



Future Perspective on Left Main Revascularization: From Evidence to Real Practice

David R. Holmes, Jr., M.D.
Mayo Clinic, Rochester

TCTAP 2017
Seoul, Korea
April 2017

Presenter Disclosure Information

David R. Holmes, Jr., M.D.

**“Future Perspective on Left Main
Revascularization: From Evidence to Real
Practice”**

The following relationships exist related to this presentation:

None



Single

Ostial

Isolated

Discrete

Shaft

Combined with other disease

Tubular

Distal

Diffuse

Post CABG or not

Calcified

Not Calcified



What Do We Know?

- 10-year follow-up
- Recent RCTs
- Unresolved issues

**New medicines and new
methods of cure always work
miracles for awhile**

**William Heberden
1710-1801**

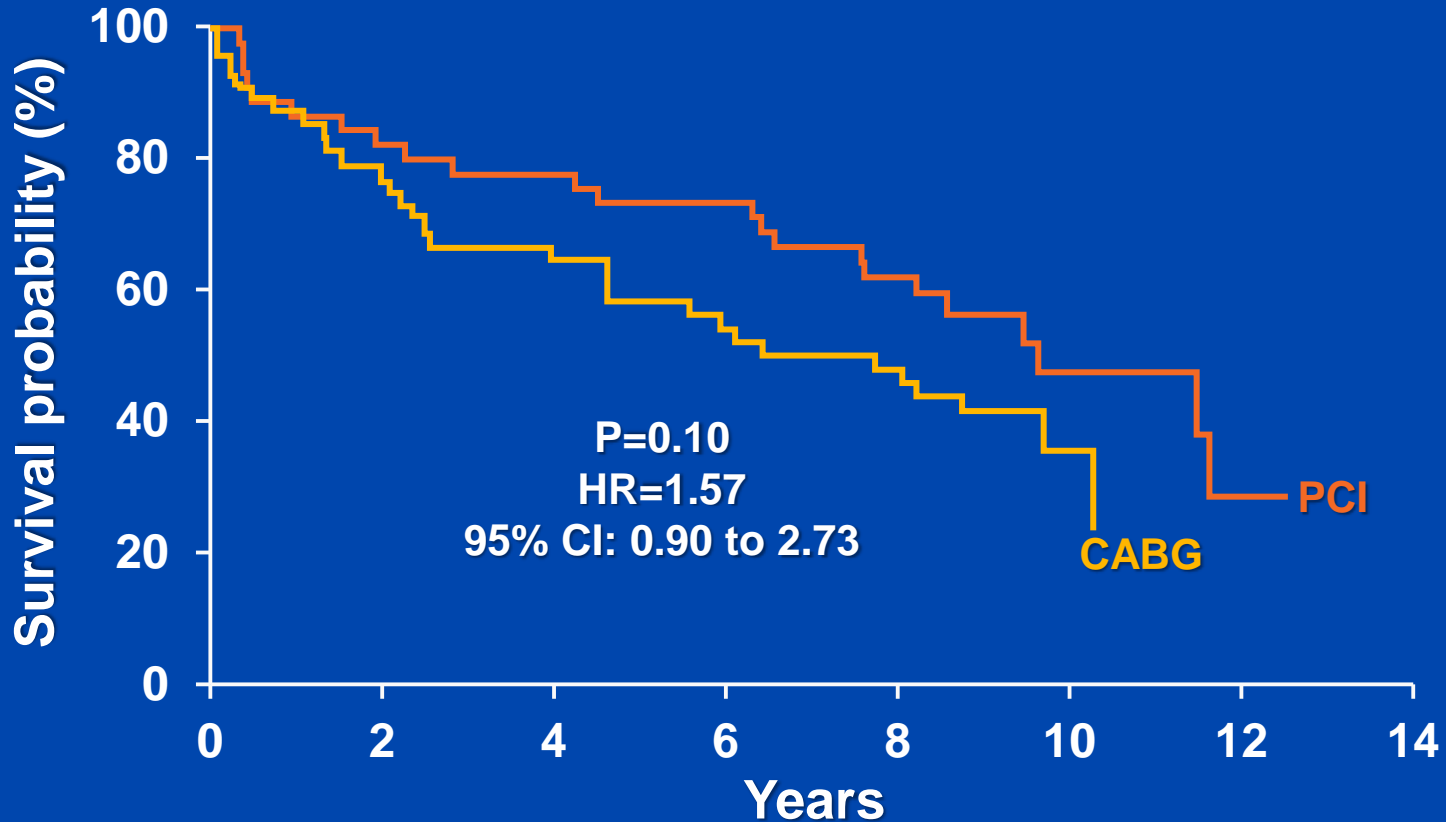
LE MANS Trial

10 Year F/U

- **Prospective multicenter trial**
 - 105 patients with LMCA low and medium complexity (SYNTAX)
- **Randomization to**
 - **Stenting – 52**
 - **CABG – 53**
- **Mean F/U**
 - **9.8 ± 1.0 years**

LE MANS Trial

Very Long-Term MACE Event-Free KM Survival Curves



No. at risk

	0	2	4	6	8	10	12	14							
CABG	48	42	37	32	31	28	26	24	23	18	4	0	0	0	0
PCI	45	39	37	35	35	33	33	30	26	13	11	9	2	1	1

Buszman et al: J Am Coll Cardiol Interv 9:318, 2016

CLINICAL RESEARCH

CORONARY

Left Main Stenting in Comparison With Surgical Revascularization

10-Year Outcomes of the (Left Main Coronary Artery Stenting) LE MANS Trial



Conclusions: In patients with unprotected left main coronary artery stenosis with low and medium complexity of coexisting coronary artery disease, stenting offers numerically, but statistically nonsignificant, favorable long-term outcome up to 10 years in terms of safety and efficacy outcome measures, therefore, constitutes an alternative therapy for CABG.

