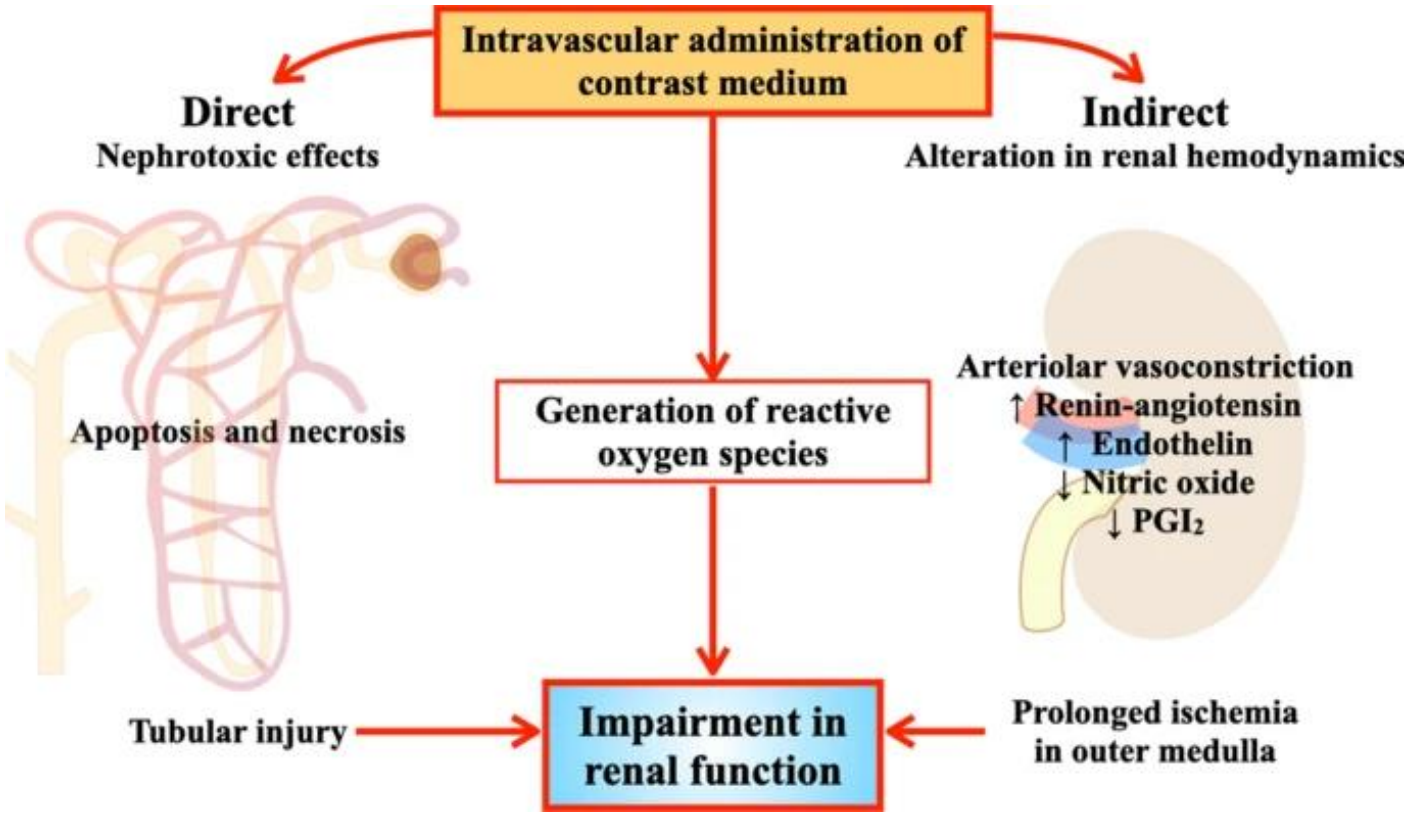
The 12th National Congress of Nephrology-Critical Care Nephrology (NIrSn)
9-11 October 2024
Zanjan, Iran

