

Diabetes and Outcomes of PCI with DES and CABG

Should Diabetes Affect Decisions on
PCI vs. CABG ?

Duk-Woo Park, MD, PhD

Asan Medical Center, Seoul, Korea

Duke Clinical Research Institute, Durham, NC

 CardioVascular Research Foundation

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Thanks Chairman

I'm going to talk about the impact of diabetes on choice of
revascularization strategy (PCI vs. CABG).

Disclosure Statement of Financial Interest

I, (DUK-WOO PARK) DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

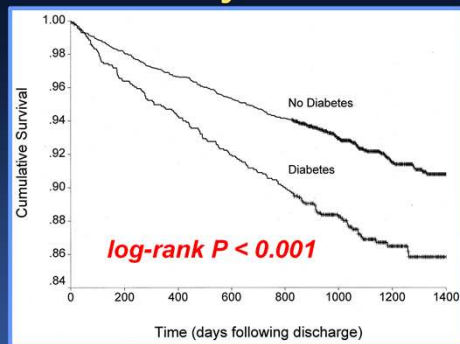
I have nothing to disclose

Diabetes Mellitus (DM) : A Growing Epidemic

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

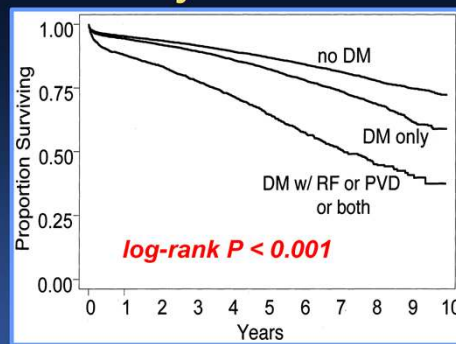
Diabetic Impact on PCI and CABG outcomes

Mortality after PCI



Wilson S R et al. *Dia Care* 2004;27:1137-1142

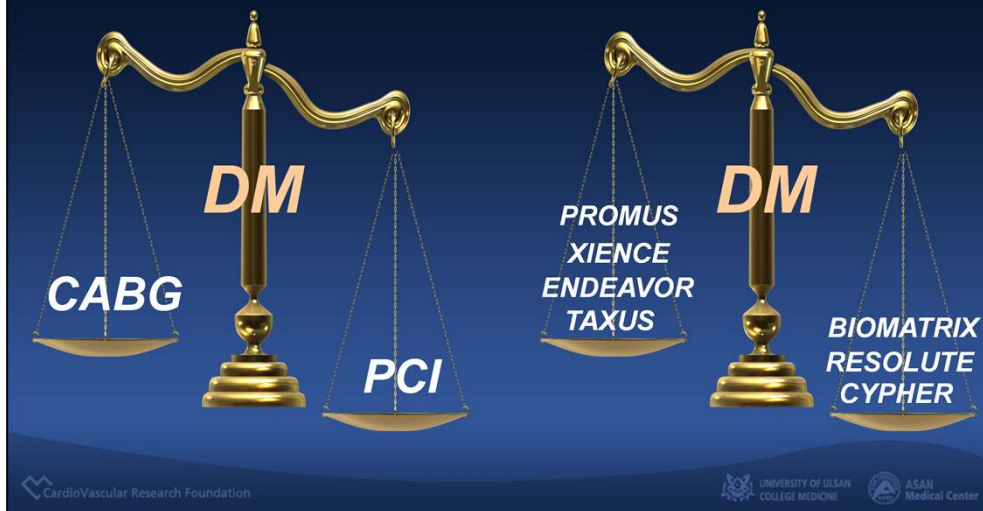
Mortality after CABG



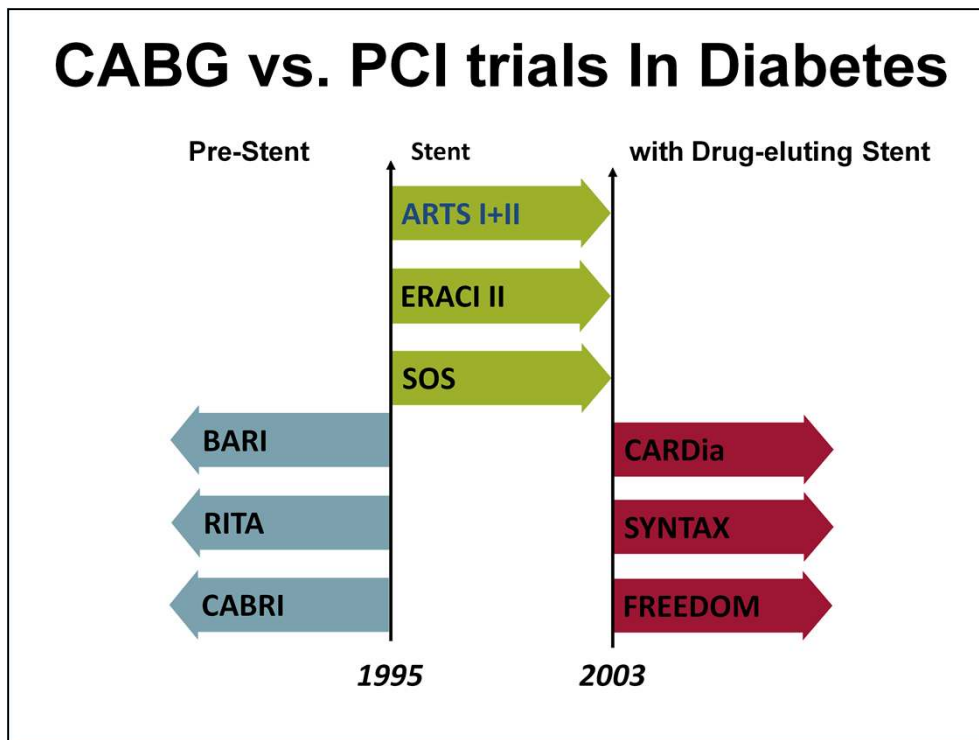
Leavitt BJ et al. *Circulation* 2004;110:II-41-44

What about diabetic impact on PCI and CABG outcomes?
compared to non-diabetic patients, diabetes itself was significantly
associated with higher risk of mortality after PCI and after CABG.

