



# Systematic review and meta-analysis of two decades of reported outcomes for robotic coronary artery bypass grafting

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**Background:** Despite the well-documented safety and feasibility of robotic coronary artery bypass grafting (CABG), widespread adoption of this approach remains limited by its steep learning curve, high procedural costs and paucity of data on longer-term efficacy. This current meta-analysis aims to provide a systematic overview of the outcomes of robot-assisted CABG, with a focus on long term graft patency and freedom from major adverse cardiac and cerebrovascular events (MACCE).

**Methods:** A systematic literature search of three electronic databases was conducted for studies reporting outcomes of robotic-assisted CABG, and were grouped based on whether patients underwent robot-assisted minimally invasive direct coronary artery bypass (RA-MIDCAB), totally endoscopic coronary artery bypass (TECAB) or were mixed. Perioperative and mid-to-long term results from included studies were pooled using meta-analysis of proportion or means in a random effects model.

**Results:** In the quantitative analysis, thirty-nine eligible studies included 6,152 patients who underwent RA-MIDCAB, 1,729 patients who underwent TECAB and 21,642 patients who underwent either form of robot-assisted CABG. A high level of heterogeneity was observed amongst baseline characteristics. Perioperative mortality and complication rates were low. Conversion rate to full sternotomy overall was less than 3.2% [95% confidence interval (CI): 2.1–5.2%,  $I^2=39\%$ ]. At a mean follow-up duration of 5.2 years, overall graft patency was 96% for both RA-MIDCAB and TECAB, and freedom from major adverse cardiac events (MACE) or MACCE was 83.2% (95% CI: 72.0–90.4%;  $I^2=90\%$ ) for RA-MIDCAB and 91.6% (95% CI: 86.6–94.9%;  $I^2=76\%$ ) for TECAB.

**Conclusions:** Robot-assisted CABG is observed to have acceptable perioperative and mid-to-long term outcomes with promising overall graft patency.

**Keywords:** Robotic coronary artery bypass grafting (robotic CABG); robot-assisted minimally invasive direct coronary artery bypass (RA-MIDCAB); totally endoscopic coronary artery bypass (TECAB)



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## Introduction

In the last two and a half decades, robotic coronary artery bypass grafting (CABG) has emerged as the most minimally invasive method of coronary bypass surgery. Loulmet and colleagues in Paris first introduced this technique in 1998, and its practicality has grown with each new generation

of robotic systems, aided by advancements in supporting technology like epicardial stabilizers and devices for distal anastomosis (1-3).

Robotic CABG encompasses robot-assisted minimally invasive direct coronary artery bypass (RA-MIDCAB) and totally endoscopic coronary artery bypass (TECAB). In RA-MIDCAB, robotic assistance is utilised in the harvest of

the internal thoracic artery (ITA) whilst the anastomosis is performed under direct visualisation through an anterior mini-thoracotomy, and is typically performed on a beating heart, facilitated by endostabilizers. In TECAB, the entire operation is performed totally endoscopically and can be done either on-pump, off-pump or on-pump with a beating heart (4).

Robotic CABG has evolved from a method capable of single-vessel to complex multi-vessel revascularisation (5). Specialised centres that regularly perform TECAB have demonstrated its effectiveness in providing multivessel, multiarterial revascularisation, even for high-risk patients such as those who are diabetic, elderly, obese and undergoing repeat procedures (6). Nowadays, robotic CABG can also be applied alongside percutaneous coronary intervention (PCI) in a hybrid coronary revascularization (HCR) approach to treat multivessel disease (2,4).

Robotic assistance is associated with less perioperative morbidity and enhanced recovery stemming from reduced surgical trauma, shorter recovery time and earlier return to normal activities (4,5). The safety and efficacy of robotic CABG has been demonstrated consistently in the literature (7-9), with decreased conversion rates and improved outcomes with experience and careful patient selection (10). Previous meta-analysis and retrospective review of TECAB and RA-MIDCAB have concluded acceptable mortality risk and early graft patency, with outcomes comparable to a traditional sternotomy approach (1,10,11).

Nevertheless, the robotic approach faces significant challenges and requires extensive training, which explains its slow adoption with only few dedicated programs continuing its use (6). A successful robotic cardiac program requires significant infrastructure costs and training of a skilled multidisciplinary team. However, although the initial procedures required longer operative times, these durations have decreased significantly over the past two decades (11), and there is some evidence to suggest that its higher procedural costs may be counterbalanced by lower complication rates and shorter length of intensive care unit (ICU) and hospital stays, providing a potentially cost neutral alternative (12).

This article aims to provide a comprehensive review of the last two decades of literature on the status and outcomes of both RA-MIDCAB and TECAB by pooling the reported peri-operative and follow-up outcomes through a meta-analytic approach, with a focus on freedom from major adverse cardiac and cerebrovascular events (MACCE) and overall graft patency.

## Methods

### Literature search

This study has been conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement (13). Ethics approval was not required for this study given all data was retrieved from previously published studies. Three electronic databases, MEDLINE via PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL), were systematically searched from their date of inception to August 2023. Search terms included “coronary artery bypass” and “robot” or “robotic” or “robot assisted” or “RA-MIDCAB” or “TECAB” or “totally endoscopic” (Appendix 1). Reference lists from previous reviews, meta-analyses and included articles were also reviewed for further suitable studies.

### Inclusion and exclusion criteria

Studies reporting outcomes on adult patients undergoing robotic CABG were included in this systematic review. For the meta-analysis, studies were grouped by the type of robot-assisted CABG procedure performed. The first group included patients who underwent RA-MIDCAB only, the second group included TECAB procedures only, and the third group included studies in which all robotic CABG procedures were combined into a single cohort. Included studies were limited to involving human subjects, had full text available, were not conference abstracts or case reports, and were written in the English language. To partially account for the impact of the learning curve, studies with ten or less patients in the cohort of successful robotic CABG were excluded. RA-MIDCAB studies were also excluded where the anastomosis was performed through a non-thoracotomy approach (i.e., through median sternotomy). Where multiple papers of overlapping cohorts were found, only the most updated, largest or cohort with the longest follow-up reported was included. In the case of multiple competing factors for inclusion, articles reporting graft patency rates were preferred.

### Data collection and quality appraisal

Three authors (B.H., J.R., K.W.) independently performed the study selection, data extraction and quality appraisal using a pre-formed template. Data items pertaining to study characteristics, patient characteristics, operative details,

peri-operative and follow-up outcomes were collected. The quality of each included study was assessed using the modified Canadian National Institute of Health Economics (CNIHE) quality appraisal checklist for case series (14). Studies were considered high quality if they scored sixteen or more points out of nineteen, moderate quality if scored twelve to fifteen, and low quality if eleven or less points were scored. Any discrepancies between the reviewers were resolved by means of discussion until consensus was reached.

### Primary and secondary outcomes

The primary outcomes investigated were mid-to-long term graft patency, freedom from reintervention and from major adverse cardiac events (MACE) or MACCE. Secondary outcomes included overall survival in the follow-up period, as well as perioperative outcomes such as in-hospital mortality, rate of myocardial infarction (MI), stroke, reoperation for bleeding, new onset arrhythmia, pulmonary complication, acute renal injury, wound infection, ICU and hospital length of stays.

