Title: Is there a renal protective effect of statins on their users in terms of no change in Glomerular filtration rate after endovascular aortic surgery

Background: Nephropathy contrast induced is very common during endovascular aortic repair surgery that can be presented with lower GFR levels as a result of acute kidney injury which is secondary to contrast that is given during this procedure. It was proven that statins have renal protective effect which is described as pleiotropic effects in which statins are prescribed as primary prevention agents in patients with high risk of vascular diseases like diabetes and coronary artery diseases. For that reason, this study was conducted to examine the hypothesis of pleiotropic effects of statins in protecting kidneys in patients underwent aortic endovascular repair in terms of there would be no decline of their GFR readings after the surgery compared to GFR readings before it.

Methods: A cohort observational retrospective study of 488 consecutive patients who underwent endovascular aortic repair between September 2012 and November 2014 in a tertiary hospital in USA. A paired t test statistical analysis method was used to assess the P value of their GFR readings changes before and after the surgery to examine the hypothesis of renal protective effect of statins in terms of there will be no change in the levels of estimated creatinine clearance.

Results: Statins use was associated with changes in GFR levels postoperatively (P=0.48) which is statistically insignificant. Acetylcysteine was given to 31.97% of statins users to decrease the severity of contrast -induced nephropathy, which was developed during surgery, compared to 7.38% who didn’t require Acetylcysteine as there was no development of contrast associated nephropathy. Among Statin users 1.02% needed emergency surgery and 3.08% died during procedure.

Conclusion: In patients underwent endovascular aortic surgery, statins therapy is not associated with a statistically significant renal protective effect postoperatively in terms of no change in GFR levels compared to preoperative levels that was correlated with the need of Acetylcysteine use in 31.97% of statins users as an antidot for contrast-induced acute kidney injury during surgery and among these patients on statins 1.02% needed emergency surgery and 3.08% died during procedure.

Introduction:

Nephropathy occurs in 1-5% of the patients undergo non-cardiac surgery and associated with high morbidity and hospitalization rate due to acute kidney injury. Statins are lipid lowering agents that lower cholesterol levels and non-cholesterol mediated mechanisms thus protect kidney in patients with cardiovascular diseases as there is high risk of developing renal impairment and cardiovascular disease progression along with dyslipidemia. Statins therapy was proven by meta-analysis to slow the reduction in the glomerular filtration rate .in addition statins decrease proteinuria in patients with cardiovascular disease high risk population such as diabetic patients and decrease cardiovascular morbidity and mortality as well1.Any GFR less than 60 ml/min per 1.73 m2 is considered to be pathological renal injury in which nephropathy is identified and staged accordingly2. Experimental models revealed that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins reduce the severity of glomerular injury thus preserve renal function 3. Statins were proven to have pleiotropic effects on renal function that clinically have positive implications on cardiovascular system in which statins not only reduce lipid levels in blood, but also have anti-inflammatory effects through inhibition of signaling molecules at many points in the inflammation pathways in which atherosclerosis resulted which is defined as a process of inflammation associated with high levels of plasma inflammatory markers and immune cells accumulation in a form of atherosclerotic plaques. Therefore, the anti-inflammatory effect of statins improves endothelial function thus these lipid lowering agents play an important role in cardiovascular risk reduction in terms of morbidity and mortality reduction in which many studies showed evidence that statins have similar anti-inflammatory effects in the pathological renal vascular system in which it exerts its renal protective benefits. Since in renal impairment disease which can be caused by inflammatory etiological source, resulting in inflammation and functional changes in the renovascular endothelium which I responsible of progression of renal injury. As a result, Statins are considered to be effective in modulating renal function by alteration of the renal inflammatory response of kidneys thus reverse acute kidney injury as well as slow the progression of chronic kidney disease therefore they are effective in the treatment of renal disese4. Acute kidney injury occurs in endovascular aortic repair as a result of contrast-induced nephropathy, embolus in renal vessels or vascular stents encroachment on renal vessels. Contrast- induced nephropathy is identified by a reduction in estimated glomerular filtration rate (estimated creatinine clearance) of > or = 25% within 96 hours of exposure to contrast agent with exclusion of other causes which is resulted due to combination of medullary ischemia and direct tubular toxicity5. Statins decrease nitric oxide production, thereby increasing flow-mediated vasodilation and endothelial function. besides they reduce vascular events and death in patients with dyslipidemia and in coronary artery diseases patients. Moreover statins with their anti-inflammatory effects, scavenge free radicals in addition to their antithrombotic properties, because of all of these protective effects they are more likely to be protective to kidneys6.This study was conducted to test the hypothesis that in patients who use statins therapy, undergoing endovascular aortic repair, there will be no change in their GFR levels after this surgery compared to their GFR level before surgery, assuming that Statins are renal protective agents in those patients and will protect them from developing contrast-induced nephropathy that can be identified through change in GFR after surgery in terms of reduction in their GFR readings compared to GFR levels preoperatively.

