Worse clinical outcomes following percutaneous coronary intervention with a high SYNTAX score
A systematic review and meta-analysis
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Abstract
Background: The synergy between percutaneous coronary intervention (PCI) with TAXUS and Cardiac Surgery (SYNTAX) score is an angiographic tool which is used to determine the complexity of coronary artery disease (CAD). We aimed to compare PCI versus coronary artery bypass surgery (CABG) in patients with a high SYNTAX score in order to confirm with evidence whether the former is really association with worse clinical outcomes.

Methods: The National database of medical research articles (MEDLINE/PubMed), EMBASE database, and the Cochrane library were searched for publications comparing PCI versus CABG in patients with a high SYNTAX score, respectively. Death, myocardial infarction (MI), stroke, repeated revascularization, and a combined outcome death/stroke/MI were considered as the clinical endpoints. RevMan software was used to analyze the data, whereby odds ratios (OR) with 95% confidence intervals (CI) were used as the statistical parameters.

Results: A total number of 1074 patients were included (455 patients with a high SYNTAX score were classified in the PCI group and 619 other patients with a high SYNTAX score were classified in the CABG group). A SYNTAX score cut-off value of ≥33 was considered relevant. Compared with CABG, mortality was significantly higher with a high SYNTAX score following PCI with OR: 1.79, 95% CI: 1.18 to 2.70; \(P = 0.006, \chi^2 = 0\). The combined outcome death/stroke/MI was also significantly higher following PCI with a high SYNTAX score, with OR: 1.69, 95% CI: 1.24 to 2.30; \(P = 0.006, \chi^2 = 0\). In addition, PCI was also associated with significantly higher MI and repeated revascularization when compared with CABG, with OR: 3.72, 95% CI: 1.75 to 7.89; \(P = 0.006, \chi^2 = 0\) and OR: 4.33, 95% CI: 1.71 to 10.94; \(P = 0.002, \chi^2 = 0.0\), respectively. However, stroke was not significantly different.

Conclusions: Compared with CABG, worse clinical outcomes were observed following PCI in patients with a high SYNTAX score, confirming with evidence, published clinical literatures. Therefore, CABG should be recommended to CAD patients who have been allotted a high SYNTAX score.

Abbreviations: CABG = coronary artery bypass surgery, CAD = coronary artery disease, PCI = percutaneous coronary intervention.

Keywords: coronary artery bypass surgery, left main coronary artery diseases, multi-vessel coronary artery disease, percutaneous coronary intervention, SYNTAX score

1. Introduction
Percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) are the 2 main revascularization procedures which are carried out in patients with left main or multi-vessel coronary artery disease (CAD).[1] Newer scientific reports have already shown that CABG might be more beneficial and effective in patients with diabetes mellitus, complicated by multi-vessel CAD.[2]

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The synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score, an angiographic tool which is used to determine the complexity of CAD has shown to facilitate the selection of patients who might benefit from either PCI or CABG. It was derived from pre-existing classifications such as the American Heart Association (AHA) classification of CAD modified for the ARTS study, the American College of Cardiology (ACC)/AHA lesion classification, the Duke classification, the International classification for patient safety, and so on. In patients who were allotted a low SYNTAX score, PCI was a good option whereas in patients who were allotted a high SYNTAX score, CABG was recommended. Even though this relevant tool has been used in clinical practice, very few research has provided evidence with data to support and further confirm this fact. Therefore, we aimed to compare PCI versus CABG in patients with a high SYNTAX score in order to confirm with evidence whether the former is truly association with worse clinical outcomes.

2. Methods

2.1. Data sources

Electronic databases: The National database of medical research articles (MEDLINE and its subgroup PubMed), EMBASE database, and the Cochrane library.

References: reference lists of relevant publications.

Official websites: official websites of most suitable journals of cardiology or cardiovascular diseases such as Circulation, the Journal of the American College of Cardiology, International Journal of Cardiology, and the American Journal of Cardiology were also searched for any relevant article.

2.2. Searched strategies

English publications were searched using the terms:
- “percutaneous coronary intervention and coronary artery bypass surgery and SYNTAX score”;
- “percutaneous coronary intervention and SYNTAX score”;
- “coronary artery bypass surgery and SYNTAX score”;
- “PCI, CABG, and SYNTAX score”; 
- “SYNTAX score and revascularization”; 
- “coronary artery disease and the SYNTAX score.”

