

Disclosures

- The presenter has no financial involvement with the product or competing products being discussed.
- The presenter received travel and lodging reimbursement from the Society of Thoracic Surgeons to attend this meeting.

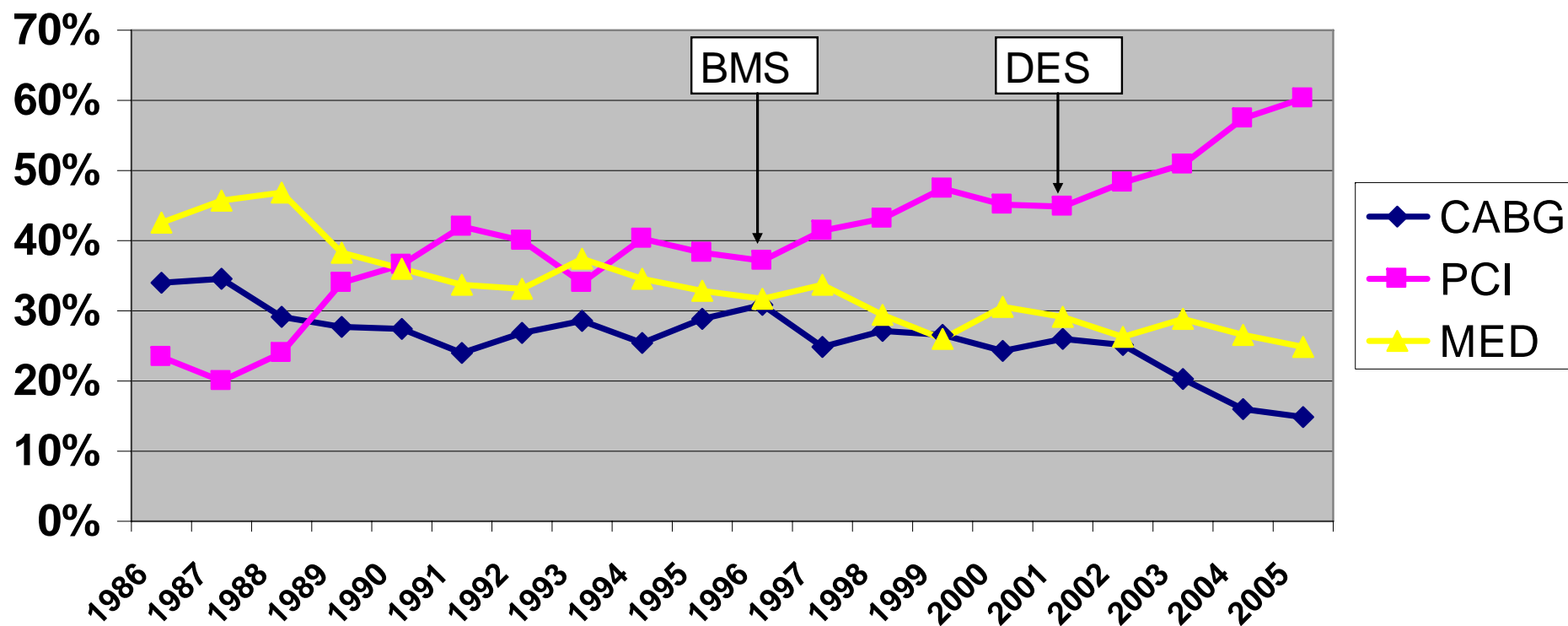
Relative Merits and Clinical Selection of CABG, Bare Metal Stents, and Drug Eluting Stents in Practice and in Evolution

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The Issue is NOT Stent safety and benefit but PATIENT safety and benefit

Trends in Treatment Selection

Duke Initial Treatment Selection All Significant CAD N=26,318



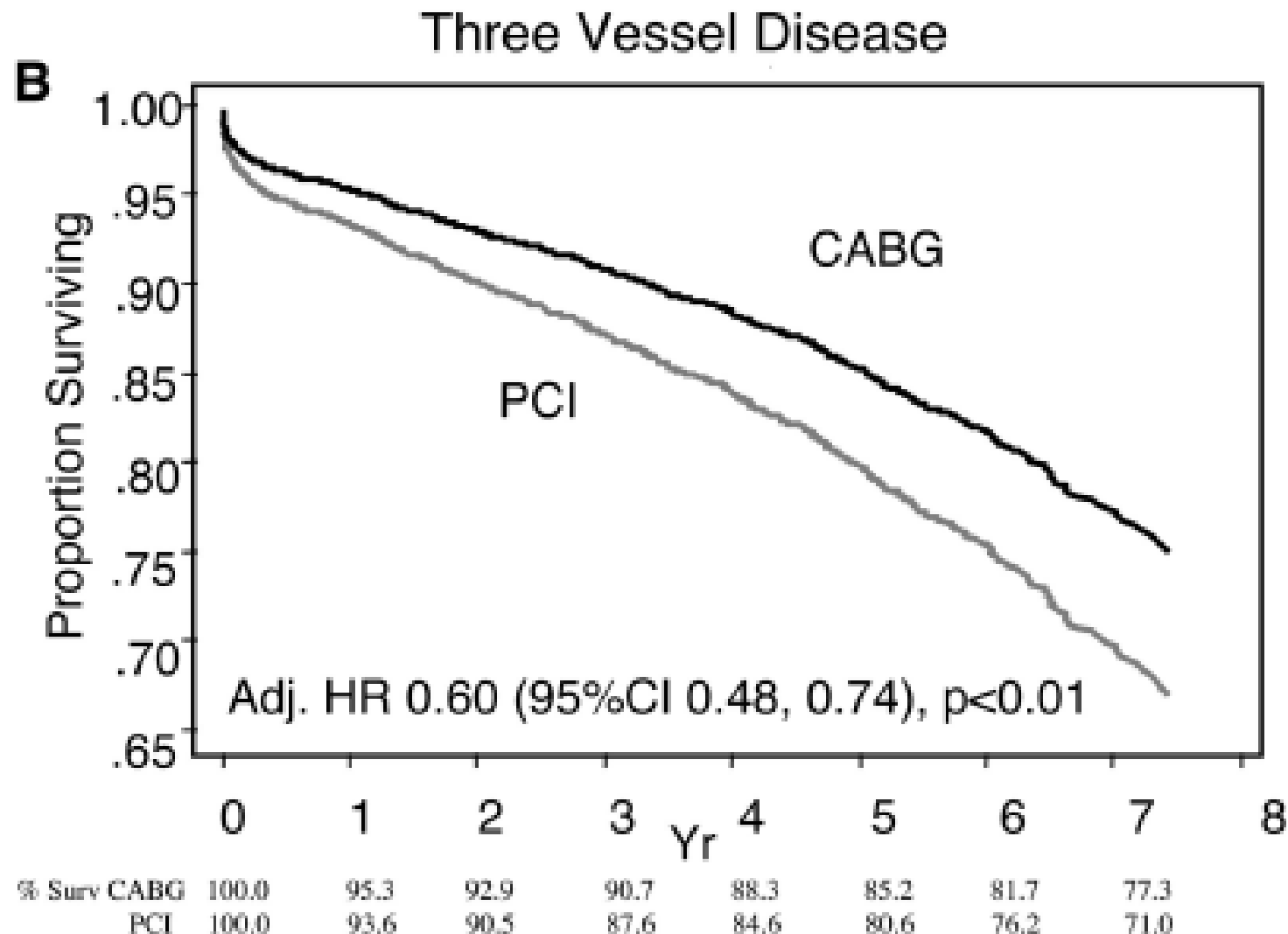
Current Perspective

- America's number 1 killer is predominantly treated with percutaneous methodology that has not been demonstrated to provide a survival advantage.
- DES introduction has broadened the indications and increased the frequency of percutaneous intervention.
- This is particularly important for the treatment of multivessel CAD, where substantial quality of life and survival benefits have been conclusively demonstrated for CABG.

Regaining Perspective

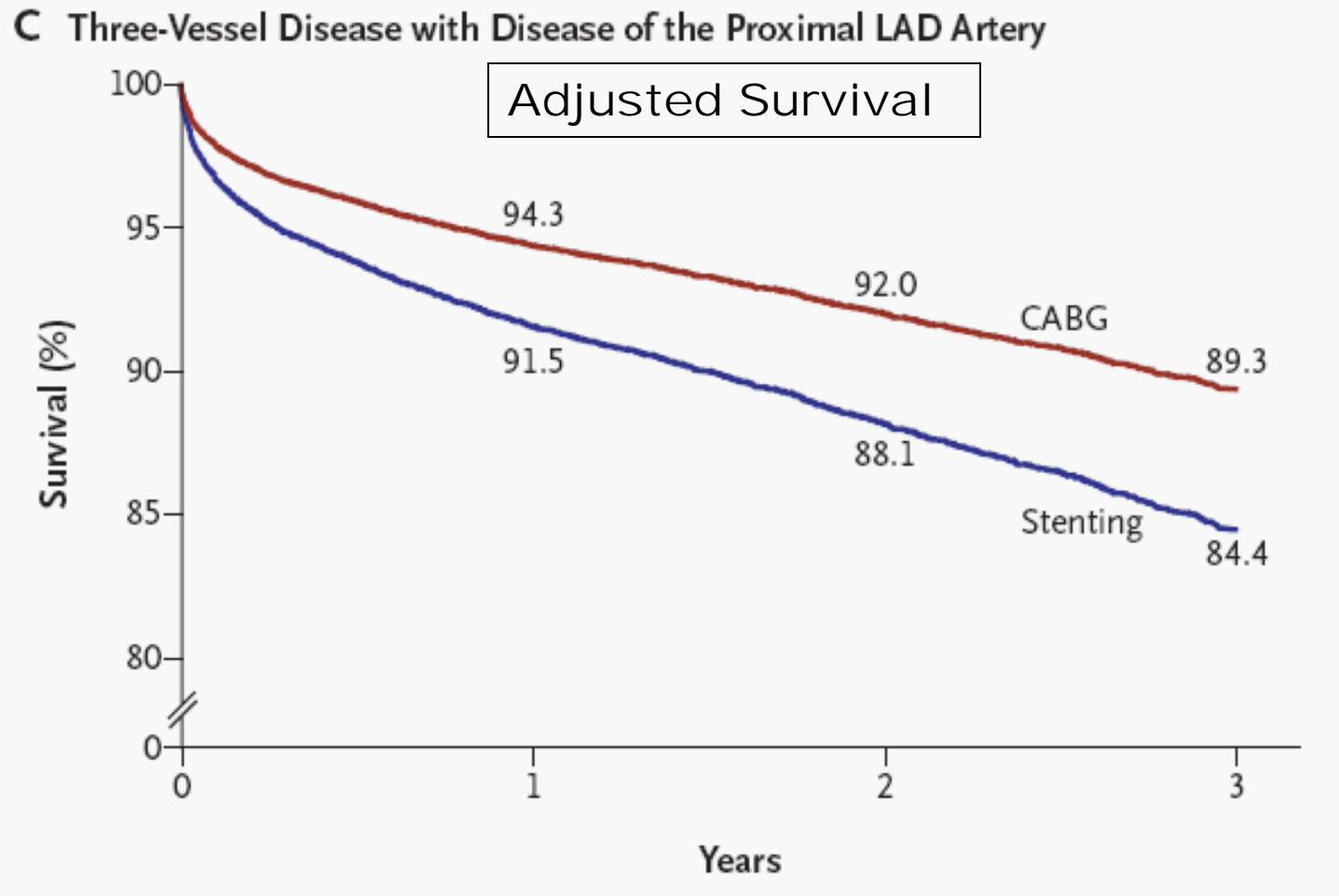
- There is a growing body of evidence indicating that:
 - DES is associated with increased mortality risk compared to BMS
 - Therefore, for the most important clinical outcome, DES is at best “non-inferior” to BMS
- Therefore, the comparison of BMS to the CABG, the standard of care, is the relevant issue and abundant long-term data are available

Northern New England Database 1994-2001 N=14,493



Circulation 2005;112[suppl I]:I-371-I-376.

New York State 1997-2000 3-Vessel Disease N=23,022



N Engl J Med 2005;352:2174-83.

