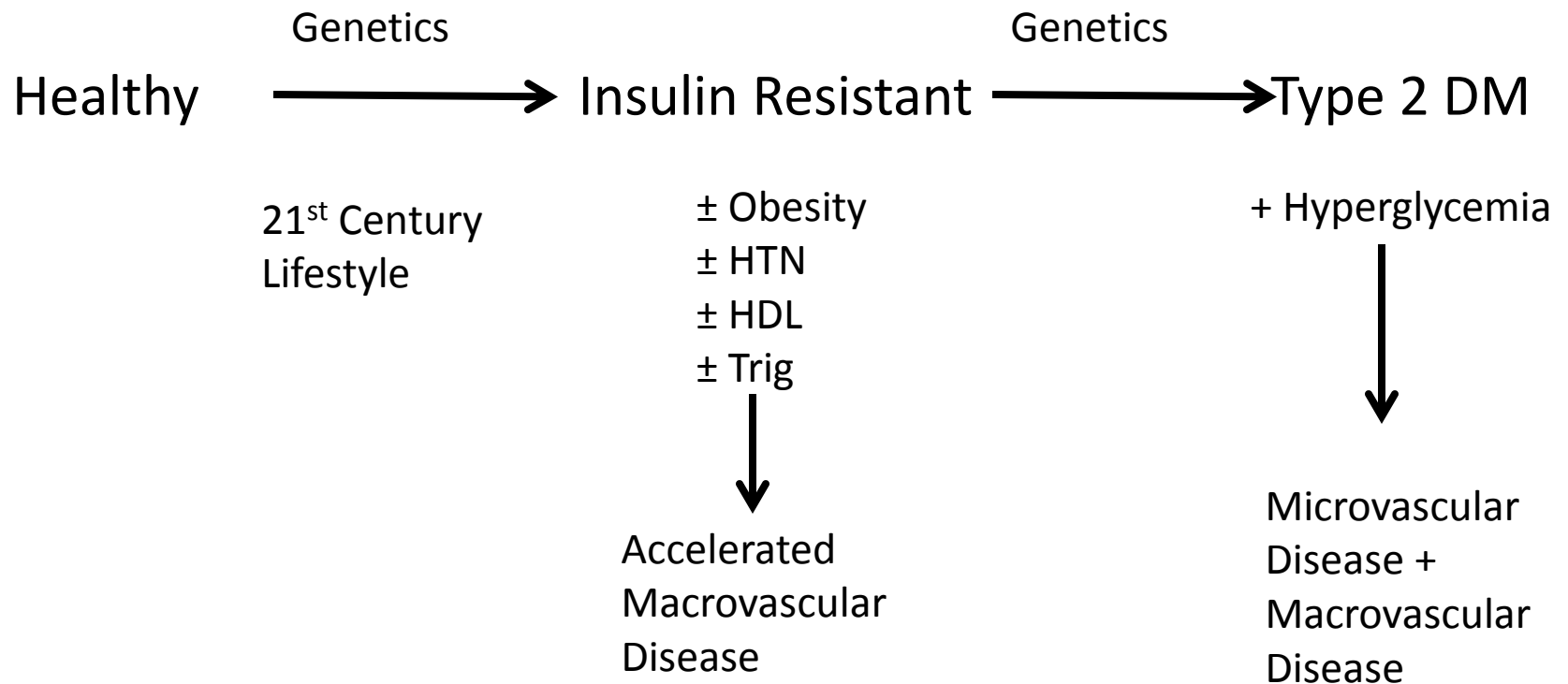
Madge Jones Professor of Medicine

Director, UVA Diabetes Center

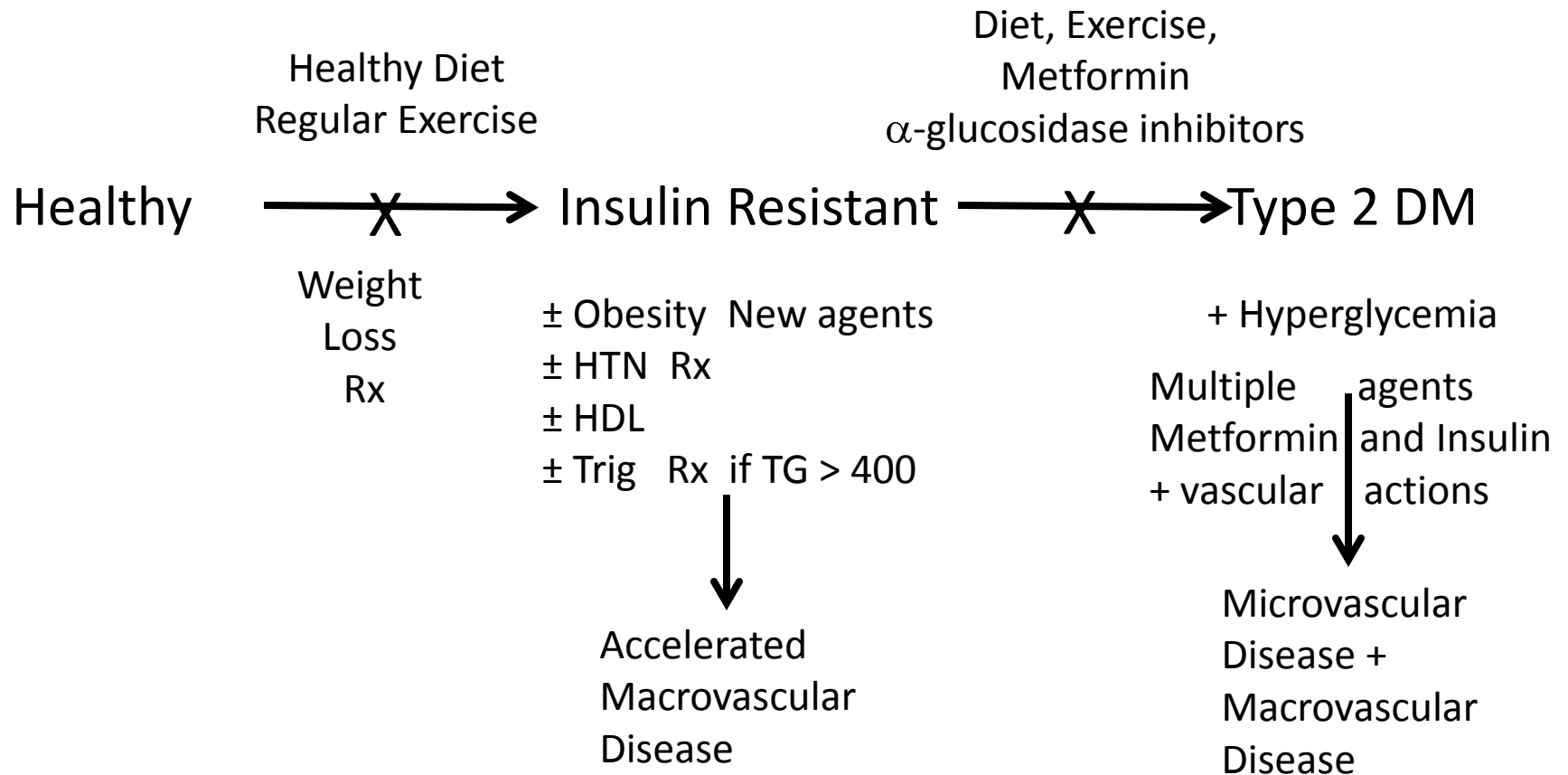
# Approaches to Diabetes Treatment 2013

- Diet and Exercise remain cornerstones
