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Impact of time factor and patient characteristics on the efficacy of PCI vs CABG for left main coronary disease

A meta-analysis

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Abstract

Background: The impact of time factor and patient characteristics on the efficacy of percutaneous coronary intervention (PCI) with drug-eluting stents vs. coronary-artery bypass grafting (CABG) for left main coronary disease is unclear.

Methods: We searched PubMed and Embase for related trials. Two outcomes of interest were major adverse cardiac or cerebrovascular events (MACCE, defined as a composite of all-cause mortality, myocardial infarction, stroke, or unplanned revascularization) and a composite of all-cause mortality, myocardial infarction, or stroke. We conducted random-effects meta-analysis stratified by follow-up duration and 7 factors of interest related to patient characteristics. Random-effects meta-regression was performed to calculate *P* values for trend and those for subgroup differences.

Results: We included 11 articles from 5 trials. Compared with CABG, PCI increased MACCE at the end of 3-year (hazard ratio [HR] 1.21, 95% confidence interval [CI] 1.04-1.40, $I^2=0$) and 5-year (HR 1.33, 95% CI 1.20–1.48, $I^2=0$) follow-up, but did not increase all-cause mortality, myocardial infarction, or stroke. The logarithm of HR of PCI vs CABG for MACCE increased as follow-up duration increased ($\beta=0.057$, $P=.025$). PCI vs CABG consistently increased 5-year MACCE across various subgroups defined by 7 factors of interest ($P_{subgroup}$ ranged from .156 to .830).

Conclusions: The long-term benefit of CABG vs PCI on MACCE in patients with left main coronary disease is consistent across patients with different clinical characteristics. The relative benefit of CABG on MACCE is driven by that of CABG on unplanned revascularization, and becomes greater as time goes on.

Abbreviations: AMS = all-cause mortality, myocardial infarction or stroke, CABG = coronary-artery bypass grafting, CI = confidence interval, HR = hazard ratio, MACCE = major adverse cardiac or cerebrovascular events, PCI = percutaneous coronary intervention, RCTs = randomized controlled trials.

Keywords: CABG, left main coronary disease, major adverse cardiac or cerebrovascular events, percutaneous coronary intervention

1. Introduction

Although large randomized controlled trials (RCTs) compared coronary-artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) using drug-eluting stents in the efficacy on left main coronary disease, the impact of time factor and patient characteristics on the efficacy of PCI vs CABG for left main coronary disease is unestablished. The main three reasons for this issue are as follows.

First, the efficacy of PCI vs CABG is inconsistent at different time points of follow-up. For example, in the EXCEL trial PCI was observed to significantly reduce the risk of major adverse cardiac or cerebrovascular events (MACCE, defined as a composite of all-cause mortality, myocardial infarction, stroke, or unplanned revascularization) compared with CABG at the end of 30-day follow-up,[1] whereas PCI was observed to increase this risk at the end of 3- and 5-year follow-up.[1,2] Besides, in the PRECOMBAT trial PCI vs CABG showed the trend of a reduction in the risk of MACCE at the end of 30-day and 6-month follow-up,[3] whereas PCI showed the trend of an increase in this risk at the end of 1-, 2-, 5, and 10-year follow-up.[3–5] Second, the efficacy of PCI vs CABG is inconsistent across different primary studies. For example, the two trials of EXCEL[2] and NOBLE[6] revealed that PCI vs CABG

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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significantly increased the risk of 5-year MACCE, whereas the two trials of SYNTAX[7] and PRECOMBAT[4] did not reveal. Besides, there was the trend of an increase in the risk of 1-year MACCE with PCI in the two trials of NCT00176397[8] and PRECOMBAT,[3] whereas there was the trend of a reduction in this risk with PCI in the two trials of EXCEL[2] and SYNTAX.[9] Third, there is a lack of statistical power in individual trials to assess the efficacy of PCI vs CABG in some subgroups. For example, in the NOBLE trial[6] CABG vs PCI significantly reduced the risk of 5-year MACCE according to the analysis on the data of all participants, whereas CABG did not significantly reduce this risk in the subgroups of participants with age < 67 years, of participants with diabetes, and of participants with a SYNTAX score of more than 22 due to the wider 95% confidence intervals (CIs) of effect size.

Thus, we conducted the present meta-analysis to assess the impact of time factor and 7 key factors relevant with patient characteristics on the efficacy of PCI vs CABG on MACCE in patients with left main coronary disease.

2. Methods

2.1. Inclusion criteria

The meta-analysis is reported according to the PRISMA statement. The PRISMA checklist for the article is presented in Table S1, http://links.lww.com/MD/F850 (Supplemental Content, which presents the PRISMA checklist). Pre-planned search strategies (see Table S2, http://links.lww.com/MD/F851, Supplemental Content, which provides the search strategies in detail) were used to search the PubMed and Embase databases until June 7, 2020 for relevant RCTs. We included RCTs which assessed the efficacy of PCI versus CABG in patients with left main coronary disease. The detailed inclusion/exclusion criteria are shown in the study protocol (registration number: INPLASY202060017; available at https://inplasy.com/inplasy-2020–6–0017). Two outcomes of interest were a primary endpoint of MACCE and a secondary endpoint of a composite of all-cause mortality, myocardial infarction, or stroke (AMS). Included RCTs were assessed for risk of bias according to the Cochrane risk of bias tool (version 5.1.0).