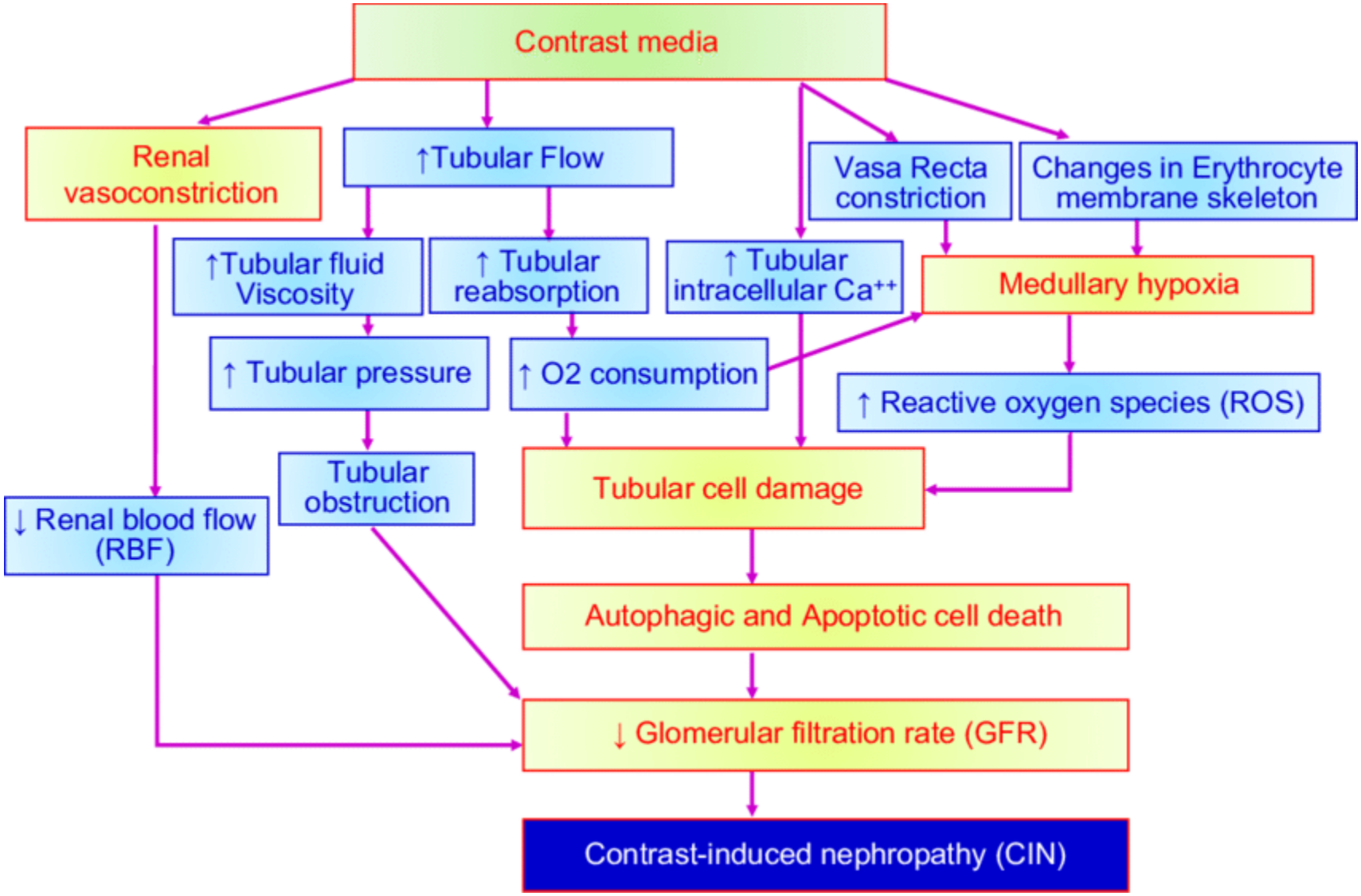
Effectiveness of Edaravone in preventing contrast-induced nephropathy in high-risk patients undergoing coronary angiography: A randomized, double-blind trial

Professor Mohammadreza Ardalan
Professor of Nephrology
Fellowship of Renal Transplant Immunology
Email: **ardalan34@yahoo.com**

