TCT AP 2019

Why The Late Benefit of CABG is Evident Over Time

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

Conflicts of Interest:
(i) **Clinical: Cardiac Surgeon**
(ii) Commercial: Consultant to Medistim, Medtronic, VGS, Stryker
(iii) Chairman of Surgical Committee of the EXCEL trial

Why The Late Benefit of CABG is Evident Over Time

THREE KEY ISSUES TO CONSIDER FOR All DATA

(i) Are RCT patients typical of routine practice (ie CAD severity) ?
No: usually highly selected with less severe coronary artery disease

(ii) Duration of follow-up ?
Must be a minimum of 5 years (ideally 10 years as in the ART)

(iii) Use of Guideline Directed Medical Therapy (GDMT) ?
Always substantially inferior in CABG vs PCI patients

Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data IN HIGHLY SELECTED PATIENTS !!

Stuart J Head, Milan Milojevic, Joost Daemen, Jung-Min Ahn, Eric Boersma, Evald H Christiansen, Michael J Domanski, Michael E Farkouh, Marcus Flather, Valentin Fuster, Mark A Hlatky, Niels R Holm, Whady A Hueb, Masoor Kamalesh, Young-Hak Kim, Timo Mäkikallio, Friedrich W Mohr, Grigorios Papageorgiou, Seung-Jung Park, Alfredo E Rodriguez, Joseph F Sabik 3rd, Rodney H Stables, Gregg W Stone, Patrick W Serruys, Arie Pieter Kappetein

[LANCET 2018]

Summary

Background Numerous randomised trials have compared coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) for patients with coronary artery disease. However, no studies have been powered to detect a difference in mortality between the revascularisation strategies.

Methods We did a systematic review up to July 19, 2017, to identify randomised clinical trials comparing CABG with PCI using stents. Eligible studies included patients with multivessel or left main coronary artery disease who did not present with acute myocardial infarction, did PCI with stents (bare-metal or drug-eluting), and had more than 1 year of follow-up for all-cause mortality. In a collaborative, pooled analysis of individual patient data from the identified trials, we estimated all-cause mortality up to 5 years using Kaplan-Meier analyses and compared PCI with CABG using a random-effects Cox proportional-hazards model stratified by trial. Consistency of treatment effect was explored in subgroup analyses, with subgroups defined according to baseline clinical and anatomical characteristics.

Findings We included 11 randomised trials involving 11 518 patients selected by heart teams who were assigned to PCI (n=5753) or to CABG (n=5765). 976 patients died over a mean follow-up of 3·8 years (SD 1·4). Mean Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score was 26·0 (SD 9·5), with 1798 (22·1%) of 8138 patients having a SYNTAX score of 33 or higher. 5 year all-cause mortality was 11·2% after PCI and 9·2% after CABG (hazard ratio [HR] 1·20, 95% CI 1·06–1·37; p=0·0038). 5 year all-cause mortality was significantly different between the interventions in patients with multivessel disease (11·5% after PCI *vs* 8·9% after CABG; HR 1·28, 95% CI 1·09–1·49; p=0·0019), including in those with diabetes (15·5% *vs* 10·0%; 1·48, 1·19–1·84; p=0·0004), but not in those without diabetes (8·7% *vs* 8·0%; 1·08, 0·86–1·36; p=0·49). SYNTAX score had a significant effect on the difference between the interventions in multivessel disease. 5 year all-cause mortality was similar between the interventions in patients with left main disease (10·7% after PCI *vs* 10·5% after CABG; 1·07, 0·87–1·33; p=0·52), regardless of diabetes status and SYNTAX score.

Interpretation CABG had a mortality benefit over PCI in patients with multivessel disease, particularly those with diabetes and higher coronary complexity. No benefit for CABG over PCI was seen in patients with left main disease. Longer follow-up is needed to better define mortality differences between the revascularisation strategies.

Who are the Trial Patients ?

✔ ☐ 11 RCT (2001-2018)

✔ ☐ 11,518 patients

✔ ☐ Individual Patient Data

BUT

✖ ☐ Mean Follow-up 3.8yr

✖ ☐ Mean Syntax 26

APART FROM THE SYNTAX TRIAL, STILL HIGHLY SELECTED PATIENT POPULATIONS !!

Compliance With Guideline-Directed Medical Therapy in Contemporary Coronary Revascularization Trials

[JACC 2018]

Ana-Catarina Pinho-Gomes, MSc(Hons),[a] Luis Azevedo, MD, PhD,[b] Jung-Min Ahn, MD,[c] Seung-Jung Park, MD, PhD,[c] Taye H. Hamza, PhD,[d] Michael E. Farkouh, MD, MSc,[e] Patrick W. Serruys, MD, PhD,[f] Milan Milojevic, PhD,[f] Arie Pieter Kappetein, MD, PhD,[g] Gregg W. Stone, MD, PhD,[h] Andre Lamy, MD, MHSc,[i] Valentin Fuster, MD, PhD,[j,k] David P. Taggart, MD(Hons), PhD[a]

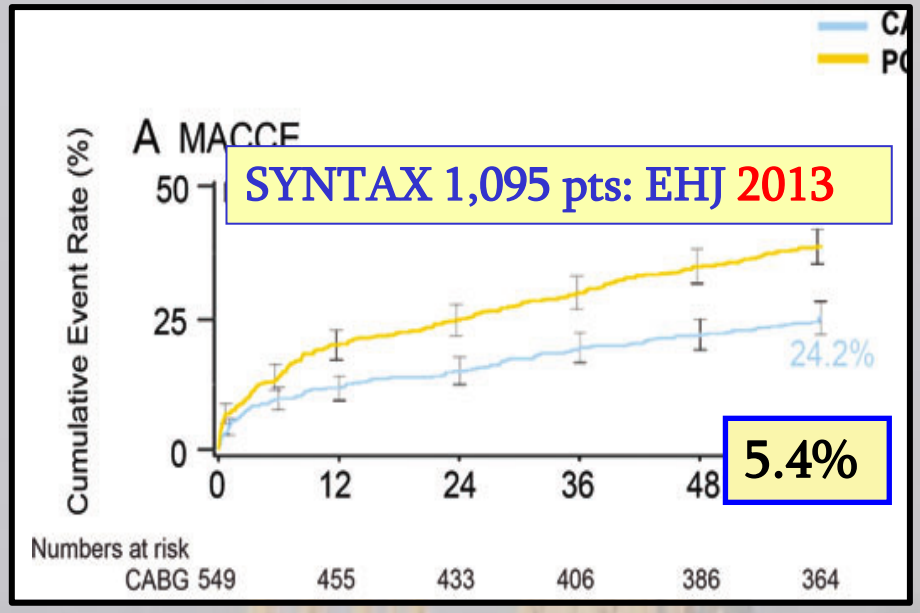
RESULTS From a total of 439 references, 5 trials were included based on our inclusion and exclusion criteria. Overall, compliance with GDMT1 was low and decreased over time from 67% at 1 year to 53% at 5 years. Compliance with GDMT2 was even lower and decreased from 40% at 1 year to 38% at 5 years. Compliance with both GDMT1 and GDMT2 was higher in PCI than in CABG at all time points. Meta-regression suggested an association between lower use of GDMT1 and adverse clinical outcomes in PCI versus CABG at 5 years.

