A network meta-analysis on comparative efficacy of statins focusing for prevention of contrast-induced acute kidney injury in chronic kidney disease patients undergoing percutaneous coronary intervention

Ilham Akbar Rahman, Yeni Purnamasari, Vicky Nanu Rewa, Hasyim Kasyim, Abd Rahman Umar, Firdaus Kasim

ABSTRACT

**Background:** The use of interventional diagnostic and therapeutic procedures required intravascular iodinated contrast are performed in millions of patients worldwide and are steadily increasing the risks of contrast-induced acute kidney injury (CI-AKI). Statins are primarily used in cardiovascular medicine for their lipid-lowering effects but they possess remarkable pleiotropic effects such as improving endothelial function as well as decreasing oxidative stress and inflammation. A network meta-analysis was carried out to evaluate the effect of different statins in prevention of CI-AKI and also to investigate which type and dose of statins maybe the best choice specifically in CKD patients who have higher risk.

**Methods:** We performed a pairwise and network meta analysis of 14 randomized studies (9847 patients) comparing a total of 6 different statins: rosuvastatin high dose, atorvastatin high dose, simvastatin high dose, rosuvastatin regular dose, atorvastatin regular dose, pravastatin regular dose versus each other and versus placebo in CKD patients undergoing PCI with iodinated contrast for prevention of CI-AKI. Google Scholar, Pubmed, Science Direct databases were searched up to May 2019. The data were pooled using STATA, and R version statistics calculating odds ratios (ORs) with 95% confidence intervals.

**Results:** Statin loading before contrast administration was associated with a significantly reduced risk of CI-AKI in patients with CKD undergoing cardiac catheterization (pooled OR= 0.51; P=0.0001). Regular dose pravastatin comprised the best effect size for a reduction in CI-AKI risk (OR = 0.32, 95% CI 0.14-0.72, p=0.006). Regular dose pravastatin and high dose atorvastatin were ranked as the highest probability to be the best treatment (Pbest) with 44% and 31% respectively for effect on CI-AKI prevention.

**Conclusion:** Preloading with statins is associated with significantly reduced risk of CI-AKI in patients with CKD undergoing cardiac catheterization. Regular dose pravastatin and high dose atorvastatin have the highest probability to be the most effective prevention strategy.

**Keywords:** Contrast-induced Acute Kidney Injury, Statin, Chronic Kidney Disease


INTRODUCTION

The practice of diagnostic and therapeutic procedures through intervention by using intravascular iodinated contrast is conducted in patients worldwide and are leading to the risks of contrast-induced acute kidney injury. The CI-AKI can cause significant burdens as with worsening renal function, prolonged hospitalization duration, increasing costs, renal morbidity and all-cause mortality. The invention of optimal strategy to prevent this complication provides an opportunity to decrease patient morbidity and mortality. Eventhough there are various preventive strategies, one of promising and potential regimen is statin.

Statin have been related for the use as cholesterol-lowering drugs in cardiovascular medicine. However, statin possess remarkable pleiotropic effects, such as intensifying endothelial function, maintaining production of nitric oxide (NO) and preventing oxidative stress. Nitric oxide which is originated from reactive oxygen species that promote atherogenesis is inhibited by statins. Departed from that postulation, statin is considered to have potential in becoming one of the best preventive strategy in CI-AKI.

CKD patients were chosen in our analysis because these type of patients have higher risk than those with normal renal function population. If we can prove the effectiveness of statin in CKD patients, than we can conclude that it will be safe and effective in normal renal function population. Various meta-analyses have investigated the effectiveness of statin in decreasing the risk of CI-AKI.
However, only few network meta analyses were established. Network meta-analyses are extension and expansion of standard pairwise meta-analyses that afford an opportunity for simultaneous pooling of data interrelated to multiple interventions, and can provide direct and indirect evidence as a combination. Therefore, we performed pairwise meta-analyses to prove overall statin effect in terms of CIAKI prevention and network meta analysis to investigate which type and dosage of statins might be the best choice for the most effective intervention.

METHODS
Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and Cochrane Collaboration recommendations were implemented to conduct this review. The explanation of PICO of the study was described in Table 1.

