TCT AP 2021

Debate Left Main PCI vs CABG:

CABG Preferred

David P Taggart MD PhD FRCS FESC
Professor of Cardiovascular Surgery, University of Oxford

Conflicts of Interest:

(i) Clinical: Cardiac Surgeon
(ii) **OXFORD CARDIOLOGISTS and SURGEONS 2nd LARGEST RECRUITERS WORLDWIDE**
(Chairman of Surgical Ctte of EXCEL but withdrew from final NEJM publication)
(iii) Commercial: Consultant to Medistim, Medtronic, VGS

Left Main: PCI vs CABG

1) Key Issues in Interpreting Data
2) PCI vs CABG in Multi-vessel CAD (No Left Main)
3) Changing Perspective of PCI in LM Disease
4) The Recent LM RCTs
5) Survival Data at 5-10 years
6) Impact of SYNTAX Scores
7) Impact of LM Location
8) Repeat Revascularization

Evidence basis CABG vs PCI: 3 Key 'Rules' of Interpretation

(i) Are RCT patients typical of real practice (CAD severity) ?

✖ No: usually very highly selected patients with less severe CAD

✔ **Underestimates the benefit of CABG in routine practice where MOST patients have more severe CAD than in RCT patients**

(ii) Duration of follow-up ?

✖ Must be a **minimum** of 5 years (ideally 10 years as in the ART)

✔ **Increasing length of follow-up = increasing benefit of CABG**

(iii) Use of Guideline Directed Medical Therapy (GDMT) ?

✖ Always **SIGNIFICANTLY** inferior in CABG vs PCI patients

✔ **CABG + GDMT: then even greater benefits over PCI**

CABG vs PCI: Multi-Vessel Disease (No Left Main)

1) CABG Improves Survival

2) CABG Reduces Myocardial Infarction

3) CABG Reduces Need for Repeat Revascularization

4) CABG Benefits are even greater in Diabetes

5) CABG Benefits even greater in impaired Left ventricular function

What Is The Situation For Left Main Disease ?

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Vol. 51, No. 9, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.09.067

STATE-OF-THE-ART PAPER AND COMMENTARY

Revascularization for Unprotected Left Main Stem Coronary Artery Stenosis

Stenting or Surgery

- <90% have multivessel CAD (CABG offers survival benefit)
- <90% of LMS are distal/bifurcation (higher risk of restenosis)
- (in EXCEL where 81% distal LM)
- BUT PCI OUTCOMES FOR ISOLATED OSTIAL/MID-SHAFT LESIONS WERE EXCELLENT (and possibly better than for CABG)

Oxford, United Kingdom; Los Angeles, California; Buffalo, New York; Greenville and Durham, North Carolina; Atlanta, Georgia; Dallas, Texas; Leuven, Belgium; and Hamilton, Ontario, Canada

For coronary artery disease with unprotected left main stem (LMS) stenosis, coronary artery bypass grafting (CABG) is traditionally regarded as the "standard of care" because of its well-documented and durable survival advantage. There is now an increasing trend to use drug-eluting stents for LMS stenosis rather than CABG despite very little high-quality data to inform clinical practice. We herein: 1) evaluate the current evidence in support of the use of percutaneous revascularization for unprotected LMS; 2) assess the underlying justification for randomized controlled trials of stenting versus surgery for unprotected LMS; and 3) examine the optimum approach to informed consent. We conclude that CABG should indeed remain the preferred revascularization treatment in good surgical candidates with unprotected LMS stenosis. (J Am Coll Cardiol 2008;51:885–92) © 2008 by the American College of Cardiology Foundation

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2008 VOL. 358 NO. 17

Stents versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease

Ki Bae Seung, M.D., Duk-Woo Park, M.D., Young-Hak Kim, M.D., Seung-Whan Lee, M.D., Cheol Whan Lee, M.D., Myeong-Ki Hong, M.D., Seong-Wook Park, M.D., Sung-Cheol Yun, Ph.D., Hyeon-Cheol Gwon, M.D., Myung-Ho Jeong, M.D., Yangsoo Jang, M.D., Hyo-Soo Kim, M.D., Pum Joon Kim, M.D., In-Whan Seong, M.D., Hun Sik Park, M.D., Taehoon Ahn, M.D., In-Ho Chae, M.D., Seung-Jea Tahk, M.D., Wook-Sung Chung, M.D., and Seung-Jung Park, M.D.

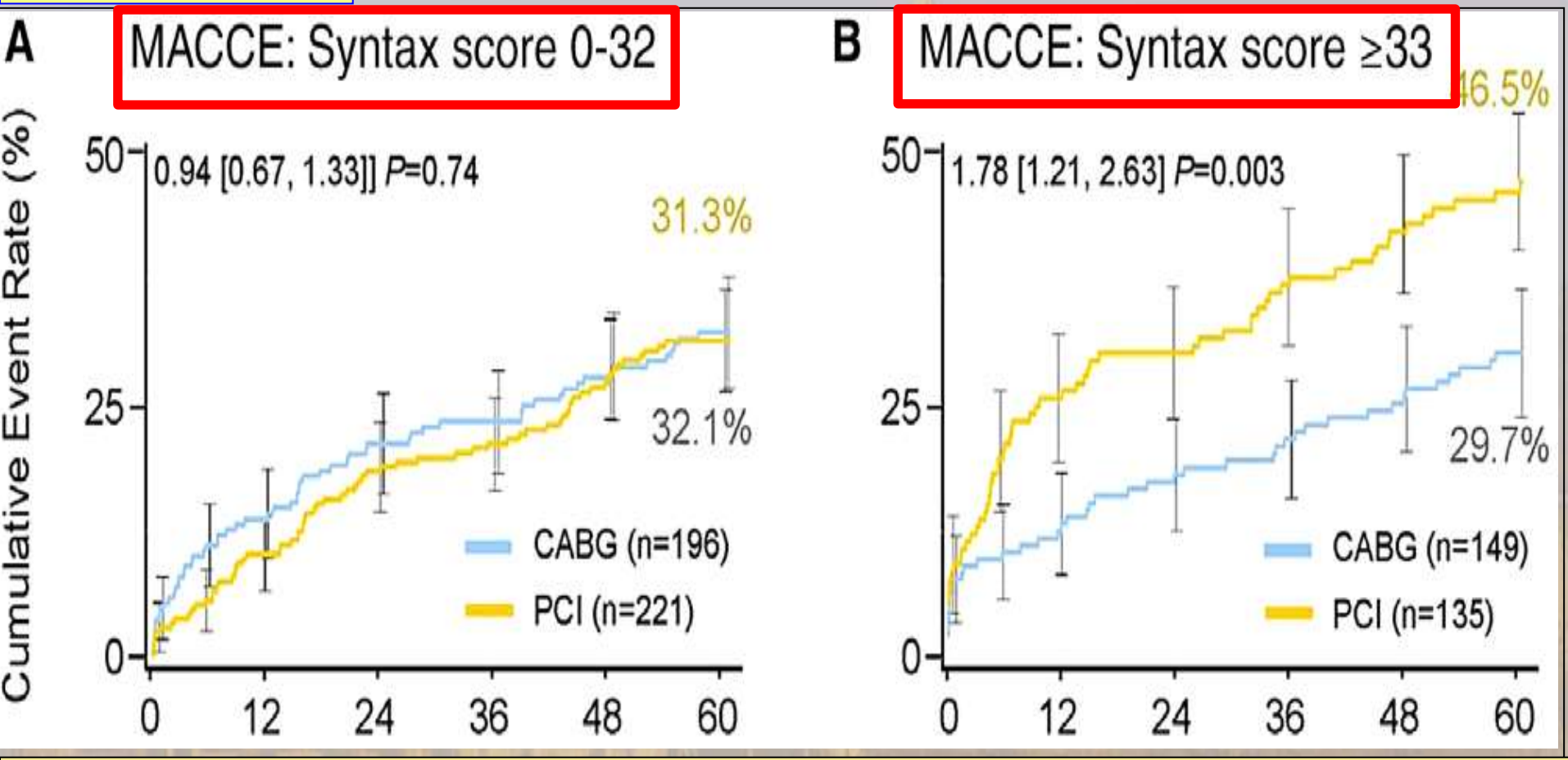
MAIN-COMPARE Registry of LM disease in 2240 Patients: 1102 stents and 1138 CABG (more severe disease) followed for 3 years

Table 3. Hazard Ratios for Clinical Outcomes after Stenting as Compared with after CABG among Propensity-Matched Patients.*

Outcome	Overall Cohort (N=542 pairs)		BMS (N=207 pairs)		DES (N=396 pairs)	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Death	1.18 (0.77–1.80)	0.45	1.04 (0.59–1.83)	0.90	1.36 (0.80–2.30)	0.26
Composite outcome of death, Q-wave myocardial infarction, or stroke	1.10 (0.75–1.62)	0.61	0.86 (0.50–1.49)	0.59	1.40 (0.88–2.22)	0.15
Target-vessel revascularization	4.76 (2.80–8.11)	<0.001	10.70 (3.80–29.90)	<0.001	5.96 (2.51–14.10)	<0.001

In Propensity-Matched Patients: Similar outcomes at 3 years for Death, and Composite Death/MI/Stroke but Much Greater Target Vessel Revascularization with Stents

LEFT MAIN
SYNTAX trial
705 RCT patients
5 years
CIRC 2014



① Accelerating Divergence of Benefits in Favour of CABG in >32
② Used to define patients in the EXCEL trial (Syntax Scores <33)
③ CABG: Competitive flow if lower SYNTAX scores (ie less proximal CAD) ?

Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease

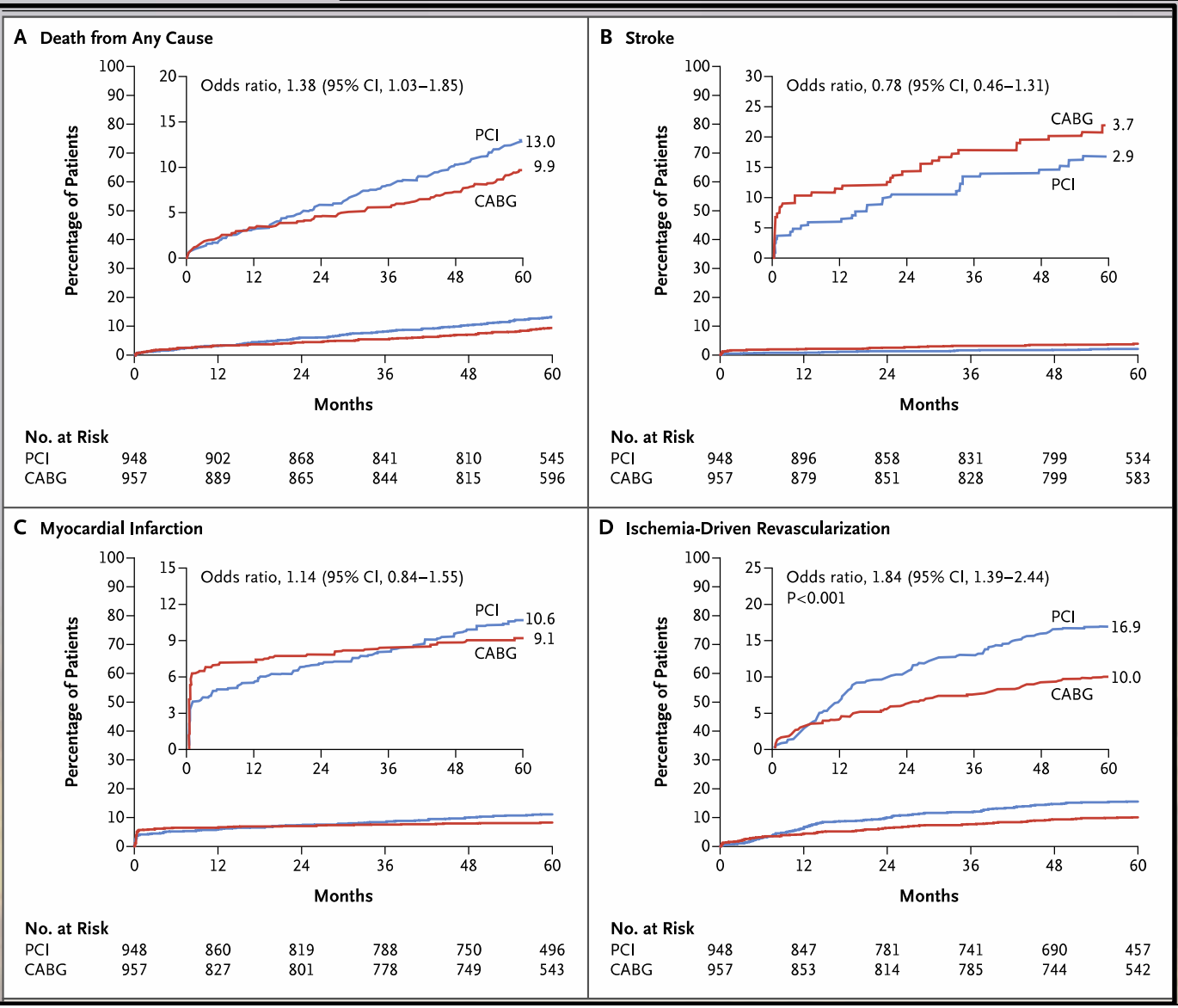
[NEJM November 7th 2019]

