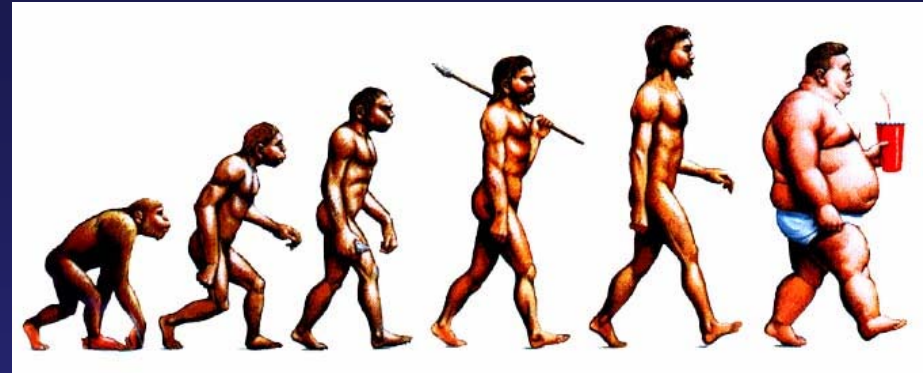# Percutaneous coronary intervention in patients with diabetes mellitus

Dr Angela Hoye
MB ChB PhD MRCP
Interventional Cardiologist
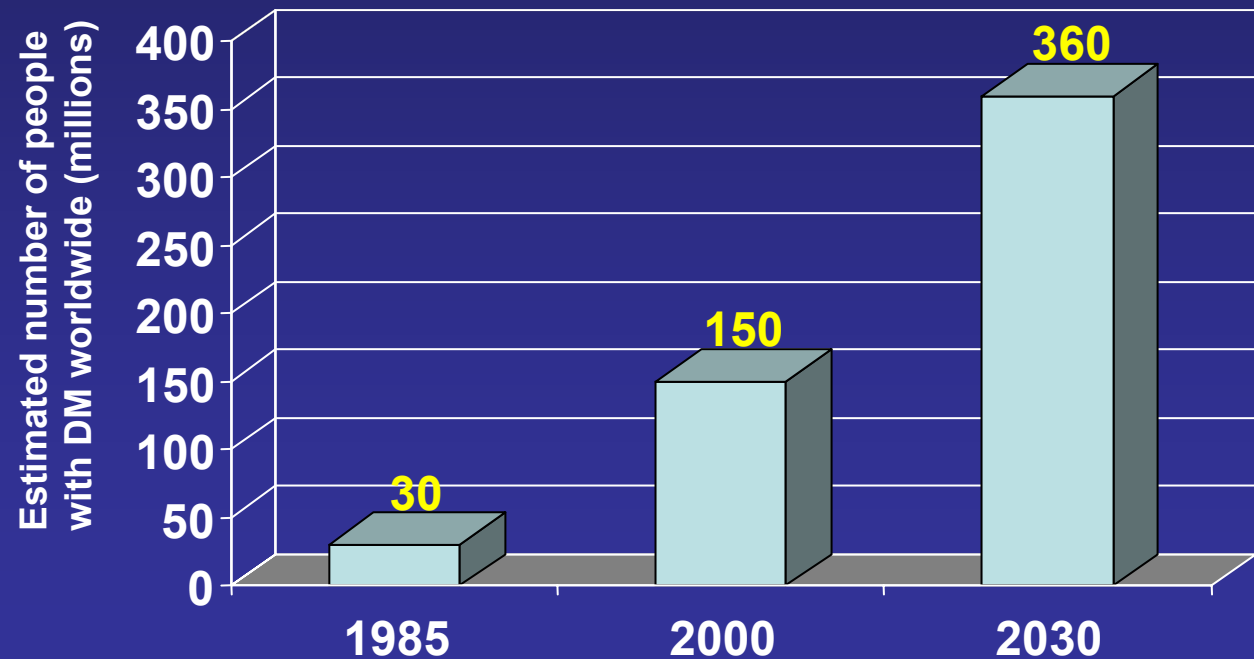**Kingston-upon-Hull, UK**

Diabetes mellitus: prevalence

The prevalence is increasing:

- within the next 25 years, the worldwide prevalence is estimated to double

Estimated number of people with DM worldwide (millions)

- 1985: 30
- 2000: 150
- 2030: 360

Wild et al Diabetes Care 2004;27:1047-53

The global burden of diabetes

Estimated top 10: Number of people with diabetes (20-79 age group), 2003 and 2025

| 2003			2025		
	Country	Persons (millions)		Country	Persons (millions)
1	India	35.5	1	India	73.5
2	China, People's Republic of	23.8	2	China, People's Republic of	46.1
3	USA	16.0	3	USA	23.1
4	Russia	9.7	4	Pakistan	11.6
5	Japan	6.7	5	Russia	10.7
6	Germany	6.3	6	Brazil	10.7
7	Pakistan	6.2	7	Mexico	9.0
8	Brazil	5.7	8	Egypt	7.8
9	Mexico	4.4	9	Japan	7.1
10	Egypt	3.9	10	Germany	7.1

- **Patients with DM have a 2-4x increased risk of cardiovascular disease and a significantly shorter life expectancy**

- **Cardiovascular disease is responsible for 75-80% deaths in diabetic patients**

Source: International Diabetes Federation

Complex coronary disease

- **Multivessel disease**
- **Diffuse disease**
- **Small vessel disease**
- **Distal disease**
- **Calcification**
- **Impaired left ventricular function**
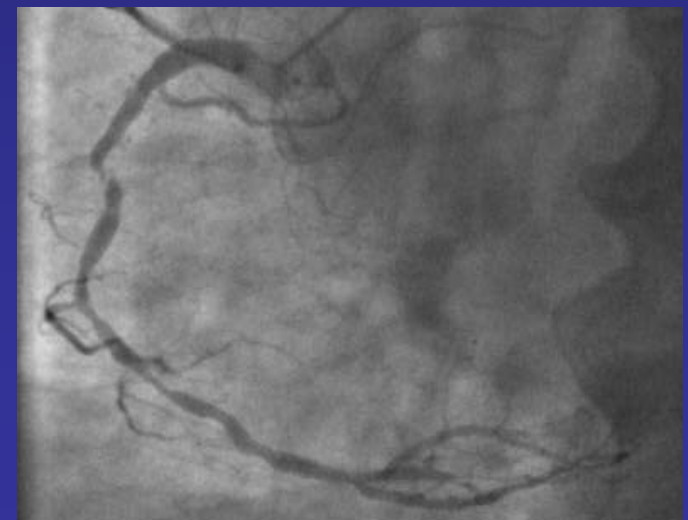
Pathophysiology

