

## Statins Against Drug-Induced Nephrotoxicity

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**ABSTRACT** - Drug-induced nephrotoxicity (DIN) accounts for up to 60% of hospital acquired acute kidney injury with considerable morbidity and mortality. Several efforts have been made to reduce drug-induced nephrotoxicity; however, DIN remains a matter of concern. Statins with their antioxidant, anti-inflammatory and anti-apoptotic effects may have the potential to protect kidney against DIN. The present review evaluated all of the available *in vitro* and *in vivo* studies that examined the use of statins as renoprotective agents against nephrotoxic drugs. Materials for this review were obtained by searching Medline, PubMed, Scopus, Cochrane central register of controlled trials, and Cochrane database of systematic reviews. Key words used as search terms included “statin”, “3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors”, “HMG-CoA reductase inhibitors”, “nephroprotective”, “renoprotective”, “drug-induced renal diseases”, “drug-induced nephrotoxicity”, “drug-induced renal toxicity”, “drug-induced nephropathy”, “drug-induced renal side effects”, and “contrast-induced nephropathy”. This search was performed without time limitation. Only English language articles were included in this review. This review concluded that chronic statin user may be less prone to contrast-induced nephropathy (CIN) compared with statin non-users. Short-term high dose statin administration may also reduce the incidence of CIN in statin naïve patients. This renoprotective effect of statins against CIN is seen in low risk patients with normal kidney function or mild kidney dysfunction, but probably not in patients with moderate to severe renal dysfunction. Based on available animal data, statins may protect kidney against gentamicin-, cisplatin- and cyclosporine-induced nephrotoxicity, however, these animal results have not yet been confirmed by human data.

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### INTRODUCTION

Drug-induced nephrotoxicity (DIN) has been reported with a great number of drugs and contributes to approximately 20% of the hospital admissions due to acute kidney injury (AKI) and up to 60% of in-hospital AKI (1). There are several mechanisms for DIN including drug-induced oxidative stress, inflammation, increased apoptosis, and direct cytotoxicity to the tubular epithelial cells (2). 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, known as statins, are widely used in the treatment of hypercholesterolemia. Statins have pleiotropic effects including antioxidant, anti-inflammatory, antithrombotic and endothelial function improving effects irrespective of their cholesterol-lowering activity (3,4). Statins show some nephroprotective effects. Some authors reported that statins decrease ischemic–reperfusion renal injury in animals due to their antioxidant and anti-inflammatory effects (5). Statins also reduce proteinuria in patients with chronic kidney disease (CKD) (6).

Some researchers proposed renoprotective effects of statins against DIN by some mechanisms including inhibition of drug accumulation in the proximal tubular cells, exerting anti-inflammatory and antithrombotic effects, up regulation of endothelial nitric oxide synthase (eNOS) and down regulation of inducible NOS (iNOS) expression (7), activation of the antioxidant defense enzymes such as heme oxygenase-1 (HO-1) (8) and thioredoxin (TRX) (9), inhibition of mitogen activated protein kinase (MAPK) and nuclear factor kappa-B (NF-κB) signaling pathways (7), reducing ischemia and angiotensin II-induced AKI (10), down regulation of angiotensin receptors (11), decreased endothelin synthesis (12), and protection against complement-related injury (13).

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This manuscript reviews all available articles on renoprotective properties of statins against nephrotoxic drugs.

### Search Method

The present review evaluated and critiqued all of the available *in vitro* and *in vivo* studies that examined the use of statins as renoprotective agents against nephrotoxic drugs. Materials for this review were obtained by searching Medline, PubMed, Scopus, Cochrane central register of controlled trials, and Cochrane database of systematic reviews. Key words used as search terms included “statin”, “3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors”, “HMG-CoA reductase inhibitors”, “nephroprotective”, “renoprotective”, “drug-induced renal diseases”, “drug-induced nephrotoxicity”, “drug-induced renal toxicity”, “drug-induced nephropathy”, “drug-induced renal side effects”, and “contrast-induced nephropathy”. This search was performed without time limitation. Only English language articles were included in this review. In each section, studies have been reviewed chronologically.

### Stain and contrast -induced nephropathy

Iodinated contrast media are widely used in diagnostic and interventional procedures with the main side effect of contrast-induced nephropathy (CIN). The incidence of CIN varies from 0.6%–2.3% in low risk patients to as high as 50% in high risk ones (14). CIN usually manifests as a nonoliguric and transient asymptomatic decline in renal function. After an initial vasodilatation, decrease in local vasodilating prostaglandins and nitric oxide and increase in vasoconstrictors (adenosine, angiotensin, endothelin, and vasopressin) result in vasoconstriction and blood flow shunt from medulla to the cortex. The medulla ischemia contributes to tubular injury. Direct toxic effect of contrast agents on renal tubular cells, increased reactive oxygen species (ROS) and proinflammatory cytokines, and enhanced oxygen consumption and intra-tubular pressure secondary to contrast-induced diuresis are other proposed mechanisms leading to CIN(15,16). Prophylactic use of antioxidant agents has been proposed as one of the modalities to decrease CIN (17).

During an animal study Al-Otaibi et al. assessed the nephroprotective effects of simvastatin against CIN. Three oral dosages of simvastatin (15, 30, and 60mg/kg) were administered for four days in

different groups of rats following CIN induction by single i.v administration of iohexil. Biochemical and histological results showed that simvastatin dose dependently attenuated contrast-induced rise in serum creatinine and urea concentrations, kidney structural changes and also ameliorated contrast-induced increase in oxidative stress as evaluated by renal lipid peroxidation, reduced glutathione, and myeloperoxidase (18).

Table 3 presents the metaanalysis and systematic reviews on the effect of statins on CIN incidence. There are different types of clinical studies on the effectiveness of statins against CIN. In almost all studies CIN has been defined as an increase in serum creatinine concentration of at least 0.5mg/dl or  $\geq 25\%$  rise from patients' baseline serum creatinine values. In all studies all included patients received hydration before receiving iodinated contrast media.

For the first time in 2004 Attallah et al retrospectively assessed 1002 stable CKD patients with serum creatinine of  $\geq 1.5$ mg/dl who were admitted for cardiac catheterization. None of these patients received statin before admission. Upon hospitalization, 250 out of the 1002 patients were prescribed statins before catheterization while others not. All patients were followed regarding serum creatinine levels and also dialysis requirement within the first week after catheterization and also one-month survival. The baseline serum creatinine level was similar between the two groups of patients (statin users and non-users). After catheterization, patients who received statin showed significantly lower serum creatinine concentrations (2.26 vs 3.1mg/dl,  $p=0.001$ ), less CIN incidence (17.2% vs 22.3% of patients,  $p=0.028$ ) and hospital stay duration (2.72 vs 3.32 days,  $p=0.01$ ). Dialysis requirement within first week after procedure (2.8% vs 5.2% of patients in statin users and non-users respectively,  $p = 0.091$ ) and one-month survival (0.97 vs 0.93,  $p=0.105$ ) were comparable between the two groups of patients (19).

Khanal et al gathered data from a prospective, audited, multicenter regional registry of patients undergoing percutaneous coronary interventions (PCI) from Michigan. Data of 28871 patients who underwent PCI and had preprocedure and peak postprocedure serum creatinine concentrations and were not receiving dialysis before PCI were used for analysis. About 38% of these patients were on statin therapy before the procedure. The mean age of patients and their preprocedure serum creatinine levels were similar between patients who were and

were not on statin. Multivariate analysis revealed that pretreatment with statin was independently associated with lower incidence of CIN (4.37% vs 5.93%,  $p < 0.0001$ ) and nephropathy requiring dialysis (0.32% vs 0.49%,  $p = 0.03$ ). After adjustments for co-morbidities or using drugs that are risk or protective factors against CIN, preprocedure statin use was still associated with a significant reduction in CIN (odds ratio [OR] 0.87, 95% confidence interval [CI] 0.77– 0.99,  $p = 0.03$ ) (20).

