

Comparing mortality and myocardial infarction between coronary artery bypass grafting and drug-eluting stenting in patients with diabetes mellitus and multivessel coronary artery disease: a meta-analysis

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Abstract

Introduction: We aim to compare the midterm outcomes between coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) in diabetic patients who had multivessel coronary artery diseases (CAD).

Material and methods: A comprehensive literature search was conducted to identify the related clinical studies with a follow-up for 1 year at least. The endpoints were death, myocardial infarction, and major adverse cardiac and cerebrovascular events (MACCE).

Results: Finally, the analysis of ten studies involving 5,264 patients showed that patients with CABG had worse baseline characteristics, a higher rate of stable angina pectoris, a higher percentage of triple-vessel disease, higher incidence of chronic total occlusion and a higher SYNTAX score. However, there was no significant difference in mortality between the two groups. Additionally, the rates of myocardial infarction and MACCE were markedly decreased in the CABG group.

Conclusions: The strategy of CABG is better than PCI for diabetic patients with multivessel CAD. The CABG can significantly reduce the rates of myocardial infarction and MACCE and is comparable in mortality despite the worse baseline characteristics.

Key words: coronary artery bypass grafting, percutaneous coronary intervention, coronary artery diseases.

Introduction

Diabetic patients experience a higher risk of coronary artery disease (CAD) and are more likely to develop more severe symptoms than non-diabetics [1, 2]. It is reported that there are more than 220 million people with diabetes worldwide and the number is expected to rise to 360 million by 2030 [3]. About one fifth of patients with unstable angina or non-ST evaluated myocardial infarction have diabetes mellitus, which is associated with advanced CAD, accounting for a higher rate of myocardial infarction and mortality [4–6]. As the leading cause of mortality among

diabetic patients, cardiovascular disease accounts for up to 80% of diabetes-related deaths [7, 8].

A clinical trial showed that there was lower mortality and repeat revascularization in diabetic patients treated with coronary artery bypass grafting (CABG) than percutaneous coronary intervention (PCI) [9]. However, drug-eluting stenting (DES) has been recently demonstrated to reduce in-stent restenosis and repeat revascularization compared to bare-metal stenting in diabetic patients. Thus, in the DES era, the optimal revascularization strategy for diabetic patients with multivessel CAD remains unknown [10–12]. We performed a meta-analysis to compare the efficacy of CABG and DES in diabetic patients with multivessel CAD.

Material and methods

Data sources

We searched Medline, EMBASE, metaRegister of Controlled Trials, and Cochrane databases from January 2003 to July 2013 for clinical studies, using the Medical Subject Heading terms “coronary artery bypass graft surgery”, “drug-eluting stent”, “diabetes mellitus” and “multivessel coronary artery disease”. The Science Citation Index was used to cross-reference studies that met the inclusion criteria.

Study selection

Studies were selected on the basis of pre-determined criteria: a clinical trial was included if it: (1) was published in journals with the full text in English, (2) compared the use of DES to CABG in diabetic patients with multivessel CAD (≥ 2 arteries), (3) had a follow-up ≥ 12 months. Studies using bare-metal stenting and describing the same article were excluded. The end points were death, myocardial infarction and major adverse cardiac and cerebrovascular events (MACCE). The MACCE was defined as a composite of all-cause death, cerebrovascular accident, myocardial infarction or repeat revascularization (any subsequent PCI or CABG procedure in any coronary vessel).

Data abstraction

We captured pre-specified data elements for each study, including baseline characteristics and clinic outcomes. Data extraction from text, tables, and figures was performed by 2 independent reviewers. Decisions were compared and a consensus was reached. Discrepancies were resolved through discussion.

Statistical analysis

The meta-analysis was conducted with Review Manager 5.2. Forest plots and funnel plots were

generated for graphical presentations, and Q statistics were computed to assess heterogeneity across the different studies. We used a fixed-effects model of meta-analysis to aggregate data; however, the randomized-effects model was used when effects were heterogeneous ($I^2 > 50\%$). The summary risk differences and odds ratios (OR) comparing CABG and DES outcomes and the 95% CI for each result were computed.