- **Atherogenic dyslipidemia**
  - high triglyceride levels: enhanced thrombogenicity, remnant triglyceride-rich lipoproteins
  - small dense LDL particles: increased penetration of arterial intima, enhanced proteoglycan binding, increased oxidation potential
  - low HDL cholesterol: reduced antioxidant and anti-inflammatory activity

- **Impaired endothelial function** - decreased nitric oxide, increased endothelin-1 and angiotensin II increases vascular tone and smooth muscle cell migration and growth

Pathophysiology

- **Prothrombotic milieu** –
  - increased platelet activation:
    - (increased number of circulating platelets, decreased platelet cAMP, increased GP IIb/IIIa receptor density, increased vitronectin circulating fibrinogen and thrombin / antithrombin II complexes, increased P-selectin)
  - coagulation cascade activation:
    - (increased fibrinogen, increased von Willebrand factor, increased FPA (increased thrombin activity), decreased activity of AT III, decreased sulfation of endogenous heparin)
  - impaired fibrinolysis:
    - (increased plasminogen activator inhibitor-1 synthesis, (directly increased by insulin & IGF-1, decreased concentration of alpha-2 antiplasmin

Prognosis of patients with DM and coronary artery disease

- **5-year survival curves for 3320 patients (24% diabetic) treated at Duke Medical Center, for multivessel disease**

Barsness et al Circulation 1997
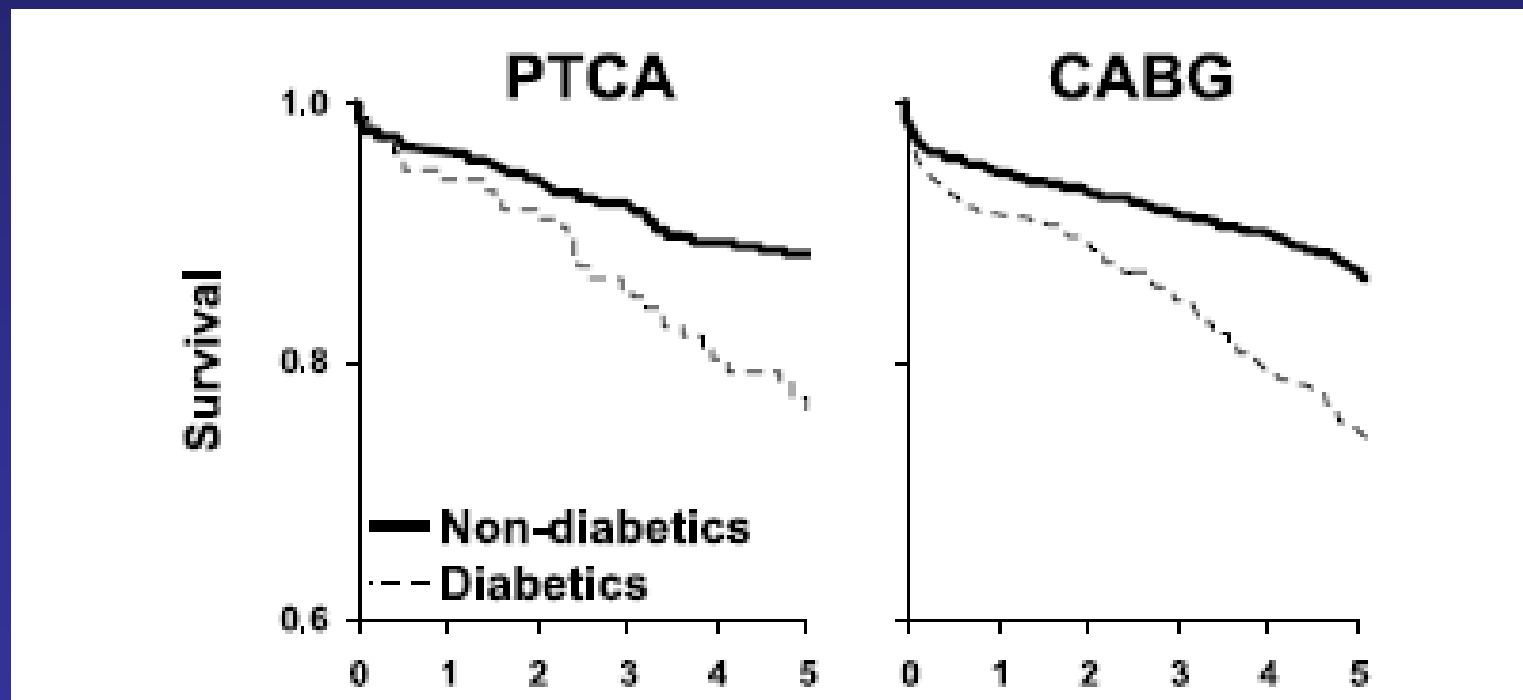
MACE following PCI in diabetic patients

- **Diabetic patients have higher rates of MACE**

- **Diabetes increases restenosis**
  - **?increased rates if on insulin therapy**

- **Diabetes is an independent predictor of TLR**

Gilbert et al Diabetes Care 2004;27:990-994, Cutlip et al JACC 2002;40:2082-9, Lemos et al Circulation 2004;109:1366-1370

Worse prognosis in ACS

- **GRACE registry: prospective multicenter study of patients with ACS**
 - diabetic versus non-diabetic pts

In-hospital outcomes	STEMI		NSTEMI		Unstable angina	
	DM	**Non-DM**	**DM**	**Non-DM**	**DM**	**Non-DM**
n	**1141**	**4262**	**1271**	**3454**	**1489**	**4499**
Death	1.48 (1.03-2.13)		1.14 (0.85-1.52)		1.41 (1.02-1.95)	
Cardiogenic shock	1.08 (0.76-1.53)		1.09 (0.79-1.50)		1.33 (0.88-2.02)	
Heart failure	1.74 (1.43-2.11)		1.88 (1.60-2.21)		1.80 (1.50-2.18)	
Renal failure	1.50 (1.00-2.23)		1.72 (1.32-2.25)		2.12 (1.45-3.08)	