In an effort to evaluate the long-term effectiveness of statin pretreatment in reducing CIN incidence, Patti et al (2008) designed a study by enrolling 434 patients undergoing PCI and followed up prospectively for 4 years. Patients were stratified into two groups according to preprocedural statin therapy (260 patients were statin-treated and 174 statin-naïve). In the statin-treated group, 59% of patients were treated by atorvastatin, 30% by simvastatin, 7% by rosuvastatin and 4% by pravastatin; mean duration of statin pretreatment was  $10.6 \pm 9.1$  months. Occurrence of major adverse cardiac events (MACEs) including cardiac death, myocardial infarction, or repeat coronary revascularization and verification of continued statin therapy were the subjects for follow-up evaluation. Results showed the protective effects of pre-PCI statin therapy against CIN that consequently leads to better long-term event-free survival. The author reported that statin-treated patients had a significantly lower incidence of CIN (3% in statin-treated vs 27% in statin-naïve patients,  $p < 0.0001$ ; 90% risk decrease) and had better postprocedural creatinine clearance ( $80 \pm 20$  vs  $65 \pm 16$  ml/min,  $p < 0.0001$ ). In patients who suffered CIN, postprocedural creatinine peak level was significantly lower in statin-treated versus statin-naïve patients ( $1.6 \pm 0.5$  vs  $2.3 \pm 1.4$  mg/dl,  $p = 0.007$ ). Hospital stay was shorter in statin-treated compared with statin-naïve patients ( $2.2 \pm 0.5$  vs  $2.4 \pm 0.6$  days,  $p = 0.01$ ). These advantages were seen in all subgroups of patient treated by statins, except in patients with a pre-existing creatinine clearance of less than 40 ml/min. Multivariate analysis showed statin pretreatment as strong predictor of decreased CIN risk (OR=0.10, 95%CI 0.02 to 0.18;  $p = 0.001$ ). CIN was a predictor of poorer outcome during follow-up. Four-year follow-ups showed significantly lower incidence of MACEs in statin-treated compared with statin naïve patients (6% vs 36%,  $p < 0.0001$ ). Event-free survival was higher in

statin-treated patients at 4 year (94% vs 66%,  $p < 0.0001$ ). The results of this study supports statins utilization as adjuvant pharmacologic therapy before PCI (21).

A Korean team (2008) conducted a prospective, randomized, placebo-controlled clinical trial (RCT), named PROMISS study, to determine the safety and efficacy of short-term administration of high dose simvastatin against CIN in 247 patients with renal insufficiency (creatinine clearance of  $\leq 60$  ml/min or baseline serum creatinine  $\geq 1.1$  mg/dl) undergoing coronary angiography using hypoosmolar contrast agent, iohexol. One hundred and twenty-four patients received simvastatin with total dose of 160 mg as 40 mg orally every 12 hours starting the evening before and ending the morning after the procedure. Others received placebo. Results did not show any difference between simvastatin and placebo groups regarding increase in serum creatinine level ( $0.002 \pm 0.164$  vs  $0.017 \pm 0.230$  mg/ml respectively,  $p = 0.559$ ). The incidence of CIN did not differ between groups (simvastatin 2.5% and placebo 3.4%,  $p = 1.00$ ). There were also no differences between the two groups in length of hospital stay (simvastatin 4.5 vs placebo 5.1 days,  $p = 0.390$ ) or 1- and 6-month clinical composite outcome of death, myocardial infarction, revascularization, cerebral infarction, or dialysis (0% in simvastatin group vs 0.8% in placebo group,  $p = 0.498$  for month 1 and simvastatin 2.4% vs placebo 4.1%,  $p = 0.5$  for month 6 of follow-up). The authors explained their different results from previous studies by retrospective designs of those studies and resultant heterogeneous patient populations due to lack of randomization and significant differences in baseline risk factors between groups (22).

Zhao et al (2008) also assessed the effect of statins pretreatment on CIN incidence among patients with acute myocardial infarction who underwent primary angioplasty. They evaluated 279 patients, of them 56 patients were taking statins (pravastatin, simvastatin, or atorvastatin) before admission. CIN incidence was significantly lower in statin users compared with statin non-users (7.1% vs 20.6%;  $p < 0.01$ ) (23).

Bouzas-Mosquera et al (2009) did not achieve Zhao results in the same patient population with larger sample size of 589 patients. In this study CIN incidence was comparable between statin users and non-users (15.9% vs 10.8%;  $p = 0.2$ ) (24).

Another study (2009) was a comparative one on the effectiveness of two doses of simvastatin in

preventing CIN in patients with acute coronary syndrome undergoing PCI. Two hundred and twenty-eight patients were randomly divided into simvastatin 20mg (n=115) or simvastatin 80mg group (n=113). Patients in simvastatin 80mg group showed lower incidence of CIN within 48hours after contrast administration (5.35% versus 15.7%) and also lower rise in serum creatinine, C-reactive protein (CRP), P-selectin, and intercellular adhesion molecule-1 levels (25).

Yoshida et al (2009) assessed the impact of chronic pravastatin treatment before scheduled coronary angiography or PCI on reduction of CIN incidence. They evaluated 431 patients with renal insufficiency, of them 194 patients were receiving pravastatin as chronic treatment of hypercholesterolemia. Results from logistic regression analysis revealed that pravastatin treatment independently related to the decreased risk of CIN (OR=0.34, p=0.011) (26).

Toso et al (2010) during a RCT on 304 patients with baseline estimated creatinine clearance of <60ml/min undergoing elective coronary angiography and/or other intervention declared an interesting data. Design of their study was very similar to PROMISS trial; however, because of older subject, lower baseline serum creatinine and cardiac ejection fraction and a higher incidence of PCI, this study population was at higher risk for CIN. Included patients divided randomly to receive atorvastatin 80 mg/day or matching placebo for 48 hours before and 48 hours after contrast medium administration. All patients in both groups received NAC 1200mg twice daily, from the day before to the day after the procedure. Results failed to show significant difference between the two groups according to mean increase in serum creatinine concentration after contrast media administration (0.59±0.17 in the placebo group vs 0.72±0.26 mg/dl in the atorvastatin group, p=0.31). CIN occurrence did not differ between the two groups (placebo 11% and atorvastatin group 10%, p=0.86). Persistent kidney injury, defined as a 1-month increase from baseline creatinine value of at least 25%, was seen in 30% and 31% of the patients in the placebo and atorvastatin group respectively (P=0.58). Like results obtained by PROMISS trial, this study showed that a short-term treatment with high-dose atorvastatin before and after contrast exposure, in addition to standard intravenous hydration and oral NAC, does not decrease CIN occurrence in patients with pre-existing CKD (27).

An American group (2010) declared the results of their retrospective study on 353 adult patients who underwent non-emergent PCI; of them 239 patients were on different doses of different statins therapy and 114 were not. In this study a new method of patient classification based on Mehran score, a weighted scoring system that is based on comorbidities and events during PCI, was applied to analyze the effect of statins. Despite of limitations of this study such as different kind and different doses of administered statins, obtained results were against statin use before non-emergent PCI. Data showed a non-significantly higher incidence of CIN in patients on statins compared with patients not used statins (24.7% vs 14%) (28).

A Turkish team (2010) compared short-term, high-dose atorvastatin plus NAC (80 mg atorvastatin plus 600 mg NAC twice daily in the first day followed by 80 mg atorvastatin for 2 days after the procedure) or only NAC in 130 participants who undergoing coronary angiography. Patients with baseline renal dysfunction were excluded from this study. Based on their results CIN incidence was non-significantly lower in atorvastatin+NAC group (3.3% vs 10%, p=0.135). Despite similar serum creatinine concentration and creatinine clearance between the two groups at the initiation of the study, serum creatinine levels were significantly lower and creatinine clearance was significantly higher in the atorvastatin+NAC group (0.84±0.18 vs 0.95±0.35mg/dl, p=0.03 and 96±22 vs 87±23ml/min, p= 0.037 respectively) (29).

Acikel et al (2010) performed a RCT on 160 patients aiming to compare the effects of two different statin therapy regimens on the development of renal function deterioration following elective coronary angiography. Patients were randomized to receive either short-term atorvastatin 40 mg/day started 3 days before coronary angiography and continued for 48 h after the procedure or did not receive any lipid-lowering medication as a control group. The study was also composed of additional 80 nonrandomized patients who had been receiving statins (different dose of different statins) by mean duration of 6.5± 4.4 months before contrast exposure as a chronic statin-treated group. There were no differences in renal function parameters such as serum creatinine and cystatin C concentrations between the short-term atorvastatin group and the chronic statin-treated group. Results was in favor of statin therapy, since post procedure serum creatinine and cystatin C levels and GFR were significantly

better in patients using atorvastatin than those in the control group ( $P=0.002$ ,  $P=0.027$  and  $P=0.004$ , respectively). Moreover, postprocedure serum creatinine and cystatin C levels were significantly lower and GFR was significantly higher in chronic statin-treated patients compared with controls control subjects ( $P=0.006$ ,  $P=0.003$ , and  $P=0.030$ , respectively). By releasing these data, authors just showed that both short-term and chronic statin therapy may have a role in protecting renal function after elective coronary angiography but they addressed the main limitation of their study as nonrandomized included patients in the long-term statin-treated group (30).

