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Native-Coronary versus Bypass-Graft PCI after CABG: A Design- and Time-Stratified Systematic Review and Meta-analysis

Hamzah Pratama Megantara
hamzahpratama10@gmail.com
University of Indonesia
Naura Anjanie
Airlangga University
Joeristanti Soelistyaningroem
Mitra Keluarga General Hospital

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Abstract

Background

Observational evidence has historically favored percutaneous coronary intervention (PCI) of the bypassed native coronary artery rather than the bypass graft after coronary artery bypass grafting (CABG). PROCTOR, the first randomized target-strategy trial, reported a directionally different one-year estimate. We evaluated whether these evidence blocks could be reconciled by study design, effect-measure family, follow-up horizon, anatomy, and registry overlap.

Methods

We systematically reviewed randomized and comparative observational studies of native-vessel versus bypass-graft PCI after CABG. Randomized and observational evidence was analyzed separately. Unadjusted binary outcomes were pooled as risk ratios (RRs) using Paule-Mandel random-effects models with Hartung-Knapp confidence intervals; adjusted hazard ratios (HRs) and odds ratios (ORs) were synthesized only within the same effect-measure family. Follow-up was classified as early, 9–12 months, or > 12 months. Risk of bias was assessed using RoB 2 and ROBINS-I, and certainty using GRADE.

Results

Thirty-five original comparative reports were identified (34 observational and one randomized trial). Twelve observational studies contributed to the primary long-term MACE synthesis, which favored native-vessel PCI (RR 0.64, 95% CI 0.53–0.77; I2 = 47.6%). At one year, PROCTOR favored graft PCI (HR 2.14, 95% CI 1.25–3.65), whereas adjusted observational estimates favored native PCI (HR 0.58, 95% CI 0.35–0.95; OR 0.79, 95% CI 0.69–0.91). Four adjusted observational mortality HRs yielded HR 0.81 (95% CI 0.69–0.95). These estimates were not pooled across design or metric.

Conclusions

Randomized and observational evidence represent clinically different target-selection scenarios and should not be combined into a single causal estimate. Current data support an individualized, anatomy- and time-dependent strategy rather than a universal native-first or graft-first rule; longer randomized follow-up is needed to determine comparative durability.

Background

Late ischemia after CABG is common because of progressive native coronary atherosclerosis and degeneration of saphenous vein grafts. Repeat surgery carries substantial risk, making PCI the predominant revascularization strategy. The clinically important question is whether to treat the diseased graft or the bypassed native coronary artery. SVG PCI may restore flow rapidly but is susceptible to distal embolization, no-reflow, periprocedural myocardial infarction, restenosis, and continuing graft degeneration. Native-vessel PCI may provide greater durability, but post-CABG native lesions are often long, calcified, tortuous, or chronically occluded and may require advanced techniques [3–5].

Until 2026, comparative evidence was entirely nonrandomized. A previous meta-analysis reported lower MACE, death, myocardial infarction, and target-vessel revascularization after native-vessel PCI [3]. However, its aggregate estimates combined heterogeneous definitions and follow-up horizons and could not eliminate confounding by indication. A later structured review identified 26 observational studies and emphasized substantial anatomic selection bias and insufficient information about whether both target vessels supplied the same ischemic territory. A 2026 contemporary narrative synthesis incorporated PROCTOR but did not perform a design-stratified quantitative update [4].

PROCTOR was the first randomized strategy trial and reported higher one-year MACE with native-vessel PCI, directionally contrasting with most observational evidence [39]. This contrast may reflect differences in eligibility, native CTO complexity, graft morphology, procedural MI definitions, and follow-up duration rather than a simple reversal of treatment effects. We therefore conducted a design-, metric-, and time-stratified systematic review and meta-analysis that represented each original report individually, mapped overlapping registries, separated unadjusted and adjusted effect measures, and distinguished early, one-year, and long-term outcomes. The primary objective was to quantify evidence within defensible strata and describe randomized–observational differences without an inappropriate overall pool or an underidentified formal interaction test.

Methods

Protocol and reporting

The review was prepared according to PRISMA 2020 [1] and the Cochrane Handbook [2]. The protocol has been prospectively registered at PROSPERO (CRD42024573145).

Eligibility criteria

We included randomized trials and comparative cohort studies enrolling adults with prior CABG who underwent PCI of a native coronary artery or bypass graft and reported at least one clinical or procedural outcome by target.\ Studies were eligible irrespective of clinical presentation. Studies comparing prior-CABG with no-CABG populations without a within-CABG target-vessel comparison were excluded. Case series without a comparator, narrative reviews, meta-analyses, editorials, protocols without outcomes, and duplicate abstracts were excluded. When multiple reports represented the same cohort, the most complete publication was retained for the relevant outcome and time horizon.

Information sources and search strategy

Literature searching was conducted on PubMed, Scopus, CENTRAL/Cochrane Library, ScienceDirect, and Google Scholar from inception to 12 August 2026, supplemented by backward and forward citation searching. Search concepts combined prior CABG, native coronary artery, bypass graft or saphenous vein graft, and PCI. Full database-specific strategies are provided in Supplementary Table S1. The supplied PRISMA flow records 900 identified records, 783 duplicates removed, 117 reports assessed for eligibility, 82 reports excluded, and 35 included reports.

Data extraction

Two reviewers independently extracted study design, period, setting, sample size, clinical presentation, age, use of drug-eluting stents and embolic protection, native-vessel CTO prevalence, target-vessel composition, outcome definitions, follow-up, raw event counts, and adjusted estimates. Each original study was represented as an individual row. Estimates from previous meta-analyses were not entered as study-level data. Discrepancies between abstracts, tables, and derived counts were flagged for full-text verification rather than silently reconciled.

Outcomes and time horizons

The primary outcome was study-defined MACE. Because definitions varied, every definition was tabulated and a harmonized sensitivity analysis was prespecified for composites containing death, myocardial infarction, and repeat revascularization. Secondary outcomes were all-cause death, spontaneous or nonprocedural myocardial infarction, target-vessel or territory revascularization, procedural myocardial infarction, stroke, major bleeding, no-reflow, technical success, and perforation. Procedural MI was not pooled with spontaneous or follow-up MI. Follow-up was classified as early (in-hospital or 30 days), intermediate (9–12 months), and long-term (> 12 months).

Overlapping cohorts

Potential overlap was assessed using institution, registry, recruitment dates, geography, clinical presentation, and sample characteristics. Three principal clusters were identified: Mount Sinai reports, Beijing reports, and UK/BCIS-related reports. The primary unadjusted analysis used a conservative representative dataset: ADAPT-DES was retained instead of the overlapping Gaglia report, and Yang et al. was retained instead of the earlier Liu W and Liu Y reports. Diagnosis-specific UK cohorts were used only when reasonably mutually exclusive, and Pan-London was reserved for adjusted long-term analyses. The Melbourne conference abstract was excluded as a duplicate of the 2025 full report. All-report, complete-cluster exclusion, and leave-one-study-out analyses tested robustness.