Franklin et al Arch Int Med 2004;164:1457-1463

Worse prognosis with AMI

- **VALIANT study of 14,703 patients with AMI**
  - **Known DM (n=3,400 23%)**
  - **Newly diagnosed DM (n=580, 4%)**
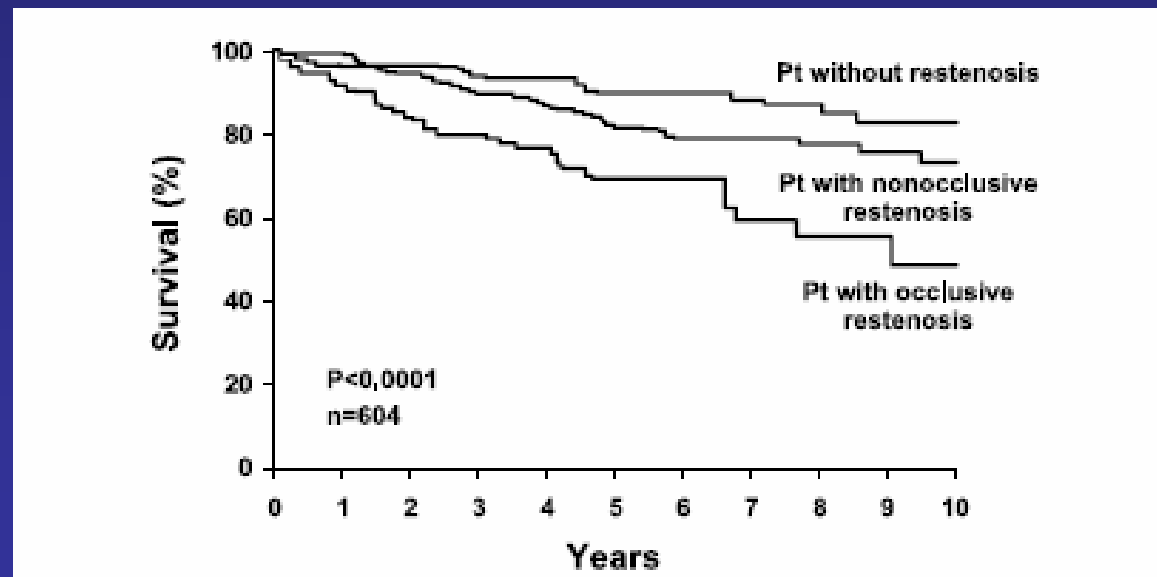 - **No DM (n=10,719)**
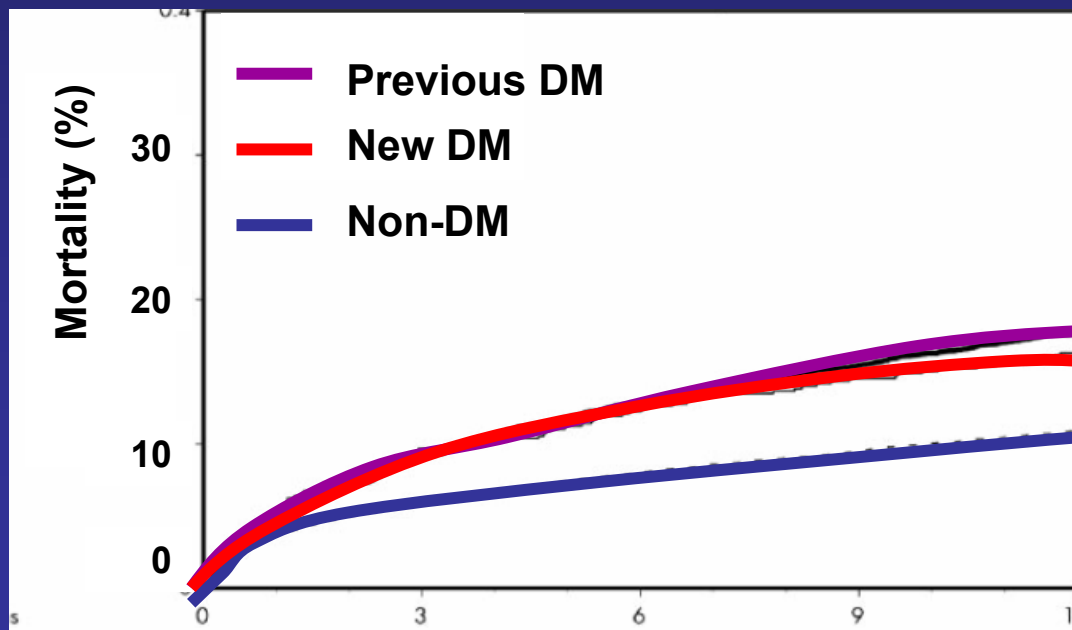
Survival at 1 year by diabetic status