### Statistical methods

Baseline patient characteristics and operative outcomes, where reported by half or more of included studies, were pooled using meta-analysis of proportions or means for categorical and continuous variables, respectively, using R (Version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria). Where values were reported as a median and range, mean and standard deviation (SD) estimates were calculated using methods described by Wan and colleagues (15). A random effects model and the restricted maximum likelihood estimate method was used to derive the pooled weighted estimates. Pooled data was presented as  $n$  (%) with 95% confidence intervals (CIs). Heterogeneity was assessed using the  $I^2$  statistic with a value of 0–49%, 50–74% and  $\geq 75\%$  deemed as low, moderate and high heterogeneity, respectively. Publication bias was assessed through the small-study effect methods with a funnel plot. Tests for funnel plot asymmetry such as Egger's regression test were only used when there were greater than ten studies to be sufficiently powered.

## Results

### Study selection

The electronic literature search yielded a total of 531 studies,

of which 460 studies from database sources and six from citations underwent title and abstract screening following exclusion of duplicates. One hundred and four articles altogether underwent full-text review, of which 62 were excluded for reasons outlined in *Figure 1*. Of the remaining 39 studies included in the meta-analysis, seventeen studies reported outcomes on RA-MIDCAB only, ten studies reported on TECAB only, three studies provided separate data for both RA-MIDCAB and TECAB, and nine studies reported outcomes for a combined robotic CABG cohort. All included studies were retrospective observational cohorts (*Table 1*), the majority of which were single institutional studies, however nine (7,10,22,24,42,44-47) were multicenter or database analyses.

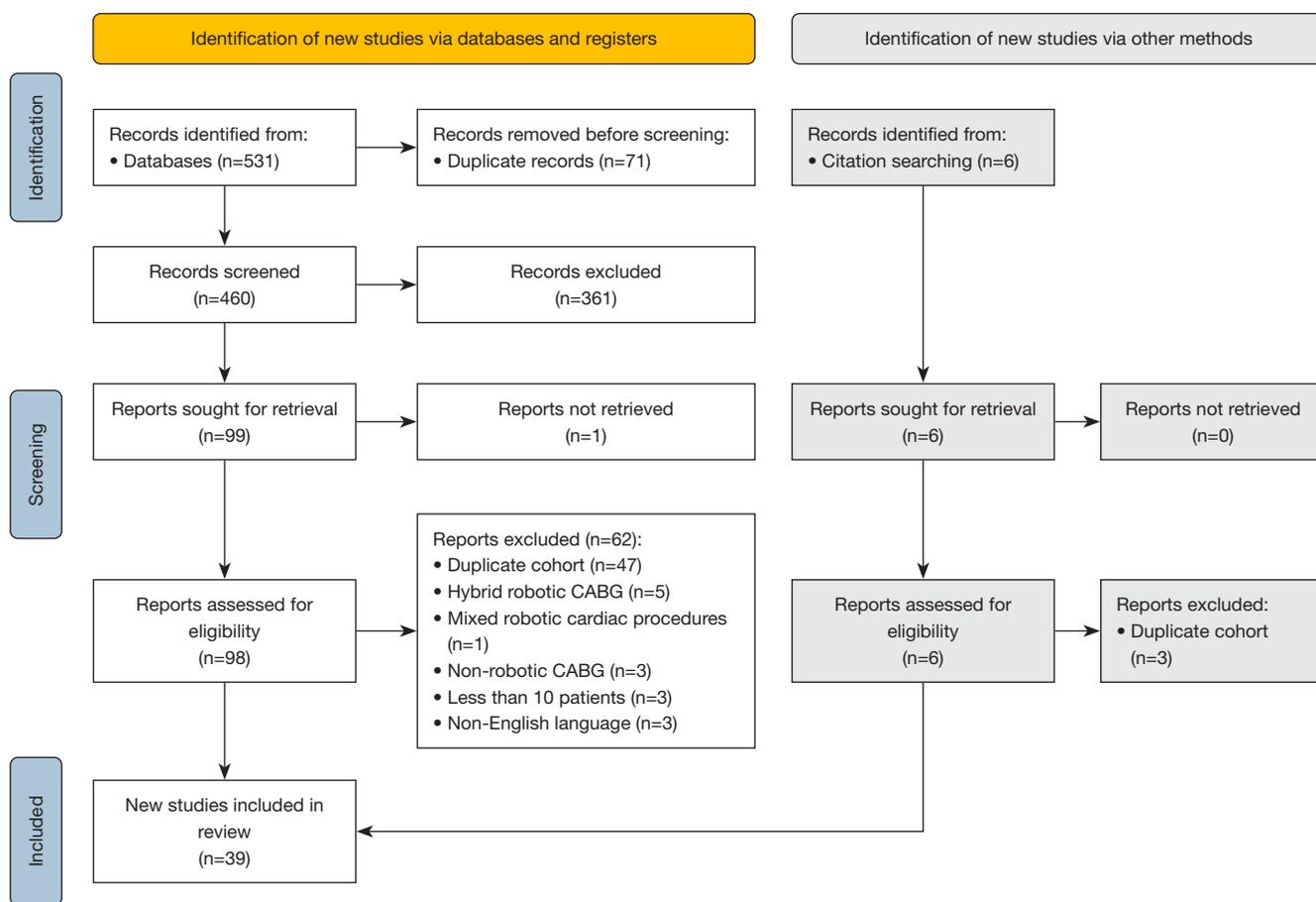
### Quality appraisal

Of the 39 studies evaluated using the CNIHE quality appraisal checklist, seven studies overall were considered high quality, 25 studies were moderate quality and seven were low quality (*Appendix 2*). The majority of studies deemed low quality were as a result of inadequate length of follow-up.

### Baseline patient characteristics

From 1998 to 2022, the reported outcomes of 6,152 patients who underwent RA-MIDCAB, 1,729 patients who underwent TECAB and 21,642 patients who underwent either form of robotic CABG were analysed separately. The pooled weighted estimates for patient and operative characteristics in each group are displayed in *Tables 2-4*.

Baseline patient demographics in terms of mean age, proportion of male patients, body mass index (BMI) and comorbidities including hypertension, diabetes, smoking history, chronic lung disease, chronic kidney disease and prior MI were similar amongst patients receiving either RA-MIDCAB or TECAB. The majority of patients were 60–65 years of age, three quarters were male, and on average were overweight, but not obese. A quarter of patients had an MI previously, with 29.7% (95% CI: 14.9–50.6%;  $I^2=95\%$ ) in the TECAB group and 37.2% (95% CI: 28.4–46.9%,  $I^2=97\%$ ) in the RA-MIDCAB group having undergone previous PCI. Approximately a third of patients in both groups were planned as part of an HCR approach, which more commonly occurred after the robotic CABG procedure. A greater proportion of TECAB recipients were observed to have single vessel disease (86.1%; 95% CI:



**Figure 1** PRISMA flow diagram of search strategy (16). CABG, coronary artery bypass grafting.

61.9–96.0%,  $I^2=98\%$ ) whereas more patients in the RA-MIDCAB group had triple vessel disease (17.0%; 95% CI: 5.9–39.9%,  $I^2=99\%$ ), which reflects the preference for RA-MIDCAB in multivessel disease. Mean left ventricular ejection fraction (LVEF) was normal and the same amongst TECAB and RA-MIDCAB recipients at approximately 57%.

### Operative characteristics

In all included articles except one (26), the da Vinci Robotic System (Intuitive Surgical, Sunnyvale, CA, USA) was used. Most procedures were performed on a beating heart (97.1% in RA-MIDCAB and 94.7% in TECAB). The mean operative time was similar for both RA-MIDCAB and TECAB at approximately 273 minutes. In the vast majority of cases, a left internal mammary artery to left anterior descending (LIMA-LAD) anastomosis was performed.