Risk of bias and certainty

RCT was evaluated using RoB 2 [40] at the outcome level. Observational studies were evaluated with ROBINS-I [41], emphasizing confounding by indication, native-vessel complexity, graft morphology, and whether both targets were technically feasible. Certainty was graded separately for randomized and observational evidence using GRADE [42]. Observational associations were not upgraded solely for large sample size because unmeasured anatomic confounding remained plausible. Complete domain-level assessments are provided in Supplementary Tables S5–S7.

Statistical analysis

All effects were oriented as native-vessel PCI versus graft PCI; values below 1 favored native PCI. Unadjusted binary outcomes were summarized as RRs. A 0.5 continuity correction was applied only when one arm had zero events; double-zero studies were excluded from relative-effect models. Random-effects models used the Paule–Mandel estimator for between-study variance and Hartung–Knapp confidence intervals [43, 44]. Fixed-effect estimates were retained as sensitivity analyses. Heterogeneity was summarized by I^2 and tau^2, but interpreted cautiously when few studies contributed. Adjusted HRs were pooled only with HRs, and adjusted ORs only with ORs. HRs, ORs, and RRs were never combined in the same pooled estimate. Randomized and observational studies were never combined into an overall causal effect. One-year estimates were displayed descriptively according to study design and effect-measure family. No formal interaction test by study design was performed because only one randomized trial was available and design was completely confounded with study-specific population, anatomical, procedural, and endpoint differences. Prespecified subgroup analyses included early versus intermediate versus long-term follow-up, adjusted versus unadjusted estimates, acute coronary syndrome, and CTO-dominant cohorts, defined as at least 50% native target lesions being CTOs. The CTO interaction was not estimated when fewer than two compatible studies were available per subgroup. Analyses were performed in Review Manager 5.4 with reproducible source data provided in the workbook.

Reporting bias

For pooled outcome blocks with at least 10 sufficiently comparable studies, small-study effects were assessed using funnel plots of log risk ratio against its standard error together with Egger regression. No formal funnel-plot asymmetry testing was performed for analyses with fewer than 10 studies or for one-year evidence blocks containing incompatible effect measures. Funnel-plot asymmetry was interpreted as a potential small-study effect rather than as diagnostic evidence of publication bias.

Use of generative artificial intelligence

OpenAI ChatGPT was used during manuscript preparation to assist with language editing, journal-format conversion, document assembly, consistency checks, and analytic-code/documentation support. AI-generated outputs were treated as drafts requiring author verification. The authors retain full responsibility for the accuracy and integrity of the content, data, analyses, citations, and conclusions.

Results

Study selection and characteristics

The supplied PRISMA flow identifies 900 records across PubMed (n = 255), ScienceDirect (n = 77), Scopus (n = 335), Cochrane/CENTRAL (n = 33), and Google Scholar (n = 200). After removal of 783 duplicate records, 117 reports were assessed for eligibility; 82 were excluded for wrong intervention (n = 24), wrong outcome (n = 28), or wrong population (n = 30), leaving 35 original comparative reports: 34 observational reports and one randomized trial (Fig. 1). Twelve observational studies contributed to the primary long-term MACE synthesis. Of the other 22 observational reports, two were excluded because of probable Beijing-cohort overlap, seven did not provide compatible arm-level long-term MACE at > 12 months or belonged to a separate adjusted/time-horizon block, and thirteen contributed only to secondary outcomes or qualitative synthesis. Complete characteristics and contribution status are shown in Table 1 and Supplementary Tables S2 and S10.

Table 1
Characteristics of all eligible original comparative reports

Study	Design	Period	Native/Graft N	Follow-up	ACS %	DES %	Native CTO %	MACE/outcome note	Overlap handling
Meliga et al. (2007)	Retrospective single-centre registry	2002–2004	13/11	3 years	29.2	100	100	CTO-specific; native and SVG strategies	No specific overlap identified
Garcia-Tejada et al. (2009)	Retrospective single-centre registry	2005–2006	53/31	1.5 years	45.2	84.0	8.4	Study-defined MACE	No specific overlap identified
Varghese et al. (2009)	Retrospective single-centre registry	2003–2006	79/63	2.5 years	79.5	74.1	2	Clinical outcomes; TVR available	No specific overlap identified
D'Ascenzo et al. (2010)	Retrospective single-centre registry	2002–2004	25/28	3 years	69.8	19.0	28	Study-defined MACE	No specific overlap identified
Welsh et al. (2010)	Post-hoc analysis of randomized-trial cohort	2004–2006	55/63	3 months	100	NR	NR	STEMI; no compatible MACE	No specific overlap identified
Brilakis et al. (NCDR) (2011)	Retrospective multicentre registry	2004–2009	187989/112913	In-hospital	74.0	68	5.4	In-hospital outcomes only	No specific overlap identified
Alidoosti et al. (2011)	Retrospective single-centre registry	2003–2007	163/63	9 months	0	42.9	NR	Study-defined MACE	No specific overlap identified
Gaglia et al. (2011)	Retrospective single-centre registry	2000–2010	4001/191	1 year	100	49.9	NR	AMI cohort; potential Mount Sinai overlap	Mount Sinai temporal overlap possible
Bundhoo et al. (2011)	Retrospective multicentre registry	2005–2008	101/60	1 year	40.3	84.9	2.5	Study-defined MACE	No specific overlap identified
Xanthopoulou et al. (2011)	Retrospective single-centre registry	2004–2008	102/88	2.3 years	71.1	32.1	4.9	Study-defined MACE	No specific overlap identified
ACROSS / Leal et al. (2012)	Retrospective single-centre registry	2003–2008	533/123	2 years	36.9	83.2	NR	Component outcomes available	No specific overlap identified
Ho et al. (2012)	Retrospective single-centre registry	2005–2008	9/16	3 years	44.0	100	0	Study-defined MACE	No specific overlap identified
Nikolsky et al. (2013)	Post-hoc analysis of randomized-trial cohort	2005–2007	50/33	3 years	100	78.0	NR	STEMI; study-defined MACE	No specific overlap identified
Liu W et al. (2013)	Retrospective single-centre registry	2005–2011	110/30	2 years	100	100	NR	Potential Beijing overlap	Beijing temporal/site overlap possible
Kohl et al. (2014)	Retrospective multicentre registry	2003–2012	104/84	5 years	100	NR	NR	STEMI; MACE event counts available in prior extraction	No specific overlap identified
Liu Y et al. (2015)	Retrospective single-centre registry	2005–2010	190/75	3 years	85.8	82.7	NR	Potential Beijing overlap	Beijing temporal/site overlap possible
Garg et al. (2015)	Retrospective single-centre registry	2007–2012	22/25	1.7 years	100	NR	NR	STEMI; death only	No specific overlap identified
VA-CART (2016)	Retrospective multicentre registry	2005–2013	7930/3616	5 years	51.3	77.8	4.5	Large national registry	No specific overlap identified

Abbreviations: ACS, acute coronary syndrome; CTO, chronic total occlusion; DES, drug-eluting stent; MACE, major adverse cardiovascular events; NR, not reported. Sample sizes are outcome-complete denominators where indicated. Primary long-term MACE accounting: 12 reports included; 2 excluded for probable overlap; 7 assigned to other time/metric blocks; 13 contributed only to secondary outcomes or qualitative synthesis.

