REMEDIAL III
REnal Insufficiency Following Contrast MEDIA Administration III TriaL
Urine flow rate-guided versus left-ventricular end-diastolic pressure-guided hydration in high-risk patients for contrast-induced acute kidney injury.

Carlo Briguori, MD, PhD

Interventional Cardiology

Mediterranea Cardiocentro, Naples, Italy

Background

- Hydration is the cornerstone in contrast-induced acute kidney injury (CI-AKI) prophylaxis[1]
- Tailored hydration regimens have been proposed to improve both efficacy and safety in the prevention of CI-AKI, such as
  - LVEDP-guided[2]
  - Urine flow rate-guided[3]

1. McCullough PA. J Am Coll Cardiol 2008;51:1419-28
2. Brar S. et al. Lancet. 2014;383(9931):1814-1823
3. Briguori C, et al. Circulation. 2011;124(11):1260-1269.

Purpose

- We performed a multicenter, randomized, single-blind, phase 3, investigator-initiated trial comparing 2 tailored-hydration regimens:
- LVEDP-guided hydration (*LVEDP-guided group*)
- UFR-guided hydration (*UFR-guided group*)
- The trial was registered with www.clinicaltrial.gov (NCT02489669)
- In all cases iobitridol (Xenetix, Guerbet, Villepinte, France) a low-osmolar, non-ionic contrast agent) was administered. Guerbet provided an unrestricted grant to the Mediterranea Cardiocentro.

	UFR-guided group	LVEDP-guided Group	
Pre-Procedure	**Reach UFR >300 mL/h**	**Start hydration 1 h before procedure**	
	Priming (in 30 minutes) • 250 mL or • 150 mL (if LVEF≤30% ot $LVEDP^{TDI}$ >14) Followed by i.v. furosemide (≥0.25 mg/kg)	**$LVEDP^{TDI}$ (E/e' ratio)** <10 11-14 >14	**Infusione rate (mL/kg/h)** 5 3 1.5
Intra-procedure	**Maintain UFR ≥450 mL/h**	**Adjust hydration rate according to LVEDP**	
	Additional furosemide dose allowed according to UFR value	**LVEDP (mm Hg)** ≤12 13-18 >18	**Infusione rate (mL/kg/h)** 5 3 1.5
Post-Procedure	**Continued for 4 h**	**Continued for 4 h**	

Study Population

Between July 15, 2015 and June 6, 2019

Inclusion Criteria

All consecutive patients with chronic kidney disease (CKD) an eGFR ≤45 mL/min/1.73 m^2
and/or
At high risk for CI-AKI according to Mehran's score ≥11 and/or Gurm's score >7

Exclusion Criteria:

- Age <18 years
- Women who are pregnant
- Acute pulmonary edema
- Acute myocardial infarction (STEMI)
- Recent contrast media exposure
- End-stage CKD on chronic dialysis
- Multiple myeloma
- Current enrolment in any other study when enrolment in the REMEDIAL III would involve deviation from either protocol
- Cardiogenic shock
- Administration of theophilline, dopamine, mannitol and fenoldopam

Primary endpoint

Composite of CI-AKI and/or acute pulmonary edema

CI-AKI:
increase in the serum creatinine concentration ≥25% and/or ≥0.5 mg/dL from baseline value at 48 hours after contrast media exposure

Acute pulmonary edema:
the sudden development of dyspnea and/or tachypnea and/or breathlessness associated with tachycardia, anxiety, cough and sweating after the initiation of the hydration regimen

Secondary endpoints

- Increase in the serum creatinine concentration ≥0.3 mg/dL at 48 hours

- Changes in the serum cystatin C concentration at 24 and 48 hours

- Rate of acute renal failure requiring dialysis

- Rate of in-hospital, 1, 6 and 12-month major adverse events (MAE), including all-cause death, dialysis, acute pulmonary edema, and sustained kidney injury (defined as a persistent ≥25% GFR reduction compared to baseline at the last available value during the follow-up)

