State-of-the-Art PCI vs. CABG in DM and MVD;

DEFINE-DM Trial

Hoyun Kim, MD
Department of Cardiology,
University of Ulsan College of Medicine,
Asan Medical Center, Seoul, Korea

Disclosure

- I have nothing to disclose.

Diabetes and Coronary Artery Disease

- Diabetes is a common comorbidity among patients with coronary artery disease.

- Diabetic patients have a more aggressive form of atherosclerosis, more extensive coronary artery disease, and higher risk of ischemic cardiovascular events and mortality.

Circulation 2015;132:923-931
Circulation 2021;144:1380-95
Circulation 2019;139:2742-53

- Diabetes is a major determinant of adverse clinical events after myocardial revascularization.

The Lancet Diabetes & Endocrinology 2013;1:317-328
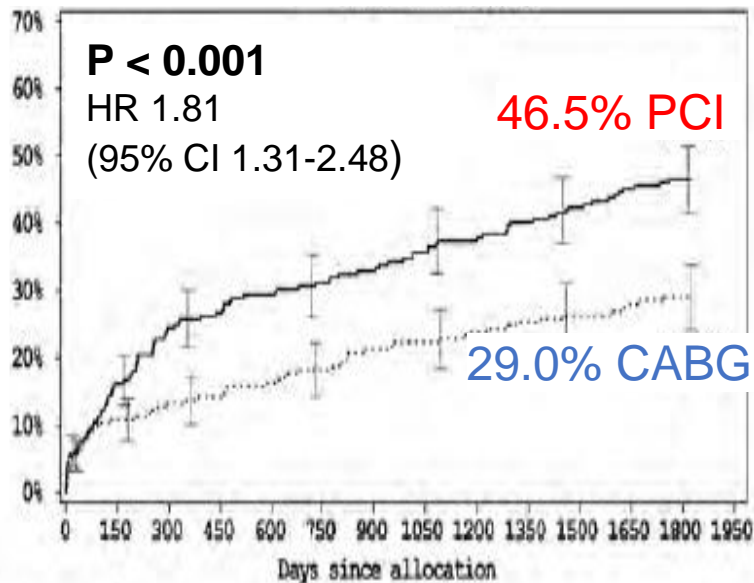*Journal of the American College of Cardiology 2019;73:1629-1632*

CVRF

Previous Trials;

PCI vs. CABG
in DM and Multivessel CAD

SYNTAX trial
DM subgroup analysis

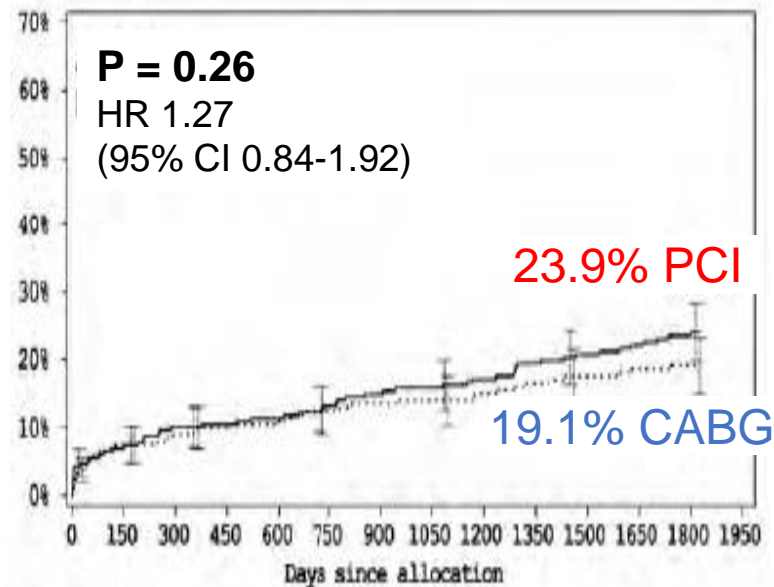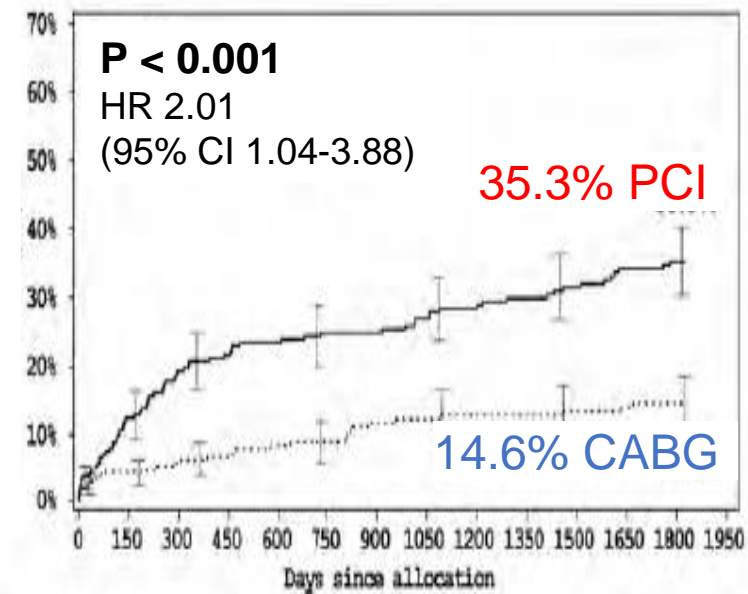*1,800 patients with LM and/or 3VD, 5-year follow-up*

452 patients with DM

Composite of Death, MI, Stroke, or Repeat Revascularization

P < 0.001
HR 1.81
(95% CI 1.31-2.48)

46.5% PCI

29.0% CABG

Days since allocation

Composite of Death, MI, or Stroke

P = 0.26
HR 1.27
(95% CI 0.84-1.92)

23.9% PCI

19.1% CABG

Days since allocation

Repeat revascularization

P < 0.001
HR 2.01
(95% CI 1.04-3.88)

35.3% PCI

14.6% CABG

Days since allocation
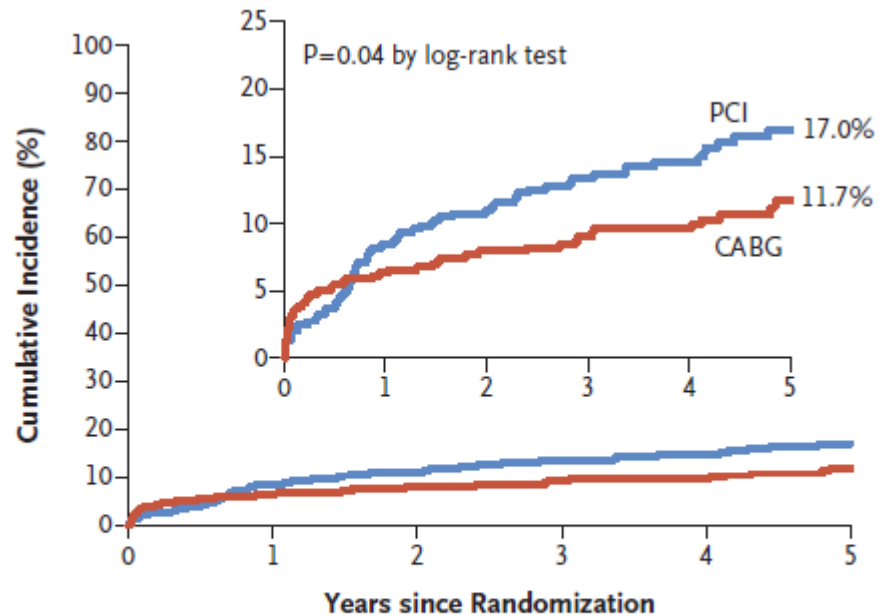
Eur J Cardiothorac Surg. 2013;43(5):1006-1013