Rate of conversion to sternotomy across RA-MIDCAB and TECAB was 2.7% (95% CI: 1.5–4.8%;  $I^2=85\%$ ) and 2.9% (95% CI: 1.1–7.3%;  $I^2=91\%$ ), respectively. In the TECAB group, conversion to RA-MIDCAB occurred at a rate of 4.7% (95% CI: 1.1–18.2%;  $I^2=93\%$ ) in reported studies. Number of patients requiring a blood transfusion perioperatively was higher for patients receiving TECAB at 17.4% (95% CI: 8.1–33.6%;  $I^2=95\%$ ) compared to 8.4% (95% CI: 6.0–11.5%;  $I^2=71\%$ ) receiving RA-MIDCAB.

### Perioperative outcomes

In-hospital mortality was 0.9% (95% CI: 0.6–1.4%;  $I^2=38\%$ ) for RA-MIDCAB recipients in 18 studies, and 1.5% (95% CI: 0.9–2.4%;  $I^2=8\%$ ) for TECAB recipients in 12 studies (Tables 5,6). In the mixed robotic CABG group comprising largely of data from national databases, the pooled in-hospital mortality was 0.9% (95% CI: 0.7–1.3%;

**Table 1** Characteristics of included studies

Primary author	Ref.	Year	Institution(s)/database	Study period	Follow-up (months)	Robotic CABG approach	No. of patients	CPB
Lo	(17)	2023	Taichung Veterans General Hospital, Taiwan	2005–2015	77.0±44.9	RA-MIDCAB	562	OPCAB
Jonsson	(18)	2023	Emory University School of Medicine, USA	2009–2020	46±35.6	RA-MIDCAB	1,000	OPCAB
Torregrossa	(19)	2022	Lankenau Heart Institute, USA	2005–2021	88.5±67.0	RA-MIDCAB	600	OPCAB
Gofus	(12)	2022	University Hospital Hradec Kralove, Czechia	2018–2021	18	RA-MIDCAB	130	OPCAB
Piperata	(20)	2022	Hopital Cardiologique de Haut-Leveque, Bordeaux University Hospital, France	2021–2022	NA	RA-MIDCAB	17	ONCAB
Varrone	(21)	2022	Surgery, Lenox Hill Hospital, Northwell Health, New York, NY, USA	1997–2021	NA	RA-MIDCAB	1,080	OPCAB
Cheng	(3)	2021	PLA General Hospital, China	2007–2017	89.7±30.4	RA-MIDCAB; TECAB	154; 126	OPCAB
Patrick	(22)	2021	STS Adult Cardiac Surgery Database (98 institutions)	2014–2019	NA	RA-MIDCAB	1,195	OPCAB [1,070], ONCAB [125]
Wu	(23)	2019	Kaohsiung Veterans General Hospital, Taiwan	2010–2016	6	RA-MIDCAB	22	OPCAB [12], ONCAB [10]
Giambruno	(10)	2018	Western University, London Health Sciences Centre (Canada), University of California Davis (USA), Saint Boniface Hospital (Canada)	1998–2016	NA	RA-MIDCAB	605	OPCAB [589], ONCAB [16]
Pasrija	(24)	2018	STS Adult Cardiac Surgery Database	2011–2014	NA	RA-MIDCAB; TECAB	50; 50	OPCAB
Roubelakis	(25)	2017	OLV Hospital, Belgium	2002–2015	60.8±120.3	RA-MIDCAB	44	OPCAB [43], ONCAB [1]
Sabashnikov	(26)	2014	Royal Brompton & Harefield NHS Foundation Trust, UK	2003–2013	57±17.3	RA-MIDCAB	236	OPCAB
Bayramoglu	(27)	2014	Florence Nightingale Hospital, Turkey	2004–2012	60.3±23.8	RA-MIDCAB	100	OPCAB
Fujita	(28)	2014	National Cerebral and Cardiovascular Center, Osaka, Japan	2004–2012	NA	RA-MIDCAB	33	OPCAB
Ishikawa	(29)	2014	Kanazawa University, Kanazawa, Japan	2005–2013	NA	RA-MIDCAB	35	OPCAB
Leyvi	(30)	2014	Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA	2007–2012	NA	RA-MIDCAB	150	ONCAB [7], OPCAB [143]
Turner	(31)	2006	Center for Advanced Surgery and Technology, Trinity Mother Frances Health System and University of Texas at Tyler, College of Nursing and Health Science, Tyler, Texas	2004–2005	NA	RA-MIDCAB	70	OPCAB
Derose	(32)	2005	St. Luke's-Roosevelt Hospital Center, USA	2002–2004	16.1±8.4	RA-MIDCAB	37	OPCAB
Falk	(33)	2000	University of Leipzig, Germany	1998–1999	3	RA-MIDCAB; TECAB	32; 22	OPCAB
Balkhy	(34)	2022	University of Chicago, USA	2018–2020	1.4±1	TECAB	192	OPCAB
Balkhy	(35)	2020	University of Chicago, USA	2013–2018	22.5±15.1	TECAB	361	OPCAB
Stastny	(36)	2018	Innsbruck Medical University, Austria	2001–2012	82.8±27.6	TECAB	208	ONCAB
Zaouter	(37)	2015	CHU de Bordeaux, Service d'Anesthésie-Réanimation II, Bordeaux, France	2011–2014	NA	TECAB	38	OPCAB

**Table 1** (continued)

Table 1 (continued)

Primary author	Ref.	Year	Institution(s)/database	Study period	Follow-up (months)	Robotic CABG approach	No. of patients	CPB
Dhawan	(38)	2012	University of Chicago, USA	2007–2009	NA	TECAB	106	OPCAB
Jegaden	(39)	2011	Hospital Louis Pradel, France	2003–2008	32.4±1.2	TECAB	59	OPCAB
Srivastava	(40)	2010	Alliance Hospital (Odessa Regional Medical Center), USA	2004–2007	17.6±23.2	TECAB	241	OPCAB
de Cannière	(7)	2007	Erasmus University Hospital, Belgium; Klinikum der Johann Wolfgang Goethe Universität, Germany; Dresden Herzzentrum, Germany; Onze Lieve Vrouweziekenhuis, Belgium; Leipzig Heart Institute, Germany	1998–2002	6	TECAB	228	OPCAB [111], ONCAB [117]
Mishra	(41)	2006	Escorts Heart Institute and Research Centre, India	2002–2005	1–24	TECAB	13	OPCAB [11], ONCAB [2]
Argenziano	(42)	2006	Milstein Hospital, USA; Henrico Doctors' Hospital, USA; Leopold-Franzen-Universität Innsbruck, Austria; Alliance Hospital, USA; St Joseph Hospital of Atlanta, USA; Saint Agnes Medical Center, USA; Lenox Hill Hospital, USA; Sacred Heart Medical Center, USA; New York Presbyterian Hospital, USA	2002–2004	3	TECAB	85	ONCAB
Al-Mulla	(43)	2022	Heart Hospital, Hamad Medical Corporation, Qatar	2009–2020	3	Mixed	71	NA
Cerny	(44)	2021	OLV Hospital, Belgium; University Hospital Hradec Kralove, Czechia; University Hospital Bordeaux, France; Erasmus University Hospital, Belgium	2016–2019	NA	Mixed	1,266	OPCAB [1,250], ONCAB [16]
Yokoyama	(45)	2021	National Inpatient Sample	2012–2017	NA	Mixed	7,355	NA
Whellan	(46)	2016	STS Adult Cardiac Surgery Database	2006–2012	NA	Mixed	9,862	OPCAB [7,655], ONCAB [2,207]
Cavallaro	(47)	2015	Nationwide Inpatient Sample	2008–2010	NA	Mixed	2,582	OPCAB [2,060], ONCAB [522]
Casula	(48)	2014	University Hospital of Central Manchester, UK	2002–2008	NA	Mixed	100	OPCAB
Currie	(49)	2012	London Health Sciences Centre, Canada	1999–2003	96±16	Mixed	82	OPCAB
Folliguet	(50)	2010	L'Institut Mutualiste Montsouris, France	2004–2008	13±36	Mixed	56	OPCAB
Mishra	(51)	2007	Escorts Heart Institute and Research Centre, India	2002–2006	1–42	Mixed	268	NA

