Percutaneous coronary intervention in diabetes mellitus

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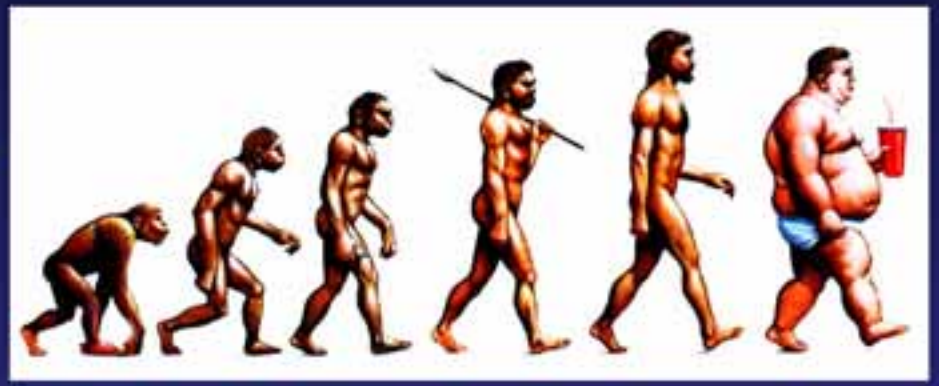
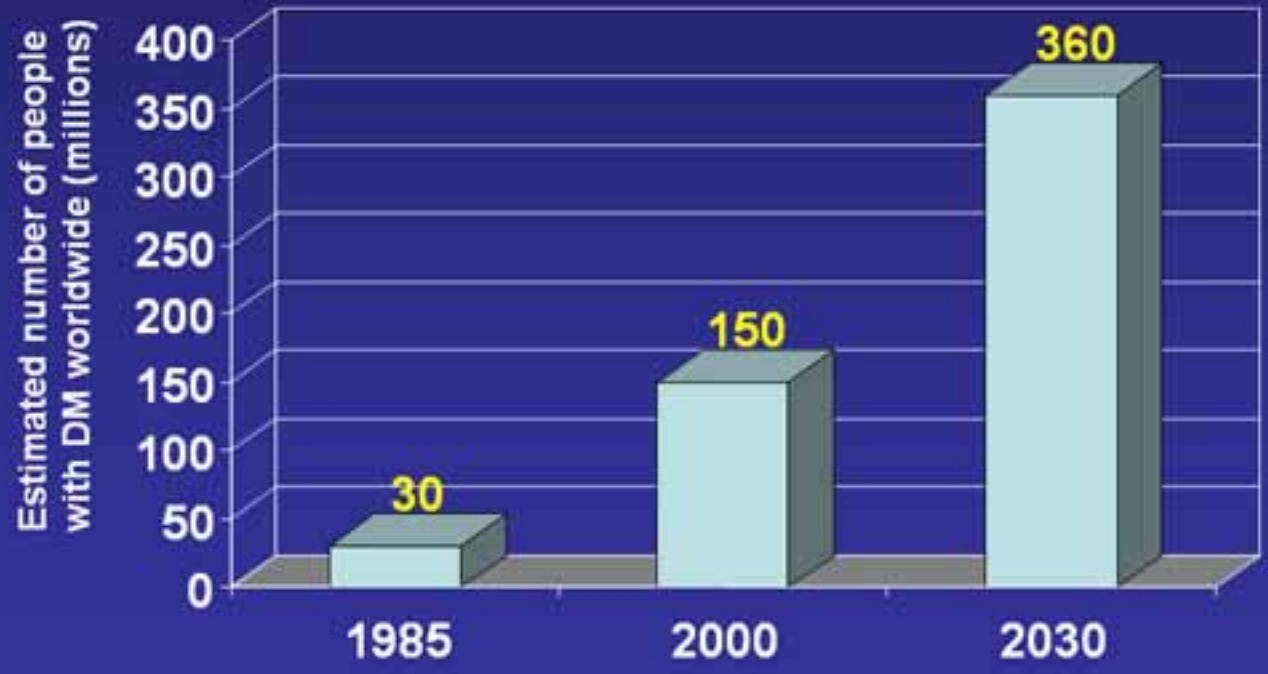
No conflicts of interest to disclose

Diabetes mellitus: prevalence

The prevalence is increasing:



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



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

Diabetes mellitus

- Cardiovascular disease is responsible for >75% deaths in diabetic patients
- Diabetic patients with clinical evidence of coronary disease have a mortality rate at 8 yrs of ~50%
- Men with DM will lose 11.6 life-years, women 14.3 life-years

Narayan et al JAMA 2003;290:1884-1890

Impaired glucose tolerance and DM

- **Atherogenic dyslipidemia** - high triglyceride levels, small dense LDL particles, low HDL cholesterol
- **Impaired endothelial function** - decreased nitric oxide, increased endothelin-1 and angiotensin II increases vascular tone and smooth muscle cell migration and growth
- **Prothrombotic milieu** - increased platelet activity, increased number of circulating platelets, increased levels of fibrinogen and factor VII, higher levels of plasminogen activator inhibitor-1, lower levels of endogenous fibrinolytic activity and antithrombin III

Complex patient group

- Older
- Hypertension
- High cholesterol
- Obesity
- Peripheral vascular disease
- Cerebrovascular disease
- Retinopathy
- Renal dysfunction – increased risk of contrast nephropathy

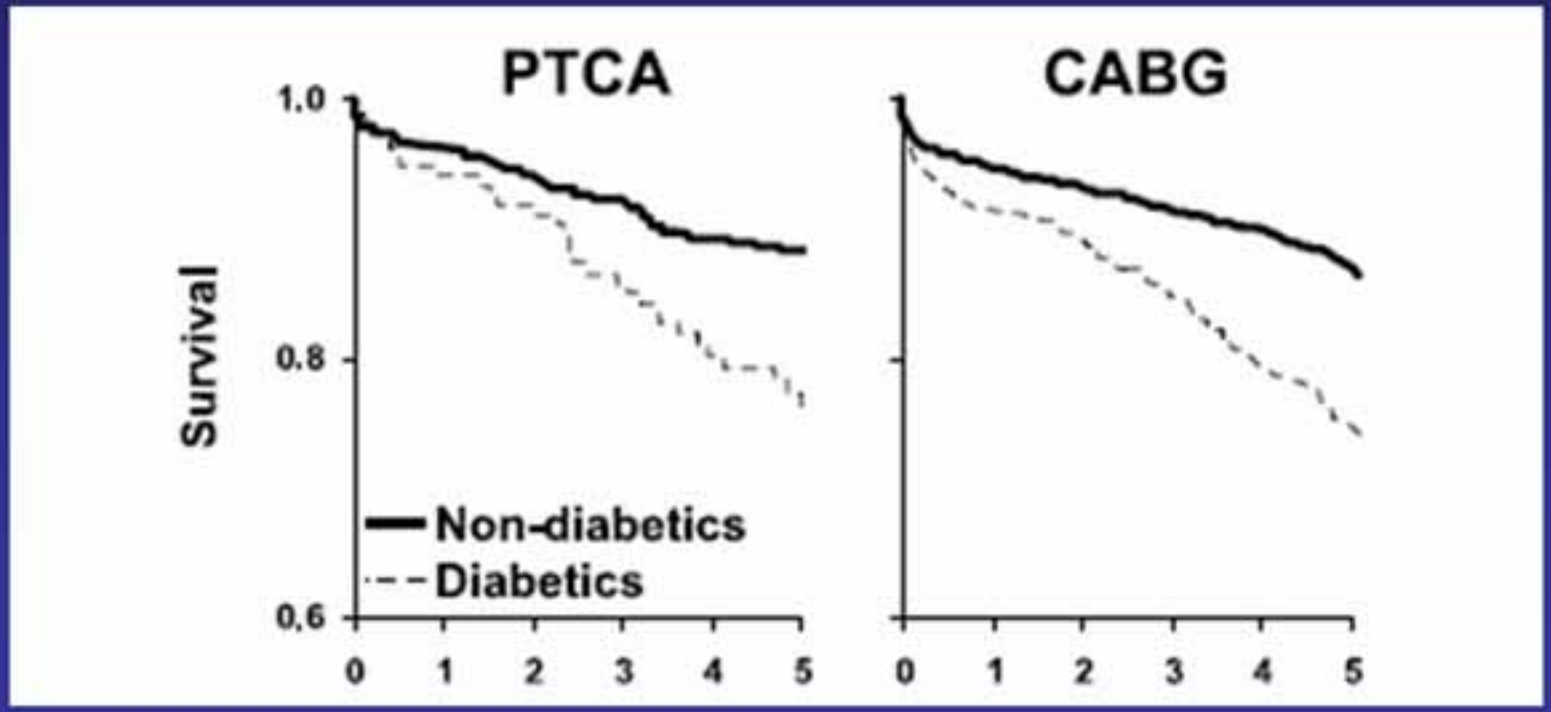
} Difficulties with vascular access

Complex coronary disease

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

Prognosis of patients with DM and coronary artery disease

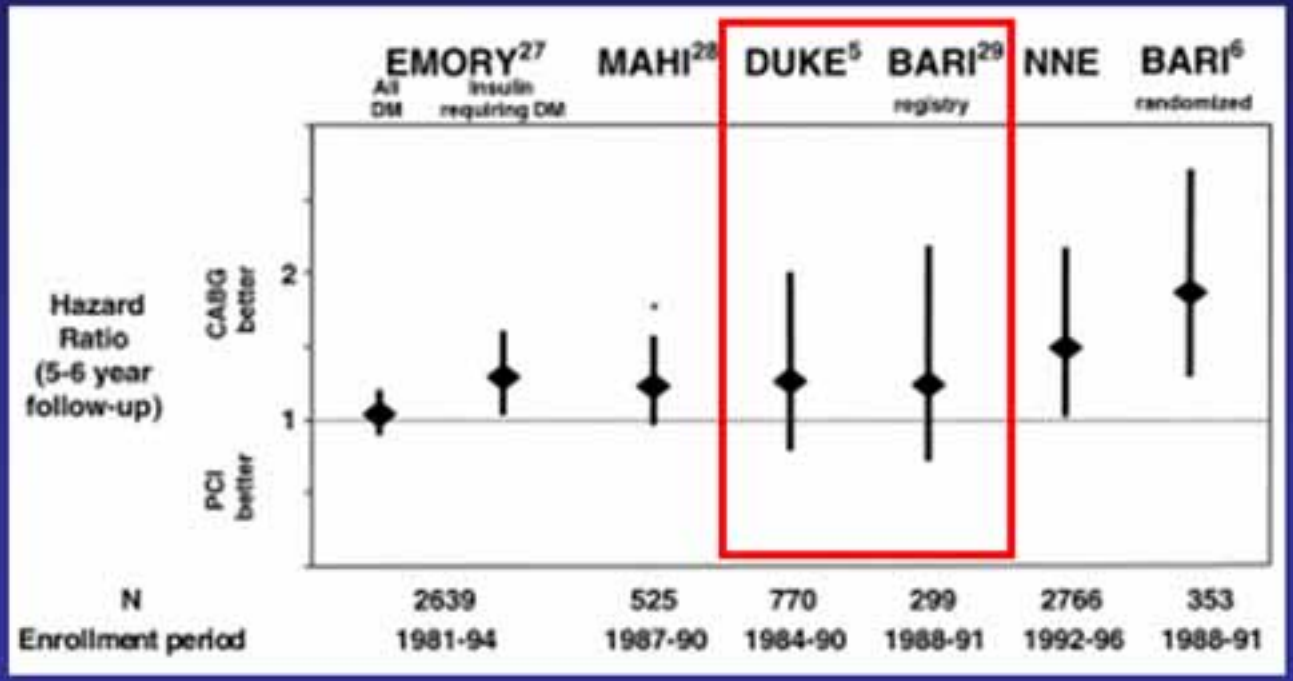
- 5-year survival curves for 3320 patients (24% diabetic) treated at Duke Medical Center, for multivessel disease



Barsness et al Circulation 1997

Historical data

- Limited due to a lack of specific randomised studies – subgroup analysis of larger studies
- Single centre experiences – real world