DM Influence on Comparative Effectiveness & Choice of Treatment

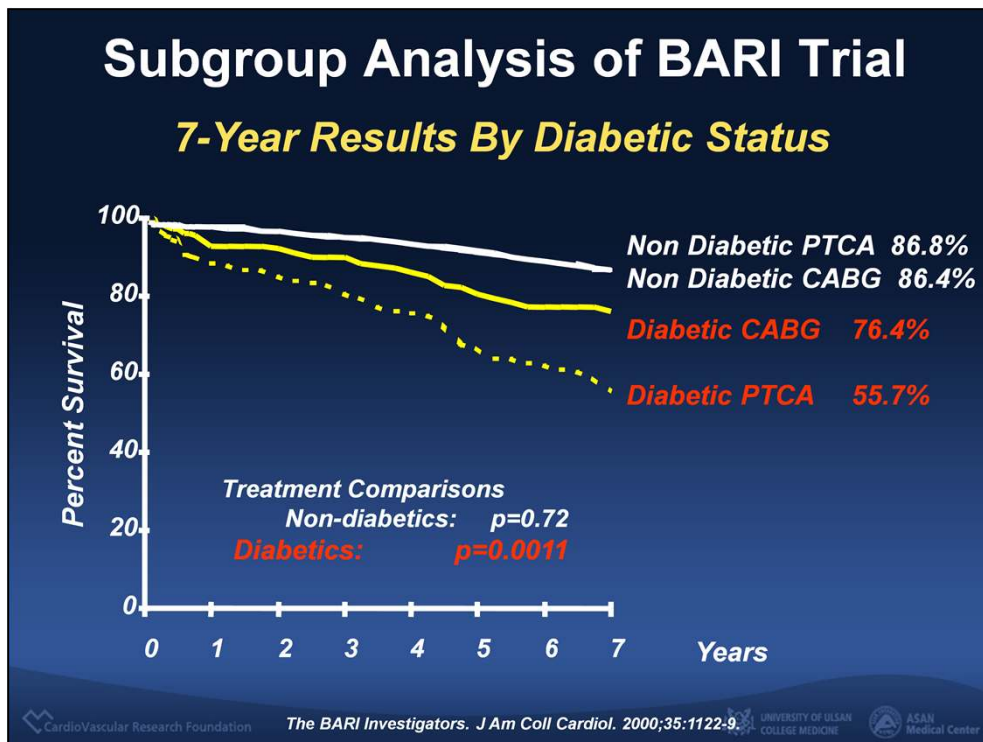


Therefore, the presence of diabetes mellitus can influence the choice of revascularization strategy and specific stent type.



CABG versus PCI trials have always been a big issue and lots of debates exist.

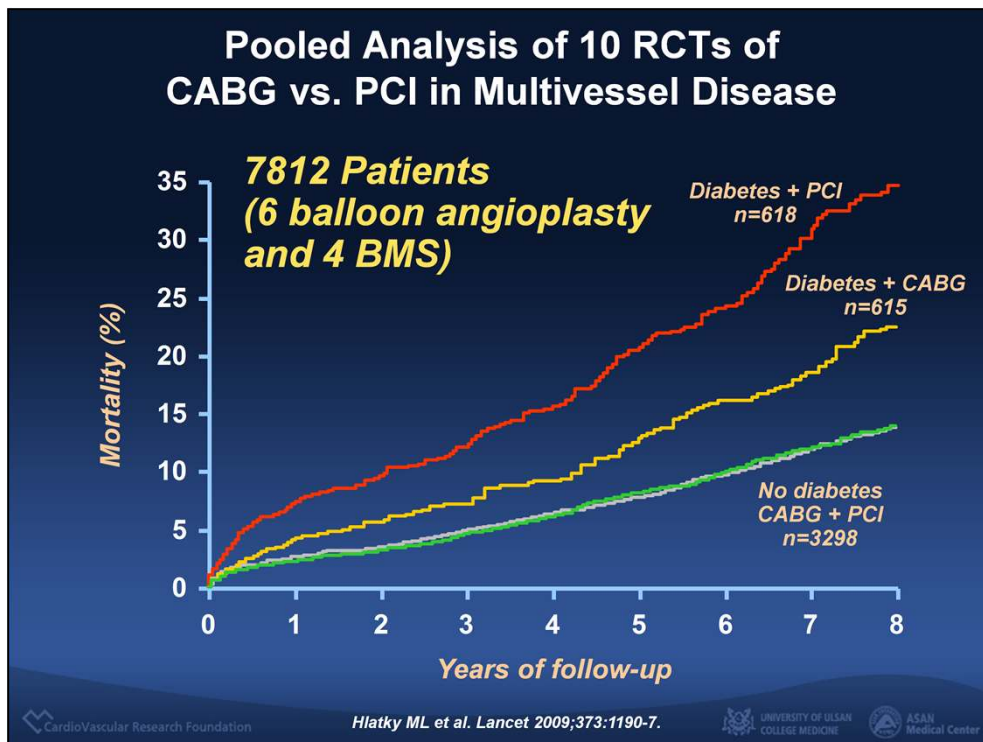
We can divide the revascularisation trials into three groups.



For a very long-time, at least more than 10 years,

Subgroup analysis of BARI trial has been regarded as a Bible of revascularization strategy for diabetic patients.

This study led to an NHLBI alert recommending that patients with diabetes and multivessel disease undergo CABG as the preferred mode of revascularization.



Similarly, large-sized pooled analysis showed similar results;
Long-term mortality is similar after CABG and PCI in nondiabetic patients,
but CABG was a better option for diabetic patients.
However, none of the trials included drug-eluting stents. So, application to
clinical practice was very limited.

