Role of Routine Follow-up Coronary Angiography After Percutaneous Coronary Intervention — Systematic Review and Meta-Analysis —

Naoki Misumida, MD; Akihiro Kobayashi, MD; Sun Moon Kim, MD; Ahmed Abdel-Latif, MD; Khaled M Ziada, MD

Background: Prior studies have shown that routine follow-up coronary angiography (CAG) following percutaneous coronary intervention (PCI) increases the incidence of revascularization without a clear reduction in major adverse clinical events. However, none of these prior studies were adequately powered to evaluate hard clinical endpoints such as myocardial infarction (MI) or death and thus the clinical utility of such practice remains to be determined.

Methods and Results: We conducted a systematic review and meta-analysis of randomized trials that compared clinical outcomes after PCI between patients who underwent routine follow-up CAG and those who only had clinical follow-up. Five randomized trials, totaling 4,584 patients met our inclusion criteria, including studies that used sub-randomization and ones that assigned consecutive patients per study protocol. Our results showed that routine follow-up CAG was associated with a lower rate of MI (odds ratio [OR] 0.65; 95% confidence interval [CI] 0.46–0.91; P=0.01) without reduction in all-cause mortality (OR 0.87; 95% CI 0.59–1.28; P=0.48), and a higher rate of target lesion revascularization (OR 1.73; 95% CI 1.42–2.11; P<0.001).

Conclusions: Our meta-analysis demonstrated that routine follow-up CAG after PCI was associated with a higher rate of revascularization, but also with a reduction in the rate of subsequent MI. Further studies investigating the potential role of routine follow-up angiography may be warranted.

Key Words: Angiographic follow-up; Myocardial infarction; Percutaneous coronary intervention; Restenosis; Routine angiography

Routine follow-up coronary angiography (CAG) after percutaneous coronary intervention (PCI) is commonly implemented to assess the efficacy and safety of new revascularization devices. Although routine angiographic surveillance has undoubtedly furnished valuable scientific data, contributing to the advancement of coronary intervention, the direct clinical benefits remain poorly defined. In fact, prior studies have shown that routine follow-up CAG following PCI increases repeat revascularization without a clear reduction in myocardial infarction (MI) or death.1–3

Accordingly, the 2012 ACCF/SACI appropriate use criteria for diagnostic catheterization rated follow-up CAG as inappropriate in stable or asymptomatic post-PCI patients, discouraging its universal application.4 However, none of the prior studies evaluating the potential benefits of routine angiographic follow-up were adequately powered to evaluate hard clinical endpoints such as MI or death. In this context, we conducted a systematic review and meta-analysis to assess the potential clinical benefits associated with routine follow-up angiography post-PCI.

Methods

We performed a meta-analysis of randomized trials in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guideline.5 The protocol for this systematic review was registered in the PROSPERO database (https://www.crd.york.ac.uk/PROSPERO; CRD42017056193). We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials through January 2017 using the following search terms: “angiographic follow-up” or “routine coronary angiography” or “follow-up coronary angiography” or “scheduled coronary angiography” or “routine angiography” or “follow-up angiography” or “angiographic surveillance” or “surveillance angiography” or “surveillance coronary angiography”. The search was restricted to randomized controlled trials and there were no language restrictions. Studies were also identified by searching references cited in the screened articles and relevant review articles.

Eligible studies were refined to randomized trials that compared clinical outcomes based on follow-up strategies...
between routine follow-up CAG and clinical follow-up only in patients who underwent PCI. We also included a study investigating revascularization devices or medications that sub-randomized patients to routine angiography or clinical follow-up only strategies and a study that non-arbitrarily assigned consecutive patients to either strategy per study protocol (such as the one that assigned the first half of the patients to protocol-mandated angiographic follow-up). We did not establish any inclusion or exclusion criteria regarding the timing for follow-up CAG.

Two investigators (N.M. and A.K.) independently assessed trial eligibility using the predefined inclusion criteria. After initial screening of all titles and abstracts of identified articles, potential studies were reviewed in full-text to determine their eligibility. Disagreements were resolved through discussion between the reviewers.

The primary outcome of interest was MI, as defined by each study, and the secondary outcome of interest were all-cause death (or cardiac death, if all-cause death was not reported) and target lesion revascularization (TLR) (or target vessel revascularization, if TLR was not reported).

