

**Original Paper**

# Is Nebivolol Really Effective in Preventing Contrast Induced Nephropathy?

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## Key Words

Contrast induced nephropathy • Neutrophil-gelatinase-associated lipocalin • Nebivolol • Renal Failure

## Abstract

**Background/Aims:** Contrast induced nephropathy (CIN) has multifactorial etiopathogenesis including oxidative stress and vasoconstriction. Nebivolol is an antioxidant and has vasodilatory effect via NO release and may prevent CIN development. We have noticed that a few number of studies that have evaluated the effectiveness of nebivolol for the prevention of CIN used serum creatinine (sCr) levels for CIN detection. However, sCr is an insensitive marker for renal damage. Therefore in this study we used serum neutrophil-gelatinase associated lipocalin (NGAL), a more sensitive marker of renal damage, to evaluate preventive role of nebivolol in CIN. **Methods:** 159 patients undergoing coronary angiography (CAG) who had at least one risk factor for CIN were divided into nebivolol (+) and (-) groups. CIN was defined as a rise in sCr of 0.5mg/dl or a 25% increase from the baseline value. Serum Cr, glomerular filtration rate (eGFR) and NGAL levels were assessed before and 48 h after CAG. Mehran risk scores were calculated for both groups. **Results:** Both groups were similar in terms of baseline characteristics, Mehran risk scores, and current medications. Clinically, CIN developed at similar rates in both groups. Serum Cr, eGFR and NGAL values were similar in both groups before and after CAG. Serum Cr and NGAL levels increased and eGFR decreased significantly compared to the levels before CAG. Patients who developed CIN were significantly older ( $p=0.003$ ), and were more likely to have DM ( $p=0.012$ ), a higher mean contrast agent volume ( $p<0.001$ ), and a higher Mehran score ( $p<0.001$ ). We did not observe any favorable effect of Nebivolol in the prevention of CIN in patients undergoing CAG. **Conclusion:** According to the results of our study Nebivolol does not seem to prevent CIN in patients undergoing CAG. However, further randomised controlled trials with more sensitive renal damage markers are obviously needed to understand the actual effect of nebivolol on CIN especially through oxidative pathways and in high risk patients.

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## Introduction

Despite advances in imaging modalities using contrast agents, contrast induced nephropathy (CIN) remains a significant problem in patients undergoing coronary angiography (CAG). The incidence of CIN in the general population ranges from 0.6 to 2.3%, but it can reach up to 50% in high-risk patients [1-3]. CIN is the third most common cause of renal failure in hospitalized patients, and it can lead to permanent impairment of renal function, with a mortality rate of up to 20% [4].

The etiopathogenesis of CIN remains unclear. Vasoconstriction of the renal microcirculation, oxidative stress, inflammation and direct tubular toxicity are the principal implicated factors [2, 4, 5]. Although a large number of medications including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) [6], fenoldopam [7], N-acetylcysteine [7], and nebivolol [8, 9] have been evaluated in terms of CIN prevention and treatment, the effectiveness of pharmacological measures excluding statins [10] and hydration [10] remains unproven.

Nebivolol is a third-generation beta-blocker with antioxidant properties that triggers vasodilatation by facilitating nitric oxide (NO) release [9, 11, 12]. Nitric oxide is an endothelium derived substance with direct vasodilatory activity. Nebivolol increases NO bioavailability through several mechanisms. It has been shown that nebivolol increases endothelial Nitric Oxide Synthase (eNOS) expression and activity [13, 14], and decreases asymmetric dimethyl arginine which is a natural eNOS inhibitor [15] and decreases degradation of eNOS [16]. Moreover, it produces systemic antioxidant effects by reducing superoxide production via inhibition of NAD(P)H oxidase activity [17, 18]. Both oxidative stress and vasoconstriction in the renal medullary capillary network may be responsible for development of CIN, and nebivolol may have protective effects on this process through abovementioned mechanisms. There have been a number of studies exploring whether nebivolol can prevent CIN or not [8, 19, 20]; but invariably, the development and severity of CIN was measured through increases of sCr. It is known that sCr levels do not rise until renal damage is advanced. Although a few studies have claimed that nebivolol is useful to prevent CIN [20], whether the drug actually inhibits CIN development or not remains unclear. We therefore explored the effectiveness of nebivolol in prevention of CIN development by using serum neutrophil-gelatinase associated lipocalin (NGAL), also known as "renal troponin" by many authors, signifying its superior features in early detection of renal damage [21]. It has been claimed that NGAL is a better predictor of acute kidney injury (AKI) than sCr in patients undergoing CAG [22].

