Supplementary Online Content

Gaudino M, Hameed I, Farkouh ME, et al. Overall and cause-specific mortality in randomized clinical trials comparing percutaneous interventions with coronary bypass surgery: a meta-analysis. Published online October 12, 2020. *JAMA Intern Med.* doi:10.1001/jamainternmed.2020.4748

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Full Search Strategy

Ovid MEDLINE® ALL - 1946 to November 21, 2019
Searched on November 24, 2019
Limited to RCTs via BMJ's study design search filter available from:
https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/

Line #	Search
1	Percutaneous Coronary Intervention/
2	(percutaneous coronary intervention* or percutaneous coronary revascularization* or PCI or percutaneous coronary angioplasty or stent or stents or stenting).tw.
3	Angioplasty, Balloon, Coronary/
4	(coronary balloon angioplasties or coronary balloon angioplasty or transluminal coronary balloon dilation or coronary artery balloon dilation or percutaneous transluminal coronary angioplasty or coronary angioplasty or coronary angioplasties or PTCA).tw.
5	or/1-4
6	Coronary Artery Bypass/
7	(coronary adj2 (bypass or graft)).tw.
8	(CABG or aorticocoronary anastomosis or total arterial revascularization or total arterial revascularisation or Multiple arterial revascularization or multiple arterial revascularisation).tw.
9	Coronary Artery Bypass, Off-Pump/
10	Internal Mammary-Coronary Artery Anastomosis/
11	((Right Internal Mammary Artery or RIMA or Coronary Internal Mammary Artery or arteria mammaria interna or arteria thoracica interna or internal thoracic artery or mammary internal artery) and (transplant* or graft* or anastomosis)).tw.
12	(surgical revascularization or cardiac muscle revascularisation or cardiac muscle revascularization or coronary revascularisation or coronary revascularization or heart muscle revascularisation or heart myocardium revascularisation or heart revascularisation or heart revascularization or internal mammary arterial anastomosis or internal mammary arterial implantation or internal mammary artery anastomosis or internal mammary artery graft or internal mammary artery implant or internal mammary artery implantation or internal mammary-coronary artery anastomosis or myocardial revascularisation or myocardial revascularization or myocardium revascularisation or myocardium revascularization or transmyocardial laser revascularisation or transmyocardial laser revascularization or vineberg operation).tw.
13	or/6-12
14	"randomized controlled trial".pt.
15	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab
16	(retraction of publication or retracted publication).pt.
17	or/14-16
18	(animals not humans).sh.
19	((comment or editorial or meta-analysis or practice-guideline or review or letter) not "randomized controlled trial").pt.
20	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.

21 17 not (18 or 19 or 20)
22 5 and 13
23 22 and 21

eTable 2. Summary of the Included Randomized Clinical Trials

Trial	Number of centers	Location	Study period	Number of patients randomized	Mean follow-up (years)
ARTS[1]	67	Europe	1997-1998	1205 (PCI: 600, CABG: 605)	5
BEST [2]	27	Asia	2008-2013	880 (PCI: 438, CABG: 442)	4.6
Blazek et al[3]	1	Germany	1997-2001	220 (PCI: 110, CABG: 110)	10.3
Boudriot et al[4]	4	Germany	2003-2009	201 (PCI: 100, CABG: 101)	1
CARDia[5]	24	United Kingdom, Ireland	2002-2007	510 (PCI: 256, CABG: 254)	2
Cisowski et al[6]	1	Poland	2000-2001	100 (PCI: 50, CABG: 50)	1
Drenth et al[7]	1	Netherlands	1997-1999	102 (PCI: 51, CABG: 51)	4
ERACI II [8]	7	North America, Europe, South America	1996-1998	450 (PCI: 225, CABG: 225)	5
EXCEL[9]	126	Europe, North America, Asia, South America	2010-2014	1905 (PCI: 948, CABG: 957)	5
FREEDOM[10]	140	United States	2005-2010	1900 (PCI: 953, CABG: 947)	3.8, 7.5
Hong et al[11]	1	South Korea	2003	189 (PCI: 119, CABG: 70)	0.5
Kim et al[12]	1	South Korea	2000-2001	100 (PCI: 50, CABG: 50)	1
LE MANS[13]	3	Poland	2001-2004	105 (PCI: 52, CABG: 53)	9.8
MASS-II[14]	1	Brazil	1995-2000	408 (PCI: 205, CABG: 203)	11.4
Myoprotect[15]	1	Germany	1998-2001	44 (PCI: 23, CABG: 21)	1
NOBLE[16]	36	Europe	2008-2015	1184 (PCI: 592, CABG: 592)	4.9
Octostent[17]	3	Netherlands	1998-2000	280 (PCI: 138, CABG: 142)	1
PRECOMBAT[18]	13	Korea	2004-2009	600 (PCI: 300, CABG: 300)	5
Stent or Surgery (SoS) [19]	53	Europe, Canada	1996-1999	988 (PCI: 488, CABG: 500)	2
SIMA [20]	6	Europe	-	121 (PCI: 62, CABG:59)	10
SYNTAX [21,22]	85	Europe, United States	2005-2007	1800 (PCI: 903, CABG: 897)	5, 10
Thiele et al [23]	1	Germany	2003-2007	130 (PCI: 65, CABG: 65)	3.6
VA CARDS [24]	22	United States	2006-2010	198 (PCI: 101, CABG: 97)	2

eTable 3. Details of Patient Characteristics

Trial	Treatment	Age, mean (SD), median [IQR]	Female (%)	BMI (SD) [IQR]	Smoking (%)	DM (%)	Insulin (%)	CAD, family history (%)	Statin (%)	HTN (%)	HCL/HLD (%)	PVD (%)	Carotid artery disease (%)	Prior Stroke (%)	Prior MI (%)	Prior TIA (%)	Prior CHF (%)	Prior PCI (%)	Prior CABG (%)	LVEF (SD) [IQR]	SA (%)	UA (%)	ACS (%)
ARTS[1]	PCI	61 (10)	23	27.2 (3.7)	28	19	-	39	-	45	58	6	-	-	44	-	-	-	-	-	57	37	-
	CABG	61 (9)	24	27.4 (3.7)	26	16	-	42	-	45	58	5	-	-	42	-	-	-	-	-	60	35	-
BEST [2]	PCI	64.0 (9.3)	30.6	24.7 (2.9)	20.1	40.4	4.6	-	-	67.6	54.6	3.4	-	8.4	5.7	-	3.7	6.8	-	59.1 (8.5)	47.9	42.1	-
	CABG	64.9 (9.4)	26.5	25.0 (2.9)	20.1	42.1	4.1	-	-	66.7	50.2	2.7	-	7.5	6.6	-	2.7	8.6	-	59.9 (8.1)	46.2	45.0	-
Blazek et al[3]	PCI	62.5 (10.2)	28	28.2 (3.8)	25	34	-	18	-	72	70	-	-	-	45	-	-	0	0	62 (15)	-	-	-
	CABG	61.6 (10.0)	15	27.2 (3.4)	25	25	-	17	-	71	73	-	-	-	45	-	-	0	0	63 (11)	-	-	-
Boudriot et al.[4]	PCI	66 [62-73]	28	27.2 [24.6-31.5]	-	40	-	-	-	82	68	-	-	3	19	-	-	-	-	65.0 [55.0-70.0]	-	-	-
	CABG	69 [63-73]	22	27.0 [24.9-30.1]	-	33	-	-	-	82	64	-	-	6	14	-	-	-	-	65.0 [55.0-68.0]	-	-	-
CARDia[5]	PCI	64.3 (8.5)	29.3	29.2 (4.9)	29.3	100	36.5	-	-	76.6	92.9	2.4	-	-	-	-	-	-	-	-	-	-	-
	CABG	63.6 (9.1)	22.1	29.4 (5.3)	29.1	100	39.1	-	-	80.6	87.3	5.2	-	-	-	-	-	-	-	-	-	-	-
Cisowski et al[6]	PCI	53.3 (10.2)	16	-	52	8	-	40	-	52	78	-	-	-	-	-	-	0	0	-	-	-	-
	CABG	54.1 (9.1)	18	-	48	6	-	44	-	56	76	-	-	-	-	-	-	0	0	-	-	-	-
Drenth et al[7]	PCI	61 (1.3)	25	-	58	18	-	50	-	33	45	-	-	0	18	-	-	0	0	-	-	-	-
	CABG	60 (1.6)	22	-	62	8	-	46	-	16	41	-	-	0	24	-	-	0	0	-	-	-	-
ERACI II[8]	PCI	62.5 (11.5)	22.7	28.8% above 30	54.3	17.3	-	-	-	71.0	62.5	19.1	-	-	28.5	-	-	-	-	-	-	92.1	-
	CABG	61.4 (10.1)	18.6	32.5% above 30	49.5	17.3	-	-	-	70.5	60.2	26.6	-	-	27.7	-	-	-	-	-	-	90.7	-

EXCEL[9]	PCI	66.0 (9.6)	23.8	28.6 (5.0)	23.4	30.2	7.7	-	-	74.2	70.5	10.2	-	-	17.8	5.5	7.1	18.4	0	57.0 (9.6)	52.7	24.1	-
	CABG	65.9 (9.5)	22.5	28.8 (4.9)	20.2	28.0	7.7	-	-	73.2	68.1	8.8	-	-	16.8	7.0	6.2	15.9	0	57.3 (9.0)	52.8	24.5	-
FREEDOM[10]	PCI	63.2 (8.9)	26.8	29.6 (5.4)	14.8	100	33.8	-	82.1	84.6	-	-	-	3.9	26.2	-	-	-	-	65.7 (12.1)	-	-	31.9
	CABG	63.1 (9.2)	30.5	29.8 (5.3)	16.6	100	30.9	-	82.6	85.1	-	-	-	3.0	25.0	-	-	-	-	66.6 (10.5)	-	-	29.5
Hong et al[11]	PCI	60.5 (9.6)	36.1	25.5 (2.9)	40.3	37.0	-	9.3	-	50.4	54.6	-	-	2.5	21.8	-	-	0	0	52.8 (8.8)	-	50.4	-
	CABG	61.4 (9.9)	35.7	26.6 (3.9)	45.7	48.6	-	10.0	-	55.7	51.4	-	-	2.9	22.9	-	-	0	0	51.9 (9.1)	-	42.9	-
Kim et al[12]	PCI	61 (12)	40	-	45	20	-	-	-	55	60	-	-	2	22	-	0	0	0	51 (11)	-	65	-
	CABG	63 (12)	30	-	55	15	-	-	-	55	70	-	-	2	22	-	0	0	0	49 (13)	-	55	-
LE MANS[13]	PCI	60.6 (10.5)	40	-	-	19	-	-	-	75	65	-	-	-	36	-	-	-	-	53.5 (10.7)	-	-	-
	CABG	61.3 (8.4)	27	-	-	17	-	-	-	70	60	-	-	-	32	-	-	-	-	53.7 (6.7)	-	-	-
MASS-II[14]	PCI	60 (9)	33.0	-	27	23	-	-	-	61	-	-	-	-	52	-	-	-	-	67 (8)	78	-	-
	CABG	60 (9)	28.0	-	32	29	-	-	-	63	-	-	-	-	41	-	-	-	-	67 (9)	86	-	-
Myoprotect[15]	PCI	69 (8)	17	-	-	39	-	-	22	96	-	-	-	-	-	-	-	-	-	52	78	-	-
	CABG	71 (7)	43	-	-	38	-	-	48	86	-	-	-	-	-	-	-	-	-	56	57	-	-
NOBLE[16]	PCI	66.2 (9.9)	20.0	27.9 (4.5)	19	15	-	58	82	65.2	-	-	-	-	-	-	-	19.6	0.7	60 [55-65]	82.1	-	17.9
	CABG	66.2 (9.4)	24.0	28.1 (4.4)	22	15	-	56	78	65.7	-	-	-	-	-	-	-	19.9	0.3	60 [52-64]	82.9	-	16.9
Octostent[17]	PCI	60.3 (9.1)	30	-	25	9	-	60	-	33	59	7	-	1	25	-	-	4	-	-	-	30	-
	CABG	58.9 (10.0)	28	-	19	14	-	62	-	31	60	7	-	2	23	-	-	5	-	-	-	34	-
PRECOMBAT[18]	PCI	61.8 (10.0)	24.0	24.6 (2.7)	-	34	3.3	-	-	54.3	42.3	5.0	-	-	3.4	-	0.0	12.7	-	61.7 (8.3)	53.3	42.7	-
	CABG	62.7 (9.5)	23.0	24.5 (3.0)	-	30	3.0	-	-	51.3	40.0	2.3	-	-	6.7	-	0.7	12.7	-	60.6 (8.5)	45.7	48.0	-

