Interactive CardioVascular and Thoracic Surgery 19 (2014) 462–473
doi:10.1093/icvts/ivu157 Advance Access publication 3 June 2014

Adjunct coronary endarterectomy increases myocardial infarction and early mortality after coronary artery bypass grafting: a meta-analysis

Erdinc Soylu, Leanne Harling*, Hutan Ashrafian, Roberto Casula, John Kokotsakis and Thanos Athanasiou

Department of Surgery and Cancer, Imperial College London, London, UK

* Corresponding author. Department of Surgery and Cancer, Imperial College London, 10th floor QEQM Building, St Mary's Hospital, Praed Street, London W2 1NY, UK. Tel: +44-203-3127651; fax: +44-203-3126302; e-mail: leanne.harling@imperial.ac.uk (L. Harling).

Received 7 January 2014; received in revised form 2 April 2014; accepted 13 April 2014

Abstract

Coronary endarterectomy (CE) may provide a useful adjunct to coronary artery bypass grafting (CABG) in patients with extensive, diffuse coronary atheroma. However, concerns regarding its morbidity and mortality have created uncertainty as to the role of CE in the current era. The aim of this study was therefore to quantitatively summarize the short- and long-term outcomes of CE. Twenty observational studies were identified by systematic literature search, incorporating 54 440 patients (7366 CABG + CE; 47 074 CABG only), which were analysed using random-effects modelling. Heterogeneity, subgroup analysis, quality scoring and risk of bias were assessed. Primary end-points were 30-day mortality and perioperative and postoperative myocardial infarction (MI). Secondary end-points were postoperative morbidity, intensive care unit (ITU) stay, hospital stay and long-term graft patency. Adjunctive CE significantly increased 30-day mortality [odds ratios (OR) = 1.69, 95% confidence interval (CI) [1.49–1.92], P <0.00001], perioperative (OR = 2.10, 95% CI [1.82–2.43], P <0.00001) and postoperative MI (OR = 3.34, 95% CI [1.74–6.41], P = 0.0003) when compared with CABG alone. Furthermore, postoperative ventricular arrhythmias, pulmonary complications, renal failure and inotrope use were significantly greater in patients undergoing adjunct CE. CE also increased ITU and hospital stay and reduced angiographic patency at the last follow-up (OR = 0.57, 95% CI [0.36–0.88]). Increased 30-day morbidity and mortality continues to raise concerns over the safety of adjunct CE. Furthermore, the procedure can be associated with worse long-term graft patency. To better determine whether CE should remain a viable adjunct to CABG, novel studies must focus on collecting prospective data with homogeneous inclusion criteria for CE as well as isolating outcomes for different coronary vessels and standardizing postoperative anticoagulation.

Keywords: Coronary endarterectomy • Coronary artery bypass grafting • CABG • Atherosclerosis

INTRODUCTION

Over recent years, the profile of patients referred for coronary artery bypass grafting (CABG) has become increasingly complex. A growing proportion of patients are older, with diffuse disease and multiple comorbidities, and many have undergone previous percutaneous coronary intervention [1]. In the past, coronary endarterectomy (CE) had been popularized to achieve complete revascularization in the setting of complex, diffuse coronary disease, where an acceptable distal target could not be found. However, although early reports demonstrated symptomatic relief from angina, an increase in perioperative myocardial infarction (MI) [2], postoperative morbidity and early mortality [3–6] led to major concerns over the safety of this procedure [7]. Despite this, the changing pattern and increasing complexity of coronary disease have led to CE being reconsidered as a treatment strategy in selected cases and, thus, reassessment of the technique, its indications and outcomes is now necessary [7].

CE can be performed using either an open or a closed approach [8]. Open endarterectomy involves incising the coronary artery throughout the length of the stenosis, proximally transecting the atheroma and carefully dissecting out the plaque, including any extensions into coronary side branches. The vessel is then closed using an autologous patch of either saphenous vein or mammary artery. Bypass grafting may be performed onto the patch where necessary [9]. Closed endarterectomy is performed through a small arteriotomy made over a proximal area of the plaque. Subsequently, careful dissection between the lamina of the vascular wall and the atheroma is followed by gentle traction on the plaque to enable the cast of atheroma to be removed. Care must be taken to minimize vascular trauma and the risk of proximal dissection. One or more small bridging arteriotomies may be required distally to facilitate plaque removal, particularly from side branches [10].

Comparative studies evaluating CE versus CABG have been criticized for their non-randomized nature and inherent selection bias [11]. As such, endarterectomy patients tend to have more complex, diffuse disease patterns compared with those undergoing CABG. Furthermore, outcomes for right and left CE may be distinctly different, with endarterectomy to the left anterior descending (LAD) artery being associated with increased morbidity and mortality compared with other vessels.

Despite several studies into role of adjunctive CE, there is continued uncertainty regarding its potential. The purpose of this study is therefore to provide a quantitative summary of the available evidence surrounding the use of CE in combination with

CABG to inform current practice. Our primary aim was to evaluate the effect of CE on the incidence of peri- and postoperative MI and early mortality. Secondarily, we considered its impact on major morbidities, length of stay and overall vessel patency at follow-up.

MATERIALS AND METHODS

Literature search

A systematic literature search was performed of the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Ovid Medline and EMBASE electronic databases using the following search terms: 'coronary vessels', 'heart' and 'endarterectomy'. The last date for this search was 23 November 2013. The primary search was supplemented with searches of: (i) PubMed-related articles; and (ii) clinicaltrials.gov. A summary of the search strategy is shown in Fig. 1.

Inclusion and exclusion criteria

All articles reporting the use of CE in the treatment of coronary artery disease, which were comparative between CE with CABG and CABG only, were included. Studies with more than two arms, comparing other interventions, such as patch reconstruction, were included, but the data were only extracted from the relevant patient groups. No language restrictions were imposed. Where data were duplicated, the most recent study or that with the largest sample size was preferentially considered.

Based on these criteria, two reviewers (E.S. and L.H.) independently selected studies for further examination by title and abstract review of all identified citations. All potentially eligible studies were retrieved and examined in full. Any disagreement was resolved by discussion with the senior author (T.A.).

Data extraction

Two authors (E.S. and L.H.) independently extracted the following data using a standardized spreadsheet: first author, year of publication, study type, number of subjects, population demographics, technique of CE, coronary vessel endarterectomized, type of conduit, use of cardiopulmonary bypass (CPB) and of antiplatelets or anticoagulants. All laboratory, physiological and clinical outcome measures used by the included studies were recorded. Specific outcome data were retrieved where possible for the following: (i) primary end-points: 30-day (early) mortality, perioperative and postoperative (as classified by the authors) MI; and (ii) secondary end-points: ventricular arrhythmias, pulmonary complications, postoperative renal failure, inotrope use, blood transfusion, intensive care unit (ICU) stay, hospital stay and long-term graft patency. Meta-analysis was performed in line with recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [12].

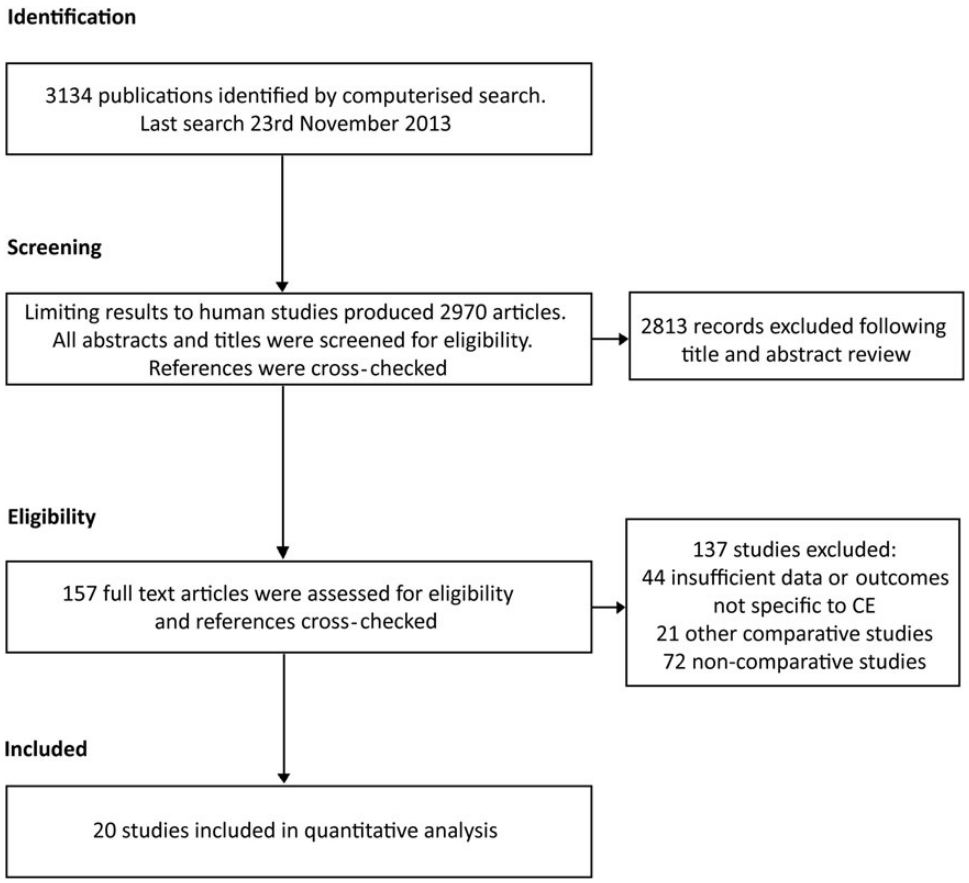


Figure 1. Search strategy.