BEST Trial

880 patients with Multivessel CAD, median 4.6 years of follow-up

438 in PCI , 442 in CABG

Primary Composite of Death, MI, or Target-vessel revascularization

Composite of Death, MI, Stroke, or Any Repeat Revascularization
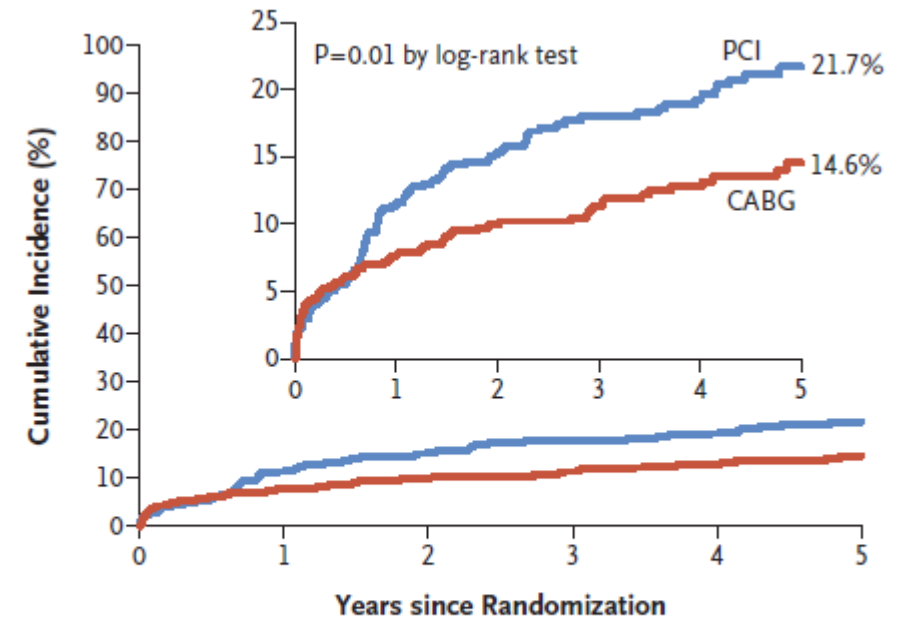
N Engl J Med 2015;372:1204-12

BEST Trial

DM Subgroup Analysis

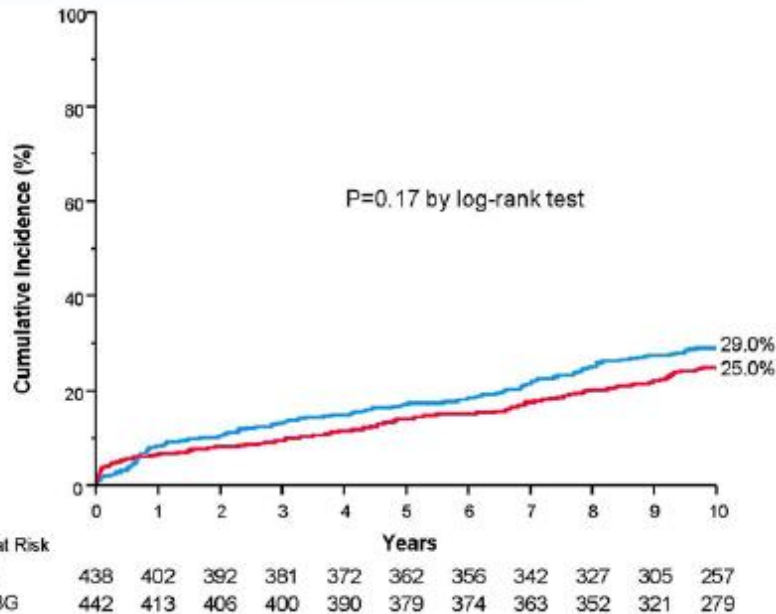| Subgroup	PCI	CABG	Hazard Ratio (95% CI)		P Value for Interaction
	no. of patients with event/total no. (%)				
Diabetes					0.06
Yes	34/177 (19.2)	17/186 (9.1)		2.24 (1.25–4.00)	
No	33/261 (12.6)	30/256 (11.7)		1.07 (0.65–1.76)	

0.1   1.0   10.0

PCI Better   CABG Better
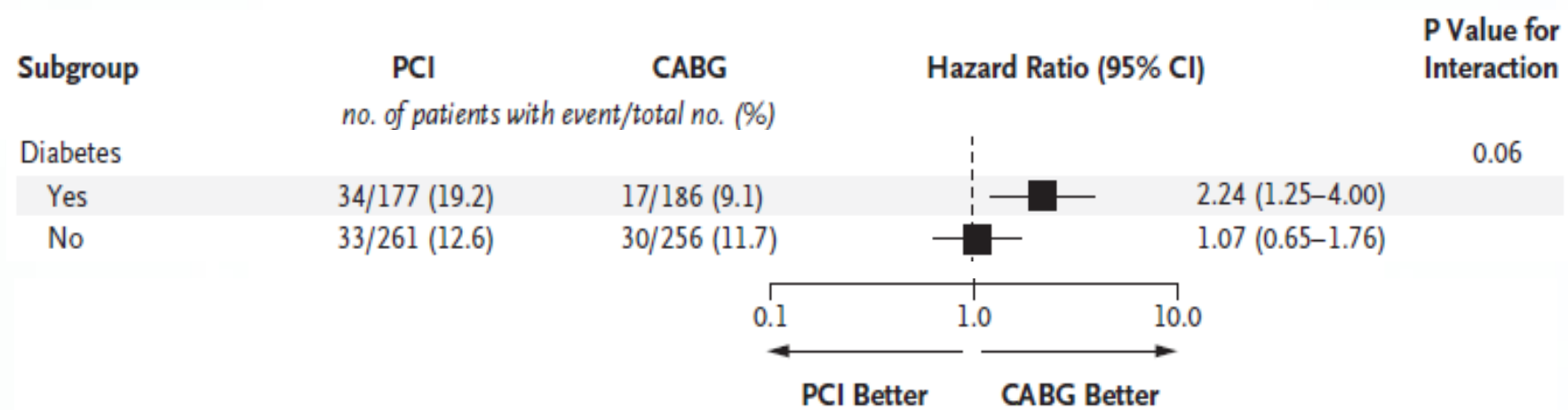
➢ In patients with diabetes and multivessel CAD, the primary composite endpoint of death, MI, or target-vessel revascularization occurred frequently in the PCI group.
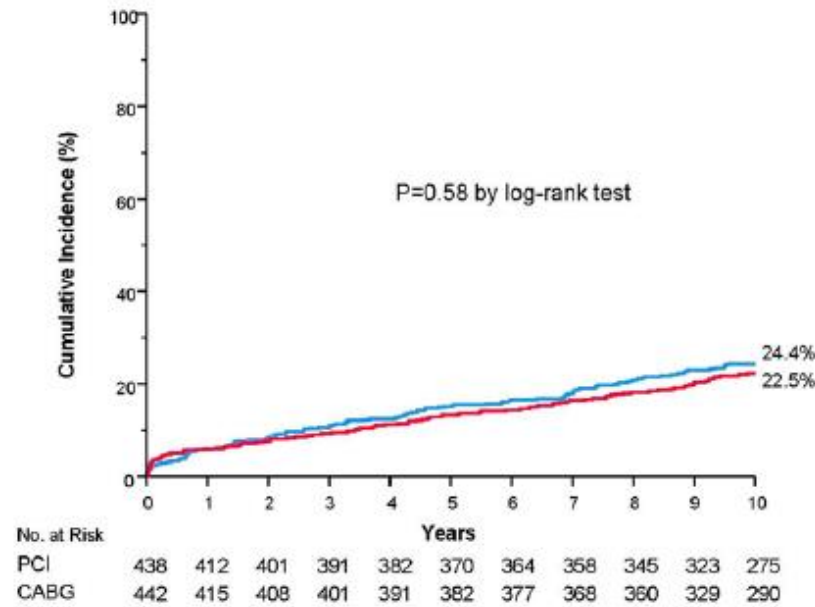
Extended follow-up of the BEST Trial