- Pharmacology
  - An expanding universe
- Costs of Rx
- Surgery – a brief discussion

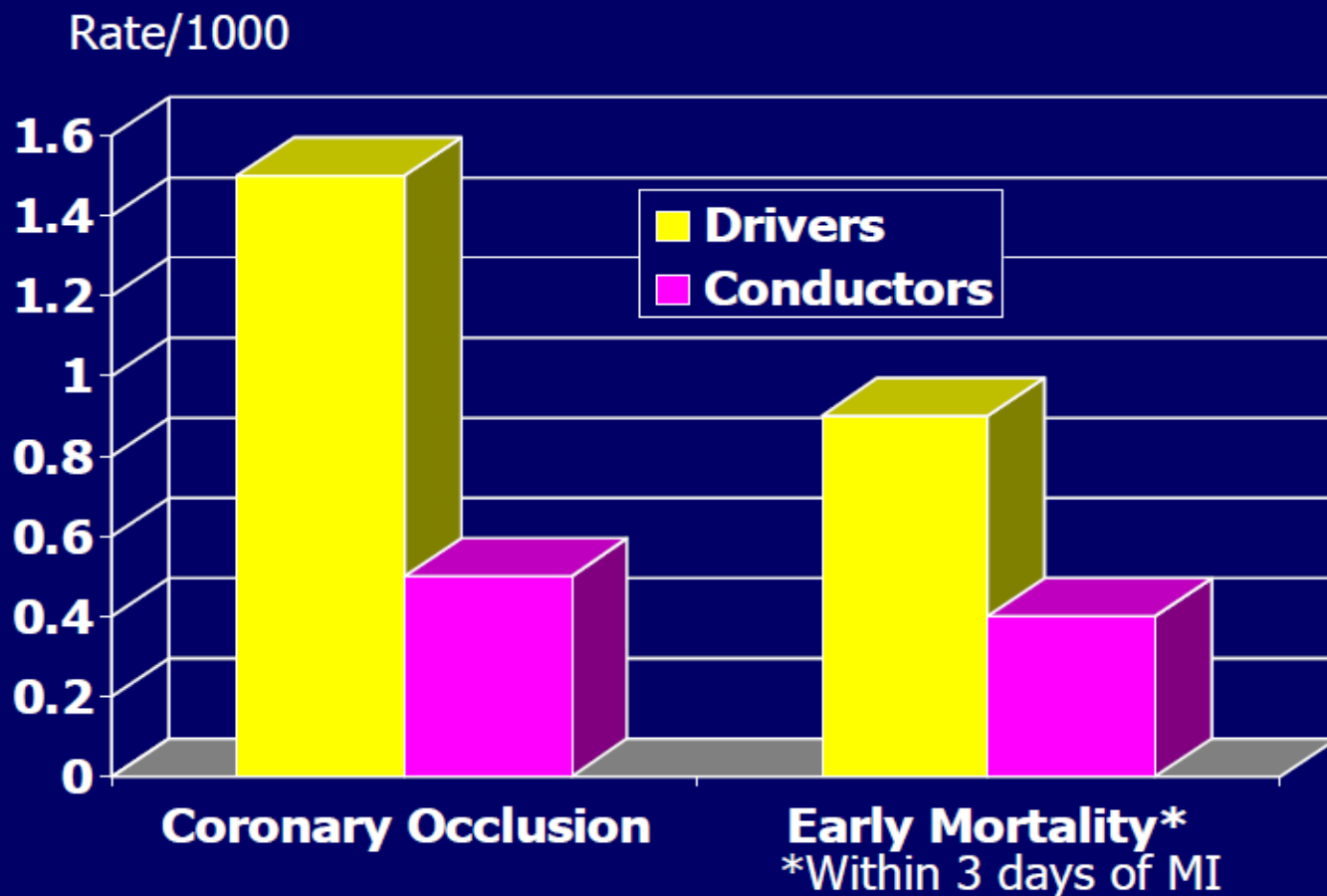
# Type 2 Diabetes – Genesis and Consequences