Statistical analysis was conducted using Review Manager® Version 5.2.0 for Windows (Cochrane Collaboration, Oxford, UK) and STATA v.11 statistical analysis software (StataCorp LP, TX, USA). Analysis was performed using a weighted random-effects model. Weighted mean difference (WMD) was calculated as the summary statistic for continuous variables, and pooled odds ratios (OR) were calculated for dichotomous variables. Both OR and WMD are reported with 95% confidence intervals (CIs). A P-value of <0.05 was considered statistically significant. Determination of heterogeneity was undertaken using the χ^2 test (Cochran's Q) and I^2 value; with I^2 ≥75% denoting a high degree of statistically significant heterogeneity.

Sensitivity analysis

To evaluate potential sources of heterogeneity, sensitivity analysis was performed for the following: (i) studies published after year 2000; (ii) study size (n ≥100); (iii) studies with quality score ≥8; and (iv) studies with matched CABG and CABG + CE groups.

Quality scoring and risk-of-bias assessment

A modified Newcastle–Ottawa scale (Supplementary Table 1) was used to assess the methodological quality of included studies. This star-based system considered the following points: (i) patient selection; (ii) intergroup comparability; and (iii) outcome assessment (maximum 3, 10 and 2 stars, respectively; total /15). The 10 single-star variables used to grade comparability among study groups included age, gender, hypertension, ejection fraction, three-vessel disease, left mainstem disease, urgent/emergent operation, myocardial viability and surgeon/hospital volume. Quality scoring of included studies was independently assessed by two authors (E.S. and L.H.), with 100% inter-rater agreement.

A domain-based evaluation of risk of bias was performed in accordance with the guidelines outlined in the Cochrane Handbook for Systematic Reviews or Interventions version 5.1.7. Two authors (L.H. and E.S.) subjectively reviewed all studies included in this review and assigned a value of 'yes', 'no' or 'unclear' to the following questions: (i) was the allocation sequence adequately generated? (ii) Was allocation adequately concealed? (iii) Was there blinding of participants, personnel and outcome assessors? (iv) Were incomplete outcome data sufficiently assessed? And (v) Are reports in the study free of the suggestion of selective outcome reporting?

'Risk-of-bias' plots were performed using Review Manager® Version 5.1.7 for Windows (The Cochrane Collaboration, Software Update, Oxford, UK). Publication bias was assessed by visual inspection of funnel plots in addition to statistical estimation of small study effects using both Begg and Mazumdar's test and Egger's test for small study effects.

RESULTS

Eligible studies, variations in technical approach and quality assessment

Twenty publications [2, 7, 11, 13–29] were identified as those fulfilling our inclusion criteria, producing a pooled data set of 54 440 patients. Of these, 7366 (13.5%) underwent CABG with CE and 47 074 (86.5%) patients underwent CABG alone. Twelve studies were of retrospective cohort design [2, 7, 11, 15, 20, 22, 24–26, 28, 29], two were prospective cohort [14, 21], five were cohort studies without further specification [16–19, 23] and one study was a retrospective analysis of prospectively collected data from a randomized control trial into on- versus off-pump coronary revascularization [13]. Full study characteristics are shown in Table 1.

One study examined only endarterectomy of the LAD artery [24] and three examined only the right coronary artery [15, 16, 20]. The remaining 16 studies looked at both right and left coronary systems [2, 7, 11, 13, 14, 17–19, 21–23, 25–29]. Nine studies reported both 'open' and 'closed' endarterectomy techniques [2, 11, 14, 17, 18, 21–23, 26], seven studies used only a 'closed' technique [7, 13, 15, 16, 19, 20, 28] and only Tasdemir *et al.* used the 'open' method [24]. Three studies did not specify endarterectomy technique used [25, 27, 29]. Notably, RCA endarterectomy was most commonly performed using the closed method [2, 7, 11, 13, 15, 16, 19, 20, 22, 23], whereas LAD endarterectomy was most commonly performed using the open method [2, 11, 22–24].

Nine studies reported using both saphenous vein and internal thoracic artery conduit [11, 13, 15, 17, 21, 23–25, 28]. Three used saphenous vein only [16, 18, 26] and the remaining eight did not specify the type of conduit used [2, 7, 14, 19, 20, 27, 29]. On-pump-only procedures were performed in 12 studies [2, 7, 11, 16, 19–22, 24–26, 28], 3 used both on- and off-pump method [13, 15, 23], and the remaining 5 did not specify [14, 17, 20, 27, 29].

Eleven studies used at least one antiplatelet drug immediately postoperatively, which was continued for varying lengths of time, ranging from 3 months to indefinitely [2, 7, 11, 13-15, 20, 22, 24, 29, 30]. Five of these also administered concurrent anticoagulant therapy consisting of either warfarin or unfractionated heparin (Table 2) [7, 13, 15, 27, 28]. Seven studies administered neither antiplatelets nor anticoagulants postoperatively [17–19, 23, 25, 26].

Preoperative matching and quality score

Three studies adequately matched CE and CABG groups for all preoperative demographics [7, 11, 19] and 14 studies compared preoperative characteristics of their study and control groups [2, 7, 11, 14, 15, 19–27], demonstrating significant differences in preoperative characteristics. Five studies did not report on preoperative characteristics [16–19, 29]. The overall quality scores are demonstrated in Table 3. Ten studies were perceived to be of relative 'high'-quality scoring ≥8 [2, 7, 11, 14, 20, 21, 23–26].

Risk-of-bias analysis

Risk-of-bias analysis revealed several areas for concern, particularly regarding randomization, allocation concealment and blinding (Fig. 2). Furthermore, no studies currently demonstrate a design to satisfactorily exclude selection, performance and detection bias. Four of the six studies reporting angiographic patency present incomplete data [15, 17, 18, 26], only performing follow-up angiographies in symptomatic patients. Only eight studies had prespecified outcomes that were adequately reported [2, 13, 18–20, 22, 25, 26]. In addition to this, four studies did not disclose preoperative and intraoperative characteristics of the patients [16–18, 29], whereas one had significant differences in control and intervention groups of the study [20]. These issues raise concerns around attrition, reporting and other bias, respectively.