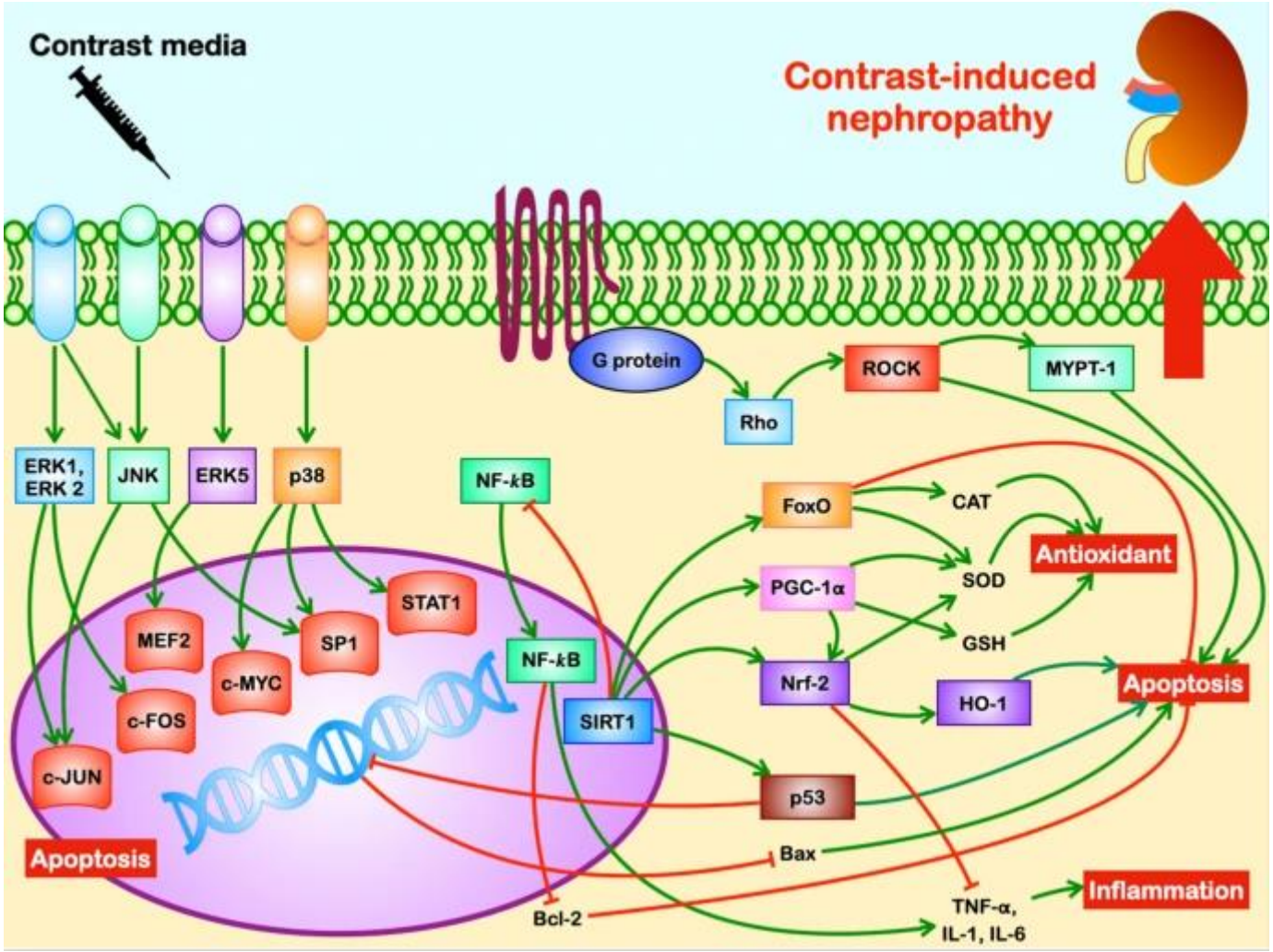
Introduction

Contrast-induced nephropathy (CIN) or acute kidney injury (CI-AKI) can occur after the administration of contrast media for therapeutic angiographic intervention or intravascular diagnostic procedures.




