Managing the post intervention period … Which therapies ?

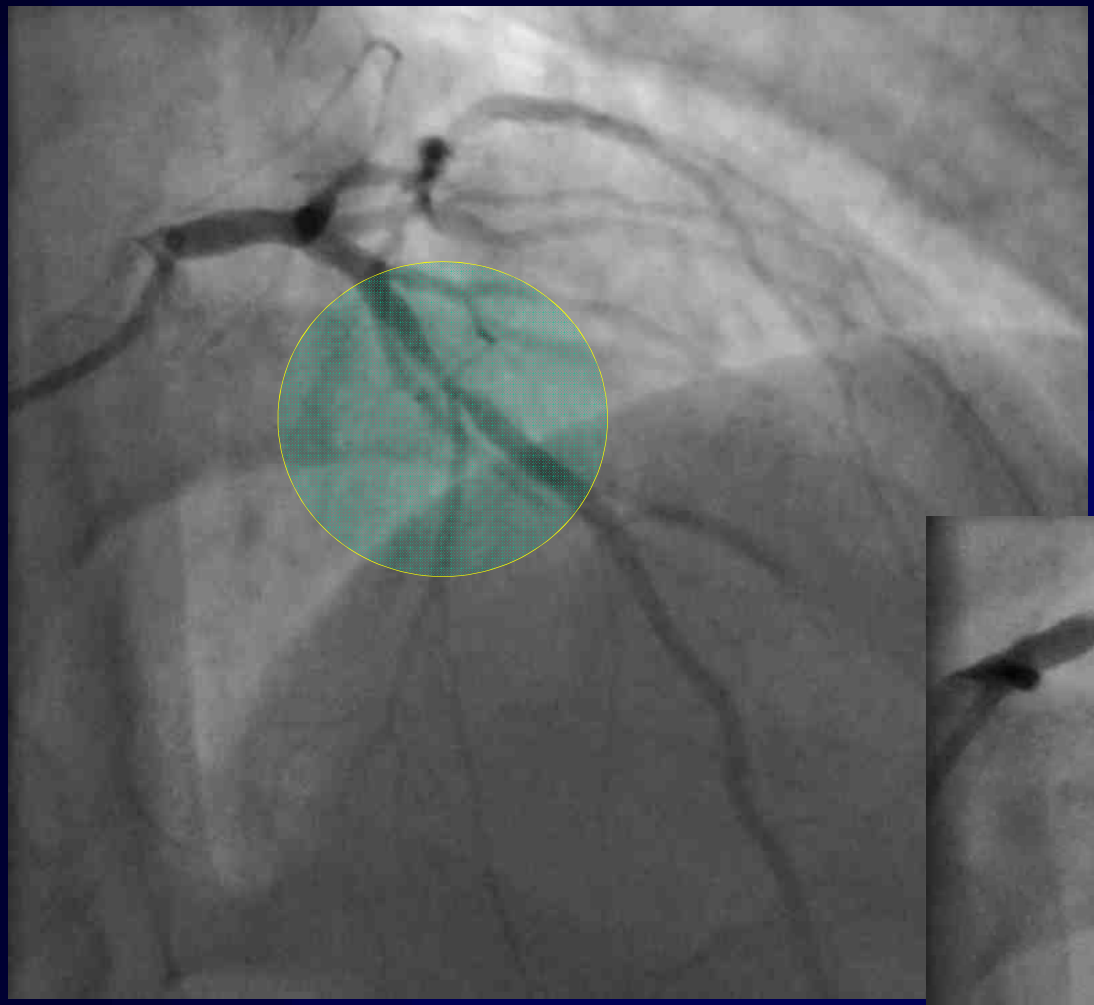
{Beyond anti-platelets}

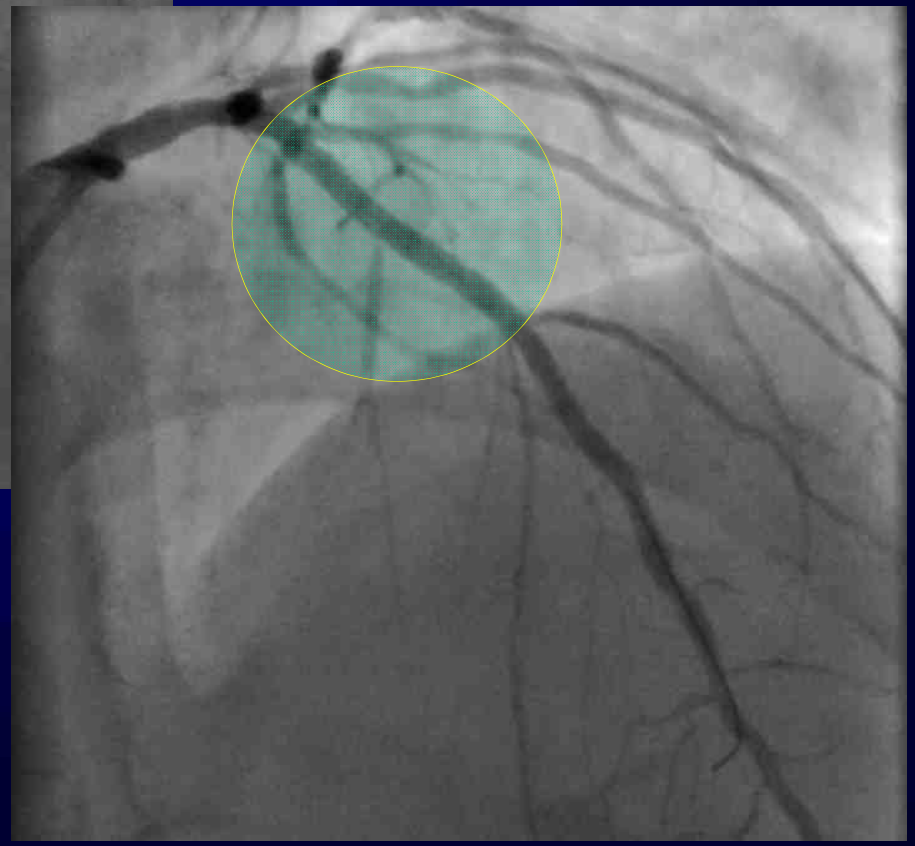
Tony Gershlick

Professor of Interventional Cardiology

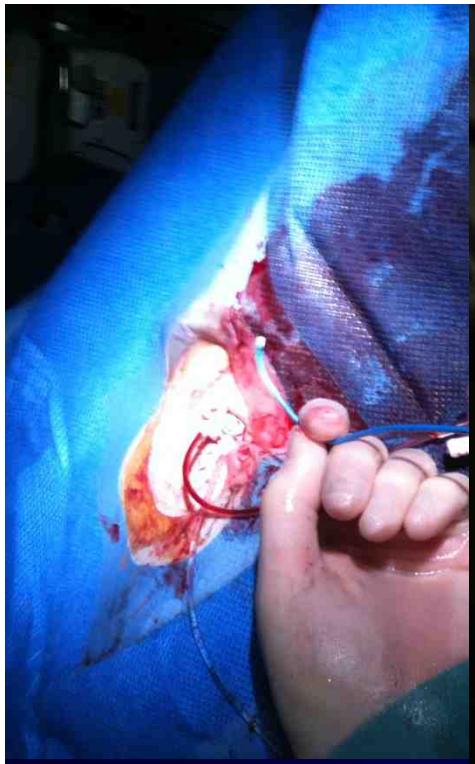
University Hospital of Leicester UK

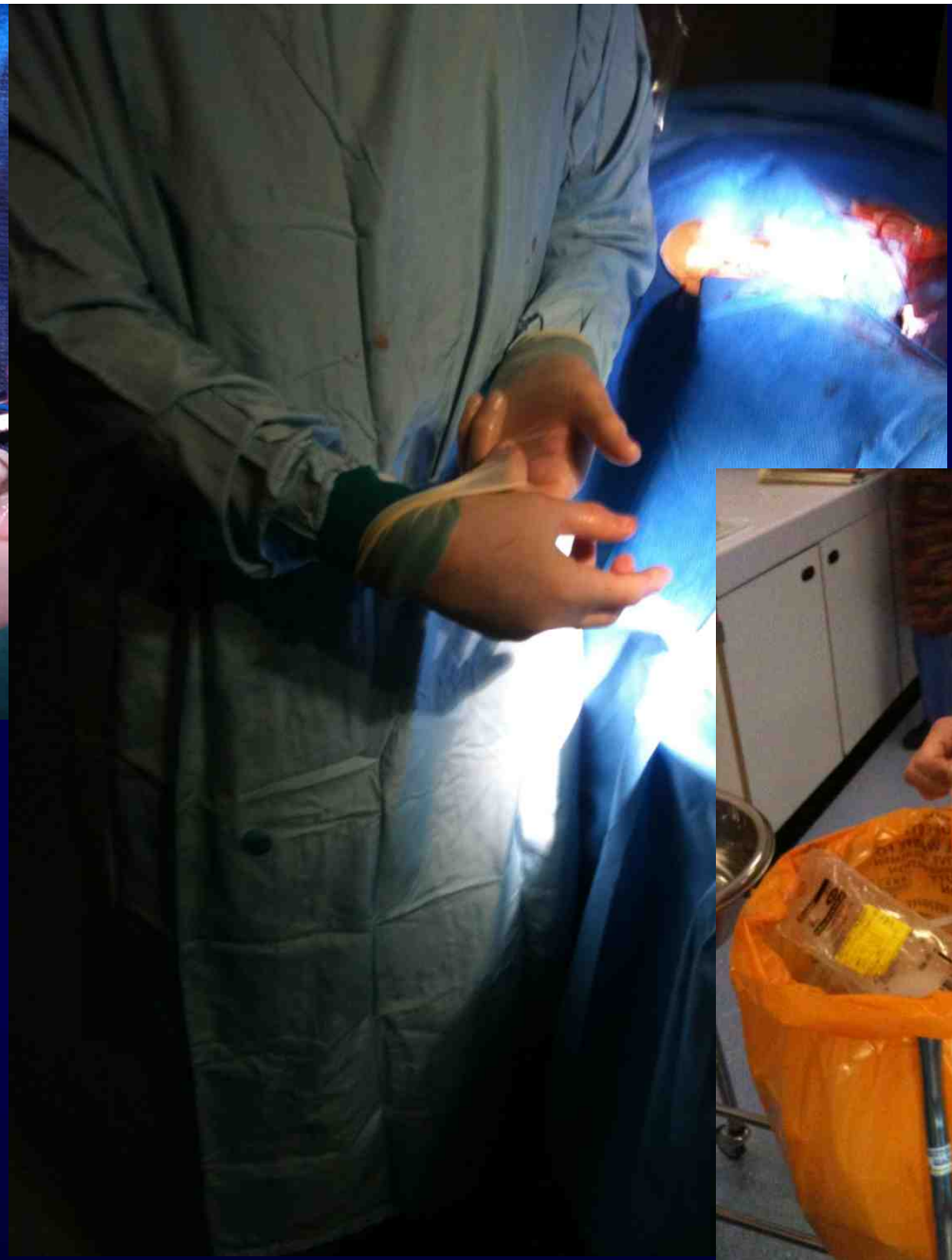
Korea 2010



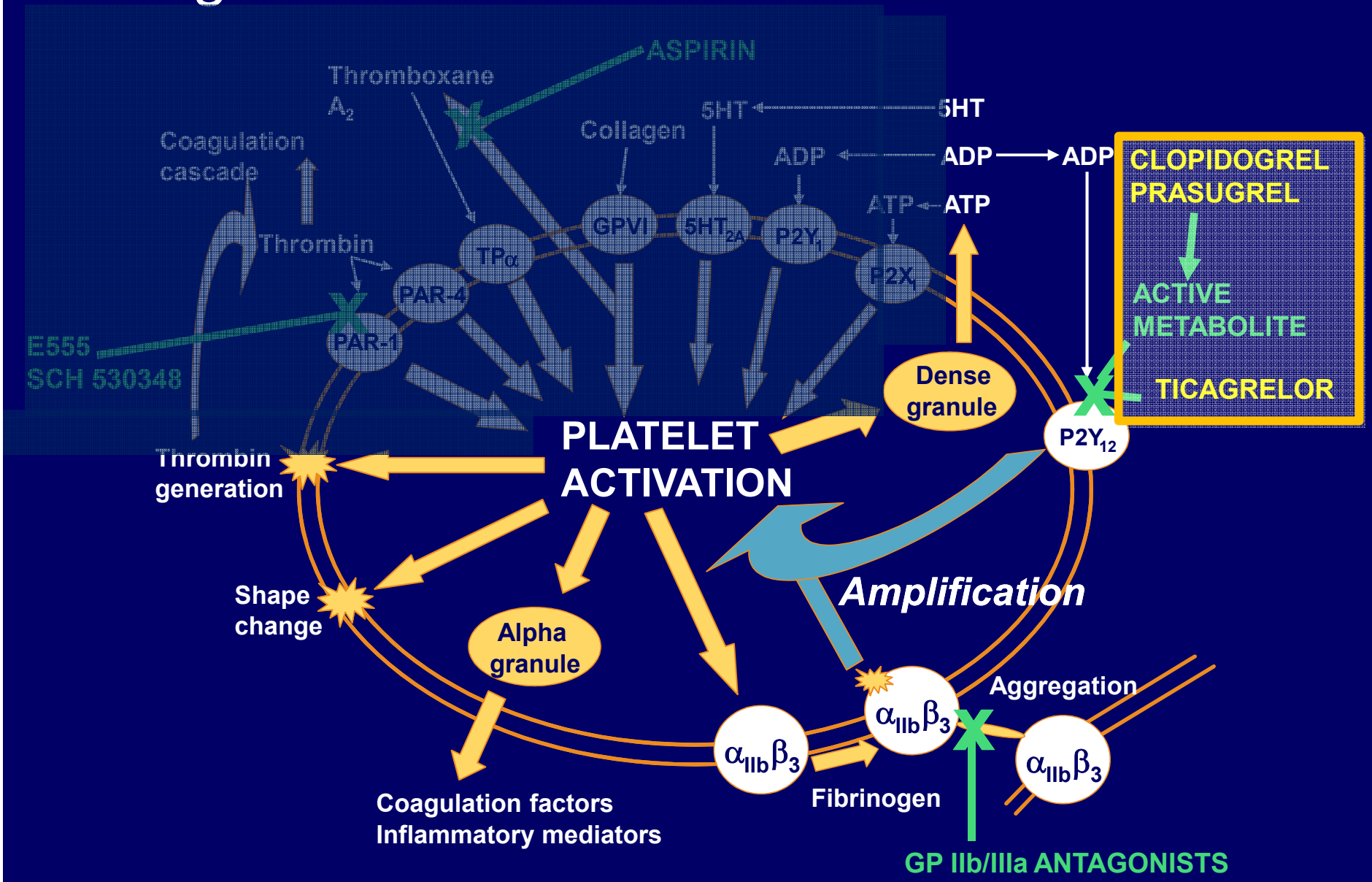


Is this the end of the case?





Targets for Platelet Inhibition



GP = glycoprotein; PAR = protease-activated receptor; TP = thromboxane A_2 / prostaglandin H_2.
Adapted from Storey RF. *Curr Pharm Des*. 2006;12:1255-1259.

- Which other therapies need we consider ?
- Why ?

- Statins
- Diabetes
- B Blockers
- Others

STATINS

Cardioprotective Effect Of **The Statins**.

pleiotropic effects

- Modify –
  inflammation, endothelial function, plaque stability, and thrombus formation

Rosenson RS, Tangney CC.. JAMA 1998; 279:1643–50.
Dangas G Thromb Haemost 2000;83:688 –92.
Davignon J. Circulation 2004;109 23 Suppl 1:III39–43.

- Both the anti-inflammatory and the endothelial effects may occur immediately after a single dose of statin.

Ostadal P Mol Cell Biochem 2003;246:45–50

- 24-h treatment with lovastatin and simvastatin induces inhibition of monocyte chemotactic protein-1 synthesis in mononuclear and endothelial cells in vitro

Romano M Lab Invest 2000;80:1095–100.

.

❑ Statins have beneficial effects on endothelial function by a rapid increase in nitric oxide bioavailability as early as 3 h after statin administration

Laufs U Circulation 1998;97:1129 –35.

❑ Nitric oxide shown act as physiological inhibitor of leukocyteendothelial cell interaction by suppressing up-regulation of several endothelial cell adhesion molecules, including P-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1

Kubes P Proc Natl Acad Sci U S A 1991;88: 4651–5.

❑ Statins attenuated neutrophil-endothelium interaction in the coronary microvasculature

Lefer AM Circulation 1999;100:178–84.
Ueda J Am Coll Cardiol 1999;34:2120 –5.

❑ Brief (10-min) exposure of the normo-cholesterolemic adult heart to atorvastatin, after a period of injurious ischemia, recruits the phosphatidyl inositol 3-kinase pathway, leading to cardioprotection

Bell. J Am Coll Cardiol 2003;41:508 –15.

Clinical data ?

Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 54, No. 23, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.07.005

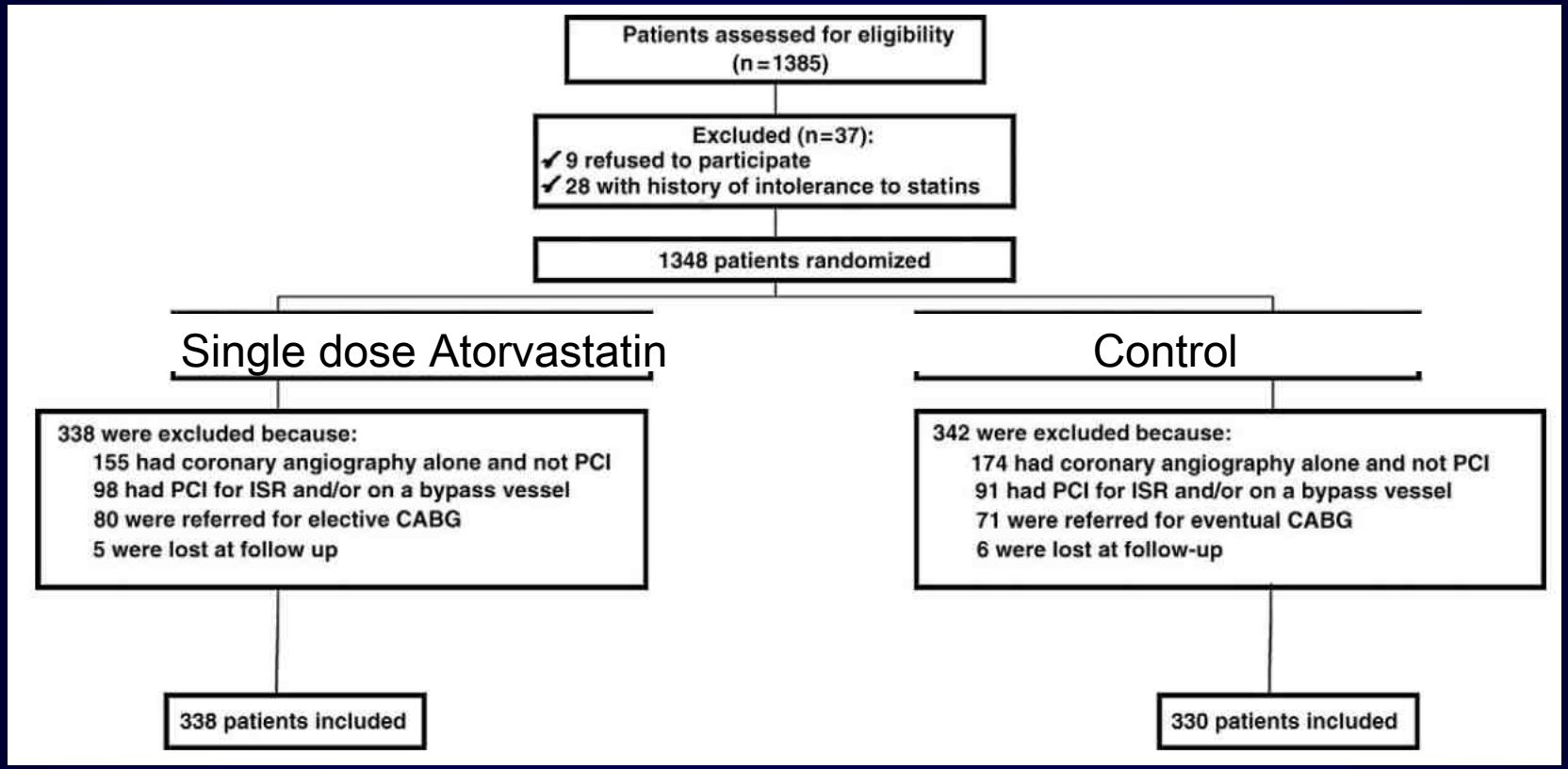
Novel Approaches for Preventing or Limiting Events (Naples) II Trial

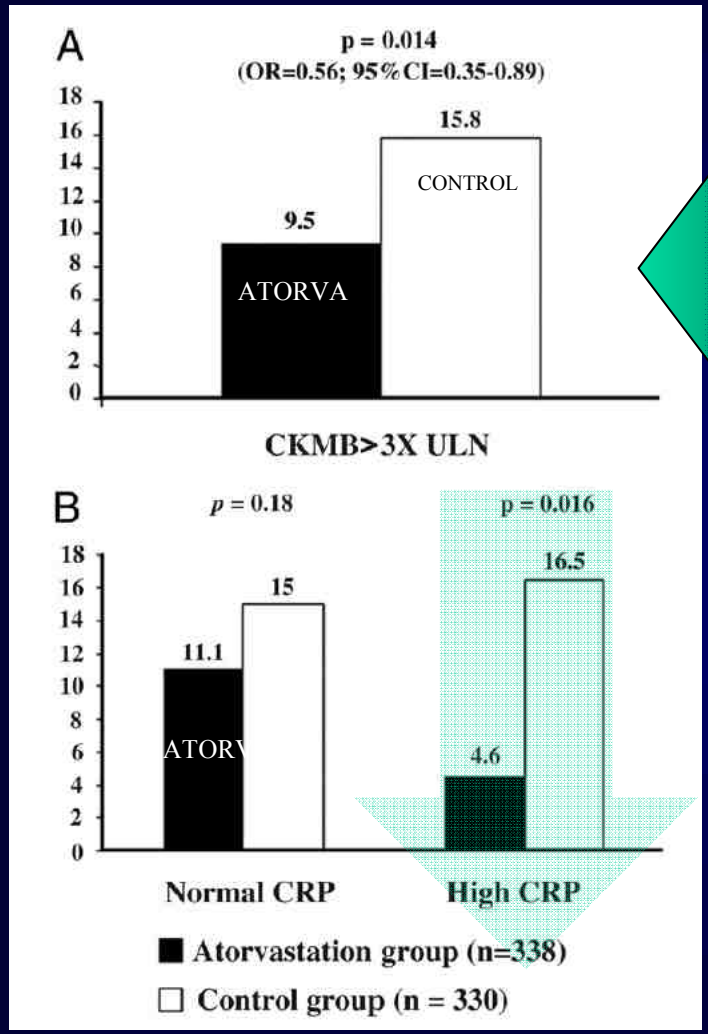
Impact of a Single High Loading Dose of Atorvastatin on Periprocedural Myocardial Infarction

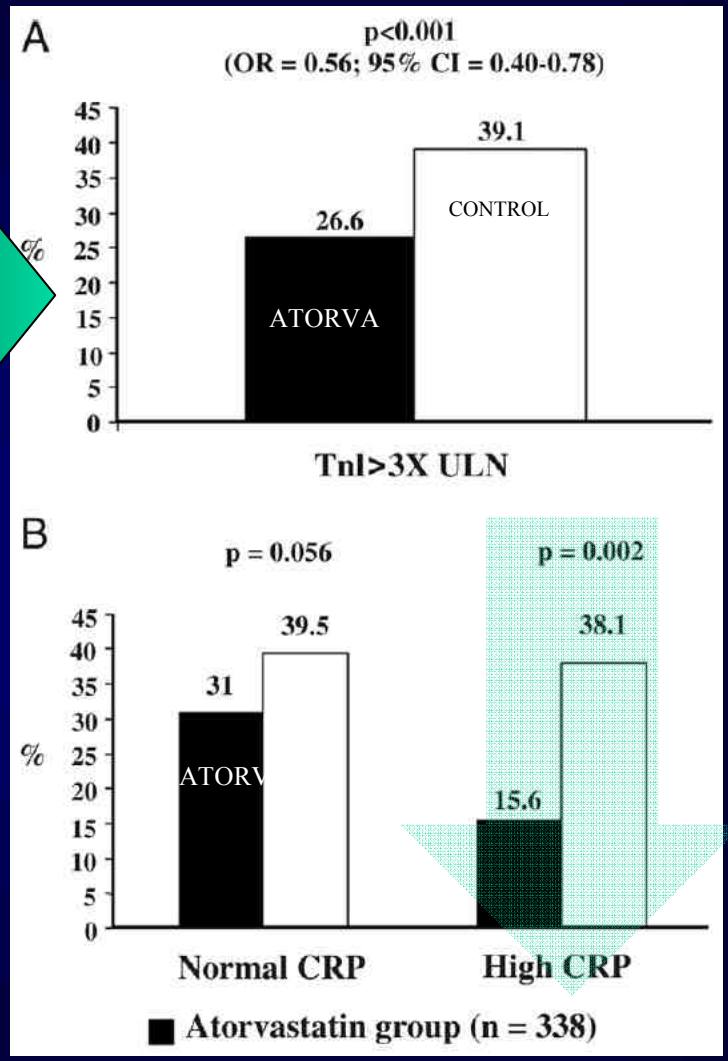
Carlo Briguori, MD, PHD,*† Gabriella Visconti, MD,* Amelia Focaccio, MD,* Bruno Golia, MD,* Alaide Chieffo, MD,† Alfredo Castelli, MD,† Marco Mussardo, MD,† Matteo Montorfano, MD,† Bruno Ricciardelli, MD,* Antonio Colombo, MD†

Naples and Milan, Italy

Statin naive PCI




A
p = 0.014
(OR=0.56; 95% CI=0.35-0.89)
18
16
14
12
10
8
6
4
2
0
15.8
CONTROL
9.5
ATORVA
CKMB>3X ULN
B
p = 0.18
p = 0.016
18
16
14
12
10
8
6
4
2
0
11.1
15
ATORV
4.6
16.5
Normal CRP
High CRP
Atorvastation group (n=338)
Control group (n = 330)


A
p<0.001
(OR = 0.56; 95% CI = 0.40-0.78)
45
40
35
30
25
20
15
10
5
0
%
39.1
CONTROL
26.6
ATORVA
TnI>3X ULN
B
p = 0.056
p = 0.002
45
40
35
30
25
20
15
10
5
0
%
39.5
31
ATORV
38.1
15.6
Normal CRP
High CRP
Atorvastatin group (n = 338)

Efficacy of Atorvastatin Reload in Patients on Chronic Statin Therapy Undergoing Percutaneous Coronary Intervention

Results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial

Germano Di Sciascio, MD,* Giuseppe Patti, MD,* Vincenzo Pasceri, MD,†
Achille Gaspardone, MD,‡ Giuseppe Colonna, MD,§ Antonio Montinaro, MD§

Rome and Lecce, Italy

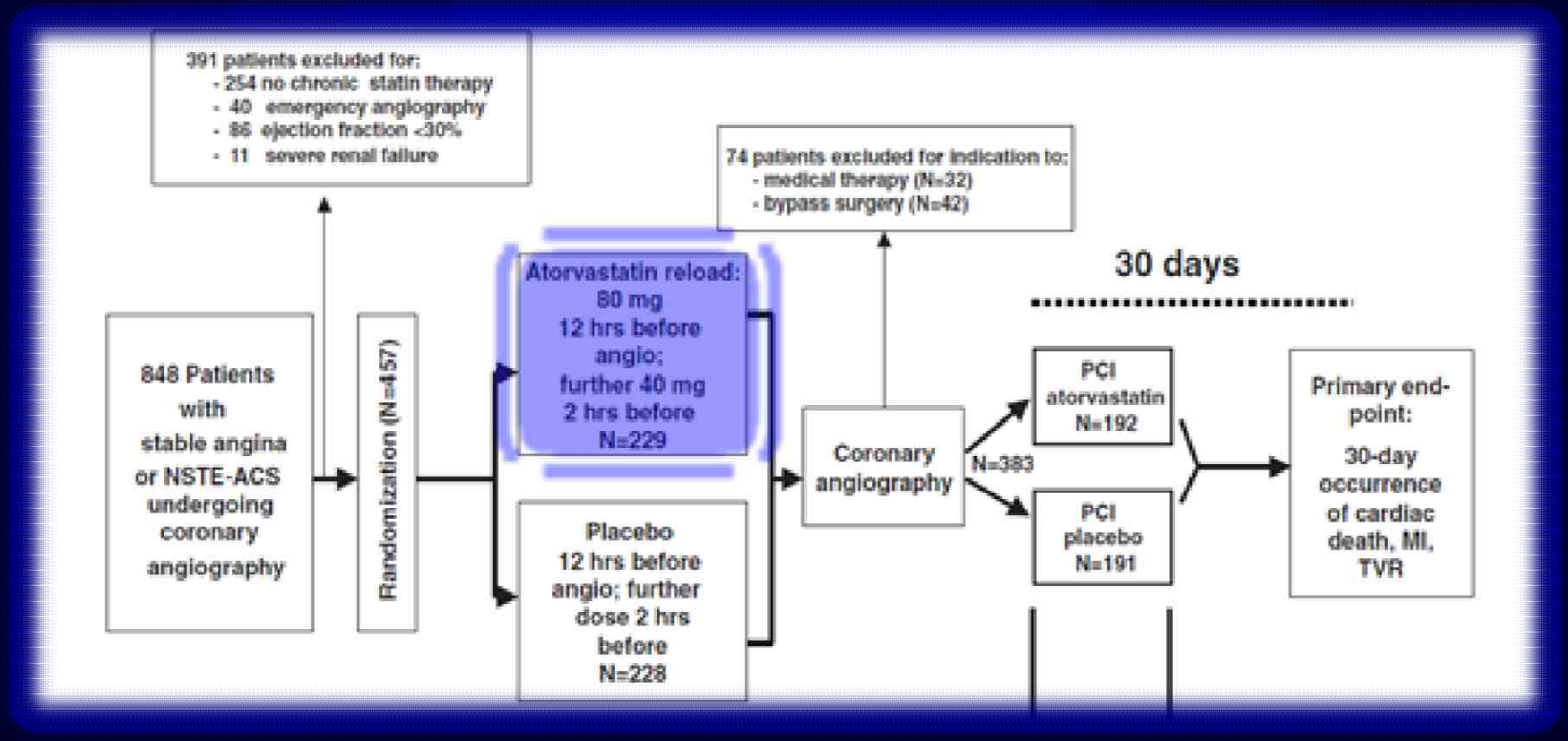


Table 3 Individual and Combined Outcome Measures of the Primary End Point at 30 Days in the Atorvastatin Reload and Placebo Groups

	Atorvastatin Reload (n = 192)	Placebo (n = 191)	p Value
Cardiac death	0	1 (0.5)	NS
Myocardial infarction	7 (3.7)	17 (8.9)	0.056
Stent thrombosis	0	1 (0.5)	NS
Target vessel revascularization	0	1 (0.5)	NS
Total MACE	7 (3.7)	18 (9.4)	0.037

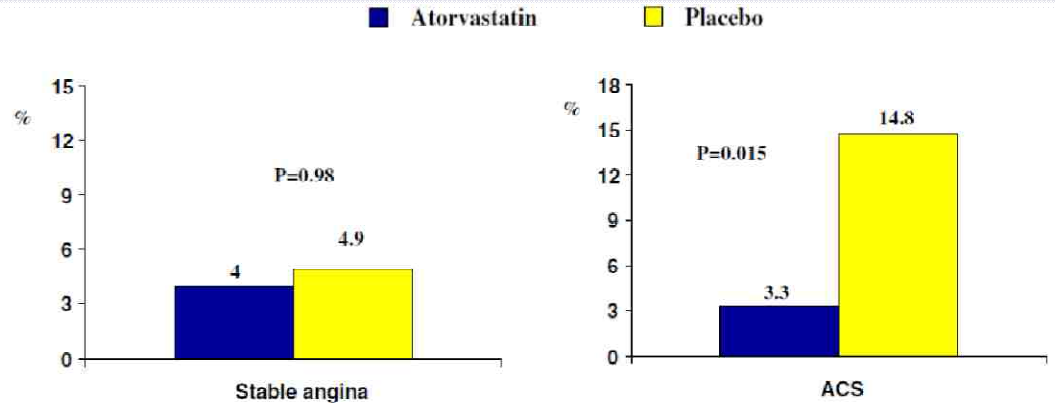


Figure 2 Secondary End Points

Conclusions The ARMYDA-RECAPTURE trial suggests that reloading with high-dose atorvastatin improves the clinical outcome of patients on chronic statin therapy undergoing PCI. These findings may support a strategy of routine reload with high-dose atorvastatin early before intervention even in the background of chronic therapy. (J Am Coll Cardiol 2009;54:558–65)

Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 54, No. 24, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.09.010

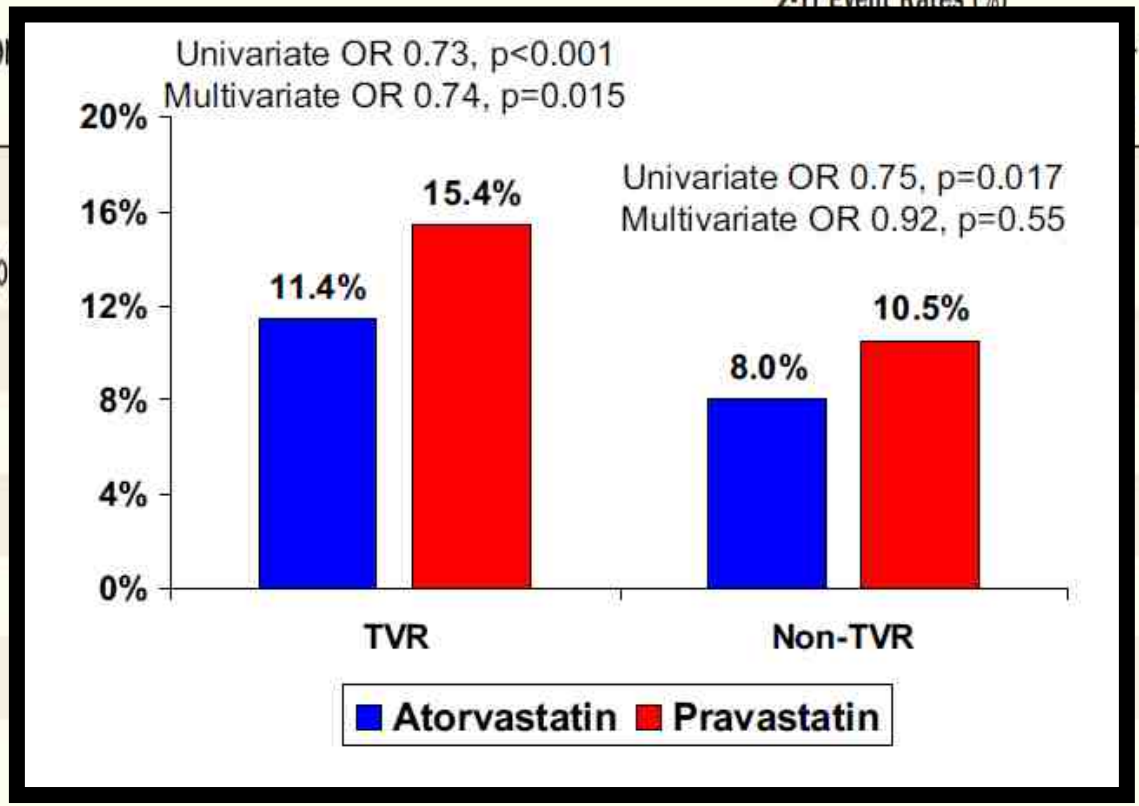
Interventional Cardiology

atorvastatin 80 mg or pravastatin 40 mg daily

Effect of Intensive Statin Therapy on Clinical Outcomes Among Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndrome

benefits in non-TVR, but not TVR, appear explained by reductions in on-treatment LDL-C and CRP, suggesting a possible pleiotropic mechanism of high-dose statin therapy.

