DIABETES AND CARDIOVASCULAR DISEASE

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Clinical Vignette

A 55 year old man presents to the office for a visit to establish care. He has history of type II DM for the last 15 years and is on oral hypoglycemic agents. He also has a history of HTN, obesity and hyperlipidemia. He does not have any specific complaints but states that he has been more tired than usual and has to stop more often when he works in the yard to catch his breath. He does not engage in any regular physical activity.

What is the main cause of mortality and morbidity in this patient?

What can you do to decrease his risk?

High level of suspicion is key for diagnosis of vascular disease

History and Physical

- Always ask about changes in functional capacity compared to 6 months or a year ago
- Always ask about possible symptoms of vascular claudication
- Always listen to the carotid arteries for bruits
- Always examine the feet and pedal pulses

Overview

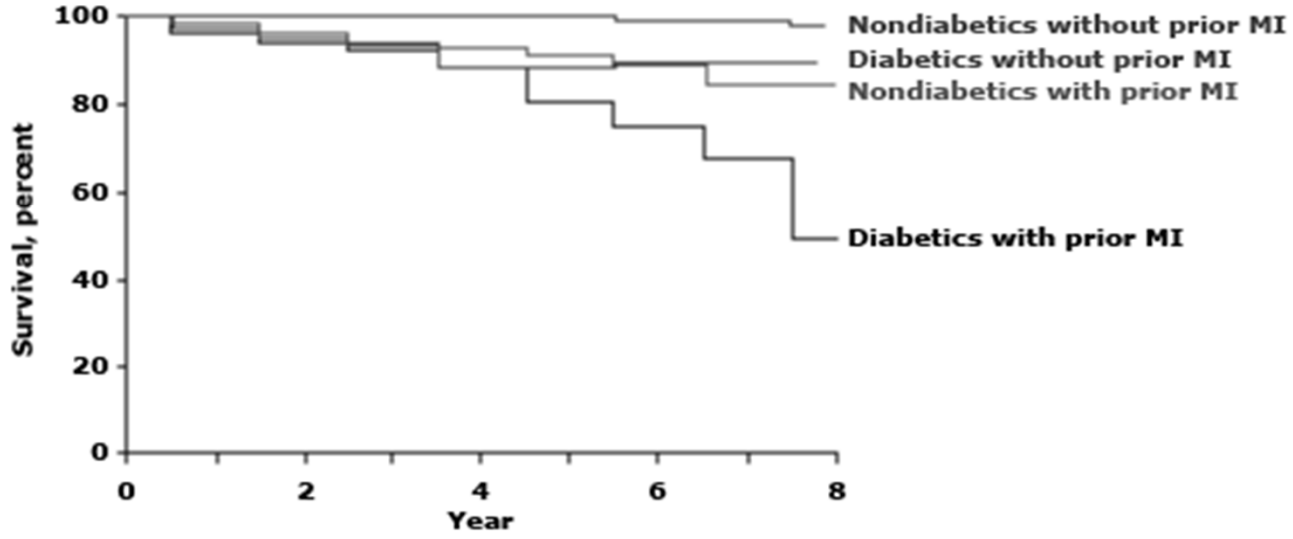
- Prevalence and extent of CVD in diabetics
- Mechanisms of increased risk
- Glycemic control and risk of CVD
- CAD and diabetes
- PAD and diabetes
- Cardiovascular effects of hypoglycemic agents

PREVALENCE AND EXTENT OF CVD IN DIABETICS

Prevalence

- CVD is the most common cause of mortality and morbidity in patients with diabetes
- At least 65% of diabetic patients die from some form of heart disease or stroke
- Adults with DM are 2 – 4 times more likely to have heart disease or stroke than adults without diabetes
- Diabetes is considered a CAD equivalent

Diabetes increases coronary heart disease mortality with and without a prior myocardial infarction (MI)



In a seven-year follow-up of 1059 subjects with type 2 diabetes and 1378 patients without diabetes, persons with diabetes, with or without a prior myocardial infarction (MI), had a greater mortality from coronary disease compared to those without diabetes (42 versus 16 percent for those with a prior MI and 15 versus 2 percent for those without a prior MI). The rate of coronary death and fatal and nonfatal MI in persons with diabetes without a prior MI was the same as in those without diabetes with a prior MI, providing part of the rationale for considering type 2 diabetes a coronary heart disease equivalent.