Contrast media
Renal vasoconstriction
↑Tubular Flow
Vasa Recta constriction
Changes in Erythrocyte membrane skeleton
↑Tubular fluid Viscosity
↑ Tubular reabsorption
↑ Tubular intracellular Ca++
Medullary hypoxia
↑ Tubular pressure
↑ O2 consumption
↑ Reactive oxygen species (ROS)
Tubular obstruction
Tubular cell damage
↓ Renal blood flow (RBF)
Autophagic and Apoptotic cell death
↓ Glomerular filtration rate (GFR)
Contrast-induced nephropathy (CIN)

Mechanism of CIN via complex pathways of ROS

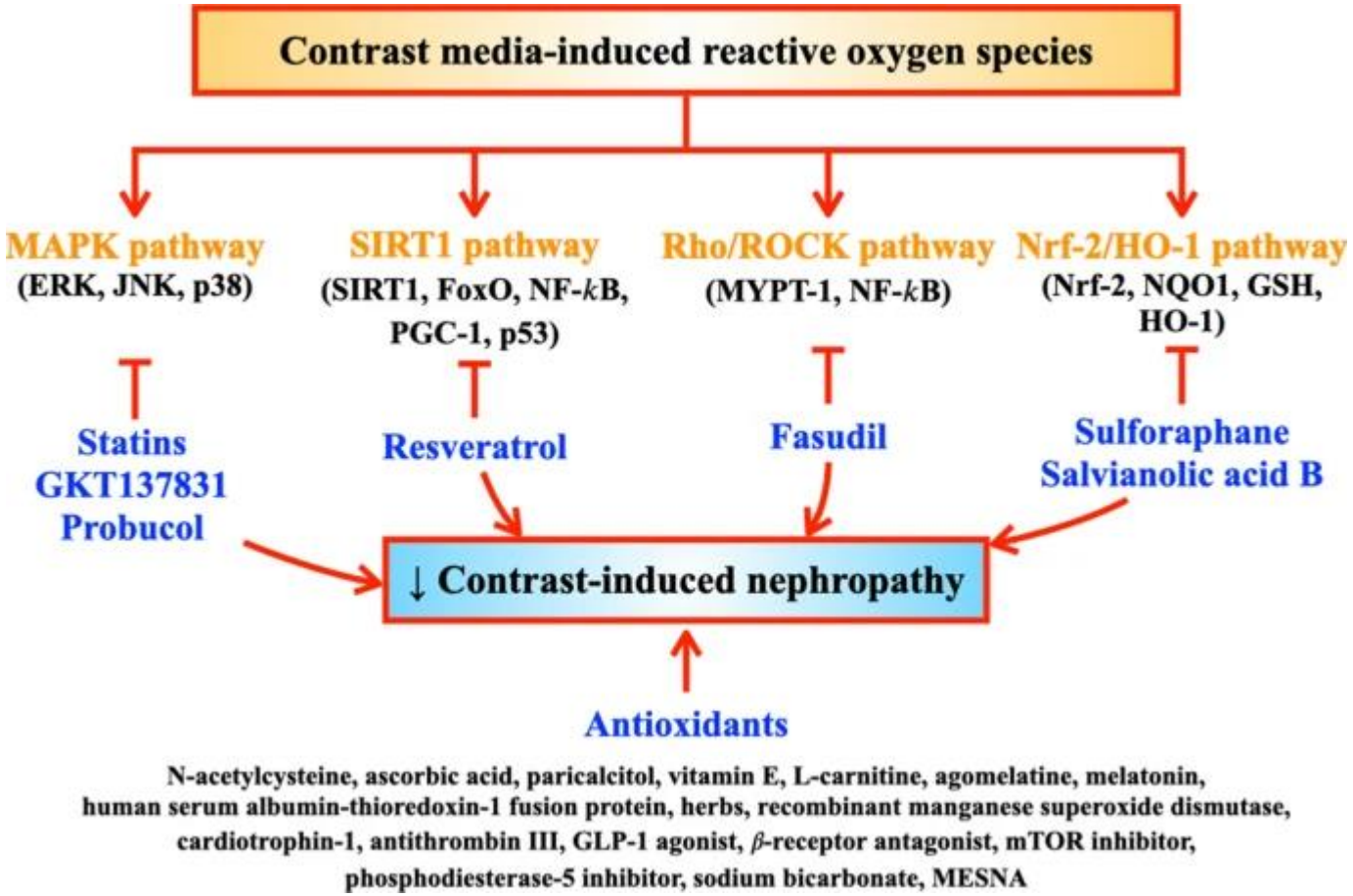


- The main molecular mechanisms that might be complicated in this process are the mitochondrial impairment and alteration/shifting of cellular metabolites (e.g., acetyl-CoA and NAD^+/NADH) acting as cofactors to alter the activities of many enzymes, for instance, sirtuins.
  - Ardalan et alJournal of cellular physiology 2020

- Moreover, alteration of mitochondrial structure over the fusion and fission mechanisms can regulate cellular signaling pathways by modifying the rate of reactive oxygen species generation and metabolic activities.

