High Dose Atorvastatin Raises Threshold of Contrast Induced Nephropathy in Diabetic Patients Undergoing Elective Coronary Intervention.

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Abstract

Background Contrast induced nephropathy (CIN) is a significant complication of angiographic procedures resulting from injection of iodinated contrast media (CM). Patients with diabetes mellitus (DM) are at the highest risk of CIN. Statins have recently been proposed for protection against CIN due to their antioxidant and anti-inflammatory properties

Aim of work To investigate the potential benefit of acute pretreatment with high dose atorvastatin (80 mg) in reduction of the incidence of CIN in diabetic patients indicated for elective coronary intervention.

Patients and Methods 200 diabetic patients with indication for coronary intervention were enrolled in the study. 100 patients will be randomly assigned to receive atorvastatin (80 mg) just before coronary intervention (statin group) and 100 patients received placebo (control group). CIN was defined as a rise of serum creatinine of more than 25% or ≥0.5 mg/dl (44 μmol/l) from baseline within 48 hours of the angiography. After the procedure, TIMI flow of the culprit vessel was reported, as well as the volume of used contrast media and time of X-ray exposure.

Results Our study reported a CIN incidence of 12, 18 and 6% among the whole study, placebo and statin groups respectively, p value 0.001. Among placebo group, CIN is likely to develop after 13.5 minutes X ray exposure time with specificity 73.2% and sensitivity 77.8%, AUC 0.879 (CI: 0.798-0.960), P value 0.001. While in statin group, CIN is likely to develop after 14.5 minutes X ray exposure time with specificity 74.5% and sensitivity 83.3%, AUC 0.818 (CI: 0.727-0.910), P value 0.009. In placebo group, CIN is likely to develop after injection of 145 ml with specificity 75.6% and sensitivity 77.8%, AUC 0.855 (CI: 0.757-0.952), P value 0.001. While in statin group, CIN is likely to develop after injection of 165 ml with specificity 84% and sensitivity 83.3%, AUC 0.878 (CI: 0.811-0.944), P value 0.002

Conclusions Acute pre-treatment with high dose atorvastatin can effectively protect against CIN and was associated with a marked decrease in the prevalence of CIN in diabetic patients undergoing coronary interventions. Moreover, pre-treatment with high-dose atorvastatin raises the threshold of X-ray exposure time and amount of contrast media beyond which CIN is likely to develop.

Background:

Contrast induced nephropathy (CIN) is a significant complication of angiographic procedures. It results from injection of contrast media (CM) [1]. The incidence of CIN after percutaneous coronary intervention (PCI) ranges between 0 and 24%, depending on the presence of associated risk factors. A higher incidence is reported after primary PCI [2].

It is a transient and recoverable form of acute renal injury [3]. However, the occurrence of CIN is linked to a prolonged hospital stay, an escalated morbidity and mortality and a higher financial burden [4].

Due to the complexity of pathophysiologic mechanism for the development of CIN, several prophylactic procedures have been implemented to avoid this unwanted side effect [5–6]. Some of these procedures have been designed as routine practice for preventing CIN such as routine intravenous volume expanders as isotonic crystalloids [7]. Other measures are under investigation, such as intravenous saline or sodium bicarbonate solution [8–10], antioxidant agents as oral N-acetylcysteine [11] or ascorbic acid [12] and administration of low- or iso-osmolar contrast media [13].

Statins have been suggested for prevention of CIN due to their antioxidant and anti-inflammatory properties [14]. However, different studies have produced inconsistent results [14–17]. Although statins were shown to protect against contrast induced acute kidney injury (CI-AKI) in patients suffering acute coronary insult and undergoing primary PCI [16–21].

Patients with diabetes mellitus (DM) are at high risk of contrast-induced acute kidney injury due to the pathophysiologic alterations caused by contrast media, including increased generation of oxygen free radicles, vascular endothelial affection, and dysregulated microcirculation. Hence, patients with chronic kidney disease and diabetes are at high risk of CI-AKI [22]. The benefit of statins is not well known for patients at increased risk for nephropathy such as diabetic patients who undergo elective coronary intervention.