Methods:

This Retrospective Observational Cohort Study included patients who had endovascular aortic repair at the tertiary American Hospital. Whether abdominal or thoracic type, between September 2012 and November 2014. Patients with a history of renal failure who require dialysis and have a history of repeated endovascular operations repair were excluded from the study. Using the Perioperative health database System at the vascular clinic of this tertiary hospital,488 consecutive patients were identified meeting the inclusion criteria for analysis. Estimated GFR was determined for each patient in this study based on CKD-EPI Equation which considers factors that impact creatinine production including age, sex and race. The equation doesn’t require weight or height variables because results are normalized to a typical adult value of 1.73 m2 of body surface area. Primary outcome was change in GFR postoperatively compared to preoperatively levels. GFR postoperatively was measured by maximum duration of 7 days after surgery in statin users to be compared to their levels before surgery to determine if there will be any change in GFR levels.

A paired t test statistical analysis method was used to assess the P value of their GFR readings changes before and after the surgery to examine the hypothesis of renal protective effect of statins in terms of there will be no change (no decrease in GFR readings) in the levels of estimated creatinine clearance as GFR is an indicator in this study to define contrast-induced nephropathy in which reductions in GFR levels will be there as a result to nephropathy. Patients’ Age, Gender, History of congestive heart failure, diabetic status, Acetylcysteine use as antidot to reverse ACI (Acute Kidney Injury) development during or after surgery, Need of Emergency Surgery during or after endovascular aortic repair and The Number of Deaths (Expired)after surgery all were assessed in correlation with statins to identify factors affecting GFR change after surgery in this statin’s population.

Results:

One hundred and ninety-two (39.34%) of that total of 488 patients studied as shown in Figure A, were taking statins therapy before operation. There were several baseline characteristics were identified preoperatively of those patients who were on statins or not as illustrated in Table 1 and 2 of patient’s demographics who were included in this study. Age distribution among patient underwent endovascular aortic surgery was assessed as presented in Figure B with a mean age of 72 years and minimum age of 22 years and maximum of age of 93 years old in which it can be concluded according to the distribution of patients ages who were included in this study that young age, middle age and old age were all involved which can reflect that this study have estimated ages between 22 years and 93 years old, that can generate results more practically than choosing only young or elderly patients in which discrimination in results can’t be excluded. It was reported in this study among statin users that male patients’ population percentage was higher than female patients as 30.12% and 9.22% respectively as shown in Figure C which reflect the truth of male population are prone to cardiovascular diseases more than female in which endovascular aortic surgery is needed in those high-risk population compared to female statins group. Diabetes status was investigated as presented in Figure D among all patients included to be 86.07% were non-diabetic, whereas only 13.93% were diabetic patients in which they have higher risk to develop acute kidney injury secondary to contrast of this surgery. As visualized in Figure E among all those diabetic patients, 9.07% were on statins, on the other hand, 4.92% were diabetic but not on statins therapy which correlate with the international guidelines of using statin in diabetic patients for primary prevention of coronary artery diseases as proved here that that majority of diabetic patients were on statins and only few were not on. For those statin users with a history of Congestive Heart Failure included in this study counts for only 2.05% as illustrated in Figure F, while the majority of statins users with a percentage of 37.3% of total population of this study, had no history of congestive heart failure which means that most of statin users without history of CHF that generate more accurate results in terms of GFR change dependent factors in which patient with congestive heart failure are prone to develop ACI secondary to contrast because of their chronic kidney disease associated with their hearty failure. In Figure G, it was obviously presented that the majority of statins users 31.97% were given Acetylcysteine for contrast-induced nephropathy in which it can be concluded that despite using statis, the majority of those patients developed nephropathy secondary to contrast in this surgery in which statins didn’t prove their renal protective effects against contrast in those populations and only 7.38% of statin users didn’t require Acetylcysteine as an antidot for contrast-induced acute kidney injury. Number of patients who needed emergency surgery due to AKI development associated with contrast use during or after surgery was of minimal percentage of 1.02% of statin users who required Emergency surgery as seen in Figure H which means that ACI was mostly reversable with the use of Acetylcysteine and almost all patients on statins 38.32% didn’t require Emergency Surgery except 1.02 % who did require for emergency surgery. Number of deaths in this retrospective study counted for 3.08 % of statins users who were expired during the surgery, while the 36.34% didn’t die as illustrated in Figure I. Finally, P value of 0.48 which is more than P value 0.05, was calculated via paired t test of GFR readings before and after surgery as seen in Figure J to conclude that it is not statistically significant in this study because there were changes in GFR readings before and after surgery which concludes that Statins therapy were not renal protective agents in those patients who underwent endovascular aortic repair as nephropathies were developed secondary to contrast, thereby GFR readings decreased after surgery and null hypothesis is not rejected.

