A clinical study about contrast nephropathy: Risk factors and the role of beta blockers

Çağdaş Akgüllü, Ufuk Eryılmaz, Hasan Güngör, Ahmet Huyut, Cemil Zencir, Tolga Hekim[1]

Department of Cardiology, Faculty of Medicine, Adnan Menderes University; Aydın-*Turkey*
[1]Department of Cardiology, Aydın State Hospital; Aydın-*Turkey*

Abstract

Objective: There is still a group of patient that have unpredictable risk for the development of contrast nephropathy (CN). There is also an effort to find more effficient strategies to prevent CN. Carvedilol, metoprolol and nebivolol seem to have theoretical potentials for the prevention of CN. In this study, we aimed to investigate their effects on the prevention of CN. We also aimed to define the risk factors associated with the development of CN in our study group.

Methods: In this prospective, cross-sectional study, the patients were divided into four groups according to whether they were taking 25 mg/day carvedilol (n:56), 5 mg/day nebivolol (n:60), 50 mg/day metoprolol (n:68) or none (n:63). We made analysis to determine the agents' efficiency on the prevention of CN. We also performed multiple logistic regression analysis including all groups to define the risk factors associated with CN.

Results: The incidents of CN were the lowest in the carvedilol group (4%) while the worst performance occurred in those taking metoprolol (10%). The difference between the groups in terms of the development of CN did not reach statistical significance (p>0.05). Multiple logistic regression analysis showed age (p=0.003), higher triglyceride levels (p=0.011) and family history of coronary artery disease (p=0.038) to be the predictors of CN.

Conclusion: In this study, we didn't find any relation between the development of CN and carvedilol, metoprolol or nebivolol usage. We found age, higher levels of triglyceride and family history of coronary artery disease to be risk factors for predicting CN.

(Anatol J Cardiol 2015; 15: 232-40)

Keywords: carvedilol, nebivolol, metoprolol, contrast nephropathy, triglyceride, coronary angiography

Introduction

Diagnostic and therapeutic invasive cardiac catheterization has become more widespread, thus causing an increase in the frequency of complications related to the use of contrast material (CM). One such complication is acute renal failure that develops after exposure to iodinized CM, which is more commonly known as contrast nephropathy (CN) (1). Although there is still no clear consensus regarding the definition of CN, the following has been frequently used in clinical investigations: an increase in the serum creatinine levels of 0.5 mg/dL (44.2 μmoL/L) or a 25% increase compared with the basal value over a 48-hour period following the administration of CM when no other viable cause for the higher levels exists (2).

The future rate of development for CN is predicted to be approximately 7% for the general population (3). Once occured, CN usually returns to normal with sufficient hydration and close clinical follow-up in most patients, however it can also lead to in-hospital mortality and morbidity (4). Currently, CN is responsible for 11-12% of the cases of renal failure that develop in the hospital and is the third most common cause of acute renal failure, with even higher numbers in the elderly, diabetes patients, those with previous renal failure, those who have experienced an acute coronary event and undergone coronary intervention, and those with heart failure. There are some scoring systems to predict high risk patients for CN. One of the most favourite score is Mehran risk score (MRS) including 8 clinical and procedural variables: age >75 years, hypotension, congestive heart failure, intra-aortic balloon pump, serum creatinine, diabetes, anemia, and volume of contrast for determining the risk for the development of CN (5).

The exact pathogenesis of CIN is controversial but several mechanisms have been proposed. Renal vasoconstriction and

Address for Correspondence: Dr. Çağdaş Akgüllü, Adnan Menderes Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 090100, Aytepe, Aydın-*Türkiye*
Phone: +90 256 444 12 56-2215 Fax: 256 213 60 64 E-mail: cagdasakgullu@gmail.com
Accepted Date: 12.03.2014 **Available Online Date:** 28.04.2014

DOI:10.5152/akd.2014.5304

renal hemodynamic disturbances, increased levels of endothelin, impaired nitric oxide production, endothelial dysfunction, direct cellular toxicity due to relatively high tissue osmolality, and reperfusion injury via free radical formation and oxidative stress (OS) are the suggested mechanisms (6, 7). Different studies with different pharmacological agents have been studied to find the most effective way for the prevention of CIN or to add any further benefit. There is controversy about the benefits of most agents however, hydration either orally or intravenous with isotonic saline is still accepted to be the most efficient way for the prevention of CIN (8).

Carvedilol, a third generation beta blocker agent with its potent antioxidant property in additon to its vasodilatory effect through its alpha blocker activity gives rise to a theoretical potential for the prevention for CN. It may prevent renal vasoconstriction as well as oxidative stress induced by CM. Nebivolol, is another third generation beta blocker with vasodilatator effects. Moreover, tissue studies have demonstrated that nebivolol increases renal blood flow and GFR by causing dilatation in the afferent and effertent arterioles. In addition to these effects, nebivolol converts reactive oxygen products formed by the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase to NO by way of endothelial constitutive NO synthase (eNOS) and increases the total antioxidant action (9). Thus, theoretically, nebivolol also appears to have the substantially strong potential to prevent CN. Metoprolol is still one of the most frequent beta blocker agents prescribed by the clinicians. It doesn't have vasodilatory effect like carvedilol and nebivolol. But,the antioxidant efficiency of this agent may lead to a theoretical potential for the prevention of CN. However, in the literature there are contradictory studies regarding the antioxidant efficiency of metoprolol (10, 11).