Table 1: Synopsis of studies

Study references (design)	*n*		Age		% Male		Matching criteria	Non-matched preoperative characteristics (P <0.05)	Inclusion	Exclusion	Technique	CE vessel	Graft	CPB
	CABG	CABG + End	CABG	CABG + End	CABG	CABG + End								
Abid *et al.* [13] (RCT of on- versus off-pump surgery, not randomized for CE)	50	50	56 ± 9.5	53.6 ± 10.2	84	90	–	31	C, F, G	a, b, c, d	LAD: closed extraction (spatula dissection + traction) + ITA bypass graft or SV patch + ITA graft; Others: closed extraction (spatula dissection + traction) + SV bypass graft	LAD, RCA, OM, D, I, Cx	SV, ITA	ON, OFF
Akchurin *et al.* [27] (Cohort-R)	102	97	56.1 ± 9.45	56.9 ± 7.46	80	89	–	7, 14, 30	–	–	–	LAD, RCA, D, Cx, PD	–	–
Asimakopoulos *et al.* [7] (Cohort-R)	56	56	59.6 ± 10.2	59.6 ± 10.8	84	84	1, 3, 17, 18	–	A, B, J, K	–	Closed extraction + (dissection + traction) + bypass graft	LAD, RCA, Cx	–	ON
Christakis *et al.* [1] (Cohort-P)	911	317	–	–	83	88	–	3, 8, 16, 19, 20	B, C, E, J, L, M	–	Closed extraction + bypass graft; open extraction + patch angioplasty + bypass graft	LAD, RCA, Cx	–	–
Demirtas *et al.* [28] (Cohort-R)	412	37	51.9 ± 15.7	53.6 ± 11.8	64	70	–	31	A, C, F	–	Closed extraction + (dissection + traction) + bypass graft	LAD, RCA, OM, D	SV, ITA	ON
Erdil *et al.* [15] (Cohort-R)	50	59	59.6 ± 9.8	59.5 ± 8.4	86	86	–	7	Br, C, G, I	–	Closed extraction (traction) + SV bypass graft	RCA	SV, ITA	ON, OFF
Gale *et al.* [16] (Cohort-R)	284	49	–	–	–	–	–	31	Br, E, F, K, O, P		Closed extraction (spatula dissection + traction) + SV bypass graft	RCA	SV	ON
Huysmans *et al.* [17] (Cohort-R)	837	250	–	56.8		88	–	31	A, E, K, O	e	Closed extraction (manual traction) + ITA or SV bypass graft; open extraction + ITA or SV graft or onlay graft	LAD, RCA	SV, ITA	–
Jonjev *et al.* [29] (Cohort-R)	249	251	–	–	–	–	–	–	–	–	Manual extraction of atheromatous material using specially designed instruments	LAD, RCA, D1, D2, Septal Branches		
Kamath *et al.* [18] (Cohort-R)	316	122	–	–	–	–	–	31	B, C, Q	g	Closed extraction (dissection and traction) + SV bypass/ or onlay graft; open extraction + SV bypass or onlay graft	LAD, RCA, Cx	SV	–
LaPar *et al.* [11] (Cohort-R)	297	99	62 ± 11.4	62.2 ± 10.4	72	71	1, 2, 3, 4, 5, 6, 7	–	A, B, C, D, E	–	RCA: closed extraction (evertion + traction) + SV bypass graft; LAD: open extraction + SV patch + ITA bypass graft	LAD, RCA, OM, D, PD, Cx	SV, ITA	ON
Larock *et al.* [19] (Cohort-R)	48	48	–	–	–	–	8, 16, 27, 28	–	–	e, j	Closed extraction (manual traction) + bypass graft	LAD, RCA, Cx	–	ON

Continued

Table 1: (*Continued*)

Study references (design)	*n*		Age		% Male		Matching criteria	Non-matched preoperative characteristics (P <0.05)	Inclusion	Exclusion	Technique	CE vessel	Graft	CPB
	CABG	CABG + End	CABG	CABG + End	CABG	CABG + End								
Livesay *et al.* [2] (Cohort-R)	27 095	3369	56 ± 9	56 ± 9	85	91	–	3, 7, 16, 22	B, C, K, O	–	LAD: open extraction + vein onlay graft; Others: closed extraction (manual or gas extraction) + bypass graft	LAD, RCA, Cx	–	ON
Miller *et al.* [20] (Cohort-R)	592	80	55 ± 1	56 ± 1	87	90	–	14, 25, 26	A, B, F, R	h	Closed extraction (eversion and traction) + bypass graft	RCA	–	ON
Shapira *et al.* [21] (Cohort-P)	757	151	65 ± 1	66 ± 10	70	72	–	7, 9, 10, 16	C, E, G, J	–	Closed extraction (spatula dissection and traction) + bypass graft; open extraction + SV patch + bypass graft or bypass graft alone	LAD, RCA, OM, D, Cx, PD, PL	SV, ITA	ON
Silberman *et al.* [22] (Cohort-R)	2071	231	19–66	–	78	76	–	6, 7, 8, 9, 23, 24	B, C, E, O	f	LAD: open extraction + vein patch or venous/arterial bypass graft; Others: arteriotomy + closed (dissection and traction) + bypass graft	LAD, RCA, OM, Cx, PD	V, A	ON
Sirivella *et al.* [23] (Cohort-R)	7396	1478	65 ± 4	67 ± 9	71	72	–	6, 7, 8, 9, 10, 11, 12, 13	C, E, G	b, e	Closed extraction (traction) + bypass graft; open extraction + SV patch + bypass graft or ITA patch graft to LAD	LAD, RCA, OM, D, Cx PD, PL	SV, ITA, RA	ON, OFF
Tasdemir *et al.* [24] (Cohort-R)	130	61	54.7 ± 11.8	53.6 ± 13.7	87	89	–	–	–	i, e	Open extraction + ITA onlay patch graft or SV onlay patch graft or SV patch or ITA graft	LAD	SV, ITA	ON
Tiruvoipati *et al.* [25] (Cohort-R)	5321	461	63.5 ± 9.2	62.9 ± 9.1	80	85	–	3, 8, 9, 14, 15	C, E, H	e	–	LAD, RCA, D, Cx	SV, ITA	ON
Walter *et al.* [26] (Cohort-R)	100	100	56	54	92	94	21	–	E, N	–	Closed extraction (spatula dissection and traction); open extraction + SV bypass or SV onlay graft	LAD, RCA, D, OM	SV	ON

Matching criteria and preoperative characteristics: 1, age; 2, Society of Thoracic Surgeons predicted risk of mortality; 3, gender; 4, year of surgery; 5, ejection fraction; 6, hypertension; 7, diabetes mellitus; 8, previous myocardial infarction; 9, peripheral vascular disease; 10, renal impairment; 11, three-vessel coronary disease; 12, left main stenosis; 13, Parsonnet score; 14, hyperlipidaemia; 15, statin use; 16, number of diseased coronary vessels; 17, left ventricular function; 18, angina class; 19, angina type; 20, NYHA class; 21, angiographic extent of diffuse disease; 22, low ejection fraction(<30%); 23, proximal left anterior descending artery stenosis; 24, reduced left ventricular function; 25, left ventricular dyssynergy; 26, pulmonary capillary wedge pressure; 27, location and severity of stenosis; 28, number of grafts; 29, smoking; 30, previous coronary artery bypass graft surgery; 31, preoperative characteristics are not compared.

Inclusion criteria: A, severe calcification or disease; B, total occlusion (r = right, l = left); C, diffuse coronary artery disease; D, vessel diameter <2 mm; E, diseased vessel supplying viable or potentially viable myocardium; F, conventional CABG not possible; G, major arteries and branches >1.5 mm in external diameter; H, adequately sized distal vessel; I, angiographic evidence of dominant right coronary occlusion with diffuse lesion; J, vessel supplying muscle with reversible ischaemia; K, multiple stenosis extending distally or significant narrowing of distal lumen; L, conventional CABG only possible to distal vessel <1.5 mm in diameter; M, distal bypass prejudicing perfusion to proximal side branches; N, three-vessel diffuse coronary artery disease; O, technical problems, e.g. plaque separation, calcified plaque at the site of arteriotomy or brittle character of coronary artery; P, normal posterior descending or posterolateral branches; Q, partial occlusion of the lumen; R, posterior descending or posterolateral branches of RCA too small or too diseased for bypass support.

Exclusion criteria: a, left ventricular ejection fraction <30%; b, non-viable myocardium; c, re-do CABG; d, concomitant valve surgery; e, concomitant procedure e.g. left ventricular aneurysmectomy or valve replacement; f, CABG without using cardiopulmonary bypass; g, no exclusion; h, non-dominant right coronary artery; i, additional endarterectomies or reconstructions of arteries other than left anterior descending; j, age >75 years.

Cohort-R: retrospective cohort study; Cohort-P: prospective cohort study; RCA: right coronary artery; LAD: left anterior descending artery; OM: obtuse marginal; D: diagonal; Cx: circumflex; PD: posterior descending; PL: posterolateral; I: intermediate; SV: saphenous vein; ITA: internal thoracic artery; RA: radial artery; V: vein; A: artery; CPB: cardiopulmonary bypass; ON: on-pump; OFF: off-pump; CABG: coronary artery bypass grafting; CE: coronary endarterectomy.

