Supplementary data

Trial details: Endpoint definition of single trials. Trial enrollment periods and inclusion and exclusion criteria

SYNTAX

Study Period: from March 2005 to April 2007
85 centres (Europe and USA) adhered to the SYNTAX protocol

Main inclusion criteria:

- Three vessel disease or left main disease (> 50% stenosis or left main equivalent)
- No previous CABG or PCI
- Patients with stable or unstable angina or with evidence of documental ischemia if asymptomatic
- Decision by local Heart Team (cardiac surgeon and interventional cardiologist) that either CABG or PCI can realize equivalent anatomical revascularization.

PRECOMBAT

Study Period: from April 2004 to August 2009
13 centers in South Korea adhered to the PRECOMBAT protocol

Main inclusion criteria:

- diagnosis of stable angina, unstable angina, silent ischemia, or non–ST-segment elevation myocardial infarction;
- new diagnosis of unprotected left main coronary artery (ULMCA) stenosis (> 50% by angiographic visual estimation);
- patients were considered by local Heart Team (cardiac surgeon and interventional cardiologist) to be a suitable candidate for either PCI or CABG.

Main exclusion criteria:

- contraindication to any of the following medications: heparin, aspirin, both clopidogrel and ticlopidine, sirolimus, stainless steel and/or contrast media;
- any previous percutaneous coronary intervention (PCI) of a ULMCA or ostial left circumflex artery or ostial left anterior descending artery within 1 year or previous CABG;
- acute MI within 1 week;
- ejection fraction < 30%;
- cardiogenic shock;
- any stroke or any cerebrovascular accident within 6 months
- Creatinine level ≥ 2.0 mg/dL or dependence on dialysis.
- Severe hepatic dysfunction

BEST

Study Period: from July 2008 – to September 2013
27 sites in South Korea, China, Malaysia, and Thailand adhered to the BEST protocol

Main key inclusion criteria:

- Age ≥ 18 years.
- Angiographically confirmed multivessel CAD (stenosis > 70%) in at least 2 major epicardial vessels (≥ 2.0 mm in diameter) in at least two separate coronary artery territories (LAD, LCX, RCA) and valuated to be equally managed with PCI or CABG).
- Indication for intervention based on symptoms of angina and/or evidence of myocardial ischemia.
- Agreement by the patient or guardian to the study protocol and the clinical follow-up.
- Provision of written informed consent.

Main key exclusion criteria:

- Known hypersensitivity or contraindication to any of: heparin, aspirin, clopidogrel, everolimus stainless steel and/or true anaphylaxis to prior contrast media
- Severe congestive heart failure. The left ventricular ejection fraction was not considered a criterion for exclusion.
- Planned simultaneous surgical procedure (e.g., valve repair/replacement, aneurysmectomy, carotid endarterectomy or carotid stent).
- Previous CABG
- Prior PCI with DES within 1 year.
- Two or more chronic total occlusions in major coronary territories.
- Acute ST-elevation myocardial infarction within 72 hours prior to enrollment.
- Abnormal creatine kinase (CK > 2× normal) and/or abnormal CK-MB levels and/or elevated troponin levels at the time of randomization.
- Previous stroke within 6 months or stroke at more than 6 months with residual neurologic involvement.
- Extra-cardiac disease with life expectancy less than 2 years, e.g., COPD, active hepatitis, hepatic failure, or severe renal disease.
- Prior history of significant bleeding
- Contraindication to either CABG or PCI/DES due to a coexisting clinical condition.
- Intolerance or contraindication to aspirin or clopidogrel.
- Suspected pregnancy.
- Concurrent enrollment in another clinical trial.
- Left main coronary artery stenosis (≥ 50% diameter).

FREEDOM

Study Period: from April 2005 – to April 2010
141 sites worldwide adhered to the FREEDOM protocol.