2.2. Statistical analysis

To evaluate the impact of time factor on the efficacy of PCI vs CABG, we conducted meta-analysis on two outcomes of interest stratified by follow-up duration, and also conducted meta-regression analysis using follow-up duration as the independent variable. To evaluate the impact of 7 important factors (i.e., age, sex, diabetes, non–left main diseased coronary arteries, acute coronary syndrome, distal left main coronary stenosis, and SYNTAX score) related to patient characteristics on the efficacy of PCI vs CABG, we conducted meta-analysis on MACCE measured at the end of 5-year follow-up in various subgroups defined by the seven factors of interest, and also conducted meta-regression analysis to calculate the p values for subgroup differences. Meta-analyses and meta-regression analyses were performed using the random-effects model. Heterogeneity was measured by I^2 statistic. Effect sizes were hazard ratios (HRs) and 95% CIs. Publication bias was examined using funnel plots and Egger tests. $P < 0.05$ represents statistical significance. All analyses were completed using Stata (version 15.1).

2.3. Ethical statement

The data analyzed in this study were extracted from previously published studies, and therefore ethical approval was not necessary.

3. Results

3.1. Characteristics of included trials

We included 11 articles[1–11] from 5 RCTs for pooled analysis after study selection, as is shown in Figure S1, http://links.lww.com/MD/F844 (Supplemental Content, which is the PRISMA flow diagram of study selection). The characteristics of included trials and the risk of bias results were the same as those in a recent meta-analysis study.[12] The data analyzed in the study are provided in Table S3, http://links.lww.com/MD/F852 (Supplemental Content, which shows the original data analyzed in the study), in which the **Sheet1** provides the data used for assessing the impact of time factor on the efficacy of PCI vs CABG, and the **Sheet2** provides the data used for assessing the impact of 7 important factors related to patient characteristics on the efficacy of PCI vs CABG.

3.2. Meta-analyses and meta-regression analyses

The 5 trials of EXCEL, NOBLE, PRECOMBAT, SYNTAX and NCT00176397 were included for the pooled analysis of assessing the impact of time factor on the efficacy of PCI versus CABG. Compared with CABG, PCI reduced MACCE at the end of 30-day follow-up (HR 0.56, 95% CI 0.40–0.79, $I^2 = 0$) whereas PCI increased MACCE at the end of 3-year (HR 1.21, 95% CI 1.04–1.40, $I^2 = 0$) and 5-year (HR 1.33, 95% CI 1.20–1.48, $I^2 = 0$) follow-up (Fig. 1), while the logarithm of HR of PCI vs CABG for MACCE increased as follow-up duration increased ($\beta = 0.057$, $P = 0.025$) (see Figure S2, Supplemental Content, http://links.lww.com/MD/F845, which shows the results of meta-regression analysis of the impact of follow-up duration on the efficacy of PCI vs CABG for MACCE). PCI vs CABG reduced 30-day AMS (HR 0.61, 95% CI 0.42–0.88), and was not significantly different with CABG in 1-year, 2-year, 3-year, 5-year, and 10-year AMS (see Figure S3, Supplemental Content, http://links.lww.com/MD/F846, which shows the results of meta-analysis of the efficacy of PCI vs CABG for AMS, stratified by follow-up duration), while the logarithm of HR of PCI vs CABG for AMS was not associated with follow-up duration ($\beta = 0.045$, $P = .135$) (see Figure S4, Supplemental Content, http://links.lww.com/MD/F847, which shows the results of meta-regression analysis of the impact of follow-up duration on the efficacy of PCI vs CABG for AMS).

The 3 trials of NOBLE, PRECOMBAT, and SYNTAX were included for the pooled analysis of assessing the impact of 7 factors of interest on the efficacy of PCI vs CABG. PCI vs CABG significantly increased 5-year MACCE regardless of age (Fig. 2; $P_{subgroup} = .591$), sex (Fig. 3; $P_{subgroup} = .574$), history of diabetes (Fig. 4; $P_{subgroup} = .886$), number of non–left main diseased coronary arteries (Fig. 5; $P_{subgroup} = .989$), existence of acute coronary syndrome (Fig. 6; $P_{subgroup} = .156$), existence of distal left main coronary stenosis (Fig. 7; $P_{subgroup} = .923$), and SYNTAX score (Fig. 8; $P_{subgroup} = .724$). **Figures S5-S11**, http://links.lww.com/MD/F848 (Supplemental Content, which shows the results of sensitivity analysis with the EXCEL trial included) showed that $P_{subgroup}$ ranged from 0.156 to 0.830, suggesting the robustness of the above findings. Publication bias

