

3 REVIEW ARTICLE

4 Mid- and long-term outcomes of on-pump 5 versus off-pump coronary artery bypass 6 grafting: a meta-analysis of randomized 7 controlled trials

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14 ABSTRACT

15 The long-term comparative outcomes of on-pump and off-pump coronary artery bypass grafting (CABG)
16 remain disputed. We performed a random-effects meta-analysis of 25 randomized controlled trials (18,729
17 patients) comparing on-pump versus off-pump CABG, searching MEDLINE/PubMed, Cochrane CENTRAL, Web
18 of Science, ProQuest, ClinicalTrials.gov, Scopus, and grey literature through June 7, 2025. Outcomes (repeat
19 revascularization, late myocardial infarction, stroke/TIA, late mortality, major adverse cardiovascular events
20 [MACE], and composite endpoints) were pooled as hazard ratios (HRs) with 95% confidence intervals (CIs),
21 expressed as on-pump versus off-pump. On-pump CABG significantly reduced late myocardial infarction (HR
22 0.58; $p = 0.01$). Off-pump CABG was associated with significantly lower MACE (HR 1.62; $p = 0.003$), with the
23 greatest benefit at 5–10 years (HR 2.18; $p < 0.00001$) and persisting beyond 10 years (HR 1.89; $p = 0.03$) and
24 with a lower composite-endpoint risk (HR 1.24; $p = 0.04$). No significant differences were found for late mor-
25 tality, repeat revascularization, or stroke/TIA. Risk of bias was moderate to high, and the certainty of evidence
26 was low to very low for most outcomes. On-pump CABG confers a long-term reduction in myocardial infarction,
27 whereas off-pump CABG is associated with a lower MACE and composite cardiovascular event burden;
28 neither technique differs for late mortality, repeat revascularization, or cerebrovascular events. Surgical strat-
29 egy should be individualized, and further high-quality trials are warranted.

30 **Keywords:** Coronary artery bypass grafting, off-pump coronary artery bypass grafting, on-pump coronary
31 artery bypass grafting, mid-term outcomes, long-term outcomes.

32 Introduction

33 Coronary artery disease (CAD) continues to be among
34 the leading causes of morbidity and mortality across
35 the world, and coronary artery bypass grafting (CABG)
36 continues to be a key component of revascularization
37 therapy, especially in patients with multivessel coronary
38 disease, left main CAD, or diabetes mellitus. CABG is
39 well established to improve survival, reduce ischemic
40 events, and enhance quality of life in well-selected patient
41 groups compared to medical therapy or percutaneous
42 coronary intervention (PCI) [1].

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Received: 01 September 2026 | **Accepted:** 24 September 2026



47	CABG has also been performed for a long time with	
48	cardiopulmonary bypass (CPB), or on-pump CABG.	
49	This involves stopping the heart and diverting blood	
50	through a heart-lung pump so that the surgeon can have	
51	a bloodless, motionless field to operate in. CPB permits	
52	meticulous formation of anastomoses and complete	
53	revascularization, particularly in those with complex	
54	coronary anatomy. However, on-pump CABG has had	
55	some theoretical complications due to the systemic	
56	inflammatory response and embolic load generated	
57	by the extracorporeal circulation. Such complications	
58	include neurocognitive dysfunction, renal dysfunction,	
59	stroke, and lengthened recovery, especially in elderly or	
60	high-risk patients [2].	
61	To reduce CPB-induced morbidity, off-pump CABG	
62	was introduced as a novel surgical technique. Surgery is	
63	performed on a beating heart in off-pump CABG without	
64	using CPB, with specialized stabilizing equipment.	
65	Theoretically, off-pump CABG has various benefits,	
66	including fewer neurological complications, reduced	
67	systemic inflammation, reduced transfusion needs, shorter	
68	intensive care and hospital stay, and earlier postoperative	
69	recovery [3]. Early observational reports and some	
70	randomized trials have reinforced these advantages,	
71	particularly among high-risk or elderly patients. However,	
72	concerns with technical challenges of off-pump CABG	
73	remain, including reduced target coronary exposure,	
74	increased risk for incomplete revascularization, and	
75	variability in surgical outcomes based on operator	
76	experience. These issues cause the potential for decreased	
77	long-term graft patency and faster rates of repeat	
78	revascularization or myocardial infarction [4].	
79	Despite the clinical significance of this topic, debate	
80	remains concerning the long-term effectiveness of on-	
81	pump versus off-pump CABG. While some randomized	
82	controlled trials (RCTs) and observational studies have	
83	provided evidence of non-inferior long-term survival	
84	and major adverse cardiovascular events with off-	
85	pump CABG, others have demonstrated increased	
86	repeat revascularization or poorer graft patency for	
87	off-pump CABG [5]. Furthermore, long-term outcome	
88	interpretation is complicated by heterogeneity in the	
89	duration of follow-up between studies. Myocardial	
90	infarction, stroke, and death may not be as accurately	
91	reported in the short follow-up studies, and the possibility	
92	of temporal divergence of benefit between the two	
93	approaches has not generally been resolved [6].	
94	To address these uncertainties, we conducted a meta-	
95	analysis of on-pump versus off-pump CABG randomized	
96	trials with mid- and long-term clinical outcomes.	
97	Specifically, we evaluated repeat revascularization, late	
98	myocardial infarction, stroke or transient ischemic attack	
99	(TIA), and all-cause late mortality. Second, we performed	
100	subgroup analyses by follow-up duration, categorized as	
101	mid-term (≥ 1 to < 5 years), intermediate long-term (≥ 5	
102	to < 10 years), and extended long-term (≥ 10 years), to	
103	determine if difference changes or does not change across	
104	time. By pooling the results of numerous well-designed	
105	trials, the aim of the study is to provide stronger guidance	
106	on the optimal surgical approach to CABG based on both	
107	the efficacy and the durability of benefit.	
	Subjects and Methods	108
	<i>Methodology</i>	109
	The conduction and reporting of this meta-analysis	110
	followed the principles of the Cochrane Handbook for	111
	Systematic Reviews of Interventions, version 6 and the	112
	Preferred Reporting Items for Systematic Reviews and	113
	Meta-Analyses (PRISMA) guidelines [7]. This study	114
	was not prospectively registered. No review protocol was	115
	prepared or published.	116
	<i>Research question</i>	117
	What are the comparative mid- and long-term clinical	118
	results of on-pump and off-pump CABG in terms of	119
	repeat revascularization, late myocardial infarction,	120
	stroke or TIA, and late mortality in patients undergoing	121
	surgical revascularization?	122
	<i>Research aim</i>	123
	To evaluate and compare the mid- and long-term clinical	124
	results of on-pump and off-pump CABG through the	125
	synthesis of RCTs.	126
	<i>Research objectives</i>	127
	• To synthesize and systematically review evidence	128
	from RCTs comparing on-pump and off-pump CABG.	129
	• To compare and estimate the hazard of repeat	130
	revascularization, late myocardial infarction, stroke	131
	or TIA, and late mortality in on-pump and off-pump	132
	CABG groups.	133
	• To perform subgroup analyses by duration of	134
	follow-up, classified as mid-term (≥ 1 to < 5 years),	135
	intermediate long-term (≥ 5 to < 10 years), and	136
	extended long-term (≥ 10 years), to determine how the	137
	relative effectiveness of the two surgical techniques	138
	changes over time.	139
	• To evaluate the durability and safety profile of both	140
	techniques for cardiovascular and cerebrovascular	141
	events over the long-term period.	142
	Inclusion Criteria	143
	<i>Types of studies</i>	144
	We considered only RCTs that directly compared on-	145
	pump versus off-pump CABG. Studies should have	146
	reported at least one of the following outcomes (repeated	147
	revascularization, late myocardial infarction, stroke or	148
	TIA, or all mortality) with a follow-up time of at least 1	149
	year. Single-center and multicenter trials were eligible.	150
	No publication status restrictions, or geographical region	151
	were imposed. Only studies published in English were	152
	included.	153
	<i>Participants</i>	154
	Trials were eligible if they enrolled adult patients (≥ 18	155
	years) with CAD who were receiving primary CABG	156
	surgery. The population could encompass multivessel	157
	disease, left main disease, diabetes, or other common	158
	comorbidities. Elective and urgent procedures were	159

160 included in the trials. Redo CABG alone, combined
161 cardiac procedures (valve replacement), or isolated
162 pediatric patients were excluded.

163 **Interventions**

- 164 • **Intervention Group:** Patients undergoing off-pump
165 CABG, i.e., CABG on a beating heart without CPB.
- 166 • **Comparator Group:** Patients undergoing on-pump
167 CABG, i.e., CABG with CPB and cardiac arrest under
168 aortic cross-clamping.
- 169 • All variations of surgical technique (e.g., use of
170 stabilizer, conduit used, and experience of surgeon)
171 were permitted, provided the primary comparison was
172 between on-pump and off-pump CABG.

173 **Exclusion Criteria**

174 Clinical trials were excluded if they had any of the
175 following:

- 176 • Non-randomized study types, e.g., observational
177 studies, case series, or registry comparisons.
- 178 • Irrelevant outcomes (i.e., did not have any
179 of the following at ≥ 1 year follow-up: repeat
180 revascularization, myocardial infarction, stroke/TIA,
181 or all-cause death).
- 182 • Shorter than 1 year of follow-up.
- 183 • Mixed interventions with no clear distinction of
184 on-pump versus off-pump groups, or where hybrid
185 revascularization was used.
- 186 • Duplicate publications or sub-analyses of the identical
187 trial dataset unless reporting additional long-term data
188 not already published.
- 189 • Studies of combined procedures, e.g., valve surgery or
190 congenital repairs, unless reporting separately isolated
191 CABG outcomes.

192 **Search Strategy**

193 **Electronic searches**

194 The following electronic databases were searched for
195 eligible studies: MEDLINE/PubMed, Cochrane Central
196 Register of Controlled Trials, Web of Science, ProQuest,
197 ClinicalTrials.gov, grey literature, and Scopus. The
198 search was set for all articles published in English from
199 inception to June 7, 2025.