Results

Eligible studies

Ten studies (2 randomized trials and 8 nonrandomized trials) were included in the meta-analysis and their baseline characteristics are presented in Table I [12–21]. There was an absence of baseline characteristics of the Banning *et al.* study, because the baseline patient demographics and lesion characteristics in CABG and DES groups were shown as a composite outcome for the diabetic cohort [18]. The rest of the initial citations were excluded based on the titles/abstracts, language, publication type, etc. A total of 5,264 patients were included in the analysis (2,585 CABG and 2,679 DES patients). In most studies, sirolimus-eluting and paclitaxel-eluting stents were provided to the patients in the PCI procedure. However, in the studies of Onuma *et al.* [14] and Yamagata *et al.* [15], PCI was performed by implantation of only sirolimus-eluting stents, whereas only paclitaxel-eluting stents were used in the study of Banning *et al.* [18]. The CABG was performed without elective extracorporeal circulation including a left internal mammary artery for revascularization of the left anterior descending coronary artery whenever possible in most cases. The mean follow-up duration was 3.2 years.

Study characteristics

The CABG group had higher percentages of stable angina pectoris (OR 1.32, 95% CI: 1.06–1.64) (Figure 1), triple-vessel disease (OR 4.59, 95% CI: 2.08–10.11) (Figure 2), chronic total occlusion (OR 1.94, 95% CI: 1.29–2.92) (Figure 3) and SYNTAX scores (mean difference 5.73, 95% CI: 1.67–9.78) (Figure 4). There is no other significant difference in baseline characteristics between the CABG group and DES group.

Clinical outcomes

We also performed a subgroup analysis comparing PCI with DES vs. CABG. Among non-randomized studies, OR was comparable between the DES group and the CABG group for the endpoints, with the exception of MACCE rate. There was a significantly higher risk for MACCE in patients treated with

Table 1. Baseline characteristics

Study/year	Farkouh et al./2012	Dominguez-Franco et al./2009	Onuma et al./2011	Yamagata et al./2010	Tarantini et al./2009	Kim et al./2012	Briguori et al./2007	Qiao et al./2009	Lee et al./2007
Location	Multicenter	Spain	Multicenter	Japan	Italy	Korea	Italy	China	United States
No. of patients	953/947	128/142	159/96	92/116	93/127	489/402	69/149	363/282	102/103
Design	Randomized trial	Retrospective study	Nonrandomized ARTS-II trial compared with the surgical group of ARTS-I	Nonrandomized registry	Prospective, nonrandomized registry	Prospective registry	Nonrandomized registry	Observational study	Nonrandomized registry
Follow-up duration [years]	3.8	2	5	3	2	5.6	1	1	1
Age	63.2/63.1	67.5/65.3	65/63	70/67	65/66.5	63.5/62.8	63/66	60.9/62.5	67/68
Men	698/658	80/93	106/66	66/85	76/103	304/275	48/107	250/221	67/67
Stable AP (%)	-/-	-/-	54/63	39/59	75.2/79.5	-/-	80/82	18.2/19.1	42/48
Unstable AP (%)	-/-	-/-	32/33	22/19	33.3/19.7	-/-	8.5/9.5	60.3/71.6	41/36
Previous MI (%)	26.2/25.0	49.2/28.9	30/49	57/63	43.0/55.9	7.1/27.1	42/37	20.9/25.2	23/17
Hypertension (%)	-/-	71.1/59.2	80/56	91/92	90.1/86.6	64.0/61.4	74/80	74.1/61.3	89/90
Smoking (%)	14.8/16.6	39.1/43.7	12/17	74/78	36.5/40.2	23.1/16.4	30.5/40	31.6/28.8	16/15
Peripheral artery disease (%)	-/-	13.3/8.5	-/-	22/17	-/-	3.5/10.7	-/-	-/-	-/-
No. of diseased vessels (%):									
2	-/-	-/-	49/64	87/2.6	54.8/16.5	52.8/16.4	50.5/13.5	51/18.1	-/-
3	82.3/84.5	57.8/81	50/35	13/97	45.2/83.5	47.2/83.6	49.5/86.5	49/81.9	-/-
Patients with CTO (%)	-/-	36.7/47.2	-/-	38/44	5.3/13.4	5.9/47.0	-/-	-/-	9/14
SYNTAX score	26.2/26.1	18.5/25.9	-/-	16/21	16/21	18.3/30.4	18/23	-/-	-/-
LVEF (%)	65.7/66.6	52.4/54.2	60/60	47/48	61.9/62.2	58.3/54.7	54/53	59.9/59.5	51/52
Insulin-requiring DM (%)	33.8/30.9	39.8/32.4	18/17	13/17	33.3/28.3	17.6/18.9	39/36	15.6/16.9	22/25