Main key inclusion criteria:

- Patients with diabetes (Type 1 or Type 2) and angiographically confirmed multivessel coronary artery disease with stenosis of more than 70% in two or more major epicardial vessels involving least two separate coronary-artery territories and without left main coronary stenosis.
- multivessel disease suitable for either approach
- Indication for revascularization based upon symptoms of angina and/or objective evidence of myocardial ischemia
- Willing to comply with all follow-up required study visits
- Signed and received copy of informed consent

Main key exclusion criteria:

- Two or more chronic total occlusions in major coronary territories.
- Abnormal creatine kinase (CK > 2x normal) level at coronary territories time of randomization.
- Extra-cardiac illness with a life expectancy lower than 5 years
- Severe congestive heart failure Prior CABG surgery
- Prior cardiac valve surgery
- Prior PCI with DES within 6 months
- Previous stroke within 6 months or patients with stroke with significant residual neurologic involvement
- In-stent restenosis of target vessel
- Left main stenosis (≥50% diameter stenosis)
- Acute ST-elevation MI within 72 h before enrollment
- Planned simultaneous surgical procedure (eg, valve repair/replacement, aneurysmectomy, carotid endarterectomy, or carotid stent)
- Contraindication to either CABG or PCI/DES
- Significant leukopenia, neutropenia, thrombocytopenia, anemia, or known bleeding diathesis
- Intolerance or contraindication to aspirin or both clopidogrel and ticlopidine.
- Dementia
- Suspected pregnancy
- Geographically inaccessible for follow-up visits required by protocol

Table 1 of the supplementary data. Algorithm literature search

Search	PUBMED	
#1	(("coronary artery bypass"[Title/Abstract] OR "cabg"[Title/Abstract]) AND 2010/01/01:2023/01/31[Date - Publication]) AND (2010/1/1:2023/1/31[pdat])	23,119
#2	(("drug eluting stent"[Title/Abstract] OR "des"[Title/Abstract] OR "stenting"[Title/Abstract]) AND 2010/01/01:2023/01/31[Date - Publication]) AND (2010/1/1:2023/1/31[pdat])	41,772
#3	(("percutaneous coronary intervention"[Title/Abstract] OR "pci"[Title/Abstract]) AND 2010/01/01:2023/01/31[Date - Publication]) AND (2010/1/1:2023/1/31[pdat])	40,603
#4	(("left main disease"[Title/Abstract] OR "left main coronary artery disease"[Title/Abstract]) AND 2010/01/01:2023/01/31[Date - Publication]) AND (2010/1/1:2023/1/31[pdat])	1,227
#5	("multivessel coronary artery disease"[Title/Abstract] AND 2010/01/01:2023/01/31[Date - Publication]) AND (2010/1/1:2023/1/31[pdat])	914
#6	#1 AND #2 AND #3 AND #4 OR #5	1064
#7	("randomised"[Title/Abstract] OR "randomized"[Title/Abstract] OR "trial"[Title/Abstract]) AND (2010/1/1:2023/1/31[pdat])	737,198
#8	("long term follow up"[Title/Abstract] OR "extended follow up"[Title/Abstract]) AND (2010/1/1:2023/1/31[pdat])	39,605
#9	#7 AND #8	6,339
#10	#6 AND #9	**27**
EMBASE		
#1	('**coronary artery bypass**' OR '**cabg**':ab,ti) AND [2010-2023]/py	67,901
#2	('**drug-eluting stent**' OR '**des**' OR '**stenting**':ti,ab) AND [2010-2023]/py	373,598
#3	('**percutaneous coronary intervention**' OR '**pci**':ti,ab) AND [2010-2023]/py	108,182
#4	('**left main disease**' OR '**left main coronary artery disease**':ti,ab) AND [2010-2023]/py	2,511
#5	'**multivessel coronary artery disease**':ti,ab AND [2010-2023]/py	1,624
#6	(**randomized** OR **randomised** OR **trial**:ab,ti) AND [2010-2023]/py	1,388,705
#7	#1 AND #2 AND #3 AND #4	449
#8	**('long term follow-up'** OR '**extended follow-up**' AND [2010-2023]/py	71,382
#9	#6 AND #7 AND #8	**72**
CENTRAL		
#1	(left main disease):ti,ab,kw OR (left main coronary artery disease):ti,ab,kw (Word variations have been searched) with Publication Year from 2010 to 2023, in Trials	1747
#2	(multivessel coronary artery disease):ti,ab,kw with Publication Year from 2010 to 2023, in Trials (Word variations have been searched)	189
#3	(percutaneous coronary intervention):ti,ab,kw OR ("PCI"):ti,ab,kw (Word variations have been searched) with Publication Year from 2010 to 2023, in Trials	11849