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

- **LARGEST, MOST DEFINITIVE TRIAL OF PCI vs CABG in LEFT MAIN**
- **SELECTED** Patients: SYNTAX SCORES <33
- 1905 patients (2600 planned but trial stopped early)
- MEAN AGE 66: (life expectancy of 15-20 years)
- MEAN SYNTAX Score 26
- Primary Outcome: Composite of Death, MI, Stroke (NOT Revasc)

Oxford 2nd largest recruiter worldwide to EXCEL trial

EXCEL: 5 YEARS 'Clinical Reality' [NEJM 2019]



Low-Risk Left Main:

1) Mean age 66 yr,
2) Low/ intermediate severity LM disease (Syntax Scores < 33)

PCI at 5years:

- ↑ **Death (38%) (Accelerating in PCI group !!!)**
- ↑ Non-procedural MI (ie real MI),
- ↑ Repeat Revasc
- = Stroke:

CONCLUSIONS In patients with left main coronary artery disease of low or intermediate anatomical complexity, there was no significant difference between PCI and CABG with respect to the rate of the composite outcome of death, stroke, or myocardial infarction at 5 years. (Funded by Abbott Vascular)

Correspondence

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PCI or CABG for Left Main Coronary Artery Disease

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To the Editor: In the {sa1q1}EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (Nov. 7 issue),[1] Stone et al. report no significant difference in the 5-year composite outcome of death, stroke, or myocardial infarction among patients with stable left main coronary artery disease who underwent either percutaneous coronary intervention (PCI) with drug-eluting stents or coronary-artery bypass grafting (CABG). We have three fundamental concerns regarding these findings.

First, the incidence of death from any cause {sa1q2}was 13.0% in the PCI group and 9.0% in the CABG group (odds ratio, 1.38; 95% confidence interval [CI], 1.03 to 1.85). Although the difference was not adjusted for multiple comparisons, the increased risk is unequivocally the most important outcome in a relatively young population (average age, 66 years), particularly since the between-group difference continued to diverge over time. Second, the cause of death was adjudicated ({sa1q3}as definite cardiovascular, definite noncardiovascular, or undetermined, with undetermined causes classified as cardiovascular), even though such adjudication is notoriously susceptible to bias, especially in an open-label trial. Third, the investigators used a new, untested definition of periprocedural myocardial infarction that clearly penalizes surgery and that is the key driver of the composite outcome that claims no difference in the two treatment strategies. The EXCEL protocol repeatedly stated that the Universal Definition of Myocardial Infarction would also be used, but such data were not provided. Consequently, the first author of this letter withdrew authorship from the manuscript.

Conflict

No potential conflict of interest relevant to this letter was reported.

Reference

1. Stone GW, Kappetein AP, Sabik JF, et al. Five-year outcomes after PCI or CABG for left main coronary disease. N Engl J Med 2019;381:1820-30. [PMID: 31562798]

EXCEL published
NEJM 7th November 2019

DT/MG Letter submitted
14th November 2019:
'3 fundamental concerns'

(i) Differential and Accelerating Death Rates in the PCI group
(ii) 'Adjudicated' Death
(iii) New untested definition of MI + failure to provide protocol specified UDMI data

Proofs of letter received
20 March 2020

Letter finally published
16 July 2020

8 months
after the trial !!

GW Stone, PW Serruys, J Sabik. NEJM July 16 2020

Table 1. Cumulative Incidence of Myocardial Infarction at 5 Years, According to Two Definitions.*

Outcome	PCI (N = 948)		CABG (N = 957)		Difference (95% CI)†
	Patients	Event Rate	Patients	Event Rate	
	no.	%	*no.*	%	*percentage points*
Protocol definition					
Procedural myocardial infarction	37	3.9	57	6.0	−2.1 (−4.1 to −0.2)
All myocardial infarction	95	10.2	84	9.0	1.2 (−1.5 to 3.9)
Third universal definition					
Procedural myocardial infarction	31	3.3	13	1.4	1.9 (0.5 to 3.3)
All myocardial infarction	89	9.6	43	4.7	4.9 (2.6 to 7.2)

* Listed are cumulative incidences of myocardial infarction in the EXCEL trial, so the data vary slightly from the Kaplan–Meier rates reported in the original article; the cumulative incidences are not calculated as the ratio of the numerator to the denominator of patients. Procedural myocardial infarction was defined according to the prespecified protocol definition used in the primary outcome analysis and according to the Third Universal Definition of Myocardial Infarction; the latter definition was a secondary outcome measure in the trial. CABG denotes coronary-artery bypass grafting, CI confidence interval, and PCI percutaneous coronary intervention.

† The between-group difference was calculated by subtracting the percentage in the CABG group from that in the PCI group.

(In contrast to the new biochemical definition of MI which was higher in CABG)
3rd UDMI DATA showed that with PCI
(i) HR for Procedural MI was 2.4
(ii) HR for All MI was 2.0

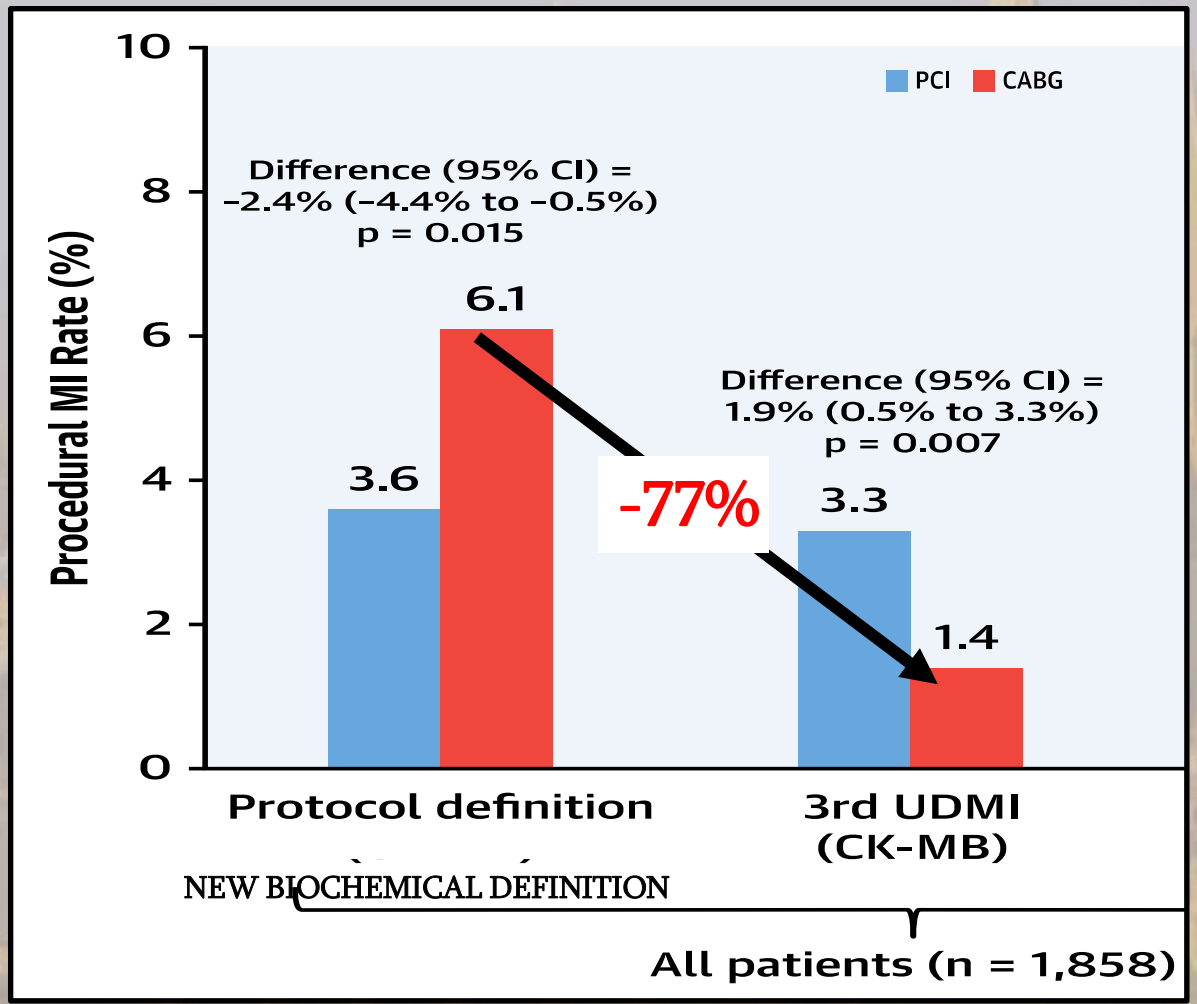
BUT
(i) Not presented to ESC/EACTS Guideline Taskforce on Myocardial Revascularization
(ii) Not presented in 2016 and 2019 NEJM publications

Implications of Alternative Definitions of Peri-Procedural Myocardial Infarction After Coronary Revascularization

[JACC Oct 6 2020]

John Gregson, PhD,[a] Gregg W. Stone, MD,[b,c] Ori Ben-Yehuda, MD,[c,d] Björn Redfors, MD, PhD,[c,d,e] David E. Kandzari, MD,[f] Marie-Claude Morice, MD,[g] Martin B. Leon, MD,[c,d] Ioanna Kosmidou, MD, PhD,[c,d] Nicholas J. Lembo, MD,[c,d] W. Morris Brown III, MD,[f] Dimitri Karmpaliotis, MD,[c,d] Adrian P. Banning, MD,[h] Jose Pomar, MD,[i] Manel Sabaté, MD,[i] Charles A. Simonton, MD,[j] Ovidiu Dressler, MD,[c] Arie Pieter Kappetein, MD, PhD,[k] Joseph F. Sabik III, MD,[l] Patrick W. Serruys, MD, PhD,[m,n] Stuart J. Pocock, PhD[a]

