

Statins and Kidney Failure

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Abstract

Use of the HMG-CoA Reductase Inhibitors, also known as statins, in patients with renal dysfunction is laden with controversy. Studies on statin use in renal patients have given varying reports. Some research has indicated that these medications may exacerbate existing renal dysfunction and induce further progression of renal disease. Furthermore, some researchers have suggested statins may actually cause some cases of renal dysfunction through the effects of rhabdomyolysis, acute interstitial nephritis, or necrotizing immune-mediated myopathy, while other researchers have asserted that the statins can have nephroprotective effects. The use of statins is believed to be ineffective in patients who are already in end-stage renal failure, but the research varies on this point, as well. There is currently a lack of researched knowledge regarding the safety and efficacy of HMG-CoA Reductase Inhibitors in patients with renal dysfunction, as well as the potential causative link between these medications and renal dysfunction.

Statins and Kidney Failure

According to the latest data from the Centers for Disease Control and Prevention (CDC), over 20 million people in the United States (U.S.) have chronic kidney disease (CKD); this accounts for more than 10% of the U.S.'s adult population (Centers for Disease Control and Prevention, 2014b). Many of these individuals are likely to have elevated serum cholesterol levels, causing CKD patients to have higher rates of cardiovascular disease (Elliott, McCaughan & Fogarty, 2014). One of the most common pharmacological treatments for patients with elevated cholesterol levels is the use of HMG-CoA Reductase Inhibitors, also known as statin drugs. Catapano (2012, Abstract) named the statins as "the most widely prescribed therapeutic class of drugs worldwide." Recent national statistics indicate that the use of statins in the U.S. is apparently increasing as more Americans are developing hypercholesterolemia and require pharmacological treatment (Centers for Disease Control and Prevention, 2014a).

Statins' Nephrotoxic Effects

Statins generally have few adverse effects; however, they can cause myotoxicity in some patients, leading to muscle breakdown. According to a systematic review published by Ganga, Slim and Thompson (2014), about 10-25% of patients treated with statins in clinical practice develop muscle problems. As muscle fibers break down, a byproduct known as myoglobin travels to the renal system where the kidneys attempt to process and eliminate the myoglobin. The healthy renal system, unprepared for myoglobin's large protein structure, may lose its ability to function in response to myoglobin accumulation in the renal glomeruli. For a renal system that is already damaged, as in someone with CKD, the kidneys may become even further damaged and

the CKD may progress to a later stage, possibly necessitating the use of renal replacement therapy (RRT), such as hemodialysis (HD), peritoneal dialysis (PD), or a renal transplant (Olyaei, Greer, Santos & Rueda, 2011). According to Auer, Sinzinger, Franklin and Berent (2014), renal compromise is the most common form of organ damage related to statin-induced myopathy.

The most severe form of statin-related myotoxicity is rhabdomyolysis. Mendes, Robles and Mathur (2014) published a comprehensive review of 112 cases of rhabdomyolysis, asserting that statin-induced rhabdomyolysis is generally rare in most of the general population, and it causes approximately 0.3-13.5 cases per 1,000,000 statin prescriptions; however, other forms of toxicity are less rare and can result in organ damage. Olyaei et al. (2011) examined case studies of kidney transplant patients and patients with CKD who received statins, and they found that patients with preexisting renal problems such as CKD actually have a much higher risk of developing statin-related myalgia, myopathy, and rhabdomyolysis than those in the general population.

Although myopathy is a known side effect of the statin drugs, and such myopathy may lead to renal dysfunction, there is limited research on the incidence of statin-caused renal dysfunction related to myopathies other than rhabdomyolysis. Ironically, some research has indicated statins might have nephroprotective effects; for this reason, statin therapy is sometimes prescribed for patients who have an increased risk for acute kidney injury (AKI), a condition of renal insufficiency that can lead to renal failure and CKD. Statin use in patients who already have renal dysfunction is also controversial due to a lack of ample research on the safety and efficacy of statin use in patients who already have renal dysfunction with or without the need for dialysis.

Intended Effects of Statins

Elevated serum cholesterol levels have long been associated with an increased risk for cardiovascular events, due to cholesterol's role in atherosclerosis, a disease process in which artery walls thicken in response to lipid accumulation and inflammatory processes within the vessels. Although dietary interventions and lifestyle modifications are generally the recommended treatment method for hypercholesterolemia, sometimes, hypercholesterolemia is very severe, or it does not respond effectively to these interventions alone, so patients may use pharmacological therapy to treat their hypercholesterolemia. The first-line pharmacological therapy for elevated cholesterol is treatment with a statin drug (Catapano, 2012). According to the CDC (2014b), a growing number of people in the United States are developing hypercholesterolemia, and consequently use statins in an attempt to control their cholesterol levels.