Literature Search Strategy and Selection Criteria
Google scholar, Pubmed and Science direct were systematically searched up to May 2019, for articles on effects of statins in prevention of CI-AKI in patients with CKD which is defined as estimated glomerular filtration rate <60mL/min/1.73 m². The following various key search terms in medical subject heading (MeSH) were used: "statin" OR "pravastatin" OR "rosuvastatin" OR "simvastatin" OR "atorvastatin", AND, "contrast", AND "nephropathy" OR "CIAKI" OR "CIN", AND "chronic kidney disease". No language limitations were applied and some of our studies were in Chinese. For the selection criteria of our research, following criteria were fundamental in studies that we searched: (1) original research and data showing the effects of statins after CM administration; (2) comparison of statins vs placebo and comparison statin vs other statin; (3) there are CKD patients involved in sample study; (4) CIAKI outcome was reported; (5) undergoing PCI procedure.

Data Extraction and Quality Assessment
Data were independently extracted by 2 authors (IAR, YP) using a standardized extraction form. Any discrepancies were resolved between the authors through consensus and consultation (VNR, HK, ARU, FK). Following informations were extracted from each trial: (1) baseline patient characteristics (mean age, creatinine clearance/serum creatinine, contrast types, and contrast volume), (2) characteristics of included studies (country, study design, total number of patients per arm, patient population), the interventions (type, and dosage of statin), (3) outcomes (number of patients experiencing CI-AKI), (4) information on blinding, random sequence generation, allocation concealment, indications of incomplete data, indications of selective reporting and other bias.

Outcome
The focused outcome of concern in our analysis was the incidence of CI-AKI in patients with CKD. CIAKI was described as an absolute increase in SCr of >0.5mg/dL (44.2mmol/L) or a relative >25% increment in Scr levels from the baseline value at 48–72 hours after contrast media administration.

Statistical Analysis
Dichotomous variables were analyzed where Odds Ratio and 95% Confidence Interval were calculated as treatment effect. STATA version 14.0 (STATA Corporation, College Station, Texas) was used to run subgroup analysis in pairwise meta-analysis. Network meta-analysis was performed using R version 1.2.1335 statistic for indirect and mixed comparisons where metafor, netmeta and gemtc package were applied calculating Odds Ratio and 95% Confidence Interval. The probability to be the best treatment (Pbest) were calculated by counting proportion of iterations in a Markov chain Monte Carlo simulation. Pairwise heterogeneity among studies was calculated with χ² test and I²>50% was considered indicative for significant heterogeneity. When significant heterogeneity occured, random effects model was used, otherwise a fixed effects model was used. Publication bias was analyzed by using funnel plot and Egger regression test along with Begg rank correlation test.

RESULTS
Search Results
The initial 245 potential records identified, 140 studies were removed due to duplication. Of 140 studies reviewed from title/abstract reading, 120 were removed. Of the 20 studies assessed by reading full articles, 6 were removed. Finally, 14 studies matched our inclusion criteria. The PRISMA flowchart shows the detailed process of studies selection as shown in Figure 1.

Selection of Eligible Studies and Patient Characteristics
The characteristics of the identified studies and patients included are shown in Table 2. Most of the studies are RCTs and the rest are cohorts published between 2011 and 2017. A total of 9847 patients were included in the analysis: 4660 for the statin group and 5187 for the control group. From 14 studies,
3 studies compared atorvastatin high dose versus placebo/no statin, \(^8\),\(^9\),\(^10\) 3 studies compared rosuvastatin high dose versus placebo, \(^11\),\(^12\),\(^13\) 1 study compared simvastatin high dose versus placebo, \(^14\) 3 studies compared rosuvastatin regular dose versus placebo, \(^6\),\(^7\),\(^15\) 1 study compared pravastatin regular dose versus placebo, \(^16\) 1 study compared atorvastatin high dose versus atorvastatin regular dose, \(^17\) 1 study compared pravastatin versus simvastatin, \(^18\) 1 study compared rosuvastatin regular dose versus atorvastatin regular dose. \(^19\) The mean age of patients ranged from 55 to 75 years, and the baseline mean creatinine clearance ranged from 42.5 to 99 mL/min. Contrast medium that were used include iodixanol, ioversol, high and low osmolar, non ionic low osmolar, lobtridol, iopamidol, iodixanol, iohexol which the average volume ranged from 72.2 to 213. CIAKI was identified as an escalation in SCr of >0.5mg/dl (44.2 mmol/L) or a >25% escalation in SCr levels from the baseline value at 48-72 hours after exposed to contrast media. CKD was identified as an eGFR <60 ml/min/1.73 m\(^2\) in two studies, \(^9\),\(^11\) as a creatinine clearance (CrCl)<60 ml/min in two studies, \(^12\),\(^13\) and as a SCr >3 mg/dl in one study. \(^8\)

**Quality Control of Studies and Publication bias**

Cochrane Collaboration’s tool was used to assess the risk of bias in the studies. Seven specific domains were used to define the risk of bias.