Aim of the work:

To investigate the potential benefit of acute pre-treatment with high dose atorvastatin (80 mg) in reduction of the incidence of CIN in diabetic patients indicated for elective coronary intervention.

Patients And Methods:

(A) Patients:

The study is a prospective, multi-center, randomized, placebo-controlled study. The ethical Committee of the Faculty of Medicine, Assiut University approved the study protocol.

200 diabetic patients with indication for coronary intervention participated in the study. 100 patients were randomly assigned to receive atorvastatin (80 mg) just before coronary intervention (statin group) and 100 patients received placebo (control group). An informed written consent for participating in the study was obtained from each participant.

Exclusion criteria:

1- Current statin treatment within the previous three months.

2- Chronic renal failure patients on renal dialysis, or serum creatinine more than 1.5 mg/dl.

3- Severe co-morbidities i.e. patients with cancer, advanced liver cirrhosis.

4- Contraindications to statin therapy.

5- Contrast media injection within the preceding 10 days.

6- Pregnancy.

7- Refusal of consent.

(B) Methodology:

All study patients were subjected to:

(1) Full clinical history: including age, sex, history of smoking, hypertension, history of previous PCI, duration of diabetes mellitus and type of anti-DM treatment.

(2) Thorough physical examination focusing on:

- - General examination including intra-procedural hemodynamic assessment.
- - Cardiac examination to elicit manifestations of heart failure.

(3) Echocardiography searching for wall motion abnormalities and estimation of left ventricular systolic function.

(4) Initial venous blood samples for determination of hemoglobin level and serum creatinine before the procedure. Follow up for serum creatinine at 48 hours post-procedure was done.

CIN was stated as a raising of serum creatinine of more than 25% or ≥ 0.5 mg/dl (44 μmol/l) from initial level within 48 hours of the angiographic procedure and after excluding other factors that may cause nephropathy such as nephrotoxic drugs [15].

(5) All patients received clopidogrel (600 mg) or ticagrelor (180 mg). Any nephrotoxic drugs (i.e., metformin, non-steroidal anti-inflammatory drugs) were withdrawn on admission.

(6) Coronary intervention was done using the same nonionic, low-osmolar contrast medium (Iopamidol; Scanlux, Sanochemia, Austria) in all cases.

After the procedure, TIMI flow of the culprit artery was assessed, as well as the volume of used contrast media and time of X-ray exposure.

(7) Statistical analysis:

Data were processed by statistical package for the social sciences (SPSS, version 20. 0). Descriptive statistics for interval and ordinal variables were calculated such as the ranges, means, and standard deviations, whereas, for categorical variables, the frequencies and percentages were reported. Student t-test or paired t-test, as appropriate, were used to compare normal and continuous variables. Chi-square

test was used for comparing categorical variables. The level of significance was stated at $P < 0.05$. Receiver operating curves (ROC) were plotted and area under the curve (AUC) was assessed for some studied variables. Sensitivity and specificity were calculated at a cutoff point. A p value of < 0.05 was considered significant.

Results:

The study enrolled 200 ischemic diabetic patients who underwent elective PCI with mean age 58.8 ± 7.8 years, males 94 (47%) and 39 (19.5%) were smokers.

(A) Baseline data:

The baseline data of the whole study population are demonstrated in table (1).

(Table 1)

Table 1: The baseline demographic, clinical, echocardiographic and laboratory data of the studied population.