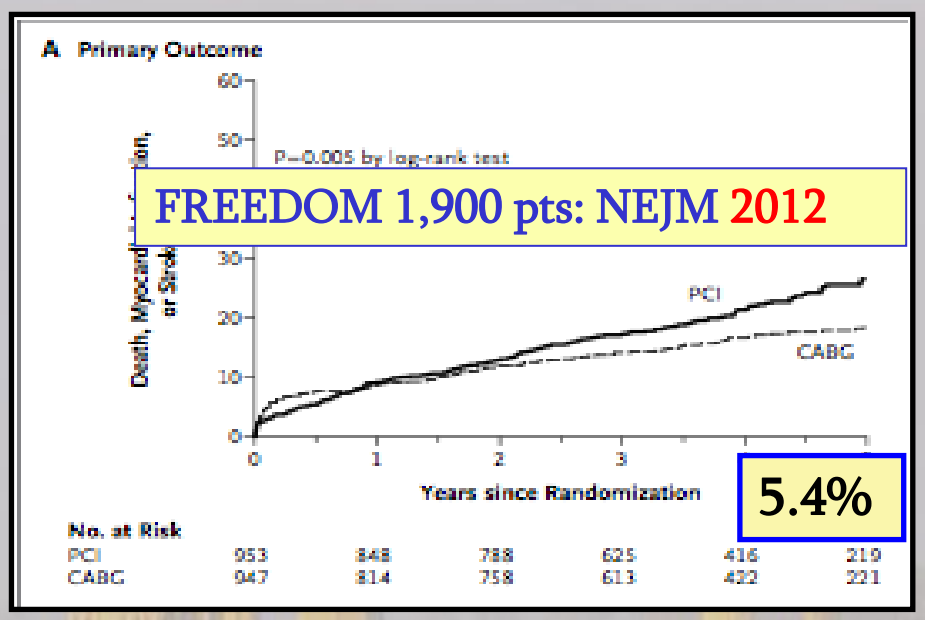
CONCLUSIONS Compliance with GDMT in contemporary clinical trials remains suboptimal and is significantly lower after CABG than after PCI, which may influence the comparison of clinical trial endpoints between those study groups.

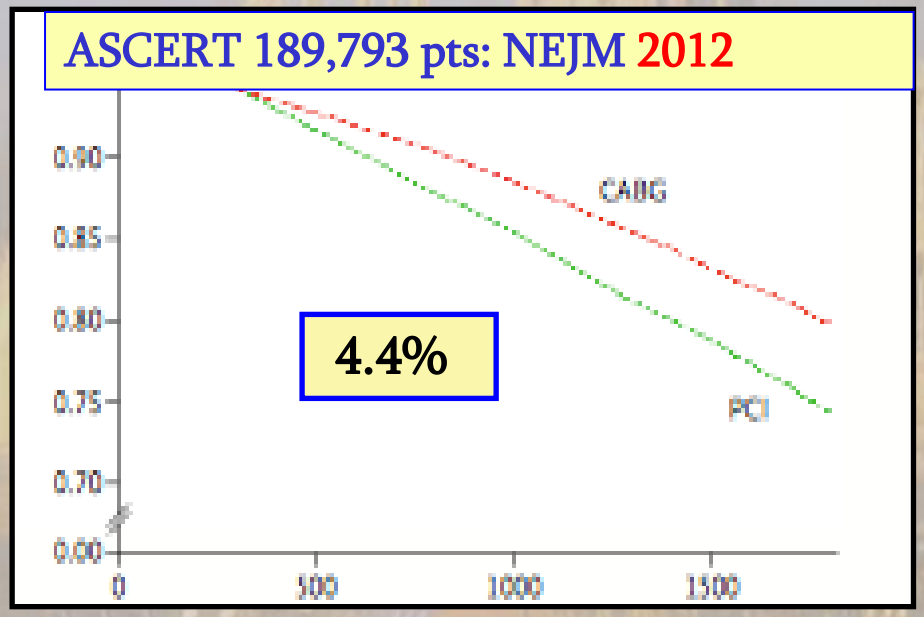
(J Am Coll Cardiol 2018;71:591–602) © 2018 by the American College of Cardiology Foundation.

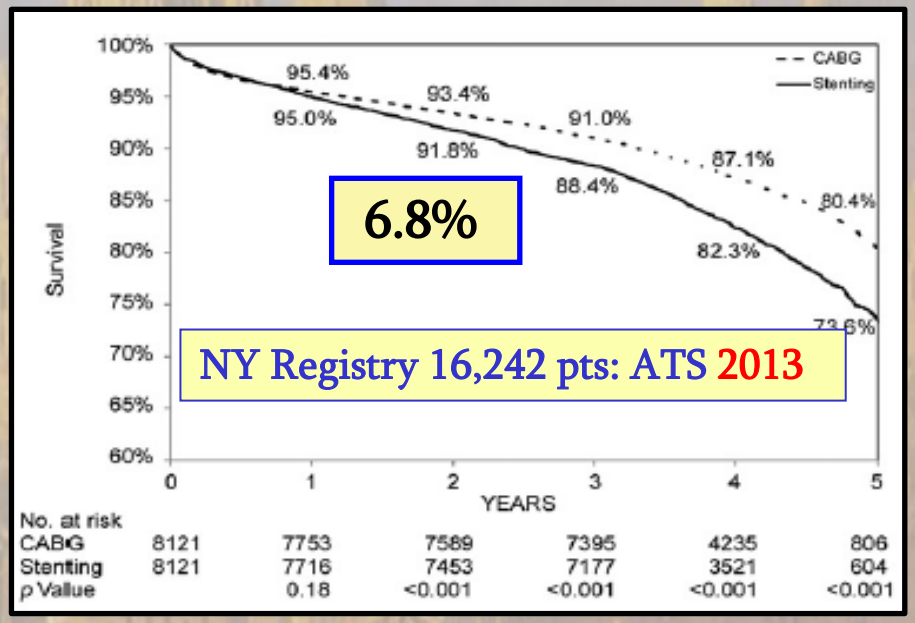
ART: GDMT 70-90% at 10 years !

