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REVIEW

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Percutaneous coronary intervention versus coronary artery bypass grafting in patients with coronary heart disease and type 2 diabetes mellitus: Cumulative meta-analysis

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Abstract

Previous meta-analyses showed that coronary artery bypass grafting (CABG) has lower all-cause mortality than percutaneous coronary intervention (PCI) for the management of coronary heart disease (CHD), but the long-term outcomes were not analyzed thoroughly in patients with type 2 diabetes mellitus (T2DM). To perform a meta-analysis of randomized controlled trials (RCTs) to explore the long-term effectiveness between CABG and PCI in patients with T2DM and study the temporal trends using a cumulative meta-analysis. PubMed, Embase, Cochrane library, and Clinical Trials Registry for eligible RCTs published up to September 2020. The outcomes were all-cause death, cardiac death, myocardial infarction, repeat revascularization, and stroke. Nine RCTs and 4566 patients were included. CABG resulted in better outcomes than PCI in terms of all-cause death (RR = 1.41, 95%CI: 1.22–1.63, $p < 0.001$), cardiac death (RR = 1.56, 95%CI: 1.25–1.95, $p < 0.001$), and repeat revascularization (RR = 2.68, 95%CI: 1.86–3.85, $p < 0.001$), but with difference regarding the occurrence of myocardial infarction (RR = 1.20, 95%CI: 0.78–1.85, $p = 0.414$), while PCI was associated with better outcomes in terms of stroke occurrence (RR = 0.51, 95%CI: 0.34–0.77, $p = 0.001$). The cumulative meta-analysis for all-cause death showed that the differences between CABG and PCI started to be significant at 3 years of follow-up, while the difference became significant at 5 years for cardiac death. In patients with CHD and T2DM, CABG results in better outcomes than PCI in terms of all-cause death, cardiac mortality, and repeat revascularization, while PCI had better outcomes in terms of stroke. The differences are mainly observed over the long-term follow-up.

KEYWORDS
coronary artery bypass graft, coronary heart disease, meta-analysis, mortality, percutaneous coronary intervention, type 2 diabetes mellitus

Qiuping Xie and Jianguo Huang equally contributed to this work.

1 | INTRODUCTION

Coronary heart disease (CHD) refers to myocardial dysfunction and organic lesions due to coronary artery stenosis and insufficient blood supply to heart areas. It has become the leading cause of death and disability worldwide.[1] CHD affects 1.7% of the world population and is responsible for 9 million deaths each year.[2] Type 2 diabetes mellitus (T2DM) is an independent risk factor of CHD.[3] About 370 million people have T2DM in the world.[4] The number of patients with coronary multi-vessel disease and T2DM is increasing year by year.[3]

Coronary artery bypass grafting (CABG) refers to cardiac surgery during which a section of a blood vessel, either an artery or vein, is grafted to serve as a new conduit for improved blood flow to the heart.[5] Percutaneous coronary intervention (PCI) is a non-surgical procedure to improve coronary blood flow at the occlusion site via maneuvers performed through a coronary catheter, including balloon inflation, stent placement, and/or atherectomy.[6] The two procedures have their pros and cons. CABG can provide long-term control of the disease, but it is a significantly invasive procedure, and there is a risk of losing graft patency over time. PCI is a minimally-invasive procedure, but in-stent restenosis can occur, which can be prevented using a drug-eluting stent (DES).[7] PCI is associated with higher restenosis and revascularization rates than with CABG during revascularization in patients with coronary multi-vessel disease complicated with T2DM; however, most data were obtained from the bare metal stent (BMS) era.[8-10] Still, because of the chronic inflammatory and oxidative stress states observed in T2DM, guidelines recommend CABG for patients with T2DM and coronary multi-vessel disease.[11] With the advent of DES, some authors believed that was is associated with a better prognosis, significantly reducing in-stent restenosis and revascularization rate after DES-PCI,[8,12] but the advent of DES might have widened the gap with respect to major adverse cardiovascular events.[13,14] In multi-vessel disease, it appears that CABG is associated with a better prognosis than PCI.[7] Furthermore, patients with T2DM require antiplatelet therapy after revascularization, and the optimal strategy is different than in non-T2DM patients,[15] which could influence the conclusions of the various studies.