Parameter	
Age in years (mean±SD)	58.8±7.8
Sex; Males (%)	94 (47)
Smokers (%)	39 (19.5)
HTN (%)	77 (38.5)
Previous PCI (%)	8 (4)
Duration of DM in years (mean±SD)	7±3.9
Insulin therapy (%)	95 (47.5)
Heart failure (%)	44 (22)
Body mass index (mean±SD)	27.2±3.3
Heart rate in beats/min. (mean±SD)	84.5±14.5
Systolic blood pressure in mmHg (mean±SD)	132.9±18.8
Diastolic blood pressure in mmHg (mean±SD)	83.9±10.4
Segmental wall motion abnormalities (%)	68 (34)
EF (%) (mean±SD)	59.3±9.8
Volume of contrast in ml (mean±SD)	121.4±48.3
Time of X-ray exposure in min. (mean±SD)	12±5.5
Coronary procedure	
PCI with one stent	133 (66.5)
PCI with two stents	53 (26.5)
PCI with more than two stents	14 (7)
TIMI flow	
TIMI I	2 (1)
TIMI II	9 (4.5)
TIMI III	189 (94.5)
Baseline serum creatinine in mg/dL (mean±SD)	119.1±16.8
Follow up serum creatinine in mg/dL (mean±SD)	136.1±25.6
Hemoglobin in mg/dL (mean±SD)	12.3±1.6

CIN (%)	24 (12)

(2) Patients randomization: Using simple randomization, the studied patients were divided into two groups according to pre-procedural statin administration. The differences between the two study groups are displayed in table (2).

(Table 2)

Table 2: Demographic, clinical, echocardiographic and laboratory data of the two groups

Parameter	Placebo group	Statin group	P value
Age in years (mean±SD)	59.3±7.1	58.3±8.5	0.4
Sex; Males (%)	47 (47)	47 (47)	1.0
Smokers (%)	19 (19)	20 (20)	0.6
HTN (%)	38 (38)	39 (39)	0.9
Previous PCI (%)	4 (4)	4 (4)	1.0
Duration of DM in years (mean±SD)	7.0±3.5	7.1±4.2	0.8
Insulin therapy (%)	53 (53)	42 (42)	0.1
Heart failure (%)	24 (24)	20 (20)	0.5
Body mass index (mean±SD)	27.2±3.1	27.2±3.4	1.0
Heart rate in beats/min. (mean±SD)	84.6±14.8	84.4±14.3	0.9
Systolic blood pressure in mmHg (mean±SD)	131.9±18.0	134.0±19.5	0.4
Diastolic blood pressure in mmHg (mean±SD)	83.4±10.6	84.4±10.3	0.5
Segmental wall motion abnormalities (%)	33 (33)	35 (35)	0.8
EF (%) (mean±SD)	59.7±9.8	59.0±9.8	0.6
Volume of contrast in ml (mean±SD)	123.0±49.1	119.8±47.6	0.6
Time of X-ray exposure in min. (mean±SD)	12.1±5.6	11.9±5.4	0.8
Coronary procedure			
PCI with one stent (%)	63 (63)	70 (70)	0.3
PCI with two stents (%)	31 (31)	22 (22)	
PCI with > two stents (%)	6 (6)	8 (8)	
TIMI flow			
TIMI I (%)	2 (2)	0 (0)	0.3
TIMI II (%)	5 (5)	4 (4)	
TIMI III (%)	93 (93)	96 (96)	
Baseline serum creatinine in mg/dL (mean±SD)	1.2±0.2	1.2±0.2	0.9
Follow up serum creatinine in mg/dL (mean±SD)	1.4±0.3	1.3±0.2	0.02*
Hemoglobin in mg/dL (mean±SD)	12.7±1.8	11.8±1.3	0.1

CIN (%)	18 (18)	6 (6)	0.0001*
* Statistically significant			

Compared to serum creatinine before the procedure, there was a statistically significant rise in serum creatinine after coronary intervention among the study groups, p value 0.001, table (3).

Table (3): Comparison of serum creatinine level before and after intervention among both study groups.

	Baseline serum creatinine	**Follow up serum creatinine**	**P value**
Placebo group	1.191 ± 0.17	1.385 ± 0.32	0.001*
Statin group	1.190 ± 0.17	1.337 ± 0.16	0.001*
* Statistically significant			

(3) Contrast induced nephropathy: The whole study group was divided into two groups according to the development of contrast induced nephropathy.