## Material and Method

Our cross-sectional case-control study was conducted in the Adiyaman University Training and Research Hospital. A total of 159 consecutive patients who underwent CAG upon a diagnosis of stable coronary artery disease (CAD), between October 2012 and September 2014, exhibiting at least one of pre-defined risk factors for development of CIN including diabetes mellitus (DM), advanced age, reduced glomerular filtration rate (GFR), and/or anemia were included. Patients with acute coronary syndrome, patients who had been exposed to nephrotoxic agents in the last 48 h prior to CAG, who had severe heart failure (ejection fraction <35%) or those known to be hypersensitive to contrast agents were excluded from the study. Patients with conditions that might alter NGAL levels, such as sepsis, urinary tract infection, and/or malignancy [23, 24], and patients who used beta-blockers other than nebivolol, were also excluded. Eligible patients who met the above criteria were divided into two groups according to nebivolol usage as Nebivolol (+) and Nebivolol (-) groups. In the nebivolol (+) group the drug had already been started by previous clinicians such as internalists or cardiologists for the probable indications of hypertension, suspected coronary artery disease or palpitation. The study was approved by the local ethic committee and a written informed consent was obtained from all patients.

Baseline clinical and demographic data and prior medical histories were recorded. Hypertension was defined as a blood pressure of  $\geq 140/90$  mm/Hg or treatment with antihypertensive agents. DM was defined

as a fasting glucose level  $\geq 126$  mg/dl or treatment with oral anti-diabetic drugs or insulin. Hyperlipidaemia was defined as suggested by the current guidelines [25]. Anemia was defined as a baseline haematocrit  $< 39\%$  for males and  $< 36\%$  for females. Smokers were defined as current tobacco users or patients who had quit smoking within 1 month prior to the procedure. Severe heart failure was identified by transthoracic echocardiography, and was defined as a left ventricular ejection fraction  $< 35\%$ , using the modified Simpson's method.

We calculated Mehran risk scores for all patients. This scoring system is the most commonly used system to determine the probability of CIN development and it includes parameters such as age, hypotension, congestive heart failure, use of an intra-aortic balloon pump, sCr level, DM status, anemia, and contrast agent volume [26]. Estimated GFRs were determined prior to each procedure using the Modification of Diet in Renal Disease (MDRD) formula [27].

CIN was defined as a sCr increase of 0.5 mg/dL or a 25% increase from the baseline value assessed at 48 hours after CAG. [4, 5]. As all patients exhibited risk factors for development of CIN, all were hydrated with isotonic saline infusion at a rate of 1 mL/kg/h for 12 h prior to and following the CAG procedure. All patients received low-osmolality contrast agent (containing iohexol) during CAG, and the given volume of contrast agent was recorded. All CAG procedures were performed and evaluated by an experienced interventional cardiologist blind to the study design. The stenotic diameter of the major epicardial coronary artery was measured and stenosis of 70% or greater was graded as critical.