Data from: Haffner SM, Lehto S, Ronnemaa T, et al. N Engl J Med 1998; 339:229.

Impact of DM

- In the Framingham Heart Study, the presence of DM doubled the age-adjusted risk for cardiovascular disease in men and tripled it in women
- Multiple other studies showed similar results
- Type I DM was associated with even higher rates of CVD
- Diabetics are more likely to have multi-vessel and microvascular CAD

Impact of DM

- Poor glycemic control incrementally increases the risk of atherosclerosis

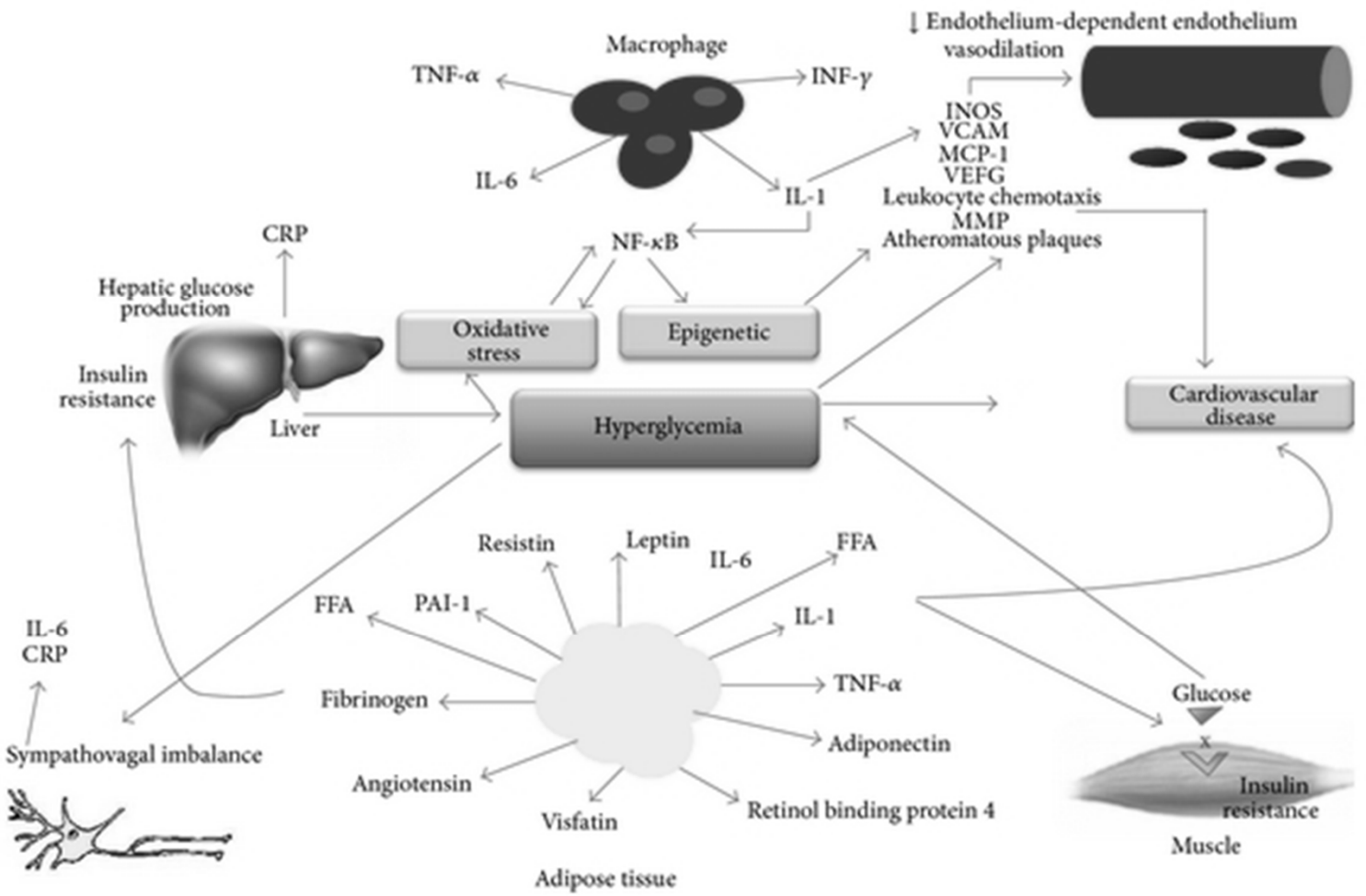
- Every 1% increase in HbA1c is associated with 26% increase in cardiovascular risk
  - Ann Intern Med. 2004;141(6):421