ARMYDA-CIN [Atorvastatin for Reduction of Myocardial Damage during Angioplasty–Contrast-Induced Nephropathy] was another trial by Patti et al (2011) to investigate the effect of short-term high-dose atorvastatin load on the incidence of CIN after PCI. Statin-naïve patients with acute coronary syndrome undergoing PCI ( $n = 241$ ) randomly received atorvastatin 80 mg 12 hours before intervention with another 40mg dose 2hours before procedure ( $n=120$ ) or placebo ( $n=121$ ). There were no differences between the two groups regarding baseline serum creatinine and CRP concentrations, creatinine clearance, and history of CKD or diabetes mellitus. Thereafter all patients irrespective of their randomization were prescribed atorvastatin 40 mg/day for long-term. CIN incidence was lower in the atorvastatin group (5% vs 13.2% ,  $p=0.046$ ). Postprocedure serum creatinine was significantly lower ( $1.06 \pm 0.35$  vs  $1.12 \pm 0.27$ ,  $p = 0.01$ ) and creatinine clearance was significantly higher ( $80.1 \pm 32.2$  vs  $72.0 \pm 26.6$  ml/min,  $p=0.034$ ) in atorvastatin compared with placebo group. Serum CRP peak levels ( $8.4 \pm 10.5$  vs  $13.1 \pm 20.8$  mg/l,  $p= 0.01$ ) and hospital stay ( $2.9 \pm 0.9$  vs  $3.2 \pm 0.8$  days,  $p = 0.007$ ) were significantly lower in atorvastatin versus placebo group. Multivariable analysis showed that short-term pretreatment with high-dose atorvastatin was independently associated with a decreased risk of CIN (OR 0.34, 95% CI 0.12 to 0.97,  $p=0.043$ ) (31).

Muñoz et al (2011) compared the effect of one of the most lipophilic statin (simvastatin) versus the most hydrophilic one (pravastatin) on CIN. They evaluated 261 patients, of them, 145 received simvastatin and 116 received pravastatin. The majority of patients underwent elective PCI. There were no differences in CIN risk factors and prophylactic strategies between the two groups.

17.9% of patients in the simvastatin group versus 8.6% in the pravastatin group ( $P < 0.05$ ) encountered CIN but none of them required dialysis. Results showed that acute kidney injury (AKI) (defined as more than 0.3mg/dL rise in serum creatinine within 48hours) occurred in 14.5% of patients in the simvastatin group compared with only 6.9% in the pravastatin group ( $P<0.05$ ). Patients on pravastatin had a significantly lower incidence of CIN compared to patients on simvastatin and the difference between statins remained an independent predictor for the development of CIN in multivariate analysis (parameter estimate 0.42,  $p=0.03$ ) (32).

RCT by Li et al (2012) investigated the effects of high dose atorvastatin on the incidence of CIN after emergency PCI. They randomly assigned 180 statin-naïve patients with acute ST-segment elevation myocardial infarction into two groups, one group received high dose atorvastatin (80 mg) within 12 hours of symptoms onset and before undergoing emergency PCI and the other one received placebo. Both groups continued by long-term atorvastatin (40 mg/day). Hence, two groups were completely similar except in getting loading dose of atorvastatin before procedure. CIN occurred lesser in atorvastatin-loaded versus the control group (2.6% vs 15.7%,  $p=0.01$ ). Postprocedural serum creatinine concentrations were significantly lower 24 and 72 hours post procedure in the atorvastatin-loaded group ( $93.4 \pm 17.1$  vs  $112.6 \pm 23.3$   $\mu\text{mol/l}$  at 48 h and  $84.2 \pm 14.2$  vs  $95.3 \pm 17.7$   $\mu\text{mol/l}$  at 72 h, both  $p < 0.0001$ ), however, peak serum cystatin C was lower in the control group ( $0.51 \pm 0.14$  vs.  $0.61 \pm 0.13$  mg/l,  $p < 0.0001$ ). Multivariate logistic regression analysis showed that high dose atorvastatin pretreatment was independently associated with a decreased risk of CIN (OR 0.084, 95% CI 0.015–0.462,  $p= 0.004$ ) (33).

Novel Approaches for Preventing or Limiting Events (NAPLES) II is a RCT on 410 patients that evaluated possible protective mechanisms of atorvastatin against CIN *in vivo* and *in vitro*. CKD patients enrolled to whether the atorvastatin group (80 mg within 24 hours before contrast media exposure;  $n=202$ ) or the control group ( $n=208$ ). In this study all patients pretreated by a high dose of oral NAC 1200 mg twice daily. The primary outcome measure was the development of CIN, defined as an increase in cystatin C concentration of 10% above the baseline value at 24 hours after administration of contrast agent. Twenty patients with CKD who were not scheduled for contrast

media exposure and not enrolled in the original NAPLES II trial were assessed to address whether a single dose of atorvastatin 80mg may affect the serum creatinine or cystatin C levels. CIN occurred in 4.5% of patients in the atorvastatin group and 17.8% of patients in the control group ( $p=0.005$ ;  $OR=0.22$ ; 95% CI, 0.07– 0.69). Based on the CIN definition in previous studies by changes in serum creatinine, there was no difference in CIN incidence between the two groups in NAPLESII trial (3.5% in atorvastatin group vs 7.7% in the placebo group  $p=0.085$ ). CIN rate was lower in high dose atorvastatin- administrated group in both diabetics and nondiabetics and in patients with moderate chronic kidney disease (creatinine clearance 31–60

ml/min/1.73 m<sup>2</sup>) but not in patients with severe CKD (creatinine clearance less than 30 ml/min/1.73 m<sup>2</sup>). In spite of some limitation and powerful aspects of the study, these results suggested that the beneficial effect of statin is observed only in patients at low to medium risk for CIN. *In vitro* results revealed that pretreatment with a high dose of atorvastatin reduced contrast-induced activation of stress kinases such as caspase-3, Jun N-terminal kinases (JNK), and p-53 and resultant apoptosis. Atorvastatin pretreatment also restored cell survival signals mediated by Akt and MAPK pathways (34).

All of the above mentioned studies on protective effect of statins against CIN have been summarized in Table 1.

**Table 1.** Studies on protective effects of statins against contrast-induced nephropathy (All patients in these studies received hydration before contrast media administration).

Type of study	Total patients	Trial design	Clinical outcome	
Retrospective	1,002	Patients with stable baseline $SCr \geq 1.5$ mg/dl, who did not receive statin and NAC underwent cardiac catheterization with non-ionic contrast agent. 250 out of the 1002 patients were prescribed statins before catheterization while others not.	Patients who received statin showed significantly lower SCr concentrations and less AKI during the first week after cardiac intervention. Dialysis requirement within the first week after procedure and one-month survival were similar between the two groups.	19
Prospective, observational	29,409	Patients who underwent PCI and had both baseline preprocedure and peak postprocedure SCr levels. About 38% of these patients were on statin therapy before the procedure and 62% were not. Demographic data and baseline SCr were similar between the two groups.	Pretreatment with statin was independently associated with lower incidence of CIN and nephropathy requiring dialysis.	20
Prospective, observational	434	Patients who underwent PCI were enrolled and followed up to 4 years. Patients were stratified into two groups according to preprocedural statin therapy (260 patients statin-treated with different types of statins for mean duration of $10.6 \pm 9.1$ months and 174 statin-naive).	Statin-treated patients had a significantly lower incidence of CIN, better postprocedural CrCl, lower postprocedure peak SCr level, and shorter hospital stay. Benefit of statin pretreatment was observed in all subgroups, except in patients with a pre-existing CrCl <40 ml/min.	21
Prospective, RCT	247	Enrolled patients had CKD and underwent coronary angiography with iso-osmolar contrast agent. 124 patients received simvastatin (160 mg total, 40 mg orally every 12 hours starting the evening before and ending the morning after the procedure) or placebo (n = 123).	There was no difference between simvastatin and placebo groups in mean peak increase in SCr measured within 48 hours after coronary angiography. There were also no differences between the two groups in CIN incidence, length of hospital stay, or 1- and 6-month clinical composite outcome of death, AMI, revascularization, cerebral infarction, or dialysis.	22