Table 2: Anticoagulant and antiplatelet therapy of included studies

Study references	Antiplatelet/anticoagulant therapy
Abid *et al.* [13]	Aspirin 75 mg and clopidogrel 150 mg 2 h postoperatively (If drainage <100 ml/h) followed by aspirin 75 mg and clopidogrel 75 mg OD for 3 months. Aspirin continued for life. 5000 IU unfractionated heparin 8-hourly postoperatively.
Akchurin *et al.* [27]	Hepatin (SC) started 6 h postoperatively and continued with warfarin or acenocoumarol (INR = 2–3) for 3–6 months and then switched to aspirin 100–125 mg daily in 71 patients in CE group. Remaining patients in CE group and 100 patients in CABG group only received aspirin 100–125 mg daily from first postoperative day
Asimakopoulos *et al.* [7]	Warfarin (INR = 2) and aspirin 75–150 mg OD for 3 months. After 3 months, warfarin stopped and aspirin continued indefinitely
Christakis *et al.* [1]	IV dipyridamole intra and postoperatively
Demirtas *et al.* [28]	Heparin (IV) started 2–3 days postoperatively continued with warfarin for a duration of 6 months in CE group
Erdil *et al.* [15]	Warfarin and ticlodipin 250 mg BD following extubation. Ticlodipin stopped at second postoperative month. Warfarin replaced with aspirin 300 mg at the end of sixth postoperative month
Gale *et al.* [16]	–
Huysmans *et al.* [17]	–
Jonjev *et al.* [29]	Antiplatelet and anticoagulant therapy administered under a special protocol—not stated
Kamath *et al.* [18]	–
LaPar *et al.* [11]	Aspirin and clopidogrel for a minimum of 3 months in CE group
Larock *et al.* [19]	–
Livesay *et al.* [2]	Aspirin and dipyridamole postoperatively.
Miller *et al.* [20]	Antiplatelets (e.g. sulfinpyrazone 200 mg QDS) for 2–3 months postoperatively
Shapira *et al.* [21]	Antiplatelets started 6 h postop
Silberman *et al.* [22]	Antiplatelets
Sirivella *et al.* [23]	–
Tasdemir *et al.* [24]	Dipyridamole 75 mg TDS and acetylsalicylic acid OD postoperatively
Tiruvoipati *et al.* [25]	–
Walter *et al.* [26]	–

CE: coronary endarterectomy; INR: international normalized ratio; CABG: coronary artery bypass grafting; OD: once daily; BD: twice daily; QDS: four times daily; IV: intravenous; SC: subcutaneous.

Visual inspection of funnel plots did not reveal any significant outliers (using 95% CIs) for any of our primary or secondary outcomes. Begg and Mazumdar's test and Egger's test similarly did not demonstrate any significant small study effects for any of the outcomes reported.

Pre- and intraoperative characteristics

Overall, pooled analysis revealed no significant difference in age, ejection fraction, obesity, smoking, diabetes mellitus, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, renal failure, heart failure and family history of coronary heart disease between CE and CABG groups. However, CE patients were more likely to have atheroma involving three or more vessels (OR = 2.06, 95% CI [1.82–2.33], P <0.00001) and concomitant peripheral vascular disease (OR = 1.80, 95% CI [1.34–2.42], P = 0.0001).

As expected, endarterectomy was associated with a significant increase in CPB and cross-clamp time (OR = 15.63, 95% CI [11.29–19.96], P <0.00001 and OR = 11.94, 95% CI [0.49–23.39], P = 0.04, respectively); however, the number of grafts per patient was not significantly different between the two groups (P = 0.83).

The overall results of for both primary and secondary end-points are shown in Table 4.

Primary end-points

Thirty-day mortality was significantly higher after endarterectomy when compared with patients undergoing CABG only (20 studies; OR = 1.69, 95% CI [1.49–1.92], P <0.00001), without significant heterogeneity (χ^2 = 11.09, I^2 <0.01%, P = 0.92; Fig. 3A).

The incidence of both peri- and postoperative MI was also significantly higher in the endarterectomy group (OR = 2.10, 95% CI [1.82–2.43], P <0.00001 and OR = 3.34, 95% CI [1.74–6.41], P = 0.0003, respectively), although significant heterogeneity was present for the postoperative MI outcome (χ^2 = 43.56, I^2 = 79%, P <0.00001) (Fig. 3B and C).

Secondary end-points

CE was associated with a significantly increased incidence of ventricular arrhythmias (OR = 1.64, 95% CI [1.01–2.65], P = 0.04), pulmonary complications (OR = 1.42, 95% CI [1.31–1.54], P <0.00001), postoperative renal failure (OR = 1.41, 95% CI [1.09–1.83], P = 0.009), inotrope use (OR = 1.61, 95% CI [1.28–2.03], P <0.0001) and blood transfusion (WMD = 4.27 95% CI [3.85–4.69], P <0.00001) when compared with CABG-only procedures, without significant heterogeneity (Table 4).

Endarterectomy also significantly increased ITU (WMD = 0.91, 95% CI [0.36–1.45], P = 0.001) and hospital stay (WMD = 1.15, 95% CI [0.58–1.72], P <0.0001) when compared with CABG only, although significant heterogeneity was present (χ^2 = 124.91, I^2 = 97%, P <0.00001; χ^2 = 30.16, I^2 = 87%, P <0.00001, respectively). Furthermore, angiographic patency at follow-up was significantly worse in the CE group compared with the CABG-only group (OR = 0.57, 95% CI [0.36–0.88], P = 0.01), without heterogeneity (Table 4).

Subgroup analysis

Full results of subgroup analysis are shown in Table 5.

Table 3: Modified Newcastle–Ottawa score of included studies

Study references	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7	Total
Abid *et al.* [13]	0	0	0	0	0	*	*	**2**
Akchurin *et al.* [27]	0	0	*	**	*	*	*	**6**
Asimakopoulos *et al.* [7]	*	*	*	**	*	*	*	**8**
Christakis *et al.* [1]	*	*	*	**	***	0	*	**9**
Demirtas *et al.* [28]	*	*	*	0	*	0	*	**5**
Erdil *et al.* [15]	*	*	0	***	*	0	*	**7**
Gale *et al.* [16]	*	*	*	0	*	0	0	**4**
Huysmans *et al.* [17]	*	*	*	0	0	0	*	**4**
Jonjev *et al.* [29]	0	*	*	0	0	0	*	**3**
Kamath *et al.* [18]	*	*	0	0	0	*	*	**4**
LaPar *et al.* [11]	*	*	*	*****	*	*	*	**11**
Larock *et al.* [19]	*	0	0	0	*	0	*	**3**
Livesay *et al.* [2]	*	*	*	**	*	*	*	**8**
Miller *et al.* [20]	*	*	*	***	***	*	*	**11**
Shapira *et al.* [21]	*	*	*	***	*****	*	*	**13**
Silberman *et al.* [22]	*	*	*	**	**	0	0	**7**
Sirivella *et al.* [23]	*	*	*	***	***	*	*	**11**
Tasdemir *et al.* [24]	*	*	*	***	**	0	*	**9**
Tiruvoipati *et al.* [25]	*	*	*	***	**	0	0	**8**
Walter *et al.* [26]	*	*	*	*****	*	*	*	**11**

* Denotes one point awarded according to the Newcastle Ottawa Scoring System outlined in supplementary table 1.