880 patients with Multivessel CAD, median 11.8 years of follow-up
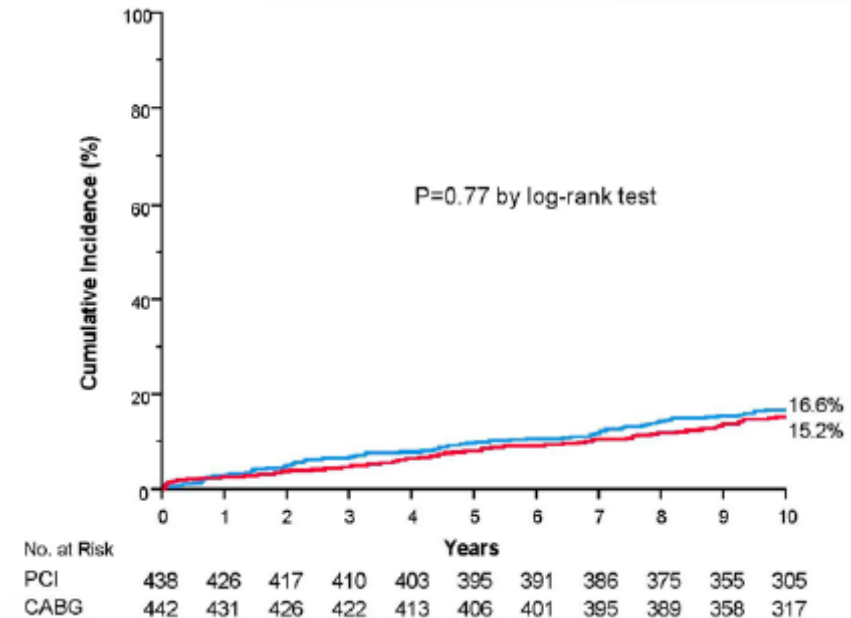
438 in PCI , 442 in CABG

Primary Composite of Death, MI, or Target-vessel revascularization — P=0.17 by log-rank test; PCI 29.0%, CABG 25.0%
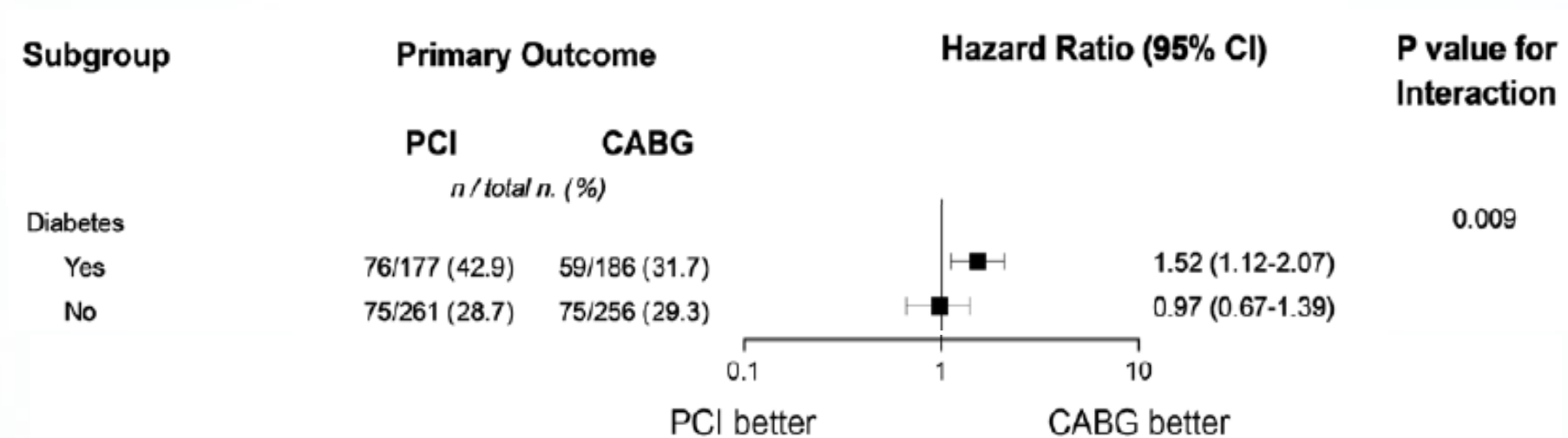
Death, MI, or Stroke — P=0.58 by log-rank test; PCI 24.4%, CABG 22.5%

Death from Any Cause — P=0.77 by log-rank test; PCI 16.6%, CABG 15.2%

Extended follow-up of the BEST Trial

DM subgroup analysis

Subgroup	Primary Outcome		Hazard Ratio (95% CI)	P value for Interaction
	PCI	**CABG**		
	n / total n. (%)			
Diabetes				0.009
Yes	76/177 (42.9)	59/186 (31.7)	1.52 (1.12-2.07)	
No	75/261 (28.7)	75/256 (29.3)	0.97 (0.67-1.39)	