2.3. Inclusion and exclusion criteria

Inclusion criteria were:
(a) Studies that consisted of patients with CAD.
(b) Studies comparing PCI versus CABG in patients with a high SYNTAX score, respectively.

Exclusion criteria were:
(a) Studies that did not involve patients with CAD.
(b) Meta-analyses or letters to editors.
(c) Studies which did not compare PCI versus CABG in patients with a high SYNTAX score, respectively.
(d) Studies which did not report the above-mentioned clinical outcomes.
(e) Duplicated studies.

2.4. Types of participants

Patients with CAD were included in this analysis as shown in Table 1. However, when CAD was further subdivided, specific patients with:
(i) Left main coronary diseases;
(ii) Multi-vessel coronary diseases;
(iii) Three-vessel coronary diseases were included.

2.5. Outcomes and follow-ups

As shown in Table 1, the outcomes which have been analyzed in this study included:
(a) Mortality (all-cause death or cardiac death);
(b) Combined outcome including death/stroke/MI;
(c) MI;
(d) Stroke;
(e) Repeated revascularization.

MACCEs which were considered equally important, could not be analyzed since they were reported in only 1 study.

The follow-up periods varied from 2 years to 5 years as shown in Table 1.

2.6. Data extraction and quality assessment

This data extraction process was carried out by 2 independent reviewers (PKB and AB).

The following information was extracted:
Time of publication;
- Names of authors and names of trials or observational studies;
- Types of participants which were included;
- Reported outcomes and follow-up time periods;
- Methodological features of the trials;
- SYNTAX scores reported;
- Total number of patients which were classified in the PCI and CABG groups respectively;
- Baseline features of the patients.
The methodological quality of the trials was assessed with reference to the Cochrane collaboration[5] and a score was allotted based on the presence of a low, moderate, or high bias risk. A minimum score of 0 (very high bias risk) and a maximum score of 12 (very low bias risk) were given.

Any disagreement which followed were discussed and solved by the third reviewer (FH).

2.7. Statistical analysis

This is a systematic review and meta-analysis of data reported in several previously published studies. Therefore, inconsistency across the studies was possible. However, 2 simple statistical tools were used to measure heterogeneity across the studies.[6] (1) The $Q$ statistic test, whereby a $P$ value less or equal to .05 was considered statistically significant.

(2) The $I^2$ statistic test. The higher the $I^2$ value, the larger will be the heterogeneity. Therefore, a low $I^2$ value could best represent a lower heterogeneity.

The statistical effects which were used were also dependent on the heterogeneity $I^2$ value:

(1) If a low $I^2$ value (<50%) was obtained for a specific group, a fixed effects model was used;

(2) If a high $I^2$ value (>50%) was obtained when analyzing a particular subgroup, a random effects model was used.

The RevMan software version 5.3 was used to analyze the data, whereby odds ratios (OR) with 95% confidence intervals (CI) were the statistical parameters.

Patients’ consents and ethical or board review approval were not required.

3. Results

3.1. Searched outcomes

The PRISMA reporting guideline was followed.[7]

Electronic databases resulted in: 269 publications. Primary exclusion based on titles and abstracts: 234 studies. Full-text articles which were assessed: 35 studies. Secondary exclusion:

- Meta-analysis (1)
- Did not compare PCI versus CABG in patients with a high SYNTAX score, but instead compared PCI or CABG separately with a low versus a high score respectively (8)
- Only compared PCI with a low score versus CABG with a high score (3)
- Duplicates (19)

Finally, only 4 studies[8–11] satisfied the inclusion and exclusion criteria and were selected for this analysis (Fig. 1).

3.2. General features of the studies which were included

As shown in Table 2, 2 studies were randomized controlled trials (SYNTAX and FREEDOM trials) and 2 studies were observational studies. A total number of 1074 patients were included (455 patients with a high SYNTAX score were classified in the PCI group and 619 patients with a high SYNTAX score were
classified in the CABG group). A SYNTAX score cut-off value of ≥33 was considered relevant in this analysis. The exact number of patients with a high SYNTAX score was not provided in study Head2014, but the percentage of similar patients with adverse clinical outcomes was reported. Therefore, we assumed the total number of patients with a high SYNTAX score in that particular study to be 100 in each group as shown in Table 2.

After a methodological assessment of the trials, a low risk of bias was observed in the SYNTAX and FREEDOM trials, and a score of 10 out of 12 points was allotted to each of them.