Study	Design	Period	Native/Graft N	Follow-up	ACS %	DES %	Native CTO %	MACE/outcome note	Overlap handling
Iqbal et al. (2016)	Retrospective multicentre registry	2007–2012	1168/1490	1 year	100	52.1	NR	BCIS STEMI cohort	UK/BCIS geographic or diagnostic overlap possible
Mavroudis et al. (2017)	Retrospective single-centre registry	2004–2010	103/89	3 years	41.4	83.0	NR	TVR-focused	No specific overlap identified
ADAPT-DES (2017)	Retrospective multicentre registry	2008–2010	1063/405	2 years	54.9	100	5.7	Potential Mount Sinai overlap	Mount Sinai temporal overlap possible
Shoaib et al. (NSTEMI) (2018)	Retrospective multicentre registry	2007–2014	8825/9544	1 year	100	70.0	NR	BCIS NSTEMI cohort	UK/BCIS geographic or diagnostic overlap possible
Liu D et al. (2019)	Retrospective multicentre registry	2009–2015	113/44	3.7 years	63.0	96.8	23.0	Diabetes subgroup	No specific overlap identified
Pan-London Registry (2020)	Retrospective multicentre registry	2005–2015	3703/8938	3 years	46.2	87.5	28.6	Potential UK registry overlap	UK/BCIS geographic or diagnostic overlap possible
Shoaib et al. (CTO) (2020)	Retrospective multicentre registry	2007–2014	2513/8619	1 year	0	67.6	100	BCIS CTO-specific cohort	UK/BCIS geographic or diagnostic overlap possible
Abdelrahman et al. (2022)	Retrospective single-centre registry	2008–2018	209/192	1 year	54.6	84.5	NR	MACE = death, MI, or revascularization; online 2020, print 2022	No specific overlap identified
Beerkens et al. (2021)	Retrospective tertiary-centre registry	2009–2017	2928/883	1 year	NR	NR	NR	Venous graft arm; arterial graft n = 172 separate; potential Mount Sinai overlap	Mount Sinai temporal overlap possible
Broughton et al. (2022)	Retrospective multicentre registry	NR	2851/1400	Long-term	NR	NR	NR	Composite MI/revascularization and mortality; no compatible raw MACE	No specific overlap identified
Ibisoglu et al. (2022)	Retrospective AMI cohort	NR	NR/NR	1 year	100	NR	NR	Group-specific outcome counts not available in accessible source	No specific overlap identified
Liu R et al. (2023)	Prospective observational cohort	2013	378/60	5 years	NR	NR	NR	5-year MI and 2-year revascularization reported	No specific overlap identified
Yang et al. (2023)	Retrospective single-centre registry	2010–2020	1072/204	43 months	Mixed	Contemporary	Native group more CTO	Potential Beijing overlap	Beijing temporal/site overlap possible
Beerkens et al. (NHR) (2024)	Nationwide prospective registry	2017–2021	9643/3179	1 year	NR	NR	NR	MACE = death or TVR; includes venous and arterial grafts	No specific overlap identified
Boddu et al. (2024)	Retrospective single-centre registry	NR	138/49	Median 60 months	NR	NR	NR	MACE = cardiac death, nonfatal MI, or TVR; outcome-complete denominators	No specific overlap identified

Abbreviations: ACS, acute coronary syndrome; CTO, chronic total occlusion; DES, drug-eluting stent; MACE, major adverse cardiovascular events; NR, not reported. Sample sizes are outcome-complete denominators where indicated. Primary long-term MACE accounting: 12 reports included; 2 excluded for probable overlap; 7 assigned to other time/metric blocks; 13 contributed only to secondary outcomes or qualitative synthesis.

Study	Design	Period	Native/Graft N	Follow-up	ACS %	DES %	Native CTO %	MACE/outcome note	Overlap handling
Cohen et al. (2025)	Retrospective multicentre registry	2005–2018	1928/836	Median 4.8 years	NR	NR	Native group more CTO	Melbourne registry; 2021 conference abstract is duplicate	Duplicate 2021 abstract excluded; 2025 full report retained
PROCTOR (2026)	Multicentre randomized open-label strategy trial	NR	108/112	1 year	NR	Contemporary	Native CTO ≈ 83%	MACE = all-cause death, nonfatal target-territory MI, or clinically driven target-territory revascularization	No specific overlap identified

Abbreviations: ACS, acute coronary syndrome; CTO, chronic total occlusion; DES, drug-eluting stent; MACE, major adverse cardiovascular events; NR, not reported. Sample sizes are outcome-complete denominators where indicated. Primary long-term MACE accounting: 12 reports included; 2 excluded for probable overlap; 7 assigned to other time/metric blocks; 13 contributed only to secondary outcomes or qualitative synthesis.