0.1   1   10

PCI better   CABG better

Extended follow-up of the BEST Trial
DM subgroup analysis

(A) Primary Composite End Point

(B) Death, Stroke, or Myocardial Infarction

(C) Death from Any Cause

(D) Any Repeat Revascularization

PCI
CABG

Circulation. 2022;146:1581–1590
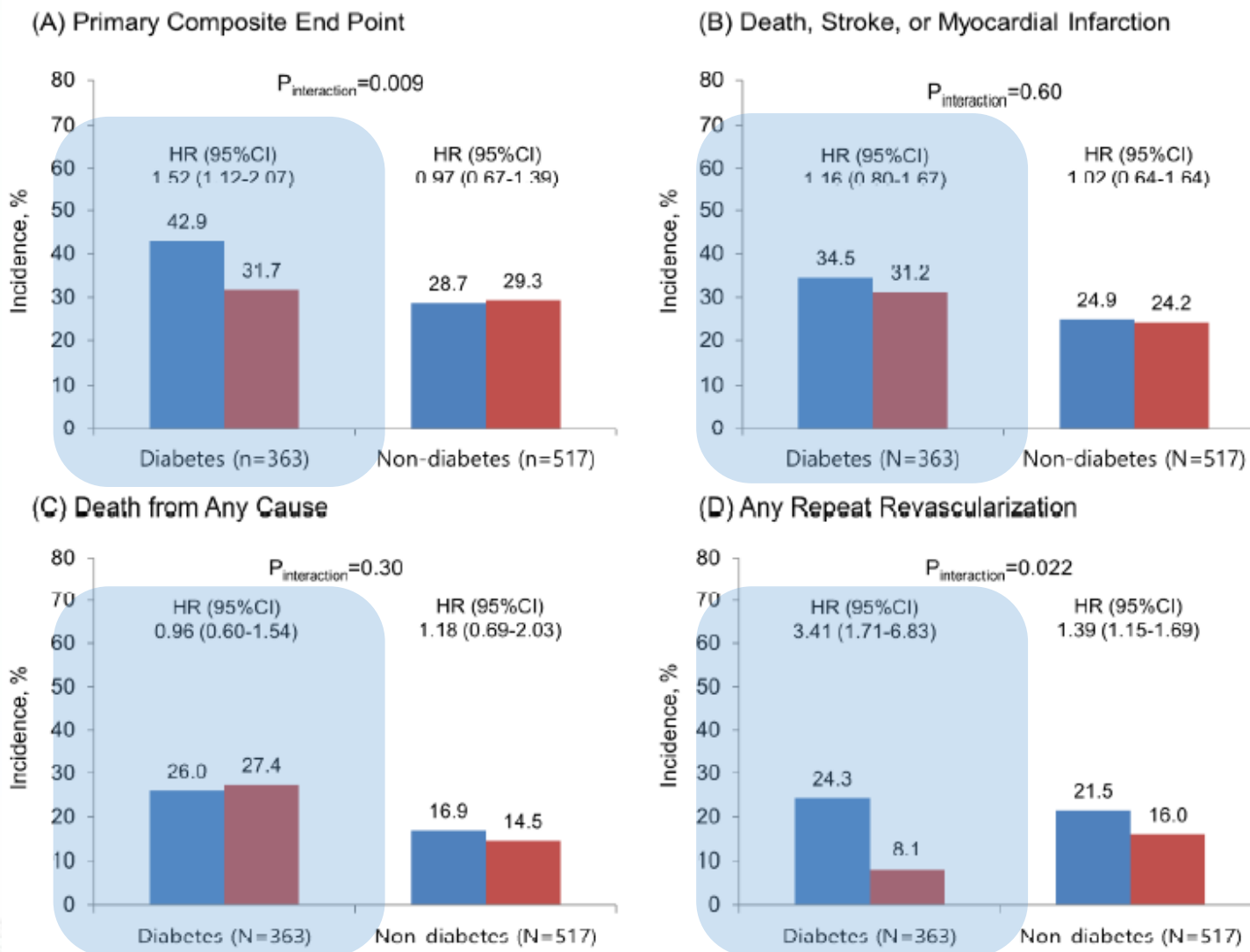
Limitations of Prior RCTs

- **The SYNTAX trial and the BEST trial have not focused on DIABETIC patients.**

   >> Subgroup analyses with underpower

- **The SYNTAX trial included patients with left main coronary artery disease.**
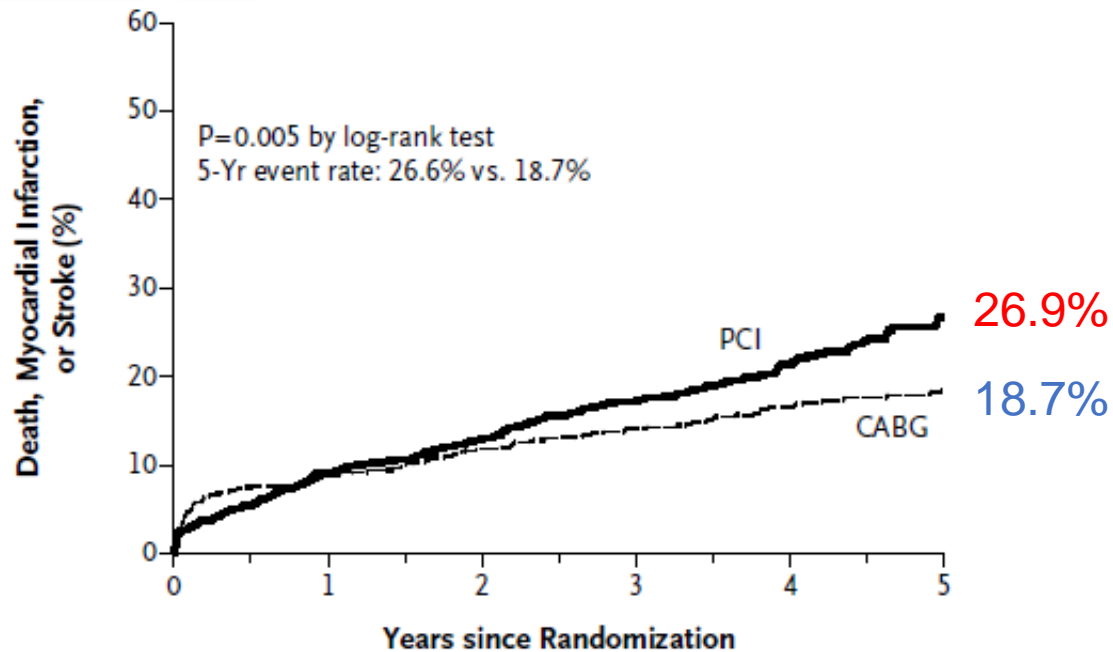
Randomized Trials
for patients with DM and multivessel CAD;
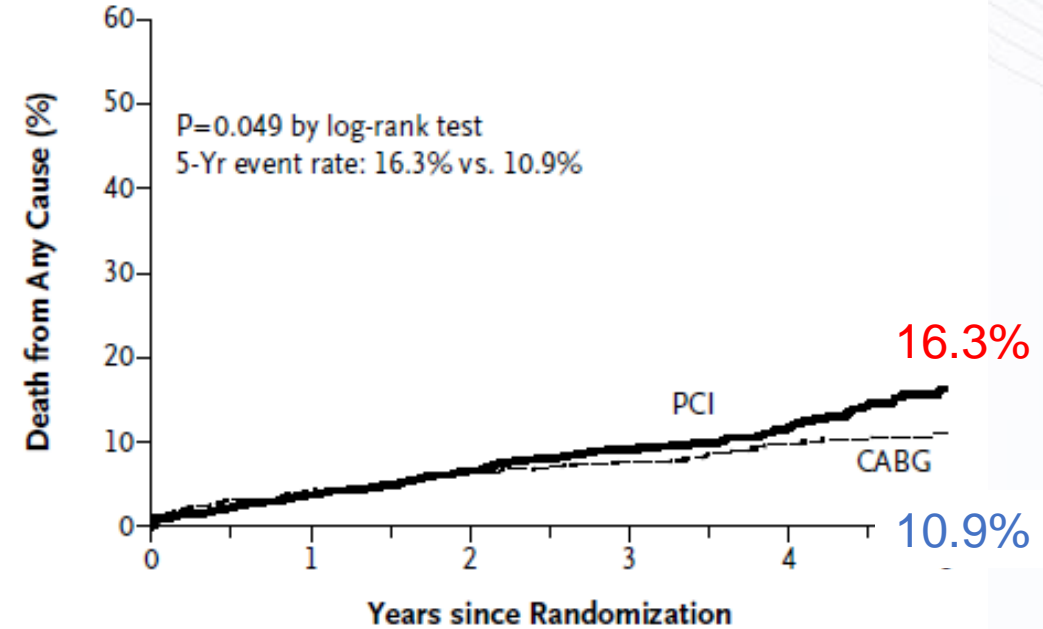
FREEDOM trial
BARI-2D trial

