TCT

CABG is Best Revascularization in Diabetes

(I have not included RCTs/Registries only reporting 1 year outcomes)

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

Conflicts of Interest:
(i) Clinical: Cardiac Surgeon
(ii) Commercial: Consultant to Medtronic, Abbott, AstraZeneca, Novadaq, VGS, Cardioguard

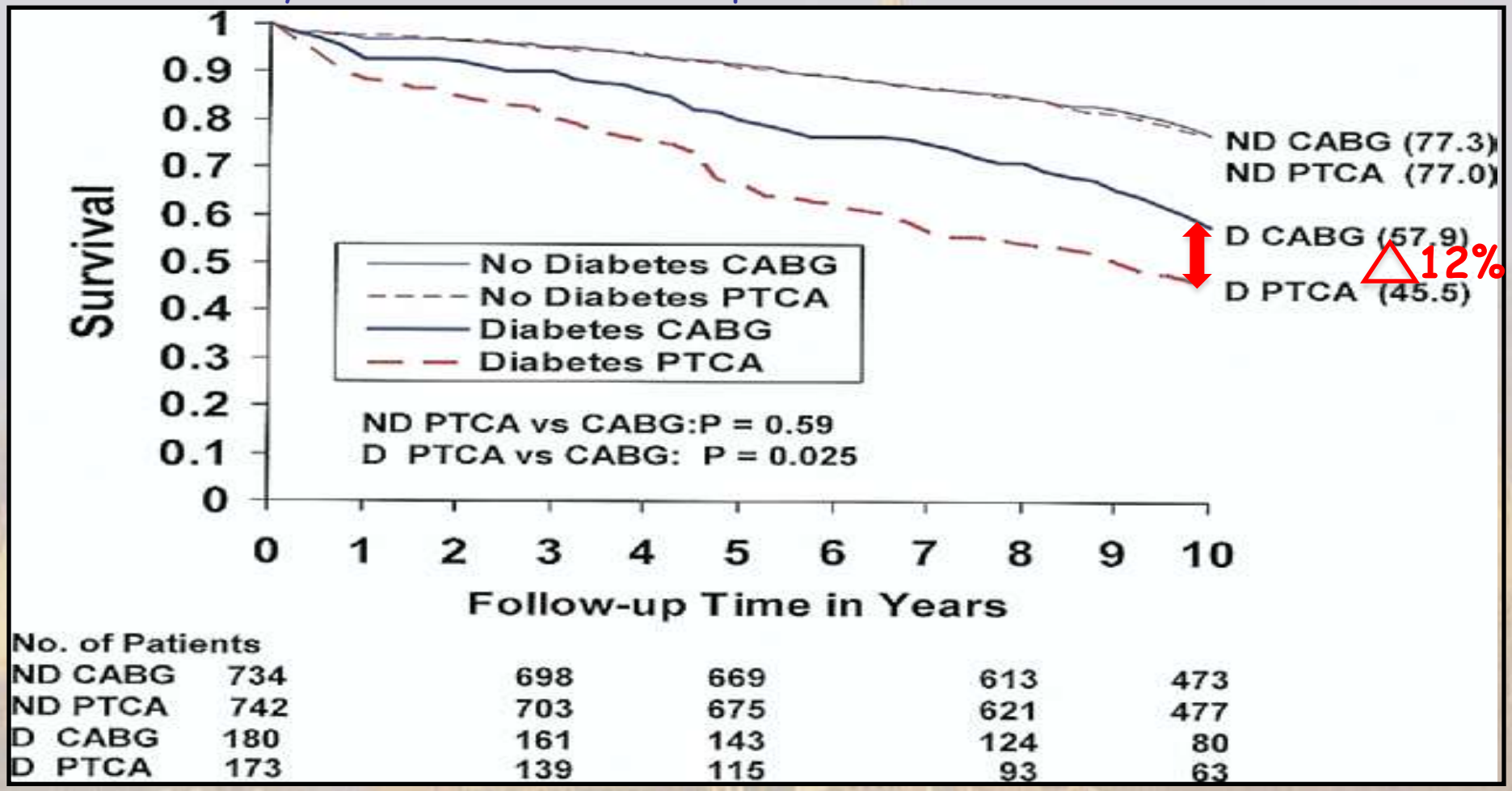
Diabetes Mellitus (DM): A Growing Epidemic

- > 170 million DM worldwide, 24 million DM in USA
- WHO estimate DM will double by 2030
- DM has 4-6 fold increase in adverse cardiovascular events
- DM present in >25% CABG and >30% ACS patients
- In DM 75% of deaths, 80% hospital admissions are CVS

The Final 10-Year Follow-Up: Results From the BARI Randomized Trial

The BARI Investigators* [J Am Coll Cardiol 2007;49:1600–6]

- 1829 patients: (12% of potentially eligible population)
- **353 diabetic patients**: (19% of All BARI patients)
- Low Severity CAD: 41% 3vCAD; 31% proximal LAD; normal LV function