CABG vs PCI with DES in Diabetes

- BMS RCTs
- CARDia
- SYNTAX
- FREEDOM



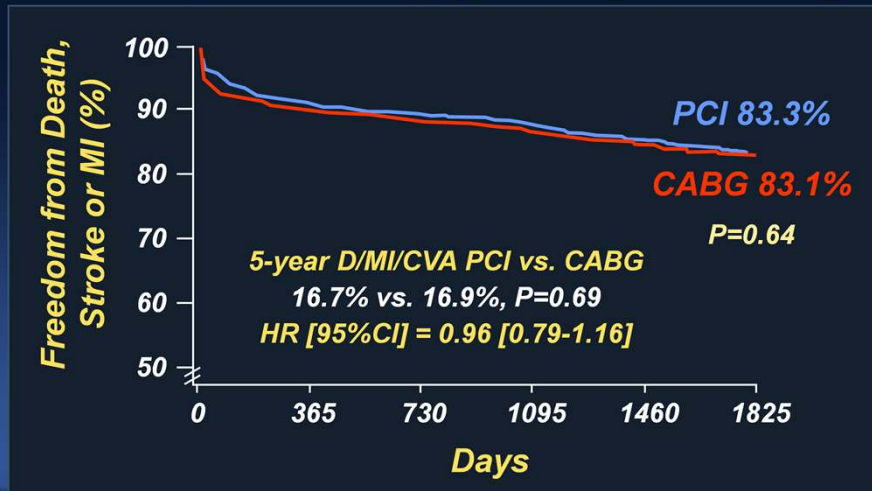
*Diabetes
should **not**
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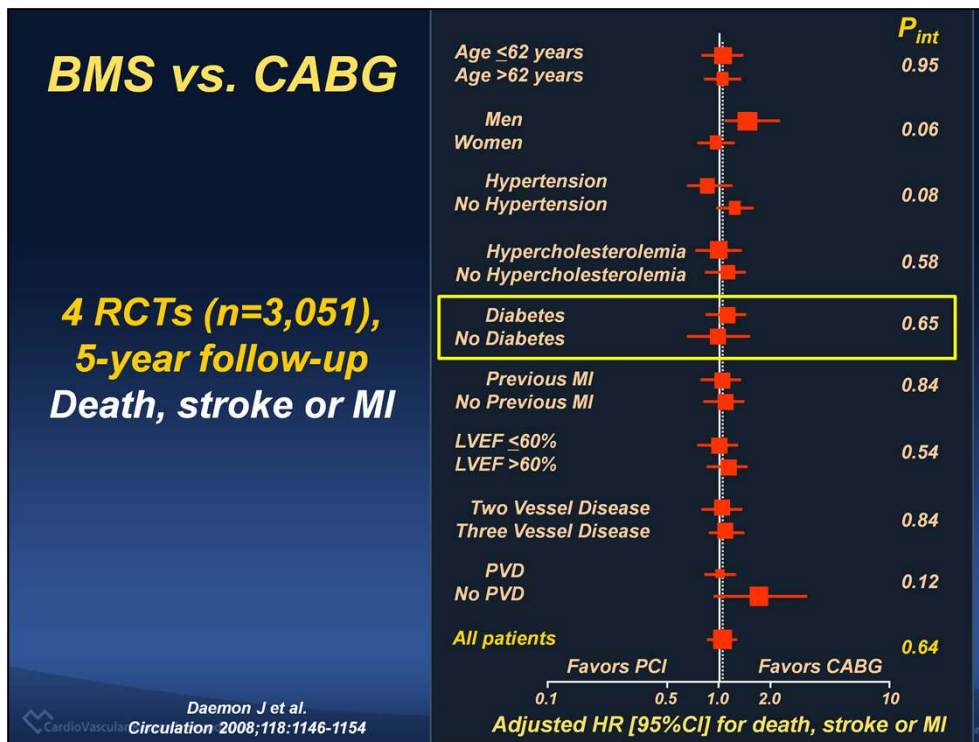
All of previous studies was already out of date.

More strong evidence from several trial were presented.