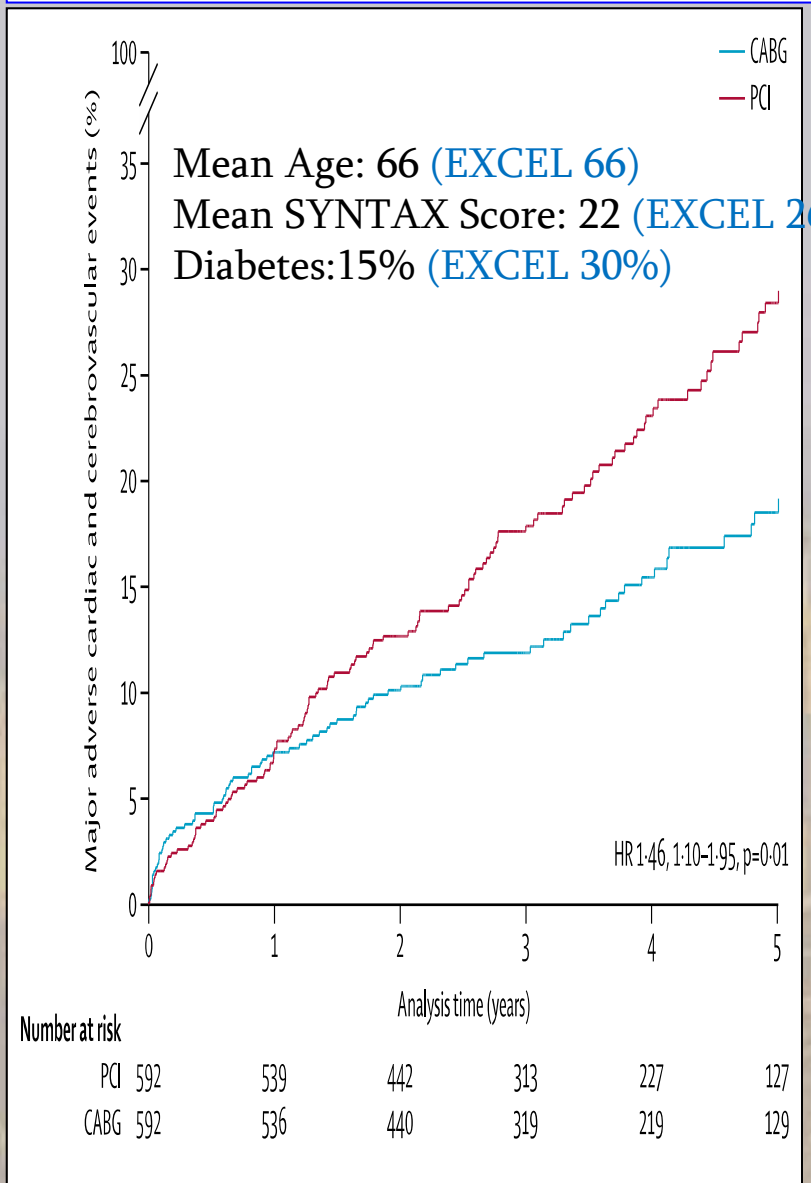
EXCEL

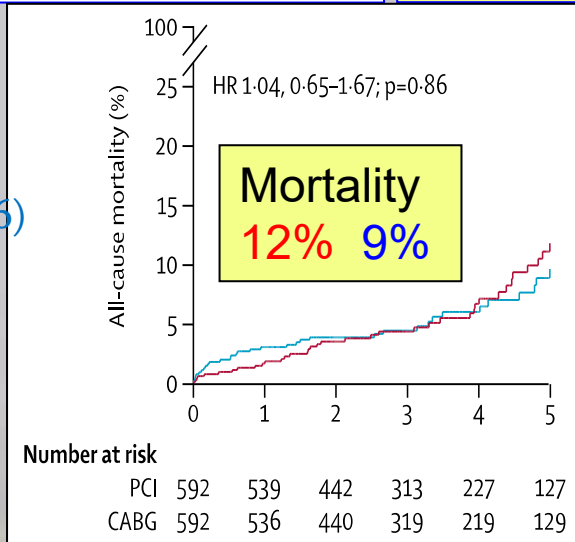


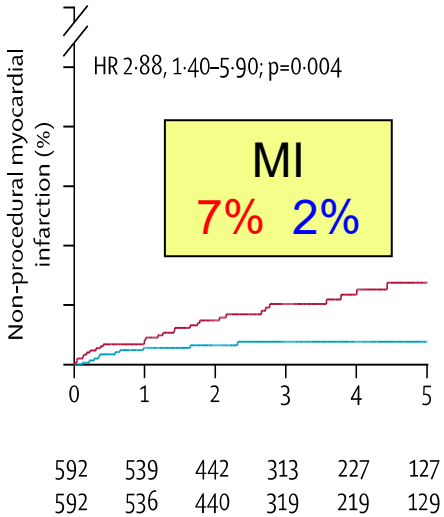
Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial

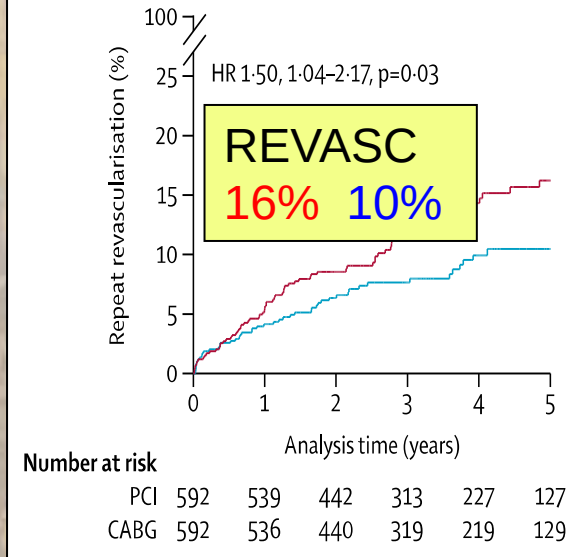
Timo Mäkikallio, Niels R Holm, Mitchell Lindsay, Mark S Spence, Andrejs Erglis, Ian B A Menown, Thor Trovik, Markku Eskola, Hannu Romppanen,

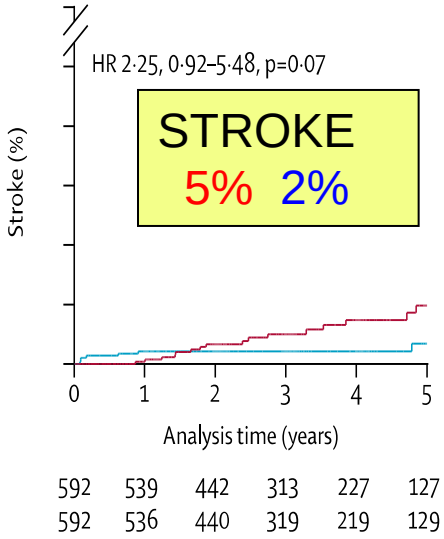
LM: NOBLE RCT
1201 Patients
No Registry Patients
Lancet 2016



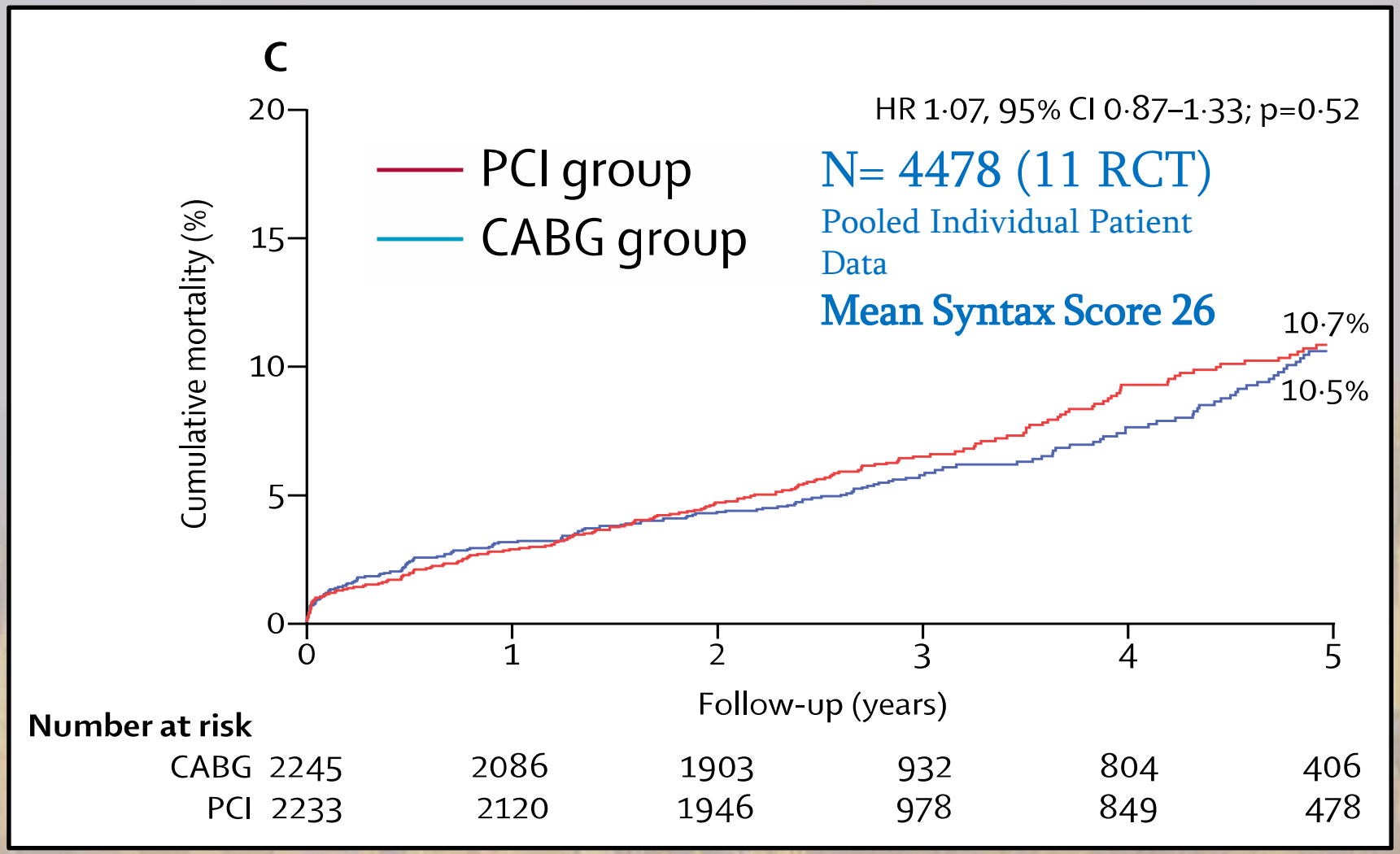






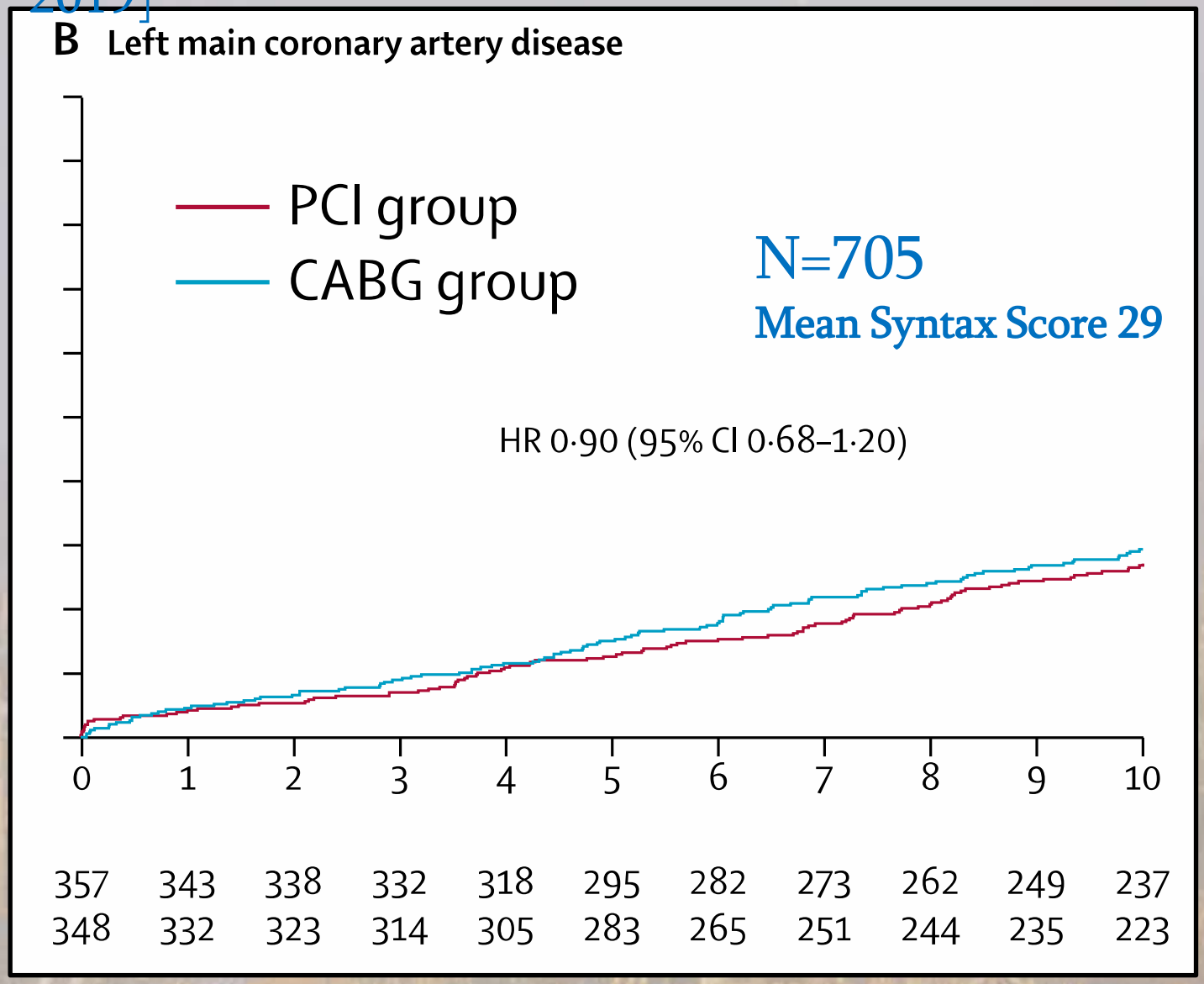


Left Main: Head et al Lancet 2018:



