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Short- and Long-Term Patient Outcomes From Combined Coronary Endarterectomy and Coronary Artery Bypass Grafting

A Meta-Analysis of 63,730 Patients (PRISMA)

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Abstract: This meta-analysis aimed to compare the short- and long-term outcomes in patients undergoing combined coronary endarterectomy and coronary artery bypass grafting (CE + CABG) versus isolated CABG, and particularly to examine subgroup patients with high-risk profile and patients with diffuse disease in the left anterior descending artery (LAD).

Studies published between January 1, 1970 and May 31, 2015 were searched in the literature databases, including Ovid Medline, Embase, PubMed, and ISI Web of Science.

A total of 30 eligible studies including 63,730 patients were analyzed.

Five authors extracted data from the included studies independently.

Meta-analysis on the total patients revealed that CE + CABG was associated with significantly increased 30-day postoperative all-cause mortality compared with isolated CABG (OR = 1.86, 95% CI: 1.66–2.08, z = 10.99, $P < 0.0001$). Subgroup analysis on patients with high-risk profile and patients with diffuse disease in the LAD showed that 30-day mortality after CE + CABG was 2.6 folds (OR = 2.60, 95% CI: 1.39–4.86, z = 2.99, $P = 0.003$) and 3.93 folds (OR = 3.93, 95% CI: 1.40–11.0, z = 2.60, $P = 0.009$) of that after isolated CABG in the respective subgroup. In contrast, the mortality was comparable in CE + off-pump CABG and CE + on-pump CABG groups (OR = 0.53, 95% CI: 0.18–1.55, z = 1.16, $P = 0.248$). In addition, the incidences of perioperative myocardial infarction (MI) and 30-day postoperative complications, including low output syndrome (LOS), MI, ventricular tachycardia (VT), and renal dysfunction after CE + CABG were significantly higher than those after isolated CABG (all $P < 0.05$). In high-risk patient subgroup, CE + CABG significantly increased the incidences of postoperative LOS, MI, and renal function compared with isolated CABG (all $P < 0.05$). The incidence of perioperative myocardial after CE + CABG was 2.86 and 2.92 times of that after isolated CABG in high-risk patients and patients with diffuse disease in LAD, respectively. Analysis on the recent reports (published later than 2000) showed consistent results as the analysis including all the eligible reports. Long-term survival was comparable in CE + CABG and isolated CABG groups (hazardous ratio = 1.16, 95% CI: 0.32–4.22, z = 0.23, $P = 0.819$).

CE + CABG appears to be associated with poor short-term outcomes, particularly in high-risk patients and patients with diffuse disease in the LAD.

Abbreviations: CABG = coronary artery bypass grafting, CAD = coronary artery disease, CE = coronary endarterectomy, CI = confidential interval, DCAD = diffuse coronary artery disease, HR = hazard ratio, LAD = left anterior descending artery, LOS = low output syndrome, MI = myocardial infarction, NS = not significance, OR = odds ratio, PCI = percutaneous coronary intervention, VA = ventricular arrhythmia.

INTRODUCTION

Coronary artery bypass grafting (CABG) is 1 of the most common surgical interventions for coronary revascularization.[1] However, it often fails to achieve satisfactory outcomes in patients with a high-risk profile, which is characterized by old age, severe left ventricular dysfunction, diffuse coronary artery disease (ie, at least 75% of the segment distal to the lesion has a vessel diameter of <2 mm),[2] comorbidities such as diabetes and peripheral vascular disease, and/or previous percutaneous coronary intervention (PCI).[3,4] Coronary endarterectomy (CE) combined with CABG (CE + CABG) had been commonly practiced in the past.[5] Theoretically, simultaneous removal of plaques in the target vessels to CABG can achieve complete revascularization, particularly for patients with diffuse coronary artery disease, who usually have limited available target vessels for CABG. However, in recent years, surgeons become increasingly cautious toward CE + CABG.[6] It has been reported that patients undergoing CE + CABG showed poorer 30-day postoperative outcomes than patients undergoing isolated CABG.[7,8] Soylu et al conducted a meta-analysis and found that CE + CABG increased early postoperative mortality and the incidence of perioperative myocardial infarction (MI).[5]

Comparison of 30-day postoperative outcomes from CE + CABG versus isolated CABG has been conducted on patients with unselected risk of coronary artery disease (CAD).[5] Patients undergoing CE usually have high-risk profile, such as having

diffuse coronary artery disease and poorer physical condition, compared with patients undergoing isolated CABG.[1] The patient preoperative clinical characteristics may not match in CE + CABG and isolated CABG groups in previous meta-analysis.[5] Thus, meta-analysis on patients with unselected risk might not accurately reveal the benefits or adverse effects of CE procedure because a poor outcomes from CE + CABG may be associated with poor patient preoperative clinical characteristics. Furthermore, the effect of CE + CABG on long-term survival is still unclear. This study aimed to compare the short- and long-term outcomes from CE + CABG versus isolated CABG, particularly in patients with high-risk profile and patients with diffuse disease in the left anterior descending artery (LAD).

METHODS

Guidelines and Data Collection

As this meta-analysis, as a systematic review, does not involve animal experiments or direct human trials, there is no need to conduct special ethic review and the ethical approval is not necessary. The design of this meta-analysis stringently followed the guidelines for Quality of Reporting of Meta-analysis.[8,9] We systematically searched Ovid Medline, Embase, PubMed, and ISI Web of Science for relevant studies published between January 1, 1970 and May 31, 2015. The search terms were "CABG," "endarterectomy," "left anterior descending," "high risk," "off-pump CABG," and "diffuse coronary artery disease." The reference lists of selected articles, conference proceedings, and personal files for relevant citations were also screened. Publication language was not restricted in the search.

Study Inclusion and Exclusion Criteria

Eligible studies met the following inclusion criteria: patients underwent CABG; CE + CABG group and isolated CABG group were compared; CE + off-pump CABG group and CE + on-pump CABG group were compared; short-term outcomes included 30-day postoperative mortality, low output syndrome (LOS), perioperative MI, postoperative renal dysfunction, postoperative MI, postoperative arrhythmia including atrial fibrillation (AF), and ventricular tachycardia (VT) were studies; long-term patient survival was investigated. The exclusion criteria were duplicate of previous publication; abstract, review, comment, and editorial; preclinical studies; missing original data; lack of isolated CABG as a control group; patients undergoing other procedures such as valve replacement and major vascular surgery in addition to CE and CABG.

Diffuse Coronary Artery Disease and High-Risk Definitions

According to the 2014 ESC/EACTS guidelines on myocardial revascularization, the definition of diffuse coronary artery disease in this study was that at least 75% of the segment distal to the lesion has a vessel diameter <2 mm.[2] The definition of high-risk patients in both CE + CABG and isolated CABG groups was that patients met 1 or more of the following criteria: ages ≥70 years; diffuse disease in at least 1 coronary artery; left main stem stenosis ≥70%; preoperative comorbidities such as diabetes, peripheral vascular disease, LOS, or MI; previous PCI or CABG; unstable angina (CCS class III and IV) or poor left ventricular function (LVEF ≤40%) as assessed by left ventriculography.