FREEDOM trial

1,900 patients with DM and Multivessel CAD, 5-year follow-up

953 in PCI , 947 in CABG

Composite of Death, MI, or Stroke

P=0.005 by log-rank test
5-Yr event rate: 26.6% vs. 18.7%

26.9%
18.7%

No. at Risk						
PCI	953	848	788	625	416	219
CABG	947	814	758	613	422	221

Death from Any Cause

P=0.049 by log-rank test
5-Yr event rate: 16.3% vs. 10.9%

16.3%
10.9%

No. at Risk						
PCI	953	897	845	685	466	243
CABG	947	855	806	655	449	238

N Engl J Med 2012;367:2375-84

28th TCTAP

FREEDOM Follow-On Study

1,900 patients with DM and Multivessel CAD

Median follow-up of 7.5 years (0 to 13.2 years)

Free from All-Cause Death
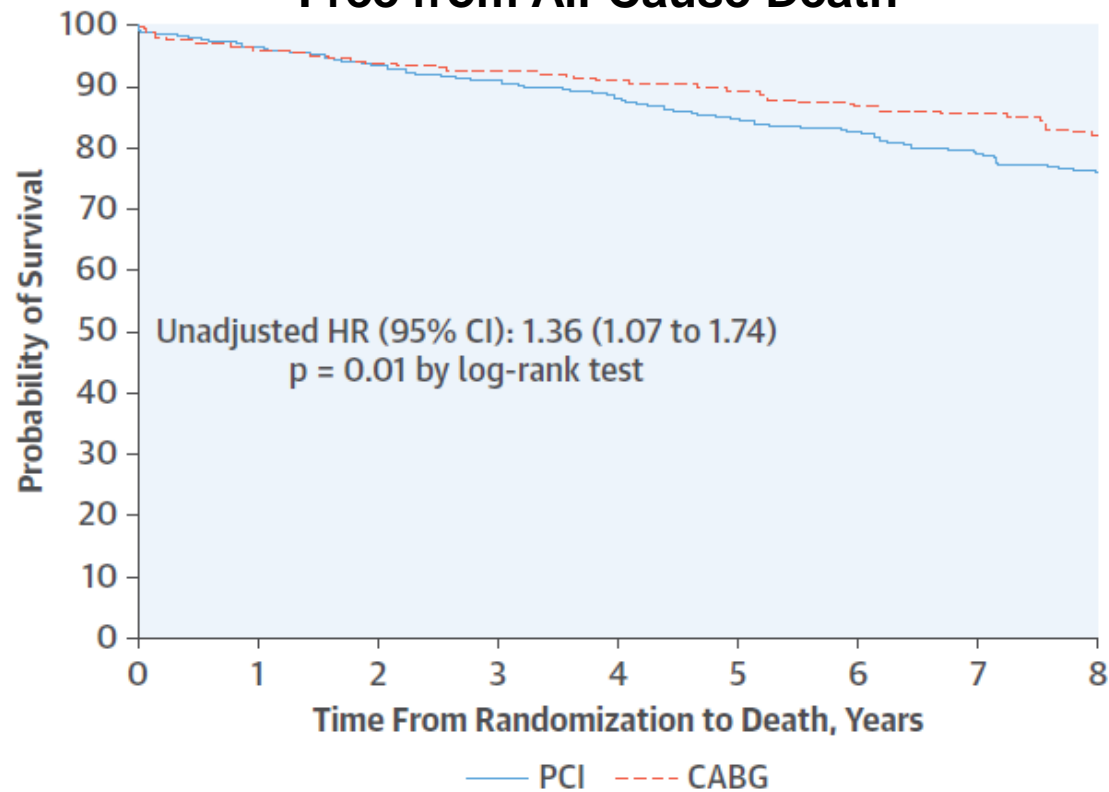
All-cause mortality