Table 2
Outcome definitions and synthesis decisions

Study	Follow-up	Reported outcome	Definition/components	Design stratum
Meliga et al. (2007)	3 years	BG 16.1; NA 18.2	CTO-specific; native and SVG strategies	Observational
Garcia-Tejada et al. (2009)	1.5 years	BG 12.9; NA 15.1	Study-defined MACE	Observational
Varghese et al. (2009)	2.5 years	Total 50%; between-group NS	Clinical outcomes; TVR available	Observational
D'Ascenzo et al. (2010)	3 years	BG 39.3; NA 28.0	Study-defined MACE	Observational
Welsh et al. (2010)	3 months	Death BG 19.0; NA 5.7	STEMI; no compatible MACE	Observational
Brilakis et al. (NCDR) (2011)	In-hospital	NR	In-hospital outcomes only	Observational
Alidoosti et al. (2011)	9 months	BG 4.8; NA 4.9	Study-defined MACE	Observational
Gaglia et al. (2011)	1 year	MACE BG 36.8; NA 24.5	AMI cohort; potential Mount Sinai overlap	Observational
Bundhoo et al. (2011)	1 year	BG 21.6; NA 8.9	Study-defined MACE	Observational
Xanthopoulou et al. (2011)	2.3 years	BG 43.2; NA 19.6	Study-defined MACE	Observational
ACROSS / Leal et al. (2012)	2 years	Death 10.9; MI 10.5; TVF 29.5; between-group NS	Component outcomes available	Observational
Ho et al. (2012)	3 years	BG 57.9; NA 10.0	Study-defined MACE	Observational
Nikolsky et al. (2013)	3 years	BG 52; NA 30	STEMI; study-defined MACE	Observational
Liu W et al. (2013)	2 years	BG 26.7; NA 18.1	Potential Beijing overlap	Observational
Kohl et al. (2014)	5 years	Death BG 25; NA 26	STEMI; MACE event counts available in prior extraction	Observational
Liu Y et al. (2015)	3 years	BG 45.3; NA 28.4	Potential Beijing overlap	Observational
Garg et al. (2015)	1.7 years	Death BG 24; NA 9	STEMI; death only	Observational
VA-CART (2016)	5 years	MACE BG 52.85; NA 37.93	Large national registry	Observational
Iqbal et al. (2016)	1 year	Death BG 11.9; NA 14.5	BCIS STEMI cohort	Observational
Mavroudis et al. (2017)	3 years	TVR BG 12.5; NA 3.6	TVR-focused	Observational
ADAPT-DES (2017)	2 years	BG 18.1; NA 8.2	Potential Mount Sinai overlap	Observational
Shoaib et al. (NSTEMI) (2018)	1 year	Death BG 7.08; NA 8.29	BCIS NSTEMI cohort	Observational
Liu D et al. (2019)	3.7 years	BG 25.0; NA 20.4	Diabetes subgroup	Observational
Pan-London Registry (2020)	3 years	Death BG 23.8; NA 13.6	Potential UK registry overlap	Observational
Shoaib et al. (CTO) (2020)	1 year	Death BG 3.1; NA 3.5	BCIS CTO-specific cohort	Observational
Abdelrahman et al. (2022)	1 year	Adjusted MACE HR available	MACE = death, MI, or revascularization; online 2020, print 2022	Observational
Beerkens et al. (2021)	1 year	No significant MACE difference	Venous graft arm; arterial graft n = 172 separate; potential Mount Sinai overlap	Observational
Broughton et al. (2022)	Long-term	Adjusted outcomes available	Composite MI/revascularization and mortality; no compatible raw MACE	Observational
Ibisoglu et al. (2022)	1 year	1-year TVR 6/95	Group-specific outcome counts not available in accessible source	Observational
Liu R et al. (2023)	5 years	No difference in 5-year MACCE	5-year MI and 2-year revascularization reported	Observational
Yang et al. (2023)	43 months	MACE 291/1072 vs 67/204	Potential Beijing overlap	Observational

Study	Follow-up	Reported outcome	Definition/components	Design stratum
Beerkens et al. (NHR) (2024)	1 year	1-year MACE 14.3 vs 19.7%	MACE = death or TVR; includes venous and arterial grafts	Observational
Boddu et al. (2024)	Median 60 months	MACE 44/138 vs 28/49	MACE = cardiac death, nonfatal MI, or TVR; outcome-complete denominators	Observational
Cohen et al. (2025)	Median 4.8 years	Adjusted long-term mortality HR available	Melbourne registry; 2021 conference abstract is duplicate	Observational
PROCTOR (2026)	1 year	MACE 37/108 vs 21/112	MACE = all-cause death, nonfatal target-territory MI, or clinically driven target-territory revascularization	Randomized

Table 3
Principal meta-analytic and design-stratified results

Outcome/time	Evidence/measure	k	Effect (95% CI)	I^2 %	Model	Interpretation
MACE, > 12 months	Observational unadjusted RR	12	0.64 (0.53–0.77)	47.6	Paule–Mandel/Hartung–Knapp	Values < 1 favor native PCI
Death, > 12 months	Observational unadjusted RR	15	0.71 (0.61–0.83)	9.8	Paule–Mandel/Hartung–Knapp	Values < 1 favor native PCI
MI, > 12 months	Observational unadjusted RR	12	0.60 (0.47–0.78)	20.4	Paule–Mandel/Hartung–Knapp	Values < 1 favor native PCI
TVR, > 12 months	Observational unadjusted RR	14	0.68 (0.57–0.83)	34.5	Paule–Mandel/Hartung–Knapp	Values < 1 favor native PCI
All-cause mortality, long-term	Observational adjusted HR	4	0.81 (0.69–0.95)	48.9	HR-only synthesis	Not mixed with OR or RR
MACE, 1 year	Observational adjusted HR	1	0.58 (0.35–0.95)	NA	Single study	Abdelrahman et al.
MACE, 1 year	Randomized HR	1	2.14 (1.25–3.65)	NA	Single trial	PROCTOR
MACE, 1 year	Observational adjusted OR	1	0.79 (0.69–0.91)	NA	Single study; kept separate from HR/RR	Netherlands Heart Registration
Procedural MI	Randomized HR	1	14.85 (1.95–112.96)	NA	Not pooled with spontaneous MI	PROCTOR 13% vs 1%
MACE, 9–12 months	Observational crude RR	2 individual studies	Bundhoo 0.41 (0.19–0.90); Alidoosti 1.03 (0.28–3.76)	NA	Displayed individually; no cross-metric pool	Different definitions and small k
Design comparison	Randomized vs observational	NA	No formal interaction test	NA	Descriptive evidence map only	One RCT; design confounded with study-specific features

Table 4
Risk of bias, overlap, and certainty summary

Evidence block	Judgment	Basis	Implication
PROCTOR randomized evidence	RoB 2: some concerns	Low risk for randomization, deviations, and missing data; some concerns for outcome measurement and selection of the 1-year reported result	Low certainty for 1-year MACE; very low for several component endpoints
Observational evidence	ROBINS-I: serious overall	Confounding by indication/anatomy remained serious across all reports; other domains were generally low to moderate	Very low certainty
Mount Sinai cluster	Potential overlap	Gaglia, ADAPT-DES, Beerkens; representative and complete-cluster sensitivity analyses	Direction unchanged
Beijing cluster	Potential overlap	Liu W, Liu Y, Yang; Yang retained in primary; complete-cluster sensitivity	Direction unchanged
UK/BCIS cluster	Potential partial overlap	Diagnosis-specific cohorts and Pan-London handled in separate outcome blocks	Residual uncertainty
Effect measures	No cross-family pooling	RR, HR, and OR analyzed separately	Reduces interpretive bias
Randomized–observational comparison	Descriptive only	One RCT and nonexchangeable HR/OR/RR observational estimates	No causal design-interaction inference

Risk of bias

PROCTOR was judged to have some concerns overall for the 1-year MACE result. Risk was low for the randomization process, deviations from intended interventions, and missing outcome data; all 220 randomized participants contributed to the 1-year analysis or died during follow-up. Some concerns remained for outcome measurement and selection of the reported result because treatment was open label, clinically driven revascularization and procedural MI could be influenced by procedural context, enrollment stopped early because of funding, and the protocol-specified primary endpoint was at 3 years whereas the current report presents 1-year outcomes. All 34 observational reports were judged at serious overall risk of bias, driven principally by confounding by indication and anatomy. Complete domain-level judgments are provided in Supplementary Tables S5–S6.