Data Extraction and Quality Assessment

Five reviewers (JW, WY, CG, MG, and YY) extracted the following data: details of the publication (first author's surname, trial acronym, enrollment period, and year of publication), patient inclusion and exclusion criteria, patient demographics, sample size in control and study groups, analyses on high-risk patients, patients with diffuse diseased in the LAD, comparison of CE + off pump CABG versus CE + on-pump CABG, and outcomes including 30-day postoperative mortality, LOS, AF, VT, and renal dysfunction, perioperative and postoperative MI, and long-term survival. When the 5 reviewers had different opinions toward some studies, the problematic studies were reviewed again and the disagreement was discussed openly until a consent was reached. Downs and Black score was used to evaluate the quality of each included study.[9] The checklist of Downs and Black score consists of 26 items distributed in 5 subscales: reporting (9 items), which estimates whether the information provided in the paper is sufficient to allow a reader to make an unbiased assessment of the findings of the study; external validity (3 items), which addresses the extent to which the findings from the study could be generalized to the population from which the study subjects were derived; bias (7 items), which addresses biases in the measurement of the intervention and the outcome; confounding (6 items), which addresses bias in the selection of study subjects; power (1 item), which attempts to assess whether the negative findings from a study could be due to chance. Except for 1 item in the reporting subscale, which was scored 0 to 2, and the single item in the power subscale, which was scored 0 to 5, all the answers to other items were scored 0 or 1. The total maximum score was therefore 31. Each reviewer scored the included studies separately, and an average score was calculated and used as the final Downs and Black score for the study. A score ≥20 represents satisfactory quality, and a score <20 represents poor quality. When the 5 reviewers have different opinions toward some studies, the problematic studies were reviewed again and the disagreement was discussed openly until a consent was reached.

Primary and Secondary Endpoints

The primary endpoint of this study was the odds ratio (OR) of 30-day postoperative all-cause mortality after CE + CABG versus isolated CABG (including subgroup analysis of 30-day mortality in high-risk patients and patients with diffuse disease in the LAD) and OR of 30-day mortality after CE + off-pump CABG versus CE + on-pump CABG. The secondary endpoints were hazard ratio (HR) of long-term survival after CE + CABG versus isolated CABG and the OR of the incidences of 30-day postoperative LOS, MI, AF, VT, renal dysfunction, and perioperative MI after CE + CABG versus isolated CABG. LOS was defined as a requirement of intra-aortic balloon pumping or infusion of norepinephrine, epinephrine, milrinone, or dobutamine after the first hour postoperatively to maintain systolic blood pressure ≥90 mm Hg. Postoperative or perioperative (as classified by the authors) MI was defined as creatine kinase–MB increase >80 µg/L or troponin T >3.0 µg/L the first 48 hr after surgery. The definition of 30-day postoperative MI was enzymatic elevation of creatine kinase–MB >10 µg/L or troponin T >0.1 µg/L together with at least 1 of the following findings: classic angina symptoms, electrocardiograph (ECG) signs of necrosis or ischemia, or coronary re-intervention. Postoperative AF was defined by the documentation of AF of any duration at any time during the postoperative period on a physician assessment, on the basis of a rhythm strip or 12-lead

electrocardiogram recording. Postoperative VT was defined as the uniform tachyarrhythmia of ventricular origin that had a duration of >20 sec after surgery, unless terminated earlier because of hemodynamic collapse. Renal dysfunction was defined as a need of acute hemodialysis, blood creatinine level ≥200 μg/L, or blood creatinine 2 times the preoperative value.

Data Analysis

The statistical analysis software Stata (version 13.1) was used for data analysis. P value was 2-sided and $P < 0.05$ was considered statistically significant. Study heterogeneity was evaluated by I^2 index. $I^2 = 25\%$ to 49%, 50% to 74%, and ≥75% was considered low, moderate, and high heterogeneity, respectively. $I^2 \geq 50\%$ was considered significantly heterogeneous. A fixed-effect model was used for meta-analysis without significant study heterogeneity. A random-effect model was used when significant heterogeneity was found in the included studies. ORs with 95% CI were reported. HR was used to assess data on time-to-event and survival. Parmar et al[10] introduced the standard approaches to extract data on time-to-event analyses. Publication bias was examined by Funnel plot and Egger's weighted regression. When the P value in the Egger's test was <0.05, the publication bias was consider significant.

RESULTS

Characteristics and Quality of the Included Studies

The flow chart for study screening is shown in Figure 1. A total of 2230 articles were retrieved by using the search terms; among them, 2192 records were excluded for the reasons listed in Figure 1. Full-text reports were obtained for 38 studies. Of the 38 reports, 5 lack control group; 3 contain overlapping data. Thus, a total of 30 observational studies, including 63,730 patients, were analyzed (Fig. 1 and Table 1).[1,6–8,11–36] Patient characteristics, endpoints in the included studies, sample size of both groups, and Downs and Black Score are presented in Table 1. Of the 30 eligible reports, 27 compared 30-day mortality after CE + CABG versus isolated CABG; 5 compared 30-day mortality after CE + off-pump CABG versus CE + on-pump CABG; 10 investigated high-risk patients undergoing CABG with or without CE (the patient preoperative clinical

characteristics were matched in CE + CABG and isolated CABG groups); 5 focused on patients with diffuse disease in the LAD undergoing CABG with or without CE (Table 1). The Downs and Black Score of the 30 articles was between 20 and 24 (Table 1), suggesting that the quality of all the 30 articles was satisfactory. Long-term survival data in the included studies, such as follow-up time, follow-up ratio, and survival, are presented in Table 2.
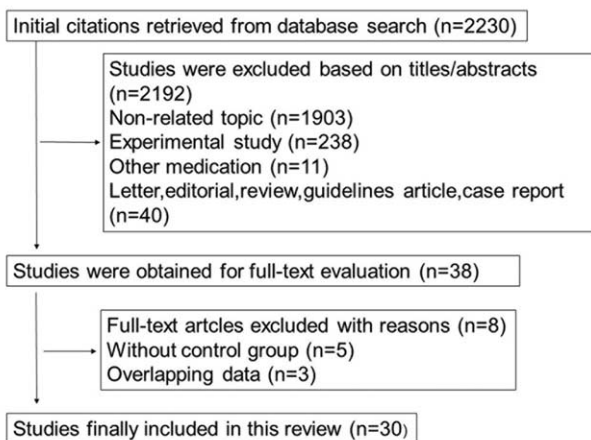
Primary Endpoints

Meta-analysis on patients with unselected risk of CAD demonstrated that CE + CABG was associated with significantly increased 30-day postoperative all-cause mortality compared with isolated CABG (OR = 1.86, 95% CI: 1.66–2.08, z = 10.99, $P < 0.0001$, Fig. 2) without study heterogeneity ($I^2 = 0.0\%$, $P = 0.555$). Meta-analysis including only the recent reports (published later than 2000) showed consistent results (OR = 1.82, 95% CI: 1.47–2.25, z = 5.57, $P < 0.0001$, Fig. 2) as the meta-analysis including all the eligible studies. Subgroup analysis on high-risk patients revealed similar results with even higher extent of increase in the mortality in CE + CABG group compared with isolated CABG group (OR = 2.60, 95% CI: 1.39–4.86, z = 2.99, $P = 0.003$, Fig. 3A) without study heterogeneity ($I^2 = 0.0\%$, $P = 0.924$), and consistent results were obtained from the meta-analysis including only the recent reports (OR = 3.10, 95% CI: 1.32–7.30, z = 2.59, $P = 0.009$, Fig. 3A). Subgroup analysis of patients with diffuse disease in the LAD showed that the mortality in LAD-CE + CABG group was 3.93 times of that in isolated CABG group (OR = 3.93, 95% CI: 1.40–11.00, z = 2.60, $P = 0.009$, Fig. 3B), and analysis on the recent reports revealed consistent results (OR = 3.66, 95% CI: 1.02–13.19, z = 1.99, $P = 0.047$, Fig. 3B). Sensitivity analysis found no significant impact of each individual study on the overall results. Neither funnel plot (Fig. 4) nor Egger's weighted regression showed significant publication bias ($P = 0.546$). Furthermore, patients undergoing CE + off-pump CABG and patients undergoing CE + on-pump CABG showed similar 30-day postoperative mortality (OR = 0.53, 95% CI: 0.18–1.55, z = 1.16, $P = 0.248$, Fig. 5).