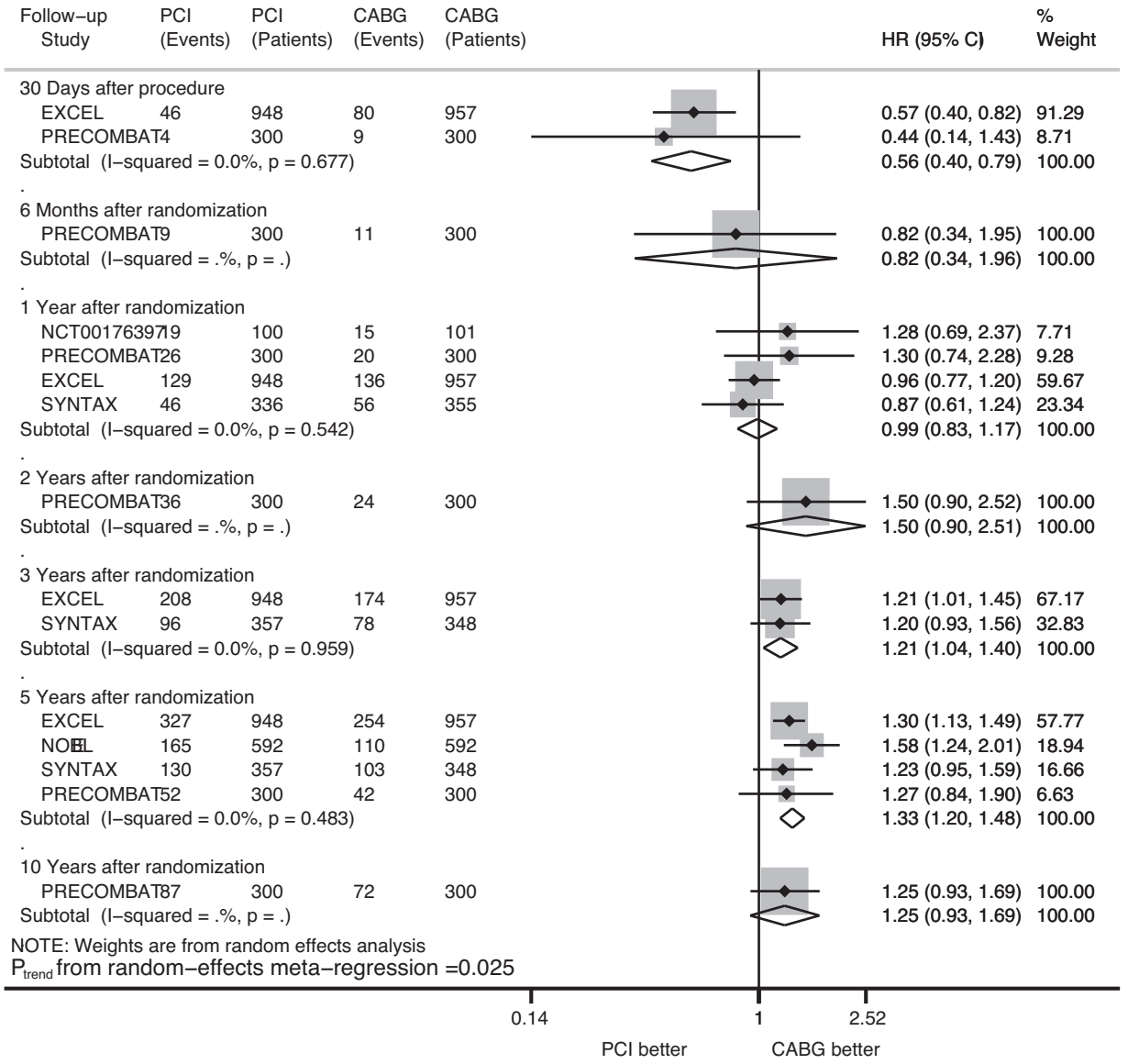

Figure 1. Meta-analysis of the efficacy of PCI versus CABG for MACCE, stratified by follow-up duration.

was not observed for 5-year MACCE in all subgroups defined by the 7 factors of interest (see **Figures S12-S28**, Supplemental Content, http://links.lww.com/MD/F849, which shows the results of publication bias detection).

4. Discussion

Compared with recent meta-analysis studies,[12–14] for the first time we assessed the impact of time factor and key factors relevant with patient characteristics on the efficacy of PCI vs CABG for left main coronary disease. Accordingly, two main findings were produced as follows. First, we found that the logarithm of HR of PCI vs CABG for MACCE increased as follow-up duration increased ($\beta = 0.057$, $P = .025$), which suggests that the benefit of CABG vs PCI on MACCE becomes greater as time goes on. Second, we found that PCI vs CABG consistently increased 5-year MACCE across various subgroups defined by 7 key factors (i.e., age, sex, diabetes, non–left main diseased coronary arteries, acute coronary syndrome, distal left main coronary stenosis, and SYNTAX score), which suggests that the superiority of CABG over PCI in 5-year MACCE is consistent across patients with different clinical characteristics.

Moreover, in our study CABG vs PCI was observed to significantly reduce 3-year and 5-year MACCE but was not observed to significantly reduce 3-year and 5-year AMS, which suggests that the benefit of CABG vs PCI on MACCE does not derive from that of CABG vs PCI on AMS. Meanwhile, Ahmad et al[12] demonstrated similar long-term mortality, stroke, and myocardial infarction after CABG vs PCI in patients with left main coronary disease, but less unplanned revascularization procedures after CABG vs PCI. Thus, we can conclude that the long-term benefit of CABG vs PCI on MACCE is driven by that of CABG vs PCI on unplanned revascularization.