Survival benefit of CABG increases with time (< 5 yrs follow-up is 'interim' analyses)







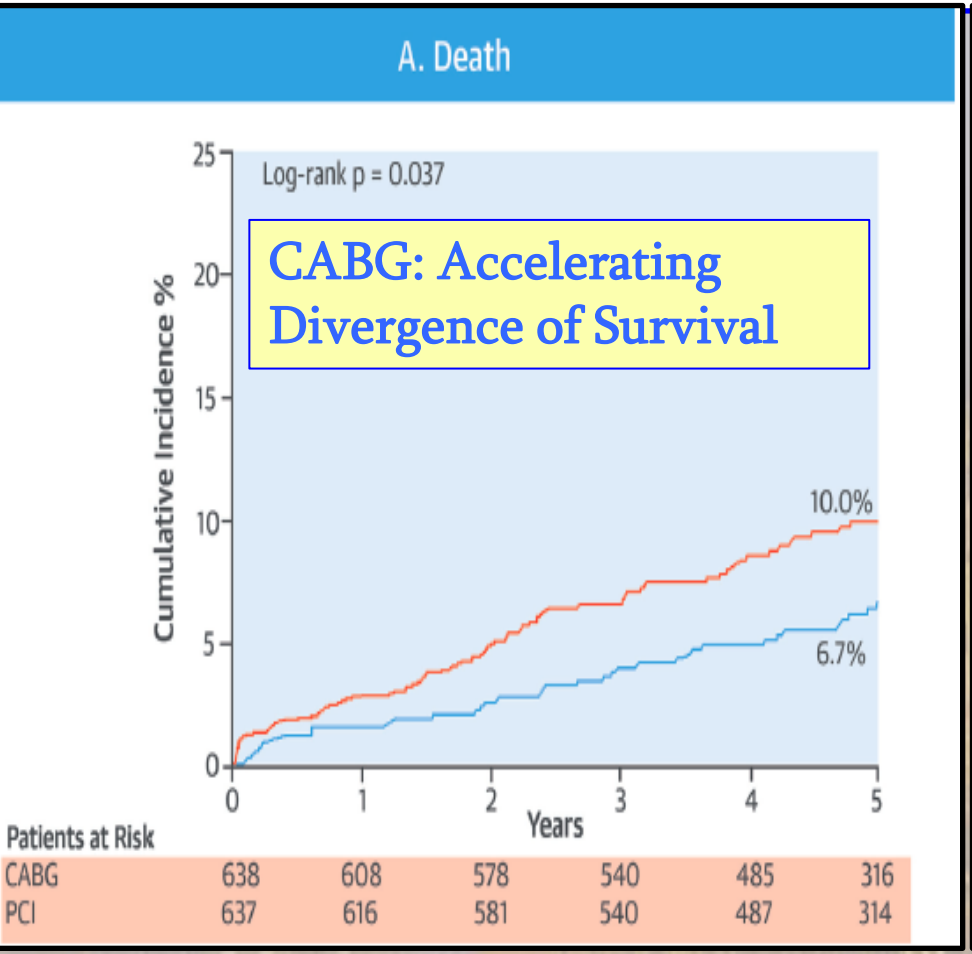


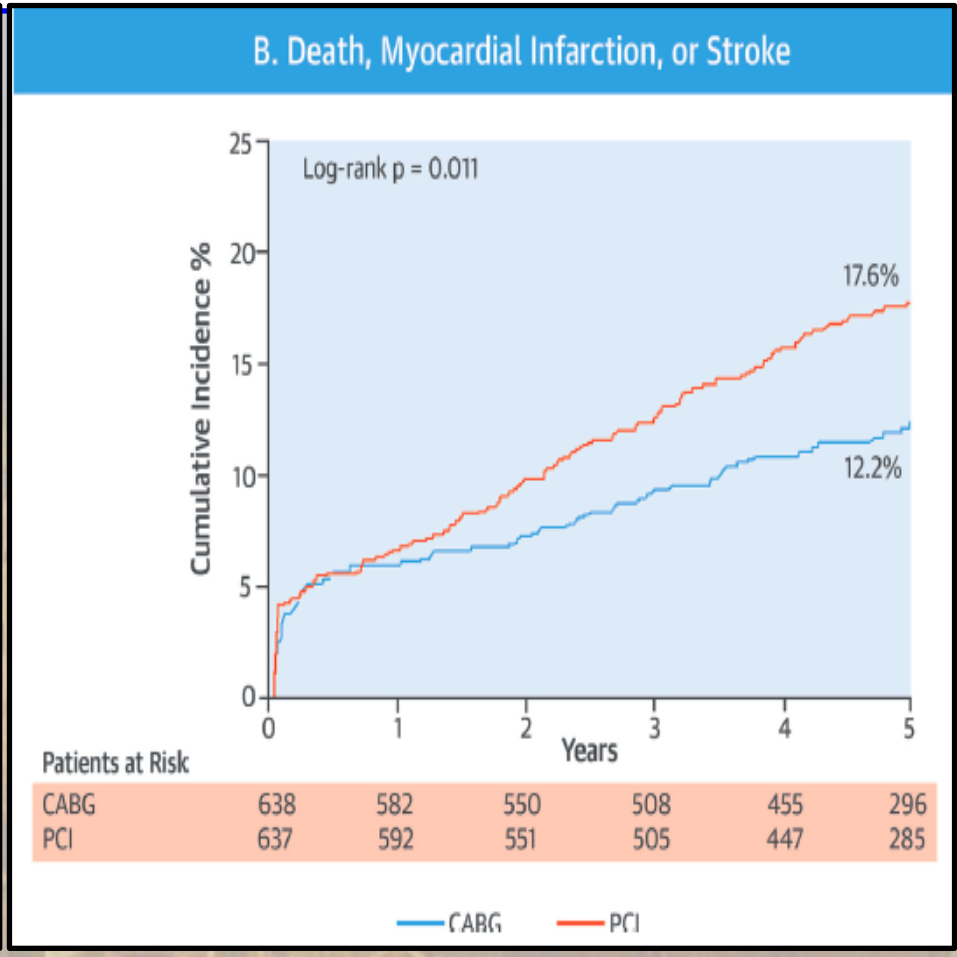
ACCELERATING DIVERGENCE OF SURVIVAL CURVES AFTER 5 YEARS !!!

