DM and Triple Vessel Disease; Old Evidence and Next New Trials? DEFINE-DM Trial

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Disclosure

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Diabetes and CAD

- Diabetes is a common comorbidity among patients with coronary artery disease (CAD).
- Diabetic patients have a more aggressive form of atherosclerosis and more extensive coronary artery disease.

Circulation 2013;128:1675-1685
Circulation 2015;132:923-931

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

The Lancet Diabetes & Endocrinology 2013;1:317-328
JACC 2019;73:1629-1632

- Patients with diabetes have higher risk of ischemic cardiovascular events and mortality than those without diabetes.

Circulation 2021;144:1380-95
Circulation 2019;139:2742-53

Old Evidence

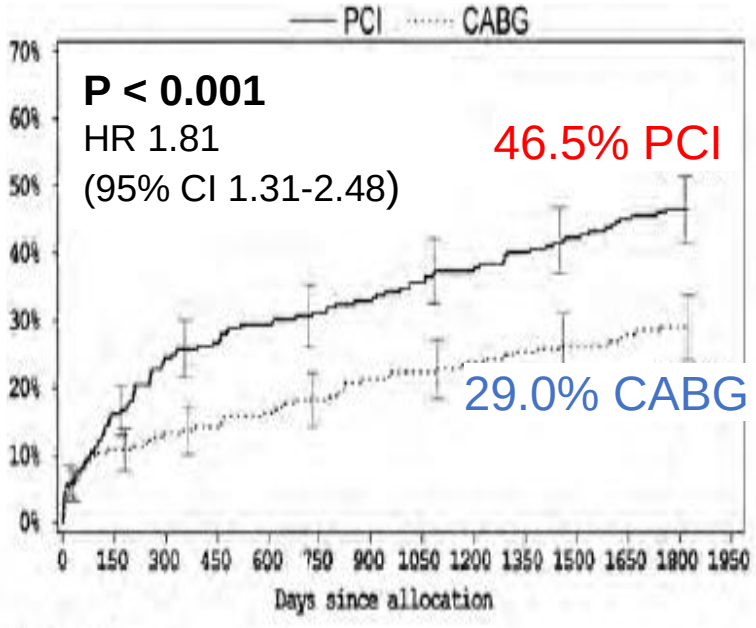
PCI vs. CABG
in DM with Multivessel CAD

SYNTAX trial
DM subgroup analysis

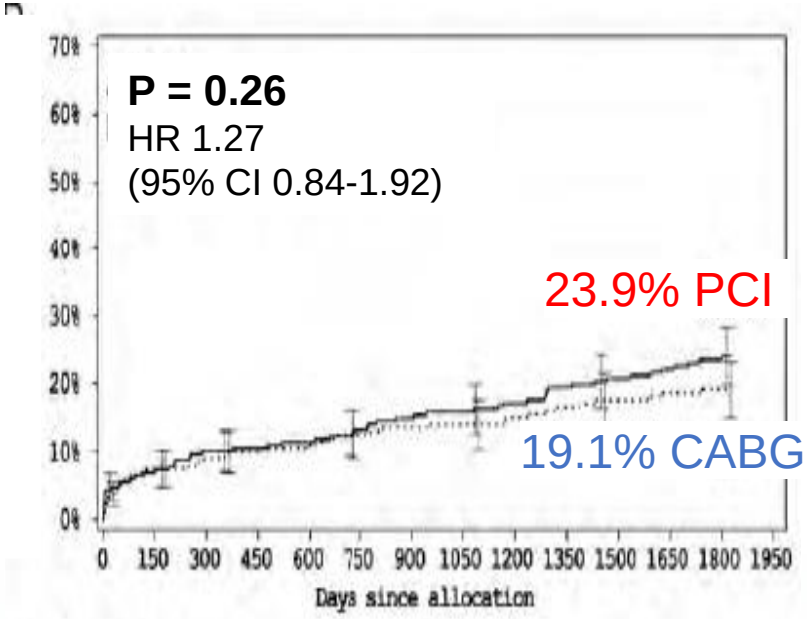
1,800 patients with LM and/or 3VD, 5-year follow-up

452 patients with DM

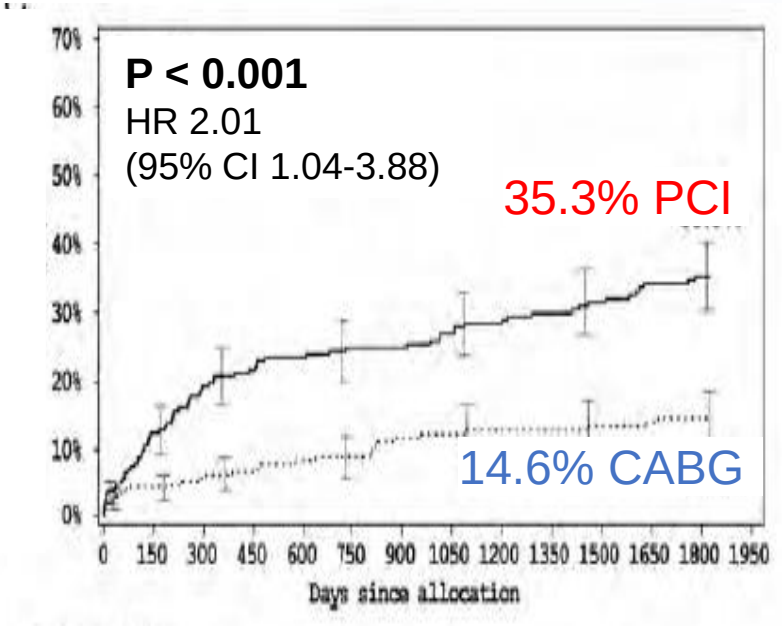
Composite of Death, MI, Stroke, or Repeat Revascularization