200 The following search terms were used: (“Coronary Artery
201 Bypass” OR “coronary artery bypass” OR CABG OR
202 “surgical revascularization”) AND ((“off-pump” OR
203 “off pump” OR “beating heart surgery” OR OPCAB
204 OR OPCABG) OR (“on-pump” OR “on pump” OR
205 “cardiopulmonary bypass” OR CPB OR conventional
206 CABG))AND(“Reoperation”OR“revascularization”[tiab]
207 OR “repeat revascularization”[tiab] OR “late myocardial
208 infarction”[tiab] OR “myocardial infarction” OR
209 infarction[tiab] OR “Stroke”OR stroke[tiab] OR TIA[tiab]
210 OR “transient ischemic attack”[tiab] OR “mortality”
211 OR death[tiab] OR survival[tiab]) AND (“Follow-
212 Up Studies”[MeSH] OR “long-term”[tiab] OR “long
213 term”[tiab] OR “mid-term”[tiab] OR “mid-term”[tiab]
214 OR “late outcomes”[tiab] OR “ ≥ 1 year”[tiab] OR “ ≥ 5
215 years”[tiab]).

216 **Other resources**

217 The first reviewer searched within the reference lists of
218 obtained articles for other potentially relevant studies
219 that were not retrieved by electronic search.

220 **Selection of studies**

221 Two reviewers independently screened studies. The first
222 reviewer screened the retrieved reports for eligibility
223 through title and abstract and full-text screening. The
224 second reviewer checked the retrieved studies and
225 discrepancies were solved through discussion with a
226 third reviewer. After removal of duplicate records and
227 review articles, the remaining records were screened
228 by title and abstract. Records considered potentially
229 relevant were retrieved as full-text reports and assessed
230 for eligibility according to the predefined inclusion and
231 exclusion criteria. Full-text reports were excluded only
232 when a specific eligibility criterion was not met, with
233 the reasons documented. The final synthesis included 25
234 eligible studies.

235 **Data extraction**

236 The first reviewer carried out data extraction from the
237 included studies using a standardized data sheet which
238 included: (a) the study’s characteristics (the author, year,
239 the country, and study design); (b) patients’ characteristics
240 (sample size, age at the time of treatment initiation, sex,
241 and patient populations); (c) procedure details (number
242 of grafts, use of arterial or venous grafts, graft patency
243 evaluation method, ejection fraction (preserved vs
244 reduced), urgent/emergency vs elective CABG, and
245 follow-up duration) , and (e) the outcomes; repeat
246 revascularization, myocardial infarction (late), stroke or
247 TIA, late mortality rate and composite endpoints. When
248 multiple publications from the same randomized trial
249 were identified, only one dataset per trial was included
250 for each outcome. The report with the longest follow-
251 up duration was selected to avoid duplication of patient
252 populations. The second reviewer checked the collected
253 data for consistency and clarity. Any disagreements were
254 settled by refereeing the third reviewer.

255 **Measured Outcomes**

256 **Primary outcomes**

- 257 ➤ *Repeat revascularization:* A definition of the need for
258 repeat coronary revascularization procedures (repeat
259 CABG or PCI) following the index procedure, during
260 follow-up.
- 261 ➤ *Major adverse cardiovascular events:* Refers
262 to the first occurrence of any of the following:
263 all-cardiovascular related mortality, non-fatal
264 myocardial infarction, or non-fatal stroke. For studies
265 that reported a composite endpoint under a different
266 name but comprising these core components, the data
267 were extracted and analyzed as MACE.
- 268 ➤ *Myocardial infarction (Late):* Refers to new-onset
269 myocardial infarction occurring after hospital
270 discharge, as reported during the mid- or long-term
271 follow-up phase.

272 ➤ *Stroke or TIA*: Any cerebrovascular event on follow-
 273 up and encompasses ischemic and hemorrhagic
 274 strokes, and TIAs confirmed by clinical diagnosis or
 275 imaging.

276 **Secondary outcomes**

277 ➤ *Late mortality rate*: All-cause mortality occurring
 278 during the mid- or long-term follow-up. Mortality
 279 was not restricted to cardiovascular causes except
 280 when the cause was defined as part of the original
 281 study.
 282 ➤ *Composite endpoints*: Refers to a combined endpoint
 283 consisting of all-cause mortality together with at
 284 least one other clinically relevant, non-fatal event,
 285 e.g. death + stroke + myocardial infarction + renal
 286 failure requiring dialysis+ revascularization) as some
 287 articles used this method of reporting.

288 **Assessment of the risk of bias**

289 The risk of bias in the included studies was assessed
 290 using the Cochrane Risk of Bias tool [8].

291 **Data synthesis**

292 Initially, 3,242 records were retrieved from electronic
 293 database searches. After removing duplicates and excluded
 294 studies, out of 100 studies screened for eligibility, 25
 295 RCTs (18729 patients) [9–33] met all inclusion criteria
 296 and were determined eligible for inclusion in the final
 297 analysis (Table 1). These 25 records corresponded to 25
 298 independent randomized trials rather than 25 separate
 299 patient cohorts; where a trial had more than one associated
 300 publication (e.g., a long-term follow-up or sub-study
 301 report), only the report with the longest follow-up was
 302 retained per outcome, as described under Data extraction
 303 above, so no patient population was double-counted
 304 within any outcome analysis., and the remaining studies
 305 were excluded as per pre-defined criteria, were ineligible
 306 study topic or intervention ($n = 13$), retrospective design
 307 ($n = 5$), duplicate publication ($n = 10$), non-English
 308 publication ($n = 2$), case series ($n = 2$), narrative review
 309 ($n = 3$), ineligible outcomes ($n = 30$), and follow-up of
 310 less than 1 year ($n = 10$), these studies were mentioned
 311 in Figure 1 [34].

312 **Statistical analysis**

313 Meta-analysis was performed using Review Manager
 314 (RevMan) 5.4 version [35]. This meta-analysis synthesized
 315 data from RCTs comparing on-pump versus off-pump
 316 CABG across multiple long-term clinical outcomes.
 317 For all outcomes, we extracted or calculated hazard
 318 ratios (HRs) with 95% confidence intervals (CIs) as the
 319 primary effect measure, as they account for both the
 320 occurrence and timing of events during variable follow-
 321 up periods. When HRs were not directly reported, they
 322 were estimated using the methods described by Tierney
 323 et al., based on Kaplan–Meier curves, log-rank statistics.
 324 All HRs were transformed to their natural logarithms,
 325 and standard errors were calculated from CIs for pooling
 326 using the generic inverse-variance method in RevMan
 327 5.4. All HRs are expressed with on-pump CABG as

the index group and off-pump CABG as the reference 328
 group; consequently, $HR < 1$ indicates a lower event 329
 risk with on-pump CABG (favoring on-pump), and HR 330
 > 1 indicates a higher event risk with on-pump CABG 331
 (favoring off-pump). Heterogeneity among studies was 332
 assessed using the I^2 statistic, with values above 50% 333
 indicating substantial heterogeneity. Where significant 334
 heterogeneity was detected, sensitivity analyses were 335
 performed to identify and address potential sources, such 336
 as exclusion of outlier studies. All statistical tests were 337
 two-sided, and a p-value of less than 0.05 was considered 338
 statistically significant, with subgroup analyses stratified 339
 by follow-up duration (1 to <5 years, 5 to <10 years, and 340
 ≥ 10 years) to explore temporal effects. Furthermore, 341
 sensitivity analysis was conducted to detect the possible 342
 source of heterogeneity by (leave one out). Risk of bias 343
 was systematically assessed for each included study 344
 using the Cochrane Risk of Bias tool. Publication bias 345
 was assessed visually using funnel plots and statistically 346
 using Egger's regression test and Begg's rank correlation 347
 test. Egger's and Begg's tests were performed using 348
 Stata 17.0 (StataCorp LP, College Station, TX, USA). 349
 The certainty of evidence for the primary outcomes was 350
 formally assessed using a graded approach (GRADE). 351

352 **Results**

A total number of 25 RCTs [9–33] with 18729 patients 353
 were included in this meta-analysis to compare the long- 354
 term outcomes following on-pump versus off-pump 355
 CABG. 356

357 **Repeat coronary revascularization**

A pooled analysis of repeat revascularization was 358
 performed using data from four studies [14,15,31,33] 359
 involving 9,942 patients. The analysis revealed no 360
 statistically significant difference in the need for repeat 361
 revascularization between on-pump and off-pump CABG 362
 (on-pump vs. off-pump: $HR\ 0.83$; 95% CI [0.54, 1.28]; 363
 $p = 0.41$). The initial analysis demonstrated moderate 364
 heterogeneity among the studies ($I^2 = 65\%$; $p = 0.04$). A 365
 sensitivity analysis was conducted, which identified the 366
 study by Koop et al. (OctoPump Trial) [31] as a major 367
 contributor to this heterogeneity. Upon its exclusion, the 368
 heterogeneity was substantially reduced ($I^2 = 35\%$), and 369
 the recalculated pooled estimate showed no evidence of 370
 a difference between the surgical techniques (on-pump 371
 vs. off-pump: $HR\ 1.00$; 95% CI [0.68, 1.45]; $p = 0.98$) 372
 (Figure 2). 373

374 **Late myocardial infarction**

Myocardial infarction was evaluated in a pooled analysis 375
 of four studies [9,12,15,19] comprising 3,021 patients. 376
 The analysis demonstrated a statistically significant 377
 reduction in myocardial infarction favoring on-pump 378
 CABG compared to off-pump surgery (on-pump vs. 379
 off-pump: $HR\ 0.58$; 95% CI [0.38, 0.88]; $p = 0.01$), 380
 where $HR < 1$ reflected lower myocardial infarction 381
 risk with on-pump CABG. No significant heterogeneity 382
 was observed among the included studies ($I^2 = 0\%$; $p =$ 383
 0.81). The results were directionally consistent across all 384
 individual trials, with hazard ratios ranging from 0.50 to 385

Table 1. Included studies in the meta-analysis.