# Type 2 Diabetes – Where and When to Intervene



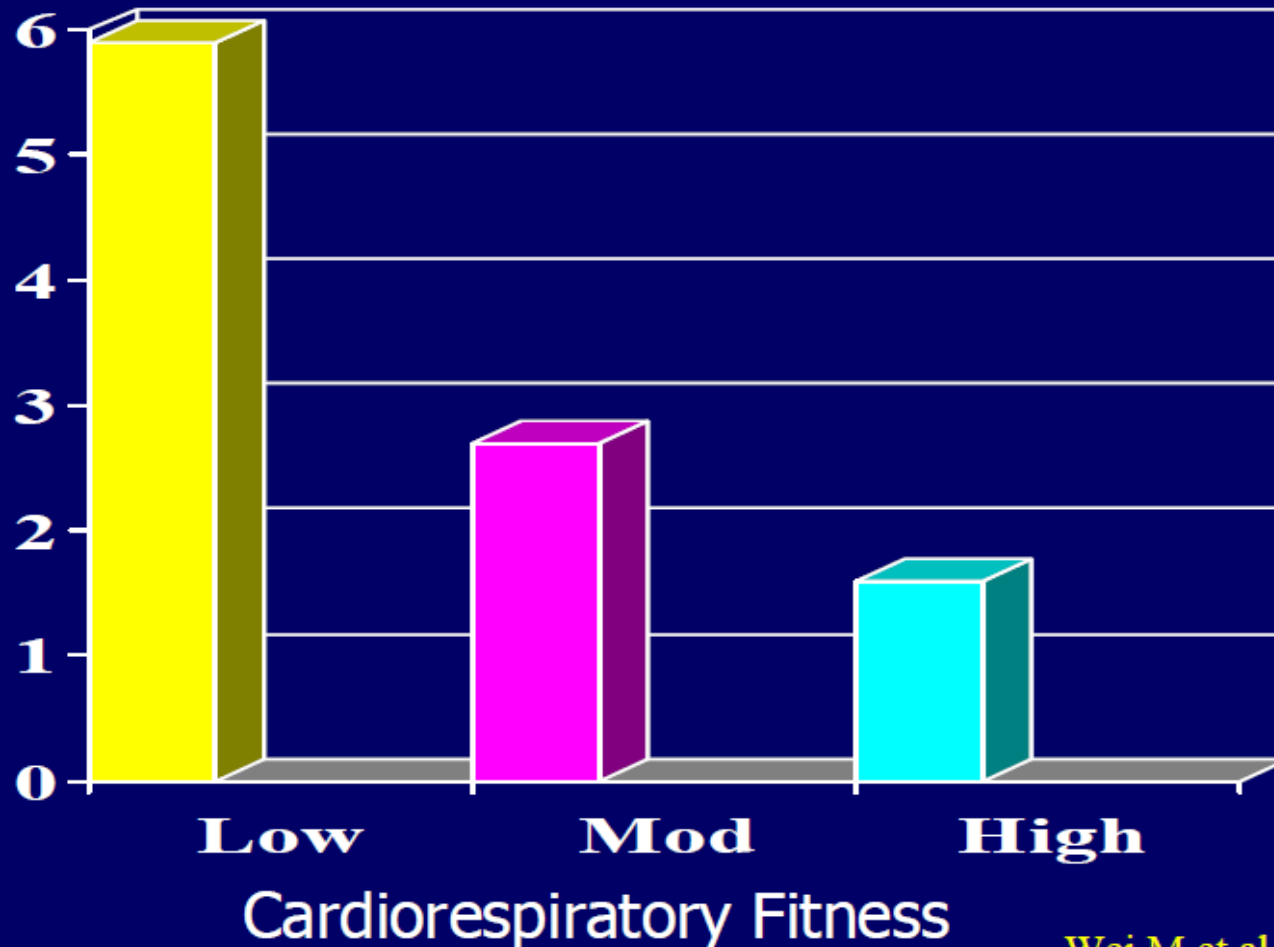
# Physical Activity at Work and Coronary Artery Disease; 31,000 London Transport Workers