Secondary Endpoints

In contrast to 30-day postoperative mortality, long-term survival was comparable in CE + CABG and isolated CABG groups (HR = 1.16, 95% CI: 0.32–4.22, z = 0.23, $P = 0.819$, Fig. 6). Analysis of the recent reports (published later than 2000) showed consistent results (HR = 1.47, 95% CI: 0.17–13.14, z = 0.35, $P = 0.728$, Fig. 6). The studies included for long-term survival analysis showed no study heterogeneity ($I^2 = 0.0\%$, $P = 0.999$) and no significant publication bias ($P = 0.057$).

Meta-analysis on the incidences of 30-day postoperative complications revealed that compared with patients undergoing isolated CABG, patients undergoing CE + CABG exhibited significantly higher incidences of perioperative MI and 30-day postoperative LOS, MI, VT, and renal dysfunction with various study heterogeneity (Table 3). The study heterogeneity was particularly high for postoperative MI (Table 3). The incidence of AF was similar in the 2 groups of patients (Table 3) without significant heterogeneity.

Subgroup analysis on high-risk patients revealed that the incidence of postoperative MI in CE + CABG group was 2.02 times of that in isolated CABG group (Table 3) without study heterogeneity. Thus, 1 of the sources of heterogeneity for postoperative MI in the analysis on all the patients was probably


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Initial citations retrieved from database search (n=2230)
        |
        |      Studies were excluded based on titles/abstracts
        |      (n=2192)
        |----> Non-related topic (n=1903)
        |      Experimental study (n=238)
        |      Other medication (n=11)
        |      Letter,editorial,review,guidelines article,case report
        |      (n=40)
        |
        v
Studies were obtained for full-text evaluation (n=38)
        |
        |      Full-text artcles excluded with reasons (n=8)
        |----> Without control group (n=5)
        |      Overlapping data (n=3)
        |
        v
Studies finally included in this review (n=30)
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FIGURE 1. Study selection flow chart.

TABLE 1. Characteristics of the Included Studies

Author	Year	Patient Characteristics	Reported Short-Term Complications	Reported Short-Term Mortality	Sample Size CE/Control	Downs and Black Score
Gale[11]	1977	(Unselected CAD) From November 1969 to March 1976, patients undergoing surgery at St Vincent's Hospital for CAD were included	Perioperative MI	CE + CABG vs isolated CABG	49/284	20
Kamath[12]	1981	(Unselected CAD) From May 1, 1978 to June 30, 1979, patients underwent revascularization for CAD at Mount Sinai Medical Center, Milwaukee	None	CE + CABG vs isolated CABG	121/316	23
Miller[13]	1981	(Unselected CAD) Patients underwent myocardial revascularization between 1971 and 1975	Perioperative MI	CE + CABG vs isolated CABG	80/592	20
Livesay[14]	1986	(Unselected CAD) Between 1970 and 1984, patients underwent surgical revascularization at the Texas Heart Institute	VA perioperative MI	CE + CABG vs isolated CABG	3369/27,095	22
Larrock[15]	1987	(High-risk patients) Forty-eight patients undergoing CE + CABG and 48 patients undergoing isolated CABG were included. Patient preoperative clinical characteristics were matched in the 2 groups. The following criteria were used for matching: location and severity of the lesion under study, presence or absence of previous AMI in the vessel area under study or elsewhere, number of coronary arteries significantly narrowed and number of grafts	None	CE + CABG vs isolated CABG	48/48	20
Walter[16]	1988	(High-risk patients) From 1981 to 1983, 100 consecutive patients with 3-vessel CAD undergoing CE + CABG and 100 patients undergoing isolated CABG were included. Patients in both groups had the same extent of diffuse 3-vessel disease, which was determined by angiography	AF VA Postoperative MI Renal dysfunction Perioperative MI	CE + CABG vs isolated CABG	100/100	21

Author	Year	Patient Characteristics	Reported Short-Term Complications	Reported Short-Term Mortality	Sample Size CE/Control	Downs and Black Score
Huysmans[17]	1988	(Unselected CAD) From 1972 to 1986, patients underwent surgical revascularization	None	CE + CABG vs isolated CABG	250/837	21
Brenowitz[18]	1988	(Unselected CAD) Since 1978, patients have had coronary artery bypass operations	None	CE + CABG vs isolated CABG	2501/2504	20
Christakis[19]	1993	(Unselected CAD) Between 1982 and 1989, consecutive patients undergoing CABG by 1 surgeon at the University of Toronto were studied	LOS	CE + CABG vs isolated CABG	317/911	22
Demirtas[20]	1994	(Unselected CAD) From January 1989 to April 1990, consecutive patients undergoing CABG were included	Perioperative MI Perioperative MI	CE + CABG vs isolated CABG	37/412	20
Christenson[21]	1995	(Unselected CAD) Between January 1990 and October 1994, patients undergoing CABG were included	Postoperative MI Postoperative MI	CE + CABG vs isolated CABG	106/2166	21
Tasdemir[22]	1996	(High-risk patients/LAD-DCAD patients) Between 1988 and 1992, 120 patients who had diffuse atherosclerotic lesions necessitating reconstruction of the LAD undergoing CABG with or without CE were included	LOS	CE + CABG vs isolated CABG	61/130	22
Shapira[23]	1999	(Unselected CAD) Patients undergoing isolated first-time CABG + CE at Boston Medical Center between July 1991 and July 1997 were compared with patients undergoing isolated CABG during the same period	Perioperative MI Postoperative MI	LAD-DCAD with CE vs LAD-DCAD without CE CE + CABG vs isolated CABG	151/757	21
Asimakopoulos[24]	1999	(Unselected CAD) Between January 1993 and August 1996, patients underwent isolated primary CABG in the Cardiothoracic Unit, Hammersmith Hospital, Imperial College School of Medicine	Renal dysfunction AF VA Postoperative MI Renal dysfunction	CE + CABG vs isolated CABG	56/56	22

Author	Year	Patient Characteristics	Reported Short-Term Complications	Reported Short-Term Mortality	Sample Size CE/Control	Downs and Black Score
Jonjev[25]	2000	(Unselected CAD) Patients were operated between January 1, 1985 and December 31, 1990 at the University Clinic of Cardiovascular Surgery, Novi Sad	None	CE + CABG vs isolated CABG	251/249	20
Silberman[7]	2002	(Unselected CAD) Between January 1993 and December 1999, patients underwent isolated CABG in Shaare Zedek Medical Center	Postoperative MI	CE + CABG vs isolated CABG	88/2071	20
Erdil[26]	2002	(High-risk patients) Between August 1998 and May 2000, 59 patients had right coronary artery endarterectomy along with RCA bypass with saphenous vein graft; 50 patients underwent RCA bypass without RCE	AF	CE + CABG vs isolated CABG	59/50	21
Naseri[35]	2003	(High-risk patients) From April 1, 1999 to March 1, 2001, patients underwent OPCAB + OPCE (group 1) or CCAB + CE (group 2) at Academic Hospital of Istanbul. Clinical characteristics, including age, sex, and risk factors, were matched in the 2 groups of patients	VA Perioperative MI None	OPCAB + CE vs CCAB + CE	44/44	20
Akchurin[27]	2003	(Unselected CAD) The study group consisted of 97 patients undergoing CABG + CE and 102 patients undergoing isolated CABG	Perioperative MI	CE + CABG vs isolated CABG	97/102	20
Fukui[1]	2005	(High-risk patients/LAD-DCAD patients) Between April 2001 and July 2004, 250 patients (29.4%) were treated utilizing a modified technique of extended LAD reconstruction, with or without endarterectomy in combination with conventional CABG	LOS	LAD-DCAD with CE vs LAD-DCAD without CE	67/183	23
Sirivella[6]	2005	(Unselected CAD) From 1985 to 2002, patients undergoing isolated coronary artery endarterectomy with CABG were included	VA Perioperative MI Renal dysfunction LOS	CE + CABG vs isolated CABG	1478/7396	20