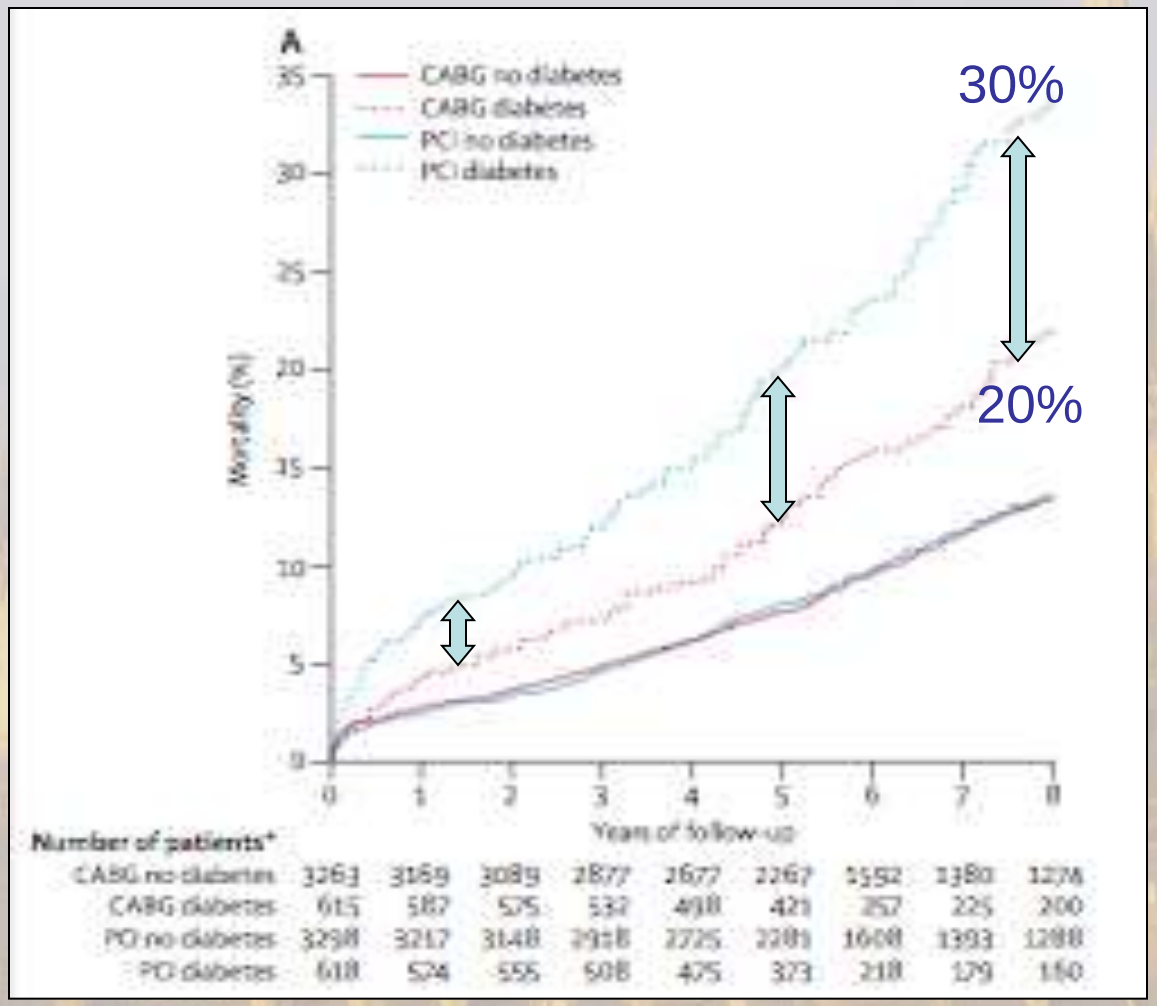
No. of Patients					
ND CABG	734	698	669	613	473
ND PTCA	742	703	675	621	477
D CABG	180	161	143	124	80
D PTCA	173	139	115	93	63

Increase in repeat revasc x4 in PCI (58% of PCI received CABG)
ITT analyses: X-overs reduce the magnitude of CABG survival benefit

Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials **Lancet 2009**

Mark A Hlatky, Derek B Boothroyd, Dena M Bravata, Eric Boersma, Jean Booth, Maria M Brooks, Didier Carrié, Tim C Clayton, Nicolas Danchin, Marcus Flather, Christian W Hamm, Whady A Hueb, Jan Kähler, Sheryl F Kelsey, Spencer B King, Andrzej S Kosinski, Neuza Lopes, Kathryn M McDonald, Alfredo Rodriguez, Patrick Serruys, Ulrich Sigwart, Rodney H Stables, Douglas K Owens, Stuart J Pocock

- OVERALL
- 7812 patients
- Median follow up 6 years
- 65%: 1 or 2 VD; all normal LV
- HR *CABG*: 0.91: p=0.12



- 1233 patients with DM
- HR for *CABG* vs PCI in DM 0.70; p=0.01
- Survival benefit of *CABG* increases with time

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 11, 2009 VOL. 360 NO. 24

A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease

The BARI 2D Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Diabetes with Coronary Disease — A Moving Target amid Evolving Therapies?

William E. Boden, M.D., and David P. Taggart, M.D., Ph.D.

BARI 2D: [NEJM 2009]

(i) optimal medical therapy vs prompt revascularization (prespecified to PCI/CABG)
(ii) Insulin vs oral hypoglycaemics

2368 patients (2001-05)	PCI (1605)	CABG (763)
Age (sd) [% male]	62 (9); [68%]	63 (8); [76%]
DM (years); [% insulin]	10(9); [31%]	11(8); [22%]
Unstable; prior revasc	11% 29%	7%; 13%
3 vessel disease	20%	52%
Significant LAD disease	10%	19%
Ejection Fraction	57 (11)	57 (11)

	Medical	PCI	Medical	CABG
	807	798	385	378
5 years Death	11.9%	12.8%	16.9%	14%
5 years MI	10.2%	11.3%	14.6%	7.4%*
5 years Stroke	2.9%	2.9%	2.6%	1.9%
5 years Death,MI,Stroke	20.8%	23.4%	29.9%	20.9%*

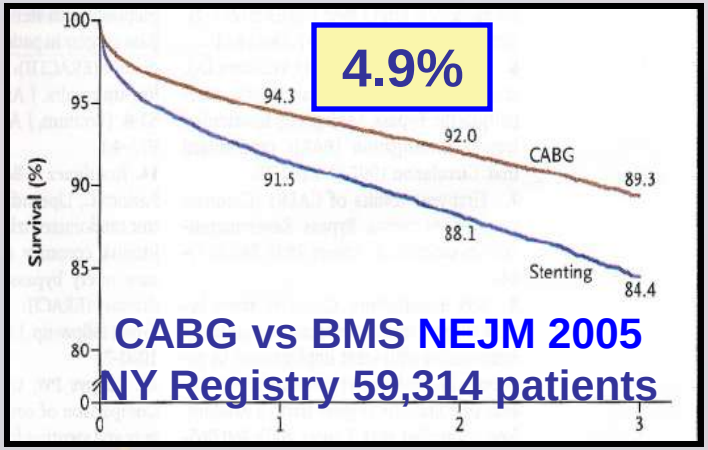
By 5 years 42% of medical group required revascularization (ITT analyses !)

- Overall Low severity CAD (NO Registry Data: what % of all DM enrolled ?)
- PCI had no benefit over medical treatment but CABG (prespecified) did
- High risk of subsequent revascularization in medical group (42%)