For routine biochemical tests, a blood sample was obtained from a peripheral vein both prior to and 48 h after the CAG procedure. Samples were drawn into standardized tubes and assayed within 1 h using routine laboratory techniques. Haematological measurements were performed with the aid of an XT-2000i analyser (Sysmex Corporation of America, Long Grove, IL, USA). As the NGAL serum level peaks around 48 h following AKI [5], serum samples were obtained from a peripheral vein prior to and 48 h after the CAG procedure, separated, and stored at  $-80^{\circ}\text{C}$  prior to determination of serum NGAL levels, which were measured using a commercial BioVendor ELISA kit capable of measuring both serum and plasma with 7,7% intraassay and 9,8% interassay CV (Human LIPOCALIN 2/NGAL ELISA Kit; BioVendor-Laboratori Medicina a.s.; Czech Republic).

#### *Statistical Analysis*

All analyses were performed using SPSS version 19 for Windows (SPSS Inc., Chicago, IL, USA). Numerical variables are presented as means  $\pm$  standard deviations, and nominals as percentages. All variables were subjected to Kolmogorov-Smirnov testing to determine whether they were normally distributed, or not. The independent samples t-test was used to compare the values of continuous variables between the two groups. Nonparametric values were compared using the Mann-Whitney U-test. The chi-squared test was used to compare categorical data. To evaluate the effects of various factors on CIN development, we performed multivariate regression analyses. The models were adjusted using various candidate factors including age, gender, DM status, baseline sCr level, the GFR, the NGAL level, contrast agent volume, the Mehran score, and the use of nebivolol. Coefficients with 95% confidence intervals (95% CIs) are presented. A p value  $< 0.05$  was considered statistically significant.

## **Results**

Patients who had used nebivolol for at least 1 month formed the nebivolol (+) group and all the others nebivolol (−) group. Demographic characteristics, current medications, and basic features of both groups are shown in Table 1. Both groups were similar in terms of age ( $68.4 \pm 8.2$  vs  $67.7 \pm 12.3$  respectively), gender, DM (44% vs 31% respectively) and hypertension frequency (48% vs 36% respectively), smoking status, and current medications ( $p > 0.05$  for all comparisons). The Mehran score ( $7.4 \pm 3.3$  vs  $7.6 \pm 3.3$  respectively) and the amount of contrast agent used ( $104.4 \pm 61.7$  ml vs  $92.4 \pm 40.5$  ml respectively) were similar between the nebivolol (+) and (−) groups (Table 1). Mean serum NGAL levels ( $89.3 \pm 56.3$  ng/ml vs  $87.8 \pm 53.7$  ng/ml prior to CAG and  $106.4 \pm 80.9$  ng/ml vs  $100.1 \pm 62.6$  ng/ml after CAG respectively), eGFR values ( $77.5 \pm 32.7$  ml/dk/ $1.73\text{m}^2$  vs  $75.1 \pm 31.9$  ml/dk/ $1.73\text{m}^2$  prior to CAG and  $64.6 \pm 23.5$  ml/dk/ $1.73\text{m}^2$  vs  $67.1 \pm 30.1$  ml/dk/ $1.73\text{m}^2$  after CAG), and sCr levels

( $1.1 \pm 0.5$  mg/dl vs  $1.1 \pm 0.6$  mg/dl prior to CAG and  $1.4 \pm 0.9$  mg/dl vs  $1.3 \pm 0.7$  mg/dl after CAG) both before and 48 h after CAG, were similar in the nebivolol (+) and nebivolol (-) groups (Table 2). Clinically, CIN developed in 8 (17%) of patients in the nebivolol (+) group and 13 (11%) in the nebivolol (-) group ( $p = 0.3$ ).

Significant impairment in post-CAG eGFR values was observed in both nebivolol (+) and nebivolol (-) groups (from  $77.5 \pm 32.7$  ml/dk/ $1.73\text{m}^2$  to  $64.6 \pm 23.5$  ml/dk/ $1.73\text{m}^2$ ,  $p = 0.01$  and from  $75.1 \pm 31.9$  ml/