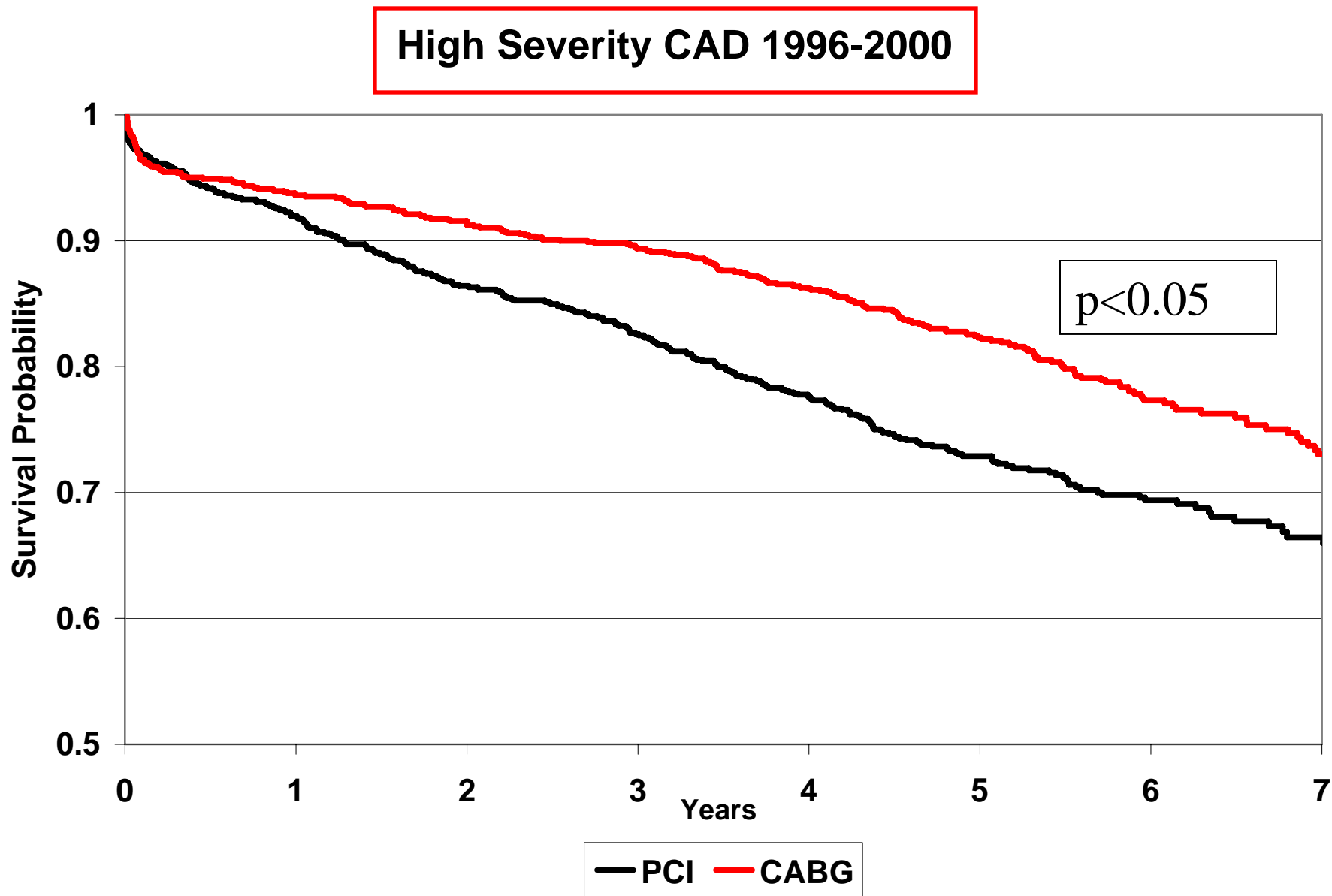
Duke Observational Data Analysis

- 1986-2000, all patients with significant CAD
- N= 18,481
- Medical Therapy 6,682
- PCI 6,292
- CABG 5,327

Severity of CAD

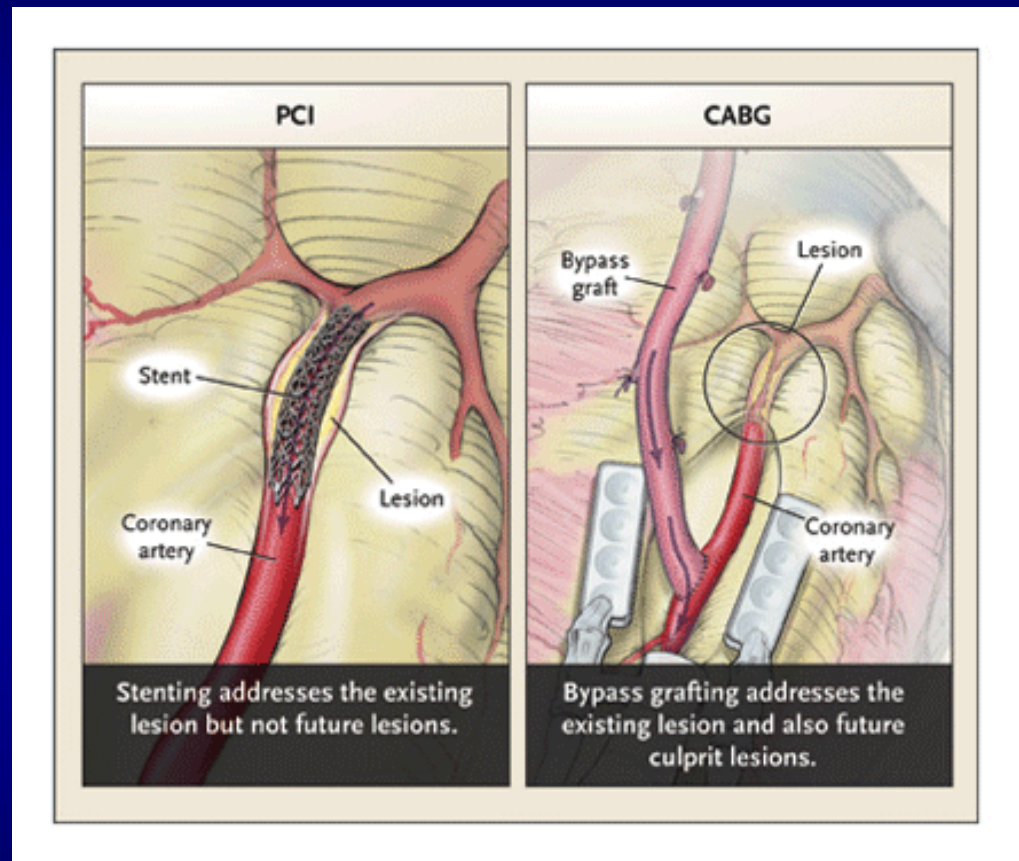
CAD Index	CAD Severity Group	Severity and Location of Stenosis
1	Low	One vessel $\geq 75\%$
2	Low	Two vessels $\geq 75\%$; None $\geq 95\%$
3	Intermediate	One vessel $\geq 75\%$; $\geq 95\%$ Proximal LAD <u>or</u> 50-74% LM
4	Intermediate	Two vessels $\geq 75\%$; at least one $\geq 95\%$
5	Intermediate	Two vessels $\geq 75\%$ with $\geq 95\%$ LAD <u>or</u> 25-49% LM <u>or</u> three vessels $\geq 75\%$ and $< 95\%$
6	Intermediate	Two vessels $\geq 75\%$ <u>with either</u> $\geq 95\%$ Proximal LAD <u>or</u> LM 50-74%
7	High	Three vessels $\geq 75\%$ <u>and</u> two or three vessels $\geq 95\%$
8	High	Three vessels $\geq 75\%$ <u>and either</u> $\geq 75\%$ Proximal LAD or 25-49% LM
9	High	Three vessels $\geq 75\%$ <u>and either</u> $\geq 95\%$ Proximal LAD or 50-74% LM

BMS vs. CABG Adjusted Survival



Why is CABG better than PCI?

- PCI treats an isolated lesion in the proximal vessel.
- CABG bypasses the proximal 2/3 of the vessel, where the current lesion *and future threatening lesions* occur.
- *This advantage of CABG will persist, even if Stent restenosis is ZERO.*