Author	Year	Patient Characteristics	Reported Short-Term Complications	Reported Short-Term Mortality	Sample Size CE/Control	Downs and Black Score
		(High-risk patients) Endarterectomy (in 1748 patients) was performed in 2201 vessels, including 714 LAD, 140 diagonal branch, 60 distal branch of main CX, 244 obtuse marginal branch, 758 RCA, and 52 posterior descending coronary artery. In 52 patients, off-pump CABG was performed	Postoperative MI			
Tiruvoipati[8]	2005	(Unselected CAD) All the patients undergoing CABG between January 1995 and December 2001 were selected for the study	Renal dysfunction VA	OPCAB + CE vs CCAB + CE CE + CABG vs isolated CABG	461/5321	21
Hussain[36]	2008	(High-risk patients) Consecutive patients underwent CABG from January 2006 to March 2007 in a prospective randomized trial at the Department of Cardiac Surgery of Punjab Institute of Cardiology, Lahore	Postoperative MI Renal dysfunction None	CE + CABG vs isolated CABG	43/72	21
Abid[28]	2009	(High-risk patients) Between December 1, 2006 and November 30, 2007, patients with severe CAD undergoing CABG with or without CE were included	LOS AF VA	CE + CABG vs isolated CABG OPCAB + CE vs CCAB + CE	50/50	21
Fukui[32]	2011	(High-risk patients/LAD-DCAD patients) A total of 213 patients underwent extensive reconstruction of the diffusely diseased LAD using an ITA graft between September 2004 and July 2009. Endarterectomy was performed in 46.0% of the patients	Postoperative MI LOS	CE + CABG vs isolated CABG	98/115	24
Lapar[30]	2011	(High-risk patients) From 2003 to 2008, 99 patients undergoing CE + CABG and 297 undergoing isolated CABG were included. The patients in CE + CABG were propensity score matched to the patients in isolated CABG group at the ratio of 1:3 based upon clinical factors	Perioperative MI AF	LAD-DCAD with CE vs LAD-DCAD without CE CE + CABG vs isolated CABG	99/297	23

Author	Year	Patient Characteristics	Reported Short-Term Complications	Reported Short-Term Mortality	Sample Size CE/Control	Downs and Black Score
Kato[33]	2012	(High-risk patients/LAD-DCAD patients) Between March 1995 and March 2001, 112 patients (mean age 63 years) underwent long segmental LAD reconstruction (>2 cm) with or without CE using the LITA	Postoperative MI Renal dysfunction Perioperative MI LOS	OPCAB + CE vs CCAB + CE CE + CABG vs isolated CABG	37/75	23
Binsalamah[29]	2014	(High-risk patients/LAD-DCAD patients) Patients who underwent CABG from 2005 to 2011 at a tertiary care university teaching hospital by a single surgeon were retrospectively reviewed. Of the 480 patients, 58 patients (12%) had CE in the LAD in addition to CABG using the left internal mammary artery	Perioperative MI VA Postoperative MI	LAD-DCAD with CE vs LAD-DCAD without CE CE + CABG vs isolated CABG	58/58	22
Qiu[34]	2014	(High-risk patients) Between January 1999 and December 2013, 212 patients underwent myocardial revascularization with CE at Nanjing first hospital to achieve a complete revascularization	Renal dysfunction None	LAD-DCAD with CE vs LAD-DCAD without CE OPCAB + CE vs CCAB + CE	92/120	21
Nemati[31]	2015	(Unselected CAD) From May 2010 to December 2011, patients undergoing CABG with CE or without CE were included	None	CE + CABG vs isolated CABG	84/967	20

AF = atrial fibrillation, AMI = acute myocardial infarction, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CCAB = conventional coronary artery bypass grafting, CE = coronary endarterectomy, DCAD = diffuse coronary artery disease, ITA = internal thoracic artery, LITA = left internal thoracic artery, LOS = low output syndrome, MI = myocardial infarction, OPCAB = off-pump coronary artery bypass grafting, OPCE = off-pump coronary endarterectomy, RCA = right coronary artery, RCE = right coronary artery endarterectomy, VA = ventricular arrhythmia.

TABLE 2. Long-Term Results

Author (Year)	Long-Term Results
Miller[13] (1981)	The total cumulative follow-up was 2969 patient-years. The average follow-up (98% complete) time was 5.7 years for CE group and 4.7 years for control group. There was no significant difference between the survival rates of the CE and control groups. At postoperative 5.6 years, the actuarial survival rate was 87 ± 4% for CE group and 83 ± 2% for control group
Livesay[14] (1986)	Follow-up information was obtained on 23,467 patients (77% of late survivors). Actuarial analysis at 5 years and longer has shown very little difference in the long-term survival rate (isolate CABG: 90%; CE + CABG: 86%)
Walter[16] (1988)	A total of 12 patients undergoing CE and 5 control patients died. At postoperative 26 months, the actuarial survival rate was 88% for CE group and 95% for control group. The difference was not statistically significant
Tasdemir[22] (1996)	Follow-up was 98.2% in group I and 100% in group II. In total, 346.5 patient-years were in group I; 319.2 patient-years were in group II. The mean follow-up period was 6.3 years in group I and 5.7 years in group II. Actuarial survival for 7 years was 94 ± 5% in group I and 74.8 ± 16.0% in group II
Asimakopoulos[24] (1999)	The mean follow-up time was 21 months (range: 2–48 months), amounting to a total of 100.5 patient-years. There was no significant difference in the actuarial survival between the 2 groups
Fukui[1] (2005)	Follow-up was completed in 95.2% (238 of 250) of the patients. During a mean follow-up period of 21.2 ± 10.7 months (range: 1–45 months), there were 13 late deaths, including 3 cardiac-related death, 3 pneumonia-related deaths, 3 multisystem failure, 2 deaths of cancer, 1 traffic accident, and 1 cerebrovascular accident. The actuarial survival after LS-CABG was 92.0% at 45 months
Lapar[30] (2011)	After a mean follow-up of 27.7 ± 0.9 months (CE = 25.8 ± 1.7 months [n = 98/99], CABG alone = 28.4 ± 1.0 months [n = 295/297]), overall survival was equivalent among patients undergoing CE + CABG or CABG alone
Kato[33] (2012)	Of the hospital survivors, 10 patients were lost to follow-up, giving a follow-up rate of 90.9% (100 of 110 patients) with a mean follow-up time of 9.0 ± 3.1 years (range: 0.7–14.8 years). There were 28 late deaths, including 5 cardiac-related deaths (heart failure in 4 patients and arrhythmia in 1 patient). Overall survival rate including hospital deaths was 91% at 5 years and 74% at 10 years, and freedom from cardiac-related death was 95% at 5 years and 92% at 10 years

