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ORIGINAL RESEARCH ARTICLE

Preventing Contrast-Induced Acute Kidney Injury in Egyptian Patients Undergoing Coronary Angiography: A Randomized Controlled Trial

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Abstract

Background and Objectives Contrast-induced acute kidney injury (CI-AKI) observed after coronary angiography (CAG) requires preventive strategies guided by clinical judgment. Evidence is still lacking regarding the prevention of CI-AKI in patients undergoing coronary angiography. This study aimed to compare the effect of a high dose of N-acetylcysteine (NAC) plus preprocedural hydration, a high dose of atorvastatin (HDS) plus preprocedural hydration, or preprocedural hydration alone on the prevention of CI-AKI in patients undergoing elective coronary angiography.

Methods A prospective multi-armed randomized comparative study was conducted on elective patients undergoing CAG. Patients were randomly assigned to either control group [$n = 40$], who received hydration with 0.9% saline started just before contrast media injection and continued for 12 h at a rate 1.0 mL/kg/min after angiography; NAC group [$n = 40$], who received oral NAC 1200 mg daily started 5 days before angiography and good hydration; or HDS group [$n = 40$], receiving one oral dose of atorvastatin 80 mg 24 h before angiography and good hydration. CI-AKI was defined as an increase in serum creatinine of > 25% of baseline or an absolute increase of 0.5 mg/dL above baseline after 48 h. Incidence of CI-AKI and incidence of complications were assessed for all groups.

Results The study included 120 patients. The incidence of CI-AKI was [32.5%] in the control group, [20%] in the NAC group, and [12.5%] in the HDS group. The incidence of CI-AKI was significantly lower in the high-dose statin group compared with the control group (risk ratio = 1.658; 95% CI 1.050–2.433). In-hospital clinical outcomes showed no statistical significance among the three groups.

Conclusions Both NAC and high-dose statins may reduce CI-AKI incidence in patients undergoing CAG, with statins showing more promising results. These findings support prophylactic strategies for CI-AKI prevention in high-risk patients undergoing CAG. In-hospital outcomes were comparable.

Clinical Trial registration Clinical-Trials.gov (ID; NCT06139952, Date; December 2023).

1 Introduction

Contrast-induced acute kidney injury (CI-AKI) is a common and potentially serious complication following percutaneous coronary angiography (CAG), which is a diagnostic procedure used to evaluate the blood flow to the heart [1]. It is defined as an impairment in renal function occurring within 3 days following the intravascular administration of contrast medium [2]. The pathophysiological mechanisms underlying CI-AKI involve hypoxic and toxic injury, characterized by disturbances in renal microcirculation, reduced oxygen delivery to the medulla, and cellular damage mediated by reactive oxygen species [3, 4]. Although CI-AKI is commonly defined as an absolute increase of 0.5 mg/dL or a relative increase of 25% in serum creatinine levels within 48–72 h after contrast exposure, it has been suggested that acute renal failure up to 7 days after contrast exposure should also be considered CI-AKI [5]. Advancements in device technology and antithrombotic strategies have led to more complex patients undergoing CAG, often being discharged within 24–48 h [6]. This makes it seem more practical to evaluate changes in serum creatinine levels during this period after contrast exposure. In addition, an effective method for predicting the risk of CI-AKI post CAG is essential for proper patient management [7].

Sarah Sabry, Mahmoud Taeima, Noha Nassar, Azza ElFiky and Ayman Saleh take full responsibility for all aspects of reliability and freedom from bias of the data presented and their discussed interpretation.

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Key Points

Contrast-induced acute kidney injury is a common renal complication after percutaneous coronary angiography, which occurs within 3 days of contrast medium administration.

There is no consensus on the best approach to prevent contrast-induced acute kidney injury.

This study compared three strategies for contrast-induced acute kidney injury prevention in the coronary angiography patient population at a single institution: hydration alone, hydration combined with oral N-acetyl cysteine, and hydration combined with oral high-dose statin therapy.

High-dose statin therapy showed the greatest reduction in kidney injury risk, suggesting it may be a promising preventive strategy. Larger trials are needed to confirm these findings.

The incidence rates of CI-AKI following CAG range from 2 to 50%, depending on the patient population and the definition of CI-AKI used [8]. The development of CI-AKI is associated with several adverse outcomes, including prolonged hospital stays, increased risk of cardiovascular events, and higher mortality rates [2].

In the literature, factors such as chronic kidney disease, diabetes, hypotension, congestive heart failure, advanced age, and anemia are linked to an increased risk of CI-AKI [9]. Since contrast media is excreted by the kidneys in an unmetabolized form, its clearance can be estimated using creatinine clearance. The relationship between contrast volume and creatinine clearance (CV/CrCl) has been suggested as a substitute measure for the area under the curve of blood contrast media concentration over time [10]. A CV/CrCl > 2.62 threshold was suggested in a study by Tan et al. to be an independent predictor of CI-AKI [11]. A recent study validated that CV/CrCl could be considered a reliable predictor for the development of CI-AKI in patients undergoing CAG [12].