... were statistically not different between groups; however, numerically the difference was in favor of stenting. Similarly, there was no difference in the occurrence of myocardial infarction (8.7 vs. 10.4%; $p = 0.62$), stroke (4.3 vs. 6.3%; $p = 0.68$), and repeated revascularization rates (26.1% vs. 31.3%; $p = 0.64$). The probability of very long-term survival up to 14 years was comparable between PCI and CABG (74.2% vs. 67.5%; $p = 0.34$; hazard ratio: 1.45, 95% confidence interval: 0.67 to 3.13); however, there was a trend toward higher MACCE-free survival in the PCI group (34.7% vs. 22.1%; $p = 0.06$; hazard ratio: 1.71, 95% confidence interval: 0.97 to 2.99).

CONCLUSIONS In patients with unprotected left main coronary artery stenosis with low and medium complexity of coexisting coronary artery disease, stenting offers numerically, but statistically nonsignificant, favorable long-term outcome up to 10 years in terms of safety and efficacy outcome measures, therefore, constitutes an alternative therapy for CABG. (*J Am Coll Cardiol Interv* 2016;9:318-27)
© 2016 by the American College of Cardiology Foundation.

From the *American Heart of Poland, Center for Cardiovascular Research and Development, Katowice, Poland; *Medical University of Silesia, Katowice, Poland; †Third Clinical Department of Cardiology of Medical University of Silesia, Silesian Center for Heart Disease, Zabrze, Poland; ‡University of Texas Health Sciences, San Antonio, Texas; and the §Surge-18 Clinic Research Foundation, Bryn Mawr, Pennsylvania. The authors have reported that they have no relationships related to the content of this paper to disclose.

Manuscript received September 26, 2015; revised manuscript received October 14, 2015; accepted October 24, 2015.



NOBLE

EXCEL

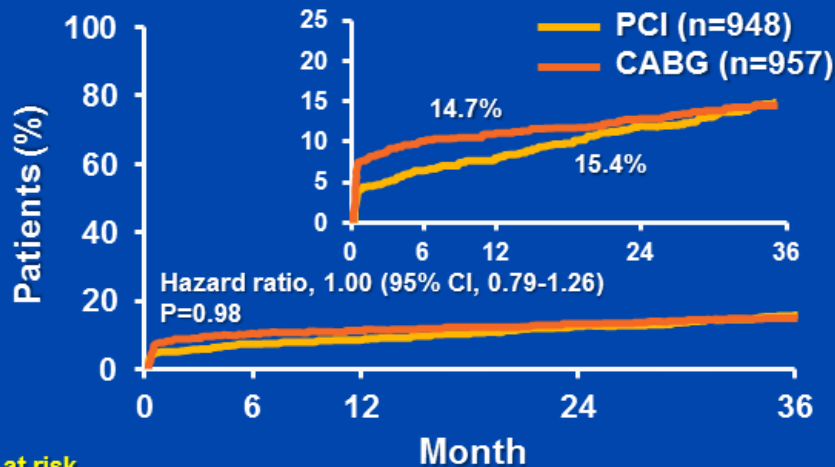
EXCEL

- **Multicenter multinational RCT – Heart Team**
 - **1,905 patients with LMCA**
 - **SYNTAX score ≤ 32**
 - **Randomization to**
 - **PCI with EES (n=948)**
 - **CABG (n=957)**
- **Primary endpoint**
 - **All cause mortality, stroke, MI at 3 years**
- **Non-inferiority study (margin 42% patients)**

EXCEL Trial

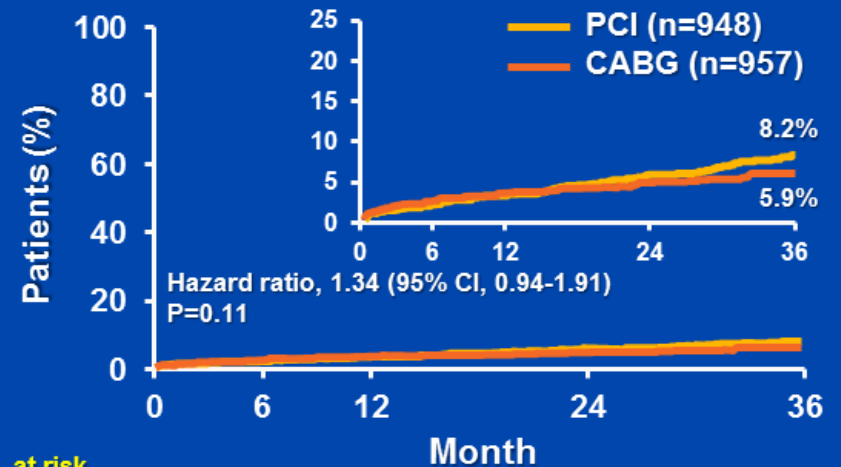
Primary Composite End Point Time to Event

Death, Stroke, or Myocardial Infarction



No. at risk		Month					
	0	6	12	24	36		
PCI	948	896	875	850	784	445	
CABG	957	868	836	817	763	468	

Death From Any Cause

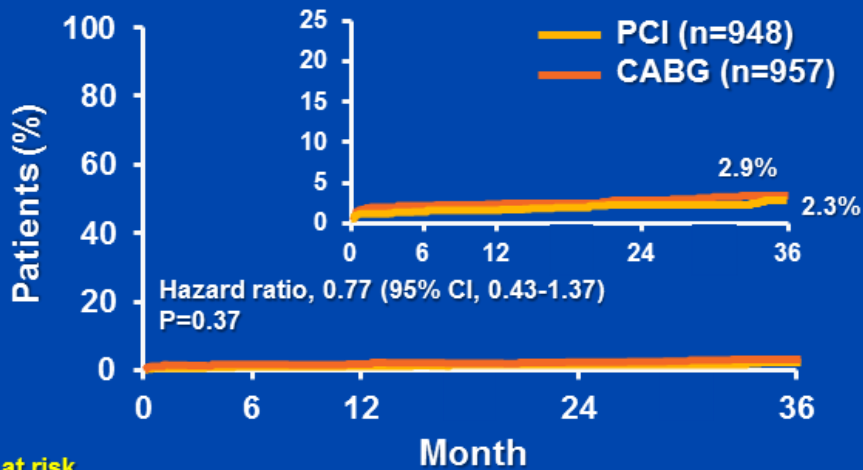


No. at risk		Month					
	0	6	12	24	36		
PCI	948	933	921	898	839	476	
CABG	957	933	910	889	835	522	