- Length of in-hospital stay

Sample size

- **Hypothesis:**
  - **Reduction in the primary endpoint from 9% in the *LVEDP-guided group* to 5% in the *UFR-guided group***
- **Sample size:**
  - **A total of 700 patients (350 each group) will be necessary to gave the study 80% power and a significance level <0.05**

Enrollment

Assessed for eligibility (n = 933)

Exclusion (n = 222)
Not meeting inclusion/exclusion criteria (n = 140)
Refused to partecipate (n = 85)

Randomization (n = 708)

$LVEDP^{TDI}$ assessment

Allocation

✓Patients allocated in the LVEDP-guided group (n= 355)
- ✓Received allocated treatment (n = 351)
- ✓Did not receive the allocated treatment (n = 4)
- ✓ Refused procedure (n = 3)
- ✓ Fever (n = 1)

✓ Patients allocated in the UFR-guided group (n= 353)
- ✓ Received allocated treatment (n = 351)
- ✓ Did not receive the allocated treatment (n = 2)
- ✓ Refused Foley catheter (n = 2
- ✓ Refused procedure (n = 0)

Follow-up

Patients lost at follow-up (n = 0)

Patients lost at follow-up (n = 0)

Analysis

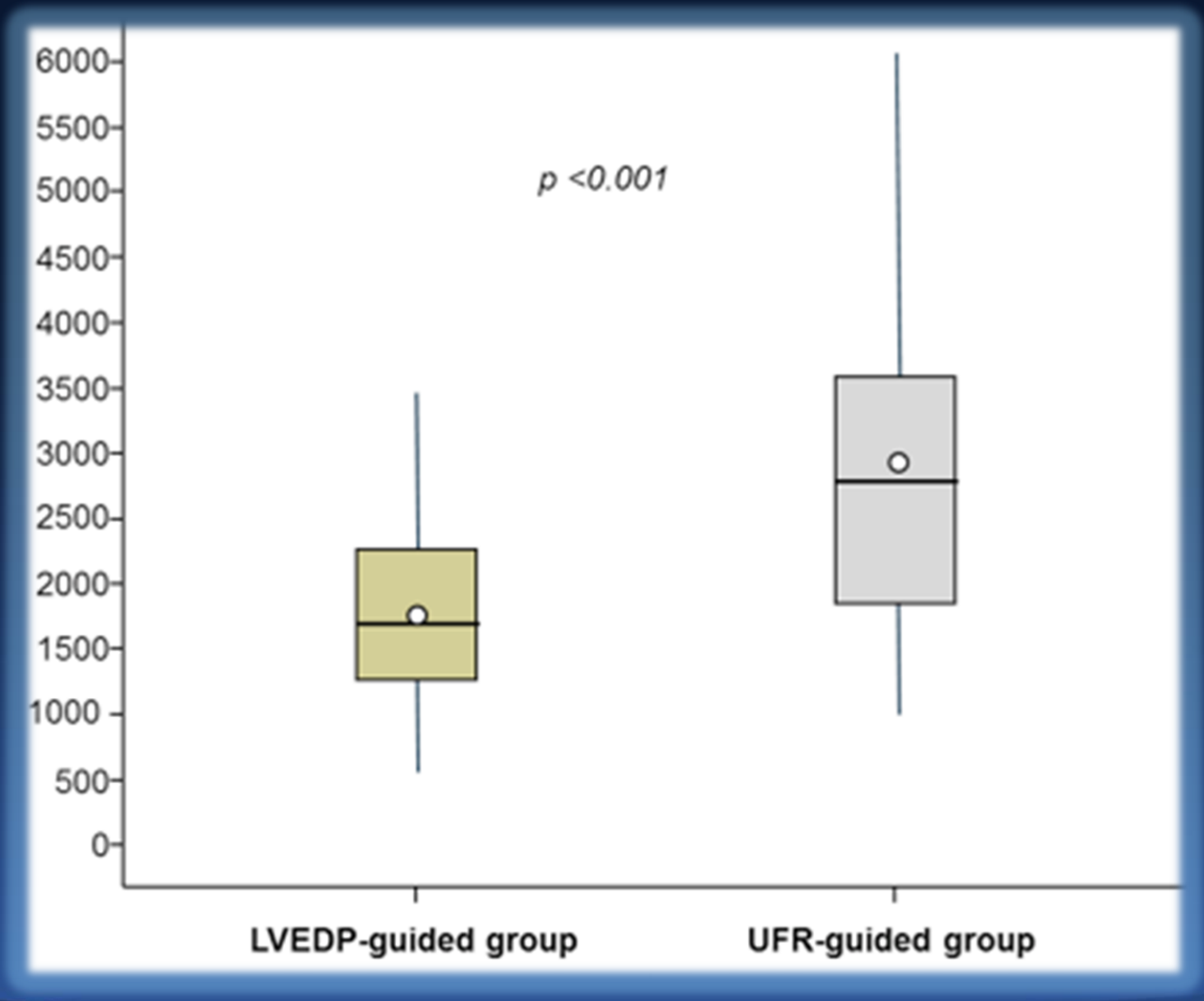
Patients analized (n = 355)
Patients excluded from primary endpoint analysis (n = 4)

