PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-Effectiveness of Follow-Up Invasive Coronary Angiography After Percutaneous Coronary Stenting: A Real-World Observational Cohort Study in Japan
AUTHORS	Shiina, Tetsuya; Goto-Hirano, Keiko; Takura, Tomoyuki; Daida, Hiroyuki

VERSION 1 – REVIEW

REVIEWER	Misumida, N Mount Sinai Hospital
REVIEW RETURNED	26-Feb-2022

GENERAL COMMENTS	I had the opportunity to review an original investigation from Shiina et al. entitled “Clinical Outcomes and Cost-Effectiveness of Follow-Up Invasive Coronary Angiography After Percutaneous Coronary Stenting in Japan” The authors investigated the cost-effectiveness of routine follow-up coronary angiogram after PCI compared to clinical follow-up without angiogram using a large-scale medical service database. Follow-up coronary angiogram without clinical indication is not routinely pursued in the US and most of the European countries, but this remains a part of daily practice in Asian countries including Japan. Since there is no proven benefits with this approach and guidelines discourage the routine application of coronary angiogram without clinical indication, the clinical impact of this analysis is limited. Nevertheless, this analysis would provide an additional piece of data on this topic, which may impact the clinical decision on routine follow-up coronary angiogram in selected countries. I have several questions concerns as below. The data source seems to be national-level data including 497 hospitals and 7 million patients. However, the included number of patients (856 patients before exclusions and 558 patients after exclusion and matching) seem very low considering its overall sample size. The distinction between “routine” versus “clinically indicated” may not be clear without actual clinical data sources. Were all patients who underwent coronary angiogram between 6-12 months included in the routine follow-up angiogram group? Or the indication for angiogram was reviewed case-by-case basis? Among the patients who underwent routine follow-up angiogram, how many of them underwent ad-hoc PCI following diagnostic angiogram?

	Although I acknowledge that clinical outcomes are not the main focus of the current analysis, the event rate seems very low, raising concern for missing events due to the nature of the study data source.

REVIEWER	Heer, Tobias Klinikum Schwabing, Cardiology
REVIEW RETURNED	27-Feb-2022

GENERAL COMMENTS	A strength of the study is that real costs for patients with and without routine coronary angiography were compared. A weakness of the study is that the number of patients is rather low. The follow-up of 3 years might be not enough to compare differences in context with revascularization as the rate of adverse events was rather low. Also, real costs will be different in other health care systems and might differ in other countries than Japan. The costs for coronary computed tomography angiography, cardiac magnetic resonance, and cardiac nuclear scan in table 3 see very low. Why are the numbers so low? CCTA more often was performed in the CF group. Did this not have more influence on the costs in this group compared to the AF group? How does the healthcare system in Japan work? Do you have DRGs? How can you calculate the costs for MACCE (table 3) and how do you explain the confidence interval (with negative costs?)? The authors found in their study that coronary revascularisation after 1 year of index PCI was performed more often in the conservative group than in the invasive group. What is the explanation for this finding?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
Dear Dr. N Misumida,
Thank you for reviewing our manuscript and providing constructive comments; all the comments were critical in improving the manuscript. We have presented point-by-point responses to all the comments as follows:

1. The data source seems to be national-level data including 497 hospitals and 7 million patients. However, the included number of patients (856 patients before exclusions and 558 patients after exclusion and matching) seem very low considering its overall sample size.

Author response: Thank you for your insightful comment. In this study, the data source was the public health service billing information, and for a particular patient, the data of a single health insurance provider were analysed. But patients who changed health insurance provider during the observation period of this study were excluded. This has had a considerable effect in decreasing the sample size of the study. Furthermore, patients who underwent PCI, coronary artery bypass grafting, or dialyses within 1 year were not included, decreasing the total assessable sample size. To highlight these points, we have added text in the revised manuscript for clarity.

Exact location and change in the revised manuscript:
Page number 8 (study design and patient selection section):

“Health insurance data of the patients who changed the insurance provider during the observation period were not included in the analysis. Further, patients who underwent PCI, coronary artery bypass grafting, or dialysis within 1 year before PCI were not enrolled.”