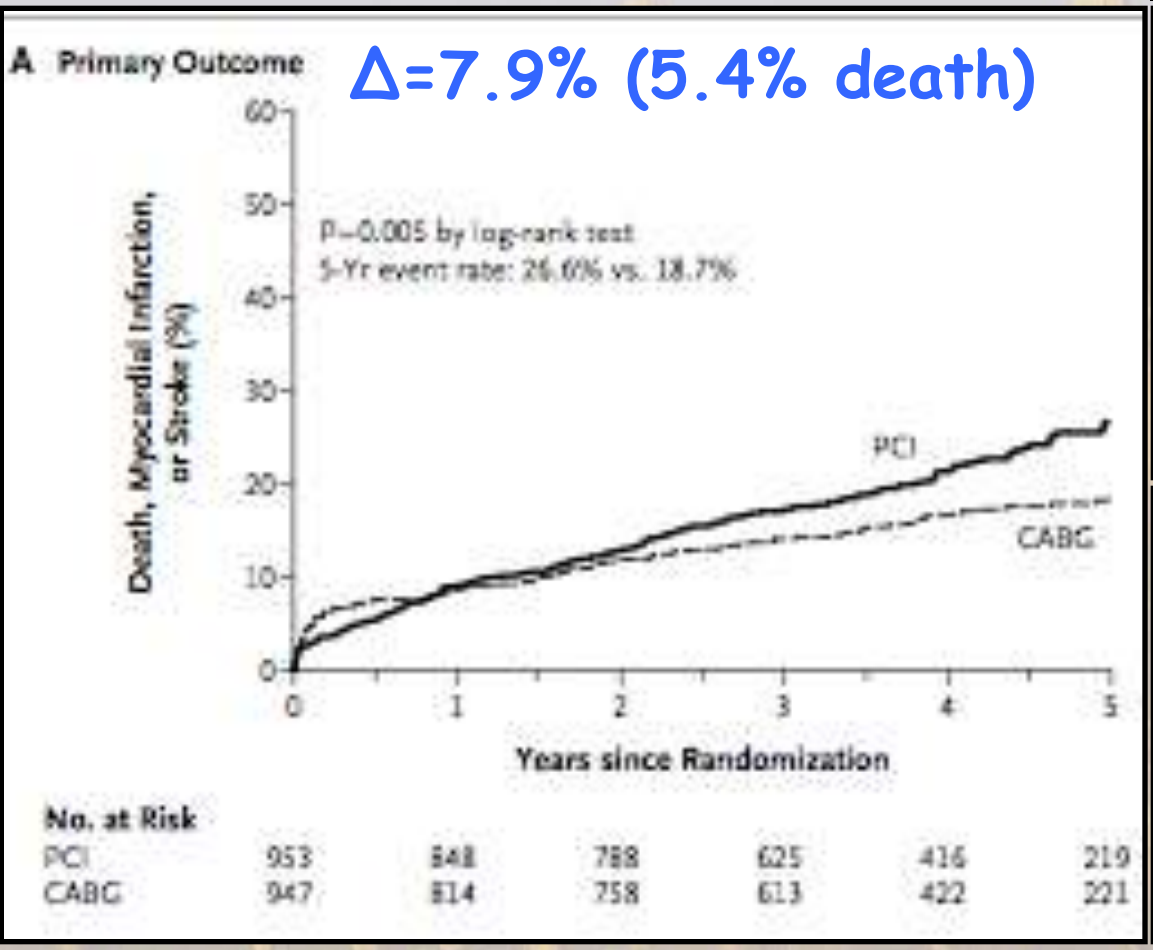
The NEW ENGLAND JOURNAL of MEDICINE [2012]

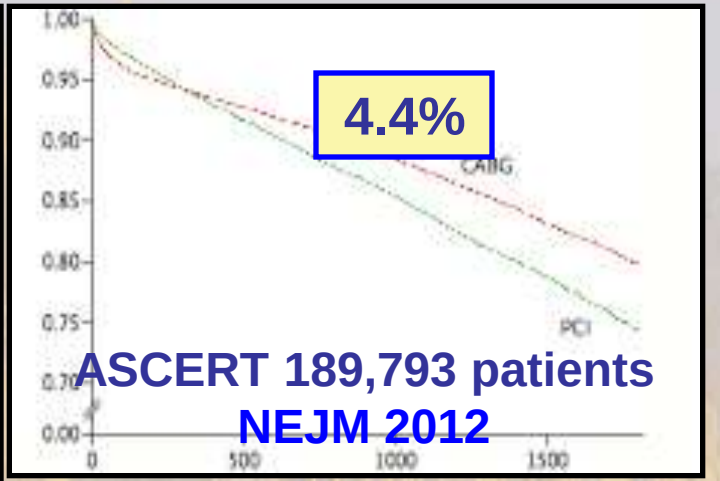
ORIGINAL ARTICLE

Strategies for Multivessel Revascularization in Patients with Diabetes

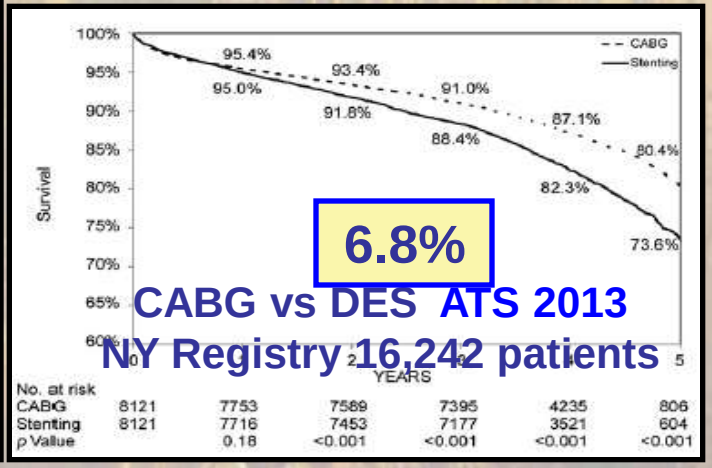


CABG vs BMS NEJM 2005
NY Registry 59,314 patients





ASCERT 189,793 patients
NEJM 2012



CABG vs DES ATS 2013
NY Registry 16,242 patients

Treatment of Complex Coronary Artery Disease in Patients with Diabetes: 5-Year Results Comparing Outcomes of Bypass Surgery and Percutaneous Coronary Intervention in the SYNTAX Trial

EJCTS 2013

A. Pieter Kappetein[1], Stuart J. Head[1], Marie-Claude Morice[2], Adrian P. Banning[3], Patrick W. Serruys[4], Friedrich-Wilhelm Mohr[5], Keith D. Dawkins[6], Michael J. Mack[7], on behalf of the SYNTAX Investigators.

	DM=452		
	CABG=221	PCI=231	
MACCE %	29	47	<0.001
All cause death/stroke/MI %	19	24	0.26
All death %	13	20	0.06
Cardiac death %	6.5	13	0.03
Stroke %	4.7	3	0.34
MI %	5.4	9	0.20
Repeat Revascularization %	15	35	<0.001
Repeat PCI %	13	29	<0.001
Repeat CABG %	1.9	8.7	0.004
Graft Occlusion/stent thrombosis %	4.3	5.3	0.61

Effectiveness of Percutaneous Coronary Intervention With Drug-Eluting Stents Compared With Bypass Surgery in Diabetics With Multivessel Coronary Disease: Comprehensive Systematic Review and Meta-analysis of Randomized Clinical Data

JAHA 2013

Abdul Hakeem, MD; Nadish Garg, MD; Sabha Bhatti, MD; Naveen Rajpurohit, MD; Zubair Ahmed, MD; Barry F. Uretsky, MD