Individual patient risk for CI-AKI after CAG can be assessed with the calculation of a simple risk score on the basis of readily available information [13]. This CI-AKI risk score can be used for both clinical and investigational purposes. Mehran risk score had been validated in a more recent study as a good score for predicting CI-AKI in patients with acute coronary syndrome who underwent CAG [14]. Accordingly, its use is supported in patients hospitalized for acute coronary syndrome to identify those at risk and to optimize CI-AKI prophylactic therapy before and after catheterization [13].

Many reports have demonstrated the protective roles of various agents [15]. Yet, guideline-directed medical therapy remains elusive [16]. So, despite advances in the administration of contrast agents, CI-AKI remains a substantial concern for patients undergoing this procedure.

Adequate preprocedural hydration is the core for the prevention of CI-AKI, and the intravenous hydration with isotonic saline (using 1ml/kg/h) should be started at 4–12 h before contrast exposure to prevent CI-AKI, as recommended by ESUR Contrast Medium Safety Committee guidelines [17].

A variety of strategies have been proposed to reduce the risk of CI-AKI, including the use of lower volumes of contrast media, the use of iso-osmolar or low-osmolar contrast agents, preprocedural hydration, and the use of pharmacological agents such as N-acetylcysteine (NAC), high-dose statins (HDS), and sodium bicarbonate [18–21].

A recent meta-analysis reported that, at high doses, atorvastatin pretreatment, usually using an 80 mg atorvastatin once-dose, was associated with a major reduction in the prevalence of CI-AKI in patients undergoing CAG [22]. So, pretreatment with high-dose atorvastatin could be employed to prevent CI-AKI.

Similarly, a meta-analysis concluded that the use of NAC in patients after angiography was associated with a considerable reduction of CI-AKI. Hence, this may provide a possible strategy to prevent the incidence of CI-AKI [23].

However, there is no consensus on the optimal approach for preventing CI-AKI. Therefore, there is a need to identify effective strategies to prevent or minimize the occurrence of CI-AKI [24].

This has the potential to make a large impact on clinical practice and may lead to the development of evidence-based guidelines for the prevention of CI-AKI in patients undergoing CAG [25]. In turn, this may improve patient outcomes and reduce healthcare costs associated with prolonged hospital stays and increased morbidity and mortality rates.

To address this knowledge gap, our study aims to compare the efficacy and safety of multiple interventions designed to reduce the risk of CI-AKI in Egyptian patients undergoing CAG.

This study was a prospective clinical trial conducted in a CAG Egyptian population. The objective was to compare three preventive strategies: preprocedural hydration alone, hydration combined with oral NAC, and hydration combined with HDS therapy. The primary outcome of the study was the incidence of CI-AKI, and secondary outcomes encompassed a range of clinical events, including the need for intra-aortic balloon pump support, arrhythmias, bleeding, mortality, nonfatal myocardial infarction, target vessel revascularization, stroke, and rehospitalization.

2 Methods

2.1 Study Design

This was a prospective, randomized, multi-armed (three arms), single-blinded (outcome assessor) controlled study conducted on elective patients undergoing CAG at the Cardiovascular Hospital, Ain Shams University (ASU). The study protocol was approved by the Research Ethics Committee for Experimental and Clinical Studies at the Faculty of Pharmacy, ASU. Before participating in the study, written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and was registered at Clinical-Trials.gov (ID: NCT06139952).

2.2 Patients and Methods

All elective patients undergoing CAG presenting to the Cardiovascular Hospital, ASU, from December 2023 to July 2024 were screened for eligibility. Patients were included if they were with isolated CAG and were between 18 and 60 years of age. Exclusion criteria comprised; pregnancy or lactation, renal dysfunction (serum creatinine level of > 2.1 mg/dl), or prior exposure to contrast media within 7 days.

These exclusion criteria (age > 60 years and serum creatinine level > 2.1 mg/dL) allowed patients undergoing CAG with renal function-related factors known to increase CI-AKI to be excluded.

Factors that may increase CI-AKI risk after CAG include (1) patient-related characteristics (i.e., age > 75 years, diabetes mellitus, chronic congestive heart failure, or admission with acute pulmonary edema, hypotension, anemia, and chronic kidney disease); and (2) procedure-related characteristics (i.e., the use of elective intra-aortic balloon pump or increasing volumes of contrast media), and are described in the risk score prediction of contrast-induced acute kidney injury after percutaneous CAG [13, 14].

Eligible patients were randomly assigned to one of the three study arms using a computer-generated randomization sequence. Block randomization with a 1:1:1 allocation ratio was applied to ensure balanced group sizes across the study arms.

The groups included: (1) control group [$n = 40$], received standard hydration with 0.9% saline started just before contrast media injection and continued for 12 h at a rate of 1.0 mL/kg/min after angiography; (2) NAC group [$n = 40$], received oral NAC 1200 mg daily started 5 days before angiography and standard hydration; or (3) HDS group [$n = 40$], receiving one oral dose of atorvastatin 80 mg 24 h before angiography and standard hydration.