25% Diabetes (1120): MORTALITY CABG 13.4% vs 16.5% PCI: p=0.054

LM: SYNTAXES at 10 years: [Thuijs et al Lancet 2019]



ORIGINAL RESEARCH ARTICLE

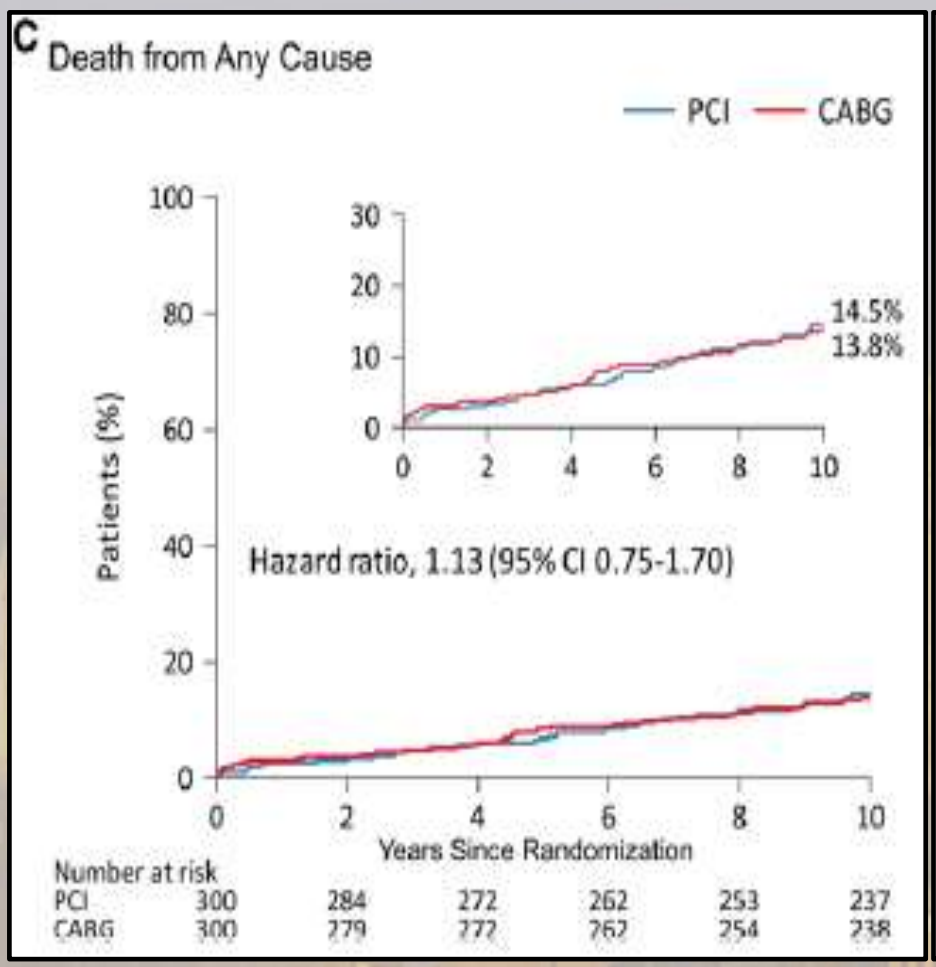
[CIRC 2020]

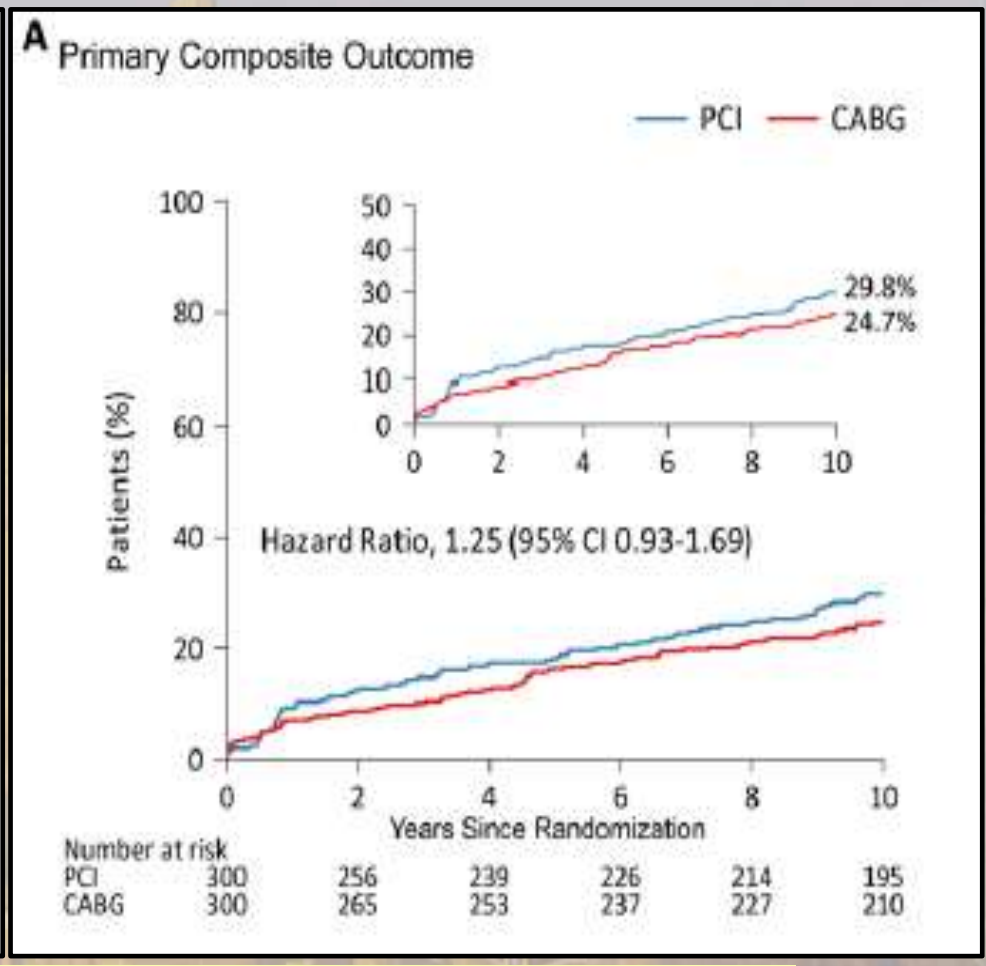
Ten-Year Outcomes After Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Disease

Extended Follow-Up of the PRECOMBAT Trial

Duk-Woo Park, MD*
Jung-Min Ahn, MD*
Hanbit Park, MD
Sung-Cheol Yun, PhD
Do-Yoon Kang, MD
Pil Hyung Lee, MD
Young-Hak Kim, MD
Do-Sun Lim, MD
Seung-Woon Rha, MD
Gyung-Min Park, MD
Hyeon-Cheol Gwon, MD
Hyo-Soo Kim, MD
In-Ho Chae, MD
Yangsoo Jang, MD
Myung Ho Jeong, MD
Seung-Jea Tahk, MD
Ki Bae Seung, MD
Seung-Jung Park, MD
On behalf of the PRECOMBAT Investigators

PRECOMBAT: N = 600: Mean SYNTAX SCORE 25





CAVG vs PCI Death, MI, Stroke Similar but REVASC 8% CABG vs 16% PCI

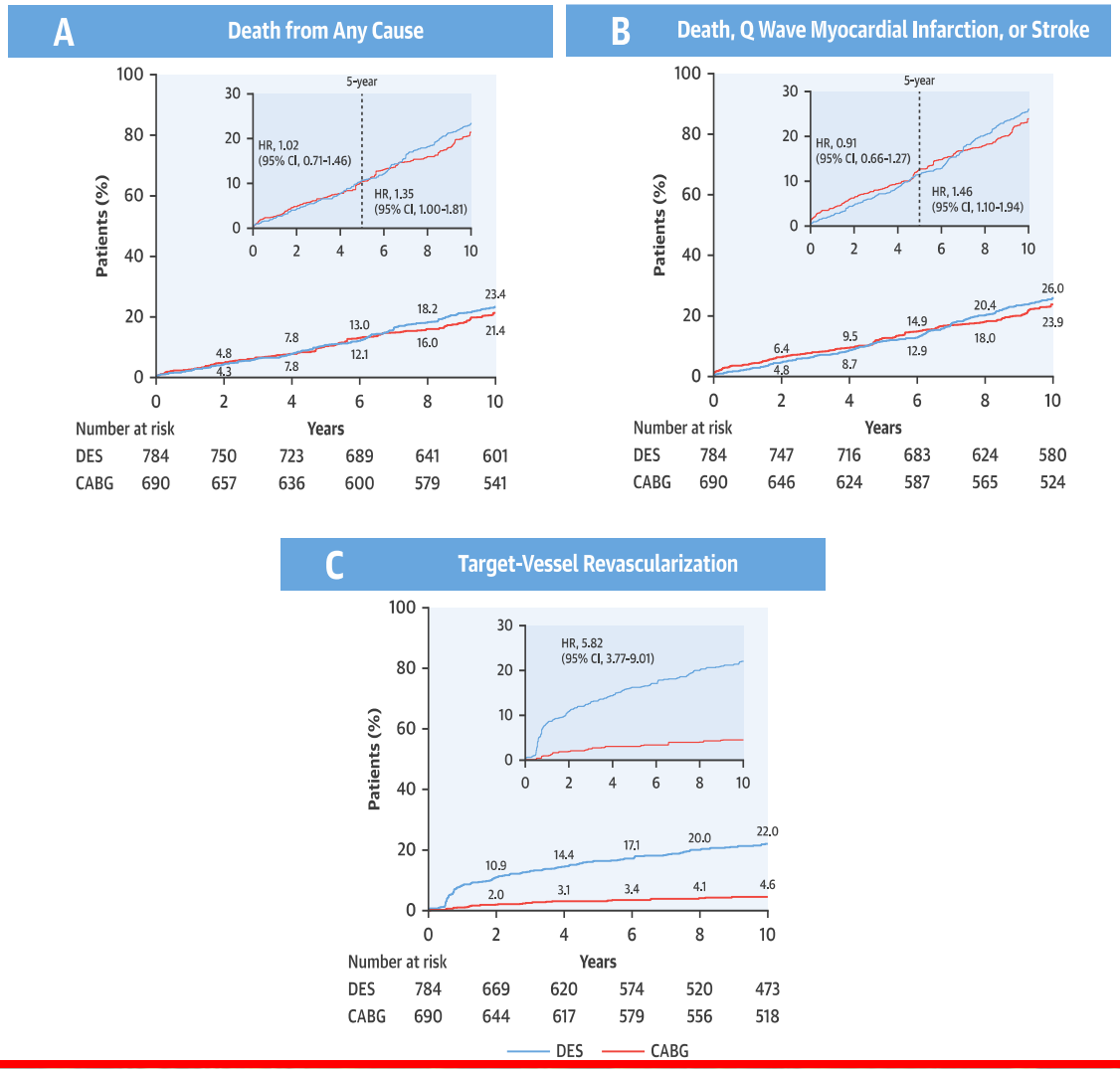
10-Year Outcomes of Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Artery Disease

JACC
DEC 2018

Duk-Woo Park, MD,[a,*] Jung-Min Ahn, MD,[a,*] Sung-Cheol Yun, PhD,[b] Yong-Hoon Yoon, MD,[a] Do-Yoon Kang, MD,[a] Pil Hyung Lee, MD,[a] Seung-Whan Lee, MD,[a] Seong-Wook Park, MD,[a] Ki Bae Seung, MD,[c] Hyeon-Cheol Gwon, MD,[d] Myung-Ho Jeong, MD,[e] Yangsoo Jang, MD,[f] Hyo-Soo Kim, MD,[g] In-Whan Seong, MD,[h] Hun Sik Park, MD,[i] Taehoon Ahn, MD,[j] In-Ho Chae, MD,[k] Seung-Jea Tahk, MD,[l] Seung-Jung Park, MD[a]

Significant increase in mortality with DES vs CABG between 5 and 10 years

CENTRAL ILLUSTRATION Long-Term Outcomes of Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Left Main Disease