**Table 1.** Baseline demographic characteristics of patient groups in terms of nebivolol usage

	Nebivolol (+) (n=45)	Nebivolol (-) (n=114)	p
Age (years)*	$68.4 \pm 8.2$	$67.7 \pm 12.3$	0.884
Sex (Male/Female)	22/23	65/49	0.381
DiabetesMellitus, n (%)	20(44%)	36(31%)	0.143
Hypertension, n (%)	22(48%)	42(36%)	0.209
Smoking, n (%)	8(17%)	27(23%)	0.526
Hyperlipidemia, n (%)	15(33%)	51(44%)	0.214
Current medications			
Statins n (%)	15(33%)	51(44%)	0.214
ASA n (%)	14(31%)	35(30%)	0.994
ACEI n (%)	8(17%)	21(18%)	0.569
ARB n (%)	7(15%)	20(17%)	0.483
OAD n (%)	13(28%)	23(20%)	0.293
Insulin n (%)	5(11%)	11(9%)	0.775
CCB	14(31%)	26(22%)	0.313

ASA:Acetylcalicic acid, ACEI:Angiotensine converting enzyme inhibitor, ARB: Angiotensine Receptor Blocker, OAD: Oral antidiabetic agent, CCB: Calcium Channel Blocker. \*Mann Whitney U test was used for age and Chi-Square test was used for other parameters

**Table 2.** Baseline laboratory and angiographic characteristics of patient groups in terms of nebivolol usage

	Nebivolol (+) (n=45)	Nebivolol (-) (n=114)	p
Mehran risk score	$7.4 \pm 3.3$	$7.6 \pm 3.3$	0.607
Contrast agent volume (ml)	$104.4 \pm 61.7$	$92.4 \pm 40.5$	0.647
sCr level prior to CAG (mg/dl)	$1.1 \pm 0.5$	$1.1 \pm 0.6$	0.957
eGFR prior to CAG (ml/dk/ $1.73\text{m}^2$ )	$77.5 \pm 32.7$	$75.1 \pm 31.9$	0.803
NGAL level prior to CAG (ng/ml)	$89.3 \pm 56.3$	$87.8 \pm 53.7$	0.678
sCr level 48 hours after CAG (mg/dl)	$1.4 \pm 0.9$	$1.3 \pm 0.7$	0.589
eGFR, 48 hours after CAG (ml/dk/ $1.73\text{m}^2$ )	$64.6 \pm 23.5$	$67.1 \pm 30.1$	0.890
NGAL level 48 hours after CAG (ng/ml)	$106.4 \pm 80.9$	$100.1 \pm 62.6$	0.507
Development of clinical CIN	8(17%)	13(11%)	0.304
WBC( $\times 10^3/\text{mm}^3$ )	$7.6 \pm 1.9$	$7.8 \pm 2.7$	0.571
PLT( $\times 10^3/\text{mm}^3$ )	$238.2 \pm 54.7$	$229.9 \pm 50.4$	0.362
Hematocrit(%)	$37.5 \pm 4.4$	$39.0 \pm 5.1$	0.128
Single vessel disease, n (%)	15(33%)	51(44%)	0.214
Two- vessel disease, n (%)	14(31%)	27(23%)	0.421
Three- vessel disease, n (%)	9(20%)	16(14%)	0.345

sCr: Serum Creatinine, GFR: Glomerular filtration rate, CAG: Coronary angiography, NGAL: Neutrophil-gelatinase-associated lipocalin, CIN: Contrast induced nephropathy, WBC: White Blood Cell, PLT: Platelets

dk/ $1.73\text{m}^2$  to  $67.1 \pm 30.1$  ml/dk/ $1.73\text{m}^2$ ,  $p = 0.009$ , respectively). NGAL levels in both groups increased significantly compared to baseline (from  $89.3 \pm 56.3$  ng/ml to  $106.4 \pm 80.9$  ng/ml,  $p = 0.026$  and from  $87.8 \pm 53.7$  ng/ml to  $100.1 \pm 62.6$  ng/ml,  $p = 0.027$ , respectively). Serum Cr levels also increased significantly in both groups after CAG (from  $1.1 \pm 0.5$  mg/dl to  $1.4 \pm 0.9$  mg/dl,  $p = 0.023$  and from  $1.1 \pm 0.6$  mg/dl to  $1.3 \pm 0.7$  mg/dl,  $p < 0.001$ , respectively) (Table 3).