- DM is the second strongest risk factor for PAD (after smoking) with higher rates of mortality and amputation

Impact of DM

- Diabetics are more likely to have silent ischemia and asymptomatic CAD
- Some diabetic patients have a blunted appreciation of ischemic pain, which may result in atypical anginal symptoms, silent ischemia, or even silent infarction
- This is thought to be caused at least in part by autonomic denervation of the heart
- Screening for CAD in diabetics is generally not recommended except in high risk pts or when starting an exercise program

MECHANISMS OF INCREASED RISK


Macrophage
TNF-α
INF-γ
IL-6
IL-1
↓ Endothelium-dependent endothelium vasodilation
INOS
VCAM
MCP-1
VEFG
Leukocyte chemotaxis
MMP
Atheromatous plaques
CRP
NF-κB
Hepatic glucose production
Oxidative stress
Epigenetic
Insulin resistance
Liver
Hyperglycemia
Cardiovascular disease
Resistin
Leptin
IL-6
FFA
FFA
PAI-1
IL-1
IL-6
CRP
Fibrinogen
TNF-α
Glucose
Adiponectin
Sympathovagal imbalance
Angiotensin
Insulin resistance
Visfatin
Retinol binding protein 4
Muscle
Adipose tissue

Mechanisms of Increased Risk

- Diabetics have higher incidence of traditional cardiovascular risk factors such as HTN

- Dyslipidemia in DM worsens CVD risk
  - Increased VLDL
  - Increased TGs
  - Small dense LDL (oxidized LDL)
  - Low HDL

- Hyperglycemia per se may play a role in promoting atherosclerosis

Endothelial Dysfunction

- Has been documented in diabetic patients with normal coronary arteries and no other risk factors
- The degree appears to be related to the duration of DM
- Insulin resistance without overt diabetes was also shown to be associated with endothelial dysfunction
- Interventions such as treatment with metformin, statins, and thiazolidinediones can improve endothelial function

Coagulation Abnormalities

- Increased levels of plasma fibrinogen which is a cardiac risk factor
- Fibrinolytic activity is reduced
- Both tissue factor and blood thrombogenicity are increased in patients with poorly controlled diabetes
- Increased platelet activation

GLYCEMIC CONTROL AND RISK OF CVD

UKPDS

- Over 5000 pts
- Followed for 10 years
- Mean age 54 ys
- Recently diagnosed DM
- Intensive treatment achieved HbA1c 7% vs. 7.9%