Composite of Death, MI, or Stroke



Repeat revascularization

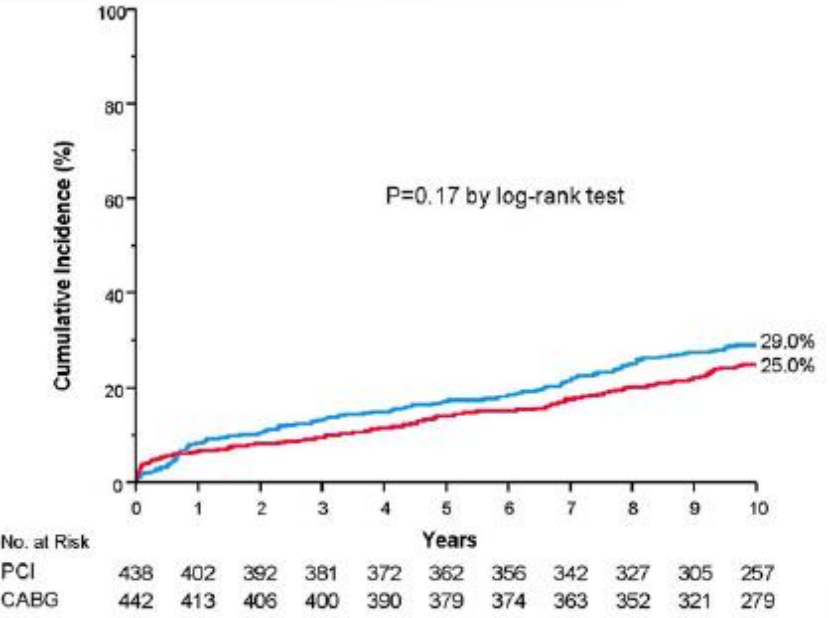


Eur J Cardiothorac Surg. 2013;43(5):1006-1013

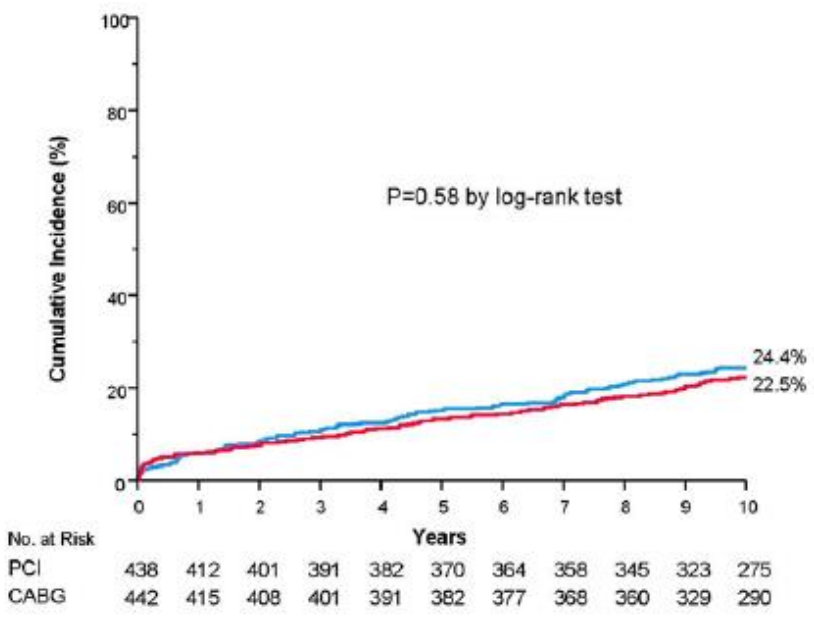
10-Yr Follow-up of the BEST Trial

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

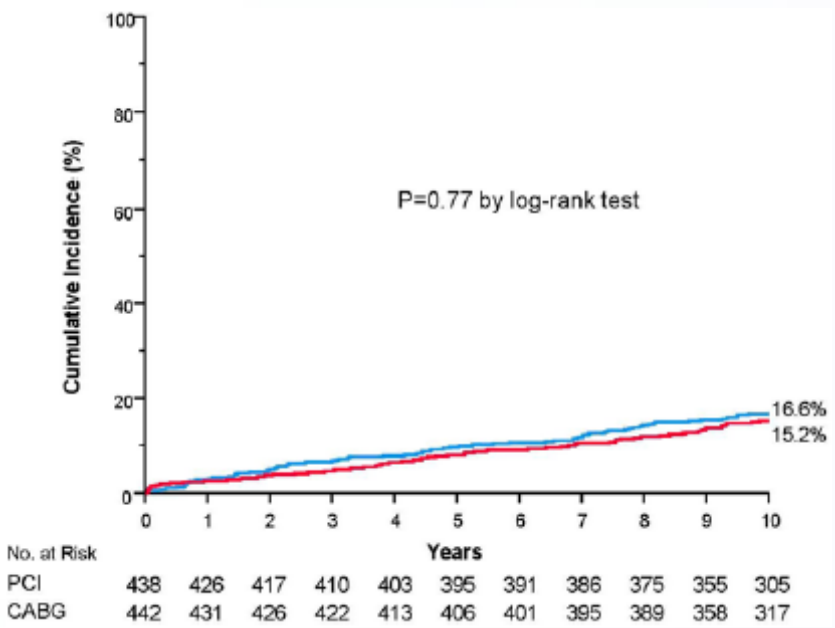
Primary Composite of Death, MI, or Target-vessel revascularization



Death, MI, or Stroke



All-Cause Death

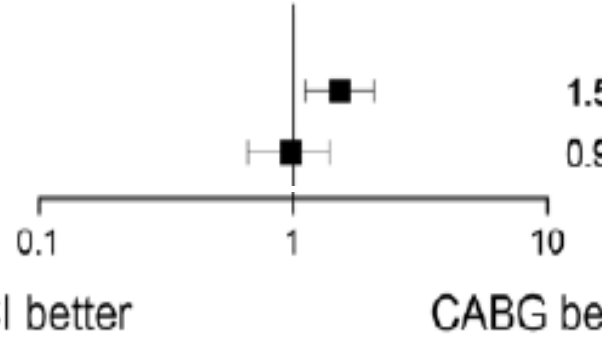


Ahn JM, DY Kang, DW Park, SJ Park et al. Circulation. 2022;146:1581–1590

10-Yr 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)	