### Table 1 PICO of the study

<table>
<thead>
<tr>
<th>Patient</th>
<th>CKD patients undergoing PCI with iodinated contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Statin</td>
</tr>
<tr>
<td>Control</td>
<td>Placebo and Each other statin</td>
</tr>
<tr>
<td>Outcome</td>
<td>Contrast Induced Acute Kidney Injury</td>
</tr>
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</table>

### Table 2 The baseline characteristics of selected studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Statin total patients</th>
<th>Control total patients</th>
<th>Intervention</th>
<th>Mean Age (years)</th>
<th>Baseline CrCl (mL/min) or SCr (µmol/L)</th>
<th>Contrast</th>
<th>Statin</th>
<th>Control</th>
<th>Study design</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintavalle, 2012</td>
<td>202</td>
<td>208</td>
<td>Atorvastatin 80 mg within 24h before CM exposure</td>
<td>70</td>
<td>42.5 mL/min</td>
<td>Iodixanol</td>
<td>177</td>
<td>184</td>
<td>RCT</td>
<td>Italy</td>
</tr>
<tr>
<td>Abaci, 2015</td>
<td>103</td>
<td>105</td>
<td>Rosuvastatin 40 mg within 24h before CM exposure and 20 mg/day for 2 days after CM exposure</td>
<td>68</td>
<td>52 mL/min</td>
<td>Ioversol</td>
<td>117</td>
<td>139</td>
<td>RCT</td>
<td>Turkey</td>
</tr>
<tr>
<td>Oliveira, 2012</td>
<td>8</td>
<td>10</td>
<td>Rosuvastatin 40 mg 2 to 6h before CM exposure</td>
<td>61</td>
<td>NR</td>
<td>High and low osmolar</td>
<td>72.2</td>
<td>78.2</td>
<td>RCT</td>
<td>Brazil</td>
</tr>
<tr>
<td>Jo, 2008</td>
<td>118</td>
<td>118</td>
<td>Simvastatin 40 mg/12h for 2 days, twice in evening before CM exposure and twice in evening after CM exposure</td>
<td>66</td>
<td>54.4 mL/min</td>
<td>Iodixanol</td>
<td>173.3</td>
<td>190.9</td>
<td>RCT</td>
<td>South Korea</td>
</tr>
<tr>
<td>Liu, 2014</td>
<td>273</td>
<td>805</td>
<td>Rosuvastatin 10 mg vs atorvastatin 20 mg 2-3 days before exposure and 2-3 days after exposure</td>
<td>65</td>
<td>99 µmol/L</td>
<td>non ionic low osmolar</td>
<td>133</td>
<td>132</td>
<td>RCT</td>
<td>China</td>
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</table>
### Table 2  Continued