Allocation concealment was maintained using sequentially numbered, sealed opaque envelopes, which were opened only at the time of patient enrollment. Randomization was overseen by an independent investigator not involved in patient recruitment or outcome assessment, thereby minimizing selection bias. Participant randomization assignments remained concealed in sealed envelopes. Owing to the nature of the interventions (oral pharmacological agents versus hydration alone), blinding of participants and treating clinicians was not feasible. Outcome assessors were independent and blinded to group allocation to minimize bias.

Patient's demographic information (age, sex, body mass index, smoking status), laboratory data (liver and kidney function tests, blood cell count, lipid levels), along with comorbid diseases, allergies, and medication were all collected from the patient record file using a predesigned follow-up sheet.

A flow diagram to illustrate patient recruitment, randomization, and follow-up is presented in Fig. 1.

2.3 Follow-up and End Points

All patients were followed for a minimum of 4 consecutive days. According to the routine practice of our institution, follow-up was scheduled daily. Patients' data were collected at baseline and at follow-up time points. Prescription and administration of interventions were made accordingly by the attending physician together with the clinical pharmacist responsible. The contrast agent used was Ioxitalamic acid (brand name Telebrix® 350mg I/mL) as an iodinated contrast medium for x-ray imaging. The primary outcome was the incidence of CI-AKI defined as an absolute increase of 0.5 mg/dL or a relative increase of 25% in serum creatinine levels within 48–72 h after contrast exposure [1, 8].

The CV/CrCl is an index recommended to quantify the contrast volume administered during interventional procedures to predict the risk of acute kidney injury [26].

In addition, secondary outcomes included the occurrence of any in-hospital clinical event during the follow up period. These include the use of an intra-aortic balloon pump, occurrence of arrhythmia, bleeding, mortality, non-fatal myocardial infarction, target vessel revascularization, stroke, and rehospitalization [27].

2.4 Statistical Analysis

Sample size was calculated using the PASS 15 software program (NCSS, LLC, Kaysville, Utah, USA), setting the type-1 error (α) at 0.05 and the power at 80%. Results from previous studies by Thayseen et al, Bidram et al, and