Observational study-defined MACE

In the conservative nonoverlapping set, 12 studies contributed long-term study-defined MACE. Native-vessel PCI was associated with fewer events (RR 0.64, 95% CI 0.53–0.77; I^2=47.6%; Fig. 2). The 9–12-month observational synthesis also favored native PCI but was less stable because few studies contributed. The all-report model, representative-dataset model, complete Mount Sinai exclusion, complete Beijing exclusion, and combined-cluster exclusion all remained on the native-favoring side of the null. No single-study omission reversed the direction of the long-term estimate (Supplementary Figures S1–S2). These findings describe association, not causal superiority.

One-year evidence according to design and effect-measure family

At one year, PROCTOR favored graft PCI (HR 2.14, 95% CI 1.25–3.65). Two adjusted observational estimates pointed toward native PCI: Abdelrahman et al. reported HR 0.58 (95% CI 0.35–0.95), and the Netherlands Heart Registration reported OR 0.79 (95% CI 0.69–0.91). Crude 9–12-month RRs were 0.41 (95% CI 0.19–0.90) in Bundhoo et al. and 1.03 (95% CI 0.28–3.76) in Alidoosti et al.; the overlap-flagged Gaglia report was displayed descriptively. Figure 3 presents these estimates by design and metric. No overall effect or formal interaction by design was calculated because the evidence contained only one randomized-controlled trial (RCT) and nonrandomized estimates differed in metric, population, target-selection process, MACE definition, and procedural complexity.

Mortality, myocardial infarction, and revascularization

Adjusted long-term mortality HRs from four observational cohorts produced a pooled HR of 0.81 (95% CI 0.69–0.95; Fig. 4). This estimate was kept separate from unadjusted RRs. Long-term unadjusted MI and TVR generally favored native PCI, although heterogeneity reflected differences in ACS presentation, endpoint definitions, and treatment era. Two compatible adjusted long-term MI HRs favored native PCI, but certainty remained very low. The Netherlands Heart Registration adjusted one-year OR was reported separately because ORs were not mixed with HRs or RRs.

Procedural versus spontaneous myocardial infarction

PROCTOR reported procedural MI in 13% of the native-strategy arm and 1% of the SVG-strategy arm (HR 14.85, 95% CI 1.95–112.96). This endpoint was not pooled with spontaneous or follow-up MI. The native arm contained a high prevalence of CTOs and frequent retrograde techniques, making the procedural MI signal clinically coherent but indirectly applicable to simpler native lesions. In observational cohorts, SVG PCI was more consistently associated with no-reflow and distal embolization, but procedural MI definitions and raw counts were insufficiently standardized for a defensible pooled estimate. The evidence therefore supports distinct early procedural hazards rather than a single undifferentiated MI endpoint.

CTO-dominant versus non-CTO cohorts

The prespecified CTO-dominant interaction could not be estimated reliably. PROCTOR was CTO dominant, and one observational CTO-specific report provided mortality but not a compatible one-year MACE definition. Most other observational reports had low or unreported native CTO prevalence. This absence of comparable subgroup data is itself important: the randomized trial and the historical observational literature did not enroll the same anatomical decision set.

Reporting bias

Funnel plots were generated for the four unadjusted long-term outcome syntheses containing at least 10 studies (Supplementary Figures S3–S6). Egger regression did not detect statistically significant small-study effects for MACE ($p = 0.462$), all-cause death ($p = 0.862$), myocardial infarction ($p = 0.179$), or target-vessel revascularization ($p = 0.812$). These findings do not exclude reporting bias because asymmetry tests have limited power and the underlying studies were heterogeneous. No asymmetry testing was performed for adjusted mortality, adjusted MI, or one-year evidence blocks because fewer than 10 compatible studies contributed (Supplementary Table S8).

Certainty of evidence

GRADE certainty was low for randomized 1-year MACE after downgrading for RoB 2 concerns and indirectness to the broader all-comer post-CABG population. Randomized all-cause mortality, target-territory MI, target-territory revascularization, and procedural MI were rated very low because of additional imprecision and/or indirectness. All observational outcome blocks were rated very low because serious residual confounding by target selection remained plausible; inconsistency, indirectness, and imprecision varied by outcome. Complete outcome-specific GRADE judgments are provided in Supplementary Table S7.

Discussion

Principal findings

This review demonstrates a clear directional contrast between PROCTOR and several observational estimates, but the available aggregate data cannot identify study design as the cause of that contrast. Long-term observational associations favor native-vessel PCI, whereas the first randomized one-year comparison favors SVG PCI in a highly selected population. Treating these estimates as exchangeable would erase the clinical differences that make the new evidence important. Our stratified approach therefore refuses an overall randomized-plus-observational pool and asks which target-selection scenario each evidence block represents. The observational literature reflects real-world target choice. Operators often select SVG PCI when the native vessel is chronically occluded, heavily calcified, diffusely diseased, or technically inaccessible. Conversely, severely degenerated or thrombotic grafts may be avoided. Even sophisticated adjustment cannot fully capture lesion feasibility, distal target quality, operator expertise, ischemic-territory equivalence, or previous failed attempts. The resulting confounding can make native PCI appear more favorable because the comparison is partly favorable native anatomy versus unfavorable graft anatomy. PROCTOR changed the decision set. Both targets had to be clinically and technically acceptable before randomization, thereby reducing target-choice confounding but selecting relatively treatable SVGs and unusually complex native targets. The high native CTO burden and frequent advanced techniques shifted early hazard toward native PCI, especially through procedural MI. At one year, the trial answers whether an immediately feasible favorable SVG should be treated instead of a difficult native target—not whether native PCI is inferior across all post-CABG patients or over five years.

Time-dependent interpretation

The results support a temporal model. Native CTO PCI may impose greater early procedural risk but, when successful, may offer a more durable substrate than a degenerating SVG. SVG PCI may be less demanding and safer early when lesions are focal, nonaneurysmal, minimally thrombotic, and have adequate runoff, yet the biological graft-failure process continues. Observational follow-up of two to five years and PROCTOR follow-up of one year therefore sample different phases of the risk curve. Longer-term PROCTOR outcomes are essential before early benefit is interpreted as durable superiority.

Clinical implications

Target selection should be individualized. Native PCI remains reasonable when the lesion is technically achievable, distal vessel quality is adequate, and durable benefit is expected. SVG PCI may be preferred when graft anatomy is favorable and the alternative native intervention is an exceptionally complex CTO, especially when rapid reperfusion is needed. High-risk graft features—including diffuse degeneration, ectasia, aneurysm, heavy thrombus, and poor runoff—should weigh against SVG PCI. The decision should incorporate intravascular imaging, embolic protection when appropriate, CTO expertise, expected survival, and patient preferences rather than follow a rigid native-first or graft-first rule.