3.3. Baseline features of the patients

A mean age ranging from 62.6 to 76.8 years was reported among the patients. More than 60% of the patients (from the PCI and CABG groups) were male patients. Study Capodanno2011 reported 67.1% of man patients within the PCI group, and 69.1% of man patients within the CABG group. Study Head2014 reported 79.3% versus 81.1% of man patients within the PCI and CABG groups, respectively. All the 4 studies consisted of a majority number of patients with hypertension, with an increased percentage of more than 80 in 3 of the studies. Study Dangas2014 involved only patients with diabetes mellitus. Smoking history was highest in study Capodanno2011. Overall, when the groups (PCI versus CABG) were compared, there were no significant differences in baseline features among patients who were treated with PCI and CABG respectively as shown in Table 3.

3.4. Main results of this analysis

Results of this analysis (Table 4) showed that compared with CABG, mortality was significantly higher following PCI (high SYNTAX Score) with OR: 1.79, 95% CI: 1.18 to 2.70; P=.006, I²=0% (Fig. 2). The combined outcome death/stroke/MI was also significantly higher following PCI with a high SYNTAX score, with OR: 1.69, 95% CI: 1.24 to 2.30; P=.009, I²=0% (Fig. 2). In addition, PCI was also associated with significantly higher MI (Fig. 2) and repeated revascularization (Fig. 3) in patients with a high SYNTAX score when compared with CABG, with OR: 3.72, 95% CI: 1.75 to 7.89; P=.006, I²=0% and OR: 4.33, 95% CI: 1.71 to 10.94; P=.002, I²=77%, respectively. However, stroke was not significantly different with OR: 0.93, 95% CI: 0.43 to 2.00; P=.85, I²=0% (Fig. 2).

3.5. Publication bias

In this analysis, we selected studies which compared PCI versus CABG with a high SYNTAX score, respectively. Adverse clinical outcomes such as mortality, death/stroke/MI, repeated revascularization, stroke, and MI were assessed. Because this analysis involved only 4 studies, the only best way to assess publication bias was through funnel plots generated from RevMan 5.3. According to the funnel plot which was generated, a low evidence of publication bias was estimated across these 4 studies which assessed all the clinical endpoints as shown in Fig. 4.

4. Discussion

In this analysis, we aimed to compare PCI versus CABG in patients who were allotted a high SYNTAX score, respectively. Our results showed that PCI with a high SYNTAX score was associated with significantly higher mortality, combined death/stroke/MI outcome, MI, and repeated revascularization. However, stroke was not significantly different. This analysis has
confirmed and has provided further evidence to the fact that CABG should benefit patients with a high SYNTAX score and that PCI should not be recommended to patients who have been allotted a high SYNTAX score, thus validating the SYNTAX score.

Another study validating the SYNTAX score also showed PCI in patients with a high SYNTAX score to be associated with worse clinical outcomes following this invasive procedure.\(^{[12]}\)
everolimus eluting stents (EES) in patients with higher SYNTAX unprotected left main CAD, and reported a lower long-term be even better in deciding the treatment strategy in patients with recently published study further showed this SYNTAX II score to observed.

to be treated by PCI, worse adverse outcomes were later disagreed to be revascularized by CABG and preferred described.\[15\]

≥ were (16 and 24), whereas the cut-off value in this analysis was

elevation acute coronary syndrome who underwent CABG.\[18\]

literature concerning the SYNTAX score and its application. This analysis con

versus CABG in patients who were speci

This research article is the first meta-analysis comparing PCI versus CABG in patients who were specifically qualified as having a high SYNTAX score. In addition, compared with previously published trials or observational studies, this analysis consisted of a larger number of patients. Another new feature could be the presence of a very low level of heterogeneity among several important subgroups assessing these clinical outcomes. The concept and idea of this research article are new, providing evidence, and analytical support to further confirm the existing literature concerning the SYNTAX score and its application. This analysis confirms the fact that patients allotted a high SYNTAX score should be revascularized by CABG which might be far more beneficial compared with PCI.

4.2. Limitations

Limitations could be the fact that a small sample size of patients was used during this analysis. Another limitation could be the fact that each subgroup analysis involved 2 or 3 studies. Moreover, patients with left main coronary disease and patients with multi-vessel coronary diseases were combined and analyzed. All the studies which were included had a follow-up period of 5 years except for 1 study, which had a follow-up period of only 2 years. Another limitation could be the fact that randomized patients and patients which were obtained from observational studies were combined and analyzed. Fortunately, a low level of heterogeneity was observed among several important subgroups.