1. (a) **Group A**: It included 176 (88%) patients without CIN after PCI procedure.
2. (b) **Group B**: It included 24 (12%) patients with CIN after PCI procedure.

The differences between the two groups are displayed in table (4).

(Table 4)

Table 4: Demographic, clinical, echocardiographic and laboratory data of the two groups.

Parameter	Group A	Group B	P value
	n = 176	n = 24	
Age in years (mean±SD)	58.8±7.7	58.9±8.3	0.9
Sex; Males (%)	80 (45.5)	14 (85.3)	0.1
Smokers (%)	32 (18.2)	7 (29.2)	0.2
HTN (%)	68 (38.6)	9 (37.5)	0.5
Previous PCI (%)	4 (2.3)	4 (16.7)	0.008*
Duration of DM in years (mean±SD)	7.2±4.0	5.9±2.0	0.1
Insulin therapy (%)	81 (46)	14 (58.3)	0.2
Heart failure (%)	29 (16.5)	15 (62.5)	0.001*
Body mass index (mean±SD)	27.1±3.3	27.3±3.3	0.8
Heart rate in beats/min. (mean±SD)	83.8±14.3	90.0±15.7	0.047*
Systolic blood pressure in mmHg (mean±SD)	132.6±18.9	135.8±17.9	0.4
Diastolic blood pressure in mmHg (mean±SD)	83.4±10.5	87.9±8.8	0.044*
Segmental wall motion abnormalities (%)	54 (30.7)	14 (58.3)	0.007*
EF (%) (mean±SD)	60.0±9.6	54.6±9.7	0.01*
Volume of contrast in ml (mean±SD)	114.2±44.8	174.6±39.7	0.001*
Time of X-ray exposure in min. (mean±SD)	11.2±5.0	18.3±5.5	0.001*
Coronary procedure			
PCI with one stent (%)	124 (70.5)	9 (37.5)	0.008*
PCI with two stents (%)	41 (23.3)	12 (50)	
PCI with > two stents (%)	11 (6.2)	3 (12.5)	
TIMI flow			
TIMI I (%)	0 (0)	2 (8.3)	0.001*
TIMI II (%)	2 (1.1)	7 (29.2)	
TIMI III (%)	174 (98.8)	15 (62.5)	
Hemoglobin in mg/dL (mean±SD)	12.3±1.6	12.0±1.9	0.3
Statin therapy (%)	94 (53.4)	6 (25)	0.009*

* Statistically significant

(4) ROC curve statistics:

We used ROC curve statistics in order to set a cut-off points for both X ray exposure time and volume of used contrast beyond them, CIN is likely to develop.

(A) X ray exposure time:

Among placebo group, CIN is likely to develop after 13.5 minutes X ray exposure time with specificity 73.2% and sensitivity 77.8%, AUC 0.879 (CI: 0.798–0.960), P value 0.001. While in statin group, CIN is likely to develop after 14.5 minutes X ray exposure time with specificity 74.5% and sensitivity 83.3%, AUC 0.818 (CI: 0.727–0.910), P value 0.009, Figure (1).

(B) Volume of contrast media:

In placebo group, CIN is likely to develop after injection of 145 ml with specificity 75.6% and sensitivity 77.8%, AUC 0.855 (CI: 0.757–0.952), P value 0.001. While in statin group, CIN is likely to develop after injection of 165 ml with specificity 84% and sensitivity 83.3%, AUC 0.878 (CI: 0.811–0.944), P value 0.002, Figure (2).

Discussion:

CIN is an outstanding complication of angiographic procedures that results from administration of iodinated contrast media [1]. CIN occurs within two days of contrast exposure, the increase in creatinine level peaks one week later and usually recovers within 10 days [23–25], with most patients regaining their baseline values. Clinical manifestations that necessitate renal replacement therapy are present in approximately 3% of patients [26–27]. The development of CIN is associated with a prolonged hospital stay, an escalated morbidity and mortality and a higher financial burden [4].