People suspected to have coronary artery disease are prescribed anti-ischemic agents before the catheterization procedure. Because β-blockers are established as an essential therapeutic option for patients suspected to have myocardial ischemia, it is critical to characterize the effects of such compounds on CN. Furthermore, comparing the effects of these three most prescribed beta blockers on CN may further help clinicians to add a cost effective potential for the protection of kidneys from CM. In this study, we aimed to determine and compare the effects of carvedilol, metoprolol and nebivolol therapy on CN. We also aimed to determine the risk factors effecting our particular study group in terms of CN.

Methods

Study design and population

This study included 247 patients who underwent coronary angiography (CAG) between January 2012 and November 2013. The patients were selected randomly and divided into four groups prospectively, and all were hydrated with intravenous 0.9% sodium chloride (NaCL) at a speed of 1 mL/kg/hour for 12 hours before and after the procedure. The therapy groups had been receiving 5mg nebivolol (n=60), 25 mg carvedilol (n=56), or 50 mg metoprolol (n=68) for at least two weeks and maximally for the last month. They continued to use their drugs at the same rate in the five-day follow-up period after the angiography. The patients in the control group (n=63) were not using any beta blocker therapy at least for the last two weeks before the procedure. We used iopromide, a nonionic (low osmolar) CM, in our study.

In this study, the dosage of 5 mg/day nebivolol and 50 mg/day metoprolol were selected in the light of previous studies (12). However, to the best of our knowledge there is not any previous study testing any dosage of carvedilol against CN in the literature. Thus, we choosed 25 mg/day as this dose is high enough to prevent angina pectoris and mostly tolareted well.

Patients with severe renal failure [glomerular filtration rate (GFR) below 30mL/min/1.73 m^2], severe, symptomatic hypotension (a systolic blood pressure below 80 mm Hg requiring positive inotropic or intra-aortic balloon support), acute coronary syndromes, accelerated angina under anti-ischemic therapy, those who had undergone urgent percutaneous transluminal angioplasty, a previuosly diagnosed chronic inflammatory disease, malignancy, and those with a history of allergies against CM or those who developed an allergy during the procedure were excluded from the study. In addition, patients who required dialysis, those who were hypoxic and dehydrated, those who had been exposed to any nephrotoxic agent or CM in the seven days prior to the procedure, those who required the use of loop diuretics, those for whom the use of beta-blockers was contraindicated, those taking theophylline/aminophylline, and those who were New York Heart Association class 3-4 were also not included.

Approval for this study was obtained from the local Ethics Committee, and informed consent was obtained from all of the study participants.

Randomization and management of medication

First contact and the enrollment process were done in our outpatient clinic. All patients corresponding to our inclusion criterias were randomly enrolled to the study. As a part of randomization process, patients were enrolled to the study in four days of the week (Monday, Tuesday, Thursday and Friday). Patients were selected for nebivolol group if they were enrolled in Monday, for carvedilol in Tuesday, for metoprolol in Thursday and for control group in Friday. The duration of beta blocker therapy before the catheterization process was standardized to be between two and four weeks. If the beta blocker group patients haven't been using any beta blocker at the beginning, then suitable therapy following the study protocol was prescribed and the catheterization was performed after two weeks. However, during the enrollment process, if the patients have been using one of the study agent in suitable dosage on condition that it had begun within the last month; they were also enrolled to the study and the catheterization procedure was performed to those when the criteria of being under the beta

blocker therapy for at least two weeks was met. To the control group, catheterization procedure was performed within a week after enrollment.

Definition

In this particular study, the CN is defined as: an increase in the serum creatinine levels of 0.5 mg/dL (44.2 μmol/L) or a 25% increase compared with the basal value over a 48-hour period following the administration of CM when no other viable cause for the higher levels exists (2).

Transthoracic echocardiography

Before the procedure, echocardiographic assessment was performed with the Philips HD11 XE ultrasound system (Philips Healthcare, Andover, MA, USA), and the left ventricular ejection fraction (LVEF) was determined using the modified Simpson's rule. In addition, the creatinine clearance was determined using the Cockroft-Gault formula (13) and the MRS was also calculated for all of the patients prior to the beginning the procedure (5).

Follow-up

The basal serum creatinine levels of the patients were measured at the beginning of the study but before the hydration process and on postprocedural days two and five. The primary endpoint of the study was the development of CN.