Study	Design/setting	Sample size (OP/CP)	Follow-up	Population	Main findings
Benedetto U. et al., EXCEL [9]	2019; multinational; post hoc RCT	923 (271 OP; 652 CP)	3 years	Left main CAD; SYNTAX ≤32	Recent MI: 11.1% OP vs 16.3% CP ($p = 0.04$). Repeat revascularization 7.0% vs 6.9% ($p = 0.37$); MACCE 11.8% vs 9.2% (HR 1.28, 95% CI 0.82–2.00; $p = 0.28$); late MI 2.4% vs 2.7% ($p = 0.74$); stroke/TIA 4.7% vs 3.8% ($p = 0.57$); symptomatic graft stenosis/occlusion 7.0% vs 4.9% ($p = 0.32$).
Diegeler A. et al., GOPCABE [10]	2013; Germany; RCT	2,539 (1,271 OP; 1,268 CP)	1 year	First-time isolated CABG; elderly	Mean grafts 2.7 OP vs 2.8 CP ($p < 0.001$). Repeat revascularization 3.1% vs 2.0% ($p = 0.11$); MACCE 13.1% vs 14.0% (HR 0.93, 95% CI 0.76–1.16; $p = 0.48$); MI 2.1% vs 2.4% ($p = 0.70$); stroke 3.5% vs 4.4% ($p = 0.26$); renal replacement 2.9% vs 3.5% ($p = 0.37$).
Forouzannia SM et al. [11]	2023; Iran; RCT	274; analyzed 263 (134 OP; 129 CP)	2.6 years (median)	Triple-vessel CAD	Grafts 3.5 ± 0.6 in both groups. MACCE 7.0% OP vs 11.2% CP (HR 0.57, 95% CI 0.24–1.32; $p = 0.192$); death 4.6% vs 5.2%; non-fatal MI 1.5% vs 3.7%; stroke/TIA 0.8% vs 1.5%; no significant between-group differences.
Hlavicka J. et al., PRAGUE-6 [12]	2016; Czech Republic; prospective single-center RCT	206 (98 OP; 108 CP)	1 year	High-risk CABG (EuroSCORE ≥6)	Grafts 2.04 OP vs 2.66 CP ($p < 0.001$). Composite death/stroke/MI/renal failure 21.4% OP vs 30.8% CP (HR 0.65, 95% CI 0.37–1.12; $p = 0.117$); death 16.3% vs 10.3% ($p = 0.210$); MI 8.2% vs 15.0% ($p = 0.148$); revascularization 5.1% vs 2.8% ($p = 0.373$).
Karolak W. et al. [13]	2007; Canada; RCT	300 (150 OP; 150 CP)	3.8 years (IQR 3.4–4.4)	Elective CABG; triple-vessel disease 67.8%–74%; EF <30% and emergencies excluded	Grafts 2.8 ± 0.9 OP vs 3.0 ± 0.9 CP ($p = NS$); arterial grafting 68% vs 64%. Repeat revascularization and MACCE were assessed; detailed long-term event estimates were not reported in the source table.
Lamy A. et al., CORONARY [14]	2013; 19 countries; RCT	4,752 (2,375 OP; 2,377 CP)	1 year	Mixed-risk CABG; age ≥70 or other risk factors	Urgent/emergency surgery 38.8%; >75% had preserved EF. Repeat revascularization 1.4% OP vs 0.8% CP (HR 1.66, 95% CI 0.95–2.89; $p = 0.07$); MACCE 12.1% vs 13.3% (HR 0.91, 95% CI 0.77–1.07; $p = 0.24$); MI 6.8% vs 7.5%; stroke 1.5% vs 1.7%; QoL no difference.
Møller CH et al., BBS [15]	2011; Denmark; RCT	341 (176 OP; 163 CP)	3.7 years (median)	High-risk; EuroSCORE ≥6; three-vessel disease	Grafts 3.2 ± 0.7 OP vs 3.3 ± 0.7 CP ($p = 0.10$). MACCE 40% vs 33% (HR 1.22, 95% CI 0.86–1.75; $p = 0.28$); MI 7.4% vs 14% (HR 0.53, 95% CI 0.27–1.04; $p = 0.06$); stroke 9.0% vs 6.7% ($p = 0.36$); reintervention 5.1% vs 6.1% ($p = 0.76$); AF 45% in both.
Nathoe HM et al., OctoPump [16]	2005; Netherlands; RCT	281 (142 OP; 139 CP)	1 year	Elective CABG; stable/unstable angina; preserved LV function	Grafts 2.4 OP vs 2.6 CP ($p = NS$). Complete arterial revascularization 84% OP vs 76% CP. Repeat revascularization 4.9% vs 1.4% ($p = 0.26$); event-free MACCE survival 88.0% vs 90.6% ($p = 0.48$); late MI 0 vs 1.4% ($p = 0.15$); stroke/TIA 0 in both; QoL QALYs 0.82 vs 0.83 ($p = 0.81$).
Sharma D. et al. [17]	2016; India; RCT	581 (293 OP; 288 CP)	1 year	Elderly (≥65 years), first-time isolated CABG	Grafts 2.6 ± 0.8 OP vs 2.8 ± 0.9 CP ($p < 0.001$). Composite endpoint 13.1% vs 13.3% ($p = 0.94$); repeat revascularization 3.3% vs 2.1% ($p = 0.34$); MI 2.2% vs 2.1% ($p = 0.97$); stroke 2.3% vs 2.7% ($p = 0.77$); MACCE no difference.
Shroyer AL et al., ROOBY [18]	2009; USA; RCT	2,203 (1,104 OP; 1,099 CP)	1 year	CABG population; 99% male	Grafts 2.9 ± 0.9 OP vs 3.0 ± 1.0 CP ($p = 0.002$); arterial grafting 59.4% vs 58.0%. Graft patency 82.6% vs 87.8% ($p < 0.01$); repeat revascularization 4.6% vs 3.4% ($p = 0.18$); late MI 2.0% vs 2.2% ($p = 0.76$); stroke 1.3% vs 0.7% ($p = 0.28$); MACCE 9.9% vs 7.4% ($p = 0.04$).
Yu L. et al. [19]	2014; China; RCT	102 (51 OP; 51 CP)	4.2 ± 1.1 years	Triple-vessel CAD with enlarged ventricles (LVEDD ≥6.0 cm)	Grafts 3.0 ± 0.6 OP vs 3.1 ± 0.5 CP ($p = 0.273$); all received LIMA + saphenous vein. Repeat PCI 2.1% vs 2.2% ($p = 0.975$); late mortality 14.9% vs 13.3% ($p = 0.742$); recurrent angina 8.9% vs 4.3% ($p = 0.368$).
Angelini GD et al., BHACAS 1 & 2 [20]	2009; UK; RCT	401 (199 OP; 202 CP)	1–8 years	Elective multivessel CABG; preserved LV function	Grafts 2.46 OP vs 2.64 CP. Graft patency 89.4% vs 89.0% (OR 1.00, 95% CI 0.55–1.81; $p > 0.99$); death HR 1.24 (95% CI 0.72–2.15; $p = 0.44$); MACCE/death HR 0.84 (95% CI 0.58–1.24; $p = 0.39$); QoL no difference.
De Melo RMV et al., MASS III [21]	2015; Brazil; post hoc RCT analysis	260 (119 OP; 141 CP)	5 years	Multivessel CAD with severe circumflex lesions (≥70%); EF ≥40%	Grafts 2.6 ± 0.57 OP vs 3.0 ± 0.65 CP ($p = 0.0001$). Repeat revascularization 5.0% in both ($p = 1.0$); MACCE 21% OP vs 12% CP (HR 1.88, 95% CI 1.02–3.48; $p = 0.041$); late MI 6.0% vs 4.3% ($p = 0.58$); heart-failure hospitalization 13.7% vs 5.8% ($p = 0.05$).

(Continued)