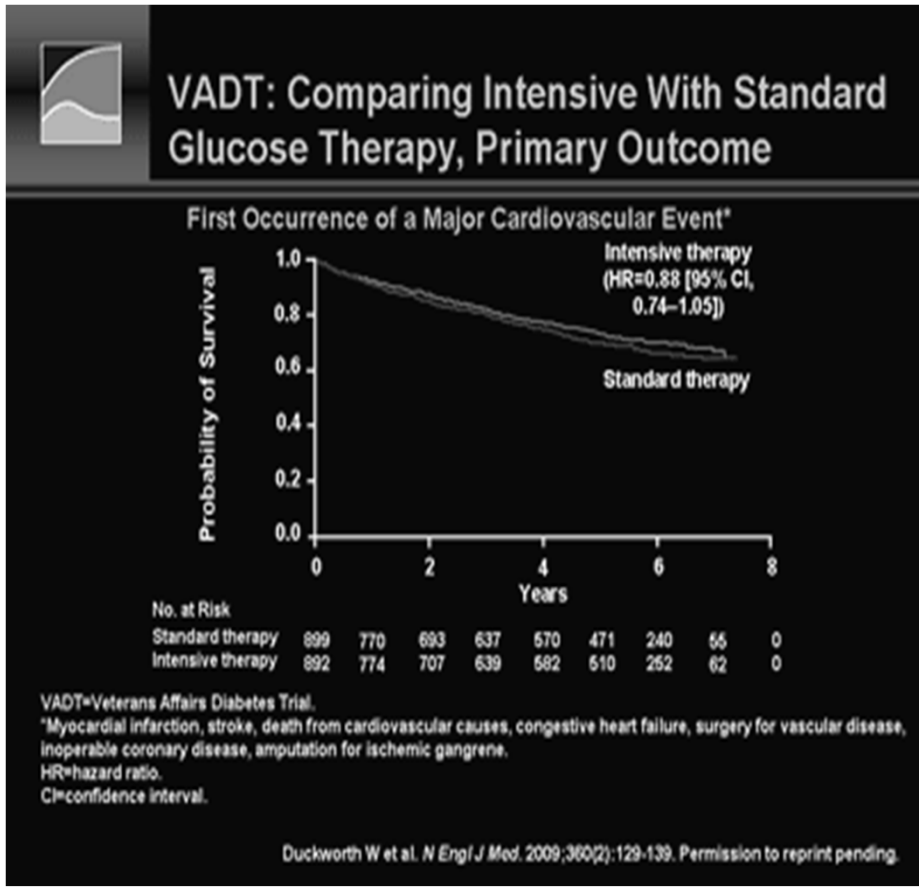
UKPDS: Glucose Control Study Results

Intensive Blood Glucose Control

	Change in risk	*P* value
Any diabetes-related endpoint	↓12%	0.029
Diabetes-related deaths	↓10%	NS
Myocardial infarction (fatal/nonfatal)	↓16%	0.052
Stroke (fatal/nonfatal)	↑11%	NS
Microvascular disease	↓25%	0.0099

UKPDS Group. *Lancet*. 1998;352:837-853.

Veterans Affairs Diabetes Trial



- 1791 pts
- Follow up for 5.6 ys
- Mean age 60 ys
- DM for 11 ys
- 40% had CVD
- HbA1c 6.9% vs. 8.4%
- No difference in micro or macro-vascular events

The ADVANCE trial

- 11,140 pts
- Follow up 5 years
- Mean age 58 ys
- Duration of DM 8 ys
- 32% had cardiovascular disease
- HbA1c 6.5% vs. 7.3%
- No significant reduction in macrovascular events
- Significant reduction in nephropathy

The ACCORD Trial

- Over 10,000 pts
- Follow up 3.4 ys
- Mean age 62 ys
- Duration of DM 10 ys
- 35% with CVD
- HbA1c 6.4% vs. 7.5%
- There was reduction in nonfatal MI
- There was increase in mortality, weight gain and risk of hypoglycemia

DCCT/EDIC

- Type I DM
- HbA1c < 7% target
- Treated for 6.5 ys and followed for another 10 ys
- Showed significant decrease in microvascular and macrovascular complications (42% reduction)

Summary

- A goal of HbA1c of < 7% is appropriate in type I and type II diabetes to reduce the risk of microvascular disease
- In type I DM, glycemic control to a goal of < 7% reduces CVD events
- This is not as clear for type II DM especially in patients with long standing DM
- More stringent glycemic control to achieve lower levels is not helpful and can be harmful (U-shaped relationship)