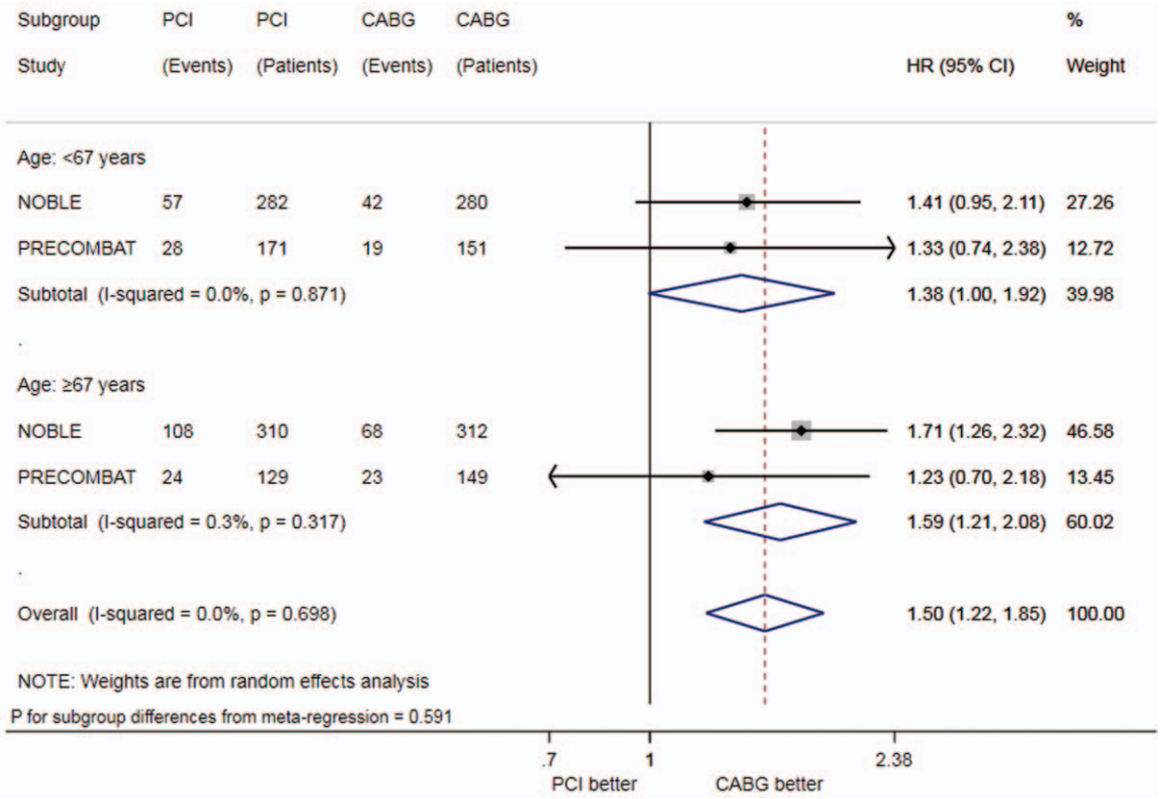

Figure 2. Meta-analysis of the efficacy of PCI versus CABG for MACCE, stratified by age.