Ardalan et al Journal of cellular physiology 2020

Intervention to reduce ROS for the prevention of CIN



Edaravone
Alsava

- A free-radical scavenger
- Reduces oxidative stress
- Prevents cellular damage caused by ROS.
- Exhibits the ability to safeguard organs against inflammation, radiation, and ischemia–reperfusion injury.

- In animal models, pre-treatment with edaravone has been shown to attenuate renal injury and histologic changes after contrast administration via increasing renal antioxidant capacity

Ardalan et al unpublished work

- This single-center double-blind randomized controlled trial study aimed to determine the effect of Alsava as an antioxidant in high-risk patients undergoing coronary angiography.
-

- Ardalan et al Pharma Res Prespect 2024

Aim of study

- Participants were recruited from Shahid Madani Heart Hospital in Tabriz, Iran, between June 2021 and November 2022.

The primary outcome measure was the onset of CIN, defined as a 25% increase in serum creatinine levels 120 h after administration of contrast media.

methods

Eligible candidates for the study included patients with CKD at Stages 3a, 3b, and 4
or
with $59 \leq$ eGFR >15 candidates for undergoing coronary angiography

Methods

- Exclusion criteria:
  - pregnancy, lactation, age over 80 years
  - hypersensitivity to contrast agents
  - a history of asthma, severe liver damage

Our study **excluded cases requiring urgent percutaneous coronary intervention** (PCI) for ST-segment elevation myocardial infarction (STEMI) that did not allow for sufficient time for appropriate hydration and drug administration.

Methods

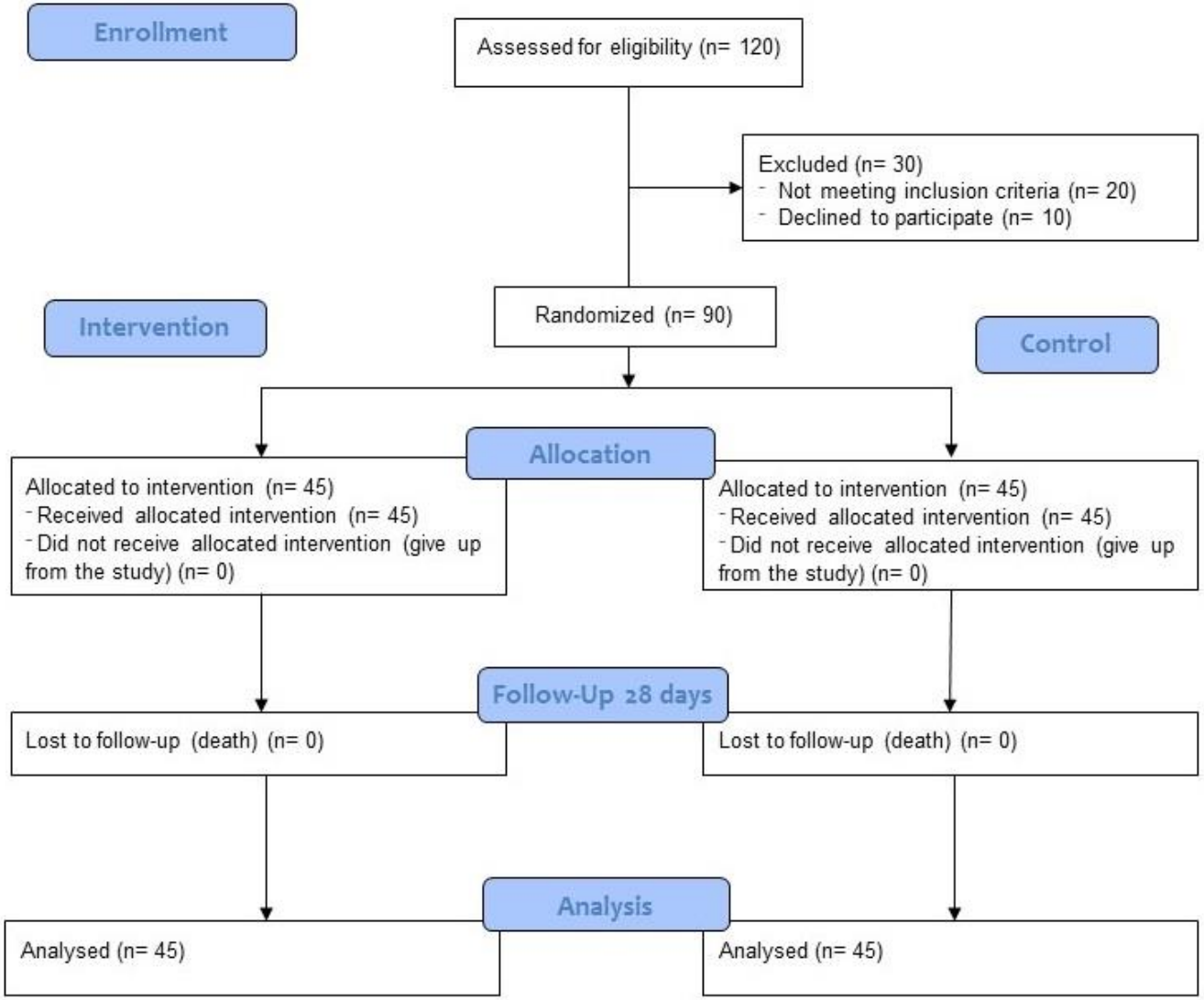
- **Hydration** was administered to all patients (n=90) who had sufficient time for preparation prior to angiography.