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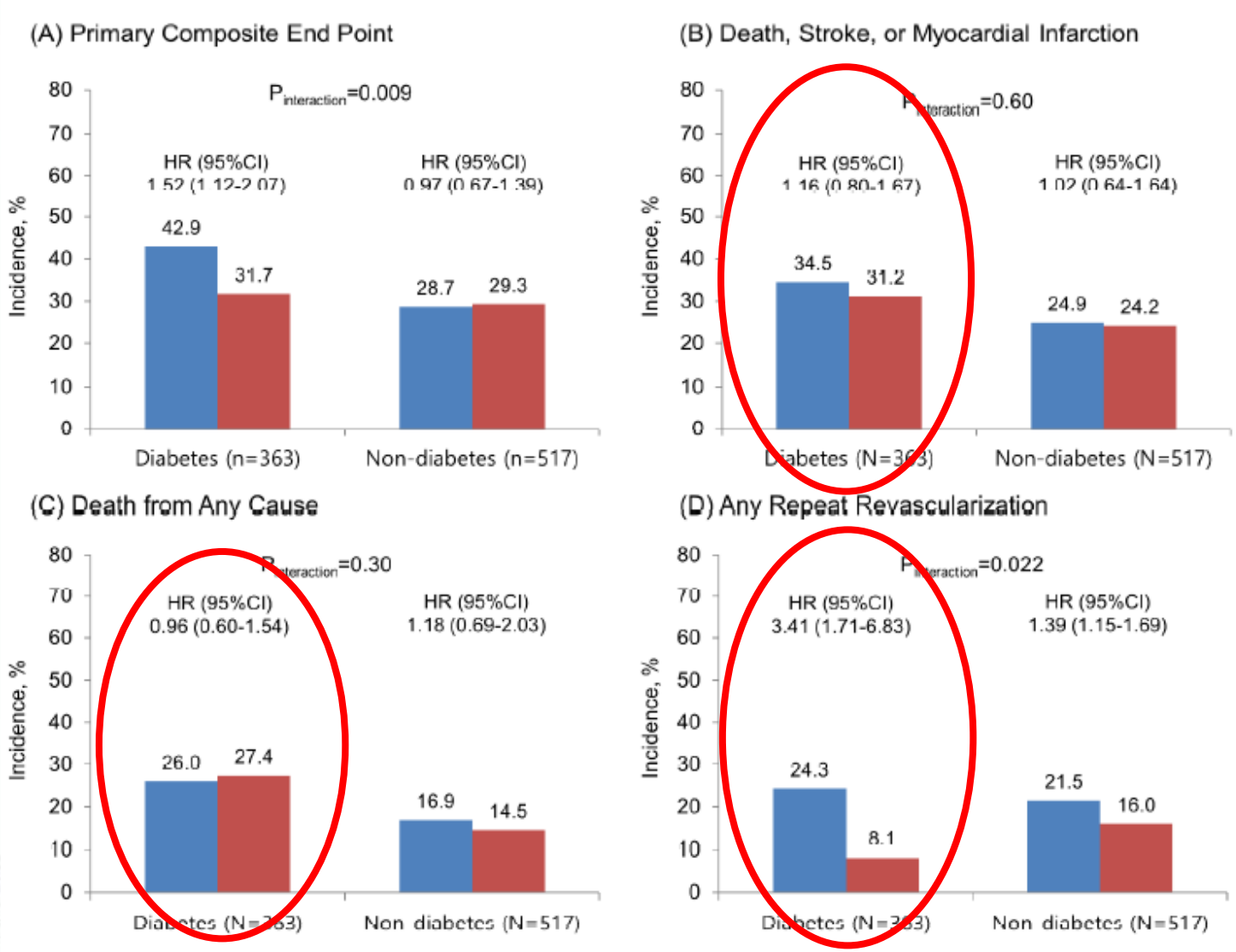
Extended follow-up of the BEST Trial

DM subgroup analysis

PCI
CABG



In Diabetic Patients after PCI and CABG,

No difference for composite of death, stroke, or MI

No difference for all-cause mortality

Only difference for repeat revascularization

Ahn JM, DY Kang, DW Park, SJ Park et al. Circulation. 2022;146:1581–1590

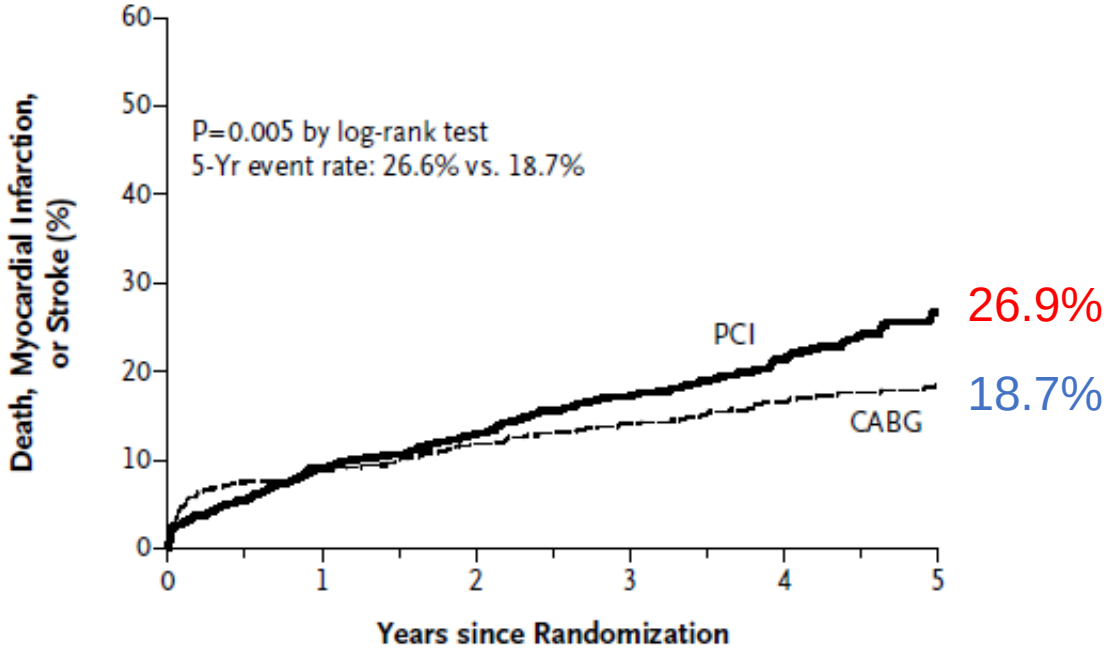
Landmark RCTs Specifically Targeting Patients with DM and multivessel CAD:

FREEDOM Trial
BARI-2D Trial

FREEDOM trial

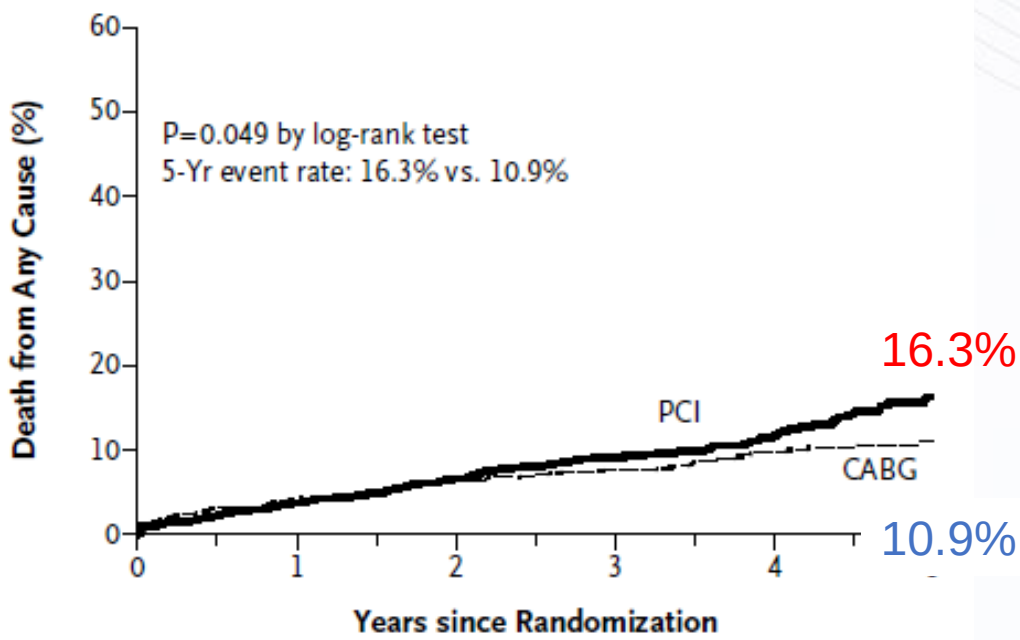
1,900 patients with DM and Multivessel CAD, 5-year follow-up
953 in PCI , 947 in CABG