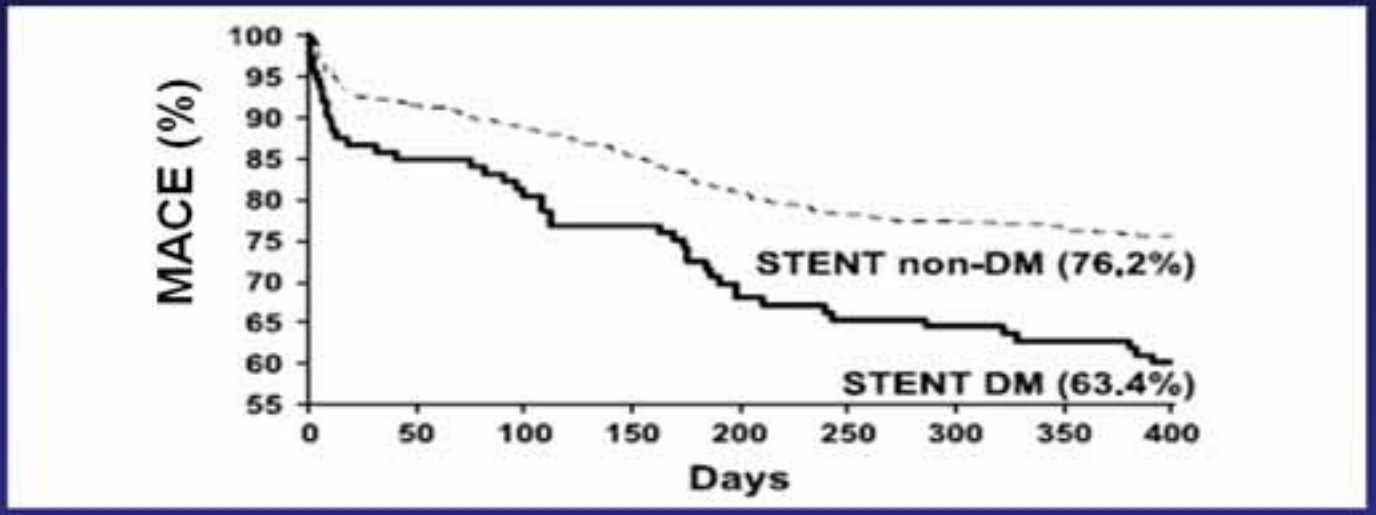


The preferred strategy - CABG

Niles et al JACC 2001;37:1008-15

MACE following PCI in diabetic patients

- ARTS I:*

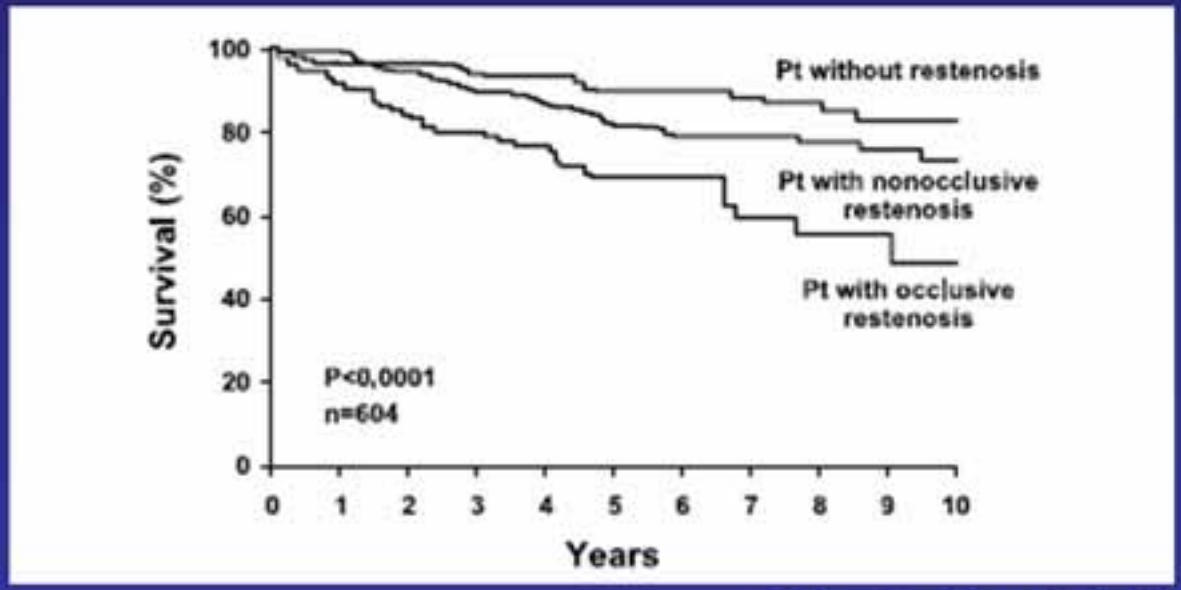


- Diabetes increases restenosis
- Meta-analysis of 6236 patients** following coronary stenting (1,166 with DM), restenosis occurred in 37% versus 26%, p<0.01
- Increased rates if on insulin therapy

*Abizaid et al Circulation 2001
**Gilbert et al Diabetes Care 2004

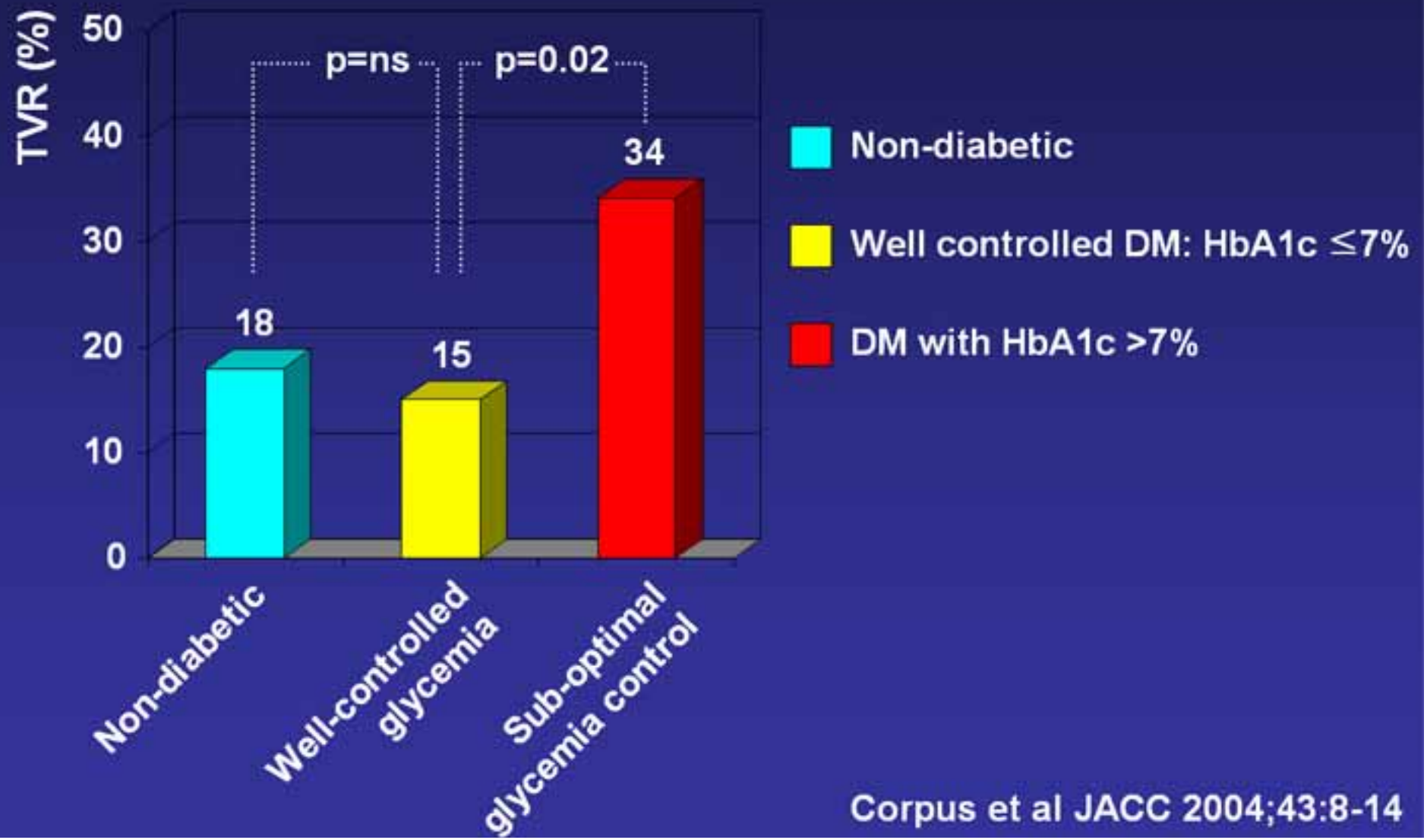
Prognosis of patients with DM and coronary artery disease

- Long-term survival rates of 604 diabetic patients following successful balloon angioplasty
- Stratified according to the results of follow-up angiography at 6-months



Van Belle et al Circulation 2001

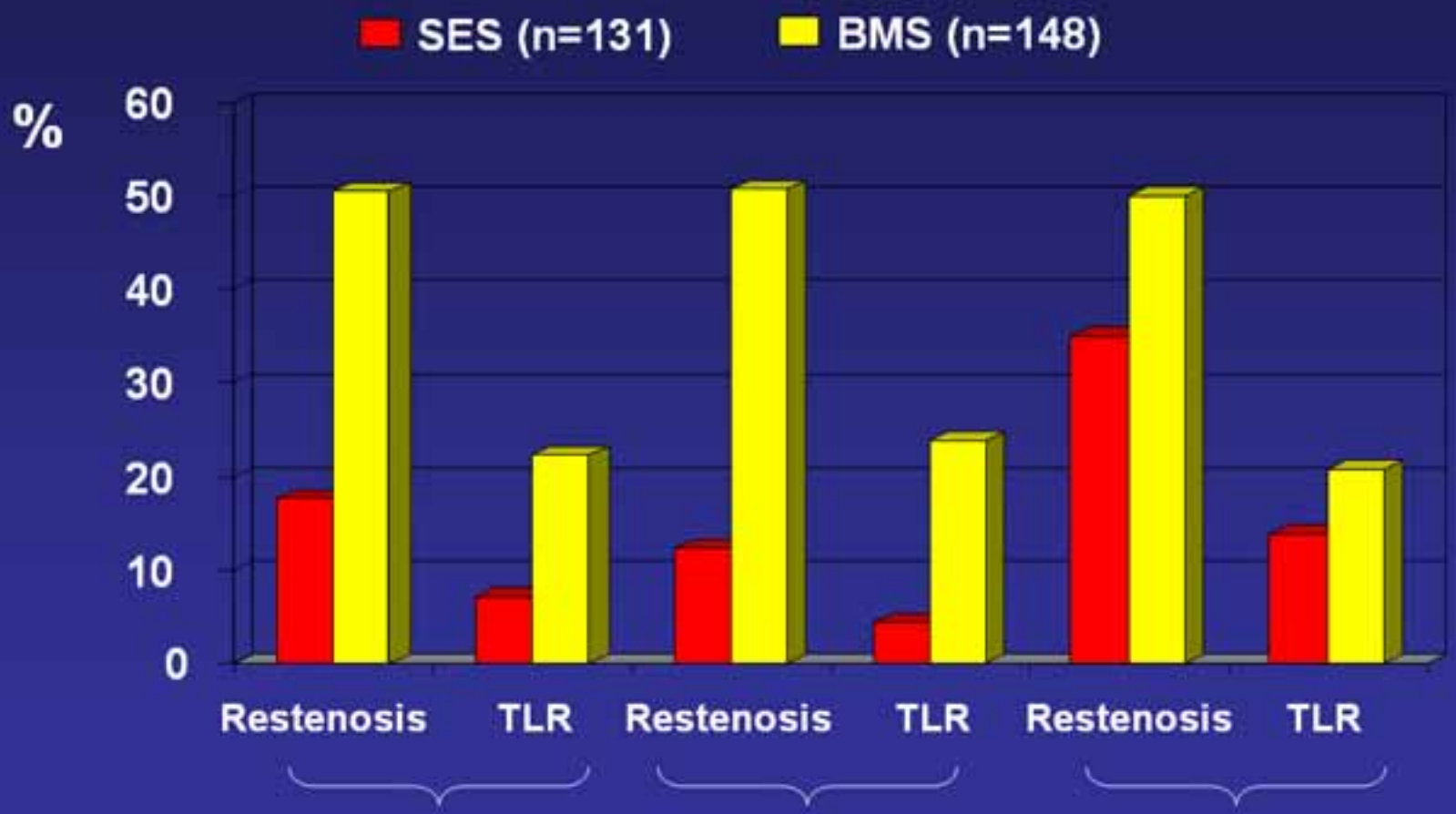
Glycemic control and target vessel revascularization