There are two ways cholesterol enters the bloodstream: through dietary, exogenous cholesterol and through endogenous cholesterol produced by the liver, which constitutes the greater part of serum cholesterol. Since cholesterol is a lipid, it cannot move freely in the blood. Instead, lipoproteins cover the cholesterol molecules within a phospholipid layer, so the cholesterol can then travel through the bloodstream to the body cells where it impacts essential cellular functions. High-density lipoproteins (HDLs) are a type of lipoprotein that consists of a high protein percentage and a low percentage of cholesterol, whereas low-density lipoproteins (LDLs) contain a minor protein component with a high cholesterol percentage. Due to their high percentage of cholesterol, LDLs are strongly involved in coronary atherosclerosis; thus, lowering LDL levels may actually reverse atherosclerotic changes in some people's vessels. In contrast to LDLs, HDLs

function to remove LDL-carried cholesterol from body cells and carry it back to the liver, where it is metabolized and eventually eliminated from the body; thus, HDLs have protective effects against atherosclerosis (Mani et al., 2014).

The effects of the statin drugs derive from the statins' inhibition of an enzyme known as HMG-CoA Reductase (3-hydroxy-3-methylglutaryl coenzyme A Reductase), which catalyzes an essential reaction in hepatic cholesterol synthesis. Although HMG-CoA Reductase inhibition actually increases the hepatic synthesis of HMG-CoA Reductase, it also causes hepatocytes to synthesize more LDL receptors, which then bind to LDL, and remove it from the bloodstream. Mani et al. (2014) published a retrospective analysis of 2,566 patients receiving statins, which suggested that by inhibiting HMG-CoA Reductase, the statin drugs might reduce cholesterol synthesis and thereby decrease atherosclerotic plaque development within blood vessels. Since cholesterol is an independent risk factor for major cardiovascular events and mortality, statin therapy is a respected form of preventive treatment for cardiovascular disease (Centers for Disease Control and Prevention, 2014a).

A recent study by Lee et al. (2011) examined atherectomy specimens from 22 patients with unstable angina and 21 patients with stable angina that had undergone surgery due to de novo coronary artery lesions. The researchers tested the specimens for the presence of antibodies specific to HMG-CoA Reductase, and they found that patients with HMG-CoA Reductase in these plaques were much more likely to have unstable versus stable angina. The study revealed that when HMG-CoA Reductase is present in atherosclerotic plaques, this enzyme might contribute to additional cholesterol synthesis and make these plaques more unstable and likely to rupture. Plaque rupture often leads to

adverse outcomes due to myocardial infarction (MI), cerebrovascular accident (CVA), and other adverse cardiovascular events (Lee et al., 2011).

Controversy over Statin's Effects on the Kidneys

Current research concerning statins' effects on the renal system is rather inconsistent, since some studies have asserted that statins can protect against renal injury and AKI, whereas others have attributed cases of AKI and advanced CKD to myopathies caused by statins (Kostapanos, Milionis & Elisaf, 2010). Statin use in patients who have preexisting renal dysfunction prior to statin therapy is particularly controversial. Ahmad (2014) asserted that although rhabdomyolysis in the general population is somewhat rare, the incidence of rhabdomyolysis in patients with CKD is much higher than in the general population and the myopathy from statin use is also relatively common; such myopathy can also progress CKD in the same way that rhabdomyolysis can progress CKD. At the same time, statins' effects in lowering serum cholesterol and preventing atherosclerotic plaque build-up might benefit the kidneys and invalidate concerns about statins' risk. Statin therapy for patients with CKD requires careful consideration into their risks and benefits to the kidneys.

The statin drugs may potentiate multiple effects on the kidney. Perhaps, the most intriguing aspect of these medications and their effects on the kidneys is the fact that they are neither inherently nephrotoxic, nor are they inherently nephroprotective. Part of the problem with determining the full extent of statin-caused renal damage derives from the fact that there are several different forms of muscle problems that relate to statin therapy, and rhabdomyolysis is only one of these. In a recent article discussing statin intolerance due to myopathies or high creatine kinase levels, Ahmad (2014) admitted that there is

still not a standardized criterion for describing or diagnosing statin intolerance. Auer et al. (2014) also discussed the discrepancies in clinical research studies and everyday practice, saying that inconsistent definitions or exclusion criteria may explain the inconsistent data. They described statin myopathy as being an entity with no clearly agree-upon definition (Auer et al., 2014).

Statin-Induced Renal Damage

Research has indicated that statins may be directly responsible for potentiating and progressing some cases of renal dysfunction. The exact mechanism by which they may exert nephrotoxic effects is unclear, however. Table 1 shows some relevant studies, detailing the methods used to collect the data, as well as the study findings.