Primary Composite of Death, MI, or Stroke



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

Death from Any Cause



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

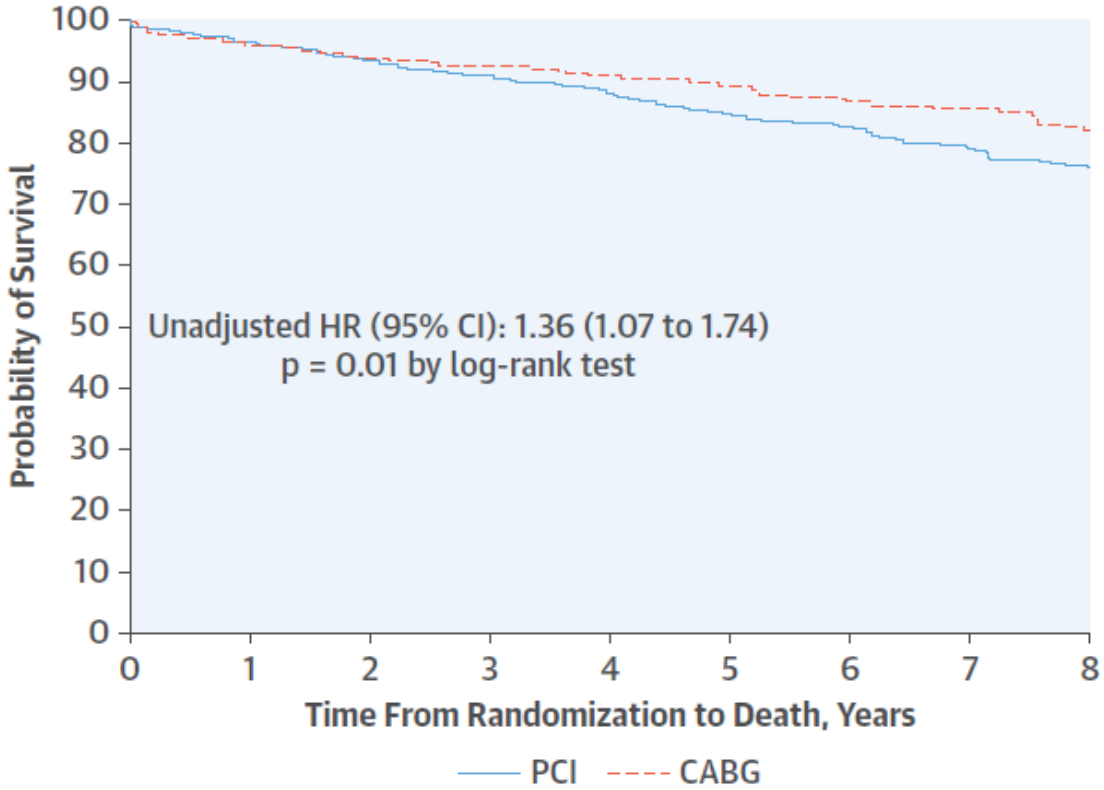
N Engl J Med 2012;367:2375-84

FREEDOM Follow-On Study

1,900 patients with DM and Multivessel CAD

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

Free from All-Cause Death



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

All-cause mortality

- PCI 24.3%
- CABG 18.3%

  (HR 1.36; P = 0.01)

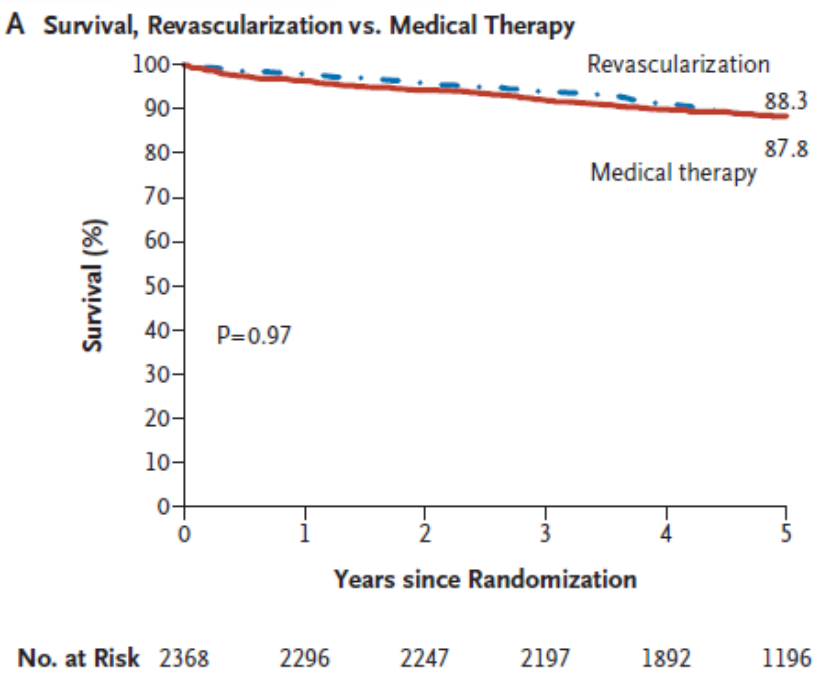
J Am Coll Cardiol. 2019;73(6):629–38

BARI 2D trial

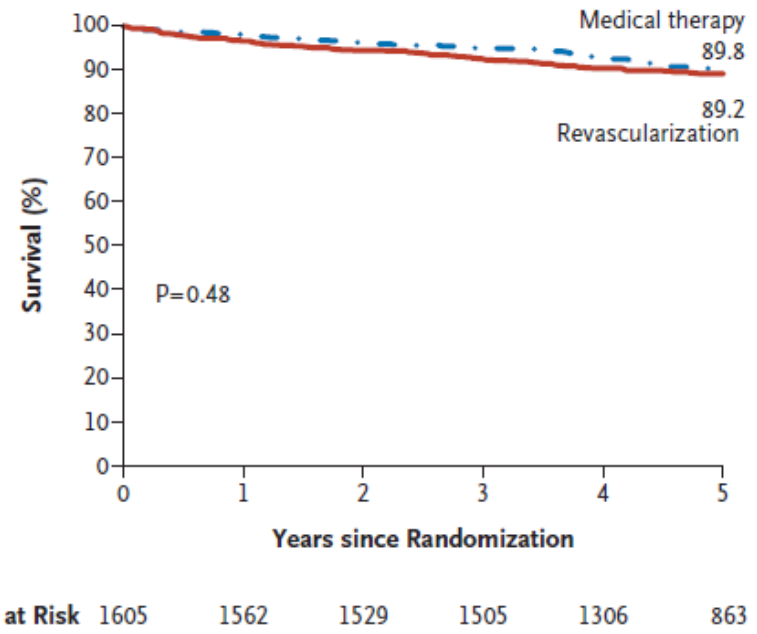
2,368 patients with type 2 DM and CAD, mean follow-up of 5.3 years