Stent or Surgery (SoS)[19]	PCI	61 (9.2)	20.0	-	16	13.9	4	48	-	43	53	6	-	1	44	1	-	-	-	57	-	19	-
	CABG	62 (9.8)	22.0	-	14	14.8	2	48	-	47	50	7	-	3	47	2	-	-	-	57	-	22	-
SIMA[20]	PCI	59 (57-62)	24	-	57	11	-	36	-	46	62	-	-	2	2	-	-	-	-	67 [65-69]			
	CABG	60 (58-63)	17	-	50	13	-	27	-	48	55	-	-	0	2	-	-	-	-	67 [65-70]			
SYNTAX[21,22]	PCI	65.2 (9.7)	23.6	28.1 (4.8)	18.5	25.6	24.6	-	-	68.9	78.7	-	8.1	3.9	31.9	4.3	4.0	-	-	-	56.9	28.9	-
	CABG	65.0 (9.8)	21.1	27.9 (4.5)	22.0	24.6	9.9	-	-	64.0	77.2	-	8.4	4.8	33.8	5.2	5.3	-	-	-	57.2	28.0	-
Thiele et al[23]	PCI	66 (59-72)	31	28.0 (3.7)	14	28	-	-	-	83	55	-	-	3	23	-		0	0	65 [60-66]	-	-	-
	CABG	66 (59-71)	29	26.9 (4.0)	18	25	-	-	-	85	55	-	-	9	23	-		0	0	65 [60-70]	-	-	-
VA CARDS[24]	PCI	62.7 (7.1)	1.0	32.8 (5.7)	27.7	100	47.9	-	-	96.0	-	10.9	-	6.9	-	-	-	34.7	3	-	-	-	-
	CABG	62.1 (7.4)	1.0	33.0 (5.7)	20.6	100	47.5	-	-	95.7	-	17.0	-	8.5	-	-	-	20.2	1.1	-	-	-	-

Trial	Treatment	Bifurcation (%)	Bifurcation or trifurcation of the distal left artery (%)	Diseased non-left main coronary arteries (0,1,2,3) (%)	NYHA Class I (%)	NYHA Class II (%)	NYHA Class III (%)	NYHA Class IV (%)	EuroSCORE (SD) [IQR]	SYNTAX score (SD) [IQR]
ARTS[1]	PCI	34	-	(0,2,68,30)	-	-	-	-	-	-
	CABG	31	-	(0,0,67,33)	-	-	-	-	-	-
BEST[2]	PCI	57.5	-	-	-	-	-	-	2.9 (2.0)	24.2 (7.5)
	CABG	58.8	-	-	-	-	-	-	3.0 (2.1)	24.6 (8.1)
Blazek et al[3]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
Boudriot et al[4]	PCI	-	-	(28,35,26,11)	-	-	-	-	-	24.0 [19.0-29.0]
	CABG	-	-	(29,27,28,17)	-	-	-	-	-	23.0 [14.8-29.0]
CARDia[5]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
Cisowski et al[6]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
Drenth et al[7]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
ERACI II[8]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-

EXCEL[9]	PCI	-	81.3	(17.2,30.8,34.3,17.)	-	-	-	-	-	32.2% (<22); 42.8% (23-32); 25.1% (>33)
	CABG	-	77.4	(17.5,30.5,30.8,19.0)	-	-	-	-	-	39.3% (<22); 37.3% (23-32); 23.4% (>33)
FREEDOM[10]	PCI	-	-	-	-	-	-	-	2.7 (2.4)	26.2 (8.4)
	CABG	-	-	-	-	-	-	-	2.8 (2.5)	26.1 (8.8)
Hong et al[11]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
Kim et al[12]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
LE MANS[13]	PCI	-	-	(0,13,27,60)	-	-	-	-	3.3 (2.3)	25.2 (8.7)
	CABG	-	-	(0,6,19,75)	-	-	-	-	3.5 (2.3)	24.7 (6.8)
MASS-II[14]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
Myoprotect[15]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
NOBLE[16]	PCI	-	-	-	53	29.6	13	5	2 [2-4]	22.5 (7.5)
	CABG	-	-	-	43	33.0	17	7	2 [2-4]	22.4 (8.0)
Octostent[17]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
PRECOMBAT[18]	PCI	66.7	-	(9.0,17.7, 33.7,40.7)	-	-	-	-	2.6 (1.8)	24.4 (9.4)
	CABG	61.0	-	(11.3, 17.7, 30.0, 41.0)	-	-	-	-	2.8 (1.9)	25.8 (10.5)
Stent or Surgery (SoS) [19]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
SIMA[20]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
SYNTAX[21,22]	PCI	72.4	-	-	-	-	-	-	3.8 (2.6)	28.4 (11.5)
	CABG	73.3	-	-	-	-	-	-	3.8 (2.7)	29.1 (11.4)
Thiele et al[23]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
VA CARDS[24]	PCI	-	-	-	5.0	22.8	8.9	0	-	21.5 (8.9)
	CABG	-	-	-	11.7	24.5	7.4	0	-	22.7 (10.6)

ACS- Acute coronary syndrome; BMI- Body mass index; CABG- Coronary artery bypass grafting; CAD- Coronary artery disease; CHF- Chronic heart failure; DM- Diabetes mellitus; HTN- Hypertension; HCL- Hypercholesterolemia; HLD- Hyperlipidemia; MI- Myocardial infarction; ; NYHA- New York Heart Association PCI-Percutaneous coronary intervention; PVD- Peripheral vascular disease; SA- Stable angina pectoris; TIA- Transient ischemic attack; UA- Unstable angina

eTable 4. Procedural Characteristics

Trial	Treatment	Aspirin (%)	Thienophyridine (%)	Ticagrelor (%)	GP Inhibitor	Statin (%)	Beta-blocker (%)	ACEI or ARB (%)	Calcium channel	No. of lesions (SD or IQR)	CR (%)	No. of stents (SD) [IQR]	DES use (%)	Type of stent	Total stent length, mm (SD)	Stent diameter, mm (SD) [IQR]	No. of non-LMCA stents (0,1,2, bifurcation) (%)	Bifurcation technique (1 stent, 2 stent) (%)	Intravascular ultrasound, (any, pre-,
ARTS[1]	PCI	100	100	-	-	-	-	-	-	2.8 (1.0)	-	2.6 (1.1)	0	BMS	47.5 (21.8)	-	-	-	-
	CABG	100	100	-	-	-	-	-	-	2.8 (1.0)	-	-	-	-	-	-	-	-	-
BEST[2]	PCI	97.0	96.6	-	-	83.1	68.5	44.5	58.0	-	53.9	3.4 (1.4)	100	DES	85.3 (38.2)	3.1 (0.3)	-	-	(76.0,-,-)
	CABG	96.6	89.3	-	-	83.5	42.8	25.3	46.4	-	62.0	-	-	-	-	-	-	-	-
Blazek et al[3]	PCI	-	-	-	-	-	-	-	-	-	-	1.2 (0.4)	0	BMS	15.1 (4.3)	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Boudriot et al[4]	PCI	-	-	-	-	97	99	98	-	-	-	-	100	DES	-	-	-	-	-
	CABG	-	-	-	-	94	95	92	-	-	-	-	-	-	-	-	-	-	-
CARDia[5]	PCI	-	-	-	-	-	-	-	-	3.6	-	-	69	BMS, DES	71	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-
Cisowski et al[6]	PCI	-	-	-	-	-	-	-	-	-	-	-	0	BMS	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Drenth et al[7]	PCI	-	-	-	-	-	-	-	-	-	-	-	0	BMS		-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ERACI II[8]	PCI	-	-	-	-	-	-	-	-	-	-	-	0	BMS	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EXCEL[9]	PCI	95.9	95.9	6.9	-	94.7	81.8	55.7	5.8	1.9 (1.1)	-	2.4 (1.5)	100	DES	49.1 (35.6)	-	-	-	(76.2,-,-)
	CABG	92.1	31.0	0.2	-	88.0	88.1	40.1	6.8	2.6 (0.8)	-	-	-	-	-	-	-	-	-
FREEDOM[10]	PCI	98.4	97.8	-	-	83.7	79.3	80.2	24.7	5.7 (2.2)	-	3.5 (1.4)	100	DES	26.1 (14.2)	-	-	-	-
	CABG	85.9	23.9	-	-	81.1	76.1	60.2	18.0	5.7 (2.2)	-	-	-	-	-	-	-	-	-
Hong et al[11]	PCI	-	-	-	-	-	-	-	-	-	-	1.2 (0.2)	100	DES	22.6 (4.8)	2.9 (0.3)	-	-	-
	CABG	-	-	-	-	-	-	-	-	-	-	-		-		-	-	-	-
Kim et al[12]	PCI	-	-	-	-	-	-	-	-	-	-	-	0	-	22 (11)	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-	-	-		-		-	-	-	-
LE MANS[13]	PCI	-	-	-	-	-	-	-	-	-	79	-	35	BMS, DES	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-	89	-	-	-	-	-	-	-	-
MASS-II[14]	PCI	-	-	-	-	-	-	-	-	-	41	2.1 (0.7)	0	BMS	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Myoprotect[15]	PCI	91	-	-	-	39	70	43	0	1.48	-	-	0	BMS	13.4 (4.0)	-	-	-	-