Statistical analysis

Descriptive values related to the obtained data were given as mean±standard deviation (SD), number, and frequency. The Kolmogorov-Smirnov test was used to examine whether or not the numerical properties were normally distributed within the groups. For those without normal distribution, the Kruskal-Wallis test was used to compare the four groups, and the Mann-Whitney U test was used to make a comparison between the patients who developed CN and those who did not. Additionally, for the properties that demonstrated normal distribution, single-tail variance analysis and Student's t test were employed to perform comparisons on the same two groups. Furthermore, the relationship between categorical properties, the development of CN, and the beta-blocker groups was examined by an appropriate chi-square analysis, and a binary logistic regression model was used in a pooled analysis to determine which risk factors affected the development of CN. A p value of <0.05 was considered to be statistically significant, and the PASW version 18 statistical software program was used for all calculations.

Results

Two hundred forty seven patients were enrolled to the study, the pateints were randomised to control (n=63), metoprolol (n=68), nebivolol (n=60) and carvedilol groups (n=56). The distribution of the categorical demographic and clinical properties of the patients by all groups along with the comparisons of the differences between the groups are shown in Table 1. We observed that there were significantly more males in the metoprolol group (n=41) than the nebivolol group (n=21), whereas there was no marked difference between genders in the carvedilol group (29 males and 27 females) and control group (39 males, 24 females). Furthermore, the rate of hypertension (HT) was significantly higher (79%) in the metoprolol group than in the nebivolol (55%), carvedilol (59%) and control (59%) groups. Similarly, the presence of hyperlipidemia (HL) was also significantly higher in the metoprolol group (44%) versus the nebivolol (15%), carvedilol (23%) and control (31%) groups. In addition, there were significantly more smokers in the metoprolol group (45%) than the nebivolol (23%) group, but the number of smokers was similar between the metoprolol group and carvedilol group (41.7%). Family history of coronary artery disease (CAD) is higher in the control group as compared with other three groups (30% versus 13% in metoprolol, 5% in nebivolol, and 9% in carvedilol groups). Patients taking oral nitrates are less in the control group compared to other three groups (5% versus 19% in metoprolol, 21% in carvedilol and 15% in nebivolol). In addition patients taking thiazide are higher in the control (20%) and metoprolol (19%) groups as compared to nebivolol (5%) and carvedilol (7%) groups (Table 2). The other categorical properties shown in the Table 1 were observed to have similar rates in the four groups.

Furthermore, no significant differences were found between the groups concerning the distribution of the other drugs used by the patients, such as statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBS), trimetazidine, acetylsalicylic acid, metformin, and insulin (Table 2). There was not any significant diffference between the therapy groups in terms of the duration of beta blocker therapy before the catheterization process (Table 1).

The descriptive values of the numerical demographic and clinical properties by beta-blocker groups along with a comparison of the results between the groups are also shown in Table 1. The mean age of the metoprolol group (59 y) was markedly higher than the carvedilol group (54 y), but this difference was not deemed to be of statistical significance when it was analyzed. However the mean age of the control group (63 y) was significantly higher then other three groups. The differences between the other groups in terms of age were also not statistically significant. The median value of the control (100 mL) and the metoprolol (100 mL) groups were significantly higher compared with the carvedilol group (80 mL) with regard to contrast dosage, but no other significant differences related to this category were seen.

The basal creatinine levels before hydration were significantly higher in control (0.85 mg/dL) and metoprolol groups compared with nebivolol group (0.75 mg/dL). Moreover the creatinine levels on the fifth day were significantly higher in the metoprolol group (0.89 mg/dL) and control group (0.87 mg/dL) compared with those taking nebivolol (0.75 mg/dL) and carvedilol (0.80 mg/dL). But there were no other significant differences with respect to the creatinine levels. In addition, no statistically

Table 1. Distribution and comparative results of the demographic and clinical properties of the groups