Furthermore, as shown in Table 1, the mean age of the study population was approximately 55 ± 7 years, and patient population up to 65 years of age were primarily enrolled. The patients in this age group often change health care providers. In 2014, 200,142 coronary stents were performed in Japan, of which 52,872 (26%) were performed in patients aged 65 years or younger, according to the National Database of Health Insurance Claims and Specific Health Check-ups of Japan. Because the same patient may receive more than one such treatment, the expected nationwide number of patients will be smaller. We have added this perspective in the discussion section of the revised manuscript.

Exact location and change in the revised manuscript:
Page number 22 (discussion section):

“In 2014, 200,142 coronary stents were performed in Japan, of which 52,872 (26%) were performed in patients aged 65 years or younger, according to the National Database of Health Insurance Claims and Specific Health Check-ups of Japan.[18] Because the same patient may receive treatment more than once, the expected nationwide number of patients will be smaller.”

2. The distinction between “routine” versus “clinically indicated” may not be clear without actual clinical data sources. Were all patients who underwent coronary angiogram between 6-12 months included in the routine follow-up angiogram group? Or the indication for angiogram was reviewed case-by-case basis?

Author response: Thank you for your insightful comment. We agree that ‘the distinction between “routine” versus “clinically indicated” may not be clear without actual clinical data sources’. All the patients who underwent coronary angiography 6 to 12 months after PCI were included in the follow-up invasive angiography group. However, this group may include patients who were not routinely indicated for angiography when analysed on a case-by-case basis. We have added this information in the revised manuscript for clarity.

Exact location and change in the revised manuscript:
Page number 23 (Study limitations, Discussion section):

All the patients who underwent invasive coronary angiography 6 to 12 months after PCI were included in the AF group, and the AF strategy may include patients who were not routinely indicated for angiography if analysed on a case-by-case basis.

3. Among the patients who underwent routine follow-up angiogram, how many of them underwent ad-hoc PCI following diagnostic angiogram?

Author response: Thank you for your comment. Of the 279 patients who underwent follow-up invasive coronary angiography, 11 underwent ad hoc PCI within 3 months after angiography. We added this description in the ‘Discussion’ section for enhanced clarity.

Exact location and change in the revised manuscript:
Page number 20 (Discussion section):

“In the AF group, 11 elective PCI procedures were performed within 3 months, suggesting the possibility of ad hoc PCI after angiography.”

4. Although I acknowledge that clinical outcomes are not the main focus of the current analysis, the event rate seems very low, raising concern for missing events due to the nature of the study data source.

Author response: Thank you for your comment and we agree on low event rate, and this has been included as a limitation in the revised manuscript.

Exact location and change in the revised manuscript:
Page number 23 (Limitations, Discussion section):
"Although the primary endpoint had a lower event rate, the nature of the study data source raised concerns regarding missing events, and the sample size was not sufficient to determine the equivalence of AF strategies."

Reviewer 2:
Dear Dr. Tobias Heer, Klinikum Schwabing,
Thank you for reviewing our paper and providing constructive comments. All your comments were critical in improving the manuscript. Please find our point-by-point responses to all the comments as follows:

1. A strength of the study is that real costs for patients with and without routine coronary angiography were compared. A weakness of the study is that the number of patients is rather low. The follow-up of 3 years might be not enough to compare differences in context with revascularization as the rate of adverse events was rather low. Also, real costs will be different in other health care systems and might differ in other countries than Japan.

Author response: Thank you for your comment, and we agree with the reviewer's point, and hence, in the revised manuscript, we have updated the strengths and limitation section to highlight these points for clarity to the readers.

Exact location and change in the revised manuscript:
Page number 5:
Revised strengths and limitations of this study:

 This study provides evidence for the economic evaluation of invasive coronary angiography 6 to 12 months after percutaneous coronary intervention from a social perspective.
 The 3-year follow-up cost was compared with the actual costs of patients with and without follow-up invasive coronary angiography using a cost-minimization analysis.
 The determination of angiographic follow-up strategy equivalence included the low event rate limitation as demonstrated in previous large randomised controlled trials.
 Factors such as the left main trunk, multivessel coronary artery disease, double stents, or renal and cardiac functions were not analysed.