CAD AND DIABETES

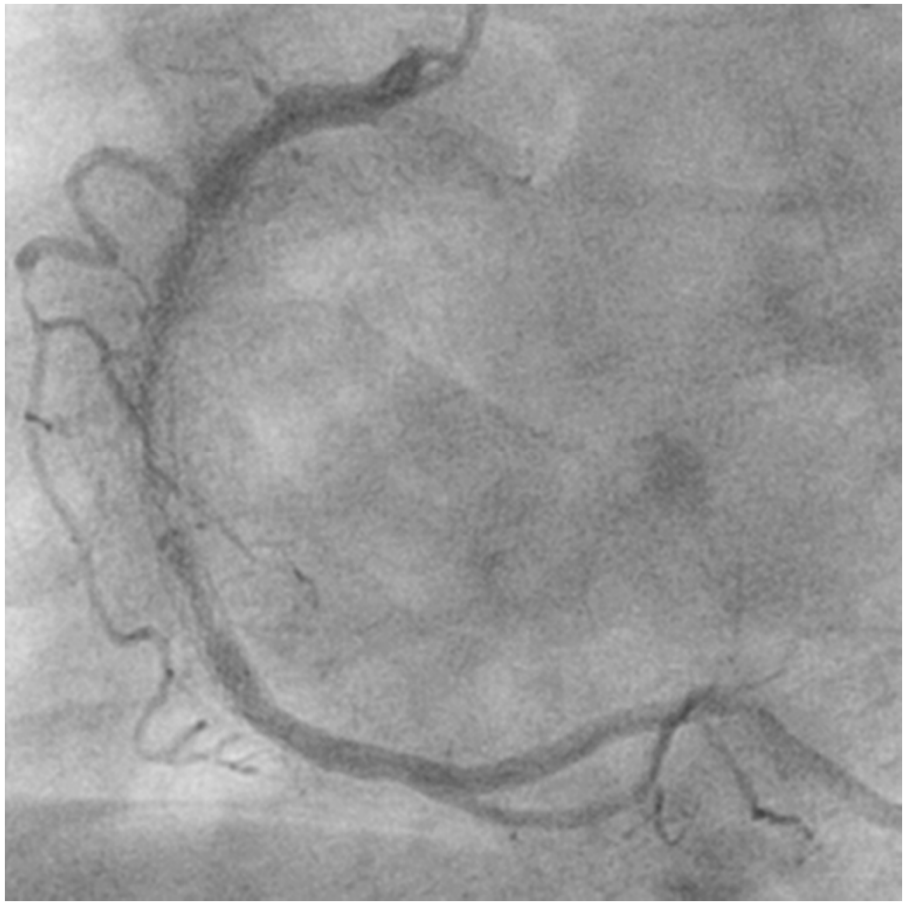
CAD and DM

- Diabetic patients with CAD have a lower long-term survival than nondiabetic patients
- Pts with DM comprise 25-30% of those who undergo revascularization
- Revascularization short and long term outcomes with PCI or CABG are worse in diabetics

PCI in Diabetics

- Higher rates of complications such as AKI
- Higher rates of in-stent restenosis
- Higher rates of disease progression
- Results are worse in patients with small vessels and more diffuse disease (such as multivessel CAD)
- In the SYNTAX trial (complex CAD) the rate of repeat revascularization at 5 yrs was higher in diabetics (29% vs. 19%)
- Second generation DES offer significant benefit over BMS and first generation DES

In-Stent Restenosis



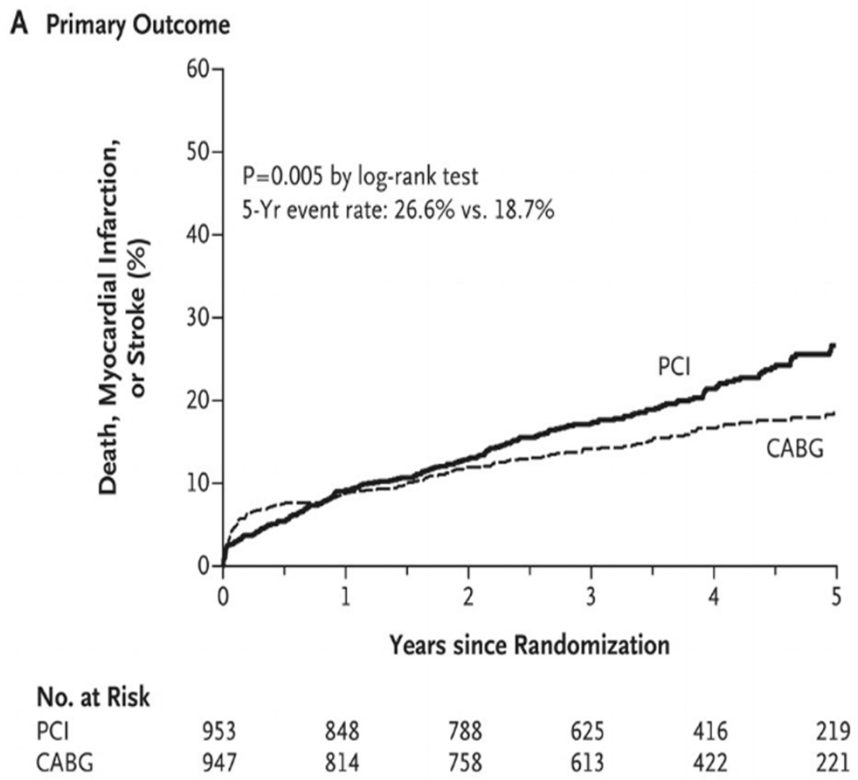
CABG in Diabetics

- Short- and long-term survival after CABG are significantly reduced in diabetic pts but no increase of in-hospital mortality
- Higher risk of renal failure and wound infection
- The risk of wound infection may be higher with bilateral IMA use

PCI vs. CABG

- PCI is the preferred method of revascularization in single vessel or simple 2 vessel disease
- Long debate about the optimal treatment for diabetics with multivessel CAD
- Prior observational and small studies showed similar rates of mortality and MI but higher rates of repeat revascularization with PCI
- The recent FREEDOM trial changed this position

