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Comparison of bypass surgery and drug-eluting stenting in diabetic patients with left main and/or multivessel disease: A systematic review and meta-analysis of randomized and nonrandomized studies

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Abstract

Background: *With advances in theinterventional field, the choice between coronary artery bypass grafting (CABG) and percutaneous coronary intervention with drug-eluting stents (PCI-DES) for the diabetic subset with left main (LM) and/or multivessel disease (MVD) remains consistently controversial.*

Methods and results: *We conducted a systematic review of randomized controlled trials (RCTs) and observational controlled trials (OCTs) comparing the two strategies for the diabetic subset with LM and/or MVD. PubMed, EMBASE, CENTRAL databases, Google Scholar and SinoMed were systematically searched for eligible studies without language and publication restrictions. We identified 19 trials (4 randomized and 15 nonrandomized), enrolling 5,805 patients in OCTs and 3,060 patients in RCTs, respectively. PCI-DES was associated with higher mortality compared with CABG (11.7% DES vs. 9.1% CABG, RR 1.23, 95% CI 1.00–1.53, $p = 0.06$). Patients after PCI-DES had higher prevalence of myocardial infarction (MI) when compared with CABG (8.5% DES vs. 4.6% CABG, RR 1.68, 95% CI 1.20–2.37, $p = 0.003$). PCI-DES patients were at substantially lower risk of stroke (2.0% DES vs. 3.9% CABG, RR 0.51, 95% CI 0.39–0.67, $p < 0.00001$), but at several-fold higher risk of repeat revascularization (19.0% DES vs. 6.3% CABG, RR 2.95, 95% CI 2.46–3.55, $p < 0.00001$). The OCT patients risked a lower mortality as compared to the RCT patients (9.6% OCTs vs. 11.9% RCTs, RR 0.81, 95% CI 0.71–0.92, $p = 0.001$).*

Conclusions: *CABG for patients with diabetes mellitus and LM and/or MVD had advantages over PCI-DES in all-cause death, nonfatal MI, and repeat revascularization, but the substantial disadvantage in nonfatal stroke. The high-selected patients (RCTs) risked a higher mortality than the real-world patients (OCTs).* (Cardiol J 2015; 22, 2: 123–134)

Key words: coronary artery bypass grafting, multivessel disease, left main, diabetes mellitus, drug-eluting stents

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Introduction

Diabetes mellitus is a powerful, independent risk factor for cardiovascular disease and accounts for about 25% of all patients requiring myocardial revascularization [1, 2]. Patients with diabetes have more extensive and diffuse coronary artery disease (CAD) than nondiabetic patients [3, 4], and have higher mortality and morbidity after revascularization procedures, including myocardial infarction (MI), restenosis after balloon angioplasty [4–7], and bare-metal stenting [8]. Despite significant improvements in the CAD mortalities in the past decades, due to atherosclerosis resulting in MI, CAD remains the leading death death worldwide [5]. Coronary artery bypass grafting (CABG) was generally regarded as a preferred revascularization strategy for patients with left main (LM) and/or multivessel disease (MVD) [9]. However, the advances in the interventional field, especially the advent and development of drug-eluting stents (DES), which significantly reduced restenosis and the need for subsequent repeat revascularizations as compared with bare metal stents (BMS), have largely cut back one of the major limitations of percutaneous coronary interventions (PCI) [10–18]. Several randomized controlled trials (RCTs), exclusively comparing CABG surgery and PCI with DES (PCI-DES) for the diabetic subset with LM and/or MVD [19–22], have reported medium- and long--term outcomes, but given high-selected patients in the RCTs, their applicability to the general population is unknown. The observational controlled trial (OCTs), unlike the RCTs, can reflect daily clinical practice in the real world. We conducted a systematic review and meta-analysis of randomized and nonrandomized studies to establish clinical efficacy and safety of PCI-DES vs. CABG in patients with diabetes and LM and/or MVD both in the real world (OCTs) and in high-selected population (RCTs).

Methods

Search strategy

We systematically searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, Google Scholar and SinoMed for relevant studies reported from January 2002 (the year when the DESs were introduced to clinical practice) to December 2013, without language and publication restrictions. To achieve the maximum sensitivity of the search strategies and identify all trials comparing PCI-DES with CABG in diabetic subset, we appropriately used both free text and thesaurus terms, including: 'multivessel disease', 'left main', 'diabetes mellitus', 'percutaneous coronary intervention', 'drug-eluting stents', and 'coronary artery bypass'. We also performed a systematic search from reference lists of selected articles, conference proceedings, and personal files for relevant citations.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they met the following criteria: 1) RCT, OCT and pre-specified subgroup analyses comparing CABG with PCI-DES for diabetics with LM and/or MVD; 2) studies published in peer-reviewed journals with full available text; and 3) follow-up period ≥ 12 months. Studies were excluded if they met any of the following criteria: 1) the subjects were not exclusively diabetics with LM and/or MVD, 2) using only BMS or involving BMS with DES in 1 PCI subject, 3) duplicate publication, 4) less than 50 patients in each cohort.

Study selection

Two reviewers screened the citations and abstracts identified by the search strategies. Full text reviews were also conducted by 2 other reviewers to establish eligibility when screening reviewers believed that a citation potentially met the inclusion criteria. Disagreements regarding inclusion were resolved via consensus.