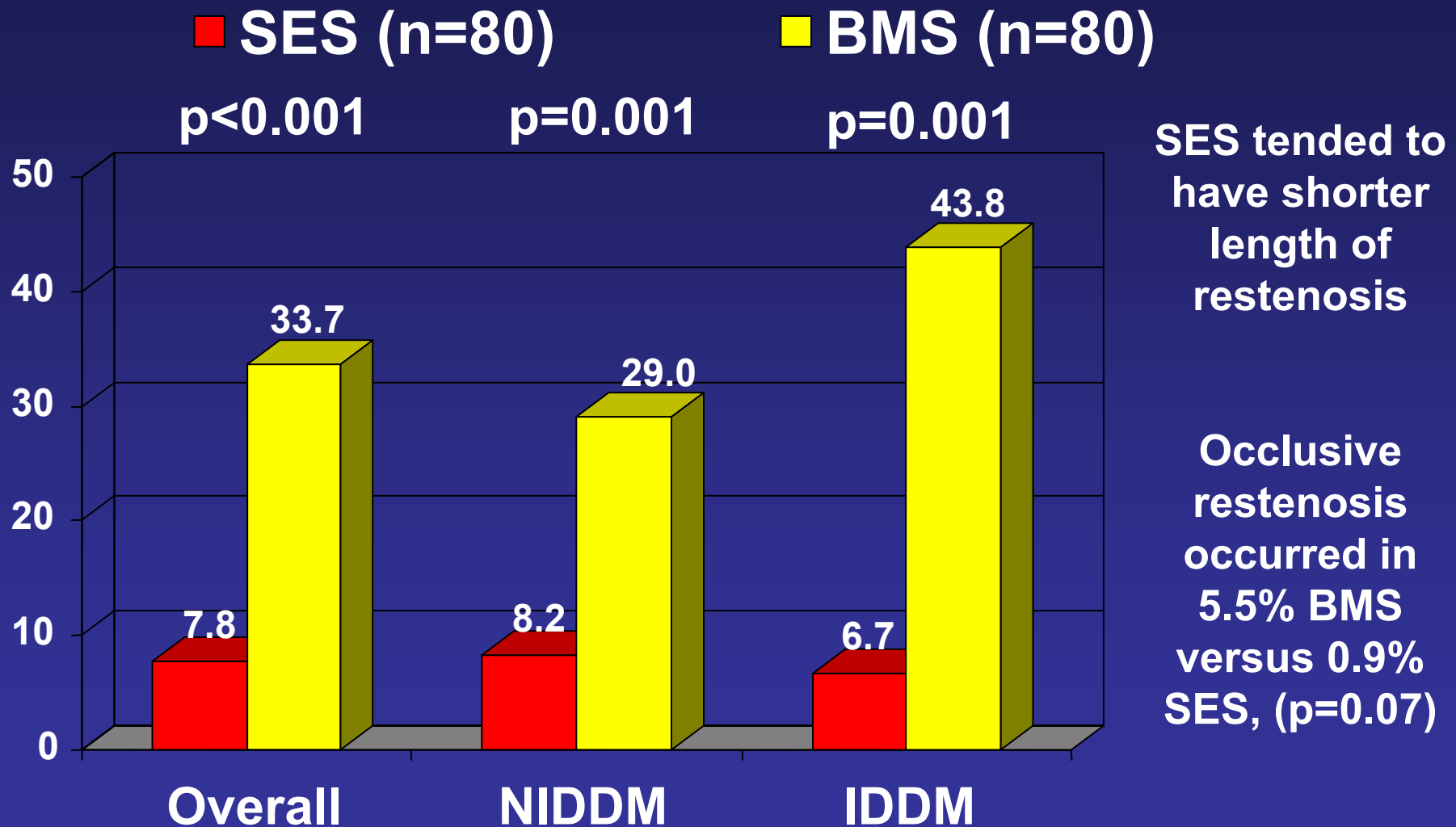p<0.001 for previous DM vs no DM

p<0.001 for new DM vs no DM

p=0.43 for previous DM vs new DM

Aguilar et al Circulation 2004;110:1572-78

Prognosis of patients with DM and coronary artery disease

- **Long-term survival rates of 604 diabetic patients following successful balloon angioplasty**
- **Stratified according to the results of follow-up angiography at 6-months**
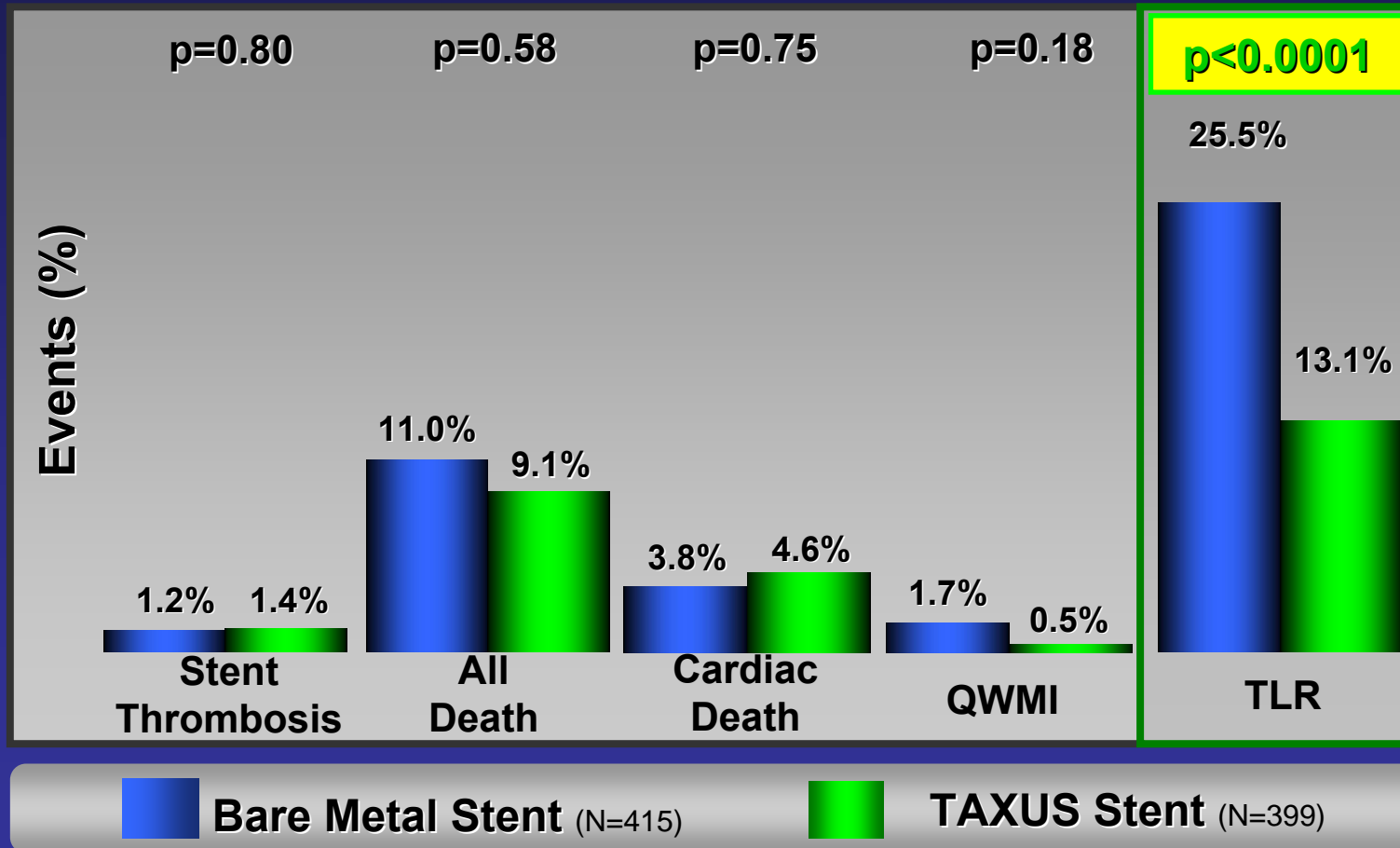
DIABETES trial: in-segment restenosis rate at 9-months