Retrospective	279	patients who underwent primary angioplasty for their first AMI were included. 56 patients were taking statins (pravastatin, simvastatin, or atorvastatin) before admission.	Patients used statins before admission had lower incidence of CIN.	<b>23</b>
Retrospective	589	Patients who underwent primary angioplasty.	They did not observe a protective effect of statin therapy on CIN development after primary angioplasty.	<b>24</b>
Prospective, RCT	228	Patients with ACS underwent PCI were randomly divided into simvastatin 20-mg treated group (n = 115) or simvastatin 80-mg treated group (n= 113).	Patients in simvastatin 80mg group showed lower incidence of CIN and also lower rise in SCr, hs-CRP, P-selectin, and intercellular adhesion molecule-1 levels.	<b>25</b>
Prospective, observational	431	Patients with renal insufficiency, of them 194 were chronic pravastatin users	Long-term pravastatin pre-treatment independently related to the decreased risk of CIN.	<b>26</b>
Prospective, RCT	304	Patients with baseline CrCl <60 ml/min were randomized to receive atorvastatin 80 mg/day or placebo for 48 hours before and 48 hours after contrast medium administration. All patients received oral NAC 1,200 mg 2 times/day.	Mean increase in SrCr and CIN incidence were not significantly different between atorvastatin and placebo groups. s	<b>27</b>
Retrospective	353	239 patients used statins before PCI and 114 were not. Patients were classified based on Mehran score for risk of development of CIN.	Data showed a non-significantly higher incidence of CIN in patients on statins compared with patients not used statins.	<b>28</b>
Prospective, RCT	130	patients underwent coronary angiography were either randomized to a short-term high dose atorvastatin plus NAC (80 mg atorvastatin plus 600 mg NAC twice daily in the first day followed with 80 mg atorvastatin for 2 days after the procedure) or only NAC.	Lower incidence of CIN, lower SCr, and higher CrCl were observed in atorvastatin+NAC group.	<b>29</b>
Prospective, RCT	160	patients underwent elective coronary angiography were randomized equally into two groups: atorvastatin 40 mg/day group (statin started 3 days before coronary angiography) and an untreated control group. An additional 80 patients were included as a chronic statin therapy group.	There were no differences in SCr and cystatin C concentrations between the short-term atorvastatin group and the chronic statin-treated group. Post procedure serum creatinine and cystatin C levels and GFR after coronary angiography, were significantly better in patients using atorvastatin than those in the control group. Post procedure serum creatinine and cystatin C levels were significantly lower and GFR was significantly higher in chronic statin-treated patients compared with controls subjects.	<b>30</b>
RCT	270	Statin-naive patients with ACS undergoing PCI (n=241) randomly received atorvastatin (80 mg 12 hours before intervention with another 40-mg preprocedure dose, n=120) or placebo (n= 121).	Postprocedure SCr was significantly lower, CrCl was significantly higher, and CIN incidence was lower in atorvastatin compared with placebo group. CRP peak levels and hospital stay were significantly lower in the atorvastatin versus placebo group. Multivariable analysis showed that short-term pretreatment with high-	<b>31</b>

			dose atorvastatin was independently associated with a decreased risk of CIN.	
Retrospective	261	The effect of one of the most lipophilic statin (simvastatin) versus the most hydrophilic statin (pravastatin) on CIN were evaluated. They assessed 261 patients, of them, 145 received simvastatin and 116 received pravastatin. The majority of patients underwent elective PCI.	Patients on pravastatin had a significantly lower incidence of CIN and AKI compared to patients on simvastatin and the difference between statins remained an independent predictor for the development of CIN in multivariate analysis.	32
Prospective, RCT	180	Statin-naïve patients with acute ST-elevated AMI randomly assigned into groups which were received whether high dose atorvastatin (80 mg) within 12h of symptom onset undergoing emergency PCI or placebo followed by long-term atorvastatin (40 mg/day).	CIN was occurred significantly lower in atorvastatin loaded versus the control group. Postprocedural SCr was significantly lower, but serum cystatin C was higher in the atorvastatin loaded group. Multivariate logistic regression analysis showed that high dose atorvastatin pretreatment was independently associated with a decreased risk of CIN.	33
Prospective, RCT	410	This study also evaluated possible mechanisms of atorvastatin against CIN in vivo and in vitro. CKD patients enrolled to whether the atorvastatin group (80 mg within 24 hours before contrast media exposure; n=202) or the control group (n=208). In this study all patients pretreated by a high dose of NAC (1200 mg PO twice daily) and sodium bicarbonate solution.	CIN incidence was significantly lower in the atorvastatin group. CIN incidence was lower in high dose atorvastatin-administrated group in both diabetics and nondiabetics and in patients with moderate but not severe CKD patients.	34
<p>ACS: acute coronary syndrome; AKI: acute kidney injury; AMI: acute myocardial infarction; CrCl:creatinine clearance; CKD: chronic kidney disease; CNI: contrast-induced nephropathy; CRP: C-reactive protein; GFR: glomerular filtration rate; NAC:N-acetylcysteine; PCI: percutaneous coronary intervention; RCT: randomized controlled trial; SCr: serum creatinine</p>				

Eventually based on conflicting data, for the first time an American group published a meta-analysis to evaluate the impact of statin therapy on the incidence of CIN in patients undergoing coronary angiography until that date (2010). They reanalyzed the data from three RCTs involving 770 patients (330 in the statin group and 340 in the control group) and 7 non-randomized studies involving 31,959 patients (11,936 statin-pretreated and 20,023 statin-naïve patients). All included studies in this metaanalysis have been summarized in the present article [19-24, 26-29]. This metaanalysis suggested that statin therapy might be associated with a significant reduction in the incidence of CIN in patients undergoing coronary angiography but advised caution because of the nonrandomized nature of most of the studies and the significant heterogeneity among the studies. According to the pooled estimate across the 3 prospective randomized controlled

trials, statin therapy reduced the incidence of CIN compared to control by 26%, where the difference between the two arms was not statistically significant (OR=0.76, 95% CI: 0.41–1.41, p=0.39). There was no significant heterogeneity in the randomized studies ( $I^2=0\%$ , p=0.48). Although the pooled analysis of the non-randomized studies (all retrospective except one which was cohort prospective) revealed a marginally significant benefit associated with statin therapy (OR=0.60, 95% CI:0.36–1.00, p=0.05) while had significant heterogeneity ( $I^2=88\%$ , p<0.00001) (35).

Thereafter Zhang et al (2011) did a meta-analysis including different types of studies such as cohort studies comparing the CIN incidence between chronic statin-users before contrast administration and a statin-naïve patients (20,21,23,26,28) as well as including RCTs comparing periprocedure short-term, high-dose versus short-term, low-dose statin



treatment or placebo (22,25,27,29, two non-English language RCTs). Among cohort studies included in this meta-analysis, 4 showed that chronic statin therapy before contrast administration had a protective effect against CIN. From 6 RCTs, 1194 patients were included. Under the fixed-effects model, a non-significant protective trend toward decreased CIN incidence was seen with periprocedural short-term, high-dose statin treatment (RR: 0.70; 95% CI: 0.48–1.02). There are some limitations in this study including combined data of cohort studies and heterogeneous RCTs and the inclusion of low-quality studies for meta-analysis (36).

Immediately after previous study, a meta-analysis on 7 RCTs (27, 29-31, two non-English articles) about periprocedural short-term atorvastatin treatment on CIN was released by a Japanese group. Results of this study were against Zhang et al's evaluation, however, just four included articles in these two meta-analyses were the same. Included articles enrolled 1251 patients undergoing percutaneous angiography or intervention. Results of pooled analysis demonstrated a statistically significant reduction in the serum creatinine changes (fixed-effects MD, -0.07 mg/dl; 95% CI, -0.08 to -0.05 mg/dl; *p* for effect <0.00001; *p* for heterogeneity=0.12), increase in the changes of creatinine clearance (random-effects MD, 6.27 ml/min; 95% CI, 1.86 to 10.68 ml/min; *p* for effect=0.005; *p* for heterogeneity<0.00001), and reduction in the incidence of CIN (fixed-effects OR, 0.56; 95% CI, 0.33 to 0.95; *p* for effect=0.03; *p* for heterogeneity=0.43) in the atorvastatin compared with control group (37).

Zhou et al (2011) performed a metaanalysis by aiming to assess the effectiveness of short-term (2–7 days), high-dose (80 mg/d) statins in the prevention of CIN. Five RCTs (22, 25, 27, 29, one non-English article that has been used in previous meta-analysis as well) with a total of 1,009 patients were included. Statins showed overall benefit in preventing CIN (RR=0.53, 0.32–0.87 with minor heterogeneity  $I^2=19\%$ ). The subgroup analysis by stratifying the data according to patients' baseline serum creatinine, manifested that two studies done in patients with CKD Stage $\geq 3$  failed to show significant difference in CIN occurrence between the statin and matching group (6.5% vs 7.2%; RR=0.89, 0.46–1.73), without evidence of heterogeneity ( $I^2=0\%$ , *p*=0.79), while the remaining three studies conducted in patients with CKD Stage<3 revealed a significantly lower

incidence of CIN in the statin groups (3.6% vs 11.9%) (RR=0.28, 0.13–0.62), without evidence of heterogeneity ( $I^2=0\%$ , *p*=0.87) (38).

Zhang et al (2011) extracted data from RCTs (27, 22, 29) with 751 subjects. Pooled analyses with random-effect model showed that neither the CIN incidence (RR=0.76, 95% CI 0.44–1.29, *p*=0.30,  $I^2=0\%$ ) nor the need for renal replacement therapy (RR=0.33, 95% CI 0.03–3.17, *p*=0.34) were different between statin or placebo groups. This is while statin pretreatment was associated with mild reduction of serum creatinine (weighted mean difference=-0.06 mg/dl, 95% CI -0.12 to 0.00 mg/dl, *p*=0.05,  $I^2=53\%$ ) (39).