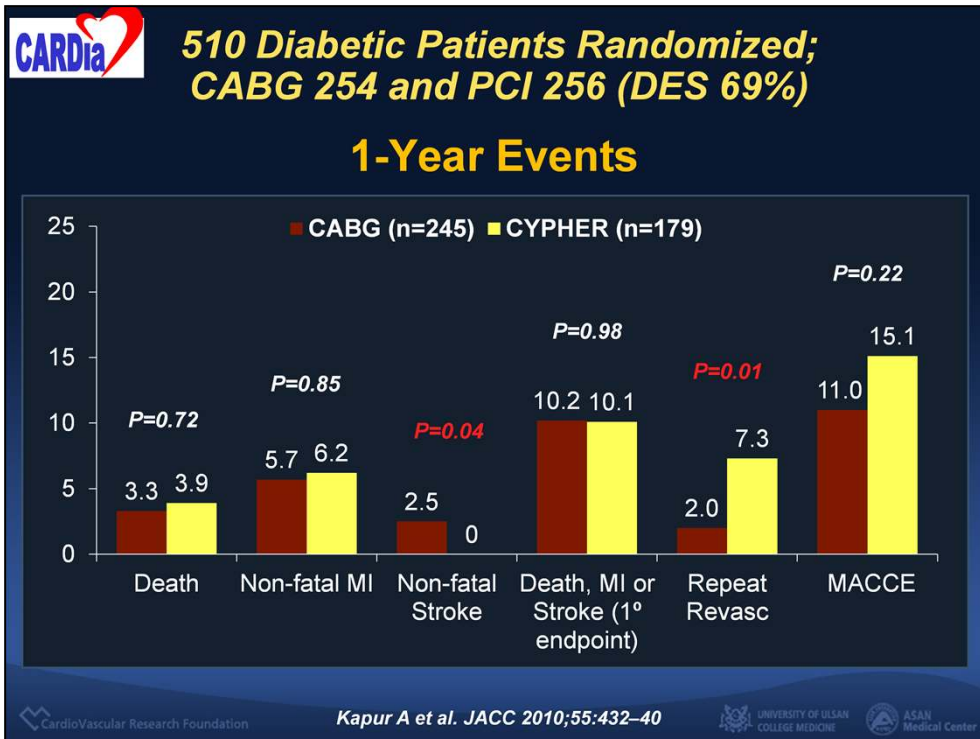
Bare Metal Stents vs. CABG

4 RCTs (ARTS, ERACI-II, MASS-II, SoS), 3,051 pts,
94% IMA, 5-year follow-up (pt level pooled analysis)





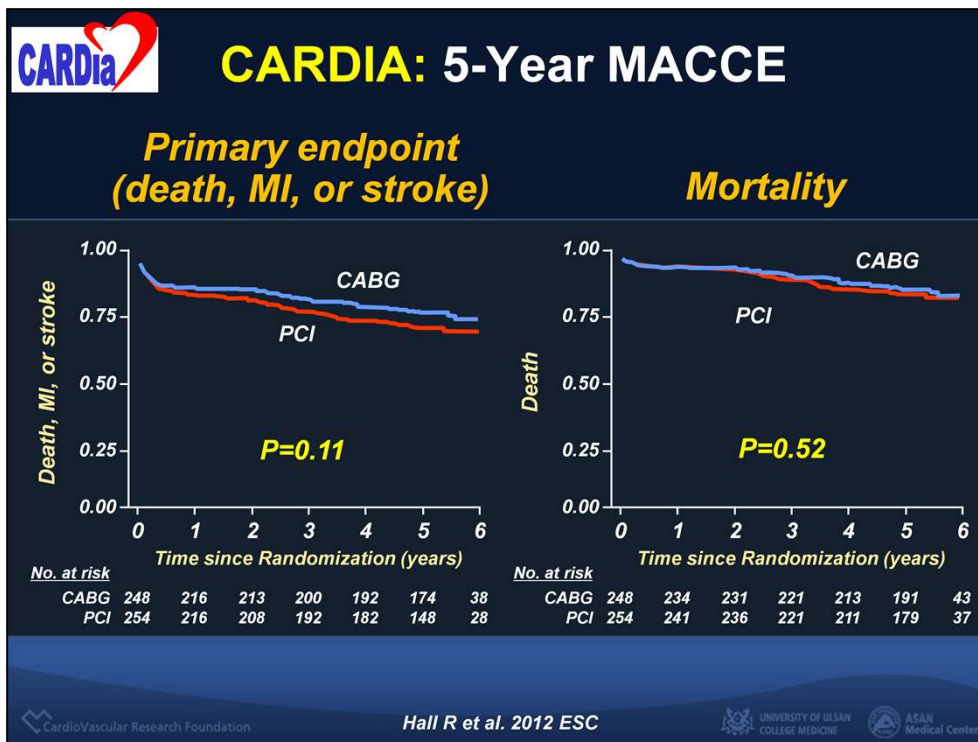
In this trial, PCI showed a similar long-term mortality compared to CABG both in diabetic and nondiabetic patients.



Cardia trial was first, diabetes-specific clinical trial.

254 treated with CABG, 256 treated with PCI.

Primary endpoint (death, MI, or stroke) was similar between the 2 groups.



For 5-year long-term follow-up, this results was maintained.

SYNTAX: Death, CVA, MI to 5 Years Impact of Diabetes

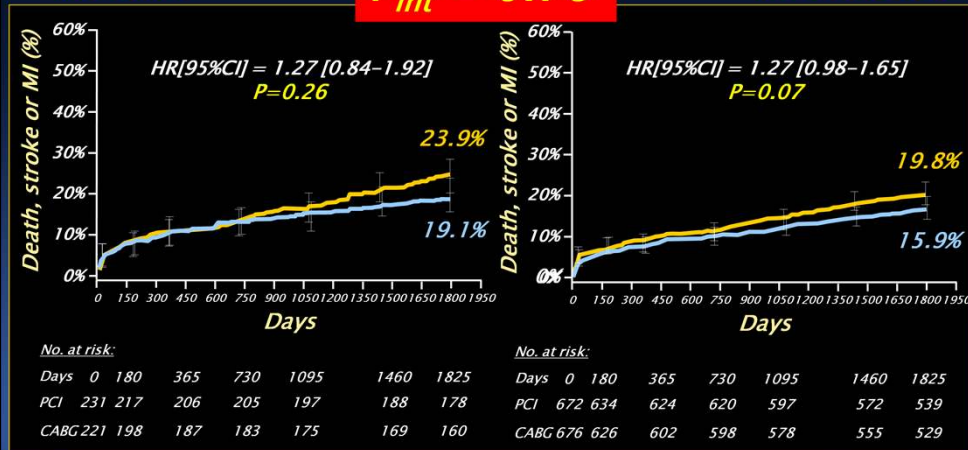
Subgroup Analysis of Diabetes
(452 DM; CABG 221 and TAXUS 231)

— CABG — TAXUS

Diabetes

$P_{int} = 0.76$

No diabetes



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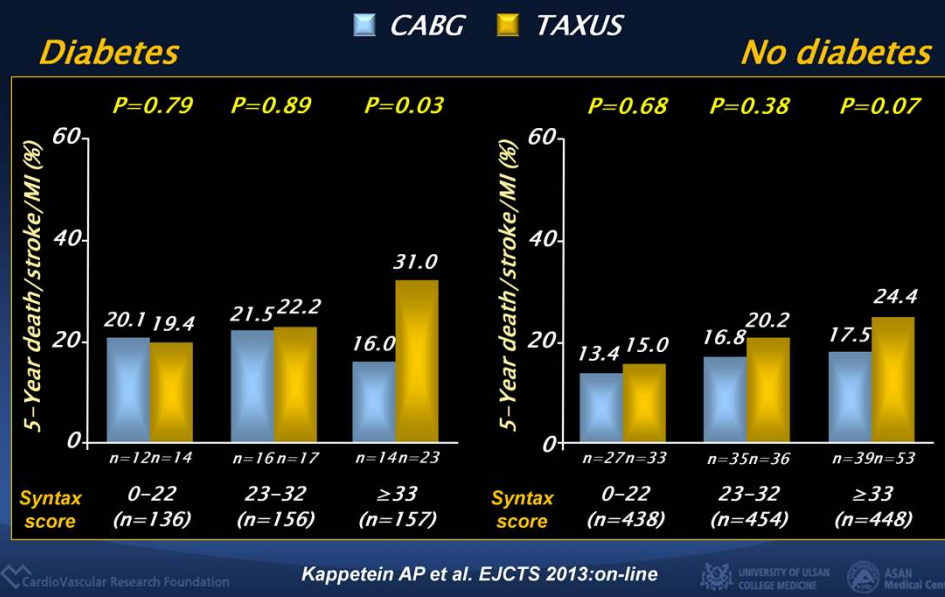
Kappetein AP et al. EJCTS 2013;on-lin

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SYNTAX trial is largest trial comparing old-version DES TAXUS and CABG for multivessel disease patients.
Total population was 1,800 patients.
Among them,

Death, CVA, MI to 5 Years: Impact of Diabetes and Syntax Score



SYNTAX score;
Low, intermediate, high

FREEDOM Trial

Patients with DM and multivesel CAD (N=1900)

Randomized 1:1

***Contemporary PCI
with DES
N=953***

***Contemporary CABG
with or without CPB
N=947***

***Contemporary background therapy
for CAD and diabetes***

Primary endpoint; composite of all-cause death, nonfatal MI, and stroke

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Farkouh ME, et al. Am Heart J. 2008;155:215-23.

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However, previous Cardia trial was underpowered and SYNTAX was subgroup analysis;

Interpretation was just hypothesis-generating.

FREEDOM Trial is landmark trial to compared DES vs. CABG for diabetic patients. .