	CABG	86	-	-	-	10	33	67	14	1.5	-	-	-	-	-	-	-	-	-
NOBLE[16]	PCI	91.0	95.6	-	18.6	-	-	-	-	2 (1-3)	91.7	-	100	DES	-	4.0 [4.0-4.5]	(52.7, 32.3, 9.3, 85.8)	(-, 29.7)	(-,45.6,72.6)
	CABG	-	-	-	-	-	-	-	-	2 (2-3)	-	-	-	-	-	-	-	-	
Octostent[17]	PCI	-	-	-	-	-	-	-	-	-	-	1.4	0	BMS	201. (10.2)	-	-	-	-
	CABG																		
PRECOMBAT[18]	PCI	98.3	97.7	-	-	71.7	60.7	39.3	61.3	-	68.3	2.7 (1.4)	100	DES	60.0 (24.1)	-	-	(29.0, 32.3)	(83.3,-,-)
	CABG	96.7	90.7	-	-	72.0	40.3	26.7	45.3	-	70.3	-	-	-	-	-	-	-	-
Stent or Surgery (SoS)[19]	PCI	-	-	-	8.2	-	-	-	-	2.7	-	2 [2-3]	0	BMS	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SIMA[20]	PCI	90	-	-	-	-	56	2	33	-	-	-	-	-	-	-	-	-	-
	CABG	87	-	-	-	-	55	0	33	-	-	-	-	-	-	-	-	-	-
SYNTAX[21,22]	PCI	96.3	96.8	1.9	-	86.7	81.3	78.6	25.8	4.3 (1.8)	61.3	4.6 (2.3)	100	DES	86.1 (47.9)	-	-	-	-
	CABG	88.5	19.5	4.8	-	74.5	78.6	68.4	18.4	4.4 (1.8)	56.3	-	-	-	-	-	-	-	-
Thiele et al[23]	PCI	100	100	-	-	99	99	100	-	-	-	-	95.4	DES, BMS	-	-	-	-	-
	CABG	100	34	-	-	97	97	97	-	-	-	-			-	-	-	-	-
VA CARDS[24]	PCI	-	-	-	-	-	-	-	-	-	-	-	100	DES	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Trial	Treatment	LIMA (%)	BIMA (%)	OPCAB (%)	LIMA+ SV grafting (%)	No. of grafts, mean (SD)	No. of arterial grafts, mean (SD)	No. of venous grafts, mean (SD)	No. of grafts, (1,2,3,4,5) (%)	Ultrasound (epi-aortic or transesophageal-aortic, epi-aortic, transesophageal)
ARTS[1]	PCI	-	-	-	-	-	-	-	-	-
	CABG	88.5	-	-	-	2.6 (1.0)	-	-	-	-
BEST[2]	PCI	-	-	-	-	-	-	-	-	-
	CABG	90.0	-	58.4	-	3.1 (0.9)	2.1 (1.1)	1.0 (0.8)	-	-
Blazek et al[3]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
Boudriot et al[4]	PCI	-	-	-	-	-	-	-	-	-
	CABG	99.0	-	-	-	-	-	-	-	-
CARDia[5]	PCI	-	-	-	-	-	-	-	-	-
	CABG	94	-	-	-	2.9	-	-	-	-
Cisowski et al[6]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
Drenth et al[7]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
ERACI II[8]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
EXCEL[9]	PCI	-	-	-	-	-	-	-	-	-
	CABG	94.9	27.7	28.3	-	2.6 (0.8)	1.4 (0.6)	1.2 (0.9)	-	(43.6, 12.6, 40.8)

FREEDOM[10]	PCI	-	-	-	-	-	-	-	-	-
	CABG	89.5	-	17.4	-	2.9 (0.8)	-	-	-	-
Hong et al[11]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
Kim et al[12]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
LE MANS[13]	PCI	72%	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
MASS-II[14]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	3.3 (0.8)	-	-	-	-
Myoprotect[15]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-
NOBLE[16]	PCI	-	-	-	-	-	-	-	-	-
	PCI	-	-	-	-	-	-	-	-	-
Octostent[17]	CABG	-	-	-	-	1.2	1.2			
	CABG	92.1	7.4	14.9	81.1	-	-	-	(3.9,49.7,37.2,4.2,0.5)	-
PRECOMBAT[18]	PCI	-	-	-	-	-	-	-	-	-
	CABG	77.7	-	51.7	-	2.7 (0.9)	2.1 (0.9)	0.7 (0.8)	-	-
Stent or Surgery (SoS)[19]	PCI	-	-	-	-	-	-	-	-	-
	CABG	79	10.2	-	-	2.8	-	-	-	-
SIMA[20]	PCI	-	-	-	-	-	-	-	-	-
	CABG	100	0	-	-	-	-	-	-	-
SYNTAX[21,22]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	24.1	14.3	-	2.8 (0.7)	-	-	-	-
Thiele et al[23]	PCI	98.5	-	95.8	-	-	-	-	-	-
	CABG									
VA CARDS[24]	PCI	-	-	-	-	-	-	-	-	-
	CABG	-	-	-	-	-	-	-	-	-

ACEI- Angiotensin-converting enzyme inhibitor; ARB- Angiotensin II receptor blockers; BIMA- Bilateral internal mammary artery; BMS: Bare-metal stent; CR- Complete revascularization; DES- Drug-eluting stent; GP- Glycoprotein IIa IIb; LIMA- Left internal mammary artery; LMCA- Left main coronary artery; OPCAB- Off-pump coronary artery bypass grafting; SV- Saphenous vein

eTable 5. Details of Medical Therapy

Trial	Description of Medical Therapy
ARTS[1]	Antianginal medication (PCI: 78.9%, CABG: 58.5%)
BEST [2]	Aspirin (PCI: 78.2%, CABG: 76.1%) Thienopyridine (PCI: 58.8%, CABG: 48.4%) Any antiplatelet drug (PCI: 92.0%, CABG: 90.8%) Beta-blocker (PCI: 50.0%, CABG: 37.0%) Calcium-channel blocker (PCI: 55.2%, CABG: 37.0%) ACE inhibitor or ARB (PCI: 34.5%, CABG: 21.7%) Statin (PCI: 79.3%, CABG: 75.0%)

Blazek et al[3]	• PCI: aspirin (100 mg/day, indefinitely); ticlopidine or clopidogrel (4 weeks, following a loading dose the day before the procedure) • CABG: aspirin (100 mg/day, indefinitely) Beta-blocker (PCI: 74%, CABG: 75%) ACE inhibitor/AT-1 antagonist: (PCI: 73%, CABG: 71%) Statin (PCI: 68%, CABG: 68%) Aspirin (PCI: 74%, CABG: 69%) Thienopyridines (PCI: 10%, CABG: 8%) Nitrates (PCI: 20%, CABG: 19%) Calcium antagonists (PCI: 22%, CABG: 15%) Antidiabetic medication (PCI: 21%, CABG: 18%)
Boudriot et al[4]	• PCI: antiplatelet therapy (>100 mg/day, indefinitely); clopidogrel (75 mg/day, ≥12 months); Glycoprotein IIb/IIIa inhibitor use was left to the discretion of the operator. • CABG: aspirin (100 mg/day, indefinitely) • BOTH: other pharmacological treatments such as statins, angiotensin-converting enzyme inhibitors, and betablockers were recommended based on current practice in both treatment groups. At discharge Aspirin (PCI: 100%, CABG: 100%) Clopidogrel (PCI: 100, CABG: 32%) Beta-blocker (PCI: 99, CABG: 95%) ACE inhibitor/AT-1 antagonist (PCI: 98%, CABG: 92%) Statins (PCI: 97%, CABG: 94%)
CARDia[5]	• Routine administration of abciximab and clopidogrel for 1 to 3 months after BMS placement or 12 months after DES placement. Aspirin (PCI: 83.4%, CABG: 87.2%) Clopidogrel (PCI: 54.4%, CABG: 10.3%) Aspirin and clopidogrel (PCI: 50.9%, CABG: 16.5%) Statins (PCI: 83.4%, CABG: 89.3%) ACE inhibitors: (PCI: 56.1%, CABG: 60.3%) Oral hypoglycemics (PCI: 65.5%, CABG: 61.1%) Insulin (PCI: 29.8%, CABG: 40.9%)
Cisowski et al[6]	• PCI: ticlopidine (4 weeks)
Drenth et al[7]	• PCI: aspirin (100 mg/day, indefinitely); ticlopidine (250 mg/day, 1 month); Glycoprotein IIb/IIIa inhibitor was not used. • CABG: (100 mg/day, indefinitely)

	No Beta blocker/Calcium antagonist/Long-acting nitrate (PCI: 24%, CABG: 29%) ≥1 Beta-blocker/Calcium antagonist/Long-acting nitrate: (PCI: 41%, CABG: 65%) ≥2 Beta blocker/Calcium antagonist/Long-acting nitrate: (PCI: 35%, CABG: 6%)
ERACI II [8]	Abciximab (PCI: 28.3%, CABG: 0.0%)
EXCEL[9]	Aspirin (PCI: 93.0%, CABG: 93.6%) P2Y12 receptor inhibitor (PCI: 61.6%, CABG: 21.0%) Clopidogrel or ticlopidine (PCI: 50.0%, CABG: 20.3%) Clopidogrel (PCI: 50.0%, CABG: 20.2%) Ticlopidine (PCI: 0.0%, CABG: 0.1%) Prasugrel or ticagrelor (PCI: 11.6%, CABG: 0.8%) Prasugrel (PCI: 8.5%, CABG: 0.4%) Ticagrelor (PCI: 3.1%, CABG: 0.4%) Beta-blockers (PCI: 86.6%, CABG: 94.3%) Calcium channel blockers (PCI: 18.3%, CABG: 19.1%) ACE inhibitors or receptor blockers (PCI: 66.7%, CABG: 59.4%) Aldosterone antagonist: (PCI: 1.6%, CABG: 1.7%) Diuretic: (PCI: 17.1%, CABG: 38.8%) Anti-arrhythmic agent: (PCI: 3.1%, CABG: 17.4%) Statins: (PCI: 97.5%, CABG: 96.2%) Chronic oral anticoagulant (PCI: 5.2%, CABG: 10.8%)
FREEDOM[10]	Aspirin (PCI: 95.3%, CABG: 95.4%) Thienopyridine (PCI: 58.7%, CABG: 22.8%) Warfarin (PCI: 1.4%, CABG: 1.7%) Statin (PCI: 91.4%, CABG: 89.9%) Beta blocker (PCI: 82.6%, 82.8%) ACE inhibitor (PCI: 67.4%, 66.7%) Angiotensin-II receptor antagonist (PCI: 31.6%, CABG: 29.4%) Calcium-channel blocker (PCI: 28.4%, CABG: 24.8%) H2-receptor blocker (PCI: 19.7%, CABG: 20.8%)
Hong et al[11]	• PCI: aspirin (indefinitely); clopidogrel or ticlopidine (6 months)
Kim et al[12]	• PCI: aspirin (100 mg/day, indefinitely), ticlopidine (250 mg/day, indefinitely) • CABG: aspirin (100 mg/day, indefinitely)
LE MANS[13]	• PCI: Acetylsalicylic acid and thienopyridine (clopidogrel or ticlopidine) was initiated at least 2 days before the procedure. Intravenous glycoprotein IIb/IIIa blockers were used at the operator's discretion only in procedures performed in patients with complex coronary lesions and unstable angina. Unfractionated heparin was used in standard doses. • CABG: Double antiplatelet treatment (≥12 months); other pharmacological treatments (e.g., statins, angiotensin-converting enzyme inhibitors, beta-blockers) were recommended based on current practice and were left to the discretion of a supervising physician. Acetylsalicylic acid (PCI: 84%, CABG: 85%)