End Point for Patients With PCI for Index Event	Log-Rank p Value
Primary end point	0.001
Death/MI/RI/UA with rehospitalizatio	<0.001
Death	0.057
MI	0.052
Stroke	0.648
Recurrent ischemia	<0.001
UA with rehospitalization	0.029
Revascularization after 30 days	0.002



Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 54, No. 4, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.04.033

CLINICAL RESEARCH — Clinical Trials

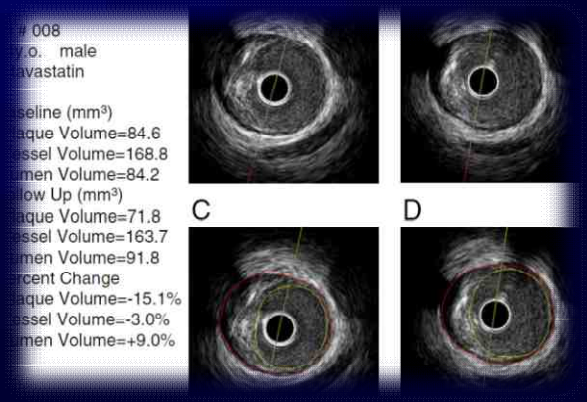
Effect of Intensive Statin Therapy on Regression of Coronary Atherosclerosis in Patients With Acute Coronary Syndrome

A Multicenter Randomized Trial Evaluated by Volumetric Intravascular Ultrasound Using Pitavastatin Versus Atorvastatin (JAPAN-ACS [Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome] Study)

Takafumi Hiro, MD,* Takeshi Kimura, MD,† Takeshi Morimoto, MD,‡ Katsumi Miyauchi, MD,§

	Both Groups (n = 252)	p Value Compared With Baseline	Pitavastatin (n = 125)	p Value Compared With Baseline	Atorvastatin (n = 127)	p Value Compared With Baseline	p Value Between Groups
Plaque volume (mm^3)	−9.4 ± 9.8	<0.001	−8.2 ± 8.9	<0.001	−10.6 ± 10.6	<0.001	0.05
Percent plaque volume (%)	−6.0 ± 6.2	<0.001	−5.7 ± 6.3	<0.001	−6.3 ± 6.1	<0.001	0.5

What about the longer term ?



Early intensive statin treatment for six months improves long-term clinical outcomes in patients with acute coronary syndrome (Extended-ESTABLISH trial): A follow-up study

Accepted 1 December 2009

Tomotaka Dohi, Katsumi Miyauchi*, Shinya Okazaki, Takayuki Yokoyama, Naotake Yanagisawa, Hiroshi Tamura, Takahiko Kojima, Ken Yokoyama, Takeshi Kurata, Hiroyuki Daida

Department of Cardiovascular Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

The primary endpoint was the first occurrence of major adverse cardiac and cerebrovascular events (MACCE) : all-cause death, recurrent ACS and stroke.

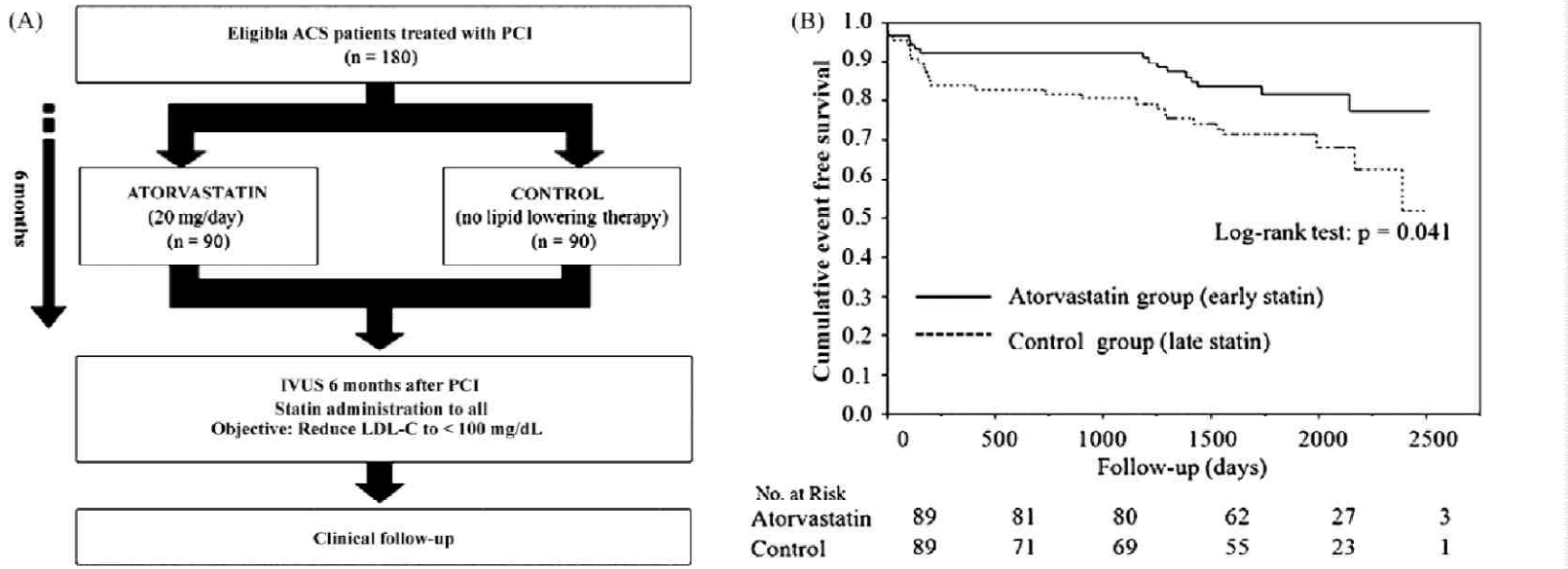
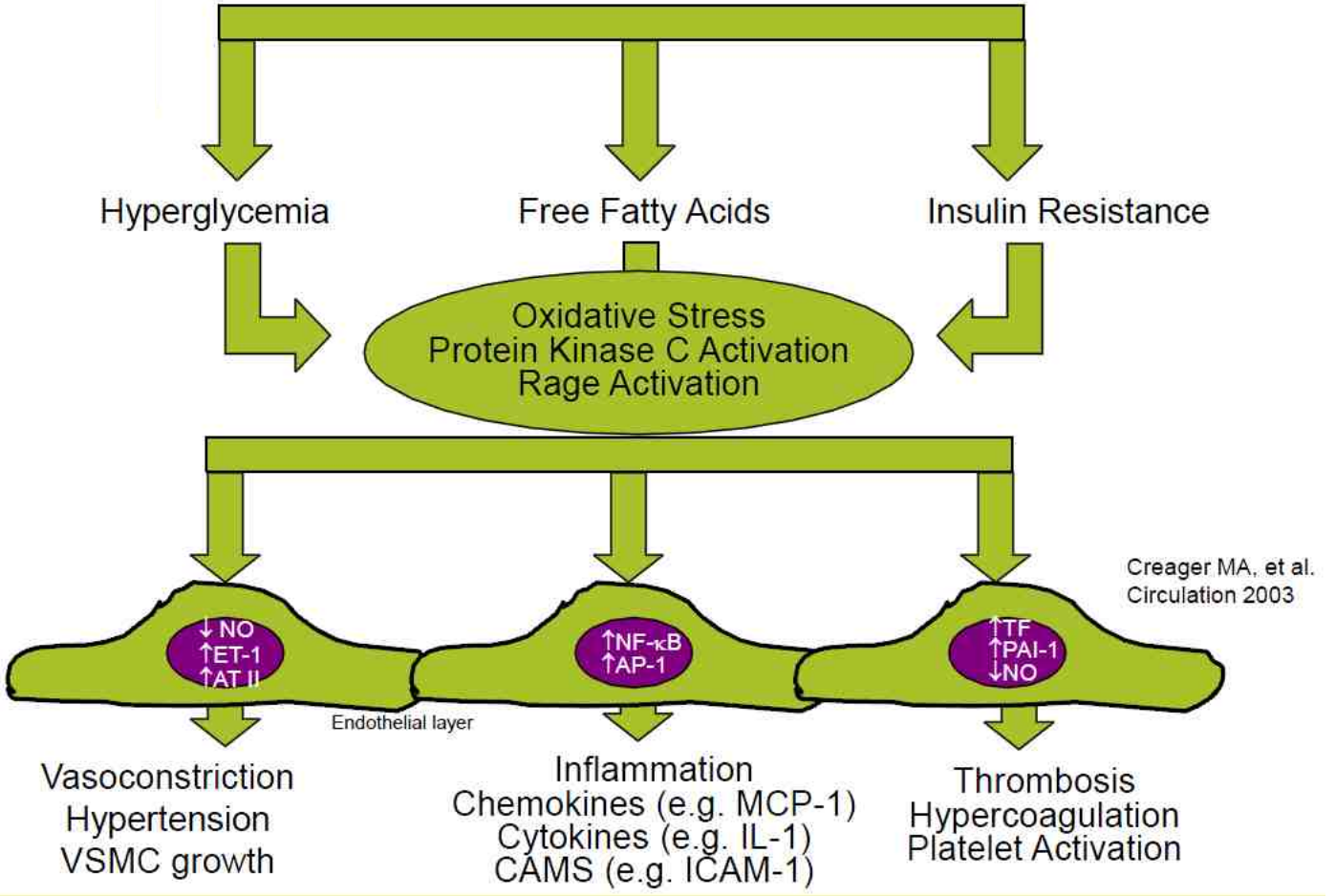


Fig. 1. (A) Summary of follow-up study of Extended-ESTABLISH trial. (B) Kaplan–Meier estimates of incidence of MACCE. Cumulative event-free survival is significantly higher in atorvastatin, than control group (log-rank test, $p = 0.041$).

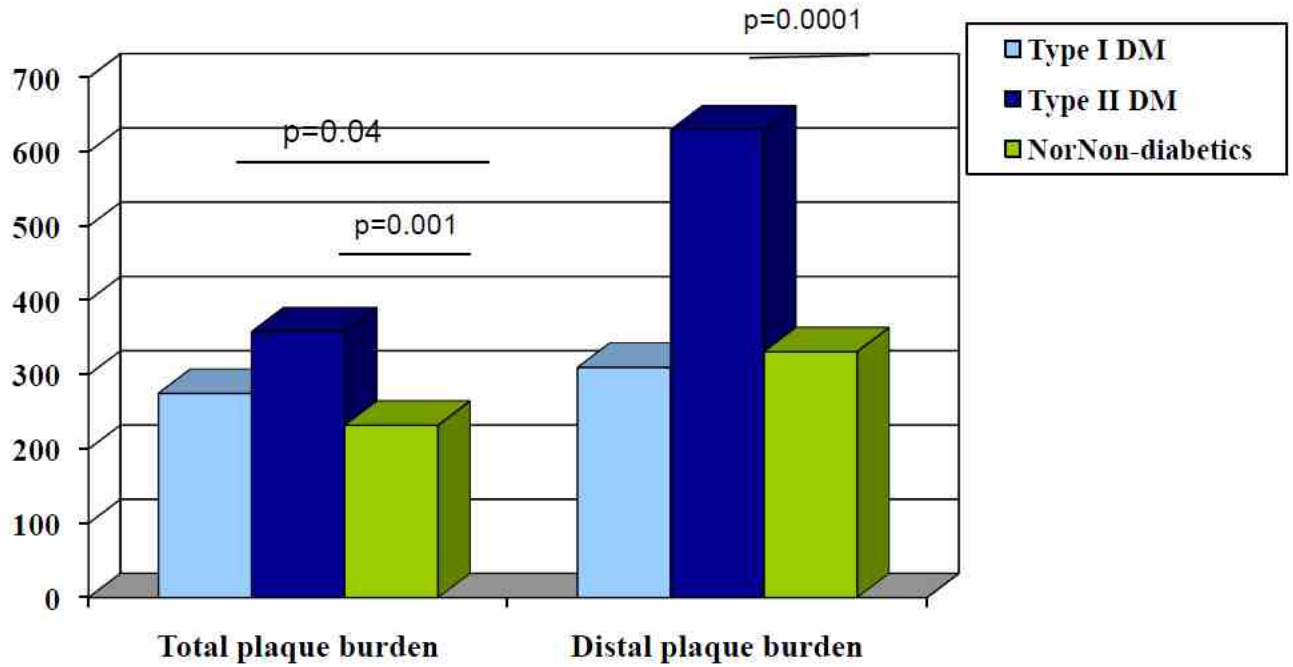
DIABETES

Diabetes Mellitus



Creager MA, et al.
Circulation 2003

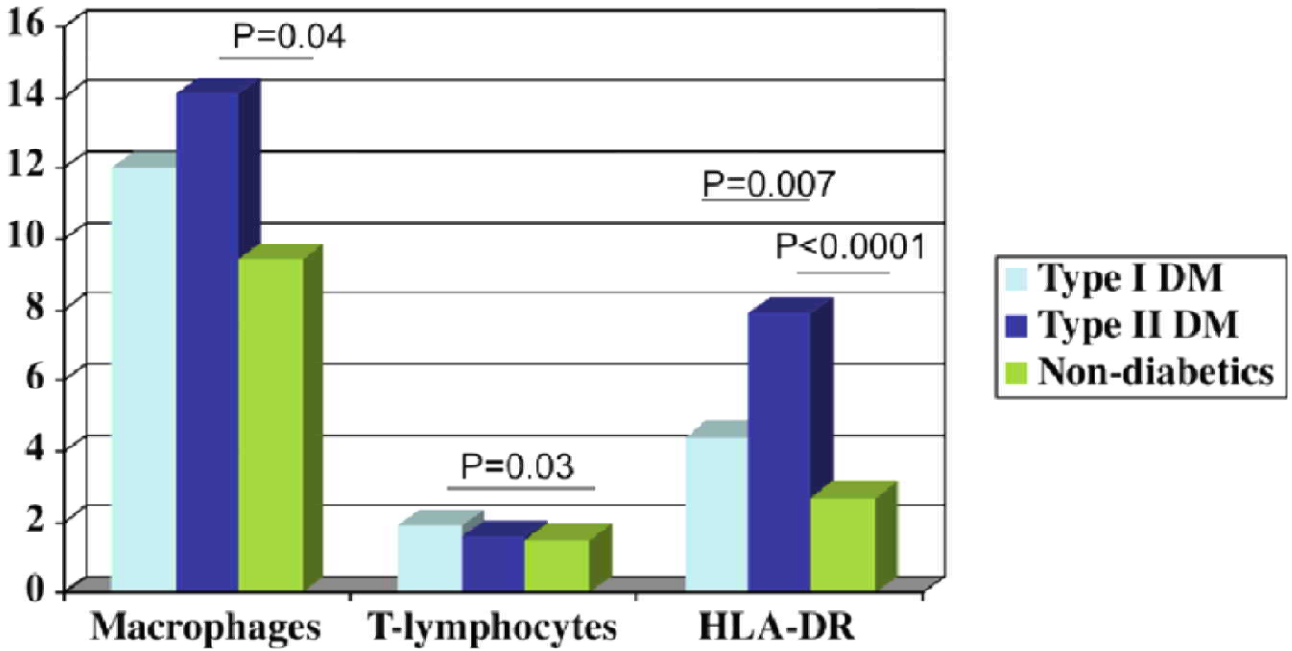
Plaque Characteristics in Diabetics and Non-diabetics



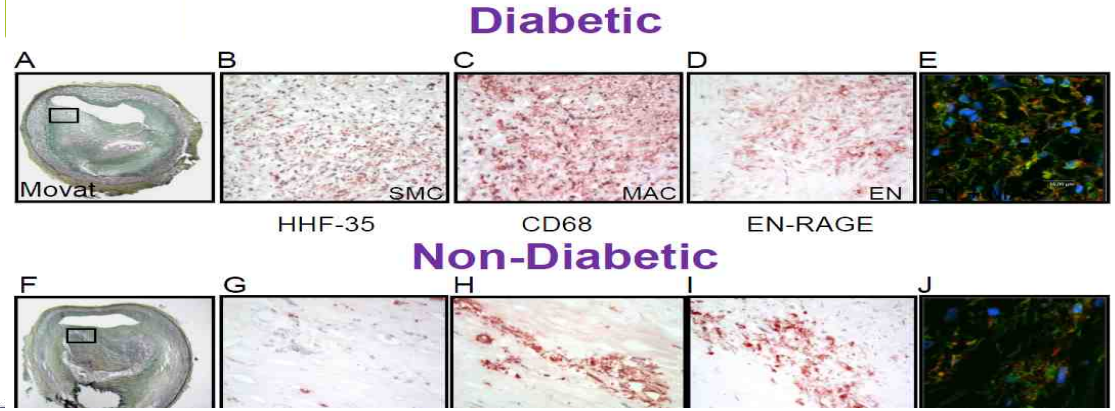
Burke , el al. ATVB 2004

Diabetics have more plaque

Semi-quantitative Score for Macrophages, T-lymphocytes and HLA-DR Expression in Diabetics and Non-diabetic plaques