Relevant data were independently extracted by 2 investigators (N.M. and A.K.). Disagreements were resolved through discussion between the reviewers. Data were abstracted to include the following information: first author’s name, year of publication, study period, country, study design, sample size, clinical characteristics of the study population, definitions of the outcomes used in each study, timing of follow-up CAG, follow-up duration, and incidence of primary and secondary outcomes of interest. Quality assessment for each study was performed using the Cochrane Collaboration’s risk of bias tool.

**Statistical Analysis**

Summary estimates were calculated as odds ratios [OR] with 95% confidence intervals [CI] using a prespecified random effects model based on DerSimonian and Laird’s meta-analytic statistical method. In addition, we performed a subgroup analysis according to stent use: (1) studies in which stents (either bare-metal [BMS] or drug-eluting [DES]) were used in more than 80% of the patients and (2) studies in which DES were used in more than 80% of the patients. We performed additional sensitivity analyses using the “one study removed” method by removing individual studies to assess the effect of each study on overall outcome. We also performed a cumulative meta-analysis to examine the stability of our results over time and different standards of therapy. Using the OR log-transformed as an independent variable, meta-regression analysis was performed with prespecified study year as a moderator to test the effect of publication year on the pooled effect measure. The I² index was used to summarize the proportion of total variability in the estimate. The I² statistic is derived from the Q statistic and describes the percentage of total variation across studies that is due to heterogeneity; values of 25%, 50%, and 75% correspond to low, moderate, and high heterogeneity, respectively.

Assessment of publication bias using Funnel plot and the Begg’s test was not performed, because of the limited number of included studies. The statistical level of significance was 2-tailed P<0.05. All statistical analyses were performed using Comprehensive Meta-analysis version 3.0 software (Biostat, Inc., NJ, USA).

**Results**

The result of our search strategy is illustrated in Figure 1. Of 843 screened articles, 20 potential studies were reviewed in full-text to determine eligibility. A total of 5 randomized controlled trials met our inclusion criteria, including 2 studies that used sub-randomization and 2 studies that non-arbitrarily assigned consecutive patients to either strategy per study protocol. The total number of patients included in our final analysis was 4,584.

The characteristics of included studies and patients are shown in Table 1 and Table 2. Two studies were deemed to have a high risk of bias because of the use of cluster assignment instead of formal randomization (Table 3). The 2 most recent studies mainly used DES, and the 2 studies conducted in the 1990s used either balloon angioplasty or BMS. The majority of the patients who were assigned to angiographic surveillance underwent follow-up angiography. Follow-up duration ranged from 1 to 4.6 years.
The major adverse clinical outcomes from each study are shown in Table 4. Figure 2 illustrates the Forest plot reporting OR with 95% CI for MI, all-cause death and TLR. Routine follow-up CAG was associated with a lower rate of MI (OR 0.65; 95% CI 0.46–0.91; P=0.01) without reduction in all-cause death (OR 0.87; 95% CI 0.59–1.28; P=0.48), and a higher rate of TLR (OR 1.73; 95% CI 1.42–2.11; P<0.001). No significant change was noted when the data were analyzed using the fixed effects model.

The results from the subgroup analysis according to the type or method of revascularization are shown in Figure 3 and Figure 4. The lower rate of MI with angiographic follow-up was also seen in subgroup analysis where stents (either BMS or DES) were used in more than 80% of patients (OR 0.60; 95% CI 0.40–0.92; P=0.02). In the subgroup analysis where DES were used in more than 80% of patients, there was a similar but statistically non-significant trend for lower rates of MI in the angiographic follow-up group (OR 0.70; 95% CI 0.41–1.18; P=0.18). A higher incidence of TLR was seen with angiographic follow-up in all tested subgroups. No significant interactions were noted in the rate of MI and TLR between studies stratified by (1) stent use (either BMS or DES) in >80% of the patients or (2) DES use in >80% of the patients. The higher incidence of TLR with routine angiographic follow-up was less apparent in studies that mainly used DES (OR 1.48; 95% CI 1.04–2.10) compared with those that used balloon angioplasty or BMS (OR 1.87; 95% CI 1.47–2.37).