EXCEL Trial

Primary Composite End Point Time to Event

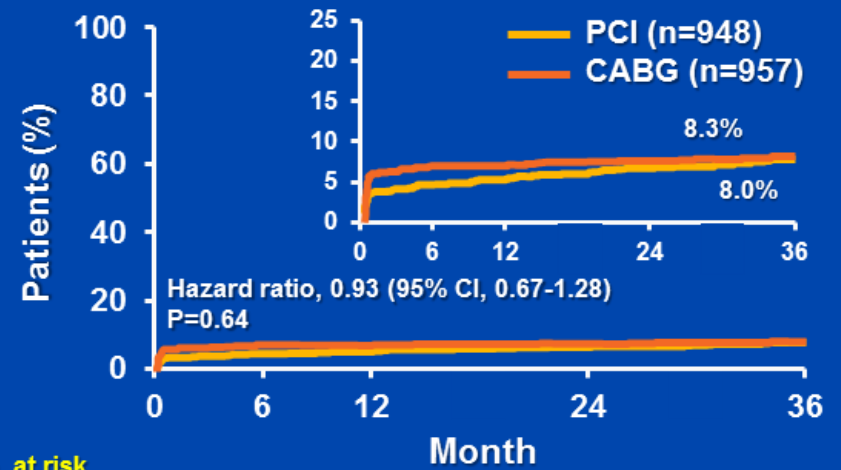
Stroke



No. at risk

	0	6	12	24	36	
PCI	948	930	915	893	839	473
CABG	957	922	899	880	823	511

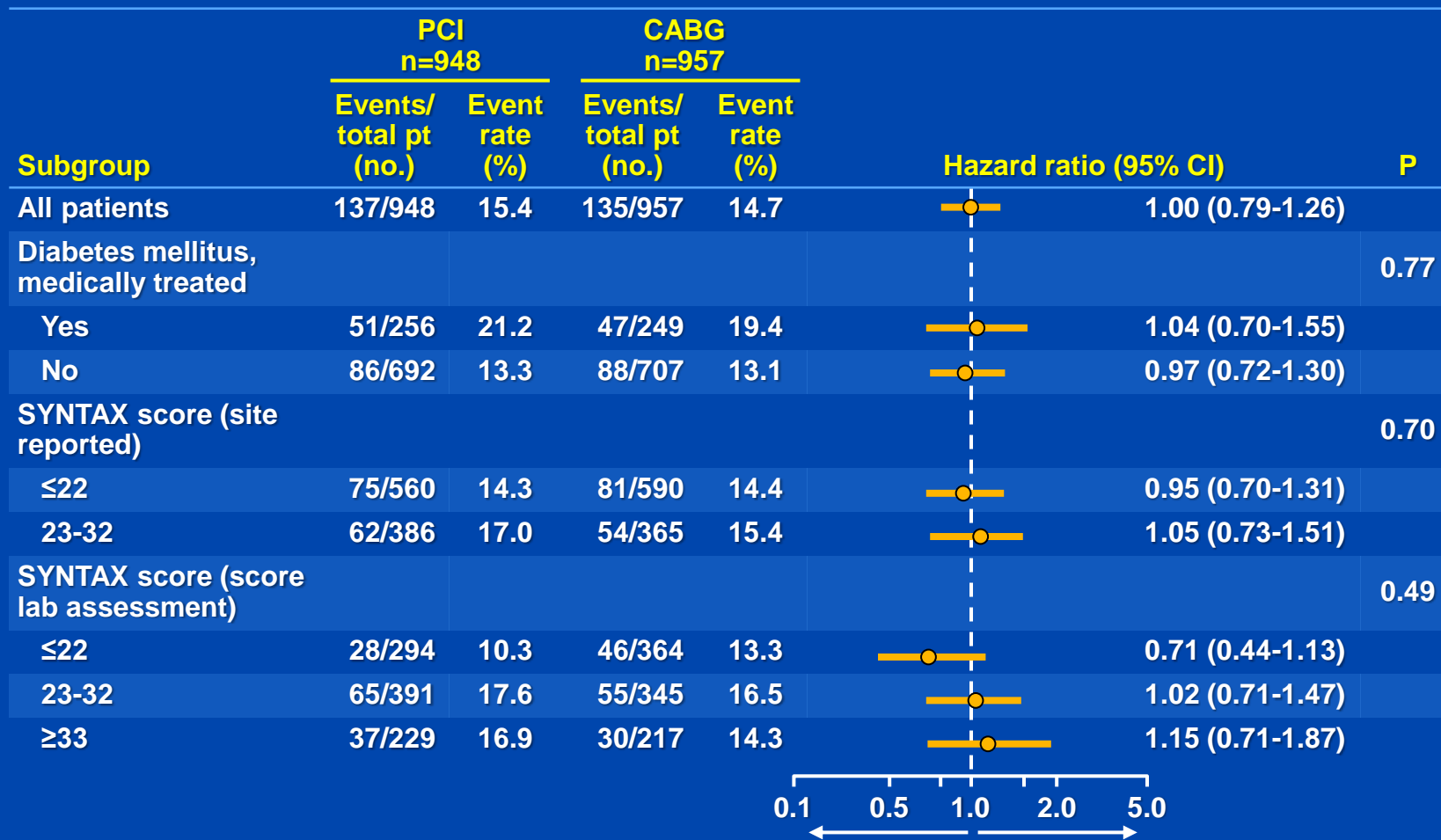
Myocardial Infarction



No. at risk

	0	6	12	24	36	
PCI	948	900	882	857	805	452
CABG	957	879	846	830	776	480

EES or Bypass Surgery for LM CAD



Stone et al: NEJM 375:2223, 2016

ORIGINAL ARTICLE

Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease

G.W. Stone, J.F. Sabik, P.W. Serruys, C.A. Simonton, P. Généreux, J. Puskas, D.E. Kandzari, M.-C. Morice, N. Lembo, W.M. Brown III, D.P. Taggart, A. Banning, B. Merkely, F. Horkay, P.W. Boonstra, A.J. van Boven, I. Ungi, G. Bogáts, S. Mansour, N. Noismuz, M. Sabaté, J. Pomar, M. Hickey, A. Gershlick, P. Buszman, A. Bochenek, E. Schampaert, P. Pagé, O. Dressler, I. Kosmidou, R. Mehran, S.J. Pocock, and A.P. Kappetein, for the EXCEL Trial Investigators*

ABSTRACT

Conclusions: In patients with left main coronary artery disease and low or intermediate SYNTAX scores by site assessment, PCI with everolimus-eluting stents was noninferior to CABG with respect to the rate of the composite end point of death, stroke, or myocardial infarction at 3 years.

At 3 years, a primary end-point event had occurred in 15.4% of the patients in the PCI group and in 14.7% of the patients in the CABG group (difference, 0.7 percentage points; upper 97.5% confidence limit, 4.0 percentage points; $P=0.02$ for noninferiority; hazard ratio, 1.00; 95% confidence interval, 0.79 to 1.26; $P=0.98$ for superiority). The secondary end-point event of death, stroke, or myocardial infarction at 30 days occurred in 4.9% of the patients in the PCI group and in 7.9% in the CABG group ($P<0.001$ for noninferiority, $P=0.008$ for superiority). The secondary end-point event of death, stroke, myocardial infarction, or ischemia-driven revascularization at 3 years occurred in 23.7% of the patients in the PCI group and in 19.7% in the CABG group ($P=0.01$ for noninferiority, $P=0.10$ for superiority).

CONCLUSIONS

In patients with left main coronary artery disease and low or intermediate SYNTAX scores by site assessment, PCI with everolimus-eluting stents was noninferior to CABG with respect to the rate of the composite end point of death, stroke, or myocardial infarction at 3 years. (Funded by Abbott Vascular; EXCEL ClinicalTrials.gov number, NCT01205776.)

N ENGL J MED NEJM-ORG

The New England Journal of Medicine

Downloaded from nejm.org at MAYO CLINIC LIBRARY on November 1, 2016. For personal use only. No other uses without permission.

Copyright © 2016 Massachusetts Medical Society. All rights reserved.

NOBLE Trial

- **Multicenter multinational RCT – Heart Team**
 - **1,201 patients with LMCA**
 - **Randomization**
 - **PCI with DES (n=598)**
 - **CABG (n=603)**
- **Primary endpoint**
 - **All-cause death, nonprocedural MI, repeat revasc, stroke**
- **Non-inferiority study**
 - **HR <1.35 yrs – 5-year follow-up**