Data are expressed as DES/CABG. AP – angina pectoris, CTO – chronic total occlusion, LVED – left ventricle ejection fraction, MI – myocardial infarction

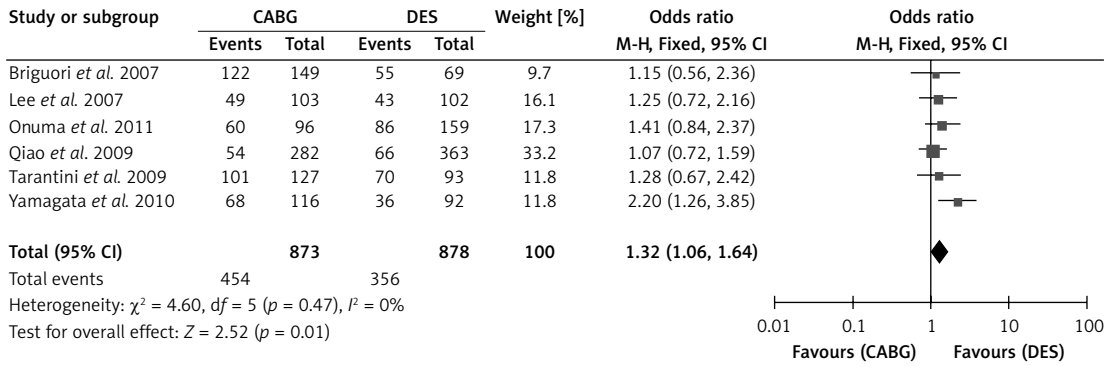


Figure 1. Odds ratio and conclusions plot of stable angina pectoris

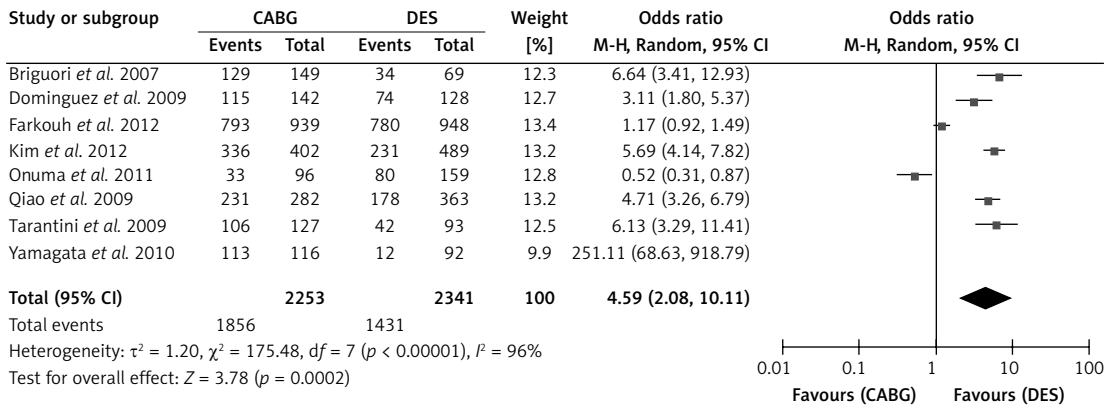


Figure 2. Odds ratio and conclusions plot of triple-vessel disease

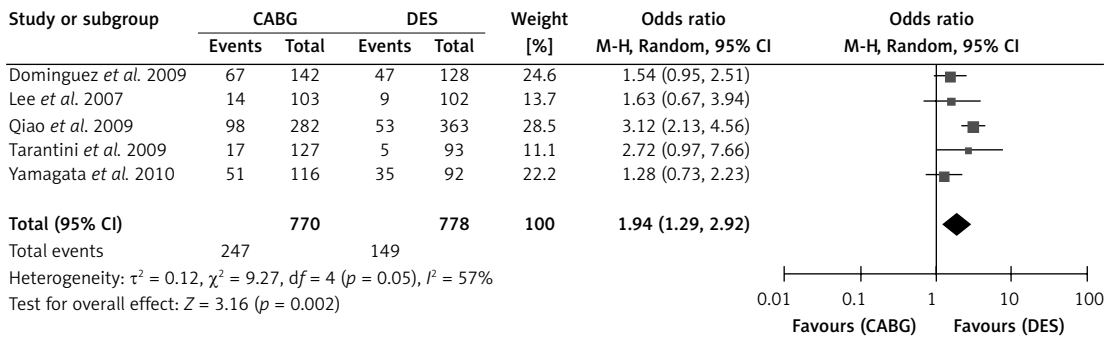


Figure 3. Odds ratio and conclusions plot of chronic total occlusion

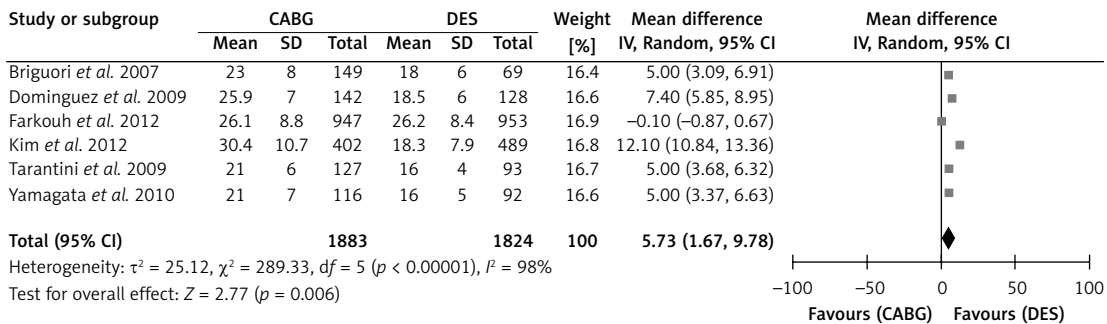


Figure 4. Mean difference and conclusions plot of SYNTAX scores

DES compared with CABG (OR 0.60, 95% CI: 0.50–0.72). However, DES was associated with significantly increased risks for all three endpoints in the randomized studies. Generally, the OR for mortality was 0.89, indicating that CABG was associated with lower mortality compared with DES, though the effect did not reach statistical significance between the two revascularizations (Figure 5 A). The χ^2 test with 9 degrees of freedom for the Q statistic was 7.14 ($p = 0.62$, $I^2 = 0\%$), indicating no significant heterogeneity among the studies. However, there was a statistically significant difference in MACCE rate: CABG could dramatically reduce the rate of MACCE (OR 0.60, 95% CI: 0.52–0.69) (Figure 6 A). There was no significant heterogeneity among the studies as the χ^2 test with 9 degrees of freedom for the Q statistic was 9.29 ($p = 0.41$, $I^2 = 3\%$). Additionally, a sig-

nificant difference in myocardial infarction between the two groups was revealed (Figure 7 A). The OR for myocardial infarction was 0.57 (95% CI: 0.44–0.75), indicating that CABG was associated with lower incidence of myocardial infarction compared with DES. The χ^2 test with 8 degrees of freedom for the Q statistic was 9.28 ($p = 0.32$, $I^2 = 14\%$), indicating no significant heterogeneity among the studies. In addition, the funnel plot for each endpoint was shown (Figures 5 B, 6 B and 7 B).