The FREEDOM Trial



- Multicenter randomized study
- 1900 pts with DM and multivessel CAD
- Randomized to CABG or PCI with DES
- Optimal medical therapy in both arms

FREEDOM Results

Table 3. **Kaplan–Meier Estimates of Major Adverse Cardiovascular and Cerebrovascular Events at 30 Days and 12 Months after the Procedure.**

Event	30 Days after Procedure			12 Months after Procedure		
	PCI	CABG	P Value	PCI	CABG	P Value
	number (percent)			*number (percent)*		
Major adverse cardiovascular and cerebrovascular events	45 (4.8)	47 (5.2)	0.68	157 (16.8)	106 (11.8)	0.004
Death	8 (0.8)	15 (1.7)	0.12	32 (3.4)	38 (4.2)	0.35
Myocardial infarction	17 (1.8)	15 (1.7)	0.82	54 (5.8)	30 (3.4)	0.02
Stroke	3 (0.3)	16 (1.8)	0.002	8 (0.9)	17 (1.9)	0.06
Repeat revascularization	31 (3.3)	10 (1.1)	0.002	117 (12.6)	42 (4.8)	<0.001

PAD AND DIABETES

PAD and DM

- PAD is a very prevalent disease especially in diabetics and the elderly
- PAD is underdiagnosed
- Most pts with PAD are asymptomatic or have atypical claudication symptoms
- The presence of PAD predicts future CVD events

PAD and DM

- Ask about symptoms of claudication (typical or atypical). High level of suspicion is needed
- Foot exam including pulse examination should be done at every visit
- ABI should be considered in the following pts
  - Abnormal lower extremity pulse exam
  - Known atherosclerosis (CAD, carotid, renal artery disease)
  - Symptoms
  - Age 50-59 with history of Diabetes or smoking
  - Age >40 with diabetes and at least one other risk factor

Critical Limb Ischemia

- This occurs in 1-2% of patients with PAD and is more common in diabetics and smokers

- Critical limb ischemia is considered to be present if:
  - Resting ischemic pain
  - Non-healing or slowly healing ulceration in the setting of severe PAD
  - Dry or wet gangrene

- If revascularization is not possible then amputation is usually needed

- Percutaneous or surgical revascularization

CARDIOVASCULAR EFFECTS OF HYPOGLYCEMIC AGENTS

Metformin

- There is significant debate whether metformin has cardiovascular benefits
- Metformin can reduce BP modestly although this effect is not proven (inconsistent results from studies)
- Metformin has a favorable effect on lipid profile
  - Reduces TGs (likely related to lower glucose levels)
  - Mild reduction in LDL
  - No significant change in HDL
- No significant effect on micro-albuminuria

Metformin

- The UKPDS demonstrated that in obese type 2 diabetics metformin reduces the risk of MI (39% reduction) more than sulfonylureas or insulin
- Metformin is not associated with weight gain and can cause some weight loss which is a clear advantage over other agents
- Has a positive effect on endothelial dysfunction and coagulation abnormalities
- **In summary, data indicate a possible favorable effect on cardiovascular outcomes**

Sulfonylureas

- Some studies suggest that sulfonylureas may be associated with poorer outcomes after an MI
- First generation sulfonylureas are associated with worse cardiac outcomes compared to metformin
- This can be related to the effect on the ATP-dependent K channels in the heart
- Newer agents which are selective for the pancreatic receptors (gliclazide and glimepiride) do not appear to have a negative effect but some concern still exists

Meglitinides

- There are no long-term studies of meglitinides to assess cardiovascular outcomes or mortality
- Since the mode of action is similar to sulfonylureas, the same concern exists
- The main side effect is hypoglycemia which appears to have a negative effect on cardiovascular outcomes