NOBLE Trial

Bottom Line

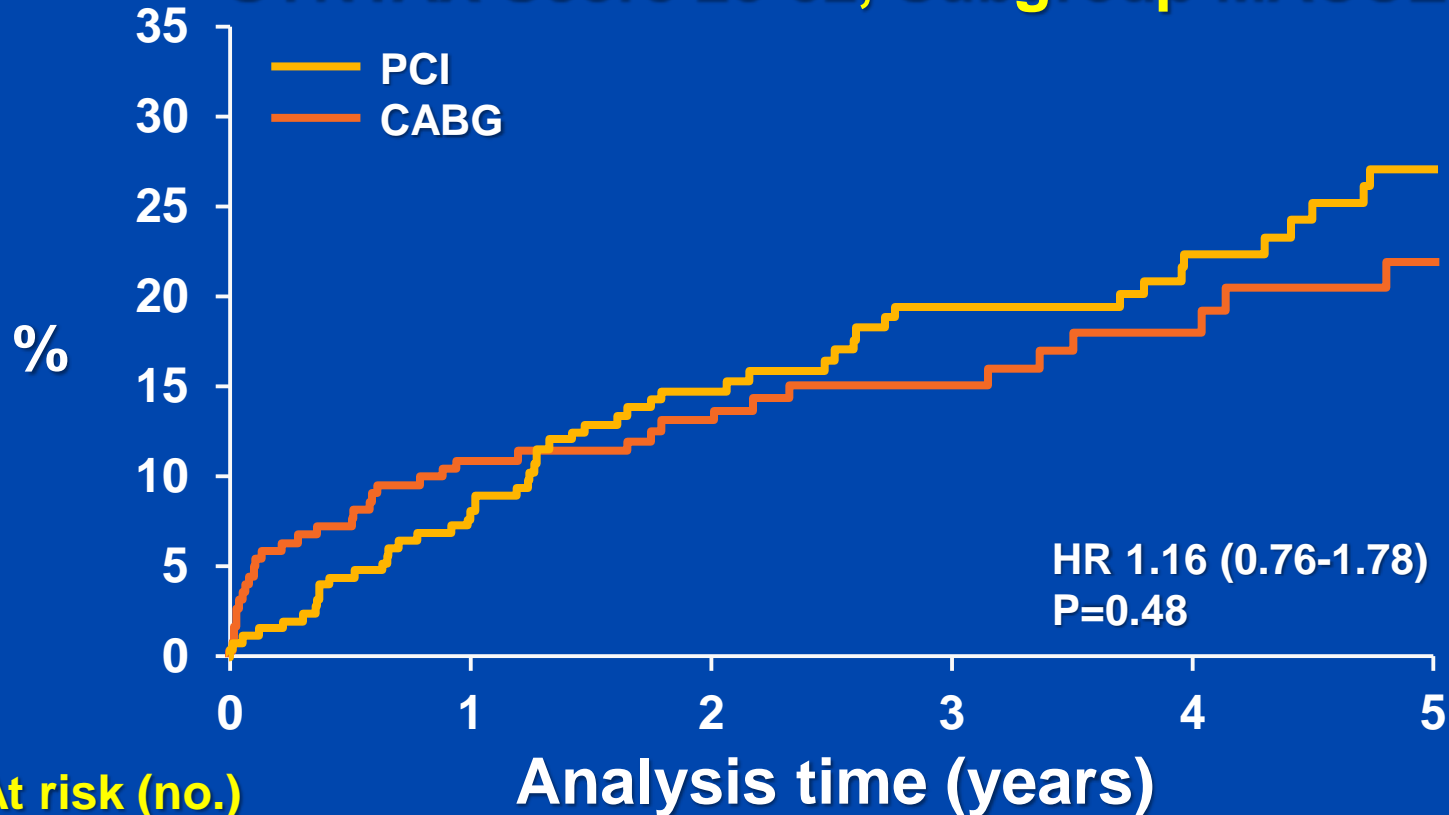
5-Year KM Estimates

	PCI	CABG	HR	P
MACCE (%)	29	19	1.48	0.0066
All-cause mortality (%)	12	9	1.07	0.77
Non-procedural MI (%)	7	2	2.88	0.0040
Any revascularization (%)	16	10	1.50	0.032
Stroke (%)	5	2	2.25	0.073

Noble Trial

Outcomes by SYNTAX Score Group

SYNTAX Score 23-32, Subgroup MACCE



At risk (no.)