Another meta-analysis on 8 RCTs (25, 27, 29,30, and three Chinese language articles two of them have been included in previous metaanalysis) among 1423 patients was performed to determine whether short-term administration of high-dose statin is superior to conventional-dose statin or placebo among patients undergoing catheterization and interventional procedures or not. Results supported that short-term high-dose statin treatment can decrease the incidence of CIN (RR: 0.51, 95% CI, 0.34-0.77; *p*=0.001) and 48 hour serum creatinine level (SMD -0.07 mg/dl; 95% CI, -0.11 to -0.04 mg/dl; *p*=0.00001). However, subgroup analysis of 2 studies could not prove reduction in CIN occurrence in patients with preexisting CKD (RR 0.90; 95% CI, 0.49-1.65; *p*=0.73). The authors noted that the definition of high dose statin is arbitrary, there have been no dose-finding studies with respect to statin for the prevention of CIN, and so-called high dosing is purely based on the original trial that used 80mg or 40mg dose per day (40).

Li et al (2012) by evaluating seven randomized controlled trials with a total of 1,399 patients [22,25,27,29,30,31] (one of the study that have been included in this meta-analysis was not reviewed in the present article due to non-English language) assessed the effectiveness of intervention with high dose statin versus low-dose statin or placebo treatment for the prevention of CIN. The overall results based on fixed-effect model manifested that the use of short-term, high-dose statin treatment was associated with a significant reduction in CIN risk (relative risk (RR) = 0.51, 95% CI 0.34–0.76, *p*=0.001;  $I^2 = 0\%$ ). The incidence of acute renal failure requiring dialysis and decrease in the plasma CRP level was not significantly different after the use of statin (RR = 0.33, 95% CI 0.05–2.10, *p*=0.24;  $I^2=0\%$  and standardized mean difference (SMD)

20.64, 95% CI:21.57 to 0.29,  $p=0.18$ ,  $I^2=97\%$ , respectively) (41).

Collecting above systematic reviews and meta-analysis, Kwok et al (2013) concluded that although statins show promising effect to reduce CIN incidence (RR 0.51, 95% CI 0.34-0.77,  $I^2=0\%$ ), however, limitations in the studies quality and heterogeneity prevent any firm confirmation (42).

### Summary of contrast -induced nephropathy

What is apparent from these meta-analyses is that making a decision and interpreting a precise conclusion is very difficult for all researchers due to different types of studies (observational studies against RCTs), different definition of dosage in the studies (such as using high dose statin for 40 mg simvastatin or atorvastatin in some studies while 80 mg in others), including patients with varying degree of risk factors for CIN (such as patients with varying baseline kidney function as a major risk factor for CIN), and using different types of statins (hydrophilic versus lipophilic statins) between these studies and even among patients within some particular studies. However, we can conclude that CIN may occur less frequently among chronic statin user compared with statin-naïve patients. Additionally, short-term administration of high dose hydrophilic statins may exert nephroprotective effects against CIN in statin-naïve patients.

### Antibiotics

#### Statins and aminoglycoside-induced nephrotoxicity

Aminoglycosides are valuable gram negative coverage antibiotics because of low rates of resistance. However, nephrotoxicity is the dose limiting factor for their therapeutic use. Aminoglycoside nephrotoxicity mediated through increasing vasoconstrictors, ROS, inflammatory cytokines and apoptosis (43). Statins possess some properties that may diminish aminoglycoside-induced nephrotoxicity. These properties include anti-oxidative effects, inhibition of aminoglycoside accumulation in the proximal tubular cells, and exerting anti-inflammatory and anti-thrombotic effects. In addition up regulation of eNOS and down regulation of iNOS expressions occur by statins administration. Statins also inhibit activation of MAPK and NF- $\kappa$ B (44,45). Aminoglycoside endocytosis through multi-ligand receptor megalin is the main step in the cellular uptake of

aminoglycoside and future nephrotoxicity. This process is modulated by intracellular concentration of isoprenoid pyrophosphates. Isoprenoid pyrophosphate derives from mevalonate through enzymatic activity of HMG-CoA reductase. Statins by inhibiting HMG-CoA reductase have the theoretical potential to reduce intracellular concentration of aminoglycoside. This hypothesis was approved in *in vitro* study of Antoine et al (45).

Ozbek et al (2009) evaluated the effect of atorvastatin against gentamicin-induced nephrotoxicity in rats. Coadministration of atorvastatin prevented gentamicin-induced increases in blood urea nitrogen (BUN) and serum creatinine levels, reduction in calculated creatinine clearance values, reduction in renal tissue glutathione (GSH) levels and elevation of kidney malondialdehyde (MDA) and NO levels. Coadministration of atorvastatin also significantly prevented gentamicin-induced tubular and glomerular degeneration. The administration of atorvastatin reduced gentamicin-induced over expressions of iNOS, p38-MAPK, and p65-NF- $\kappa$ B in rats. The authors concluded that atorvastatin can prevent gentamicin-induced renal injury via the inhibition of MAPK and NF- $\kappa$ B signaling pathways and iNOS expression (44).

During a rat study, Jabari et al evaluated the preventive effects of low, medium and high dose simvastatin (2mg/kg/d, 10mg/kg/d, and 20 mg/kg/d respectively) against nephrotoxicity of low- and high-dose gentamicin (50mg/kg/d and 80mg/kg/d respectively). Simvastatin administration started prophylactically several days before gentamicin injection and continued all over gentamicin administration days. Increasing simvastatin dosage up to 10 mg/kg/day dose-dependently improved gentamicin-induced changes in renal histopathology and function test (46).

There is an ongoing clinical trial on the protective role of atorvastatin against aminoglycoside-induced nephrotoxicity (47). The result of this human study seems to be the first results on the clinical effect of statin against aminoglycoside induced nephrotoxicity and infection outcome.

#### Statin and vancomycin-induced nephrotoxicity

Vancomycin is antibiotic of choice to treat methicillin resistant *S. aureus* infections with nephrotoxicity as its major adverse effect. Prevalence of vancomycin-induced nephrotoxicity when is used as monotherapy is 5 to 10%; while in high dosage or combination with other nephrotoxic

agents, nephrotoxicity incidence increases to 14-35% (48). Vancomycin decreases activities of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) (49-50) and increases oxidative stress and free radicals (48, 50-51) as possible mechanisms of vancomycin-induced nephrotoxicity. Vancomycin alters the energy-dependent reabsorptive function of proximal tubular cells and also mitochondrial function (52).

Panonnunmal et al during an animal study evaluated the renoprotective effects of atorvastatin against vancomycin-induced AKI. Atorvastatin started several days before vancomycin injection and continued during vancomycin treatment and several days after that. Vancomycin decreased renal function as evidenced by increase in BUN and serum creatinine and decrease in creatinine clearance. Vancomycin also induced hypokalemia, oliguria, urinary sodium wasting, renal oxidative stress, and also some tubular and glomerular structural damages. Vancomycin-induced renal oxidative stress presented as increased renal tissue MDA, and decreased expression of antioxidant enzymes including SOD, CAT, and GSH in the kidney tissue. All vancomycin-induced renal functional, structural, and oxidative changes were mostly or completely prevented by atorvastatin administration. Authors concluded that renoprotective effect of atorvastatin against vancomycin-induced AKI is mediated through its antioxidant effect (53).

### **Platinum derivatives cytotoxic drugs**

#### **Statin and cisplatin-induced nephrotoxicity**

Cisplatin is a cytostatic agent in the treatment of solid tumors, including cancers of the ovary, testis, bladder, head and neck, lung, cervix and endometrium. Nephrotoxicity is the major side effect with the incidence of 6-13% (1) that limits cisplatin use. Cisplatin-induced nephrotoxicity consisted of AKI, distal renal tubular acidosis, renal concentrating defect, transient proteinuria, hyperuricemia, fanconi-like syndrome, hypomagnesemia, hypocalcemia, renal salt wasting, erythropoietin deficiency, thrombotic microangiopathy, and CKD. After accumulation by renal parenchymal epithelial cells, cisplatin is metabolically converted to a more potent toxin, forms inter- and intra strand cross-links with DNA and subsequent DNA injury, mitochondrial DNA and respiration damage, activation of apoptotic pathways, and initiation of inflammatory responses

(54) and oxidative/nitrosative injury (55). It has been reported that hydroxyl radicals' generation following cisplatin administration directly or indirectly activates p38 MAPK that plays pivotal role in cisplatin-mediated kidney injury and inflammation (56). Statins have been suggested as anticancer agents based on preclinical evidence of their anti-proliferative, pro-apoptotic, anti-invasive, and radio-sensitizing properties (57). Ligands of peroxisome proliferator-activated- $\alpha$  (PPAR- $\alpha$ ) have been reported to prevent cisplatin-induced nephrotoxicity (59) and statins as ligands of PPAR- $\alpha$  may possess renoprotective effect against platinum agents' nephrotoxicity. Several studies evaluated the renoprotective effects of different statins against cisplatin-induced nephrotoxicity that are reviewed here.