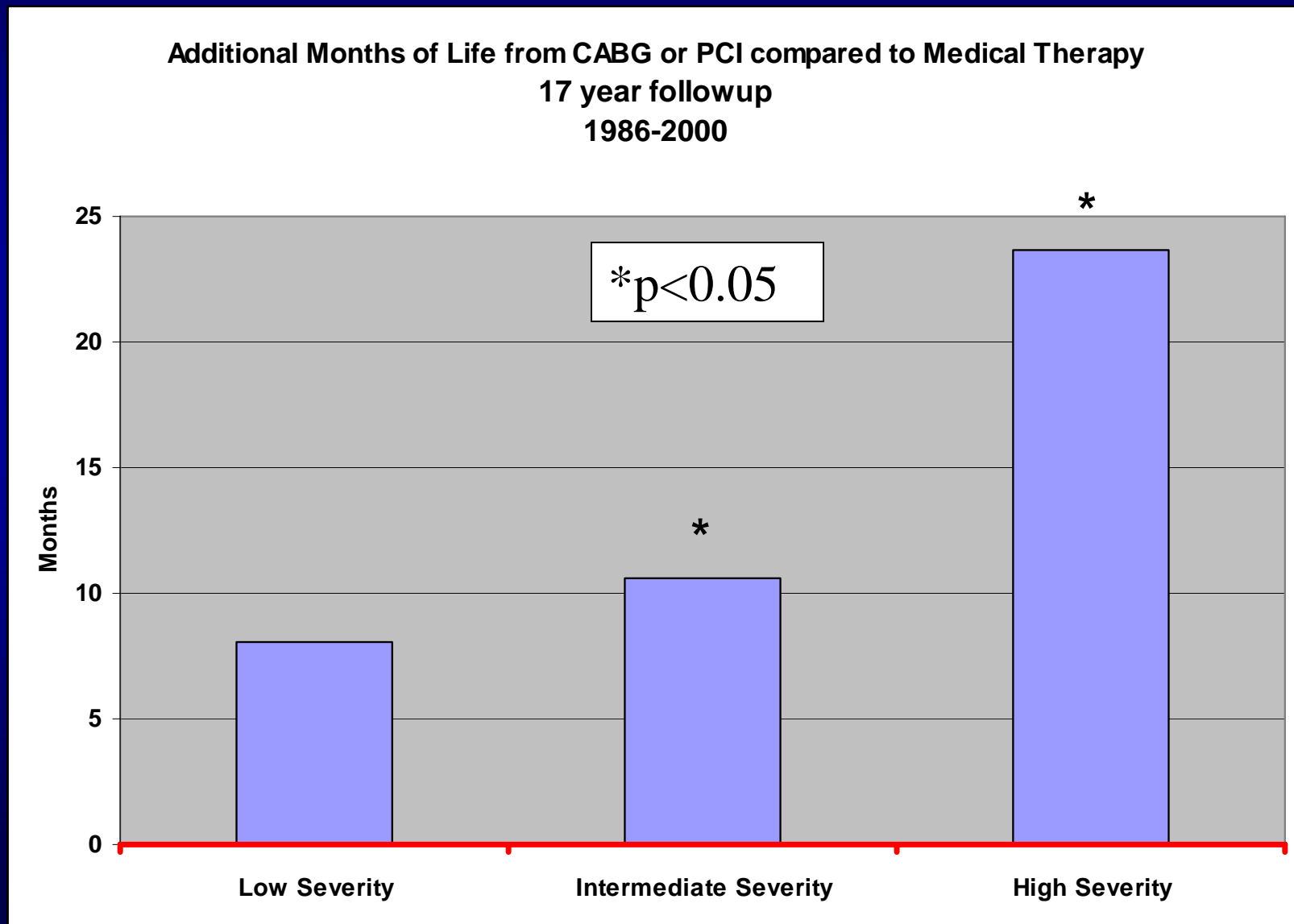


Gersh and Frye NEJM, May 2005

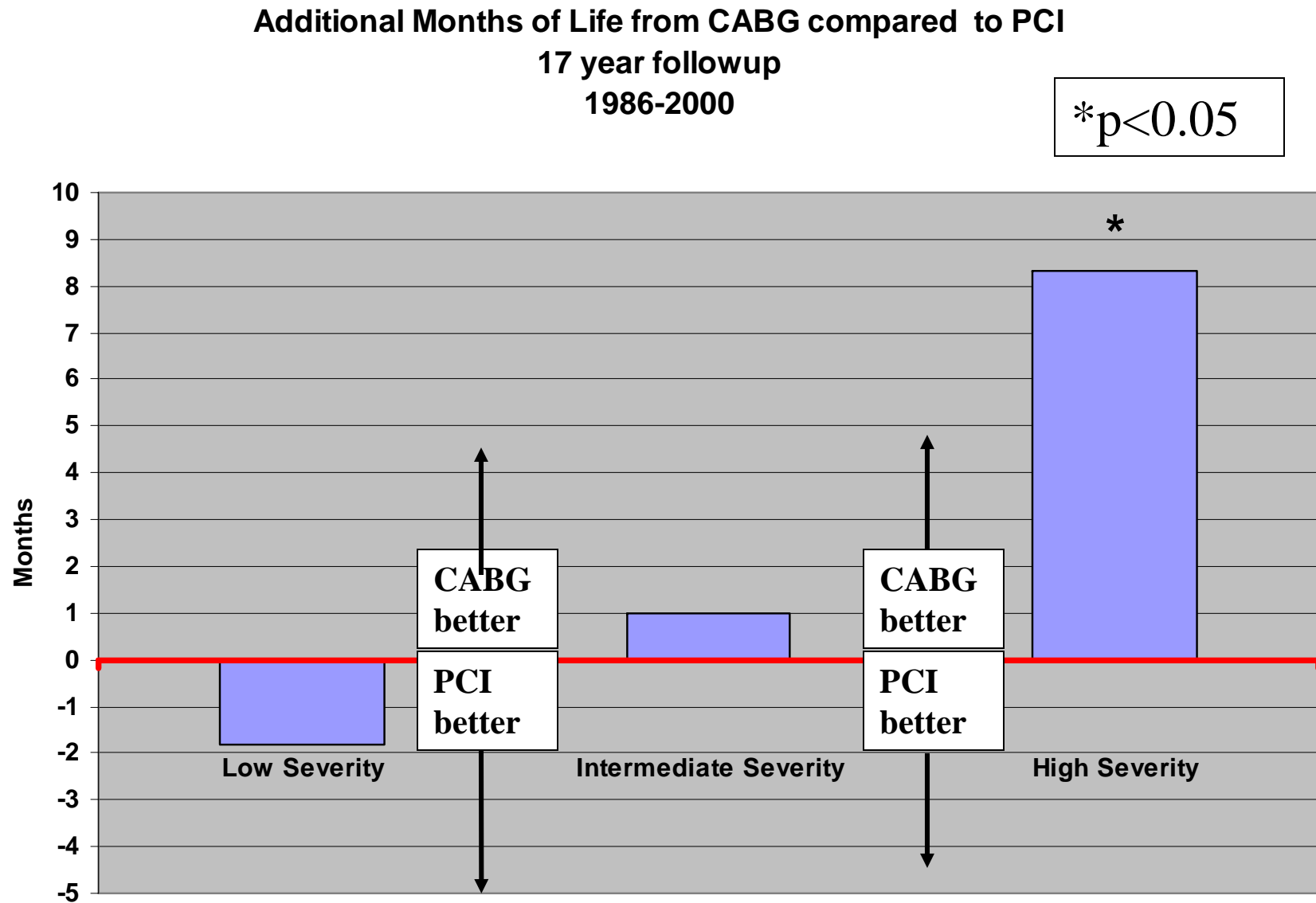
Why is CABG Superior in Multivessel Disease?

- Complete Revascularization
- Grafting and graft failure does not effect the native coronary circulation
- CABG risk increases little with increasing CAD
- PCI risk appears to be additive, increasing arithmetically with each stent, unlike CABG
- CABG survival benefit increases with increasing CAD

Life Prolongation by Revascularization (PCI or CABG)



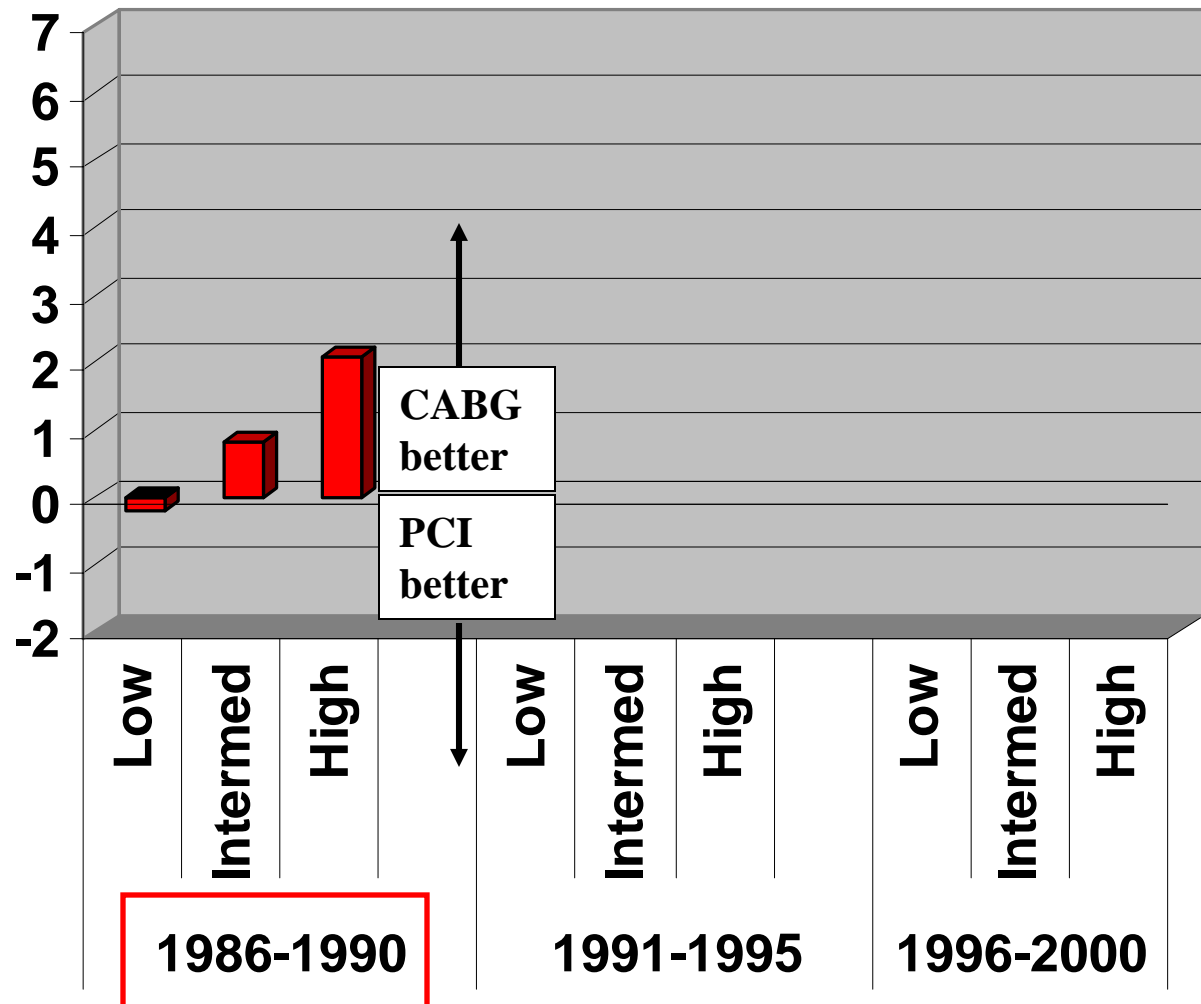
Relative Benefit Contribution, 1986-2000