Table 1 Studies that suggest statins may contribute to all types of renal insufficiency					
Study/Year	Population	Intervention/Methods	Comparison	Outcome	Time
Data analysis by Murugan et al./ 2012	Patients hospitalized with community-acquired pneumonia N=1,836; ≥18 years	Multicenter, prospective observational inception cohort study 413 patients received statin therapy prior to hospitalization for pneumonia	1,423 patients did not receive statin therapy prior to hospitalization for pneumonia	Patients who used statins prior to hospitalization had an increased incidence of AKI	One-year follow-up period
Data analysis by Zhang et al./ 2009	Saarland inhabitants who participated in the ESTHER Study from July 2000 to December	Cross-sectional, multivariate analysis 848 participants reported regular statin usage	4,134 participants reported having hypertension, a known CKD risk factor 3,977	Statin usage was an independent risk factor for the presence of CKD	Two-year follow-up period

	2002 N=9,806; 50-74 years; 55% female		participants reported having diagnosed hyperlipide mia		
PLANET I/ 2006	Patients with urinary protein/cre atinine ratios of 500-5,000 mg/g and a fasting LDL cholesterol of ≥ 90 mg/dL N=325	Randomized, prospective study Patients in the experimental group received 80 mg atorvastatin per day	Patients in the control groups either received 40 mg rosuvastatin per day or 10 mg rosuvastatin per day	Atorvastatin use reduced proteinuria by approximately 20%, but there was no effect on the rate of decline in glomerular filtration rate (GFR) Rosuvastatin did not affect proteinuria, but it decreased GFR by 8 mL/minute every year Renal adverse reactions were higher with rosuvastatin use	52- week follow- up period

As demonstrated in Table 1, Murugan et al. (2012) studied a large cohort of 1836 patients with community-acquired pneumonia. Of the 1836 total patients studied, 413 patients received a statin prior to their hospitalization. The purpose of the study was to determine if statin use decreased patients' risk for pneumonia-induced AKI as well as examining whether one-year and cause-specific mortality in AKI patients decreased with statin therapy. As described in Table 1, the study revealed that the 413 patients who took a statin before coming to the hospital did not have a lower risk for AKI; however, if they did develop AKI, they had a slightly lower risk of death at one year. One-third of the

deaths in AKI patients related to cardiovascular disease. The researchers concluded that statin usage did not decrease the risk for AKI and did not correlate with a decreased risk of death at one year (Murugan et al., 2012).

Another study by Zhang et al. (2009) that analyzed multiple variables including older age, cardiovascular history, DM and the use of statins concluded that statin use may increase the risk of CKD. The researchers included the analysis of studies such as the ESTHER Study (*Epidemiologische Studie zu Chancen der Verhuetung, Fruherennung und optimierten Therapie chronischer Erkrankungen in der aelteren Bevoelkerung*), which collected data on a large sample of patients who ranged in age from 50 to 74 years old and had CKD. The study revealed statistically significant increases in the incidence of CKD for patients who had formerly taken statins, as Table 1 further describes. The researchers therefore advised older adults to cautiously consider the effects of these medications on their renal systems (Zhang et al., 2009).

In 2013, Olyaei et al. conducted a literature review of studies that analyzed statin use in patients with CKD and end-stage renal disease (ESRD). They discussed several newly published studies including Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease PLANET I and PLANET II. In these studies groups of 325 and 220 patients respectively were selected based on the presence of a urinary protein/creatinine ratio of 500 to 5,000 milligrams (mg) per gram and a fasting LDL-cholesterol level of greater than or equal to 90 mg/dL. Participants were divided into randomized groups that either received daily 80 mg doses of atorvastatin, daily 10 mg doses of rosuvastatin, or daily 40 mg doses of rousvastatin. The study revealed that atorvastatin therapy generally decreased participants' incidence of

proteinuria; however, atorvastatin therapy did not affect the rate of GFR decline. In contrast, rosuvastatin causes GFR to decline by 8 milliliters per minute each year, while having no effect on urinary excretion of protein. Based on these results as shown in Table 1, Olyaei et al. (2013) concluded that statin therapy for patients with CKD is complex and may not be as safe or effective as statin therapy in non-CKD patients.

Possible Nephroprotective Effects

In contrast to the studies that emphasize the potential nephrotoxic effects of the statins, some studies have indicated that statin medications may be useful in preventing or slowing renal dysfunction and may even have nephroprotective effects, especially when used before surgery. Surgical patients have an increased risk for developing AKI due to fluid loss as well as pharmacologic therapy that may be used during surgery. On some occasions, healthcare providers have chosen to give statin medications in an attempt to decrease this risk (Lee et al., 2011). The exact mechanism of nephroprotection is not clear; however, several clinical trials have shown a possible benefit to such prophylactic therapy. Below, Table 2 outlines various trial findings, describing the data collection methods, as well as the results.