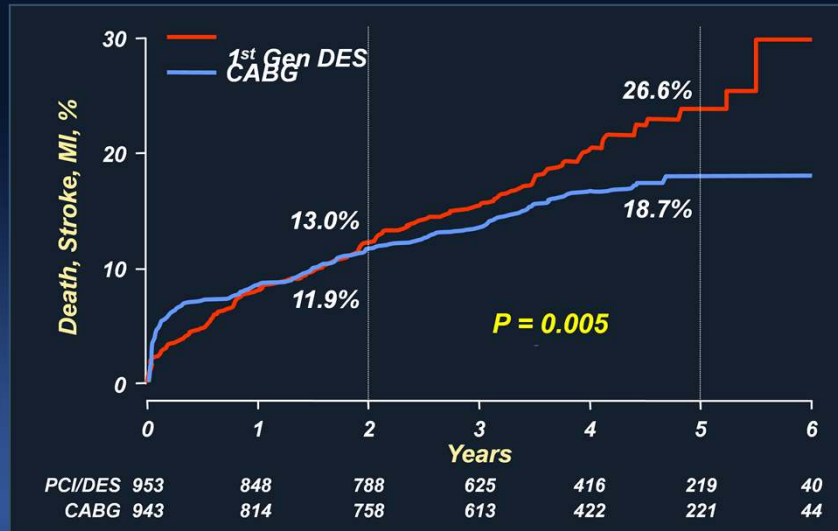
FREEDOM: 1900 pts with diabetes +MVD randomized to SES/PES vs. CABG

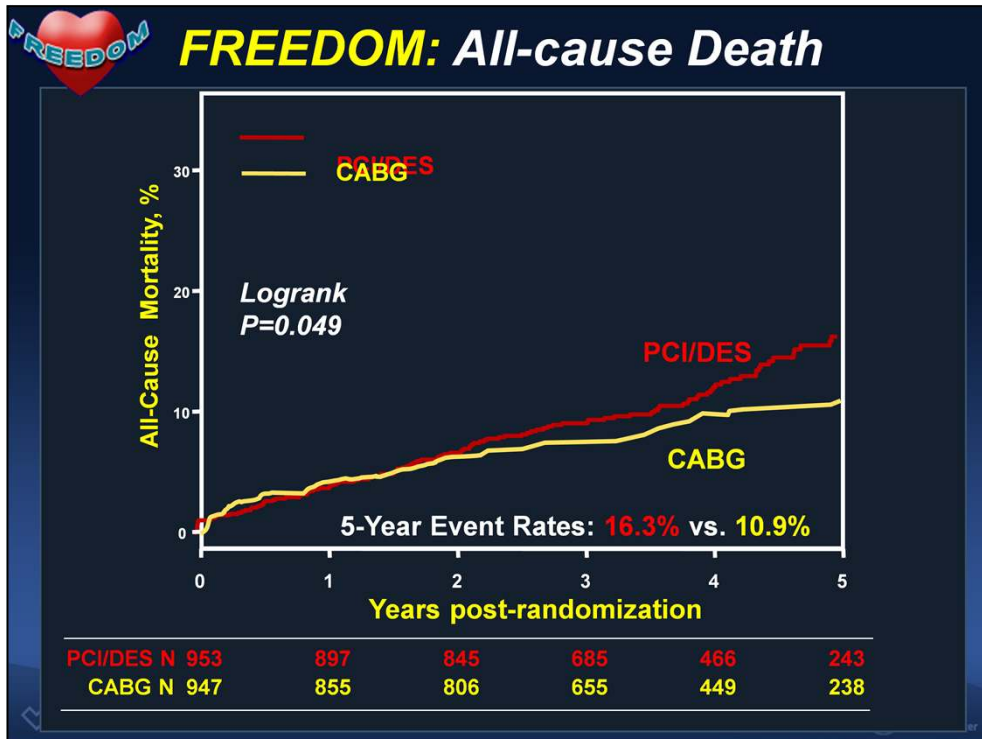
Characteristic	SES/PES (N=953)	CABG (N=947)	P-value
Age (years)	63.2 ± 8.9	63.1 ± 9.2	0.78
Male sex	73.2%	69.5%	0.08
Use of insulin	33.8%	30.9%	0.19
Duration of diabetes – yrs	10.1 ± 8.9	10.31 ± 9.0	0.49
Hemoglobin A1c – %	7.8 ± 1.7	7.8 ± 1.7	0.86
Unstable angina	31.9%	29.5%	0.25
3VD	82.3%	84.5%	0.22
EuroSCORE	2.7 ± 2.4	2.8 ± 2.5	0.52
SYNTAX score	26.2 ± 8.4	26.1 ± 8.8	0.77