Corpus et al JACC 2004;43:8-14

Diabetic population of SIRIUS

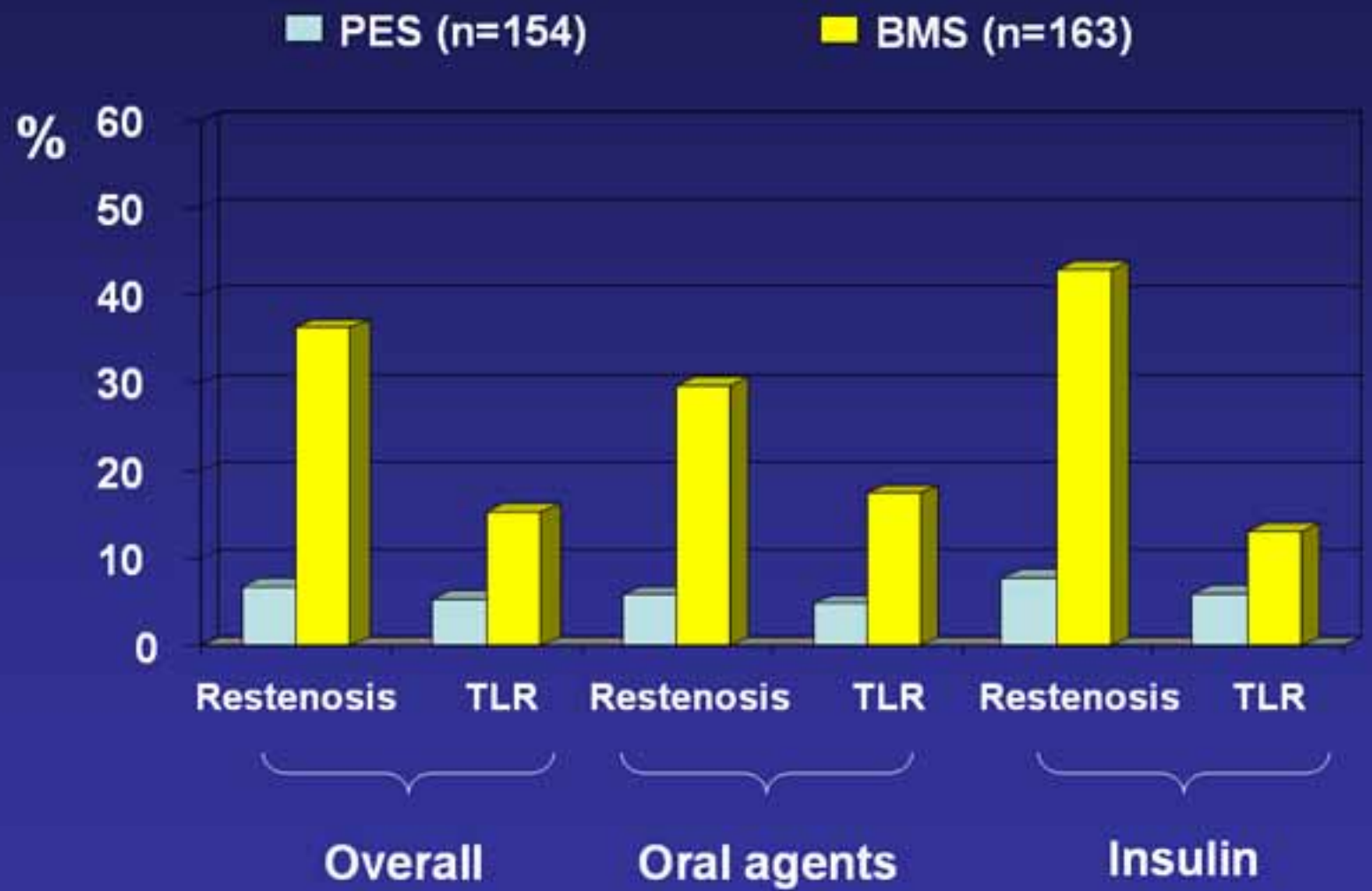
- 26% total population



Moses et al NEJM 2003;349:1315

Diabetic population of TAXUS IV

- 32% total population



Stone et al NEJM 2004;350:221

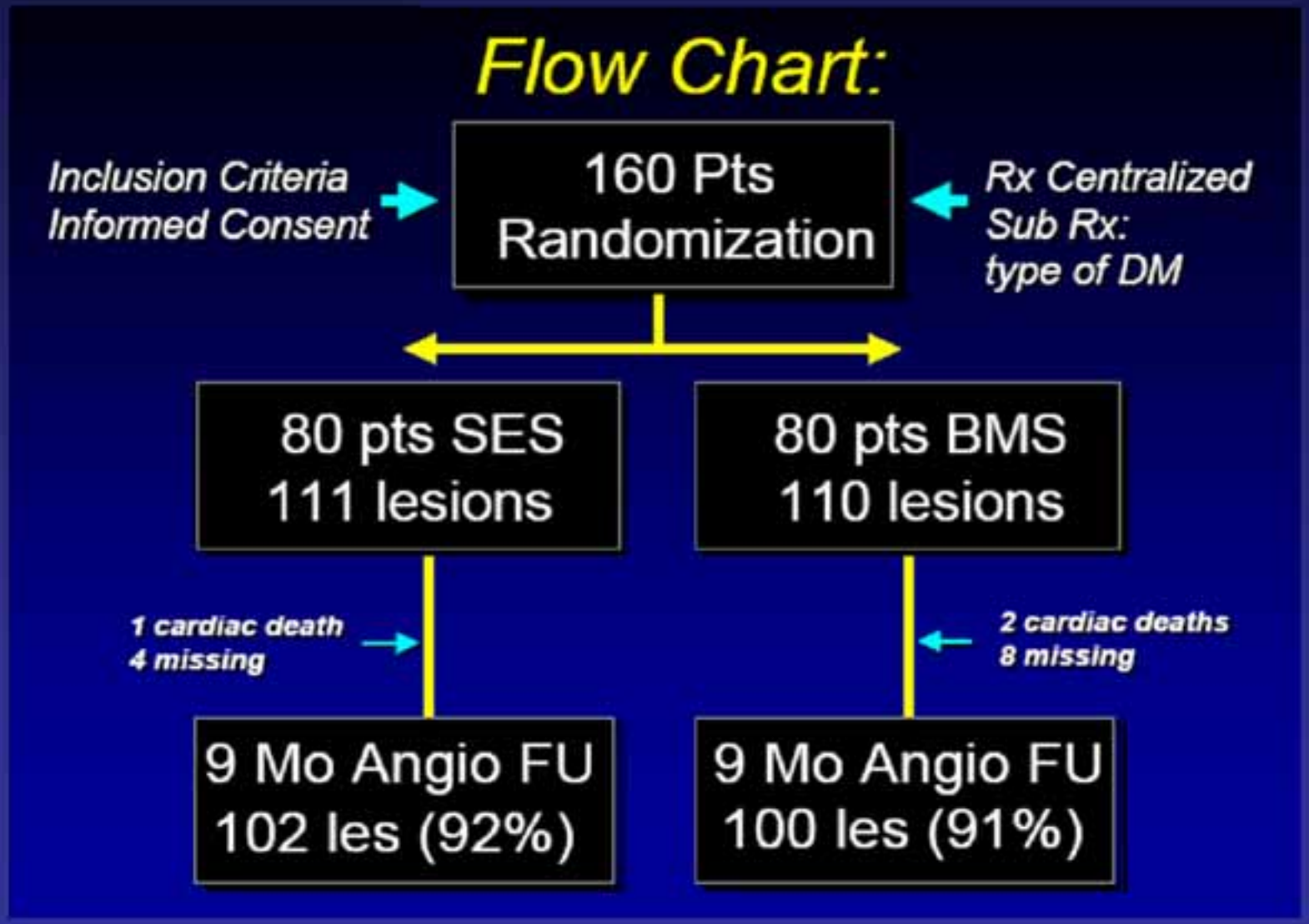
DIABETes and sirolimus Eluting Stent trial

- Prospective multicenter randomized study of the SES versus BMS implantation in diabetic patients

- Primary endpoint was in-segment late lumen loss at 9-month follow-up

Sabate et al Circulation 2005;112:2175-2183

DIABETES trial



Sabate et al Circulation 2005;112:2175-2183

DIABETES trial

	SES Lesion n=111	BMS Lesion n=110
Lesion length (mm)	14.6 ± 8	15.3 ± 8
RVD (mm)	2.33 ± 0.6	2.35 ± 0.6
B2/C (%)	79	81
Calcification (%)	43	36
Chronic total occlusion (%)	13	14
Stent diameter (mm)	2.8 ± 0.3	3.0 ± 0.4 *p=0.0001
Stent length (mm)	22 ± 10	23 ± 13

Sabate et al Circulation 2005;112:2175-2183

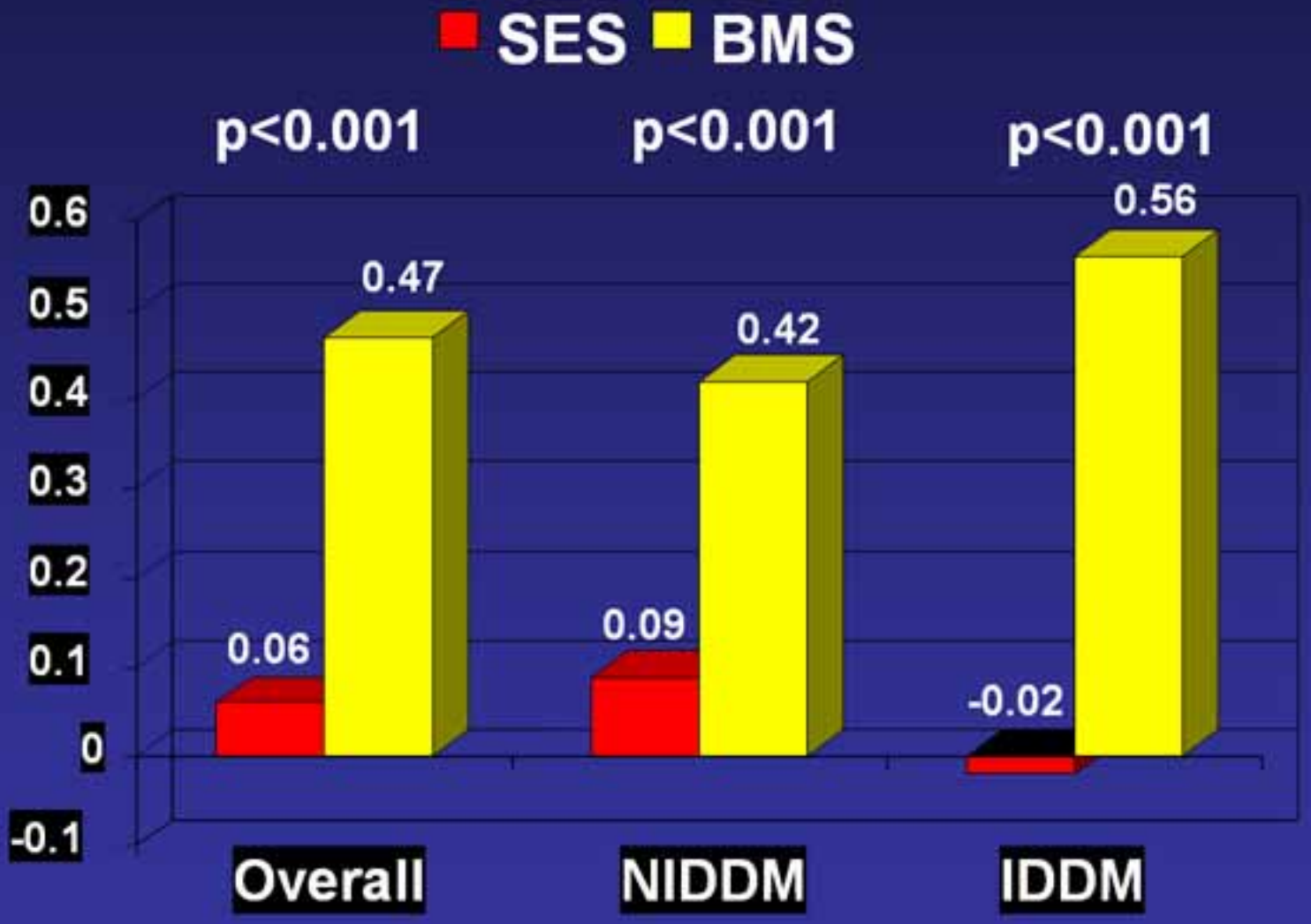
DIABETES trial

	SES n=80	BMS n=80
Insulin	32%	34%
Non-insulin	68%	66%
Glycosylated hemoglobin A_{1C} (%)	7.4 ± 1.5	7.3 ± 1.4
IIb/IIIa inhibitor use	64	54
Multivessel disease	61%	69%

- 66% vessel smaller than 2.5mm
- 43% lesion longer than 20mm
- 32% had a creatinine clearance <60mL/min
- 51% poor glycemic control with a glycosylated HbA_{1c} >7%