Morris JN et al. *Lancet* 1953

# Fitness and Incident Type 2 Diabetes; 8633 Healthy U.S. Men

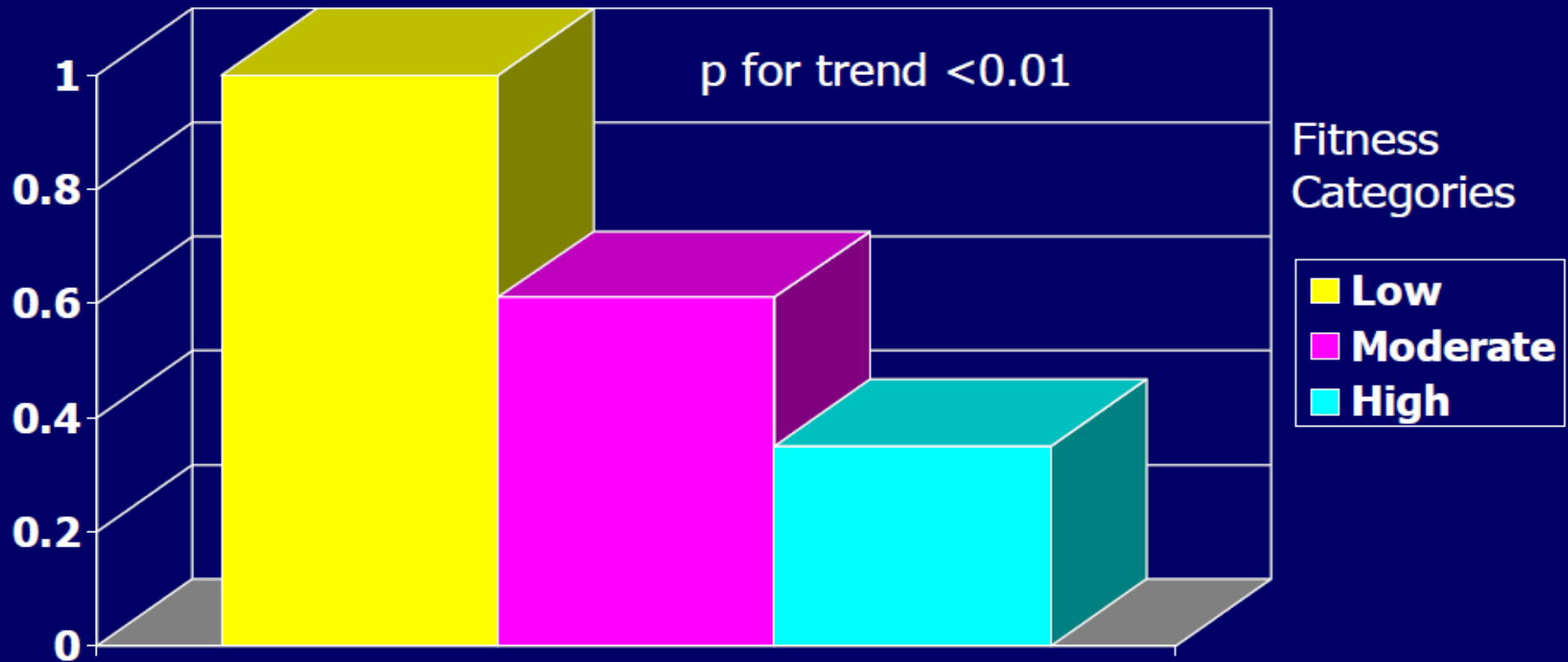
Diabetes incidence/1000 men



# Fitness and Risk of Incident Hypertension

## 4884 Healthy Women; 5yr follow-up

Relative Risk  
for Hypertension

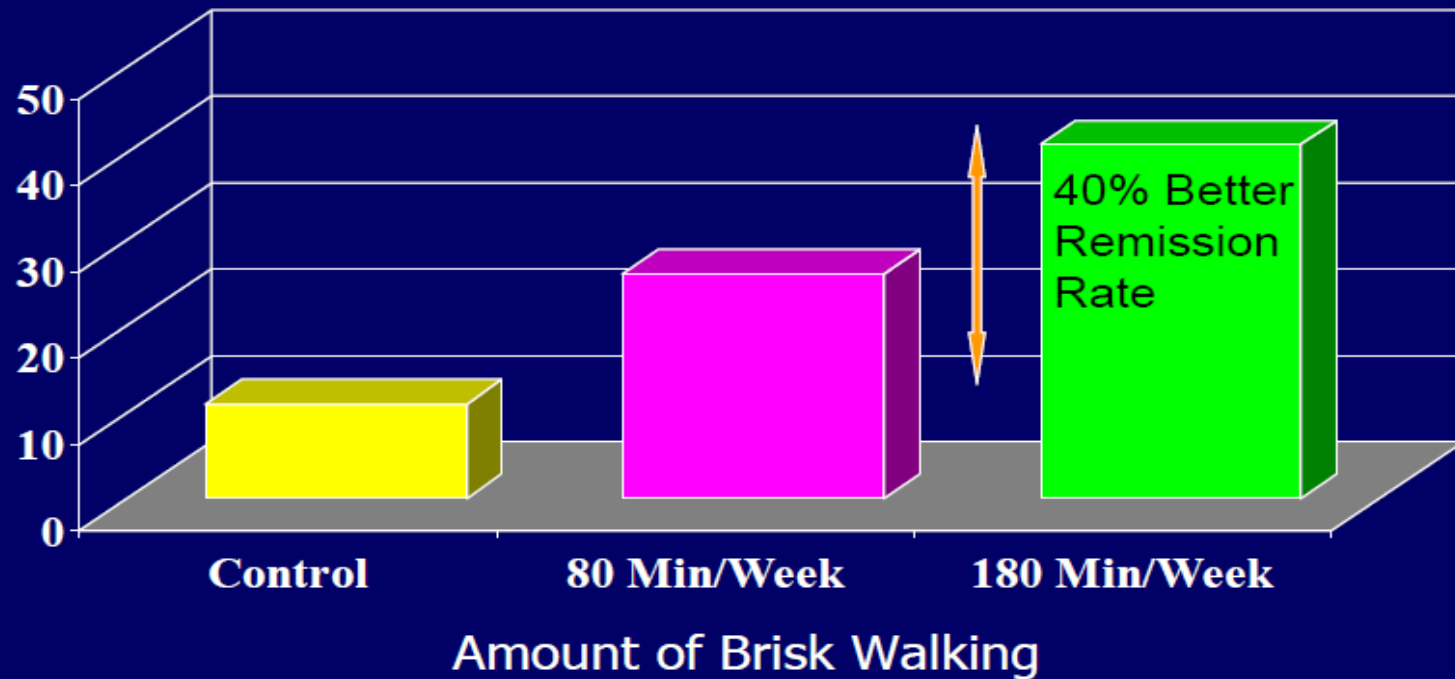


Controlled for BMI, age, hx htn

Barlow CE et al. *Am J Epidemiol* 2006; 163:142-50

# Exercise Is As Good As Other Treatments for Clinical *Depression*

% of Patients with Remission of Depression