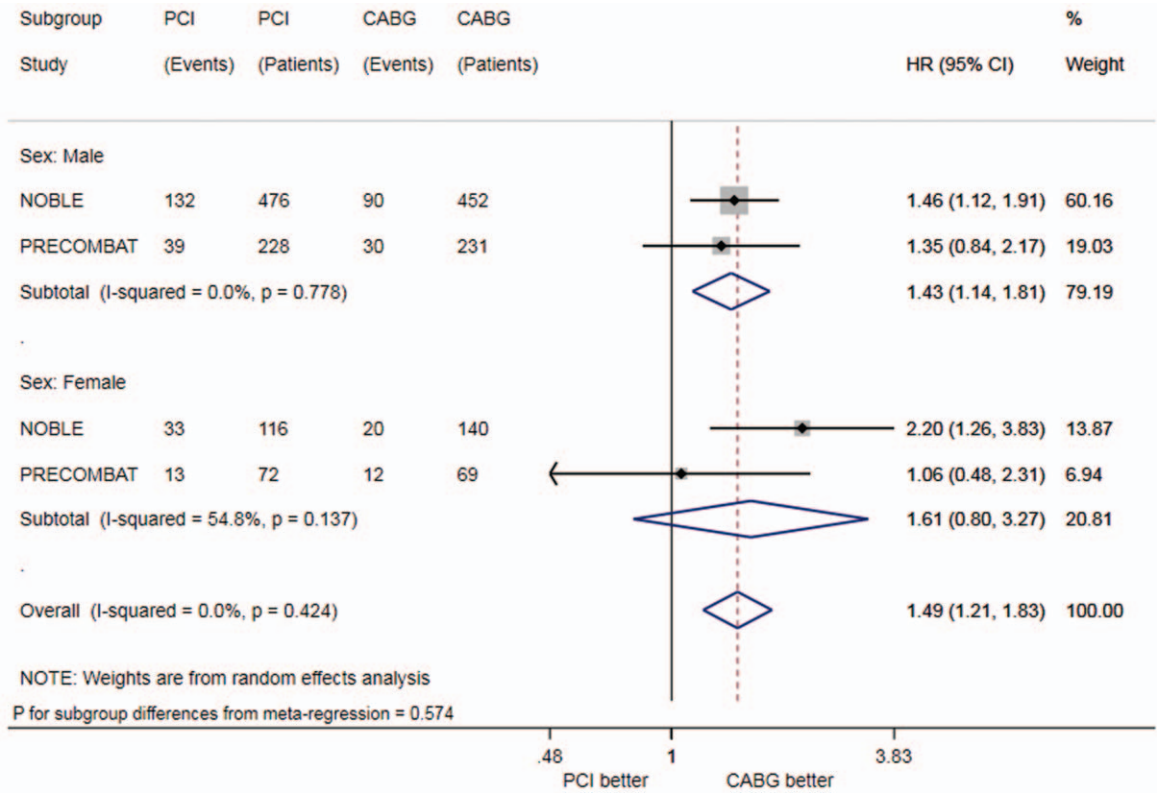

Figure 3. Meta-analysis of the efficacy of PCI versus CABG for MACCE, stratified by sex.

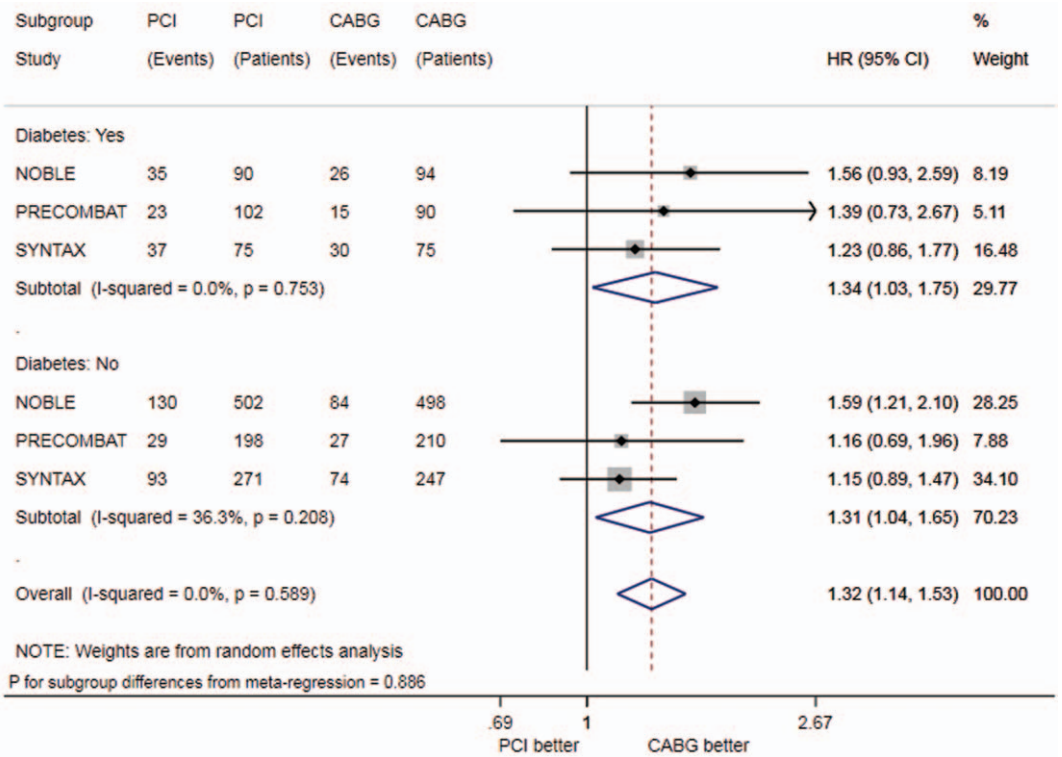

Figure 4. Meta-analysis of the efficacy of PCI versus CABG for MACCE, stratified by diabetes.