At risk (no.)	0	1	2	3	4	5
PCI	249	224	181	129	104	62
CABG	220	192	152	113	76	47

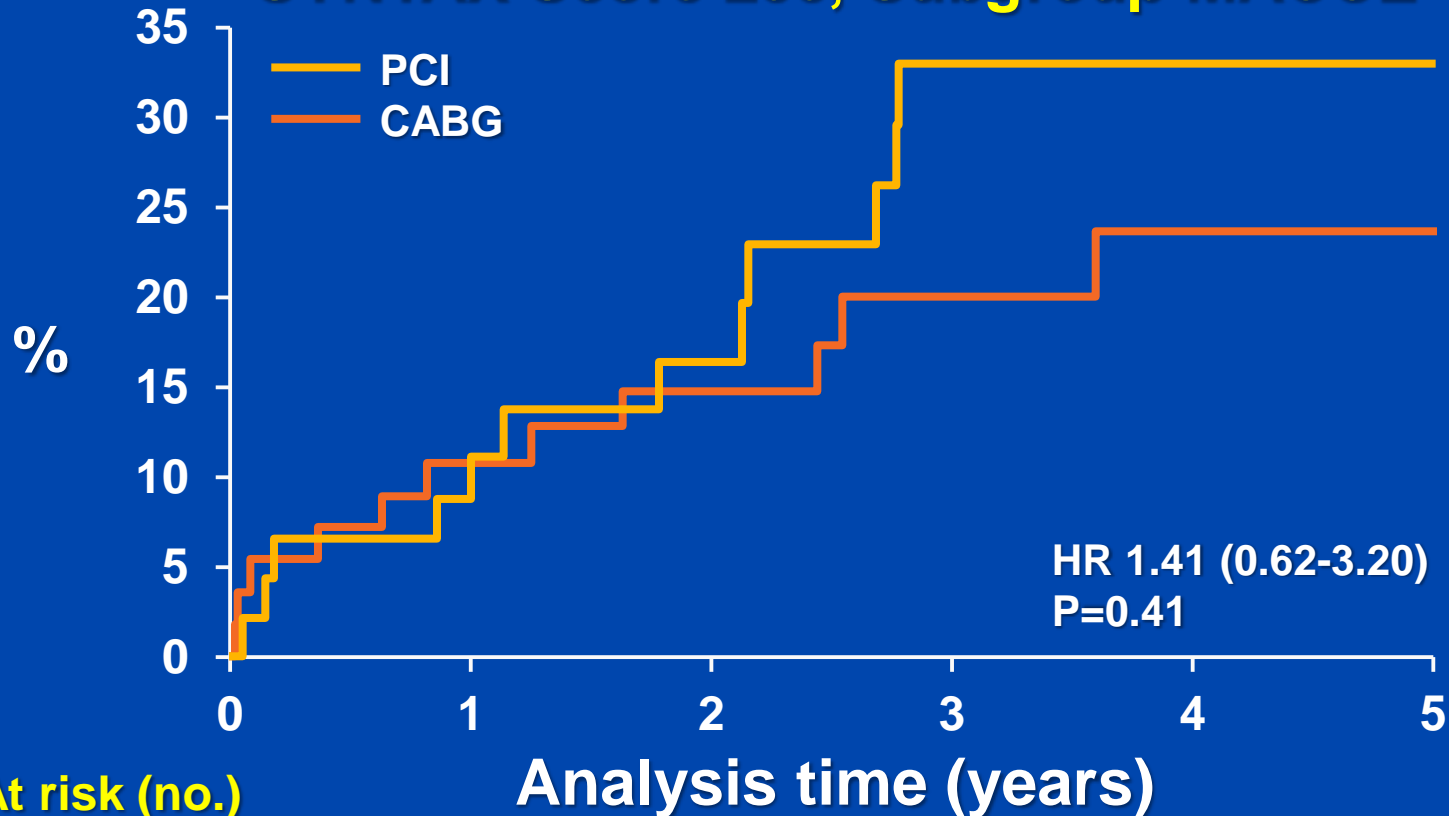
Analysis time (years)

Makikallio et al: www.thelancet.com [http://dx.doi.org/10.1016/S0140-6736\(16\)32052](http://dx.doi.org/10.1016/S0140-6736(16)32052)

Noble Trial

Outcomes by SYNTAX Score Group

SYNTAX Score ≥ 33 , Subgroup MACCE



At risk (no.)