Sensitivity analyses using the “one study removed” method did not show significant changes in the summary OR estimates for any outcome assessed (Figure S1).
Cumulative meta-analysis showed a relatively stable accumulation of evidence for reduction of MI and increase in TLR associated with angiographic follow-up (Figure S2). Meta-regression analysis showed that treatment effect does not change significantly depending on publication year (Figure S3).

**Discussion**

Our meta-analysis of 5 randomized trials including 4,584 patients confirmed that routine follow-up CAG following PCI was associated with a higher rate of repeat revascularization. Importantly, our analysis also demonstrated a lower rate of MI associated with routine follow-up CAG post-PCI. Subgroup analysis according to stent use and type of stent showed a similar reduction in MI and increase in TLR associated with routine angiographic follow-up. To our knowledge, this is the first meta-analysis that addresses the potential clinical benefits associated with routine follow-up angiography post-PCI.

Prior studies have repeatedly demonstrated that routine angiographic surveillance increases the rate of TLR without a clear reduction in major adverse cardiac events. However, none of those studies were adequately powered to evaluate hard clinical endpoints such as death or MI. It is important to emphasize that a negative result from an underpowered study does not prove “absence of benefit.” For example, among 17 randomized trials investigating the mortality benefit of β-blocker in heart failure patients between the years 1985 to 1997, only 1 study showed a significant reduction in mortality with β-blocker use while 13 studies demonstrated a similar but statistically non-

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**Table 2. Characteristics of the Patients in Each Study Included in a Meta-Analysis of Routine Follow-up Coronary Angiography After PCI**

<table>
<thead>
<tr>
<th>Author</th>
<th>Age (years)</th>
<th>Male</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>Dyslipidemia</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruygrok et al</td>
<td>59</td>
<td>79%</td>
<td>40%</td>
<td>12%</td>
<td>NA</td>
<td>26%</td>
</tr>
<tr>
<td>ten Berg et al</td>
<td>60</td>
<td>78%</td>
<td>21%</td>
<td>9%</td>
<td>29%</td>
<td>31%</td>
</tr>
<tr>
<td>Pinto et al</td>
<td>62</td>
<td>72%</td>
<td>70%</td>
<td>24%</td>
<td>67%</td>
<td>44%</td>
</tr>
<tr>
<td>Lansky et al</td>
<td>63</td>
<td>69%</td>
<td>75%</td>
<td>29%</td>
<td>72%</td>
<td>23%</td>
</tr>
<tr>
<td>Shiomi et al</td>
<td>69</td>
<td>79%</td>
<td>76%</td>
<td>45%</td>
<td>78%</td>
<td>18%</td>
</tr>
</tbody>
</table>

**Table 3. Bias Risk Assessment of the Studies Included in a Meta-Analysis of Routine Follow-up Coronary Angiography After PCI**

<table>
<thead>
<tr>
<th>Author</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blind participants and personnel</th>
<th>Blind outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruygrok et al</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>ten Berg et al</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Pinto et al</td>
<td>High risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Lansky et al</td>
<td>High risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Shiomi et al</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**Table 4. Clinical Outcomes in Each Study Included in a Meta-Analysis of Routine Follow-up Coronary Angiography After PCI**

<table>
<thead>
<tr>
<th>Author</th>
<th>MI</th>
<th>All-cause death</th>
<th>TLR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Angiographic follow-up</td>
<td>Clinical follow-up</td>
<td>Angiographic follow-up</td>
</tr>
<tr>
<td>Ruygrok et al</td>
<td>2/357 (0.6%)</td>
<td>4/349 (1.1%)</td>
<td>3/357 (0.8%)</td>
</tr>
<tr>
<td>ten Berg et al</td>
<td>17/531 (3.2%)</td>
<td>21/527 (4.0%)</td>
<td>6/531 (1.1%)</td>
</tr>
<tr>
<td>Pinto et al</td>
<td>12/536 (2.3%)</td>
<td>27/582 (4.7%)</td>
<td>6/536 (1.1%)</td>
</tr>
<tr>
<td>Lansky et al</td>
<td>21/522 (4.0%)</td>
<td>23/412 (5.6%)</td>
<td>9/522 (1.7%)**</td>
</tr>
<tr>
<td>Shiomi et al</td>
<td>6/349 (1.7%)</td>
<td>9/351 (2.6%)</td>
<td>30/349 (8.6%)</td>
</tr>
</tbody>
</table>