Işeri et al examined the protective effect of simvastatin against cisplatin-induced renal toxicity in rats. Simvastatin initiated prophylactically 5 days before a single injection of cisplatin and continued for 10 consecutive days. Cisplatin impaired kidney function as shown by increased BUN and serum creatinine concentrations and decreased creatinine clearance. This renal dysfunction was improved by simvastatin administration. Simvastatin decreased cisplatin-induced increase in myeloperoxidase (MPO) activity in the kidney but did not improve cisplatin-induced changes in renal MDA and GSH contents. Simvastatin attenuated cisplatin-induced increase in kidney tissues collagen content as indicator of fibrotic activity, and reactive oxygen metabolites. Kidney histological damages were completely reversed by simvastatin. (59).

Another animal study by Fujieda et al evaluated the effect of pravastatin on cisplatin-induced nephrotoxicity. In this study low dose pravastatin was started for long time of two weeks before cisplatin-induced AKI. Cisplatin caused renal tubular damage with high renal MDA level, increased p53 up-regulated modulator of apoptosis (PUMA) expression, p53- and terminal deoxynucleotidyl transferase dUTP nick end-labeling (TUNEL)-positive cell counts, and decreased renal GSH level, GPx mRNA expression, and activity. Renal tissue sections showed cisplatin-induced structural damage to the proximal tubular cells. Pretreatment with pravastatin significantly improved cisplatin-induced renal dysfunction and proteinuria and attenuated cisplatin-induced immunohistological changes in p53- and TUNEL-positive apoptotic cells in renal proximal tubular

cells. Prophylactic administration of pravastatin also significantly prevented cisplatin-induced oxidative damage as shown by modulation in cisplatin-induced changes in renal MDA and GSH levels and kidney tissue GPx expression and activity. The authors concluded that pravastatin prevents cisplatin-induced cell apoptosis through p53 signaling pathways and also via its antioxidant activity. In this study pravastatin partially, but not completely prevented cisplatin-induced nephrotoxicity. The authors hypothesized that statins induced decrease in the mTOR response may exert some renal ischemia-reperfusion injury that may partly mask the nephroprotective effects of statin (60). This hypothesis was originated from Roudier's (61) and Finlay's (62) reports on statins effect on mTOR pathway. However this is an area of conflict as some authors reported that pravastatin might decrease renal reperfusion injury effect through inhibition of fransylation and prenylation of some signal transduction protein with subsequent interference with some inflammatory pathways (63).

In the third animal study by An et al the protective effects of high dose pravastatin administration shortly before cisplatin-induced acute nephrotoxicity was evaluated. Pravastatin pretreatment significantly diminished cisplatin-induced increase in BUN and serum creatinine and histological damage to renal tubules. Cisplatin significantly increased renal MDA level, decreased kidney GSH level, and inhibited activities of antioxidant enzymes including CAT, SOD and GPx. All these oxidative changes significantly attenuated by pravastatin administration. Cisplatin increased kidney iNOS expression and peroxynitrite formation. These cisplatin-induced oxidative and nitrosative stimulations were partially suppressed by pravastatin. Pravastatin also reduced cisplatin-induced p38 MAPK activation in the kidney tissues. The authors concluded pretreatment with pravastatin can prevent cisplatin-induced nephrotoxicity via inhibiting oxidative and nitrosative stress (64).

Khoshnoud et al assessed the impact of simvastatin on cisplatin-induced nephrotoxicity in rats using three different doses of 1, 2, or 4mg/kg simvastatin that were much lower than the 10mg/kg dose that has been used in İşeri's study. In this study cisplatin-induced kidney dysfunction was not improved by simvastatin administration at any dosage (65). Inconsistent with previous studies (59, 60, 64) in this study simvastatin in any dosage could not prevent cisplatin-induced lipid peroxidation. In

this study cisplatin did not decrease renal GSH level while simvastatin at dose of 4mg/kg significantly increased kidney tissue concentration of GSH. Renal histopathological changes were just prevented by simvastatin at dosage of 4mg/kg (65).

We think that the failure of simvastatin to prevent cisplatin-induced nephrotoxicity in this study (65) is mainly related to the lower dose of simvastatin that have been administered in this study compared to others (59). Moreover İşeri et al in their study administered daily simvastatin injection five days before single dose injection of cisplatin and continued simvastatin administration for five days after cisplatin injection as well (59) but in Khoshnoud study (65) only a single low dose of simvastatin one hour before single injection of cisplatin was used that may result in failure to see renoprotective effects of simvastatin. Additionally cisplatin dose in khoshnoud study [65] was two times the dose in İşeri et al (59) study.

It seems that protective effect of statins against platinum agents-induced nephrotoxicity is dose- and duration-dependent.

#### **Stain and carboplatin-induced nephrotoxicity**

In an *in vitro* and *in vivo* study by Cheng et al carboplatin caused AKI and increased renal ROS production, caspase-3 expression and subsequent apoptotic cells. Preadministration of pravastatin significantly prevented carboplatin-induced kidney dysfunction and apoptosis and improved carboplatin-induced histomorphologic changes and animal survival. Their *in vitro* survey on molecular mechanism of renoprotective effect of pravastatin against carboplatin-induced nephrotoxicity in rat NRK-52E renal tubular epithelial cells explored that pravastatin decreased ROS production, increased expression of HO-1, cyclooxygenase-2(COX-2), and 6-keto prostaglandin F1- $\alpha$  (the stable hydrolysis product of PGI<sub>2</sub>), enhanced nuclear translocation of PPAR- $\alpha$ , and increased HO-1 promoter and peroxisome proliferator response element (PPRE) activities. The authors showed interaction of PPAR- $\alpha$  and PPRE on the HO-1 promoter in nuclear extracts from NRK-52E cell line following pravastatin treatment. Their *in vivo* experiences also showed that pravastatin induced overexpression of PPAR- $\alpha$  and HO-1 in wild-type mice. HO-1 expression was significantly diminished in PPAR- $\alpha$ -knockout mice. Authors concluded that pravastatin can partially prevent carboplatin-induced nephrotoxicity and apoptosis through PPAR- $\alpha$ -

dependent pathway. The non-complete renoprotective effect of pravastatin has been explained by its mTOR-induction activity by the authors as presented in cisplatin section as well (66).

### Statin and calcineurin inhibitor-induced nephrotoxicity

Cyclosporine as the first discovered calcineurin inhibitor (CNI) initially was used in human kidney transplantation in the late 1970s. Cyclosporine-induced acute and chronic nephrotoxicity are major concerns in transplantation. Cyclosporine-induced acute nephrotoxicity includes reversible decrease in GFR with alterations in renal vascular resistance, tubular vacuolization, and thrombotic microangiopathy. Chronic Cyclosporine nephrotoxicity consisted of irreversible renal functional deterioration as a result of irreversible and progressive tubular atrophy, interstitial fibrosis, and glomerulosclerosis. Cyclosporine decreases vasodilating prostaglandins and NO, and increases endothelin-1 (ED-1), thromboxane, angiotensin II, aldosterone, TGF- $\beta$ , and ROS (67).

Li et al assessed the effect of two doses of 5 and 20mg/kg of pravastatin on interstitial inflammation and fibrosis in a rat model of chronic cyclosporine-induced nephropathy. Chronic nephrotoxicity was induced by 4 weeks administration of cyclosporine 15mg/kg/day. High dose, but not low dose, pravastatin normalized cyclosporine-induced

changes in serum creatinine level and creatinine clearance. Pravastatin ameliorated cyclosporine-induced arteriopathy and tubulointerstitial fibrosis. Immunohistochemistry revealed a significant increase in CRP and ED-1-positive cells, increased osteopontin mRNA expression in kidney cortex, TGF- $\beta$  mRNA over-expression and eNOS protein under-expression by cyclosporine administration. All these changes were prevented dose-dependently by pravastatin. Cyclosporine injection increased the number of renin positive glomeruli. Pravastatin coadministration did not affect intrarenal renin immunoreactivity or the number of renin-positive glomeruli (68). During another animal study, Nam et al showed that high dosage of 15mg/kg of rosuvastatin prevented cyclosporine-induced tubular apoptosis and decreased cyclosporine-induced tubular atrophy and interstitial fibrosis. Rosuvastatin decreased intrarenal inflammation and fibrosis through decline in the expression of ED-1, TGF- $\beta$ ,  $\alpha$ -smooth muscle actin, Bax/Bcl-2 ratio, Smad 2/3, Smad 4, P-JNK (69). Based on these studies, anti-inflammatory, anti-apoptotic, and anti-fibrotic effects of statins against cyclosporine nephrotoxicity seems to be dose dependent. Therefore, high dose hydrophilic statins may decrease chronic cyclosporine-induced nephrotoxicity.