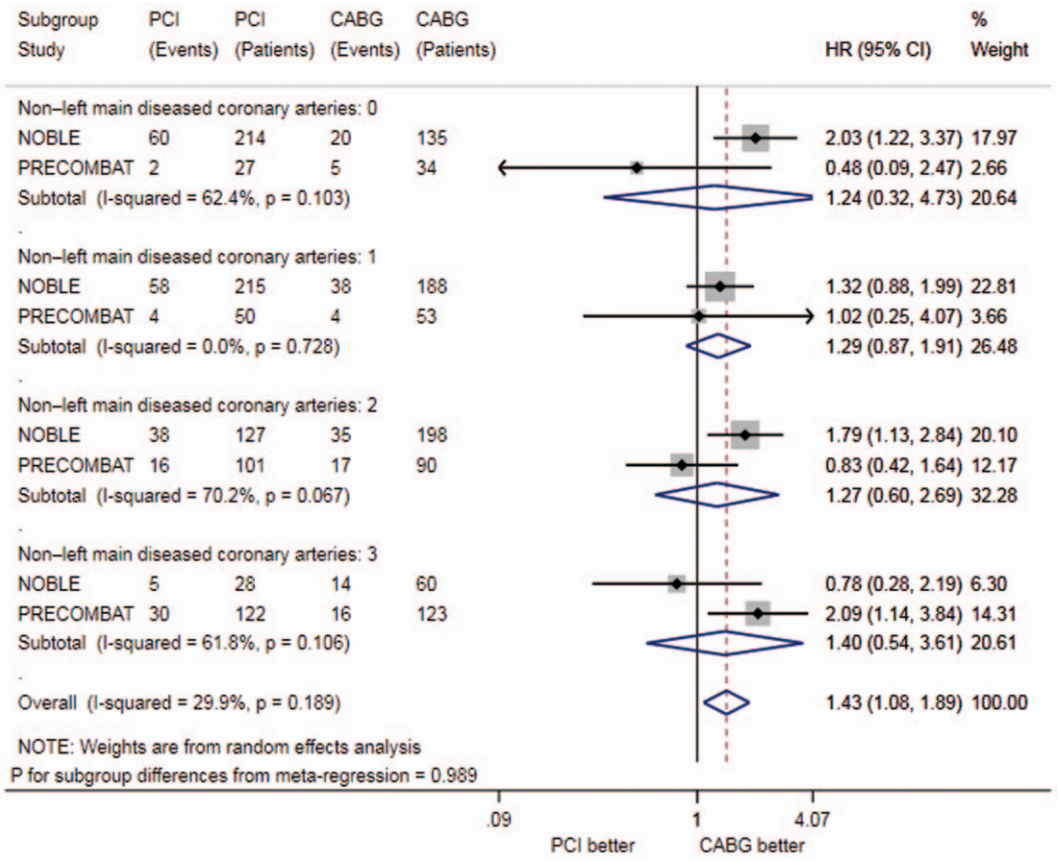

Figure 5. Meta-analysis of the efficacy of PCI versus CABG for MACCE, stratified by non–left main diseased coronary arteries.

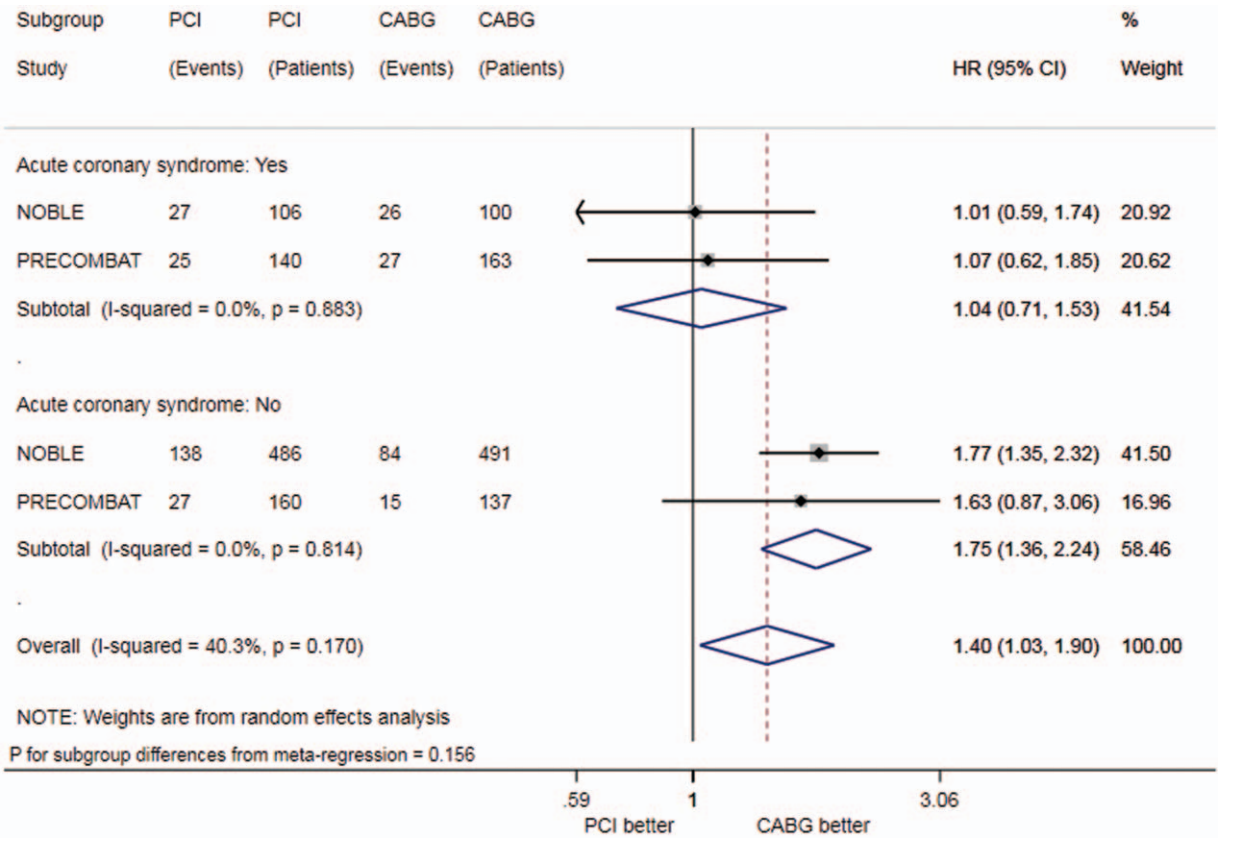

Figure 6. Meta-analysis of the efficacy of PCI versus CABG for MACCE, stratified by acute coronary syndrome.