**Table 3.** Comparisons of Cr, GFR and NGAL values before and 48 hour after of CAG between Nebivolol (+) and (-) groups

	sCr level prior to CAG (mg/dl)	sCr level 48 hours after CAG (mg/dl)	p	eGFR prior to CAG (ml/dk/1.7 3m <sup>2</sup> )	eGFR, 48 hours after CAG (ml/dk/ 1.73m <sup>2</sup> )	p	NGAL level prior to CAG (ng/ml)	NGAL level 48 hours after CAG (ng/ml)	p
Nebivolol (+) n=45	1.1 ± 0.5	1.4 ± 0.9	.023	77.5 ± 32.7	64.6 ± 23.5	.018	89.3 ± 56.3	106.4 ± 80.9	0.026
Nebivolol (-) N=114	1.1 ± 0.6	1.3 ± 0.7	< .001	75.1 ± 31.9	67.1 ± 30.1	0.009	87.8 ± 53.7	100.1 ± 62.6	0.027

sCr: Serum Creatinine, eGFR: Glomerular filtration rate, NGAL: Neutrophil-gelatinase-associated lipocalin, CAG: Coronary angiography. Paired sample t test was used

**Table 4.** Baseline demographic, angiographic, and laboratory data on patient groups in terms of clinical CIN development

	CIN (+) n=21	CIN (-) n=138	p
Age (years)	74.6 ± 11.2	66.9 ± 11.0	0.003
Sex, M/F*	14/7	73/65	0.347
Diabetes mellitus, n (%)	13(61%)	43(31%)	0.012
Hypertension, n (%)	5(23%)	59(42%)	0.151
Hyperlipidemia, n (%)	8(38%)	58(42%)	0.815
Smoking (%)	4(19%)	31(22%)	0.896
Currentmedication*			
Statin n (%)	8(38%)	58(42%)	0.815
ASA n (%)	5(23%)	44(31%)	0.614
ACEI n (%)	2(9%)	26(18%)	0.374
ARB n (%)	3(14%)	24(17%)	0.992
OAD n (%)	4(19%)	32(23%)	0.786
CCB n (%)	4(19%)	36(26%)	0.597
Insulin n (%)	1(4%)	15(10%)	0.697
Nebivolol usage (n)	8 /21	37/138	0.285
Single-vessel disease, n (%)	8(38%)	58(42%)	0.815
Two-vessel disease, n (%)	5(23%)	36(26%)	0.986
Three-vessel disease, n (%)	2(9%)	23(16%)	0.533
Contrast agent volume	159.2 ± 71.8	86.1 ± 33.9	< .001
Mehran risk score	11.5 ± 2.8	6.9 ± 2.9	< .001
sCr level prior to CAG (mg/dl)	1.7 ± 0.7	1.1 ± 0.4	< .001
eGFR prior to CAG (ml/dk/1.73m <sup>2</sup> )	50.1 ± 30.0	79.7 ± 30.6	< .001
NGAL level prior to CAG (ng/ml)	143.1 ± 75.1	79.9 ± 45.3	< .001
sCr level 48 hours after CAG (mg/dl)	2.7 ± 1.1	1.1 ± 0.4	< .001
eGFR, 48 hours after CAG (ml/dk/1.73m <sup>2</sup> )	35.2 ± 9.4	71.1 ± 27.2	< .001
NGAL level 48 hours after CAG (ng/ml)	196.3 ± 80.7	87.4 ± 53.1	< .001
WBC (x10 <sup>3</sup> /mm <sup>3</sup> )	7.6 ± 3.2	7.8 ± 2.4	0.701
PLT (x10 <sup>3</sup> /mm <sup>3</sup> )	234.7 ± 47.1	231.9 ± 52.4	0.729
Hematocrit(%)	39.3 ± 4.2	38.4 ± 4.8	0.557