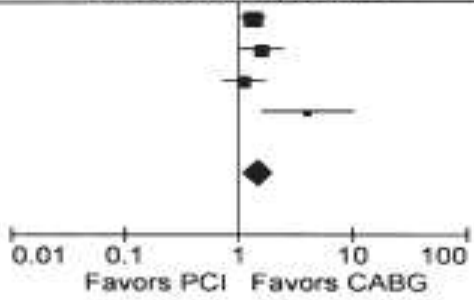
(A)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
FREEDOM trial	114	953	83	947	37.7%	1.36 [1.04, 1.78]	2012
SYNTAX TRIAL	44	231	26	221	25.9%	1.62 [1.03, 2.54]	2012
CARDIA Study	37	254	32	248	26.4%	1.13 [0.73, 1.75]	2013
VA CARDS	21	101	5	97	9.9%	4.03 [1.58, 10.27]	2013
Total (95% CI)		1539		1513	100.0%	1.51 [1.09, 2.10]	
Total events	216		146				

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.28$, df = 3 (P = 0.10); $I^2 = 52\%$

Test for overall effect: Z = 2.47 (P = 0.01)

Death



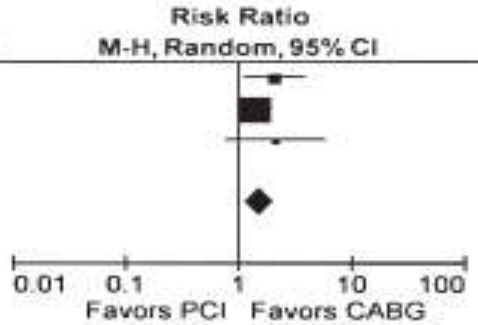
(B)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
SYNTAX TRIAL	28	231	13	221	21.1%	2.06 [1.10, 3.87]	2012
FREEDOM trial	73	953	52	947	70.9%	1.40 [0.99, 1.97]	2012
VA CARDS	11	101	5	97	8.1%	2.11 [0.76, 5.86]	2013
Total (95% CI)		1285		1265	100.0%	1.57 [1.17, 2.09]	
Total events	112		70				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.49$, df = 2 (P = 0.47); $I^2 = 0\%$

Test for overall effect: Z = 3.03 (P = 0.002)

Cardiac Death



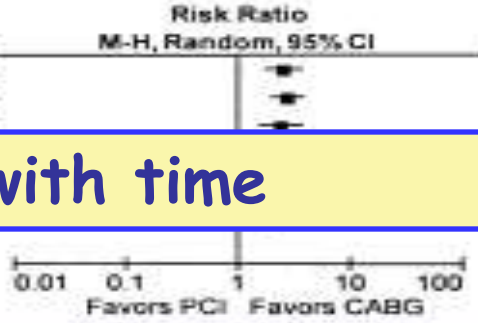
Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
SYNTAX TRIAL	75	231	28	221	25.5%	2.56 [1.73, 3.80]	2012
FREEDOM trial	117	953	42	947	26.1%	2.77 [1.97, 3.89]	2012
CA							
VA							
To							
Total events	268		122				

Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 25.69$, df = 3 (P < 0.0001); $I^2 = 88\%$

Test for overall effect: Z = 1.97 (P = 0.05)

Benefits of surgery increase with time

REVASC



Effectiveness of Percutaneous Coronary Intervention With Drug-Eluting Stents Compared With Bypass Surgery in Diabetics With Multivessel Coronary Disease: Comprehensive Systematic Review and Meta-analysis of Randomized Clinical Data

JAHA 2013

Abdul Hakeem, MD; Nadish Garg, MD; Sabha Bhatti, MD; Naveen Rajpurohit, MD; Zubair Ahmed, MD; Barry F. Uretsky, MD

	CABG	PCI	4 years follow-up	
numbers	1513	1539		
MACCE %	16.8	22.5	1.34 (1.16-1.54)	<0.0001
DEATH %	9.7	14	1.51 (1.09-2.01)	0.01
MI %	5.9	10.3	1.44 (0.79-2.6)	.23
STROKE %	3.8	2.3	.59 (0.39-0.90)	0.01
REVASC %	8	17.4	1.85 (1.0-3.4)	0.05

Benefits of surgery increase with time

Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomised controlled trials.

Verma S, Farkouh ME, Yanagawa B, Fitchett DH, Ahsan MR, Ruel M, Sud S, Gupta M, Singh S, Gupta N, Cheema AN, Leiter LA, Fedak PW, Teoh H, Latter DA, Fuster V, Friedrich JO. **[Lancet Diab Endocrin 2013]**

- 8 RCTs with 7468 participants, of whom 3612 had diabetes.
  - 4 RCTs used BMS (ERACI II, ARTS, SoS, MASS II)
  - 4 RCTs used DES (FREEDOM, SYNTAX, VA CARDS, CARDia).

- At mean/median 5-year:
  - ✓ CABG had lower all-cause mortality vs PCI (RR 0·67, 95% CI 0·52-0·86; p=0·002)
  - ✓ No differences in outcome whether PCI used BMS or DES.

INTERPRETATION:
In the modern era of stenting and optimum medical therapy, revascularisation of patients with diabetes and multivessel disease by CABG decreases long-term mortality by about a third compared with PCI using either BMS or DES. CABG should be strongly considered for these patients.

Meta-analysis of 14 trials comparing bypass grafting vs drug-eluting stents in diabetic patients with multivessel coronary artery disease. **[Nutr Metab Cardiovasc Dis 2014]**

De Luca G, Schaffer A, Verdoia M, Suryapranata H.

- 14 trials (4 RCT and 10 non-RCT) with 7072 patients.

- At 5 years CABG had:

✓ reduced mortality (7.3% vs 10.4%, OR [95%CI] = 0.65[0.55-0.77], p < 0.000
  RCTs (OR[95%CI] = 0.64[0.50-0.82], p = 0.0005)
  Non-RCTs (OR[95%CI] = 0.75[0.6-0.94)], p = 0.01)

✓ reduced MACCE (14.9% vs 22.9%, OR[95%CI] = 0.59[0.51-0.67], p < 0.00001

✓ reduced TVR (5.2% vs 15.7%, OR[95%CI] = 0.30[0.25-0.36], p < 0.00001

✗ increased risk of CVA (3.6% vs 1.4%, OR[95%CI] = 2.34[1.63-3.35], p < 0.0001

- A significant relationship was observed between risk profile and benefits in mortality with CABG (p < 0.001).

CONCLUSIONS:
The present meta-analysis demonstrates that among diabetic patients with multivessel disease and/or left main disease, CABG provides benefits in mortality and TVR, especially in high-risk patients but it is counterbalanced by a higher risk of stroke.

WHY DOES CABG HAVE SUCH A SURVIVAL BENEFIT OVER PCI ?

Anatomically, atheroma is mainly located in the proximal coronary arteries

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

458 THE NEW ENGLAND JOURNAL OF MEDICINE Aug. 25, 1988

2 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

impairs re-endothelialization, creates pro-thrombotic environment, impairs endothelial function downstream

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)

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

Summary and Conclusions

- Consistent evidence from RCTs, Meta-analyses and Propensity Matched Registries that CABG, in comparison to PCI, by 5 years

✓ results in better survival (>5%)
✓ reduces the risk of MI (by at least 50%)
✓ reduces the risk of repeat revascularization (by at least 50%)
X at the cost of a 1.5% increase in stroke over 5 years.