Previous meta-analyses included randomized controlled trials (RCTs) and showed that CABG has lower all-cause mortality than PCI,[7,16-18] but the long-term outcomes were not analyzed thoroughly in patients with T2DM. Herein, we performed this updated meta-analysis only based on RCTs study to explore the long-term effectiveness between CABG and PCI in patients with CHD and T2DM. Moreover, a cumulative meta-analysis was performed to study the temporal trends.

2 | METHODS

2.1 | Literature search

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] A systematic search was performed in the PubMed, Embase, Cochrane library, and Clinical Trials Registry for available papers published up to September 2020. The terms "PCI" or "percutaneous intervention", "CABG" or "coronary artery bypass grafting", "coronary disease", and "T2DM" or "type 2 diabetes mellitus" were used. The reference lists from the retrieved studies were reviewed to identify any new eligible study. The eligibility criteria were (1) population: patients with coronary artery disease and T2DM, (2) intervention: CABG, (3) control: PCI, (4) outcome: all-cause mortality, cardiovascular-cause mortality, myocardial infarction (MI), repeat revascularization, and stroke, (5) study design: RCT, and (6) full text in English. Two authors (** and **) independently performed the literature search and selection.

2.2 | Data extraction

Two authors (** and **) independently extracted the study characteristics (first author's name, trial's name, recruitment period, sampling size, age, sex, intervention arms, and follow-up) and outcomes (if the study reported hazard ratios (HRs), the HRs and 95% confidence interval (CI) were extracted; if not, relative risks (RRs) and 95%CI were calculated based on the events in the two arms). When a paper reported multiple populations, the outcomes and population of interest were selected. Discrepancies were solved by discussion.

2.3 | Quality of the evidence

The methodological quality of the RCTs was evaluated by two authors (** and **) independently with the quality assessment tool from the Cochrane manual. Discrepancies were solved by discussion.

2.4 | Statistical analysis

RRs and corresponding 95% CIs were used to summarize the results. Statistical heterogeneity among the studies was calculated using Cochran's Q-test and the I^2 index. An $I^2 > 50\%$ and Q-test $p < 0.10$ indicated high heterogeneity. Considering the vast patient population that originated from different regions and the distinct variables that were adjusted for in different studies, the random-effects model was used to avoid the risk of overestimating the associations. Besides, a cumulative meta-analysis was conducted to study the temporal trends.[20] The possible publication bias could not be evaluated by funnel plots and Egger's test because the number of studies included in each meta-analysis was <10, in which case the funnel plots and Egger's test could yield misleading results. All analyses were performed using STATA SE 14.0 (StataCorp, College Station, TX).

3 | RESULTS

3.1 | Characteristics of the studies

Figure S1 presents the study selection process. The initial search produced 1090 records. After removing the duplicates, 905 records were screened, and 776 were excluded. Then, 129 full-text articles were assessed for eligibility and 120 were excluded (conference abstract and review, $n = 21$; study aim/design, $n = 40$; population, $n = 14$; intervention, $n = 11$; outcomes, $n = 29$; non-English, $n = 5$).

Finally, nine RCTs were included[14,21-30] (Table S1). There were 2266 patients in the CABG arm and 2300 in the PCI arm. Figure S2 shows that all nine trials carried a high risk of bias in at least one category.

3.2 | CABG, PCI, and all-cause death

The meta-analysis performed at the longest follow-up shows that CABG was associated with better survival than PCI (RR = 1.41, 95% CI: 1.22–1.63, $p < 0.001$; $I^2 = 3.3\%$, $P_{heterogeneity} = 0.407$) (Figure 1(A)). When analyzing by the type of stent, CABG was still associated with a better survival than DES PCI (RR = 1.50, 95%CI: 1.22–1.83, $p < 0.001$; $I^2 = 0.8\%$, $P_{heterogeneity} = 0.401$) and angioplasty (RR = 1.29, 95%CI: 1.03–1.61, $p = 0.025$), but there was no difference with bare-metal stent (BMS) PCI (RR = 1.58, 95%CI: 0.89–2.80, $p = 0.119$; $I^2 = 39.7\%$, $P_{heterogeneity} = 0.190$) (Figure 1(A)). The cumulative meta-analysis shows that the trials reporting outcomes at 1 month, 1 year, and 3 years showed no significant differences between CABG and PCI. Still, the differences started to be significant at 3 years in one trial, 5 years in three out of six trials, at 6 years in one trial, and 10 years in two trials (Figure 1(B)).