Data extraction

Three reviewers independently extracted data from the eligible studies. The following information were extracted from each study: first author, year of publication, duration of follow-up, number of participants in each group (CABG or PCI-DES), baseline characteristics, and outcome events including: all-cause mortality (the primary outcome), non-fatal MI, non-fatal stroke and repeat revascularization (Table 1). Each OCT was named by the family name plus the publication year (family name + year) respectively, and the RCT was presented as its own study name. For studies reported in > 1 publications, we extracted data from the most complete publication and used other publications as supplements. We also tried our best to contact the authors by email for information if their articles did not report the information in detail.

Statistical methods

Data were summarized using descriptive statistics. Discrete variables were presented as proportions (%, count/sample size) and compared

Table 1. Baseline characteristics of clinical studies.

Study or subgroup	Location or centers (n)	Subjects (n) (DES/CABG)	Design	Follow-up	Type of revascularization	Coronary lesion
Ben-Gal, 2006 [23]	Israel	86/86	OCT	18 months	DES/CABG	Single, multivessel and/or LM disease
Briguori, 2007 [24]	Italy	69/149	OCT	1 year	DES/OPCABG	MVD and critical stenosis involving proximal LAD
Contini, 2012 [25]	Italy	359/359	OCT	5 years	DES/CABG	MVD
Domínguez-Franco, 2008 [26]	Spain	128/142	OCT	24 months	DES/CABG	MVD (≥ 2 vessels with a > 70% *de novo* stenosis involving the proximal LAD)
Javaid, 2007 [27]	United States	344/257‡,	OCT	12 months	DES/CABG	MVD
Kim, 2009 [28]	12	251/256	OCT	3 years	SES, PES/ /CABG	Unprotected LMCAD (defined as stenosis ≥ 50%)
Lee, 2007 [29]	United States	102/103	OCT	1 year	DES/CABG	MVD
Luo, 2012 [30]	China	99/127	OCT	25.3 months	DES/CABG	Unprotected LMCAD (defined as stenosis ≥ 50%)
Moshkovitz, 2012 [31]	Israel	271/226	OCT	62 months	DES/BITA	MVD
Onuma, 2011 [32]	Netherlands	159 /96	OCT	5 years	SES/CABG	MVD
Park, 2011 [33, 34]	Korea	489/402	OCT§	5.6 years	DES/CABG	MVD
Qiao, 2009 [35]	China	363/282	OCT	12 months	DES/CABG	MVD
Tarantini, 2009 [36]	Italy	93/127	OCT	2 years	DES/CABG	MVD
Yamagata, 2010 [37]	Japan	92/116	OCT	42 months	SES/OPCAB	MVD
Zhao, 2011 [38]	China	56/116	OCT	28.5 months DES; 28.4 months CABG	DES/CABG	LMCAD
CARDia [22]	24	256/254	RCT	5.1 years	BMS, DES/ /CABG*	MVD or complex single-vessel CAD
FREEDOM [21]	140	953/947	RCT	3.8 years	SES, PES/ /CABG	MVD
SYNTAX [20]	85	231/221	RCT§	5 years	PES/CABG	LM (isolated or in addition to 1-, 2-, or 3-vessel disease) or isolated 3-vessel disease
VA CARDS [19]	22	101/97	RCT	2 years	DES/CABG	Severe CAD

OCT — observational controlled trial; RCT — randomized controlled trial; CABG — coronary artery bypass grafting; OPCABG — off-pump CABG; DES — drug-eluting stents; SES — sirolimus-eluting stent; PES — paclitaxel-eluting stents; LAD — left anterior descending artery; BITA — bilateral internal mammary artery; LM — left main disease; MVD — multivessel disease; CAD — coronary artery disease; ‡combining 2-vessel subgroups and 3-vessel subgroups; §pre-specified subgroup-analysis; *bare metal stents 31%, drug eluting stents 69%

by the χ^2 test or Fisher's exact test, where appropriate. Continuous variables were presented as mean ± standard deviation and compared using the Student's t-test. The verified data were analyzed using Revman software (version 5.2). The endpoints of each study were analyzed using risk ratio (RR) with 95% confidence interval (CI). The Cochrane χ^2 (Cochrane Q) test was used to assess