- At five years survival curves continue to diverge implying that the survival benefit of CABG will continue to increase

FOR PATIENTS WITH DIABETES WHO REQUIRE

REVASCULARIZATION CABG IS A CLEAR WINNER

Impact of Coronary Lesion Complexity on Drug-Eluting Stent Outcomes in Patients With and Without Diabetes Mellitus: Analysis from 18 Pooled Randomized Trials. Kedhi E, Généreux P, Palmerini T, McAndrew TC, Parise H, Mehran R, Dangas GD, Stone GW **[JACC 2014]**

- Pooled patient-level data from 18 prospective RCT.
  - Two propensity matched groups by lesion complexity (ACC/AHA class A/B1 vs. B2/C).
  - Remaining baseline differences were adjusted for by multivariable analysis.

- DM was present in 3,467 (18.8%) of 18,441 patients.
  - **At 1-year** DM was a predictor of
  - Cardiac death or myocardial infarction (MI), HR [95%CI]=1.40 [1.09, 1.81]
  - TLR, HR [95%CI]=1.34 [1.05, 1.70]
  - TVR, HR [95%CI]=1.40 [1.15, 1.72]),

- TLR and TVR rates were significantly higher in DM vs. non-DM patients with ACC/AHA type B2/C lesions (8.0% vs. 4.5% and 10.6% vs. 5.9%, both $p<0.0001$), but not in type A/B1 lesions (4.6% vs. 4.8%, $p=0.87$, and 7.4% vs. 6.8%, $p=0.47$)

.

Drug-eluting Stents versus Coronary Artery Bypass Grafting in Diabetic Patients with Multi-vessel Disease: A Meta-analysis **[Heart Lung Circ 2014]** Lim JY, Deo SV, Kim WS, Altarabsheh SE, Erwin PJ, Park SJ.

- 14 studies (5 RCT; 9 OBS) > 5000 patients.

- 30-day mortality lower in the DES cohort [OR 0.49(0.27, 0.88); p=0.02; I2=0%].
- 30-day stroke higher in CABG (1.8%) vs DES/ (0.17%; p<0.01).

- One-year stroke similar in both cohorts [OR 0.84(0.19, 3.74); p=0.82].

- At three to five years for DES vs CABG
- MACCE OR 1.71 (1.27 - 2.3)
- repeat intervention OR 3.02 (2.13 - 4.28; p<0.01].

Randomized Comparison of PCI with CABG in Diabetic Patients: 1 Year Results of the CARDia Trial. JACC 2010

- 'early termination due to slow recruitment over 5 years: 510 of 600 patients

	PCI (256)	CABG (254)
Age (% male)	64 (71%)	64 (78%)
urgent	22%	24%
Insulin dependent	31% (10 years)	31% (10 years)
3vd	65%	58%
EF	59%	60%

Death	3.2%	3.3%
MI	8.4%	5.7% (Δ -32%)
CVA	0.4%	2.5%
1 year death/MI/CVA	11.6%	10.2%
Revascularization	12%	2%
Composite	18%	11%

- No Registry Data (what % of diabetic patients enrolled ?)
  - Approx 26000 DM had CABG in same period in UK ie <0.5% enrolled

Routine clinical practice in DM: PCI vs CABG

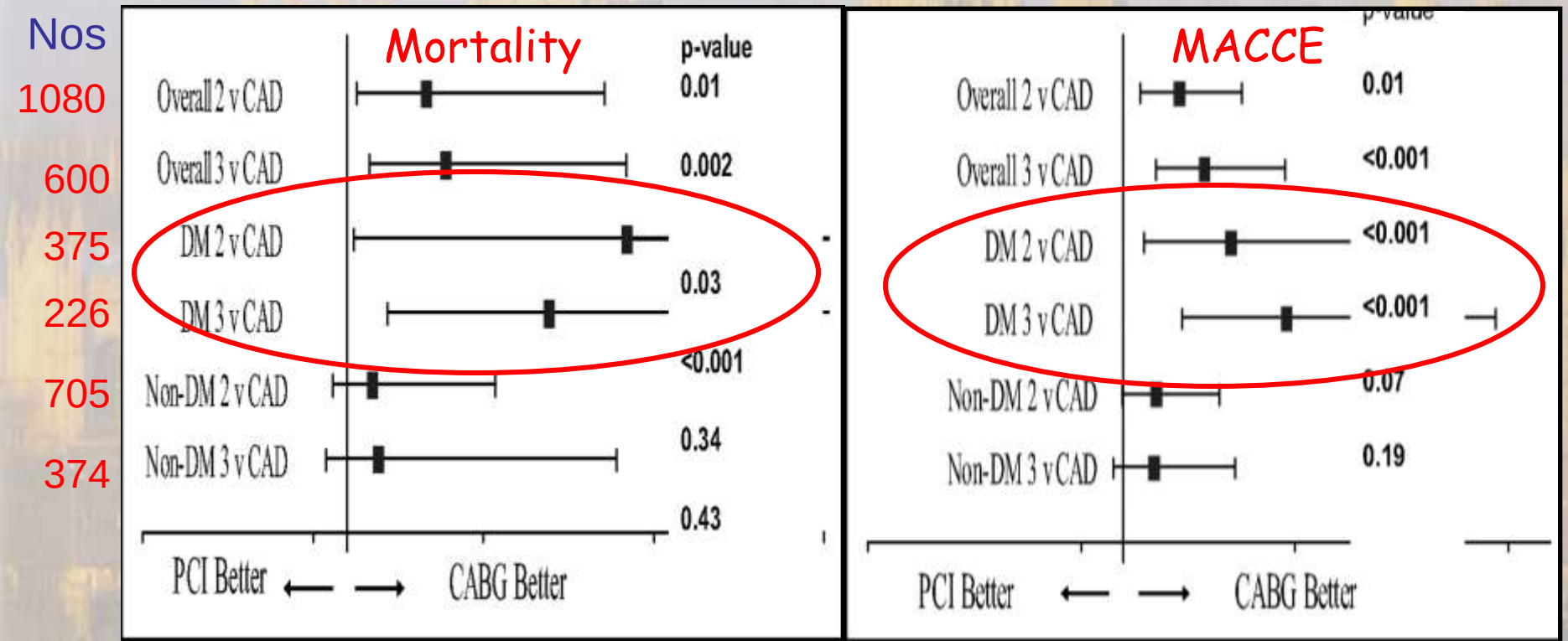
Survival of Patients With Diabetes and Multivessel Coronary Artery Disease After Surgical or Percutaneous Coronary Revascularization: Results of a Large Regional Prospective Study