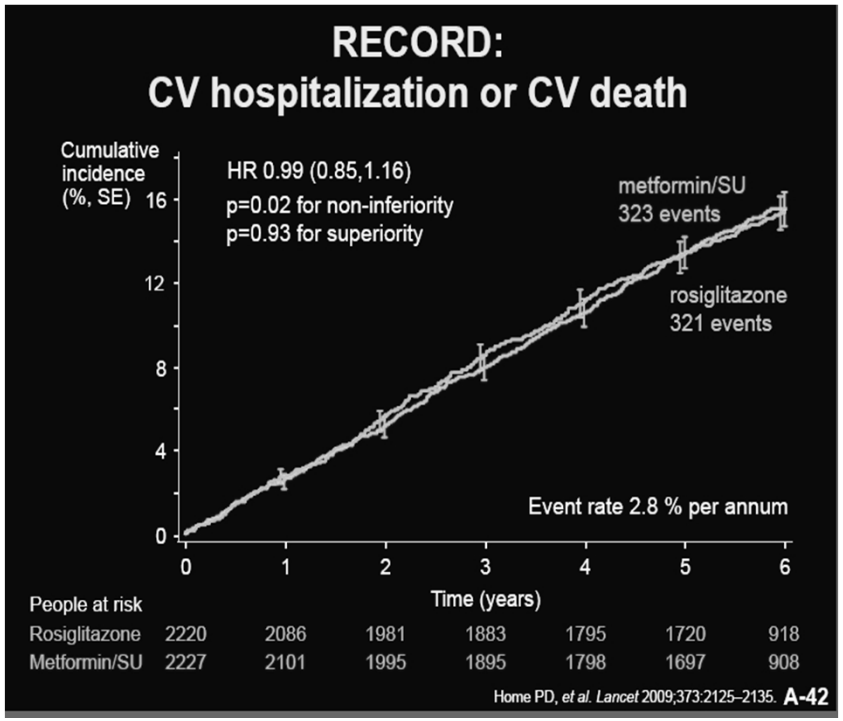
Thiazolidinediones

- Favorable effect on BP
- Reduction of albuminuria
- Improvement in endothelial function
- Some anti-inflammatory action with reduction in CRP and TNF-@

Thiazolidinediones

- Rosiglitazone and pioglitazone have similar effects on glycemic control but their effects on serum lipid concentrations are different
- Pioglitazone exerts a less unfavorable effect on lipid profile
- Both agents increase the risk of heart failure and weight gain
- Rosiglitazone appears to increase the risk of MI and cardiac mortality (several observational studies and meta-analyses)

The RECORD Study



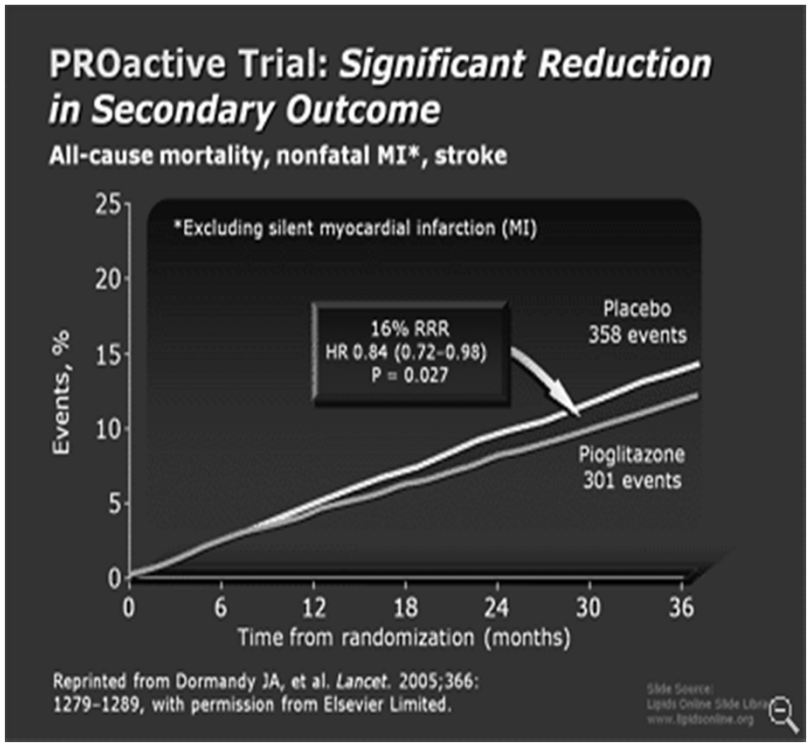
Led to reversal of restriction on rosiglitazone prescription by the FDA

- The only study designed to study the effect of rosiglitazone on cardiovascular events
- Over 4400 pts from Europe and Australia
- Mean 5.5 years of follow up
- Persistent increased risk of HF
- The risk of MI was inconclusive (HR 1.14)