Patients analized (n = 353)
Patients excluded from primary endpoint analysis (n= 2)

Clinical and biochemical characteristics

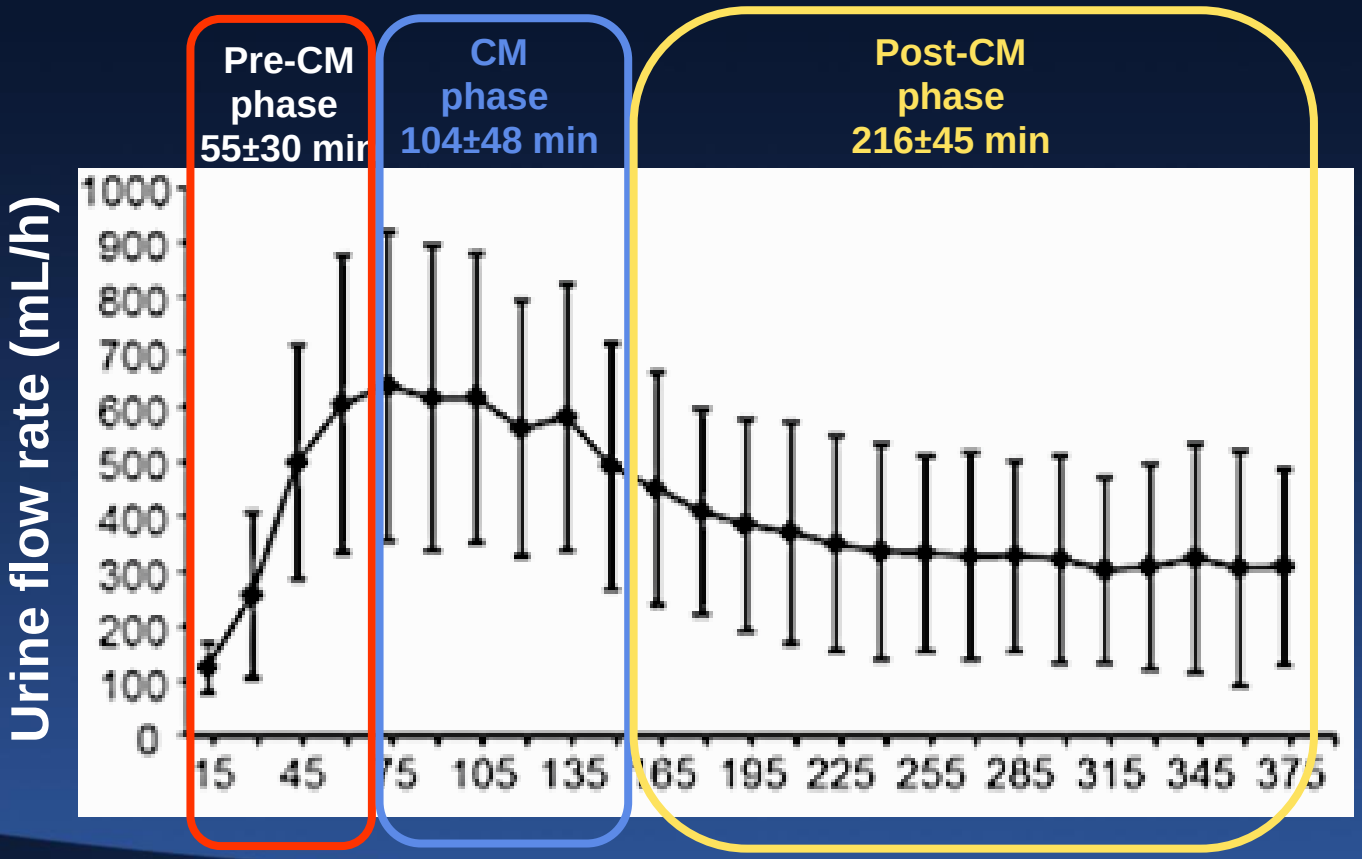
	LVEDP-guided group(n= 355)	*UFR-guided group (n= 353)*	*P* Value
Age (years)	74 ± 8	74 ± 8	0.61
Male	233 (65.5%)	207 (59%)	0.07
Body-mass Index (Kg/m2)	29±5	28±4	0.40
Left Ventricular Ejection Fraction (%)	49±10	50±11	0.19
Left ventricular end diastolic pressure (mmHg) **<12** **13-18** **>18**	14±7 174 (49.5%) 102 (29%) 75 (21.5%)	14±7 167 (47.5%) 107 (30.5%) 77 (22%)	0.81
Systemic Hypertension	323 (91%)	321 (91%)	0.89
Diabetes Mellitus	177 (50%)	175 (49.5%)	0.88
Peripheral Chronic Artery Disease	71 (20%)	74 (21%)	0.78
Gurm risk score **≥7**	5±5 89 (25%)	6±5 109 (31%)	0.44 0.09
Mehran risk score **≥11**	10±3 159 (45%)	10±3 151 (43%)	0.96 0.70
Performed procedure* **Coronary angiography** **PCI** **Coronary angiography and ad hoc PCI** **Peripheral procedure**	 126 (36%) 42 (12%) 173 (49%) 10 (3%)	 126 (36%) 42 (12%) 171 (48.5%) 12 (3.5%)	 0.75 0.49 0.41 0.43
Radial approach	325 (92.5%)	331 (64%)	0.45
Volume of contrast media (mL)* **Contrast volume >3 times GFR**	72±49 0.18	67±47 69 (19.5%)	0.18 0.46
Serum creatinine (median; Q1-Q3, mg/dL)	1.68 (1.25-1.97)	1.67 (1.45-2.02)	0.60
GFR (mL/min/1.73 m^2) **≤30**	36±3 78 (22%)	36±3 95 (27%)	1.00 0.13
Serum cystatin C (median; Q1-Q3, mg/dL)	1.74 (1.50-2.01)	1.75 (1.50.2.11)	0.24
Hemoglobin (g/dL)	12.6±1.7	12.7±1.8	0.38