	Clopidogrel (PCI: 5%, CABG: 5%) Angiotensin receptor blocker (PCI: 68%, CABG: 65%) ACE inhibitor (PCI: 5%, CABG: 5%) Beta-blocker (PCI: 84%, CABG: 80%) Statin (PCI: 84%, CABG: 85%)
MASS-II[14]	• All: optimal medical regimen of titrated nitrates, aspirin, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, or a combination of these drugs unless contraindicated. • Lipid-lowering agents, particularly statins, were also prescribed, along with a low-fat diet, on an individual basis. Aspirin (PCI: 80%, CABG: 70%, Overall: 77%) Long-acting nitrates (PCI: 41%, CABG: 12%, Overall: 42%) Beta-blockers (PCI: 61%, CABG: 44%, Overall: 58%) Calcium channel antagonists (PCI: 30%, CABG: 44%, Overall: 45%) HMG-CoA reductase inhibitors (PCI: 73%, CABG: 49%, Overall: 63%) ACE inhibitors (PCI: 30%, CABG: 21%, Overall: 27%) Insulin (PCI: 9%, CABG: 11%, Overall: 11%) Oral hypoglycemic agents (PCI: 14%, CABG: 35%, Overall: 37%)
Myoprotect[15]	None reported
NOBLE[16]	• All: aspirin (75–150 mg/day, indefinitely); clopidogrel (75 mg/day, 12 months if acute coronary syndrome is present) • PCI: clopidogrel (75 mg/day, 12 months); prasugrel or ticagrelor could be substituted for clopidogrel at the discretion of the PCI operator.
Octostent[17]	• PCI: glycoprotein IIb/IIIa receptor blocker was administered in 16 patients (12.2%).
PRECOMBAT[18]	Beta-blocker (PCI: 55.3%, CABG: 44.0%) Calcium channel-blocker (PCI: 61.7%, CABG: 46.3%) ACE inhibitor (PCI: 15.1%, CABG: 9.2%) Angiotensin II-receptor antagonist (PCI: 24.5%, CABG: 18.0%) Statin: (PCI: 72.1%, CABG: 48.0%)
Stent or Surgery (SoS)[19]	Antianginal medications (number of drugs) 0 (PCI: 18.5%, CABG: 35.1%) 1 (PCI: 44.4%, CABG: 44.2%) 2 (PCI: 28.9%, CABG: 18.3%) 3 (PCI: 7.9%, CABG: 2.2%) 4 (PCI: 0.2%, CABG: 0.0%)
SIMA[20]	Antiplatelet therapy (94% PCI and 96% CABG) Lipid-lowering therapy increased gradually from 24% at 2 years to 89% (88% PCI and 91% CABG) Beta-blockers, angiotensin-converting enzyme inhibitors, and calcium antagonists : more than 50% of the patients without differences between the 2 groups
SYNTAX[21,22]	Acetylsalicylic acid (Aspirin) (PCI: 87.1%, CABG: 85.0%) Thienopyridine (PCI: 32.0%, CABG: 12.1%)

	Other antiplatelet (PCI: 4.1%, CABG: 3.3%) Acetylsalicylic acid (Aspirin) and Antiplatelet (PCI: 27.4%, CABG: 9.1%)
Thiele et al[23]	PCI: aspirin (100 mg/day, indefinitely); clopidogrel (75 mg/day, ≥12 months) CABG: aspirin (100 mg/day, indefinitely)
VA CARDS[24]	None reported

ACE: Angiotensin converting enzyme; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention

eTable 6. Details of Trial End Points

Trial	Primary outcomes	Secondary outcomes
ARTS[1]	freedom from major adverse cardiac and cerebrovascular events including all-cause mortality, transient ischemic attacks, myocardial infarction, repeat revascularization	angina status, use of medications, costs, cost effectiveness, and quality of life; a combined end point of mortality, myocardial infarction, or stroke; and the rates of mortality, myocardial infarction, stroke, and revascularization procedures.
BEST [2]	composite of all-cause mortality, myocardial infarction, or target-vessel revascularization	safety composite of all-cause mortality, myocardial infarction, or stroke and a composite of mortality, myocardial infarction, stroke, or any repeat revascularization
Blazek et al[3]	freedom from major adverse cardiac events, defined as death from any cause, myocardial infarction, and the need for repeated target vessel revascularization	individual component of the primary endpoint
Boudriot et al[4]	all-cause mortality, myocardial infarction, and the need for repeat revascularization within twelve months	individual components of the composite end point
CARDia[5]	composite of all-cause mortality, myocardial infarction, and stroke	repeat revascularization
Cisowski et al[6]	all-cause mortality, myocardial infarction, and reoccurrence of angina pectoris (ie, a major adversecoronary event) that required hospital treatment and repeat revascularization of the target vessel	
Drenth et al[7]	major adverse cardiac and cerebrovascular events, defined as cardiac death, myocardial infarction, stroke, and need for repeat target vessel revascularization	angina pectoris class and need for antianginal medication at four years of follow-up
ERACI II [8]	Composite of all-cause mortality, Q-wave myocardial infarction, stroke, and need for repeat revascularization procedures at 30 days, 1 year, 3 years, and 5 years of follow-up.	angina status and functional class at one, three, and five years of follow-up; completeness of revascularization, determined by stress thallium at one month; and follow-up cost and cost-effectiveness of both technique
EXCEL[9]	composite of all-cause mortality, stroke, myocardial infarction	primary outcome at 30 days and composite of all-cause mortality, stroke, myocardial infarction and repeat revascularization. The cause of mortality was adjudicated as definite cardiovascular, definite noncardiovascular, or undetermined, and undetermined cases were conservatively classified as cardiovascular.
FREEDOM[10]	composite of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke	major adverse cardiovascular and cerebrovascular events 30 days and 12 months after the procedure (including components of the primary outcome as well as repeat revascularization) and annual all-cause and cardiovascular mortality
Hong et al[11]	cardiac death, myocardial infarction, and the need for repeated revascularization of the target vessel	
Kim et al[11]	Major adverse cardiac events, all-cause mortality, percutaneous coronary intervention, coronary bypass,ST elevation myocardial infarction, non-ST elevation myocardial infarction, intraaortic balloon pump, pulmonary edema, bleeding complication,economic data like admission length, intensive care unit length of stay, post-operative length of stay	Mortality, cause of mortality and target vessel revascularization
LE MANS[13]	left ventricular ejection fraction assessed by 2-dimensional echocardiography at 1 year	all-cause mortality, myocardial infarction, target vessel revascularization, and stroke
MASS-II[14]	all-cause mortality, Q-wave myocardial infarction, or refractory angina that required revascularization	angina status, mortality due to a cardiac cause, and a cerebrovascular accident
Myoprotect[15]	event-free survival including from causes like mortality, myocardial infarction, or need for target lesion revascularization at 1 year	quality-of-life evaluation and total treatment costs
NOBLE[16]	composite of all-cause mortality, non-procedural myocardial infarction, any repeat coronary revascularization	individual components of the primary major adverse cardiac and cerebrovascular endpoint, definite stent thrombosis, and symptomatic graft occlusion

Octostent[17]	freedom from all-cause mortality, stroke, acute MI, and repeat revascularization at 12 months	survival free of stroke and acute myocardial infarction, freedom from angina and medication, quality of life, and cost-effectiveness
PRECOMBAT[18]	composite of all-cause mortality, myocardial infarction, stroke, ischemia driven revascularization	individual components of the primary endpoint; a composite of mortality, myocardial infarction, or stroke; and clinically driven target vessel revascularization
Stent or Surgery (SoS) [19]	repeat revascularization	all-cause mortality
SIMA[20]	all cause mortality, myocardial infarction, and the need for additional revascularization	angina functional class
SYNTAX[21,22]	all-cause mortality, stroke, myocardial infarction, and repeat revascularization	major adverse cardiac and cerebrovascular event rates at different time intervals
Thiele et al[23]	freedom from major adverse cardiovascular events, which included cardiovascular mortality, myocardial infarction, and the need for repeated target vessel revascularization within twelve months.	each individual component of the composite end point and periprocedural adverse events occurring within thirty days after randomization
VA CARDS[24]	composite of all-cause mortality or nonfatal myocardial infarction	all-cause mortality, cardiac mortality, nonfatal myocardial infarction, and stroke

eTable 7. Adjudication of Cause of Death in the Randomized Clinical Trials

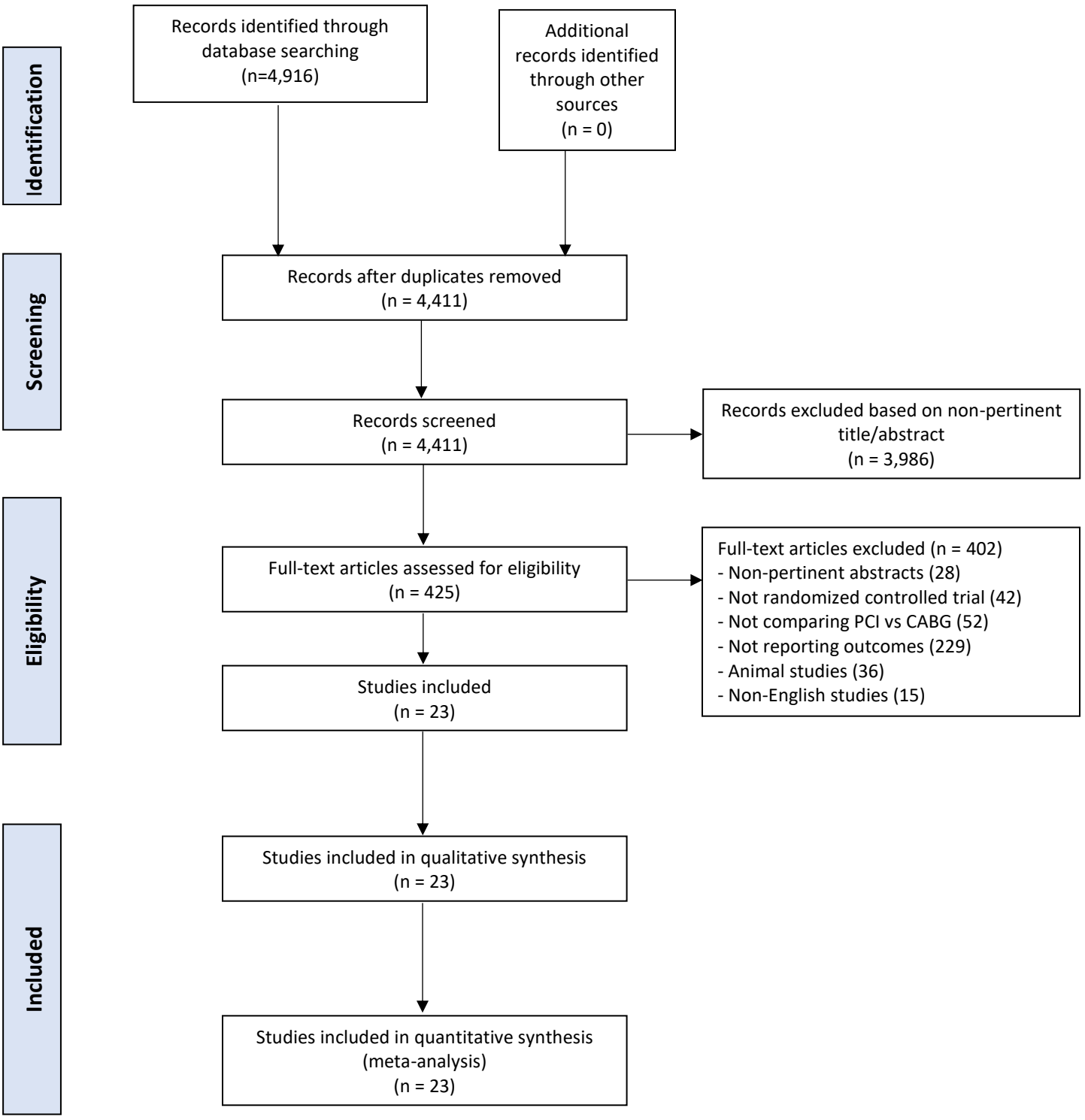
Trial	Adjudication process
ARTS[1]	An independent committee adjudicated clinical events and electrocardiograms.
BEST[2]	All the clinical end points were assessed by the event-adjudication committee, whose members were unaware of the study-group assignments.
Blazek et al[3]	All events were adjudicated by an event monitoring committee consisting of an experienced cardiologist and cardiovascular surgeon.
Boudriot et al[4]	All clinical outcomes were adjudicated by a clinical event committee consisting of a cardiothoracic surgeon and a cardiologist blinded to treatment allocation.
CARDia[5]	All major events including death, myocardial infarction, stroke, bleeding, and repeat revascularization were reviewed by the Critical Events Adjudication Committee, which consisted of cardiologists and surgeons who were blinded to treatment allocation. There were 2 adjudicators for each event, with a third used if required. An independent Data and Safety Monitoring Board comprising 2 cardiologists and 1 surgeon reviewed trial data according to protocol.
Cisowski et al[6]	The same committee consisting of cardiac surgeon and cardiologist, who were not involved into the study, assessed the angiograms.
Drenth et al[7]	Clinical events were checked by contact with the treating physicians and adjudicated by an event-monitoring committee of an experienced cardiologist and cardiac surgeon.
ERACI II[8]	The Clinical Events Committee reviewed the major adverse events and was blinded to the initial treatment strategy received.
EXCEL[9]	Trial monitors collected source documents of all primary and secondary outcome events for adjudication by an independent events committee.
FREEDOM[10]	An events committee provided central independent adjudication of all occurrences of the primary end points in an unblinded fashion.
Hong et al[11]	None reported
Kim et al[12]	None reported
LE MANS[13]	All clinical outcomes were analyzed by the clinical events committee. Information on any adverse event (including cardiac and noncardiac death, myocardial infarction, stroke, or repeated revascularization) was confirmed with hospital discharge files where the adverse event took place and was analyzed by the Clinical Events Committee.
MASS-II[14]	None reported
Myoprotect[15]	None reported