Variables	Control (n=63)	Metoprolol (n=68)	Nebivolol (n=60)	Carvedilol (n=56)	*P*
Age, years	63±10*	59±10	58±11	55±10	<0.001
Male gender, n (%)	39 (61.9)	41 (60.3)	21 (35)	29 (51.8)	0.010
Weight, kg	80	82	78	80.5	0.514
	(70-87)	(72.25-87)	(70-86)	(74-90)	
Height, cm,	167	165	163	165	0.049
	(160-175)†	(158-170)	(157-167.75)	(160-171)	
Body mass index, kg/m^2	28.10	30,10	29,70	29,00	0.196
	(25.50-31.60)	(27.73-32.80)	(25.10-33.60)	(26.40-32.58)	
Hypertension, n (%)	37 (58.7)	54 (79.4)	33 (55)	33 (58.9)	0.015
Hyperlipidemia, n (%)	20 (31.7)	30 (44.1)	9 (15)	13 (23.2)	0.002
Diabetes, n (%)	22 (34.9)	19 (27.9)	20 (33.3)	12 (21.4)	0.370
Smoking, n (%)	23 (36.5)	31 (45.6)	14 (23.3)	23 (41.1)	0.061
Familial history, n (%)	19 (30.2)	9 (13.2)	3 (5)	5 (8.9)	<0.001
Ejection fraction, %	56	61	63.5	60	0.008
	(48-65)†	(50-65)	(55-67)	(50-65)	
Mehran risk score	4	3	4	2	0.074
	(1-7)	(1-5)	(1-6)	(1-4)	
Contrast nephropathy, n (%)	5 (7.9)	7 (10.3)	5 (8.3)	2 (3.6)	0.588
Contrast dosage, mL	90	100	100	80	0.004
	(80-180)	(80-150)	(80-100)	(80-100)‡	
Creatinine clearance, mL/min	85.46±19.66	90.21±22.70	94.64±25.98	95.90±24.54	0.059
Beta blocker therapy duration before catheterization, day	-	16 (14-18)	16 (14-18)	16 (14-18)	0.967
Basal creatinine, mg/dL	0.85	0.82	0.75	0.79	0.002
	(0.76-0.98)†	(0.71-1.00)§	(0.69-0.85)	(0.70-0.88)	
Second day creatinine, mg/dL	0.85	0.85	0.81	0.80	0.060
	(0.77-1.10)	(0.72-1.07)	(0.70-0.90)	(0.70-0.94)	
Fifth day creatinine, mg/dL	0.87	0.85	0.75	0.80	<0.001
	(0.79-1.10)*	(0.74-1.00)§	(0.70-0.88)	(0.70-0.90)	
Glucose, mg/dL	105.00	98.00	100.00	98.00	0.700
	(92-151)	(92.25-119.25)	(91-127.50)	(88.50-116.75)	
High density lipoprotein, mg/dL	43.00	38.00	40.00	39.50	0.064
	(37-51)	(32.25-46.75)	(33-48)	(35-46)	
Low density lipoprotein, mg/dL	114.97±33.33	118.43±35.55	115.52±34.33	117.02±40.53	0.948
Triglyceride, mg/dL	142.00	149.50	137.00	157.50	0.816
	(106-192)	(99.00-191.75)	(95.25-177.75)	(97.50-222)	
Hemoglobin, gr/dL	13.00	13.15	12.80	12.75	0.370
	(11.90-14.10)	(12.025-14.275)	(11.85-13.75)	(11.82-14.02)	
Hematocrit, %	38.14±3.96	39.92±4.46	39.10±4.33	38.97±4.75	0.144

*Control group is different from the nebivolol and carvedilol groups.
†There is a statistically significant difference between the control and nebivolol groups.
‡Carvedilol group is different from the control and metoprolol groups.
§Metoprolol and nebivolol groups are different.
The percentage, mean or median values were accepted to be statistically significantly different where p<0.05

Table 2. Data are presented as number (percentage). The percentage values were accepted to be statistically significantly different where p<0.05

Variables	Control (n=63)	Metoprolol (n=68)	Nebivolol (n=60)	Carvedilol (n=56)	*P*
Statin, n (%)	21 (33.3)	35 (51.5)	25 (41.7)	26 (46.4)	0.196
ACEI, n (%)	22 (34.9)	28 (41.2)	16 (26.7)	15 (26.8)	0.237
ARB, n (%)	14 (22.2)	19 (27.9)	14 (23.3)	15 (26.8)	0.860
Thiazide, n (%)	13 (20.6)	13 (19.1)	3 (5)	4 (7.1)	0.016
Trimetazidine, n (%)	0 (0)	4 (5.9)	4 (6.7)	2 (3.6)	0.235
ASA, n (%)	59 (93.7)	63 (92.6)	57 (95)	54 (96.4)	0.845
Klopidogrel, n (%)	19 (30.2)	19 (27.9)	12 (20)	12 (21.4)	0.497
Oral nitrate, n (%)	3 (4.8)	13 (19.1)	9 (15)	12 (21.4)	0.048
Metformin, n (%)	16 (25.4)	11 (16.2)	12 (20)	6 (10.7)	0.202
Insulin, n (%)	5 (7.9)	5 (7.4)	3 (5)	1 (1.8)	0.476

ACEI - angiotensin converting enzyme inhibitors; ARB - angiotensin receptor blockers; ASA - acetylsalicylic

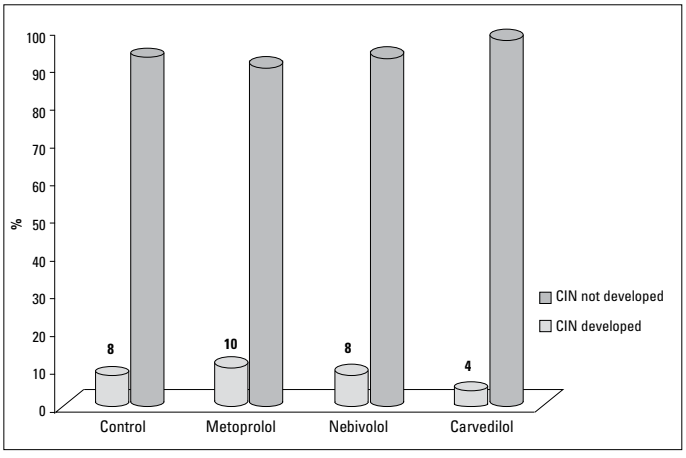

Figure 1. A comparison of three groups in terms of contrast nephropathy and incidence distribution according to the groups
No significant differences was found between the groups in terms of the development of contrast nephropathy (p=0.588)

significant differences were found between the groups in terms of the MRS or any of the other properties in Table 1.

