

# Fenoldopam to prevent renal replacement therapy after cardiac surgery. Design of the FENO-HSR study

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## ABSTRACT

**Introduction:** Acute kidney injury requiring renal replacement therapy is a serious complication following cardiac surgery associated with poor clinical outcomes. Until now no drug showed nephroprotective effects. Fenoldopam is a dopamine-1 receptor agonist which seems to be effective in improving postoperative renal function. The aim of this paper is to describe the design of the FENO-HSR study, planned to assess the effect of a continuous infusion of fenoldopam in reducing the need for renal replacement therapy in patients with acute kidney injury after cardiac surgery.

**Methods:** We're performing a double blind, placebo-controlled multicentre randomized trial in over 20 Italian hospitals. Patients who develop acute renal failure defined as R of RIFLE score following cardiac surgery are randomized to receive a 96-hours continuous infusion of either fenoldopam (0.025-0.3 µg/kg/min) or placebo.

**Results:** The primary endpoint will be the rate of renal replacement therapy. Secondary endpoints will be: mortality, time on mechanical ventilation, length of intensive care unit and hospital stay, peak serum creatinine and the rate of acute renal failure (following the RIFLE score).

**Conclusions:** This trial is planned to assess if fenoldopam could improve relevant outcomes in patients undergoing cardiac surgery who develop acute renal dysfunction. Results of this double-blind randomized trial could provide important insights to improve the management strategy of patients at high risk for postoperative acute kidney injury.

**Keywords:** *fenoldopam, cardiac surgical procedures, acute renal failure, cardiac surgery, anesthesia, renal replacement therapy.*

## INTRODUCTION

Acute renal failure (ARF) is a common as well as life threatening complication in patients undergoing cardiovascular surgery (1-3). Despite improvements in intensive care treatments and dialysis technology,

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the mortality associated with acute renal failure requiring renal replacement therapy (RRT) remains unacceptably high, though once discharged from hospital long-term mortality is low with satisfactory quality of life in patients discharged from hospital alive (4).

However no drug showed nephroprotective properties translating into a reduction in the incidence of renal replacement therapy and mortality in a cardiovascular setting (5).

Fenoldopam mesylate is a benzazepine derivative and a dopamine A-1 (DA-1) receptor agonist that seems to be effective in improving postoperative renal function (5). Fenoldopam exerts hypotensive effects characterized by a decrease in peripheral vascular resistance, with increased renal blood flow, diuresis and natriuresis; all these effects are primarily related to activation of DA-1 receptors. Other beneficial renal effects of fenoldopam could be related to other pharmacological properties that are still under investigation such as an anti-inflammatory effect (6).

A meta-analysis (7) of 16 randomized controlled trials including 1290 patients (622 receiving fenoldopam and 668 receiving placebo or best available treatment, mostly low dose dopamine) was recently conducted. Five trials were performed in cardiac surgery, three in vascular surgery, two in liver and one in renal transplants, while five trials were performed in the intensive care unit (ICU) either in selected patients with sepsis (two studies) or in the overall ICU population.

Fenoldopam dosage varied across studies, between 0.025 µg/kg/min and 0.3 µg/kg/min (in one study), mostly being administered at a dosage of 0.1 µg/kg/min. All but 2 studies had a > 12 h fenoldopam infusion, with 8 studies reporting ≥2 days infusion (median duration 48 h).

Overall analysis showed that, in compari-

son to best medical therapy, fenoldopam usage reduces the risk of RRT (34/525 [6.5 %] in the fenoldopam group vs 59/569 [10.4 %] in the control arm, OR = 0.54 [0.34-0.84],  $p = 0.007$ ).

In a second meta-analysis (8) 13 clinical studies comparing fenoldopam to placebo or standard treatment in cardiovascular surgery were included.

The studies enrolled a total of 1.059 patients (528 received fenoldopam and 531 placebo or best available treatment). Fenoldopam dosage varied across studies, being always > 0.03 µg/kg/min and most often 0.1 µg/kg/min, reaching 0.3 µg/kg/min in a single study.