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Statin total patients</th>
<th>Control total patients</th>
<th>Intervention</th>
<th>Mean Age (years)</th>
<th>Baseline CrCl (mL/min) or Scr (µmol/L)</th>
<th>Contrast</th>
<th>Statin (mean, mL)</th>
<th>Control (mean, mL)</th>
<th>Study design</th>
<th>Country</th>
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<tbody>
<tr>
<td>Patti, 2011</td>
<td>35</td>
<td>39</td>
<td>Atorvastatin 80 mg 12h before CM exposure and with 40 mg preprocedure</td>
<td>66</td>
<td>&lt;60 mL/min</td>
<td>Iobitridol</td>
<td>209</td>
<td>213</td>
<td>RCT</td>
<td>Italy</td>
</tr>
<tr>
<td>Toso, 2010</td>
<td>152</td>
<td>152</td>
<td>Atorvastatin 80 mg/day for 48h before and 48h after CM exposure</td>
<td>75</td>
<td>46 mL/min</td>
<td>Iodixanol</td>
<td>151</td>
<td>164</td>
<td>RCT</td>
<td>Italy</td>
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<tr>
<td>Han, 2014</td>
<td>1498</td>
<td>1500</td>
<td>Rosuvastatin 10 mg every evening from 2 days before to 3 days after CM exposure</td>
<td>61</td>
<td>NR</td>
<td>Iodixanol</td>
<td>120</td>
<td>110</td>
<td>RCT</td>
<td>China</td>
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<tr>
<td>Liu, 2014</td>
<td>604</td>
<td>600</td>
<td>Rosuvastatin 10 mg twice in evening before CM exposure and three doses after CM exposure</td>
<td>70</td>
<td>96 mL/min</td>
<td>Iodixanol</td>
<td>NR</td>
<td>NR</td>
<td>Cohort</td>
<td>China</td>
</tr>
<tr>
<td>Yoshida, 2009</td>
<td>194</td>
<td>237</td>
<td>Pravastatin 10 – 20 mg/day 28 days before CM exposure</td>
<td>70</td>
<td>40 mL/min</td>
<td>non ionic low osmolar</td>
<td>124</td>
<td>123</td>
<td>Cohort</td>
<td>Japan</td>
</tr>
<tr>
<td>Saied, 2017</td>
<td>23</td>
<td>18</td>
<td>Atorvastatin 80 mg 12h before and procedural 40 mg before CM exposure</td>
<td>55</td>
<td>95 mL/min</td>
<td>Iopamidol</td>
<td>118</td>
<td>117</td>
<td>RCT</td>
<td>Egypt</td>
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<tr>
<td>Wu, 2014</td>
<td>1183</td>
<td>1126</td>
<td>Rosuvastatin 10 mg every evening and twice before CM exposure and 10 mg/day 3 days after CM exposure</td>
<td>61</td>
<td>74 mL/min</td>
<td>Iodixanol</td>
<td>160</td>
<td>157</td>
<td>RCT</td>
<td>China</td>
</tr>
<tr>
<td>Munoz, 2011</td>
<td>15</td>
<td>17</td>
<td>Pravastatin 10 – 80 mg vs simvastatin 5 – 80 mg prior to CM exposure</td>
<td>59</td>
<td>93 µmol/L</td>
<td>Iodixanol and iohexol</td>
<td>NR</td>
<td>NR</td>
<td>Cohort</td>
<td>USA</td>
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<tr>
<td>Leoncini, 2014</td>
<td>252</td>
<td>252</td>
<td>Rosuvastatin 40 mg on admission and 20 mg/day in evening before CM exposure and 20 mg/day after CM exposure</td>
<td>66</td>
<td>&lt;60 mL/min</td>
<td>Iodixanol</td>
<td>149.7</td>
<td>138.2</td>
<td>RCT</td>
<td>Italy</td>
</tr>
</tbody>
</table>
including: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Low risk of bias, high risk of bias, or an unclear risk of bias were used as classifications to assess the risk. Study quality was adequate in almost cases according to the Cochrane Collaboration tool. No significant publication bias was found using funnel plot (Figure 2) or proved by the Egger regression test and Begg rank correlation tests according to the outcome of CI-AKI (Egger: P=0.87, Begg: P= 1.00).

**Figure 1** Flow chart of systematic literature identification and selection process implementing PRISMA (Preferred Reporting Items for Systematic Review and Meta Analysis) Guide

**Study End Points**

Pairwise meta-analysis as subgroup analysis was first performed and results demonstrated that
statin preloading was associated with a decreased risk of CI-AKI (OR: 0.51, 95%CI: 0.40 – 0.65; P<0.05) based on statin type subgroup analysis (Figure 3). No significant heterogeneity for this analysis was detected (I²=30%). Atorvastatin high dose comprised lower CI-AKI risks compared to placebo (OR: 0.46, 95%CI: 0.28 – 0.74, P<0.05). Rosuvastatin high dose and regular dose resulted in lower CI-AKI risks compared to placebo (OR: 0.48, 95%CI: 0.29 – 0.81, P<0.05; OR: 0.61, 95%CI: 0.42 – 0.87, P<0.05 respectively). Simvastatin high dose generated lower CI-AKI risks compared to placebo (OR: 0.74, 95%CI: 0.16 – 3.40, P<0.05). Pravastatin regular dose produced the highest risk reduction compared to placebo (OR: 0.32, 95%CI: 0.14 – 0.72, P<0.05). On drugs dosage subgroup analysis, it was found that high dose statin was more effective than regular dose statin (OR: 0.48, 95%CI: 0.34 – 0.68, P<0.05 and OR: 0.55, 95%CI: 0.39 – 0.76, P<0.05, respectively) as shown in Figure 4.