Hydration volume

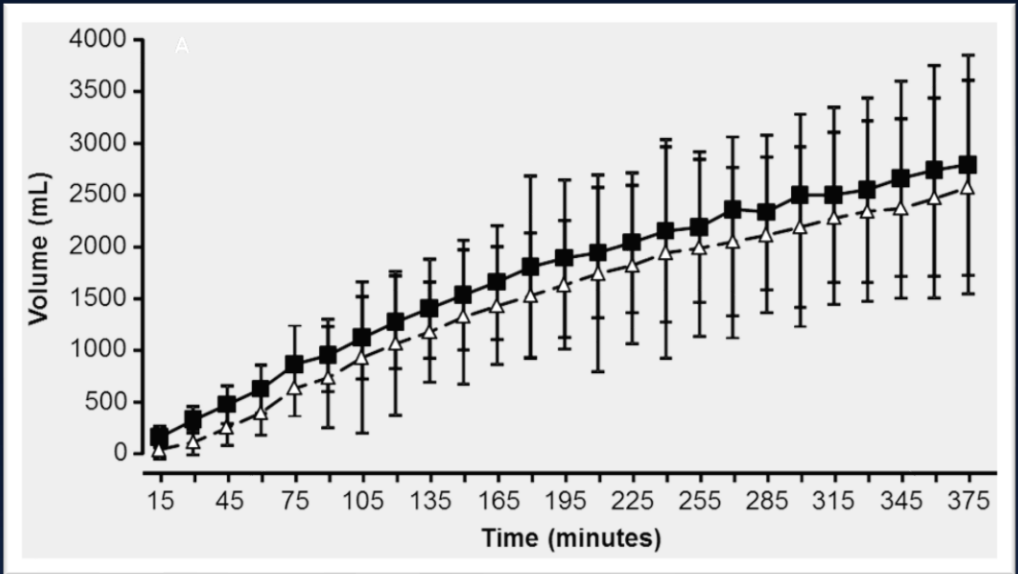


RenalGuard therapy phases

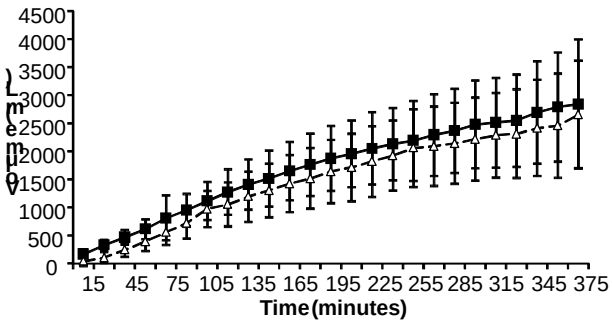
Mean UFR was 416±158 mL/h
Target UFR ≥300 mL/h was reached in 95% of patients.
Intraprocedural UFR was ≥450 mL/h was reached in 228 (65%) patients.