Propensity Matching Selected Patients With Lower Severity Disease !
(Original CABG Cohort Had More Severe CAD)
1474/2240 (66%)

AGE: 62
DM: 30%
EF: 60%
LM Ostium/Shaft: 48%
LM only: 12%
+1 VD: 17%
+ 2VD: 32%
+ 3VD: 38%

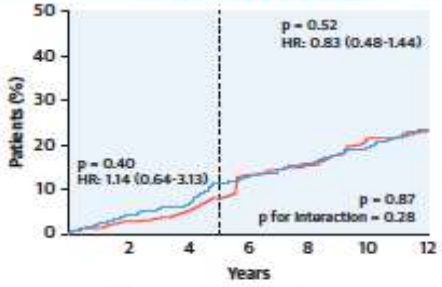
Long-Term Outcomes After PCI or CABG for Left Main Coronary Artery Disease According to Lesion Location

[JACCCI 2020]

Junho Hyun, MD, Ju Hyeon Kim, MD, Yeongjin Jeong, MD, KyungJin Choe, MD, Junghoon Lee, MD, Yujin Yang, MD, Tae Oh Kim, MD, Hanbit Park, MD, Sang-Cheol Cho, MD, Euihong Ko, MD, Do-Yoon Kang, MD, Pil Hyung Lee, MD, Jung-Min Ahn, MD, Seung-Jung Park, MD, Duk-Woo Park, MD, on behalf of the MAIN-COMPARE Registry

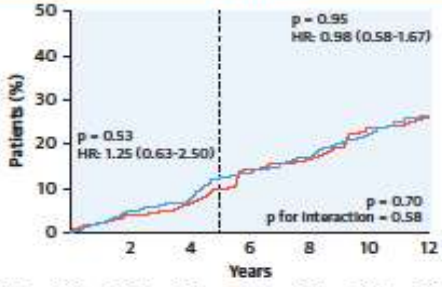
Ostial or Shaft Disease

A Death From Any Cause



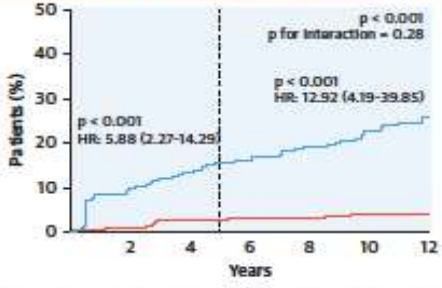
PCI	339	326	317	296	286	273	260
CABG	324	315	308	281	274	255	249

C Death, Q-Wave Myocardial Infarction, or Stroke



PCI	339	324	314	294	282	264	249
CABG	324	311	304	278	270	247	241

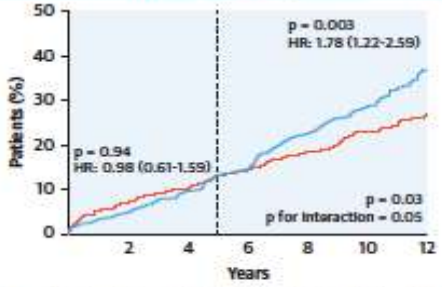
E Target Vessel Revascularization



PCI	339	306	294	285	275	262	251
CABG	324	320	315	314	314	311	311

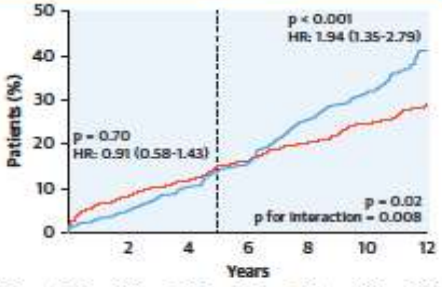
Distal Bifurcation Disease

B Death From Any Cause



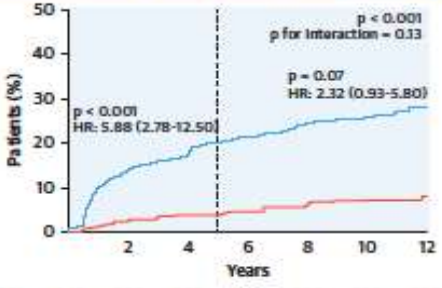
PCI	445	423	403	381	344	319	281
CABG	366	340	329	314	299	283	268

D Death, Q-Wave Myocardial Infarction, or Stroke



PCI	445	422	399	377	332	305	262
CABG	366	336	324	307	292	276	260

F Target Vessel Revascularization



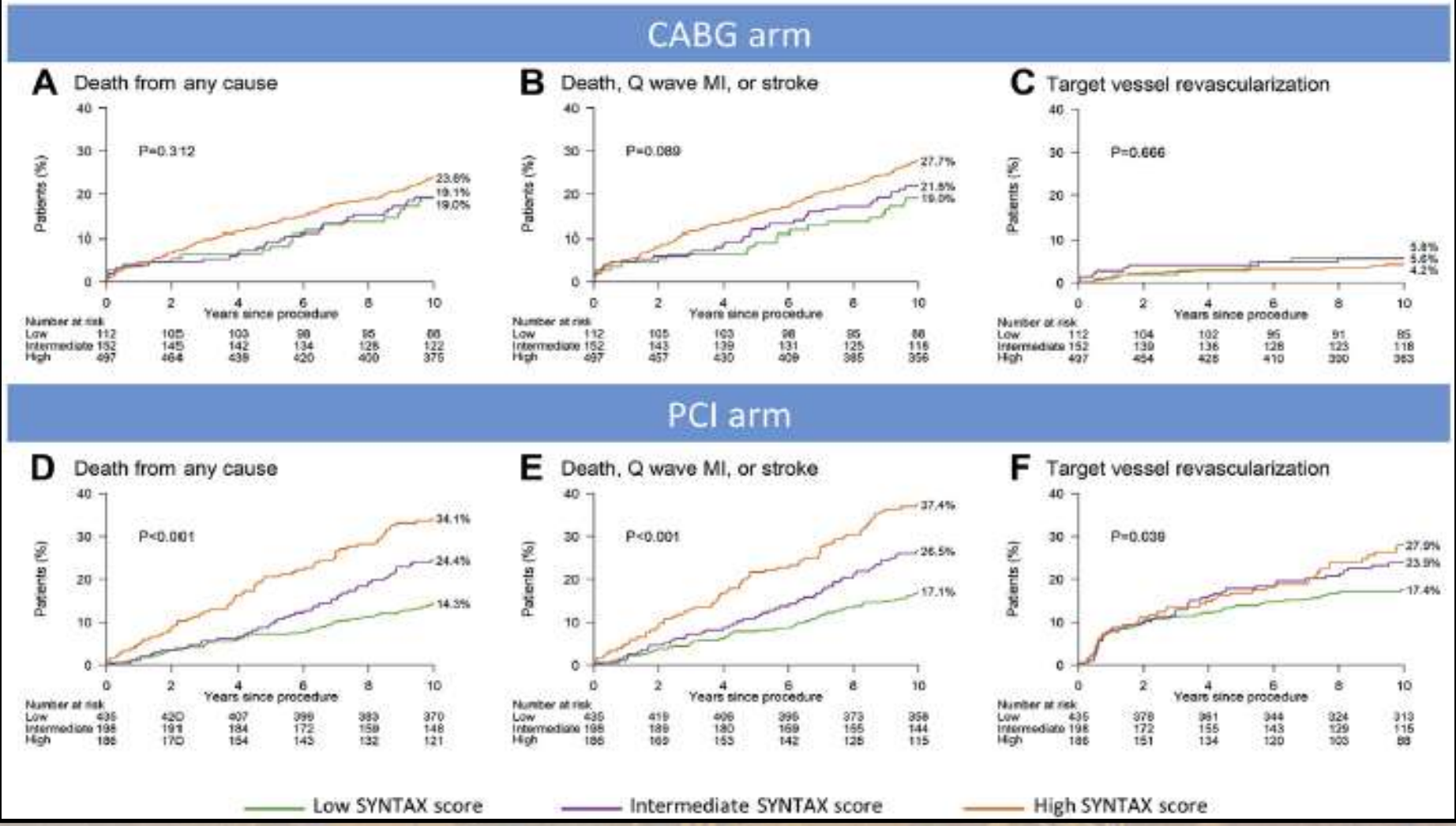
PCI	445	383	369	349	336	330	320
CABG	366	357	352	349	344	340	337

Impact of SYNTAX Score on 10-Year Outcomes After Revascularization for Left Main Coronary Artery Disease

[JACCCI 2020]

Yong-Hoon Yoon, MD,[a] Jung-Min Ahn, MD,[b] Do-Yoon Kang, MD,[b] Hanbit Park, MD,[b] Sang-Cheol Cho, MD,[b] Pil Hyung Lee, MD,[b] Seung-Whan Lee, MD,[b] Seong-Wook Park, MD,[b] Duk-Woo Park, MD,[b] Seung-Jung Park, MD[b]

FIGURE 3 10-Year Kaplan-Meier Curves for Clinical Events Stratified by SYNTAX Score Category in CABG and PCI Groups



(i) Clear Benefit of CABG in High SS (ii) SS discriminative for PCI but not

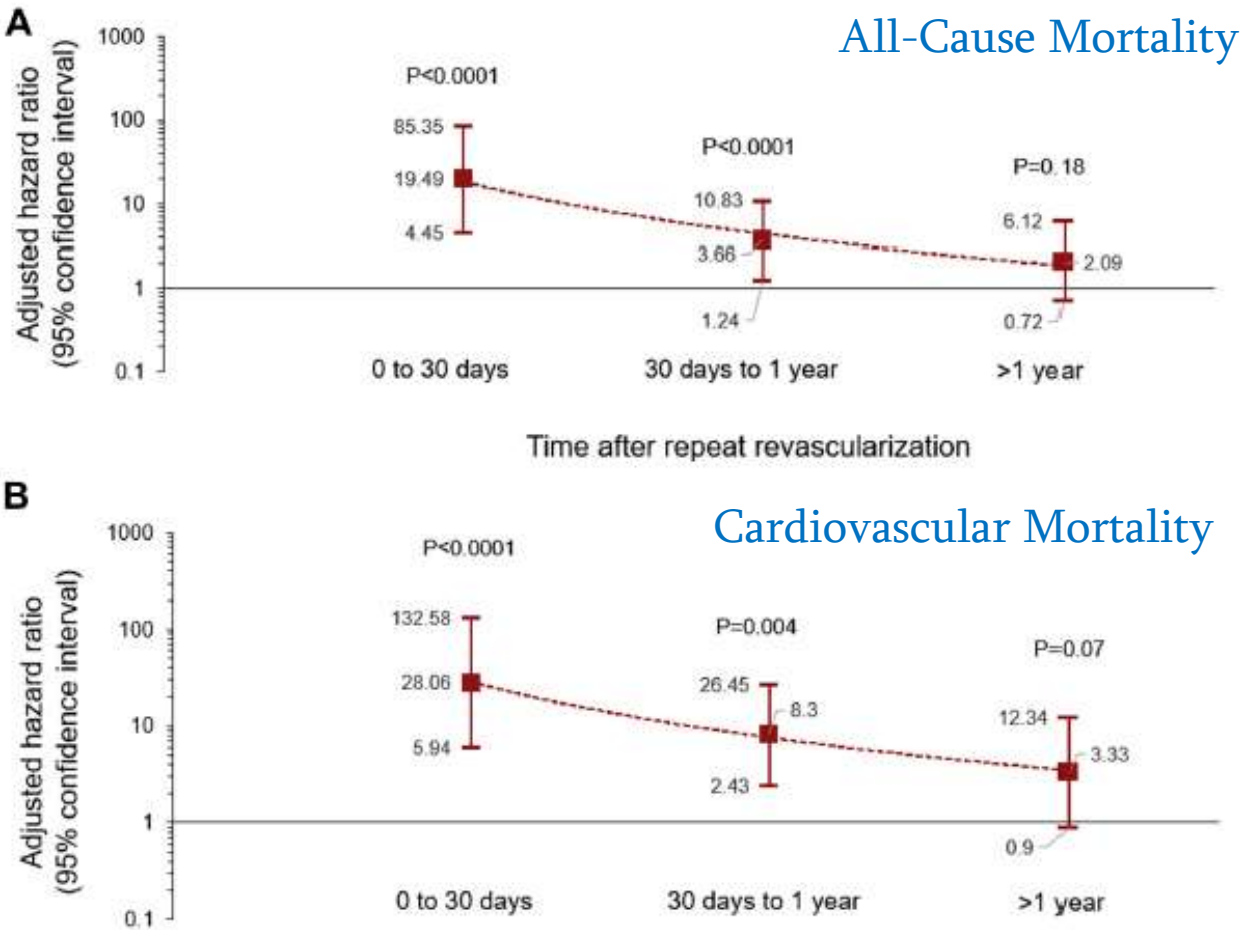
Mortality After Repeat Revascularization Following PCI or CABG for Left Main Disease

The EXCEL Trial

[JACCCI 2020]

Gennaro Giustino, MD,* Patrick W. Serruys, MD, PhD,† Joseph F. Sabik III, MD,‡ Roxana Mehran, MD,*,§ Akiko Maehara, MD,¶,# John D. Puskas, MD,‖ Charles A. Simonton, MD,** Nicholas J. Lembo, MD,** David E. Kandzari, MD,†† Marie-Claude Morice, MD,‡ David P. Taggart, MD, PhD,§§ Anthony H. Gershlick, MD,¶¶ Michael Ragosta III, MD,‖ Irving L. Kron, MD,‖ Yanghe Liu, MS,## Zixuan Zhang, MS,## Thomas McAndrew, PhD,## Ovidiu Dressler, MD,## Philippe Généreux, MD,*,## Ori Ben-Yehuda, MD,*,† Stuart J. Pocock, PhD,## Arie Pieter Kappetein, MD, PhD,†† Gregg W. Stone, MD*,†,##

FIGURE 2 Early and Late Risk for Mortality After Any Repeat Revascularization in the Overall Population



Repeat Revascularization is NOT a Benign Phenomenon

Left Main: The Continuing Debate: What to Believe ?