3.3 | CABG, PCI, and cardiac death

Figure 2(A) shows that CABG led to better survival than PCI in cardiac death (RR = 1.56, 95%CI: 1.25–1.95, $p < 0.001$; $I^2 = 0\%$, $P_{heterogeneity} = 0.774$). The same associations were observed when comparing CABG with DES PCI (RR = 1.50, 95%CI: 1.14–1.96, $p = 0.003$; $I^2 = 0\%$, $P_{heterogeneity} = 0.678$) and angioplasty (RR = 1.70, 95%CI: 1.15–2.52, $p = 0.008$). The cumulative meta-analysis showed that the differences were not significant at 1 month and 1, 2, and 3 years, but it was significant at 5 years in two of three studies and 10 years in one study (Figure 2(B)).

3.4 | CABG, PCI, and MI

There were no differences between CABG and PCI regarding the occurrence of MI (RR = 1.20, 95%CI: 0.78–1.85, $p = 0.414$; $I^2 = 65.8\%$, $P_{heterogeneity} = 0.008$), and when considering DES PCI (RR = 1.26, 95%CI: 0.76–2.10, $p = 0.367$; $I^2 = 72.7\%$, $P_{heterogeneity} = 0.006$) and BMS PCI (RR = 0.96, 95%CI: 0.37–2.51, $p = 0.931$; $I^2 = 43.9\%$, $P_{heterogeneity} = 0.182$) (Figure 3(A)). The cumulative meta-analysis showed that only two of three studies reported benefits from CABG at 5 years.

3.5 | CABG, PCI, and repeat vascularization

The meta-analysis performed at the longest follow-up shows that CABG was associated with a lower occurrence of repeat revascularization (RR = 2.68, 95%CI: 1.86–3.85, $p < 0.001$; $I^2 = 55.5\%$, $P_{heterogeneity} = 0.036$) (Figure 4). When analyzing by the type of stent, CABG was still associated with a better survival than DES PCI (RR = 2.29, 95%CI: 1.52–3.45, $p < 0.001$; $I^2 = 56.9\%$, $P_{heterogeneity} = 0.054$) and BMS PCI (RR = 4.37, 95%CI: 2.54–7.51, $p < 0.001$; $I^2 = 0\%$, $P_{heterogeneity} = 0.702$) (Figure 4).