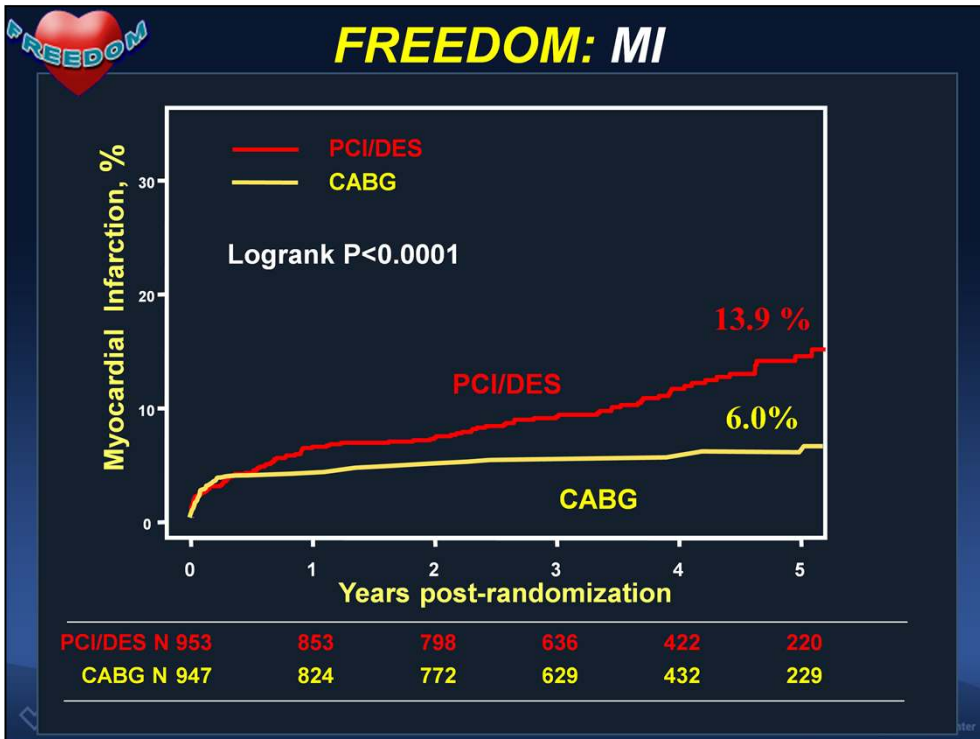


1° Endpoint: Death, Stroke, or MI

FU: minimum 2 years, median 3.8 years

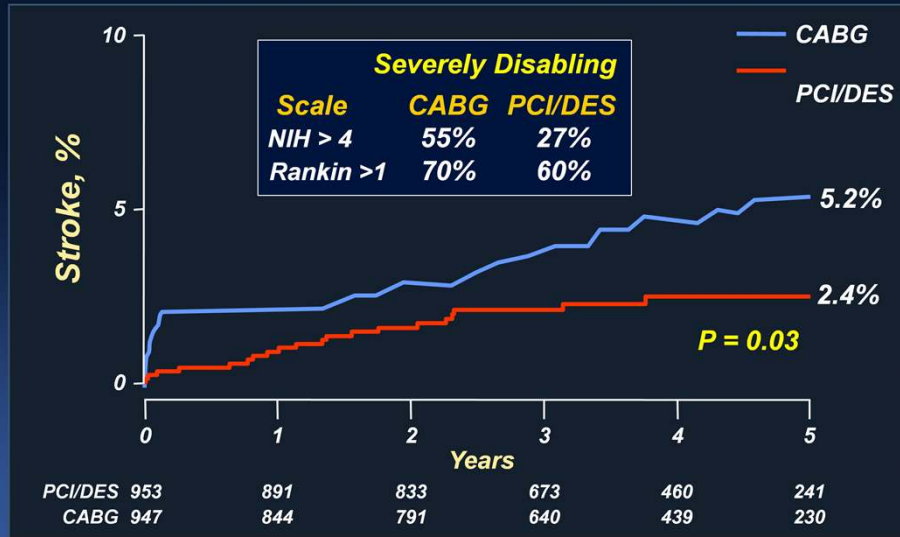


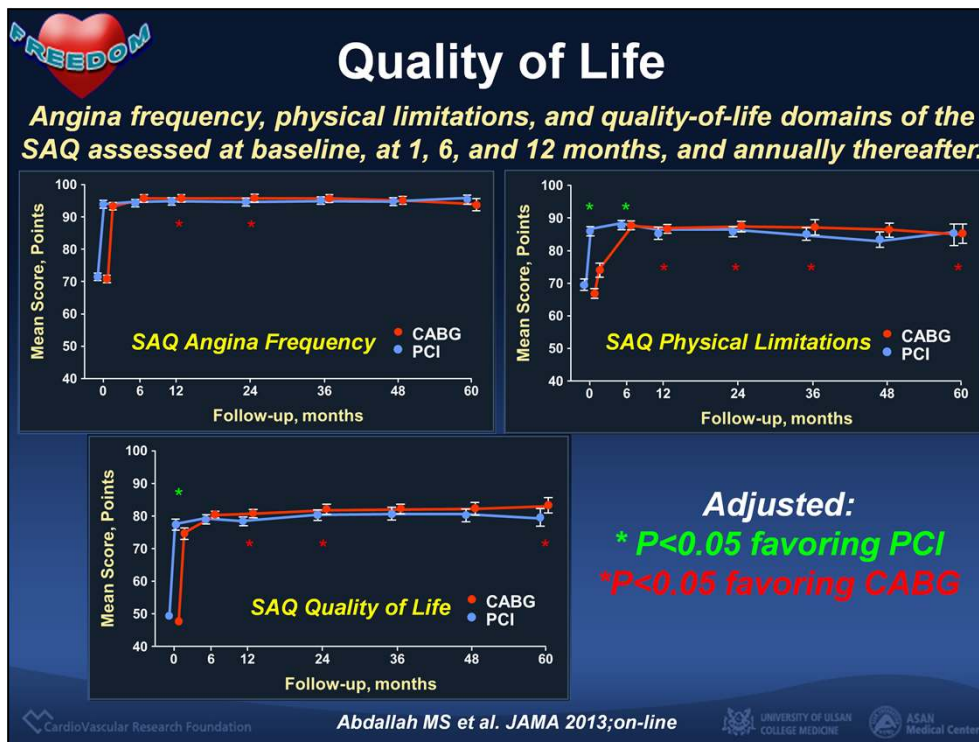






FREEDOM: Stroke





PCI resulted in more rapid improvement in health status and quality of life compared with CABG,

However, these benefits were transient and largely restricted to the first month of follow-up.

Between 6 months-2 years, health status was slightly better with CABG across a range of cardiac specific domains including angina relief, physical function, and overall quality of life.

Beyond 2 years, there were no consistent differences in any health status or quality-of-life domains between the CABG and PCI strategies.



CABG Again Outshines Stenting for Some Patients With Coronary Artery Blockage

Mike Mitka, MSJ

LOS ANGELES—A study of patients with diabetes in need of multivessel revascularization has shown that coronary artery bypass graft (CABG) surgery produces better outcomes than percutaneous coronary intervention (PCI). The study, highlighted here in November during the annual Scientific Sessions of the American Heart Association (AHA), adds to the growing list of investigations showing superiority of CABG over PCI in a variety of patient populations.

Yet mounting evidence suggests that PCI continues to be performed at rates higher than is appropriate. So why does it remain difficult for interventional cardiologists to embrace this corner of the evidence-based medicine world?

At the AHA meeting, attendees heard the results from the Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial. The FREEDOM researchers randomized 1900 patients with diabetes and

"CABG surgery is the preferred intervention for patients with diabetes and multivessel disease," said Valentin Fuster, MD, PhD, senior author of FREEDOM

103 549 patients who underwent PCI for treatment of 2-vessel or 3-vessel coronary artery disease without acute myocardial infarction from 2004 through 2008 (Weintraub WS et al. *N Engl J Med*. 2012;366[16]:1467-1476).

William S. Weintraub, MD, one of ASCERT's principal investigators and director of the Christiana Center for Outcomes Research in Wilmington, Del, said the FREEDOM trial should reinforce the superiority of CABG in revascularization of complicated patients. "Overall, surgery has been in decline for a number of years, and we've moved to less invasive procedures fairly easily," said Weintraub in an interview. "But with FREEDOM, you are moving the needle back toward surgery."