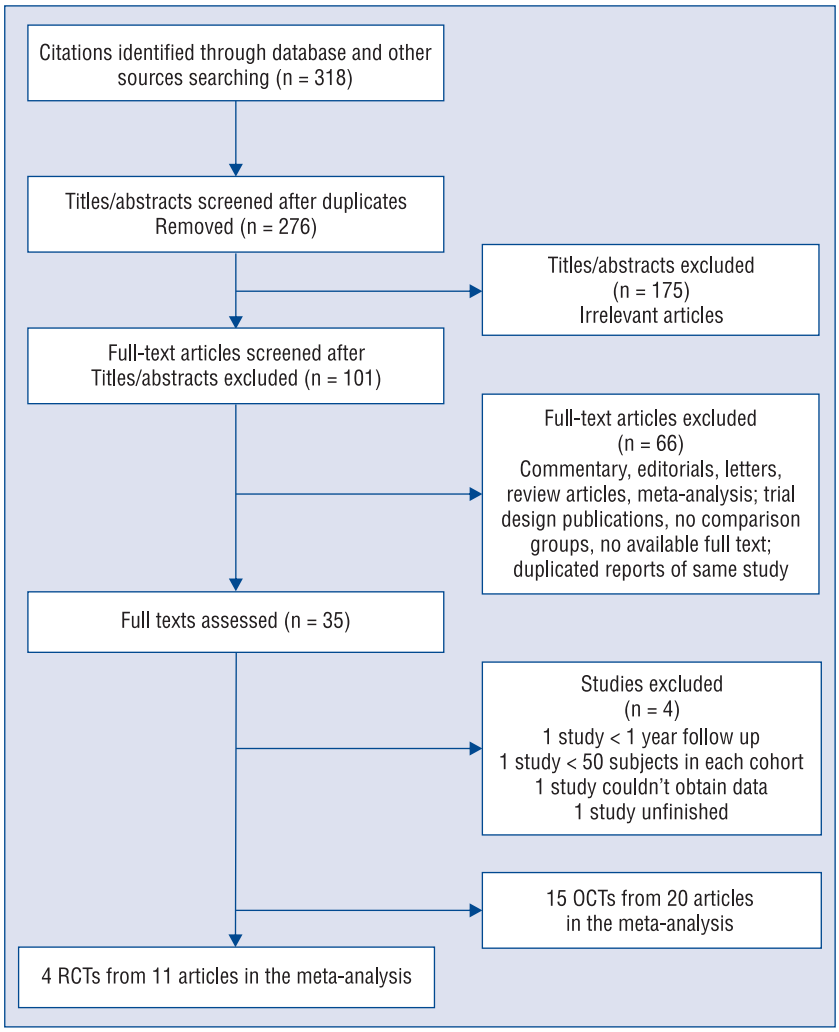

Figure 1. Flow diagram for inclusion of studies; OCTs — observational controlled trials; RCTs — randomized controlled trials.

the between-trial heterogeneity. The I^2 statistic was calculated as a measure of the proportion of the overall variation attributable to the between-trial heterogeneity rather than to chance, and we used the reported guidelines for low (I^2 = 25–49%), moderate (I^2 = 50–74%), and high ($I^2 \geq 75\%$) heterogeneity [39]. The overall effect size (RR) was calculated by fixed-effect model with the Mantel-Haenszel method when there was no significant heterogeneity ($p > 0.10$ or $I^2 < 50\%$), or with DerSimonian-Laird weights for the random-effects model when there was a significant heterogeneity ($p \leq 0.10$ or $I^2 \geq 50\%$). Forest plots were then created for graphical presentations of clinical outcomes. Publication bias with respect to the primary outcome (all-cause death) was assessed visually using a funnel plot. When there is no publication bias, studies of all sizes are scattered equally right and left of the line indicating the pooled estimate of natural log RR. For each endpoint we conducted subgroup analyses in RCTs and OCTs respectively, apart from an overall analysis. A sensitivity analysis was performed when the between-trial heterogeneity was significant.

Results

We identified 19 eligible studies (4 randomized [19–22] and 15 nonrandomized [23–38]) (Fig. 1) enrolling 5,805 patients in OCT subgroup (PCI-DES: 2,961; CABG: 2,844) and 3,060 in RCT subgroup (PCI-DES: 1,541; CABG: 1,519), respectively. The mean follow-up durations ranged from 1 year to 5.6 years. In the OCTs, with the exception of the propensity score-matched studies [23, 25], the CABG cohorts had higher prevalence of the triple vessel and/or LM disease, higher EuroSCORE and/or higher SYNTAX Score, but not in the RCTs (Table 2).

Table 2. EuroSCORE and angiographic characteristics.

Study or subgroup	3-vessel or LM disease [%]		P	EuroSCORE		P	SYNTAX score		P
	PCI-DES	CABG		PCI-DES	CABG		PCI-DES	CABG	
CARDia [22]	64.8	59.7	0.15	NA	NA	NA	NA	NA	NA
FREEDOM [21]	82.3	84.5	0.22	2.7 ± 2.4	2.8 ± 2.5	0.52	26.2 ± 8.4	26.1 ± 8.8	0.77
VA CARDS [19]	NA	NA	NA	NA	NA	NA	21.5 ± 8.9	22.7 ± 10.6	0.41
Briguori, 2007 [24]	NA	NA	NA	3.4 ± 2.3	3.8 ± 2.2	0.055	NA	NA	NA
Dominguez-Franco, 2009 [26]	57.8 7.8 (LM)	81 37.3 (LM)	< 0.001 < 0.001	4.6 ± 2.7	4.2 ± 2.9	0.21	18.5 ± 6	25.9±7	< 0.001
Javaid, 2007 [27]	11.3	72.8	< 0.00001	NA	NA	NA	NA	NA	NA
Kim, 2009 [28]	32.7 100 (LM)	74.6 100 (LM)	< 0.00001 1.00	4.0 (2.0–6.0)	5.0 (3.0-6.0)	0.001	NA	NA	NA
Luo, 2012 [30]	32.3	71.7	< 0.00001	5.0 (3.0–7.0)	5.0 (3.0–6.0)	0.363	NA	NA	NA
Moshkovitz, 2012 [31]	42.4 4.1 (LM)	78.8 27 (LM)	0.000 0.000	NA	NA	NA	NA	NA	NA
Onuma, 2011 [32]	31.4	36.5	0.41	NA	NA	NA	NA	NA	NA
Park, 2011 [33, 34]	47.2	83.6	< 0.001	0.7 ± 2.5	4.5 ± 2.7	< 0.001	18.3 ± 7.9	30.4 ± 10.7	< 0.001
Qiao, 2009 [35]	49	81.9	< 0.00001	NA	NA	NA	NA	NA	NA
Tarantini, 2009 [36]	45.2	83.5	0.0001	5.2 ± 2	5.5 ± 2	0.3	16 ± 4	21 ± 6	0.001
Yamagata, 2010 [37]	13	97	< 0.001	NA	NA	NA	16±5	21 ± 7	< 0.05