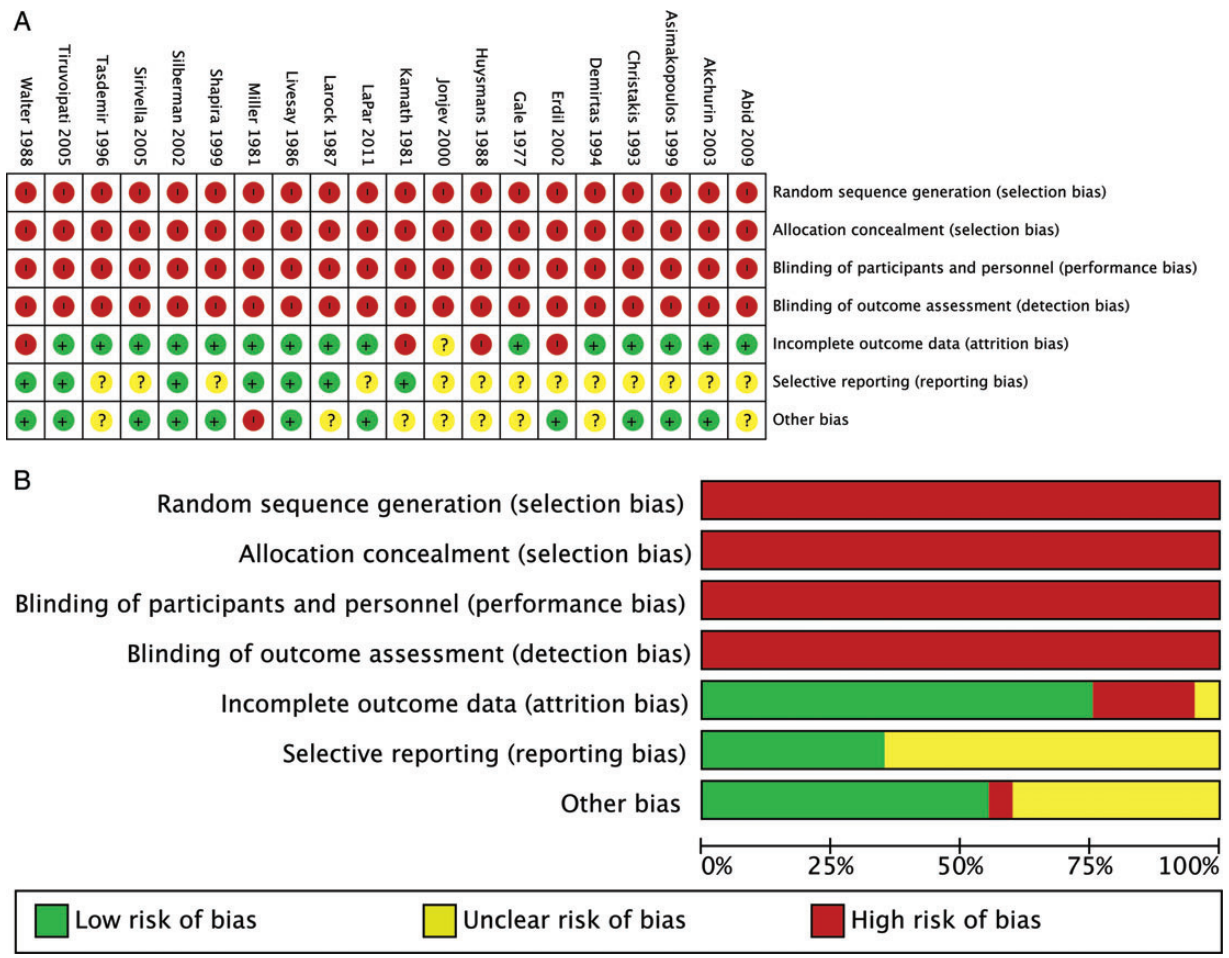


Figure 2: Risk of bias analysis. (**A**) Risk of bias summary: the authors 'judgements about each risk-of-bias item for the included studies. (**B**) Risk-of-bias graph: the authors' judgements about each risk-of-bias item presented as percentages across all included studies.

Table 4: Results of primary and secondary end-points (all studies)

Outcome	Subgroup	*n*			Overall effect		Heterogeneity		
		Studies	Study	Control	Mean difference	OR (95% CI)	*P*	χ^2	I^2 (%)	*P*
Incidence of 30-day mortality	Overall	20	7366	47 074	–	1.69 (1.49–1.92)	<0.00001	11.09	<0.01	0.92
Incidence of perioperative MI	Overall	11	4518	30 810	–	2.10 (1.82–2.43)	<0.00001	9.69	<0.01	0.47
Incidence of postoperative MI	Overall	10	2703	16 374	–	3.34 (1.74–6.41)	0.0003	43.56	79	<0.00001
Incidence of ventricular arrhythmias	Overall	5	626	5477	–	1.64 (1.01–2.65)	0.04	0.49	<0.01	0.92
Incidence of pulmonary complications	Overall	4	5098	35 348	–	1.42 (1.31–1.54)	<0.00001	0.88	<0.01	0.83
Incidence of postoperative renal failure	Overall	4	2094	13 070	–	1.41 (1.09–1.83)	0.009	1.14	<0.01	0.77
Incidence of inotrope use	Overall	3	1688	8203	–	1.61 (1.28–2.03)	<0.0001	2.39	16	0.3
Number of blood units transfused	Overall	2	1629	8153	4.27	–(3.85–4.69)	<0.00001	0.62	<0.01	0.43
Length of ICU stay	Overall	5	1837	8550	0.91	–(0.36–1.45)	0.001	124.91	97	<0.00001
Length of hospital stay	Overall	5	1837	8550	1.15	–(0.58–1.72)	<0.0001	30.16	87	<0.00001
Angiographic patency at last follow-up	Overall	5	215	410	–	0.57 (0.36–0.88)	0.01	1.88	<0.01	0.76

MI: myocardial infarction; CI: confidence interval; ICU: intensive care unit; OR: odds ratio.

Studies published on or after the year 2000. Thirty-day mortality remained significantly greater in endarterectomy patients compared with CABG only (eight studies, OR = 1.77, 95% CI [1.43–2.18], *P* <0.00001) without significant heterogeneity. Similarly, postoperative MI remained higher in CE patients (five studies, OR = 2.08 95% CI [1.06–4.08], *P* = 0.03), although this remained heterogeneous (I^2 = 82%). No significant difference in the incidence of perioperative MI was seen between CE and CABG groups (OR = 1.53, 95% CI [0.53–4.44], *P* = 0.43), without significant heterogeneity (I^2 <0.01), although only three studies were included in this subgroup [11, 15, 27].

Larger (n ≥100) and high-quality studies. CE was associated with a significantly greater 30-day mortality (*P* <0.00001), perioperative (*P* = 0.0009) and postoperative (*P* = 0.03) MI when only larger studies (*n* ≥100) were analysed; however, heterogeneity remained for the postoperative MI outcome (Table 5). The same effect was observed when only high-quality studies (quality score ≥8) were analysed; however, heterogeneity was no longer found to be present for the postoperative MI outcome.

Of interest, subgroup analysis of larger studies (*n* ≥100) also demonstrated significantly increased ITU and hospital stay with endarterectomy procedures (*P* <0.00001), while removing previous heterogeneity for both outcomes (Table 5).

Analysis of studies using matched groups or propensity score matching. Only three studies performed matched analysis of CABG and CABG + CE groups [7, 11, 19]. Analysis of these three studies as a separate subgroup was only possible for 30-day mortality and postoperative MI outcomes, given the limited data available. There was a tendency towards increased postoperative MI in the CE group although this did not reach statistical significance (OR = 4.99, 95% CI [0.80–31.24], *P* = 0.09) and moderate heterogeneity was present (I^2 = 56%, χ^2 = 4.58, *P* = 0.10). No significant difference in 30-day mortality was observed in subgroup analysis of matched studies (OR = 2.46, 95% CI [0.75–8.06], *P* = 0.14), without significant heterogeneity (I^2 <0.01%, χ^2 = 1.85, *P* = 0.40). Notably, however, the study by Larock *et al.* included in this subgroup was performed in 1987 and has a particularly low-quality score. Exclusion of this study from the matched subgroup results in similar findings to our overall analysis, including a significantly higher postoperative MI in the CABG + CE group (OR = 2.02, 95% CI [1.09–3.75], *P* = 0.03) without significant heterogeneity (I^2 <0.01%, χ^2 = 0.77, *P* = 0.38), and a trend towards increased 30-day mortality (OR = 3.38, 95% CI [0.94–12.10], *P* = 0.06), again without significant heterogeneity (I^2 <0.01%, χ^2 = 0.09, *P* = 0.76).

DISCUSSION

Over the past three decades, there has been a re-emergence of CE. However, the incidence of CE performed in combination with CABG varies from 3.7 to 42%, reflecting a lack of consistency for its indications [25]. Despite the higher operative risk associated with CE, good long-term results have supported its selective use in diffuse coronary artery disease where the distal vessel is unsuitable for CABG alone [2, 31]. In this study, we evaluated the safety and efficacy of CE, focusing on its short-term morbidity, mortality and long-term coronary vessel patency.

Our results quantitatively demonstrated an increase in the incidence of postoperative MI and 30-day mortality following integration of CE with CABG. These results remained significant in subgroup analyses of studies published on or after the year 2000, larger studies (*n* ≥100) and those with quality scores ≥8.