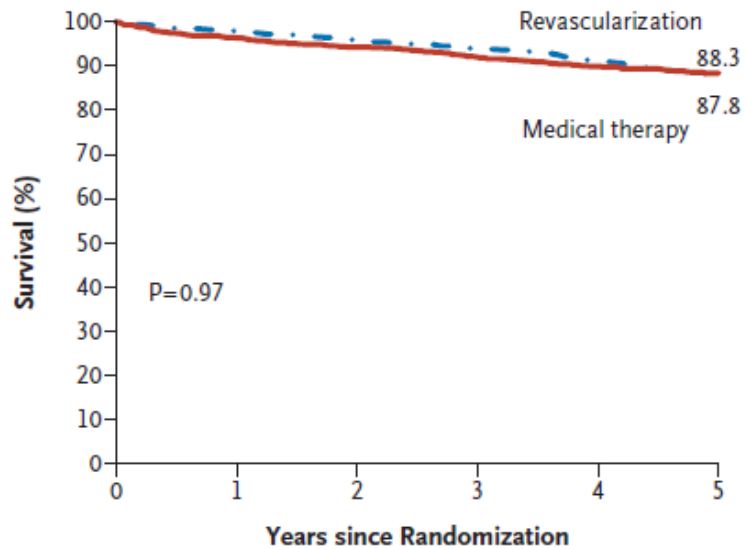- PCI 24.3%

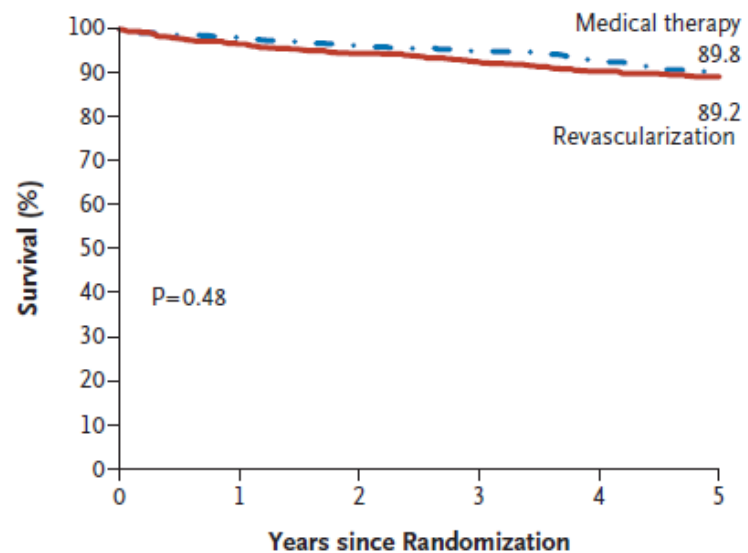- CABG 18.3%

  (**HR 1.36**; P = 0.01)

BARI 2D trial

2,368 patients with type 2 DM and CAD, mean follow-up of 5.3 years

763 in CABG stratum (385 medical, 378 CABG), 1605 in PCI stratum (807 medical, 798 PCI)

Survival Revascularization vs. Medical

Survival in PCI stratum

Survival in CABG stratum

N Engl J Med 2009;360:2503-15

BARI 2D trial

2,368 patients with type 2 DM and CAD, mean follow-up of 5.3 years

763 in CABG stratum (385 medical, 378 CABG), 1605 in PCI stratum (807 medical, 798 PCI)
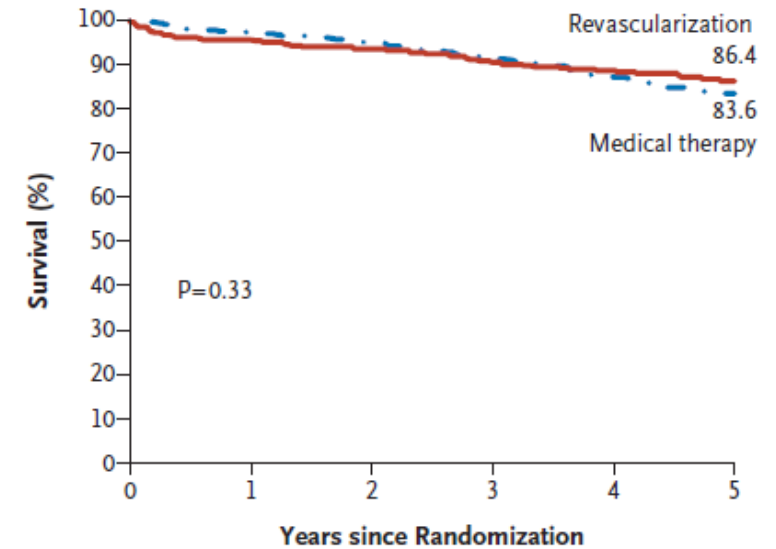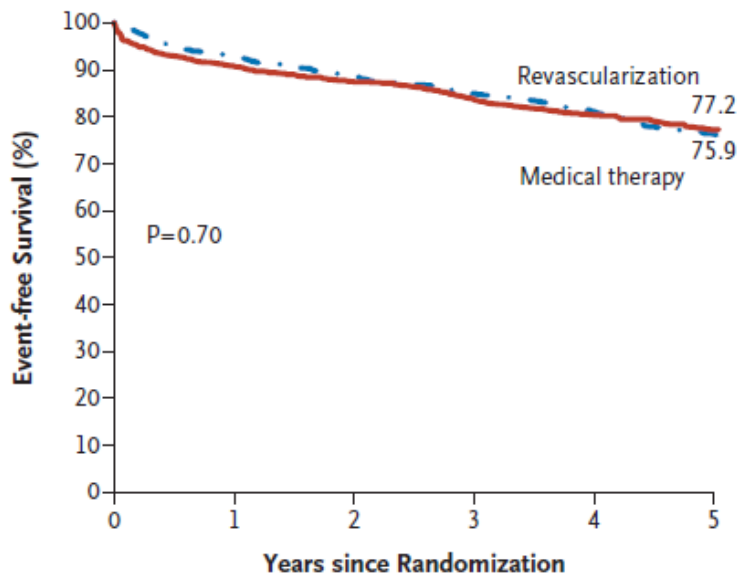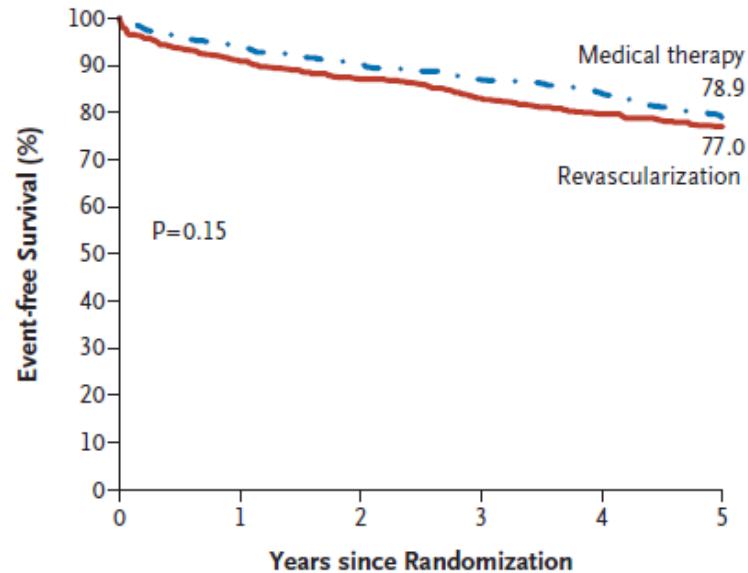

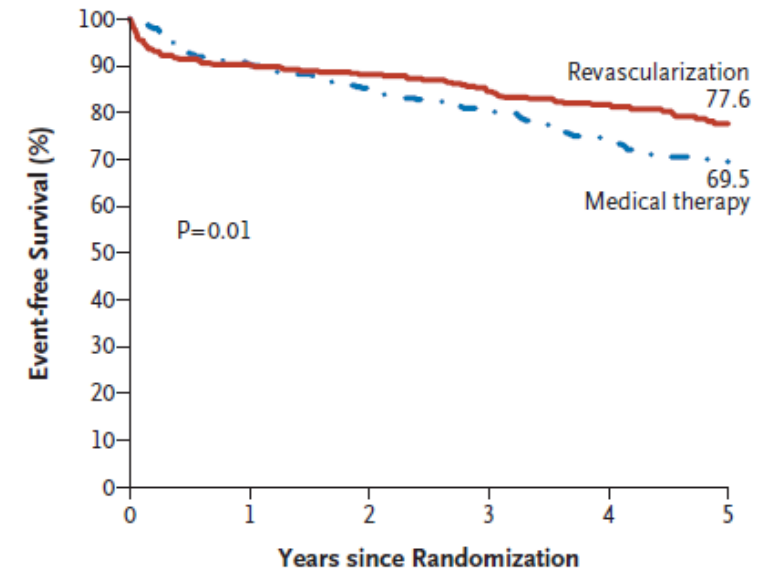**Freedom from MACE
Revascularization vs. Medical**