- They were given a **0.9% saline solution at a rate of 1 mL/kg/h for 12 h before and 24 h after the angiography procedure**.

- In the intervention group, a single dose of **edaravone (60 mg**, Zistdaru Co. Tehran, Iran) was intravenously infused within 60 min, 1 h prior to the angiography.
- Patients in the control group received a placebo under similar conditions.
  - Ardalan et al Pharma Res Prespect 2024

Eligible chronic kidney disease (CKD) patients (eGFR= 39.43 ml/min)

CONSORT diagram



Results

TABLE 1 Demographic and baseline clinical information of the participants.

Variables	Subgroups	All participants ($n=90$)	Groups		p-value
			Control ($n=45$)	Intervention ($n=45$)	
Gender	Male	66 (73.3)	38 (57.6)	28 (42.4)	**.031**
	Female	24 (26.7)	7 (29.2)	17 (70.8)	
Age (years)		65.17 ± 9.981	65.42 ± 10.94	64.9 ± 19.03	.810
Height (cm)		169 (151–185)	169 (151–178)	171 (155–185)	.218
Weight (kg)		78 (58–98)	78 (59–98)	78 (58–98)	.903
BMI (kg/m^2)		26.4 (20.4–38.6)	26 (20.4–38.6)	26 (21–38)	.315
Systolic BP (mmHg)		134.6 ± 10.7	131.6 ± 13.5	135.1 ± 7.2	.807
Diastolic BP (mmHg)		77.9 ± 8.4	77.9 ± 8.4	74.8 ± 7.5	.650
eGFR ($ml/min/1.73m^2$)		39.43 (15.45–55.22)	40.46 (21.86–55.22)	38.64 (10.45–49.88)	.229
Severity of heart disease	Elective	9 (10)	0	9 (100)	**<.001**
	UA	23 (25.6)	8 (34.8)	15 (65.2)	
	NSTEMI	23 (25.6)	12 (52.2)	11 (47.8)	
	STEMI	35 (38.9)	25 (71.4)	10 (28.6)	
PCI		42 (46.7)	22 (52.4)	20 (47.6)	.833
Contrast (mg/mL)	PCI positive	120 (25–150)	120 (90–150)	110 (25–145)	.40
	PCI negative	30 (20–150)	30 (25–150)	27.50 (20–120)	**.008**
LVEF (%)		45 (20–60)	40 (20–55)	50 (25–60)	**.001**
WBC ($10^9/L$)		9.85 (3.90–20)	12.80 (3.90–18.70)	8 (4.40–20)	**<.001**
Hb (mg/dL)		13.75 (8.20–18.80)	13.50 (10.40–18.00)	13.80 (8.20–18.80)	.728
Platelet ($10^9/L$)		201.50 (104–592)	211 (128–437)	192 (104–592)	.345
Potassium (mg/dL)		4.26 ± 0.41	4.25 ± 0.45	4.28 ± 0.38	.756
Sodium (mg/dL)		139.87 ± 3.904	139.47 ± 2.95	140.27 ± 2.83	.193
INR		1.06 (0.9–1.45)	1.05 (0.90–1.32)	1.10 (0.96–1.45)	.563
Smoker		30 (33.3)	17 (43.3)	13 (56.7)	.503