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; OPCAB, off-pump coronary artery bypass grafting; ONCAB, on-pump coronary artery bypass grafting; NA, not applicable; TECAB, totally endoscopic coronary artery bypass.

$I^2=66\%$ ). On average, perioperative stroke occurred in less than 1% of patients, perioperative MI in less than 2%. Other perioperative complications such as acute renal injury, new onset atrial fibrillation, wound infection, pulmonary complications, re-operation for bleeding and requirement for prolonged ventilation greater than 24 hours

was observed at a higher rate in the TECAB group (Table 6). However, length of ICU and hospital stay was observed to be longer in the RA-MIDCAB group at 40.8 hours (95% CI: 25.3–56.3;  $I^2=99\%$ ) and 7.6 days (95% CI: 5.2–10.0;  $I^2=100\%$ ), respectively, compared to 32.8 hours (95% CI: 24.3–41.3;  $I^2=76\%$ ) and 6.0 days (95% CI: 3.8–8.3;  $I^2=99\%$ ),

**Table 2** Pooled weighted estimate of available baseline patient and operative characteristics of RA-MIDCAB

Characteristics	Pooled weighted estimate (95% CI)*	I <sup>2</sup> % statistic (No. of studies reported)
<b>Baseline patient characteristics</b>		
Age (years)	64.5 (61.9–67.2)	99% (20/20)
Male gender (%)	75.8 (73.0–78.4)	79% (20/20)
BMI (kg/m <sup>2</sup> )	27.5 (26.6–28.3)	99% (12/20)
Single vessel disease (%)	75.5 (49.5–89.7)	99% (13/20)
Double vessel disease (%)	18.9 (7.8–39.2)	99% (10/20)
Triple vessel disease (%)	17.0 (5.9–39.9)	99% (9/20)
LAD lesion (%)	91.2 (61.9–98.5)	100% (10/20)
Smoker (%)	44.7 (37.4–52.3)	94% (13/20)
Diabetes mellitus (%)	39.4 (30.8–48.7)	98% (17/20)
Hypertension (%)	78.5 (71.0–84.5)	95% (14/20)
Chronic lung disease (%)	11.2 (7.3–16.6)	94% (11/20)
Chronic kidney disease (%)	5.7 (2.3–13.5)	97% (12/20)
Prior MI (%)	26.9 (17.7–38.5)	98% (13/20)
Prior PCI (%)	37.2 (28.4–46.9)	97% (11/20)
LVEF (%)	57.0 (53.2–60.7)	98% (12/20)
HCR (%)	31.1 (24.2–38.9)	92% (9/20)
<b>Operative characteristics</b>		
Operative time (min)	273.4 (125.6–421.3)	100% (10/20)
Off-pump	5,976/6,152 (97.1%)	–
LIMA-LAD anastomosis (%)	98.3 (96.2–99.2)	81% (13/20)
Conversion to sternotomy (%)	2.7 (1.5–4.8)	85% (14/20)
Blood transfusion (%)	8.4 (6.0–11.5)	71% (9/20)

\*, data are presented as pooled weighted estimate (95% CI) with the exception of n/N (%) for “Off-pump”. RA-MIDCAB, robot-assisted minimally invasive direct coronary artery bypass; CI, confidence interval; BMI, body mass index; LAD, left anterior descending; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; HCR, hybrid coronary revascularisation; LIMA, left internal mammary artery.

**Table 3** Pooled weighted estimate of available baseline patient and operative characteristics of TECAB

Characteristics	Pooled weighted estimate (95% CI)*	I <sup>2</sup> % statistic (No. of studies reported)
<b>Baseline patient characteristics</b>		
Age (years)	61.9 (59.8–64.1)	94% (13/13)
Male gender (%)	76.8 (69.7–82.6)	87% (12/13)
BMI (kg/m <sup>2</sup> )	28.2 (25.8–30.6)	97% (6/13)
Single vessel disease (%)	86.1 (61.9–96.0)	98% (9/13)
Double vessel disease (%)	11.1 (2.2–40.0)	98% (7/13)
Triple vessel disease (%)	4.2 (2.3–7.5)	46% (6/13)
LAD lesion (%)	95.7 (87.7–98.6)	93% (9/13)
Smoker (%)	4.0 (2.5–4.0)	86% (8/13)
Diabetes mellitus (%)	3.2 (2.5–4.0)	87% (10/13)
Hypertension (%)	75.8 (66.2–83.4)	92% (10/13)
Chronic kidney disease (%)	3.6 (1.3–10.0)	92% (6/13)
Prior MI (%)	25.1 (20.3–30.7)	66% (8/13)
Prior PCI (%)	29.7 (14.9–50.6)	95% (5/13)
LVEF (%)	56.9 (53.8–60.0)	96% (11/13)
HCR (%)	29.2 (21.6–38.1)	91% (8/13)
<b>Operative characteristics</b>		
Operative time (min)	272.9 (226.0–319.9)	99% (10/13)
Off-pump	1,638/1,729 (94.7%)	–
LIMA-LAD anastomosis (%)	95.2 (89.9–97.8)	88% (11/13)
Conversion to sternotomy (%)	2.9 (1.1–7.3)	91% (12/13)
Conversion to RA-MIDCAB (%)	4.7 (1.1–18.2)	93% (6/13)
Blood transfusion (%)	17.4 (8.1–33.6)	95% (6/13)

\*, data are presented as pooled weighted estimate (95% CI) with the exception of n/N (%) for “Off-pump”. TECAB, totally endoscopic coronary artery bypass; CI, confidence interval; BMI, body mass index; LAD, left anterior descending; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; HCR, hybrid coronary revascularisation; LIMA, left internal mammary artery; RA-MIDCAB, robot-assisted minimally invasive direct coronary artery bypass.