Study	Design/setting	Sample size (OP/CP)	Follow-up	Population	Main findings
Diegeler A. et al., GOPCABE [22]	2019; Germany; RCT	2,370 (1,179 OP; 1,191 CP)	5 years	Elderly (≥ 75 y), elective/urgent CABG	Repeat revascularization 4.1% OP vs 3.2% CP ($p = 0.228$); MACCE 34% vs 33% (HR 1.03, 95% CI 0.89–1.18; $p = 0.704$); MI 2.1% vs 1.5% ($p = 0.181$).
Hueb W. et al., MASS III [23]	2010; Brazil; RCT	308 (155 OP; 153 CP)	5 years	Stable multivessel CAD; preserved LVEF	Grafts 2.49 OP vs 2.97 CP ($p < 0.001$); arterial grafting 89–91%. Repeat revascularization 6.5% vs 5.9% ($p = 0.84$); MACCE HR 0.71 (95% CI 0.41–1.22; $p = 0.21$); late MI 6.5% vs 1.9% ($p = 0.05$); stroke/TIA 1.9% vs 3.2% ($p = 0.50$); late AF 35% vs 4% ($p < 0.001$).
Lamy A. et al., CORONARY [24]	2016; 19 countries; expertise-based RCT	4,752 (2,375 OP; 2,377 CP)	4.8 years	Isolated CABG with ≥ 1 risk factor (age ≥ 70 , diabetes, CKD, etc.)	Grafts 2.9 $\pm$ 1.0 OP vs 3.0 $\pm$ 1.0 CP ($p = 0.15$). Composite endpoint 23.1% OP vs 23.6% CP (HR 0.98, 95% CI 0.87–1.10; $p = 0.72$); repeat revascularization 2.8% vs 2.3% ($p = 0.29$); MI 7.5% vs 8.2% ($p = 0.41$); stroke 2.3% vs 2.8% ($p = 0.32$); QoL no difference. Graft patency was reported as inferior with OP at 1 y in prior CORONARY reports.
Puskas JD et al., SMART [25]	2011; USA; RCT	200 (100 OP; 100 CP)	7.5 years	Unselected multivessel CAD	Grafts 3.39 OP vs 3.40 CP; arterial grafting 40–41%. Late graft patency 76.0% OP vs 83.5% CP ($p = 0.44$); repeat revascularization 2.3% in both; MACCE survival 83.7% vs 73.7% ($p = 0.09$); ischemia 35.3% vs 41.0% ($p = 0.62$); recurrent angina 25.6% vs 11.4% ($p = 0.09$).
Shroyer AL et al., ROOBY-FS [26]	2017; USA; RCT	2,203 (1,104 OP; 1,099 CP)	5 years	Veterans with CAD; 94% multivessel disease	Grafts lower with OP ($p < 0.001$); 1-year patency 82.6% OP vs 87.8% CP ($p < 0.001$); Repeat revascularization 13.1% vs 11.9% ($p = 0.39$); 5-year MACCE 31.0% vs 27.1% (RR 1.14, 95% CI 1.00–1.30; $p = 0.046$); late MI 12.1% vs 9.6% ($p = 0.05$).
Yang L. et al., CORONARY [27]	2020; China; RCT sub-study	206 (107 OP; 99 CP)	6.7 years patency, 6.5 years clinical	Elective CABG with risk factors	MACCE 28.0% OP vs 23.0% CP ($p = 0.283$); repeat revascularization 4.6% vs 2.9% ($p = 0.402$); stroke 8.6% vs 7.5% ($p = 0.705$).
Zhou Z. et al., STICH [28]	2023; China; post hoc RCT analysis with propensity matching	456 (152 OP; 304 CP)	8.7 years	Ischemic cardiomyopathy; LVEF $\leq 35\%$	Distal anastomoses 2.24 $\pm$ 1.09 OP vs 3.03 $\pm$ 1.00 CP ($p < 0.001$); multiple arterial grafting 17.1% vs 8.6% ($p = 0.01$). Perioperative MACCE 3.3% vs 7.2% ($p = 0.09$); death/CV hospitalization HR 0.94 (95% CI 0.74–1.19; $p = 0.61$); functional improvement comparable.
Hueb W. et al., MASS III [29]	2019; Brazil; RCT	308 (155 OP; 153 CP)	10 years	Multivessel CAD; stable angina; preserved LVEF ($>40\%$)	Grafts 2.55 $\pm$ 0.84 OP vs 3.15 $\pm$ 0.92 CP ($p < 0.001$). Repeat revascularization 7.2% in both ($p = 0.15$); 10-years MACCE 36% OP vs 30.4% CP (HR 0.88, 95% CI 0.86–1.02; $p = 0.41$); late MI 7.7% vs 5.2% ($p = 0.18$); stroke/TIA 3.9% vs 5.2% ($p = 0.22$); late AF 21.3% vs 2.6% ($p < 0.001$).
Kageyama S. et al., SYNTAXES [30]	2023; multinational; post hoc RCT analysis	1,800; analyzed 1,756 (725 CP; 128 OP; 903 PCI comparator)	11.2 years (median)	Three-vessel and/or left main disease	10-years mortality: 28.4% OP vs 23.0% CP; CP vs PCI HR 0.75 (95% CI 0.62–0.93; $p = 0.009$), OP vs PCI HR 0.98 (95% CI 0.69–1.40; $p = 0.911$). Cerebrovascular events 0% OP vs 1.8% CP. OP showed no survival benefit vs PCI; CP had superior survival vs PCI.
Koop Y. et al., OctoPump [31]	2024; Netherlands; RCT with 20-y follow-up via data linkage	257 (129 OP; 128 CP)	20 years	First-time isolated CABG; CAD; preserved LV function	20-years mortality 46.5% OP vs 50.0% CP (adjusted HR 0.82, 95% CI 0.57–1.18); repeat revascularization 18.6% vs 19.5% (adjusted HR 1.05, 95% CI 0.59–1.85).
Quin JA et al., ROOBY-FS [32]	2022; USA; RCT 10-y follow-up	2,203 (1,104 OP; 1,099 CP)	10 years	Veterans with non-emergent CAD	Repeat revascularization 20.6% OP vs 19.1% CP (RR 1.02; $p = 0.39$); PCI 19.0% vs 18.3% ($p = 0.66$); repeat CABG 2.3% vs 1.2% ($p = 0.05$); HF hospitalization/ NYHA improvement 62.6% vs 62.0% ($p = 0.85$); late AF no difference ($p = 0.32$); CCS improvement 70.0% vs 71.4% ($p = 0.77$).
Tadokoro N. et al., JOCRI [33]	2023; Japan; RCT 15-y follow-up	123 (61 OP; 62 CP)	13.8 $\pm$ 2.8 years	Double/triple-vessel disease; first-time CABG	Grafts 3.7 $\pm$ 1.0 OP vs 3.5 $\pm$ 0.9 CP; complete graft patency 64% vs 68%. 15-years survival 77.7% OP vs 75.3% CP ($p = 0.85$); MACCE-free survival 62.5% vs 55.6% ($p = 0.27$); PCI 13% vs 23% ($p = 0.23$); no significant long-term differences.

OP = off-pump CABG; CP = on-pump CABG; CABG = coronary artery bypass grafting; CAD = coronary artery disease; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; QoL = quality of life; HR = hazard ratio; RR = risk ratio; OR = odds ratio; CI = confidence interval; NM = not mentioned.

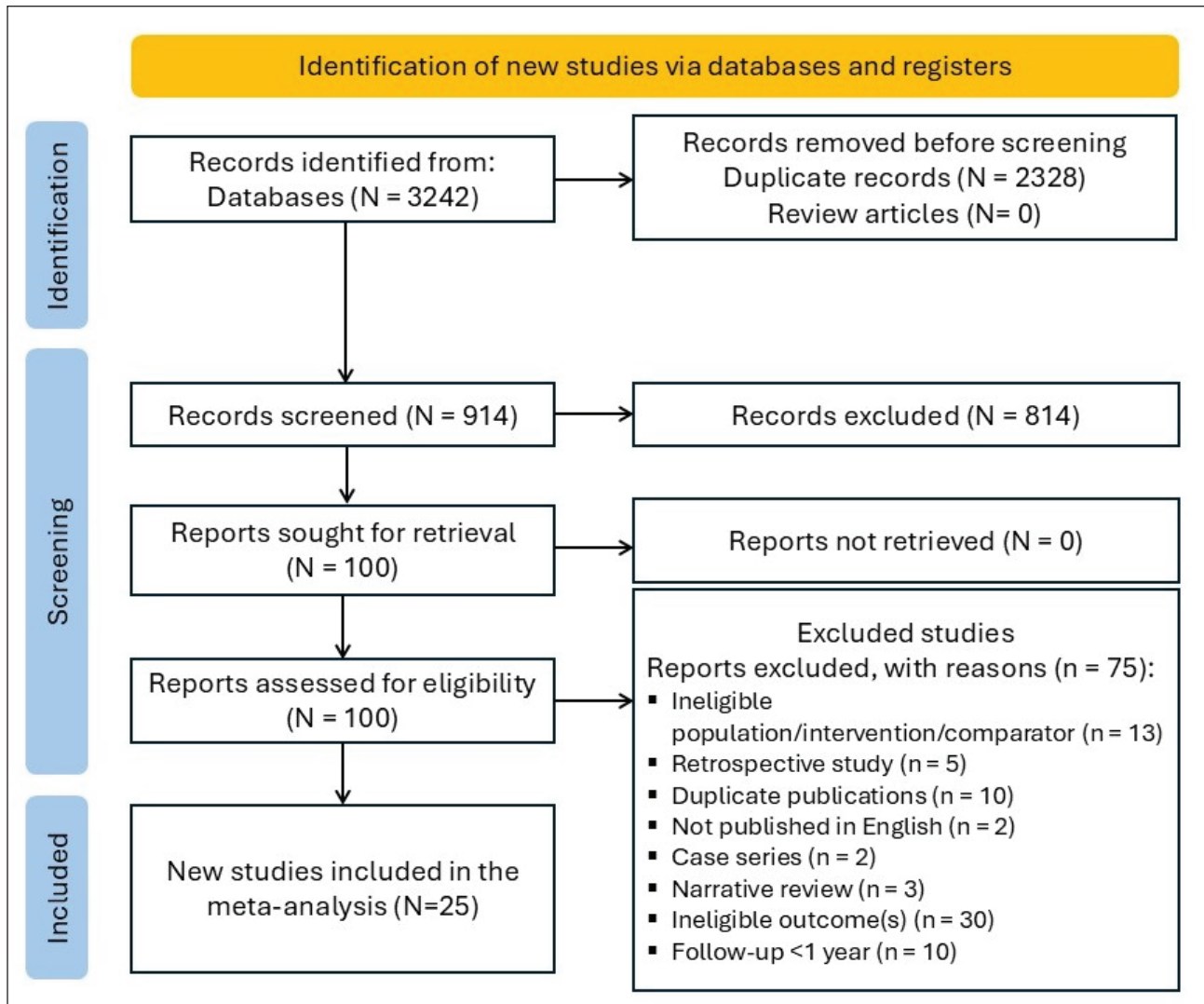


Figure 1. PRISMA flow chart illustrating the study selection process for the meta-analysis of randomized controlled trials comparing on-pump versus off-pump coronary artery bypass grafting.

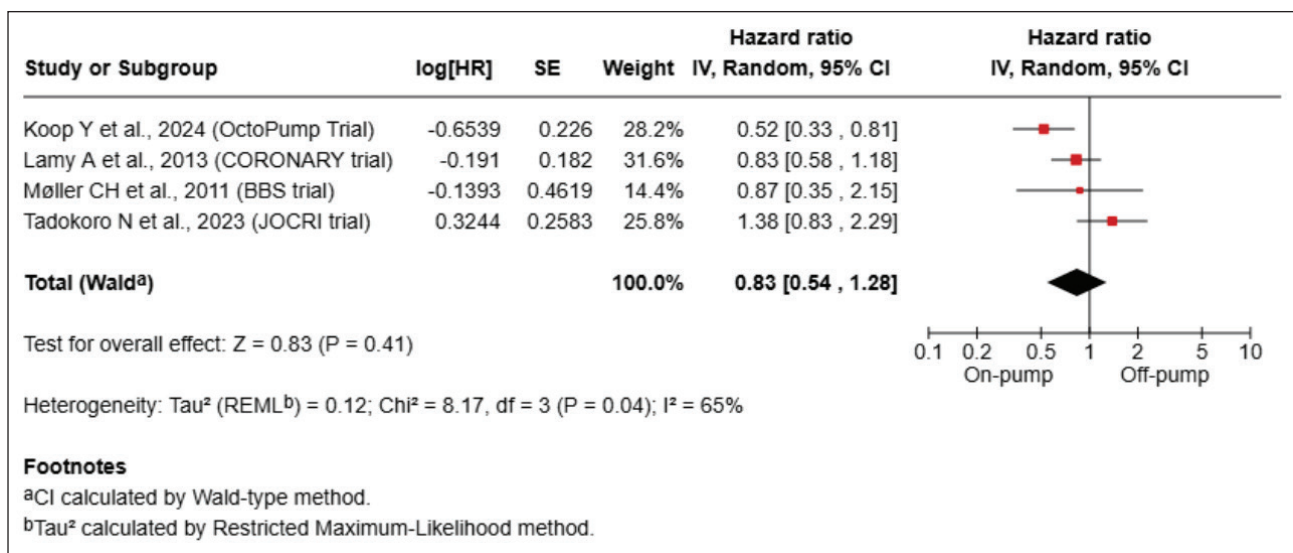


Figure 2. Forest plot summarizing the effect of on-pump versus off-pump coronary artery bypass grafting on the incidence of repeat revascularization across four randomized controlled trials, hazard ratios are expressed as on-pump versus off-pump, HR < 1 indicates fewer repeat revascularization events with on-pump CABG.