We found that CN developed at a lower rate in the carvedilol group compared with the control, nebivolol and metoprolol groups (4% versus 8%, 8%, and 10%, respectively); however, the difference between the groups did not reach statistical significance (p=0.588). The distribution of the incidence of CN by groups is shown in Figure 1.

The distribution of categorical demographic and clinical properties according to the development of CN and a comparison of the group results are shown in Table 3. We found that the rate of the patients with a positive familial history of CAD was significantly higher in the group who developed CN (30%,) versus those without CN (6%). Clopidogrel usage is also significantly higher in the group who developed CN (47% versus 23%) (Table 4). But no statistically significant correlation was found between the other categorical properties and CN development. In addition, there were also no significant relationships between the other drugs used by the patients and CN development (Table 4).

The descriptive values of the numerical demographic and clinical properties according to the development of CN and a comparison of the results are also shown in Table 3. We observed that the mean age (59 vs. 65) was statistically significantly higher in the group who developed CN. Otherwise, no significant differences were found between the study participants either with or without CN.

To determine the risk factors contributing to the development of CN, we performed multipl stepwise logistic regression analysis including the characteristics defined in Table 3 and Table 4. We did not find relation between total MRS and CN development risk. And among the components of MRS, we only found age to be related to CN risk. We also found that higher levels of triglyceridemia and family history of CAD raise the risk of CN (Table 5). We found that increase in age leads to a 1.081 (95% C.I: 1.027-1.139) fold increase on the development risk of CN. Moreover we found that an increase in triglyceride level leads to a 1.005 (95% C.I: 1.001-1.009) fold increase in risk. We also showed that family history of CAD leads to a 3.159 (95% C.I: 1.065-9.367) fold increase in risk for CN.

Discussion

As far as we know, this is the first study to determine higher levels of triglyceride to be a significant independent risk factor for the development of CN. Moreover, we also found that age and family history of CAD to be independent risk factors for CN. This study is also the first to determine and compare the potential of three different beta blockers utilized for the prevention of CN development. We showed that pre-medication with carvedilol, metoprolol or nebivolol before the procedure, have no significant effect on the development of CN. The differences between the groups regarding CN, did not reach statistical significance.

In a study by Rodriguez et al. (14) they determined that carvedilol successfully prevented the development of cisplatin-induced nephropathy (14). However, beside its theoretical ben-

Table 3. Distribution of the properties of the study population according to the development of contrast nephropathy

	Patients who did not develop contrast nephropathy (n=228)	Patients who developed contrast nephropathy (n=19)	*P*
Age, years	59±10	65±11	0.008
Height, cm	165.00	164.00	0.370
	(160.00-170.00)	(157.00-169.00)	
Weight, kg	80.00	80.00	0.767
	(71.25-88.75)	(71.00-87.00)	
Body mass index, kg/m^2	29.40	29.10	0.798
	(26.20-32.67)	(25-33.10)	
Ejection fraction, %	60.00	52.00	0.089
	(50.00-65.00)	(50.00-62.00)	
Mehran risk score	3.00	5.00	0.072
	(1.00-5.75)	(1.00-7.00)	
Contrast dosage, mL	90.00	100.00	0.103
	(80.00-120.00)	(80.00-240.00)	
Creatinine clearance, mL/min	91.76±23.52	86.57±22.92	0.356
Basal creatinine, mg/dL	0.79	0.85	0.054
	(0.70-0.92)	(0.80-1.09)	
Glucose, mg/dL	100.50	101.00	0.790
	(91.25-128.00)	(95.00-132.00)	
High density lipoprotein, mg/dL	41.00	38.00	0.305
	(34.25-48.00)	(34.00-40.00)	
Low density lipoprotein, mg/dL	116.91±35.22	111.89±41.45	0.557
Tryglyceride, mg/dL	143.00	154.00	0.780
	(99.00-200.50)	(107.00-172.00)	
Hemoglobin, g/dL	13.02±1.71	12.76±1.26	0.524
Waist circumference, cm	102.00	102.00	0.534
	(94.00-112.00)	(84.00-114.00)	
Gensini score	5 (0-22)	24 (6-64.5)	0.020
Male gender, n (%)	118 (51.8)	12 (63.2)	0.473
Diabetes, n (%)	65 (28.5)	8 (42.1)	0.324
Hypertension, n (%)	145 (63.6)	12 (63.2)	1.00
Hyperlipidemia, n (%)	65 (28.5)	7 (36.8)	0.613

*Control group is different from the nebivolol and carvedilol groups. [†]There is a statistically significant difference between the control and nebivolol groups. [‡]Carvedilol group is different from the control and metoprolol groups. [§]Metoprolol and nebivolol groups are different.
The percentage, mean or median values were accepted to be statistically significantly different where p<0.05

eficial effects depending its antioxidant and vazodilatory effects, we failed to show carvedilol to be effective for the prevention of CN. We also failed to demonstrate nebivolol to show any benefit for the prevention of CN. However, in contrast with our findings, it was previously reported by Günebakmaz et al. (15) that nebivolol was effective to prevent CN at a high rate. Moreover, in a study by Avcı et al. (12) nebivolol was also found to be have a higher success rate for the prevention of CN when compared to metoprolol.