#4	("drug eluting stent"):ti,ab,kw OR (des):ti,ab,kw OR (stenting):ti,ab,kw with Publication Year from 2010 to 2023, in Trials (Word variations have been searched)	13973
#5	("coronary artery bypass"):ti,ab,kw OR (cabg):ti,ab,kw with Publication Year from 2010 to 2023, in Trials (Word variations have been searched)	7608
#6	(randomized):ti,ab,kw OR (trial):ti,ab,kw OR (randomised):ti,ab,kw with Publication Year from 2010 to 2023, in Trials (Word variations have been searched)	902056
#7	#1 AND #3 AND #4 AND #5	226
#8	#7 OR #2	410
#9	#8 AND #6	**376**

Table 2 of the supplementary data. Risk of bias assessment using the Cochrane Collaboration revised tool for randomized control trials (RoB 2)

Study	D1	D2	D3	D4	D5	Overall
FREEDOM 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
SYNTAX 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
PRECOMBAT 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
BEST 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
EXCEL 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
NOBLE 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Low risk
Some concerns
High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Table 3 of the supplementary data. Restricted mean survival time (RMST)

RMST	CABG	PCI	RMST difference	p-value
5-years	4.71 (95%CI, 4.67-4.75) years	4.64 (95%CI, 4.60-4.68) years	0.07 years (25 days) (95%CI, 0.01-0.125;)	*P* =.02
8-years	7.16 (95%CI, 7.08-7.24) years	7.30 (95% CI, 7.23-7.38) years	0.14 years (1.7 months) (95%CI, 0.03-0.25;)	*P* = .009
10-years	8.93 (95%CI, 8.83-9.03) years	8.73 (95%CI, 8.62-8.84) years	0.20 years (95%CI, 0.05-0.35;)	*P* = .007

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; CI, confidence interval.

Figure 1 of the supplementary data. The PRISMA flow chart of study selection process