All animal studies on nephroprotective effects of statins against drug-induced nephrotoxicity except of CIN have been summarized in Table 3.

**Table 3.** Summarized studies on renoprotective effects of statins against drug-induced nephrotoxicity other than CIN

Animal model	Nephrotoxic agent	Statin administration plan	Monitored indices	Results	Ref
Male Wistar albino rats	Gentamicin 100mg/kg/d for 10 days	i.p. Atorvastatin suspension via NG tube 10mg/kg/d for 10 days	BUN, SCr, CrCl; renal tissue MDA, NO, and GSH; Renal histopathological examination	Atorvastatin prevented gentamicin-induced rises in BUN and SCr and decrease in CrCl. Atorvastatin also prevented gentamicin-induced elevation in renal tissue MDA and NO and decrease in kidney GSH, and decreased gentamicin induced tubular and glomerular histologic damage	44
Sprague-Dawley rats	Gentamicin 50mg/kg/d or 80mg/kg/d injection for 8days	Simvastatin 2, 10, or 20mg/kg/d for 12 days via gavage, started 4days before gentamicin	SCr, CrCl, kidney histology	Between dosage of 2-10mg/kg/d simvastatin dose-dependently prevented gentamicin-induced decrease in CrCl and increase in SCr and proximal tubular cell necrosis	46
Proximal tubule cell lines	Gentamicin 0.25mg/ml	Coadministration of simvastatin 10 $\mu$ M or rosuvastatin 30	Intracellular gentamicin concentration; GTP-binding protein prenylation	All three statins reduced Intracellular gentamicin concentration and GTP-binding protein prenylation	45

		$\mu\text{M}$ or pravastatin 30 $\mu\text{M}$			
<b>Wistar rats</b>	Vancomycin 200mg/kg i.p. BD for 7 days	Atorvastatin 10mg/kg/d orally 5days before to 5 days after vancomycin treatment course	SCr, BUN, CrCl, serum potassium, urinary sodium and potassium, renal tissue MDA, SOD, CAT, GSH, histopathological examination	Atorvastatin mostly or completely prevented vancomycin- induced renal functional, structural and oxidative stress changes	<b>53</b>
<b>Sprague–Dawley rats</b>	Cisplatin single dose 2.5mg/kg i.v.	Simvastatin 10mg/kg initiating five days before cisplatin injection and continued for 10 days	BUN, SCr, CrCl, Kidney MDA and GSH, histopathological examination	Simvastatin improved cisplatin-induced kidney dysfunction and also decreased kidney MPO activity but did not change renal MDA content and GSH activity. Simvastatin decreased kidney fibrosis and histological damage.	<b>59</b>
<b>Male Wistar rats</b>	Cisplatin single dose 10mg/kg i.v.	Pravastatin 6mg/kg via gavage for 19 days started 13 days before cisplatin injection	BUN, SCr, proteinuria, proximal tubular cells apoptosis, serum lipids, renal MDA and GSH level, renal GPx mRNA expression and activity	Pretreatment with pravastatin significantly improved cisplatin-induced renal dysfunction and proteinuria and attenuated cisplatin-induced cell apoptosis as changes in p53- and TUNEL-positive apoptotic cells in renal proximal tubular cells. Pravastatin significantly prevented cisplatin-induced changes in renal MDA and GSH levels, GPx expression and activity	<b>60</b>
<b>Mice</b>	Cisplatin 5mg/kg/d i.p. for 5 days	Pravastatin 80mg/kg oral gavage for 5 days; administered 2 hours before cisplatin injection	BUN, SCr, renal MDA and GSH level, renal SOD, CAT, GPx, and MAPK activities, iNOS expression and peroxynitrite formation	Pravastatin pretreatment significantly diminished cisplatin-induced increase in BUN and SCr, histological damage to renal tubules, prevented cisplatin-induced increased in renal MDA level, decrease in kidney GSH level, and inhibited activities of antioxidant enzymes including CAT, SOD and GPX, increase in kidney iNOS expression and peroxynitrite formation and MAPK activity	<b>64</b>
<b>Male Sprague–Dawley rats</b>	Cisplatin 5mg/kg single i.p. dose	Simvastatin single oral dose of 1,2,or 4mg/kg 1h prior cisplatin injection	BUN, SCr, kidney tissue MDA and GSH levels, renal histopathological examination	Simvastatin at any dosages did not prevent cisplatin-induced increase in BUN and SCr concentrations, or cisplatin-induced lipid peroxidation, cisplatin did not decrease renal GSH level while simvastatin 4mg/kg significantly increased kidney tissue concentration of GSH. Renal histopathological changes were just prevented by simvastatin at dosage of 4mg/kg.	<b>65</b>
<b>NRK-52E renal tubule epithelial cell line; Male C57/B6, H129 wild-type mice; H129</b>	Carboplatin 50-800 $\mu\text{M}$ in <i>in vitro</i> study and single dose 100mg/kg i.p. in <i>in vivo</i> study	Pravastatin 50 $\mu\text{M}$ in <i>in vitro</i> study and 1mg/kg i.p. in <i>in vivo</i> study	BUN, serum creatinine, renal ROS production, caspase-3 activity, and apoptosis; Expression of HO-1, COX-2, PPAR- $\alpha$ in renal tubule cell line and rat kidney	Pravastatin pretreatment significantly prevented carboplatin-induced kidney dysfunction and apoptosis and improved carboplatin-induced histomorphologic changes and animal survival. In NRK-52E cell line and in rats pravastatin decreased ROS	<b>66</b>

<b>PPAR<math>\alpha</math>-knockout mice</b>					production and increased expression of HO-1, COX-2, PPAR- $\alpha$ .		
<b>Male Sprague-Dawley rats</b>	Cyclosporine 15mg/kg s.c. for 4 weeks	Pravastatin 20mg/kg po	5,	SCr, osteopontine, and eNO expression; histopathological examination	CrCl; TGF- $\beta$ , and mRNA	High dose pravastatin normalized cyclosporine-induced changes in SCr and CrCl. Pravastatin dose-dependently ameliorated cyclosporine-induced arteriopathy and tubulointerstitial fibrosis, increase in CRP and ED-1-positive cells, increased renal osteopontin mRNA and TGF- $\beta$ mRNA over-expression and eNOS protein under-expression, but did not change intrarenal renin immunoreactivity or the number of renin-positive glomeruli	<b>Li et al (68)</b>
<b>Male Sprague-Dawley rats</b>	Cyclosporine 10mg/kg gavage for 4 weeks	Rosuvastatin 15mg/kg s.c.		SCr, CrCl; expression of ED-1, TGF- $\beta$ , $\alpha$ -smooth muscle actin, Bax/Bcl ratio, Smad2/3, Smad 4, P-JNK; histopathological examination		Rosuvastatin decreased cyclosporine-induced renal dysfunction, tubular apoptosis, tubular atrophy, and interstitial fibrosis through decline in expression of ED-1, TGF- $\beta$ , $\alpha$ -smooth muscle actin, Bax/Bcl ratio, Smad2/3, Smad 4, P-JNK	<b>69</b>

BUN: blood urea nitrogen; CAT: catalase; COX-2: cyclooxygenase-2; CrCl: creatinine clearance; CIN; contrast-induced nephropathy; CRP: C-reactive protein; ED-1: endothelin-1; eNOS: endothelial nitric oxide synthase; GPx: glutathione peroxidase; GSH: reduced glutathione; HO-1: heme oxygenase-1; iNOS: inducible nitric oxide synthase; i.p.: intraperitoneal; i.v.: intravenous; K: potassium; MAPK: mitogen activated protein kinase; MDA: malondialdehyde; MPO: myeloperoxidase; Na: sodium; NG: nasogastric; NO: nitric oxide; PPAR- $\alpha$ : peroxisome proliferator-activated- $\alpha$ ; ROS: reactive oxygen species; s.c.: subcutaneous; SCr: serum creatinine; SOD: superoxide dismutase; TGF- $\beta$ : transformin growth factor- $\beta$ ; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end-labeling;

### Conclusion and Expert opinion

Drug-induced nephrotoxicity accounts for about 60% of hospital-acquired AKI with high mortality and morbidity (1). Several drugs with antioxidant, anti-inflammatory, and anti-apoptotic effects have been evaluated to prevent drug-induced nephrotoxicity (70-73). Statins that widely used in the treatment of hypercholesterolemia have pleiotropic effects including antioxidant, anti-inflammatory, antithrombotic and endothelial function improving actions (3-4). Statins show some nephroprotective effects against ischemia-reperfusion renal injury in animals (5) and also reduce proteinuria in various types of CKD patients (6).