Results

TABLE 2 The history of underlying diseases of the patients.

Groups	Underlying diseases				
	Hypertension	Diabetes	Hyperlipidemia	IHD	Heart failure
All participants	68 (75.55)	40 (44.44)	37 (4.11)	25 (27.77)	5 (5.55)
Edaravone	33 (48.5)	18 (45)	16 (43.2)	9 (36)	2 (40)
Control	35 (51.5)	22 (55)	21 (56.8)	16 (64)	3 (60)
P-value	0.807	0.525	0.392	0.517	1
Elective	4 (5.9)	0	1 (2.7)	1 (4)	0
UA	18 (26.5)	10 (25)	8 (21.6)	4 (16)	2 (40)
NSTEMI	21 (30.9)	13 (32.5)	12 (32.4)	5 (20)	1 (20)
STEMI	25 (36.8)	17 (42.5)	16 (43.2)	15 (60)	2 (40)
P-value	0.039	0.031	0.165	0.076	0.936
CIN	4 (5.9)	3 (7.5)	1 (2.7)	1 (4)	0
Non-CIN	64 (94.1)	37 (92.5)	36 (97.3)	24 (96)	5 (100)
P-value	1	0.652	0.401	1	1

No statistical difference was observed in terms of the underlying diseases between the two studied groups ($p \geq 0.392$)

The occurrence of CIN was observed in 5.5% (n= 5) of the studied population: **2.2% of patients in the intervention group** (n= 1) and **8.9% of controls (n= 4)**.

However, it is worth noting that this reduction did not reach statistical significance.

Results

TABLE 3 Comparing the studied variables between the groups with or without CIN.

Variables	subgroups	Groups		P-value
		Non-CIN (n= 85)	CIN (n= 5)	
Gender	Male	61 (71.76)	5 (100)	**0.319**
	Female	24 (28.24)	0	-
Age (Years)		65.01±10.10	67.80±7.98	**0.407**
Height (cm)		169 (151-185)	169 (166-177)	**0.647**
Weight (Kg)		76 (58-98)	79 (78-91)	**0.086**
BMI (Kg/m^2)		26 (20.4-37.6)	30 (26.4-35)	**0.075**
PCI		41 (48.24)	1 (20)	**0.367**
Groups	Control	41 (48.24)	4 (80)	**0.361**
	Edaravone	44 (51.76)	1 (20)	
Severity of heart disease	Elective	9 (10.58)	0	**0.442**
	UA	23 (27.06)	0	
	NSTEMI	21 (24.71)	2 (20)	
	STEMI	32 (37.65)	3 (60)	
Contrast (ml)		45 (20-150)	30 (30-150)	**0.901**
LVEF (%)		45 (20-60)	40 (20-50)	**0.144**
WBC (10^9/L)		10 (3.9-20)	9.3 (405-16.5)	**0.647**
Hb (mg/dl)		13.7 (8.2-18.8)	13.8 (10.7-16)	**0.833**
Platelet (10^9/L)		200 (104-592)	272 (163-306)	**0.195**
Potassium (mg/dL)		4.25±0.38	4.380.82±0.82	**0.008**
Sodium (mg/dL)		139.89±2.96	139.4±1.51	**0.159**

TABLE 4. The effect of edaravone on kidney function in the studied groups.

Kidney parameters	Intervention stage	Groups: Control group	Groups: Intervention group	*p*-value
Creatinine	Before treatment	1.70 (1.45–2.80)	1.67 (1.4–4.2)	.536
	After treatment	1.66 (1.25–3.30)	1.50 (1.1–4.7)	**.043**
	p-value	.709	**<.001**	-
BUN	Before treatment	28 (13–27)	32 (10–84)	.183
	After treatment	27 (15–74)	25 (14–97)	.926
	p-value	.861	**.004**	-

Note: Data presented as median (minimum-maximum). Mann–Whitney tests were used to compare the results between the groups. p-value < 0.05 was considered statistically significant.