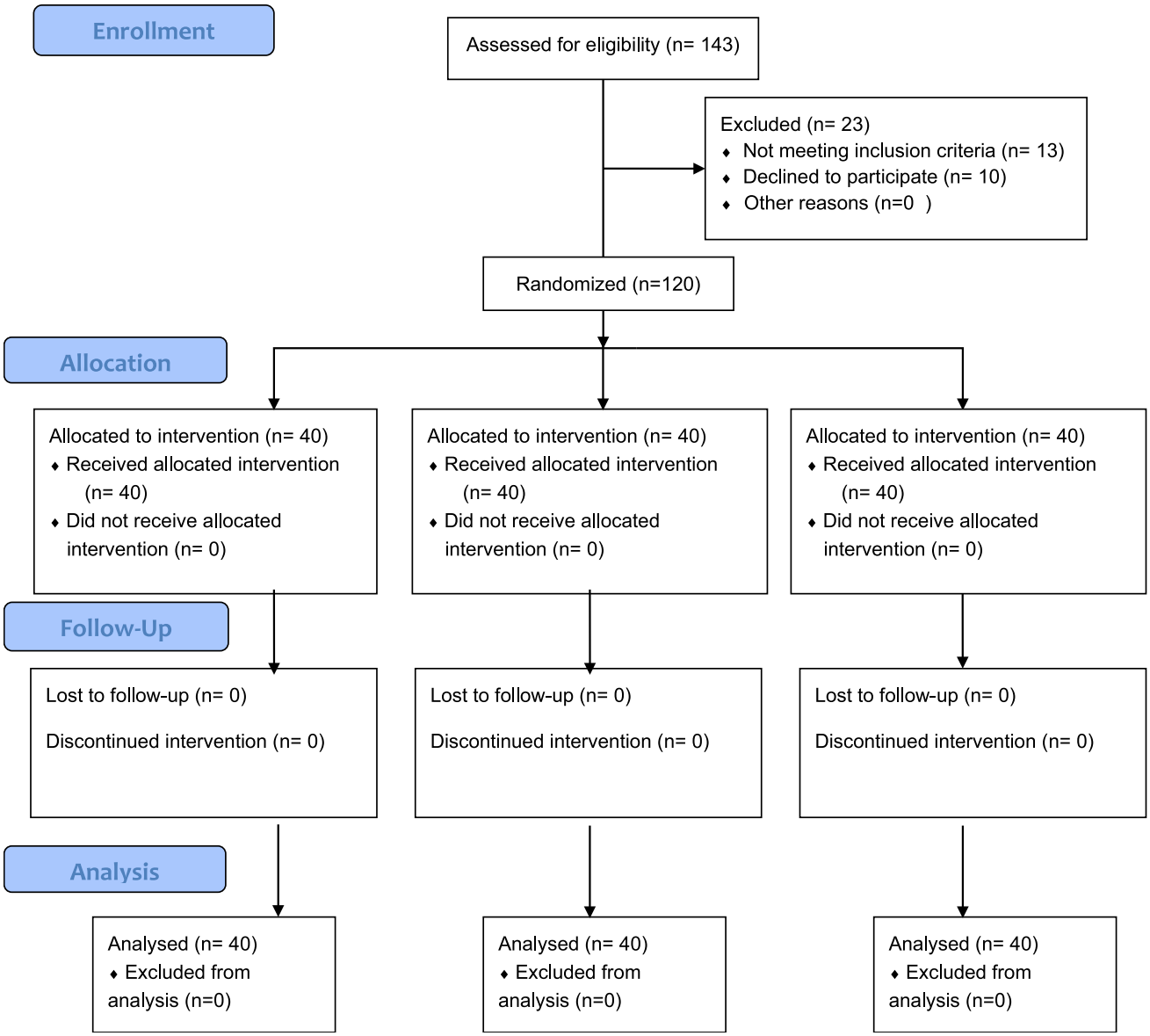

Fig. 1 Enrollment, and data collection (CONSORT 2010 flow diagram)

Wu et al, showed that the expected incidence of CI-AKI in the control group is 55%, in the NAC group is 20% and in the high-dose atorvastatin group is 1% [28–30]. Calculations according to these values produced a sample size of 40 cases per group (120 total), considering a 20% dropout rate. This dropout rate was assumed to account for potential losses to follow-up, incomplete data collection, and protocol deviations, which are commonly observed in prospective interventional studies conducted in routine clinical settings and in comparable studies involving elective patients undergoing CAG. This was made to ensure adequate statistical power for the final analysis despite anticipated attrition.

GraphPad Prism software, version 9.0 (GraphPad Software, Boston, MA, USA), was used for statistical analysis. Results were presented as numbers and proportions (categorical), median and interquartile range (IQR) (nonparametric) or mean and standard deviation (parametric), as appropriate. The data were tested for normality using the Shapiro–Wilk and Kolmogorov–Smirnov tests and comparisons were assessed using the chi-square test, Kruskal–Wallis, or one-way analysis of variance (ANOVA), as appropriate. A p value < 0.05 was considered statistically significant.

3 Results

From December 2023 to July 2024, out of a total of 143 elective patients undergoing CAG screened, only 120 patients fulfilled the inclusion criteria and were recruited. The analysis included all randomized patients.

The clinical principal investigator was responsible for generating the allocation sequence, participants' enrollment, and randomly assigning participants to interventions.

3.1 Patient Characteristics

A total of 120 individuals (74 males and 46 females) were included in this study. Baseline characteristics and demographics were comparable between groups. There were no allergies observed in the groups.

Baseline laboratory values were also comparable between groups, but some showed substantial differences between groups, such as serum hemoglobin, serum creatinine, creatinine clearance, uric acid, and white blood cell count. Yet, these values were all within normal ranges.

The identified comorbidities included hypertension, diabetes, hyperlipidemia, hypothyroidism, atrial fibrillation, and rheumatic heart disease. The Mehran Risk scores evaluated in patients were comparable across the three groups. All medications administered were comparable between groups. Patients' demographics, baseline characteristics, and comedications are presented in

Table 1.

3.2 Angiographic and Procedural Characteristics

The median number of stents used was comparable across all groups. The median contrast volume used was similar in the Control and NAC groups (200 mL, IQR 170–220) and slightly higher in the HDS group (215 mL, IQR 180–240), but this difference was not statistically significant ($p = 0.462$).

However, the CV/CrCl ratio showed significant differences among the groups. The median CV/CrCl was lowest in the control group (1.747, IQR 1.302–2.516), followed by the NAC group (2.069, IQR 1.720–8.833), and highest in the HDS group (2.422, IQR 1.676–3.080) ($p = 0.018$). Pairwise comparisons revealed significant differences between control and NAC groups ($p = 0.0315$) and between control and HDS groups ($p = 0.0085$), but not between NAC and HDS groups ($p = 0.4594$).

The proportion of patients with a CV/CrCl ratio > 2.62 also differed significantly among the groups ($p = 0.014$). This proportion was lowest in the control group (15%), followed by the NAC group (30%), and highest in the HDS group (45%). Pairwise comparison showed a significant difference between control and HDS groups ($p = 0.007$), but not between control and NAC groups ($p = 0.18$) or NAC and HDS groups ($p = 0.248$). The angiographic and procedural characteristics are listed in Table 2.

3.3 Incidence of CI-AKI

At the end of the follow-up period, out of the 120 patients, a total of 26 (21.6%) patients developed CI-AKI. A comparison between groups indicated that the control group patients showed a higher incidence of CI-AKI, compared with the NAC group and the HDS group patients (13 (32.5%), eight (20%), and five (12.5%) respectively. The overall difference between the three groups approached statistical significance ($p = 0.09$). Further pairwise comparisons revealed a statistically significant difference in CI-AKI incidence between the control and HDS groups (32.5% versus 12.5%, $p = 0.005$). However, the differences between the control and NAC groups ($p = 0.064$) and between NAC and HDS groups ($p = 0.546$) were not statistically significant. These results suggest that adding HDS may be effective in reducing the incidence of CI-AKI compared with the control, while the effect of NAC is less pronounced. The incidence of CI-AKI in groups is presented in Table 3.