■ SES (n=80)   ■ BMS (n=80)

p<0.001   p=0.001   p=0.001

SES tended to have shorter length of restenosis

Occlusive restenosis occurred in 5.5% BMS versus 0.9% SES, (p=0.07)

Overall: SES 7.8, BMS 33.7
NIDDM: SES 8.2, BMS 29.0
IDDM: SES 6.7, BMS 43.8

Sabate et al Circulation 2005;112:2175-2183

DIABETES trial: clinical outcomes at 9-months

	SES n=80	BMS n=80	p value
Death, n (%)	1 (1.3)	2 (2.5)	ns
Q-MI, n (%)	1 (1.3)	0	ns
Non-Q MI, n (%)	1 (1.3)	5 (6.3)	ns
TLR, n (%)	5 (6.3)	25 (31.3)	<0.0001
MACE, n (%)	8 (10.0)	29 (36.3)	<0.0001

TAXUS™ Stent in diabetics

TAXUS 4 yr meta-analysis: All Diabetics
TAXUS II[1] (4 yr) , IV[2] (4 yr), V[3] (2yr), VI[4] (3 yr) studies (N=814)

p=0.80   p=0.58   p=0.75   p=0.18   **p<0.0001**

Events (%)

25.5%
13.1%
11.0%
9.1%
3.8%   4.6%
1.7%
0.5%
1.2%   1.4%

Stent Thrombosis   All Death   Cardiac Death   QWMI   TLR

Bare Metal Stent (N=415)   **TAXUS Stent** (N=399)

Prothrombotic milieu: increased risk of stent thrombosis

- **Independent predictors of stent thrombosis**
- **2229 pts undergoing "real world" DES implantation**

Predictor	HR (95% CI)	P value
Premature APT discontinuation	89.78 (29.90-269.60)	<0.001
Renal failure	6.49 (2.60-16.15)	<0.001
Bifurcation lesion	6.42 (2.93-14.07)	<0.001
Diabetes	3.71 (1.74-7.89)	0.001
LV EF per 10% decrease	1.09 (1.05-1.13)	<0.001

Prothrombotic milieu: increased risk of stent thrombosis

- **8,146 patients treated with DES implantation (SES, n=3823, PES n=4323)**

- **Angiographically confirmed stent thrombosis occurred in 152 patients (cumulative incidence at 3 years 2.9%)**

- **Independent predictors of stent thrombosis**
  - **ACS at presentation (HR 2.28, 95% CI 1.29-4.03)**
  - **Diabetes (HR 2.03, 95% CI 1.07-3.83)**

Anti-platelet therapy

- **Diabetic platelets are different!**
  - Platelets have reduced membrane fluidity perhaps reflecting glycation of membrane proteins, and also related to increased intracellular calcium mobilization
  - Arachidonic acid metabolism is increased, leading to enhanced thromboxane A2 production
  - Reduced intracellular magnesium concentration – consistent with increased platelet hyperaggregability and adhesiveness
  - Diabetic platelets produce less NO (platelets contains less NO synthase) and prostacyclin, which normally inhibit platelet-endothelium interactions and promote endothelium-mediated vasodilation
  - Platelets have increased expression of activation-dependent adhesion molecules eg GPIIb/IIIa, thrombospondin, and P-selectin
  - Patients with DM have a greater rate of platelet turnover

GPIIb/IIIa inhibitor use in diabetic patients with ACS

- **6,458 diabetic patients**

  - GPIIb/IIIa inhibitor use reduced 30-day mortality (4.6% versus 6.2% (OR 0.74; 95% CI 0.59-0.92, p=0.007))

  - 1,279 diabetic patients had PCI during index admission, in this subgroup, GPIIb/IIIa inhibitor use reduced 30-day mortality (1.2% versus 4.0% (OR 0.30; 95% CI 0.14-0.69, p=0.002))

Roffi et al Circulation 2001;104:2767-2771
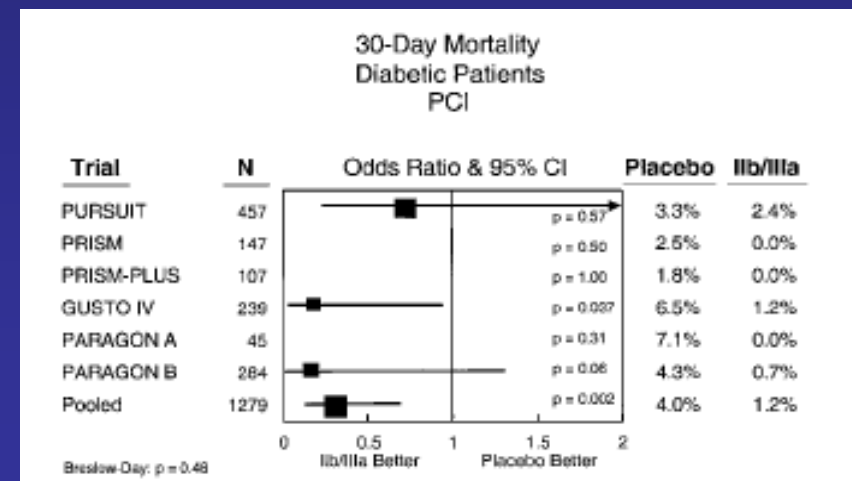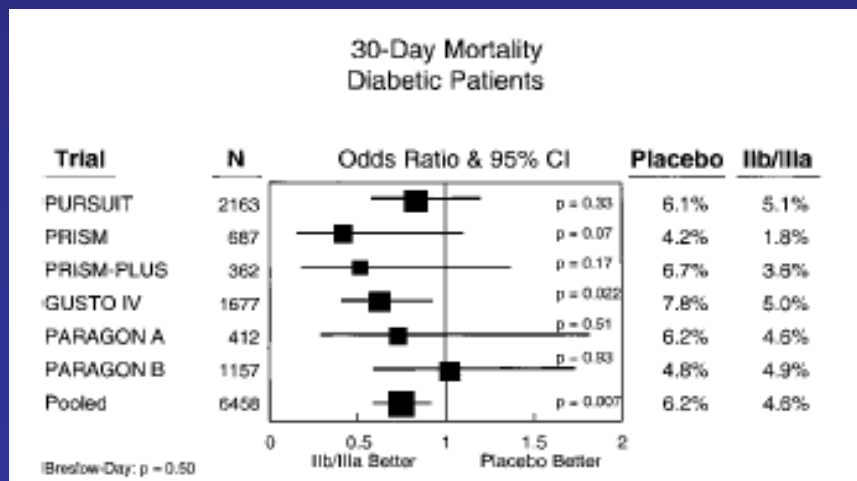
GPIIb/IIIa inhibitor use in DM: abciximab