2. The costs for coronary computed tomography angiography, cardiac magnetic resonance, and cardiac nuclear scan in table 3 see very low. Why are the numbers so low? CCTA more often was performed in the CF group. Did this not have more influence on the costs in this group compared to the AF group?

Author response: Thank you for your insightful comments. Since the costs mentioned in Table 3 denote the per capita in AF and CF groups, it was divided by the number of patients [performed on a limited number of patients], resulting in a lower cost. In the revised manuscript, headings in Table 3 are changed to 'per capita' for clarity, and the footnotes were also revised to indicate the mean cost for the groups. We have also added the mean cost of coronary CT angiography ($400), cardiac magnetic resonance ($378), and nuclear scan ($801) to Table 3 in the revised manuscript. Coronary CT angiography was performed more frequently in the CF group. However, the cumulative cost in this group was not significantly affected. On the other hand, future widespread application of functional ischemic assessment may reduce the differences in cumulative costs. We have added this explanation to the 'Discussion' section of the revised manuscript

Exact location and change in the revised manuscript:
Page number 23 (Discussion section):
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"The impact of event hospitalisation costs on cumulative costs was limited, but future widespread application of functional ischemic assessment may reduce the differences in the cumulative costs."

3 How does the healthcare system in Japan work? Do you have DRGs? How can you calculate the costs for MACCE (table 3) and how do you explain the confidence interval (with negative costs?)?

Author response: Thank you for your valuable questions. Most acute inpatient care services in Japan are reimbursed under the Diagnosis Procedure Combination (Diagnosis Procedure Combination/Per-Diem Payment System (DPC/PDPS)), a comprehensive daily evaluation system. The cost of surgery, including PCI and invasive angiography, is calculated based on fee-for-service payment model to arrive at the total cost. MACCE costs are calculated based on the hospitalisation costs for nonfatal myocardial infarction, emergency coronary revascularisation, stroke, heart failure, and death events. The number of patients treated for MACCE was 13 in each group, and the small size of patients with the 3-year cumulative event increased standard deviation of the mean cost of hospitalisation. We have added this explanation to the 'Discussion' section of the revised manuscript.

Exact location and change in the revised manuscript:
Page number 21,22 (Discussion section):

"Most acute inpatient care services in Japan are reimbursed under the Diagnosis Procedure Combination (DPC/PDPS: Diagnosis Procedure Combination / Per-Diem Payment System), a comprehensive daily evaluation system. The cost of surgery, including PCI and invasive angiography, is calculated based on fee-for-service payment model to arrive at the total cost.[17] Major adverse cardiac event costs were calculated based on the hospitalisation costs for nonfatal myocardial infarction, emergency coronary revascularisation, stroke, heart failure, and death events. In this study, the number of patients treated for MACCE was 13 in each group, and the small size with the 3-year cumulative event increased the standard deviations of the mean costs of hospitalisation."

4. The authors found in their study that coronary revascularisation after 1 year of index PCI was performed more often in the conservative group than in the invasive group. What is the explanation for this finding?

Author response: Thank you for your comment. Late progression of new or non-target lesions may explain why the trends in previous studies differ from those in this real-world study. A higher rate of non-target lesion revascularisation (TLR) was observed in the late CF group in both the ReACT trial and a sub-study of the SPRITIII (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions) trial. These points are already described in the 'Discussion' section of the originally submitted manuscript.

Exact location and change in the revised manuscript:
Page 20 (Discussion section):

“However, the rate of coronary revascularisation increased with the CF (14.3% vs 18.5%; log-rank p = 0.077). Late progression of new or non-target lesions may explain why trends in previous studies differ from those in the present real-world study. A higher rate of non-target lesion revascularisation (TLR) was observed in the late CF group in both the ReACT trial and a sub-study of the SPRITIII (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions) trial.[2,3]”

VERSION 2 – REVIEW

REVIEWER	Misumida, N Mount Sinai Hospital
REVIEW RETURNED	30-Jun-2022

GENERAL COMMENTS	The authors have satisfactorily responded to all my concerns and questions. The inherent limitations of the study due to the nature of the study (small sample size after exclusion, lack of clinical adjudication regarding "routine" versus “clinically indicated” angiogram, as well as lower than expected event rates) were mentioned as limitations of the study. I have no further comments. Thank you very much for the opportunity to review this manuscript.