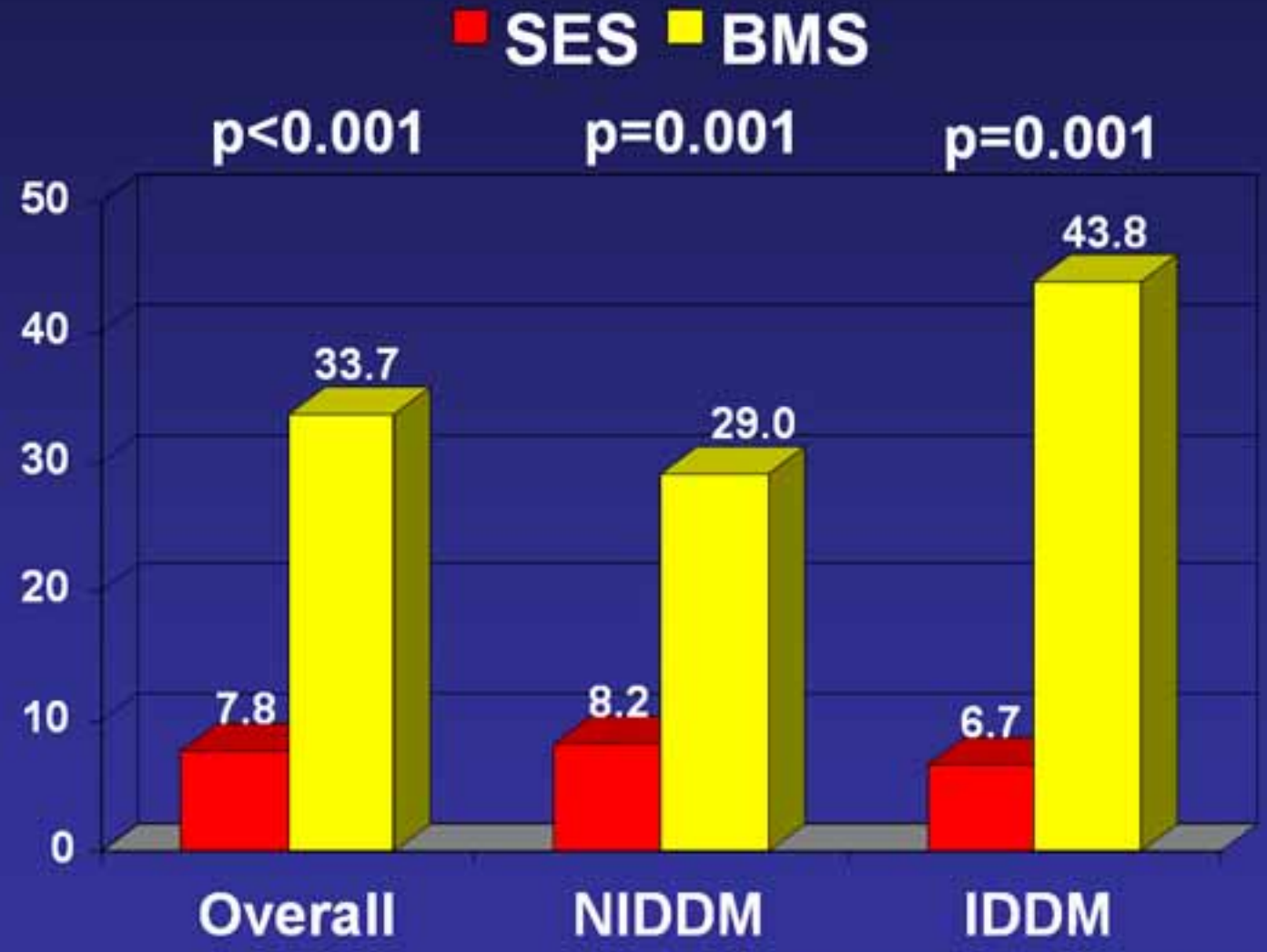
Sabate et al Circulation 2005;112:2175-2183

DIABETES trial: in-segment late loss at 9-months



Sabate et al Circulation 2005;112:2175-2183

DIABETES trial: in-segment restenosis rate at 9-months



SES tended to have shorter length of restenosis

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

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

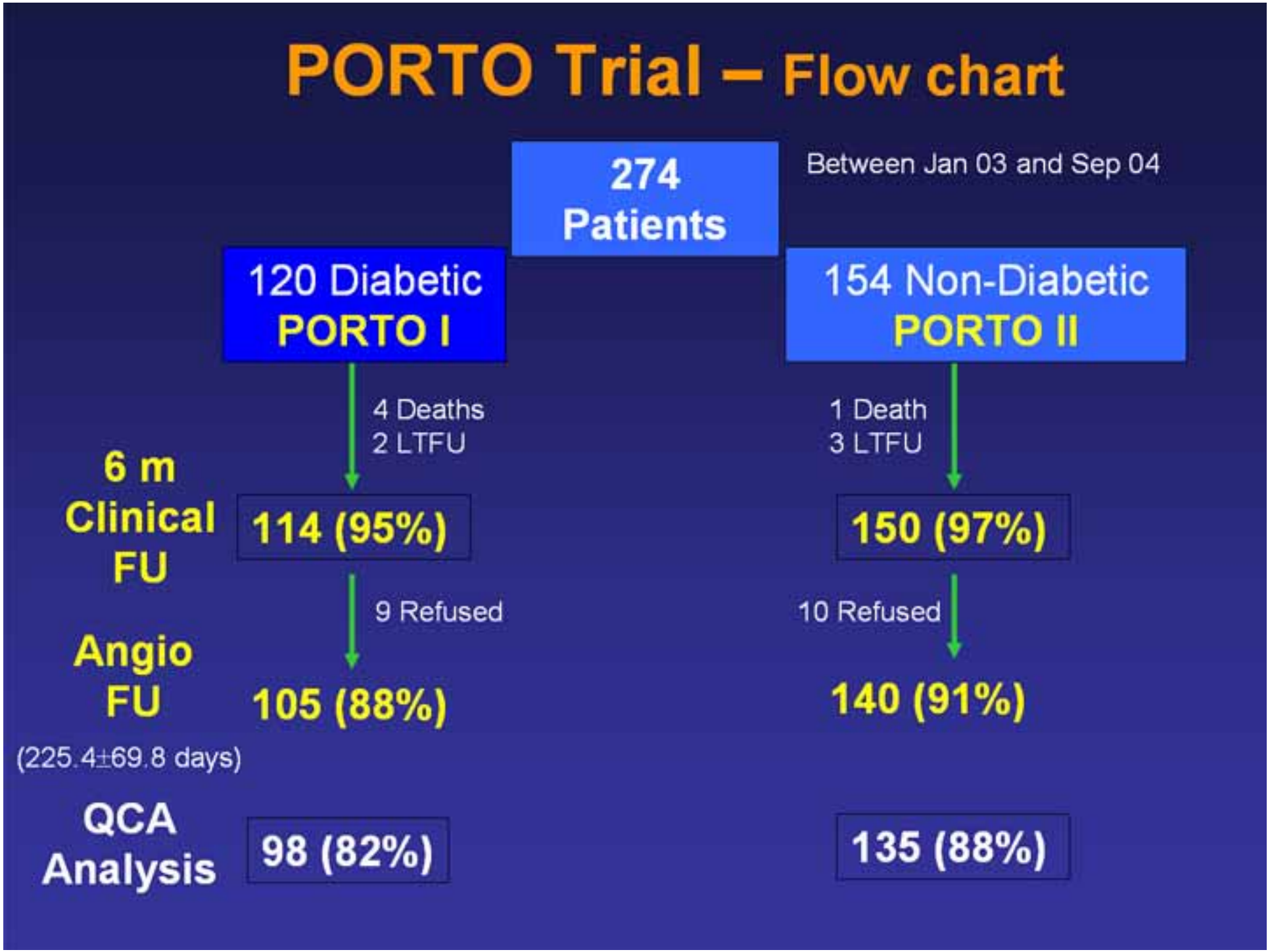
Sabate et al Circulation 2005;112:2175-2183

PORTO Trial

- Multicenter Portugese study of SES in small (≤ 2.50mm) native coronary arteries of diabetic (PORTO I) and non-diabetic (PORTO II) patients
- Lesion length ≤33mm
- Primary endpoint: in-stent Late Lumen Loss at 6-month angiographic follow-up
- Independent core lab

Seabra-Gomes EURO-PCR 2005

PORTO Trial – Flow chart



PORTO Trial – PCI data

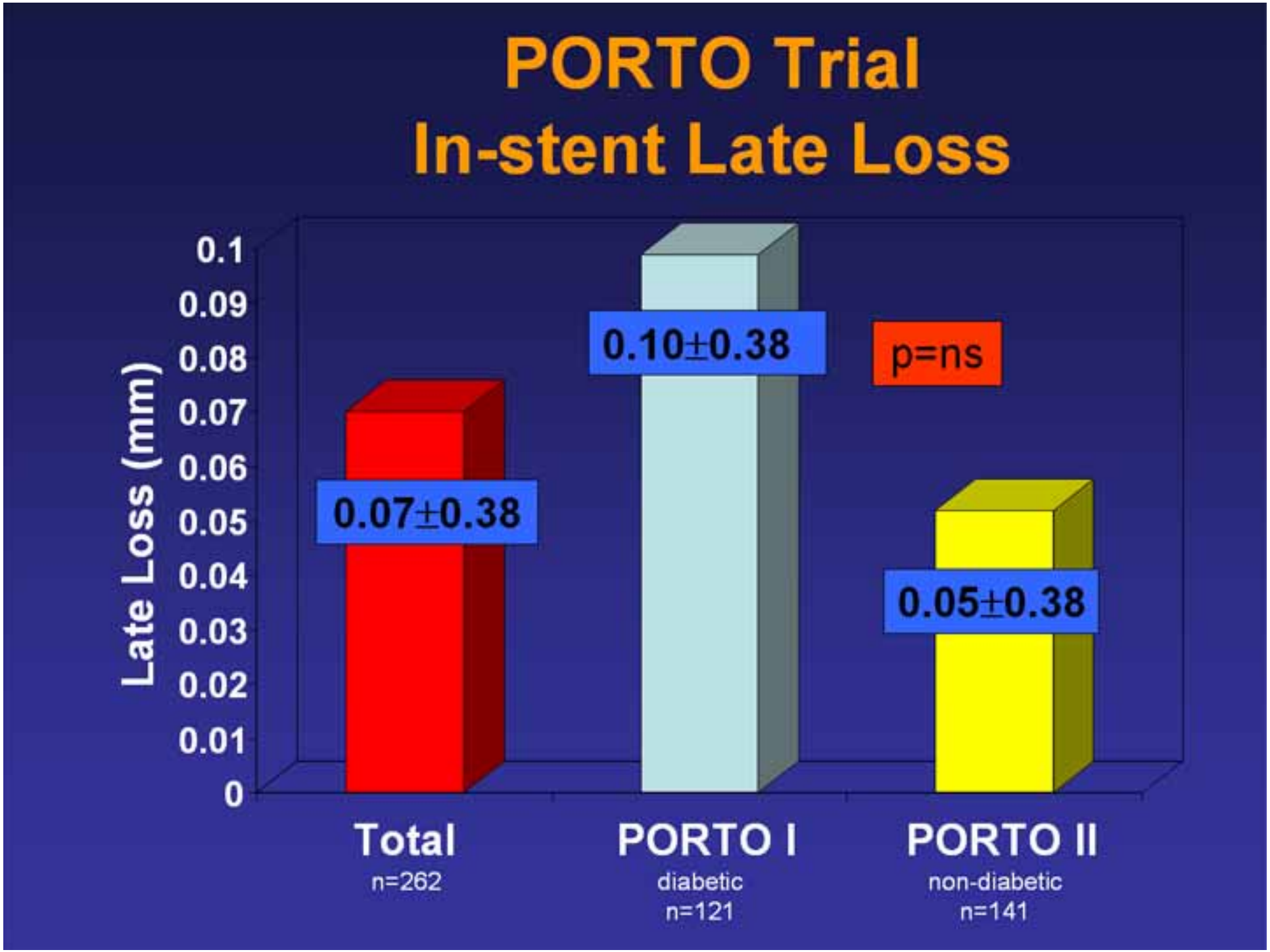
	Total	PORTO I (diabetic)	PORTO II (non-diabetic)
PCI for 2-3 target vessels	8.4%	12.5% *	5.2%
IIb/IIIa use	19.7%	23.3%	16.9%
No. Of SES	347	170	177
Only 1 stent used	93.2%	91.6%	94.7%
Stents 2.25mm	29.7%	38.2% ***	21.5%
Stents ≥ 23mm	25.6%	24.7%	26.5%