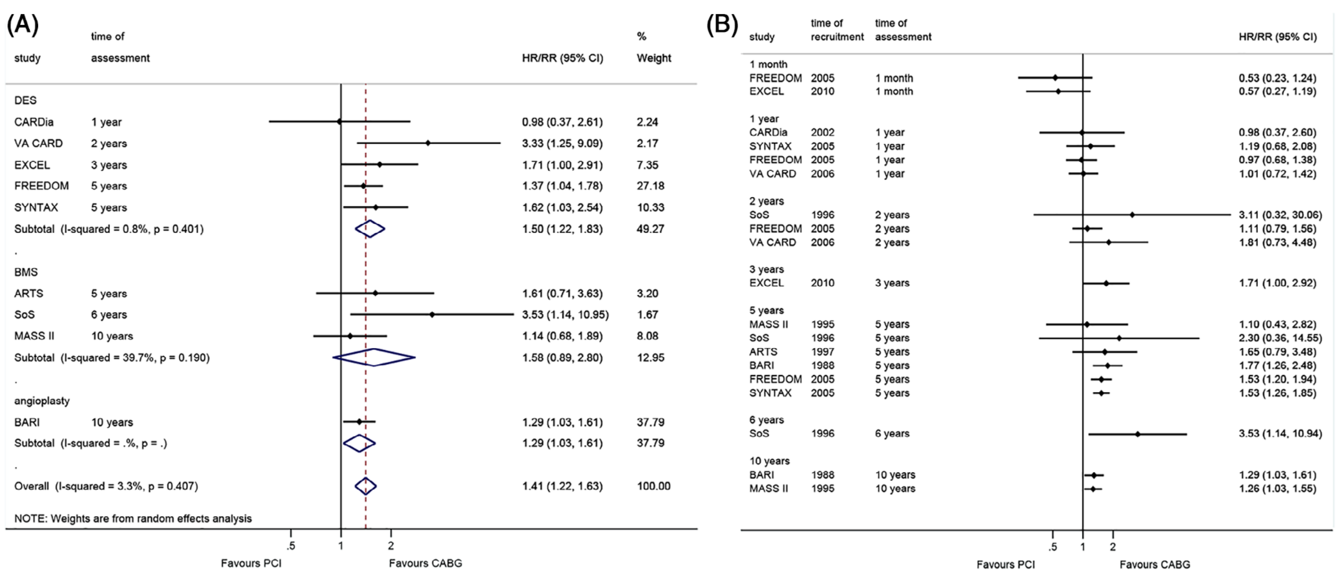

FIGURE 1 Effect of coronary artery bypass graft and percutaneous coronary intervention on all-cause death. (A). within the longest follow-up. (B). cumulative meta-analysis

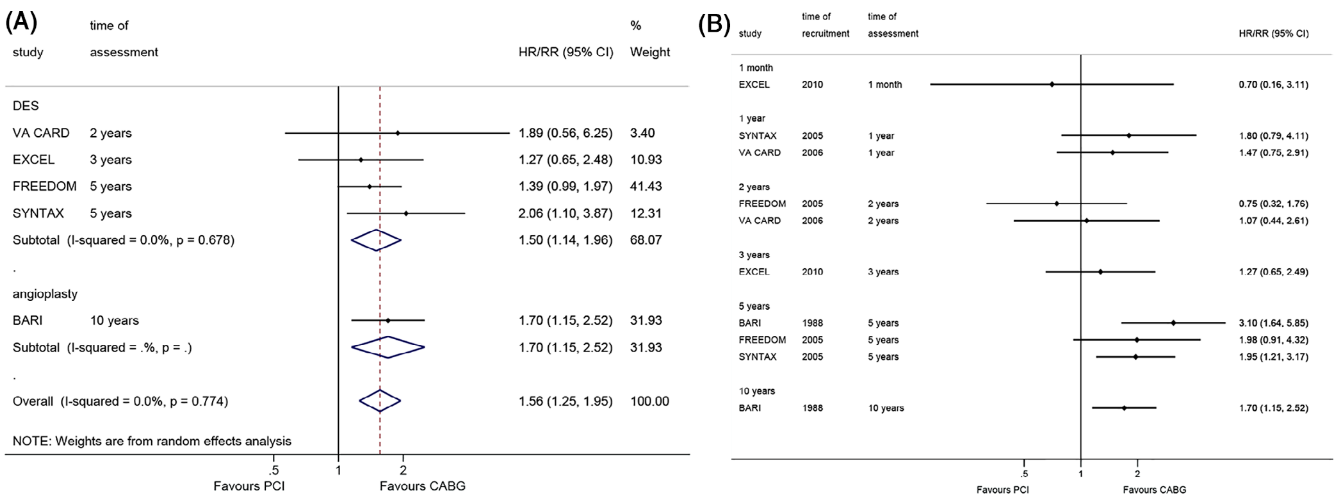

FIGURE 2 Effect of coronary artery bypass graft and percutaneous coronary intervention on cardiac death. (A). within the longest follow-up. (B). cumulative meta-analysis