NOBLE[16]	An independent clinical events committee consisting of cardiologists and a cardiac surgeon adjudicated all possible events concerning cause of death, stroke, myocardial infarction, revascularisation, graft occlusion, and stent thrombosis
Octostent[17]	An independent committee blinded to the treatment allocation evaluated all events.
PRECOMBAT[18]	The event adjudication committee, whose members were blind to the study group assignments, assessed all clinical endpoints.
Stent or Surgery (SoS)[19]	Deaths were reported by the clinical events committee.
SIMA[20]	None reported
SYNTAX[1,21]	An independent clinical events committee adjudicated all primary clinical events, and patient safety was assessed at prespecified intervals by an independent data monitoring committee. An independent clinical events committee (including cardiologists, cardiac surgeons, and a neurologist (list in the Supplementary Appendix) adjudicated all primary clinical end points, staged procedures, and cases in which the sternum was reopened.
Thiele et al[23]	All clinical outcomes were adjudicated by a clinical event committee consisting of a cardiothoracic surgeon and a cardiologist.
VA CARDS[24]	A data monitoring committee reviewed safety and outcome measures semiannually. A 3-member endpoint committee blinded to treatment assignment adjudicated all MIs and strokes. Where records related to a death in follow-up were available, the endpoint committee reviewed them to assign a presumed cardiac versus noncardiac cause.

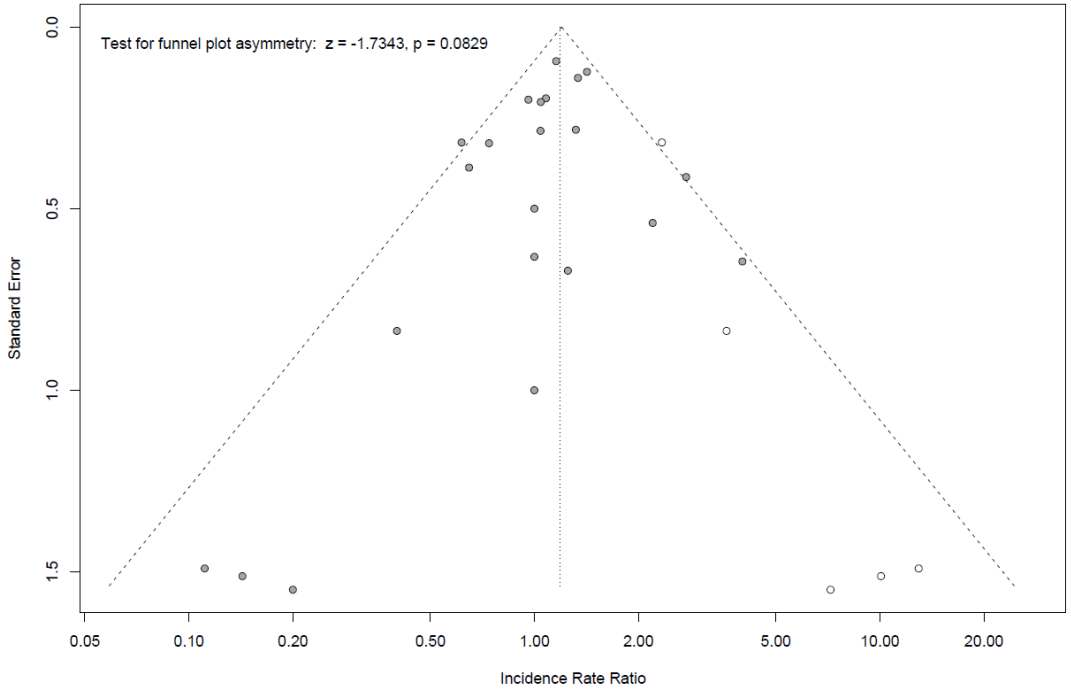
eTable 8. Details of Noncardiac Mortality in Percutaneous Coronary Intervention (PCI) vs Coronary Artery Bypass Grafting (CABG) Randomized Clinical Trials

Trial Name	PCI	CABG
ARTS[1]	Reported cardiac and non-cardiac deaths	Reported cardiac and non-cardiac deaths
BEST [2]	Reported "non-cardiac death" but did not specify cause	Reported "non-cardiac death" but did not specify cause
Blazek et al[3]	Reported cardiac death from which non-cardiac death was calculated	Reported cardiac death from which non-cardiac death was calculated
Drenth et al[7]	Reported cardiac and non-cardiac death	Reported cardiac and non-cardiac death
ERACI II [8]	Four non-cardiac deaths were due to renal insufficiency, lung cancer, pulmonary emphysema, and mesenteric infarction	Causes of non-cardiac deaths were pulmonary emphysema, stroke, renal insufficiency, and prostate and lung cancer
EXCEL[9]	Pulmonary: 8 infection: 14 gastrointestinal: 1 malignancy: 29 accident/trauma:3 non-cardiovascular organ failure: 2 other non-cardiovascular cause: 0 undetermined cause: 16	Pulmonary: 5 infection: 7 gastrointestinal: 2 malignancy: 23 accident/trauma:2 non-cardiovascular organ failure: 0 other non-cardiovascular cause: 2 undetermined cause: 9
FREEDOM[10]	Reported cardiac death from which non-cardiac death was calculated	Reported cardiac death from which non-cardiac death was calculated
Kim et al[12]	cancer deaths: 1; CVA death: 1; unknown cause: 0	cancer deaths: 0; CVA death: 0; unknown cause: 1
MASS-II[14]	Reported cardiac death from which non-cardiac death was calculated	Reported cardiac death from which non-cardiac death was calculated
NOBLE[16]	Vascular death: 2 Reported cardiac and vascular death from which non-cardiac death was calculated	Vascular death: 1 Reported cardiac and vascular death from which non-cardiac death was calculated
PRECOMBAT [18]	Reported "non-cardiac death" but did not specify cause	Reported "non-cardiac death" but did not specify cause
Octostent[7]	Reported all-cause mortality, cardiovascular mortality and other mortality	Reported all-cause mortality, cardiovascular mortality and other mortality
Stent or Surgery (SoS) [19]	Other vascular: 2 cancer: 9 unknown: 2	Other vascular: 1 cancer: 3 unknown: 0
SIMA[20]	Reported all-cause, cardiac and non-cardiac mortality	Reported all-cause, cardiac and non-cardiac mortality
SYNTAX[21,22]	Reported cardiac death from which non-cardiac death was calculated	Reported cardiac death from which non-cardiac death was calculated
VA CARDS[24]	Reported cardiac death from which non-cardiac death was calculated	Reported cardiac death from which non-cardiac death was calculated

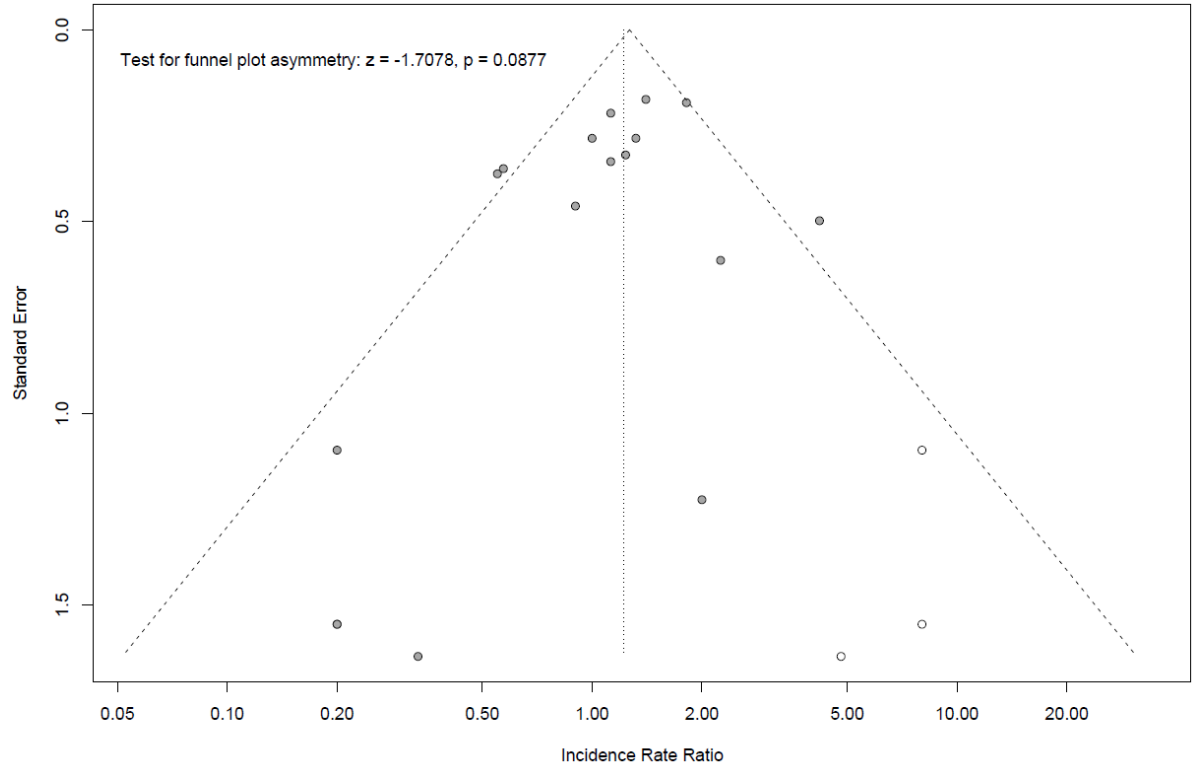
eFigure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flowchart of Our Analysis