Table 2 Studies that suggest statins have nephroprotective effects					
Study/Year	Population	Intervention/Methods	Comparison	Outcome	Time
Data analysis by Layton et al./ 2013	Patients who underwent CABG surgery N=17,077; 52.5-76.4 years;	Retrospective cohort study of CABG patients 3,085 patients received statins <20 days prior to non-emergent CABG surgery	Control group of 13,992 patients did not receive statins prior to non-emergent CABG	Statin use prior to non-emergent CABG was consistently linked with a decreased risk of AKI	Data was collected on a ten-year period from 2000 to 2010

	33% female		surgery		
Data analysis by Brunelli et al./ 2012	Patients who underwent major open abdominal, cardiac, thoracic, or vascular procedures N=78,100; 43.5-75.3 years; 45.6% female	Retrospective cohort study of surgical patients 10,779 patients received at least one dose of atorvastatin, Fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin between hospital admission and surgery	Control group of 67,321 patients did not receive statins prior to surgery	Statin users had an 18-22% reduction in the development of AKI within 72 hours following surgery High-potency statins seem to have more protective power against AKI	Data was collected on a ten-year period from 2000 to 2010
Data analysis by Luk et al./ 2010	Chinese patients with type 2 diabetes recruited between 1996 and 2005 N=5,264; 45-66 years; 53% female	Prospective cohort study of the Hong Kong Diabetes Registry 1,275 patients received statins	3,989 patients did not receive statins	Statin users had a 68% reduction in the incidence of renal dysfunction	2.77-7.04 year follow-up period
Data analysis by Zhang et al./ 2011	Patients who underwent radiocontrast procedures and were enrolled in randomized, controlled trials	Meta-analysis of randomized, controlled trials 370 patients received statins prior to contrast procedures	381 patients did not receive statins prior to their contrast procedures	Statin use was not associated with a significant decrease in the incidence of contrast-induced nephropathy Some evidence exists that statin pretreatment may slightly decrease	2.7 days to 10.6 month pretreatment period; One-month follow-up

	N=751			serum creatinine levels in patients undergoing radiocontrast procedures	period
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The findings of a study conducted by Layton et al. (2013), outlined in Table 2, supported the use of statins prior to coronary artery bypass grafting (CABG) surgery, since these medications may decrease the risk of AKI postoperatively. For this study, the researchers analyzed health care claims from large, employer-based and Medicare databases for the presence of a protective impact on the kidneys from statin therapy. Patients who were undergoing CABG surgery were selected as the sample group. The researchers found a very significant decrease in the incidence of AKI for patients who underwent statin therapy and consequently asserted that statins can protect the renal system for patients undergoing CABG surgery. Layton et al. (2013) theorized that the results would probably be similar for other types of surgery.

Brunelli et al. (2012) published the findings of their retrospective analysis of a cohort of 98,939 patients, 10,779 of whom received preoperative statin therapy before cardiac, thoracic, or vascular surgery. As shown in Table 2, this preoperative statin use was particularly advantageous in preventing renal damage in patients who underwent vascular surgery and least advantageous to patients who underwent cardiac surgery. Brunelli et al. (2012) therefore concluded that preoperative statin use might have the potential to decrease the incidence of AKI.

Luk et al. (2010) performed a prospective cohort study on the effects of statin use for 5,264 patients in China with type II diabetes mellitus (DM) over a nine-year period.

As outlined in Table 2, the study disclosed that the incidence of renal dysfunction decreased by 68% in patients who received statin therapy. The researchers consequently asserted that statin use might lower the risk of renal dysfunction and nephropathy related to type II DM (Luk et al., 2010).

In an attempt to study the incidence of contrast-induced nephropathy in statin users, Zhang et al. (2011) conducted a meta-analysis of available data on randomized, controlled trials of patients who received statin therapy prior to radiocontrast studies. The results of the four selected trials, displayed in Table 2, revealed a lack of evidence that statin pretreatment before contrast procedures could decrease the incidence of contrast-induced nephropathy. There was, however, some evidence that statin therapy might cause a slight decrease in serum creatinine levels. The researchers concluded that statins may help prevent nephropathy related to contrast dye used in radio-contrast studies, although more research is necessary before this practice is considered evidence-based.

Statin Use in Renal Patients

The initiation of statin therapy in patients with pre-existing renal dysfunction is laden with controversy. Several recent studies have led researchers to theorize that statins are actually not always very effective in lowering lipids in patients with all stages of CKD, including both dialysis patients and patients who do not require dialysis. Some studies have also concluded that since the nature of statin therapy requires that it be used for chronic treatment of hypercholesterolemia, the risks may not outweigh the benefits for patients with preexisting renal problems because long-term statin therapy increases the risks of myopathy leading to renal dysfunction.

A meta-analysis of randomized, controlled studies by Nikolic et al. (2013) found that the cardiovascular benefits of statins, which include influencing C-reactive protein levels, require that long-term therapy be maintained; unfortunately, such long-term therapy also significantly increases the risk of myopathy, which can lead to renal dysfunction, AKI, and possibly CKD. Nikolic et al. (2013) analyzed trials involving CKD patients who received statin therapy from 1966 to May 2012. Their final review incorporated the results of sixteen trials and 3,594 subjects. The trial findings showed a statistically significant decrease in total cholesterol, triglycerides, and LDL levels for early-stage CKD patients who took statins. Patients who took statins for a longer duration had even greater benefits related to the prolonged therapy. Dialysis patients had less significant decreases in the levels of these independent cardiovascular risk factors. The researchers stated that for these patients, the magnitude of total cholesterol and LDL was lower and triglycerides actually had a modest increase. When patients received short-term statin therapy, they were more likely to have increased HDL levels with an average increase of 0.7 mg/dL. In contrast, patients who received long-term statin therapy were likely to experience an average reduction of 2.4 mg/dL.