**Table 4** Pooled weighted estimate of available baseline patient and operative characteristics of a mixed robotic CABG population

Characteristics	Pooled weighted estimate (95% CI)*	I <sup>2</sup> % statistic (No. of studies reported)
<b>Baseline patient characteristics</b>		
Age (years)	62.2 (58.8–65.7)	99% (8/9)
Male gender (%)	83.0 (75.9–88.3)	99% (9/9)
Single vessel disease (%)	77.8 (42.0–94.4)	99% (4/9)
Double vessel disease (%)	15.9 (5.4–38.6)	98% (4/9)
Triple vessel disease (%)	11.8 (5.9–22.0)	85% (4/9)
Diabetes mellitus (%)	3.1 (2.2–4.0)	99% (8/9)
Hypertension (%)	69.9 (49.5–84.6)	100% (5/9)
Chronic lung disease (%)	14.1 (9.5–21.0)	99% (5/9)
Chronic kidney disease (%)	6.5 (2.4–16.7)	100% (4/9)
Prior MI (%)	22.9 (11.4–40.7)	100% (6/9)
HCR (%)	11.4 (6.8–18.8)	84% (5/9)
<b>Operative characteristics</b>		
Operative time (min)	249.8 (117.6–381.9)	99% (4/9)
Off-pump	11,215/13,962 (80.3%)	–
Conversion to sternotomy (%)	3.3 (2.1–5.2)	34% (5/9)
Blood transfusion (%)	12.4 (9.1–16.7)	93% (4/9)

\*, data are presented as pooled weighted estimate (95% CI) with the exception of n/N (%) for “Off-pump”. CABG, coronary artery bypass grafting; CI, confidence interval; MI, myocardial infarction; HCR, hybrid coronary revascularisation.

respectively, in the TECAB group.

### Mid-to-long term outcomes

Eleven studies in the RA-MIDCAB group reported mid-to-long term follow-up data (*Table 5*). The mean follow-up time was 62.6 months in the RA-MIDCAB group with 96.2% completeness of follow-up. Overall all-cause mortality in this follow-up period was 9.3% (95% CI: 2.3–31.3%; I<sup>2</sup>=99%), however cardiac cause of mortality was 2.7% (95% CI: 0.6–10.5%; I<sup>2</sup>=73%). Freedom from MACE or MACCE was 83.2% (95% CI: 72.0–90.5%; I<sup>2</sup>=90%), with a post-operative stroke and MI rate of 2.0% (95% CI: 1.5–2.8%; I<sup>2</sup>=0%) and 2.7% (95% CI: 1.5–4.7%; I<sup>2</sup>=64%),

**Table 5** Pooled weighted estimate of perioperative and follow-up outcomes of RA-MIDCAB

Outcome	Pooled weighted estimate (95% CI)	I <sup>2</sup> % statistic (No. of studies reported)
<b>Perioperative outcome</b>		
Early mortality (%)	0.9 (0.6–1.4)	38% (18/20)
Perioperative stroke (%)	0.9 (0.6–1.3)	17% (14/20)
Perioperative MI (%)	1.3 (0.9–1.8)	0% (13/20)
Re-operation for bleeding (%)	1.9 (1.5–2.5)	13% (12/20)
Arrhythmia (%)	7.9 (3.6–16.2)	97% (10/20)
Pulmonary complication (%)	2.5 (1.1–5.6)	73% (8/20)
Acute renal injury (%)	1.2 (0.7–2.3)	72% (13/20)
Wound infection (%)	1.3 (0.6–2.7)	67% (13/20)
ICU length of stay (hours)	40.8 (25.3–56.3)	99% (11/20)
Hospital length of stay (days)	7.6 (5.2–10.0)	100% (15/20)
<b>Mid-to-long term outcomes</b>		
Mean follow-up time (months)	62.6 (38.0–87.3)	– (7/11)
Completeness of follow-up (%)	96.2 (85.5–99.1)	– (8/11)
All-cause mortality (%)	9.3 (2.3–31.3)	99% (8/11)
Cardiac mortality (%)	2.7 (0.6–10.5)	73% (4/11)
Freedom from MACE or MACCE (%)	83.2 (72.0–90.5)	90% (4/11)
Reintervention (%)	5.5 (2.6–11.3)	93% (7/11)
Overall graft patency (%)	96.2 (93.8–98.2)	0% (5/11)
Stroke (%)	2.0 (1.5–2.8)	0% (6/11)
MI (%)	2.7 (1.5–4.7)	64% (7/11)

RA-MIDCAB, robot-assisted minimally invasive direct coronary artery bypass; CI, confidence interval; MI, myocardial infarction; ICU, intensive care unit; MACE, major adverse cardiac events; MACCE, major adverse cardiac and cerebrovascular events.

respectively, in the follow-up period. The overall graft patency rate, as assessed in a total of 403 patients with either computed tomography (CT) or angiography, was 96.2% (95% CI: 93.8–98.2%; I<sup>2</sup>=0%), and the rate of coronary re-intervention was 5.5% (95% CI: 2.6–11.3%; I<sup>2</sup>=93%).

In the nine studies reporting on mid-to-long term outcomes of TECAB, the mean follow-up time was 48.9 months with 94.1% completeness of follow-up (*Table 6*). All-cause

**Table 6** Pooled weighted estimate of perioperative and follow-up outcomes of TECAB

Outcome	Pooled weighted estimate (95% CI)	I <sup>2</sup> % statistic (No. of studies reported)
<b>Perioperative outcome</b>		
Early mortality (%)	1.5 (0.9–2.4)	8% (12/13)
Perioperative stroke (%)	0.9 (0.5–1.8)	0% (8/13)
Perioperative MI (%)	1.6 (0.9–2.9)	0% (7/13)
Re-operation for bleeding (%)	3.1 (1.6–6.0)	73% (10/13)
Arrhythmia (%)	10.6 (7.9–14.0)	42% (7/13)
Pulmonary complication (%)	3.6 (2.3–5.5)	10% (6/13)
Acute renal injury (%)	3.1 (1.5–6.2)	51% (5/13)
Wound infection (%)	1.8 (0.4–6.9)	50% (5/13)
ICU length of stay (hours)	32.8 (24.3–41.3)	76% (9/13)
Hospital length of stay (days)	6.0 (3.8–8.3)	99% (10/13)
<b>Mid-to-long term outcomes</b>		
Mean follow-up time (months)	48.9 (6.1–91.8)	– (5/9)
Completeness of follow-up (%)	94.1 (85.1–97.8)	– (4/9)
All-cause mortality (%)	3.4 (1.1–9.9)	42% (4/9)
Freedom from MACE or MACCE (%)	91.7 (86.7–94.9)	76% (5/9)
Reintervention (%)	4.1 (2.2–7.5)	63% (6/9)
Overall graft patency (%)	96.4 (93.0–98.9)	71% (9/9)
Recurrent angina (%)	3.5 (0.7–15.3)	77% (4/9)

TECAB, totally endoscopic coronary artery bypass; CI, confidence interval; MI, myocardial infarction; ICU, intensive care unit; MACE, major adverse cardiac events; MACCE, major adverse cardiac and cerebrovascular events.

mortality was 3.4% (95% CI: 1.1–9.9%; I<sup>2</sup>=42%) and freedom from MACE or MACCE was 91.7% (95% CI: 86.7–94.9%; I<sup>2</sup>=76%). Recurrent angina was experienced in 3.5% of patients and rate of postoperative MI was 1.3%. Overall graft patency, as assessed in 900 patients, and reintervention rate were similar to the RA-MIDCAB group.