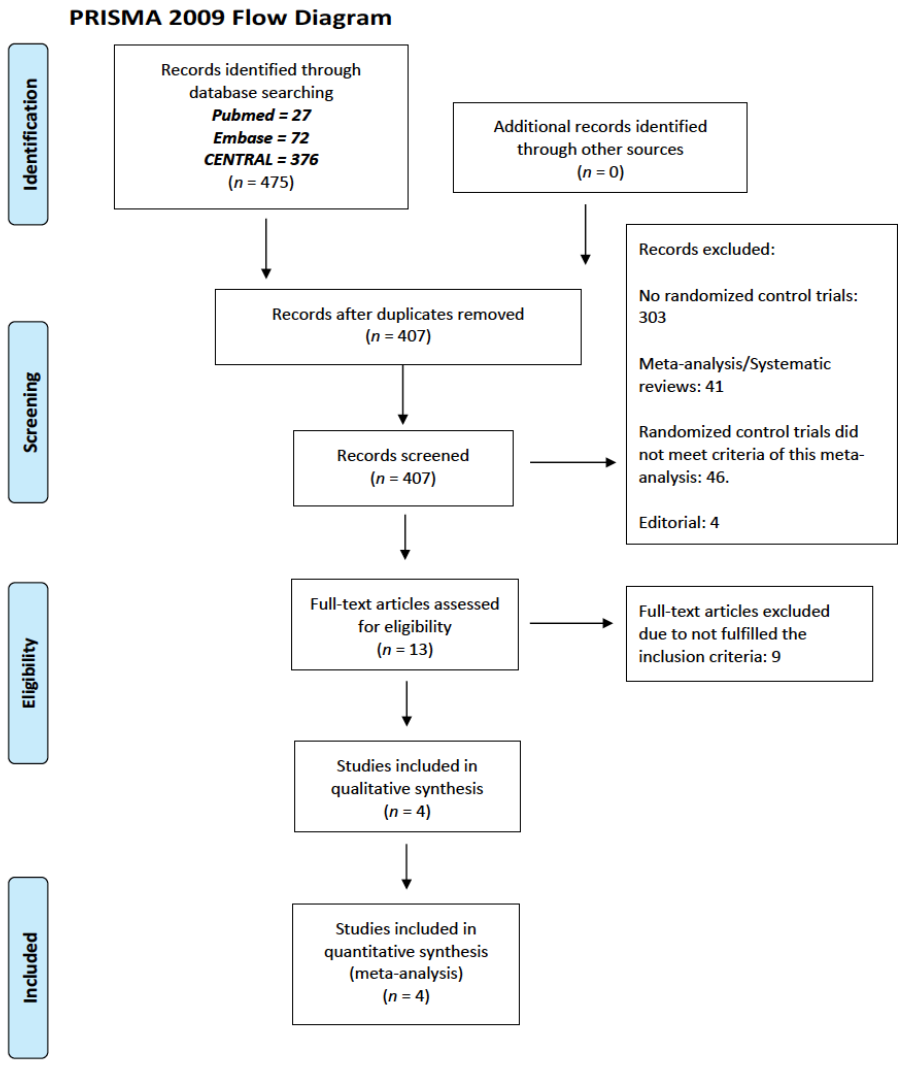

Figure 2 of the supplementary data

Log-minus-log survival curves. If the assumption of proportional hazard is valid, the lines should be parallel. The plot shows the two lines are not parallel and cross each other. Therefore, the hazard ratio is not constant over time. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; ln, natural log.

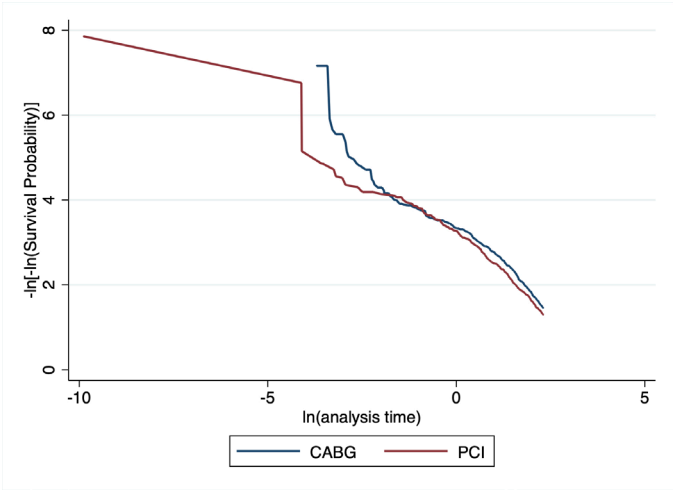

Figure 3 of the supplementary data. Predicted versus observed survival functions. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

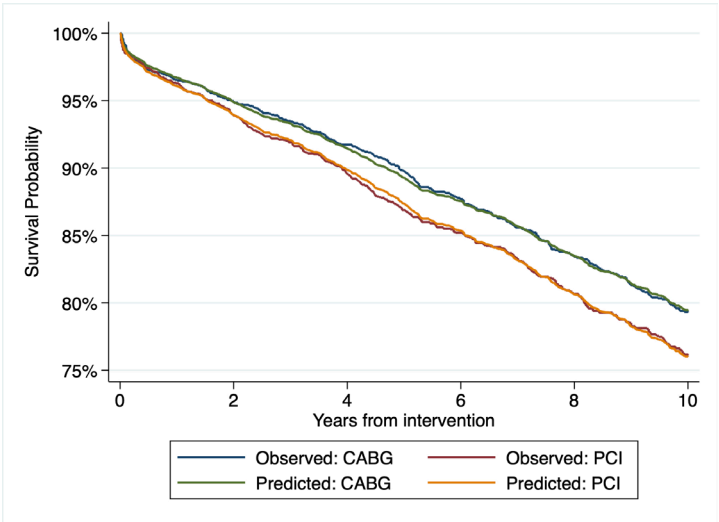

Figure 4 of the supplementary data. Scaled Schoenfeld residuals. PH, proportional hazard