Although the risk of developing CIN is low in patients with good renal status, it is remarkably higher in those with conditions such as diabetes mellitus or chronic kidney disorder [4, 28]. Many clinical trials and meta-analysis have confirmed that the incidence of CIN is increasingly common among patients with diabetes mellitus [29]. Given the adverse outcome of this issue, every effort should be done to decrease the incidence of CIN among those high-risk patients.

The pathophysiology of CIN is still unclear due to its multifactorial and complicated nature. Possible suggested theories include renal vasoconstriction leading to medullary ischemia, diminished nitric oxide generation, release of oxygen harmful radicals, direct tubular cell affection, inflammation, and nephrotoxicity [30].

Hence, several different protocols have been tried to prevent onset of CIN [5, 6]. Some of these prophylactic measures have become routine work for preventing CIN such as, intravenous volume expansion with isotonic crystalloid solution [7] whereas others are still under investigation, including intravenous saline or sodium bicarbonate solution [8–10], antioxidant agents as oral N-acetylcysteine [11] or ascorbic acid [12] and administration of low- or iso-osmolar contrast media [13].

Statins have been studied for a protective effect against CIN since their pleiotropic effects could protect the kidneys even in patients with chronic kidney disease (CKD) [21, 31–32]. Besides cholesterol lowering effects, statins have additional effects that can counteract the pathophysiology of CIN. These include increasing vascular smooth muscle relaxation, tracking oxygen free radicals, decreasing inflammation, and augmenting endothelial nitric oxide generation. Statins have antithrombotic effects and reduce acute renal injury [30]. Statins also enhance signaling pathways and hinder epithelial tubular renal cell apoptosis [33].

Among available statins, atorvastatin has multiple favorable pleiotropic effects of 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors. Atorvastatin can enhance endothelial function, ensure coronary plaque stabilization, decrease the proliferation of vascular smooth muscle cells and platelet aggregation, and suppress inflammation and oxidative stress [34]. Atorvastatin lessens kidney hypoperfusion after contrast media administration by down regulation of angiotensin receptors and decreasing generation of endothelin-1 [35]. The anti-inflammatory property of atorvastatin prevents damage of the renal cells through suppression of pro-inflammatory cytokines. This phenomenon activates the nuclear factor-kappa B pathway and induces the expression of tissue factors by macrophages [36]. Renal protective effect by atorvastatin after PCI is probably due to such attenuation of expression (though other pleiotropic effects may be responsible). Recently the possible role of atorvastatin in preventing renal damage in patients undergoing angiographic procedures has been studied.

The aim of the current study was to evaluate the beneficial effect of high dose atorvastatin just before elective coronary intervention in diabetic patients, a high-risk group of patients, who are liable for developing CIN. Our study also investigated the incidence of CIN after elective coronary intervention among this patient group. To our knowledge, this is the first placebo-controlled study to investigate the possible role of a high single dose atorvastatin just prior to elective PCI among diabetic patients in order to prevent CIN.

Our study reported a CIN incidence of 12, 18 and 6% among the whole study, placebo and statin groups respectively. Obviously those who randomly received statin just prior to the procedure were protected against CIN, p value 0.001.

Toso et al. in 2010 conducted a study on about 300 patients who had baseline CKD and undergoing coronary intervention. They stated that a short-term use of high doses of atorvastatin before and after contrast injection, with the use of routine intravenous hydration and oral N-acetylcysteine, does not affect CIN occurrence in patients with pre-existing CKD, [37]. This study failed to show any beneficial effect of atorvastatin, may be due the nature of the studied population i.e. patients with well-established CKD.