Comparison with previous reviews

The present work adds individual-report representation, explicit registry-overlap management, separation of adjusted and unadjusted effect measures, follow-up-specific models, a descriptive one-year evidence map, procedural-versus-spontaneous MI separation, RoB 2, ROBINS-I, and GRADE. It deliberately avoids a formal design-interaction claim that cannot be identified from one randomized trial and nonexchangeable observational estimates.

Strengths and limitations

This review has several strengths, including explicit separation of randomized and observational evidence, effect-measure-specific synthesis, follow-up stratification, registry-overlap adjudication, procedural-versus-spontaneous MI separation, and outcome-level RoB 2, ROBINS-I, and GRADE assessment. Several limitations remain. First, observational estimates are highly vulnerable to residual confounding by indication and incomplete anatomic granularity. Second, MACE definitions, follow-up horizons, and treatment eras varied, and several evidence blocks contained few compatible studies. Third, aggregate data cannot resolve patient-level effect modification by native CTO complexity, graft morphology, distal vessel quality, or operator expertise. Fourth, exact patient overlap could not always be established across registry reports, although prespecified sensitivity analyses were used. Fifth, PROCTOR remains the only randomized target-strategy trial and currently contributes one-year evidence, limiting long-term causal inference. Finally, the supplied review files contain protocol-source and workflow discrepancies that must be reconciled against native search, screening, extraction, and adjudication records before submission; these discrepancies are documented rather than silently harmonized.

Conclusions

Native-vessel and bypass-graft PCI should not be considered universally superior strategies after CABG. Long-term observational evidence was associated with fewer adverse events after native-vessel PCI, although these findings remain highly susceptible to confounding by anatomical complexity and target selection. In contrast, PROCTOR showed lower one-year MACE with graft PCI in a selected population in whom both targets were considered feasible, largely because complex native-vessel intervention was associated with more procedural myocardial infarction. Taken together, the available evidence supports an individualized, anatomy- and time-dependent approach: graft PCI may offer an early advantage when the alternative native lesion is technically complex, whereas the long-term comparative durability of both strategies remains uncertain. Target selection should therefore integrate native-vessel complexity, graft quality, procedural risk, and expected durability rather than follow a universal native-first or graft-first strategy. Further randomized studies with longer follow-up should stratify native CTO complexity and graft morphology and distinguish procedural from spontaneous myocardial infarction.

Abbreviations

ACS, acute coronary syndrome; BCIS, British Cardiovascular Intervention Society; CABG, coronary artery bypass grafting; CI, confidence interval; CTO, chronic total occlusion; DES, drug-eluting stent; EPD, embolic protection device; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; NCDR, National Cardiovascular Data Registry; OR, odds ratio; PCI, percutaneous coronary intervention; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions; RoB 2, revised Cochrane risk-of-bias tool for randomized trials; RR, risk ratio; SVG, saphenous vein graft; TVR, target-vessel revascularization.

Declarations

Author Contribution

HPM contributed to conceptualization, methodology, investigation, data curation, formal analysis, visualization, and writing of the original draft. NA contributed to study screening, data verification, risk-of-bias assessment, and writing—review and editing. JS contributed to supervision, validation, clinical interpretation, and writing—review and editing. All authors reviewed and approved the final manuscript.

Data Availability

The data supporting the findings of this systematic review and meta-analysis are derived from previously published studies. The extracted aggregate data, effect-size calculations, and analysis outputs are provided within the supplementary materials, including the accompanying meta-analysis workbook. No individual participant-level data were used.

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Figures

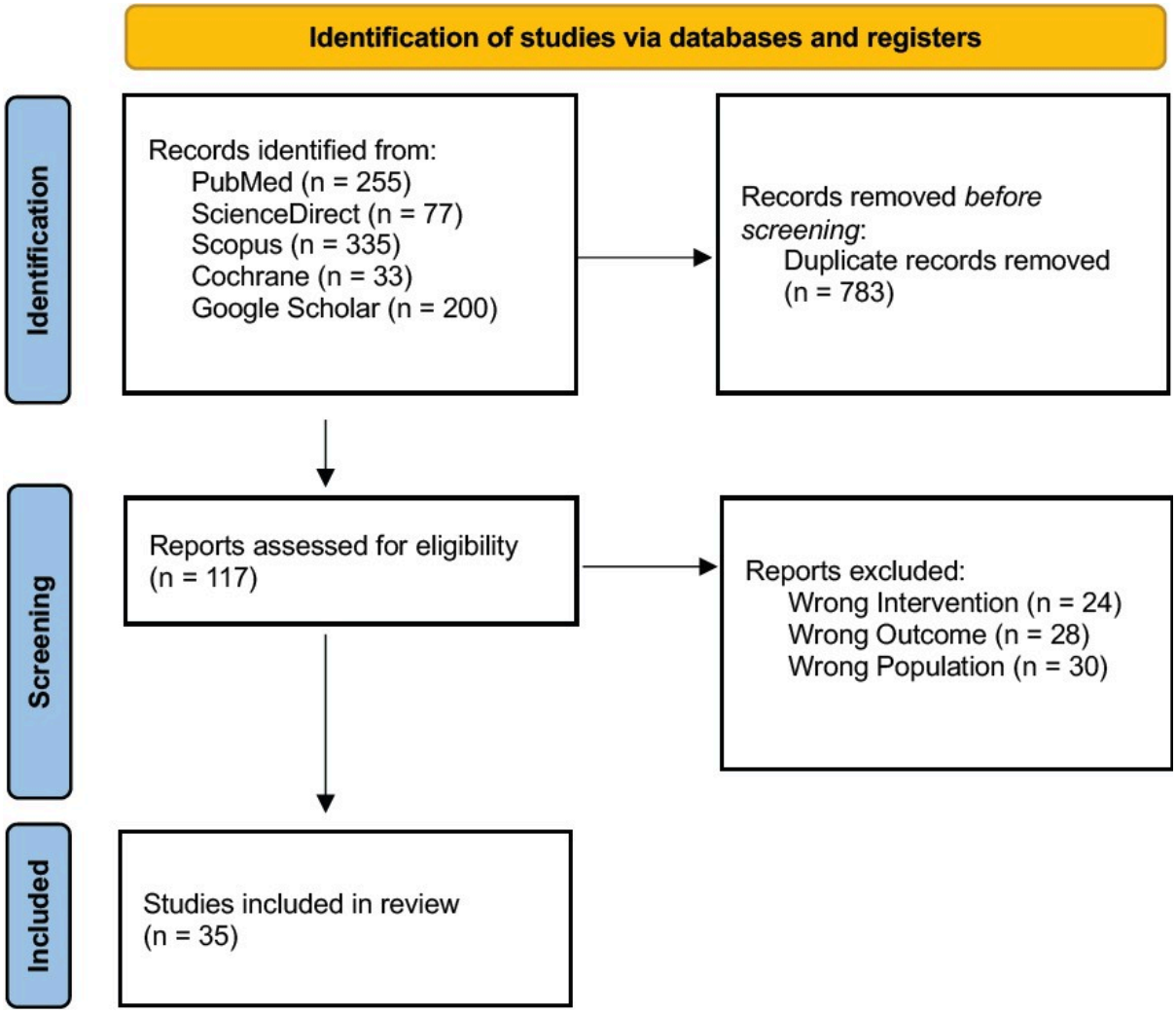


Figure 1

PRISMA 2020 study-selection flow diagram. Records were identified from PubMed, ScienceDirect, Scopus, Cochrane/CENTRAL, and Google Scholar. The supplied flow counts show 900 records identified, 783 duplicates removed, 117 reports assessed for eligibility, 82 reports excluded, and 35 studies included (34 observational reports and one randomized trial).