Discussion and Conclusion:

Preoperative statins therapy failed to maintain the GFR in patients undergoing endovascular aortic repair. The results of our study are with agreement of recent meta-analysis study that showed that statins therapy did not decrease the incidence of contrast-induced nephropathy after coronary angiography7.in contrary, our results contrast those reported by Khanal et al who proved a significant lower incident of contrast nephropathy in Statins patients undergoing percutaneous coronary interventions 8. However, that study didn’t report the perioperative hydration status as this is an important factor to be considered before exposure to contrast media that affect GFR levels as negative fluid balance put patients under risk of developing contrast nephropathy. GFR is used as indicator of nephropathy associated with contrast as it is more sensitive indicator than serum creatinine alone to changes in renal function since GFR may be decreased by more than 75% before serum creatinine becomes anormal and elevated. Welten et al reported that statins didn’t reduce the incidence of AKI after open vascular surgery, although the statin use in that study was associated in early recovery of kidney injury9. In our study in patients undergoing endovascular aortic repair, statins did not show a protective renal effect on their renal function that was proved by reductions in their GFR levels after surgery in which statins didn’t improve short term renal outcomes and did not improve the worsening of renal function that was proved by the increase use of Acetylcysteine in 31.97 of statins users as antidote of GFR worsening secondary to contrast which conclude that statins did not exert protective renal effect and did not reverse the developing of contrast induced nephropathy. In addition our results suggest that factors such as age, gender, diabetic status, history of congestive heart failure may considered as more important determinants of post operative GFR than the use of statin therapy and baseline GFR which let us comes to the conclusion that preoperative renal reserve may be more important factor in predicting renal outcomes than a single renal protective intervention which is the statins therapy which couldn’t be the protective interventional factors as it was assumed and hypothesized. The number of emergency cases was small which account to 1.02% of statins users which indicates that contrast nephropathy which occurred in these population was reversable by Acetylcysteine antidot and hydration. Estimation of patients expired was minimal in statins users compared to non-statins users with 3.08% and 6.78% respectively. Our hypothesis of No change in GFR for patients on statins is rejected and the null hypothesis is not rejected, as Statins have protective renal effect which is proven by many studies that are mentioned earlier, therefore GFR is expected to not be reduced after endovascular aortic surgery (in which Acute Kidney Injury as nephropathy can occur secondary to contrast that is given before the surgery as a result GFR may decrease after surgery).In our study null hypothesis can't be rejected as P value is > 0.05 which is 0.48 as GFR changed after procedure despite patients were on statins which have renal protective effects against nephropathy secondary to contrast after endovascular aortic procedure in which patients were given Acetylcysteine to reduce the severity of contrast induced nephropathy in which out of 192 patients who were statin users, 31.97% of those statins users, were given Acetylcysteine to reduce severity of contrast associated nephropathy and only 7.38% of statin users who didn't need to be given Acetylcysteine as they didn't develop contrast induced nephropathy which was measured by change in GFR before and after endovascular aortic surgery.

Limitations:

This is an observational retrospective cohort study in which its results are subjected to potential bias in selection of participants, confounding and measurement bias. Therefore, a randomized controlled trials are needed to reduce these kinds of biases and compare statins users for the renal protective effect of statins before and after surgery prospectively.

In summary:

Our results did not support the theory that GFR will not be changed in patients who take preoperative statins than after surgery. In patients underwent endovascular aortic surgery, statins therapy is not associated with a statistically significant renal protective effect postoperatively P value is 0.48 in terms of no change in GFR levels compared to preoperative levels that was correlated with the need of Acetylcysteine use in 31.97% of statins users as an antidot for contrast-induced acute kidney injury during surgery and among these patients on statins 1.02% needed emergency surgery and 3.08% died during procedure.

Figures and Tables:

Figure A

Chart, bar chart

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Table 1. Demographics of Patients underwent Endovascular Aortic SurgeryTable

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Table 2. Statistics of Demographic characteristics of patients underwent Endovascular Aortic Surgery.A picture containing table

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Figure B.

Chart, histogram

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Figure C

Chart, bar chart

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Figure D

Chart, bar chart

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Figure E

Chart

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Figure F

Chart, bar chart

Description automatically generated

Figure G

Chart, waterfall chart

Description automatically generated

Figure H

Chart, bar chart

Description automatically generated

Figure I

Chart, bar chart

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Figure J

Graphical user interface, text, application, email

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