**Freedom from MACE
(death, MI, or stroke) in PCI**

**Freedom from MACE
(death, MI, or stroke) in CABG**

N Engl J Med 2009;360:2503-15

2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization

	COR	LOE

➢ In patients with diabetes and multivessel CAD with involvement of LAD, who are appropriate candidates for CABG, CABG is recommended in preference to PCI to *reduce mortality and repeat revascularization*

1	A

➢ In patients with diabetes and multivessel CAD amenable to PCI and an indication for revascularization and are poor candidates for surgery, PCI can be useful to *reduce long-term ischemic outcomes*

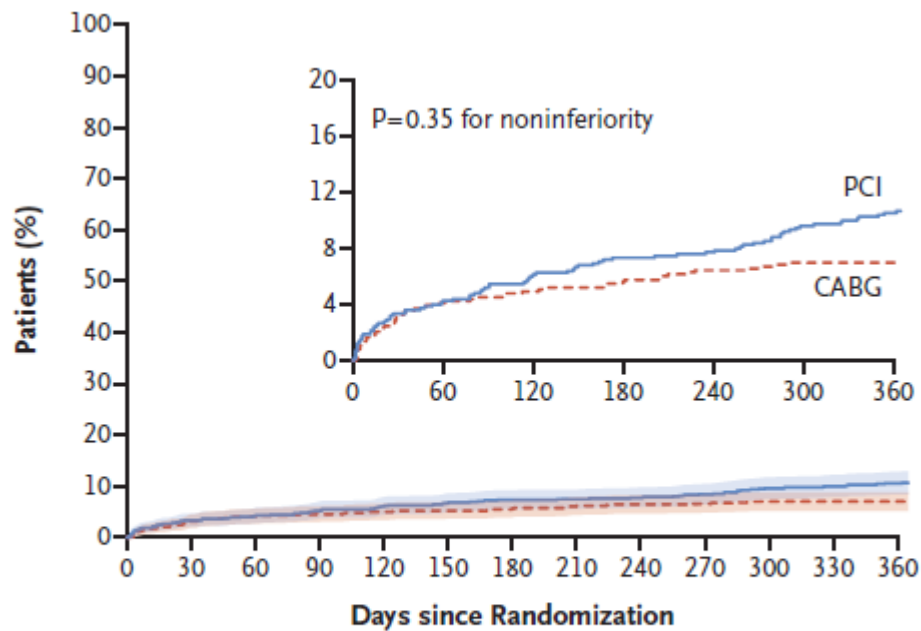| 2a	B-NR

Limitations of Prior RCTs

- **Not focus on patients with diabetes**
  - SYNTAX, BEST

- **Just subgroup analyses with underpower**
  - SYNTAX, BEST

- **Not use current generation DES**
  - FREEDOM, SYNTAX

- **Not frequently use intracoronary imaging**
  - SYNTAX, FREEDOM

- **Not use OMT (e.g., SGLT-2 inhibitors) of current practice**
  - FREEDOM, BARI 2D

FAME 3 Trial

1,500 patients with 3VD

757 in FFR-guided PCI using 2nd generation DES, 743 in CABG

MACCE (death, MI, stroke, or repeat revascularization) at 1 year

P=0.35 for noninferiority

Subgroup	PCI	CABG	PCI	CABG	Adjusted Hazard Ratio (95% CI)
	total no.		1-yr incidence (%)		
All patients	757	743	10.6	6.9	
Age					
≥65 yr	434	409	9.4	8.1	
<65 yr	323	334	12.1	5.4	
Sex					
Female	141	124	11.3	13.7	
Male	616	619	10.4	5.5	
Diabetes					
No	543	529	9.4	7.0	
Yes	214	214	13.6	6.5	
NSTE-ACS					
No	456	454	10.1	5.9	
Yes	300	287	11.3	8.4	
LVEF					
>50%	616	610	10.4	6.6	
30–50%	137	130	10.9	8.5	
Previous PCI					
No	658	637	9.3	6.8	
Yes	98	104	19.4	7.7	
SYNTAX score					
0–22	237	245	5.5	8.6	
23–32	365	343	13.7	6.1	
≥33	132	122	12.1	6.6	

PCI Better — CABG Better

N Engl J Med 2022;386:128-37

FAME 3 Trial

1,500 patients with 3VD

757 in FFR-guided PCI using 2nd generation DES, 743 in CABG

Table 2. Angiographic and Procedural Characteristics.*

Characteristic	PCI (N=757)	CABG (N=743)
PCI characteristics		
Staged procedure — no./total no. (%)	166/750 (22.1)	NA
No. of stents	3.7±1.9	NA
Median total length of stents placed (IQR) — mm	80 (52–116)	NA
Intravascular imaging used — no./total no. (%)	87/744 (11.7)	NA

However,

>> Intravascular imaging was only used in 11.7%

N Engl J Med 2022;386:128-37
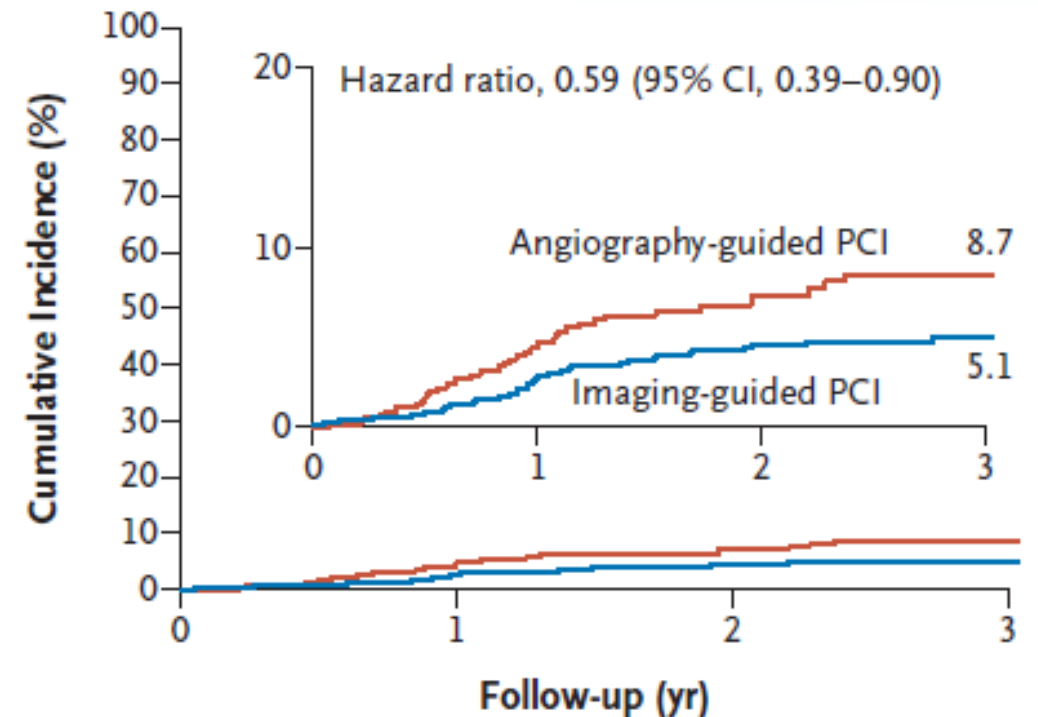
RENOVATE-COMPLEX-PCI Trial