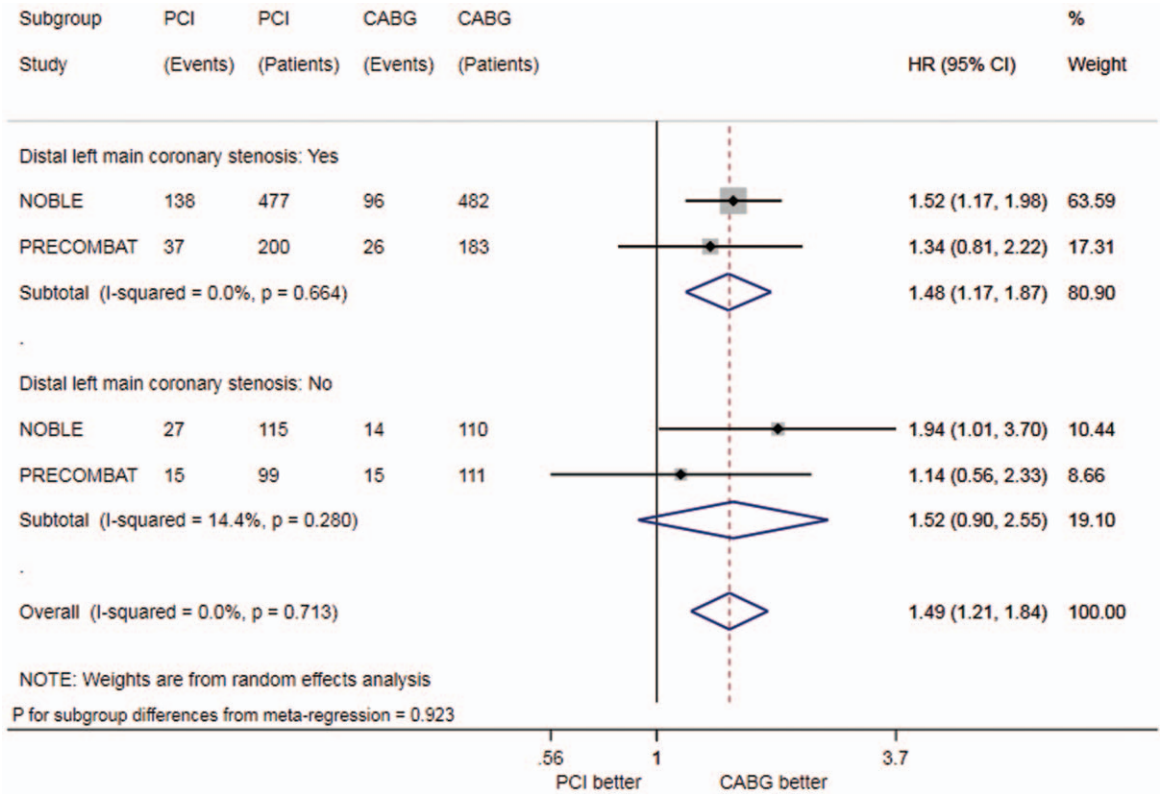

Figure 7. Meta-analysis of the efficacy of PCI versus CABG for MACCE, stratified by distal left main coronary stenosis.