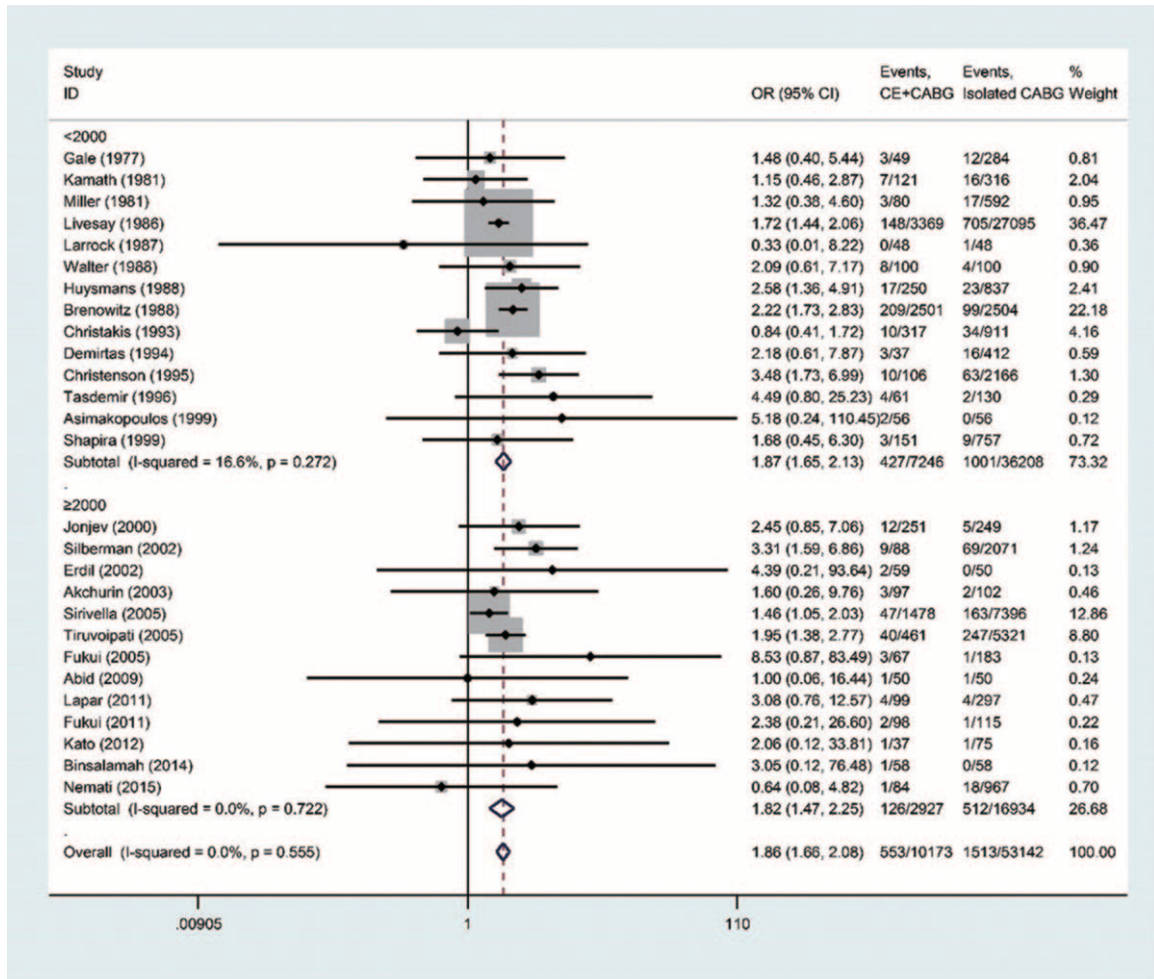CE = coronary endarterectomy, LS-CABG = long segmental coronary artery bypass grafting.
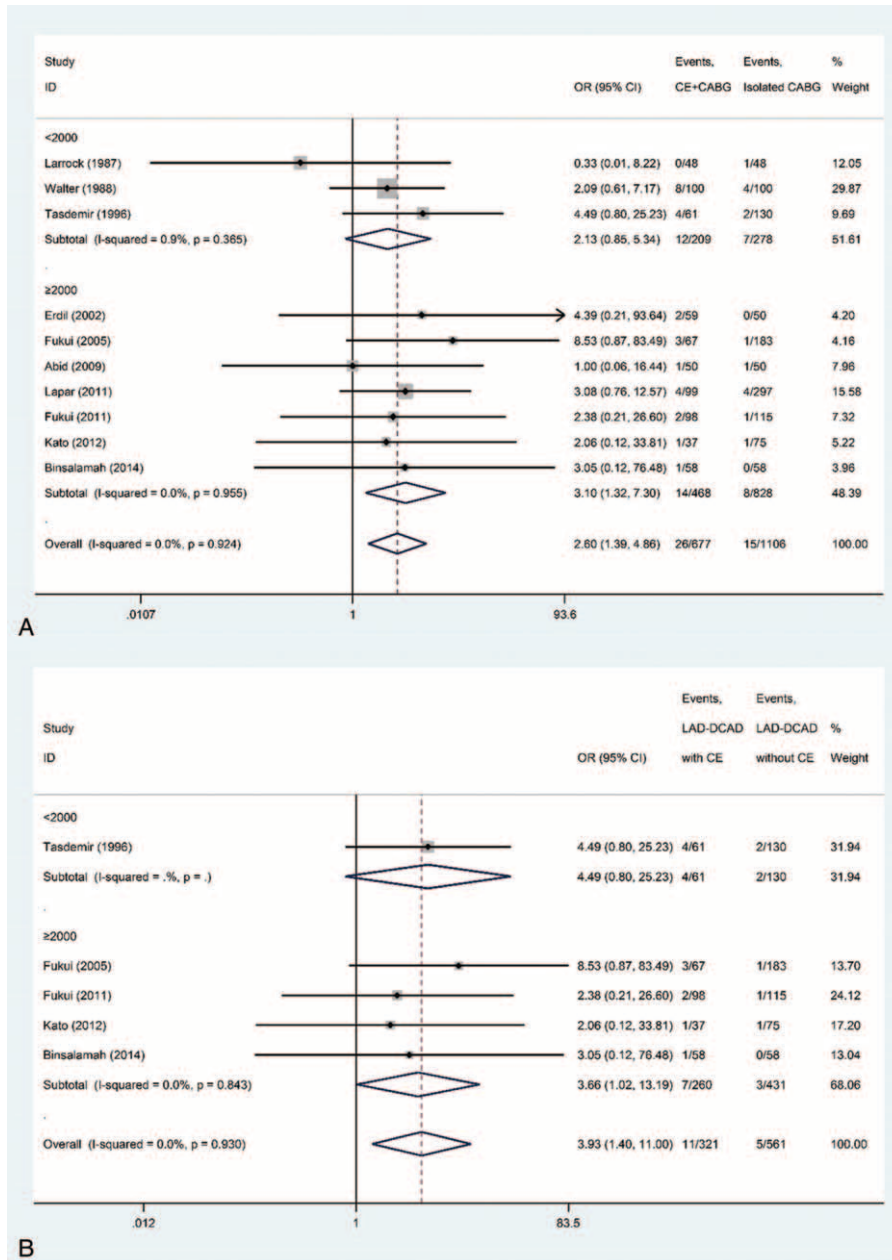
FIGURE 2. Analysis of 30-day mortality after CE + CABG versus isolated CABG. CABG = coronary artery bypass grafting, CE = coronary endarterectomy, CI = confidence interval, OR = odds ratio.

attributable to reports including patients with unselected risk of CAD. In addition, in the high-risk patient subgroup, the incidences of perioperative MI and 30-day postoperative renal dysfunction and LOS in CE + CABG group were significantly higher than those in isolated CABG group (Table 3). The incidence of 30-day postoperative VT was similar in the high-risk patients undergoing CE + CABG versus isolated CABG (Table 3). In the subgroup analysis of patients with diffuse disease in the LAD, the incidence of perioperative MI in LAD-CE +CABG group was 2.92 times of that in isolated CABG group (Table 3).