A network meta-analysis was then conducted, comparing different effects of atorvastatin high dose, atorvastatin regular dose, simvastatin high dose, rosuvastatin regular dose, rosuvastatin high dose and pravastatin regular dose as shown in figure 5. Head to head comparison of each statin was presented at network league table according to table 3. By using rank probability (Pbest) in Markov chain Monte Carlo simulation as shown in table 4, we found results that pravastatin regular dose (OR: 0.33, 95%CI: 0.10 – 1.09, Pbest 44%) and atorvastatin high dose (OR: 0.36, 95%CI: 0.17 – 0.77, Pbest 31%) comprised the highest probability to be the best treatment. Simvastatin high dose (OR: 0.71, 95%CI: 0.16 – 3.13, Pbest 9.4%), rosuvastatin high dose (OR: 0.57, 95%CI: 0.23 – 1.41, Pbest 8.9%), rosuvastatin regular dose (OR: 0.72, 95%CI: 0.34 – 1.52, Pbest 3.9%), atorvastatin regular dose (OR: 1.08, 95%CI: 0.34 – 3.44, Pbest 1.6%) followed treatment rankings respectively.

**DISCUSSION**

The strength of this study was the application of network meta-analysis, which has advantage to assess comparative efficacy of several statins and synthesize treatment effects across a network of studies both RCTs and cohorts. This method could analyze all possible statins comparisons in a way of direct and indirect comparisons so as to increase the force of the tests and investigate the most effective therapy. Therefore, the effects which could not be identified through a direct meta-analysis could be identified through network meta-analysis.

The present network meta-analysis could represent comprehensive comparison of several statins at different types and doses in preventing CI-AKI in...
patients with CKD undergoing PCI. The main findings of current network meta-analysis of 14 studies involving 9847 patients concludes that administration of statin before PCI procedure is associated with lower risk of CI-AKI in CKD patients undergoing PCI with iodinated contrast media. The risk reduction of CIAKI was 47% with number needed to treat (NNT) 41 when statins were compared with placebo/no statin in CKD patients. Subgroup analysis finds that pravastatin regular dose comprised the highest risk reduction in terms of occurrence of CI-AKI. Our rank probability (Pbest) test by using Markov chain Monte Carlo simulation suggests that pravastatin regular dose and atorvastatin high dose comprised the highest probability to be the most effective treatment. Together these findings indicate that statin can be used as premedication before PCI procedure even in a higher risk patients which are CKD patients.

The CI-AKI, as a severe complication after the use of contrast media procedure, is an important problem in today's era, as it causes negative outcome and prolonged hospitalization, increasing morbidity and mortality, specifically in CKD patients who have higher risk in developing CI-AKI. CI-AKI is defined as a rise in blood urea nitrogen (BUN) and SCr, or a reduction in eGFR occurred approximately 24-72 hours after contrast administration. It is measured that incidence of CI-AKI is about 2% to 7% in patients undergoing elective coronary angiography/percutaneous coronary intervention and is higher in CKD patients which is a greatest independent risk factor for CI-AKI. Therefore, prevention may result in significant impact and benefits.

The mechanisms which are responsible in development of CI-AKI have not been fully understood. However, several studies previously have suggested several ways in which contrast media could alter the renal hemodynamics and thus, could play major role in the pathogenesis of CI-AKI: blood flow reduction in renal medullary, GFR, red blood cell speed and velocity, and oxygen pressure, reduction in nitric oxide (NO), causing severe local hypoxia resulting in ischemic injury, endothelin increase, which is a solid endogenous vasoconstrictor, inflammation and cellular production of reactive oxygen species (ROS) leading to oxidative stress, leading in direct tubular epithelial and vascular endothelial damage.