1,639 patients, at median f/u of 2.1 years

1092 in imaging-guided PCI, 547 angiography-guided PCI

TVF (cardiac death, TV MI, CD-TVR)
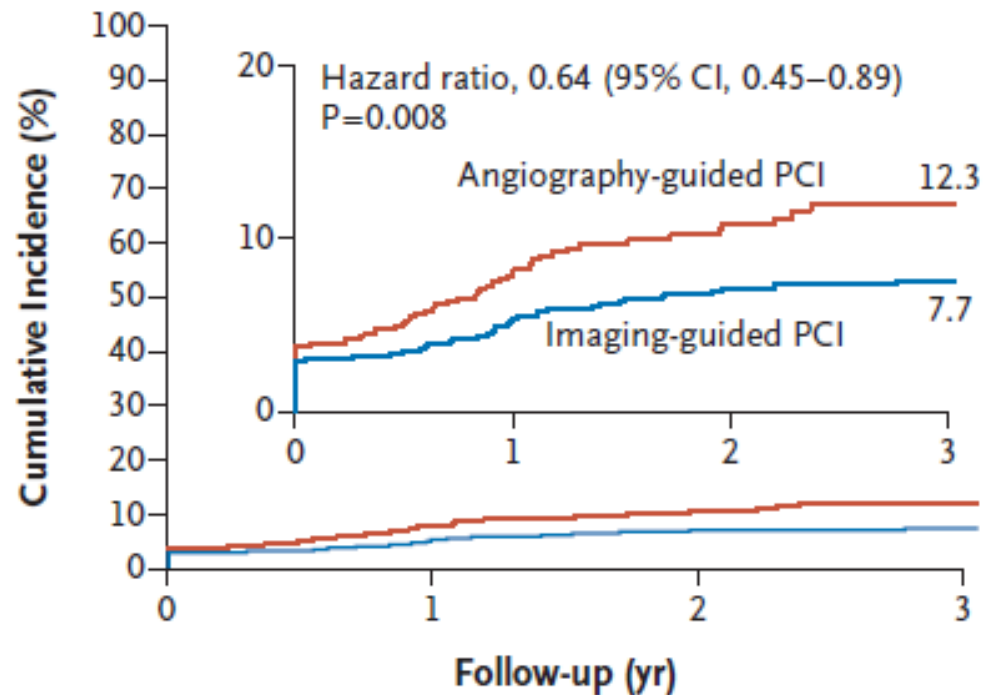
TVF without periprocedural MI

N Engl J Med 2023;388:1668-79.

Which would be better ?

Imaging- and Physiology-guided state-of-the-art PCI
or
CABG

DEFINE-DM Trial

Diabetes-Centered Evaluation of Revascularization Strategy of Functional and Imaging-CombiNEd State-of-the-Art Percutaneous Coronary Intervention or Coronary-Artery Bypass Grafting in Patients with Diabetes Mellitus and Multivessel Coronary Artery Disease

Seung-Jung Park (Trial Chair)

Duk-Woo Park (Trial PI)

Heart Institute, Asan Medical Center,

University of Ulsan College of Medicine, Seoul, Korea

CVRF

Objective

- To compare outcomes of imaging- and physiology-guided state-of-the-art PCI with CABG in patients with diabetes and multivessel CAD with LAD involvement.

- A multicenter, international, randomized, controlled non-inferiority trial. Approximately 1,200 patients will be enrolled from international heart centers.

Trial Design

Diabetes-Centered Evaluation of Functional and Imaging-CombiNEd
State-of-the-Art Percutaneous Coronary Intervention or Coronary-Artery Bypass
Grafting in Patients with Diabetes Mellitus and Three-Vessel Coronary Artery Disease

DEFINE-DM Trial

**1,200 Patients with Diabetes and Multivessel CAD with LAD Involvement
Who Were Equally Eligible for PCI or CABG**

1:1 randomization in random block sizes of 6 and 8, with stratification according to the participating center

**Imaging- and Physiology-Guided
State-of-the Art PCI
(N = 600)**

**Standard CABG
(N = 600)**

The primary end point was the composite of
death from any cause, myocardial infarction, or stroke at 2 year.

Study Participants

Consecutive patients with diabetes and multivessel CAD (angiographic DS ≥50%)

with LAD involvement who are equivalently eligible for PCI or CABG

Inclusion Criteria

- Patients at least 20 years of age
- Patients with type 2 diabetes
- Patients with significant multivessel CAD (defined as ≥50% diameter stenosis by visual estimation) of major epicardial vessel with LAD involvement equally suitable to both PCI and CABG

Exclusion Criteria

- Unprotected left main coronary artery disease requiring revascularization
- Complex CAD anatomy of lesion characteristics that PCI is not suitable
- ST elevation MI
- Cardiogenic shock or severe LV dysfunction (LVEF <30%)
- Requirement of other cardiac or non-cardiac surgical procedure
- Life expectancy < 2 years for concurrent medical condition

Study Endpoints

Primary

- The primary endpoint is the rate of major adverse cardiac or cerebrovascular events (MACCE) at 2 years.

- MACCE are defined as a composite of hard clinical endpoints of death from any causes, MI, or stroke.

Study Endpoints

Secondary

- Each individual component of primary composite outcome

- Death from any causes, cardiovascular causes, or non-cardiovascular causes

- MI (any, spontaneous or procedural)

- Composite of death, MI, stoke, or repeat revascularization

- Stent thrombosis

- Symptomatic graft occlusion or stenosis

- Bleeding complications (BARC criteria)

- Periprocedural major adverse events (major arrhythmia, any unplanned surgery or therapeutic radiologic procedure, acute renal failure, infection requiring antibiotics, etc.)

- Length of hospital stay

- Rehospitalization

- Functional class (assessed by the CCS classification)

- Angina-related quality of life index (by the Seattle Angina Questionnaire [SAQ]) or health-related quality of life index (by the EQ-5D)

Conclusion

- The results of previous trials suggest CABG is better than PCI in patients with DM and multivessel disease.

- However, there are limitations for accepting those results in the contemporary PCI era.

- DEFINE-DM trial would provide valuable evidence for comparing imaging- and physiology-guided state-of-the-art PCI and CABG in patients with DM and multivessel disease.