As a result of their meta-analysis, Nikolic et al. (2013) concluded that patients who are not on dialysis are likely to experience significant lipid profile changes, whereas patients on dialysis may not experience statistically significant lipid profile changes; non-dialysis patients also generally experience improved outcomes related to longer-term therapy, whereas dialysis patients actually have surprisingly decreased effectiveness related to longer-term therapy; perhaps this means that dialysis patients who wish to

receive the cardiovascular benefits of statin therapy should only receive the statins for a very short duration (Nikolic et al., 2013).

While controversy still prevails over the effectiveness of statins at lowering lipids, there is a small amount of recent research that seems to indicate that in some cases of renal dysfunction, statins may not cause a therapeutic decrease in the risk for cardiovascular events, even if they may lower lipids. These studies raise the question of whether statin therapy is worthwhile, since it may increase the patient's risk of progressive renal dysfunction without truly having a therapeutic benefit on the patient's cardiovascular health.

Natsuaki et al. (2012) detailed the results of the CREDO-Kyoto PCI/CABG Registry Cohort-2 study, which indicated statin usage does not significantly decrease the risk for major adverse cardiovascular events in patients with severe CKD. Statin use consistently related to a decreased risk of AKI, defined using serum creatinine changes as outlined by Acute Kidney Injury Network and Risk-Injury-Failure staging systems, and on the need for RRT.

Olyaei, Greer, Santos, & Rueda (2011) completed a meta-analysis of the relevant literature that included the results of primary intervention studies and secondary intervention studies. Studies included the Study of Heart and Renal Protection (SHARP trial), described in Table 3, and the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trial, also outlined in Table 3. A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis (AURORA trial), which is outlined in Table 4, was also analyzed. Olyaei et al. (2011) asserted that patients in all stages of CKD are more likely to develop myalgia, myopathy and rhabdomyolysis from

statin therapy than patients who do not have some form of renal dysfunction; this study also concluded that CKD patients who are taking statins to lower their cholesterol should receive the lowest possible dose (Olyaei et al., 2011).

The question remains: if myopathy and renal damage are valid concerns for those taking statins, how can healthcare providers advocate for their patients' safety? In a recent article depicting their retrospective research study, Sai et al. (2013) advocated a standardized detection algorithm, which would allow physicians and other healthcare providers to detect statin-induced myopathy (SIM) based on the electronic medical record (EMR). The researchers collected data from the EMRs of 5,109 patients who had taken statins. They monitored the EMRs for changes including increased creatine kinase (CK) and were able to accurately detect five cases of suspected SIM (Sai et al., 2013). Such an algorithm may make it possible for conditions such as rhabdomyolysis to be diagnosed earlier than they would be otherwise, so they can be treated earlier and cause less long-term damage to the renal system.

Possible Effectiveness of Statin Therapy in Renal Patients

Some studies of statin therapy in renal patients suggest that the benefits of statin therapy are significant enough to warrant statin use even in patients with various types of renal dysfunction. Among these, the Study of Heart and Renal Protection (SHARP trial) and Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL trial) stand out as the most prominent clinical trials. The IDEAL trial, in particular, which was published in 2010, is still held up as a relevant research study in the discussion of statin therapy in renal patients. Below, Table 3 outlines the results of various studies, describing the data collection methods and the findings.

Table 3 Studies that suggest the effectiveness of statins in lowering cardiovascular risk for patients with renal dysfunction

Study/ Year	Population	Intervention/ Methods	Comparison	Outcome	Time
The SHARP trial/ 2011	Patients with preexisting CKD and no known history of MI or coronary revascularization 33% of total study population was receiving maintenance HD or PD N=9,270; 40-70+ years; 37% female	Randomized, double-blind study 4,650 patients received a combination of simvastatin plus ezetimibe	Control group of 4,620 patients received a matching placebo	The experimental group had a 17% reduction in major atherosclerotic events There were no statistically significant differences between the results of participants on dialysis and those who were not on dialysis	4-9 year follow-up period
The IDEAL trial/ 2005	Patients with history of MI who underwent statin therapy for elevated serum cholesterol levels between 1999 and 2005 N=8,888; 52-71 years; 19% female	Open-label, blinded, end-point, randomized, controlled trial 4,439 patients received 80 mg atorvastatin daily	Comparison group of 4,449 patients received 20 mg simvastatin daily	Atorvastatin users had lower mean LDL levels than simvastatin users 898 atorvastatin users experienced a coronary event during therapy, versus 1,059 simvastatin users	Median 4.8-year follow-up period
The CREDO-Kyoto PCI/CABG Registry Cohort-2/ 2012	Patients with advanced CKD undergoing coronary revascularization N=14,706; 53-75 years; 28% female	Retrospective cohort study 7,228 patients received statin therapy	Control group of 7,478 patients did not receive statin therapy	Statin users without CKD and with mild CKD had a significantly decreased incidence of major adverse cardiovascular events There was no significant risk	699-1,245 day follow-up period

				decrease in patients with severe CKD or HD patients	
The SWEDE HEART Registry Study/ 2011	Survivors of MI 178 patients received dialysis prior to admission N=42,814	Patients received statins at discharge from MI-hospitalization	Control group of patients did not receive statins at discharge	Statin users with stages 2-4 of renal insufficiency had improved one-year survival rates	Follo w-up period