Five studies with a mixed robotic CABG cohort reported on mid-to-long term outcomes with a mean follow-up time of 54.5 months and a 95.1% completeness of follow-up (Table 7). Overall all-cause mortality was 1.3% (95% CI: 0.04–26.4%; I<sup>2</sup>=80%) with freedom from MACE or

**Table 7** Pooled weighted estimate of perioperative and follow-up outcomes of a mixed robotic CABG population

Outcome	Pooled weighted estimate (95% CI)	I <sup>2</sup> % statistic (No. of studies reported)
<b>Perioperative outcome</b>		
Early mortality (%)	0.9 (0.7–1.3)	66% (8/9)
Perioperative stroke (%)	0.7 (0.3–2.1)	97% (5/9)
Re-operation for bleeding (%)	3.2 (1.5–6.8)	99% (8/9)
Acute renal injury (%)	5.3 (2.4–11.3)	99% (4/9)
Hospital length of stay (days)	5.9 (4.0–7.8)	100% (9/9)
<b>Mid-to-long term outcomes</b>		
Mean follow-up time (months)	54.5 (47.2–58.1)	– (2/5)
All-cause mortality (%)	1.3 (0.04–26.4)	80% (2/5)
Freedom from MACE or MACCE (%)	88.8 (82.7–93)	2% (2/5)
Reintervention (%)	4.7 (2.5–8.5)	0% (3/5)
Overall graft patency (%)	90.7 (84.6–94.5)	0% (3/5)

CABG, coronary artery bypass grafting; CI, confidence interval; MACE, major adverse cardiac events; MACCE, major adverse cardiac and cerebrovascular events.

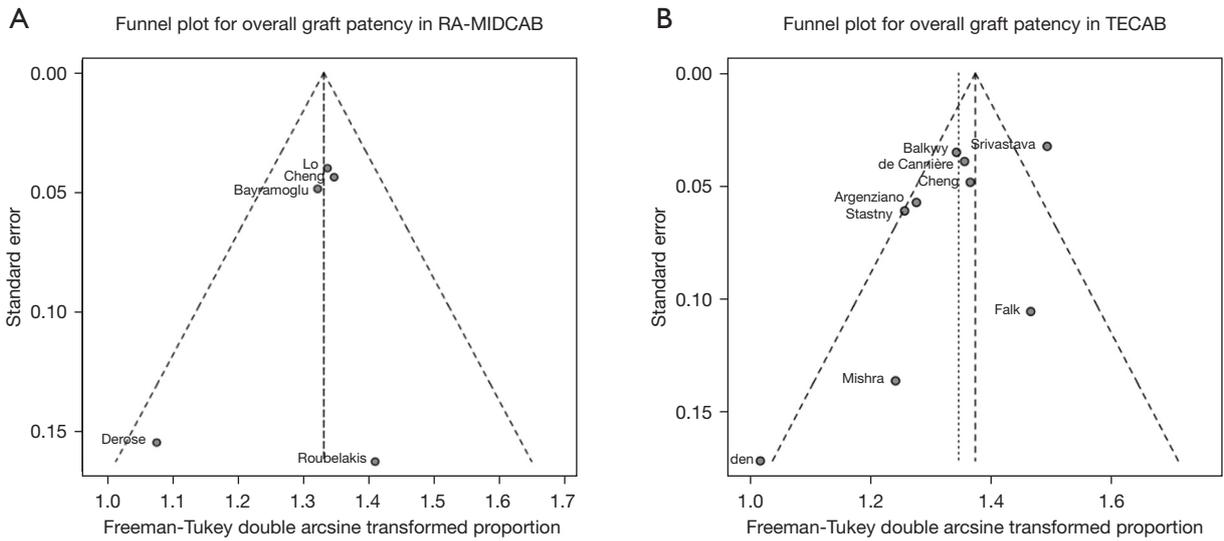
MACCE of 88.8% (95% CI: 82.7–93%; I<sup>2</sup>=2%). The overall graft patency as assessed in 144 patients was 90.7% (95% CI: 84.6–94.5%; I<sup>2</sup>=0%) and coronary reintervention was required in 4.7% (95% CI: 2.5–8.5%; I<sup>2</sup>=0%) of recorded patients.

### Publication bias

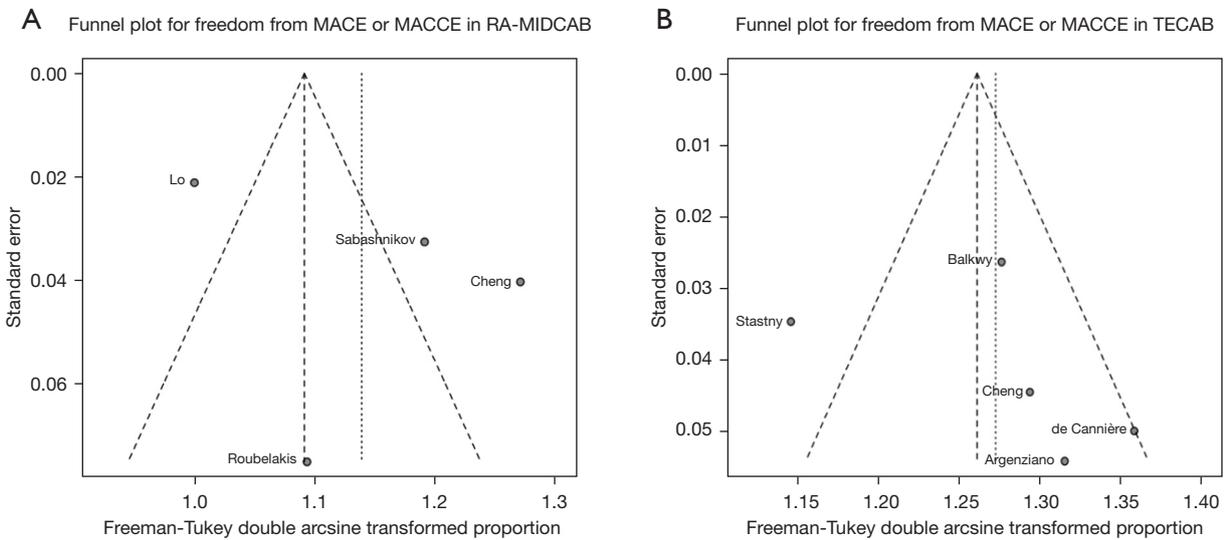
On visual inspection of funnel plots for primary outcomes, there was asymmetry in all funnel plots except for overall graft patency in the RA-MIDCAB group (Figures 2,3). There were insufficient studies for Egger's regression test to be applied.

### Discussion

In this current era, there exists a multitude of alternative, less invasive approaches to the “gold standard” on-pump sternotomy CABG, including off-pump, minimally invasive and totally endoscopic techniques. Despite these growing advances, there has been a slow uptake and plateau of robotic assistance for CABG, with many sites discontinuing



**Figure 2** Funnel plot for publication bias in overall graft patency outcome in (A) RA-MIDCAB and (B) TECAB. RA-MIDCAB, robot-assisted minimally invasive direct coronary artery bypass; TECAB, totally endoscopic coronary artery bypass.



**Figure 3** Funnel plot for publication bias in freedom from MACE or MACCE outcome in (A) RA-MIDCAB and (B) TECAB. MACE, major adverse cardiac events; MACCE, major adverse cardiac and cerebrovascular events; RA-MIDCAB, robot-assisted minimally invasive direct coronary artery bypass; TECAB, totally endoscopic coronary artery bypass.

the procedure for at least one year (46). A multitude of factors may be contributing to this, such as the perceived steep learning curve, albeit less so in those already adept with minimally invasive technology. Moreover, comparison of minimally invasive techniques with conventional CABG in the literature have often yielded equivalent results, hence surgeons may remain reluctant to adopt these more

technically demanding approaches (30). The heterogeneity of the patient cohort seen in this meta-analysis may reflect that at current, no single cohort for whom robotic CABG is most suitable has been identified and this may also contribute to low adoption rates.