NA — not available; LM — left main disease; PCI-DES — percutaneous coronary intervention with drug-eluting stents; CABG — coronary artery bypass grafting

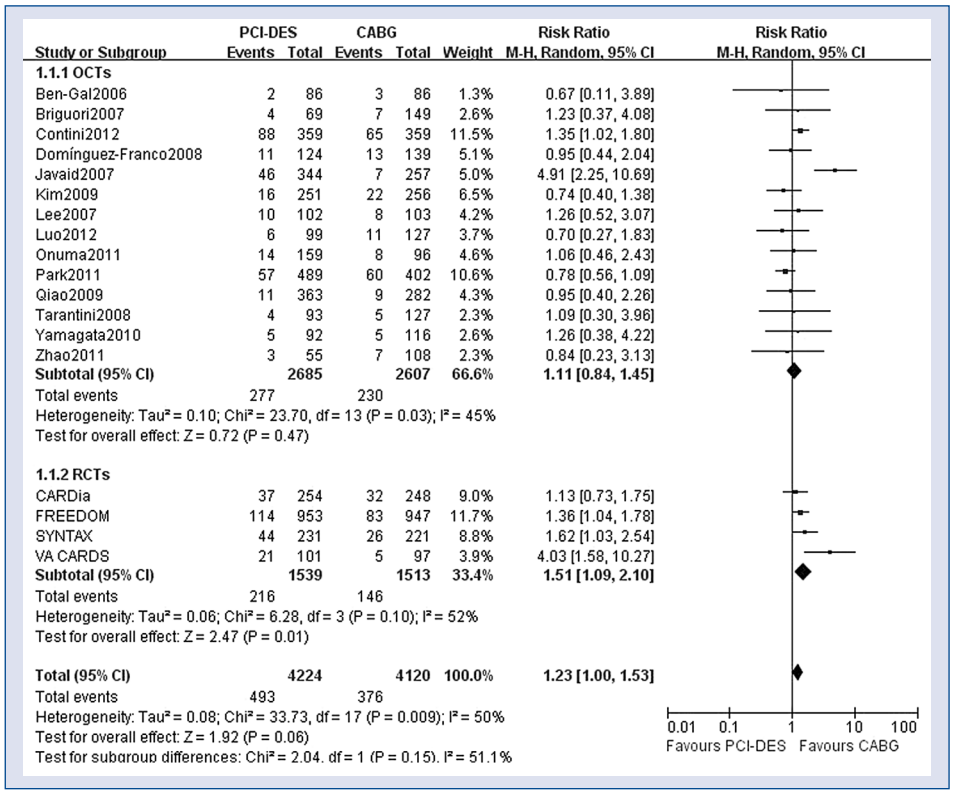

Figure 2. All-cause mortality at longest follow-up. The individual trials and subtotal risk ratios and 95% confidence intervals (CI) comparing the outcome of death for percutaneous coronary intervention with drug-eluting stents (PCI-DES) vs. coronary artery bypass grafting (CABG).

The CARDia trial included patients initially undergoing PCI with BMS (BMS 31%, DES 69%) [22]. The VA CARDS trial was stopped because of slow recruitment after enrolling only 25% of the intended sample size, leaving it severely underpowered for the primary composite endpoint of death plus nonfatal MI [19].

All-cause death

Random-effects meta-analysis yielded two different outcomes for all-cause death in RCTs and OCTs subgroup. The prevalence of death in RCTs subgroup was 14.0% in the PCI-DES cohort and 9.6% in CABG cohort with an RR of 1.51 (95% CI 1.09–2.10, p = 0.01). A moderate heterogeneity among the RCTs, mainly driven by including the VA CARDS trial, was revealed by sensitivity analysis (I^2 = 52%, p = 0.10). After excluding VA CARDS trial, random-effects model generated an RR 1.36, 95% CI 1.11–1.66 for death (p = 0.003) with no residual heterogeneity (I^2 = 0%, p = 0.53). While the OCT subgroup analysis indicated a comparable mortality between PCI-DES and CABG (10.3% DES vs. 8.8% CABG, RR 1.08, 95% CI 0.83–1.42, p = 0.55), heterogeneity analysis revealed a low heterogeneity among the OCTs (I^2 = 45%, p = 0.03) which was largely due to the inclusion of the Javaid, 2007 trial. After the exclusion of this trial, random-effects meta-analysis yielded an RR 1.02 (95% CI 0.85–1.22) for death (p = 0.80) with no residual heterogeneity (I^2 = 0%, p = 0.73).

When pooling all the RCTs and OCTs, random-effects model yielded an RR 1.23 (11.7% DES vs. 9.1% CABG, 95% CI 1.00–1.53, p = 0.06) for death. After excluding the VA CARDS trial and the Javaid, 2007 trial, the overall mortalities of the two arms reached statistical difference (RR 1.15, 95% CI 1.01–1.31, p = 0.04) with no residual heterogeneity between trials (I^2 = 0%, p = 0.51) (Fig. 2, Table 3). There was an asymmetry of the points on visual estimation of the funnel plot, which indicated the possibility of publication bias with respect to the primary outcome (all-cause death) (Fig. 3).