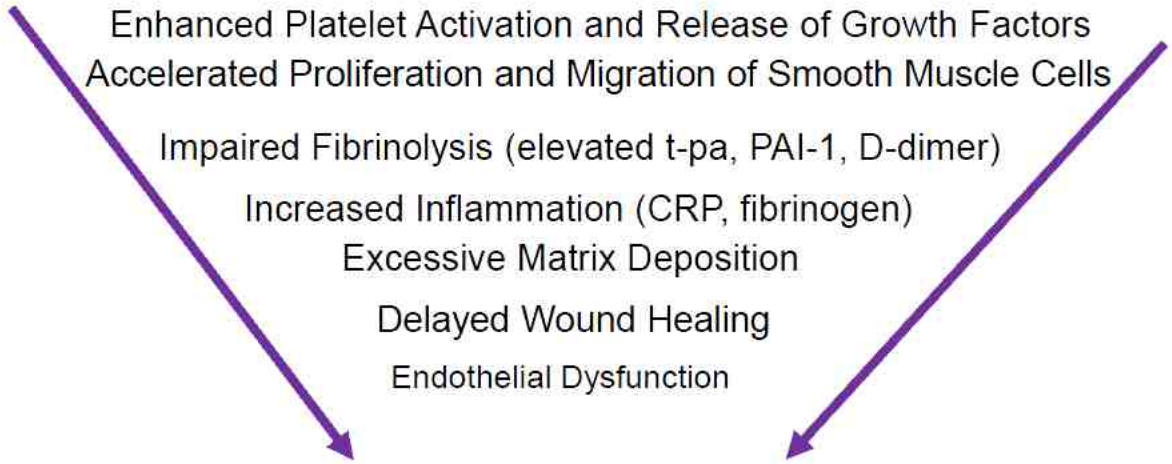


It is more inflammatory



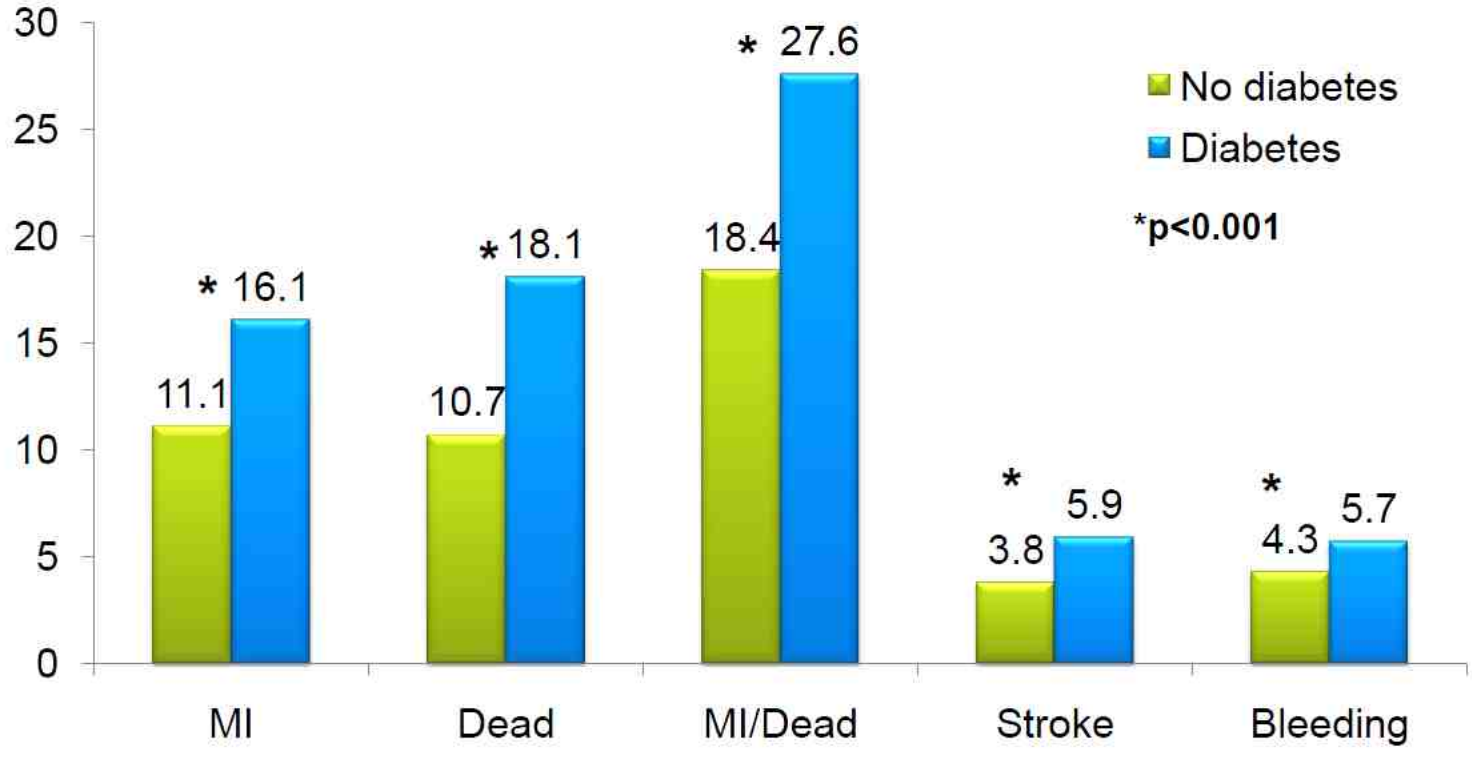
R09

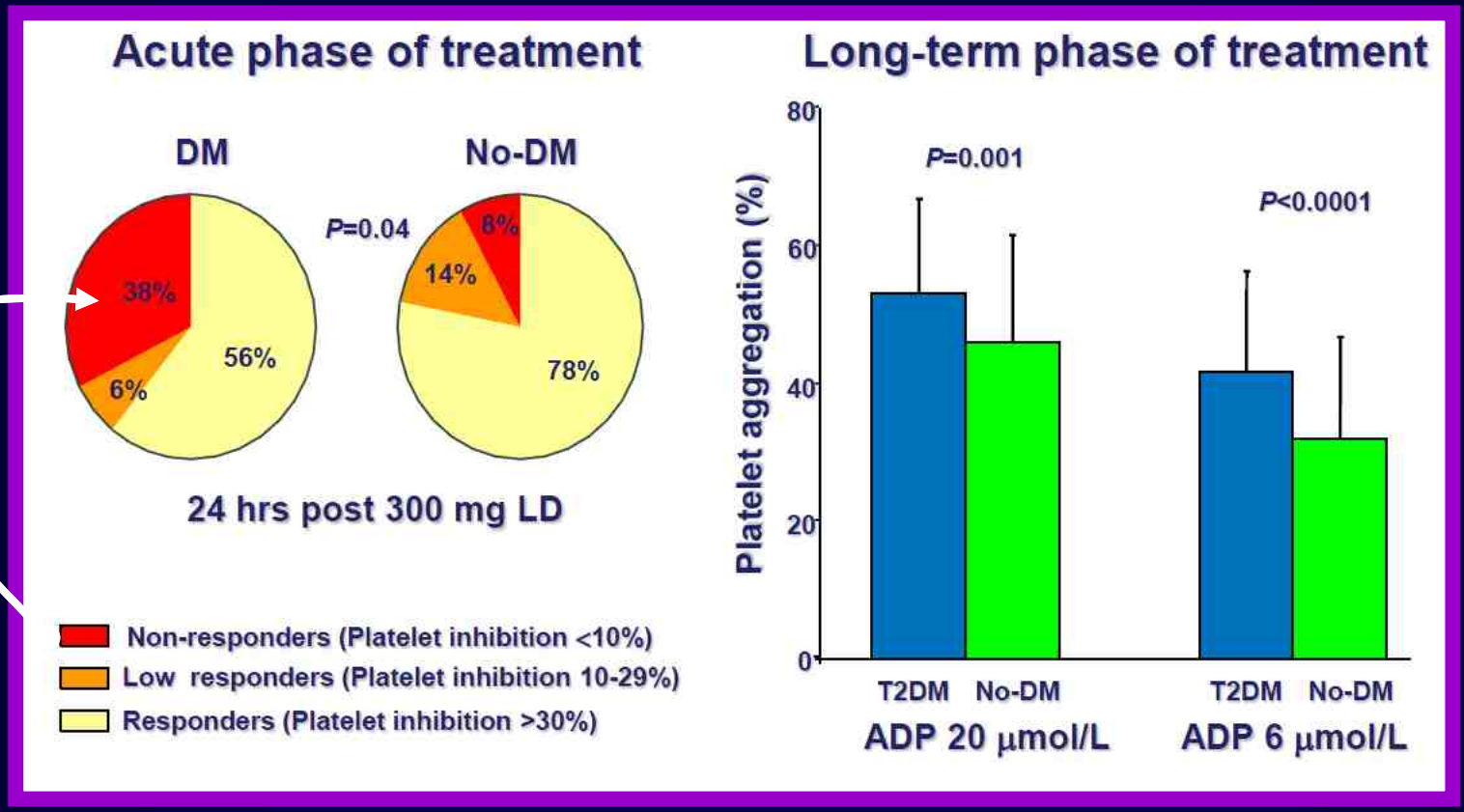
Consequences of Insulin Resistance In Type II Diabetes



Abnormal Response to Vascular Injury

Complications within 2 years after PCI in 224,833 patients from the SCAAR registry

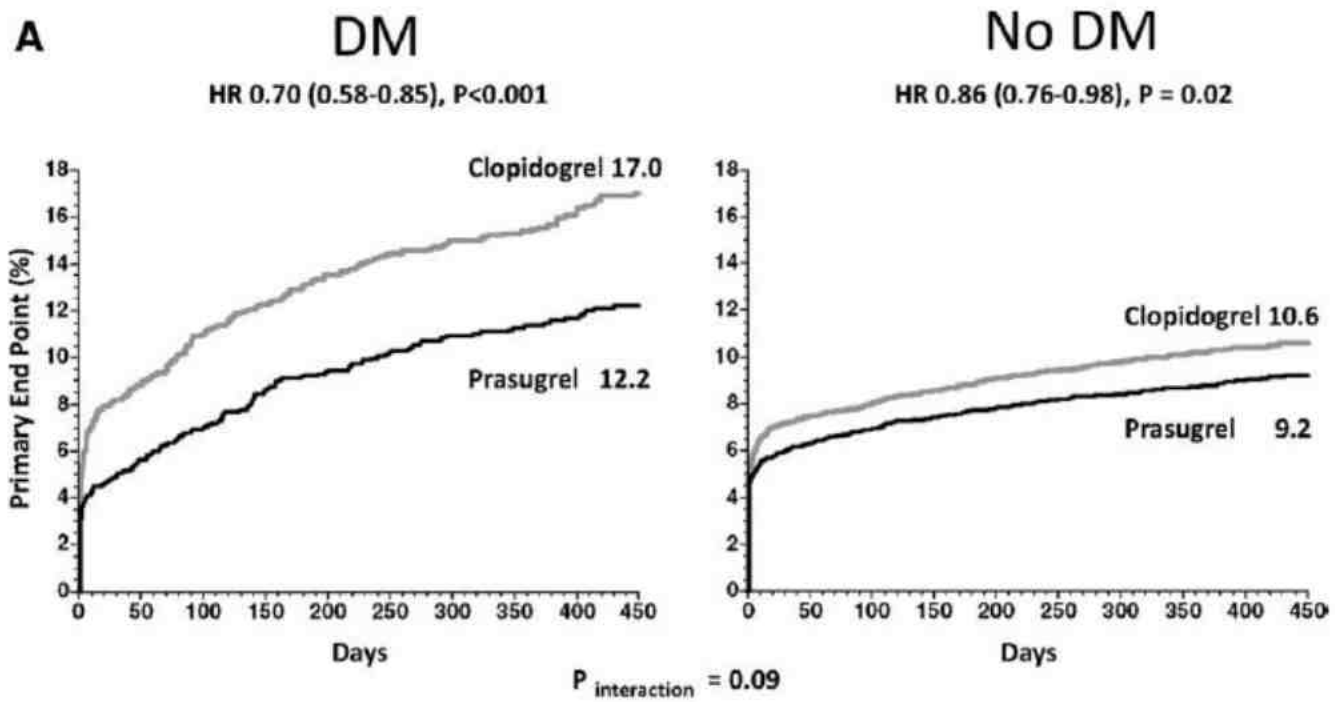




Diabetics have more resistant platelets

TRITON TIMI 38: Diabetics

MACE

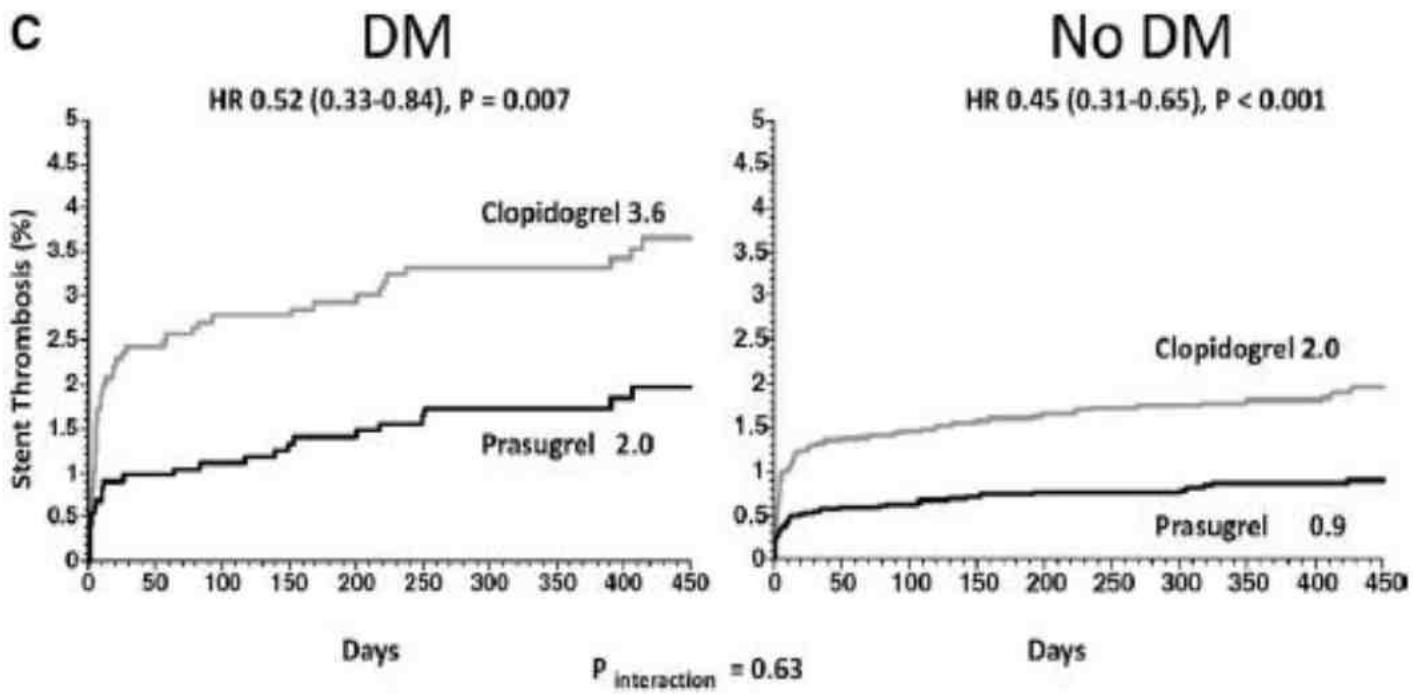


Wiviott et al. Circulation 2008.