ASA:Acetylcyclic acid, ACEI:Angiotensine converting enzyme inhibitor, ARB: Angiotensine Receptor Blocker, OAD: Oral antidiabetic agent, CCB: Calcium Channel Blocker, Cr: Creatinine, GFR: Glomerular filtration rate, CAG: Coronary angiography, NGAL: Neutrophil-gelatinase-associated lipocalin, CIN: Contrast induced nephropathy, WBC: White Blood Cell, PLT: Platelets,  
\*: Chi-Square test was used

When patients were divided into two groups based on clinical CIN development, no significant difference was detected between the groups in terms of nebivolol usage (38% in CIN (+) group and 26% in CIN (-) group) (Table 4). Patients who developed CIN were significantly older (p = 0.003), were more likely to have DM (p = 0.012), used a higher amount of contrast agent (p < 0.001), and had a higher Mehran score (p < 0.001) (Table 4) than CIN (-) patients.

We performed a multiple logistic regression analysis to identify risk factors contributing to the development of CIN. Baseline serum eGFR prior to CAG (OR: 0.971, 95% CI: 0.944-0.998,  $p = 0.038$ ), NGAL level prior to CAG

**Table 5.** Multiple logistic regression to define risk factors contributing to development of CIN

Variables	OR	95 % CI	p
sCr level prior to CAG (mg/dl)	0.325	0.079-1.330	0.118
eGFR prior to CAG (ml/dk/1.73m <sup>2</sup> )	0.971	0.944-0.998	0.038
NGAL level prior to CAG (ng/ml)	1.014	1.001-1.027	0.031
Contrast agent volume	1.028	1.011-1.046	0.001
Mehran risk score	1.339	1.028-1.744	0.030
Age	0.993	0.922-1.069	0.854
DM	3.662	0.869-15.436	0.077
Nebivolol usage	2.136	0.414-11.018	0.365

sCr: Serum Creatinine, GFR: Glomerularfiltration rate, CAG: Coronaryangiography, NGAL: Neutrophil-gelatinase-associated lipocalin

(OR: 1.014, 95% CI: 1.001-1.027,  $p = 0.031$ ), contrast agent volume (OR: 1.028, 95% CI: 1.011-1.046,  $p = 0.001$ ), and Mehran risk score (OR: 1.339, 95% CI: 1.028-1.744,  $p = 0.030$ ) were independent predictors of CIN development (Table 5). We found no relationship between the sCr level prior to CAG ( $p = 0.118$ ), age ( $p = 0.854$ ), DM (OR: 3.662, 95% CI: 0.869-15.436,  $p = 0.077$ ), or usage of nebivolol ( $p = 0.365$ ) and the risk of CIN development.

## Discussion

In our present study, we evaluated whether nebivolol is protective or not for the development of CIN. We observed similar rates of CIN in both the nebivolol (+) and nebivolol (-) groups. Previous studies on this matter have used a classical CIN definition that primarily takes sCr levels into account. However, since sCr elevation may be delayed, or may not rise even as GFR falls or may rise unpredictably at anytime within 1 to 10 days of CIN development, it is not a good marker for early determination of renal damage. More sensitive markers than sCr should be used for evaluation of nebivolol on CIN development. Accordingly in our study we preferred serum NGAL levels in evaluating the development of CIN. We discovered that serum NGAL levels did not differ between nebivolol (+) and nebivolol (-) groups.

Patients that developed CIN were older and had a higher incidence of DM, a higher Mehran score, higher baseline sCr and NGAL levels, and a lower baseline eGFR than patients that did not develop CIN. We did not find any relationship between nebivolol usage and the risk of CIN development using multiple logistic regression analysis.