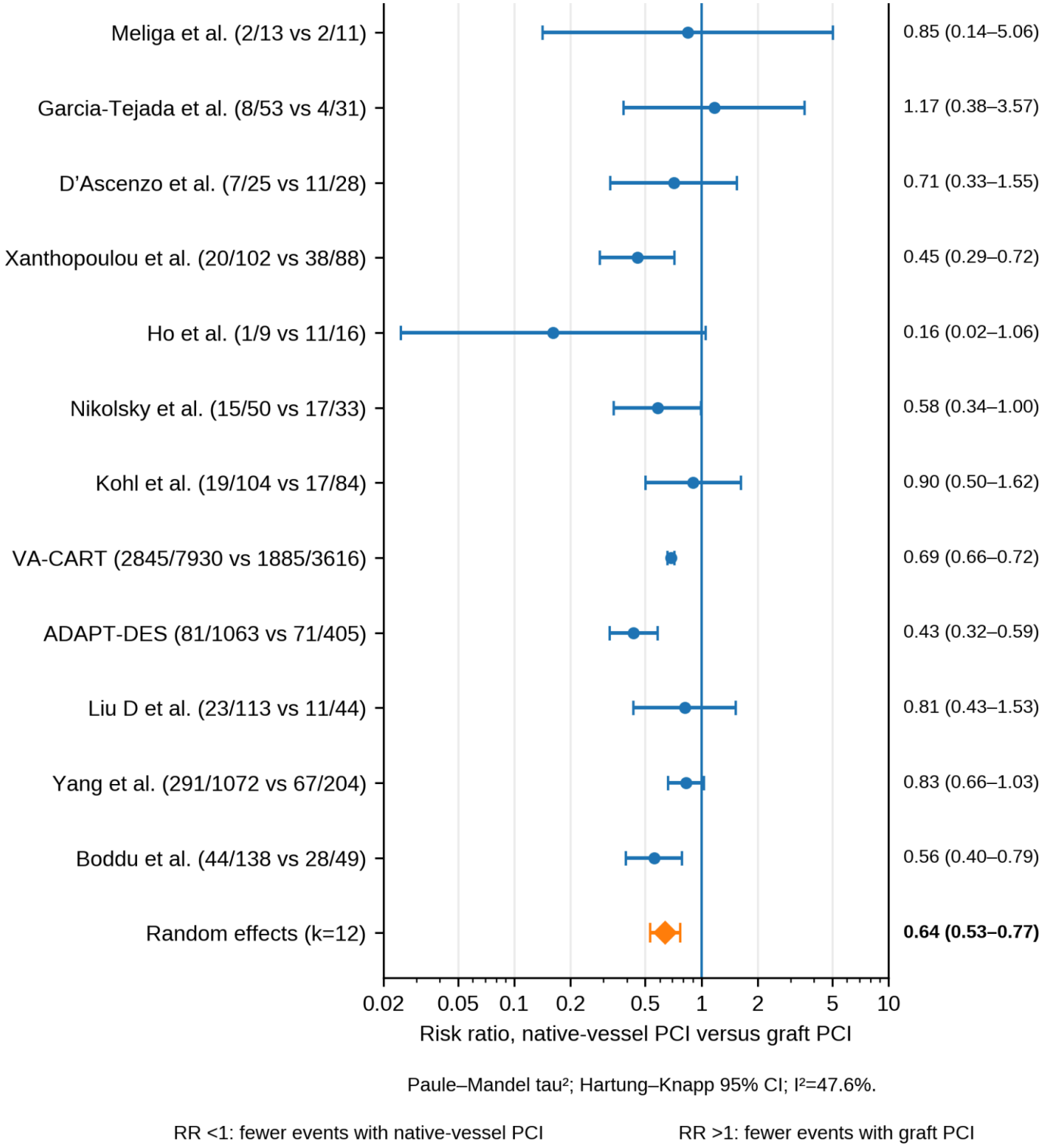


Figure 2

Long-term observational MACE. Forest plot of 12 observational studies reporting study-defined major adverse cardiovascular events beyond 12 months. Risk ratios compare native-vessel PCI with bypass-graft PCI; values below 1 favor native PCI. The conservative representative-dataset analysis excludes reports with probable overlap. Random-effects models use the Paule-Mandel estimator and Hartung-Knapp confidence intervals.