Despite this, there has been a growing number of participating centers since recent renewed interest owing

to technological advancements, more structured training pathways and reconfirmation of superiority of CABG over PCI in various clinical scenarios (35,44). Advanced robotic systems now provide enhanced high-definition three-dimensional (3D) visualisation together with improved control, dexterity and precision from four robotic arms (12). Moreover, at two and a half decades since the first adoption of this technique, the long-term data that was previously lacking is now increasingly available and showing encouraging outcomes. In a propensity-matched analysis of robotic versus conventional CABG by Kofler and colleagues, there was no difference in perioperative outcomes, long-term survival or freedom from MACCE, with rates of MI (1.4%), stroke (0.7%), early mortality (1.3%) comparable to the current meta-analysis (52). In more recent and larger propensity-matched analysis of the US National Inpatient Sample from 2012 to 2017, robotic CABG was found to be associated with lower in-hospital mortality, rate of acute kidney injury, transfusion, post-operative bleeding and hospital length of stay compared to conventional CABG (45).

Although all-cause mortality in the follow-up period of this pooled meta-analysis is high, at 9.3% for RA-MIDCAB and 3.4% for TECAB, this is likely confounded by deaths unrelated to a primary coronary cause. Thus, freedom from MACCE and long-term graft patency may be more relevant indicators for long-term effectiveness and durability of revascularisation compared to overall survival. In this pooled meta-analysis, freedom from MACE or MACCE of 83.2% and 91.7% in RA-MIDCAB and TECAB, respectively, at a mean follow-up of 5.2 years appears greater than five-year MACCE-free survival of 81% of conventional CABG from the more recent NOBLE randomised trial (53).

Graft patency is also an important indicator of the durability of robotic CABG. In this pooled meta-analysis, the overall graft patency rate was excellent at 96% for both RA-MIDCAB and TECAB, as assessed through either invasive or CT angiography in a mean follow-up period up to five years. This is comparable to the ten-year patency rate of the LIMA graft in conventional CABG of 90% (54,55). Balkhy *et al.* propose that anastomotic connectors may be instrumental in achieving reproducible long-term patency results in multivessel off-pump TECAB (35).

High rates of conversion have previously been used as a point of criticism against robotic CABG, however this has expectantly decreased over the last two decades with growing experience (11). The rate of conversion to sternotomy as observed in this meta-analysis is now much

lower at less than 3%, compared to 10% in published large series from a decade ago (56,57), and 23–33% in TECAB studies a decade before that (7).

As for unexpected results, the reduction in hospital length of stay appears modest when compared to conventional CABG, indicating that realistically patients may still require six-to-seven postoperative days in hospital. However, in high-volume centers, length of stay can be significantly reduced, with patients staying an average of four days (46). While we expect to use fewer blood products with less invasive surgeries, a surprising number of TECAB patients needed blood transfusions and surgical revisions for bleeding, more so than those undergoing RA-MIDCAB. As previously discussed by Kofler *et al.*, this may be a result of the learning curve of different surgeons and the longer operative times given TECAB is technically more challenging (52). Rate of wound infection is another parameter for which sternal-sparing techniques are expected to reduce, and hence has been touted as beneficial for obese patients whom have a high risk of wound complications. Superficial wound infection in this current meta-analysis was observed at a rate ranging from 0.4–6.9% in this pooled meta-analysis which appear equivocal to deep sternal wound infection (DSWI) rates in the literature (58). However, infection of the port or thoracotomy wound may pose relatively lower risk of serious complication compared to DSWI which has a mortality rate of up to 30% (59).

It is important to note that outcomes of robotic CABG derive from a highly selected pool of low-risk patients, whom are relatively younger and have fewer comorbidities, hence comparisons with conventional CABG must be interpreted with caution (46,60). Furthermore, patients undergoing robotic CABG are largely those with single vessel LAD disease that would usually not be considered for conventional CABG (30). Lin *et al.* therefore compared these two approaches in patients with multi-vessel disease only and found that in real world practice, robotic CABG could be an effective option in patients with fewer clinical complexities (61).

Though the low rate of perioperative complications observed in this pooled meta-analysis is comparable to previous meta-analyses demonstrating the short-term safety and efficacy of these procedures, perioperative complications appeared to occur at a slightly lower rate in RA-MIDCAB compared to TECAB. This may be due to RA-MIDCAB being performed preferentially than TECAB, as it may be safely and efficiently performed even early in a surgeon's experience (31). Though not analysed in this study, TECAB

is also associated with significantly higher hospital costs, the bulk of which lay in operating room equipment such as distal anastomotic devices (24). Nevertheless, the cost of TECAB may be warranted in more complex, multiarterial revascularisation, which although is possible with RA-MIDCAB, has significant complexity with each additional anastomosis (24).

Furthermore, although MIDCAB is already an attractive alternative to conventional CABG and technologically least complex of all minimally invasive CABG procedures, robotic assistance provides 3D telemanipulation that further minimises access trauma of the LIMA harvest by avoiding larger incisions and wider rib spreading (12,62). In a propensity-matched study by Gofus *et al.* comparing conventional versus robot-assisted MIDCAB, RA-MIDCAB had lower 24-hour post-operative blood loss and potentially faster recovery, however mortality and risk of perioperative complications were comparative (12).

Robotic assistance has also been adopted in HCR, a revolutionary strategy in which a minimally invasive form of bypass grafting is combined with PCI for the treatment of multivessel disease. Studies on robotic HCR show excellent short-term outcomes with no hospital mortality, post-operative MI ranging from 0–3.7%, stroke ranging from 0–1.7% and freedom from reintervention ranging from 73.4–100% in one meta-analysis (63). With careful patient selection, robotic HCR is an attractive strategy that can achieve complete revascularisation whilst integrating the long-term benefit of bypass grafting with less invasiveness of PCI to non-LAD targets (64).

### Limitations

All included studies were retrospective and observational in nature resulting in methodological limitations which render firm conclusions difficult to be drawn. As expected from inherent selection bias that cannot be adjusted for by any statistical methodologies, there was considerable statistical heterogeneity observed in the pooling of baseline patient characteristics, which showed that patients undergoing robotic CABG may not be a generalizable cohort. This is partly owed to pooling of outcomes across two and half decades, encompassing several generations of evolution in robotic instruments and surgical technique. Moreover, several larger studies are from high volume, experienced centers and hence their outcomes may also not be generalizable. Results may be confounded by several factors including conversions, hybrid procedures, whether

cardiopulmonary bypass was used and whether cases were from the learning curve. Finally, not all articles reported on consecutive patients, which introduces reporting bias in a selected patient population.