Nonfatal myocardial infarction

The RCT subgroup analysis demonstrated no difference in MI incidence (10.3% DES vs. 5.9% CABG, RR 1.44, 95% CI 0.79–2.60, p = 0.23), with a significant between-trial heterogeneity

Table 3. Sensitivity analysis.

	Outcome (total subjects)	PCI-DES (%)	CABG (%)	RR 95% [CI]	P	Heterogeneity
OCT analysis after excluding: Javaid, 2007 trial	Death (n = 4,691)	231/2,341 (9.9%)	223/2,350 (9.5%)	1.02 [0.86–1.22]	0.80	I^2 = 0% P = 0.73
RCT analysis after excluding: VA CARDS trial	Death (n = 2,854)	195/1,438 (13.56%)	141/1,416 (9.96%)	1.36 [1.11–1.66]	0.003	I^2 = 0% P = 0.53
	Myocardial infarction (n = 2,854)	153/1,438 (10.64%)	75/1,416 (5.30%)	2.01 [1.54–2.62]	< 0.00001	I^2 = 0% P = 0.83
	Repeat revascularization (n = 2,854)	249/1,438 (17.32%)	93/1,416 (6.57%)	2.61 [2.09–3.27]	< 0.00001	I^2 = 0% P = 0.89
Overall analysis after excluding: VA CARDS trial	Death (n = 7,545)#	426/3,779 (11.27%)	364/3,766 (9.67%)	1.15 [1.01–1.31]	0.04	I^2 = 0% P = 0.51
	Myocardial infarction (n = 7,467)	326/3,786 (8.61%)	159/3,681 (4.32%)	1.91 [1.43–2.57]	< 0.0001	I^2 = 43% P = 0.04
	Repeat revascularization (n = 8,643)	834/4,394 (18.98%)	255/4,249 (6.00%)	2.99 [2.62–3.42]	< 0.00001	I^2 = 0% P = 0.57

#Excluding VA CARDS trial and Javaid, 2007 trial; RCTs — randomized controlled trials; OCTs — observational controlled trial; RR — risk ratio; CI — confidence interval; PCI-DES — percutaneous coronary intervention with drug-eluting stents; CABG — coronary artery bypass grafting

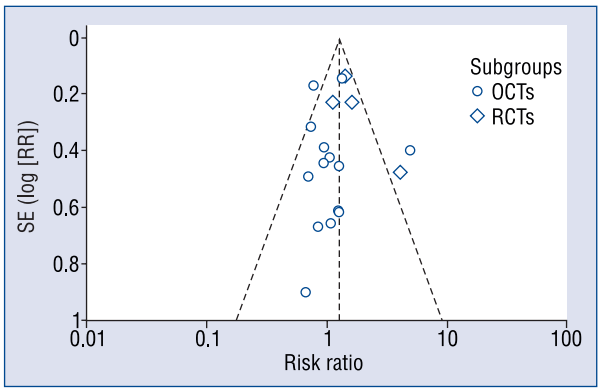

Figure 3. Funnel plot for assessment of publication bias of trials for the endpoint of all-cause death; OCTs — observational controlled trial; RCTs — randomized controlled trials.

(I^2 = 75%, p = 0.007). Sensitivity analysis showed that this heterogeneity was largely contributed by the inclusion of the VA CARDS trial, where MI rate after CABG was much higher than that after PCI-DES, unlike other RCTs. When excluding this trial, random-effects meta-analysis demonstrated a statistical difference (10.6% DES vs. 5.3% CABG, RR 2.01, 95% CI 1.54–2.62, p < 0.00001) with no residual heterogeneity (I^2 = 0%, p = 0.83). The OCT subgroup analysis showed that MI after PCI-DES was more prevalent as opposed to CABG (7.4% DES vs. 3.7% CABG, RR 1.82, 95% CI 1.15–2.86, p = 0.01) with a moderate heterogeneity (I^2 = 54%, p = 0.01), for which no special trial was mostly responsible.

Regardless of the inclusion or exclusion of the VA CARDS trial, random-effects meta-analysis showed that the overall MI rate was consistently higher in PCI-DES patients (inclusion: 8.5% DES vs. 4.6% CABG, RR 1.68, 95% CI 1.20––2.37, p = 0.003; exclusion: 8.6% DES vs. 4.3% CABG, RR 1.91, 95% CI 1.43–2.57, p < 0.0001) (Fig. 4, Table 3).

Nonfatal stroke

Fixed-effects meta-analysis revealed that both in the RCTs and OCTs subgroup PCI-DES was associated with much lower risk of stroke compared with CABG (RCTs: 2.3% DES vs. 3.8% CABG, RR 0.59, 95% CI 0.39–0.90, p = 0.01; OCTs: 1.8% DES vs. 4.0% CABG, RR 0.46, 95% CI 0.32–0.66, p < 0.0001) with no heterogeneity between trials (RCTs: I^2 = 0%, p = 0.94; OCTs: I^2 = 0%, p = 0.57). When pooling two subgroups, PCI-DES patients kept a consistently lower frequency of stroke (2.0% DES vs. 3.9% CABG, RR 0.51, 95% CI 0.39–0.67, p < 0.00001) with no heterogeneity between trials (I^2 = 0%, p = 0.80) (Fig. 5).