Fred H. Edwards, MD, another principal investigator with ASCERT and emeritus professor in the department of surgery at the University of Florida Academic Health Center in Jacksonville, said his trial and FREEDOM should give clinicians the evidence they need to make better-informed deci-



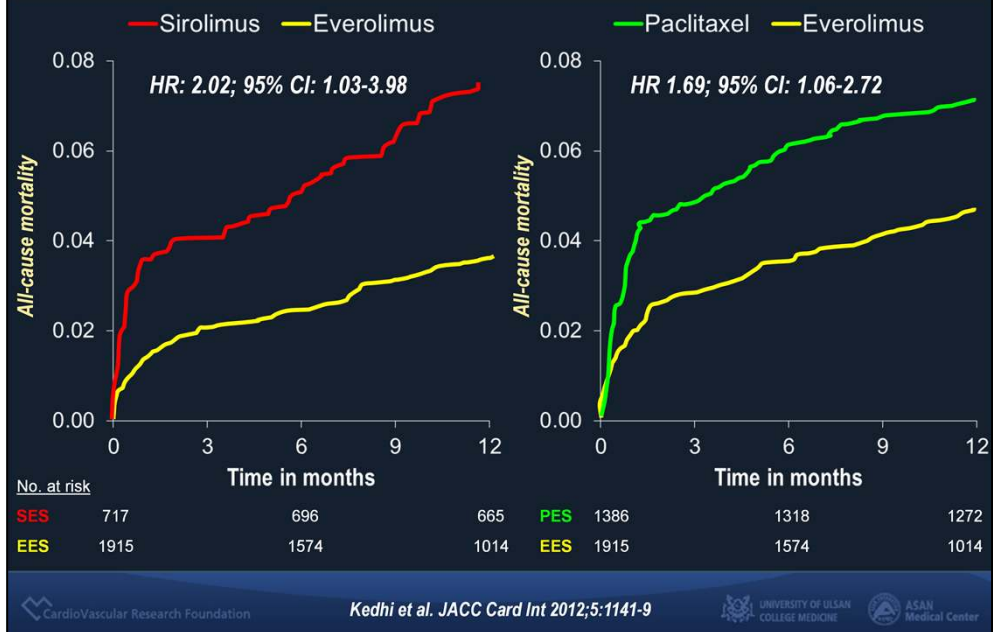
New findings suggest that coronary artery bypass graft surgery produces better outcomes than stenting in patients with diabetes who require multivessel revascularization.

JAMA, January 2, 2013—Vol 309, No. 1

Question still remains:

- ➔ Diabetic with single vessel CAD
- ➔ Outcomes with 2nd and 3rd generation DES
- ➔ Outcomes with more potent antiplatelet

EES in Patients with Diabetes: **SCAAR**



A Pooled Analysis of 3 Registry (5775 Individual Patient Data)

	MAINCOMPARE Registry	ASAN-Multivessel Registry	ASAN-MAIN Registry
Study type	Multi-center, observation	Single-center, observation	Single-center, observation
# of patients	PCI 1102 CABG 1138	PCI 1547 CABG 1495	PCI 276 CABG 469
Target subjects	Left main	Multivessel	Left main
Age	62	63	61
Male	72%	71%	72%
Diabetes	32%	29%	32%
Duration (median)	5.2 years	5.6 years	7.5 years
Publications	NEJM 2008;358:1781-92 JACC 2010;56:117-124	Circulation 2008;117:2079-86 JACC 2011;57:128-37	JACC 2010;56:1366-75

What about Asian Data...

We performed a pooled analysis of 5775 patients from 3 large observational involving patients with multivessel or left main disease.

Adjusted Outcomes

Subjects	HR	95% CI	P-value	Interaction P (DM vs. NON-DM)
Death				
Non-DM	1.15	0.88-1.50	0.39	0.27
DM	1.15	0.88-1.51	0.30	
DM, insulin	0.88	0.48-1.62	0.68	
DM, non-insulin	0.89	0.58-1.39	0.61	
Death, Q-MI, Stroke				
Non-DM	0.99	0.78-1.26	0.96	0.97
DM	1.00	0.79-1.26	0.97	
DM, insulin	0.89	0.51-1.56	0.68	
DM, non-insulin	1.05	0.70-1.58	0.81	
Repeat revascularization				
Non-DM	3.55	2.61-4.83	<0.001	0.08
DM	3.56	2.62-4.83	<0.001	
DM, insulin	6.42	2.83-14.53	<0.001	
DM, non-insulin	5.71	3.50-9.31	<0.001	

The long-term risks of mortality and composite serious outcomes were not different between PCI and CABG in non-diabetic and diabetic patients.

These relative treatment effects were not modified by diabetic status.

MAIN-COMPARE Registry ; DM and Left Main Revascularization

Outcomes	Crude		Multivariate Adjusted		Interaction p for Diabetic Status	Inverse Probability of Treatment Weighted		Interaction p for Diabetic Status
	HR (95% CI)	p Value	HR (95% CI)	p Value		HR (95% CI)	p Value	
Overall								
Death	0.747 (0.507–1.101)	0.14	1.109 (0.735–1.674)	0.621†	0.902	0.954 (0.623–1.462)	0.828	0.156
Death, QMI, or stroke	0.737 (0.518–1.048)	0.089	1.070 (0.735–1.556)	0.724†	0.684	0.962 (0.652–1.419)	0.846	0.934
TVR	3.863 (2.344–6.367)	<0.0001	5.102 (2.973–8.756)	<0.0001§	0.233	4.309 (2.278–8.151)	<0.0001	0.919
Diabetic patients								
Death	0.744 (0.391–1.417)	0.369	0.793 (0.396–1.586)	0.511		0.547 (0.24–1.245)	0.150	
Death, QMI, or stroke	0.764 (0.434–1.345)	0.351	0.926 (0.522–1.644)	0.793¶		0.782 (0.377–1.621)	0.509	
TVR	5.898 (2.277–15.275)	0.0003	6.213 (2.397–16.106)	0.0002¶		7.668 (2.757–21.32)	<0.0001	
Nondiabetic patients								
Death	0.755 (0.464–1.229)	0.258	1.05 (0.623–1.768)	0.856**		1.004 (0.586–1.718)	0.989	
Death, QMI, or stroke	0.733 (0.467–1.149)	0.176	1.030 (0.636–1.670)	0.903††		0.963 (0.586–1.583)	0.882	
TVR	3.168 (1.758–5.710)	0.0001	4.273 (2.264–8.066)	<0.0001††		2.943 (1.357–6.384)	0.006	

EDITORIAL COMMENT

Diabetes Mellitus Does Not Unsweeten Left Main Intervention*

David O. Williams, MD,† J. Dawn Abbott, MD‡
Boston, Massachusetts; and Providence, Rhode Island

unprotected LMCA disease. First, in the subset of patients that had LMCA disease, there was no significant difference in composite rate of major adverse cardiac or cerebrovascular events at 1 year between the PCI and coronary artery bypass grafting (CABG) groups (15.8% vs. 13.7%, $p = 0.44$, respectively). Rates of repeat revascularization, however, were significantly higher among PCI patients (11.8% vs. 6.5%, $p = 0.02$), whereas stroke was more common among CABG patients. These data support the use of PCI with drug-eluting stents (DES) as a reasonable alternative to CABG for patients with LMCA disease. A second observation, however, qualifies this conclusion. When SYNTAX investigators analyzed outcomes according to LMCA disease involvement and the extent of associated coronary

These findings were even consistent with significant left main disease.