0.89, and the pooled estimate indicated a 42% relative reduction in the risk of myocardial infarction associated with the on-pump technique (Figure 3).

Long-term risk of stroke or transient ischemic attack

The pooled analysis of stroke and TIA comprised three studies [9,12,15] with 1,470 participants. No statistically significant difference was found between on-pump and off-pump CABG for this cerebrovascular outcome (on-pump vs. off-pump: HR 1.19; 95% CI [0.73, 1.95]; $p = 0.49$), which reflects higher stroke/TIA risk with on-pump CABG that did not reach statistical significance. No significant heterogeneity was detected among the studies ($I^2 = 0\%$; $p = 0.43$). The results of the individual trials were consistent, with HRs ranging from 0.44 to

1.43, though all confidence intervals crossed unity, indicating no conclusive evidence of benefit or harm for either surgical technique on the risk of stroke or TIA (Figure 4).

Major adverse cardiovascular events

For MACE, a pooled analysis of nine studies [9–11,15,20,23,24,29,33] (incorporating data from 13,247 patients) was performed. The overall analysis demonstrated a statistically significant increase in MACE risk with on-pump CABG relative to the off-pump technique (on-pump vs. off-pump: HR 1.62; 95% CI [1.18, 2.21]; $p = 0.003$), favoring the off-pump approach. However, the evidence was characterized by considerable heterogeneity, which could not be resolved through sensitivity analysis ($I^2 = 94\%$; $p < 0.00001$).

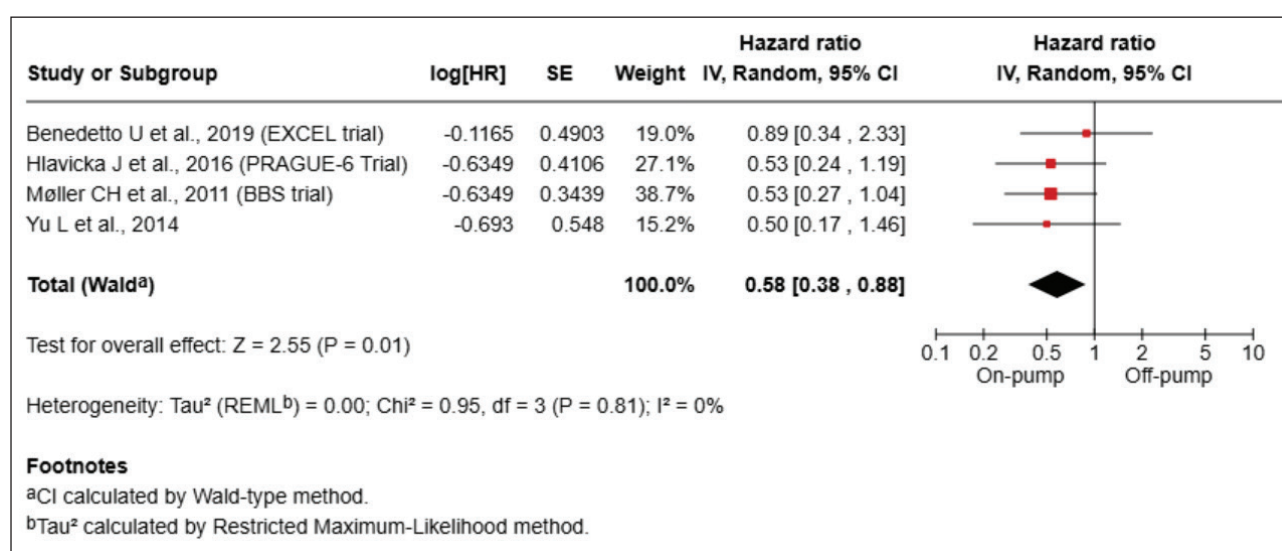


Figure 3. Forest plot showing the comparison of late myocardial infarction incidence between on-pump and off-pump coronary artery bypass grafting in 4 randomized controlled trials, hazard ratios are expressed as on-pump versus off-pump, $HR < 1$ indicates lower late MI risk with on-pump CABG.

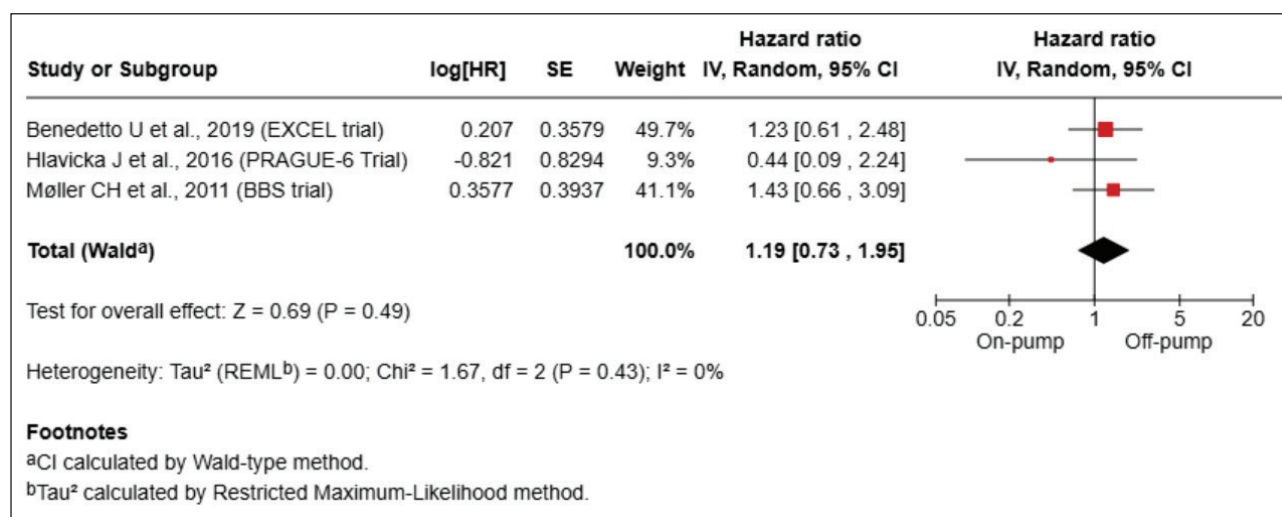


Figure 4. Forest plot displaying the long-term risk of stroke or transient ischemic attack following on-pump versus off-pump coronary artery bypass grafting in 3 randomized controlled trials, hazard ratios are expressed as on-pump versus off-pump, $HR < 1$ indicates lower cerebrovascular risk with on-pump CABG.

Subgroup analysis based on follow-up duration revealed a significant interaction (test for subgroup differences: $\chi^2 = 12.05$, $df = 2$, $p = 0.002$; $I^2 = 83.4\%$), indicating that the treatment effect varied over time. No significant difference between techniques was observed in the mid-term period (≥ 1 to < 5 years: on-pump vs. off-pump HR 0.92; 95% CI [0.62, 1.36]; $p = 0.66$), with moderate heterogeneity ($I^2 = 47\%$). In contrast, a significant benefit favoring off-pump CABG emerged in the intermediate long-term period (≥ 5 to < 10 years: HR 2.18; 95% CI [1.61, 2.95]; $p < 0.00001$), despite high heterogeneity within this subgroup ($I^2 = 85\%$), and this benefit persisted into the extended long-term period (≥ 10 years: HR 1.89; 95% CI [1.07, 3.35]; $p = 0.03$), again with substantial heterogeneity ($I^2 = 81\%$) (Figure 5).

Late mortality in on-pump versus off-pump CABG

A total of 12 studies [9,12,15,19–22,24,28,31–33], comprising 15,512 patients, were pooled to assess the

effect of on-pump versus off-pump CABG on long-term all-cause mortality. The pooled analysis demonstrated no statistically significant difference in mortality between the two surgical strategies (on-pump vs. off-pump: HR 1.20; 95% CI [0.92, 1.55]; $p = 0.17$), where the point estimate HR > 1 numerically reflects higher all-cause mortality risk with on-pump CABG, though this did not reach statistical significance. Substantial heterogeneity was observed among the studies ($I^2 = 90\%$; $p < 0.00001$). A sensitivity analysis revealed that exclusion of the study by Lamy et al. (CORONARY trial) [24] reduced heterogeneity to 59%, while the result remained non-significant (on-pump vs. off-pump: HR 1.07; 95% CI [0.91, 1.27]; $p = 0.41$).