3.4 In-Hospital Outcomes

Various in-hospital clinical outcomes were assessed, including the use of an intra-aortic balloon pump, occurrence of arrhythmia, bleeding, mortality, nonfatal myocardial infarction, target vessel revascularization, stroke, and rehospitalization. None of these clinical outcomes showed statistically significant differences among the three groups, ($p > 0.05$ for all). In-hospital outcomes are presented in Table 4.

In summary, this study found that using HDS markedly reduced the incidence of CI-AKI compared with the control group, while the effect of NAC was less pronounced.

4 Discussion

This study aimed to compare the effectiveness of NAC and HDS against a control group in reducing the occurrence of CI-AKI in patients undergoing percutaneous CAG. Our findings provide valuable insights into the prevention of CI-AKI and contribute to the ongoing debate about optimal prophylactic strategies.

Our study found an overall CI-AKI incidence of 21.6%, with notable variations among the groups (Control: 32.5%, NAC: 20%, HDS: 12.5%). This overall incidence falls within the range previously reported, which may occur in 11–40% of patients [31]. The relatively high incidence in our control group, despite receiving adequate periprocedural hydration, underscores the

Table 1 Patients' demographics, baseline characteristics, and comedications

Parameter	Control ($n = 40$)	NAC ($n = 40$)	HDS ($n = 40$)	p value
Demographic				
Sex, male, n (%)[$]	29 (72.50)	24 (60)	21 (52.50)	0.178
Age, median (IQR)[#]	49 (46.25–53.25)	50 (37.75–55.00)	51 (43.25–56.75)	0.456
Height, mean ± SD[!]	170.8 ± 8.046	167.5 ± 8773	167.4 ± 8.894	0.131
Weight, mean ± SD[!]	79.88 ± 11.56	81.88 ± 10.47	80.40 ± 13.21	0.735
BMI, median (IQR)[#]	27.39 (24.99–29.66)	28.66 (26.41–30.70)	28.26 (25.79–31.15)	0.103
Allergy, n (%)[$]	0 (0)	0 (0)	0 (0)	–
Baseline laboratory				
CRP, median (IQR)[#]	20.75 (14.83–27)	19.0 (14.18–30.85)	18.50 (11.78–25.88)	0.442
Hb g/dl, median (IQR)[#]	13.90 (12.0–15.28)	12.0 (11.20–13.35)	12.0 (10.93–13.88)	0.003*
Hematocrit %, median (IQR)[#]	42.05 (38.65–45.73)	41.0 (38.38–46.93)	42.40 (38.33–46.60)	0.942
INR, median (IQR)[#]	1.010 (1.0–1.050)	1.020 (0.9925–1.070)	1.020 (1.00–1.095)	0.584
Platelet*1000/μL, mean ± SD[!]	386.1 ± 56.19	387.3 ± 61.34	385.4 ± 60.59	0.989
ALT IU/L 56 (SGPT), median (IQR)[#]	22.50 (15.25–27.75)	22 (17.0–27.0)	25.0 (19.00–28.00)	0.361
AST IU/L 40 (SGOT), median (IQR)[#]	24.0 (20.25–30.75)	22.50 (18.0–28.75)	27.0 (17.50–33.75)	0.305
HDL 35 to 90 mg/dL, median (IQR)[#]	54.50 (41.25–70.75)	49.50 (37.50–64.75)	54.50 (38.25–65.25)	0.501
LDL, mean ± SD[!]	135.1 ± 27.18	134.6 ± 27.14	134.7 ± 25.37	0.995
Total Cholesterol, mean ± SD[!]	192.6 ± 34.85	194.4 ± 35.50	194.8 ± 29.51	0.465
S.Cr mg/dL, median (IQR)[#]	0.9 (0.7–1.275)	1.10 (1.00–1.475)	1.075 (1.00–1.300)	0.011*
Cr Cl mL/min, mean ± SD[!]	119.7 ± 58.21	94.48 ± 28.73	92.96 ± 31.89	0.007*
BUN, median (IQR)[#]	18 (10.25–22.00)	16.5 (12.25–26.00)	17.5 (11.00–25.00)	0.777
WBC*1000 cells/mm^3, median (IQR)[#]	10.8 (7.625–14.78)	8.45 (6.175–10.40)	8.75 (6.050–11.20)	0.004*
Uric acid, median (IQR)[#]	4.6 (3.40–5.775)	5.45 (4.40–6.50)	5.5 (4.00–7.00)	0.031*
Blood Glucose, median (IQR)[#]	114.5 (86.50–144.50)	101 (83.00–135.00)	109 (94.00–127.00)	0.860
Comorbidities				
Diabetes mellitus, n (%)[$]	12 (30)	10 (25)	13 (32.5)	0.754
Hypertension, n (%)[$]	18 (45)	21 (52.5)	19 (47.5)	0.792
Hypothyroidism, n (%)[$]	3 (7.5)	2 (5)	3 (7.5)	0.875
Hyperlipidemia, n (%)[$]	5 (12.5)	8 (20)	6 (15)	0.646
Smoking, n (%)[$]	16 (40)	16 (40)	15 (37.5)	0.966
Previous CABG, n (%)[$]	0 (0)	0 (0)	0 (0)	–
Previous MI, n (%)[$]	2 (5)	3 (7.5)	3 (7.5)	0.875
CHF, n (%)[$]	11 (27.5)	10 (25)	14 (35)	0.592
AF, n (%)[$]	4 (10)	6 (15)	3 (7.5)	0.547
Total number of comorbidities, median (IQR)[#]	2 (1-2)	2 (1–2)	2 (1-2)	0.978
Mehran's score, median (IQR)[#]	7.1 (2.125–9.7)	7.1 (4.1–10)	7.4 (4.725–9.650)	0.592
Coadministered medications				
Calcium channel blockers, n (%)[$]	5 (12.5)	3 (7.5)	2 (5)	0.466
Statins, n (%)[$]	5 (12.5)	8 (20)	6 (15)	0.646
Oral antidiabetics, n (%)[$]	12 (30)	10 (25)	13 (32.5)	0.754
Insulin, n (%)[$]	2 (5)	3 (7.5)	3 (7.5)	0.875
Diuretics, n (%)[$]	11 (27.5)	10 (25)	14 (35)	0.946
Nitrates, n (%)[$]	4 (10)	1 (2.5)	5 (12.5)	0.242
Throid replacement therapy, n (%)[$]	3 (7.5)	2 (5)	3 (7.5)	0.875
ACEI, n (%)[$]	16 (40)	13 (32.5)	14 (35)	0.776
ARB, n (%)[$]	7 (17.5)	5 (12.5)	9 (22.5)	0.500
β-blockers, n (%)[$]	12 (30)	13 (32.5)	12 (30)	0.962
PPI, n (%)[$]	16 (40)	14 (35)	14 (35)	0.866
Other antiarrhythmics, n (%)[$]	6 (15)	6 (15)	7 (17.5)	0.939