Diabetics : more potent APT

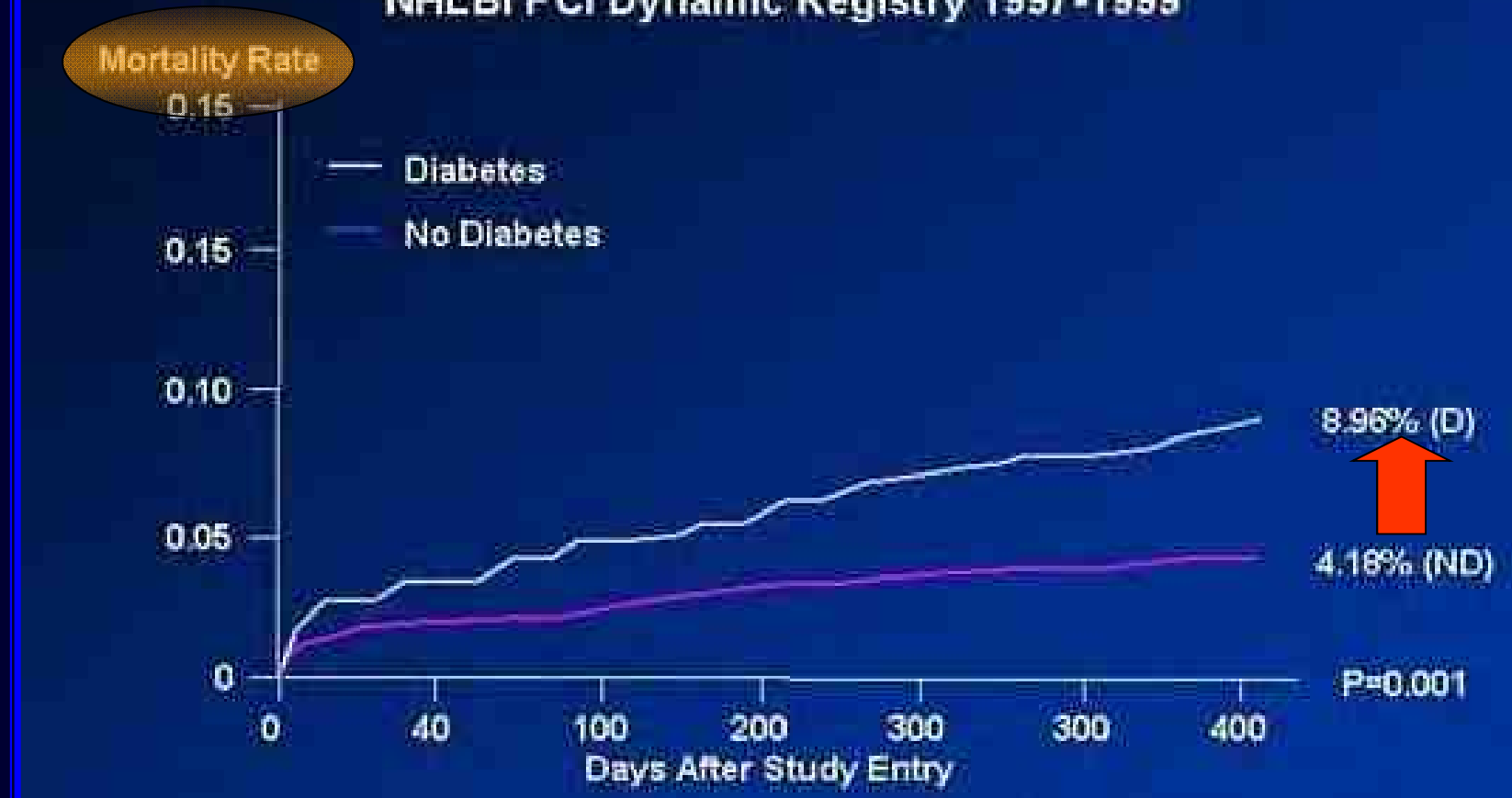
TRITON TIMI 38: Diabetics

STENT THROMBOSIS



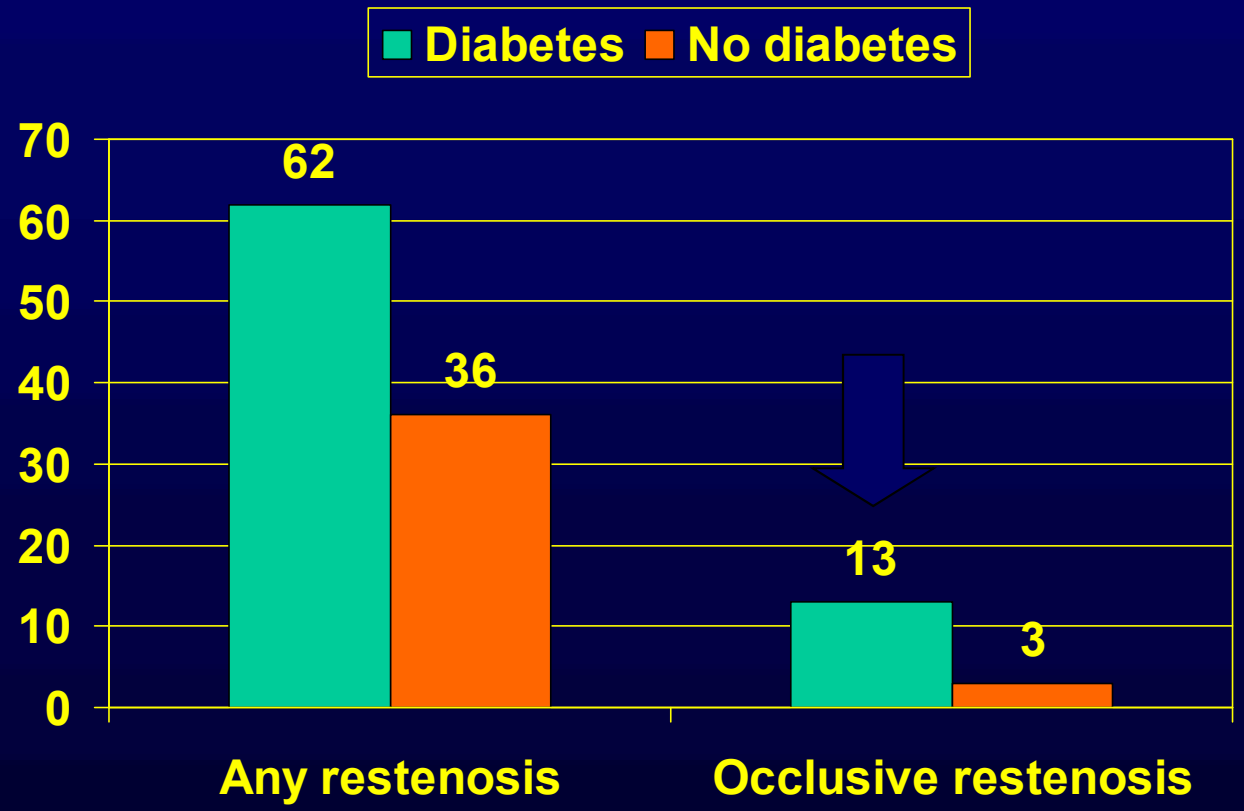
Wiviott et al. Circulation 2008.

Diabetes Doubles Mortality Risk After Successful PCI



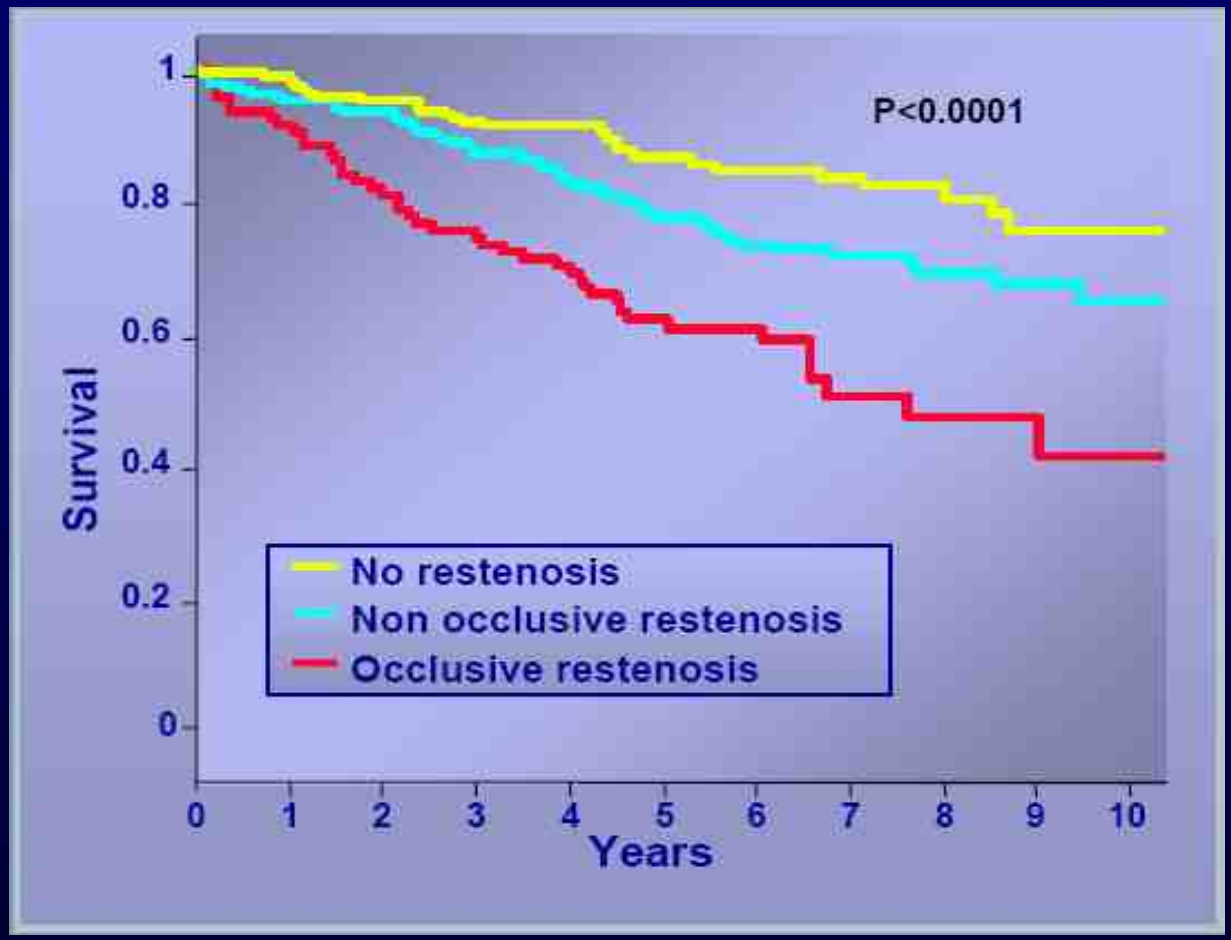
Laskey, WK, et al, Am J Cardiol 2002;90:1062-1067

Occlusive restenosis: a specific feature of diabetic patients



Van Belle et al, Circulation 2001; 103: 1218-24

Long term Survival of diabetics according to restenosis at 6 months

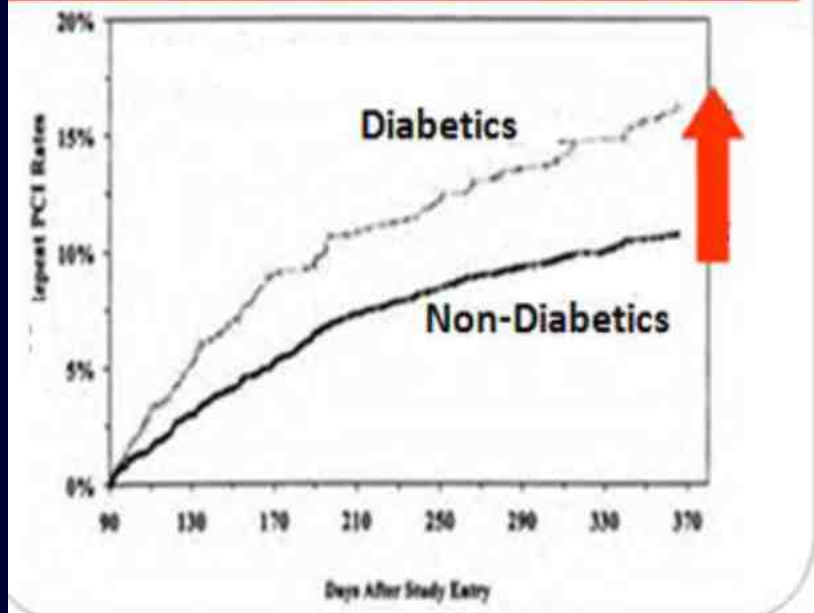


N=637

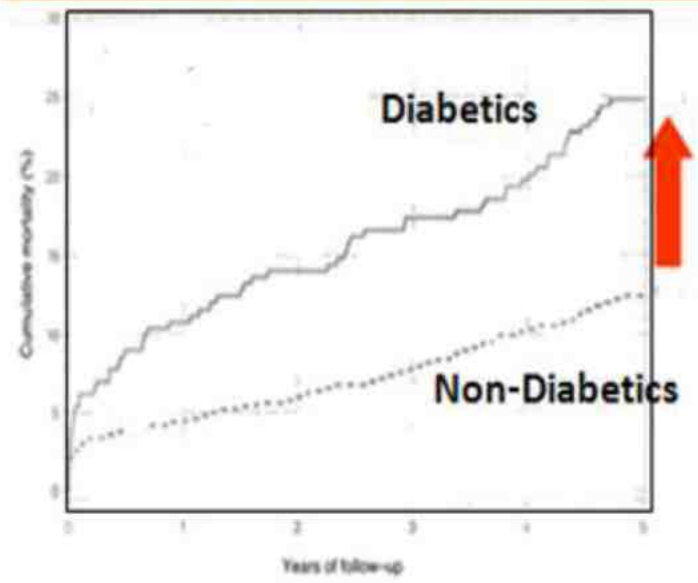
Van Belle et al Circulation 2001; 103:1218-24

Diabetes is a problem for either revascularisation option

Need for repeat procedure after PCI in diabetic population



Five year mortality CABG with and without DM



Takara *et al. Cardiovascular Diabetology* 2010, **9**:1
http://www.cardiab.com/content/9/1/1

CARDIO VASCULAR DIABETOLOGY

ORIGINAL INVESTIGATION **Open Access**

Long-term prognosis of diabetic patients with acute myocardial infarction in the era of acute revascularization

Ayako Takara[1], Hiroshi Ogawa[*2], Yasuhiro Endoh[1], Fumiaki Mori[2], Jun-ichi Yamaguchi[2], Atsushi Takagi[2], Ryo Koyanagi[2], Tsuyoshi Shiga[2], Hiroshi Kasanuki[2], Nobuhisa Hagiwara[2]

Between January 1999 and June 2001, 3021 consecutive patients from 17 participating hospitals in Japan were registered

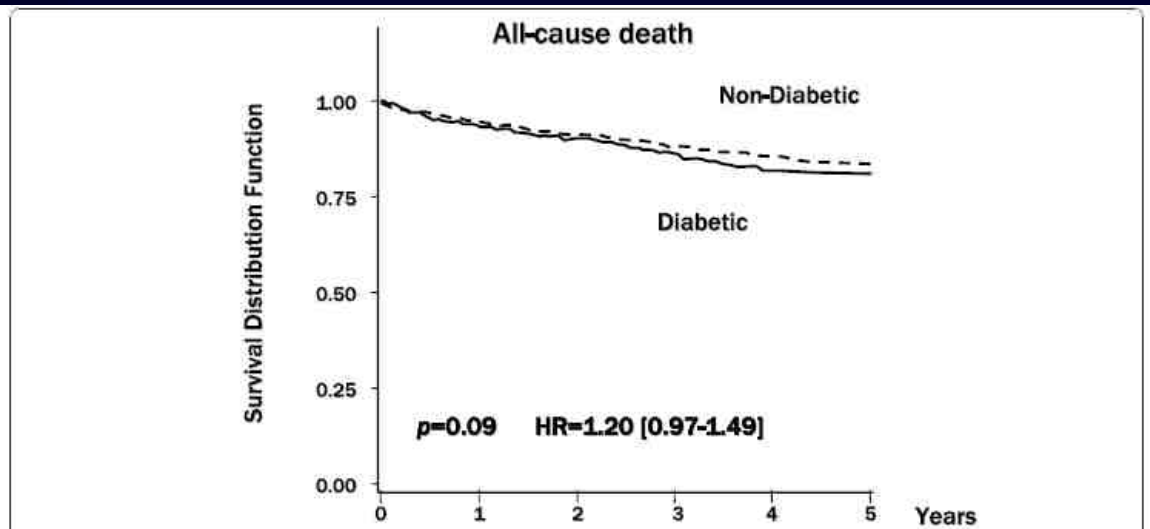


Figure 1 Kaplan-Meier survival curves for all-cause mortality among AMI patients with or without diabetes. The solid line indicates AMI patients with diabetes; the dotted line indicates those without diabetes.

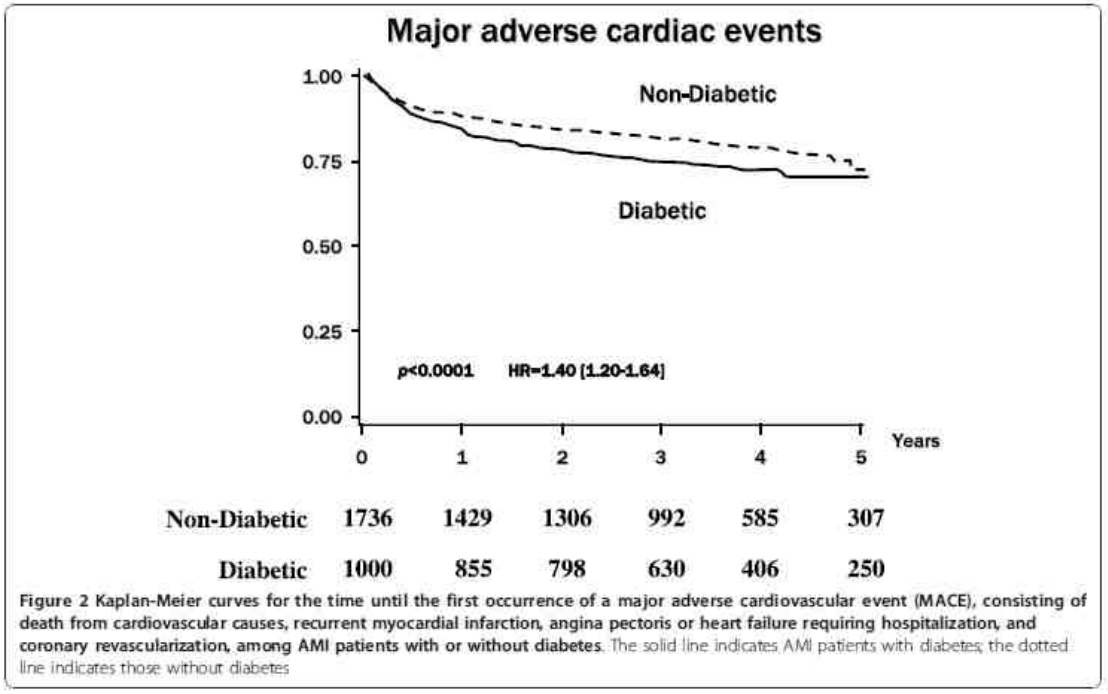


Figure 2 Kaplan-Meier curves for the time until the first occurrence of a major adverse cardiovascular event (MACE), consisting of death from cardiovascular causes, recurrent myocardial infarction, angina pectoris or heart failure requiring hospitalization, and coronary revascularization, among AMI patients with or without diabetes. The solid line indicates AMI patients with diabetes; the dotted line indicates those without diabetes

- Any elevation in glycemia, even subdiabetic, increases risk of CV disease and events*

- Goal for Hgb A1Cin DCCT/EDIC Study** (DEMD of NIH) was <6.05% and ESC advises Hg A1C <6.1-6.5%

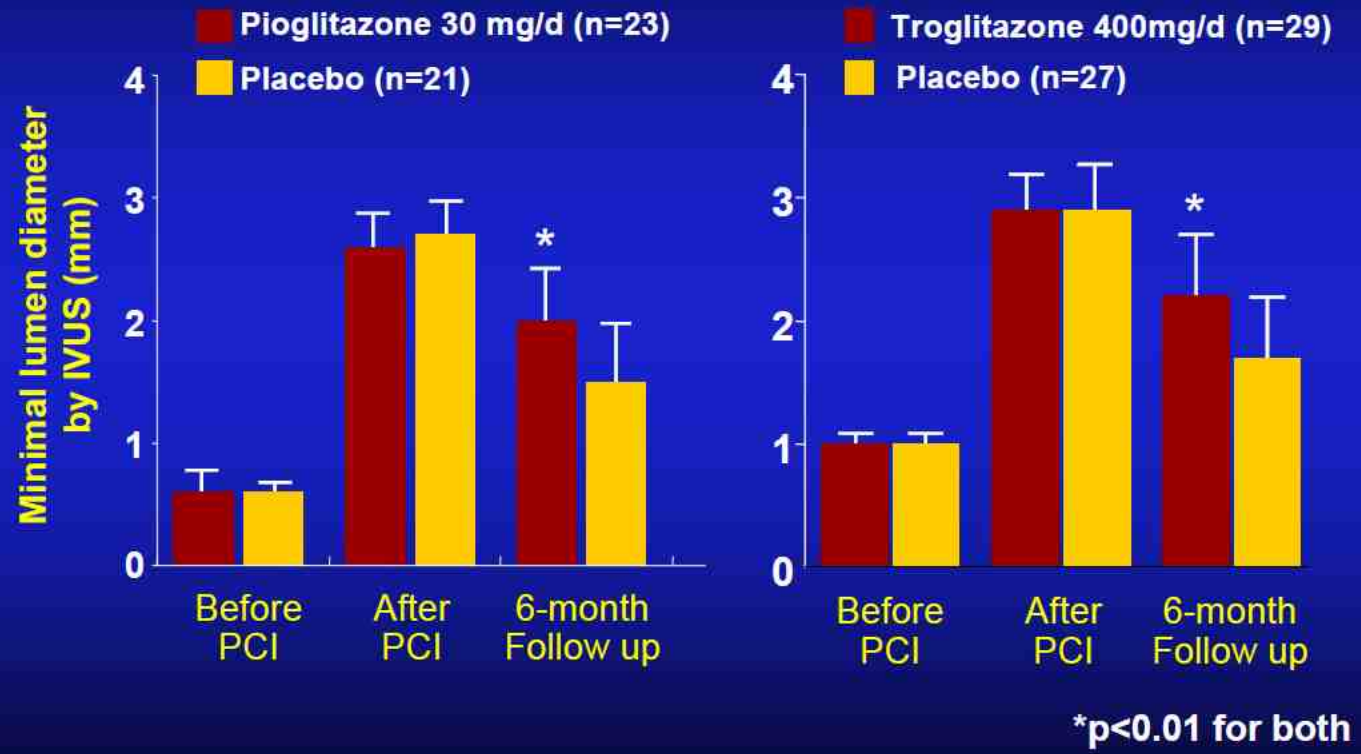
- DCCT/EDIC Study of 1441 patients with Type 1 DM randomized to intensive vs conventional therapy and followed 17 yrs