- **Pooled data from EPIC, EPILOG, and EPISTENT**
- **Abciximab versus placebo in patients undergoing elective or urgent PCI**
- **1,462 patients with DM**
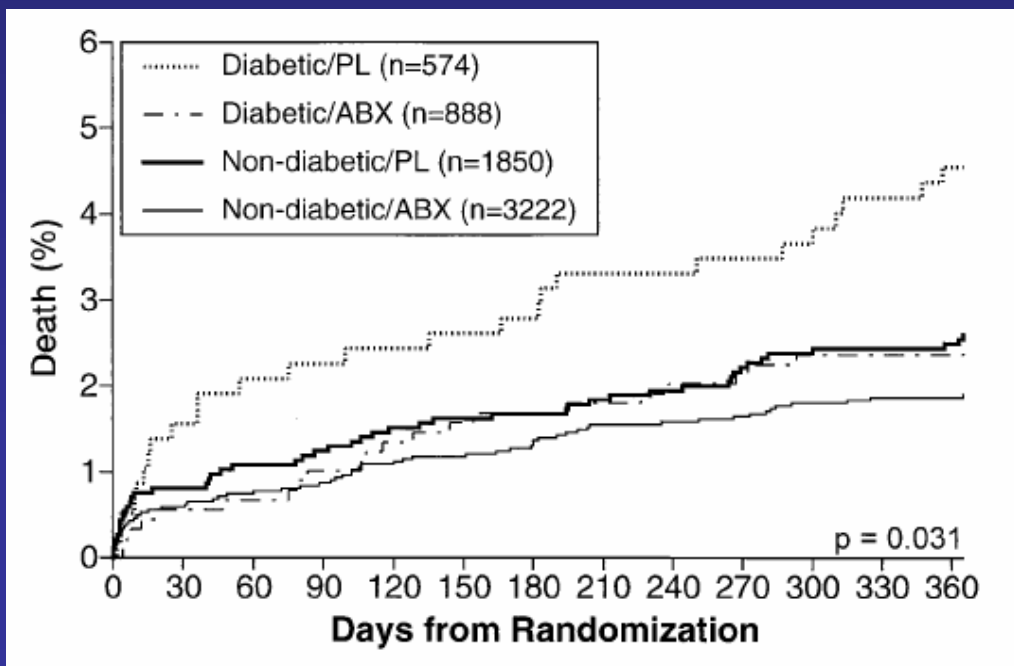
- **Abciximab reduced mortality from 4.5% to 2.5%, p=0.03**

Bhatt et al JACC 2000;35:922-8

OPTIMUS

- **Type 2 diabetics (n=40) with CAD and previous PCI, with a suboptimal response to clopidogrel**
- **Randomised to 150mg od versus 75mg od clopidogrel, with assessment of platelet function**