In 2015 Bidram et al carried out their study on 200 patients with no obvious risk factors for CIN who underwent only diagnostic coronary angiography. All study population received standard intravenous hydration. They intervened 12 hours before the procedure by giving high dose atorvastatin (80 mg). Their results didn't reveal any association between pre-angiography high dose atorvastatin and prevention of CIN. Also, pre-operative short-term high dose atorvastatin administration was related to a marked decrease in serum creatinine level and improved in GFR after the procedure, [38].

On the other hand, Khosravi et al. in 2016 used a high dose (80 mg) atorvastatin in prevention of CIN among high risk patients (diabetic and/or CKD) undergoing coronary intervention. They confirmed the favorable effect of atorvastatin in prevention of CIN, [39].

However, in all above studies, they administered atorvastatin 12–48 hours before the procedure, in contrast to ours that administered the drug immediately before the procedure. Also their study population received intravenous isotonic saline and/or N-acetylcysteine, creating some doubt about the proper effects of atorvastatin, [37–39].

A meta-analysis that was published in 2018 reported that compared to placebo, high-dose atorvastatin decreased the risk of CIN. Only few data present on high-dose atorvastatin compared with low-dose atorvastatin, so a meta-analysis could not be done, [40].

In our study, a comparison of the creatinine values before and after coronary intervention showed rise in the serum creatinine level among both study groups, p value 0.001. This indicates that every coronary intervention procedure still carries some risk of having harm to kidneys especially in those high risk diabetic patients.

Our study is the first to clearly demonstrate that using atorvastatin before the procedure raised the cut-off point of both X ray time exposure and amount of used contrast medium for developing CIN.

Limitations:

One of the limitations of our study is the lack of follow up to determine the proper effect of atorvastatin on renal function.

Conclusions:

Pre-treatment with high dose atorvastatin can effectively protect against CIN. At high doses, atorvastatin pretreatment was associated with a marked decrease in the prevalence of CIN in diabetic patients undergoing coronary interventions. Moreover, pretreatment with high-dose atorvastatin raises the threshold of X-ray exposure time and amount of contrast media beyond which CIN is likely to develop.

Abbreviations

CIN: Contrast induced nephropathy

CM: Contrast media

DM: Diabetes mellitus

PCI: Percutaneous coronary interventions

CI-AKI: Contrast induced acute kidney injury

ROC: Receiver operating characteristic

AUC: Area under the curve

CI: Confidence interval

CKD: Chronic kidney disease

Declarations:

* The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Assiut University, 18th November 2019.

* A written informed consent was taken from every participant.

* The written consent of our institution involves a consent for publication of the processed obtained data without any names or private data of the participants.

* All data of the study is available upon request. Data generated or analyzed during this study are included in this published article.

* All authors declare no financial or non-financial conflict of interests.

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* All study authors contributed in all study steps. A.A. postulated the study design, data collection and final manuscript edition. L.A. carried out data analysis and writing paper draft. R.G. shared in PCI procedure. A.H. shared in recruitment and randomization of the cases. M.A.E performed data preparation, analysis and statistical operations. A.I. shared in PCI procedure.