Despite several preventive strategies have been put forward, only few provided clinical efficacy. Although statin was used as lipid lowering drugs, statins possess a remarkable pleiotropic effects, including increasing endothelial function by inhibiting the release of free reactive oxygen species, stimulating the production of NO, upregulating and increasing endothelial functions capacity, anti-inflammatory effects, and effective as antioxidant. Most probably, these mechanisms aim at above mentioned. Therefore, statins are considered and have potential to be associated with the prevention of CI-AKI after iodinated contrast exposure by counteracting of the possible common pathways of the CIAKI process. Study conducted by Khana et al. in retrospective cohort study previously reported that patients who underwent PCI receiving chronic statin therapy before the PCI procedure had a significantly lower incidence of CIN. Nevertheless, statins type and dosage of statins are yet to investigate.

The differences and comparisons between different type of statins may be related to their lipophilicity, LDL cholesterol-lowering effects, anti-inflammation effects and renal effects. Pravastatin regular dose comprised the highest probability to be the best treatment and atorvastatin high dose comprised the highest probability to be the second best treatment. Pravastatin (10mg/day) was effective in decreasing proteinuria by inhibition of renal endothelin-1 production. The reason why pravastatin may be most effective than other statins in prevention of CIAKI and renal protection is probably due to its water-soluble structure where pravastatin is the most hydrophilic statin currently available. Previously reported studies on human in-vitro and in-vivo mice postulated that lipophilic statins are less efficacious in counteracting pro-inflammatory mechanisms and in several cases may even stimulate pro-inflammatory responses.

Finally, standard doses (10-20 mg/day) of pravastatin have no adverse effects on organs (insulin secretion from the pancreatic β cells, sugar uptake by fat cells or muscles). Atorvastatin high dose may be more effective than simvastatin high dose due to its higher anti-inflammatory and antioxidant features. In animal studies, atorvastatin showed that it could prevent contrast induced epithelial tubular renal cell apoptosis by extracellular signal-regulated kinase pathways. In addition, several actions are involved in renal protective effect of atorvastatin mainly improving endothelial function, anti-inflammation and antithrombotic actions. Moreover in our study, it has been shown that high dose of statin was more effective than regular dose of statin (figure 4) which this was similar to the study reported by Zhou et al. in 2018. This may indicate that the pleiotropic effects of statin is influenced by drugs dosage. The proangiogenic effect of atorvastatin was found at 10 nmol/L in human umbilical endothelial cells (ECs) in vitro experimentation. Previous studies also reported that compared with low-dose statins, high dose
statsins were associated with significant reduction in pro-inflammatory cytokines production, such as interleukin (IL-8), urokinase plasminogen activator (uPA), high sensitivity of CRP and the production of P-selectin and intercellular adhesion molecule-1 (ICAM-1). IL-8 plays a major role in the renal response to several internal and external disruption which can lead to chronic kidney disease. Chronic kidney disease was also associated with IL-8 and P-selectin through the interaction of mononuclear (MCs)-ECs. Endothelial dysfunction was due to overrelease of NO caused by increased expression of P-selectin and ICAM-1. Previous study reported that uPA was associated to be linked in the development of kidney disease and could be a potential biomarker to predict AKI after cardiac surgery. 

CONCLUSION

Premedication with statin in preprocedural iodinated contrast media exposure is associated with significantly reduced risk of CI-AKI in patients with CKD undergoing percutaneous coronary intervention. Regular dose pravastatin and high dose atorvastatin have the highest probability to be the most effective prevention strategy.

CONFLICT OF INTEREST

The authors declare nothing to disclosure regarding conflict of interest.

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AUTHOR CONTRIBUTIONS

Authors and co-authors to be specified as having contributed equally to the work or having jointly supervised the work. Corresponding authors have specific responsibilities (described below).

Regarding the authors’ contributions to this paper, Ilham Akbar Rahman and Yeni Purnamasari wrote the drafted of the manuscript; Vicky Nanu Rewa, Hasyim Kasiyim, Abd Rahman Umar and Firdaus Kasim revised the manuscript; Ilham Akbar Rahman and Yeni Purnamasari contributed to the data collection, statistical analysis, and results interpretation. Firdaus Kasim planned and ran statistical analysis. Ilham Akbar Rahman, Yeni Purnamasari, Vicky Nanu Rewa proposed the idea, concept, and study design. All authors participated in manuscript discussion and revision. All authors approved the final manuscript.

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