Nathaniel W. Niles, MD,* Paul D. McGrath, MD, FACC,† David Malenka, MD, FACC,*

JACC 2001

- **2766 risk matched DIABETICS: PCI ↑ 5 yr mortality x 2 – 4**

Javaid et al. [Circ 2007] 1680 patients DES vs CABG 1 year follow up



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 24, 2008 VOL. 358 NO. 4

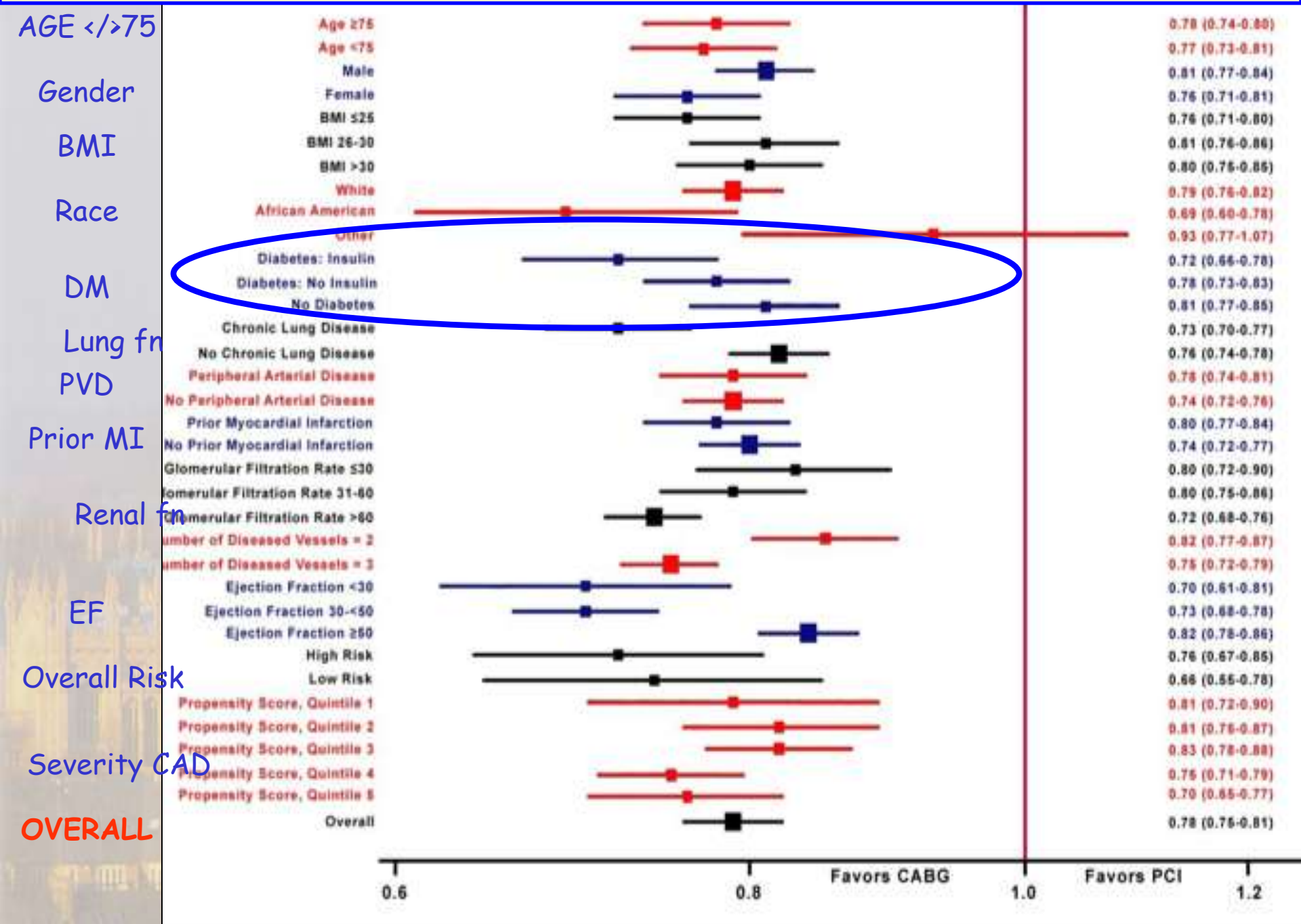
Drug-Eluting Stents vs. Coronary-Artery Bypass Grafting in Multivessel Coronary Disease

Edward L. Hannan, Ph.D., Chuntao Wu, M.D., Ph.D., Gary Walford, M.D., Alfred T. Culliford, M.D., Jeffrey P. Gold, M.D., Craig R. Smith, M.D., Robert S.D. Higgins, M.D., Russell E. Carlson, M.D., and Robert H. Jones, M.D.

Table 3. Hazard Ratios for Death and for Death or Myocardial Infarction after CABG and after Treatment with a Drug-Eluting Stent, According to Selected Subgroups of Patients.*

Variable	No. of Patients	Mean Follow-up	Death			Death or Myocardial Infarction		
			No. of Events	Adjusted Hazard Ratio (95% CI)†	P Value	No. of Events	Adjusted Hazard Ratio (95% CI)†	P Value
		mo						
Diabetes								
CABG	2844	18.9	242	0.97 (0.77–1.20)	0.75	304	0.84 (0.69–1.01)	0.07
Stent	3256	18.5	224	Reference		343	Reference	
Ejection fraction <40%								
CABG	1614	18.6	181	0.77 (0.59–1.00)	0.05	213	0.67 (0.53–0.84)	<0.001
Stent	1059	17.8	144	Reference		183	Reference	
Age ≥80 yr								
CABG	760	18.0	107	0.74 (0.55–1.00)	0.05	125	0.74 (0.56–0.96)	0.03
Stent	1266	17.8	175	Reference		216	Reference	

189,793 PPM patients from ACC (PCI) and STS (CABG) databases: NEJM 2012



Comparative Effectiveness of Multivessel Coronary Bypass Surgery and Multivessel Percutaneous Coronary Intervention