Intensive therapy (A1C<6.05%) reduced risk
cardiovascular disease by 42% (P=0.02)
severe clinical events (MI, stroke, or CV death) by 57%

* *Khaw KT et al Ann Intern Med 2004;141:413-20.*

** *DCCT/EDIC Study Res Grp N Engl J Med 2005 (Dec 22);353:2643-*

Thiazolidinediones Reduce Late Luminal Loss After PCI/Stent



Tagaki T et al. Am Heart J. 2003;146:e5.
Tagaki T et al, JACC 2000; 36:1529-1535

Complementary effects of sirolimus-eluting stents and glycoprotein IIb/IIIa inhibitors for percutaneous coronary intervention in diabetic patients: one-year follow up of a single-centre registry

P de Araujo Goncalves, R Seabra-Gomes, R Teles, M Almeida, C Aguiar, L Raposo, J Ferreira, F Pereira Machado

Heart 2006;92:1155–1156. doi: 10.1136/hrt.2005.079780

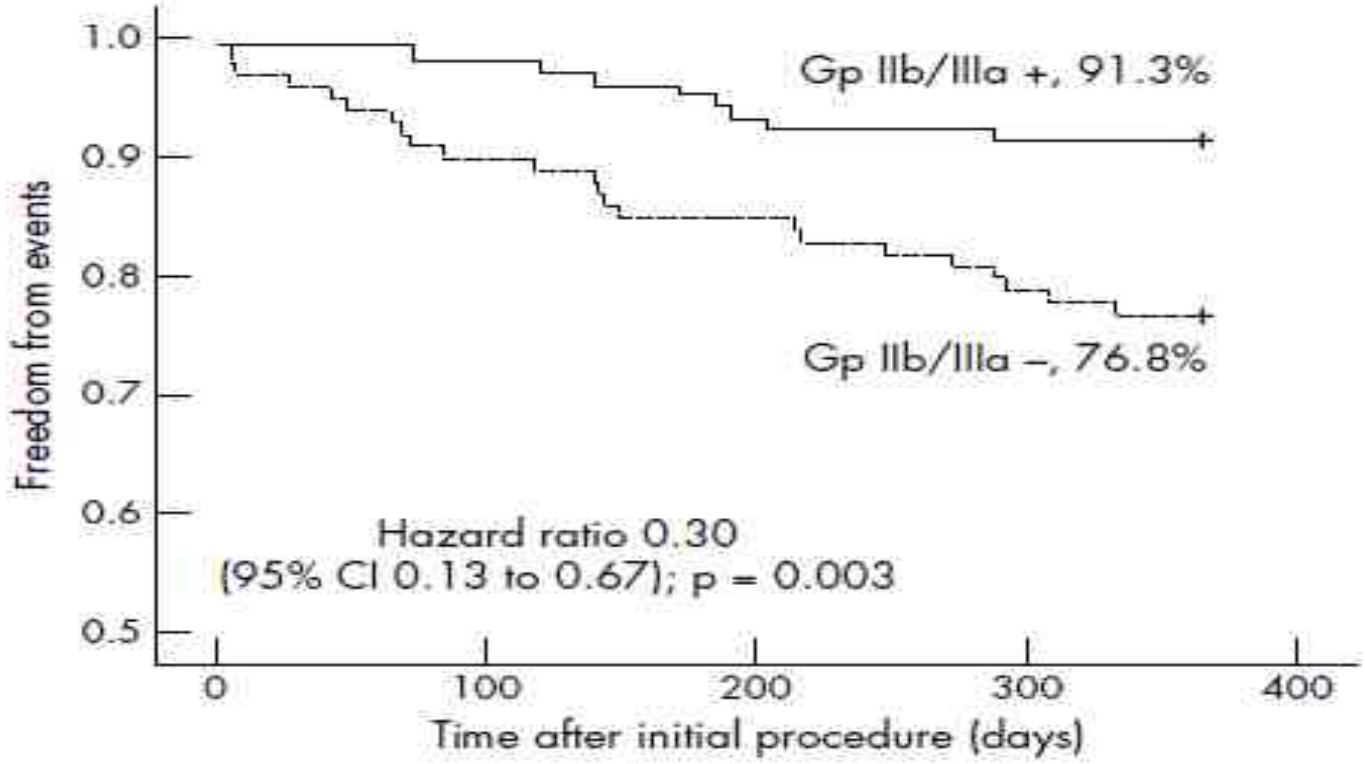


Figure 1 Major adverse cardiac event-free survival at one year. CI, confidence interval; Gp, glycoprotein.

What else ?

Patterns of use and potential impact of early β-blocker therapy in non–ST-elevation myocardial infarction with and without heart failure: The Global Registry of Acute Coronary Events

Michael Emery, MD,[a] José López-Sendón, MD,[b] Philippe Gabriel Steg, MD,[c] Frederick A. Anderson, Jr, PhD,[d] Omar H. Dabbous, MD, MPH,[d] Aliocha Scheuble, MD,[c] and Kim A. Eagle, MD,[a] for the GRACE Investigators
Ann Arbor, MI; Madrid, Spain; Paris, France; and Worcester, MA

Figure 2

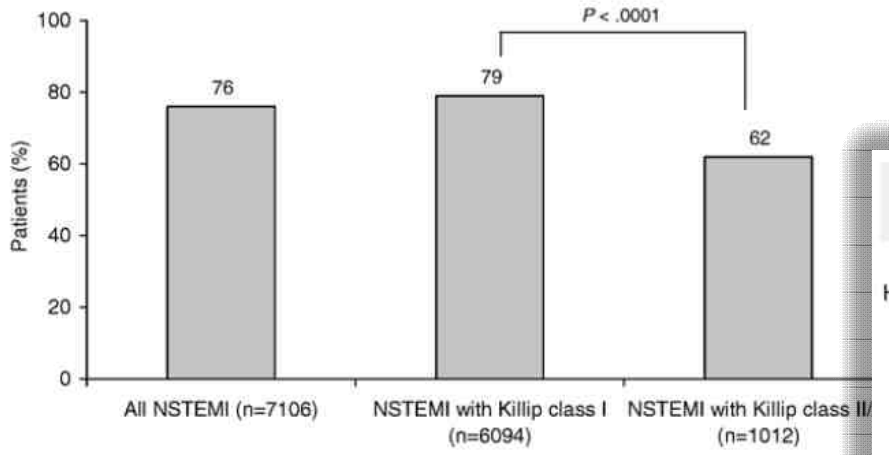
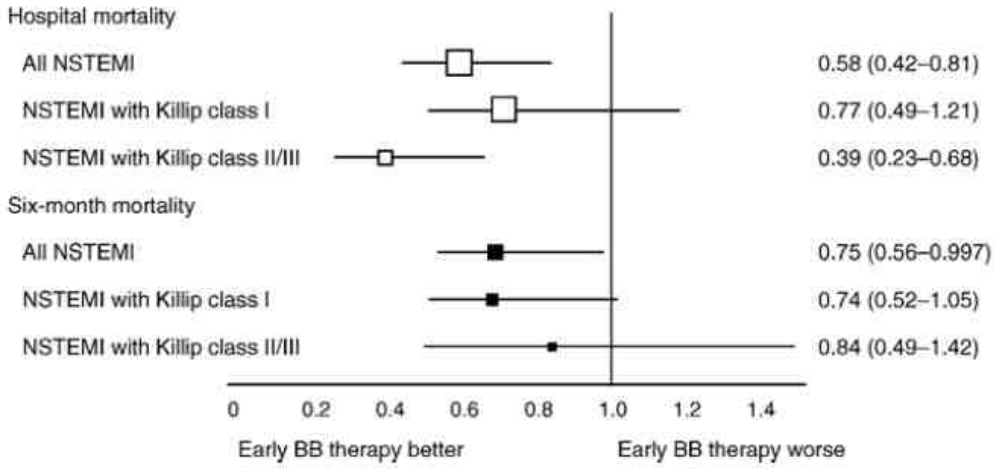


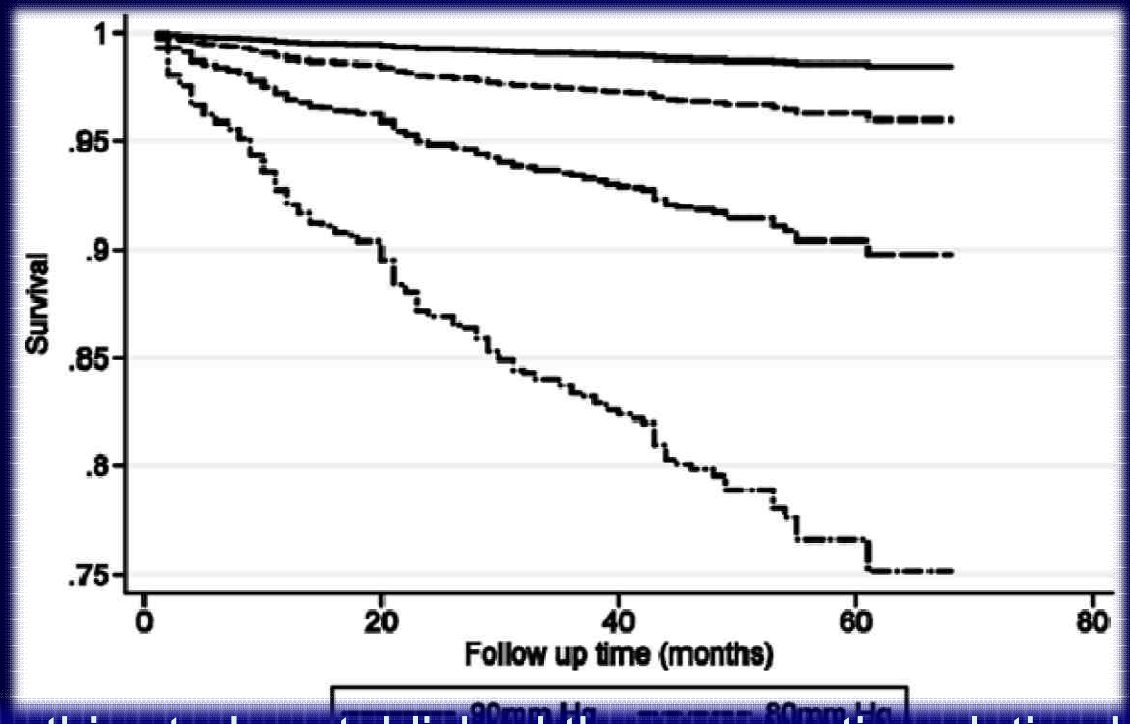
Figure 3



Relation Between Blood Pressure at Hospital Discharge After an Acute Coronary Syndrome and Long-Term Survival

Cheuk-Kit Wong, MDa,*, Peter Herbison, MScb, and Eng Wei Tang, MMeda

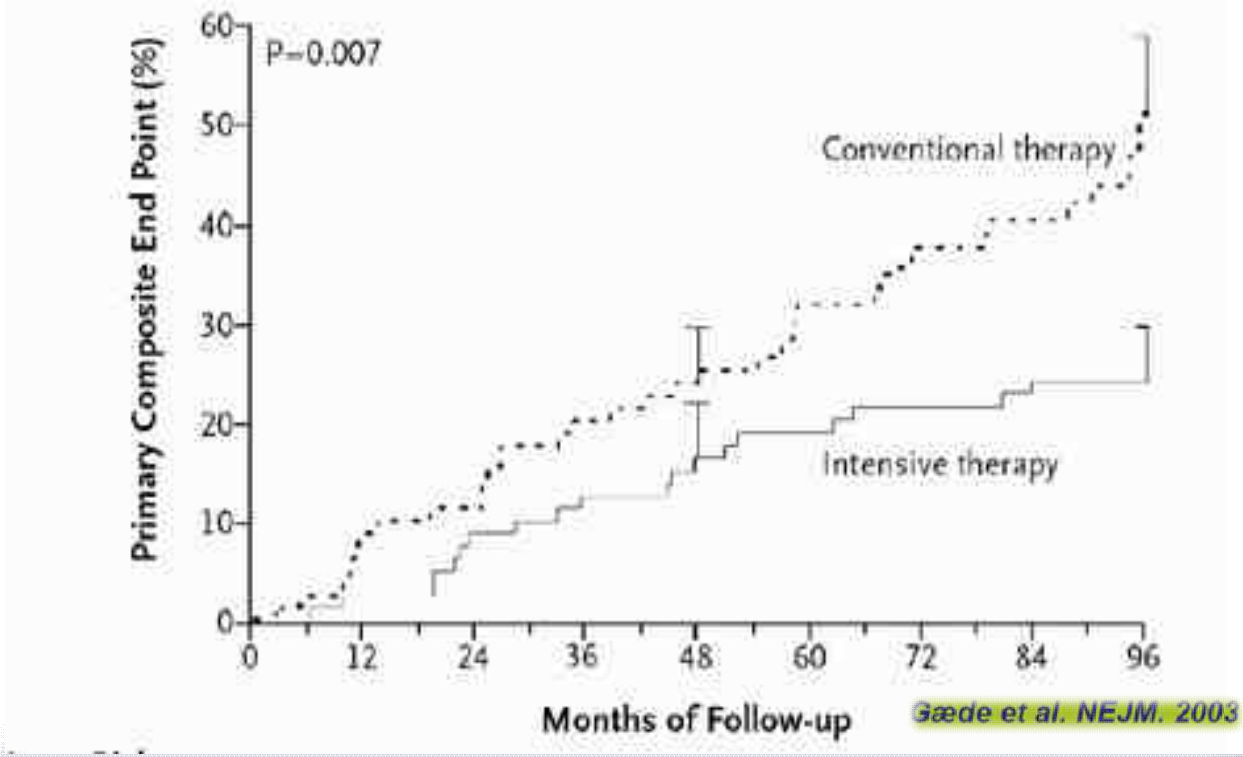
Am J Cardiol2008;101:1239 –1241



In conclusion, this study established the prognostic relation between diastolic BP and survival after ACS independent of the use of cardio-protective medications and the GRACE discharge risk score

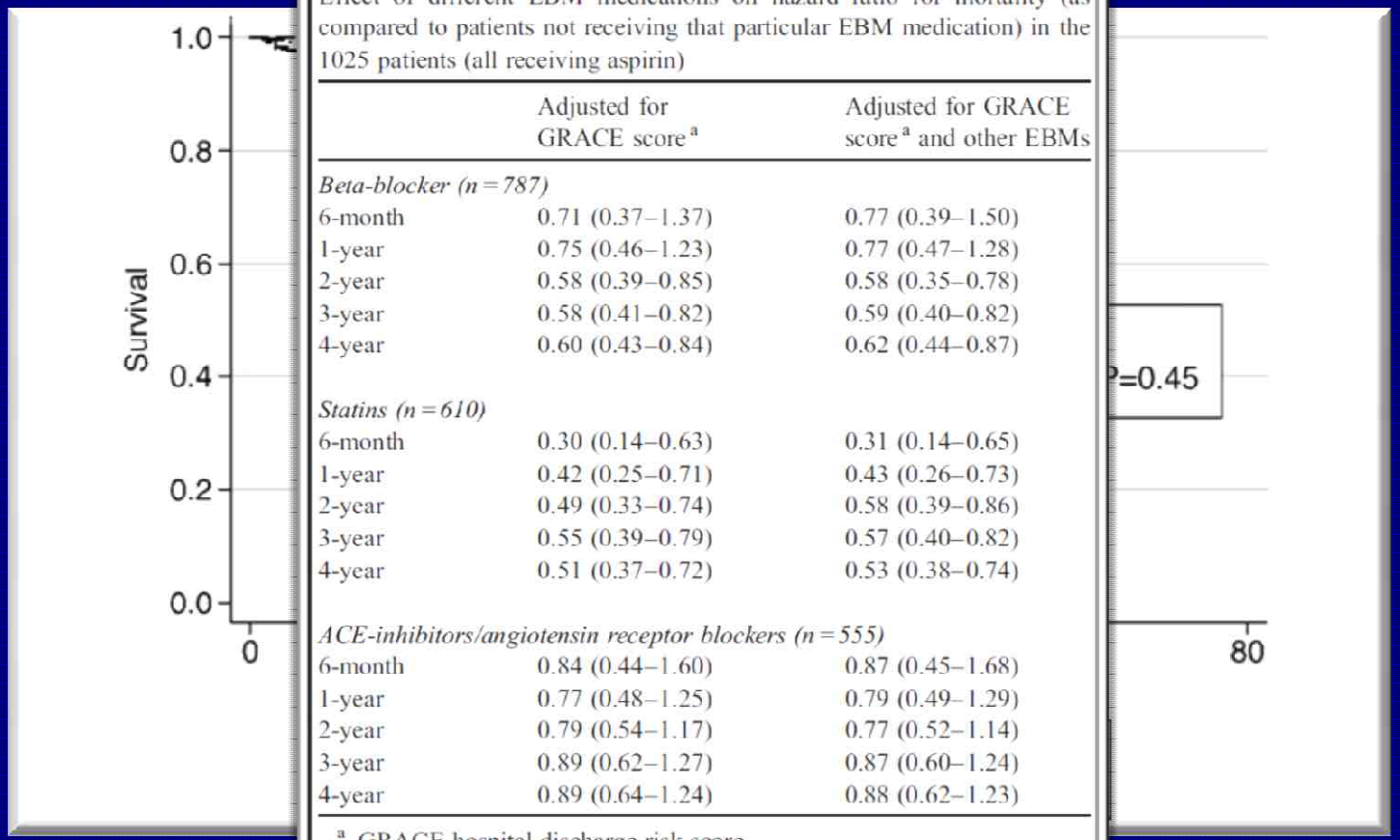
Putting it all together

Multi-factorial Strategy



The use of different evidence-based medications: 5-year survival after an acute coronary syndrome: An observational study Cheuk-Kit Wong

International Journal of Cardiology 132 (2009) 197–202



Effect of different EBM medications on hazard ratio for mortality (as compared to patients not receiving that particular EBM medication) in the 1025 patients (all receiving aspirin)

	Adjusted for GRACE score[a]	Adjusted for GRACE score[a] and other EBMs
Beta-blocker (n = 787)		
6-month	0.71 (0.37–1.37)	0.77 (0.39–1.50)
1-year	0.75 (0.46–1.23)	0.77 (0.47–1.28)
2-year	0.58 (0.39–0.85)	0.58 (0.35–0.78)
3-year	0.58 (0.41–0.82)	0.59 (0.40–0.82)
4-year	0.60 (0.43–0.84)	0.62 (0.44–0.87)
Statins (n = 610)		
6-month	0.30 (0.14–0.63)	0.31 (0.14–0.65)
1-year	0.42 (0.25–0.71)	0.43 (0.26–0.73)
2-year	0.49 (0.33–0.74)	0.58 (0.39–0.86)
3-year	0.55 (0.39–0.79)	0.57 (0.40–0.82)
4-year	0.51 (0.37–0.72)	0.53 (0.38–0.74)
ACE-inhibitors/angiotensin receptor blockers (n = 555)		
6-month	0.84 (0.44–1.60)	0.87 (0.45–1.68)
1-year	0.77 (0.48–1.25)	0.79 (0.49–1.29)
2-year	0.79 (0.54–1.17)	0.77 (0.52–1.14)
3-year	0.89 (0.62–1.27)	0.87 (0.60–1.24)
4-year	0.89 (0.64–1.24)	0.88 (0.62–1.23)

[a] GRACE hospital discharge risk score.