Table 1 (continued)

Parameter	Control ($n = 40$)	NAC ($n = 40$)	HDS ($n = 40$)	p value
Aspirin, n (%)[$]	15 (15)	14 (35)	16 (40)	0.899
Clopidogrel, n (%)[$]	2 (5)	3 (7.5)	3 (7.5)	0.875
Total number of drugs, median (IQR)[#]	3 (1–4)	2 (1–4.750)	3 (1–5)	0.604

BMI body mass index, *CIN* contrast-induced nephropathy, *CRP* C-reactive protein, *Hb* hemoglobin, *INR* international normalized ratio, *AST* aspartate transaminase, *ALT* alanine transaminase, *HD* high-density lipoprotein, *LDL* low-density lipoprotein, *S.Cr* serum creatinine, *Cr Cl* creatinine clearance, *BUN* blood urea nitrogen, *WBC* white blood cells, *CABG* coronary artery bypass grafting, *MI* myocardial infarction, *CHF* congestive heart failure, *AF* atrial fibrillation, *V/CrCl* contrast volume:creatinine clearance ratio, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *PPI* proton-pump inhibitor

*Statistically significant

[$]Chi square

[!]One way ANOVA

[#]Kruskal–Wallis

Table 2 Angiographic and procedural characteristics

Parameter	Control ($n = 40$)	NAC ($n = 40$)	HDS ($n = 40$)	p value
No. of stents (median, IQR)	1 (1–1)	1 (1–1)	1 (1–1)	0.676[#]
Contrast volume (median, IQR)	200 (170–220)	200 (170–220)	215 (180–240)	0.462[#]
Contrast volume/Creatinine clearance ratio (V/CrCl) (median, IQR)	1.747 (1.302–2.516)	2.069 (1.720–8.833)	2.422 (1.676–3.080)	0.018*[#]
	1.747 (1.302–2.516)	2.069 (1.720–8.833)		0.0315*[$]
		2.069 (1.720–8.833)	2.422 (1.676–3.080)	0.4594[$]
	1.747 (1.302–2.516)		2.422 (1.676–3.080)	0.008*[$]
V/CrCl>2.62 (n, %)	6 (15)	12 (30)	18 (45)	0.014*[%]
	6 (15)	12 (30)		0.18[!]
		12 (30)	18 (45)	0.248[!]
	6 (15)		18 (45)	0.007*[!]