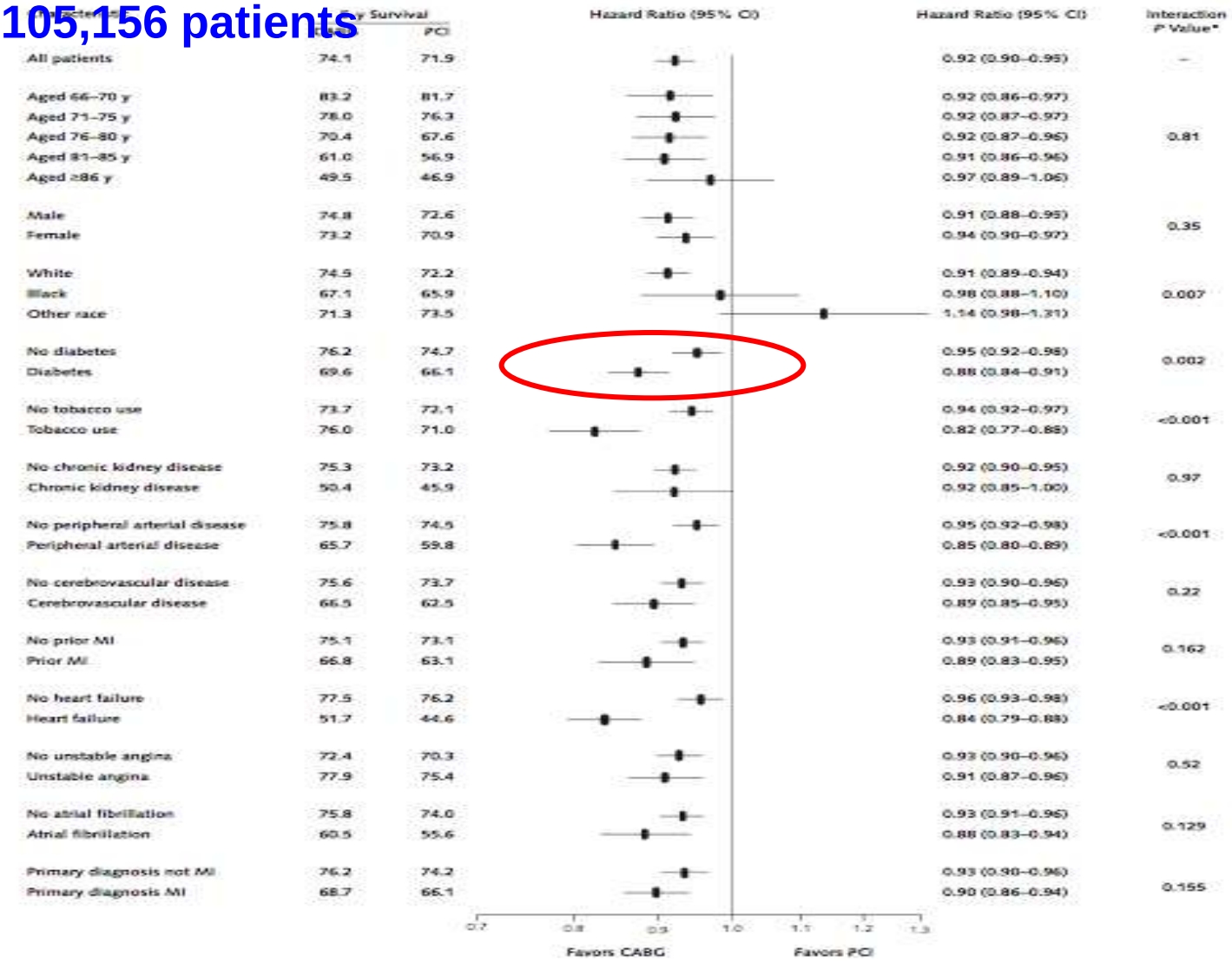
AIM 2013

A Cohort Study

Mark A. Hlatky, MD; Derek B. Boothroyd, PhD; Laurence Baker, PhD; Dhruv S. Kazi, MD, MS; Matthew D. Solomon, MD, PhD;

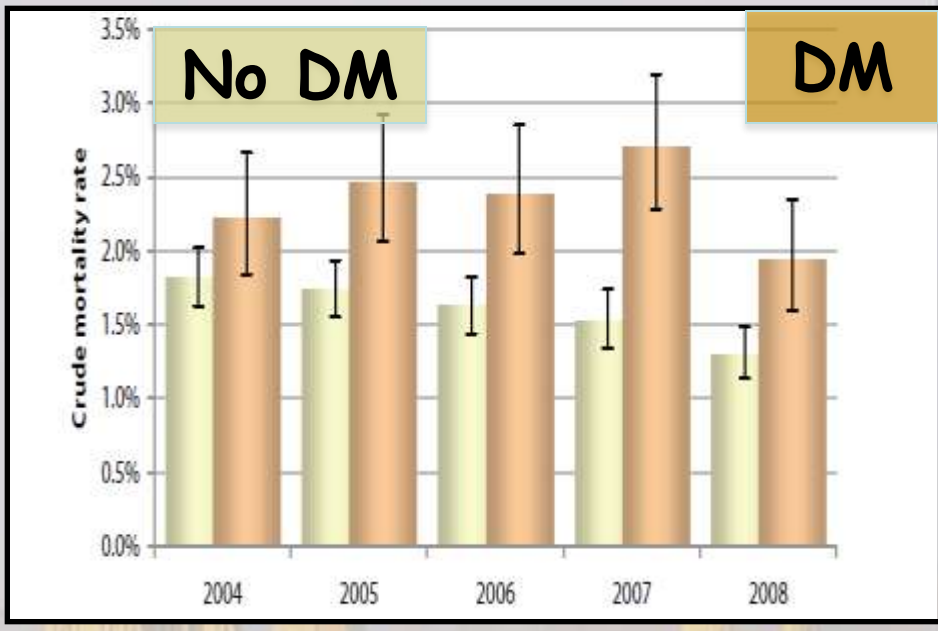
Figure 2. 5-y Kaplan–Meier survival estimates and CABG–PCI hazard ratios and associated 95% CIs in subgroups of the propensity score–matched cohort.