- **Inhibition of late platelet aggregation between baseline and at 30 days, assessed after 30μmol/L and 5 μmol/L ADP**
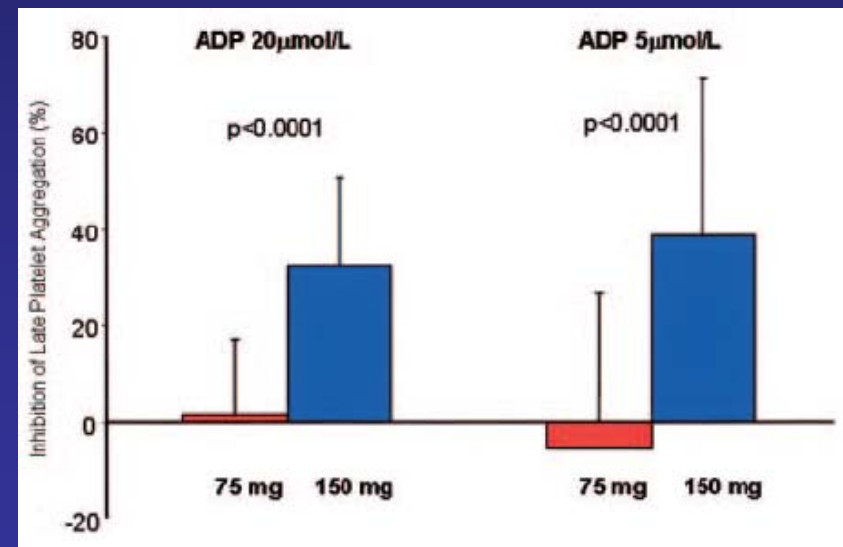
Angiolillo et al Circulation 2007;115:708-716
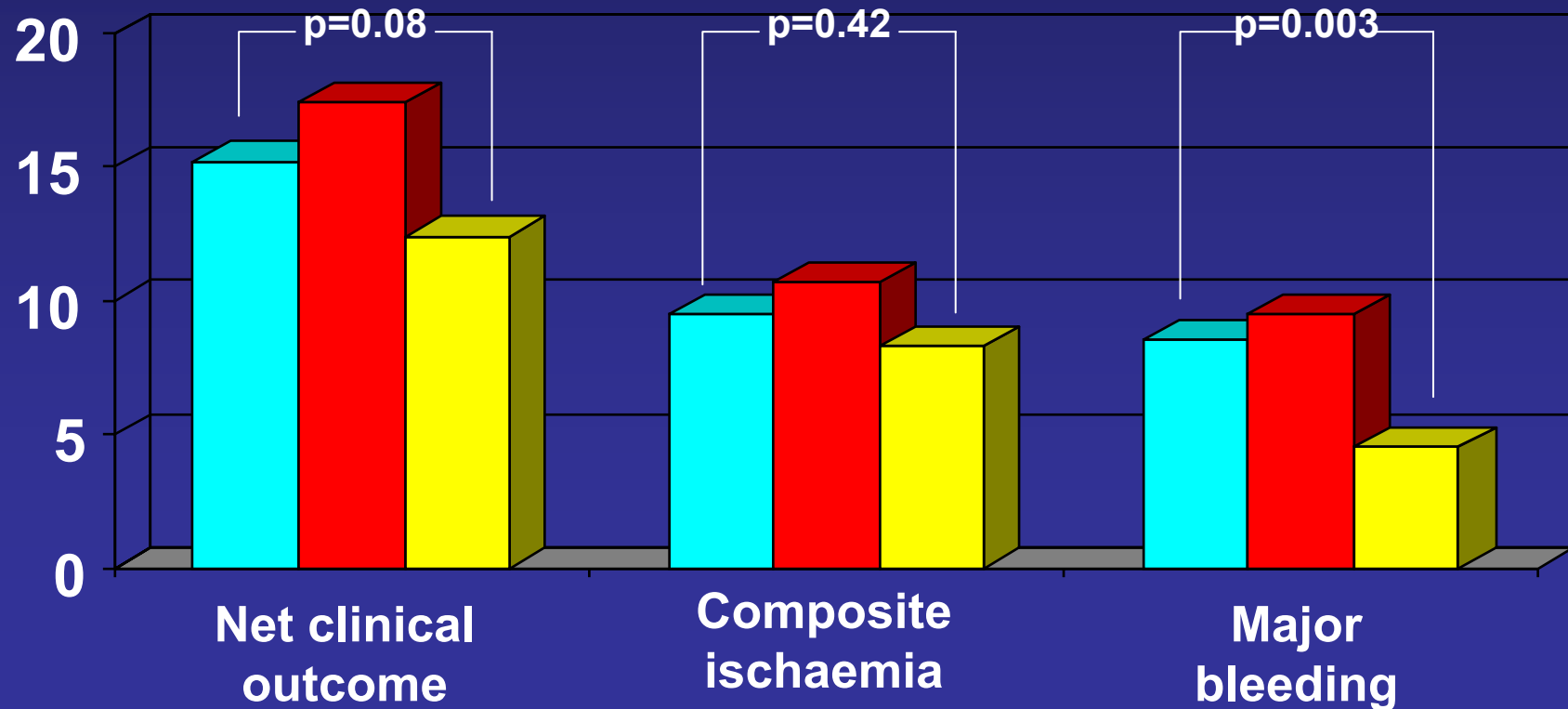
The importance of glycemic control

- **160 patients with DM randomised to conventional therapy vs intensive therapy of cardiovascular risk factors**
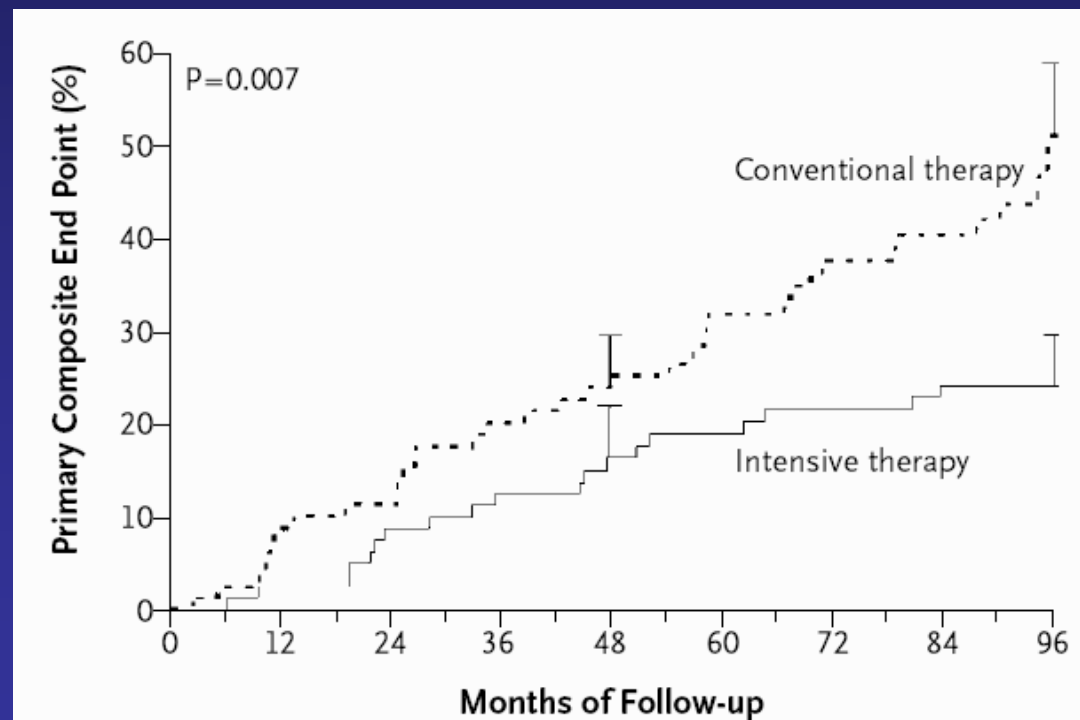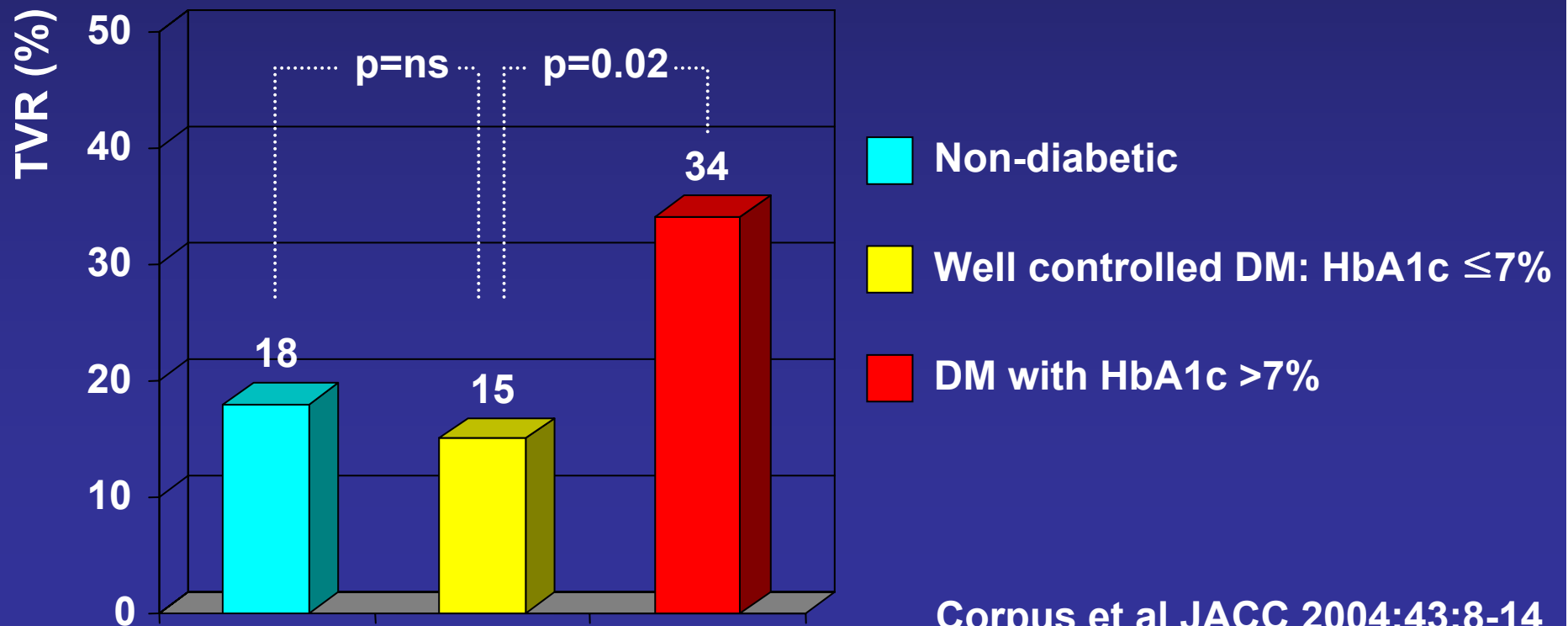