### Conclusions

Robotic CABG in this pooled meta-analysis is observed to have acceptable perioperative mortality and complication rates reinforcing it as a safe and feasible approach. Overall graft patency, freedom from MACCE and reintervention appear in favour of long-term durability. With a multitude of alternate approaches to coronary bypass grafting in this age, careful patient selection remains paramount for achieving a successful outcome. Robotic CABG, especially TECAB, is the least invasive approach to CABG and has a promising role in HCR, however its continued uptake requires support from both the surgical community and industry alike.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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## Appendix 1 Search strategy

**PubMed (Medline)** - searched 17 August 2023

(coronary artery bypass[Title/Abstract]) AND ((robot[Title/Abstract]) OR (robotic[Title/Abstract]) OR (robot assisted[Title/Abstract]) OR (RA-MIDCAB[Title/Abstract]) OR (TECAB[Title/Abstract]) OR (totally endoscopic[Title/Abstract]))

**Embase** - searched 18 August 2023

1. \*coronary artery bypass graft/
2. \*heart muscle revascularization/
3. \*robotics/ or \*robot assisted surgery/
4. robot\* assisted midcab.mp.
5. tecab.mp.
6. totally endoscopic.mp.
7. 1 or 2
8. 3 or 4 or 5 or 6
9. 7 and 8
10. limit 9 to (full text and human and English language)

**Cochrane Central Register of Controlled Trials (CENTRAL)** - searched 18 August 2023

- #1 MeSH descriptor: [Coronary Artery Bypass] explode all trees
- #2 MeSH descriptor: [Robotic Surgical Procedures] explode all trees
- #3 midcab
- #4 tecab
- #5 #1 and (#2 or #3 or #4)

Appendix 2 Quality assessment using the modified Canadian National Institute of Health Economics (CNIHE) quality appraisal checklist for case series																					
Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Total	Quality
Lo, 2023	1	0	0	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	15	Moderate
Jonsson, 2023	1	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	16	High
Torregrossa, 2022	1	1	0	0	1	0	1	1	0.5	1	1	1	1	1	0	1	1	1	1	14.5	Moderate
Gofus, 2022	1	0	0	1	1	0.5	1	1	0	0.5	1	1	1	1	1	1	1	1	1	15	Moderate
Piperata, 2022	1	0	0	0	1	0.5	1	1	0	1	1	1	1	0.5	0	1	1	1	1	13.5	Moderate
Varrone, 2022	0.5	0	0	1	1	0.5	1	1	0	0.5	1	1	1	0.5	0	1	1	1	1	13	Moderate
Cheng, 2021	1	0	0	0	1	1	1	1	1	0.5	1	1	1	1	1	1	0.5	1	1	15	Moderate
Patrick, 2021	1	0	1	0	1	1	0.5	0	0	0	1	1	1	0.5	0	1	0.5	1	0.5	11	Low
Wu, 2019	1	0	0	1	1	1	1	1	0.5	1	1	1	1	1	1	1	1	1	1	16.5	High
Giambruno, 2018	0.5	0	0	0	0.5	0.5	1	1	1	1	1	1	0.5	0.5	0	0.5	1	1	0	11	Low
Pasrija, 2018	1	0	1	1	1	0.5	1	1	0.5	1	1	1	1	0.5	0	0.5	1	1	0.5	14.5	Moderate
Roubelakis, 2017	0.5	0	0	0	1	0	1	1	1	0	1	1	1	1	1	1	1	1	0.5	14	Moderate
Sabashnikov, 2014	1	0	1	0	1	1	1	1	1	0	1	1	1	1	0	1	1	1	0.5	14.5	Moderate
Bayramoglu, 2014	1	0	0	0	1	0.5	1	1	0	1	1	1	1	1	1	1	1	1	1	14.5	Moderate
Fujita, 2014	1	0	0	1	1	0	1	1	0	0	1	1	1	0.5	0	0.5	1	1	1	12	Moderate
Ishikawa, 2014	1	0	0	1	0.5	0	1	1	1	0	1	1	0	0.5	0	1	1	1	0	11	Low
Leyvi, 2014	1	1	0	1	1	0.5	1	0.5	1	1	1	1	1	0.5	0	1	1	1	1	15.5	Moderate
Turner, 2006	1	0	0	1	0	1	1	1	0	0	1	1	1	0.5	1	0	1	1	0	11.5	Moderate
Derose, 2005	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	16	High
Falk, 2000	1	0	0	0	0.5	0	1	1	0	0	1	1	1	1	0	1	1	1	0	10.5	Low
Balkhy, 2022	1	0	0	0	1	1	1	1	0.5	1	1	1	1	0.5	0	1	1	1	1	14	Moderate
Balkhy, 2020	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5	16.5	High
Stastny, 2018	1	1	0	1	1	1	1	1	0.5	1	1	1	1	1	0	1	1	1	0.5	16	High
Zaouter, 2015	1	0	0	0	0.5	1	0.5	1	1	0.5	1	1	0.5	0.5	0	0	1	1	0	11	Low
Dhawan, 2012	1	0	0	0	1	0.5	1	1	0	1	1	1	1	0.5	0	1	1	1	1	13	Moderate
Jegaden, 2011	0.5	1	0	0	1	0	1	1	0	0	1	1	1	1	0	1	1	1	0.5	12	Moderate
Srivastava, 2010	1	0	0	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	0.5	14.5	Moderate
de Cannière, 2007	1	0	1	0	0.5	0.5	1	0.5	1	1	1	1	1	1	1	1	0.5	1	1	15	Moderate
Mishra, 2006	0.5	0	0	0	1	1	1	1	0.5	0	1	1	0	1	1	0.5	1	1	0	11.5	Moderate
Argenziano, 2006	1	1	1	0	1	1	1	1	0.5	1	1	1	1	1	1	1	1	1	0.5	17	High
Al-Mulla, 2022	1	0	0	1	1	0.5	1	0	0.5	1	1	1	1	1	0	0.5	1	1	1	13.5	Moderate
Cerny, 2021	0.5	0	1	0	0.5	0	0.5	0.5	0	1	1	1	1	0.5	0	0.5	1	1	1	11	Low
Yokoyama, 2021	0.5	0	1	0	1	1	1	0	0	1	1	1	1	0.5	0	0	1	1	0.5	11.5	Moderate
Whellan, 2016	1	0	1	0	1	0.5	1	0.5	0	1	1	1	1	0.5	0	1	1	1	0	12.5	Moderate

Appendix 2 (continued)

**Appendix 2** (*continued*)

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Total	Quality
Cavallaro, 2015	1	0	1	0	1	1	1	0	0	1	1	1	1	0.5	0	1	1	1	0	12.5	Moderate
Casula, 2014	1	0	0	1	1	1	1	1	0.5	1	1	1	0	1	0	1	1	1	0.5	13	Moderate
Currie, 2012	1	0	0	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	14	Moderate
Folliguet, 2010	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	16	High
Mishra 2007	0.5	0	0	0	1	1	1	1	0	0	1	1	0	1	1	0	1	1	0	10.5	Low

**Modified Canadian National Institute of Health Economics (CNIHE) quality appraisal checklist**

- Q1. Was the hypothesis/aim/objective of the study clearly stated?
- Q2. Was the study conducted prospectively?
- Q3. Were the cases collected in more than one centre?
- Q4. Were patients recruited consecutively?
- Q5. Were the characteristics of the patients included in the study described?
- Q6. Were the eligibility criteria (i.e., inclusion and exclusion criteria) for entry into the study clearly stated?
- Q7. Did patients enter the study at a similar point in the disease?
- Q8. Was the intervention of interest clearly described?
- Q9. Were additional interventions (co-interventions) clearly described?
- Q10. Were relevant outcome measures established a priori?
- Q11. Were the relevant outcomes measured using appropriate objective/subjective methods?
- Q12. Were the relevant outcome measures made before and after the intervention?
- Q13. Were the statistical tests used to assess the relevant outcomes appropriate?
- Q14. Was follow-up long enough for important events and outcomes to occur?
- Q15. Were losses to follow-up reported?
- Q16. Did the study provided estimates of random variability in the data analysis of relevant outcomes?
- Q17. Were the adverse events reported?
- Q18. Were the conclusions of the study supported by results?
- Q19. Were both competing interests and sources of support for the study reported?