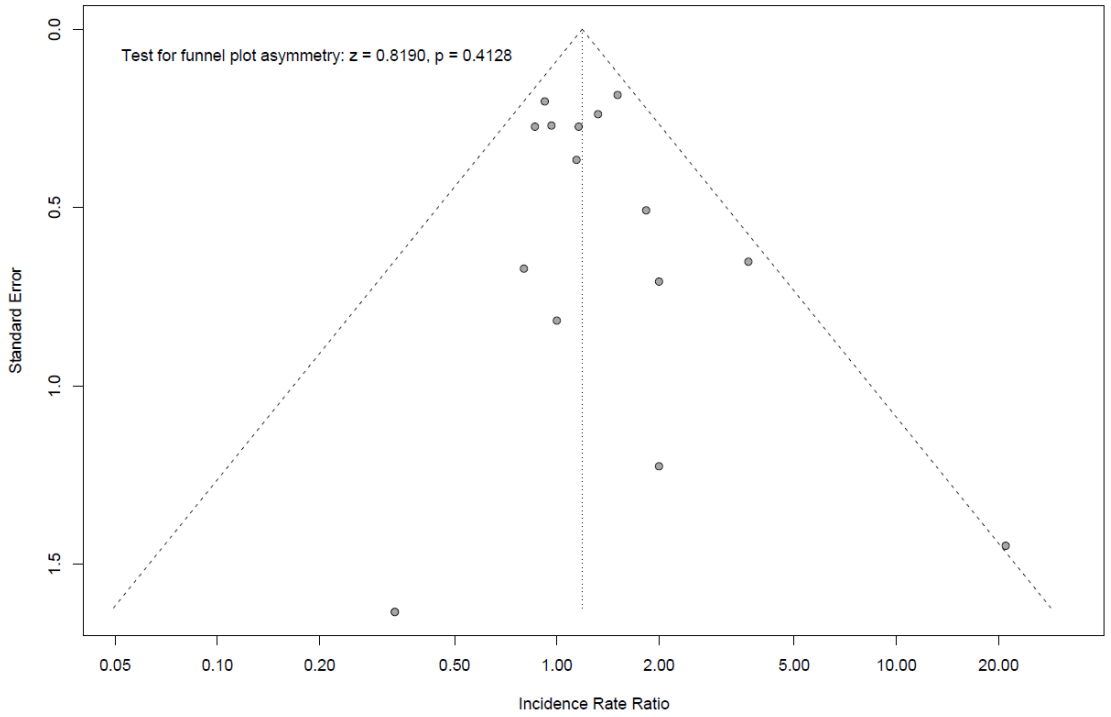
eFigure 2. Funnel Plot for Studies Reporting All-Cause Mortality



eFigure 3. Funnel Plot for Studies Reporting Cardiac Mortality

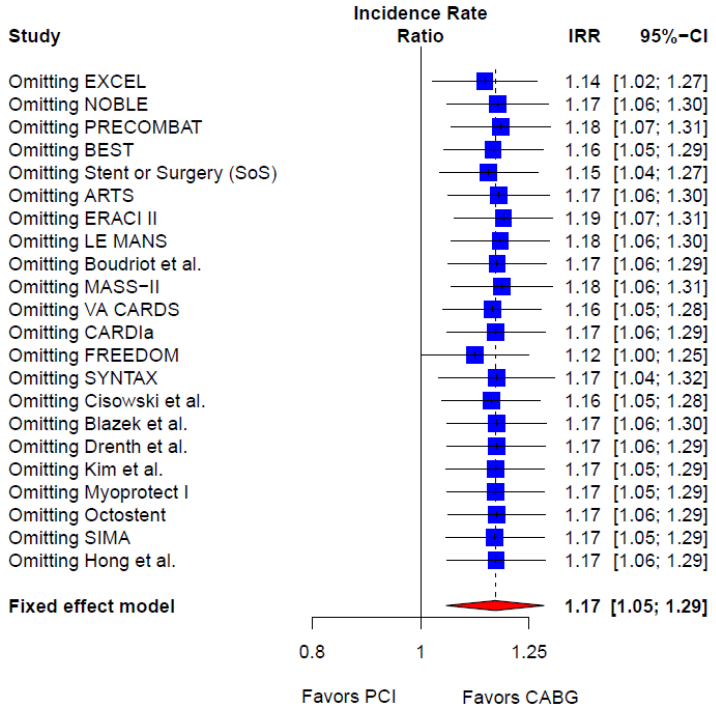


eFigure 4. Funnel Plot for Studies Reporting Noncardiac Mortality

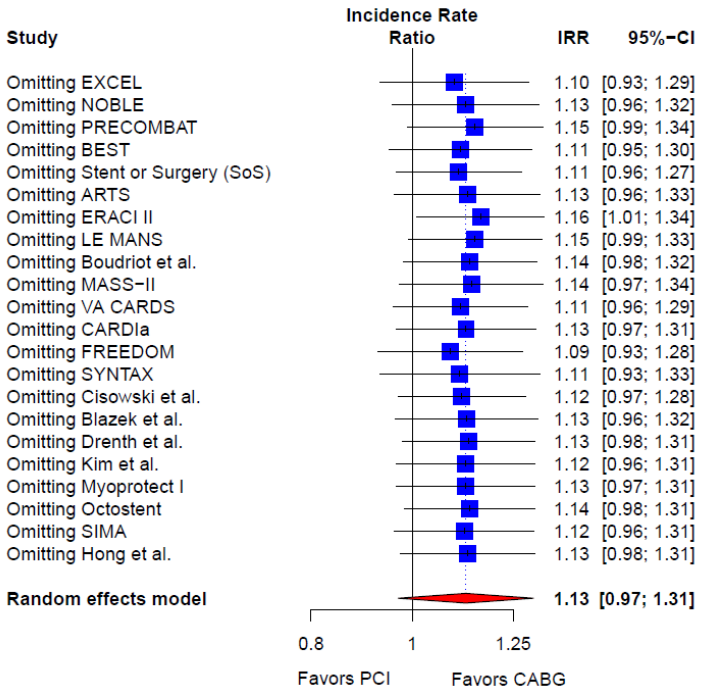


eFigure 5. Leave-One-Out Analysis for All-Cause Mortality for Fixed-Effects Model (A) and Random-Effects Model

A.



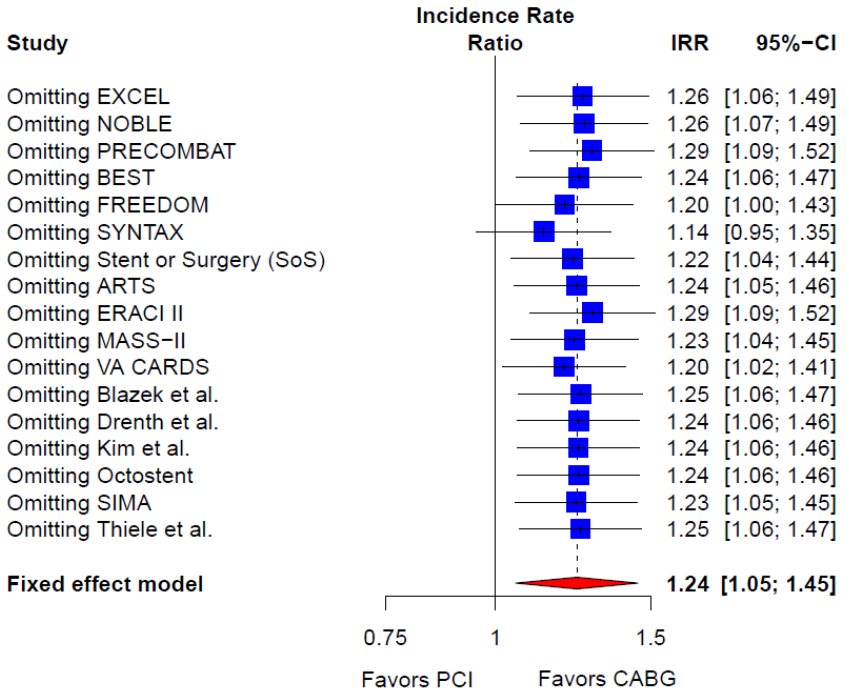
B.



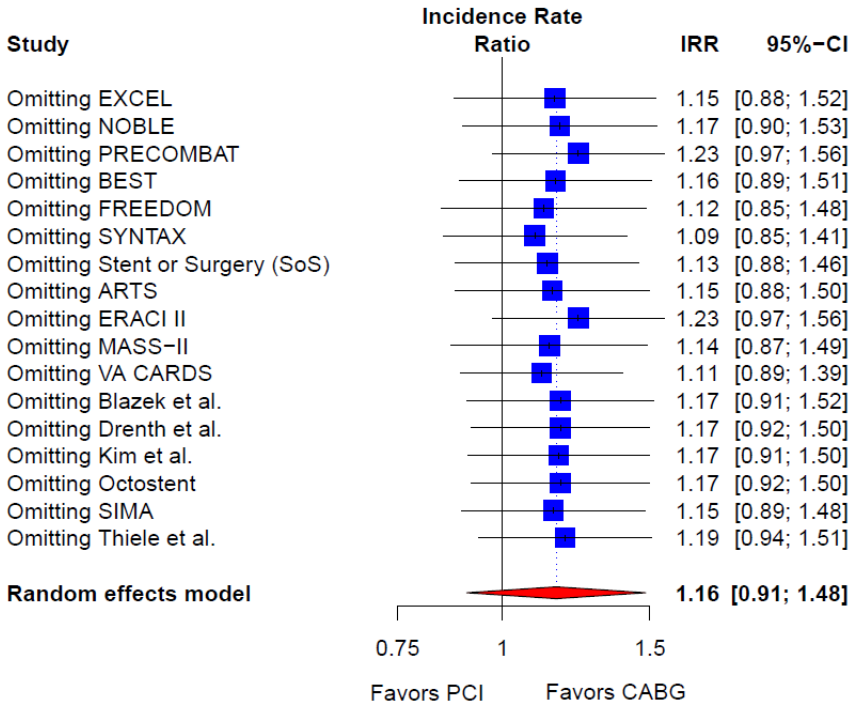
CABG: coronary artery bypass grafting; CI: confidence interval; IRR: incidence rate ratio; PCI: percutaneous coronary intervention.

eFigure 6. Leave-One-Out Analysis for Cardiac Mortality for Fixed-Effects Model (A) and Random-Effects Model (B)

A.



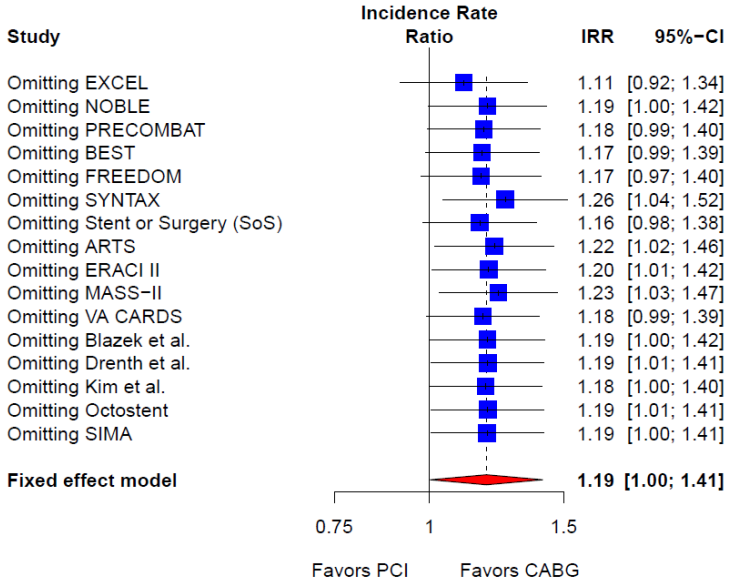
B.