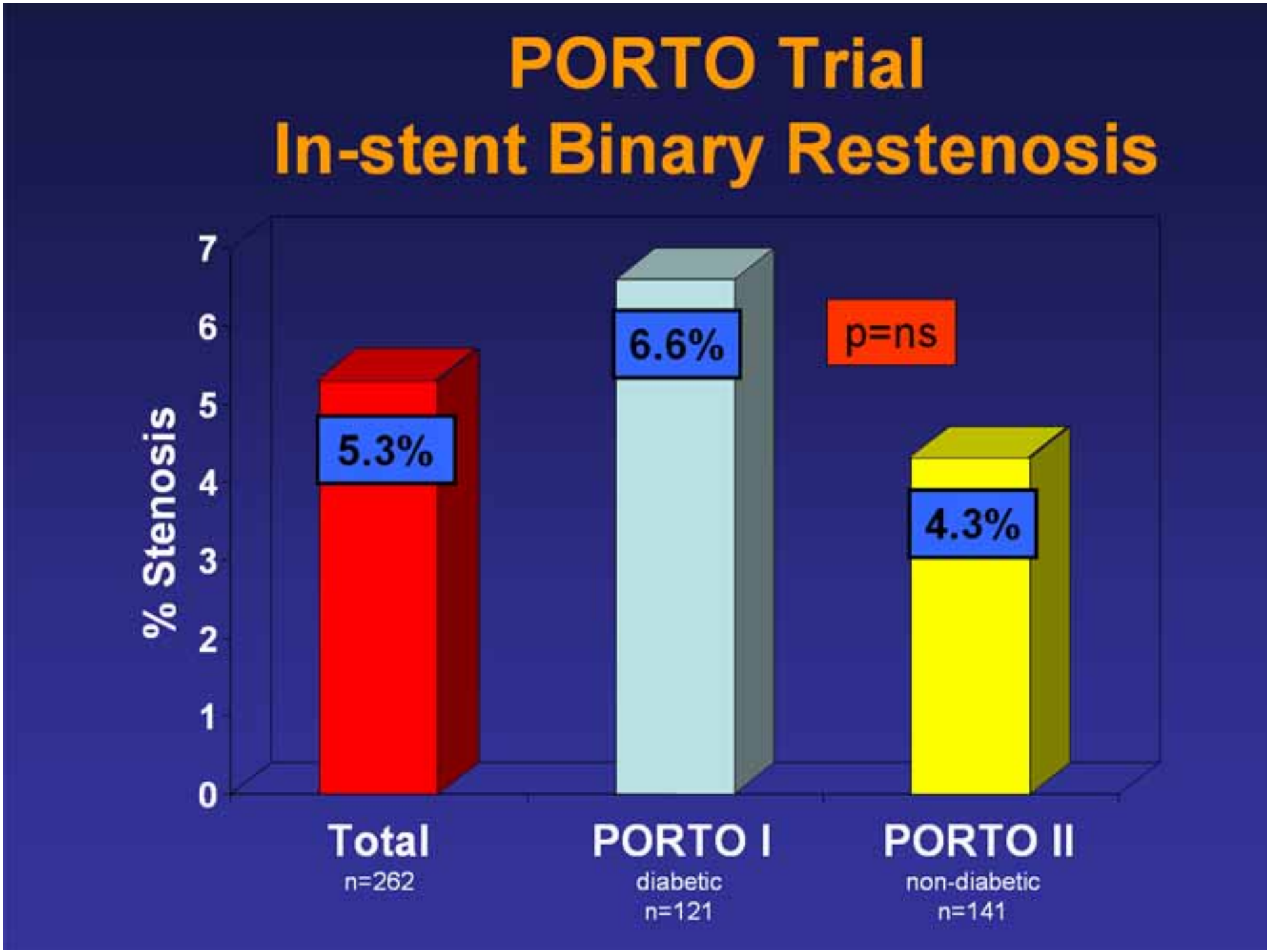
* $p < 0.05$ *** $p < 0.001$

PORTO Trial – QCA data

Pre PCI	Total n=262	PORTO I (diabetic) n=121	PORTO II (non-diabetic) n=141
Reference Vessel Diameter (mm)	2.09±0.32	2.04±0.31 *	2.13±0.34
Lesion length (mm)	11.08±6.0	11.16±6.1	11.01±5.9
Diameter stenosis (%)	58.9±11.7	59.3±11.4	58.6±12.0
MLD (mm)	0.86±0.28	0.83±0.27	0.88±0.28

* $p < 0.05$


PORTO Trial
In-stent Late Loss
Late Loss (mm)
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0.07±0.38
0.10±0.38
p=ns
0.05±0.38
Total
n=262
PORTO I
diabetic
n=121
PORTO II
non-diabetic
n=141


PORTO Trial
In-stent Binary Restenosis
% Stenosis
0
1
2
3
4
5
6
7
5.3%
6.6%
4.3%
p=ns
Total
n=262
PORTO I
diabetic
n=121
PORTO II
non-diabetic
n=141

PORTO Trial – clinical adverse events at 6 months

	Total	PORTO I (diabetic)	PORTO II (non-diabetic)
Death (%)	1.8	3.3	0.6
Cardiac Death (%)	1.1	1.7	0.6
Non-fatal AMI (%)	1.1	1.7*	0.6**
TLR (%)	0.8	1.7*	0
TVR (%)	1.1	2.5	0
MACE (%)	2.9	5.0	1.3
Stent Thrombosis (%)	0.7	0.8*	0.6**

* SAT, day 9, after anti-platelet therapy discontinuation
** Late, day 44, on anti-platelet therapy

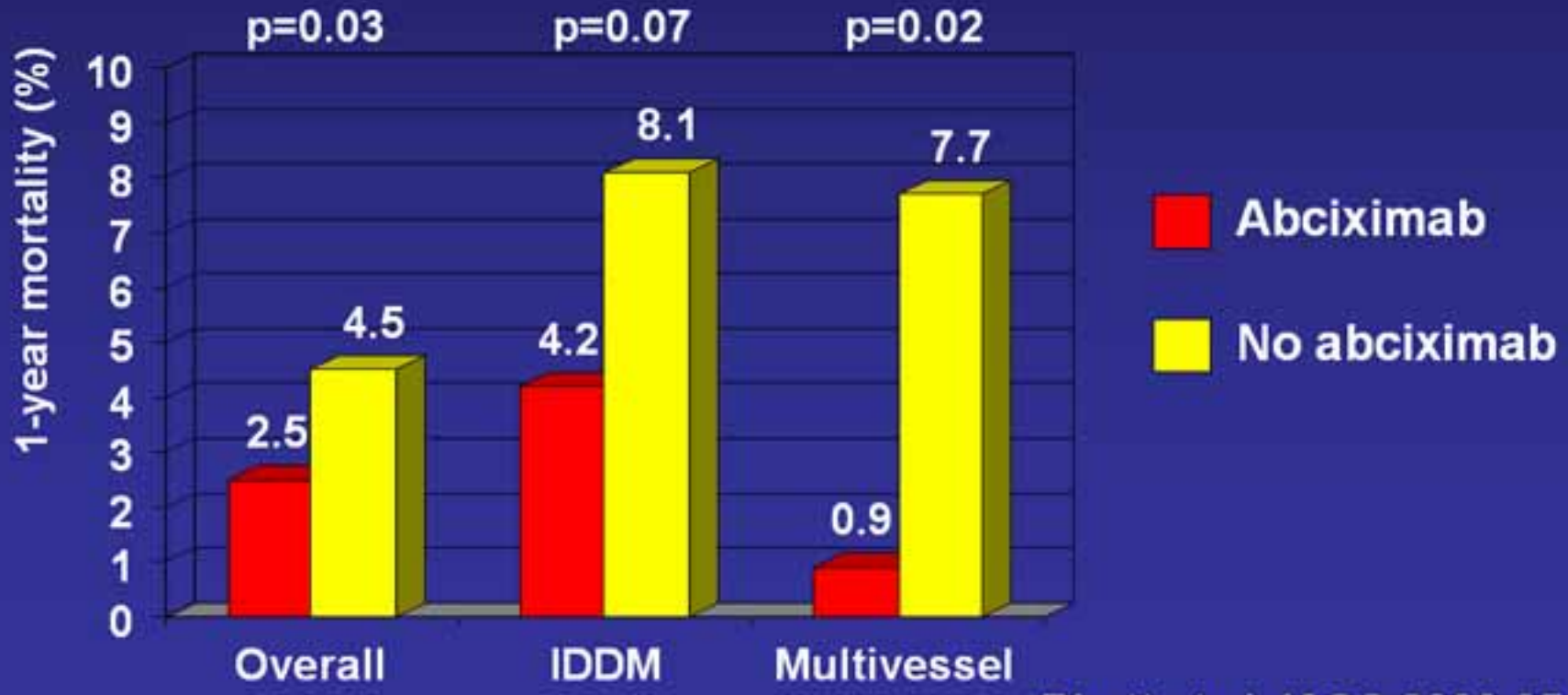
Diabetes mellitus in the era of DES in the "real world"

- DM remains an independent predictor of adverse events:
  - Rotterdam Registries (RESEARCH and T-SEARCH)
  - Milan registry*
  - German registry
  - Multicenter PCI Database Registry of Korea
  - e-Cypher*

* DM was an independent predictor of stent thrombosis

Use of abciximab in diabetics

- 1,462 diabetic patients from EPIC, EPILOG, and EPISTENT
- Mortality rate was increased in those with a significant procedural release of CK

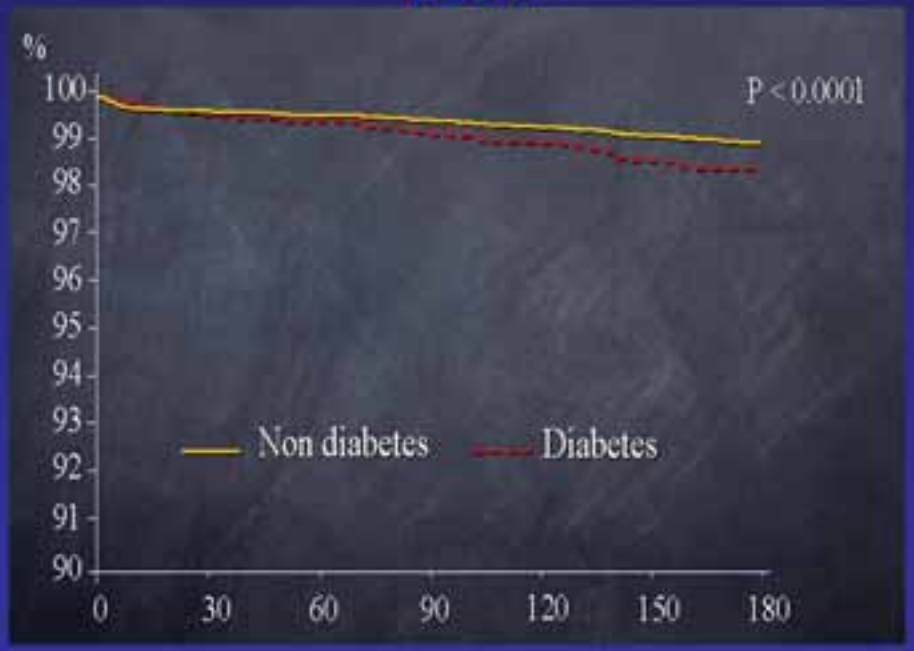


Bhatt et al JACC 2000;35:922-8

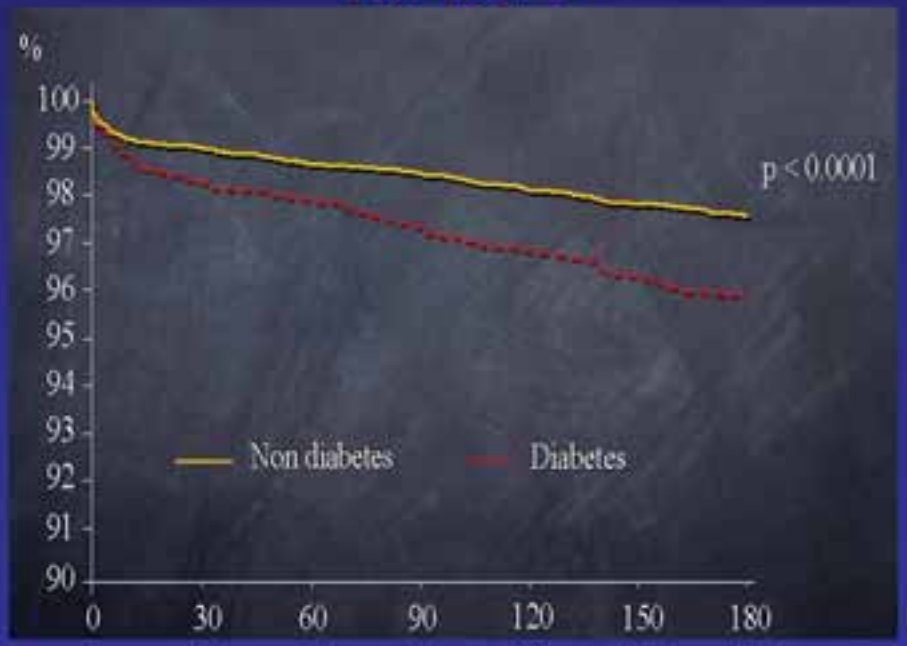
e-Cypher: survival-free of MACE

3171 diabetics (86%FU) versus 7988 non-diabetics (87%FU)