763 in CABG stratum (385 OMT vs. 378 CABG), 1605 in PCI stratum (807 OMT vs. 798 PCI)

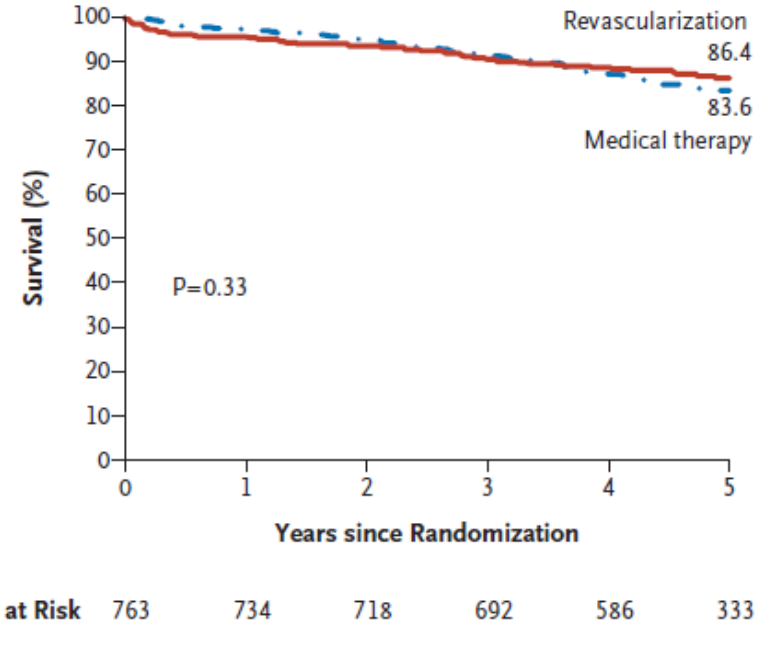
Survival in **Overall stratum**: Revascularization vs. OMT



Survival in **PCI stratum:** Revascularization vs. OMT



Survival in **CABG stratum**: Revascularization vs. OMT



N Engl J Med 2009;360:2503-15

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

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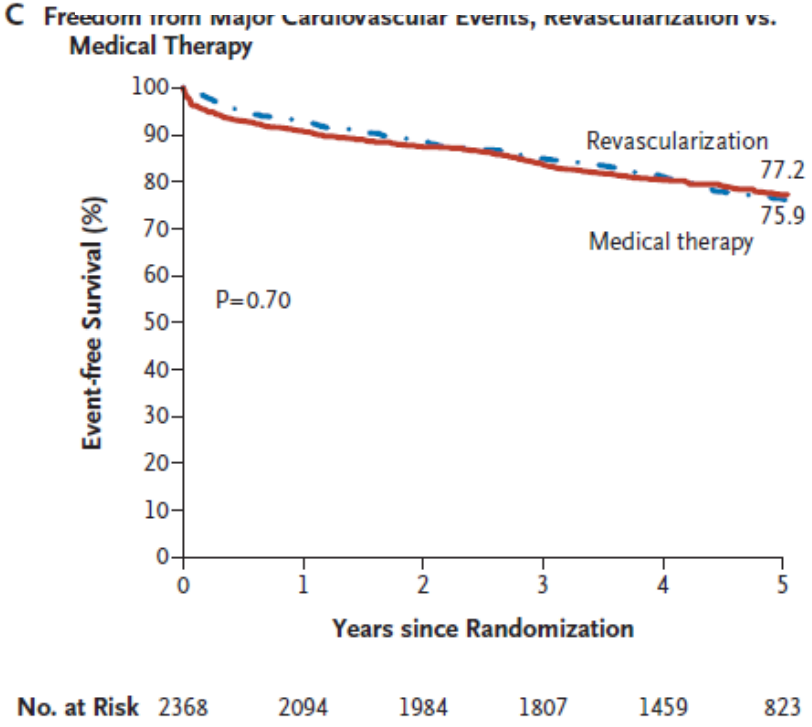
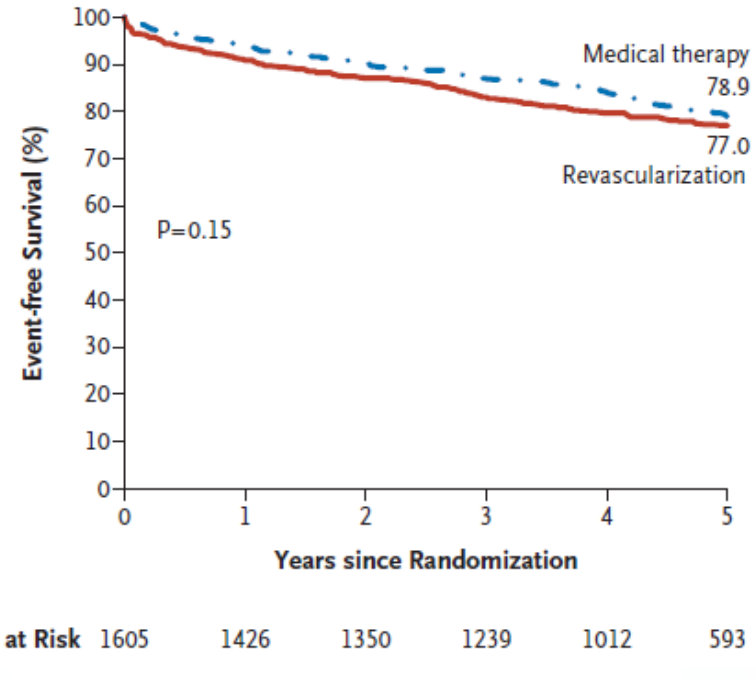
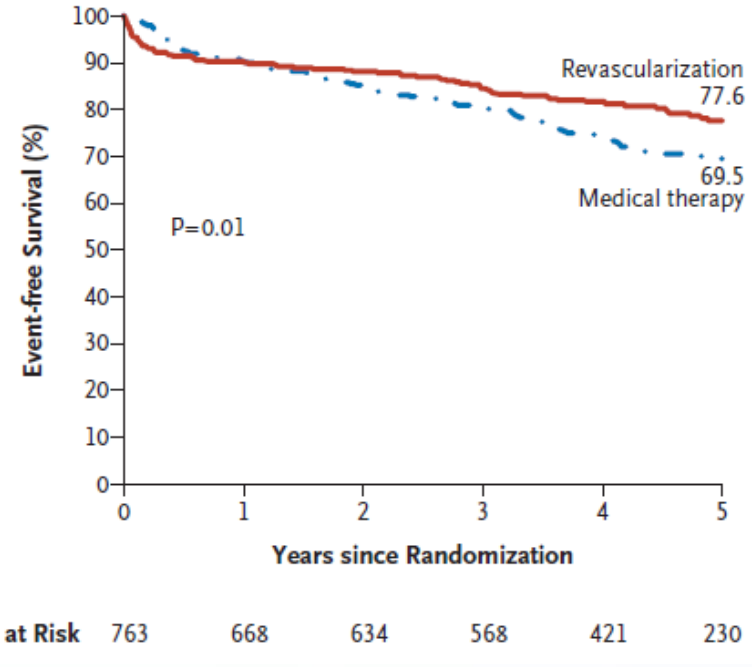
MACE-free in Overall stratum: Revascularization vs. OMT