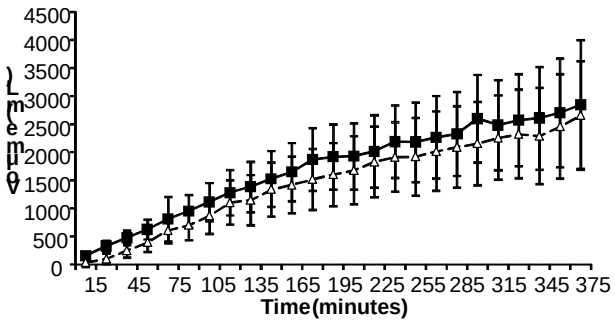
Infusion/urine output balance



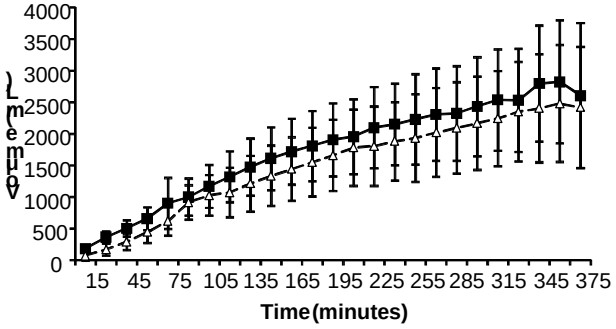
Subgroup with LVEDP ≤12 mmHg



Subgroup with LVEDP 13-18mmHg



Subgroup with LVEDP >18 mmHg



■ Infusion △ Urine

Side effects

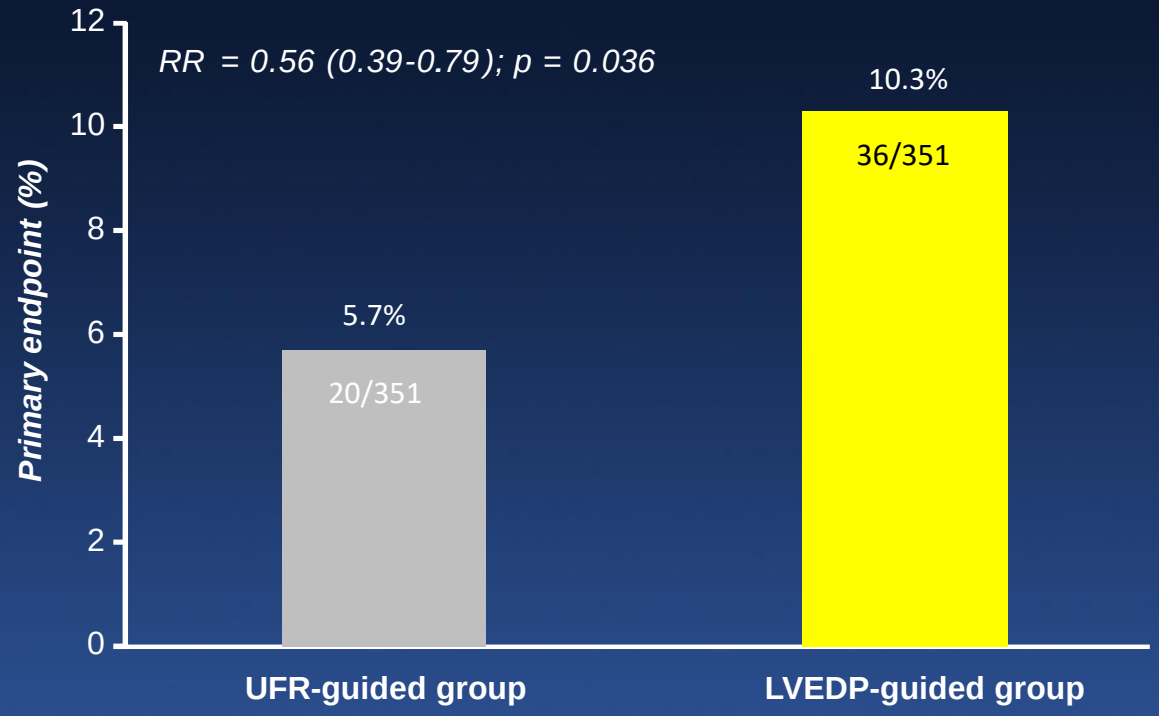
- Three patients in the *UFR-guided group* (0.8%) experienced complications related to Foley insertion, that is:
  - hematuria (n = 1)
  - pain on micturition (n = 2)
  - No patient had urinary tract infection

- Hypokalemia occurred in 22 (6.2%) patients in the *UFR-guided group* and in 8 (2.3%) patients in the *LVEDP-guided group* (RR = 2.70; 95% CI 1.21-6.37; p = 0.013). Potassium replacement was necessary in 18 (5.1%) in the UFR-guided group and in 5 (1.4%) patients in the LVEDP-guided group (RR = 3.74; 95% CI = 1.37-10.13; p = 0.009)