PCI	46	39	31	18	12	7
CABG	56	49	42	28	19	9

Makikallio et al: www.thelancet.com [http://dx.doi.org/10.1016/S0140-6736\(16\)32052](http://dx.doi.org/10.1016/S0140-6736(16)32052)

Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial



Timo Makikallio, Niels R Holm, Mitchell Lindsay, Mark S Spencer, Arshajj English, Ian B A Menson, Thor Trovik, Markku Eskola, Haruru Ramppanen, Thomas Kellerth, Jan Rokkvi, Lisette O Jensen, Gintaras Kalnasnikas, Mikael B A Lind, Markku Penttinen, Anders Herøvd, Adrian Bonning, Aqar Zaman, James Cotton, Erlend Eriksen, Sulev Mangu, Henni T Sorensen, Per H Nielsen, Matti Niemelä, Kari Kivinen, Jens F Lassen, Michael Maeng, Keith Oldroyd, Geoff Bey, Steven J Walsh, Colin G Hanratty, Ondrej Korman, Petrus Stradins, Teije K Steigen, Ole Frøbert, Alistair N J Graham, Peter C Frødenes, Matthias Corbucci, (28) Erikator, Ulfur Svein, Juhani Henttonen, Visa Anttila, David Hickey-Smith, Leif Thuesen

Interpretation: The findings of this study suggest that CABG might be better than PCI for treatment of left main stem coronary artery disease.

$p=0.0015$). Comparing PCI with CABG, 5 year estimates were 12% versus 9% (1.07, 0.67–1.72, $p=0.77$) for all-cause mortality, 7% versus 2% (2.88, 1.40–5.90, $p=0.0040$) for non-procedural myocardial infarction, 16% versus 10% (1.50, 1.04–2.17, $p=0.032$) for any revascularisation, and 5% versus 2% (2.25, 0.93–5.48, $p=0.073$) for stroke.

Interpretation The findings of this study suggest that CABG might be better than PCI for treatment of left main stem coronary artery disease.

Funding Biosensors, Aarhus University Hospital, and participating sites.

Introduction

Treatment of unprotected left main coronary artery disease with percutaneous coronary intervention (PCI) has increased rapidly during the past decade, following the favourable results of randomised trials^{1,2} and observational registry studies comparing PCI and coronary artery bypass grafting (CABG).^{3,4} At present, both options are used to treat left main coronary artery disease.⁵ Present guidelines recommend PCI in patients with left main coronary artery disease and coronary pathology favourable to PCI (ie, in the absence of complex and diffuse lesions).⁶ The guidelines are based primarily on the prespecified and powered subgroup of 705 patients with left main coronary artery disease in the

SYNTAX trial,^{2,3} which compared PCI and the drug-eluting Taxus stent with CABG in patients with three-vessel or left main coronary artery disease. The guidelines also refer to the findings of the randomised trials LE MANS (100 patients),⁷ PRECOMBAT (600 patients),⁸ and Boudriot and colleagues (201 patients)⁹ trials, which included patients with left main coronary artery stenosis. In the randomised trials, the non-inferiority margin was wide, because of relatively small patient sample sizes, and thus the trials were not powered to definitively determine the best treatment for unprotected left main coronary artery disease.

In the NOBLE trial, we postulated that PCI with drug-

(M) Lindsay MD, Professor K Oldroyd MD, G Bey MD, Belfast Heart Centre, Belfast Trust, Belfast, Northern Ireland (M Spencer MD, S Walsh MB, C G Hanratty MD, A N J Graham MD), Latvia Centre of Cardiology, Pini Stradins Clinical Hospital, Riga, Latvia (Professor A Eriksen PhD, J Frøbert MD, P Stradins PhD), Coagivon Cardiac Centre, Coagivon, Northern Ireland (I B A Menson FRCP), Department of Cardiology, University of Northern Norway, Tromsø, Norway (T Trovik PhD, T E Steigen PhD), Department of Cardiovascular Surgery, University of Medicine, Tromsø, Norway (P C Frødenes PhD), Heart Hospital, Tampere University Hospital, Tampere, Finland (M Eskola PhD, O Kujala PhD), Heart Center, Kuopio University Hospital, Kuopio, Finland (H Ramppanen PhD).



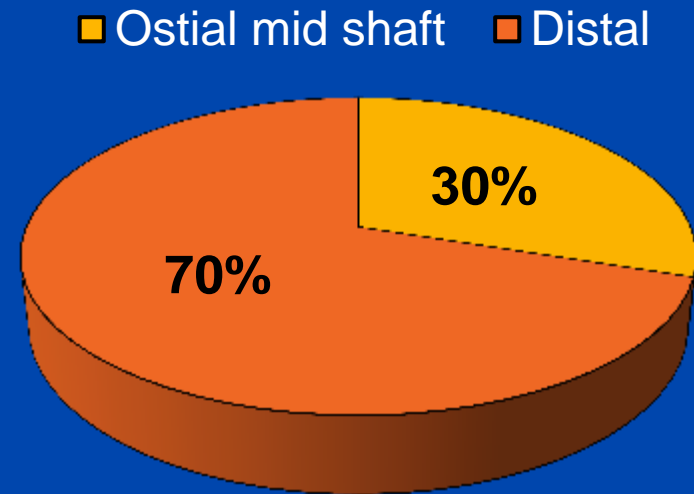
What Do We Know?