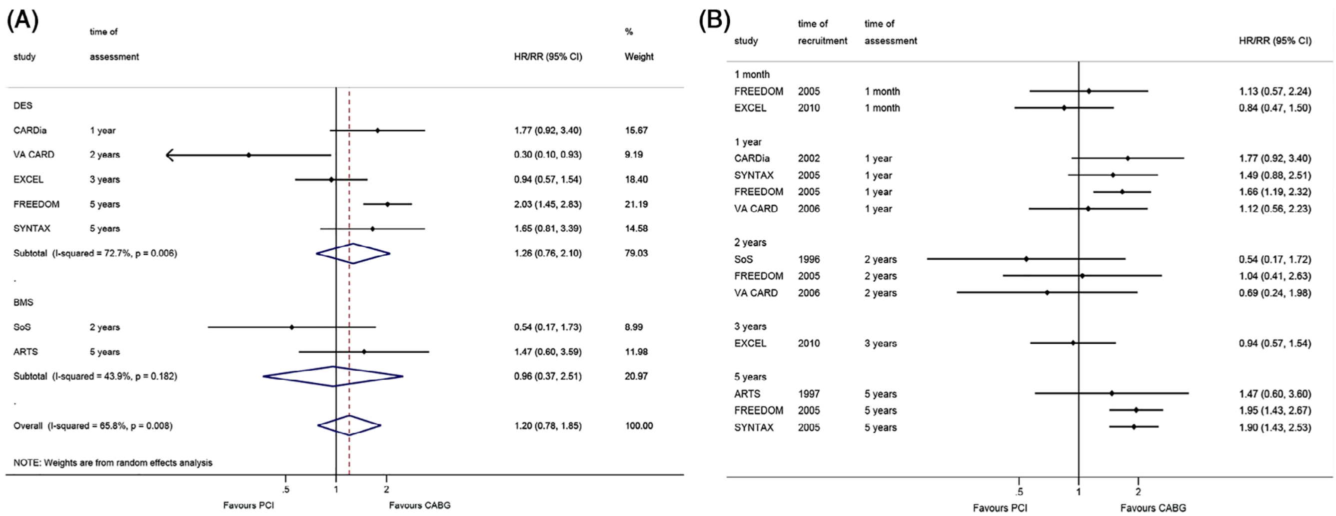

FIGURE 3 Effect of coronary artery bypass graft and percutaneous coronary intervention on myocardial infarction. (A). within the longest follow-up. (B). cumulative meta-analysis

3.6 | CABG, PCI, and stroke

At the longest follow-up, DES PCI was associated with a lower occurrence of stroke (RR = 0.51, 95%CI: 0.34–0.77, $p = 0.001$; $I^2 = 0\%$, $P_{heterogeneity} = 0.715$) (Figure 5).

4 | DISCUSSION

Previous meta-analyses showed that CABG has lower all-cause mortality than PCI for the management of CHD,[7,16-18,31,32] but the long-term outcomes were not analyzed thoroughly in patients with T2DM. Therefore, this meta-analysis of RCTs to explore the long-term effectiveness between CABG and PCI in patients T2DM and to study the temporal trends using a cumulative meta-analysis. The results show that in patients with CHD and T2DM, CABG results in better outcomes than PCI in terms of all-cause death, cardiac mortality, and repeat revascularization, while PCI had better outcomes in terms of stroke. The differences are mainly observed over the long-term follow-up.

In the pre-DES era, previous meta-analyses did not found significant differences in long-term survival between PCI and CABG in diabetic patients, and that was also recently observed in both cardiac and non-cardiac mortality where better survival with CABG was seen only in the DES era.[13,33-36] Still, multiple previous meta-analyses suggested better outcomes of CABG than PCI.[7,16-18,31,32] Spadaccio et al[7] showed that CABG had better outcomes than DES PCI regarding MI, stroke, and repeat revascularization. Athappan et al[16] performed a meta-analysis of three RCTs and showed that the rates of major adverse cardio-cerebrovascular events (MACCES) and repeat