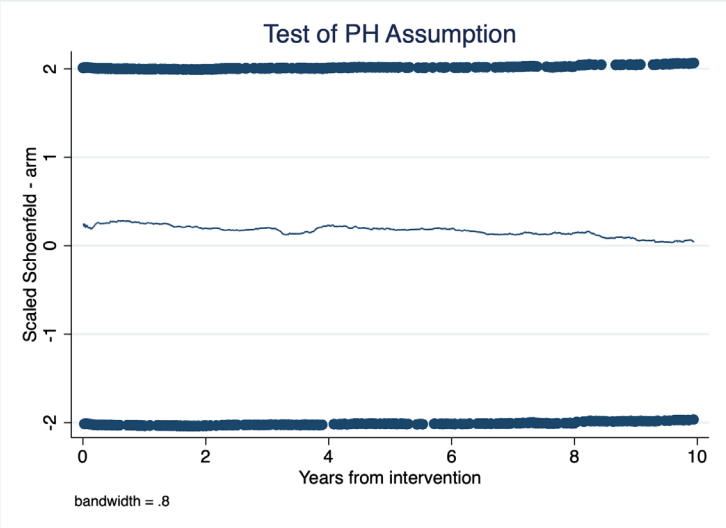

Figure 5 of the supplementary data. Time-to-event reconstructed curves for repeat coronary revascularization. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

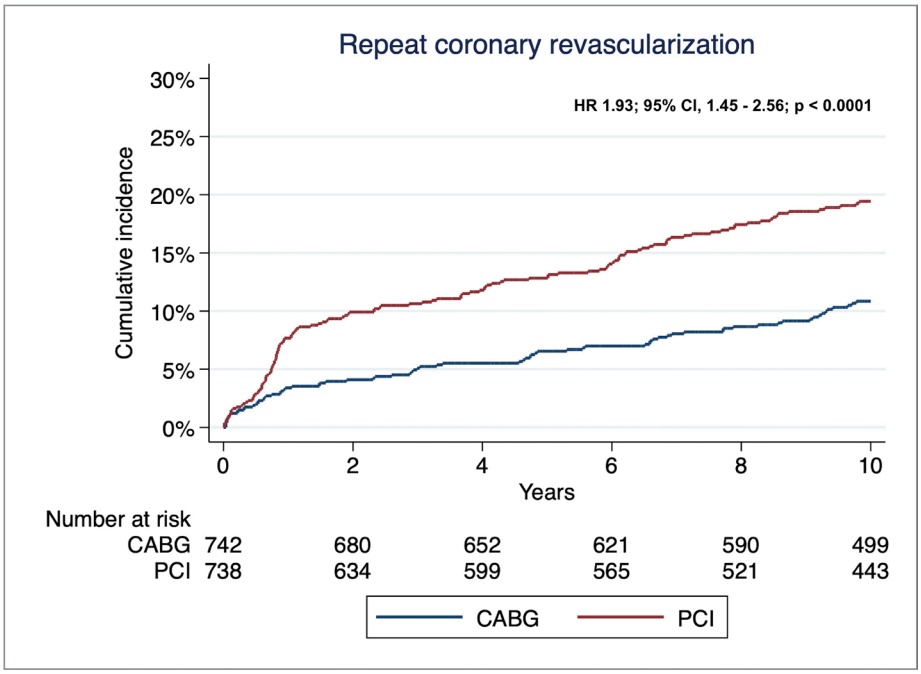

Figure 6 of the supplementary data. Time-to-event reconstructed curves for composite endpoints of all-cause mortality, myocardial infarction or stroke. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention. HR, hazard ratio; CI, confidence interval.