Abbreviation: BUN, blood urea nitrogen.

Discussion

- Meta-analysis studies have delineated the potential advantages of **antioxidants,** (Statin), vitamins (C, E, D) in addition to hydration in the reduction of the risk associated with CIN. PRESERVE trial, which encompasses a large sample size, has failed to identify any nephroprotective effect of N-acetylcysteine (NAC) against CIN.
  - Ardalan et al Pharma Res Prespect 2024

The beneficial effects of edaravone may stem from its antioxidative, anti-inflammatory properties, and preservation of microcirculation, thereby mitigating the occurrence of CIN, the evidence remains limited, our study represents the first of its kind in this field. Ardalan et al Pharma Res Prespect 2024

Conclusion

Our study showed that the administration of Edaravone one hour before infusion of contrast media causes reduced incidence of CIN.

Ardalan et al Pharma Res Prespect 2024

- Contrast-induced nephropathy as an indicator of diffuse endothelial dysfunction: Introducing novel therapeutic options for decreasing the long-term mortality.
  - Ardalan, Rastegar, et al Medical Hypotheses 2007

- Multiple studies have documented the association of CA-AKI with short- and long-term mortality ,nosocomial death ,three-fold greater risk of death, stroke, myocardial infarction, and/or kidney failure at 1 year

- the causal nature of the associations of CA-AKI, defined by small upticks in serum creatinine, with such serious adverse outcomes remains unproven.

- It is plausible that transient CA-AKI represents a marker of patients more vulnerable to adverse events because of greater underlying comorbidity, more severe acute illness, and/or les.

- Recognition of this is critical as that overestimate the risk for CA-AKI, leading to an underutilization of clinically indicated and potentially lifesaving contrast-enhanced procedures. The practice, which has been termed "renalism," . Rudnick et al M. CJASN 2007

- The term nephroptosis was an old belief, with nephropexy the most common surgical procedures in the 19th century, over one hundred and seventy surgical techniques have been described in an effort to fixate the kidney. Some gradually doubted the belief as a clinical entity and led to divided opinions, I have no belief in its existence as a pathological incident

II. MOVABLE KIDNEY.

(Floating Kidney; Palpable Kidney; Ren mobilis; Nephroptosis).

The kidney is held in position by its fatty capsule, by the peritonæum which passes in front of it, and by the blood-vessels. Normally the kidney is firmly fixed, but under certain circumstances one or another organ, more rarely both, becomes movable. In very rare cases the kidney is surrounded, to a greater or less extent, by the peritonæum, and is anchored at the hilus by a mesonephron. Some would limit the term floating kidney to this condition.

Movable kidney is almost always acquired. It is more common in

* New York Medical Journal, 1883.

women. Of the 667 cases collected in the literature by Kuttner, 584 were in women and only 83 in men. It is more common on the right than on the left side. Of 727 cases analyzed by this author, it occurred on the right in 553 cases, on the left in 81, and on both sides in 93. The greater frequency of the condition in women may be attributed to compression of the lower thoracic zone by tight lacing, and, more important still, to the relaxation of the abdominal walls which follows repeated pregnancies. This does not account for all the cases, as movable kidney is by no means uncommon in nulliparæ. Drummond believes that in a majority of the cases there is a congenitally relaxed condition of the peritoneal attachments. The condi-

THE PRINCIPLES AND PRACTICE OF MEDICINE

DESIGNED FOR THE USE OF PRACTITIONERS AND STUDENTS OF MEDICINE

BY

WILLIAM OSLER, M. D.

Fellow of the Royal Society; Fellow of the Royal College of Physicians, London; Professor of Medicine in the Johns Hopkins University and Physician-in-chief to the Johns Hopkins Hospital, Baltimore; formerly Professor of the Institutes of Medicine, McGill University, Montreal; and Professor of Clinical Medicine in the University of Pennsylvania, Philadelphia

THIRD EDITION

NEW YORK
D. APPLETON AND COMPANY
1899