Pioglitazone

- Appears to have a different risk profile than rosiglitazone
- Most studies show no difference or decrease in cardiovascular events with pioglitazone

The PROACTIVE Trial



- Specifically designed to examine the effects of pioglitazone on cardiovascular outcomes
- Over 5000 pts
- High risk for cardiovascular events (prior MI, CVA, CABG, PAD)
- The study was stopped early due to reduction in the primary endpoint
- There was increase in HF risk
- The incidence of angina was lower

Thiazolidinediones Summary

- Use of rosiglitazone is not recommended due to increased risk of HF and likely of ischemic events

- Pioglitazone is not associated with increased risk of CV events and may have a protective effect but still has risk of HF and fluid retention in addition to other non CV risks such as reduction in bone density and fractures

GLP-1 Analogs

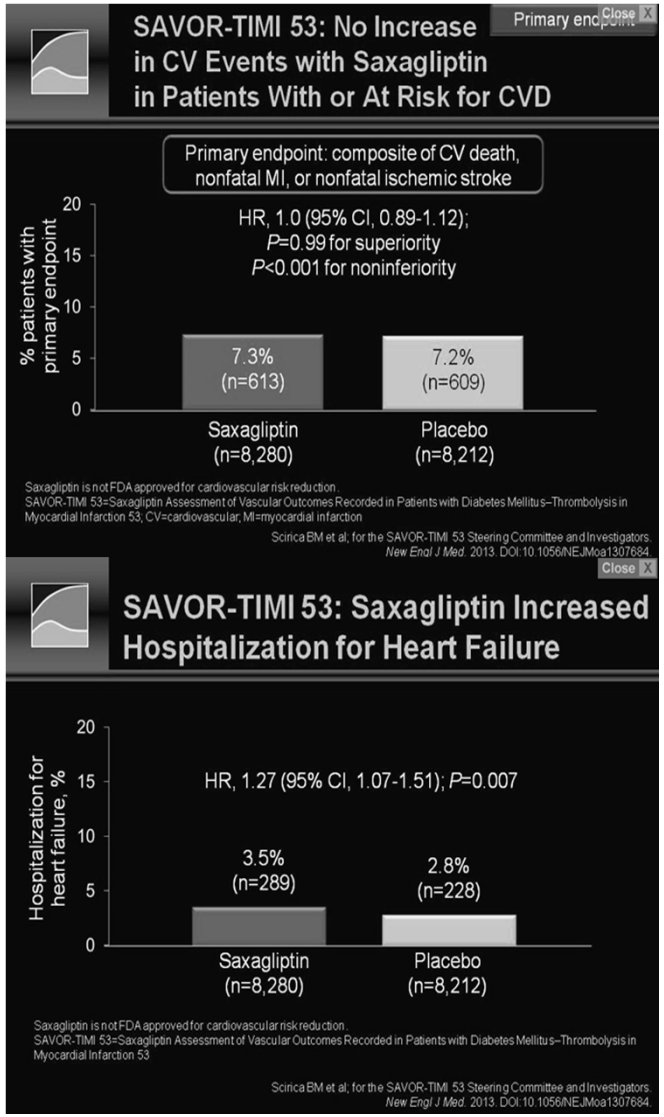
- There is no long term data on CV outcomes (large clinical trials are underway)
- The short term data are promising
- A recent meta-analysis of 37 studies with follow up at least 6 months showed:
  - MACE HR of 0.78 (not statistically significant)
  - Significant reduction in MACE in comparison to placebo and pioglitazone
  - No effect on mortality

DDP-4 Inhibitors

- Long term studies are needed to asses CV effects of these agents

- Short term studies do not show significant concern with CV safety

SAVOR-TIMI 53



- Over 16,000 pts with DM and history of CV disease or multiple risk factors
- Saxagliptin vs. placebo
- Median follow up 2.1 years
- Primary endpoint was composite of CV death, nonfatal MI and nonfatal stroke
  - N Engl J Med 2013; 369:1317-1326

Conclusion

- DM and CVD are both common and represent a high risk group of patients
- High level of suspicion for CAD and PAD is needed in diabetic patients
- Glycemic control is important in reducing microvascular complications although reduction in macrovascular complications has not been proven (very tight control can increase the risk of hypoglycemia and worsen CV risk)
- Always keep in mind the CV status when prescribing medications for diabetes (both ischemic and HF)
- There is concern with CV events with TZDs and sulfonylureas but the newer agents appear promising

Thank You

Questions???