Survival Difference by Era and CAD Severity, CABG vs. PCI

Additional
Months of Life
per 7 Years by
CABG

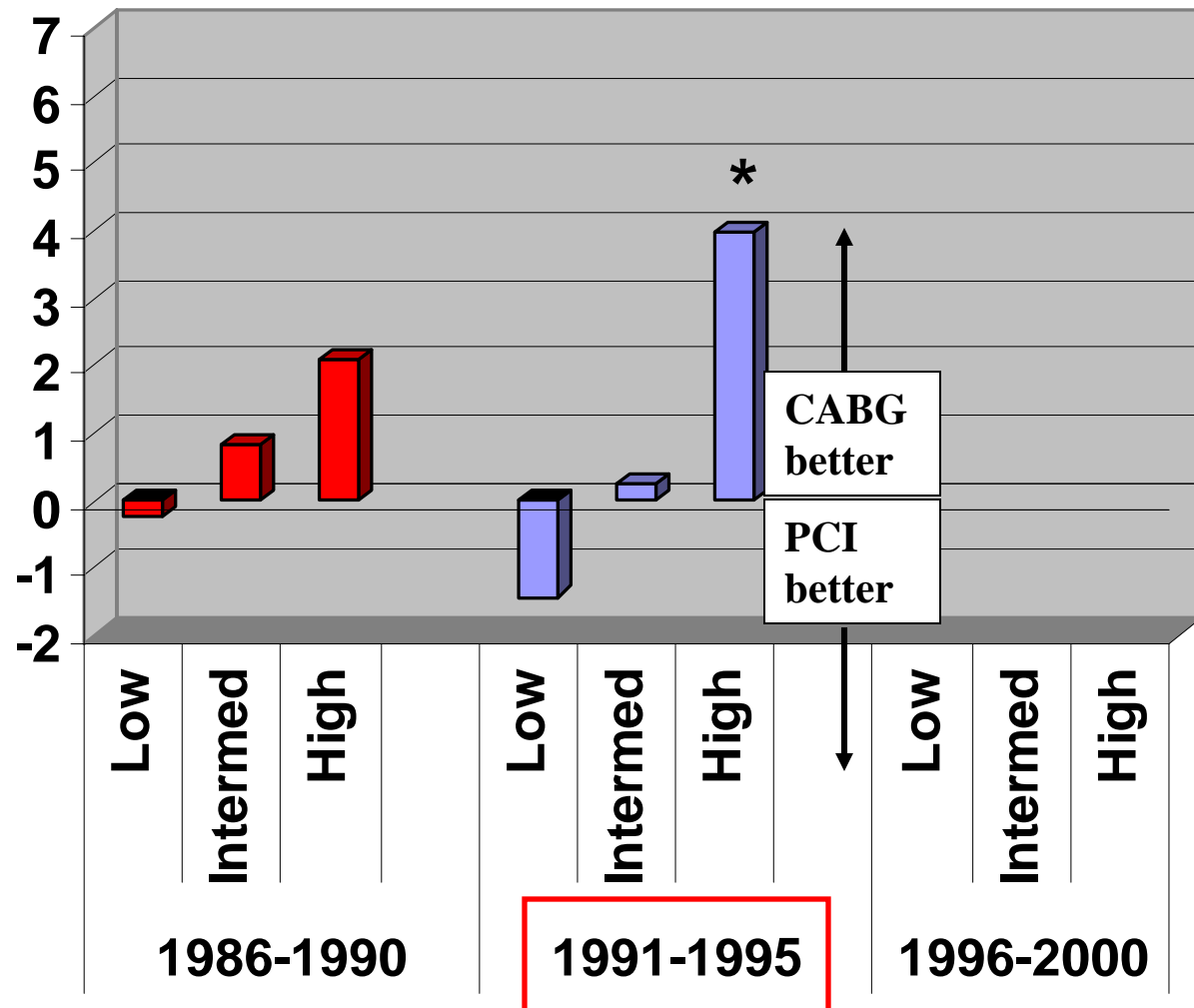
* $p < 0.05$
CABG vs PCI



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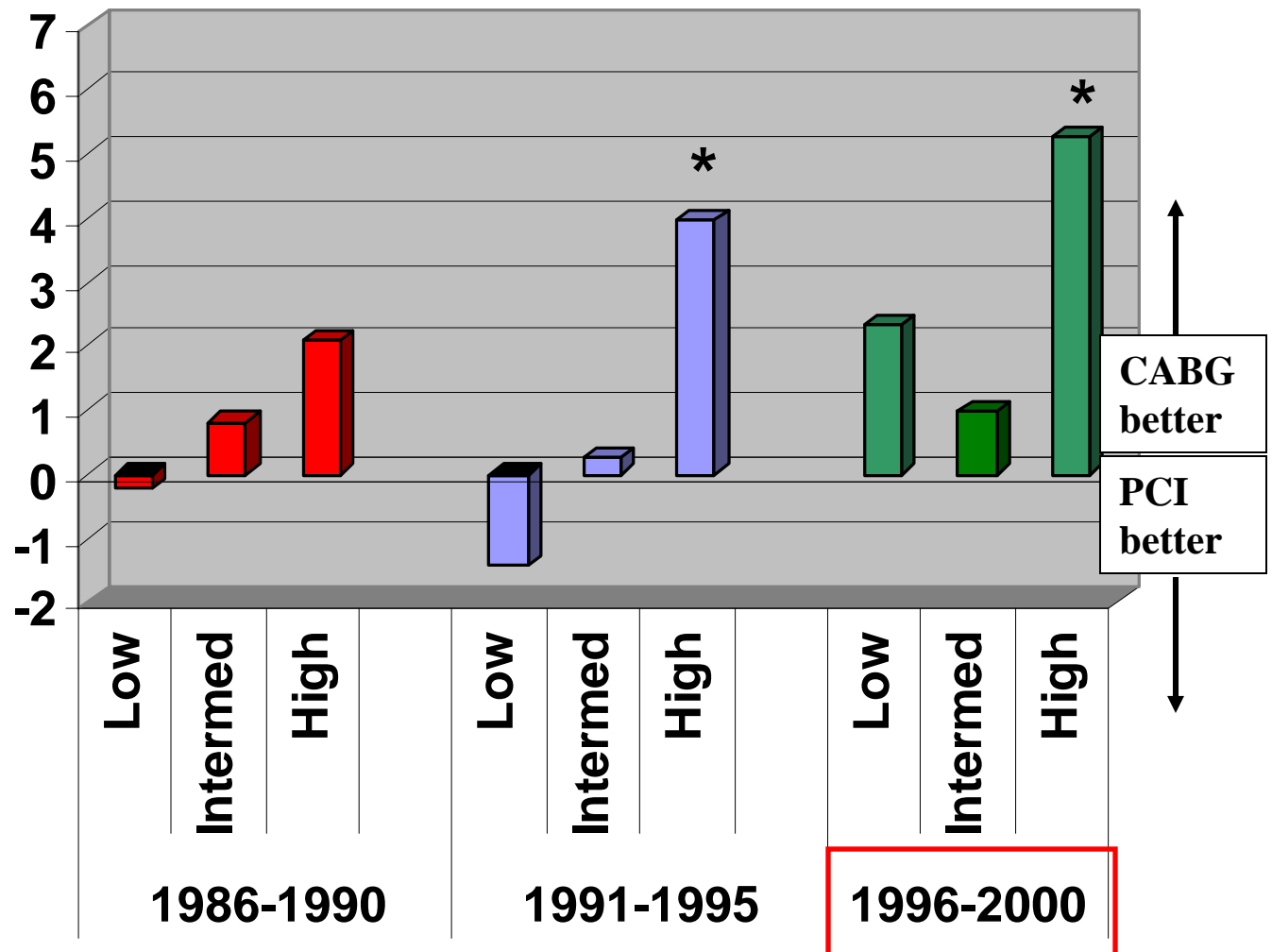
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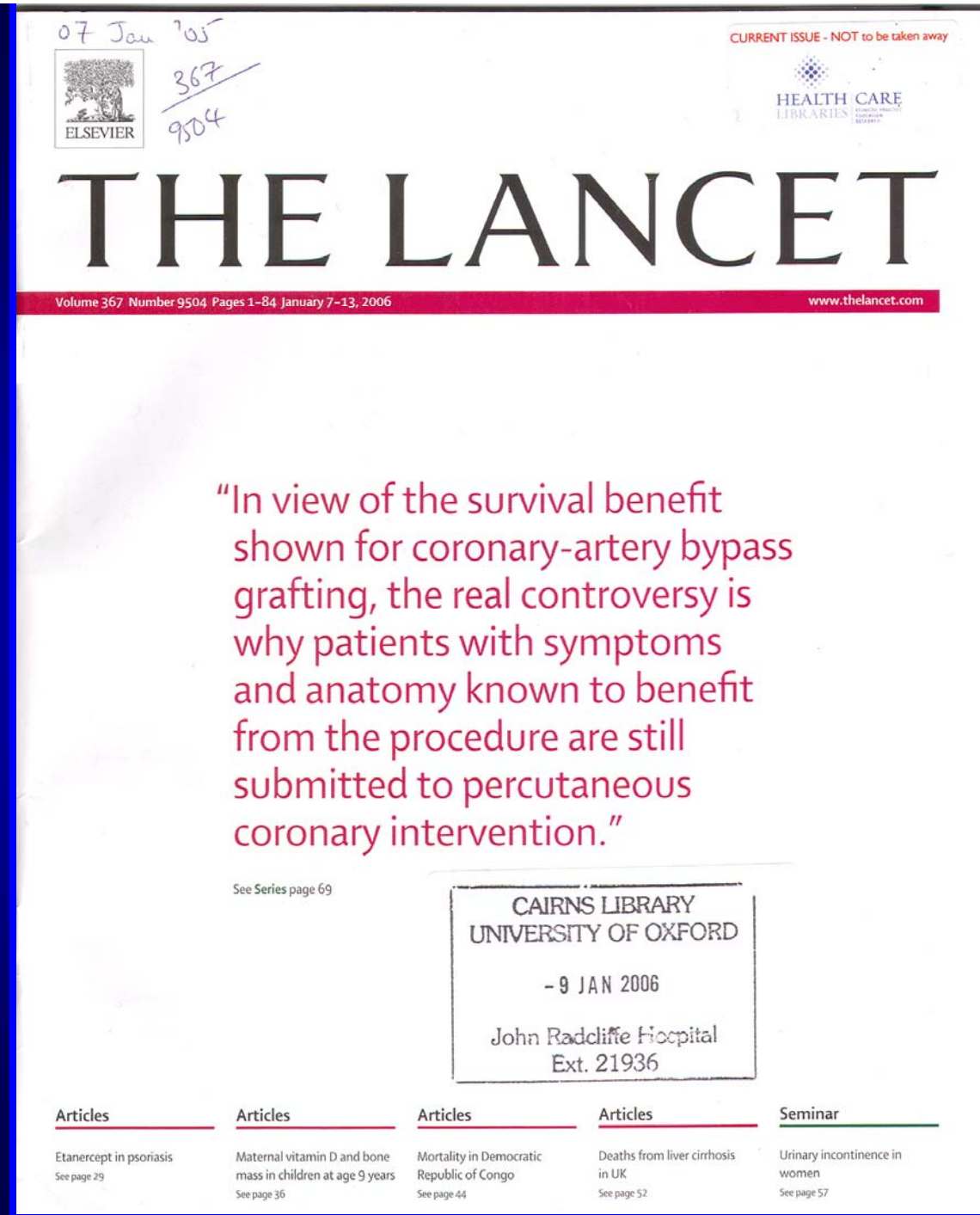
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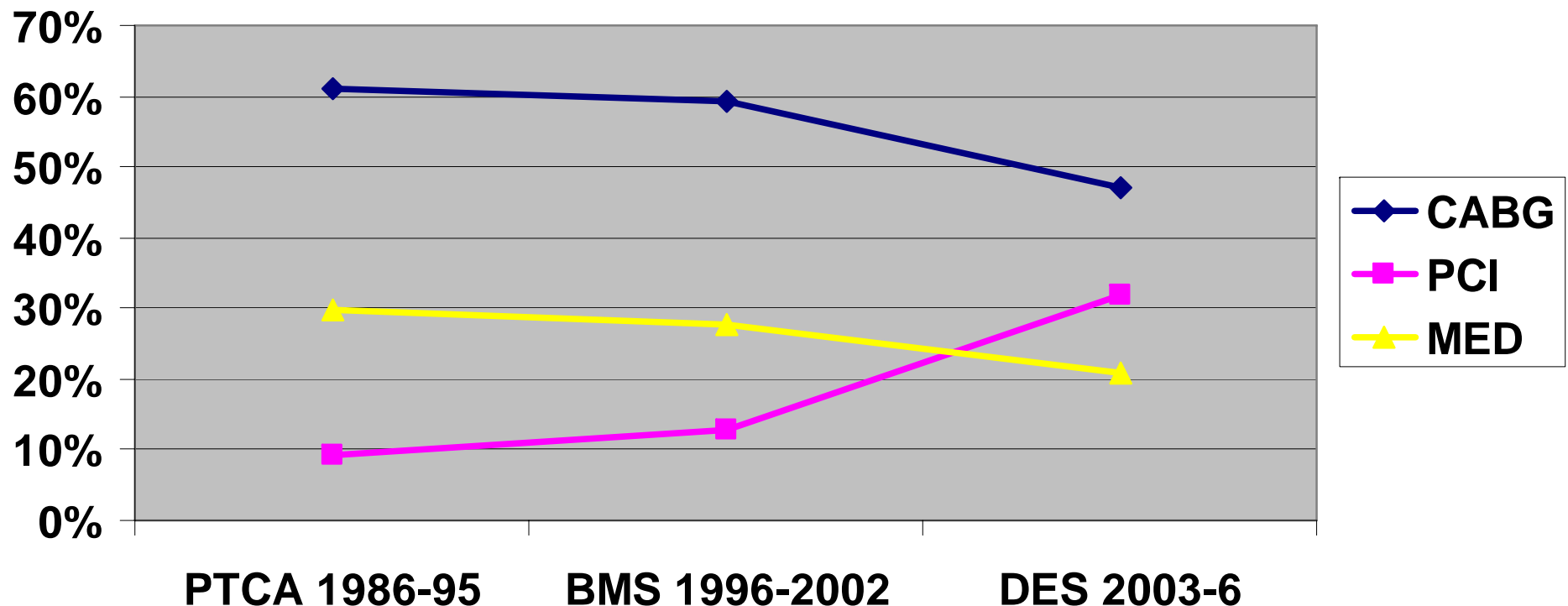


The Cover of LANCET January 2006:



Trends in Treatment Selection for High Severity CAD (25% of Real World Patients)

Duke Initial Treatment Selection
High Severity CAD N=6,226



Absolute Survival Advantage CABG vs BMS

Survival Advantage of CABG vs BMS for 3 Vessel Disease					
Patients	Source	1 year	3 years	5 Years	7 years
14,493	NNE	1.7%	3.1%	4.6%	6.3%
23,022	NY State	2.8%	4.9%		
1,722	Duke	1.6%	6.8%	9.4%	6.6%
39,237	Overall	2.3%	4.3%	5.1%	6.3%

- A significant survival advantage for CABG has been demonstrated, and appears to increase with longer follow up.

Mortality Impact

(Assumes DES equivalent to BMS)

	Worldwide Estimates	US Estimates	Data and Sources
DES implanted/Year	1,500,000	850,000	Multiple estimates
Number of Patients/Year	1,038,361	586,207	1.45 Stents/Patient*
Number with 3VD/Year	163,958	92,621	15.8 % of PCI*
Premature deaths at 1 year	3,826	2,168	NNE, NY State, Duke
Premature deaths at 3 years	16,383	9,283	NNE, NY State, Duke
Annualized	6,507	3,687	

* Williams, DO and Abbott, JD. DEScover trial 1 year results.

N=6,906 at 140 sites 2004-5. Presented at TCT 2006

“Am I more likely to be dead if I am treated with a DES?”

- The answer is YES if you have 3 vessel disease and are enabled to have DES or BMS implantation rather than CABG.