NAC N-Acetylcysteine group, *HDS* high dose of atorvastatin group, *IQR* interquartile range, *V/CrCl* contrast volume:creatinine clearance ratio

*Statistically significant

[#]Kruskal–Wallis

[$]Mann Whitney *U*

[%]Chi square

[!]Fisher's exact

Table 3. Incidence of contrast induced acute kidney injury

Parameter	Control ($n = 40$)	NAC ($n = 40$)	HDS ($n = 40$)	p value	Effect size (95% CI)
CI-AKI (n, %)	13 (32.5)	8 (20)	5 (12.5)	0.09[#]	
	13 (32.5)	8 (20)		0.064[$]	1.353 (0.835–2.037)
	13 (32.5)		5 (12.5)	0.005*[$]	1.658 (1.050–2.433)
		8 (20)	5 (12.5)	0.546[$]	

NAC N-Acetylcysteine group, *HDS* high dose of atorvastatin group, *CI-AKI* contrast-induced acute kidney injury

*Statistically significant

[#]Chi-square

[$]Fisher's exact

Table 4. In-hospital clinical outcomes

Parameter	Control ($n = 40$)	NAC ($n = 40$)	HDS ($n = 40$)	p value	Effect size (95% CI) Control versus NAC	Effect size (95% CI) Control versus HDS
Intra-aortic balloon pump, n (%)[$]	6 (15)	5 (12.5)	6 (15)	0.934	1.107 (0.549–1.777)	1.000 (0.491–1.645)
Arrhythmia, n (%)[$]	2 (5)	3 (7.5)	3 (7.5)	0.875	0.790 (0.229–1.626)	0.790 (0.229–1.626)
Bleeding, n (%)[$]	3 (7.5)	4 (10)	4 (10)	0.905	0.846 (0.306–1.593)	0.846 (0.306-1.593)
Mortality, n (%)[$]	2 (5)	1 (2.5)	1 (2.5)	0.772	1.351 (0.414–2.147)	1.351 (0.414–2.147)
Nonfatal myocardial infarction, n (%)[$]	0 (0)	1 (2.5)	1 (2.5)	0.601	0.000 (0.000–1.628)	0.000 (0.000–1.628)
Target vessel revascularization, n (%)[$]	1 (2.5)	0 (0)	1 (2.5)	0.601	2.026 (0.414–5.065)	1.000 (0.187–1.973)
Stroke, n (%)[$]	1 (2.5)	1 (2.5)	2 (5)	0.772	1.000 (0.187–1.973)	0.658 (0.120–1.661)
Rehospitalization, n (%)[$]	1 (2.5)	1 (2.5)	2 (5)	0.772	1.000 (0.1873–1.973)	0.658 (0.120–1.661)

NAC N-Acetylcysteine group, *HDS* high dose of atorvastatin group

[$]Chi square

substantial risk of CI-AKI in patients undergoing CAG and highlights the importance of effective preventive strategies.

Our results showed a reduction in CI-AKI incidence with NAC (20%) compared with the control group (20%, 32.5%, $p = 0.064$). Yet, this reduction did not reach a statistical difference. However, this finding contributes to the ongoing debate about the efficacy of NAC in preventing CI-AKI. While our results suggest a potential benefit, they contrast with the findings of the large-scale ACT trial, which found no extensive benefit of NAC in preventing CI-AKI [32]. However, our findings align more closely with the meta-analysis by Subramaniam et al. (2016), which suggested a potential benefit of NAC [33], particularly in high-risk patients. The discrepancies in these findings might be attributed to differences in patient risk profiles, NAC dosing regimens, or timing of administration. Our study adds to this body of evidence and suggests that NAC may have a role in CI-AKI prevention. However, additional research is warranted to better define the extent of its protective effect and to establish the optimal dosing regimen required to achieve this benefit.

While the pairwise comparison between the control and HDS groups showed a statistically significant reduction in CI-AKI incidence, the overall comparison among the three groups did not reach significance. Therefore, these findings should be interpreted cautiously, considering the sample size and study design. The major finding of our study was the lowest CI-AKI incidence observed in the HDS group (12.5%). This result aligns with and extends the findings of previous studies on high-dose statin pretreatment. For instance, the PRATO-ACS study demonstrated that high-dose rosuvastatin strongly reduced the risk of CI-AKI in acute coronary syndrome patients [34]. Similarly, a meta-analysis confirmed the protective effect of short-term high-dose statin pretreatment in high-risk patients, such as chronic kidney disease and diabetes patients [35]. Our findings provide further evidence supporting the use of high-dose statins as a preventive strategy against CI-AKI in patients undergoing CAG regardless of the patient's risk.

Interestingly, our study found higher CV/CrCl in the intervention groups, particularly in the HDS group, despite their lower CI-AKI incidence. This observation seems to contradict the established understanding that higher contrast volume increases CI-AKI risk, as demonstrated by Mehran et al. [13]. This could be explained by the possibility that the protective effects of NAC and HDS are robust enough to mitigate the increased risk associated with higher contrast volumes. This finding highlights the complex interplay between contrast volume, preventive interventions, and CI-AKI risk, suggesting that effective prophylaxis may allow for the use of a bit higher contrast volumes, if needed, without increasing CI-AKI risk.