Subgroup analysis stratified by follow-up duration indicated no significant mortality difference across mid-term (≥ 1 to < 5 years: on-pump vs. off-pump HR 1.17; 95% CI [0.68, 1.99]; $p = 0.57$; $I^2 = 70\%$), intermediate long-term (≥ 5 to < 10 years: on-pump vs. off-pump HR 1.41; 95% CI [0.91, 2.16]; $p = 0.12$; $I^2 = 94\%$), or extended

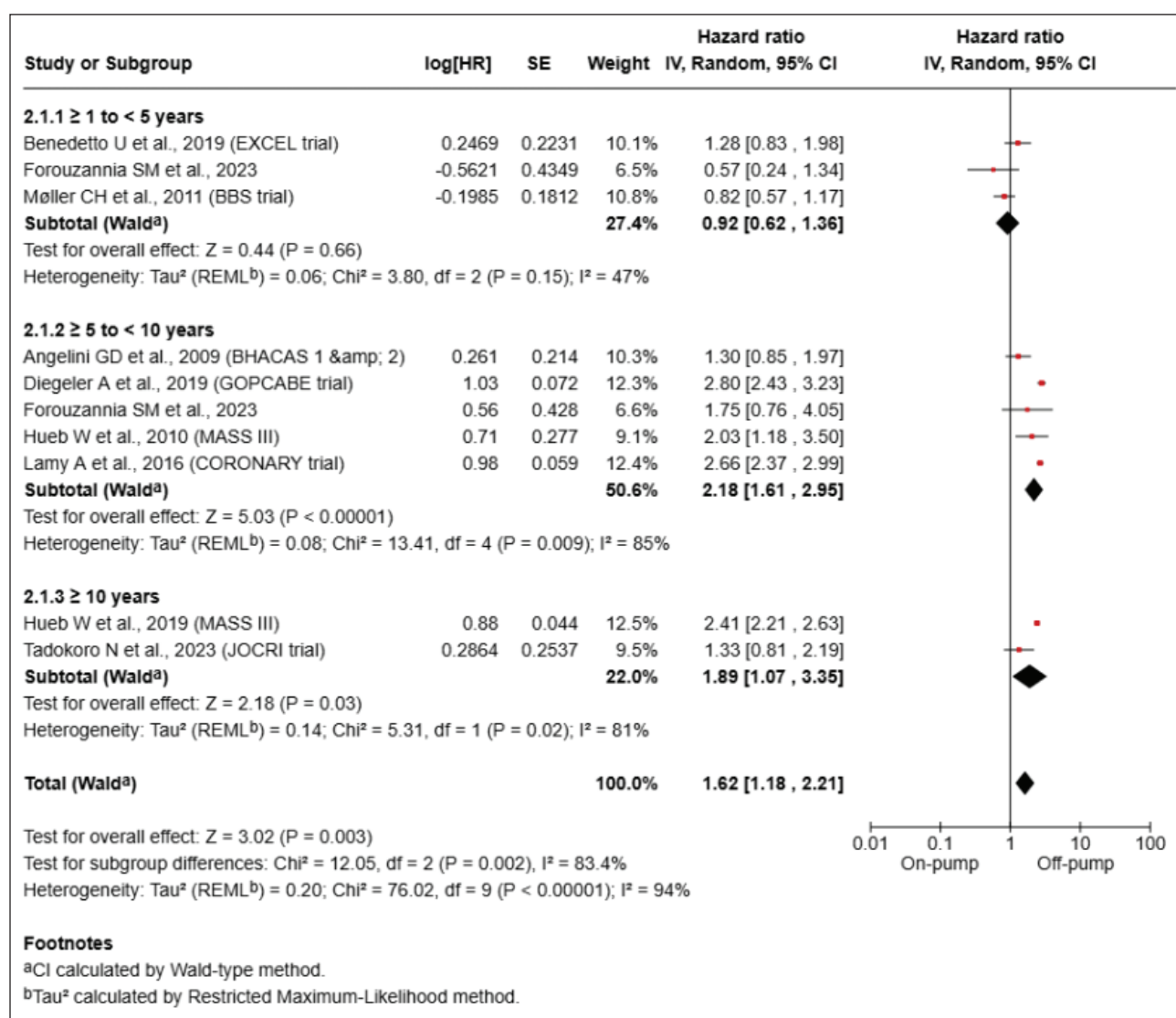


Figure 5. Forest plot evaluating the impact of on-pump versus off-pump coronary artery bypass grafting on major adverse cardiovascular events, based on data from 9 randomized controlled trials, hazard ratios are expressed as on-pump versus off-pump, HR < 1 indicates lower MACE risk with on-pump CABG.

long-term follow-up (≥ 10 years: on-pump vs. off-pump HR 0.97; 95% CI [0.74, 1.28]; $p = 0.85$; $I^2 = 53\%$). The test for subgroup differences was not significant ($\text{Chi}^2 = 2.08$, $\text{df} = 2$, $p = 0.35$, $P = 3.6\%$), suggesting follow-up time did not modify the treatment effect. Planned subgroup analyses based on patient risk profile or surgical characteristics were not feasible due to inconsistent reporting across the included trials (Figure 6).

Composite endpoints

Analysis of composite endpoints, including combined mortality and other major non-fatal events, was performed across 11 studies [9,12,14,20–22,28,29,31–33] involving 14,935 patients. The pooled analysis indicated a statistically significant increase in composite events with on-pump compared to off-pump CABG, favoring off-pump surgery (on-pump vs. off-pump: HR 1.24; 95% CI [1.01, 1.52]; $p = 0.04$). Considerable heterogeneity

was observed among the included studies ($P = 87\%$; $p < 0.00001$). A sensitivity analysis excluding the study by Zhou et al. [28] resolved this heterogeneity ($P = 1\%$), yielding a more precise and still significant estimate in favor of off-pump surgery (on-pump vs. off-pump: HR 1.08; 95% CI [1.01, 1.16]; $p = 0.02$).

Subgroup analysis by follow-up duration showed no significant interaction (test for subgroup differences: $\text{Chi}^2 = 1.37$, $\text{df} = 2$, $p = 0.50$, $P = 0\%$), suggesting a consistent treatment effect over time. A significant benefit for off-pump CABG was observed in the extended long-term period (≥ 10 years: on-pump vs. off-pump HR 1.15; 95% CI [1.04, 1.28]; $p = 0.009$) with no heterogeneity in this subgroup ($P = 0\%$). The point estimates for the mid-term (≥ 1 to < 5 years: on-pump vs. off-pump HR 0.94; 95% CI [0.47, 1.87]; $p = 0.86$; $P = 75\%$) favored on-pump, and the intermediate long-term period (≥ 5 to < 10 years: on-pump vs. off-pump HR 1.40; 95% CI [0.96, 2.04];

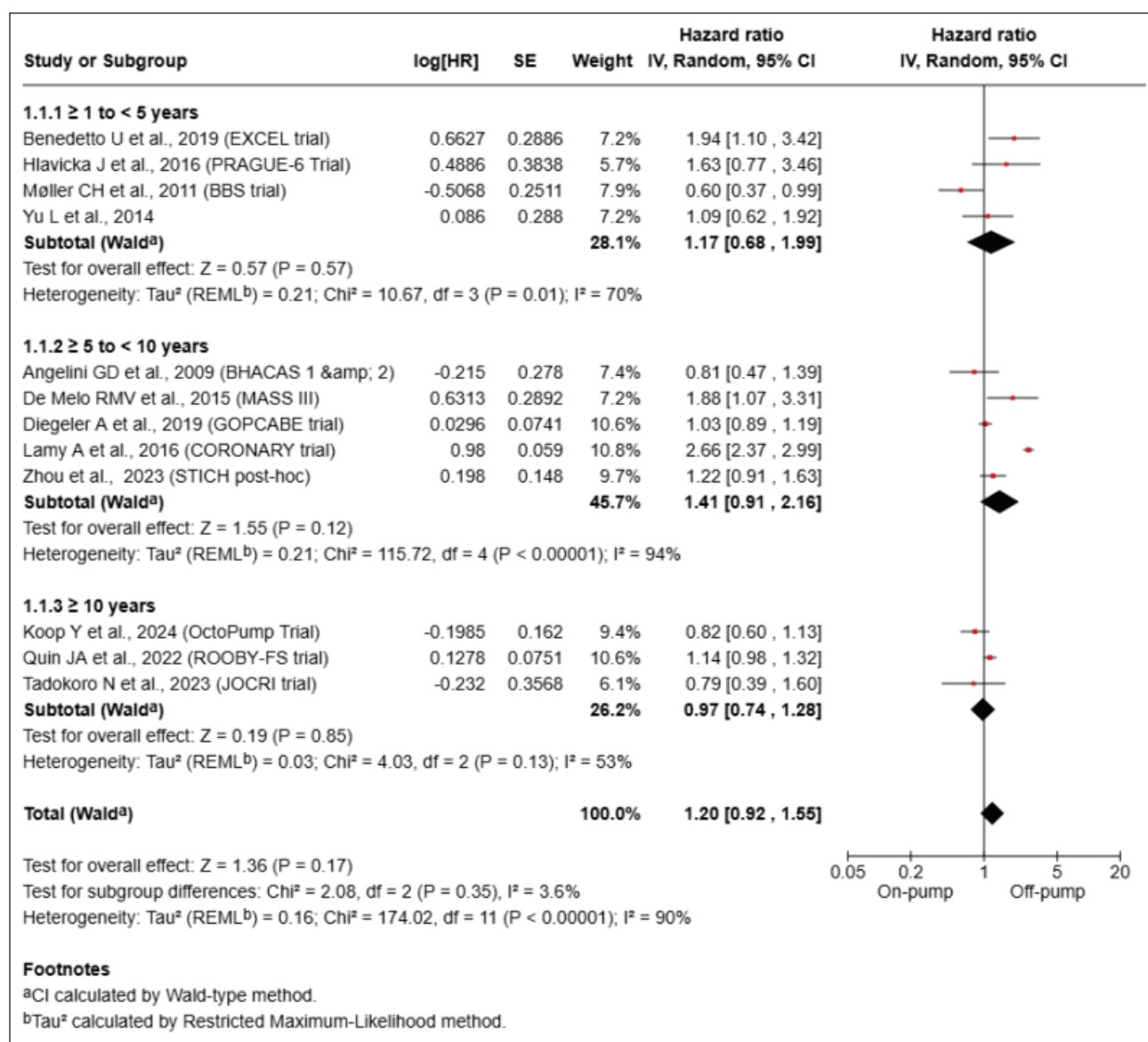


Figure 6. Forest plot demonstrates late all-cause mortality with on-pump versus off-pump coronary artery bypass grafting, based on data from 12 randomized controlled trials, hazard ratios are expressed as on-pump versus off-pump, HR < 1 indicates lower mortality risk with on-pump CABG.