Long-Term Mortality After Coronary Revascularization in Nondiabetic Patients With Multivessel Disease

[JACC 2016]

Mineok Chang, MD,[a] Jung-Min Ahn, MD,[a] Cheol Whan Lee, MD,[a] Rafael Cavalcante, MD,[b] Yohei Sotomi, MD,[c] Yoshinobu Onuma, MD,[b] Erhan Tenekecioglu, MD,[b] Minkyu Han, PhD,[d] Duk-Woo Park, MD,[a] Soo-Jin Kang, MD,[a] Seung-Whan Lee, MD,[a] Young-Hak Kim, MD,[a] Seong-Wook Park, MD, PhD,[a] Patrick W. Serruys, MD, PhD,[b,e] Seung-Jung Park, MD, PhD[a]





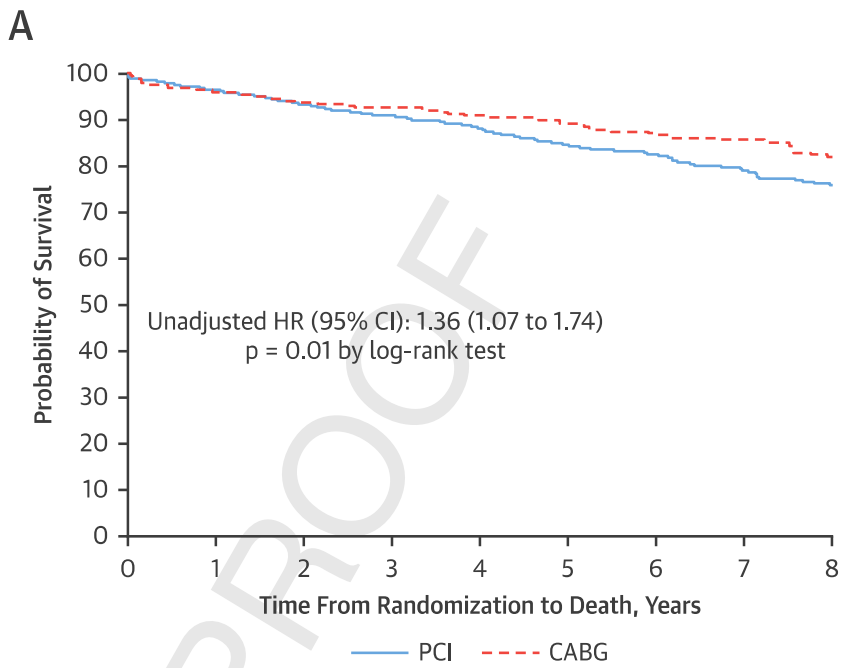
CONCLUSIONS CABG, as compared with PCI with drug-eluting stents, significantly reduced the long-term risk of mortality in nondiabetic patients with multivessel CAD. (J Am Coll Cardiol 2016;68:29-36)

Long-Term Survival Following Multivessel Revascularization in Patients With Diabetes

The FREEDOM Follow-On Study

Michael E. Farkouh, MD, MSc,[a] Michael Domanski, MD,[b] George D. Dangas, MD, PhD,[c] Lucas C. Godoy, MD,[a,d] Michael J. Mack, MD,[e] Flora S. Siami, MPH,[f] Taye H. Hamza, PhD,[f] Binita Shah, MD, MS,[g] Giulio G. Stefanini, MD,[h] Mandeep S. Sidhu, MD,[i] Jean-François Tanguay, MD,[j] Krishnan Ramanathan, MBChB,[k] Samin K. Sharma, MD,[c] John French, MBChB, PhD,[l] Whady Hueb, MD, PhD,[d] David J. Cohen, MD, MSc,[m] Valentin Fuster, MD, PhD,[c,n] for the FREEDOM Follow-On Study Investigators

FIGURE 2 Kaplan-Meier Estimates of Survival in the 2 Treatment Groups

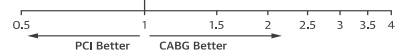


Number of patients at risk

PCI	953	897	845	745	611	460	333	260	206
CABG	947	854	807	721	589	445	313	252	191

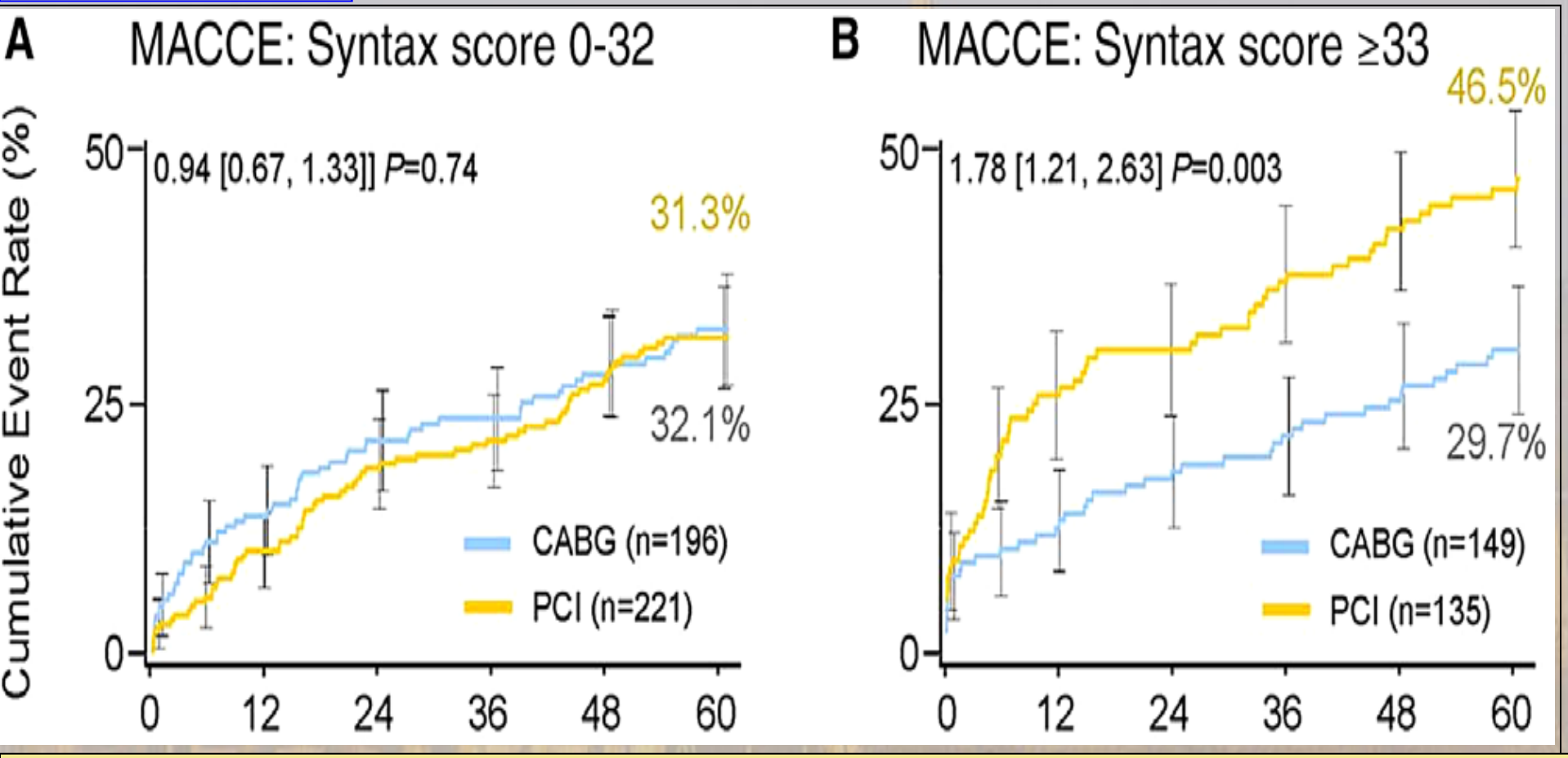
FIGURE 3 Subgroup Analysis of All-Cause Mortality for the Whole Cohort