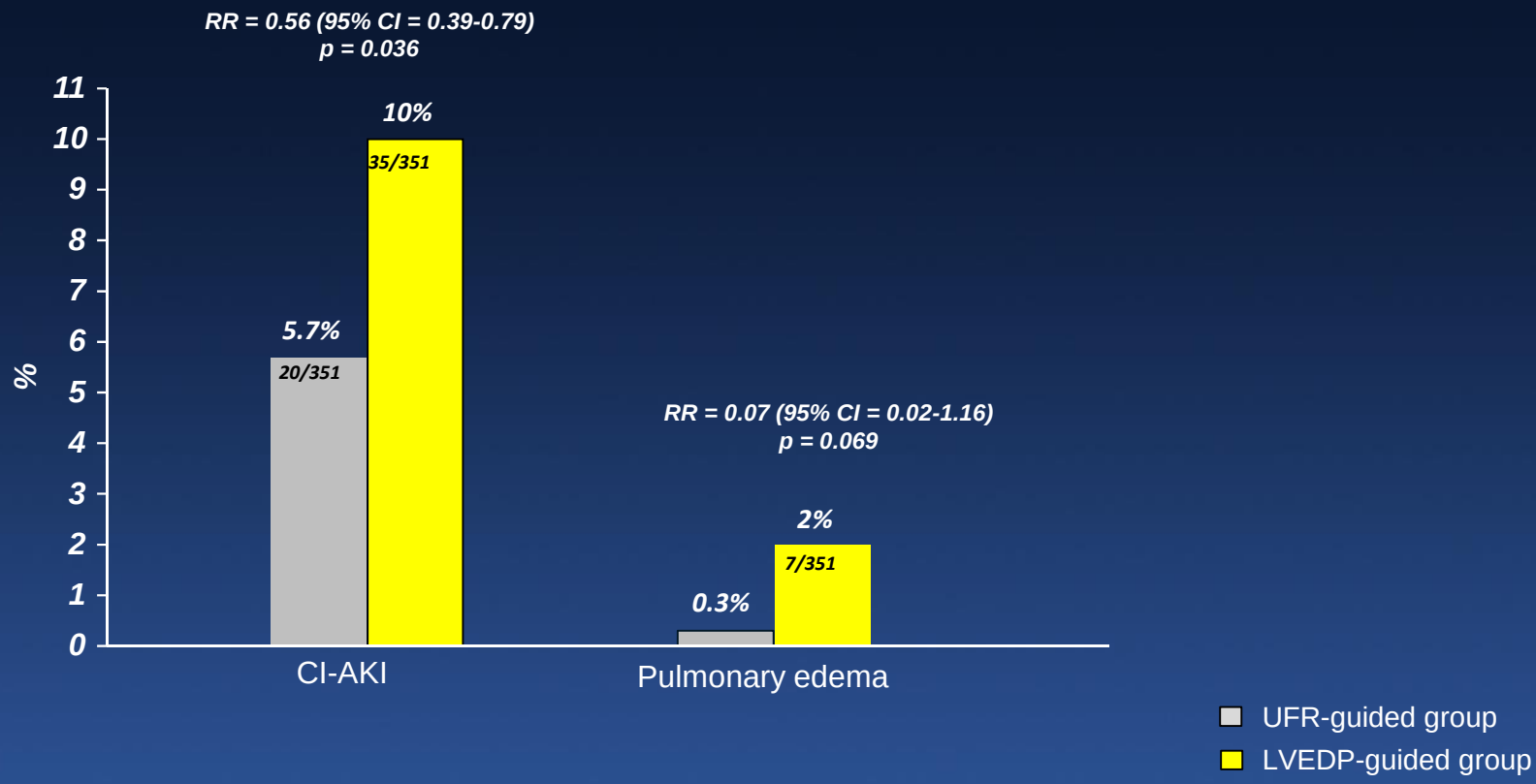
- Hypernatriemia was observed in 1.2% of patients in the LVEDP-guided group and in 1.2% patient in the UFR-guided group (p = 1.00)

Primary endpoint

NNT to prevent one event with the Renalguard therapy = 22



Primary endpoint



Primary endpoint

Pre-specified subgroups

	LVEDP-guided group(n= 355)	*UFR-guided group (n= 353)*	*Relative risk (95% CI)*	*P value for heterogeneity*
LVEDP (mmHg)				0.85
≤12	14/174 (8%)	7/167 (4.2%)	0.52 (0.37-0.74)	…
13-18	14/102 (13.7%)	7/107 (6.5%)	0.48 (0.34-0.67)	…
>18	6/75 (10.7%)	6/77 (7.8%)	1.03 (0.73-1.45)	
GFR (mL/min/1.73 m^2)				0.31
>30	26/178 (9.4%)	12/257 (4.7%)	0.32 (0.26-0.40)	…
≤30	10/73 (13.7%)	8/94 (8.5%)	0.62 (0.50-0.78)	…