Meta-analysis on the recent studies (published later than 2000) showed that patients undergoing CE + CABG exhibited higher incidences of perioperative MI and 30-day postoperative LOS, MI, VT, and renal dysfunction compared with patients undergoing isolate CABG (Table 4). These results are consistent with the results from the analysis including all the eligible reports (Table 3). Subgroup analysis of high-risk patients demonstrated that the incidences of perioperative MI, 30-day postoperative LOS, and MI in CE + CABG group was 2.56, 2.32, and 1.95 folds of those in isolated CABG group, respectively, without significant heterogeneity (Table 4).

DISCUSSION

CE combined with CABG to achieve complete revascularization has been practiced for more than 40 years.[6,18] However, CE has been found to be associated with poor 30-day postoperative outcomes,[14,37] which seriously dampens the enthusiasm of cardiac surgeons toward this procedure.[6] Similar to previous reports,[5] this present study also showed that CE + CABG was associated with significantly increased 30-day postoperative all-cause mortality and higher incidences of postoperative LOS, MI, VT, and renal dysfunction. Meta-analysis only including the recent eligible reports (published later than 2000) showed consistent results as the meta-analysis including all the eligible studies. To rule out the possibility that the poor short-term outcomes after CE + CABG might be associated with the poor physical condition of patients in CE + CABG group,[8] in this study, we performed subgroup analysis on high-risk patients with matched preoperative clinical characteristics in CE + CABG and isolated CABG groups. We found that 30-day mortality and incidences of postoperative complications after CE + CABG were dramatically higher than those after isolated CABG in high-risk patients. Similar results were observed in the subgroup analysis of patients with diffuse disease in LAD. These results
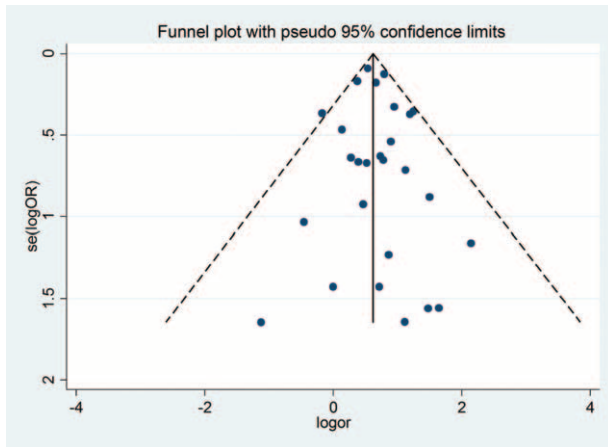
FIGURE 3. Subgroup analysis of 30-day postoperative mortality. (A) Subgroup analysis of 30-day mortality in high-risk patients. (B) Subgroup analysis of 30-day postoperative mortality in patients with diffuse disease in the LAD. CI = confidence interval, LAD = left anterior descending artery, OR = odds ratio.

indicate that CE procedure may result in poor short-term postoperative outcomes, particularly in patients with high-risk profile or with diffuse disease in the LAD.

The poor short-term postoperative outcomes in patients undergoing CE + CABG, particularly in high-risk patients, might result from endothelium damage during CE. Intact coronary endothelium can produce vasoactive factors to neutralize leukocyte adhesion and platelet aggregation, consequently reducing inflammation and thrombosis in blood vessels.[38] The damage caused by CE leads to endothelium dysfunction. Acute perioperative MI, a key complication associated with CE failure, might

be associated with thrombosis, which can be induced by removal of the endothelial lining during CE.[30] In addition, the time of cardiopulmonary bypass (CPB) during CE + CABG is usually longer than that during isolated on-pump CABG, consequently deteriorating CPB-induced ischemia-reperfusion injury (IRI) and leading to poor outcomes.[7] Endothelium damage and IRI reduce or inactivate vasoactive factors, consequently increasing neutrophil–endothelium adhesion, thrombosis, inflammation, and the incidences of postoperative complications.[39] Furthermore, MI caused by residual lesion-induced occlusion also contribute to the postoperative morbidity and mortality of CE.[40,41]

**FIGURE 4.** Funnel plot for the assessment of publication bias on 30-day postoperative all-cause mortality.

In this report, we also performed subgroup analysis on patients with diffuse disease in the LAD. The effects of LAD-CE + CABG on patient outcomes are still controversial. Byrne et al[42] showed that patients undergoing LAD-CE + CABG had low hospital mortality and morbidity. On the other hand, Silberman et al[7] suggested that patients with diffuse disease in the LAD might have a high risk for perioperative MI and death after CE. Our results also showed that LAD-CE + CABG dramatically increased 30-day postoperative mortality and incidence of 30-day postoperative complications compared with isolated CABG. The increased 30-day postoperative mortality associated with LAD-CE might result from residual

lesions in the LAD. Lawrie et al[40] investigated the independent influence of site of residual disease on late survival and found that residual lesions in the LAD artery or circumflex coronary arteries were significant predictors of survival, whereas residual lesions in the right coronary artery exerted a lesser effect. Our study also found that short-term postoperative mortality was similar in CE + off-pump CABG and CE + on-pump CABG groups. Similarly, Qiu et al[34] also showed that on-pump and off-pump CE appeared to have similar early and mid-term outcomes. Sirivella et al[6] reported that on-pump versus off-pump CE technique did not alter patient outcomes.