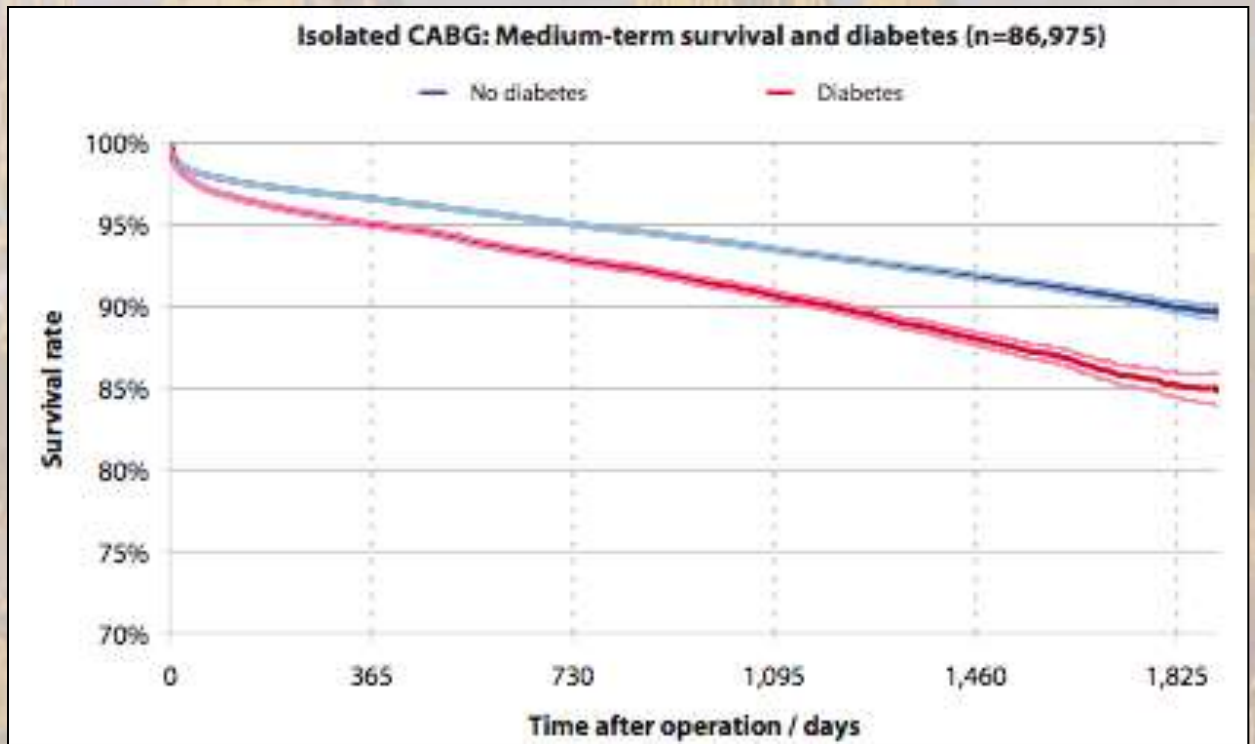
105,156 patients



6th UK and Ireland SCTS Database (2009)

		MORTALITY	
	5 yr: 2004-08	All	Elective
Total	114300	1.8%	1.1%
NonDM	88280 (77%)	1.6%	1.0%
DM	26020 (23%)	2.6%	1.6%





Fundamental Question

WHY DOES CABG HAVE SUCH A SURVIVAL BENEFIT OVER PCI ?

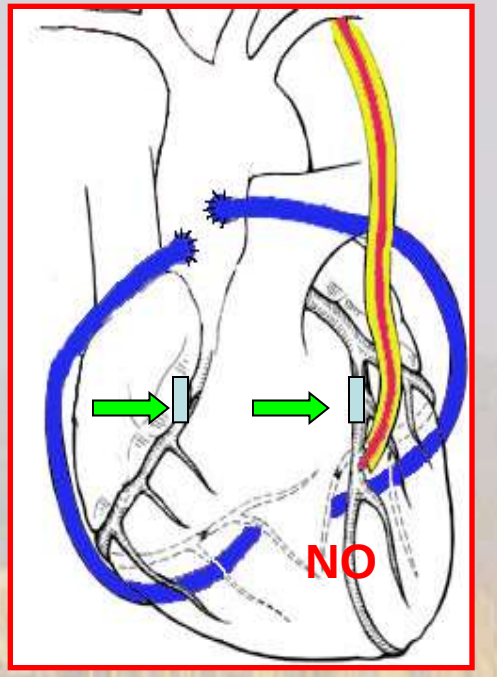
Anatomically, atheroma is mainly located in the proximal coronary arteries

During CABG placing bypass grafts to the **MID CORONARY VESSEL** has **TWO** effects

(i) Complexity of '**CULPRIT**' lesion irrelevant

(ii) over the long term, CABG offers prophylaxis against **FUTURE** 'culprit' lesions by protecting whole zones of vulnerable proximal myocardium in diffusely unstable coronary endothelium (especially diabetes)

- In contrast, PCI with stents ( ) only treats **'SUITABLE'** localised proximal 'culprit' lesions but has **NO PROPHYLACTIC BENEFIT** against new disease (proximal to, within or distal to the stent)



2. IMA graft is a permanent 'Nitric Oxide Eluting Stent' that ensures its own patency and protects native coronary circulation (NEJM 1988)

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)

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

Evidence Basis for an Intervention (CABG vs PCI)

	RCT The Gold standard	Registries (Propensity Matched)
Strengths	No Bias	>10,000s of Patients Represent real clinical practice (1/20 RCT of CABG vs PCI) Relatively Cheap
Potential Weaknesses	Small numbers of patients Small % of eligible population Atypical patient populations Short duration of follow-up Large numbers of cross-overs (19/20 RCT of CABG vs PCI) EXPENSIVE	Confounding/Bias

Always must consider TWO CRUCIAL factors
(i) % of eligible population included in trials
(ii) Length of follow-up

Summary and Conclusions

- Consistent evidence from RCTs, Meta-analyses and Propensity Matched Registries that CABG results in better survival and reduced MI and repeat revasc in comparison to PCI
- Strongest RCT evidence from Hlatky collaborative analyses
  - Significant survival benefit for DM with CABG at 6 years (HR 0.7)
- Propensity Matched Registry Data (reflecting real clinical practice) consistently show survival benefit of CABG over PCI in DM
- BARI 2D (low severity of CAD)
  - No benefit of PCI vs OMT
  - CABG reduced risk of MI (and also reduced absolute mortality by3%)
- SYNTAX trial showed that at 5 years DM patients have better survival, reduced MI and repeat revasc with CABG vs PCI
- FREEDOM trial confirms 5% survival benefit of CABG
- In ALL 78,000 elective CABG patients in UK (2004-08) 1.1% mortality
- Survival benefit of CABG vs stents accrues with time

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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.,

Increased EDRFs (especially NO) produced by IMA results in superior graft patency and additionally protects native coronary artery circulation

% progression of native CAD		
	IMA	SVG
Kitamura (1987)	18	46
Loop (1996)	39	67
Manninen (1998)	26	45
Hamada (2001)	12	38
Borges (2010)	17	44
AVERAGE	22	48

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; Gaku Nakazawa, MD; Felix C. Tanner, MD; Renu Virmani, MD

- impairs re-endothelialization,
- creates pro-thrombotic environment
- impairs distal endothelial function

9.1.2 Type of intervention: coronary artery bypass grafting vs. percutaneous coronary intervention

All RCTs have shown higher rates of repeat revascularization procedures after PCI, compared with CABG, in diabetic patients.[29] A recent meta-analysis on individual data from 10 RCTs of elective myocardial revascularization[29] confirms a distinct survival advantage for CABG over PCI in diabetic patients. Five-year mortality was 20% with PCI, compared with 12.3% with CABG (OR 0.70, 95% CI 0.56–0.87), whereas no difference was found for non-diabetic patients; the interaction between diabetic status and type of revascularization was significant. The AWESOME trial[113] randomized high-risk patients

Table 16 Specific recommendations for diabetic patients

CABG should be considered, rather than PCI, when the extent of the CAD justifies a surgical approach (especially MVD), and the patient's risk profile is acceptable.	IIa	B	29, 34, 113, 116