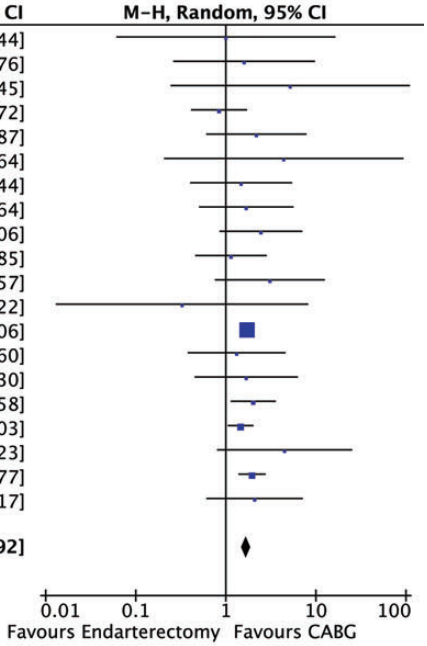
An increase in the incidence of MI after endarterectomy is supported by a number of larger studies [31–34]. However, although reports in recent years suggest comparable morbidity and mortality rates after CE combined with CABG [11], this meta-analysis reveals that the procedure continues to significantly increase both morbidity and mortality associated with myocardial revascularization, supporting long-standing concerns over the risk associated with the procedure.

Despite improvements in surgical techniques, CE causes mechanical trauma to the coronary vessel, leading to a loss of endothelial integrity and function [35, 36]. Furthermore, the procedure

A

Study or Subgroup	Endarterectomy+CABG Events	Total	CABG Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Abid 2009	1	50	1	50	0.2%	1.00 [0.06, 16.44]
Akchurin 2003	3	97	2	102	0.5%	1.60 [0.26, 9.76]
Asimakopoulos 1999	2	56	0	56	0.2%	5.18 [0.24, 110.45]
Christakis 1993	10	317	34	911	3.2%	0.84 [0.41, 1.72]
Demirtas 1994	3	37	16	412	1.0%	2.18 [0.61, 7.87]
Erdil 2002	2	59	0	50	0.2%	4.39 [0.21, 93.64]
Gale 1977	3	49	12	284	1.0%	1.48 [0.40, 5.44]
Huysmans 1988	4	250	8	837	1.1%	1.68 [0.50, 5.64]
Jonjev 2000	12	251	5	249	1.5%	2.45 [0.85, 7.06]
Kamath 1981	7	122	16	316	2.0%	1.14 [0.46, 2.85]
LaPar 2011	4	99	4	297	0.8%	3.08 [0.76, 12.57]
Larock 1987	0	48	1	48	0.2%	0.33 [0.01, 8.22]
Livesay 1986	148	3369	705	27095	50.6%	1.72 [1.44, 2.06]
Miller 1981	3	80	17	592	1.1%	1.32 [0.38, 4.60]
Shapira 1999	3	151	9	757	1.0%	1.68 [0.45, 6.30]
Silberman 2002	15	231	69	2071	5.0%	2.01 [1.13, 3.58]
Sirivella 2005	47	1478	163	7396	15.3%	1.46 [1.05, 2.03]
Tasdemir 1996	4	61	2	130	0.6%	4.49 [0.80, 25.23]
Tiruvoipati 2005	40	461	247	5321	13.6%	1.95 [1.38, 2.77]
Walter 1988	8	100	4	100	1.1%	2.09 [0.61, 7.17]
Total (95% CI)		**7366**		**47074**	**100.0%**	**1.69 [1.49, 1.92]**
Total events	319		1315			

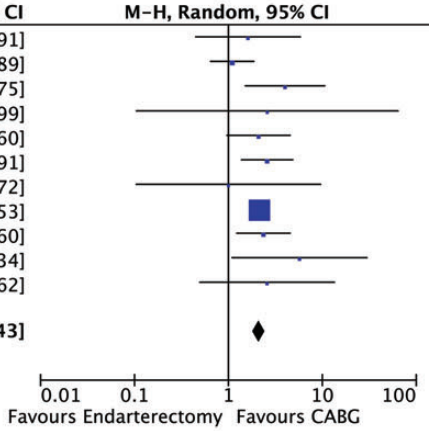
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.09$, df = 19 (P = 0.92); $I^2 = 0\%$
Test for overall effect: Z = 8.01 (P < 0.00001)



B

Study or Subgroup	Endarterectomy+CABG Events	Total	CABG Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Akchurin 2003	6	97	4	102	1.2%	1.62 [0.44, 5.91]
Christakis 1993	19	317	50	911	7.0%	1.10 [0.64, 1.89]
Demirtas 1994	6	37	19	412	2.1%	4.00 [1.49, 10.75]
Erdil 2002	1	59	0	50	0.2%	2.59 [0.10, 64.99]
Gale 1977	10	49	31	284	3.3%	2.09 [0.95, 4.60]
Huysmans 1988	17	250	23	837	5.0%	2.58 [1.36, 4.91]
LaPar 2011	1	99	3	297	0.4%	1.00 [0.10, 9.72]
Livesay 1986	182	3369	705	27095	74.5%	2.14 [1.81, 2.53]
Miller 1981	13	80	45	592	4.7%	2.36 [1.21, 4.60]
Tasdemir 1996	5	61	2	130	0.7%	5.71 [1.08, 30.34]
Walter 1988	5	100	2	100	0.8%	2.58 [0.49, 13.62]
Total (95% CI)		**4518**		**30810**	**100.0%**	**2.10 [1.82, 2.43]**
Total events	265		884			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.69$, df = 10 (P = 0.47); $I^2 = 0\%$
Test for overall effect: Z = 10.09 (P < 0.00001)



C

Study or Subgroup	Endarterectomy+CABG Events	Total	CABG Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Abid 2009	2	50	1	50	5.1%	2.04 [0.18, 23.27]
Asimakopoulos 1999	3	56	0	56	3.7%	7.39 [0.37, 146.52]
Demirtas 1994	8	29	5	278	10.9%	20.80 [6.25, 69.22]
LaPar 2011	18	99	31	297	14.9%	1.91 [1.01, 3.59]
Larock 1987	11	48	0	48	4.0%	29.75 [1.70, 521.15]
Shapira 1999	5	151	9	757	11.6%	2.85 [0.94, 8.62]
Silberman 2002	23	231	43	2071	15.6%	5.22 [3.08, 8.83]
Sirivella 2005	62	1478	252	7396	16.8%	1.24 [0.93, 1.65]
Tiruvoipati 2005	7	461	53	5321	13.8%	1.53 [0.69, 3.39]
Walter 1988	2	100	0	100	3.6%	5.10 [0.24, 107.62]
Total (95% CI)		**2703**		**16374**	**100.0%**	**3.34 [1.74, 6.41]**
Total events	141		394			

Heterogeneity: $Tau^2 = 0.64$; $Chi^2 = 43.56$, df = 9 (P < 0.00001); $I^2 = 79\%$
Test for overall effect: Z = 3.63 (P = 0.0003)

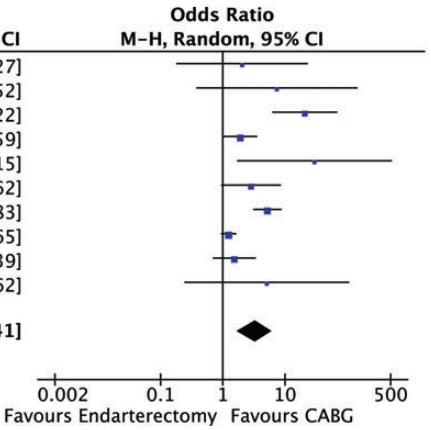


Figure 3: Forest plots showing comparative (**A**) 30-day mortality; (**B**) perioperative myocardial infarction and (**C**) postoperative myocardial infarction between adjunct CE and CABG alone. CE: coronary endarterectomy; CABG: coronary artery bypass grafting; 95% CI: 95% confidence interval.