$p = 0.08$) favored off-pump, although both were not statistically significant, with considerable heterogeneity in the latter subgroup ($I^2 = 94\%$) (Figure 7).

Risk of bias

The overall risk of bias across the included studies in this meta-analysis is judged as moderate to high. Most studies demonstrated adequate random sequence generation, indicating a low risk of selection bias in that domain. However, allocation concealment was often inadequately reported, with several studies rated as unclear, introducing potential selection bias. Performance bias was high across the majority of studies due to the lack of blinding of participants and personnel, a common challenge in surgical trials. Similarly, detection bias was frequently present, as many studies lacked blinded outcome assessment. In contrast, attrition bias and reporting bias were generally low, with most studies reporting complete outcome data and no evidence of selective reporting.

Other potential sources of bias were minimal, though one study [30] had unclear assessments in this domain due to site heterogeneity in off-pump use. Overall, the prevalent lack of blinding and occasional concerns with allocation concealment contribute to a moderate to high risk of bias in this meta-analysis (Figures 8 and 9). Certainty of evidence for the primary outcomes was formally assessed using GRADE and is presented below (Supplementary Table S1).

Publication bias assessment

Visual inspection of the funnel plots does not suggest a strong signal of publication bias across the three outcomes, although some asymmetry is noted and should be interpreted cautiously given the limited number of studies. For late mortality, the studies are generally distributed around the pooled effect estimate, with small studies (higher SE) appearing on both sides of the null line and no clear clustering in a single direction,

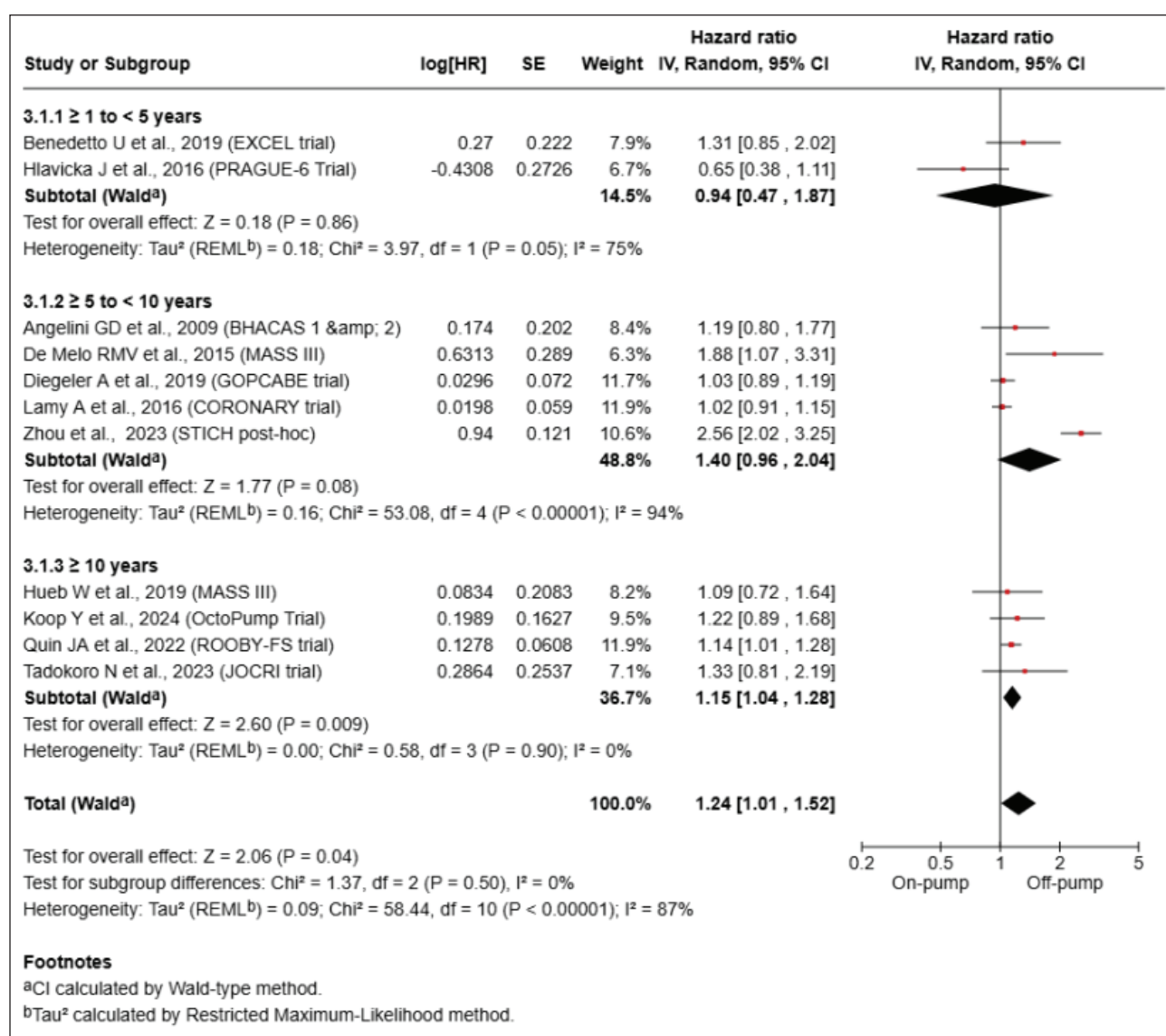


Figure 7. Forest plot showing composite cardiovascular endpoints with on-pump versus off-pump coronary artery bypass grafting in 11 randomized controlled trials, hazard ratios are expressed as on-pump versus off-pump, $HR > 1$ indicates a higher composite event burden with on-pump CABG, favoring off-pump surgery.

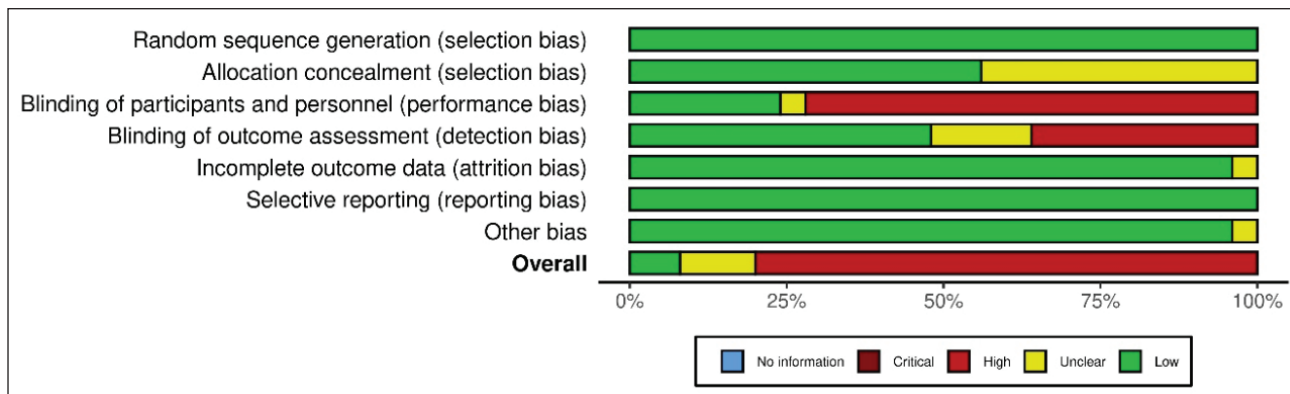


Figure 8. Risk of bias graph illustrating the distribution of bias judgements across all included randomized controlled trials.

Study	Risk of bias							Overall
	D1	D2	D3	D4	D5	D6	D7	
Angelini GD et al., BHACAS 1 & 2 [20]	+	-	+	+	+	+	+	-
Benedetto U. et al., EXCEL trial [9]	+	+	+	+	+	+	+	+
De Melo RMV et al., MASS III [21]	+	-	×	-	+	+	+	×
Diegeler A. et al., GOPCABE trial [22]	+	+	+	×	+	+	+	×
Diegeler A (2) et al., GOPCABE trial [10]	+	+	+	×	+	+	+	×
Forouzannia SM et al. [11]	+	-	+	+	+	+	+	-
Hlavicka J. et al., PRAGUE-6 Trial [12]	+	-	×	×	+	+	+	×
Hueb W. (2) et al., MASS III [23]	+	-	×	-	+	+	+	×
Hueb W. et al., MASS III [29]	+	-	×	-	+	+	+	×
Kageyama S. et al., SYNTAXES trial [30]	+	-	×	×	+	+	-	×
Karolak W. et al. [13]	+	-	×	×	+	+	+	×
Koop Y. et al., OctoPump Trial [31]	+	+	×	×	+	+	+	×
Lamy A. (2) et al., CORONARY trial [14]	+	+	×	+	+	+	+	×
Lamy A. et al., CORONARY trial [24]	+	+	×	+	+	+	+	×
Møller CH et al., BBS trial [15]	+	+	+	+	+	+	+	+
Nathoe HM et al., OctoPump Trial [16]	+	+	×	×	+	+	+	×
Puskas JD et al., SMART trial [25]	+	-	×	+	+	+	+	×
Quin JA et al., ROOBY-FS trial [32]	+	+	×	+	+	+	+	×
Sharma D. et al. [17]	+	+	-	-	+	+	+	-
Shroyer AL (2) et al., ROOBY trial [18]	+	+	×	+	+	+	+	×
Shroyer AL et al., ROOBY-FS trial [26]	+	+	×	+	+	+	+	×
Tadokoro N. et al., JOCRI trial [33]	+	-	×	+	+	+	+	×
Yang L. et al., CORONARY trial [27]	+	+	×	×	-	+	+	×
Yu L et al. [19]	+	+	×	+	+	+	+	×
Zhou Z et al., STICH trial [28]	+	-	×	×	+	+	+	×

D1: Random sequence generation (selection bias)
D2: Allocation concealment (selection bias)
D3: Blinding of participants and personnel (performance bias)
D4: Blinding of outcome assessment (detection bias)
D5: Incomplete outcome data (attrition bias)
D6: Selective reporting (reporting bias)
D7: Other bias