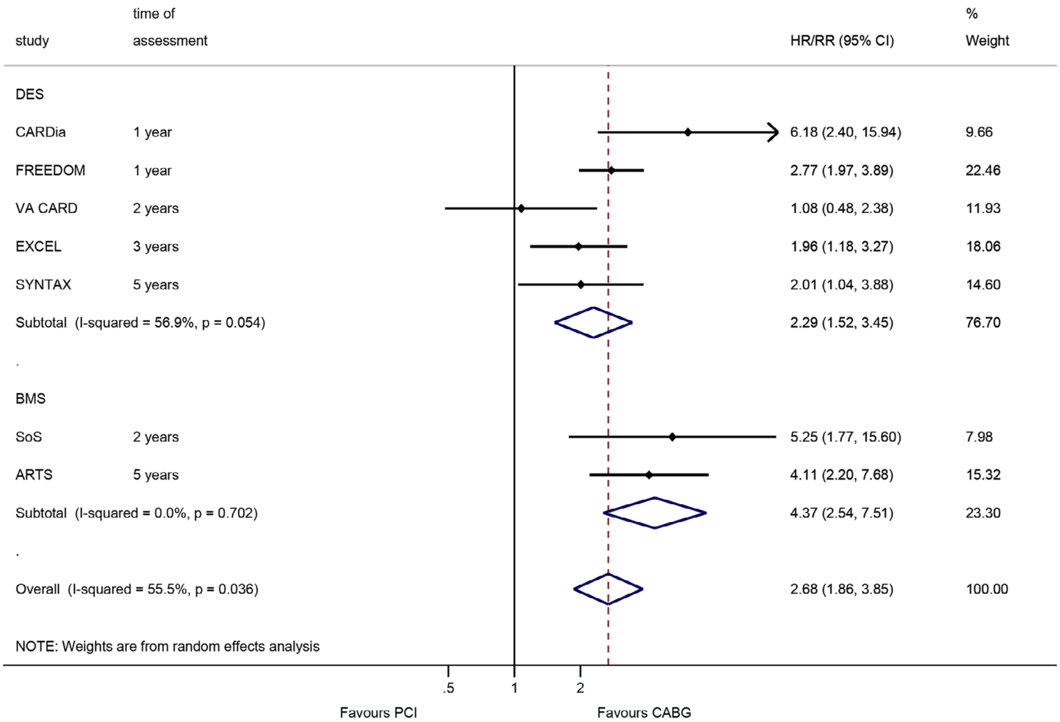

FIGURE 4 Effect of coronary artery bypass graft and percutaneous coronary intervention on repeat revascularization (within the longest follow-up)

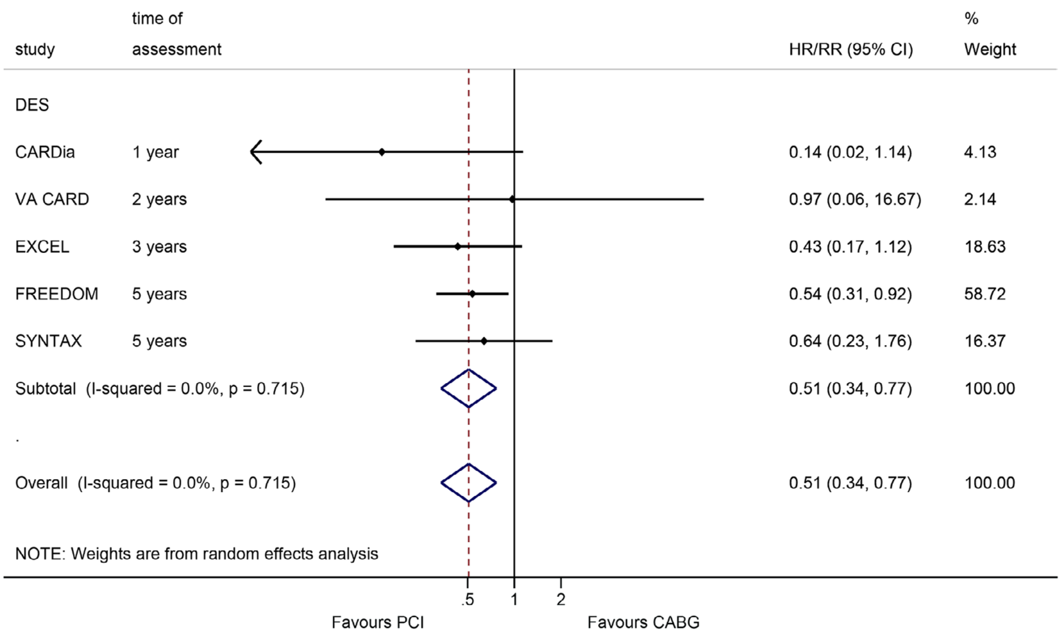

FIGURE 5 Effect of coronary artery bypass graft and percutaneous coronary intervention on stroke (within the longest follow-up)