We also didn't demonstrate a beta 1-selective adrenoceptor blocking agent metoprolol to be effective for the prevention of CN. Previously it was demonstrated in a study by Çiçek et al. (16) that this agent might decrease OS that developed secondary to coronary angioplasty. However, there are contradictory studies regarding the antioxidant efficiency of metoprolol in the literature (10, 11). Moreover, Módolo et al. (17) discovered that this beta blocker could not protect the kidneys from ischemic episodes in a study performed on dogs. We didn't find significant difference between the beta blocker groups regarding CN however, different dosages of these beta blocker agents other then our study protocol may have differing effect on CN. Moreover, longer durations

Table 4. Distribution of the medications of the study population according to the development of contrast nephropathy

	Patients who did not develop contrast nephropathy (n=228)	Patients who developed contrast nephropathy (n=19)	*P*
Statin, n (%)	96 (42.1)	11 (57.9)	0.274
ACEI, n (%)	74 (32.5)	7 (36.8)	0.891
ARB, n (%)	57 (25)	5 (26.3)	1.00
Thiazide, n (%)	30 (13.2)	3 (15.8)	0.726
Trimetazidine, n (%)	10 (4.4)	0 (0)	1.00
ASA, n (%)	215 (94.3)	18 (94.7)	1.00
Klopidogrel, n (%)	53 (23.2)	9 (47.4)	0.028
Oral nitrate, n (%)	33 (14.5)	4 (21.1)	0.500
Metformin, n (%)	39 (17.1)	6 (31.6)	0.126
Insulin, n (%)	13 (5.7)	1 (5.3)	1.00
Metoprolol, n (%)	61 (26.8)	7 (36.8)	0.497
Nebivolol, n (%)	55 (24.1)	5 (26.3)	0.786
Carvedilol, n (%)	54 (23.7)	2 (10.5)	0.259

The percentage values were accepted to be statistically significantly different where $p<0.05$
ACEI - angiotensin converting enzyme inhibitors; ARB - angiotensin receptor blockers; ASA - acetylsalicylic

of beta blocker therapy before the catheterization procedure may also have the potential to lead different results.

To determine the risk factors contributing to the development of CN, we performed multipl logistic regression analysis including the characteristics defined in Table 3, 4. We did not find relation between total MRS and CN development risk. And among the components of MRS, we only found age to be related to CN risk. However in our present study, because of the study design, patients with decompansated heart failure, who had intra-aortic balloon pump were excluded. Haemodynamically compromised patients were also excluded from the study. These components together constitutes a big place in MRS, and exclusion of these components may have big potential to alter the effeciency of MRS to detect high risk patients for the development of CN.

We also found that higher levels of triglyceride, age and family history of coronary heart disease to raise the risk of CN. Of interest previously Andrade et al. (18) showed that hypercholesterolemia in rats aggravates radiocontrast nephrotoxicity. Later, the study of Yang et al. (19) also confirmed that finding and demonstrated that dietary hypercholesterolemia aggravates contrast media induced nephropathy in rats. Recently same group also showed that rats fed with high cholesterol for 8 weeks have significantly increased ratio of CN (20). They speculated that renal nitric oxid production abnormalities due to high cholesterol level might be associated with CN. In fact there is a growing body of interest on the relation between hyperlipidemia and renal disease. Spencer et al. (21) demonstrated that hyperlipidemia and hyperglycemia act sinergistically to induce renal disease in experimental model of mice. In

Table 5. The results of the analysis of multiple stepwise logistic regression model for the risk factors contributing to the development of contrast nephropathy

			95% C.I for Odds ratio	
	Odss ratio	*P*	Lower	Upper
Age, years	1.081	0.003	1.027	1.139
Tryglyceride, mg/dL	1.005	0.011	1.001	1.009
Family history, positive	3.159	0.038	1.065	9.367
Constant	0.000	0.000		

1999 Massy et al. (22) demonstrated borderline significance of hypertriglyceridemia to be related with the progression of renal disease in chronic renal failure patients. An epidemiologic data from the Physician's Health Study and the Atherosclerosis Risk in Communities Study showed that low levels of high density lipoprotein (HDL) cholesterol levels and hypertryglyceridemia but not increased low density lipoprotein (LDL) cholesterol levels in apparently healthy men independently predict renal dysfunction after a mean follow up 2.9 years (23). Similarly, early treatment diabetic retinopathy study showed that patients who had dyslipidemia at the beginning of study, had higher risk of progression to end-stage renal disease (24).