Baigent et al. (2011) detailed the findings of the randomized placebo-controlled study known as the SHARP trial. The SHARP trial studied 9,270 patients with CKD with no known history of MI or coronary revascularization who received either daily doses of simvastatin 20 mg plus ezetimibe 10 mg or a matching placebo. 4,650 patients received the combination-drug, whereas 4,620 patients received a placebo. Researchers followed up with these patients after an average period of 4.9 years since the beginning of the trial to monitor for the occurrence of a first-time major atherosclerotic event, which was predefined by the study as a nonfatal myocardial infarction or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure. Patients who received the simvastatin-ezetimibe combination experienced a 17% proportional reduction in major atherosclerotic events. Only 131 of the patients who took the simvastatin-ezetimibe combination medication experienced non-hemorrhagic stroke, as compared to 174 of the patients who took the placebo. Likewise, only 284 patients who received simvastatin-ezetimibe therapy required arterial revascularization procedures as opposed to 352 of the patients who received the placebo. Baigent et al. (2011) therefore concluded simvastatin effectively reduced the risk of cardiovascular events in CKD patients when paired with

ezetimibe; these researchers therefore recommend the use of this particular statin combination drug for lowering cholesterol in patients with CKD.

The findings from the SHARP trial are highly respected in the medical community and have integrated themselves in many cases into evidence-based practice (EBP) related to statin therapy. A systematic review and meta-analysis by Palmer et al. (2012) asserted that SHARP had a low risk of reporting bias, which reaffirms its credibility. In their discussion, however, Palmer et al. pointed out that dialysis patients who receive statins do not have a clear clinical reduction in major cardiovascular events, a fact that appears to contradict SHARP's findings (Palmer et al., 2012).

Numerous articles and reviews have been published on the findings from the SHARP trial, with different conclusions made in each case. Auer et al. (2014) recently analyzed the findings from the SHARP trial and came to the conclusion that there is a need for further research regarding statin-caused myopathy. They reiterated the concern that statin-related myopathy and renal dysfunction will only increase as more and more people receive statin therapy (Auer et al., 2014). In contrast, Jenkins and Goldsmith (2012) published an analysis of the SHARP trial that concluded the benefits of statin therapy warrant that CKD patients should undergo prophylactic statin therapy, regardless of whether their LDL cholesterol levels are high, since CKD patients are inherently predisposed to atherosclerosis and cardiovascular events. An analysis of the SHARP trial by Holme et al. (2011) suggested that in CKD patients statin therapy may decrease risk for some particular types of cardiovascular events, while not decreasing the risk of major coronary events; in contrast, statin therapy in non-CKD patients decreases the risk for major coronary events, as well as all other cardiovascular events except stroke.

Bae et al. (2012) performed a retrospective cohort study that included the analysis of 12,636 patients with acute myocardial infarction (AMI) in the Korea AMI Registry from 2005 to 2008. Of the patients in the registry, 93% had coronary angiography and 91% of the patients who had coronary angiography had percutaneous coronary intervention (PCI) as well. This study revealed that patients who took beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers with statins had a significantly lower risk of major adverse cardiac events in the one-month and one-year follow-up periods. According to the findings of this study, statins might effectively decrease risk for major adverse cardiovascular events; this study also asserted that patients' estimated glomerular filtration rate (eGFR) can be used as an indicator of their risk for mortality related to cardiovascular events (Bae et al., 2012).

In 2011, Szummer et al. completed a retrospective cohort study that confirmed statin therapy after a MI is effective in decreasing the incidence of death from cardiovascular events and in protecting against renal dysfunction and failure from AKI and CKD. The researchers analyzed data from the national SWEDEHEART Registry related to 42,814 consecutive MI survivors who did not take statin therapy prior to hospitalization for their MIs. They found that patients in the early stages of CKD had a significant decrease in their overall mortality. The study published by Szummer et al. (2011) also indicated that statins might have the potential for improving the one-year survival rate of patients who are in stages 2-4 of kidney failure.