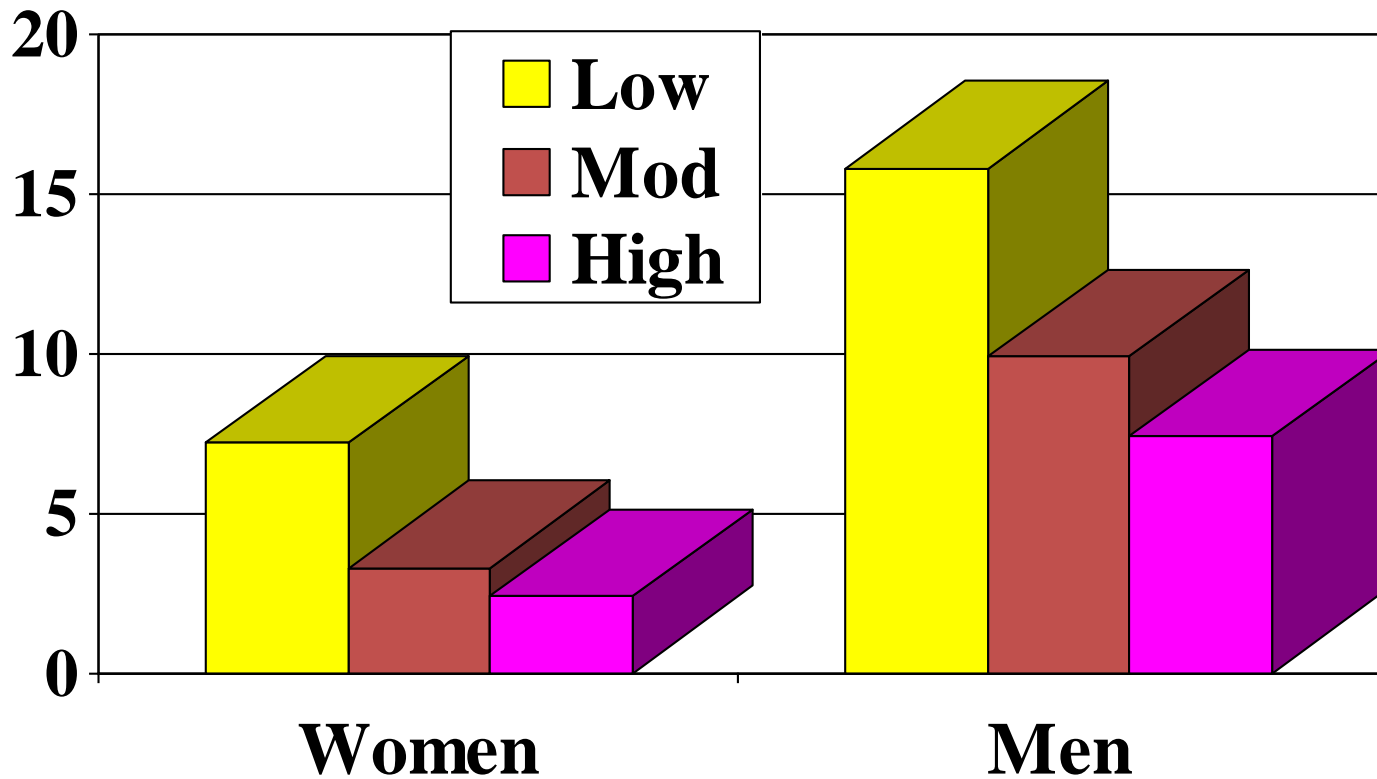


Drug therapy and cognitive behavioral therapy produce remission in approximately 40% of clinically depressed individuals



# CVD Death Rates\* by Fitness Groups, 7,080 Women and 25,340 Men, ACLS

Deaths/10,000 PY

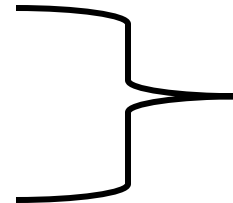


Adjusted for age, exam year, and other risk factors

Blair SN et al. *JAMA* 1996; 276:205-10

# Newer Pharmacologic Agents

- DPP-4 Inhibitors
- GLP-1R Agonists
- Dopamine D2 mimetic
- SGLT-2 inhibitors
- ?Newer insulins