Our study found no substantial differences in in-hospital clinical outcomes among the groups, despite the variations in CI-AKI incidence. This finding is consistent with the results of the PRESERVE trial, which also found no extensive difference in adverse clinical outcomes despite interventions to prevent CI-AKI [36]. While the reduction in CI-AKI incidence is a positive finding, the lack of difference in short-term clinical outcomes raises questions about the immediate clinical significance of CI-AKI prevention strategies. However, it's important to note that our study was not powered to detect differences in these secondary outcomes, and longer-term follow-up may be necessary to observe potential clinical benefits.

The protective effects of NAC and HDS observed in our study can be explained by their proposed mechanisms of action. NAC is thought to prevent CI-AKI through its antioxidant properties and by improving renal hemodynamics [37]. High-dose statins, on the other hand, are believed to exert their protective effects through antiinflammatory and antioxidant actions, as well as by improving endothelial function [38]. The superior protection observed with HDS in our study suggests that the pleiotropic effects of statins may be particularly effective in preventing CI-AKI.

Beyond statins and NAC, several other agents have been investigated for their potential role in CI-AKI prevention.

Agents such as ascorbic acid, probucol, melatonin, and allopurinol have been evaluated in different patient populations, with varying degrees of success in reducing oxidative stress and improving renal outcomes [15, 39, 40]. While some trials demonstrated modest protective effects, others reported no considerable benefit [41, 42]. Taken together, these mixed results highlight the complexity of CI-AKI pathophysiology and suggest that while antioxidant strategies hold promise, their clinical utility remains uncertain. Continued investigation is needed to identify the most effective agents, optimal dosing regimens, and patient populations that may derive the greatest benefit.

Our findings have several implications for clinical practice. The marked reduction in CI-AKI incidence with HDS pretreatment suggests that this could warrant further investigation as a potential preventive approach in patients undergoing CAG. Although the study findings are encouraging, they are preliminary and should not be used to guide clinical practice at this stage. Therefore, the choice of preventive strategy should be tailored to individual patient characteristics and risk factors. The Mehran risk score could be a useful tool for risk stratification and guiding preventive measures [13]. In addition, our findings suggest that effective prophylaxis may allow for the use of higher contrast volumes, when necessary, without substantially increasing CI-AKI risk.

5 Limitations and Future Directions

While our study provides valuable insights, it has several limitations. The sample size, although adequately powered for our primary outcome, was relatively small. Larger, multicenter randomized controlled trials are needed to confirm these findings and provide more definitive evidence. This study focused on clinical outcomes without incorporating correlated kidney injury biomarkers. So, future studies should integrate biomarker testing to provide deeper insights into CI-AKI development. In addition, our study focused on short-term outcomes, and long-term follow-up would be valuable to assess the potential impact of CI-AKI prevention on long-term renal function and cardiovascular outcomes. Future studies should also explore the potential benefits of combination therapy (e.g., NAC + HDS) and investigate a wider range of medications and doses for CI-AKI prophylaxis.

6 Conclusions

Our study demonstrates that both NAC and high-dose statin interventions may effectively reduce CI-AKI incidence in patients undergoing CAG, with high-dose statins showing particularly promising results. Interestingly, both interventions were associated with higher contrast volume ratios and a greater proportion of patients with CV/CrCl ratio > 2.62, particularly in the HDS group. Despite this, they showed the lowest incidence of CI-AKI, with no substantial variations in in-hospital clinical outcomes among the groups. These findings suggest that HDS intervention may offer protective effects against CI-AKI, even with higher contrast use, without increasing the risk of adverse clinical outcomes.

These findings contribute to the growing body of evidence that requires confirmation in larger trials for CI-AKI prevention in high-risk patients undergoing CAG. While the immediate clinical impact, as measured by in-hospital outcomes, was not significant, the reduction in CI-AKI incidence is an important finding that warrants further investigation. As we continue to refine our understanding of CI-AKI prevention, personalized prophylactic strategies based on individual patient risk factors may become an integral part of care for patients undergoing contrast-enhanced procedures.

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Declarations

Authors' contribution All authors contributed to the study's conception and design. Patients' data collection and monitoring were performed by Sarah Sabry. The analysis was performed by Mai Khaled and Mahmoud Taeima. The first draft of the manuscript was written by Sarah Sabry and Noha Nassar, Azza ElFiky, and Ayman Saleh edited and revised previous versions of the manuscript. All authors read and approved the final version and agree to be accountable for the work.

Availability of data and material The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Conflict of interest Authors have no conflicts of interest to declare that are relevant to the content of this article. All authors certify that they are not involved in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki and was registered at Clinical-Trials.gov (ID: NCT06139952). The study protocol was approved by the Research Ethics Committee for Experimental and Clinical Studies at the Faculty of Medicine, Ain Shams University. (Ethics approval number: Ph.D. (No. 51), 8 October 2017).

Consent to participate Written informed consent was obtained from all participants before they participated in the study.

Consent for publication Written informed consent was obtained from each participant by a signed declaration.

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