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.

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Disclosure Statement of Financial Interest

I, Carlo Briguori DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

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.

Hydration regimen

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

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

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)

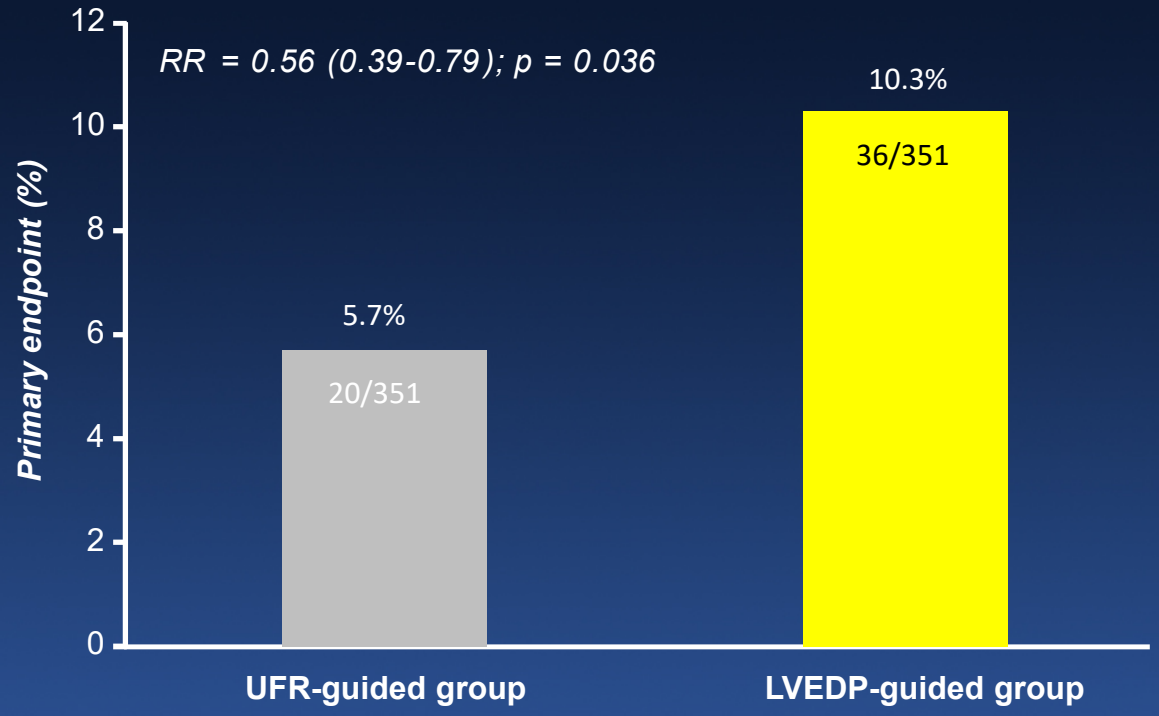
Patients analized (n = 353)
Patients excluded from primary endpoint analysis (n= 2)

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 m²) **≤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

Primary endpoint

NNT to prevent one event with the Renalguard therapy = 22



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 m²)				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)	…

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.