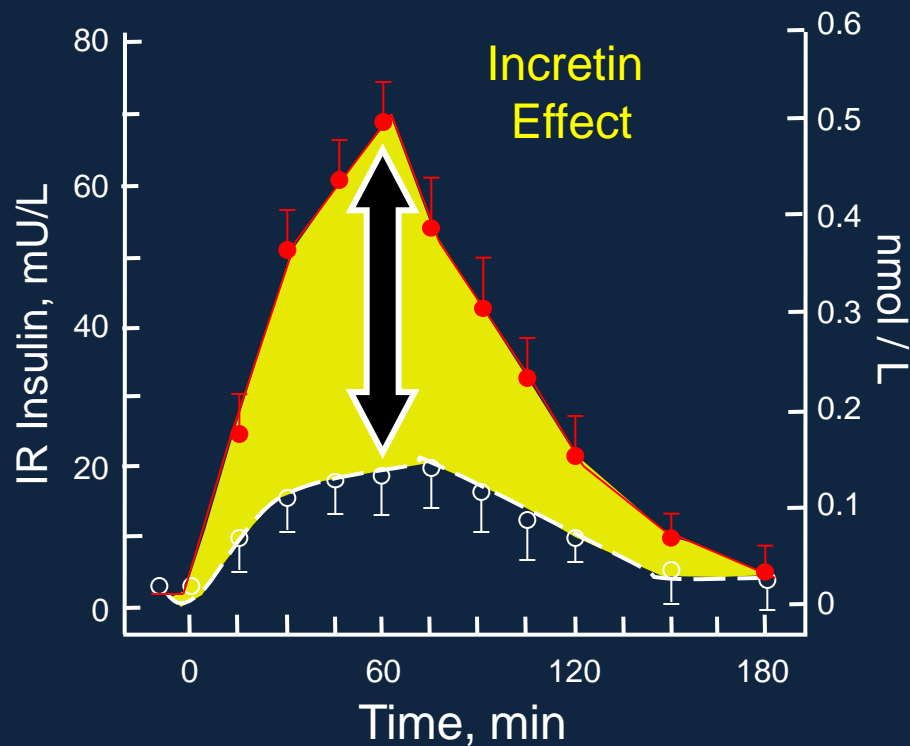


Incretin Rx

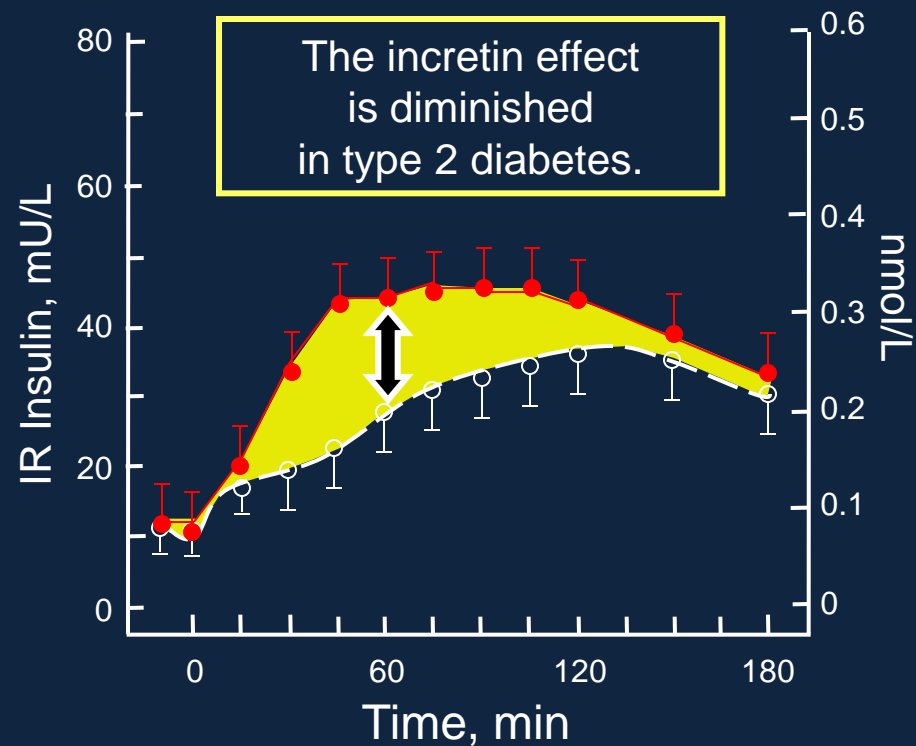
Metformin remains first line therapy

# The Incretin Effect in Subjects Without and With Type 2 Diabetes

Control Subjects  
(n=8)



Patients With Type 2 Diabetes  
(n=14)



- Oral glucose load
- Intravenous (IV) glucose infusion

# GLP-1R Agonists

- Exenatide (Byetta<sup>®</sup>)
- Exenatide LAR (Bydureon)
- Liraglutide (Victoza<sup>®</sup>)

# DPP4 Inhibitors

- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Allogliptin (Nesina)
- Linagliptin (Trajenta)

# Liraglutide (Victoza<sup>®</sup>)

- LEAD-5 trial (n=581)
  - Liraglutide 1.8 mg, glargine, placebo
  - Background: metformin 1000 mg BID, glimepiride 4 mg daily
  - A1C:
    - -1.33% vs glargine -1.09% (p = 0.0015)
    - -1.33% vs placebo -0.24% (p < 0.0001)
  - Weight:
    - -1.8 kg vs glargine +1.6 kg (p < 0.0001)
    - -1.8 kg vs placebo -0.42 kg (p < 0.0001)

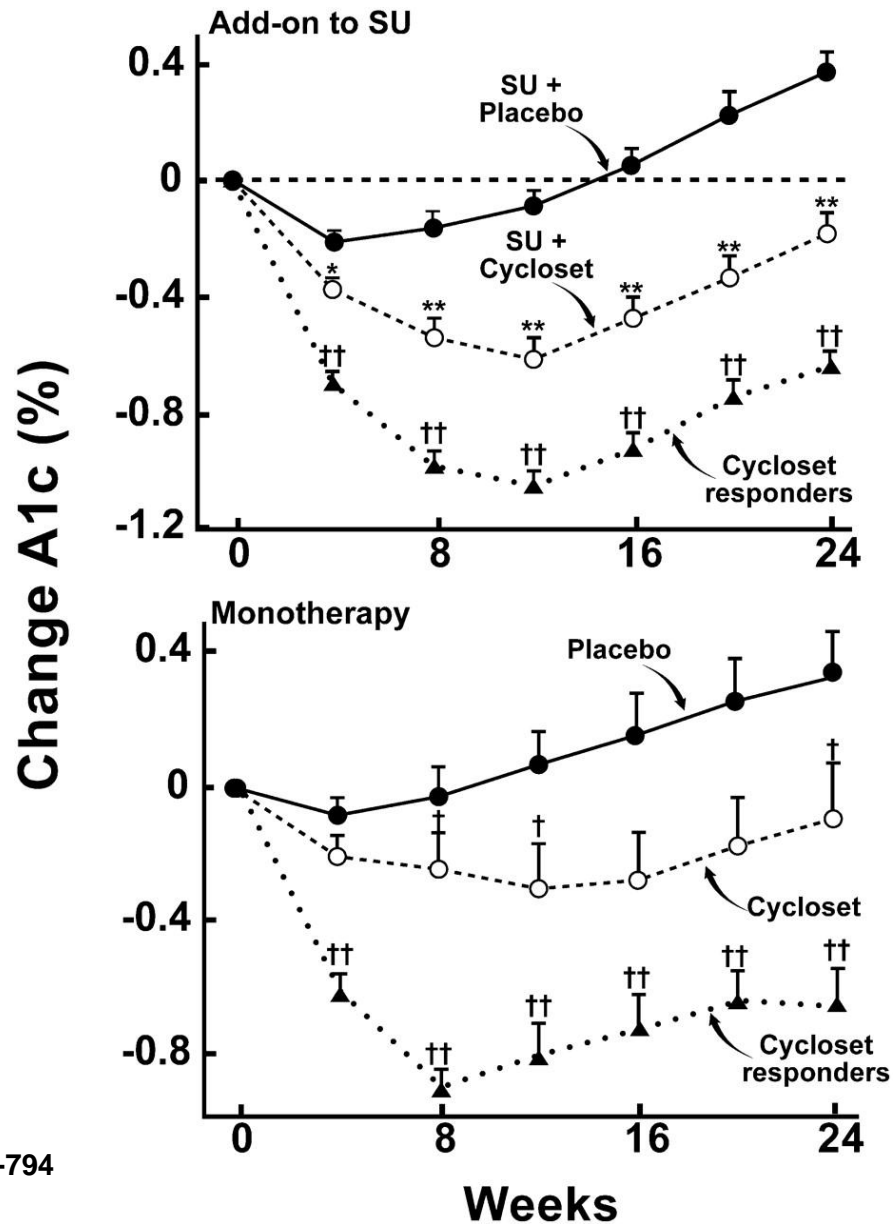
## DPP-4 Inhibitors and GLP-1R Agonists – Safety Concerns: Pancreatitis and pancreatic neoplasia.