Subgroup	PCI Total N	CABG Total N	PCI 8-yr Event Rate	CABG 8-yr Event Rate	Interaction p Value
Overall	953	947	24.3	18.3	
Extended follow-up					0.71
Yes	478	465	23.7	18.7	
No	475	482	32.5	12.1	
Age at randomization					0.001
≤63.3	473	477	21.4	9.4	
>63.3	480	470	27.0	27.3	
Ever Smoked					0.01
Yes	507	529	30.7	19.4	
No	446	418	17.5	17.0	
Sex					0.26
Male	698	658	23.3	15.8	
Female	255	289	26.6	24.1	
Race					0.99
White	726	726	24.6	19.0	
Black	60	59	24.3	14.2	
Hispanic					0.31
Yes	326	330	23.4	19.7	
No	627	617	25.4	17.9	
Region					0.02
North America	387	383	26.0	13.8	
Other	566	564	23.0	21.5	
SYNTAX					0.41
≤22	329	340	23.9	17.6	
23-32	438	406	23.8	14.8	
≥33	182	192	24.2	26.9	
LVEF					0.33
<40	21	11	55.6	20.0	
≥40	620	639	19.9	16.4	
Disease type					0.93
2-vessel disease	168	146	19.9	11.9	
3-vessel disease	780	793	24.7	19.7	
LAD involvement					0.43
Yes	862	875	23.4	18.6	
No	87	64	28.2	15.2	
History of stroke					0.57
Yes	37	28	38.2	26.7	
No	916	919	23.8	18.1	
Renal insufficiency					0.58
Yes	73	56	52.9	56.9	
No	880	891	22.0	16.2	
Use of insulin					0.64
Yes	322	293	33.6	28.2	
No	630	654	19.9	14.0	
Glycated hemoglobin					0.20
<7	323	307	18.7	19.4	
≥7	551	568	27.1	17.6	



'CONCLUSIONS In patients with DM and MVD, coronary revascularization with CABG lea to lower all-cause mortality than with PCI-DES in long-term follow-up'.

LEFT MAIN
SYNTAX trial
705 RCT patients
5 years
CIRC 2014



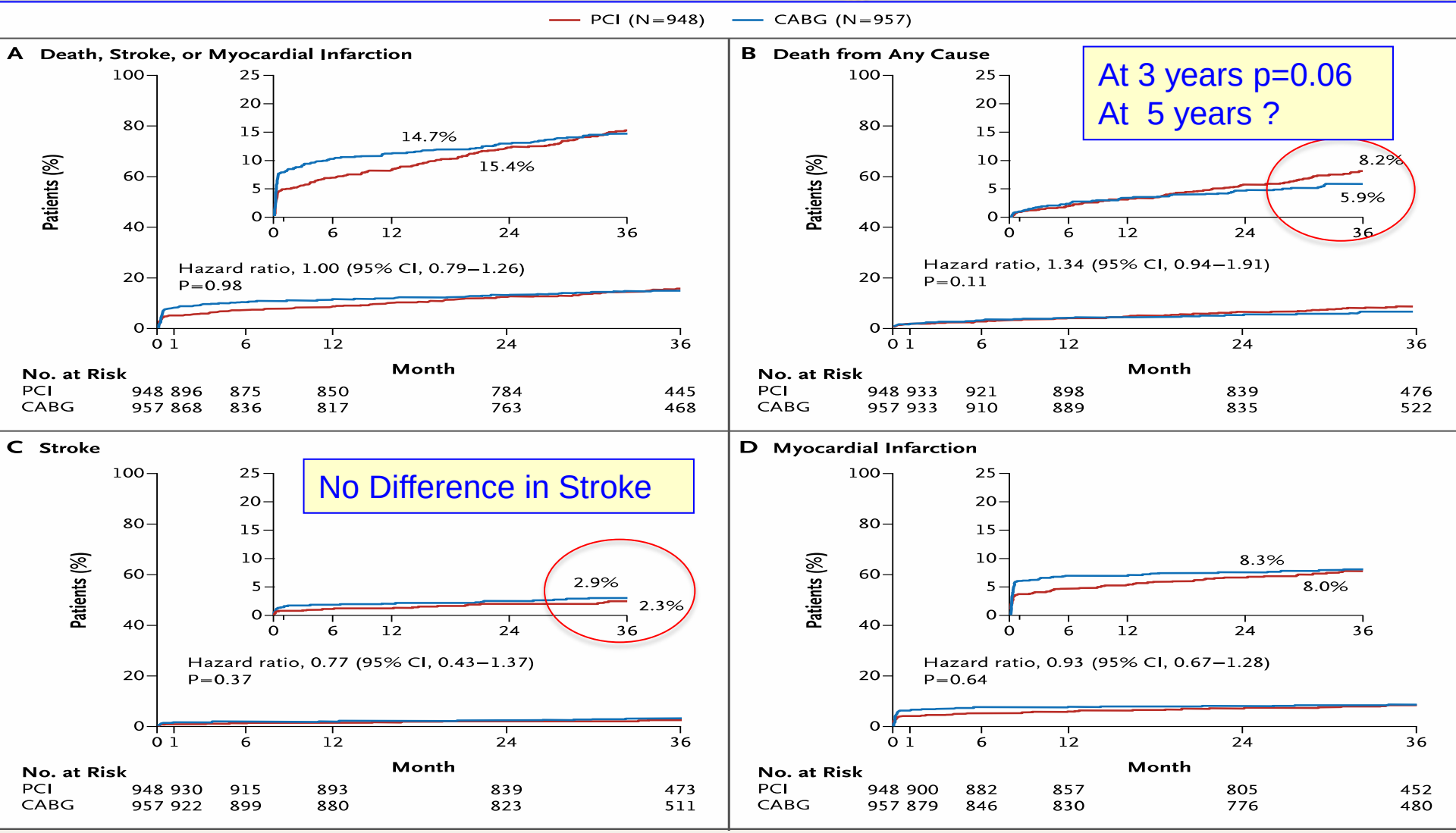
① Accelerating Divergence of Survival Curves in Favour of CABG in >32
② CABG: Competitive flow if low SYNTAX scores ie less proximal CAD ?
③ Used to define patients in the EXCEL trial (Syntax Scores <33)