3,687 Premature
Deaths Each Year





Conclusion

- The potential of the DES to resolve the mortality disadvantage of BMS in multivessel disease has resulted in massive expansion of DES indications and use.
- It is an inescapable conclusion that this potential HAS NOT BEEN REALIZED!

Background

- CABG is the gold standard therapy for multivessel CAD, and the indications for performance have generally evolved into settings shown by RCT to prolong life
- Percutaneous intervention (Balloon angioplasty->BMS->DES) has been approved for use in coronary lesions, with the indications for performance related to the ability to maintain coronary patency
- There is a difference between treating coronary arteries and treating patients

Bare Metal Stent Era Conclusions

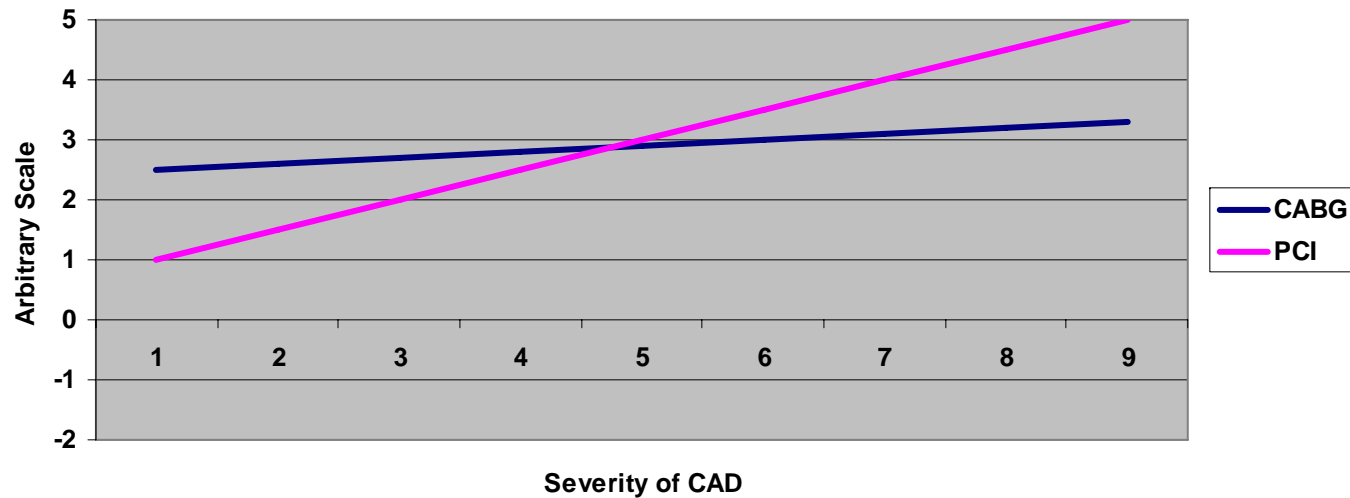
- CABG provides longevity benefit for multivessel disease, as well as more durable symptom relief
- Results are completely relevant today for patients with severe multivessel disease, in view of the absence of clinically important superiority of DES and the emerging mortality signal.

Coronary Artery Disease is the Number One Cause of Death in America

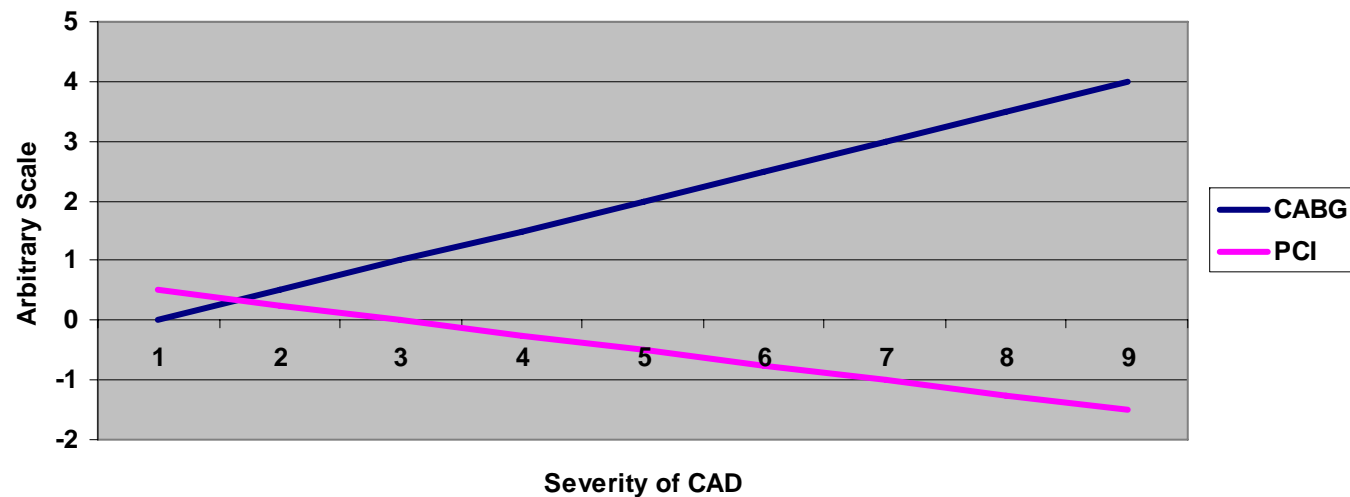
- Neither BMS or DES has been shown to reduce mortality, and are at best equivalent to CABG in highly selected patients with excess CABG risk and suitable PCI anatomy.
- As professionals charged with preserving the public health, how can we recommend any therapy other than CABG for multivessel disease?
- It is clear that if advances in coronary stenting are on the horizon, but they should be unequivocally demonstrated in less severe forms of CAD, where failure will not be associated with excess mortality.

PCI vs. CABG vs. Extent of CAD

PCI vs CABG Procedural Risk



PCI vs CABG Procedural Benefit



Charisma Trial End Points

Median Follow-up 28 months

Table 4. Composite and Individual Primary and Secondary End Points.

End Point	Clopidogrel plus Aspirin (N=7802) <i>no. (%)</i>	Placebo plus Aspirin (N=7801)	Relative Risk (95% CI)*	P Value
Efficacy end points				
Primary efficacy end point	534 (6.8)	573 (7.3)	0.93 (0.83–1.05)	0.22
Death from any cause	371 (4.8)	374 (4.8)	0.99 (0.86–1.14)	0.90
Death from cardiovascular causes	238 (3.1)	229 (2.9)	1.04 (0.87–1.25)	0.68
Myocardial infarction (nonfatal)	146 (1.9)	155 (2.0)	0.94 (0.75–1.18)	0.59
Ischemic stroke (nonfatal)	132 (1.7)	163 (2.1)	0.81 (0.64–1.02)	0.07
Stroke (nonfatal)	150 (1.9)	189 (2.4)	0.79 (0.64–0.98)	0.03
Secondary efficacy end point†	1301 (16.7)	1395 (17.9)	0.92 (0.86–0.995)	0.04
Hospitalization for unstable angina, transient ischemic attack, or revascularization	866 (11.1)	957 (12.3)	0.90 (0.82–0.98)	0.02
Safety end points				
Severe bleeding	130 (1.7)	104 (1.3)	1.25 (0.97–1.61)	0.09
Fatal bleeding	26 (0.3)	17 (0.2)	1.53 (0.83–2.82)	0.17
Primary intracranial hemorrhage	26 (0.3)	27 (0.3)	0.96 (0.56–1.65)	0.89
Moderate bleeding	164 (2.1)	101 (1.3)	1.62 (1.27–2.08)	<0.001

N Engl J Med 2006;354:1706-17.

Class I

A drug-eluting stent should be considered as an alternative to the bare-metal stent in subsets of patients in whom trial data suggest efficacy. (*Level of Evidence: A*)

Class IIb

A drug-eluting stent may be considered for use in anatomic settings in which the usefulness, effectiveness, and safety have not been fully documented in published trials. (*Level of Evidence: C*)

New recommendation since the 2001 ACC/AHA Guidelines for Percutaneous Coronary Intervention. Evidence continues to accumulate that supports the use of drug-eluting stents (DES) versus bare-metal stents in certain subsets in which DES results and outcomes are better (70, 71, 85–97).

The data that a DES can improve clinical outcomes for PCI are generally strong. However, DESs have not undergone evaluation for use in all clinical situations and anatomic settings.

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Purpose

Assess the effectiveness of treatment of coronary artery disease related to:

1. Choice of initial treatment

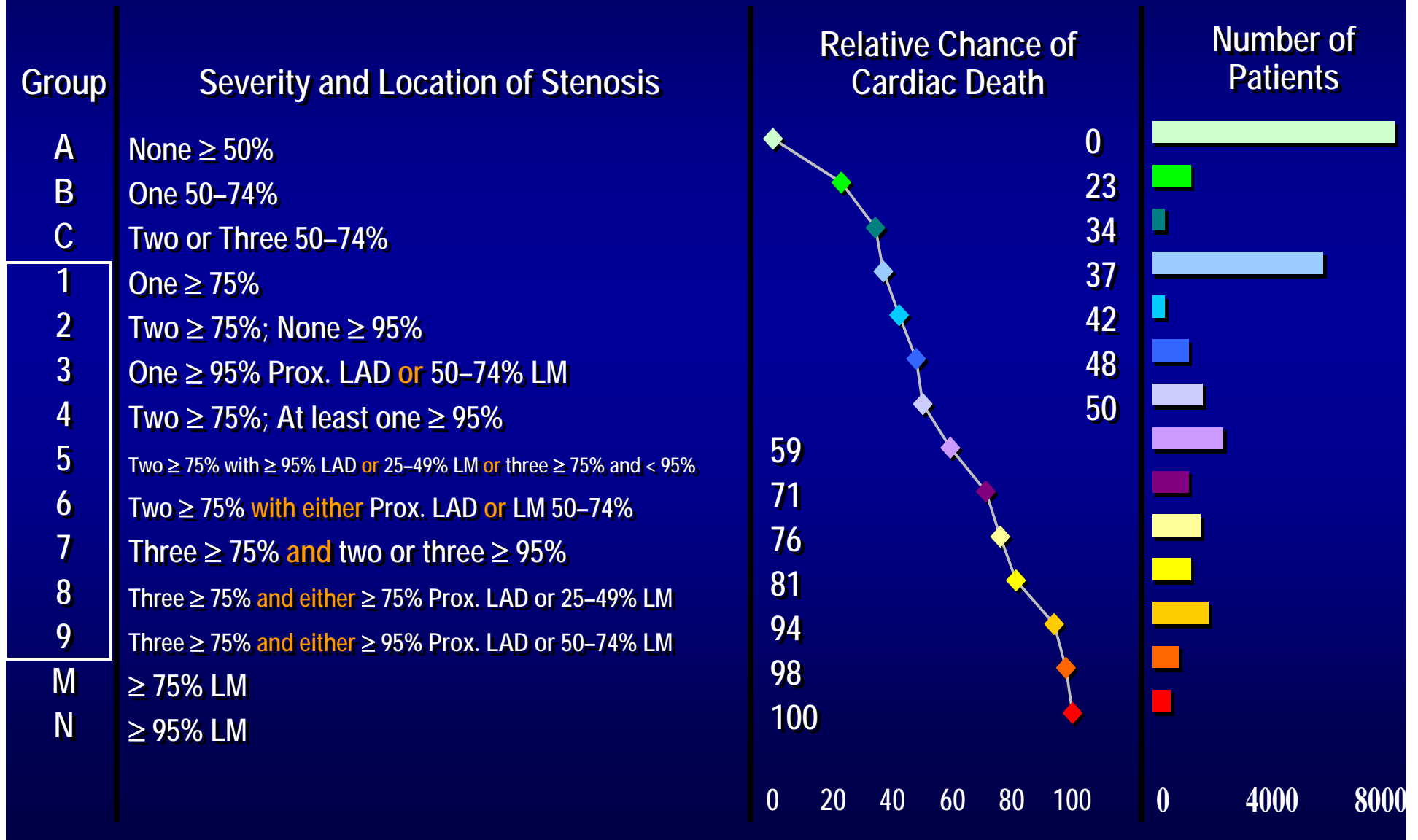
- Medical Therapy (MED)
- Percutaneous Intervention (PCI)
- Surgery (CABG)