- Agents can increase proliferation of rodent pancreatic cells.
- One human pathologic study showed increase in pancreatic alpha cells in humans and question of ductal cell proliferation.
- Review of clinical trials (>8,000 patients) does not currently support either neoplasia or pancreatitis concern for DPP-4 or GLP-1R agonists, however monitoring will continue.

# Dopamine D2 Agonist

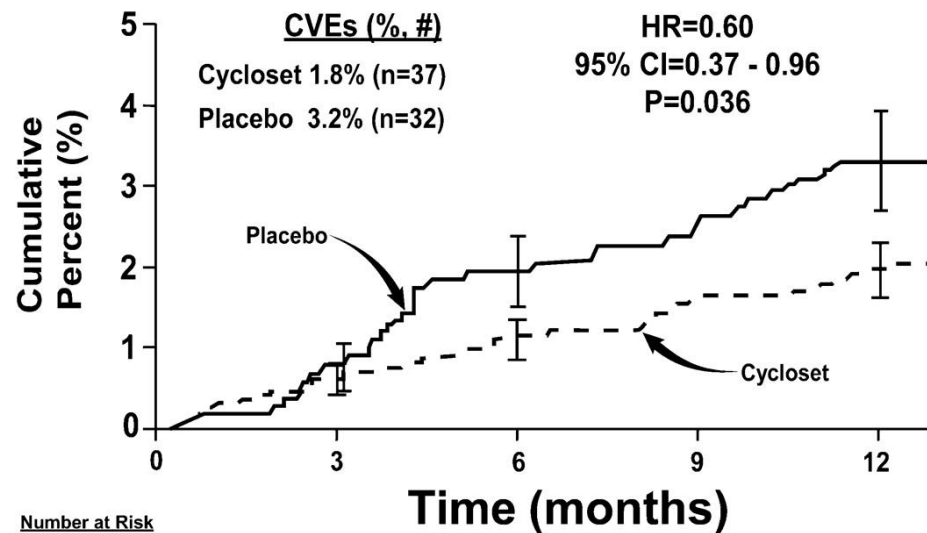
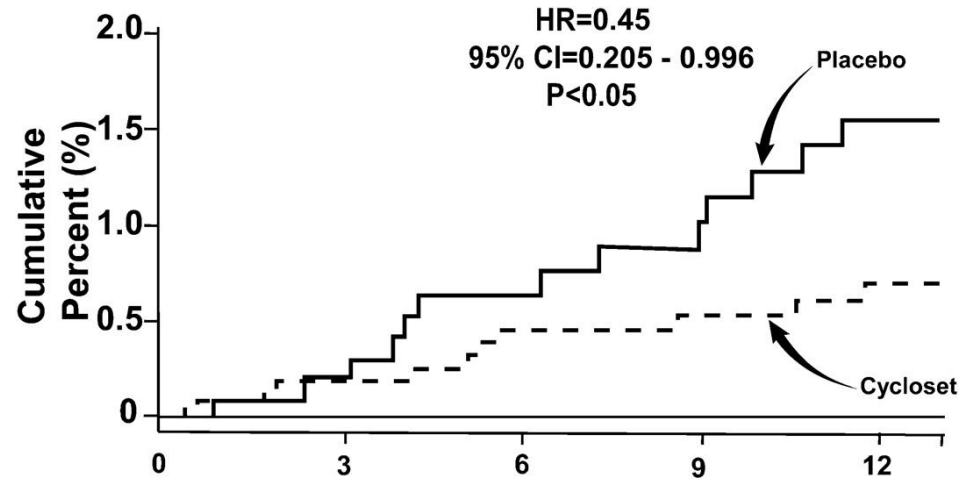
- Short-acting bromocriptine (Cycloset)
- Acts centrally by unclear mechanisms
- One agent in class and no congeners in development
- Very modest decrease in A1c (0.4-0.6 vs placebo)
- Nausea and orthostasis are issues
- Favorable CV risk profile

# Change in HbA1c in Cycloset (total group) and placebo-treated diabetic subjects.





**Top: Kaplan-Meier plot of time to first cardiovascular (MACE) event (myocardial infarction, stroke, and death) in type 2 diabetic subjects treated with Cycloset or placebo for 52 weeks**



Number at Risk

	0	3	6	9	12
Bromo- cristine	2054	1822	1691	1453	1453
Placebo	1016	950	898	793	793

# SGLT-2 Inhibitors

- Demonstrated in 1990 that phloridzin lowered glucose and improved insulin sensitivity in pancreatectomized rats.
- Canagliflozin (Invokana) first approved agent in US (others marching along)
- Blocks renal Na-glucose co-transporter in proximal tubule
- Decreases T<sub>max</sub> for glucose reabsorption (typically 180-200 mg/dL in healthy, 240 in DM) and the increased glycosuria lowers the plasma glucose

# Clinical Application

- Indications:
  - Diabetes mellitus type 2 as an adjunct to diet and exercise (monotherapy or in combination with metformin and/or sulfonylurea)
- Place in therapy:
  - New third-line agent after metformin and sulfonylurea failure
    - Possibly in front of DPP-IV inhibitors like sitagliptin

# Clinical Application

- **Contraindications:**
  - History of serious hypersensitivity reactions
  - Severe renal impairment (GFR < 30 ml/min, ESRD / on dialysis)
- **Warnings**
  - Genital mycotic infections (uncircumcised men or prior mycotic infections increase risk)
  - Hyperkalemia
  - Hypersensitivity (generalized urticaria - discontinue if occurs)
  - Hypoglycemia
- **Precautions**
  - Use with caution in elderly patients as symptomatic hypotension may occur.