Discussion

In clinical practice, most patients are treated with PCI for single-vessel disease and with CABG for severe CAD, such as triple-vessel or severe left main disease [22]. Due to the lack of random al-

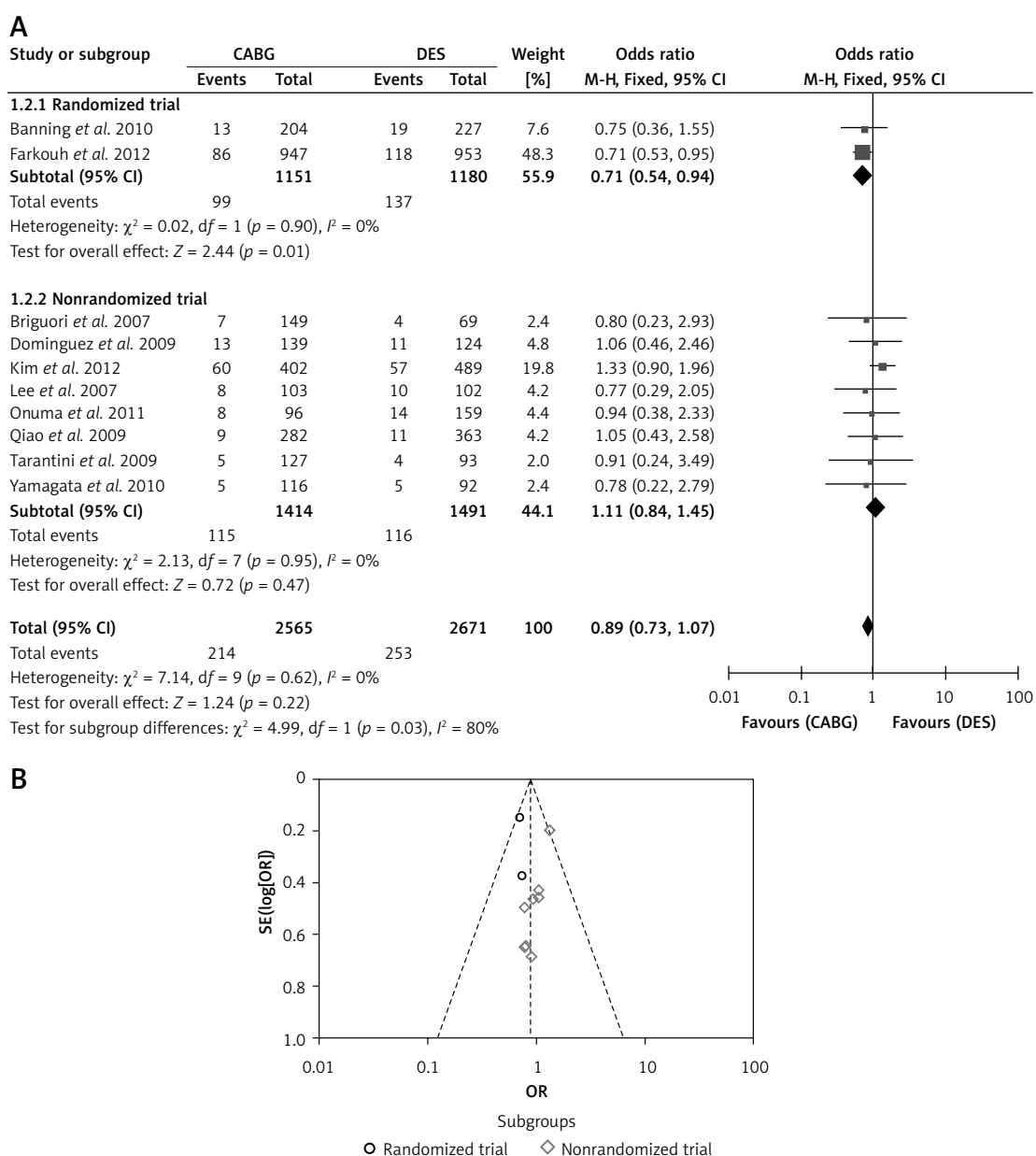


Figure 5. Forest plot (A) and funnel plot (B) of mortality

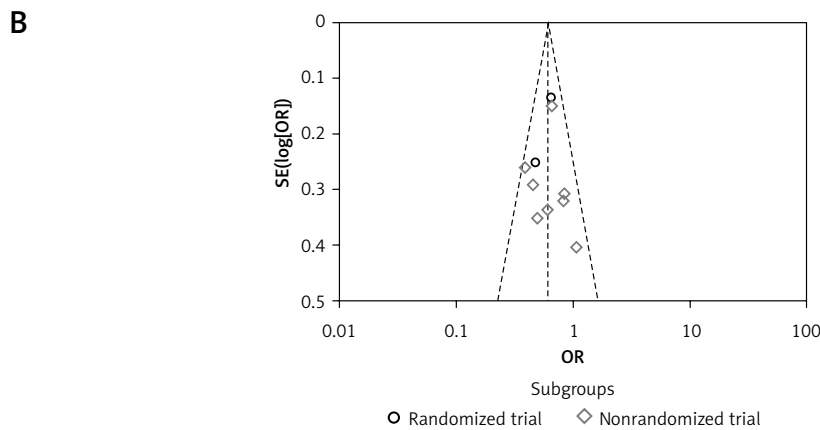
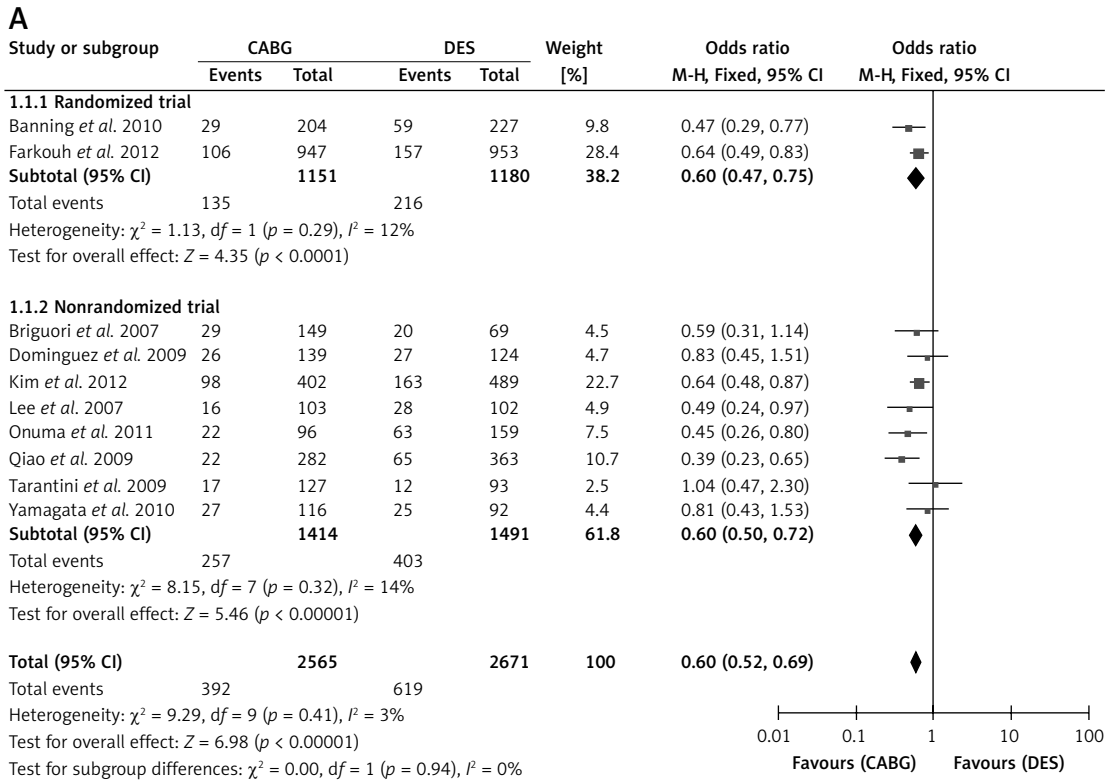