2. Era of treatment selection

3. Severity of CAD

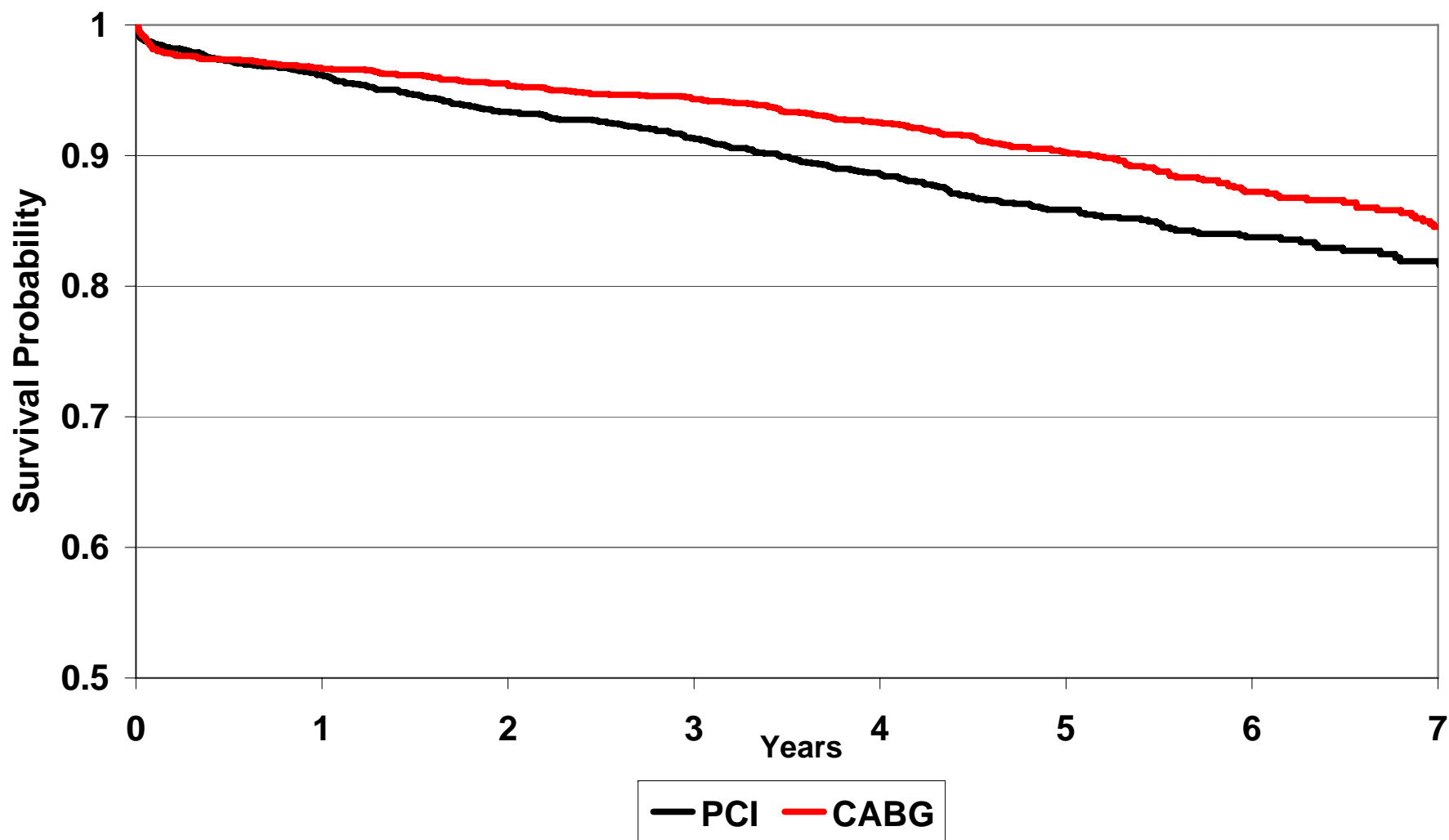
Influence of Severity and Location of Stenosis on Cardiac Death

Over a 7-Year Mean Follow-up in 29,082 Patients Catheterized for CAD at Duke
Between 1986–2000 and Treated Without Revascularization