# Drug Facts

- Pharmacokinetics

- A – Bioavailability ~65% (not affected by food);  $T_{Max}$  ~1-2 hrs
- D – ~99% protein-bound (mainly albumin)
- M – O-glucuronidation by UGT1A9 and UGT2B to 2 inactive metabolites (Minor oxidation through CYP3A4)
- E – Feces (41.5% unchanged), Urine 35% (< 1% unchanged);  $T_{1/2}$  ~10.6-13.1 hours

## Canagliflozin

# Adverse Effects

- Common Adverse Effects:

Adverse Reaction	Canagliflozin	Placebo
UTI	5.9%	4.0%
Female mycotic infection	10.4%	3.2%
Male mycotic infection	4.2%	0.6%
Polyuria	5.3%	0.8%

- Pancreatitis
- Moderate renal impairment (18-22.5%)

# Canagliflozin

- 100 mg orally once daily initially
  - May increase to 300 mg once daily if additional glycemic control required
  - In setting of renal insufficiency (estimated GFR of 45-59 mL/min) a max dose of 100 mg once daily is recommended
  - Not indicated in severe renal impairment (GFR < 45, ESRD / dialysis)
- Cost – \$ 316/ month accessed 05/30/2013

# SGLT-2 Inhibitors Summary

- Four other agents in late stage trials
- Moderate to good A1c effect (1-1.5 %)
- Favorable effect on weight (decrease 2-4%)
- Increased incidence UTI and vaginal yeast infections.
- Dose adjustment for CRF



# Medication Costs

Metformin and Sulfonylureas as low as \$5/mo

Pioglitazone (generic) \$20/mo

DPP-4 inhibitors - ~ \$260/ mo

GLP-1R agonists -Victoza - ~\$500/mo for full dose,  
Byetta ~ \$400/mo, Bydureon \$400/mo

Cycloset - ~ \$80/mo

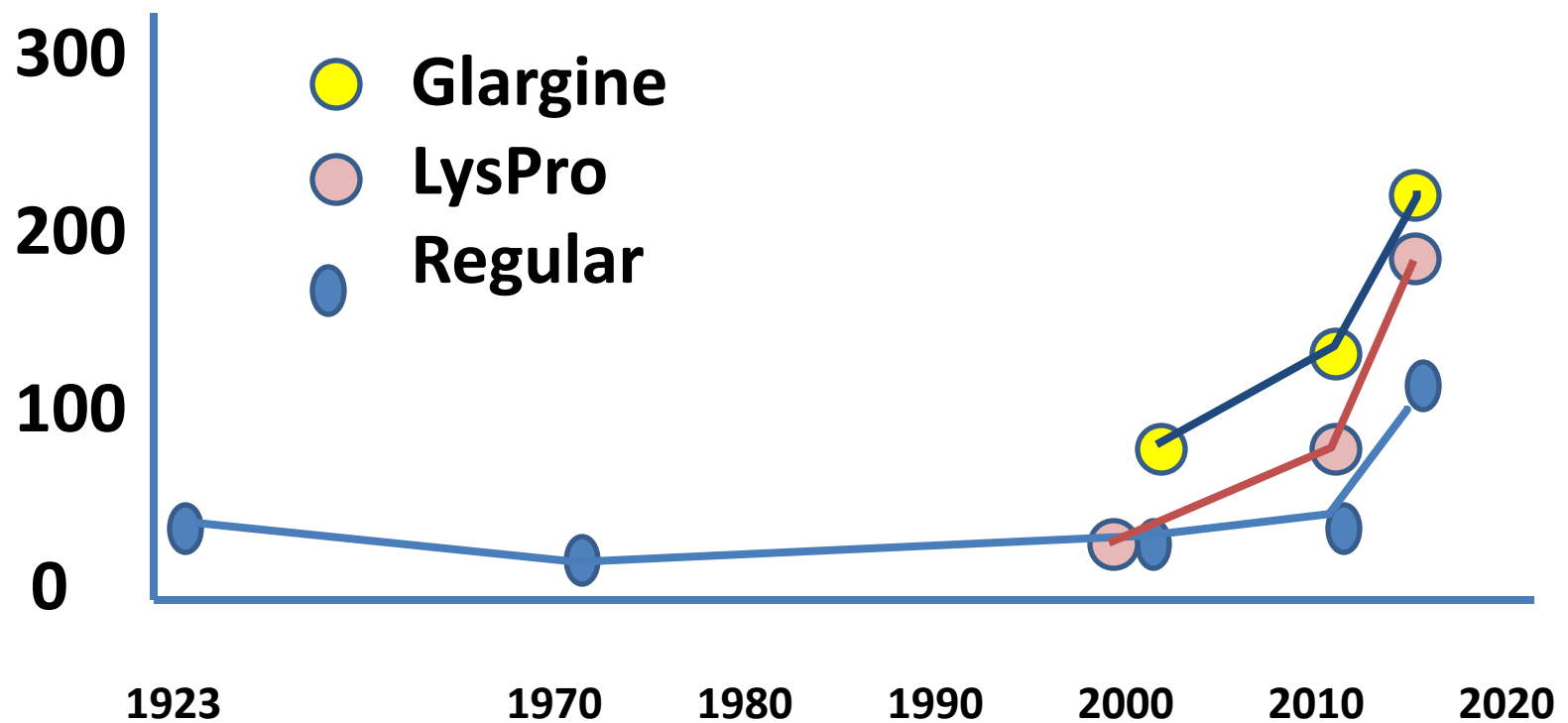
SGLT-2 Inhibitor - ~ \$320/mo

Gym membership ~ \$80/ mo

# New Insulins

- Insulin remains the single most potent agent to treat diabetes.
- Trials underway with very long acting basal insulins (every 3 days or once a week).
- Very short acting prandial insulin also under development and testing.

# Cost of Insulin (\$ vial 1000 U)



# Cost of insulin - 2013

- Regular and NPH ~ 0.075 \$/unit (up from 0.025\$ in last 3 yrs)
- Rapid acting insulins ~ 0.175 \$/ unit
- Long-acting insulins ~ 0.21 \$ /unit
  
- For the very insulin resistant patient (e.g. on 300 units daily) – basal bolus Rx will cost > \$22,000/yr!!

# Surgery for DM2

- Gastric bypass- most long term data available.
- Gastric Banding- can be effective
- Sleeve Gastrectomy – emerging experience appears encouraging