Judgement
× High
- Unclear
+ Low

Figure 9. Risk of bias summary displaying individual bias domain assessments for each included randomized controlled trial.

indicating no obvious small-study effects. For MACE, there is mild asymmetry, with a tendency for smaller studies to report slightly higher hazard ratios; however, the spread remains relatively balanced and does not show a clear absence of studies in any specific region of the plot. For the composite endpoints, the funnel plot appears reasonably symmetrical around the summary effect, with variability increasing as expected among studies with larger standard errors, again without a distinct gap suggestive of selective non-publication. Overall, while minor asymmetry is observed, likely reflecting clinical heterogeneity and the small number of included studies rather than true publication bias, the funnel plots do not provide compelling visual evidence of substantial publication bias for any of the three outcomes (Figures S1-3). Egger's test confirmed small-study effects for late mortality (intercept -2.46 , $p = 0.021$) and MACE (intercept -3.20 , $p < 0.001$), raising the possibility that publication bias, clinical heterogeneity, or both may have influenced the pooled estimates for these two outcomes. No such effect was detected for composite endpoints (intercept 1.21 , $p = 0.84$). Begg's test was non-significant across all three outcomes ($\tau -0.06$ to 0.27 ; $p = 0.28-0.84$), though this test is known to have limited power with a small number of studies and should not be taken as ruling out asymmetry where Egger's test already flagged it. Overall, publication bias cannot be excluded for late mortality and MACE, and these results should be interpreted with appropriate caution.

Certainty of evidence (GRADE)

Certainty was assessed using GRADE across all six outcomes (Supplementary Table S1). Late myocardial infarction was rated low, downgraded for risk of bias and imprecision (few studies/patients). MACE was rated very low, downgraded for risk of bias, very serious inconsistency ($I^2 = 94\%$, unresolved, with a significant time-dependent subgroup effect), and publication bias (Egger's $p < 0.001$). Composite endpoints were rated very low, downgraded for risk of bias, inconsistency (largely attributable to one outlier study), and indirectness, given the heterogeneous, incompletely reported components underlying this outcome. Late mortality was rated very low, downgraded for risk of bias, very serious inconsistency ($I^2 = 90\%$), imprecision, and publication bias (Egger's $p = 0.021$). Repeat revascularization and stroke/TIA were both rated very low, downgraded for risk of bias and imprecision, with repeat revascularization additionally downgraded for inconsistency.

Discussion

This meta-analysis of 25 RCTs, encompassing 18,729 patients, provides a comprehensive evaluation of the long-term comparative efficacy and safety of on-pump CABG versus off-pump CABG. The central findings indicate a trade-off: while off-pump CABG did not demonstrate superiority in reducing mortality, stroke, or repeat revascularization, it was associated with a significantly higher risk of late myocardial infarction and, in specific timeframes, a higher incidence of MACE compared to on-pump CABG, whereas composite

endpoint analysis demonstrated a higher event burden with on-pump CABG over the extended long-term.

The absence of a significant difference in long-term all-cause mortality (late mortality) (HR 1.20 , 95% CI $[0.92, 1.55]$, $p = 0.17$) is consistent with several pivotal large-scale trials and previous meta-analyses with extended follow-up, such as the 5-year results of the ROOBY trial and the CORONARY trial [24,26]. This suggests that the early theoretical neuroprotective and renal protective benefits of avoiding CPB do not translate into a long-term survival advantage. Similarly, the analysis found no difference in the risk of stroke or TIA, aligning with the hypothesis that cerebral embolic events are more closely related to aortic manipulation, common to both techniques, than to the use of CPB itself [10]. The need for repeat revascularization was also equivalent, which, after resolving heterogeneity, suggests modern surgical techniques and medical therapy yield comparable long-term graft patency, a finding echoed in the 10-year follow-up of the DOORS trial [36].

However, the significantly increased risk of late myocardial infarction with off-pump CABG (HR 0.58 for on-pump, $p = 0.01$) is a critical and concerning finding. This is likely attributable to inferior long-term graft patency, particularly of saphenous vein grafts, and possibly incomplete revascularization, which has been more frequently reported with the off-pump technique [26,37]. The technical challenge of performing precise anastomoses on a beating heart may compromise graft longevity, a factor that manifests clinically as an increased incidence of myocardial infarction over time. This finding is a key driver of the differences observed in the composite outcome analyses.

A 2024 meta-analysis by He et al., which included 28 RCTs and 16,090 patients, concluded that off-pump CABG was associated with a significant increase in long-term mortality (RR 1.09 , $p = 0.02$) [38]. In contrast, another 2024 meta-analysis by Comanici et al., incorporating 22 studies (including 3 RCTs and numerous propensity-matched observational studies) with 69,449 patients, found no significant difference in 10-year all-cause mortality (HR 1.00 , $p = 0.95$) [39]. The discrepancy with our null mortality result may be partly explained by the different composition of evidence bases. He et al.'s analysis was restricted to RCTs, which, while high in internal validity, may have included trials where surgeon inexperience with off-pump techniques (evidenced by high crossover rates) negatively impacted outcomes. This meta-analysis included only RCTs, which may better reflect real-world outcomes after the learning curve. Furthermore, our analysis uniquely identified a significant increase in late myocardial infarction with off-pump surgery, a finding not emphasized in the other two meta-analyses. This specific ischemic risk likely contributes to the increased MACE and composite endpoint rates we observed and may be a mechanistic link to the mortality signal seen in some trials. Therefore, the collective evidence suggests that while experienced centers can achieve comparable long-term survival with off-pump CABG, this technique consistently carries a

higher residual risk of ischemic events, which is a critical consideration for long-term patient management.

The analysis of MACE revealed a complex, time-dependent relationship. A significant benefit for off-pump CABG was isolated to the intermediate long-term period (5 to <10 years, HR 2.18, $p < 0.00001$). This period may represent the critical window where differences in graft patency and completeness of revascularization become clinically apparent, before competing risks of non-cardiac mortality attenuate the effect in the very long term (≥ 10 years). The extreme heterogeneity ($I^2 = 94\%$) in the overall MACE analysis underscores the variability in how MACE is defined across trials and the diverse patient populations studied, limiting the strength of this pooled conclusion but highlighting the importance of the subgroup finding.

Sensitivity analyses supported this robustness: excluding the large CORONARY and Zhou et al. trials, which drove most of the heterogeneity in the mortality and composite-endpoint analyses, still yielded a significant composite-endpoint estimate favoring off-pump CABG (HR 1.08, $p = 0.02$), consistent with a genuinely higher late myocardial infarction risk with off-pump CABG and a higher overall composite event burden with on-pump CABG over extended follow-up.

Several important limitations must be acknowledged. First, the overall risk of bias in the included studies is moderate to high, primarily due to the inherent lack of blinding in surgical trials and often unclear allocation concealment. This could influence subjective outcome assessments. Second, while visual funnel plot inspection did not show severe asymmetry, formal statistical tests (Egger's test) suggested potential small-study effects for mortality and MACE. However, these tests are underpowered with a limited number of studies, and the observed asymmetry may reflect clinical heterogeneity, such as varying surgeon expertise, rather than publication bias. Surgeon proficiency is a paramount confounding factor in off-pump CABG outcomes, and its variable representation across studies is a major source of heterogeneity that this meta-analysis could not quantitatively adjust for [40]. Additionally, this review was not prospectively registered, and no protocol was made publicly available, which may introduce the risk of reporting bias. Furthermore, the certainty of evidence for the primary outcomes, formally assessed using GRADE, was low or very low for most outcomes (Supplementary Table S1), which limits the strength of the clinical recommendations that can be drawn. Finally, planned subgroup analyses based on patient risk profiles (e.g., SYNTAX score, diabetic status) or surgical characteristics (e.g., number of grafts, use of multiple arterial conduits) were not feasible due to inconsistent reporting, precluding more personalized conclusions.

Conclusions

On-pump CABG was associated with a significant reduction in late myocardial infarction (on-pump vs. off-pump: HR 0.58; $p = 0.01$). In contrast, on-pump CABG was associated with a significantly higher risk of MACE

compared with off-pump CABG (on-pump vs. off-pump: HR 1.62; $p = 0.003$), a difference most pronounced during the intermediate long-term follow-up period of 5 to <10 years (HR 2.18; $p < 0.00001$) and persisting into extended long-term follow-up (≥ 10 years: HR 1.89; $p = 0.03$), indicating a net advantage of off-pump CABG for MACE. Similarly, analysis of composite cardiovascular endpoints demonstrated a significantly higher event burden with on-pump compared to off-pump CABG (on-pump vs. off-pump: HR 1.24; $p = 0.04$), with this difference persisting over extended long-term follow-up (≥ 10 years: HR 1.15; $p = 0.009$), again indicating a net advantage of off-pump CABG for composite outcomes. No significant differences were observed in late all-cause mortality (on-pump vs. off-pump: HR 1.20; $p = 0.17$), repeat revascularization (on-pump vs. off-pump: HR 0.83; $p = 0.41$), or stroke/TIA (on-pump vs. off-pump: HR 1.19; $p = 0.49$). These findings indicate a nuanced trade-off: on-pump CABG confers a lower risk of late myocardial infarction, whereas off-pump CABG is associated with a lower risk of MACE, particularly over the intermediate-to-long term, as well as a lower overall composite cardiovascular event burden over the extended long term. The choice of surgical strategies should therefore be individualized, accounting for patient risk profile, surgeon expertise, and the relative clinical priority of specific long-term outcomes.

List of Abbreviation

CABG	Coronary artery bypass grafting	
CAD	Coronary artery disease	
CI	Confidence interval	
CPB	Cardiopulmonary bypass	
HR	Hazard ratio	
MACE	Major adverse cardiovascular event	
PCI	Percutaneous coronary intervention	
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses	
RCT	Randomized controlled trial	
SE	Standard error	
TIA	Transient ischemic attack	

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for participation

Not applicable

Consent for publication

Not applicable.

Ethical approval

Not applicable

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- Supplementary content (If any) is available online.*
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