- 10-year follow-up
- Recent RCTs
- Unresolved issues

Ostial/Mid Shaft vs Distal ULMCA PCI Delta Registry

- All-comer international registry
 - 1,612 patients with ULMCA disease

- Aim: compare outcome ostial/mid shaft vs distal



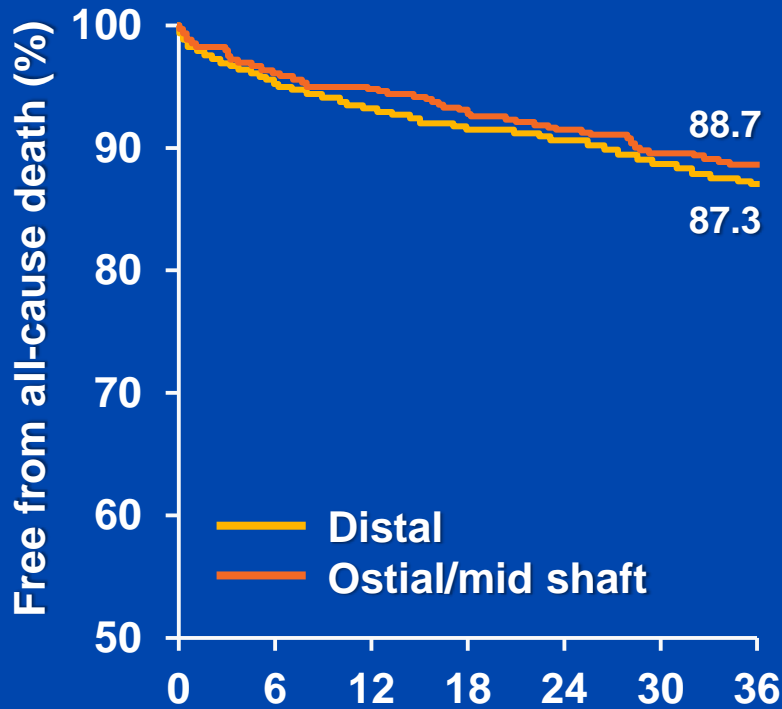
Naganuma et al: JACC Intv 6:1242, 2013

Ostial/Mid Shaft vs Distal ULMCA PCI

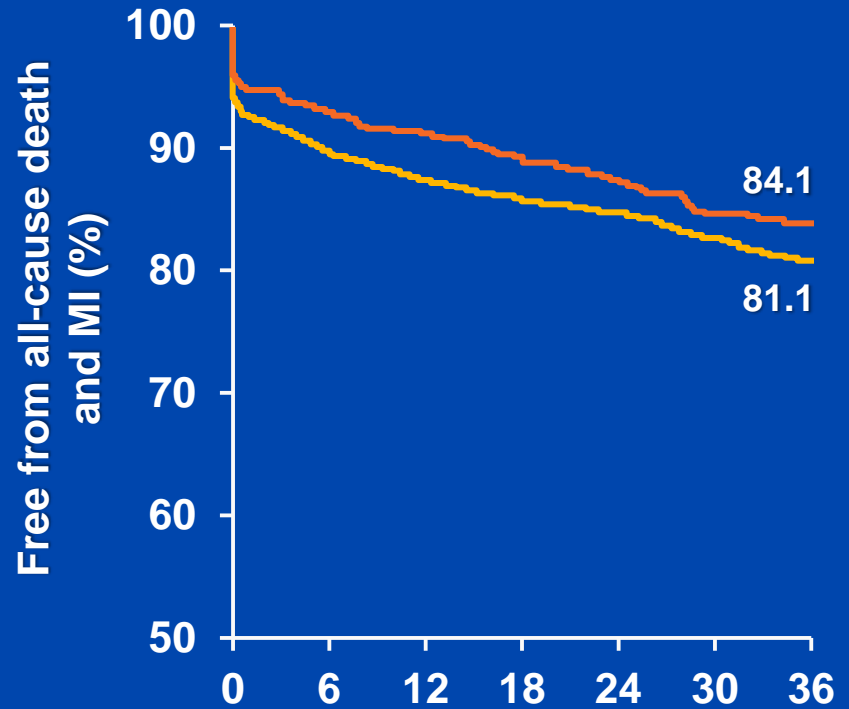
In-Hospital & Follow-Up MACE

	Ostial/Mid Shaft ULMCA PCI (n=482)	Distal ULMCA PCI (n=1,130)
Events at follow-up		
All-cause death	46 (9.5)	156 (13.8)
Cardiac death	26 (5.4)	74 (6.5)
Noncardiac death	20 (4.1)	82 (7.3)
MI	20 (3.9)	36 (3.2)
TLR	26 (6.0)	143 (12.6)
TVR	45 (9.3)	200 (17.7)
MACE	92 (19.1)	322 (28.5)

Ostial/Mid Shaft vs Distal ULMCA PCI



No. at risk	Months						
— Distal	1130	1038	996	948	908	842	748
— Ostial/mid shaft	482	459	444	414	400	376	341



No. at risk	Months						
— Distal	1130	979	936	889	849	784	692
— Ostial/mid shaft	482	445	430	400	384	358	325

Naganuma et al: JACC Intv 6:1242, 2013

Ostial/Mid Shaft vs Distal ULMCA PCI

Predictors of MACE

	HR	95% CI	P
Age, yrs	1.01	0.99-1.02	0.180
LVEF	0.99	0.98-0.99	0.030
EuroSCORE	1.02	0.99-1.05	0.273
Distal ULMCA	1.40	1.08-1.80	0.010
Elective	0.87	0.68-1.11	0.256
IABP	2.28	1.65-3.14	<0.001
Stent diameter	0.57	0.42-0.77	<0.001

Long-Term Clinical Outcomes After Percutaneous Coronary Intervention for Ostial/Mid-Shaft Lesions Versus Distal Bifurcation Lesions in Unprotected Left Main Coronary Artery

The DELTA Registry (Drug-Eluting Stent for Left Main Coronary Artery Disease): A Multicenter Registry Evaluating Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting for Left Main Treatment

Conclusions: This study demonstrates that PCI for ostial/mid-shaft lesions is associated with better clinical outcomes than are distal bifurcation lesions in ULMCA, largely because there is a lower need to repeat revascularization in ostial/mid-shaft lesions.