Repeat revascularization

The RCT subgroup analysis showed that patients after PCI-DES risk a several-fold higher

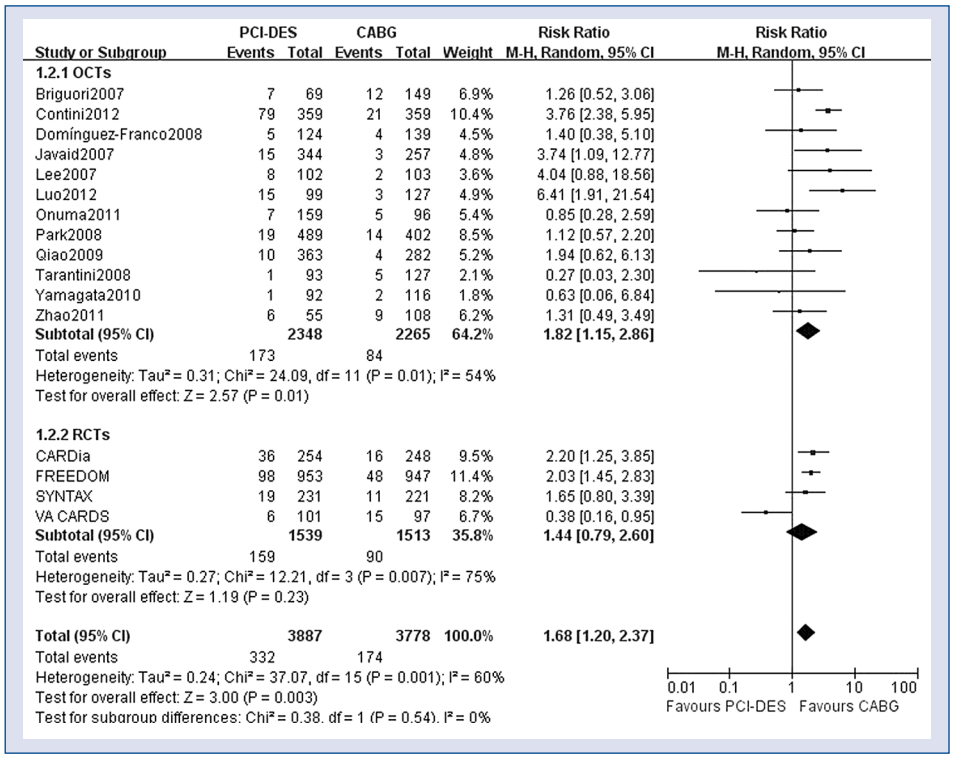

Figure 4. Nonfatal myocardial infarction at longest follow-up. The individual trials and subtotal risk ratios and 95% confidence intervals (CI) comparing the outcome of myocardial infarction for percutaneous coronary intervention with drug-eluting stents (PCI-DES) vs. coronary artery bypass grafting (CABG).

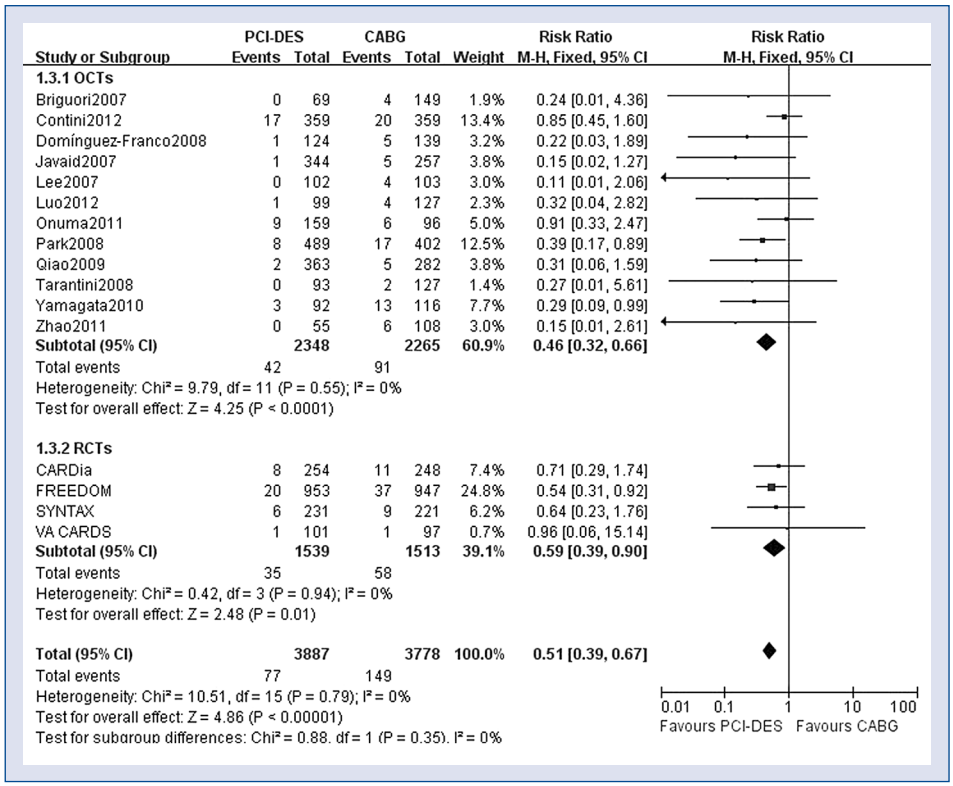

Figure 5. Nonfatal stroke at longest follow-up. The individual trials and subtotal risk ratios and 95% confidence intervals (CI) comparing the outcome of stroke for percutaneous coronary intervention with drug-eluting stents (PCI-DES) vs. coronary artery bypass grafting (CABG).