Mortality after drug-eluting stents vs. coronary artery bypass grafting for left main coronary artery disease: a meta-analysis of randomized controlled trials

[EHJ published online 2nd March 2020]

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Received 2 February 2020; revised 10 February 2020; editorial decision 13 February 2020; accepted 13 February 2020

Conclusion

5 RCTs
N=4,612

The totality of randomized clinical trial evidence demonstrated similar long-term mortality after PCI with DES compared with CABG in patients with LMCAD. Nor were there significant differences in cardiac death, stroke, or MI between PCI and CABG. Unplanned revascularization procedures were less common after CABG compared with PCI. These findings may inform clinical decision-making between cardiologists, surgeons, and patients with LMCAD.

Meta-analysis 'Magic' (i): EHJ 2020: 14 Authors (many eminent cardiologists, no surgeons)

Dilute the Largest, Most Definitive LM Trial (EXCEL) with 4 older, smaller, weaker studies until mortality benefit of CABG disappears !

Meta-analysis 'Magic' (ii): A record speed of acceptance and publication ?

11 days from submission to review, to revision, to-resubmission to acceptance

1) Received 2/2/20
2) Revised 10/2/20
3) Accepted 13/2/20
4) Published 02/03/20

Left Main: The Continuing Debate: What to Believe ?

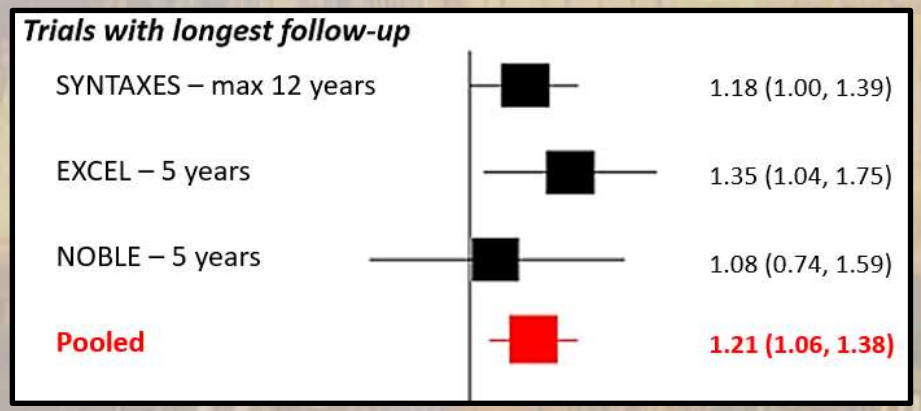
JAMA Internal Medicine | Original Investigation [July 1st 2020]

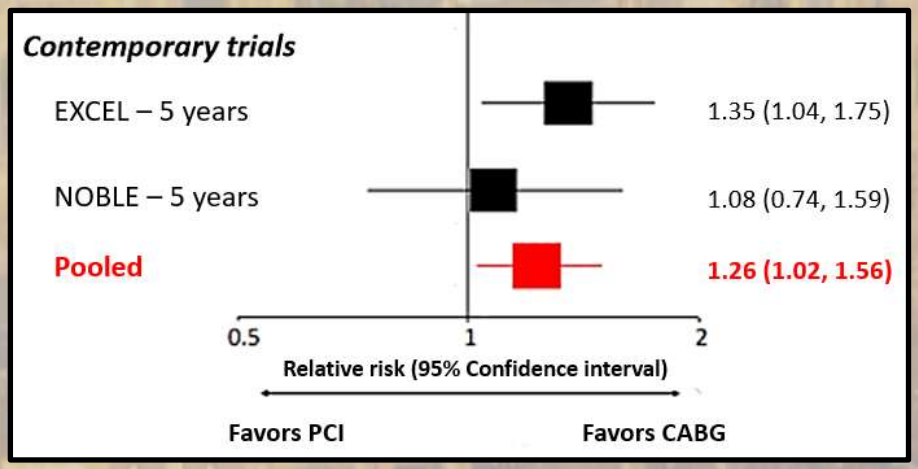
Bayesian Interpretation of the EXCEL Trial and Other Randomized Clinical Trials of Left Main Coronary Artery Revascularization

James M. Brophy, MD, PhD

CONCLUSIONS AND RELEVANCE Bayesian analysis assisted in RCT data interpretation and specifically suggested, whether based on EXCEL results alone or on the totality of available evidence, that PCI was associated with inferior long-term results for all events, including mortality, compared with CABG for patients with left main coronary artery disease.

Gaudino M, Freemantle N, Farkouh ME, JTCVS (2020 in print)

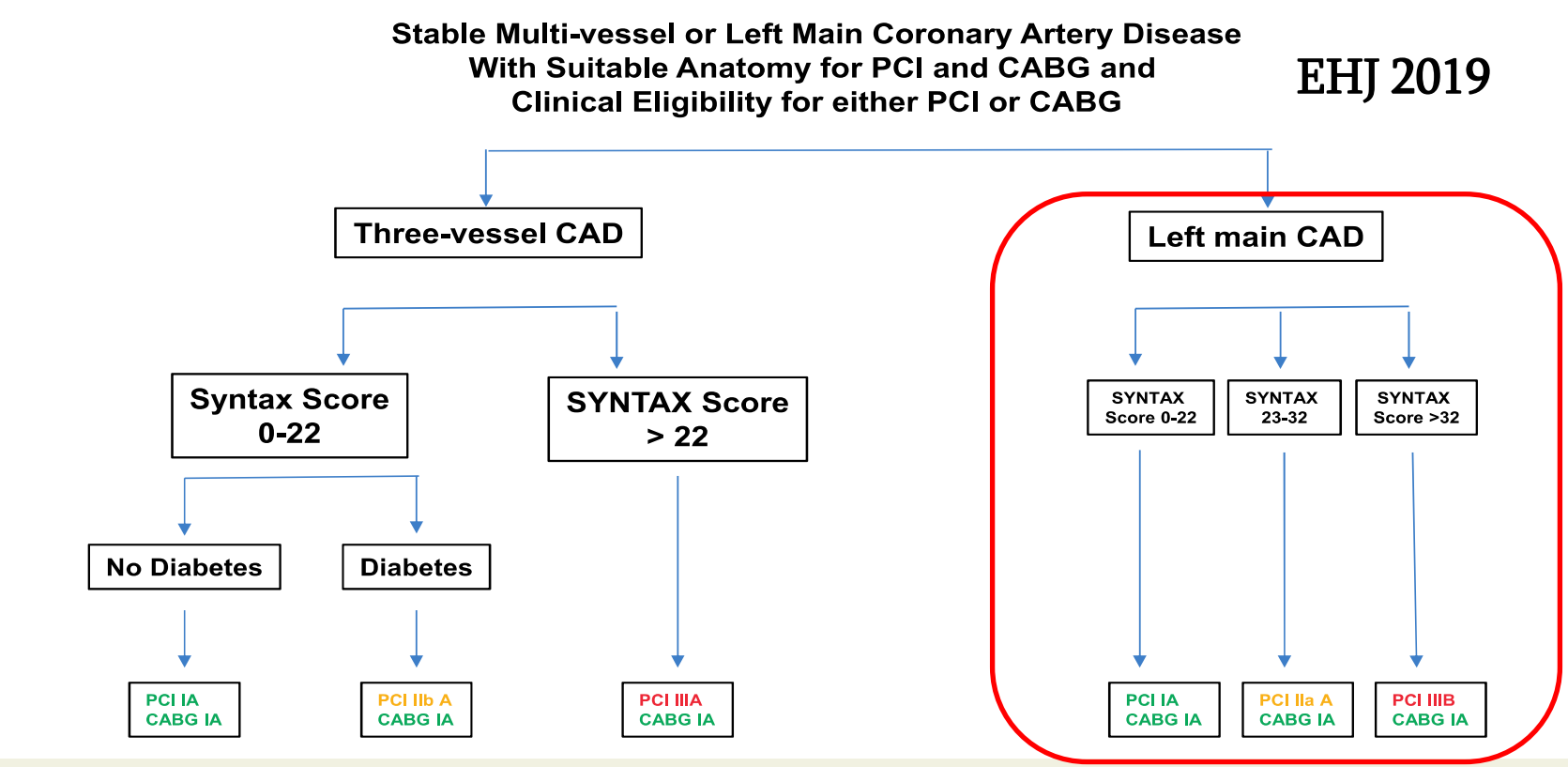




Patients with SYNTAX scores <33

2018 ESC/EACTS Guidelines on myocardial revascularization

Left main CAD	CABG		PCI	
Left main disease with low SYNTAX score (0 - 22).[69,121,122,124,145–148]	I	A	I	A
Left main disease with intermediate SYNTAX score (23 - 32).[69,121,122,124,145–148]	I	A	IIa ?	A
Left main disease with high SYNTAX score (≥33).[c] [69,121,122,124,146–148]	I	A	III	B



Take home figure Algorithm to guide the choice of revascularization procedure across major categories in patients with multivessel or left main coronary artery disease. Class recommendations correspond to the 2018 ESC/EACTS Guidelines on myocardial revascularization. CABG, coronary artery bypass grafting; CAD, coronary artery disease; LAD, left anterior descending artery; PCI, percutaneous coronary intervention.