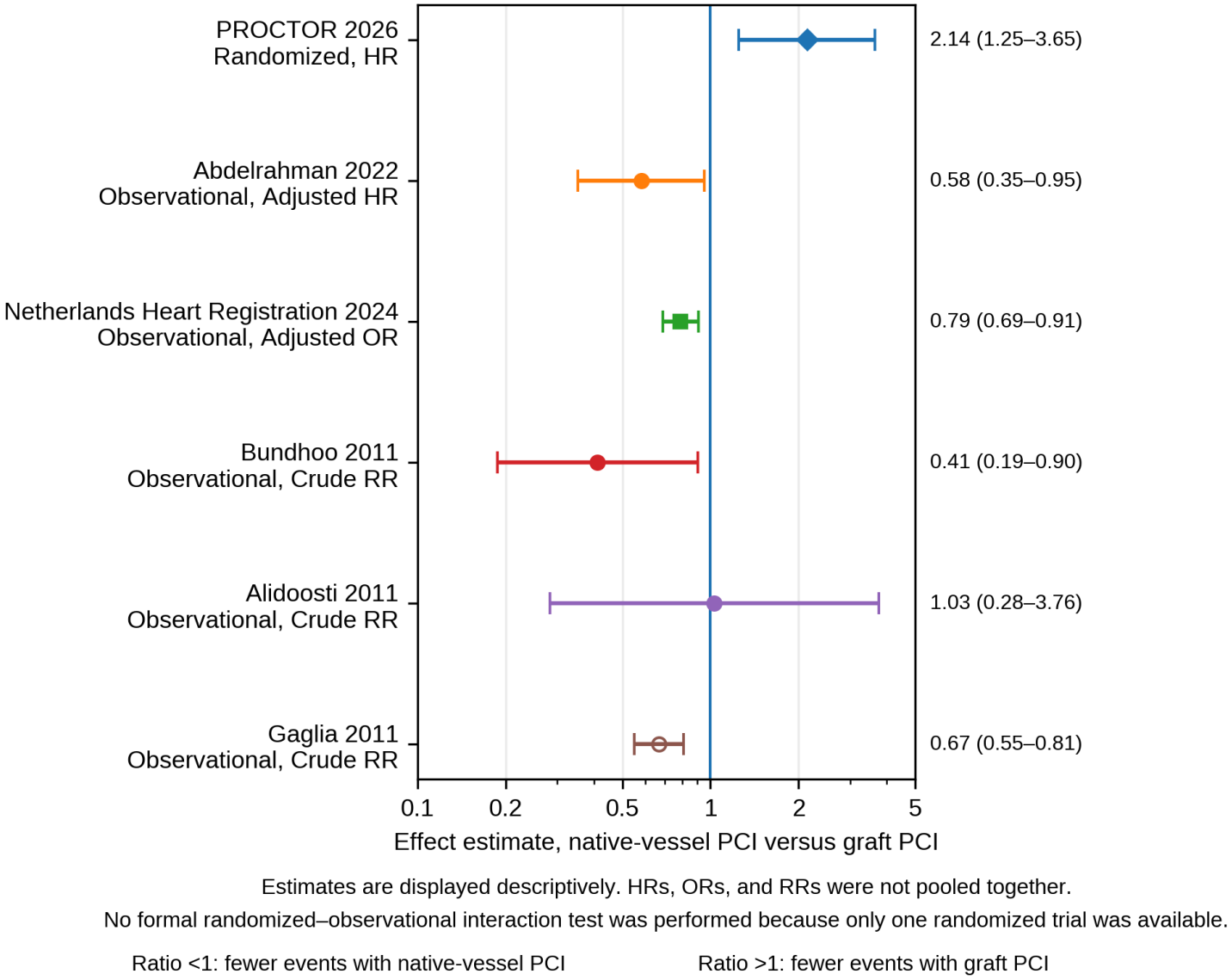


Figure 3

One-year design- and metric-stratified MACE evidence. Randomized HR, observational adjusted HR, observational adjusted OR, and crude RRs are displayed descriptively on a common ratio scale. HRs, ORs, and RRs were not pooled across metric or study design, and no formal randomized-observational interaction test was calculated. Values below 1 indicate fewer events with native-vessel PCI; values above 1 indicate fewer events with graft PCI.

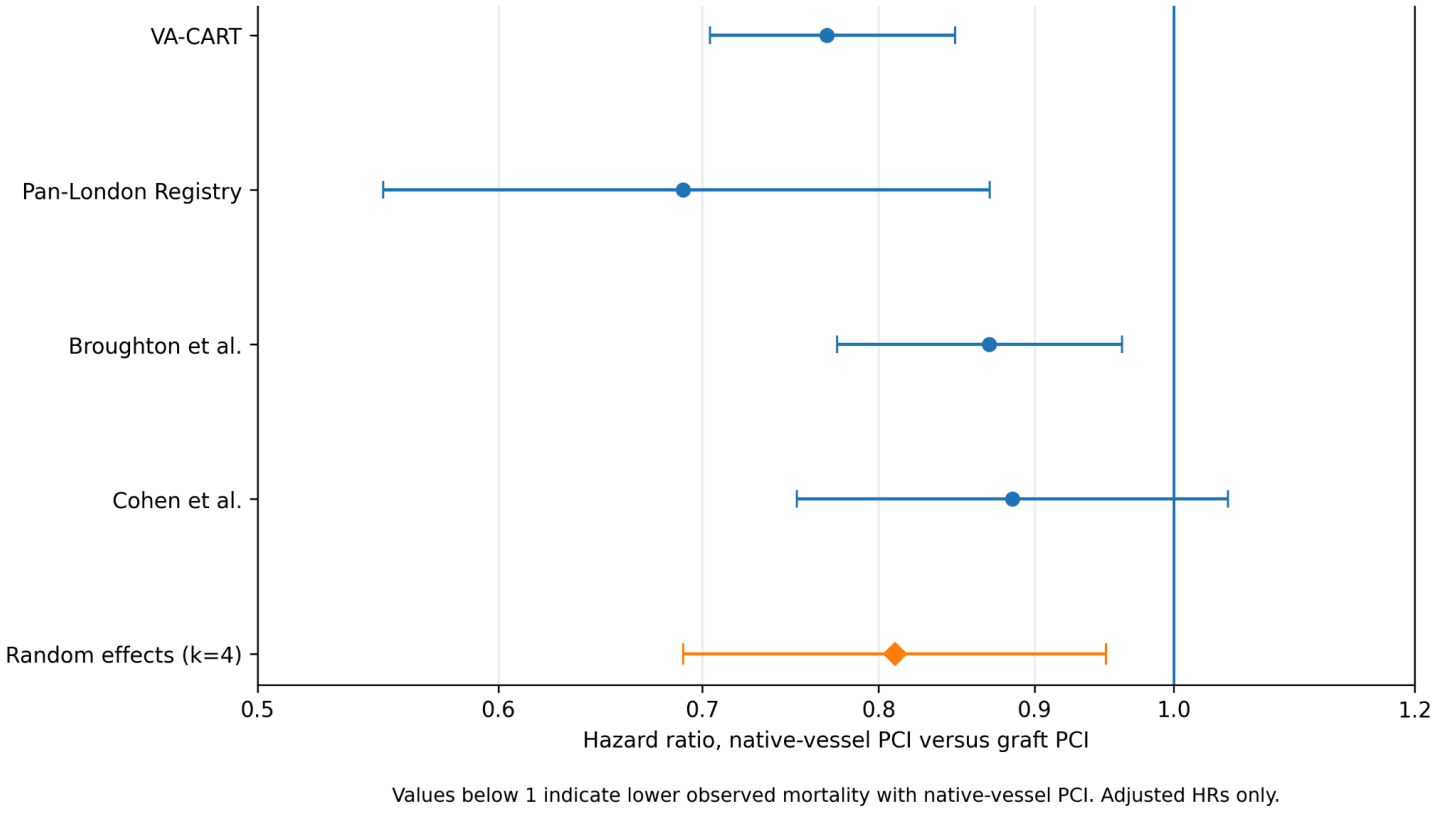


Figure 4

Adjusted long-term all-cause mortality. Forest plot of four adjusted observational hazard ratios for long-term all-cause mortality. HRs are oriented as native-vessel PCI versus bypass-graft PCI and pooled only with other adjusted HRs.

Supplementary Files

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- 06PRISMA2020ChecklistEHJ.docx
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