Although short-term outcomes from CE + CABG appeared to be poorer than those from isolated CABG, our findings demonstrated that long-term survival was comparable in CE + CABG and isolated CABG groups. Previous reports also demonstrated that long-term survival was similar in CE + CABG and CABG groups.[1,30] Since patients requiring CE + CABG usually have high-risk diffuse CAD,[1] a comparable survival in CE + CABG and isolated CABG groups may indicate the beneficial effects of complete revascularization of CE + CABG. However, long-term complications, such as MI, angina, heart failure, and cardiovascular mortality, are still unknown for patients undergoing CE + CABG. Soylu et al[5] showed that the angiographic patency at follow-up was worse in CE + CABG group. Moreover, in this present study, the meta-analysis to compare long-term survival between CE + CABG group and isolated CABG group was on patients with unselected risks, and a subgroup analysis in patients with high-risk profile was not feasible because of lacking sufficient eligible reports. Thus, whether CE procedure can exert long-term survival benefit in high-risk patients remain inconclusive and require further investigations.
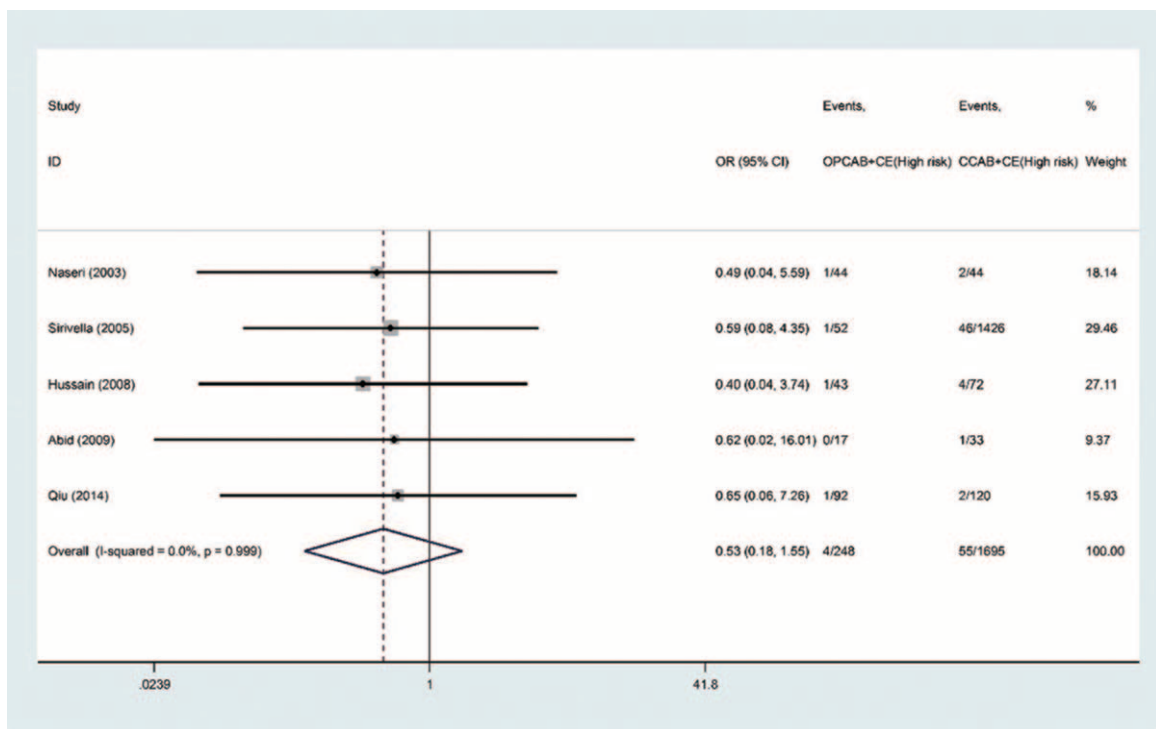
FIGURE 5. Analysis of 30-day mortality after CE + off-pump CABG versus CE + on-pump CABG. CABG = coronary artery bypass grafting, CE = coronary endarterectomy, CI = confidence interval, OR = odds ratio.
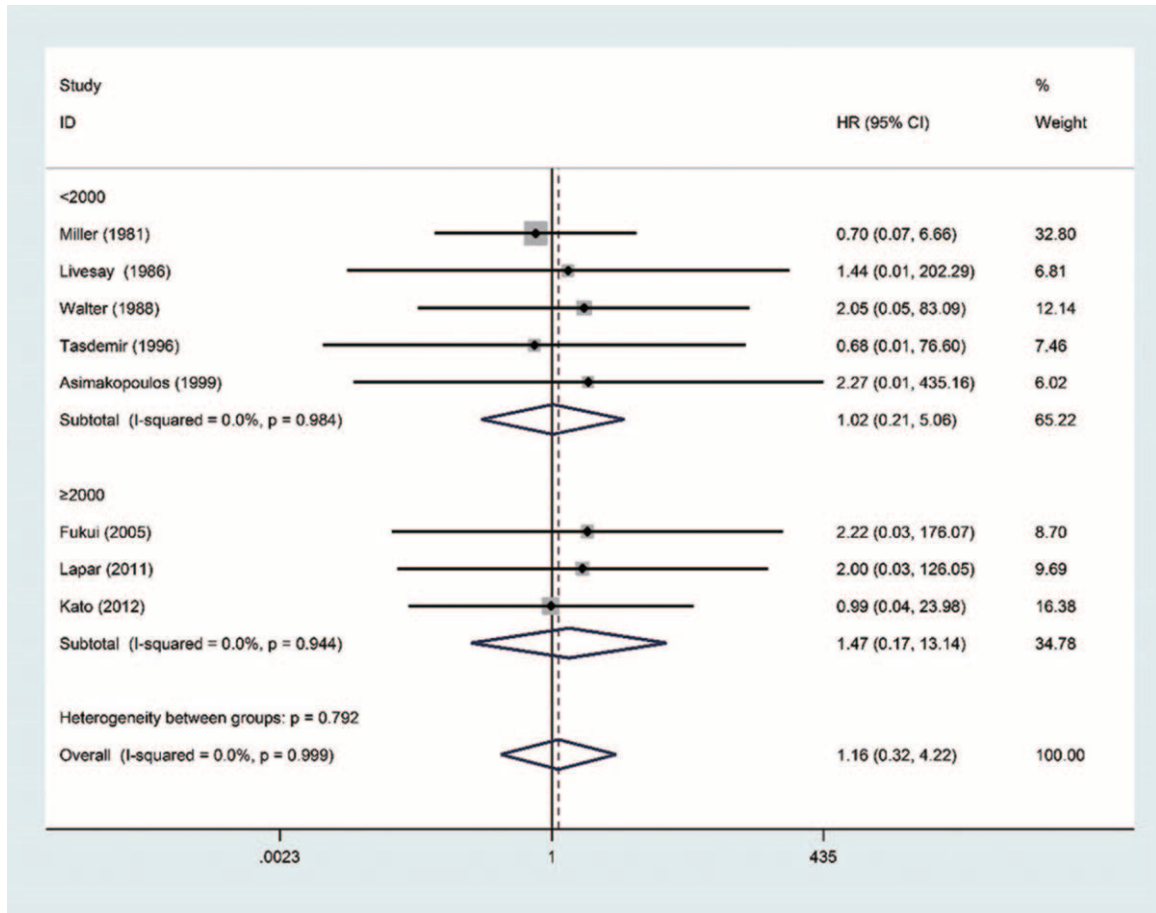
FIGURE 6. Analysis of long-term survival after CE + CABG compared with isolated CABG. CABG = coronary artery bypass grafting, CE = coronary endarterectomy, CI = confidence interval, HR = hazard ratio.

Surgeons should assess the benefits and adverse effects of CE adequately and optimize the surgical strategy to achieve satisfactory clinical outcomes. Guidelines for CE are currently not available. Fukui et al[1] recommended CE as the only revascularization method suitable for diffusely diseased vessels with either continuous calcified, soft, or hard fibrous plaques. It has been found that removal of the endothelial lining or residual obstruction caused postoperative morbidity and mortality after CE.[30,41] Our results also showed that in high-risk patients, the incidence of perioperative MI after CE + CABG was markedly higher than that after isolated CABG. Thus, we believe that unnecessary CE should be avoided. CE should be only used on patients who have diffuse CAD and whose CAD cannot be treated effectively by CABG alone. Because incomplete revascularization is 1 of the most critical factors influencing long-term mortality and morbidity,[40] to achieve complete revascularization, CE is recommended as an adjunct to CABG for this group of high-risk patients.[1,6] For patients who require CE, surgeons should maximally reduce the risk of postoperative complications, such as thrombosis, by using proper surgical techniques and aggressive postoperative anticoagulant and antiplatelet therapies.[5] Soylu et al[43] found that open-CE + CABG appeared to reduce 30-day mortality compared with closed-CE + CABG in patients with diffuse coronary artery disease. Tasdemir et al[22] suggested that compared with closed-CE, open-CE, in which the arterial lumen can be exposed, better facilitate a complete removal of plaques and avoid postoperative thrombotic occlusion. Nishi et al[44] reported that the incidences of postoperative MI, intra-aortic balloon pump use, and stroke were lower with open-CE than closed-CE. Thus, to achieve adequate revascularization in high-risk patients, surgeons should consider patient clinical presentation, extent and relevance of ischemia, and other comorbidities when optimizing a therapeutic strategy.[45]