Effect of different EBM medications on hazard ratio for mortality (compared to patients not receiving that particular EBM medication) in the 1025 patients (all receiving aspirin)

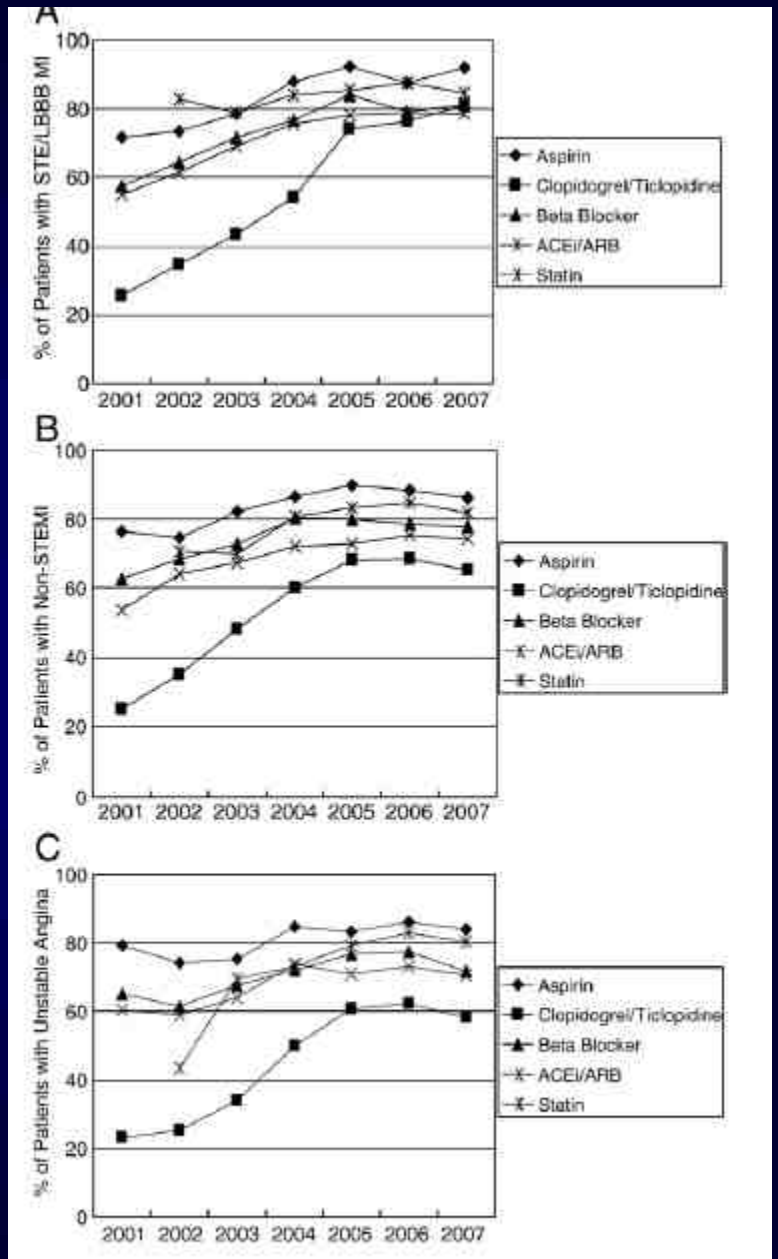
The expanded Global Registry of Acute Coronary Events: Baseline characteristics, management practices, and hospital outcomes of patients with acute coronary syndromes

Shaun G. Goodman, MD, MSc,[a] Wei Huang, MS,[b] Andrew T. Yan, MD,[a] Andrzej Budaj, MD, PhD,[c] Brian M. Kennelly, MD, PhD,[d] Joel M. Gore, MD,[b] Keith A. A. Fox, MB, ChB, FRCP,[e] Robert J. Goldberg, PhD,[b] and Frederick A. Anderson, Jr, PhD[b], for the Expanded Global Registry of Acute Coronary Events (GRACE[2]) Investigators[f] *Ontario, Canada; Worcester, MA; Warsaw, Poland; Newport Beach, CA; and Scotland, United Kingdom*

Am Heart J 2009;158:193-201.

ASPIRIN
CLOPIDOGREL

STATIN
BB
ACE



Medical therapy prescribed at discharge in patients with (**A**) STEMI or LBBB, (**B**) NSTEMI, and (**C**) unstable angina.

PROSPECT: MACE

3-year follow-up, hierarchical

	All	Culprit lesion related	Non culprit lesion related	Indeter-minate
Cardiac death	1.9% (12)	0.2% (1)	0% (0)	1.7% (11)
Cardiac arrest	0.3% (2)	0.3% (2)	0% (0)	0% (0)
MI (STEMI or NSTEMI)	2.7% (17)	1.7% (11)	1.0% (5)	0.2% (1)
Rehospitalization for unstable or progressive angina	15.4% (101)	10.4% (69)	10.7% (66)	0.8% (5)
Composite MACE	20.4% (132)	12.9% (83)	11.8% (74)	2.7% (17)
Cardiac death, arrest or MI	4.9% (31)	2.2% (14)	1.0% (6)	1.9% (12)

ASPIRIN 75 mg od
life

CLOPIDOGREL 75 mg od or
Prasugrel or Ticagrelor
12 months

STATIN
life

Beta Blocker
life

Best glycemic drug
life

Anti-hypertensive
life

Pre discharge chart

Pay attention to secondary prevention !!

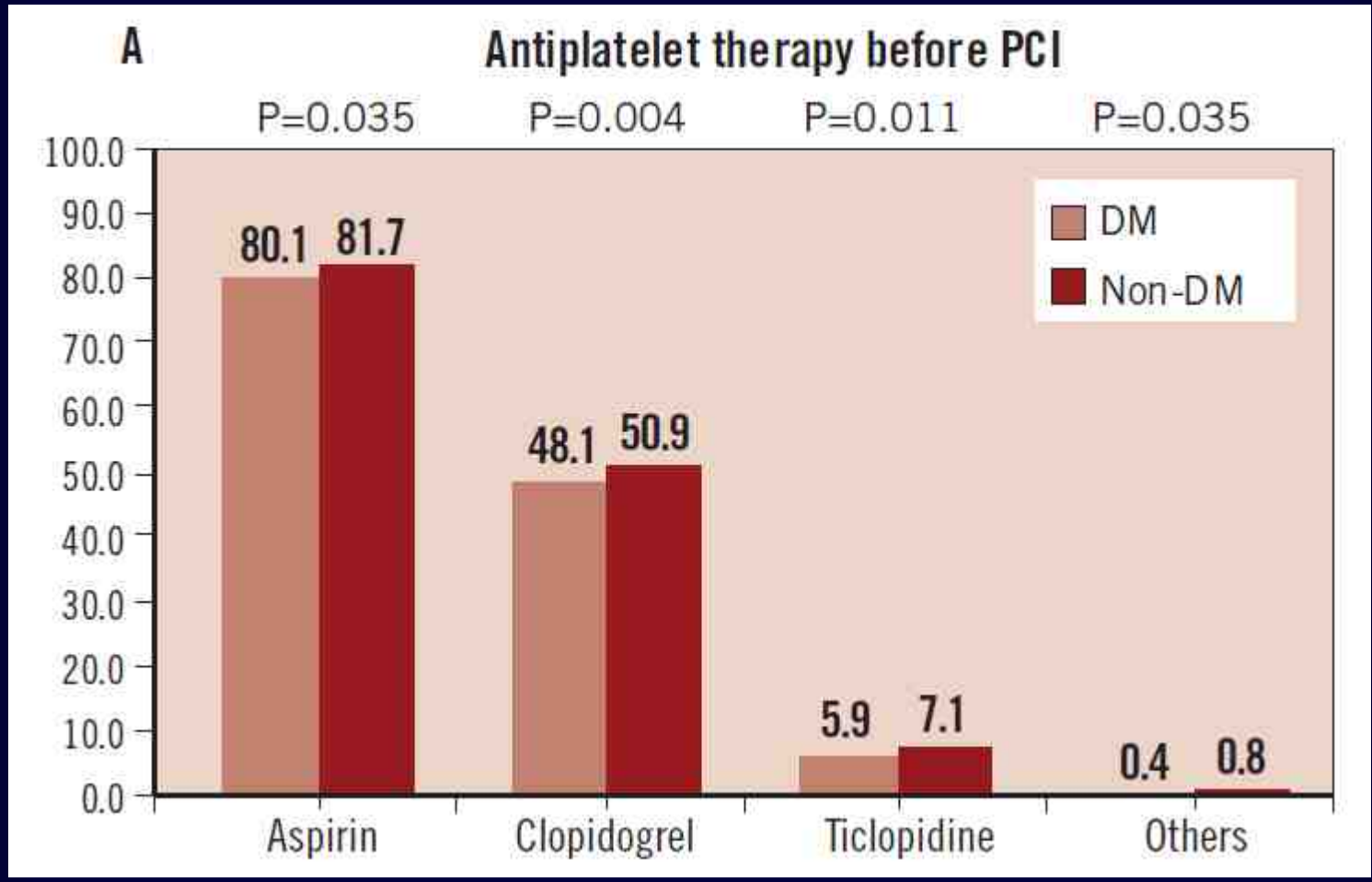

A
Antiplatelet therapy before PCI
P=0.035
P=0.004
P=0.011
P=0.035
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
80.1
81.7
48.1
50.9
5.9
7.1
0.4
0.8
DM
Non-DM
Aspirin
Clopidogrel
Ticlopidine
Others

Table 5. Predictors of hospital mortality.

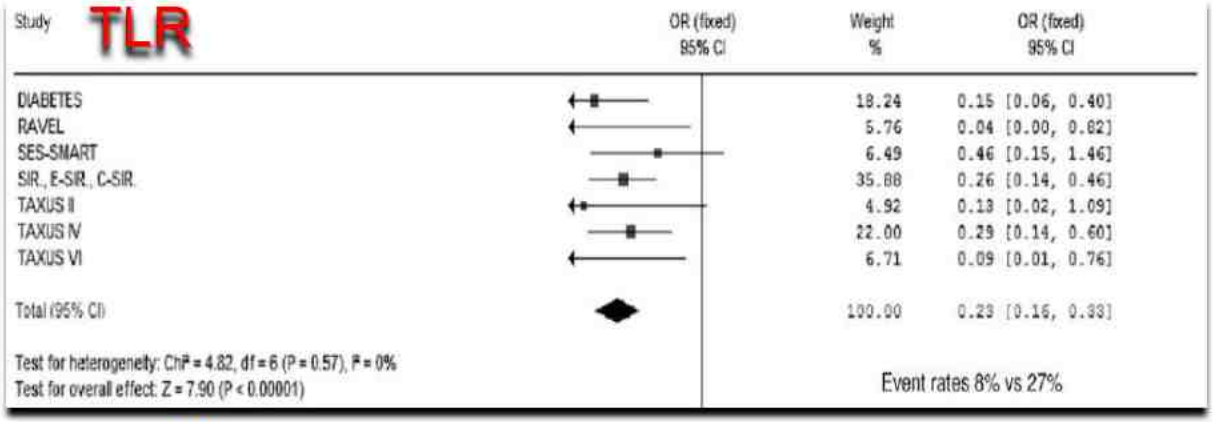
Variable	OR	95%-CI
Diabetes	1.40	1.03-1.92
Age (per 10-year increase)	1.78	1.54-2.07
Male gender	0.76	0.55-1.03
Ongoing ACS	6.56	4.06-10.60
Elective PCI	0.53	0.27-1.03
Current smoker	2.21	1.55-3.15
Previous stroke	2.01	1.23-3.27
Congestive heart failure	1.60	0.97-2.63

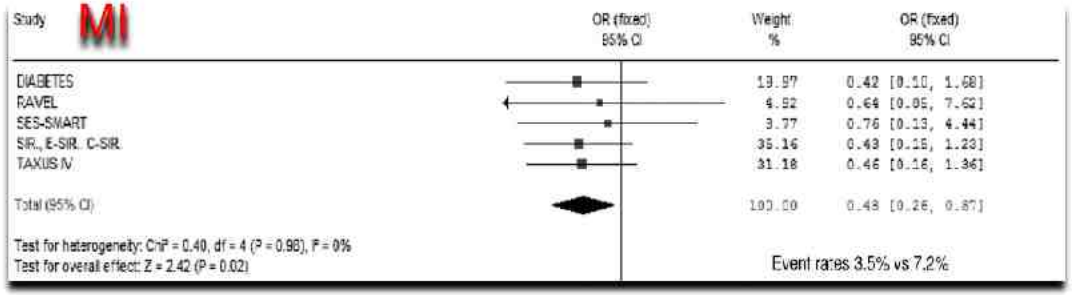
09

Meta-Analysis Comparison (Nine Trials) of Outcomes With Drug-Eluting Stents Versus Bare Metal Stents in Patients With Diabetes Mellitus

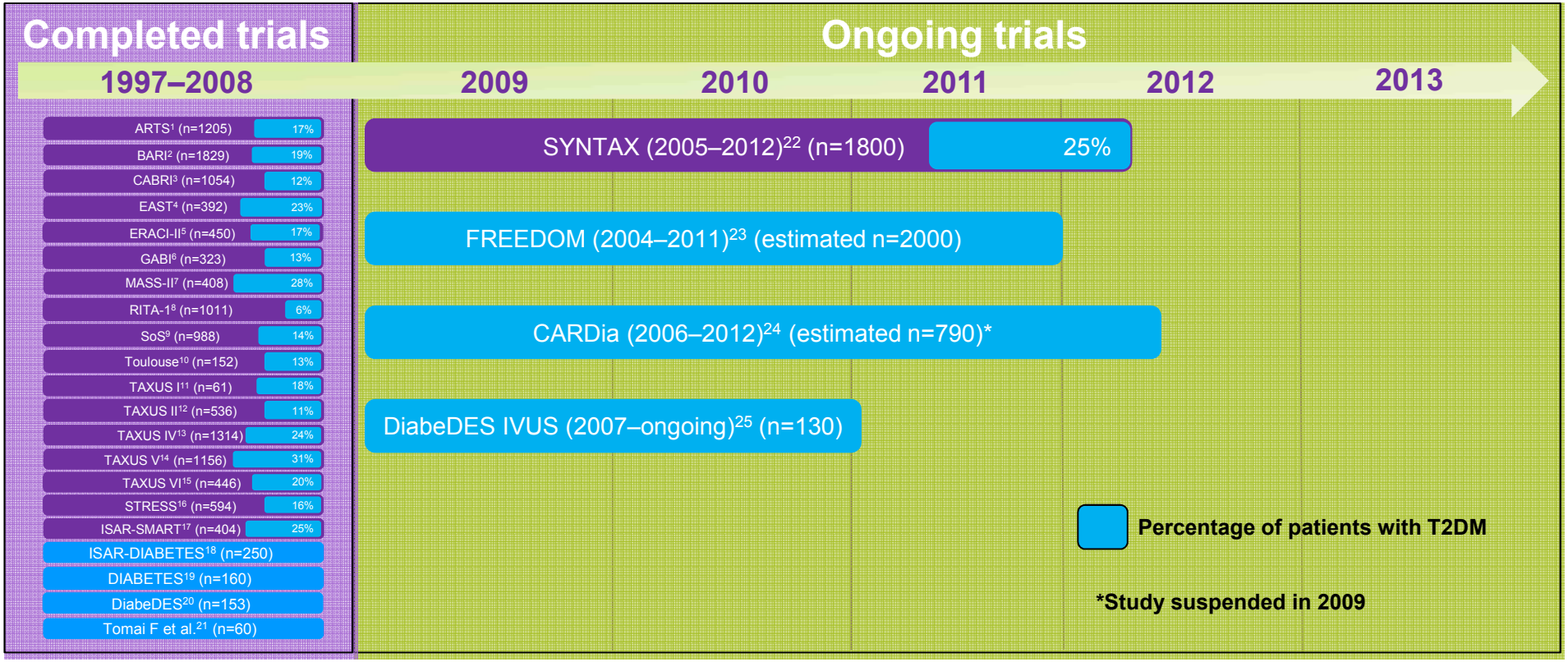
Giuseppe Patti, MD, Annunziata Nusca, MD, and Germano Di Sciascio, MD*