  - **Bp**
  - **Lipids**
  - **Diet**
  - **HbA1c**

- **Primary endpoint was composite of death, MI, stroke, revascularisation, amputation**

Gaede et al NEJM 2003;348:383-93

Fluvastatin after PCI: LIPS study

- **DM n=202, no DM n=1475**
- **Fluvastatin 80mg od versus placebo**
- **MACE: death, MI, reintervention**

➢ **Diabetes increased the rate of MACE almost 2-fold in patients treated with placebo (RR 1.78, 95% CI:1.20-2.64, p=0.0045)**

➢ **However, in diabetic patients, fluvastatin reduced the risk of MACE by 51% (p=0.009)**

Legend: No diabetes - placebo (n = 751); No diabetes - fluvastatin (n = 724); Diabetes - placebo (n = 82); Diabetes - fluvastatin (n = 120). Y-axis: Patients without event (%). X-axis: Time (years).

Arampatzis et al AHJ 2005;149:329-35

The CARDia Trial

- **Multi-centre, randomised, prospective study of revascularization in diabetics in the UK**
- **Multivessel disease or complex single vessel disease**
- **DES (with abciximab) versus CABG (use of LIMA, on or off pump)**
- **Evaluation of 600 patients (so far recruited approx 90%)**
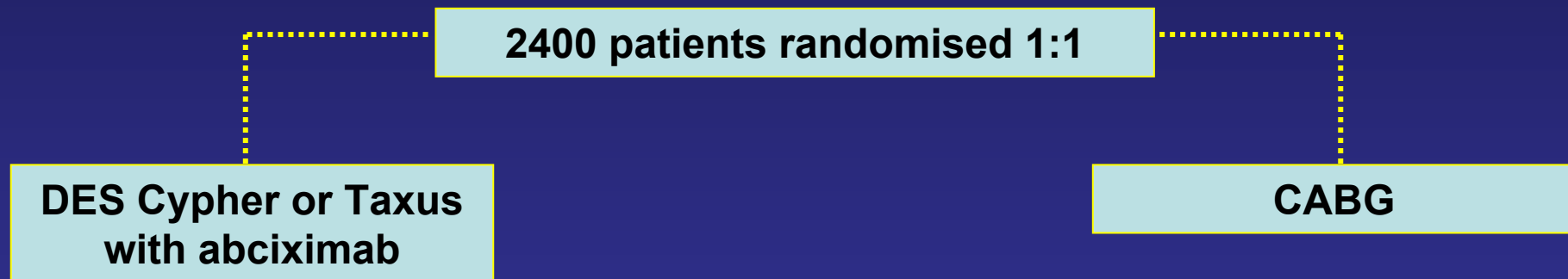- **Primary endpoint: composite of death, AMI, or stroke at 1 year**

FREEDOM trial (sponsored by NHLBI)

DES versus CABG in diabetics with multivessel disease

PI: Valentin Fuster

Eligibility: DM patients with ≥2 vessel disease suitable for stent or surgery

Exclude: AMI and / or cardiogenic shock

2400 patients randomised 1:1

DES Cypher or Taxus with abciximab		CABG

Primary endpoint: 3 yr composite of death, AMI, or stroke

Medical therapy: HbA_{1c} **<7.0%**

target BP <130/80mmHg

target LDL <70mg/dL

All patients to receive both aspirin and clopidogrel for 1 year

Conclusions

- **Outcomes in diabetic patients are worse whether treated by PCI or CABG compared with non-diabetics**
  - **More complex disease**
  - **Less complete revascularization**
  - **Increased lesion progression**

- **DES are effective in DM, however DM remains an independent predictor of MACE and TLR**

- **Remember to optimise medical therapy**
  - **Pre-procedure eg renal function, clopidogrel loading**
  - **Peri-procedure eg GPIIb/IIIa inhibitor / bivalirudin**
  - **Post-procedure eg glycemic control, BP control**