TLR



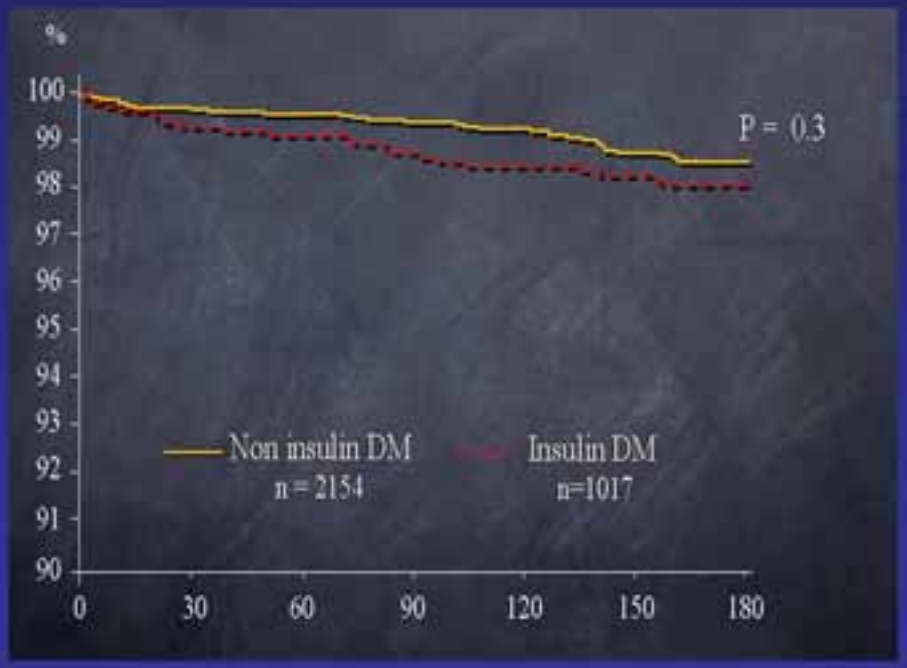
MACE



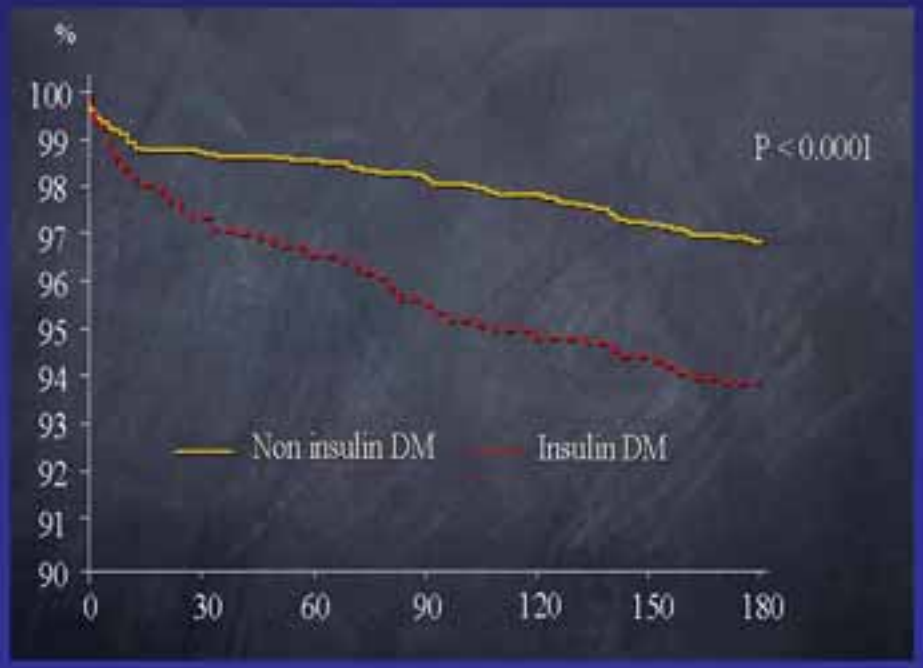
Guagliumi: presented at TCT 2004

e-Cypher: survival-free of adverse events with respect to type of therapy for diabetes

TLR



MACE



Guagliumi: presented at TCT 2004

Multicenter PCI Database Registry of Korea

- 211 patients with DM (25% total population)
- Restenosis in 15% non-diabetic versus 21% diabetic ($p<0.001$)
- Multivariate predictors of restenosis in the diabetics:
  - Current smoking
  - High CRP
  - Longer stent length
  - Smaller vessel diameter
  - Minimal lumen diameter
  - Use of PES

Hong et al Heart Epub Jan 2006

Which DES? ISAR-DIABETES

- Randomised controlled trial of 250 patients with DM and coronary disease to therapy with either SES or PES
- Primary endpoint was in-segment late loss
- Secondary endpoints of in-segment restenosis, and TLR at 9-months

- Aspirin indefinitely, clopidogrel 75mg for at least 6 months, abciximab in those with ACS

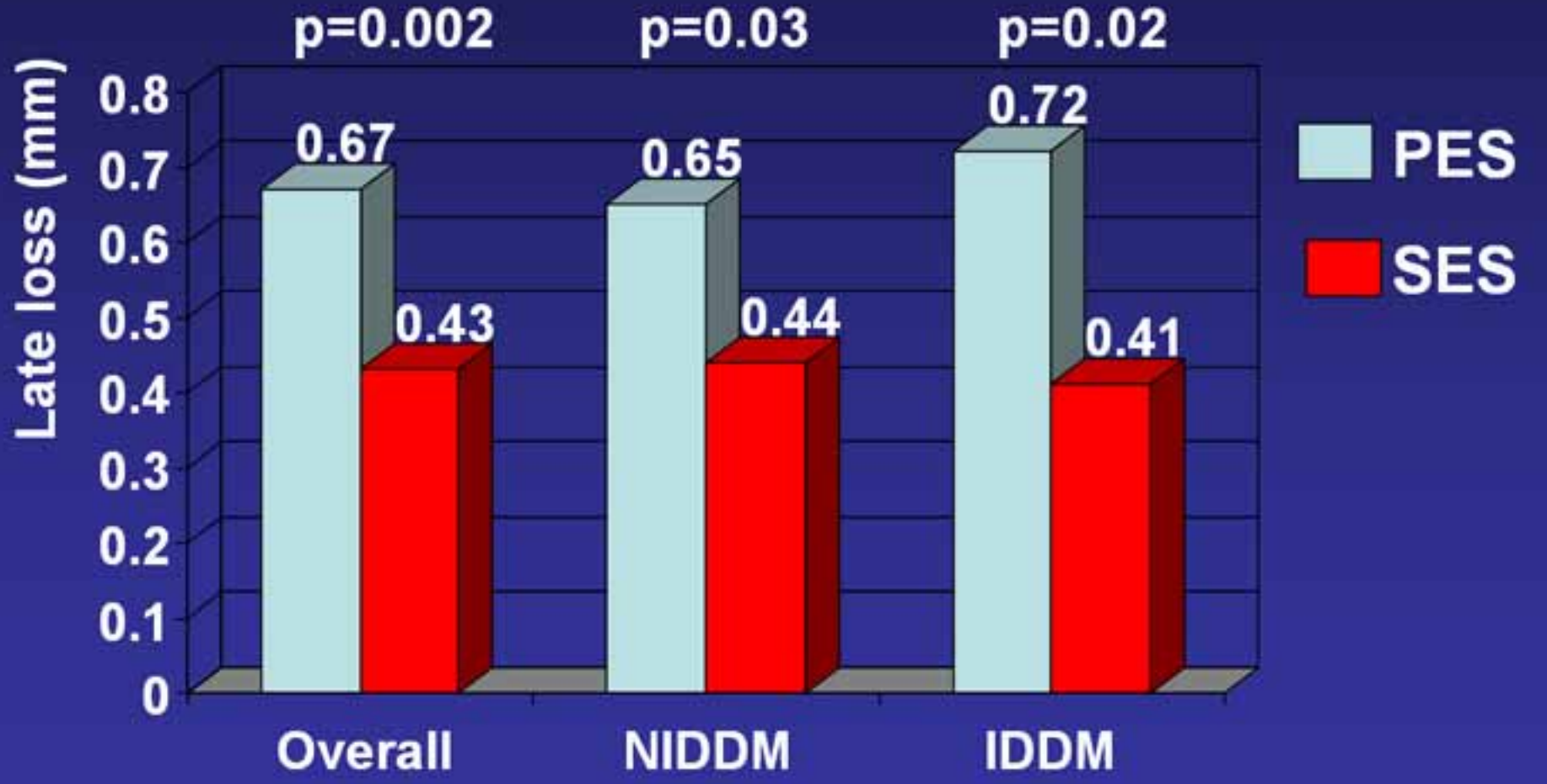
Dibra et al NEJM 2005;353:663-70

ISAR-DIABETES

	PES n=125	SES n=125
Diabetes therapy: diet alone	19	19
oral agents	52	44
insulin	29	37
Glycosylated hemoglobin (%)	7.4 ± 1.6	7.3 ± 1.1
B2/C lesions (%)	74	82
RVD (mm)	2.75 ± 0.56	2.70 ± 0.50
Lesion length (mm)	12.4 ± 7.7	13.8 ± 7.6
Length of stented segment (mm)	22.1 ± 9.3	23.8 ± 10.2

Dibra et al NEJM 2005;353:663-70

ISAR-DIABETES: in-segment late loss



Dibra et al NEJM 2005;353:663-70

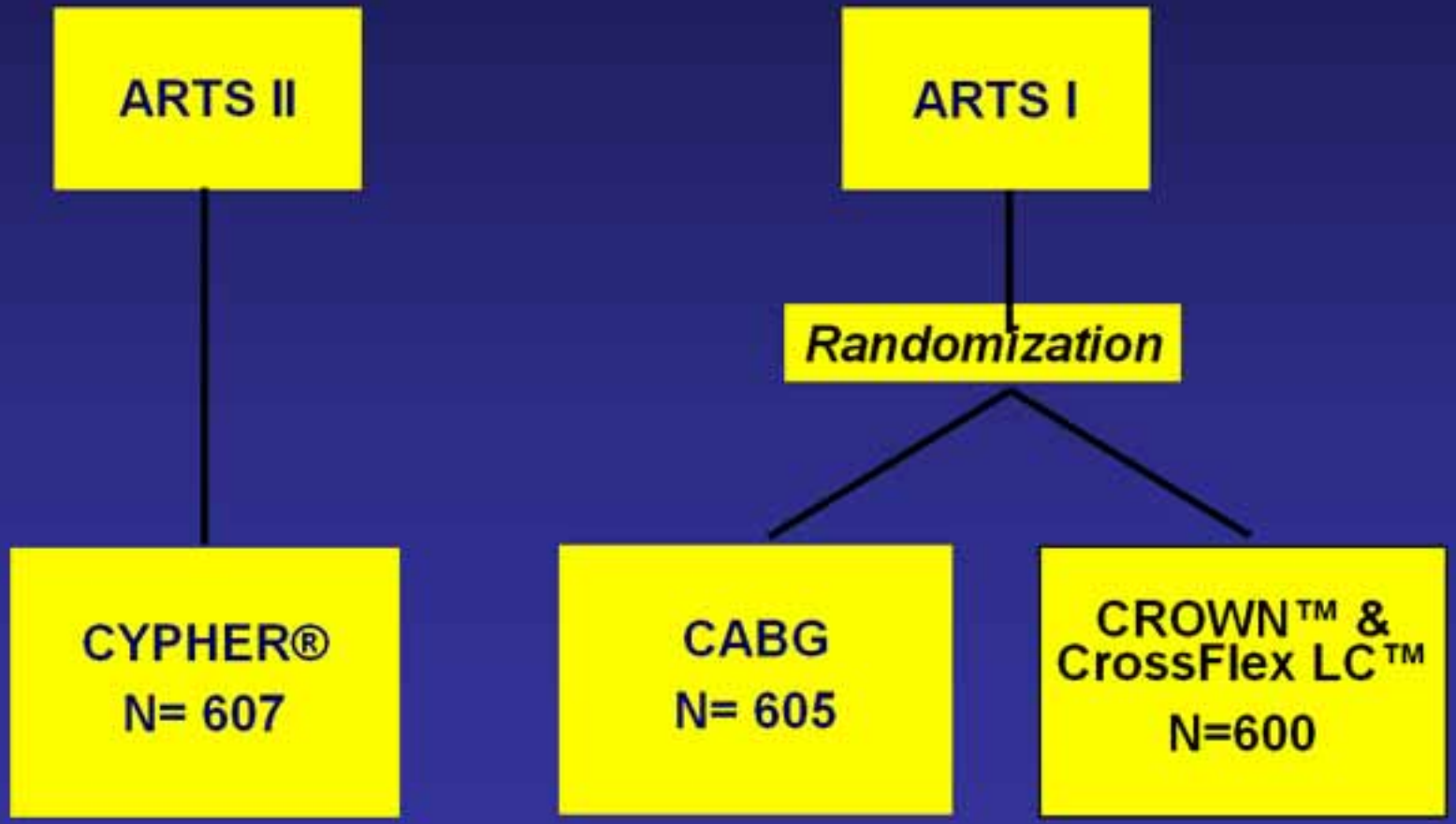
ISAR-DIABETES: clinical outcomes at 9-months