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,

LM: **SYNTAX <33**
1903 RCT patients
1000 Registry Patients
NEJM 2016

CAUTION: ONLY 3 YEARS FOLLOW-UP !!!!



EXCEL

Primary Endpoint Landmark Analysis (post hoc)

4 YEARS

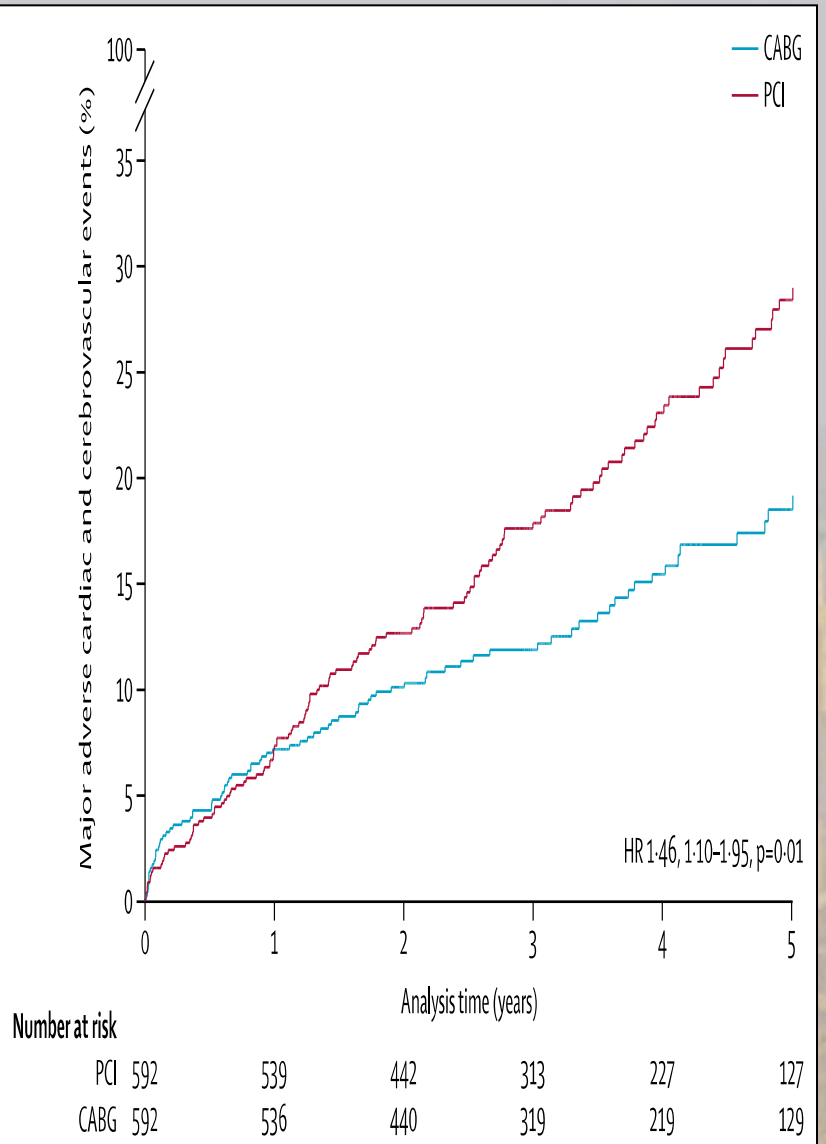
	From randomization to 30 days				From 30 days to 4 years			
	PCI (n=948)	CABG (n=957)	HR [95%CI]	P value	PCI (n=933)	CABG (n=929)	HR [95%CI]	P value
Death, stroke or MI	4.9%	7.9%	0.61 [0.42, 0.88]	0.008	14.8%	10.1%	1.48 [1.14, 1.93]	0.003
- Death	1.0%	1.1%	0.90 [0.37, 2.22]	0.82	9.4%	6.5%	1.47 [1.05, 2.05]	0.02
- Stroke	0.6%	1.3%	0.50 [0.19, 1.33]	0.15	2.0%	2.2%	0.94 [0.49, 1.79]	0.85
- MI	3.9%	6.2%	0.63 [0.42, 0.95]	0.02	5.7%	3.0%	1.92 [1.19, 3.08]	0.006