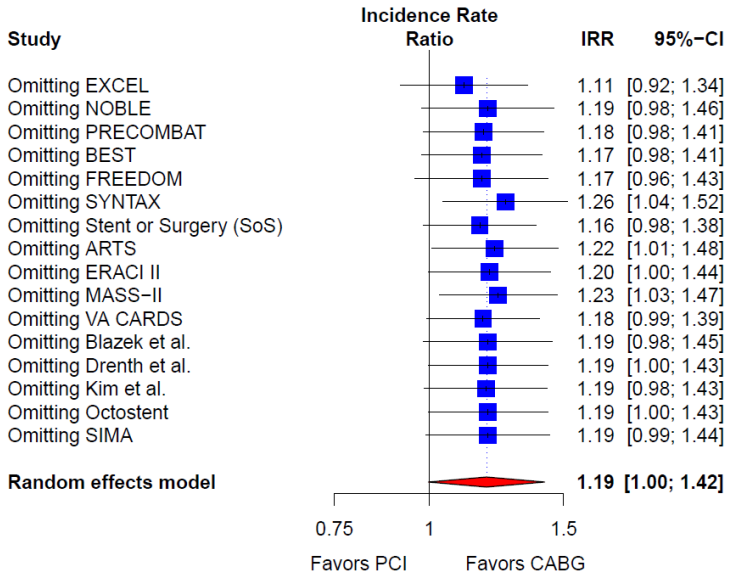
CABG: coronary artery bypass grafting; CI: confidence interval; IRR: incidence rate ratio; PCI: percutaneous coronary intervention.

eFigure 7. Leave-One-Out Analysis for Noncardiac Mortality for Fixed-Effects Model (A) and Random-Effects Model (B)

A.

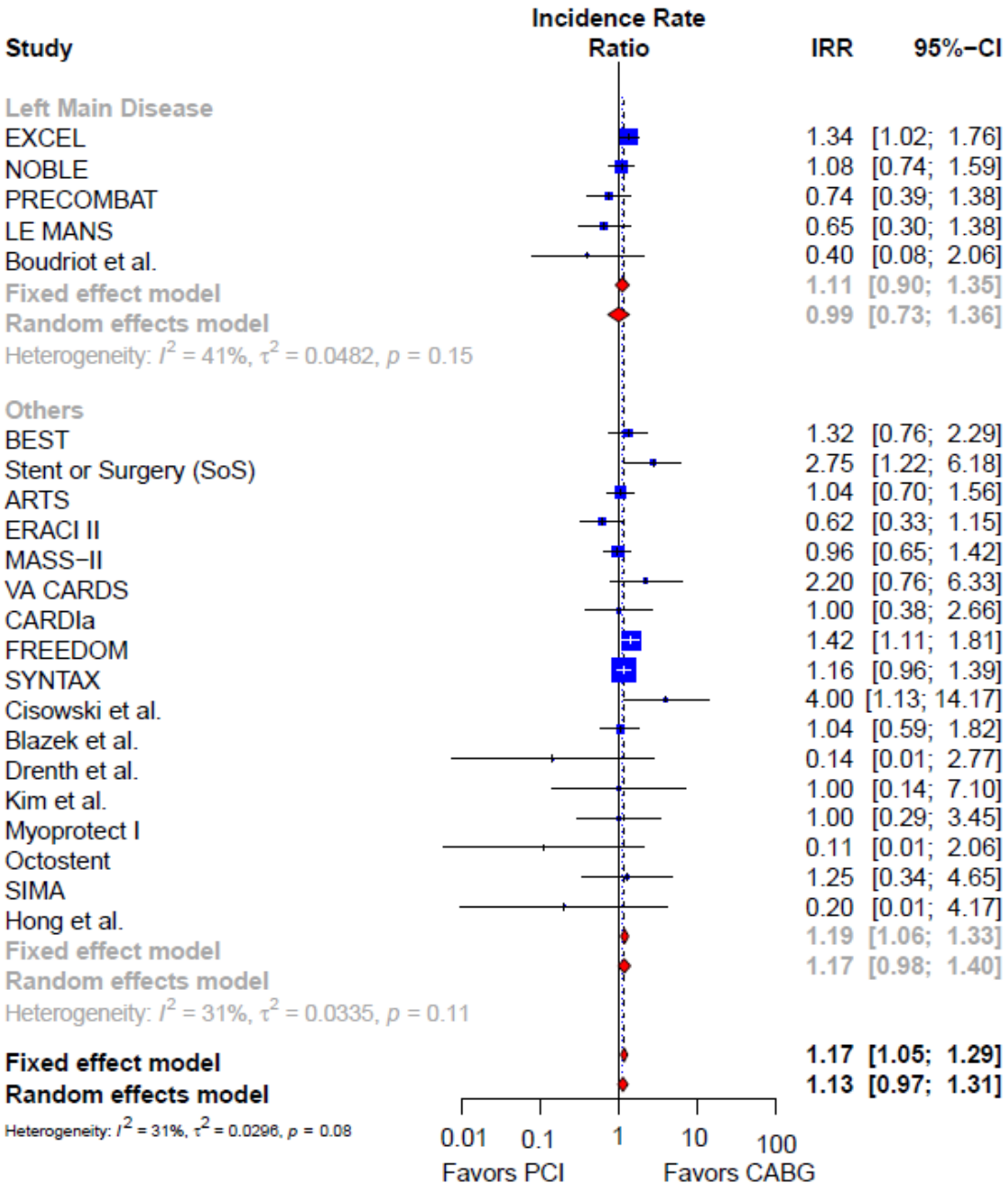


B.



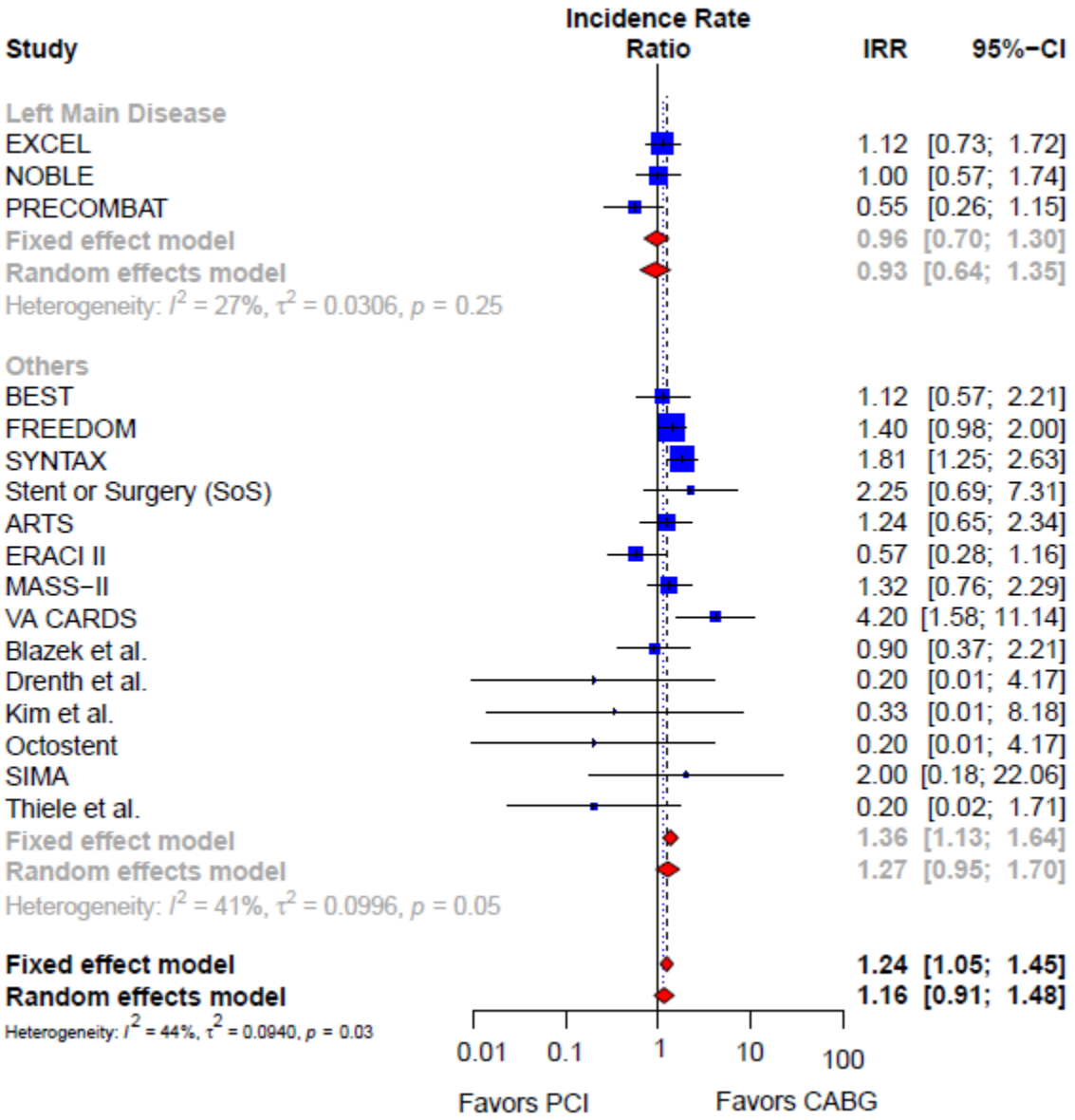
CABG: coronary artery bypass grafting; CI: confidence interval; IRR: incidence rate ratio; PCI: percutaneous coronary intervention.

eFigure 8. Subgroup Analysis for All-Cause Mortality for Trials Including Patients With Left Main Disease vs Non–Left Main Disease