	PES n=125	SES n=125	p value
Death, n (%)	6 (4.3)	4 (3.2)	0.52
AMI, n (%)	3 (2.4)	5 (4.0)	0.72
TLR, n (%)	15 (12.0)	8 (6.4)	0.13

Dibra et al NEJM 2005;353:663-70

Multivessel disease: ARTS II

- Single arm, multicenter trial
- 607 patients in 45 centers from 19 countries



Serruys et al EuroInterv.2005;2:147-156

ARTS II - Patient Population

- Patients between 18 and 80 years with MVD
- Stable, unstable angina or silent ischemia
- One lesion located in LAD
- Patients were stratified by clinical site in order to ensure inclusion of at least 1/3 3-vessel disease and 2/3 2-vessel disease to obtain a population comparable to ARTS I (2.7 lesions / patients)
- No previous PCI, CABG or stroke
- No MI within the preceeding week

ARTS II - Patient Population

Same inclusion criteria as in ARTS I

- Patients between 18 and 80 years with MVD
- Stable, unstable angina or silent ischemia
- One lesion located in LAD
- Patients were stratified by clinical site in order to ensure inclusion of at least 1/3 3-vessel disease and 2/3 2-vessel disease to obtain a population comparable to ARTS I (2.7 lesions / patients)
- No previous PCI, CABG or stroke
- No MI within the preceeding week

ARTS II – Diabetic population

Patient characteristics (main differences)	ARTS II 159-patients 568-lesions	ARTS I (CABG) 96-patients 290-lesions	ARTS I (PCI) 112-patients 309-lesions
Male (%)	77	79	73
Age (years)	65	63	63
Hypertension	80	56	64
Hypercholesterolemia	74	49	55
Lesion characteristics			
Lesion length > 20mm (%)	15	6	6
Calcified lesion (%)	33	15	13
Type C lesion	17	7	7
# of lesions > 50%DS	3.6 ± 1.3	3.0 ± 1.1	2.9 ± 1.2
# of treated lesions	3.2 ± 1.2	2.8 ± 0.8	2.5 ± 1.1

ARTS II – Diabetic population

Patient characteristics (main differences)	ARTS II 159-patients 568-lesions	ARTS I (CABG) 96-patients 290-lesions	ARTS I (PCI) 112-patients 309-lesions
Male (%)	77	79	73
Age (years)	65 ↗	63	63
Hypertension	80 ↗	56	64
Hypercholesterolemia	74 ↗	49	55
Lesion characteristics			
Lesion length > 20mm (%)	15 ↗	6	6
Calcified lesion (%)	33 ↗	15	13
Type C lesion	17 ↗	7	7
# of lesions > 50%DS	3.6 ± 1.3 ↗	3.0 ± 1.1	2.9 ± 1.2
# of treated lesions	3.2 ± 1.2 ↗	2.8 ± 0.8	2.5 ± 1.1

Figures in red indicate statistical difference (95% CI) between ARTS II and ARTS I groups

ARTS II – Diabetic population

Hierarchical MACCE upto 1 year	ARTS II N=159	ARTS I (CABG) N=96	ARTS I (PCI) N=112
Death	2.5%	3.1%	6.3%
CVA	0.0%	5.2%	1.8%
MI	0.6%	2.1%	6.3%
Death/CVA/MI	3.1%	10.4%	14.1%
Revascularization	12.6%	4.1%	22.3%
(re) CABG	3.1%	1.0%	8.0%
(re) PCI	9.4%	3.1%	14.3%
Any MACCE	15.7%	14.6%	36.6%

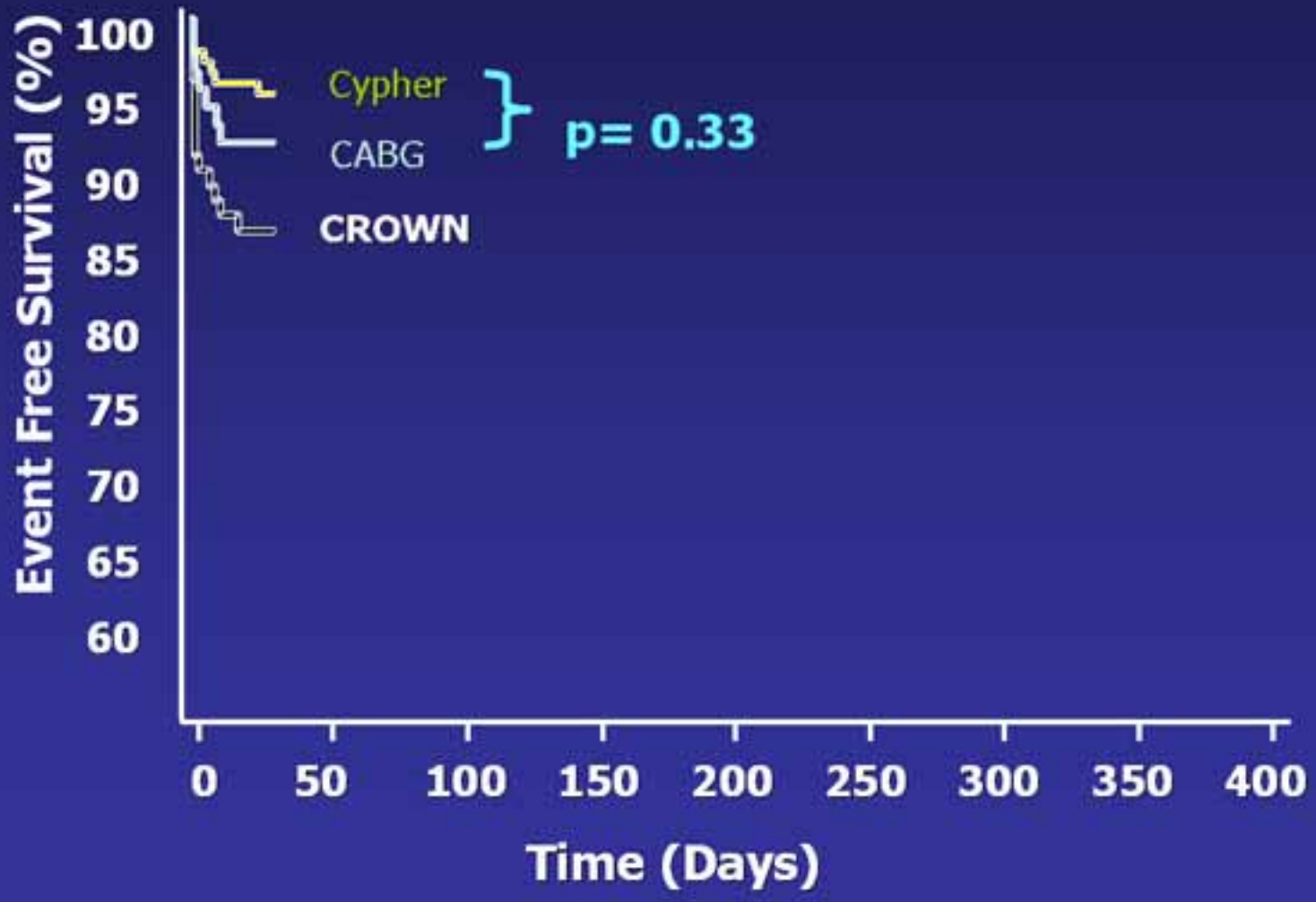
ns

p<0.001

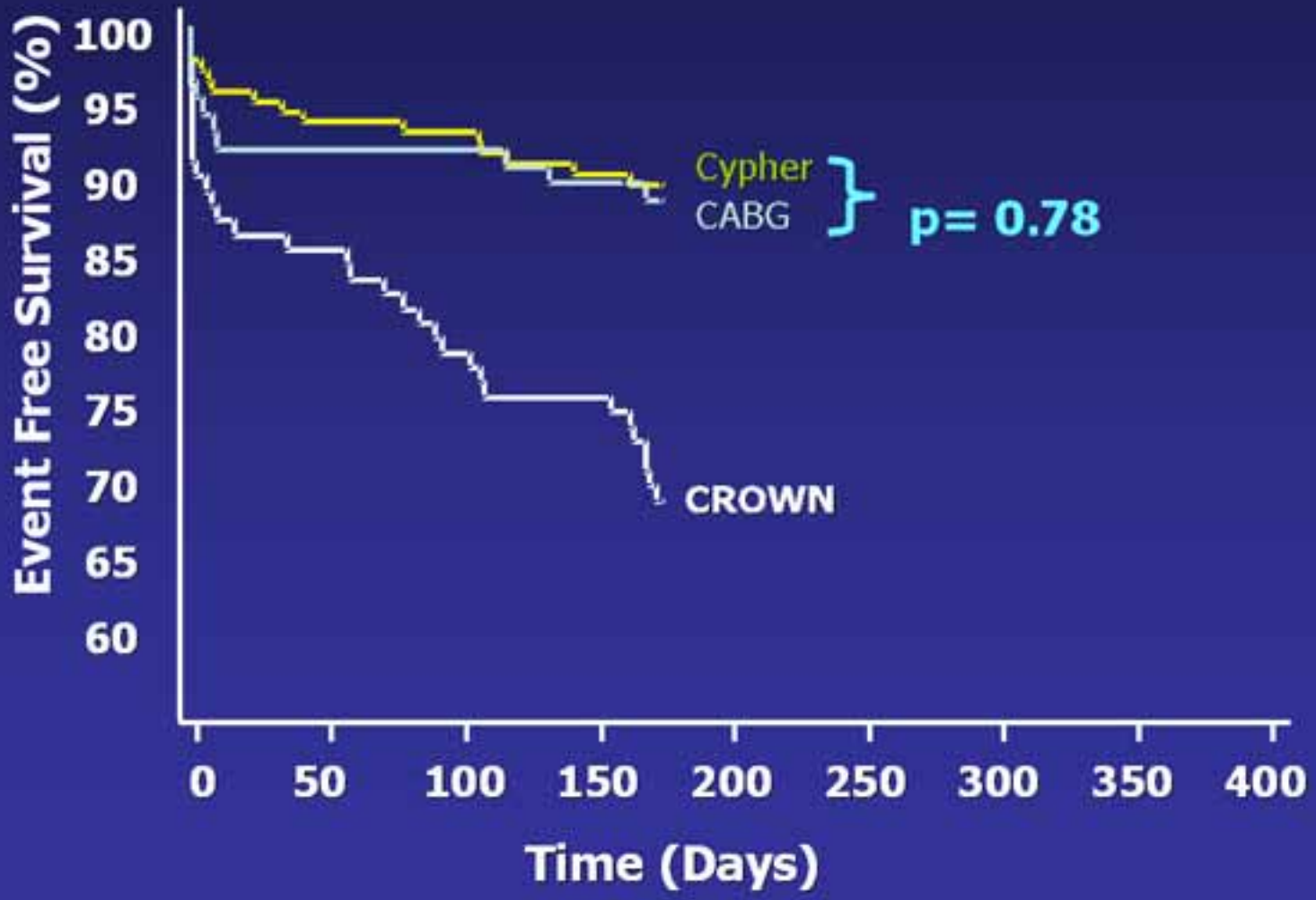
No significant difference in MACCE (p=0.86) between ARTS II and ARTS I (CABG)

Significant difference in MACCE (p=<0.001) between ARTS II and ARTS I (PCI)