MACE-free in PCI stratum: Revascularization vs. OMT



MACE-free in CABG stratum: Revascularization vs. OMT



***MACE = a composite of death, MI, or stroke**

N Engl J Med 2009;360:2503-15

Contemporary Revascularization Guidelines

2018 ESC Guideline

	CABG		PCI	
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

2021 ACC/AHA/SCAI Guideline

	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

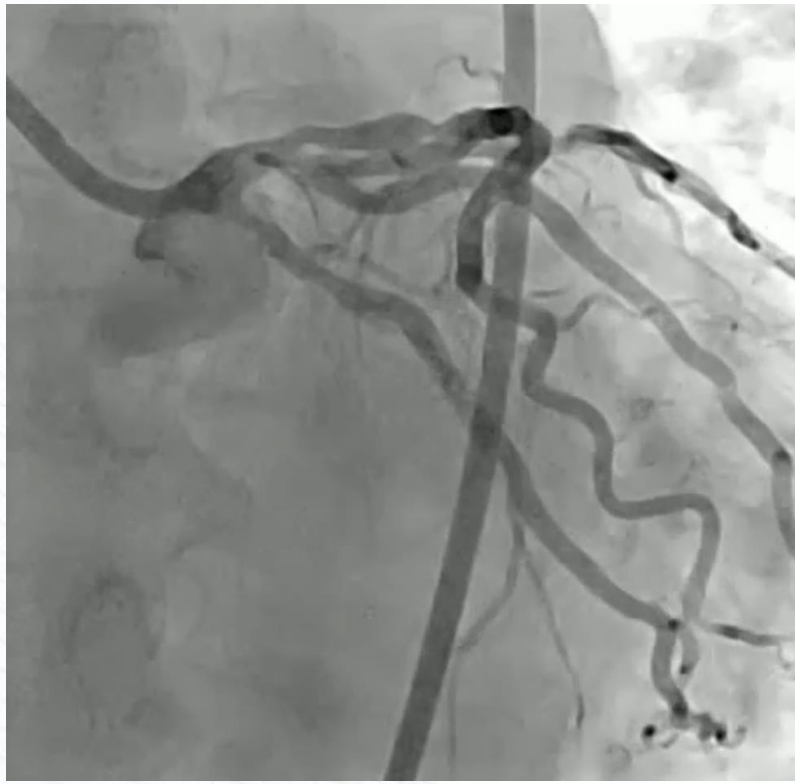
- **Not focus on patients with diabetes**
  - SYNTAX, BEST
- **Just subgroup analyses with study underpower**
  - SYNTAX, BEST
- **Not use current generation DES**
  - FREEDOM, SYNTAX
- **Not frequently use intracoronary imaging and physiology**
  - SYNTAX, FREEDOM
- **Not use GDMT (e.g., SGLT-2 inhibitors or GLP-1 RA) of current practice**
  - FREEDOM, BARI 2D

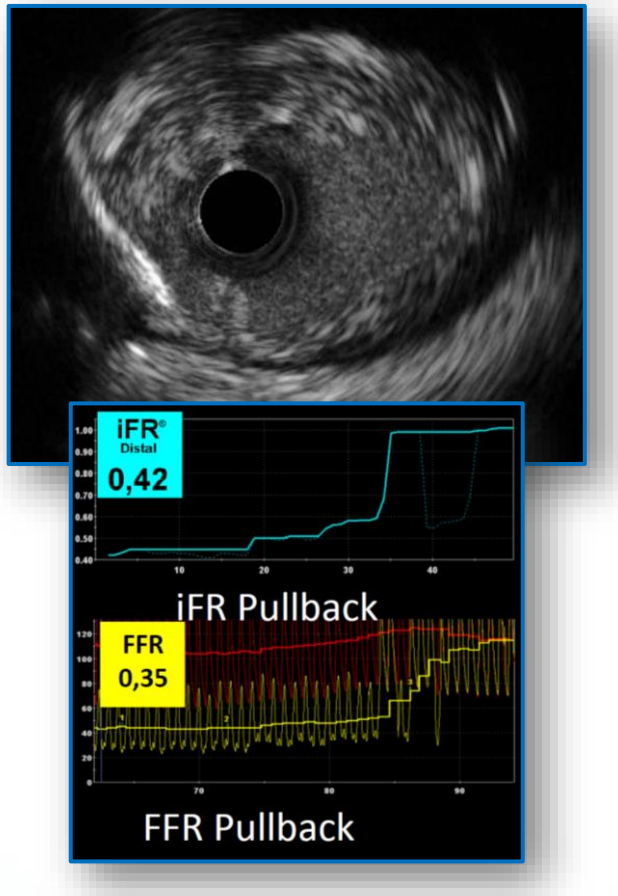
DRIVING THE FUTURE of PRECISION MEDICINE