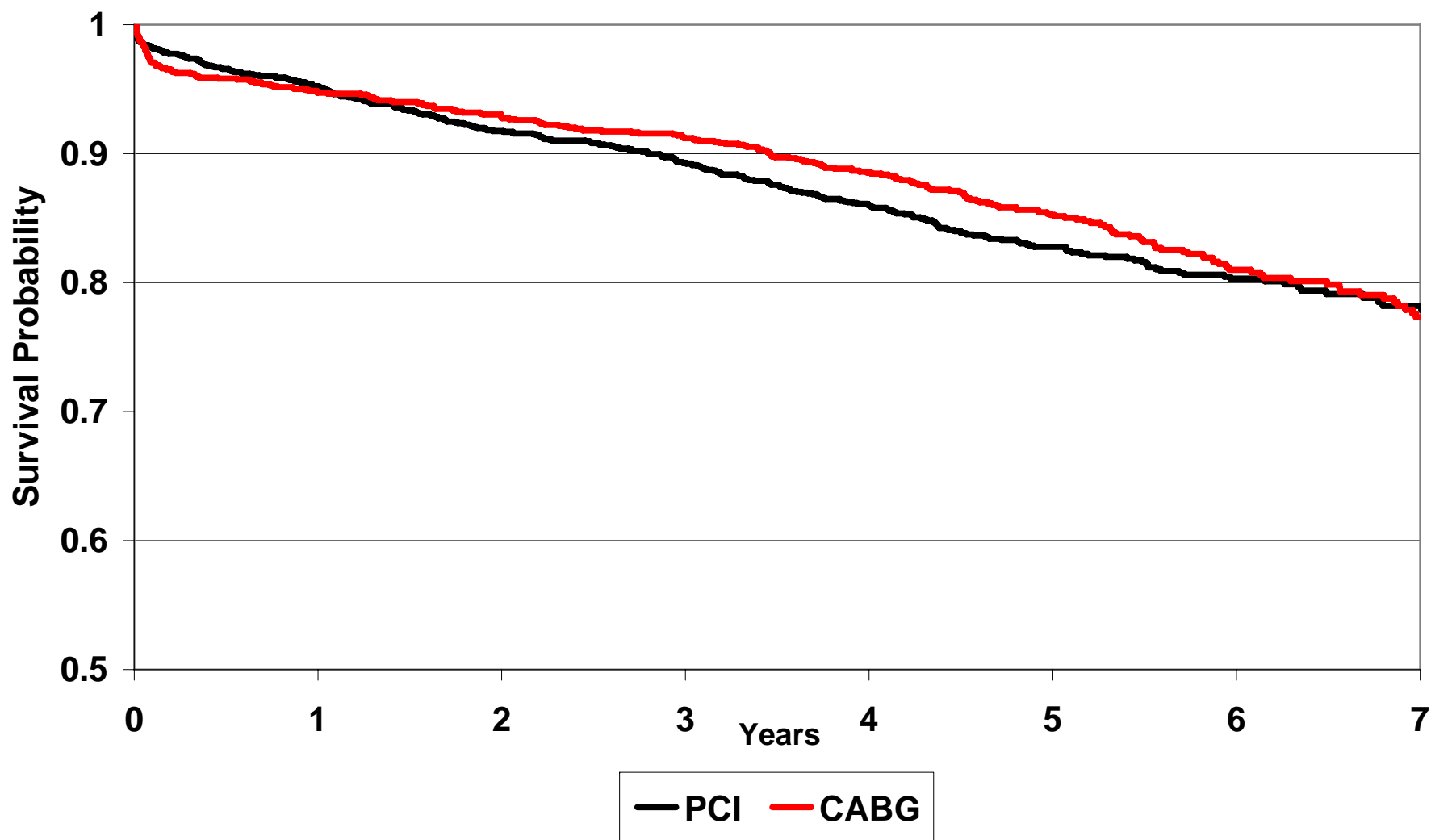
BMS vs. CABG Adjusted Survival

Low Severity CAD 1996-2000

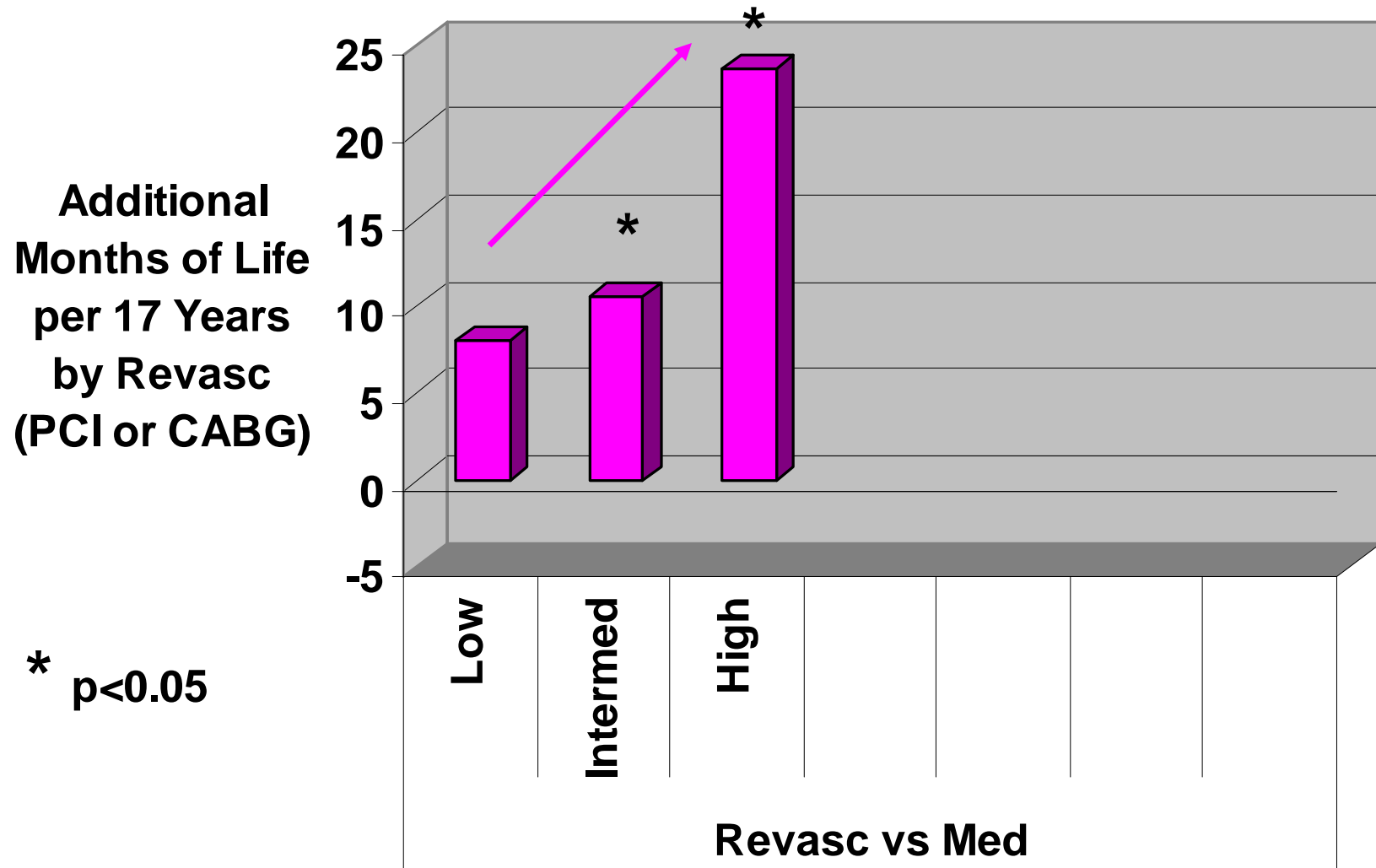


BMS vs. CABG Adjusted Survival

Intermediate Severity CAD 1996-2000



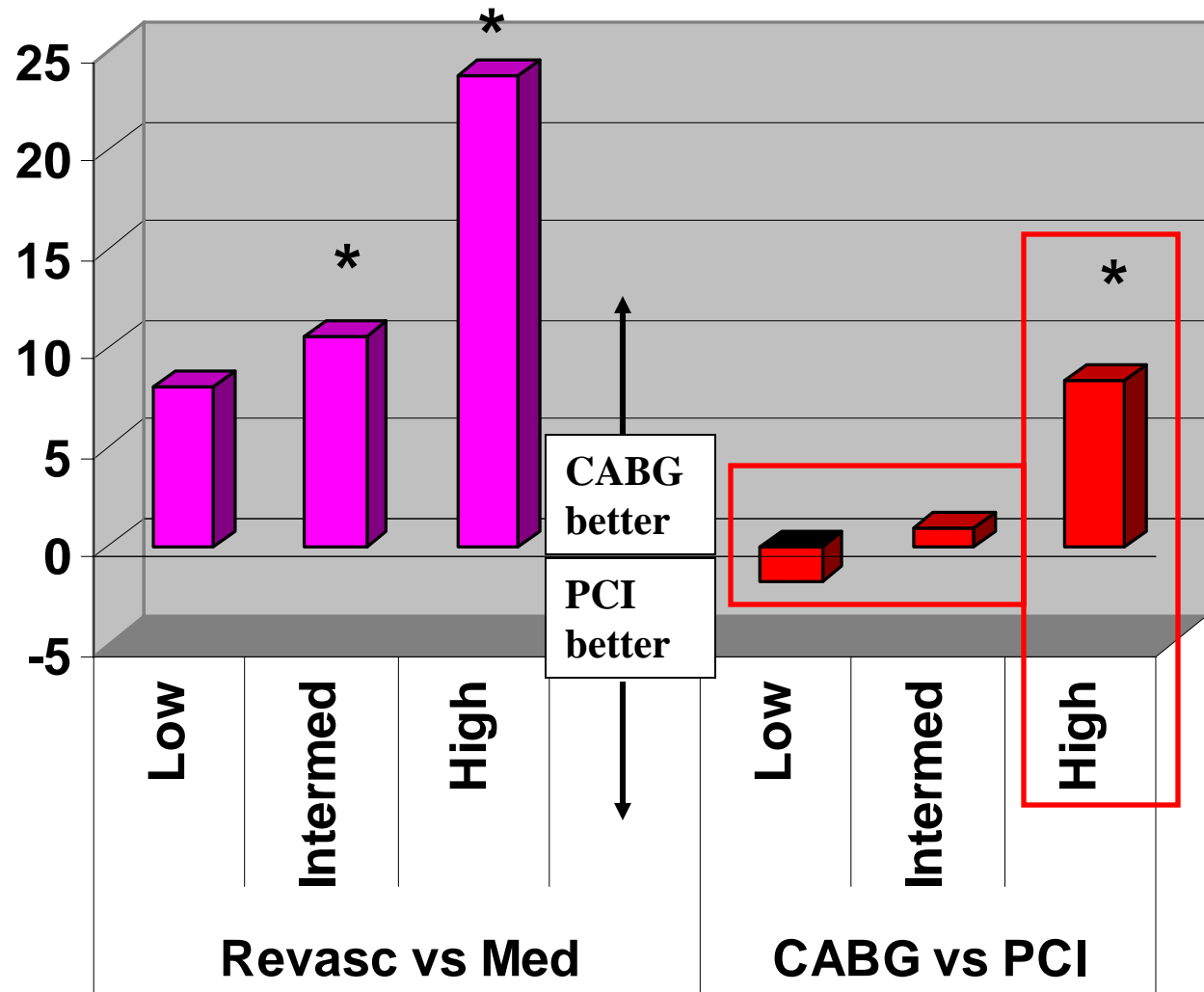
Survival Benefit Attribution 1986-2000



Survival Benefit Attribution 1986-2000

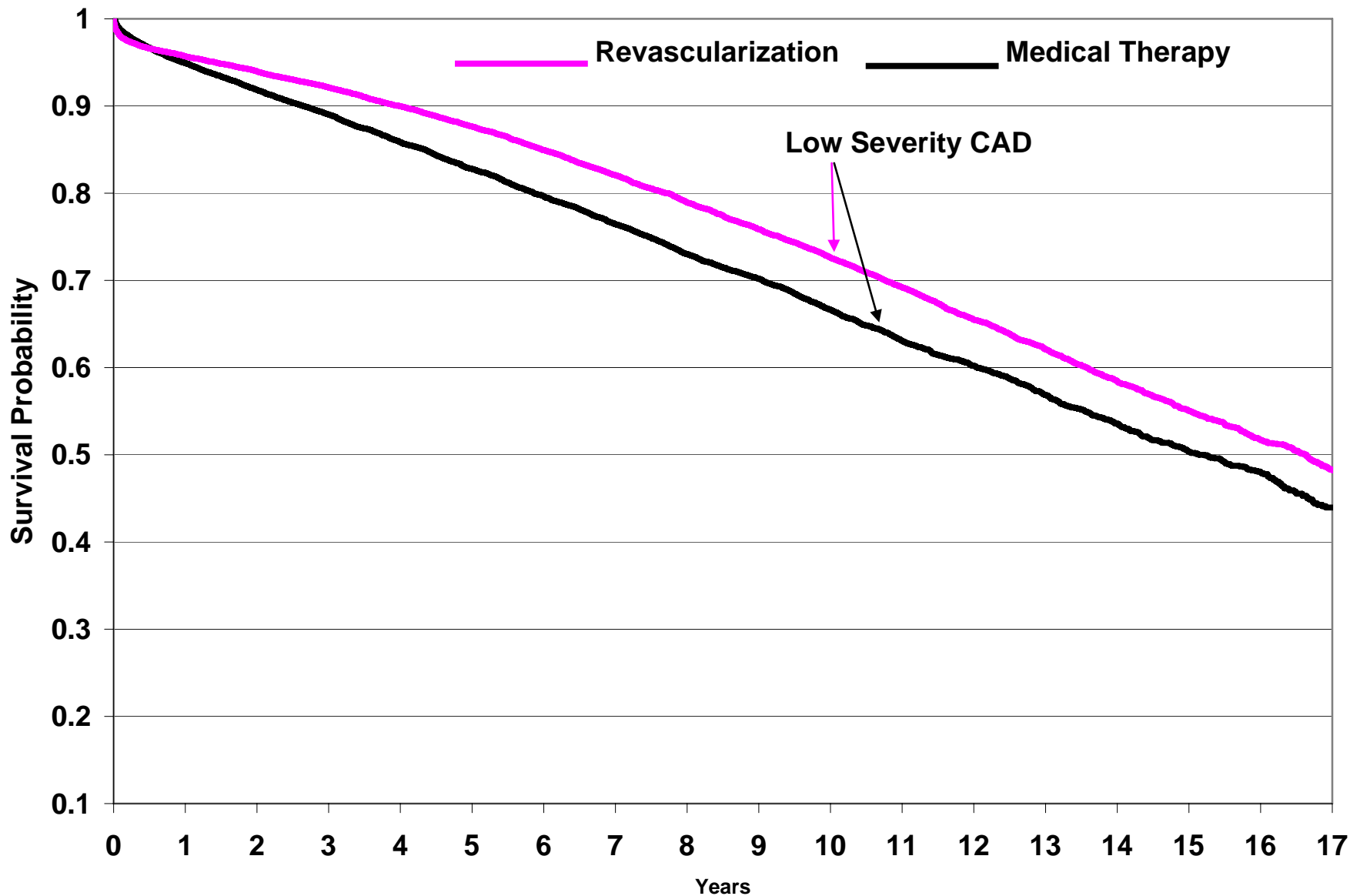
Additional
Months of Life
per 17 Years
by CABG

* $p < 0.05$

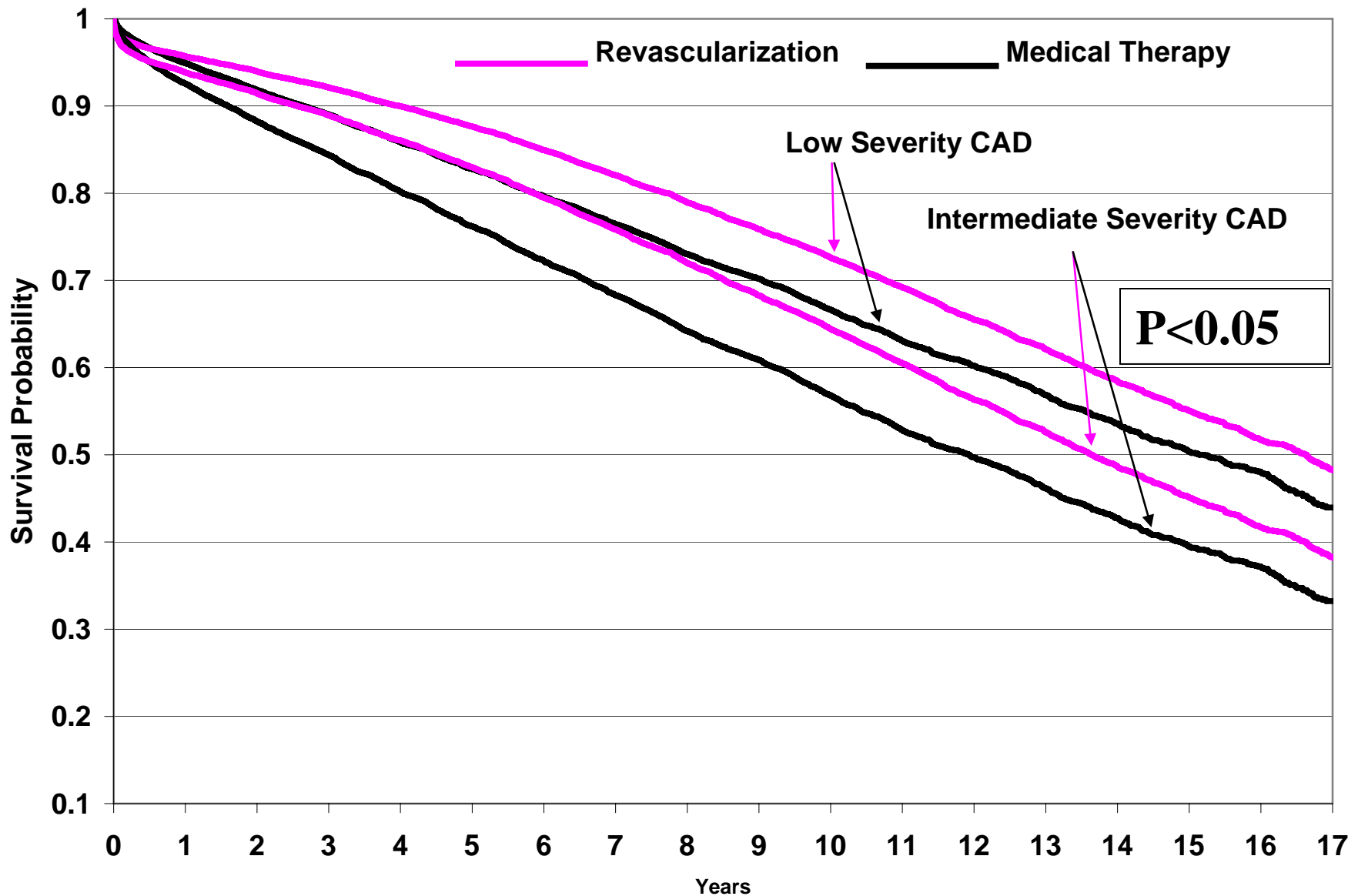


What is the role of Medical Therapy?