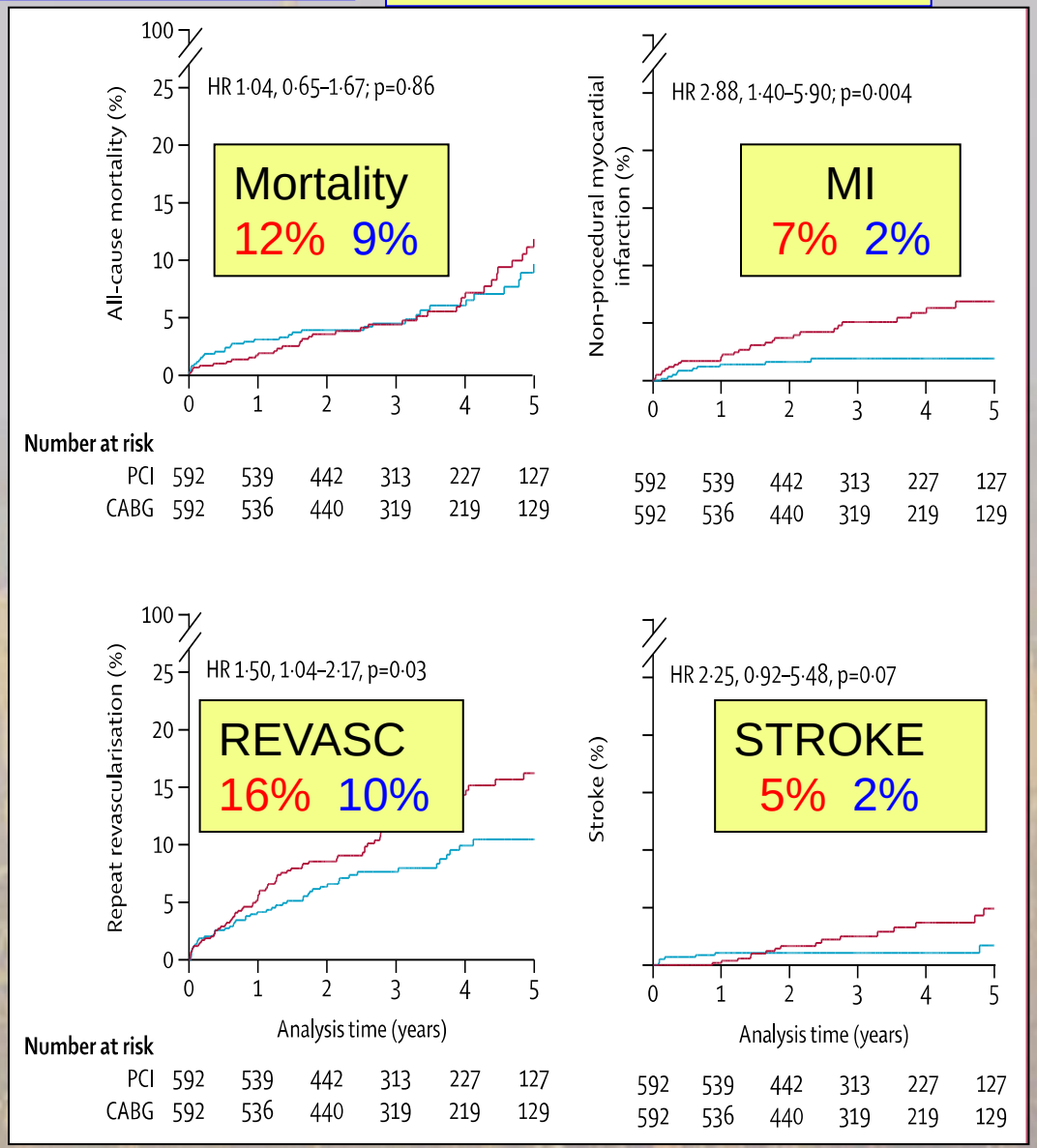
Continuing Divergence in Favour of CABG for Death and MI and Same Incidence of Stroke

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:
1201 RCT patients
No Registry Patients
Lancet 2016



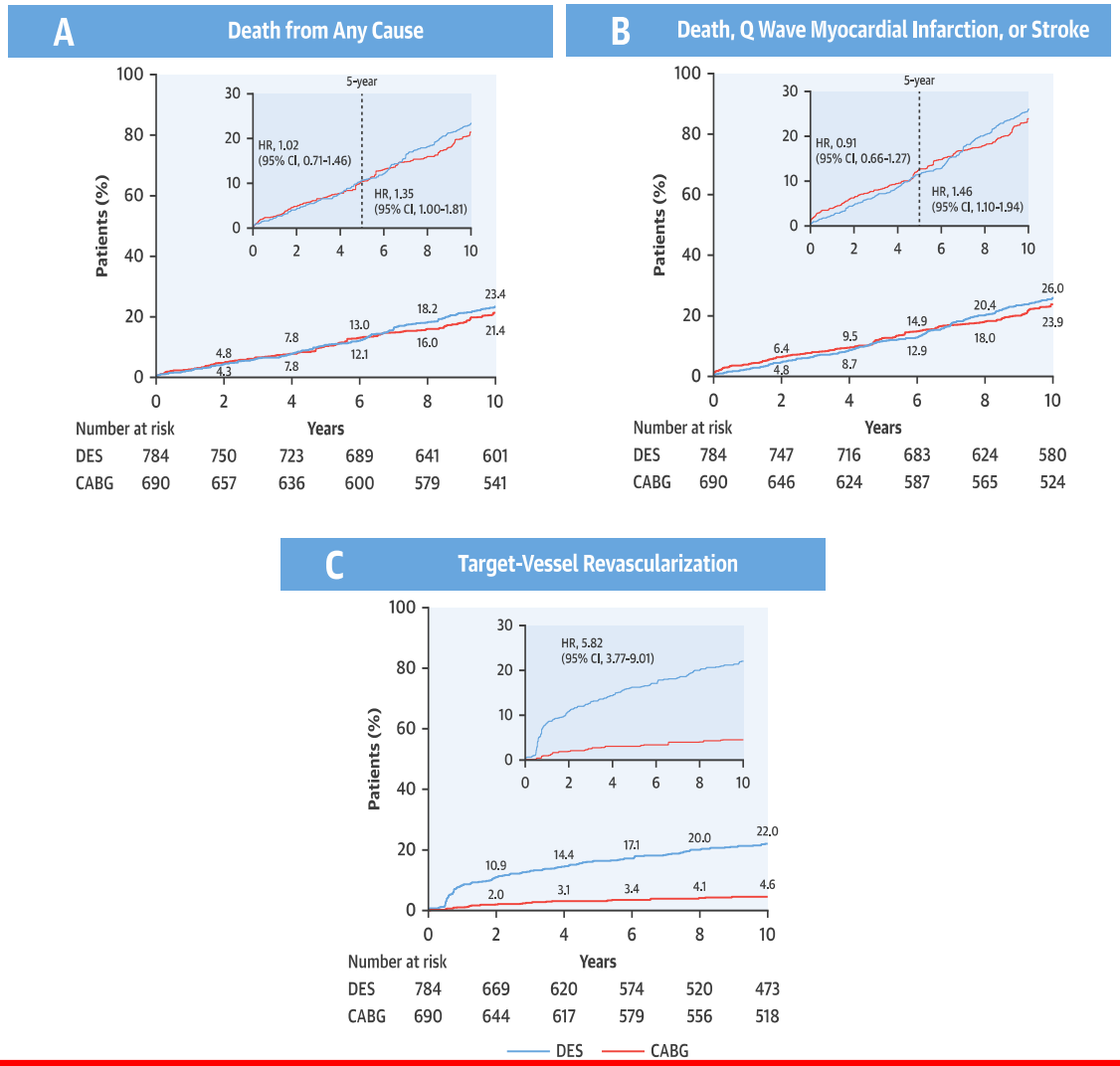


10-Year Outcomes of Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Artery Disease