Table 5: Results of subgroup analyses

Outcome	Subgroup	*n*			Overall effect				Heterogeneity		
		Studies	Study	Controls	WMD	OR	OR (95% CI)	*P*	χ^2	I^2 (%)	*P*
30-day mortality	≥year 2000	8	2726	15 536		1.77	(1.43–2.18)	<0.00001	3.31	<0.01	0.86
	n ≥100	10	6730	45 053		1.68	(1.47–1.91)	<0.00001	6.77	<0.01	0.66
	Quality score ≥8	10	6172	42 655		1.68	(1.47–1.93)	<0.00001	7.84	<0.01	0.55
	Matched studies	3	203	401		2.46	(0.75–8.06)	0.14	1.85	<0.01	0.40
Perioperative MI	≥year 2000	3	255	449		1.53	(0.53–4.44)	0.79	0.24	<0.01	0.89
	n ≥100	4	4036	28 943		1.89	(1.30–2.76)	0.0009	5.88	49	0.12
	Quality score ≥8	9	4026	29 125		1.92	(1.37–2.70)	0.0002	7.39	32	0.19
Postoperative MI	≥year 2000	5	2319	15 135		2.08	(1.06–4.08)	0.03	22.63	82	0.0002
	n ≥100	5	2421	15 645		2.37	(1.08–5.19)	0.03	23.8	83	<0.0001
	Quality score ≥8	6	2345	13 927		1.44	(1.12–1.86)	0.004	5.1	2	0.4
	Matched studies	3	203	401		4.99	(0.80–31.24)	0.09	4.58	56	0.10
Ventricular arrhythmias	≥year 2000	3	570	5421		1.62	(0.99–2.65)	0.05	0.46	<0.01	0.8
	Quality score ≥8	3	517	5377		1.51	(0.87–2.61)	0.14	0.06	<0.01	0.8
Pulmonary complications	*n* ≥100	4	5098	35 348		1.42	(1.31–1.54)	<0.00001	0.88	<0.01	0.83
	Quality score ≥8	4	5098	35 348		1.42	(1.31–1.54)	<0.00001	0.88	<0.01	0.83
Postoperative renal failure	≥year 2000	3	2038	13 014		1.43	(1.10–1.85)	0.007	0.34	<0.01	0.84
	n ≥100	2	1939	12 717		1.41	(1.08–1.85)	1.41	0.24	0.62	0
	Quality score ≥8	4	2189	13 771		1.19	(0.25–5.71)	0.82	378.92	99	<0.00001
Inotrope use	≥year 2000	2	1537	7446		1.50	(1.29–1.74)	<0.00001	0.01	<0.01	0.92
	n ≥100	2	1629	8153		1.71	(1.17–2.50)	0.005	2.37	58	0.12
	Quality score ≥8	2	1629	8153		1.71	(1.17–2.50)	0.005	2.37	58	0.12
Number of blood units transfused	*n* ≥100	2	1629	8153	4.27		(3.85–4.69)	<0.00001	0.62	<0.01	0.43
	Quality score ≥8	2	1629	8153	4.27		(3.85–4.69)	<0.00001	0.62	<0.01	0.43
Length of ICU stay	≥year 2000	4	1686	7793	0.75		(0.15–1.35)	0.01	120.43	98	<0.00001
	n ≥100	2	1629	8153	1.61		(1.41–1.80)	<0.00001	0.08	<0.01	0.77
	Quality score ≥8	3	1728	8450	1.42		(0.99–1.85)	<0.00001	21.47	91	<0.0001
Length of hospital stay	≥year 2000	4	1686	7793	1.15		(0.50–1.80)	0.0005	30.15	90	<0.00001
	n ≥100	2	1629	8153	1.64		(1.30–1.98)	<0.00001	0.85	<0.01	0.36
	Quality score ≥8	3	1728	8450	1.43		(1.12–1.73)	<0.00001	4.21	52	0.12
Angiographic patency at last follow-up	*n* ≥100	2	106	222		0.56	(0.31–0.99)	0.05	0.71	<0.01	0.4
	Quality score ≥8	3	100	241		0.57	(0.29–1.09)	0.09	1.00	<0.01	0.61

OR: odds ratio; WMD: weighted mean difference; CI: confidence interval; MI: myocardial infarction; ICU: intensive care unit.

itself can result in atheroemboli and even produce intimal tears within the coronary vessel [33]. As such, CE is associated with an increased tendency to *de novo* thrombogenesis and embolization from dislodged atheromatous material, which can result in MI and subsequent mortality. Furthermore, CE of the LAD is thought to confer higher morbidity and mortality when compared with other vessels [2, 7, 22, 33], potentially as a result of atheroembolization into multiple septal branches. However, these results are conflicted by other studies [25, 37] and independent analysis of this subgroup was not possible because of insufficient data and combined reporting of outcomes for both left and right coronary systems.

Preventative measures for reducing perioperative MI have included initial coronary reperfusion with cardioplegia solution and suction of debris through the arteriotomy [19, 21, 24, 26]; however, the uptake of such techniques is not universal and their effectiveness is unknown. Routine use of antiplatelet agents or other anticoagulants could further reduce postoperative MI by counteracting the increased tendency to thrombogenesis within endarterectomized vessels. However, our results highlight the lack of uniformity in anticoagulant administration and, as such, the need for a more standardized management protocol.

In the early postoperative period, the results of this meta-analysis also demonstrated significantly worse morbidity in terms of ventricular arrhythmias, pulmonary complications, renal failure, inotrope use and blood transfusion requirements. Furthermore, this translates into an increased ITU and hospital stay in patients undergoing CE. This is in part likely to be a result of a greater preoperative atherosclerotic burden in CE patients affecting coronary, peripheral and renal vasculature. Furthermore, the increased complexity of the CE procedure and consequent longer aortic cross-clamp, cardioplegia and bypass time could lead to prolonged renal hypoperfusion and increased postoperative clotting dysfunction.

In the long term, this study also highlights potentially lower patency rates of grafts observed with adjunct CE when compared with CABG alone. Graft patency can be influenced by several factors, including the type of conduit, intraoperative graft flow, flow in the endarterectomized vessel, diameters of reconstructed artery and distal native artery, previous MI in the territory of endarterectomized vessel and the use of antithrombotic therapy [19, 23, 24, 33, 38]. However, denudation of the coronary endothelium by endarterectomy promotes thrombogenesis and releases a cascade of inflammatory mediators, including homocystiene, interleukin-1β and matrix metalloproteinases [39]. This process not only produces oxidative stress leading to prolonged consumption of endogenous antioxidants [40], but also increases nitric oxide (NO) synthease inhibitor production, thus reducing NO availability [39, 40]. In this way, CE might not only result in increased vascular smooth muscle cell proliferation and gradual reocclusion of the endarterectomized vessel, but also create

systemic oxidative stress, which in turn might influence late luminal patency of other coronary grafts.

Strengths and limitations

This meta-analysis incorporated a total of 54 440 patients, which would be difficult to accumulate prospectively. However, a number of limitations should be considered. Firstly, all 20 studies included in this review were observational; only 2 of which were prospective [14, 21]. One study was a retrospective review of prospective data taken from a randomized controlled trial of off- versus on-pump CPB [13]. Ten of the 20 studies were determined to be of low-quality according to a modified Newcastle–Ottawa scale, with no studies adequately reporting or performing randomization, allocation concealment or blinding. Given that all studies were small and none were randomized controlled trials, it is possible that small study effects might have biased our results despite our attempts to assess this using funnel plot analysis, Egger and Begg and Mazumdar's tests. In addition, only three studies adequately matched CABG and CABG + CE groups, leading to potential selection bias.

Secondly, patients undergoing CE were significantly more likely to have atheroma involving three or more vessels (P <0.00001) and were exposed to a significantly longer CPB time (P <0.00001). Furthermore, the use of both off- and on-pump techniques combined with a mixture of arterial and venous conduits adds several unquantifiable confounders, particularly when assessing long-term patency. Thirdly, although higher postoperative mortality has previously been associated with CE of LAD over other coronary vessels, is it was not possible to separate this subgroup from the overall outcome data. Furthermore, only 12 studies reported their postoperative anticoagulation strategies, which varied from dual antiplatelet to lifelong warfarin therapy. Finally, patency rate at follow-up was mostly based on angiographic studies conducted in only symptomatic patients, potentially leading to an overestimation of long-term patency as a result of both attrition and reporting bias.

CONCLUSION

This meta-analysis suggests that adjunctive CE significantly increases 30-day mortality and peri- and postoperative MI following CABG. Furthermore, our findings demonstrated the procedure to be associated with significantly higher postoperative morbidity and lower long-term graft patency. However, it should be noted that, although these studies represent a large cohort of procedures carried out over a long time period, there remains a lack of prospective evidence, and a wide range of confounding factors might influence these results, including CE technique, location of endarterectomized vessel, the use of CPB and variations in postoperative anticoagulation. To better determine whether CE should still remain a viable adjunct to CABG, novel studies should focus on collecting prospective data with standardized inclusion criteria for CE as well as isolating outcomes for different coronary vessels, and standardizing postoperative anticoagulation regimens.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

ACKNOWLEDGEMENTS

We would like to thank Ranka Primorac and Vadzim Chalau for their invaluable help in translating the foreign language studies included in this meta-analysis.

Conflict of interest: none declared.