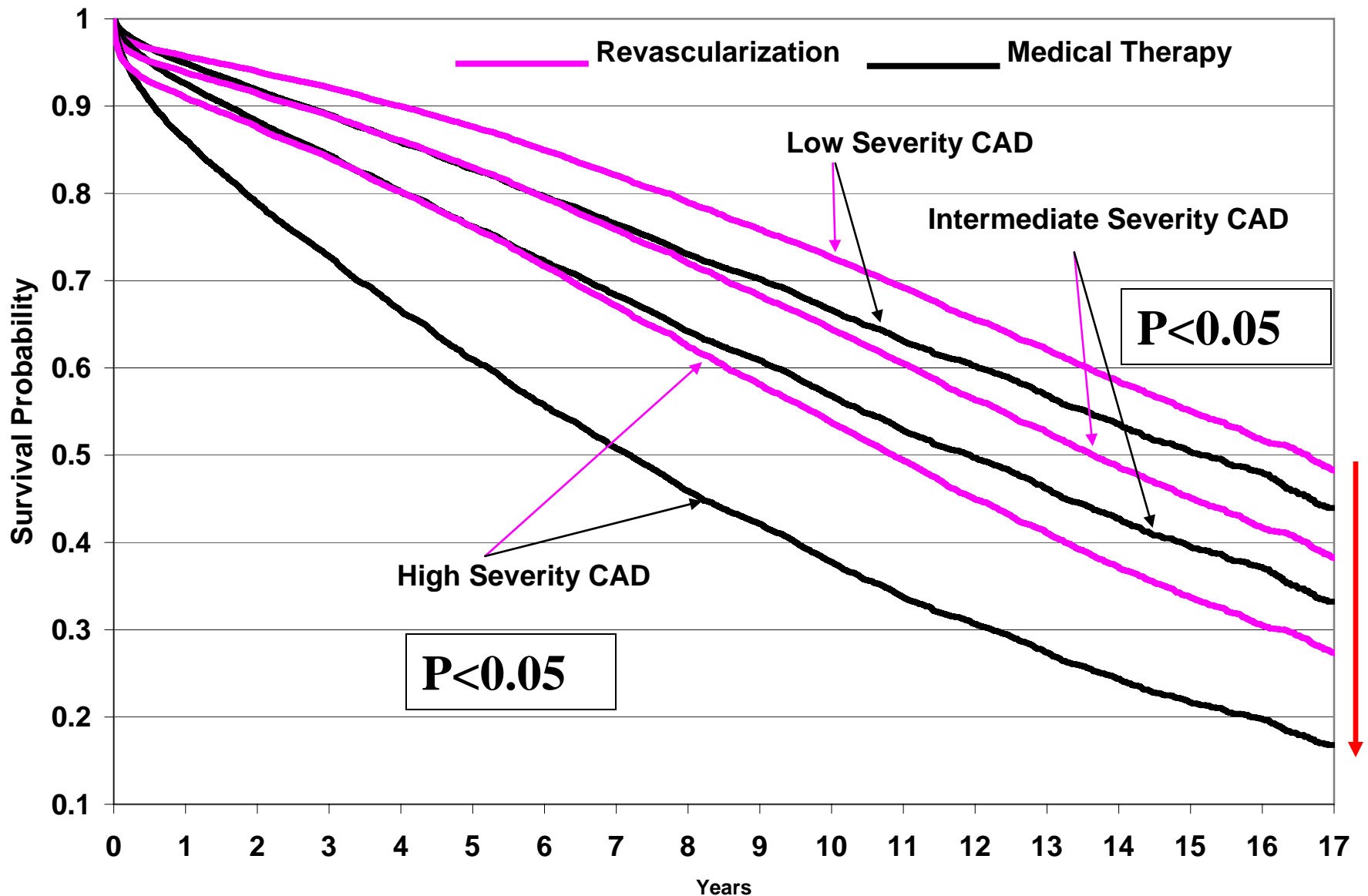
Revascularization vs. Medical Therapy 1986-2000



Revascularization vs. Medical Therapy 1986-2000



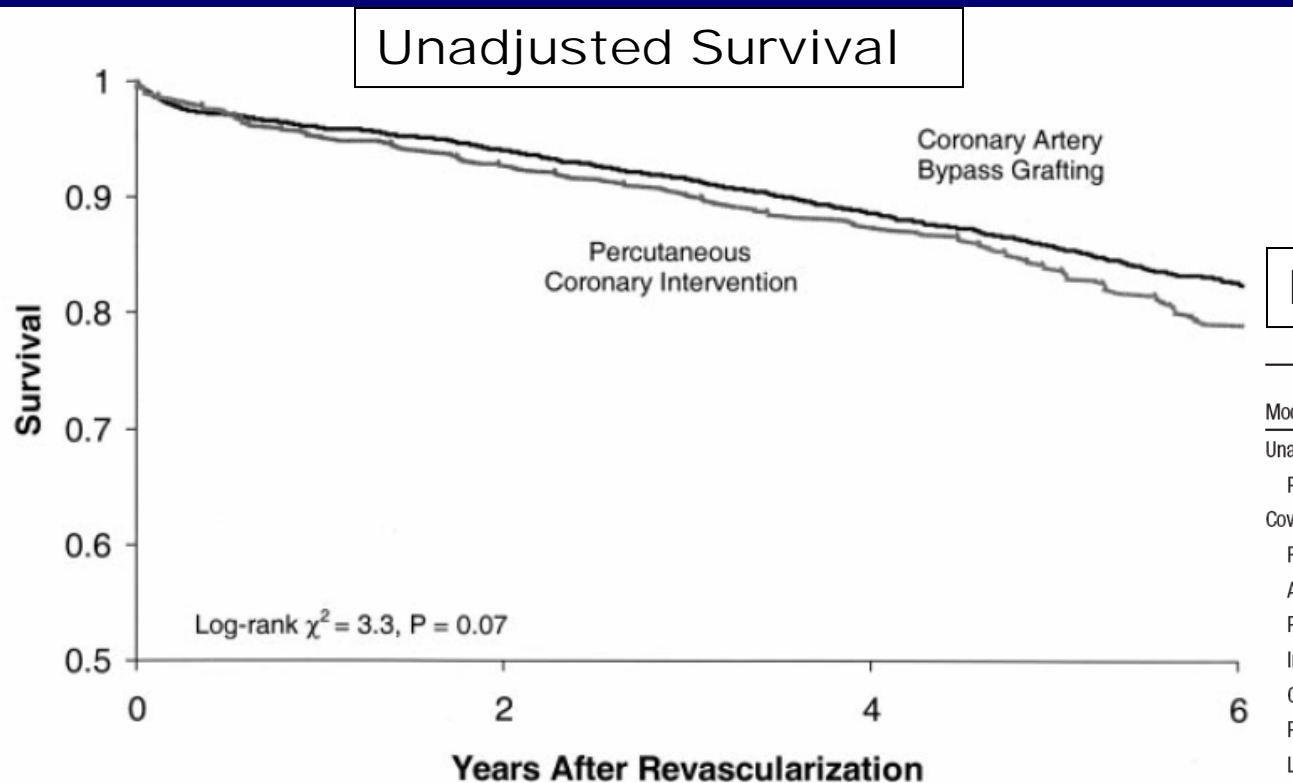
Revascularization vs. Medical Therapy 1986-2000



- We have heard the descriptor “rare” used over and over again in the past 2 days—this is not rare
- The minimization of the DES problem and ignores the issue that they are equivalent to BMS for mortality, and the promise that they would be appropriate for multivessel disease has not been realized.

Cleveland Clinic 1995-1999

N=6,033 Multivessel Disease



Propensity Adjustment

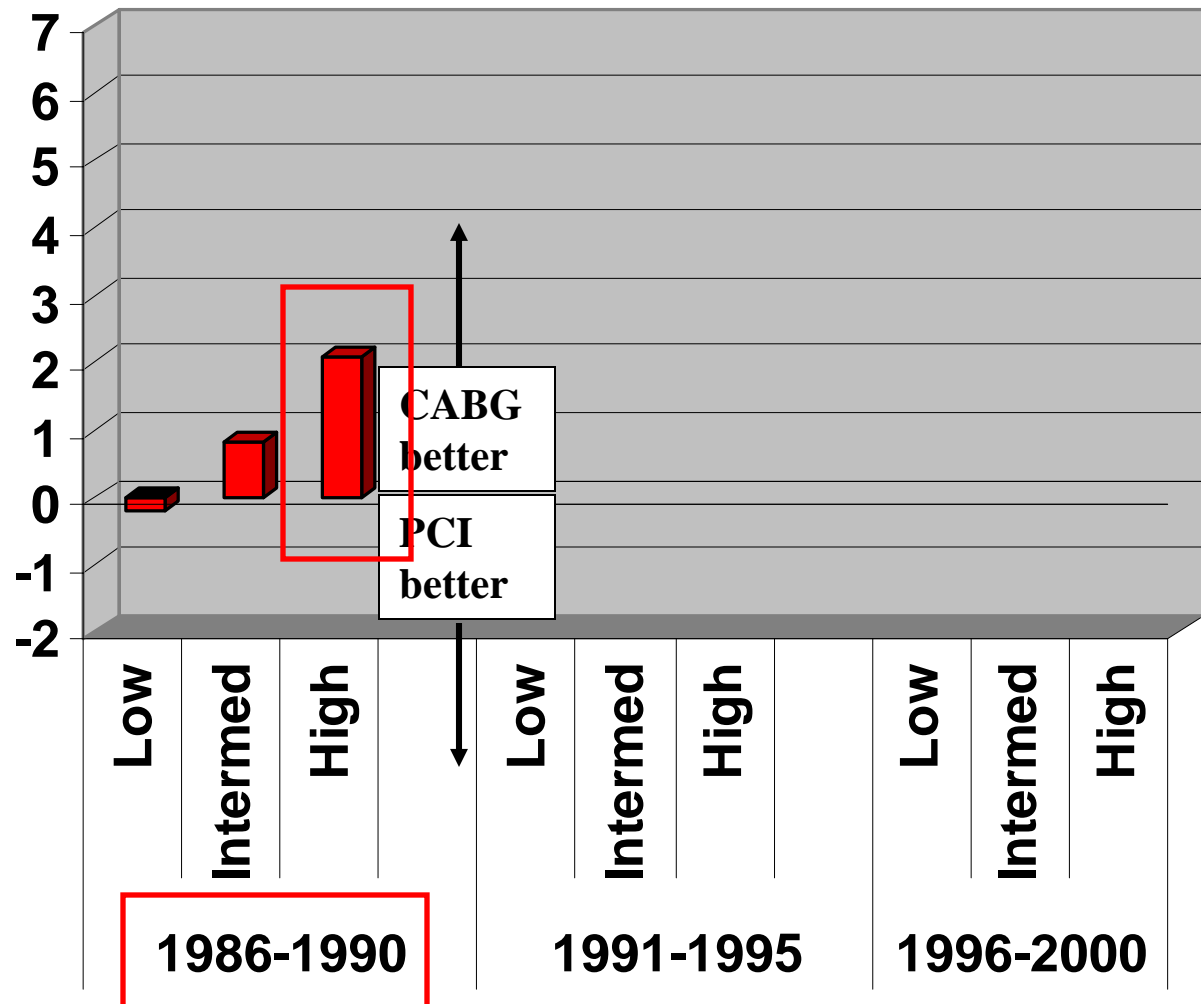
Model/Variable	Hazard Ratio (95% CI)	P
Unadjusted		
PCI	1.13 (0.99–1.40)	0.07
Covariate adjusted		
Renal insufficiency	3.72 (3.12–4.42)	<0.0001
Age in years	1.53 (1.42–1.64)	<0.0001
PCI	2.12 (1.74–2.58)	<0.0001
Insulin-treated diabetes	1.72 (1.45–2.04)	<0.0001
Chronic lung disease	1.61 (1.38–1.88)	<0.0001
Peripheral vascular disease	1.54 (1.34–1.78)	<0.0001
Left ventricular ejection fraction (10% decrease)	1.22 (1.11–1.34)	<0.0001
Non-insulin-treated diabetes	1.35 (1.16–1.57)	0.0001
Angiographic score (10% increase)	1.05 (1.01–1.08)	0.007
Left main disease	1.23 (1.05–1.44)	0.01
Propensity adjusted		
PCI	2.30 (1.85–2.86)	<0.0001
Propensity score (0.1 increase)	0.83 (0.79–0.87)	<0.0001

Circulation 2004;109:2290-2295

Survival Difference by Era and CAD Severity, CABG vs. PCI

Additional
Months of Life
per 7 Years by
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* $p < 0.05$
CABG vs PCI



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