One suggested mechanism is direct injury of the deposition of lipids and lipoproteins to glomerular and peritubular capillaries through a fenestrated endothelium. Some in vitro studies have demonstrated that phenomenon of entrapment of circulating plasma lipoproteins in the glomeruli (25). Another suggested mechanism is the non-immune glomerular injury through the macrophages. Of interest, the primary role for macrophages as mediators of lipid-induced nephropathy was previously described by Joles et al. (26). Morover the suggested mechanism for the aggravation of CN in the course of hyperlipidemia is renal vasoconstruction. Some micropuncture measurments have shown that hypercholesterolemia in rats induces marked vasoconstruction of renal blood (27). In vitro studies showed that vessels isolated from normal animals exhibit an endothelial dysfunction within a short period of exposure to cholesterol (28). In the course of hyperlipidemia, nitric oxide system is suggested to play major role in the contrast induced nephropathy (20). These findings together constitutes a logical base for the explenation of our results.

We found family history of coronary heart disease to be an independent risk factor for the development of CN. This may take attention to the importance of healthy endothelium for the protection against both CN and CAD. This chronic and acute diseases share the common pathological pathway of endothelial dysfunction. Family history of coronary artery disease may predict the development of CN as it may sign to a tendency for latent generalised endothelial dysfunction including kidneys. Of interest, Uçar et al. (29) demonstrated that increased aortic stiffness, which is accepted to be an indirect marker for endothelial dysfunction, may predict CN development in patients with stable angina pectoris. Moreover, a recent study took attraction to the close relation between the functions of this two organs. Bensal

et al. (30) found that among young and middle-aged adults with cystatin C-derived estimated glomerular filtration rate (eGFR-cys) greater than 60 mL/min/1.73 m^2, annual decline in eGFRcys is an independent risk factor for subsequent coronary artery calcium.

In our study higher levels of triglyceride raised to be novel risk factors for the development of CN. We think it is important as it can be easily modified with the help of lipid lowering drugs or life style changes. We also found that family history of coronary heart disease is also a risk factor for CN, suggesting there may be a genetical tendency for the development of CN.

Study limitations

The major limitation of the current study was the relatively small number of patients. This might have led to fail to demonstrate the difference between the groups by means of CN development. The cross sectional design of the study makes it open to any interactions. The exclusion criterias of the study design prevent generalization of our findings to the rest of population. Beside the randomised fashion of the study, there were significant differences for some characteristics which may have strong potency to influence CN development between the groups: male gender is more frequent in contol and metoprolol, hypertension is more frequent in metoprolol; hyperlipidemia is more frequent in control and metoprolol, age is older in control and metoprolol, EF is lower in control, contrast volume is less in carvedilol. However, there wasn't any significant difference between the groups by means of Mehran score which is evaluating cumulative risk taking lots of variables into consideration together for the development of CN.

Conclusion

We conclude that hypertriglyceridemia appeared to be a risk factor for the development of CN. We failed to demonstrate the efficiency of pre-medication with carvedilol, metoprolol or nebivolol to prevent CN. We believe that the frequency of CN, which can develop after CAG procedures and result in dialysis or mortality, can be decrased by modifying some risk factors such as hypertriglyceridemia.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - Ç.A.; Design - Ç.A.; Supervision - U.E.; Resource - Ç.A.; Materials - A.H.; Data collection &/or processing - C.Z.; Literature search - H.G.; Writing - Ç.A., U.E.; Critical review - T.H.