To our best knowledge, this is the first meta-analysis focusing on high-risk patients to compare the short- and long-term outcomes from CE + CABG versus isolated CABG. In the subgroup analysis of high-risk patients, the preoperative clinical characteristics were matched in CE + CABG and isolated CABG groups. Thus, this current meta-analysis may accurately reveal the benefits (possible long-term survival benefit owing to a complete revascularization) or adverse effects (poor short-term outcomes) associated with CE procedure. Furthermore, this is also the first meta-analysis to confirm that CE + CABG is associated with dramatically higher 30-day postoperative mortality compared with isolated CABG in patients with diffuse disease in the LAD. The consistent results from the meta-analysis only including the recent eligible studies (published later than 2000) and from the meta-analysis including all the eligible studies suggest that evolution of

TABLE 3. Meta-Analysis on Short-Term Postoperative Complications Including All the Eligible Reports

Complications	Events CE + CABG	Events Isolated CABG	OR (95% CI)	z	P Value	Heterogeneity	Publication Bias/P Value of Egger's Test
LOS	103/2108	236/8857	1.45 (1.13, 1.86)	2.93	0.003	No, $I^2 = 0.0\%$, $P = 0.872$	No/0.082
Postoperative MI	126/2684	440/18,684	3.17 (1.75, 5.75)	3.79	<0.0001	High, $I^2 = 76.2\%$, $P < 0.0001$	No/0.059
Ventricular tachycardia	918/4199	6644/32,930	1.11 (1.02, 1.20)	2.54	0.011	NS, $I^2 = 2.4\%$, $P = 0.411$	No/0.184
Renal dysfunction	107/2667	460/14,365	1.50 (1.20, 1.88)	3.53	<0.0001	No, $I^2 = 0.0\%$, $P = 0.795$	No/0.800
Atrial fibrillation	46/364	62/553	1.31 (0.85, 2.01)	1.22	0.223	NS, $I^2 = 4.2\%$, $P = 0.383$	No/0.721
Perioperative MI	266/4470	875/30,346	2.07 (1.79, 2.40)	9.86	<0.0001	NS, $I^2 = 21.4\%$, $P = 0227$	No/0.905
Subgroup analysis of high-risk patients							
LOS	27/313	32/554	1.86 (1.06, 3.25)	2.17	0.030	No, $I^2 = 0.0\%$, $P = 0.867$	
Postoperative MI	23/307	32/505	2.02 (1.12, 3.64)	2.33	0.020	No, $I^2 = 0.0\%$, $P = 0.929$	
Ventricular tachycardia	32/313	31/458	1.08 (0.63, 1.84)	0.27	0.789	NS, $I^2 = 22.1\%$, $P = 0.274$	
Renal dysfunction	28/521	26/835	2.04 (1.15, 3.63)	2.43	0.015	No, $I^2 = 0.0\%$, $P = 0.648$	
Atrial fibrillation	39/308	55/497	1.37 (0.86, 2.18)	1.85	0.064	NS, $I^2 = 24.2\%$, $P = 0.266$	
Perioperative MI	29/422	18/653	2.86 (1.57, 5.21)	3.67	<0.0001	NS, $I^2 = 16.4\%$, $P = 0.308$	
Subgroup analysis of patients with diffuse disease in LAD							
LOS	25/263	32/504	1.76 (0.99, 3.12)	1.94	0.053	No, $I^2 = 0.0\%$, $P = 0.851$	
Perioperative MI	23/263	16/503	2.92 (1.53, 5.63)	3.21	0.001	NS, $I^2 = 49.3\%$, $P = 0.116$	

CABG = coronary artery bypass grafting, CE = coronary endarterectomy, CI = confidence interval, LAD = left anterior descending artery, LOS = low output syndrome, MI = myocardial infarction, NS = not significance, OR = odds ratio.

TABLE 4. Meta-Analysis on Short-Term Complications Including the Recent Reports (Published Later Than 2000)

Complications	Events, CE + CABG	Events, Isolated CABG	OR (95% CI)	z	P Value	Heterogeneity
LOS	40/1730	100/7816	1.68 (1.15, 2.46)	2.66	0.008	No, $I^2 = 0.0\%$, $P = 0.831$
Postoperative MI	101/2234	379/15,193	2.18 (1.13, 4.19)	2.33	0.020	High, $I^2 = 74.9\%$, $P = 0.001$
Ventricular tachycardia	31/674	119/5679	1.71 (1.08, 2.71)	2.27	0.023	No, $I^2 = 0.0\%$, $P = 0.946$
Renal dysfunction	85/2360	416/13,452	1.45 (1.14, 1.86)	2.97	0.003	No, $I^2 = 0.0\%$, $P = 0.845$
Perioperative MI	26/457	21/822	2.16 (1.20, 2.90)	2.56	0.010	NS, $I^2 = 23.4\%$, $P = 0261$
Subgroup analysis of high-risk patients						
LOS	13/252	11/424	2.32 (1.00, 5.34)	1.97	0.049	No, $I^2 = 0.0\%$, $P = 0.833$
Postoperative MI	21/207	32/405	1.95 (1.07, 3.55)	2.17	0.030	No, $I^2 = 0.0\%$, $P = 0.960$
Ventricular tachycardia	17/213	9/358	2.24 (0.95, 5.26)	1.85	0.064	No, $I^2 = 0.0\%$, $P = 0.991$
Renal dysfunction	18/421	23/735	1.72 (0.90, 3.31)	1.63	0.103	No, $I^2 = 0.0\%$, $P = 0.679$
Perioperative MI	19/261	14/423	2.56 (1.27, 5.61)	2.62	0.009	NS, $I^2 = 44.5\%$, $P = 0.145$

CABG = coronary artery bypass grafting, CE = coronary endarterectomy, CI = confidence interval, LAD = left anterior descending artery, LOS = low output syndrome, MI = myocardial infarction, NS = not significance, OR = odds ratio.

surgical technology and patient care appear not affect the study endpoints significantly, further confirm the poor short-term outcomes associated with CE + CABG.

The major limitation of this meta-analysis is that all the included studies are observational studies. In addition, 3 studies contributed almost 3 quarters of the data for evaluation of the primary endpoint, 30-day postoperative mortality. Randomized control trials to compare the short- and long-term outcomes from CE + CABG versus isolated CABG are still lacking. Thus, the limitations associated with observational studies, such as difficulties to draw causal inferences and the potential biased effects of confounding factors on study endpoints, cannot be avoided. In addition, most of the included observational studies are small-scale studies, and only 4 studies contain relatively large sample size (more than 1000 participants). Meta-analysis including high-quality prospective randomized control studies in addition to observational studies is required to further confirm the findings of this present study. Furthermore, because of limited data availability, only a few short-term postoperative complications including 30-day postoperative MI, AF, VT, and renal dysfunction were examined in this study. The effects of CE + CABG on other postoperative complications need to be investigated in future studies. Long-term outcomes in addition to survival, such as incidence of long-term MI and angina, should be also investigated in future. Last, in the subgroup analysis of patients with diffuse disease in the LAD, 3 of the 5 included articles were from the same group (Dr Takanashi's group). Thus, future large-scale studies are required to verify the conclusion.

CONCLUSIONS

In this study, we found that CE + CABG was associated with significantly increased 30-day postoperative mortality and higher incidences of short-term postoperative complications compared with isolated CABG, particularly in the subgroup patients with high-risk profile and patients with diffuse disease in the LAD. Although the comparable long-term survival in CE + CABG and isolated CABG groups may indicate beneficial effects of complete revascularization by CE + CABG on patients requiring CE, further investigations are required to

verify this conclusion. Thus, to achieve satisfactory efficacy, surgeons should carefully weigh possible benefits and adverse effects of CE and prepare the surgical strategy adequately.

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