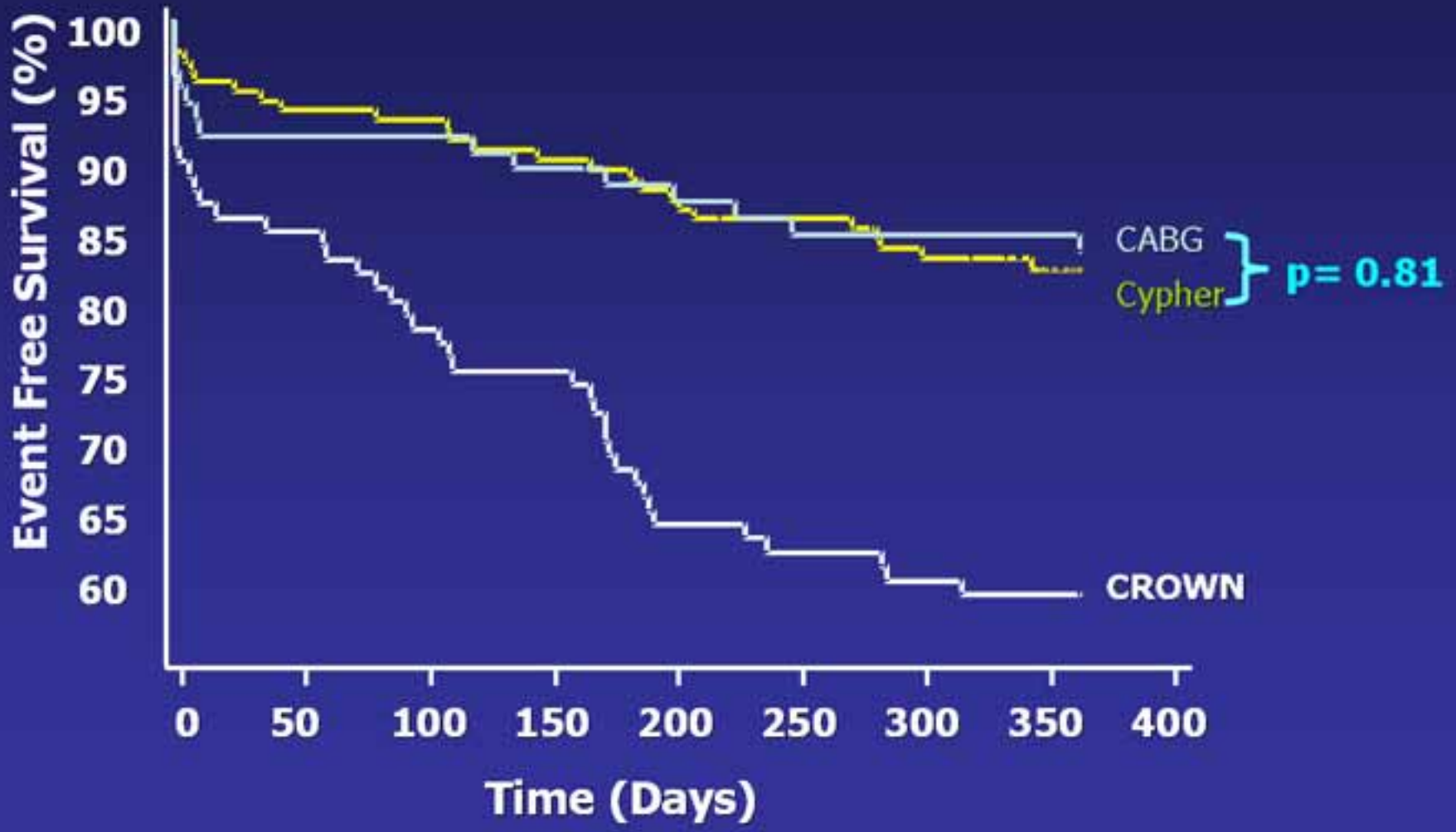
ARTS I versus ARTS II: MACCE-free survival in the diabetics



ARTS I versus ARTS II: MACCE-free survival in the diabetics



ARTS I versus ARTS II: MACCE-free survival in the diabetics

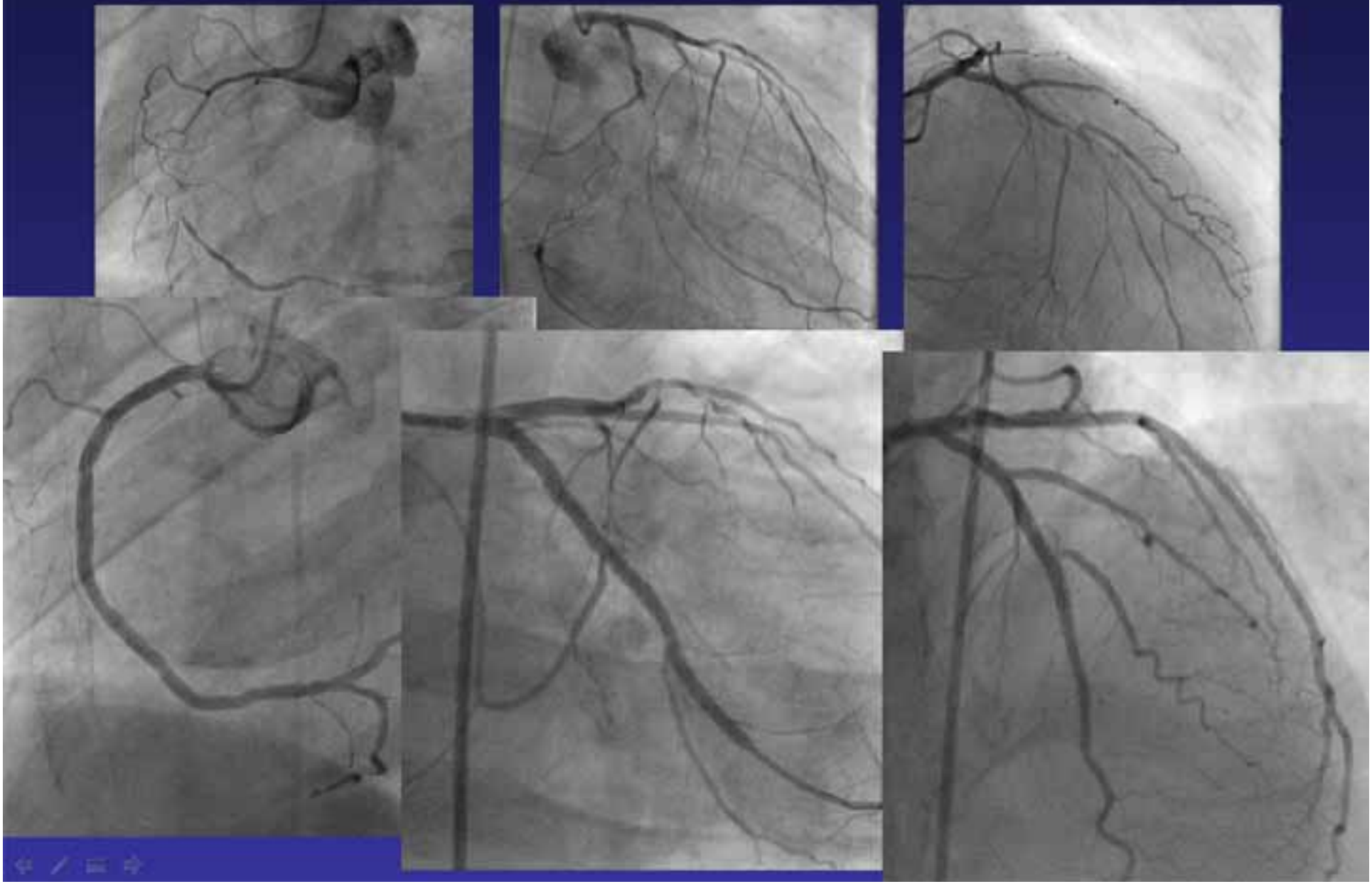


Case Example

- 57-year old man, bus driver
- 1-year history of stable angina
- Tablet controlled diabetic (for 2 years)
- Ex-smoker
- Hypercholesterolemia
- Very early abnormal ETT

- Angiography demonstrated good LV function, 3 vessel coronary disease

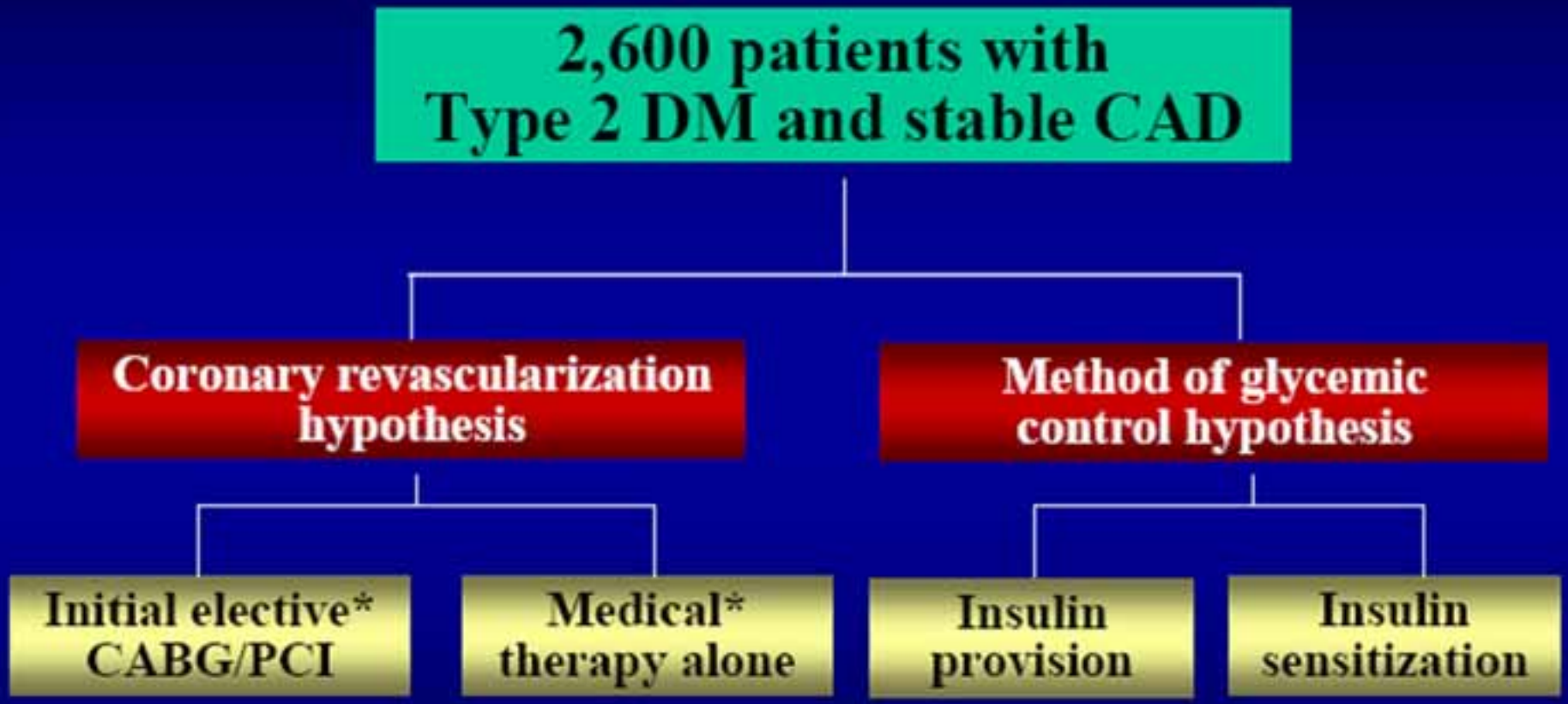
Case example



The future

- **BARI 2D** (sponsored by NHLBI): revascularization versus no revascularization in insulin versus no insulin-treated diabetic patients with mild / moderate symptoms
- **FREEDOM** (sponsored by NHLBI): SES plus abciximab versus CABG in multivessel disease
- **CARDia:** DES versus CABG in multivessel or complex single vessel disease

BARI II-D Trial: Completed



*Aggressive medical therapy in both arms

Target HbA_{1c} <7.5%

Primary endpoint – 5-Year Mortality

NHLBI sponsored FREEDOM trial

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

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 70%)
- Primary endpoint: composite of death, AMI, or stroke at 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, and reduce restenosis and TLR compared with BMS
- But DM is still a predictor of MACE and TLR
- Insulin-treated diabetics may have a poorer outcome

Conclusions: importance of optimal medical therapy

- **Prothrombotic** - optimal anti-platelet therapy
  (high dose clopidogrel pre-loading - ISAR-SWEET)
- **Renal dysfunction** - prehydrate ± N-acetylcysteine
  - ACE-inhibitor especially in the presence of proteinuria
- **Hypertension** - aim for bp <130/80
- **High cholesterol** - aggressive statin therapy
  - LDL <100mg/dL
  - HDL >40mg/dL
  - Triglycerides <150mg/dL
- **Obesity** - exercise programme & diet
- **Glycemic control** - $HbA1_c$ <7.0%