References

1. Goldfarb S, Mccullough P, Mcdermott J, Gay SB. Contrast-induced acute kidney injury: specialty-specific protocols for interventional radiology, diagnostic computed tomography radiology, and interventional cardiology. Mayo Clin Proc 2009; 84: 170-9. [CrossRef]
2. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. Kidney Int Suppl 2006; 100: S11-5. [CrossRef]
3. McCullough PA, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, et al. CIN Consensus Working Panel. Epidemiology and prognostic implications of contrast-induced nephropathy. Am J Cardiol 2006; 98: 5-13. [CrossRef]
4. Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 2000; 36: 1542-8. [CrossRef]
5. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, et al. A simple risk score for prediction of contrast induced nephropathy after coronary intervention: development and initial validation. J Am Coll Cardiol 2004; 44: 1393-9. [CrossRef]
6. Aydoğdu S. Contrast-induced nephropathy. Turk Kardiyol Dern Ars 2013; 41: 28-30. [CrossRef]
7. Wong PC, Li Z, Guo J, Zhang A. Pathophysiology of contrast-induced nephropathy. Int J Cardiol 2012; 158: 186-92. [CrossRef]
8. Gami AS, Garovic VD. Contrast nephropathy after coronary angiography. Mayo Clin Proc 2004; 79: 211-9. [CrossRef]
9. Oelze M, Daiber A, Brandes RP, Hortmann M, Wenzel P, Hink U, et al. Nebivolol inhibits superoxide formation by NADPH oxidase and endothelial dysfunction in angiotensin II-treated rats. Hypertension 2006; 48: 677-84. [CrossRef]
10. Jenkins RR, Del Signore CM, Sauer P, Skelly C. The effect of beta blocking drugs on lipid peroxidation in rat heart in vitro. Lipids 1992; 27: 539-42. [CrossRef]
11. Liu XK, Engelman RM, Agrawal HR, Das DK. Preservation of membrane phospholipids by propranolol, pindolol, and metoprolol: a novel mechanism of action of beta-blockers. J Mol Cell Cardiol 1991; 23: 1091-100. [CrossRef]
12. Avcı E, Yeşil M, Bayata S, Postacı N, Arıkan E, Cirit M. The role of nebivolol in the prevention of contrast-induced nephropathy in patients with renal dysfunction. Anatol J Cardiol 2011; 11: 613-7.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41. [CrossRef]
14. Rodrigues MA, Rodrigues JL, Martins NM, Barbosa F, Curti C, Santos NA, et al. Carvedilol protects against cisplatin-induced oxidative stress, redox state unbalance and apoptosis in rat kidney mitochondria. Chem Biol Interact 2011; 189: 45-51. [CrossRef]
15. Günebakmaz Ö, Kaya MG, Koç F, Akpek M, Kasapkara A, İnanç MT, et al. Does nebivolol prevent contrast-induced nephropathy in humans. Clin Cardiol 2012; 35: 250-4. [CrossRef]
16. Çiçek D, Tamer L, Pekdemir H, Cin VG, Yıldırım H, Kara AA, et al. Coronary angioplasty induced oxidative stress and its relation with metoprolol use and plasma homocysteine levels.Anatol J Cardiol 2006; 6: 308-13.
17. Módolo NS, Castiglia YM, Ganem EM, Braz JR, Vianna PT, Vane LA. Acute renal ischemia model in dogs: effects of metoprolol. Ren Fail 2001; 23: 1-10. [CrossRef]
18. Andrade L, Campos SB, Seguro AC. Hypercholesterolemia aggravates radiocontrast nephrotoxicity: protective role of L-arginine. Kidney Int 1998; 53: 1736-42. [CrossRef]

19. Yang DW, Jia RH, Yang DP, Ding GH, Huang CX. Dietary hypercholesterolemia aggravates contrast media-induced nephropathy. Chin Med J (Engl) 2004; 117: 542-6.
20. Yang D, Lin S, Yang D, Wei L, Shang W. Effects of short- and long-term hypercholesterolemia on contrast-induced acute kidney injury. Am J Nephrol 2012; 35: 80-9. [CrossRef]
21. Spencer MW, Mühlfeld AS, Segerer S, Hudkins KL, Kirk E, LeBoeuf RC, et al. Hyperglycemia and hyperlipidemia act synergistically to induce renal disease in LDL receptor-deficient BALB mice. Am J Nephrol 2004; 24: 20-31. [CrossRef]
22. Massy ZA, Nguyen Khoa T, Lacour B, Descamps-Latscha B, Man NK, Jungers P. Dyslipidaemia and the progression of renal disease in chronic renal failure patients. Nephrol Dial Transplant 1999; 14: 2392-7. [CrossRef]
23. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kidney Int 2000; 58: 293-301. [CrossRef]
24. Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Report No. 26. Kidney Int 2004; 66: 1173-9. [CrossRef]
25. Schlondorff D. Cellular mechanisms of lipid injury in the glomerulus. Am J Kidney Dis 1993; 22: 72-82. [CrossRef]
26. Joles JA, Kunter U, Janssen U, Kriz W, Rabelink TJ, Koomans HA, et al. Early mechanisms of renal injury in hypercholesterolemic or hypertriglyceridemic rats. J Am Soc Nephrol 2000; 11: 669-83.
27. Kaplan R, Aynedjian HS, Schlondorff D, Bank N. Renal vasoconstriction caused by short-term cholesterol feeding is corrected by thromboxane antagonist or probucol. J Clin Invest 1990; 86: 1707-14. [CrossRef]
28. Cooke JP, Dzau J, Creager A. Endothelial dysfunction in hypercholesterolemia is corrected by L-arginine. Basic Res Cardiol 1991; 86 Suppl 2: 173-81.
29. Uçar H, Gür M, Yıldırım A, Börekçi A, Gözükara MY, Şeker T, et al. Increased Aortic Stiffness Predicts Contrast-Induced Nephropathy in Patients With Stable Coronary Artery Disease Undergoing Percutaneous Coronary Intervention. Angiology 2013 Sep 26 [Epub ahead of print].
30. Bansal N, Vittinghoff E, Peralta CA, Shlipak MG, Grubbs V, Jacobs DR, et al. Estimated kidney function based on serum cystatin C and risk of subsequent coronary artery calcium in young and middle-aged adults with preserved kidney function: results from the CARDIA study. Am J Epidemiol 2013; 178: 410-7. [CrossRef]