Lim et al. (2012) conducted a study that supported the use of statins in patients with various types of renal dysfunction including CKD, since this study found statin therapy improved outcomes in CKD patients. The researchers studied a retrospective

cohort of 12,853 patients with AMI. They divided the cohort into four different groups: those who did not have any form of renal dysfunction and received statins, those who neither received statin therapy nor had renal dysfunction, those who both received statin therapy and had renal dysfunction, and those who had renal dysfunction but did not have renal dysfunction. The researchers then analyzed the separate groups for the primary end points of death and hospitalization complications, as well as secondary end points of MACE during the one-year post-AMI follow-up period. The study revealed that both patients with renal dysfunction and patients who did not have renal dysfunction experienced a decrease in the incidence of MACE during the follow-up period. Lim et al. (2012) therefore concluded that statin therapy could be beneficial for both patients with and without renal dysfunction. One limitation of this study is the fact that renal dysfunction was not clearly defined and may have only included patients in the very early stages of CKD, which would have impacted the results of the study.

A systematic review and meta-analysis of various studies with CKD patients who took statins revealed some interesting findings. Palmer et al. (2012) discussed the findings of trials such as SHARP, AURORA, and 4D (Deutsche Diabetes Dialyse Studie). The researchers concluded that based on the latest research findings, statin therapy in CKD patients who are in the early stages of the disease and do not yet require dialysis can reduce cardiovascular events and mortality (Palmer et al., 2012).

Most of the reviewed studies agreed that although statin use may potentially be helpful for patients in stages 2-4 of CKD, patients on dialysis or other forms of renal replacement therapy (RRT) may derive little to no cardiovascular benefit from statin use and may in fact do themselves more harm than good.

Possible Ineffectiveness of Statin Therapy in Renal Patients

Although some research seems to support statin therapy’s efficacy and safety for patients with renal impairment, other studies are not so supportive. At any rate, the overwhelming majority of studies have suggested that patients with ESRD, and particularly those on HD, might not experience the desired effects of these drugs. Also, the risks of causing a preexisting renal dysfunction to progress further may outweigh the benefits of statin therapy for patients who may not even have ESRD but have some level of renal impairment. Below, Table 4 describes the various studies that suggest statin therapy may be ineffective in patients with renal dysfunction, as well as the data-collecting methods and study outcomes.

Table 4 Studies that suggest statins are ineffective in lowering cardiovascular risk for patients with renal dysfunction					
Study/Year	Population	Intervention/Methods	Comparison	Outcome	Time
The AURORA trial/ 2009	Patients with ESRD who had received routine HD for at least three months N=2,776 50-80 years 38% female	Randomized, double-blinded placebo-controlled multicenter trial study Patients in the experimental group received rosuvastatin as primary prevention against a major cardiovascular event	Patients in the control group received a placebo	Experimental group had 43% reduction in LDL-C level and 27% reduction in total cholesterol levels No statistically significant decrease in the incidence of a major cardiovascular event (defined as nonfatal MI, nonfatal stroke, or death related to cardiovascular disease) 396 rosuvastatin users had a major	Three-year follow-up period

				cardiovascular event; 408 placebo users had a major cardiovascular event	
The 4D Study (Deutsche Diabetes Dialyse Studie)/ 2005	Patients with type 2 diabetes mellitus who had received HD for more than two years Baseline cholesterol was between 80 and 90 N=1,255	Randomized, multi-centered, double-blinded, placebo-controlled prospective study 619 patients received atorvastatin	636 patients received a placebo	There was no significant reduction in the risk of major cardiovascular events	Two-year follow-up period

Risks versus Benefits of Statin Use in Renal Patients

Much debate exists regarding the safety and efficacy of the statin HMG-CoA Reductase Inhibiting medications in relation to the kidneys. An issue of particular concern is the question of whether these medications may potentially protect the kidneys from damage and thereby slow the progression of CKD, possibly increasing longevity. Another area of ambiguity is that of the effectiveness of these medications in lowering cholesterol and preventing adverse cardiovascular events for patients with various forms of renal dysfunction, including AKI and CKD. Based on the evidence that is currently available, it is safe to say that statin usage may have limited safety and efficacy in treating hyperlipidemia in patients with renal dysfunction

Ethical Considerations

Although the researchers obtained informed consent before conducting the study, the SHARP and AURORA trials, like so many other trials, raise several ethical considerations; namely, is it ethical for researchers to experiment with patients' lives by giving them a placebo—and exempting them from getting what is more likely an effective treatment? This question is not an easy one, but the researchers for any study should consider it before proceeding with the study. Certain study designs may also help eliminate the ethical dilemma raised by studies that provide participants with a placebo instead of an equally effective therapy. According to Sullivan (2011), a trial that utilizes an equally effective medication considered the standard of care instead of a placebo is called an active-controlled trial. An active-controlled trial would be ethically appropriate in cases of hypercholesterolemia in which medication is necessary; patients in the control group would still receive treatment for their hypercholesterolemia while serving as the comparison for groups receiving the statin medications.