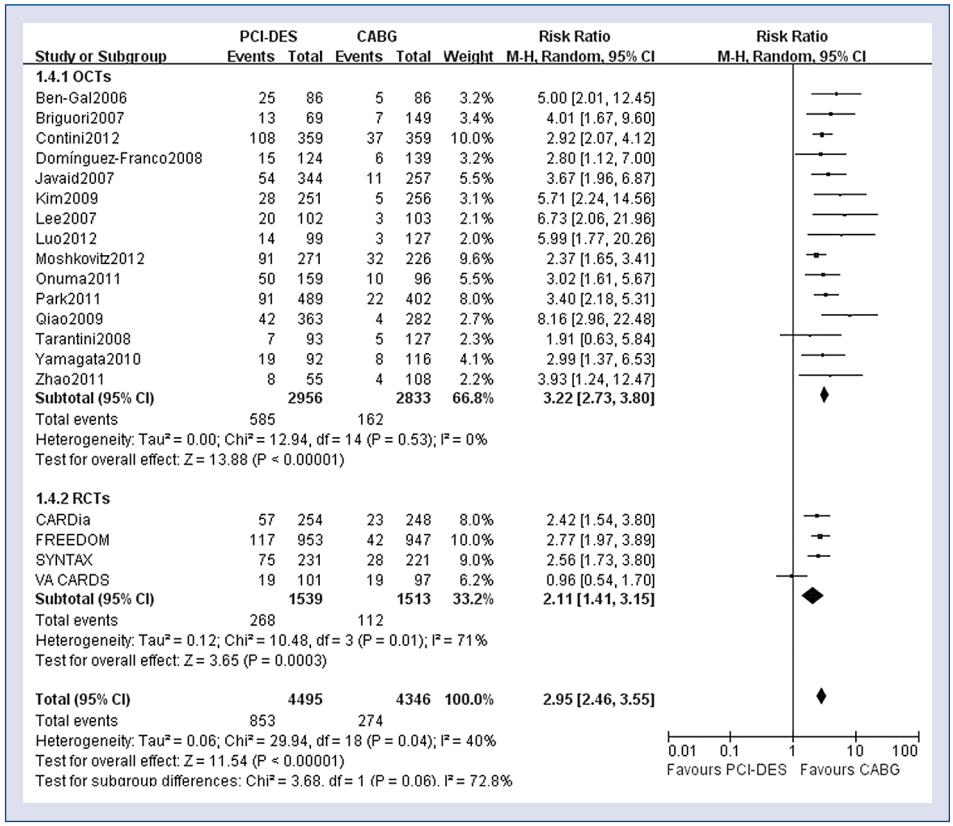

Figure 6. Repeat revascularization at longest follow-up. The individual trials and subtotal risk ratios and 95% confidence intervals (CI) comparing the outcome of repeat revascularization for percutaneous coronary intervention with drug-eluting stents (PCI-DES) vs. coronary artery bypass grafting (CABG).

rate of subsequent revascularization (17.4% DES vs. 7.4% CABG, RR 2.11, 95% CI 1.41–3.15, p = 0.0003), even if including the VA CARDS trial which primarily contributed to the significant heterogeneity among RCTs (I^2 = 71%, p = 0.01). After exclusion of this trial, the point estimate for repeat revascularization reached a statistical significance (17.32% DES vs. 6.57% CABG, RR 2.61, 95% CI 2.09–3.27, p < 0.00001) with no residual heterogeneity (I^2 = 0%, p = 0.89). The OCT subgroup analysis suggested patients after PCI-DES was at a substantially higher risk of repeat revascularization (19.8% DES vs. 5.7% CABG, RR 3.22, 95% CI 2.73–3.80, p = 0.0001) with no heterogeneity among OCTs (I^2 = 0%, p = 0.53).

Random-effects meta-analysis showed that the overall incidence of subsequent revascularization was consistently much higher in PCI-DES cohort regardless of the inclusion or exclusion of the VA CARDS trial (inclusion: 19.0% DES vs. 6.3% CABG, RR 2.95, 95% CI 2.46–3.55, p < 0.00001; exclusion: 19.0% DES vs. 6.0% CABG, RR 2.99, 95% CI 2.62–3.42, p < 0.0001) (Fig. 6, Table 3).

Discussion

To the best of our knowledge, this study, incorporating more than 8,000 patients, is the first systematic review and meta-analysis of both the randomized and nonrandomized studies that compared PCI-DES vs. CABG in diabetic subset with LM and/or MVD. Not only did this meta-analysis conclude the overall efficacy and safety of the two revascularization strategies in the general population, but also compared the two strategies in real-world patients (OCTs) and in high-selected patients (RCTs), respectively.

It is well known that the RCTs are the most convincing in all types of studies, while the OCTs, unlike the RCTs which enroll the high-selected subjects, can reflect daily clinical practice where the choice between two revascularization strategies mostly depends on the clinician's discretion and the patient's will. Actually, compared with nondiabetic patients, diabetics risk higher mortality after either DES or CABG, which demonstrated that neither CABG nor PCI could eliminate the

increased mortality risk conferred by diabetes mellitus [40]. However, CABG was generally considered a preferred revascularization strategy for patients with LM and/or MVD [9]. In the daily practice, the clinicians preferred CABG for the patients with more complex lesions regardless of diabetes mellitus status, whereas patients who have local diseases and less extensive lesions were more likely to undergo DES. Thus, in the OCTs, the CABG cohorts had higher-risk profiles for clinical and angiographic characteristics, which were revealed by the higher EuroSCORE and/or higher SYNTAX score, and by the higher prevalence of triple and/or left main CAD in the CABG cohort (Table 2).