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Figures

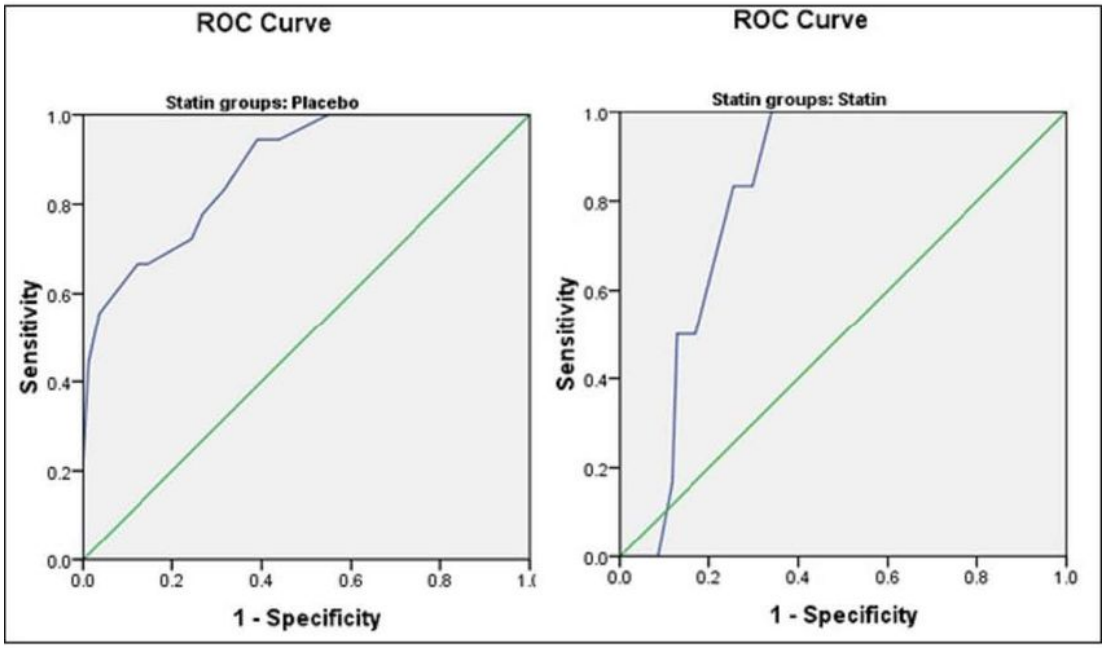

Figure 1

Figure 1

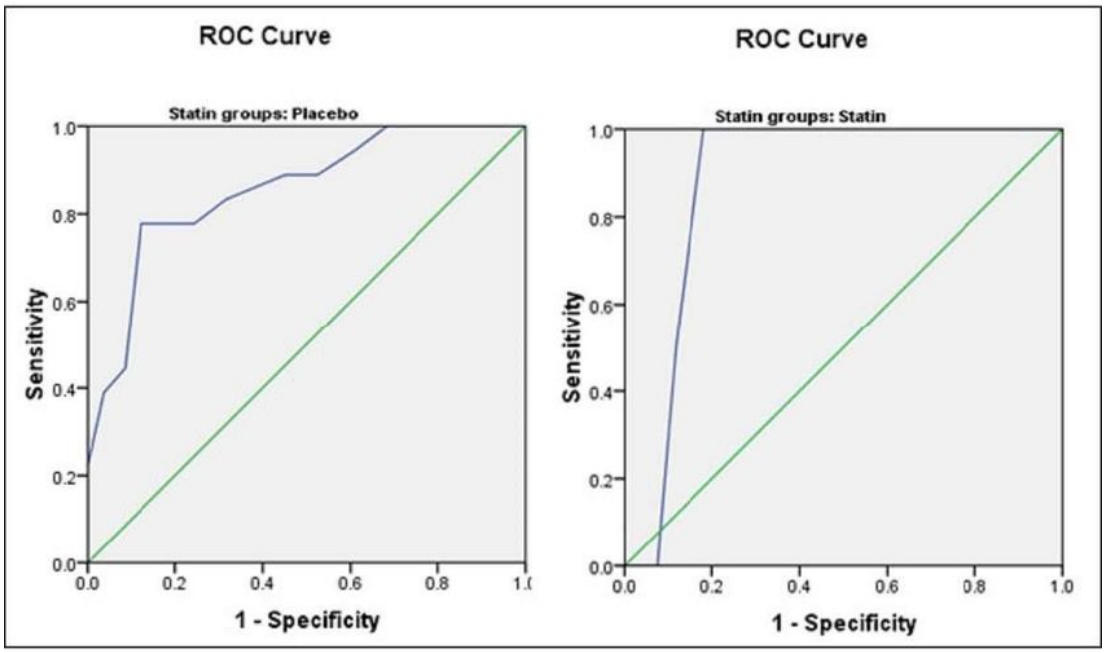

Figure 2

Figure 2