Am J Cardiol 2008;102:1328–1334





Revascularisation of patients with T2DM – select clinical trials and registries



Registries

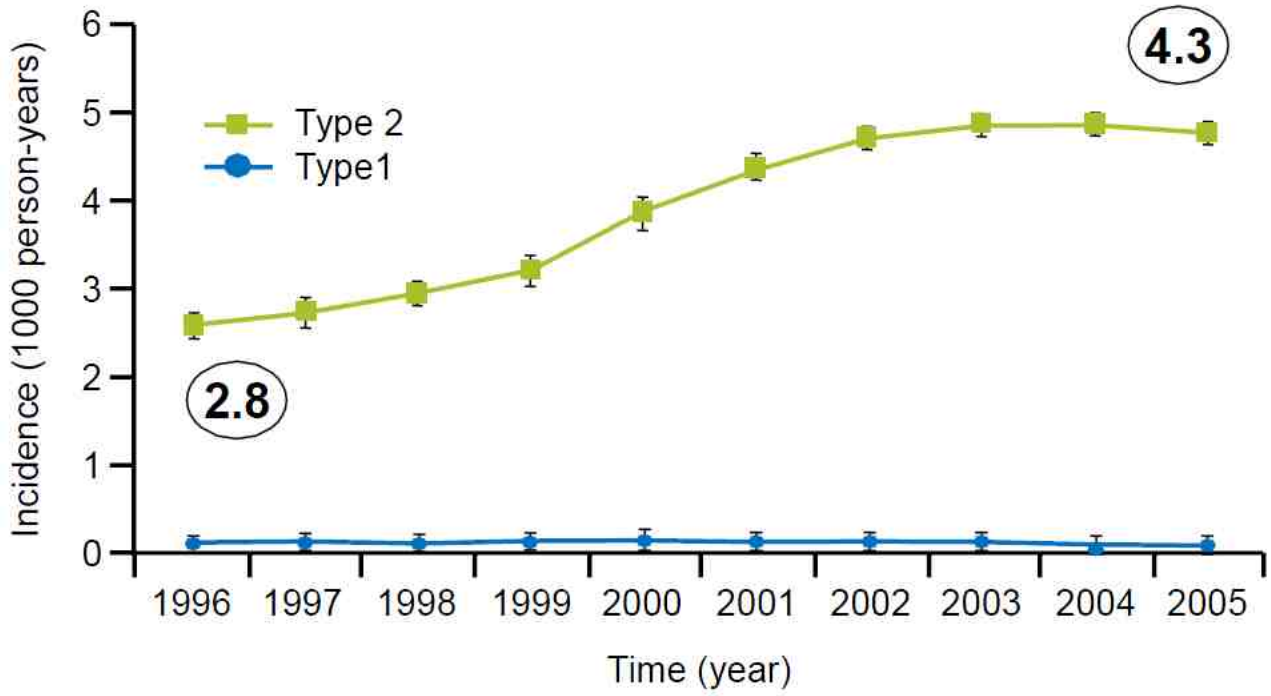
MAS-DAC[26] (n=21,045) 29%	Duke[34] (n=3220) 24%	Mayor M et al.[40] (n=1558) 34%
NHLBI Dynamic[27] (n=9170) 28%	GUH / MAHI[35] (n=15,809) 12%	REAL[41] (n=12,155) 14%
SCAAR[28,29] (n=47,967) 20%	BARI-R[36] (n=2010) 17%	RESEARCH/T-SEARCH[42] (n=3540) 20%
RIKS-HIA[30, 31] (n=70,882) 21%	NNE[37] (n=14,493) 31%	C/T-REWARDS[43] (n=2974) 36%
EMORY[32] (n=10,433) 11%	APPROACH[38] (n=11,661) 15%	MEDIX/FEDIX (estimated n=1000)
LDCMC[33] (n=272) 24%	Western Denmark[39] (n=12,395) 11%	

IVUS, intravascular ultrasound; T2DM, type 2 diabetes mellitus.

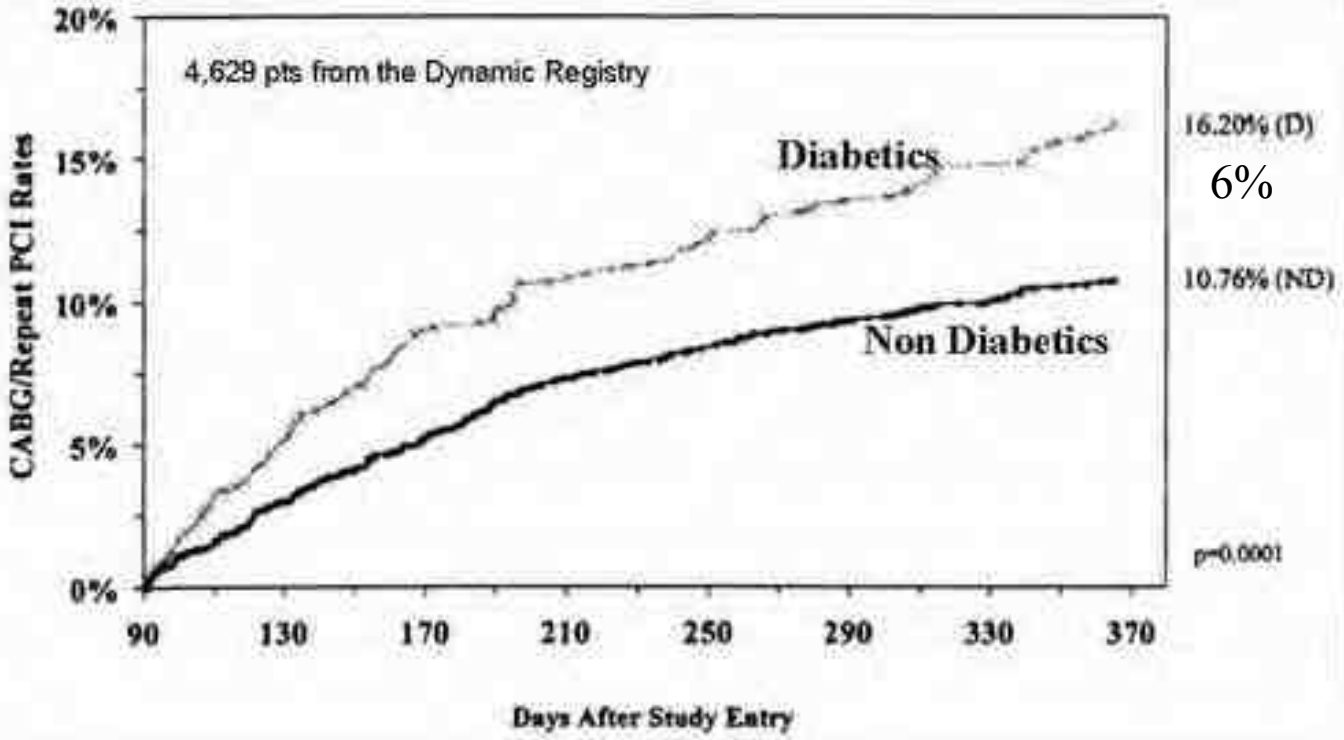
- Am J Cardiol. 2009 Jul 1;104(1):41-5.
- Prognostic value of hemoglobin A1C levels in patients with diabetes mellitus undergoing percutaneous coronary intervention with stent implantation.
- Lemesle G, Bonello L, de Labriolle A, Maluenda G, Syed AI, Collins SD, Ben-Dor I, Torguson R, Kaneshige K, Xue Z, Suddath WO, Satler LF, Kent KM, Lindsay J, Pichard AD, Waksman R.
- Department of Internal Medicine, Division of Cardiology, Washington Hospital Center, Washington, DC, USA.
- Abstract
- The optimal glycosylated hemoglobin (HbA1C) target in diabetic patients is a subject of ongoing controversy that may be especially pertinent in diabetic patients with coronary artery disease. This study aimed to determine the prognostic value of preprocedural HbA1C levels in diabetic patients undergoing percutaneous coronary intervention (PCI) with stent implantation. From 2002 to 2007, a cohort of 952 consecutive diabetic patients underwent PCI with stent implantation in our center. We compared patients with a normal preprocedural HbA1C (< or = 7%, n = 429) with patients with an increased HbA1C (>7%, n = 523). One-year rate of major adverse cardiovascular events (MACEs) including death, myocardial infarction, and target vessel revascularization was indexed. Baseline characteristics were similar between groups, except for body mass index, which was higher in the high HbA1C group (32.2 vs 31.2 kg/m(2), p = 0.03). Patients in the high HbA1C group were more likely insulin dependent (45.5% vs 26.3%, p <0.001). Rates of MACEs were similar (23.7% vs 20.8%) in the high HbA1C and low HbA1C groups (p = 0.45). By multivariate analysis, age, renal failure, clinical presentation as myocardial infarction, and history of congestive heart failure were independently associated with MACEs. In contrast, HbA1C was not associated with patient outcome. In conclusion, this study suggests that HbA1C is not a predictor of cardiac events in diabetic patients with advanced coronary artery disease. These results could explain, at least in part, recent findings of randomized clinical trials that suggest the absence of benefit in macrovascular complications of a strict glycemia control.

EUROPCR09

54% increase in diabetes in UK



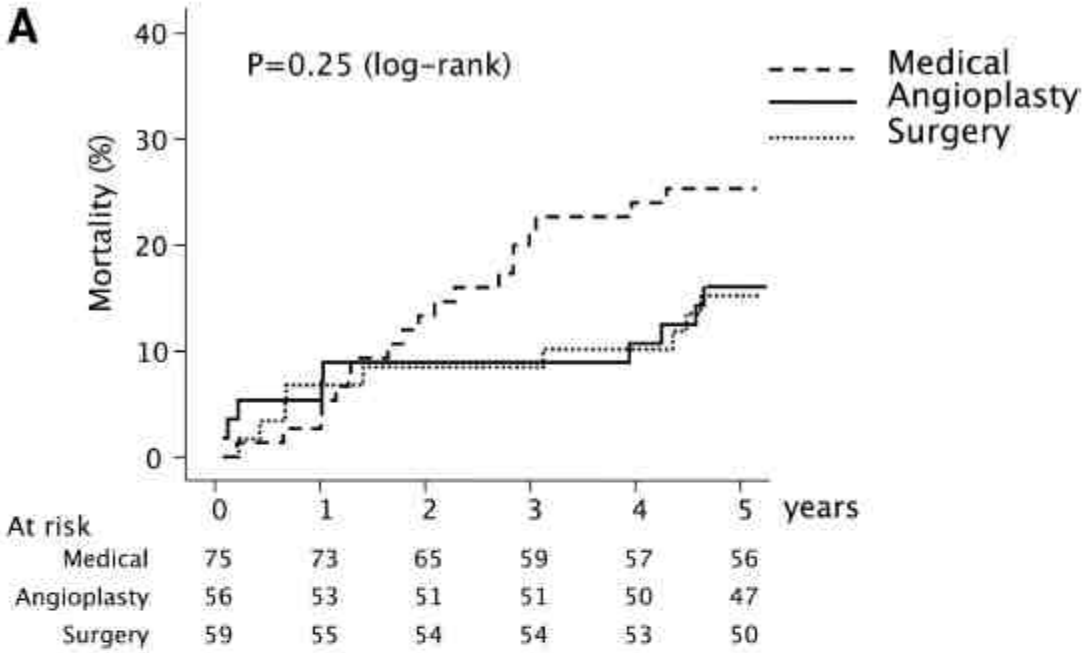
Repeat PCI or CABG following PCI

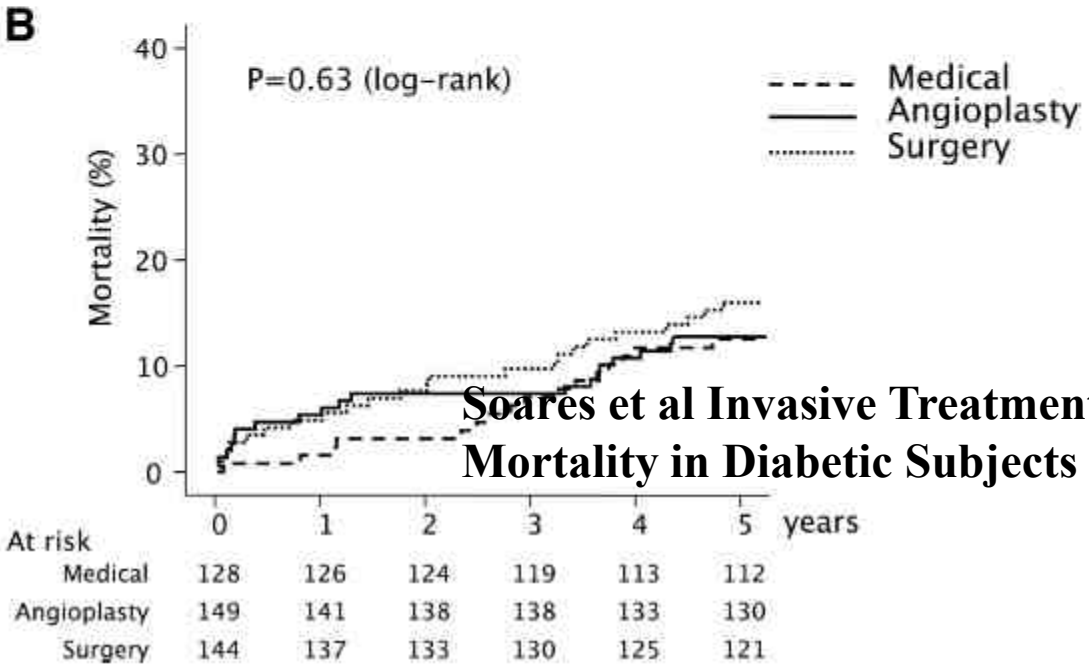


Laskey et al, *Am J Cardiol* 2002;90:1062-67

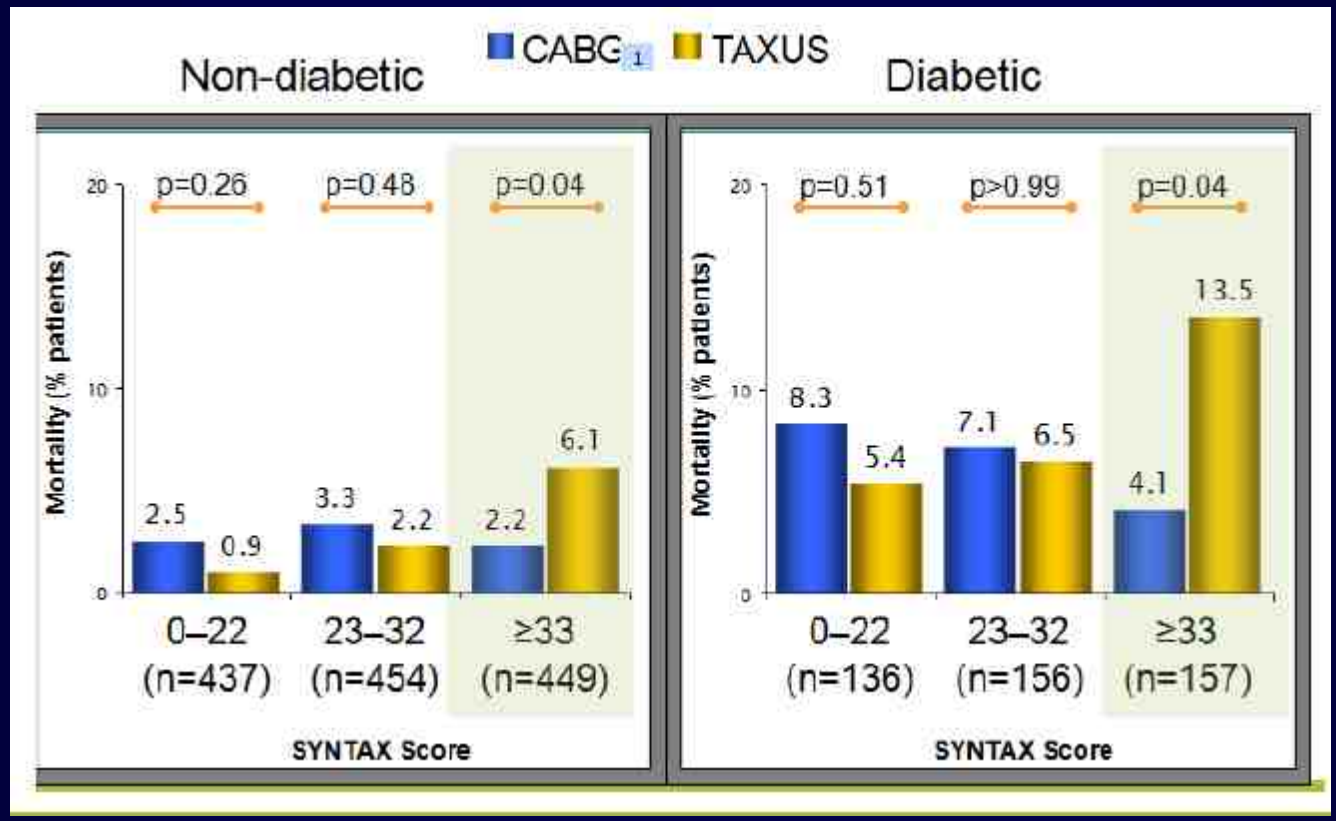
Multifactorial therapeutic strategy is essential

- ✓ Betablockers, statins, ACE inhibitors
- ✓ Achieve targets: LDL, BP, glycaemia, weight, lifestyle counselling





Soares et al Invasive Treatment Reduces Mortality in Diabetic Subjects


CABG
TAXUS
Non-diabetic
Diabetic
Mortality (% patients)
20
10
0
p=0.26
p=0.48
p=0.04
2.5
0.9
3.3
2.2
2.2
6.1
0–22
(n=437)
23–32
(n=454)
≥33
(n=449)
SYNTAX Score
p=0.51
p>0.99
p=0.04
8.3
5.4
7.1
6.5
4.1
13.5
0–22
(n=136)
23–32
(n=156)
≥33
(n=157)
SYNTAX Score