CIN is a significant adverse event associated with administration of contrast agent and is the third most common cause of acute renal failure [28]. Many factors including hypovolemia, contrast agent volume, impaired baseline GFR, advanced age and anemia facilitate the development of CIN. A number of studies exploring the prevention and elimination of known risk factors for CIN have been published previously [29-31]. The third-generation beta blocker nebivolol exhibits high-level  $\beta_1$  selectivity, and antioxidant effects, and increases NO synthesis by activating NO synthase. Nebivolol has also been shown to trigger vasodilatation of both the afferent and efferent arterioles of the rat juxtaglomerular nephrons [10-12]. Avci et al [8] compared postangiographic results of 55 patients who used nebivolol for 1 week and 35 patients who used metoprolol in their study, where they used the classical definition of CIN. They showed that the occurrence of CIN was significantly lower in the nebivolol group. But, as noted by Bowden's editorial comment, the nonrandomized design and small sample size of this study may have had led to bias [32]. Toprak et al. [19] previously described the beneficial effects of, and a protective role for, nebivolol in CIN. No difference between a contrast agent (CM) and a contrast agent + nebivolol (NCM) group was detected in 6th day sCr levels, but intravenous nebivolol reduced the severity of renal histopathological changes

and the levels of oxidative stress markers in the NCM group. As a limitation, our study design did not allow us to measure oxidative stress parameters or histopathological changes. However, we assessed CIN development by both sCr and NGAL levels, and found no difference between the nebivolol (+) and nebivolol (–) groups. As the drug has both antioxidant and vasodilator properties, nebivolol would be expected to prevent development of CIN, but we did not observe such an effect. A possible explanation for this observation might be the already high Mehran risk scores of our patients, and the multifactorial etiopathogenesis of CIN development. Similar to our results, Akgüllü et al. have discovered that pre-procedural nebivolol did not affect CIN development [33]. The cited authors measured sCr levels on both days 2 and 5. We did not evaluate sCr levels after 48 hours, but we did measure NGAL levels on day 2 (48 hour after CAG), which can detect CIN even a few hours after contrast agent administration [34]. The NGAL levels measured 48 h after CAG did not differ between the nebivolol (+) and nebivolol (–) groups. Akgüllü et al [35] have recently performed an animal study, and showed that carvedilol and nebivolol may prevent contrast media related renal damage by decreasing oxidative stress.

We observed that the baseline eGFR, Mehran score, contrast agent volume, and NGAL level prior to CAG, independently predicted CIN development. When the patients were divided into two groups in terms of CIN development, although the CIN (+) group included more patients with DM who had higher basal sCr levels, neither of these variables predicted CIN development. We think that this might be secondary to our small sample size. Although previous studies have suggested that nebivolol prevents CIN, our study did not confirm this observation. But we believe that our results are still noteworthy since we used NGAL which is a more specific and a sensitive early AKI marker for the determination of renal damage. Additionally, in our study, the baseline sCr, DM frequency, age, sex and most importantly the Mehran risk scores were similar in both groups. We believe that this minimized the effects of these parameters to the final outcome. Therefore we hold that our results support the hypothesis that nebivolol doesn't play a role in CIN prevention. However further randomised controlled trials using sensitive renal damage markers with a large number of patients are clearly needed.

Our study has several limitations such as small sample size reflecting the experience of only one centre and a lack of long term follow up data for sCr after CAG. In addition, we evaluated patients who had been using nebivolol for at least 1 month, which might be long enough to develop a tolerance to the vasodilatory effects of the drug. Therefore, short-term nebivolol use, or a single dose given prior to the procedure, might yield different results.

It is known that CIN is more likely to develop following emergency coronary interventions. Since all our patients had undergone elective CAG, we were not able to measure the preventive effect of Nebivolol in an emergency CAG setting. Finally, we did not collect urine samples or measure oxidative markers because of resource constraints.

## Conclusion

The pathogenesis of CIN is multifactorial and remains poorly understood. Therefore many precautions should be taken to prevent CIN. Based on our results it seems that nebivolol does not help to prevent CIN in patients undergoing CAG. Further prospective randomized studies are needed.

## Disclosure Statment

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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