Background Limited data are available regarding clinical outcomes following DES implantation at the different ULMCA sites.

Methods Patients with ULMCA stenosis treated by PCI with DES were analyzed in this multinational registry.

Results A total of 1,612 patients were included: 482 were treated for ostial/mid-shaft lesions versus 1,130 for distal bifurcation lesions. At a median follow-up period of 1,250 (interquartile range: 987 to 1,564) days, PCI for distal bifurcation lesions was associated with a higher incidence of major adverse cardiac events (propensity-score adjusted hazard ratio [HR]: 1.48, 95% confidence interval [CI]: 1.16 to 1.89; $p = 0.001$), largely because of the higher target vessel revascularization rate observed in this group as compared to the ostial/mid-shaft lesions group (propensity-score adjusted HR: 1.68, 95% CI: 1.19 to 2.38; $p = 0.003$). These results were sustained following propensity-score matched analysis. With regard to all-cause death and the composite endpoint of all-cause death and myocardial infarction, propensity-score adjusted analysis suggested a trend toward higher rates of these in the distal ULMCA PCI group, although this was not observed in the propensity-score matched analysis.

Conclusions This study demonstrates that PCI for ostial/mid-shaft lesions is associated with better clinical outcomes than are distal bifurcation lesions in ULMCA, largely because there is a lower need for repeat revascularization in ostial/mid-shaft lesions. (J Am Coll Cardiol Intv 2013;6:1242-9) © 2013 by the American College of Cardiology Foundation

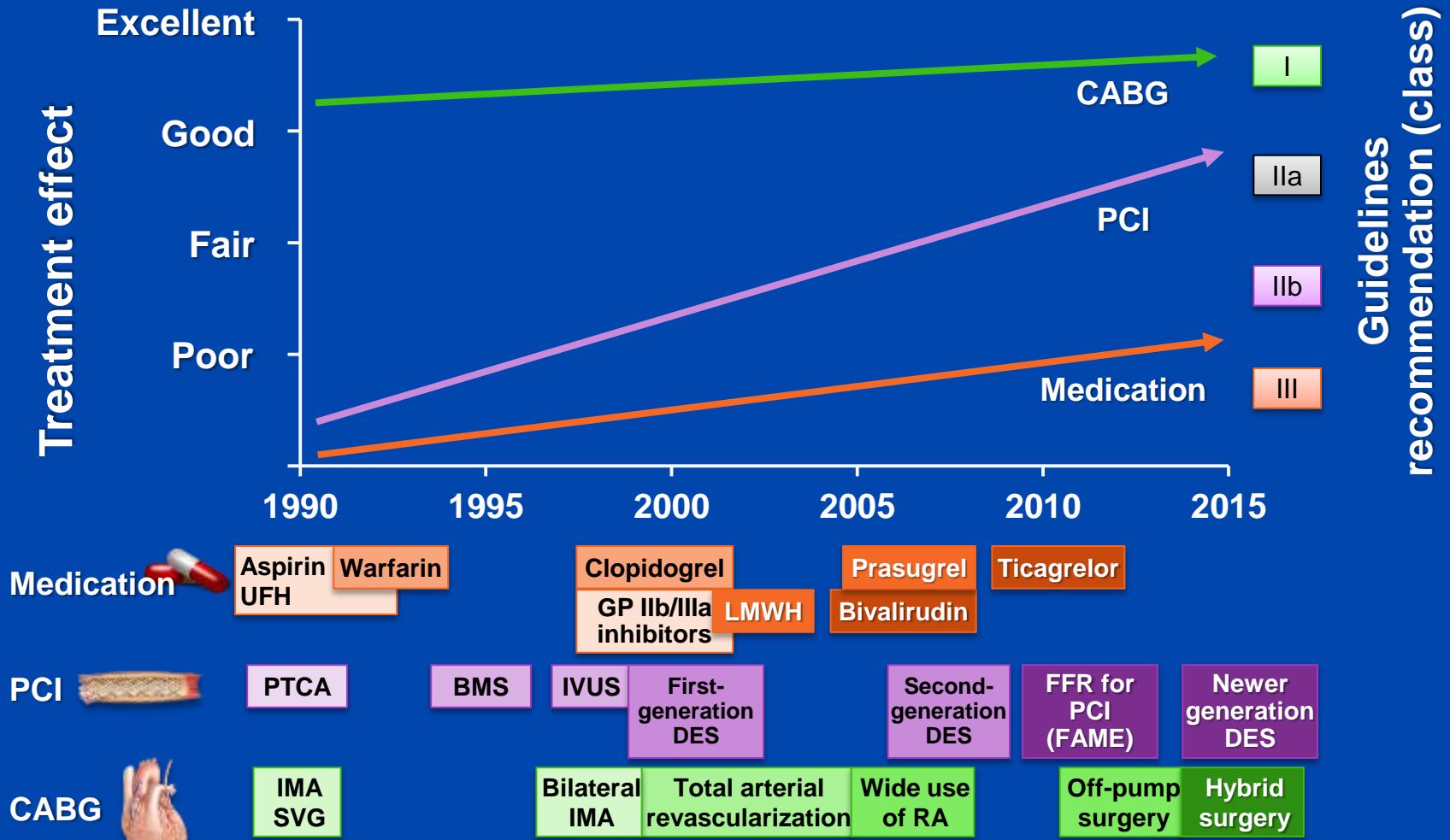
What Do We Know?

- 10-year follow-up
- Recent RCTs
- Unresolved issues

Summary

- **LMCA disease is the only lesion subset for which revascularization is unequivocally accepted as improving survival over medical therapy**
- **LMCA comes in many flavors of lesions and patient subsets**
- **Treatment has to be individualized and optimized**

Left Main Coronary Artery Disease PCI Guidelines



Lee et al: JACC 68(11):1233, 2016