Some studies have evaluated protective effects of statins against drug-induced nephrotoxicity. Studies on drugs other than contrast agents have only been done in animals. Only studies on contrast-induced nephropathy have been performed in clinical settings with conflicting results. These contradictory results are due to different studies' designs (retrospective, prospective observational, or randomized controlled trials), and different types, doses or duration of statin

administration. Approximate similarities between these different studies are similar definition for CIN and hydration of all patients before contrast media administration. Almost all retrospective and prospective observational studies showed lower incidence of CIN in chronic statin users compared with those not on statin (19-21, 23, 26, 32). Some discrepancy between few other retrospective studies (24, 28) may be due to including patients with different types of risk factors for CIN occurrence. It seems that statin therapy is more protective against CIN in patients with normal renal function or mild kidney dysfunction but not in patients with moderate to severe CKD. Among available randomized clinical trials it appears that high-dose statin therapy is more efficacious than low-dose statin in reducing CIN incidence. Different types of statins may show different efficacy as seen more protection against CIN by more hydrophilic statin, pravastatin, compared with more lipophilic one, simvastatin (22, 25, 27, 29-31, 33-34). We have to consider that publication bias may result in more accessible to studies that support nephroprotective effect of statins against CIN. Due to widespread use of statins in

patients suffering coronary artery diseases, randomized, placebo-controlled trials to assess the impact of statins in CIN prevention during cardiovascular procedures are difficult to perform. However based on our comprehensive review, it seems that chronic statin users may suffer fewer incidences of CIN or peak serum creatinine concentrations following coronary angiography compared with statin naïve patients. Among short term statin recipients, patients who were administered high-dose of more hydrophilic statins such as pravastatin and atorvastatin showed more promising impacts against CIN. Statins may protect kidney against CIN only in patients with mild, but not moderate to severe renal dysfunction.

Regarding antibiotics, all three available animal studies (22-26) on statin renoprotective effects against gentamicin-induced nephrotoxicity showed promising results. Antioxidant action of statins may play role in its nephroprotective effect. The results of ongoing clinical trial (47) will clarify the real clinical effect of statin against gentamicin-induced nephrotoxicity. Considering the results generated from statins effects against other nephrotoxic agents such as contrast media and also animal studies on aminoglycoside-induced nephrotoxicity, we have to consider that using different doses (low versus high doses) of different types (hydrophilic versus lipophilic) of statins may show different impacts against aminoglycoside or vancomycin-induced nephrotoxicity. Additionally in animal studies statins were administered prophylactically several days before antibiotic administration. Predicting the time to need aminoglycoside or vancomycin administration in clinical settings is hard and statins would be of clinical importance if they could show the nephroprotective effects against aminoglycoside/vancomycin nephrotoxicity upon concurrent not prophylactic administration.

Based on available animal studies statins showed protective effects against nephrotoxicity of platinum agents probably through their anti-oxidative effects (59-60, 64, 66). It seems that protective effect of statins against platinum agents-induced nephrotoxicity is dose- and duration dependent. Using higher dose of statins several days before and throughout platinum agents' injection period exerts more nephroprotective effects.

Since statins have been widely used in cancer patients and have also shown anti-cancer effect in some studies (57, 74-76), there is no fear regarding reducing cytotoxic effects of cisplatin by statin co-

administration. It seems to be the time to design a clinical trial on nephroprotective effect of statins against valuable cytotoxic agent cisplatin to possibly overcome its main clinical use limitation of nephrotoxicity.

Based on the available animal studies, high dosage of hydrophilic statins may attenuate cyclosporine-induced chronic nephrotoxicity. As obvious, hyperlipidemia is a prevalent co-morbidity in patients who undergo solid organ transplantation mainly heart and kidney transplantation. Hyperlipidemia is also a common side effect of immunosuppressive drugs including calcineurin inhibitors and steroids. Statins have been introduced as treatment of choice in these patients (77-78). Additionally, it has been shown that statins improve graft survival in heart transplant recipients (79-80). Therefore, statin administration in kidney or heart transplant recipients under cyclosporine therapy would be of several advantages. More hydrophilic statins have less pharmacokinetic interactions with cyclosporine and resultant side effects such as rhabdomyolysis. Among these hydrophilic statins we have to consider the important side effects of rosuvastatin-induced proteinuria and acute kidney injury (81). It is proposed to evaluate the protective effect of statins against cyclosporine-induced nephrotoxicity at-least through retrospective and prospective observational studies on patients of big transplant centers who are receiving statins for other clinical indications. These preliminary findings may be a basis for decision on performing controlled clinical trials.

### **Proposed Research**

Most retrospective studies and controlled clinical trials have shown protective effect of statins against contrast-induced nephropathy in low risk patients. Based on their data, assessment of protective effect of statins against CIN in high-risk patients is proposed in larger clinical trials using high dose of more hydrophilic statins such as pravastatin and atorvastatin.

Due to dose-dependent effect of statins against nephrotoxicity of contrast media, aminoglycosides, platinum agents and cyclosporine, we propose dose finding studies for clear definition of high dose statins against nephrotoxicity of these drugs.

Regarding different impacts of hydrophilic and lipophilic statins against drug-induced nephrotoxicity, we recommend animal and clinical



studies to better differentiate between nephroprotective effects of different types of statins.

We recommend designing animal studies using concurrent, not prophylactic administration of statin with aminoglycoside/vancomycin to clarify nephroprotective effects of statins in real clinical settings.

Considering animal findings and pleiotropic effects of statins, designing clinical trials on protective effect of statins against cisplatin- and cyclosporine-induced nephrotoxicity are recommended.

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**Table 2.** Metaanalysis of protective effects of statins against contrast-induced nephropathy

Number of study included	Number of patients	Goal of study	Results	Authors' mentioned limitations	Ref
10 studies (3 randomized and 7 non-randomized)	32,729	To evaluate the impact of statin therapy on the incidence of CIN in patients undergoing coronary angiography	Overall, statin therapy might be associated with a significant reduction in the incidence of CIN in patients undergoing coronary angiography. According to the pooled estimate across the 3 RCTs, statin therapy reduced the incidence of CIN non-significantly.	Inclusion of both randomized and non-randomized studies, differences in the definitions of CIN among the studies, variations in the type, duration, and dose of statins.	35
6 cohort studies and 6 RCTs	1,194 from RCTs	To evaluate the effects of statin pre-treatment on CIN incidence	Among 6 cohort studies included in this meta-analysis, 4 showed that chronic statin therapy before contrast administration had a protective effect against CIN. Based on RCTs, a non-significant protective trend toward decreased CIN incidence was seen with periprocedural short-term, high-dose statin treatment.	Combined data of cohort studies and heterogeneous RCTs, inclusion of low-quality studies for meta-analysis	36
7 RCTs	1251	To assess the effects	Results showed a statistically significant	Not mentioned	37

5 RCTs	1,009	of periprocedural short-term atorvastatin treatment on CIN To assess the effectiveness of short-term, high-dose statins in the prevention of CIN.	reduction in the SCr changes, increase in CrCl, and reduction in the incidence of CIN with statin. Overallly statins showed preventing effect against CIN. Stratifying the data according to baseline SCr manifested that two studies done in patients with CKD Stage $\geq$ 3 failed to show statistically significant difference in CIN occurrence between the statin and matching group, while the remaining three studies conducted in patients with CKD Stage $<$ 3 revealed a significantly lower CIN incidence in the statin groups.	Low quality of included studies, limited number of available studies, publication bias of articles with positive results	38
4 RCTs	751	To evaluate the effects of statin pretreatment for the prevention of CIN.	Neither the CIN incidence nor the needs for renal replacement therapy were different between stain or placebo groups.	Bias due to low studies and patients included, differences in characteristics among included studies, heterogeneity across included studies.	39
8 RCTs	1,423	To determine whether short-term high-dose statin is superior to conventional-dose statin or placebo among patients undergoing catheterization and interventional procedures	Short-term high-dose statin treatment can decrease the incidence of and 48-hour SCr level. However, subgroup analysis of 2 studies could not prove reduction in CIN occurrence in patients with preexisting renal impairment.	Lack of patient specific data, inclusion of studies of variable quality, high dose of statin definition arbitrary, small sample size in included studies	40
7 RCTs	1,399	Assess the effectiveness of short-term high-dose statin treatment for the prevention of CIN	Short-term, high-dose statin treatment was associated with a significant reduction in CIN risk. The incidence of AKI requiring dialysis and decrease in the plasma CRP level were not significantly different with statin use.	Few trials designed to investigate the effect of statins on clinical outcomes such as AKI requiring dialysis, length of hospital stay and in-hospital mortality, different type of statins for varied periods of time.	41

AKI: acute kidney injury; CIN: contrast-induced nephropathy; CrCl: creatinine clearance; CRP: C-reactive protein; RCT: randomized controlled trial; SCr: serum creatinine;