REFERENCES

[1] Christakis GT, Ivanov J, Weisel RD, Birnbaum PL, David TE, Salerno TA. The changing pattern of coronary artery bypass surgery. Circulation 1989;80: I151–161.
[2] Livesay JJ, Cooley DA, Hallman GL, Reul GJ, Ott DA, Duncan JM *et al*. Early and late results of coronary endarterectomy. Analysis of 3,369 patients. J Thorac Cardiovasc Surg 1986;92:649–60.
[3] Dilley RB, Cannon JA, Kattus AA, MacAlpin RN, Longmire WPJ. The treatment of coronary occlusive disease by endarterectomy. J Thorac Cardiovasc Surg 1965;50:511–26.
[4] Dumanian V. Endarterectomy of the branches of the left coronary artery in combination with an aorta-to-coronary artery reversed saphenous vein graft. J Cardiovasc Surg 1974;15:154–7.
[5] Groves LK, Loop FD, Silver GM. Endarterectomy as a supplement to coronary artery-saphenous vein bypass surgery. J Thorac Cardiovasc Surg 1972; 64:514–22.
[6] Klie JH, Johnson L, Smulyan H, Potts JL, Obeid AI, Fruehan CT *et al*. Gas endarterectomy of right coronary artery; the importance of proximal bypass graft. Circulation 1974;49:63–7.
[7] Asimakopoulos G, Taylor KM, Ratnatunga CP. Outcome of coronary endarterectomy: a case-control study. Ann Thorac Surg 1999;67:989–93.
[8] Schmitto JD, Kolat P, Ortmann P, Popov AF, Coskun KO, Friedrich M *et al*. Early results of coronary artery bypass grafting with coronary endarterectomy for severe coronary artery disease. J Cardiothorac Surg 2009;4:52.
[9] Beretta L, Lemma M, Vanelli P, DiMattia D, Bozzi G, Broso P *et al*. Coronary "open" endarterectomy and reconstruction: short- and long-term results of the revascularization with saphenous vein versus IMA-graft. Eur J Cardiothorac Surg 1992;6:382–6; discussion 387.
[10] Tyska AL, de Carvalho Cabral MM, Hayashi EK, Nogueira GA, Machado MB, de Castro Machado LM *et al*. Coronary endarterectomy: technique and results in a case-control study. Rev Bras Cir Cardiovasc 2003;18:45–52.
[11] LaPar DJ, Anvari F, Irvine JNJ, Kern JA, Swenson BR, Kron IL *et al*. The impact of coronary artery endarterectomy on outcomes during coronary artery bypass grafting. J Card Surg 2011;26:247–53.
[12] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9, W264.
[13] Abid AR, Farogh A, Naqshband MS, Akhtar RP, Khan JS. Hospital outcome of coronary artery bypass grafting and coronary endarterectomy. Asian Cardiovasc Thorac Ann 2009;17:59–63.
[14] Christakis GT, Rao V, Fremes SE, Chen E, Naylor CD, Goldman BS. Does coronary endarterectomy adversely affect the results of bypass surgery? J Card Surg 1993;8:72–8.
[15] Erdil N, Cetin L, Kucuker S, Demirkilic U, Sener E, Tatar H. Closed endarterectomy for diffuse right coronary artery disease: early results with angiographic controls. J Card Surg 2002;17:261–6.
[16] Gale AW, Chang VP, Shanahan MX, Windsor HM. Right coronary endarterectomy: a procedure with increased risk of perioperative infarction. Aust N Z J Surg 1977;47:515–8.
[17] Huysmans HA, Aytug Z, Buis B, Verwey H. Treatment of peripheral coronary artery disease by endarterectomy. Adv Cardiol 1988;36:13–8.
[18] Kamath ML, Schmidt DH, Pedraza PM, Blau FM, Sampathkumar A, Grzelak LL *et al*. Patency and flow response in endarterectomized coronary arteries. Ann Thorac Surg 1981;31:28–35.
[19] Larock MP, Burguet W, Grenade T, Trotteur G, Magotteaux P, Limet R *et al*. Usefulness of thromboendarterectomy in association with coronary artery bypass grafting. Am J Cardiol 1987;60:1025–9.
[20] Miller DC, Stinson EB, Oyer PE, Reitz BA, Jamieson SW, Moreno-Cabral RJ *et al*. Long-term clinical assessment of the efficacy of adjunctive coronary endarterectomy. J Thorac Cardiovasc Surg 1981;81:21–9.
[21] Shapira OM, Akopian G, Hussain A, Adelstein M, Lazar HL, Aldea GS *et al*. Improved clinical outcomes in patients undergoing coronary

artery bypass grafting with coronary endarterectomy. Ann Thorac Surg 1999;68:2273–8.
[22] Silberman S, Dzigivker I, Merin O, Shapira N, Deeb M, Bitran D. Does coronary endarterectomy increase the risk of coronary bypass? J Card Surg 2002;17:267–71.
[23] Sirivella S, Gielchinsky I, Parsonnet V. Results of coronary artery endarterectomy and coronary artery bypass grafting for diffuse coronary artery disease. Ann Thorac Surg 2005;80:1738–44.
[24] Tasdemir O, Kiziltepe U, Karagoz HY, Yamak B, Korkmaz S, Bayazit K. Long-term results of reconstructions of the left anterior descending coronary artery in diffuse atherosclerotic lesions. J Thorac Cardiovasc Surg 1996;112:745–54.
[25] Tiruvoipati R, Loubani M, Lencioni M, Ghosh S, Jones PW, Patel RL. Coronary endarterectomy: impact on morbidity and mortality when combined with coronary artery bypass surgery. Ann Thorac Surg 2005;79: 1999–2003.
[26] Walter PJ, Armbruster M, Amsel BJ, Scheld HH. Endarterectomy in patients with diffuse coronary artery disease. Adv Cardiol 1988;36:41–53.
[27] Akchurin RS, Brand Ia B, Barskova T. Assessment of efficacy of endarterectomy of coronary arteries. Khirurgiia 2003;10:21–4.
[28] Demirtas M, Tarcan S, Sungu U. Results of endarterectomy combined with angioplasty in aortocoronary bypass. Ann Cardiol Angeiol 1994;43: 526–31.
[29] Jonjev Z, Redzek A, Radovanovic N. Late results of myocardial revascularization in patients with coronary artery endarterectomy. Med Pregl 2000; 53:373–7.
[30] Shapira N, Lumia FJ, Gottdiener JS, Germon P, Lemole GM. Adjunct endarterectomy of the left anterior descending coronary artery. Ann Thorac Surg 1988;46:289–96.
[31] Sundt TM, Camillo CJ, Mendeloff EN, Barner HB, Gay WAJ. Reappraisal of coronary endarterectomy for the treatment of diffuse coronary artery disease. Ann Thorac Surg 1999;68:1272–7.
[32] Abrahamov D, Tamaris M, Guru V, Fremes S, Christakis G, Bhatnagar G *et al*. Clinical results of endarterectomy of the right and left anterior descending coronary arteries. J Card Surg 1999;14:16–25.
[33] Djalilian AR, Shumway SJ. Adjunctive coronary endarterectomy: improved safety in modern cardiac surgery. Ann Thorac Surg 1995;60: 1749–54.
[34] Marinelli G, Chiappini B, Di Eusanio M, Di Bartolomeo R, Caldarera I, Marrozzini C *et al*. Bypass grafting with coronary endarterectomy: immediate and long-term results. J Thorac Cardiovasc Surg 2002;124:553–60.
[35] Akgun S, Isbir CS, Yildirim T, Civelek A, Arsan S. Results of adjunctive coronary endarterectomy in 548 patients. Heart Surg Forum 2008;11: E66–70.
[36] Zamir AG, Iqbal A, Ahmad SA, Rashid A, Khan AA. Coronary endarterectomy for severe diffuse coronary artery disease. J Coll Physicians Surg Pak 2009;19:338–41.
[37] Brenowitz JB, Kayser KL, Johnson WD. Results of coronary artery endarterectomy and reconstruction. J Thorac Cardiovasc Surg 1988;95:1–10.
[38] Tabata M, Shekar PS, Couper GS, Aranki SF. Early and late outcomes of multiple coronary endarterectomy. J Card Surg 2008;23:697–700.
[39] Qureshi I, Chen H, Brown AT, Fitzgerald R, Zhang X, Breckenridge J *et al*. Homocysteine-induced vascular dysregulation is mediated by the NMDA receptor. Vasc Med 2005;10:215–23.
[40] Mezzetti A, Guglielmi MD, Pierdomenico SD, Costantini F, Cipollone F, De Cesare D *et al*. Increased systemic oxidative stress after elective endarterectomy: relation to vascular healing and remodeling. Arterioscler Thromb Vasc Biol 1999;19:2659–65.