Figure 6. Forest plot (A) and funnel plot (B) of MACCE rate

location, patients in observational studies tend to present a large bias. As a result, patients with focal disease are more likely to undergo PCI and those with extensive CAD are likely to undergo CABG. The strategy of revascularization is driven by angiographic data, such as extent, location and nature of the lesion.

A meta-analysis by Lee *et al.* showed that there was no significant difference in death and myocardial infarction between the CABG group and the DES group when the mean follow-up was 18 months (range 12 to 36), which led to the conclusion that PCI with DES was safe and might represent a viable alternative to CABG for patients with diabetes and multivessel CAD [10]. However, in the FREEDOM trial by Farkouh *et al.*, 1,900 patients with diabetes and multivessel CAD at 140

centers were enrolled and randomly assigned to undergo either PCI with DES or CABG. The primary outcome measure was a composite of death from any cause, nonfatal myocardial infarction, and nonfatal stroke. They demonstrated that CABG was superior to PCI for diabetic patients with advanced CAD considering the mortality and myocardial infarction [12]. Accordingly, the optimal revascularization strategy for diabetic patients with multivessel CAD remains uncertain.

In our meta-analysis, we conducted a comparison of baseline characteristics between the PCI group and the CABG group. Patients in the CABG group had worse characteristics before being treated, with a higher percentage of stable angina pectoris, triple-vessel disease and chronic total occlusion, and higher SYNTAX scores. Although