*Event numbers calculated by reported incidences, **target vessel revascularization, ***cardiac death. TLR, target lesion revascularization. Other abbreviations as in Table 1.
Role of Routine Follow-up CAG

The devices and medications used in the 2 trials from the 1990s were very different from contemporary practice. Stent use was infrequent and P2Y12 inhibitors (except for ticlopidine) were unavailable during that time. In addition, balloon angioplasty, the mainstay of coronary revascularization during this time, is known to be associated with a significantly higher rate of restenosis and ischemia-driven revascularization compared with stenting.¹³ Thus, the results from these earlier trials may not apply to current practice. Nevertheless, the subgroup analysis of studies that used stents in >80% of the patients showed a similar reduction in MI, supporting the presence of this association applicable to current practice. The reduction in MI was not statistically significant when the inclusion was restricted to the studies that primarily used DES in our analysis. This appears to simply stem from small sample size and small numbers of the clinical events. For example, the most recent trial showed a very low incidence of MI over a median follow-up period of 4.6 years (1.7% vs. 2.6%).¹¹

The absence of significant difference in the reduction of MI in the DES era may also be related to the reduced incidence of restenosis and late stent thrombosis with recent advancement in stent and polymer designs,¹⁴ although our cumulative meta-analysis based on the publication year, as well as the meta-regression analysis, did not show significant effect of the year of publication on the OR of the clinical outcomes. Further studies in the current DES era are awaited.

Despite the observed association between angiographic follow-up and reduction in MI, the presence of an association does not necessarily indicate a causal relationship.

significant trend towards mortality reduction.¹² However, when a meta-analysis combining the 17 trials was performed, β-blockade treatment was associated with a significant reduction in death with an OR of 0.69 (95% CI 0.54–0.88).¹²

All 5 studies included in our analysis showed a similar trend for reduction in MI with routine angiographic follow-up. No heterogeneity was noted among studies, supporting the robustness of the association between angiographic follow-up and reduction in MI. This interesting and somewhat surprising finding may illustrate an opportunity to further improve clinical outcomes after PCI. Nevertheless, these results should be interpreted with caution given the several reasons described next.

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Despite the observed association between angiographic follow-up and reduction in MI, the presence of an association does not necessarily indicate a causal relationship,

**Figure 2.** Forest plot of myocardial infarction, all-cause mortality, and TLR. Routine follow-up angiography was associated with significant reduction in (A) myocardial infarction (OR 0.65; 95% CI 0.46–0.91, P=0.01), but no significant change in (B) all-cause mortality. Routine follow-up angiography was associated with significant increase in (C) TLR (OR 1.73; 95% CI 1.42–2.11, P<0.001). CI, confidence interval; df, degrees of freedom; MH, Mantel-Haenszel; OR, odds ratio; TLR, target lesion revascularization.
Hypothetically, if a direct causal benefit from angiographic follow-up was present, the extent of benefit may vary according to lesion characteristics, yielding a larger benefit to a subgroup of patients. For example, in patients with a large area of myocardium at risk, such as those with left main disease, either percutaneous or surgical revascularization is recommended to improve survival. Thus, angiographic follow-up in these high-risk patients with subsequent revascularization for hemodynamically significant restenosis may be beneficial. Our meta-analysis did not show a difference in mortality; however, this could be related to a low overall event rates and short-term follow-up. In addition, patients who underwent left main stenting and who may have benefited from such practice were excluded from most of the studies. In the past, according to 2005 ACC/AHA PCI guidelines follow-up angiography was recommended (Class IIa) between 2 and 6 months after PCI in patients who underwent unprotected left main revascularization. This recommendation was removed in the 2009 focused update.26 To date, no prior study has prospectively evaluated the clinical effect of follow-up CAG in such high-risk patients. In a recent observational study, the lack of angiographic follow-up was associated with increased mortality in patients who underwent PCI for left main lesion after adjusting for propensity score.27 Although the observed survival benefit was likely inflated because of possible confounders. For example, significant differences in medication regimens may have existed between the 2 groups that underwent angiographic follow-up or clinical follow-up only. Patients who underwent repeat PCI for restenosis during angiographic surveillance may have been treated with a prolonged dual antiplatelet therapy (DAPT), which has been shown to reduce MI based on recent large-scale randomized trials.15,16 In addition, a recent study showed that patients who were treated with 24 months DAPT after PCI for restenosis had a lower rate of death and MI compared with those treated with 6 months of DAPT.17 Unfortunately, the details of the medications used in each study, especially DAPT, were not reported in the studies included in our analysis.