Treatment Effect Gap Over Time in Diabetes



Potential Explanation for this.....

1. Marked advances in PCI devices and adjunctive pharmacology
2. Marked improvement in background intensive medical therapy

Over time,.. treatment effect gap between CABG and PCI was alleviated over the time.

A potential explanation is that marked advances in PCI devices and adjunctive pharmacology may lessen the relative benefits of CABG over PCI.

And, background intensive medical therapy ensure the clinical equivalence between CABG and PCI for mortality and hard clinical end points.

Evidence-based Medicine

The Diabetic Pt: CABG vs. PCI

- With current DES, the benefits of PCI compared to CABG in terms of lesser invasiveness, fewer major peri-procedural complications, reduced stroke, better early QOL, more rapid return to work, etc., outweigh the greater rate of repeat revascularization, as long as mortality is not increased. **Thus, I (and my pts) currently prefer PCI in nearly all pts with SYNTAX score ≤ 22 , and most with SYNTAX score 22 – 33.**
- Most pts with SYNTAX score ≥ 33 who are good surgical candidates should be referred to CABG

Suggestions for DM Revascularization in Current Practice

		Severity of Diabetes Status		
		NON-DM	OHA	Insulin
Lesion Complexity	High	CABG	CABG	CABG
	Medium	PCI / CABG	PCI / CABG	CABG
	Low	PCI / CABG	PCI / CABG	PCI / CABG

- *In practice, individualized judgment is still required*
- *Anatomic and other patient variables still matter*

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Both severity of diabetic status and lesion complexity simultaneously influence the relative benefit between CABG and PCI.

Therefore, it should be considered when evaluating treatment options in diabetic patients with multivessel disease.

Question or Comments ?

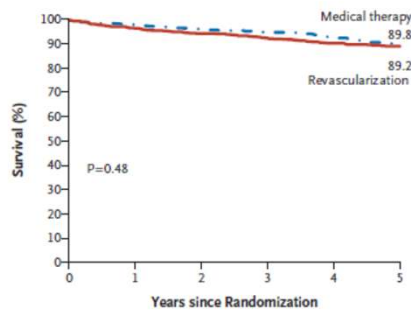


BACK-UP SLIDES

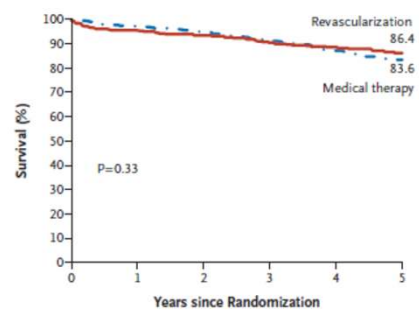
BARI-2D

***2,368 stable CAD patients randomized
between CABG vs OMT or PCI vs OMT***

Survival in PCI Stratum



Survival in CABG Stratum



BARI 2D Investigators. N Engl J Med 2009;360:2503-15.



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%)

FREEDOM Conclusions

CABG in the Default Therapy for Nearly All Patients with Diabetes

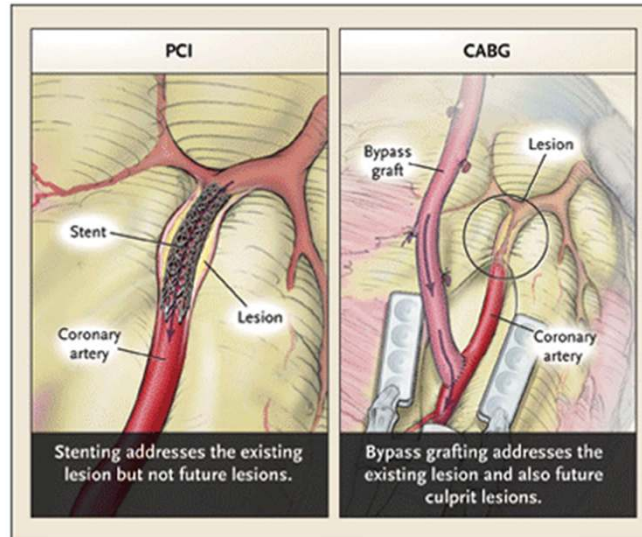
- For Diabetics with multivessel CAD (non-LM), CABG was superior to 1st Generation DES (TAXUS Express 43%, Cypher 57%)
- Among patients with lesion complexity (Syntax <22) DES may be an alternative to CABG
- Question still remains:
 - Diabetic with single vessel CAD
 - Outcomes with 2nd and 3rd generation DES
 - Outcomes with more potent antiplatelet

		Diabetes	
		Oral Meds	Insulin
Lesion complexity	High	CABG	CABG
	Medium	CABG	CABG
	Low	TAXUS or CABG	CABG

This slide uses the SYNTAX score to demonstrate that diabetic patients with a SYNTAX score in the highest tercile, that is, over 33 will benefit from CABG. It also suggests that all patients with insulin treated diabetes may do better with CABG.

How do we explain this?



Gersh and Frye. New Engl J Med 2005;352:2235



Revascularisation in Diabetes

Recommendations	Class	Level
Optimal medical treatment should be considered as preferred treatment in patients with stable CAD and DM unless there are large areas of ischaemia or significant left main or proximal LAD lesion.	IIa	B
CABG is recommended in patients with DM and multivessel or complex (SYNTAX Score >22) CAD to improve survival free from major cardiovascular events.	I	A
PCI for symptom control may be considered as an alternative to CABG in patients with DM and less complex multivessel CAD (SYNTAX score ≤22) in need of revascularization.	IIb	B
Primary PCI is recommended over fibrinolysis in DM patients presenting with STEMI if performed within recommended time limits.	I	B
In DM patients subjected to PCI, DES rather than BMS are recommended to reduce risk of target vessel revascularization.	I	A
Renal function should be carefully monitored after coronary angiography/PCI in all patients on metformin.	I	C
If renal function deteriorates in patients on metformin undergoing coronary angiography/PCI it is recommended to withhold treatment for 48 h or until renal function has returned to its initial level.	I	C