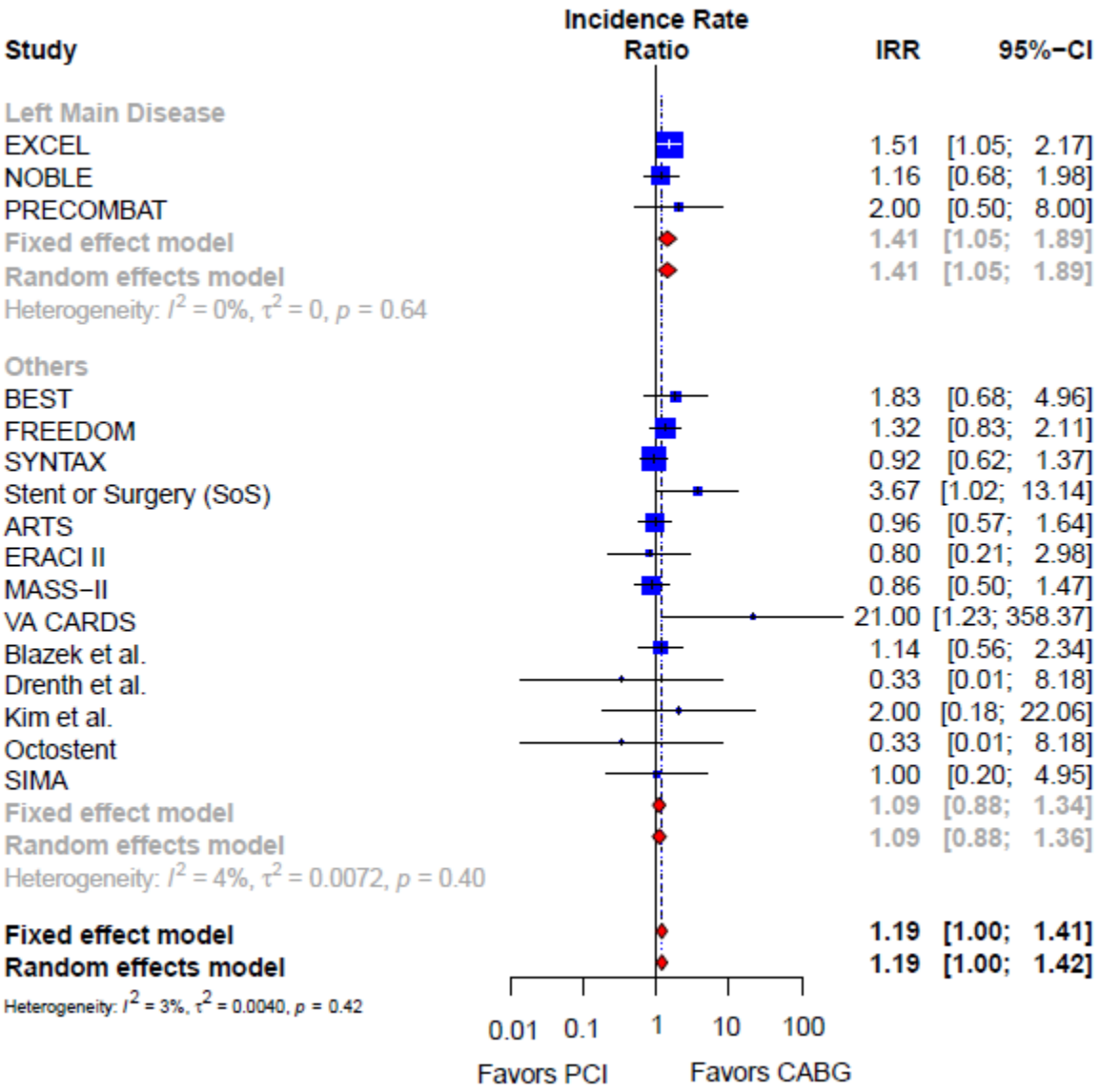
CABG: coronary artery bypass grafting; CI: confidence interval; IRR: incidence rate ratio; PCI: percutaneous coronary intervention.

eFigure 9. Subgroup Analysis for Cardiac Mortality for Trials Including Patients With Left Main Disease vs Non–Left Main Disease



CABG: coronary artery bypass grafting; CI: confidence interval; IRR: incidence rate ratio; PCI: percutaneous coronary intervention.

eFigure 10. Subgroup Analysis for Noncardiac Mortality for Trials Including Patients With Left Main Disease vs Non–Left Main Disease



CABG: coronary artery bypass grafting; CI: confidence interval; IRR: incidence rate ratio; PCI: percutaneous coronary intervention.

eMethods. The Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2)

Study details

Reference

Park S-J, Ahn J-M, Kim Y-H, Park D-W, Yun S-C, Lee J-Y, et al. Trial of everolimus-eluting stents or bypass surgery for coronary disease. N Engl J Med. 2015 Mar 26;372(13):1204–12.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias

Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)	
✓	Journal article(s) with results of the trial
☐	Trial protocol
☐	Statistical analysis plan (SAP)
☐	Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐	Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐	"Grey literature" (e.g. unpublished thesis)
☐	Conference abstract(s) about the trial
☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options

3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low

Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Rodriguez AE, Baldi J, Fernández Pereira C, Navia J, Rodriguez Alemparte M, Delacasa A, et al. Five-year follow-up of the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). J Am Coll Cardiol. 2005 Aug 16;46(4):582–8.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of ***adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)
✓ Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options

3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Stone GW, Kappetein AP, Sabik JF, Pocock SJ, Morice M-C, Puskas J, et al. Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease. N Engl J Med. 2019 Sep 28;0(0).

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

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Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of ***adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial

☐	Trial protocol
☐	Statistical analysis plan (SAP)
☐	Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐	Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐	"Grey literature" (e.g. unpublished thesis)
☐	Conference abstract(s) about the trial
☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, et al. Strategies for Multivessel Revascularization in Patients with Diabetes. N Engl J Med. 2012 Dec 20;367(25):2375–84.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias	Non-cardiac mortality
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of ***adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial

☐	Trial protocol
☐	Statistical analysis plan (SAP)
☐	Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐	Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐	"Grey literature" (e.g. unpublished thesis)
☐	Conference abstract(s) about the trial
☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Hueb W, Lopes N, Gersh BJ, Soares PR, Ribeiro EE, Pereira AC, et al. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation. 2010 Sep 7;122(10):949–57.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of ***adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial

☐	Trial protocol
☐	Statistical analysis plan (SAP)
☐	Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐	Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐	"Grey literature" (e.g. unpublished thesis)
☐	Conference abstract(s) about the trial
☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Holm NR, Mäkikallio T, Lindsay MM, Spence MS, Erglis A, Menown IBA, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. The Lancet. 2019

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias	Non-cardiac mortality
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of ***adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial

☐	Trial protocol
☐	Statistical analysis plan (SAP)
☐	Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐	Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐	"Grey literature" (e.g. unpublished thesis)
☐	Conference abstract(s) about the trial
☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Cisowski M, Drzewiecki J, Drzewiecka-Gerber A, Jaklik A, Kruczak W, Szczeklik M, et al. Primary stenting versus MIDCAB: preliminary report–Comparision of two methods of revascularization in single left anterior descending coronary artery stenosis. Ann Thorac Surg. 2002 Oct;74(4):1334–9

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of ***adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial

☐	Trial protocol
☐	Statistical analysis plan (SAP)
☐	Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐	Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐	"Grey literature" (e.g. unpublished thesis)
☐	Conference abstract(s) about the trial
☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. Lancet Lond Engl. 2002 Sep 28;360(9338):965–70.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of ***adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial

☐	Trial protocol
☐	Statistical analysis plan (SAP)
☐	Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐	Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐	"Grey literature" (e.g. unpublished thesis)
☐	Conference abstract(s) about the trial
☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Mohr FW, Morice M-C, Kappetein AP, Feldman TE, Ståhle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. The Lancet. 2013 Feb;381(9867):629–38.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of ***adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial

☐	Trial protocol
☐	Statistical analysis plan (SAP)
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☐	Company-owned trial registry record (e.g. GSK Clinical Study Register record)
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☐	Personal communication with the sponsor

Risk of bias assessment

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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Kamalesh M, Sharp TG, Tang XC, Shunk K, Ward HB, Walsh J, et al. Percutaneous coronary intervention versus coronary bypass surgery in United States veterans with diabetes. J Am Coll Cardiol. 2013 Feb 26;61(8):808–16.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias	Non-cardiac mortality
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of ***adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial

☐	Trial protocol
☐	Statistical analysis plan (SAP)
☐	Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐	Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐	"Grey literature" (e.g. unpublished thesis)
☐	Conference abstract(s) about the trial
☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Serruys PW, Ong ATL, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJRM, et al. Five-Year Ou Stenting Versus Bypass Surgery for the Treatment of Multivessel Disease. J Am Coll Cardiol. 20

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial
- ☐ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Risk of bias assessment

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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Boudriot E, Thiele H, Walther T, Liebetrau C, Boeckstegers P, Pohl T, et al. Randomized Compa Coronary Intervention With Sirolimus-Eluting Stents Versus Coronary Artery Bypass Grafting i Stem Stenosis. J Am Coll Cardiol. 2011 Feb;57(5):538–45.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

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- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
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- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Buszman PE, Buszman PP, Banasiewicz-Szkróbka I, Milewski KP, Żurakowski A, Orlik B, et al. Le Comparison With Surgical Revascularization. JACC Cardiovasc Interv. 2016 Feb;9(4):318–27.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial
- ☐ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
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- ☐ Personal communication with the sponsor

Risk of bias assessment

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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Kapur A, Hall RJ, Malik IS, Qureshi AC, Butts J, de Belder M, et al. Randomized Comparison of F Intervention With Coronary Artery Bypass Grafting in Diabetic Patients. J Am Coll Cardiol. 201

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial
- ☐ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Risk of bias assessment

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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Blazek S, Holzhey D, Jungert C, Borger MA, Fuernau G, Desch S, et al. Comparison of Bare-Met Invasive Bypass Surgery for Stenosis of the Left Anterior Descending Coronary Artery. JACC Ca Jan;6(1):20–6.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial
- ☐ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Risk of bias assessment

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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Drenth DJ, Veeger NJGM, Middel B, Zijlstra F, Boonstra PW. Comparison of late (four years) fu between percutaneous transluminal angioplasty intervention and off-pump left internal mam for isolated high-grade narrowing of the proximal left anterior descending coronary artery. Ar Dec;94(11):1414–7.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
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Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

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- ☐ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Risk of bias assessment

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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Hong SJ, Lim D-S, Seo HS, Kim Y-H, Shim WJ, Park CG, et al. Percutaneous coronary interventic implantation vs. minimally invasive direct coronary artery bypass (MIDCAB) in patients with le coronary artery stenosis. Catheter Cardiovasc Interv. 2005 Jan;64(1):75–81.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial
- ☐ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Kim JW, Lim DS, Sun K, Shim WJ, Rho YM. Stenting or MIDCAB using ministernotomy for revas anterior descending artery? Int J Cardiol. 2005 Mar;99(3):437–41.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial
- ☐ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Risk of bias assessment

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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Ahn J-M, Roh J-H, Kim Y-H, Park D-W, Yun S-C, Lee PH, et al. Randomized Trial of Stents Versus Main Coronary Artery Disease: 5-Year Outcomes of the PRECOMBAT Study. J Am Coll Cardiol. 206.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial
- ☐ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Risk of bias assessment

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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Pohl T, Giehrl W, Reichart B, Kupatt C, Raake P, Paul S, et al. Retroinfusion-supported stenting percutaneous intervention and bypass surgery: Results of the prospective randomized myopr Cardiovasc Interv. 2004 Jul;62(3):323–30.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial
- ☐ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Risk of bias assessment

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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Thiele H, Neumann-Schniedewind P, Jacobs S, Boudriot E, Walther T, Mohr F-W, et al. Randor Minimally Invasive Direct Coronary Artery Bypass Surgery Versus Sirolimus-Eluting Stenting in Anterior Descending Coronary Artery Stenosis. J Am Coll Cardiol. 2009 Jun;53(25):2324–31.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial
- ☐ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Goy J-J, Kaufmann U, Hurni M, Cook S, Versaci F, Ruchat P, et al. 10-year follow-up of a prospe comparing bare-metal stenting with internal mammary artery grafting for proximal, isolated c coronary artery stenosis the SIMA (Stenting versus Internal Mammary Artery grafting) trial. J A 2;52(10):815–7.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: PCI Comparator: CABG

Specify which outcome is being assessed for risk of bias: Non-cardiac mortality

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.: Manuscript results

Is the review team's aim for this result…?

- ✓ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- ✓ Journal article(s) with results of the trial
- ☐ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Risk of bias assessment

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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Study details

Reference	Eefting F, Nathoe H, van Dijk D, Jansen E, Lahpor J, Stella P, et al. Randomized Comparison Bet Pump Bypass Surgery in Patients Referred for Angioplasty. Circulation. 2003 Dec 9;108(23):28

Study design

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- ☐ Cluster-randomized parallel-group trial
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- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Y
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		PY
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		Y
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	N/A	N/A

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N/A
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	N/A	N/A
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N/A	N/A
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N/A	Y
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A	N/A
Risk-of-bias judgement	N/A	N/A
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	N/A

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	N/A	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A	N/A
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N/A
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

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