revascularization were high after PCI. Ali et al[17] showed that CABG had advantages over PCI in MACCES, repeat vascularization, and MI, while the stroke risk was lower with PCI. Ahmad et al[18] reported no differences in any outcomes between PCI and CABG. Gallo et al[31] showed no differences between CABG and PCI in 5-year mortality, while CABG was associated with a higher risk of stroke at 1 and 12 months, while PCI was associated with higher risks of MI and repeat revascularization at 5 years. Zhai et al[32] performed a meta-analysis of RCTs and observational studies in diabetic patients. They showed that CABG was superior to PCI in diabetic patients but that the risk of stroke was higher. Globally, those previous meta-analyses performed in various patient populations with CHD and including various study designs support the present meta-analysis that included only diabetic patients and RCTs. The combined results suggest better CABG outcomes regarding mortality, MI, and repeat vascularization, but a higher risk of stroke. This is supported by a 12-year follow-up study from the MAIN COMPARE registry.[37] This study could not examine the causes of this increased risk of stroke, but it could coincide with antiplatelet therapy discontinuation after 1 year.[38,39] This could also be due to cerebral embolism due to manipulating aortic atherosclerotic plaques during CABG[40,41] and cerebral hypoperfusion during CABG.[42,43]

The incidence of CHD in diabetic patients is 2–4 times higher than that in non-diabetic individuals, and the odds of multi-vessel disease and a higher degree of disease are higher than in non-diabetics.[44-46] Many studies showed that CABG seems to be a better choice than PCI in elderly patients with CHD and T2DM, especially in the case of multi-vessel CHD.[47,48] For example, previous reports regarding the data on heart disease (diabetic coronary revascularization) trials and 5-year results showed that the incidence of MACCES associated with PCI was significantly higher than that of CABG patients with T2DM.[49] Bundhun et al.[50] stated that MACCES, as well as repeated revascularization, were significantly lower in the CABG group than those in the PCI group, supporting the present study, albeit MACCES could not be analyzed here because of too vast differences in the definitions of MACCES among the included studies. According to Kappetein et al.,[12] PCI resulted in a high incidence of MACCES and repeated vascular reconstruction within 5 years in diabetic and non-diabetic patients. Therefore, although PCI is a potential treatment, CABG should be considered as the first choice for vascular reconstruction in patients with more complex anatomical diseases, especially in patients with diabetes mellitus.

In patients whose 3-5-year health status exceeds the survival period (recognizing the 1-year health status of CABG), the perioperative risk associated with CABG might require attention (i.e., in elderly patients). In this study, the cumulative meta-analysis approach suggests that the differences between CABG and PCI became significant at 3 years. This contradicts a meta-analysis by Athappan et al.,[16] who showed that the differences between CABG and PCI disappeared after 5 years. Those conflicting results could be due to the different studies being included and the meta-analysis method (cumulative meta-analysis, in the present study). Hence, carefully weighing the operative risks with the expected survival is essential to select the best approach.

There are some limitations that must be considered. First, heterogeneity was observed for many analyses, and the random-effect model was used in all analyses because of the heterogeneity of the included patient populations. This avoids over-estimating the associations but results in weaker associations than the actual associations. Besides, heterogeneity might be because positive results have a higher chance of publication. In addition, limiting the articles to English could lead to the omission of valuable results that could tip the balance. Second, studies from more countries should be analyzed since there are disparities among countries regarding economy and guidelines. Third, due to heterogeneity in definitions of composite outcomes such as MACCE, the present meta-analysis did not analysis these data. Finally, no patient-level data were available and could be analyzed. Further research on composite outcomes over long-term follow-up with larger sample sizes is warranted in the future.

In conclusion, in patients with CHD and T2DM, CABG results in better outcomes than PCI in terms of all-cause death, cardiac mortality, and repeat revascularization, while PCI had better outcomes in terms of stroke. The differences are mainly observed over the long-term follow-up and when comparing with patients with a DES. This study also suggests that a BMS is no worse than a DES in diabetics. Future studies could examine outcomes like MACCE, surgical complications, in-hospital mortality, quality of life, and overall costs of CABG vs. PCI in patients with CHD and T2DM.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data set supporting the results of this article are included within the article and supplementary materials.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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