Presumably, the primary purpose of follow-up CAG in post-PCI patients is to assess the presence of restenosis in stable patients, because acute coronary syndrome (ACS) or refractory angina would warrant repeat CAG regardless of planned follow-up strategy. Early intervention for restenosis following routine angiography can potentially prevent future cardiovascular events, as restenosis may manifest as ACS.18 Several studies suggested that PCI reduces the incidence of ACS in patients with stable angina.19,20 However, in terms of hard clinical endpoints such as MI or death, the current evidence does not support a benefit of PCI in stable patients except for anatomically high-risk subgroup such as those with left main disease.21–23 Further investigation is warranted to evaluate a potential causality between reduction of MI and angiographic follow-up.

Figure 3. Forest plot of myocardial infarction (MI) according to subgroups. The reduction in MI was significant among studies where stents (either bare-metal or drug-eluting [DES]) were used in more than 80% of patients (OR 0.60; 95% CI 0.40–0.92; P=0.02). In subgroup analysis where DES were used in more than 80% of patients, there was a similar but statistically non-significant trend for lower rates of MI in the angiographic follow-up group (OR 0.70; 95% CI 0.41–1.18; P=0.18). Importantly, no significant interactions were noted in the rate of MI between studies stratified by (1) DES use in >80% of the patients or (2) stent use (either bare-metal or DES) in >80% of the patients. Abbreviations as in Figure 2.
Role of Routine Follow-up CAG

In summary, our meta-analysis showed that routine follow-up CAG after PCI was associated with a lower risk of MI and a higher rate of TLR. Considering the potential value of routine angiographic follow-up in reducing MI vs. evidence of increased repeat procedures, and given the hypothesis generating nature of our data, it is prudent to individualize the application of follow-up angiography practice according to various risk factors predicting future ischemic events and possible restenosis. Further studies examining the potential role of routine follow-up angiography, especially in high-risk patients, may be warranted.

Study Limitations
Our meta-analysis has several limitations. First, 2 studies were deemed to have a high risk of bias because of the use of cluster assignment instead of formal randomization. The open-label nature of the trials may also be a potential source for bias. Second, the follow-up duration was not uniform across the studies, which were relatively short, limiting the evaluation of any long-term effect associated with follow-up angiography. Third, although the clinical benefits of invasive intervention should be carefully evaluated by balancing its benefits and risks, the rates of complications related to angiographic follow-up were only available in a limited number of studies. Fourth, as discussed, the results from the trials conducted in 1990s may not apply to current practice. Lastly, we could not evaluate or exclude the possibility of publication bias related to the limited number of included studies.

In summary, our meta-analysis showed that routine follow-up CAG after PCI was associated with a lower risk of MI and a higher rate of TLR. Considering the potential value of routine angiographic follow-up in reducing MI vs. evidence of increased repeat procedures, and given the hypothesis generating nature of our data, it is prudent to individualize the application of follow-up angiography practice according to various risk factors predicting future ischemic events and possible restenosis. Further studies examining the potential role of routine follow-up angiography, especially in high-risk patients, may be warranted.

Acknowledgments
A.A.-L. is supported by the University of Kentucky Clinical and Translational Science Pilot Award (UL1TR000117), the UK COBRE Early Career Program (P20 GM103527) and the NIH Grant R56 HL124266.

Disclosure of Any Relationship With Industry
None.

References
2. Ten Berg JM, Kelder JC, Suttorp MJ, Verheugt FW, Tijs Plokker HW. Influence of planned six-month follow-up angiography...


**Supplementary Files**

**Supplementary File 1**

Figure S1. ‘One study removed’ analysis of (A) myocardial infarction, (B) all-cause mortality and (C) target lesion recanalization showing no significant effect on the removal of any study on the overall cumulative odds ratio estimates.

Figure S2. Cumulative meta-analysis of (A) myocardial infarction, (B) all-cause mortality and (C) target lesion recanalization stratified by the year of publication.

Figure S3. Meta-regression analysis using the log-transformed odds ratio as dependent variable and the year of publication as moderator.