Summary and Conclusions: LM CABG vs PCI

Multi-Vessel Disease (No Left Main):

1) **CABG: Clearly superior for All SYNTAX scores and Especially in DM**

Left Main Disease (of whom up to 90% also have Multi-Vessel CAD):

1) CABG: Clearly Superior For Severe Disease (Syntax scores >32)

2) The two largest, definitive trials of PCI vs CABG in patients with Low/Intermediate Severity LM Disease (SYNTAX scores < 33) show CABG to be superior for Mortality (EXCEL) and Non-procedural MI and Repeat Revascularization (EXCEL and NOBLE)

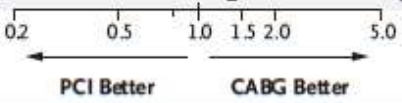
3) Conflicting LM mortality data for PCI and CABG in patients with low/intermediate SYNTAX Scores between 5 and 10 years, but increasing evidence of equivalence between therapies

4) LM Location (ostial/mid shaft vs bifurcation) is vital to subsequent outcomes and CABG appears superior for bifurcation lesions while PCI may offer equal outcomes in non-bifurcation lesions, and especially in the absence of significant additional proximal CAD (but still a much higher need for repeat revasc)

5) Repeat revascularization is not an entirely benign phenomenon

Personal View: Current data still suggests a cautious approach to the use of stents in patients with Low/Intermediate severity Left Main Disease **and especially in distal/ bifurcation lesions and in younger patients with anticipated long life expectancy.**

Subgroup	PCI (N=948)		CABG (N=957)		Odds Ratio (95% CI)
	Events/total patients no.	Event rate %	Events/total patients no.	Event rate %	
All patients	203/948	22.0	176/957	19.2	1.19 (0.95–1.50)
Age (median cutoff)					
≥67 yr	123/466	27.2	98/472	21.8	1.39 (1.02–1.89)
<67 yr	80/482	16.9	78/485	16.6	1.00 (0.71–1.40)
Sex					
Male	145/722	20.6	134/742	18.7	1.12 (0.86–1.46)
Female	58/226	26.3	42/215	21.1	1.39 (0.88–2.20)
Diabetes mellitus, medically treated					
Yes	72/256	29.0	62/249	25.5	1.24 (0.83–1.86)
No	131/692	19.4	114/707	16.9	1.17 (0.89–1.55)
Chronic kidney disease					
Estimated GFR ≤60 ml/min	54/164	34.0	37/144	27.6	1.44 (0.86–2.39)
Estimated GFR >60 ml/min	147/770	19.5	135/791	17.6	1.13 (0.87–1.47)
Left ventricular ejection fraction					
≥50%	158/782	20.6	144/796	18.7	1.14 (0.88–1.46)
<50%	33/111	31.5	26/115	24.2	1.35 (0.73–2.49)
Geographic region					
North America	89/381	24.2	61/371	17.3	1.57 (1.09–2.26)
Europe	111/534	21.1	102/541	19.6	1.09 (0.81–1.48)
Other	3/33	9.6	13/45	29.6	0.24 (0.06–0.96)
Non–left main diseased coronary arteries (core laboratory assessment)					
0	33/163	20.7	23/167	14.3	1.55 (0.86–2.78)
1	60/292	21.2	61/292	21.9	0.94 (0.62–1.40)
2	79/325	25.0	50/295	17.8	1.58 (1.06–2.36)
3	31/162	19.2	37/182	20.7	0.93 (0.54–1.59)
Left main bifurcation or trifurcation stenosis ≥50% (core laboratory assessment)					
Yes	171/771	22.7	136/741	19.0	1.24 (0.96–1.60)
No	32/171	19.2	35/195	18.9	1.05 (0.62–1.79)
SYNTAX score (site reported)					
≤22	119/560	21.9	106/588	18.7	1.21 (0.90–1.62)
23–32	84/386	22.2	70/366	20.0	1.16 (0.81–1.67)
SYNTAX score (core laboratory assessment)					
≤22	49/294	17.2	58/364	16.7	0.99 (0.65–1.51)
23–32	91/392	23.7	69/346	20.7	1.22 (0.85–1.74)
≥33	56/228	25.0	42/216	20.0	1.36 (0.86–2.15)



2018 ESC/EACTS Guidelines on myocardial revascularization

Recommendations according to extent of CAD	CABG		PCI	
	Class[a]	Level[b]	Class[a]	Level[b]
One-vessel CAD				
Without proximal LAD stenosis.	IIb	C	I	C
With proximal LAD stenosis.[68,101,139–144]	I	A	I	A
Two-vessel CAD				
Without proximal LAD stenosis.	IIb	C	I	C
With proximal LAD stenosis.[68,70,73]	I	B	I	C
Left main CAD				
Left main disease with low SYNTAX score (0 - 22).[69,121,122,124,145–148]	I	A	I	A
Left main disease with intermediate SYNTAX score (23 - 32).[69,121,122,124,145–148]	I	A	IIa ?	A
Left main disease with high SYNTAX score (≥33).[c] [69,121,122,124,146–148] 66%	I	A	III	B
Three-vessel CAD without diabetes mellitus				
Three-vessel disease with low SYNTAX score (0 - 22).[102,105,121,123,124,135,149]	I	A	I	A
Three-vessel disease with intermediate or high SYNTAX score (>22).[c] [102,105,121,123,124,135,149] 79%	I	A	III	A
Three-vessel CAD with diabetes mellitus				
Three-vessel disease with low SYNTAX score 0–22.[102,105,121,123,124,135,150–157]	I	A	IIb ?	A
Three-vessel disease with intermediate or high SYNTAX score (>22).[c] [102,105,121,123,124,135,150–157]	I	A	III	A

CABG would be better if more arterial grafts and greater use of medical therapy !!

Table 2. Primary and Secondary Outcomes over Three Periods.*

Variable	PCI		CABG		Hazard Ratio (95% CI)
	Events	Event Rate	Events	Event Rate	
	no./no. of patients	%	*no./no. of patients*	%	
Outcomes at 30 days					
Death, stroke, or myocardial infarction	46/948	4.9	75/957	8.0	0.61 (0.42–0.88)
Death	9/948 *	1.0	10/957	1.1	0.90 (0.37–2.21)
Stroke	6/948	0.6	12/957	1.3	0.50 (0.19–1.32)
Myocardial infarction	37/948	3.9	59/957	6.3	0.63 (0.42–0.94)
Death, stroke, myocardial infarction, or ischemia-driven revascularization	46/948	4.9	80/957	8.5	0.57 (0.40–0.82)
Ischemia-driven revascularization	6/948	0.6	13/957	1.4	0.46 (0.17–1.21)
Definite stent thrombosis or symptomatic graft stenosis or occlusion	3/948	0.3	11/957	1.2	0.27 (0.08–0.97)
Outcomes from 30 days to 1 yr					
Death, stroke, or myocardial infarction	38/948	4.1	35/957	3.8	1.07 (0.68–1.70)
Death	22/948	2.4	23/957	2.5	0.94 (0.53–1.69)
Stroke	5/948	0.5	7/957	0.8	0.71 (0.22–2.23)
Myocardial infarction	16/948	1.7	10/957	1.1	1.58 (0.72–3.48)
Death, stroke, myocardial infarction, or ischemia-driven revascularization	83/948	8.9	56/957	6.1	1.48 (1.05–2.07)
Ischemia-driven revascularization	59/948	6.4	28/957	3.1	2.10 (1.34– 3.30)
Definite stent thrombosis or symptomatic graft stenosis or occlusion	0/948	0	22/957	2.4	—
Outcomes from 1 yr to 5 yr					
Death, stroke, or myocardial infarction	133/933	15.1	83/929	9.7	1.61 (1.23–2.12)
Death	88/933	10.0	56/929	6.6	1.57 (1.12–2.19)
Stroke	16/933	1.9	15/929	1.8	1.06 (0.52–2.15)
Myocardial infarction	43/933	5.1	20/929	2.4	2.16 (1.27–3.67)
Death, stroke, myocardial infarction, or ischemia-driven revascularization	198/933	22.4	118/929	13.8	1.74 (1.38–2.18)
Ischemia-driven revascularization	100/933	11.6	49/929	5.8	2.10 (1.49–2.95)
Definite stent thrombosis or symptomatic graft stenosis or occlusion	7/933	0.8	25/929	3.0	0.28 (0.12–0.64)

Primary and Secondary Outcomes over 3 periods

0-30 DAYS
No difference:
Death, Stroke, Revasc
but higher MI in CABG using new definition

30 DAYS-1Year
No difference:
Death, Stroke, MI,
but higher revasc in PCI group

1-5 Years
PCI Large Increase:
Death, MI, Revasc
(no difference in stroke)

CONCLUSION: 'No Difference' ?????

EXCEL: The Controversy

Four Major Concerns in EXCEL 5-Year Analysis:

1) Interpretation of the Mortality Data
('one of 20 underpowered secondary endpoints')

2) Persistent Failure to Publish Protocol Specified MI Data
(eventually 8 months later at insistence of NEJM editors)

3) Changed Statistical Analysis: Non-Inferiority (3 yrs) to Superiority (5 yrs)

4) Failure to Share Trial Data

Controversy Extended to both the Medical Domain (EACTS, ESC, AATS, STS) and Public Domain (BBC Dec 2019, March 2020)

3 REASONS WHY CABG HAS A SURVIVAL BENEFIT OVER PCI

1 **Anatomically, atheroma is mainly located in the proximal coronary arteries**
Placing bypass grafts to the **MID CORONARY VESSEL** has **TWO** effects
(i) Complexity of proximal '**CULPRIT**' lesion is irrelevant
(ii) Over the long term offers prophylaxis against **FUTURE** proximal 'culprit' lesions
In contrast, PCI only treats **'SUITABLE'** localised proximal 'culprit' lesions but has **NO PROPHYLACTIC BENEFIT** against new proximal disease

2

THE NEW ENGLAND JOURNAL OF MEDICINE Aug. 25, 1988

IMA elutes NO into coronary circulation reducing risk of further disease

DIFFERENCE BETWEEN ENDOTHELIUM-DEPENDENT RELAXATION IN ARTERIAL AND IN VENOUS CORONARY BYPASS GRAFTS

THOMAS F. LÜSCHER, M.D., DENNIS DIEDERICH, M.D., ROBERT SIEBENMANN, M.D., KURT LEHMANN, M.D.,

Drug-Eluting Stent and Coronary Thrombosis
Biological Mechanisms and Clinical Implications [CIRC 2007]

Thomas F. Lüscher, MD; Jan Steffel, MD; Franz R. Eberli, MD; Michael Joner, MD;

impairs re-endothelialization, downstream endothelial function and creates pro-thrombotic milieu

3 PCI means incomplete revascularization (Hannan Circ 2006)
Of 22,000 PCI 69% had incomplete revascularization
>2 vessels (+/- CTO) HR for mortality 1.4 (95% CI = 1.1-1.7)
Residual SYNTAX score >8 increases mortality and MACCE (Farooq, Serruys CIRC 2013)

PCI will 'never' match the results of CABG for LM/MVD (POBA;BMS;DES)

Excel: The Facts vs The Fiction

1. The largest and most definitive trial of PCI vs CABG in LM disease
   (4 PI, investigators, patients deserve enormous credit for driving this pivotal trial)

2. Academic: I was Chairman of the Surgical Committee of the EXCEL Trial during the design and recruitment phase

3. Oxford: 2nd largest recruiter of EXCEL patients worldwide (n=100), (demonstrating sincere commitment of Oxford Cardiologist/Surgeons !)

4. I withdrew my authorship from the final NEJM manuscript (2019) over INTERPRETATION of the data

5. **There was NO attempt in the EXCEL trial to manipulate/distort the data that was actually presented**

6. **BUT, by failing to present vital MI protocol specified data,there was, by omission, manipulation/distortion of the 'true' interpretation of the trial**

Circulation

[Dec 2018]

WHITE PAPER

Myocardial Revascularization Trials

Beyond the Printed Word

ABSTRACT: This article reviews the context and evidence of recent myocardial revascularization trials that compared percutaneous coronary intervention with coronary artery bypass grafting for the treatment of left main and multivessel coronary artery disease. We develop the rationale that some of the knowledge synthesis resulting from these trials, particularly with regard to the claimed noninferiority of percutaneous coronary intervention beyond nondiabetic patients with low anatomic complexity, may have been affected by trial design, patient selection based on suitability for percutaneous coronary intervention, and end point

Marc Ruel, MD, MPH
Volkmar Falk, MD, PhD
Michael E. Farkouh, MD, MS
Nick Freemantle, PhD
Mario F. Gaudino, MD
David Glineur, MD, PhD
Duke E. Cameron, MD
David P. Taggart, MD