5. Conclusions

Compared with CABG, worse clinical outcomes were observed following PCI in patients with a high SYNTAX score, confirming with evidence, published clinical literatures and validating the SYNTAX score. Therefore, CABG should be recommended to CAD patients who have been allotted a high SYNTAX score.

References

[1] Bundhun PK, Pursun M, Teeluck AR, et al. Adverse cardiovascular outcomes associated with coronary artery bypass surgery and percutaneous coronary intervention with everolimus eluting stents: A meta-analysis. Sci Rep 2016;6:35869.

[2] Bundhun PK, Wu ZJ, Chen MH. Coronary artery bypass surgery compared with percutaneous coronary interventions in patients with insulin-treated type 2 diabetes mellitus: a systematic review and meta-analysis of 6 randomized controlled trials. Cardiovasc Diabetol 2016; 15:2.

[3] Mack M, Baumgarten H, Lytle B. Why surgery won the SYNTAX trial and why it matters. J Thorac Cardiovasc Surg 2016;152:1237–40.

[4] Yadav M, Palmerini T, Caiaret a, et al. Prediction of coronary risk by SYNTAX and derived scores: synergy between percutaneous coronary intervention with taxus and cardiac surgery. J Am Coll Cardiol 2013; 62:1212–9.

[5] Higgins JP. Assessing risk of bias in included studies. Cochrane Handbook for Systematic Reviews of Interventions. 2008;Wiley, 187–241.

[6] Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. BMJ 2001;323:101–5.

[7] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.

[8] Capodanno D, Caggegi A, Miano M, et al. Global risk classification and clinical SYNTAX (synergy between percutaneous coronary intervention with TAXUS and cardiac surgery) score in patients undergoing percutaneous or surgical left main revascularization. JACC Cardiovasc Interv 2011;4:237–47.

[9] Dangas GD, Farkouh ME, Sleeper LA, et al. Long-term outcome of PCI versus CABG in insulin and non-insulin-treated diabetic patients: results from the FREEDOM trial. J Am Coll Cardiol 2014;64:1189–97.

[10] Head SJ, Davierwala PM, Serruys PW, et al. Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. Eur Heart J 2014;35:2821–30.

[11] Shiomi H, Morimoto T, Furukawa Y, et al. CREDO-Kyoto PCI-CABG registry cohort-2 investigators. Comparison of percutaneous coronary intervention with coronary artery bypass grafting in unprotected left main coronary artery disease—5-year outcome from CREDO-Kyoto PCI-CABG registry Cohort-2. Circ J 2015;79:1282–9.

[12] Kim YH, Park DW, Kim WJ, et al. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score for prediction of
outcomes after unprotected left main coronary revascularization. JACC Cardiovasc Interv 2010;3:612–23.
[13] Serruys PW, Onuma Y, Garg S, et al. ARTS II Investigators 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Coll Cardiol 2010; 55:1093–101.
[14] Witberg G, Lavi I, Gonen O, et al. Long-term outcomes of patients with complex coronary artery disease according to agreement between the SYNTAX score and revascularization procedure in contemporary practice. Coron Artery Dis 2014;25:296–303.
[15] Farooq V, Head SJ, Kappetein AP, et al. Widening clinical applications of the SYNTAX Score. Heart 2014;100:276–87.
[16] Cerit I, Duygu H, Gülseren K, et al. Is SYNTAX score predictive of atrial fibrillation after on-pump coronary artery bypass graft surgery? Korean Circ J 2016;46:798–803.
[17] Bundhun PK, Yanamala CM, Huang F. Percutaneous coronary intervention, coronary artery bypass surgery and the SYNTAX score: A systematic review and meta-analysis. Sci Rep 2017;7:43801.
[18] Redfors B, He CH, Palmerini T, et al. The SYNTAX score does not predict risk of adverse events in patients with non-ST elevation acute coronary syndrome who undergo coronary artery bypass graft surgery. J Invasive Cardiol 2016;28:42–9.
[19] Kurniawan E, Ding FH, Zhang Q, et al. Predictive value of SYNTAX score II for clinical outcomes in octogenarian undergoing percutaneous coronary intervention. J Geriatr Cardiol 2016;13:733–9.
[20] Campos CM, van Klaveren D, Farooq V, et al. EXCEL Trial Investigators Long-term forecasting and comparison of mortality in the evaluation of the Xience Everolimus Eluting Stent vs. Coronary Artery Bypass Surgery for effectiveness of left main revascularization (EXCEL) trial: prospective validation of the SYNTAX Score II. Eur Heart J 2015;36:1231–41.