Method

This integrative review incorporated a search of several nursing and medical databases, including CINAHL and PubMed, for randomized controlled trials and meta-analyses of recent trials. As Table 5 shows, the search used the key words: *statins*, *HMG-CoA Reductase Inhibitors*, *renal insufficiency*, *AKI*, *rhabdomyolysis*, *statin-caused myopathy*, *renal failure*, and *CKD*. Phrases paired various types of renal insufficiency with the two names used to identify the statin drugs: statins and HMG-CoA Reductase Inhibitors. The most productive searches were those using the phrases: *CKD and statins*, *CKD and HMG-CoA Reductase Inhibitors*, *AKI and statins*, *AKI and HMG-CoA*

Reductase Inhibitors, renal insufficiency and statins, renal insufficiency and HMG-CoA Reductase Inhibitors, rhabdomyolysis and statins, and rhabdomyolysis and HMG-CoA Reductase Inhibitors. A total of 563 articles surfaced. Of the articles that surfaced, only 30 articles fit the two-fold selection criteria of patients with CKD who have taken statins *or* patients who have taken statins and developed AKI, which later led to increased risk for CKD.

Key Search Terms (2010-2015)	Table 5 Search Results					
	Cochrane Review	OVID	EBSCO host (CINAHL; Nursing & Allied Health Collection)	Pub Med	Total	<u>Relevant Articles</u>
HMG-CoA Reductase Inhibitor, statin, renal insufficiency, renal failure, chronic kidney disease, acute kidney injury, statin-caused myopathy, rhabdomyolysis	8	224	247	84	563	30

Study Selection

Studies were selected based on their relevance to the topic of statins and their relationship to renal impairment and CKD. Studies of patients with CKD who used statins were included, as were studies of patients with AKI who used statins. Studies of patients who developed renal insufficiency, AKI, or CKD with a possible relation to the use of statins were also included. Studies that discussed statin therapy apart from renal dysfunction were excluded. Studies of statin use in patients who did not have renal dysfunction, either prior to statin use or related to statin-caused myopathy were excluded

as well. Studies with a sample size of less than 40 were also excluded. Data extraction occurred based on articles that depicted the following outcomes: rhabdomyolysis after statin therapy in CKD patients, myopathy after statin therapy in patients with renal impairment, AKI incidence related to statin therapy, AKI prevention related to statin therapy and reduction in cardiovascular disease-related mortality in CKD patients after statin therapy.

Data Analysis

Studies were analyzed and divided into groups based on whether the findings fit into one of the following categories: statins having a positive effect on patients' renal function, statins having a negative effect on patients' renal function, statins decreasing the risk of cardiovascular disease and/or mortality in patients with renal impairment, statins having no effect on the risk of cardiovascular disease and/or mortality in patients with renal impairment and statins increasing the risk of cardiovascular disease and/or mortality in patients with renal impairment. None of the analyzed studies suggest that statin therapy increases the risk of cardiovascular disease and mortality in patients with impaired renal function; therefore, this category was not included in the final integrative review.

Implications for Nursing Practice

An important consideration for nurses is the possibility of a reliable algorithm for detecting myopathy related to statin use, as discussed earlier. Such a tool may prove very useful in preventing serious renal damage before it occurs. If an algorithm becomes available, nurses should learn how to use it in daily practice so they can integrate this knowledge into their physical assessments of patients receiving statins and hopefully help

to detect myopathies related to statin usage. Evidence-based practice can incorporate the use of a warning system in the EMR. An EMR warning system would be easy for nurses and other healthcare providers to use, while tracking CK levels and perhaps including renal-specific indicators such as creatinine clearance rate and blood urea nitrogen (BUN). A well-designed warning system might also incorporate basic laboratory data such as the complete blood count (CBC) and symptoms of myopathy such as myalgia, nausea and vomiting, fever, and tachycardia (Sai et al., 2013). With a proper warning system in the EMR, nurses could play a vital part in monitoring for renal injury and dysfunction while continuing to carry out their routine patient assessments and interventions. While an EMR warning system for statin-induced myotoxicity and renal dysfunction has not yet been extensively developed and implemented, healthcare providers may be able to design one in the near future that could help prevent needless renal dysfunction and morbidity.

Nurses also have a responsibility to educate patients about the medications they receive. Patient education should include teaching about the unique impact these medications may have on individual patients because of personal idiosyncratic factors such as CKD. Patients with CKD should learn that there are certain inherent risks if they choose to begin therapy with statin drugs. As shown in this integrative review, patients with preexisting renal dysfunction who take statin drugs may be more likely to experience further progression of their already-present renal dysfunction. There does not appear to be a difference in the impact of various statins on renal function. Although CKD and renal impairment does not contraindicate the use of statin therapy to treat hypercholesterolemia, healthcare providers should be prepared to educate these patients about the risks versus the benefits of statin therapy.

Patients with renal impairment may also require dosage modification due to their impaired renal function, and nurses, as the healthcare providers who perform the last safety check prior to medication administration, need to be aware of this so that they will know to advocate for their patients and question an inappropriate dose for a patient with renal impairment. Since the nurses are often the last ones to see a medication's dosage before it is given and they are often the ones giving medications such as the statin medications in the hospital setting, it is important for them to know what the appropriate dosages are and how they would be modified in the case of renal dysfunction. Nurses should be aware of the risks of statin use for patients with CKD and other forms of renal dysfunction and they should be prepared to inform patients with renal dysfunction of these risks.

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