Characteristics of patients with acute pulmonary edema

Patient	Group	Age	Sex	LVEF	LVEDP	GFR	SBP	Mehran score	Gurm score	Contrast volume	procedure	CIAKI
1	*UFR-guided*	*69*	*M*	*40*	*23*	*27*	*120*	*11*	*8.5*	*25*	*Coronary angiography*	*Yes*
2	*LVEDP-guided*	*80*	*F*	*55*	*15*	*35*	*120*	*15*	*16.6*	*130*	*PCI*	*Yes*
3	*LVEDP-guided*	*72*	*M*	*45*	*14*	*36*	*130*	*11*	*22.1*	*60*	*Coro and ad-hoc PCI*	*Yes*
4	*LVEDP-guided*	*80*	*M*	*35*	*24*	*34*	*140*	*12*	*3.5*	*40*	*Coro and ad-hoc PCI*	*Yes*
5	*LVEDP-guided*	*79*	*F*	*60*	*18*	*31*	*140*	*15*	*15.9*	*90*	*Coro and ad-hoc PCI*	*Yes*
6	*LVEDP-guided*	*80*	*F*	*69*	*18*	*40*	*110*	*10*	*3.5*	*80*	*Coronary angiography*	*No*
7	*LVEDP-guided*	*62*	*M*	*55*	*18*	*44*	*160*	*5*	*9.5*	*80*	*Coro and ad-hoc PCI*	*Yes*
8	*LVEDP-guided*	*55*	*F*	*28*	*33*	*12*	*160*	*11*	*15.6*	*40*	*Coronary angiography*	*Yes*

Secondary endpoints

	UFR-guided group(n= 355)	*LVEDP-guided group (n= 353)*	*Relative risk (95% CI)*	*P value*
Changes in creatinine at 48 hours				
Increase ≥ 0.3 mg/dL **Increase ≥ 0.5 mg/dL** **Increase ≥ 25%**	36 (10.3%) 18 (5.0%) 20 (5.7%)	58 (16.6%) 33 (9.4%) 35 (10%)	0.45 (0.36-0.88) 0.55 (0.44-0.68) 0.57 (0.46-0.72	0.015 0.041 0.048
Changes in cystatin C at 24 hours				
Increase ≥10% **Increase ≥25%**	22 (4.0%) 4 (1.0%)	33 (8.5%) 11 (3.0%)	0.67 (0.53-0.84) 0.36 (0.29-0.46)	0.019 0.11
Changes in cystatin C a 48 hours				
Increase ≥10% **Increase ≥25%**	28 (8.0%) 10 (2.8%)	45 (12.6%) 21 (5.9%)	0.62 (0.50-0.78) 0.48 (0.38-0.60)	0.047 0.065

1-month MAE

	LVEDP-guided group (n=355)	UFR-guided group (n=353)	p
Cumulative major adverse events	43 (12%)	25 (7.1%)	0.030
Death	9 (2.5%)	5 (1.4%)	
Dialysis	6 (1.7%)	4 (1.1%)	
Sustained kidney damage	30 (8.5%)	15 (4.3%)	
Acute pulmonary edema	8 (2.2%)	2 (0.6%)	

Conclusions

- UFR-guided approach (carried out by the RenalGuard system) is superior to the LVEDP-guided hydration regimen to prevent the composite of CI-AKI and/or acute pulmonary edema in high-risk patients.
- A strict control of potassium balance is required during RenalGuard therapy.

REMEDIAL III Investigators

Mediterranea Cardiocentro, Naples

- C. Briguori
- A. Focaccio
- G. Visconti
- F. De Micco
- C. D'Amore
- P. Elia

Federico II University of Naples

- G. Esposito
- R. Piccolo

Multimedica IRCCS, Milan

- F. Airoldi
- D. Tavano

Policlinico di Bari, Bari

- N. Signore
- A. Dachille