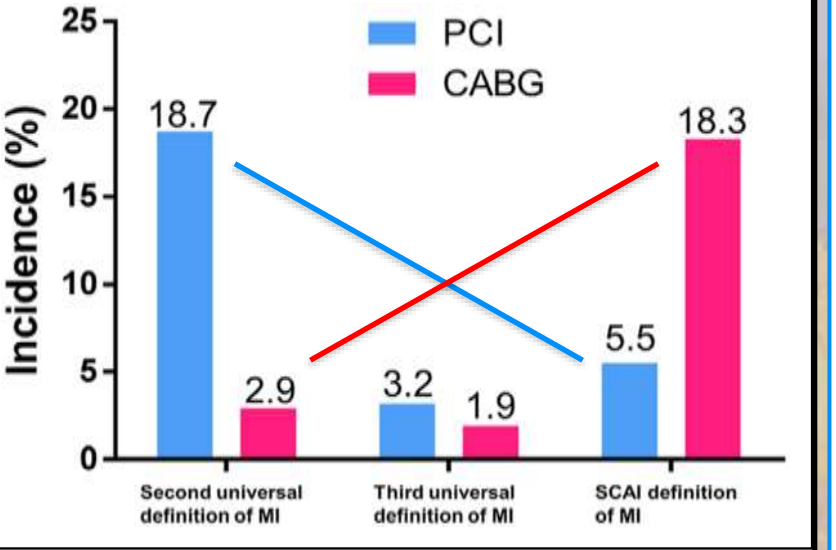
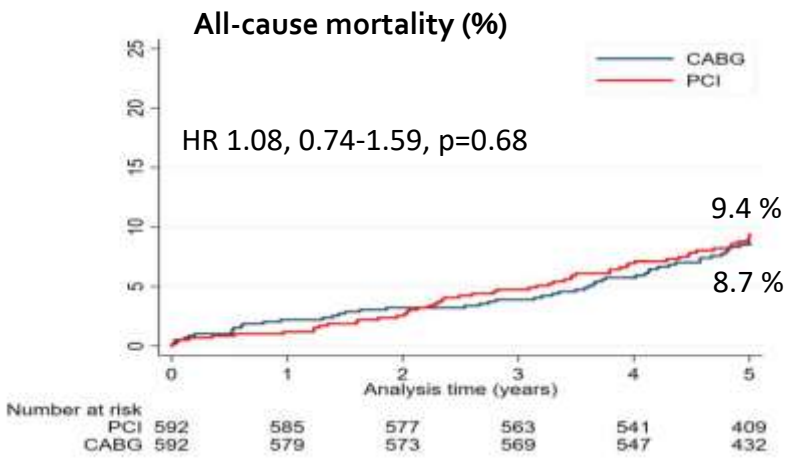
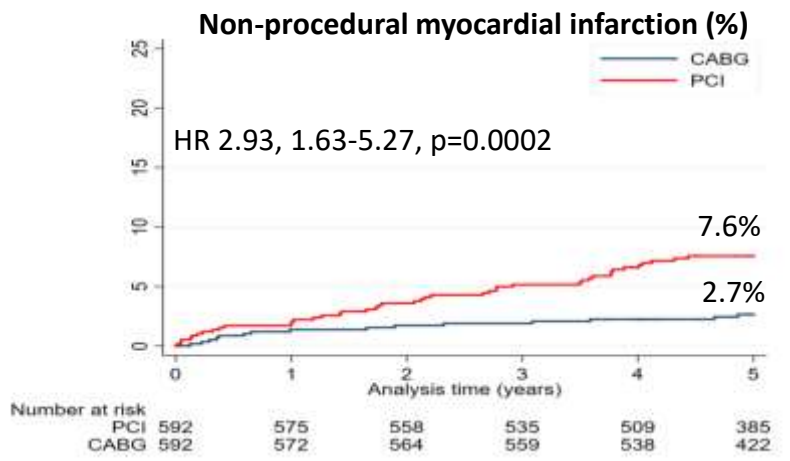
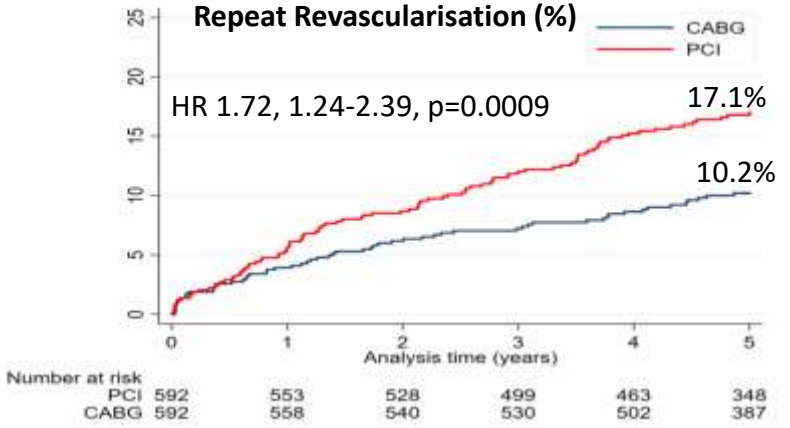


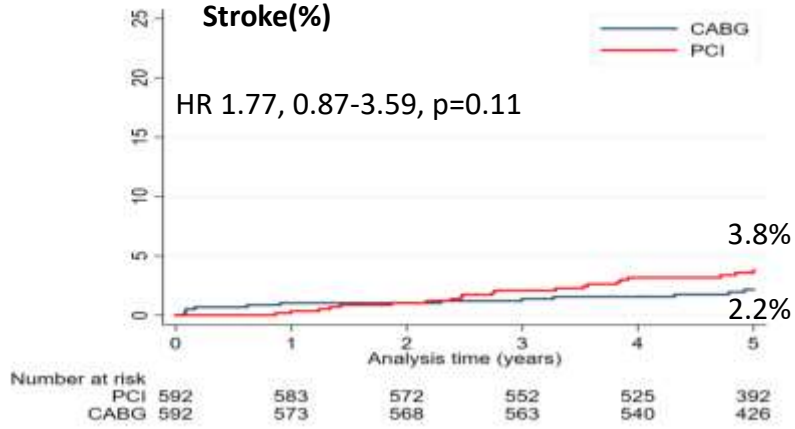
Figure 1. Rates of periprocedural myocardial infarction (MI) according to various definitions in 7697 patients who received percutaneous coronary intervention (PCI; n=4514) or coronary artery bypass grafting (CABG; n=3183) between 2003 and 2013 and for whom serial measurements of creatine kinase-MB were available.
SCAI indicates Society for Cardiovascular Angiography and Interventions.
Reproduced from Cho et al[15] with permission. Copyright © 2017, Elsevier.

'Hence a change in the definition of Periprocedural MI, from the original EXCEL trial protocol, contemporary with the 2nd Universal Definition, to the SCAI definition used in the analyses, affected the composite primary end point and the non-inferiority result of the EXCEL study. Without this modification it is plausible that the composite primary end point of MACCE, which included periprocedural MI in the first 30 days, would have changed in favor of CABG.'









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Two Definitions of MI in EXCEL Protocol (Appendix A NEJM 2019)

EXCEL Clinical Trial Protocol Version 4.0: 22nd July 2011 [NEJM 2019]
'Protocol Defined MI: MI Adjudicated per Universal Definition'
'All MI (periprocedural, spontaneous, Q-wave and non Q-wave) including large and small' (And repeated in the protocol)

Expert Consensus Document

Universal Definition of Myocardial Infarction

Kristian Thygesen; Joseph S. Alpert; Harvey D. White;
on behalf of the Joint ESC/ACCF/AHA/WHF Task Force
for the Redefinition of Myocardial Infarction

[CIRC 2007]

'If troponin assays are not available, the best alternative is CKMB'

EXCEL PROTOCOL: Definition of Myocardial Infarction [16.1.2.,p 92]
Different criteria for spontaneous and peri-procedural MI will be utilized.
New biochemical definition (SCAI definition eventually published in JACC 2013)

NEJM 2019: 'Third, a specific bio-marker-based definition of large periprocedural myocardial infarction was used in the present trial; this definition differs from the criteria used in the 3rd UDMI (which was developed while the current trial was ongoing)'.
(Genuine Confusion and Misunderstanding of which UDMI !!)

BUT: EXCEL Protocol SPECIFIED reporting of BOTH the standard (UDMI) and new (SCAI) definition of procedural MI. (To allow comparison of these definitions (i) within EXCEL and (ii) with other studies); only the new definition, that drove the composite end point was reported

NOBLE

Conclusions:
NOBLE 5-year follow-up

- The NOBLE trial has reached the predefined number of endpoints and is conclusive
- PCI remained inferior to CABG in 5-year MACCE
- CABG was superior to PCI – also in the group with SYNTAX score <23
- All-cause mortality was similar for PCI and CABG
- PCI resulted in higher rates of non-procedural myocardial infarctions and repeat revascularization

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GW Stone, PW Serruys, J Sabik. NEJM July 16 2020

Table 1. Cumulative Incidence of Myocardial Infarction at 5 Years, According to Two Definitions.*

Outcome	PCI (N = 948)		CABG (N = 957)		Difference (95% CI)†
	Patients	Event Rate	Patients	Event Rate	
	no.	%	*no.*	%	*percentage points*
Protocol definition					
Procedural myocardial infarction	37	3.9	57	6.0	−2.1 (−4.1 to −0.2)
All myocardial infarction	95	10.2	84	9.0	1.2 (−1.5 to 3.9)
Third universal definition					
Procedural myocardial infarction	31	3.3	13	1.4	1.9 (0.5 to 3.3)
All myocardial infarction	89	9.6	43	4.7	4.9 (2.6 to 7.2)

* Listed are cumulative incidences of myocardial infarction in the EXCEL trial, so the data vary slightly from the Kaplan–Meier rates reported in the original article; the cumulative incidences are not calculated as the ratio of the numerator to the denominator of patients. Procedural myocardial infarction was defined according to the prespecified protocol definition used in the primary outcome analysis and according to the Third Universal Definition of Myocardial Infarction; the latter definition was a secondary outcome measure in the trial. CABG denotes coronary-artery bypass grafting, CI confidence interval, and PCI percutaneous coronary intervention.

† The between-group difference was calculated by subtracting the percentage in the CABG group from that in the PCI group.

3rd UDMI DATA:

(i) HR for Procedural MI with PCI: 2.4 (higher than that reported by the BBC)

(ii) HR for All MI: 2.0

BUT

(i) Data PIs repeatedly said did not exist (and called the BBC 'fake information' in BMJ)

(ii) Not presented to ESC/EACTS Guideline Taskforce on Myocardial Revascularization

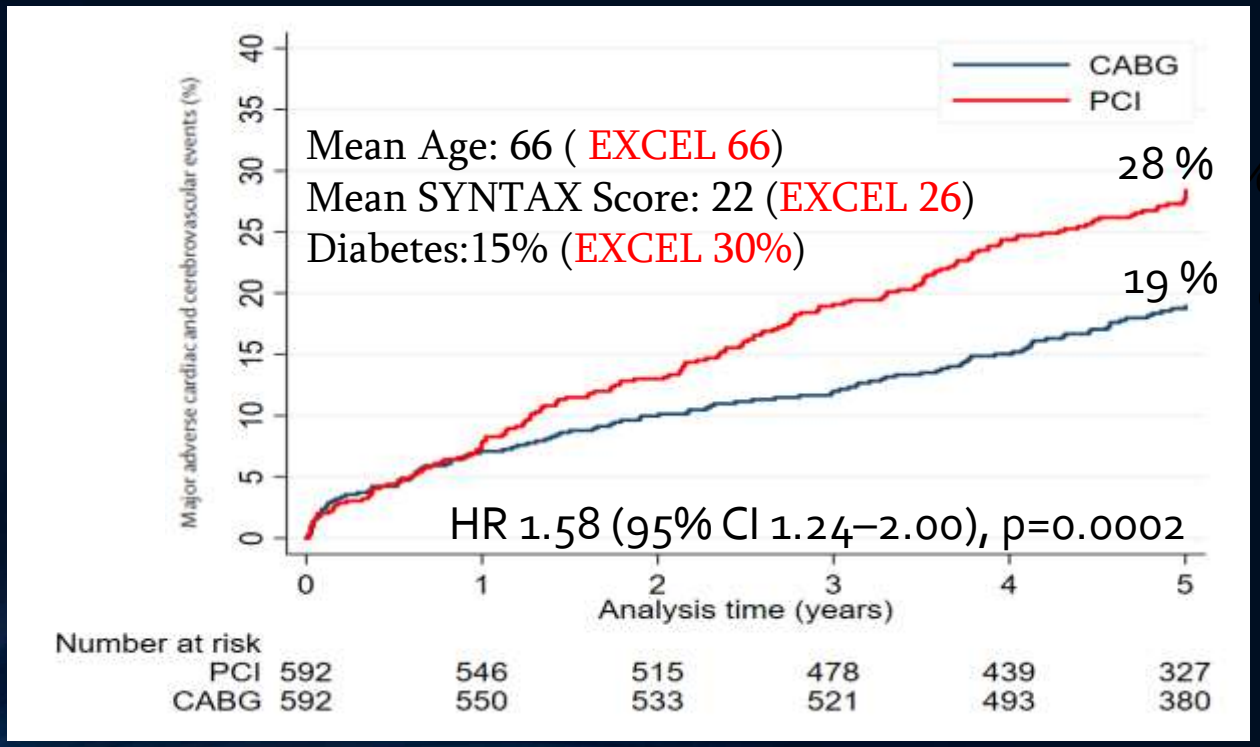
(iii) Not presented in 2016 and 2019 NEJM publications

(iv) No explanation or clarification of repeated misrepresentation

Lessons for all RCTs, Journal Publications (NEJM !), Guidelines, Patients: TRUST

Results TCT 2019
Primary endpoint: MACCE

NOBLE vs EXCEL



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Left Main Disease