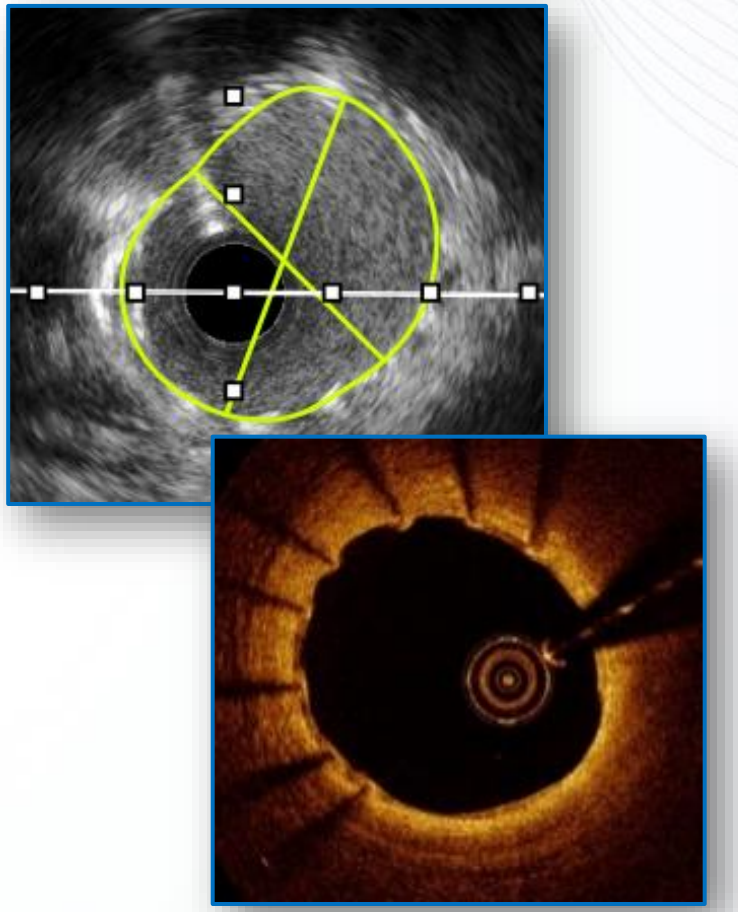
ASSESSMENT INTERVENTION

Lesion Selection Guidance Optimization

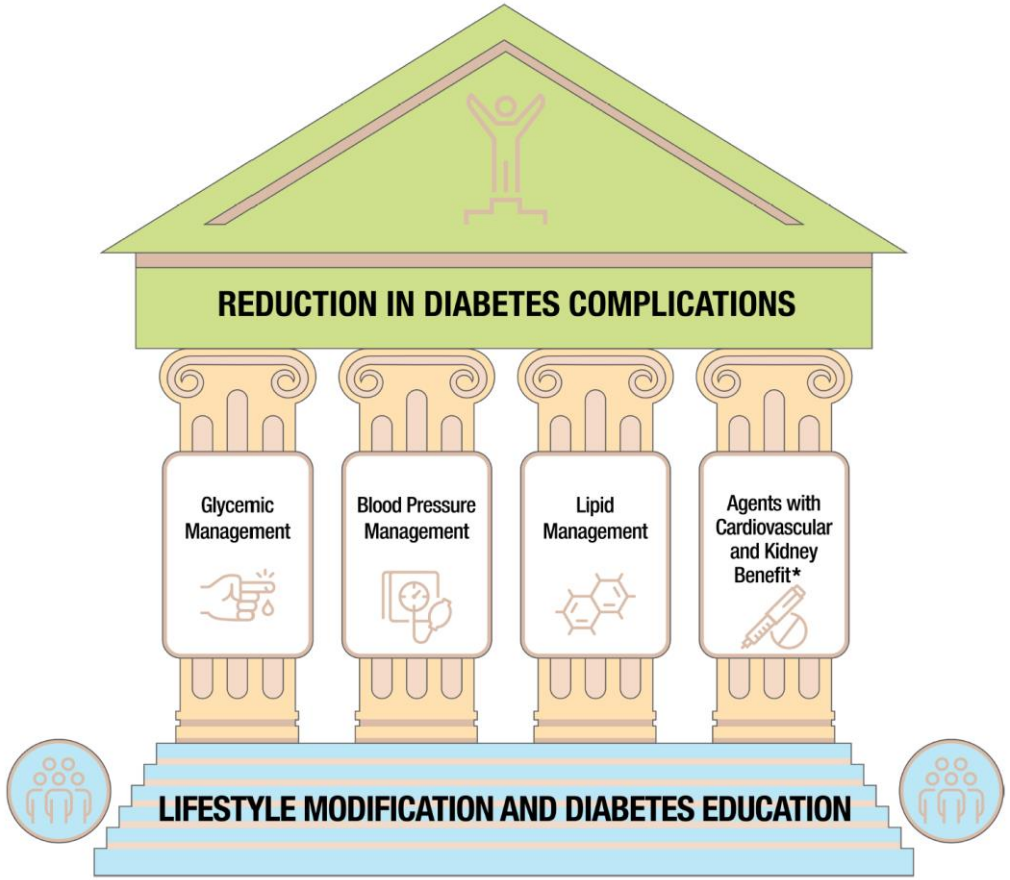
For Contemporary PCI

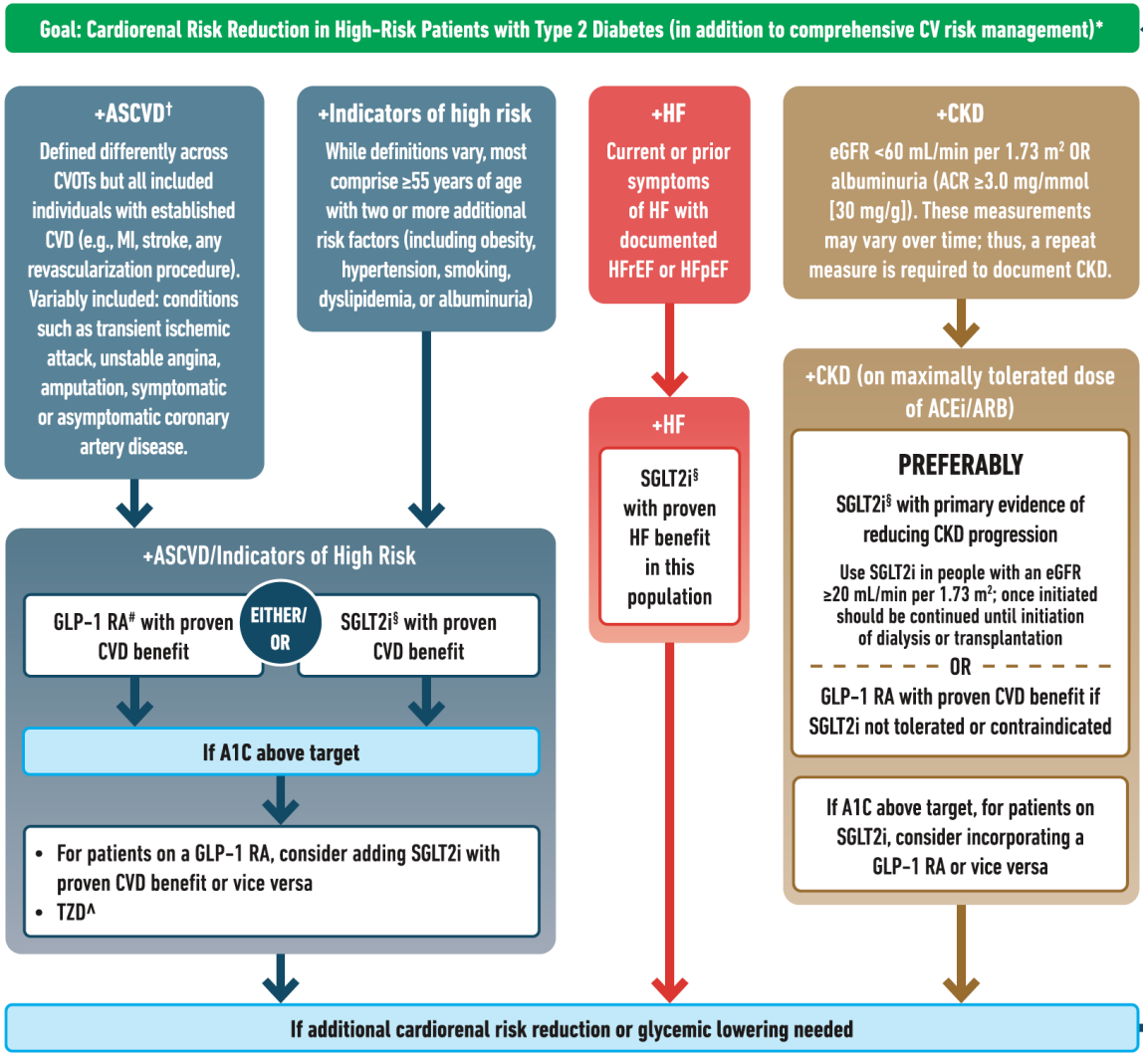






Remarkable Advances in Diabetic Management



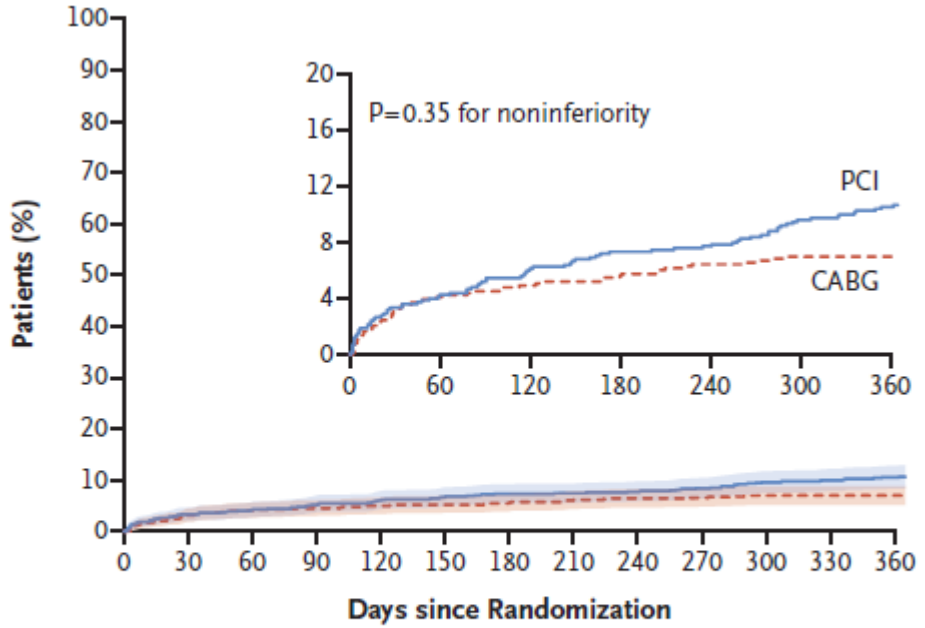


FAME 3 Trial

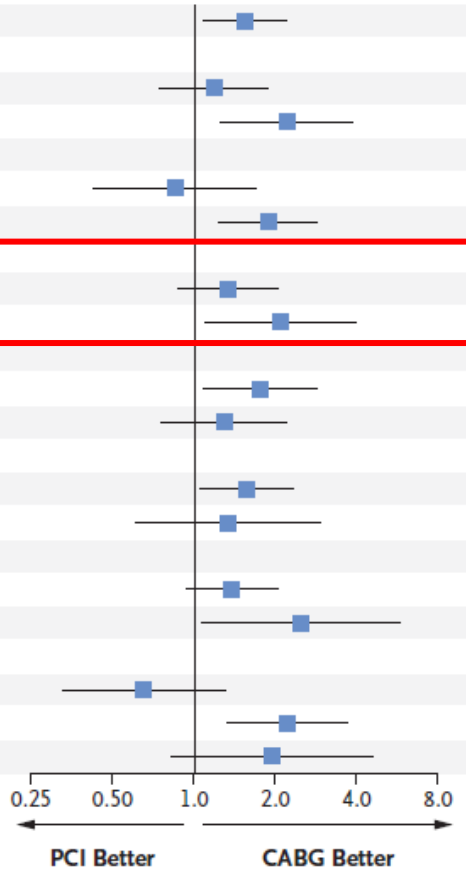
1,500 patients with 3VD

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

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



Subgroup	PCI (total no.)	CABG (total no.)	PCI (1-yr incidence %)	CABG (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



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 only used in 11.7%

>> Just subgroup analysis for patients with diabetes

N Engl J Med 2022;386:128-37

What Would be Next New Trials in Patients with DM and Multivessel CAD?

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

Trial Hypothesis

- **Trial Hypothesis**: advanced state-of-the-art PCI using intracoronary imaging (e.g., IVUS or OCT), intracoronary physiology (e.g., FFR or iFR), contemporary DES and GDMT with advanced cardiovascular and anti-diabetic medications (e.g., SGLT-2 inhibitors or GLP-1 RA) in patients with type 2 diabetes and multivessel CAD with LAD involvement will result in similar outcomes to CABG in a contemporary trial.

Trial Design

Diabetes-Centered **E**valuation of **F**unctional and **I**maging-Combi**NE**d State-of-the-Art Percutaneous Coronary Intervention or Coronary-Artery Bypass Grafting in Patients with **D**iabetes **M**ellitus 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.

Inclusion / Exclusion Criteria

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 disease requiring revascularization
- Complex CAD anatomy of lesion characteristics that PCI is not suitable