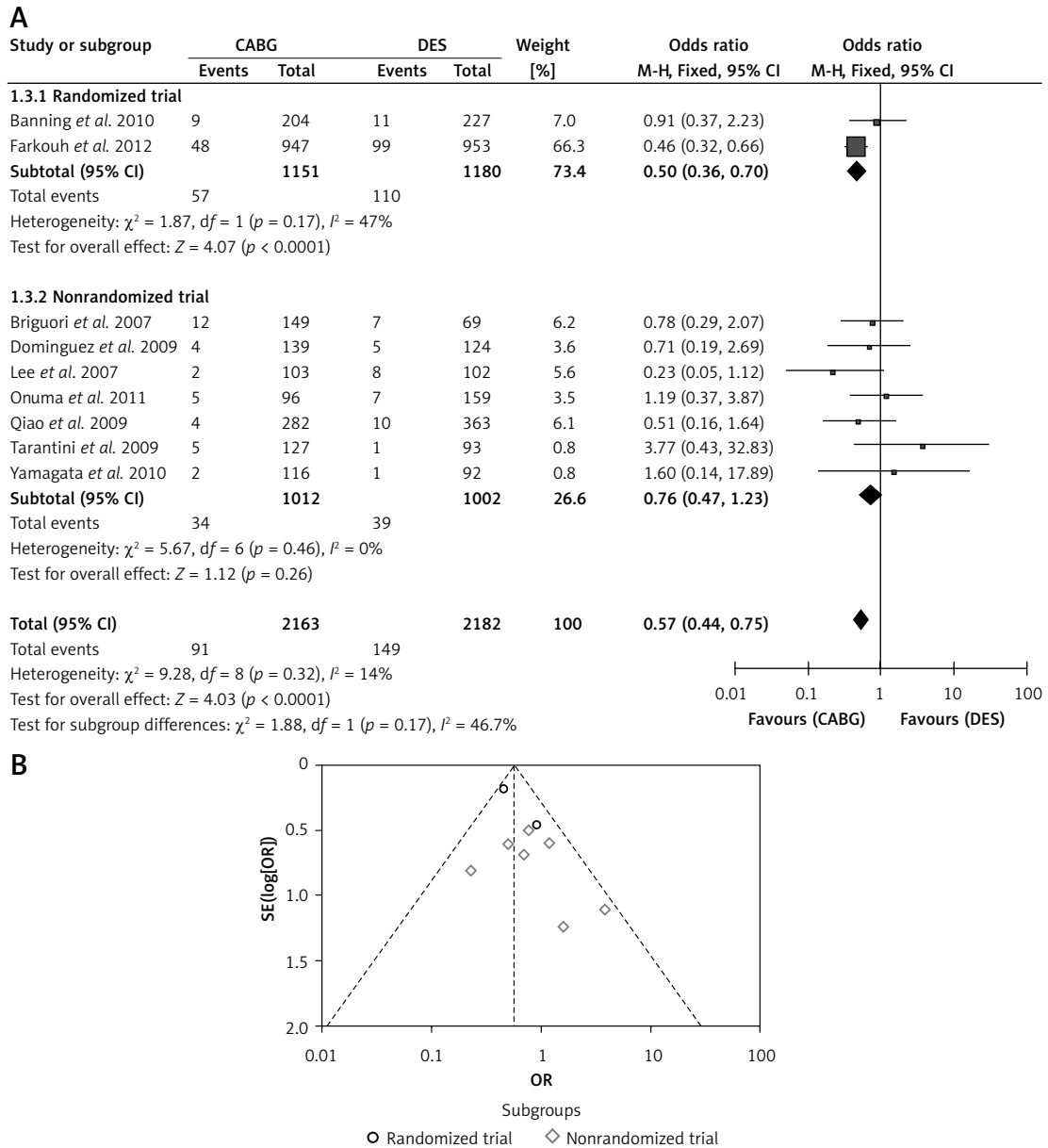


Figure 7. Forest plot (A) and funnel plot (B) of myocardial infarction

the mortality was similar in the two groups, the CABG strategy showed superiority for diabetic patients because of the lower rate of myocardial infarction, MACCE and worse baseline characteristics. Therefore, our study, like the FREEDOM trial, further confirmed that CABG had better midterm outcomes than DES.

The major difference between our study and the meta-analysis by Lee *et al.* was the duration of follow-up. The mean follow-up period of the Lee *et al.* meta-analysis was 18 months vs. 3.2 years in ours. Besides, recently published data comparing PCI and CABG were also updated and included in our analysis. In the Lee *et al.* analysis, 5 observational studies (a total of 1543 patients) from January 2003 to July 2009 were included [14, 16, 19–21], while five more studies including 3721

participants published recently were included in our meta-analysis [12, 13, 15, 17, 18], 2 of which were randomized trials. Moreover, the results of clinical outcomes showed an obvious discrepancy between our analysis and that of Lee *et al.*, as noted above.

The 2011 ACCF/AHA guideline showed that CABG (especially with one or both internal mammary arteries) led to more complete revascularization and a decreased need for additional procedures when compared with PCI [23]. Due to the diffuse nature of diabetic CAD, the relative benefits of CABG over PCI may well persist for patients even in the era of DES. The study is not without limitations. First, this meta-analysis adopted the published event rates instead of specific individual data for each trial. Second, there were limited

clinical trials included in the analysis and the numbers of patients in each cohort were small. Finally, some results of endpoints were not available, such as data of myocardial infarction in the study by Kim *et al.* [17].

In conclusion, the meta-analysis suggested that the strategy of CABG is better than PCI with DES for diabetic patients with multivessel CAD. In spite of the worse baseline characteristics, the CABG approach could significantly reduce the rate of myocardial infarction and major adverse cardiac cerebrovascular events, while obtaining a similar mortality when compared with PCI.

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