Several previous meta-analyses comparing PCI-DES vs. CABG for diabetics showed that no significant differences in death and MI were found, but the lower risk of repeat revascularization and the higher risk of stroke in CABG patients had been definitely revealed [41, 42]. The FREEDOM trial was the biggest prospective RCT comparing the two revascularization modalities for diabetic patients with MVD exclusively. The significantly higher mortality and MI but the lower rate of stroke in the PCI-DES group was observed actually at its 5-year follow-up, even though this trial was underpowered to detect a difference in all-cause mortality [21]. However, the debate had not been discontinued. Subsequently, the SYNTAX trial compared CABG with PCI using paclitaxel-eluting stents (PCI-PES) for patients with LM and/or three-vessel disease, and its subgroup analysis for the diabetic subset revealed that the mortalities of two strategies were not statistically different (19.5% DES vs. 12.9% CABG, $p = 0.065$), but this analysis was also underpowered and limited by being post hoc exploratory subgroup analysis [20, 43]. The Hakeem et al. trial [44], the first meta-analysis of RCTs on this topic, revealed that CABG improved survival, decreased MI and repeat revascularization, but increased the risk of stroke compared with multivessel PCI with first-generation DES. Generally, it was definite that patients after CABG patients risked more strokes and less repeat revascularization compared with PCI-DES patients. Through the sensitivity analyses and the subgroup analyses (the same results from two subgroup analyses), this meta-analysis further confirmed that CABG had significant advantage in repeat revascularization but the substantial disadvantage in stroke.

The funnel plot showed that the studies were mainly scattered left of the line, which revealed that publication bias possibly existed and the advantage of CABG in all-cause death was likely underestimated (Fig. 3). However, the RCT subgroup analysis and the overall sensitivity analysis demonstrated that CABG had an advantage over PCI-DES with the respects of all-cause death. The RCT subgroup analysis showed that CABG improved survival compared with PCI-DES, while the OCT subgroup analysis demonstrated the comparable mortality between two strategies (Fig. 2, Table 3). The different outcomes between the OCT and RCT subgroup analysis were likely to be driven by the higher-risk profiles for clinical and angiographic characteristics in CABG cohort in the OCTs, while the RCTs had comparable risk factor between two cohorts (Table 2), which was possibly another reason for the asymmetry of the funnel plot. The comparable survival between two strategies in OCT subgroup and the lower mortality of the OCT patients than RCT patients (9.6% OCTs vs. 11.9% RCTs, RR 0.81, 95% CI 0.71–0.92, $p = 0.001$) suggested that the preferred choice of CABG for diabetic patients with higher-risk profiles in daily clinical practice was reasonable in terms of all-cause death. Conclusively, CABG had advantage over PCI-DES with respect of the primary endpoint despite the different results between RCTs and OCTs subgroup analyses.

Only the VA CARDS trial conducted the aggressive search for silent MI, while other RCTs included silent MI when discovered but not mandated serial electrocardiography and nuclear studies, which was one of the reasons that the MI rate following CABG was much higher than that after PCI-DES [19], which pronouncedly differed from other RCTs. However, regardless of inclusion or exclusion of the VA CARDS trial, our study confirmed consistently that PCI-DES was associated with higher MI rate compared with CABG. The CABG advantage over PCI-DES in MI was also revealed by the Lee et al. [42] trial which was a meta-analysis including OCTs only and by the Hakeem et al. trial [44] which was a meta-analysis including RCTs only. Generally, the advantage of CABG in MI was definite, but it was unknown whether this advantage was kept when silent MI was aggressively searched for.

Limitations of the study

We acknowledged that our study had several limitations. Firstly, the observational studies enrolled in this mate-analysis had their inherent limitations, namely design bias, selection bias, treatment bias and publication bias. Substantial between-studies heterogeneity in terms of both study design and the effect sizes of each end point

were observed in this review. Furthermore, this meta-analysis contained trials regardless of the baseline characteristics of patients, medication treatment after revascularization, duration of follow-up and location of occlusion, which might bring about more heterogeneity. Thus, despite our choice of random effects models, the incorporating of disparate studies could not accurately summarize the overall effect of two strategies, and also limits the generalizability of our results. Secondly, the first-generation DES, used mostly in the included studies, could not fully reflect the clinical practice in the newer-generation DES era. Recent data from a Swedish registry, enrolling 4,751 diabetic patients, showed that the use of the second-generation stents (everolimus-eluting stent) was associated with improved outcomes compared with the first-generation (PES and sirolimus-eluting stents), but the result was mainly driven by lower rates of stent thrombosis and death [45]. Whether CABG keeps the priority to the PCI-DES is unknown. Thirdly, several trials reporting the in-hospital and 30-day follow-up result showed that CABG was associated with increased major adverse cardiac events, death, stroke. The meta-analysis for these short-term endpoints was not conducted by our study, which makes it difficult to evaluate the efficacy and safety of the two strategies entirely.

Conclusions

CABG for patients with diabetes mellitus and LM and/or MVD had advantages over PCI-DES in all-cause death, nonfatal MI, and repeat revascularization, but one substantial disadvantage in nonfatal stroke. The high-selected patients (RCTs) risked a higher mortality than the real-world patients (OCTs).

Conflict of interest: None declared

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