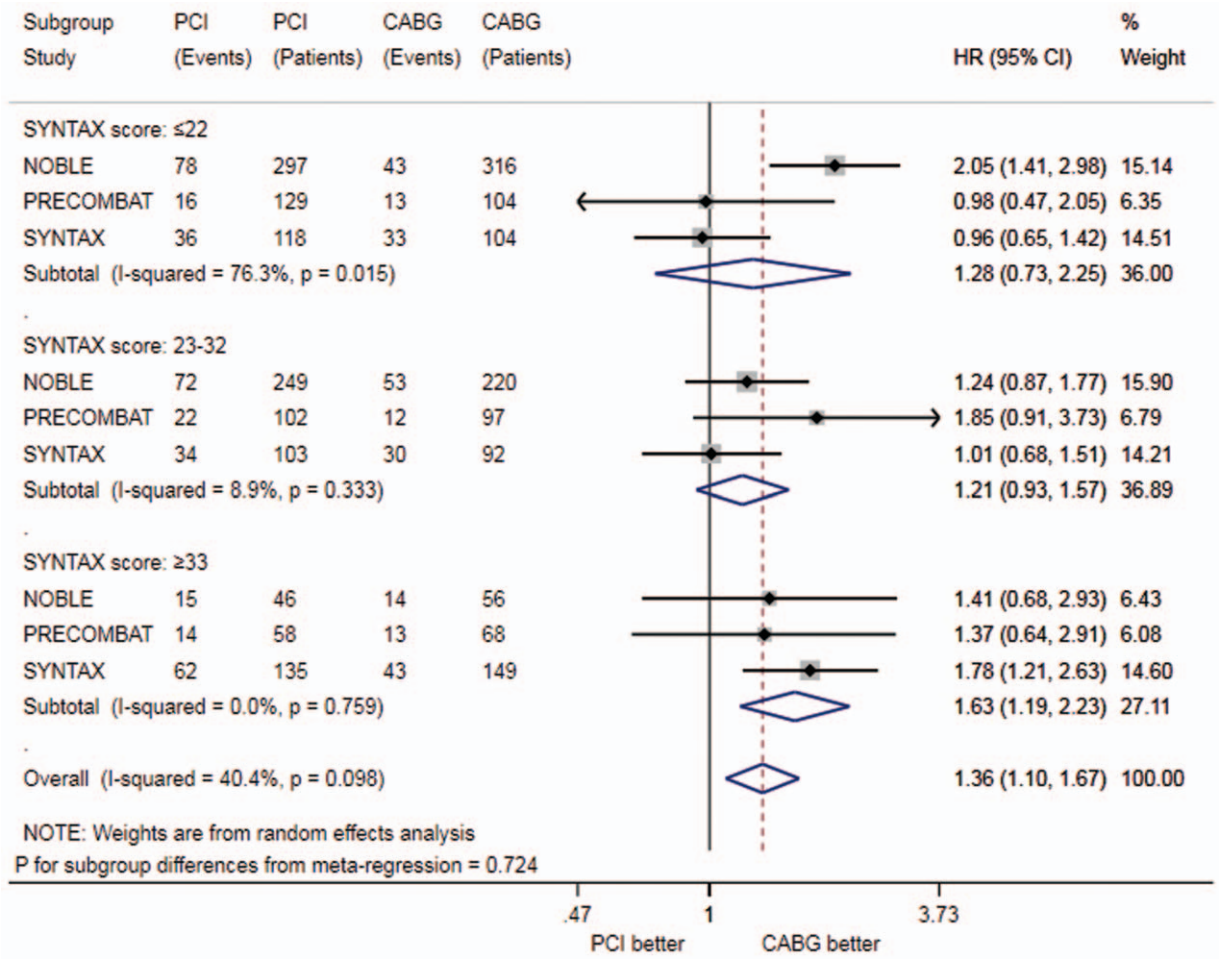

Figure 8. Meta-analysis of the efficacy of PCI versus CABG for MACCE, stratified by SYNTAX score.

Among the 5 trials included in our meta-analysis, only the SYNTAX trial[9] compared PCI using TAXUS stents with CABG, whereas the other four trials[1,3,6,8] compared PCI using non-TAXUS stents with CABG. There was no heterogeneity ($I^2=0$) observed in the meta-analyses of 1-year, 3-year, and 5-year MACCE (Fig. 1 in our manuscript), although those meta-analyses incorporated studies of TAXUS stents (i.e., SYNTAX[9]) and studies of non-TAXUS stents (i.e., NCT00176397[8], PRECOMBAT[3], EXCEL[1], and NOBLE[6]). It suggested that PCI with different types of stents (TAXUS stents or non-TAXUS stents) did not affect the efficacy of PCI on MACCE. Similarly, there was no heterogeneity ($I^2=0$) found in Figure 2, Figures 4 and 5 in the meta-analysis by Ahmad et al[12], which suggested that PCI with different types of stents did not affect the efficacy of PCI on cardiac death, myocardial infarction, and unplanned revascularization. Although some heterogeneity was observed in the meta-analyses of stroke (Fig. 3) and death (**Take home Figure**) in Ahmad et al's article[12], the overlap of 95% confidence intervals of treatment effects from individual trials suggested that the heterogeneity did not derive from the SYNTAX trial[9] (i.e., the trial of TAXUS stents). Thus, we have reasons to believe that PCI with different types of stents (TAXUS stents or non-TAXUS stents) do not affect the efficacy of PCI on the two composite outcomes assessed in our study, although there are significant differences between PCI with TAXUS stents and PCI with non-TAXUS stents in some other aspects such as safety. Accordingly, the findings based on meta-analysis incorporating trials of TAXUS stents and trials of non-TAXUS stents in our study are suitable for both the population with TAXUS stents and the population with non-TAXUS stents.

This study has three main limitations. First, we observed substantial statistical heterogeneity in a few of the subgroups evaluated in this meta-analysis, and the substantial heterogeneity observed needs to be further clarified by more specific subgroup analysis. Second, although the results of funnel plots and Egger tests in this study did not reveal any potential publication bias, funnel plots and Egger tests lack in statistical power when a meta-analysis such as our meta-analysis includes less than 10 original studies. Third, although there was not substantial statistical heterogeneity observed in the meta-analyses incorporating the data of TAXUS stents and that of non-TAXUS stents, TAXUS stents are different with non-TAXUS stents in some features such as safety. Thus, the findings of our meta-analysis should be interpreted with caution, and need to be validated by an updated meta-analysis only including the more trials of non-TAXUS stents.

In conclusion, the long-term benefit of CABG vs PCI on MACCE in patients with left main coronary disease is consistent across patients with different clinical characteristics. The relative benefit of CABG on MACCE is driven by that of CABG on

unplanned revascularization, and becomes greater as time goes on.

Author contributions

Conceptualization: Mei Qiu.
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Formal analysis: Liangliang Ding.
Validation: Zelin Zhan, Hairong Zhou.
Writing – original draft: Mei Qiu.
Writing – review & editing: Liangliang Ding, Zelin Zhan, Hairong Zhou.

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