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]

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 Cohor
Had More Severe CAD
1474/2240 (66%)

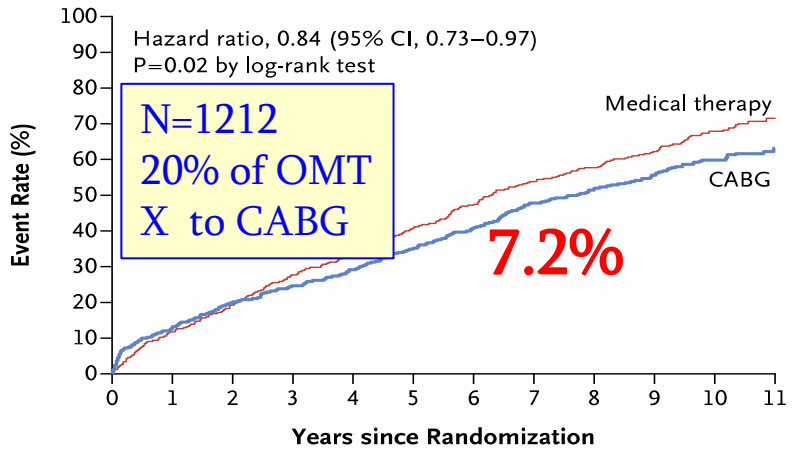
AGE: 62
DM: 30%
EF: 60%
LM Ostium/Shaft: 48%
LM only: 12%
+1 VD: 17%
+ 2VD: 32%
+ 3VD: 38%

ORIGINAL ARTICLE [NEJM 2016]

Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy

Eric J. Velazquez, M.D., Kerry L. Lee, Ph.D., Robert H. Jones, M.D.,

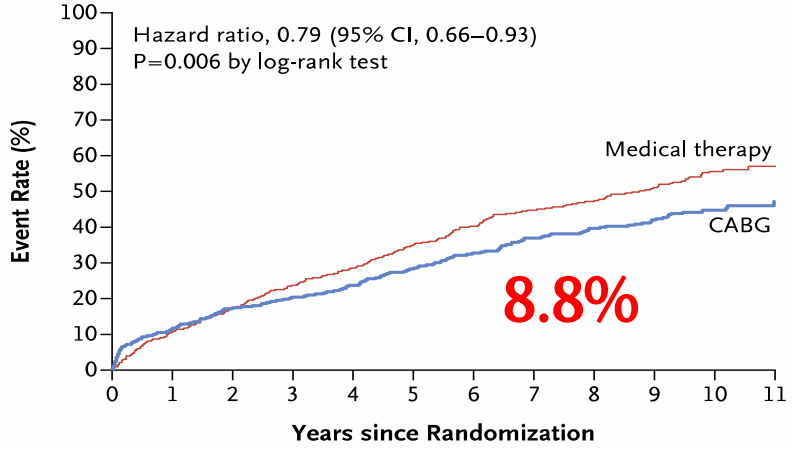
A Death from Any Cause (Primary Outcome)



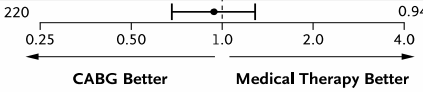
No. at Risk

Medical therapy	602	532	487	435	404	357	315	274	248	164	82	37
CABG	610	532	487	460	432	392	356	312	286	205	103	42

B Death from Cardiovascular Causes



Subgroup	No. of Patients	Hazard Ratio (95% CI)	P Value for Interaction
All patients	1212	0.84 (0.73–0.97)	
Age			0.18
≥60 yr	589	0.91 (0.75–1.10)	
<60 yr	623	0.75 (0.60–0.93)	
Sex			0.50
Male	1064	0.85 (0.73–0.99)	
Female	148	0.73 (0.46–1.16)	
Race or ethnic group			0.02
Hispanic, Latino, or nonwhite	421	0.67 (0.52–0.86)	
White	791	0.95 (0.80–1.12)	
Region or country			0.28
Poland	319	1.01 (0.77–1.33)	
United States	120	0.85 (0.55–1.31)	
Canada	123	0.77 (0.48–1.22)	
Western Europe	112	1.08 (0.68–1.69)	
Other	538	0.72 (0.57–0.89)	
NYHA heart failure class			0.74
I or II	765	0.85 (0.71–1.02)	
III or IV	447	0.81 (0.65–1.01)	
LVEF			0.31
≤28%	653	0.77 (0.64–0.92)	
>28%	559	0.89 (0.71–1.11)	
End-systolic volume index			0.68
≤78 ml/m^2	564	0.85 (0.68–1.06)	
>78 ml/m^2	551	0.80 (0.65–0.98)	
Stratum			0.03
A	1061	0.89 (0.77–1.04)	
B	151	0.55 (0.36–0.84)	
Diabetes			0.95
Yes	478	0.84 (0.67–1.04)	
No	734	0.84 (0.69–1.01)	
CCS angina class			0.52
No angina or I	629	0.80 (0.65–0.97)	
II, III, or IV	583	0.88 (0.72–1.09)	
No. of diseased vessels with ≥75% stenosis			0.04
0, 1, or 2	769	0.93 (0.77–1.11)	
3	442	0.68 (0.54–0.86)	
LM >50% or PLAD >75% stenosis			0.81
No	373	0.81 (0.62–1.05)	
Yes	838	0.85 (0.71–1.00)	
Mitral regurgitation			0.34
None or trace	435	0.92 (0.71–1.17)	
Mild (≤2+)	554	0.74 (0.60–0.92)	
Moderate or severe (3+ or 4+)	220	0.94 (0.68–1.29)	



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

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] [102,105,121,123,124,135,14 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 !!