- STEMI
- 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 a composite of of hard clinical endpoints of **death from any causes, MI, or stroke** at 2 years.

Secondary

- Each individual component of primary composite outcome
- Composite of death, MI, stoke, or repeat revascularization
- Stent thrombosis or symptomatic graft occlusion or stenosis
- Bleeding complications (BARC criteria)
- Periprocedural major adverse events
- 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)

Sample Size and Statistics

- The trial use a “**noninferiority design**”.
- Assuming 12% of 2-year primary outcome events (death, MI, or stroke) in the CABG arm (which was based on FEEDOM trial),
- Given a clinically irrelevant hazard ratio of 1.45, a one-sided 2.5% significance level and 85% power,
- The sample size necessary is 582 patients per group (1164 for the entire study).
- To account for patients lost to follow-up (we anticipate a <5% loss to follow-up), **1,200 patients will be enrolled from 50 sites over 4 years**. We assumed 4 years of enrollment time and 2 years follow-up for all patients (total time would be 6 years).

Key Message

- Old evidence suggested CABG was always better than PCI in patients with DM and multivessel CAD. This was unanimously adopted in the contemporary revascularization guidelines (CABG – class 1, PCI – class 2 or 3).
- However, there are several limitations for interpreting prior RCTs and still unmet needs in the contemporary advanced PCI era.
- We need next new trials comparing imaging/physiology-guided **"state-of-the-art PCI"** combined with advanced GDMT of newer anti-diabetic and cardioactive drugs vs. contemporary CABG in patients with diabetes and multivessel disease.
- This will be validated from the **DEFINE-DM** trial.