All but 2 studies had a ≥24 hours fenoldopam infusion, with 5 studies reporting ≥2 days of continuous application. Overall analysis showed that, in comparison to best medical therapy, fenoldopam was associated with a significant reduction in the rates of all major endpoints. Specifically, fenoldopam usage reduced the risk of RRT (30/528 [5.7 %] in the fenoldopam group vs 71/531 [13.4 %] in the control arm; OR = 0.37 [0.23-0.59],  $p < 0.001$ , number needed to treat = 13) and of in-hospital mortality (28/501 [5.6 %] in the fenoldopam group vs 55/503 [10.9 %] in the control arm (OR = 0.46 [0.29-0.75],  $p = 0.02$ , number needed to treat = 19).

Several studies suggested that fenoldopam could have a nephroprotective action in a cardiac surgery setting, even when it is used before surgery (9-12), but they were not powered enough to detect an improvement in clinical relevant outcomes, such as the need for renal replacement therapy or mortality.

Scientific literature is not unanimous about the protective properties of fenoldopam, and there are also studies which showed no improvement with administration of fenoldopam in high-risk patients undergoing cardiac surgery (13).

## METHODS

### *Study aim*

Based on previous concerning the administration of fenoldopam in patients at high risk for ARF (14), we are planning to initiate a large (1000 planned patients) multicentre, prospective, randomized, double-blind, placebo controlled clinical study enrolling patients undergoing cardiac surgery who will develop acute renal dysfunction. Our aim is to confirm the promising results of the cited meta-analyses and to add evidence based medicine to the supposed renal protective properties of fenoldopam in critically ill patients (7, 8).

### *Patients selection*

We will enroll consecutive patients undergoing cardiac surgery who will develop an acute renal failure after cardiac surgery. Candidates for this study meeting the following criteria will be included: patients who are able to understand and sign an informed consent, aged 18 years or older, undergoing cardiac surgery who will develop, during the ICU stay an acute renal dysfunction designed as "R" of RIFLE score (50 %

postoperative increase in serum creatinine and/or diuresis < 0,5 ml/kg/h for 6 hours) (Table 1).

Conversely, the following exclusion criteria will be applied: previous unusual response to fenoldopam, glaucoma, expected ICU stay less than 24 hours after randomization, RRT already started or planned before randomization, "do not resuscitate" patients, participation in other randomized studies (within the previous 30 days), fenoldopam administration within the previous 30 days, preoperative RRT or dialysis.

### *Study procedure*

All patients planned to undergo cardiac surgery who won't have exclusion criteria will be approached by a member of the research team to sign the informed consent. Failure to obtain a signed informed consent will make the patient ineligible for the study.

Treatment assignment between fenoldopam and placebo will be determined by a randomization in a ratio of 1:1. Randomization will be performed by centrally provided sealed opaque envelopes. To ensure that almost equal number of patients will receive either treatment, randomization blocks of

**Table 1** - RIFLE score for acute renal failure.

	<b>GFR* criteria</b>	<b>UO† criteria</b>	
Risk	increased creatinine x1.5 or GFR* decrease > 25 %		UO† < 0.5 ml/kg/min for 6 hours
Injury	increased creatinine x2 or GFR* decrease > 50 %	UO† < 0.5 ml/kg/min for 12 hours	
Failure	increased creatinine x3 or GFR* decrease > 75 % or creatinine ≥4 mg/dl (acute rise of ≥0.5 mg/dl)	UO† < 0.3 ml/kg/min or anuria for 12 hours	for 24 hours
Loss	Persistent ARF# = complete loss of renal function > 4 weeks		
ESRD	End-stage renal disease		
Abbreviations * Glomerular Filtration Rate † Urine Output # Acute Renal Failure			

**Table 2** - A clinical score to predict acute renal failure after cardiac surgery according to Thakar et al. (15).

Risk Factor	Points
Female gender	1
Congestive heart failure	1
Left ventricular ejection fraction < 35 %	1
Preoperative use of Intra Aortic Balloon Pump	2
Chronic Obstructive Pulmonary Disease	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only	1
Coronary Artery Bypass Graft + valve	2
Other cardiac surgeries	2
Preoperative creatinine 1.2 to < 2.1 mg/dl	2
Preoperative creatinine $\geq 2.1$ mg/dl	5

20 patients will be used. Fenoldopam and placebo (normosaline) will be identical in shape, color, appearance and size.

Enrolled patients will be randomized in the ICU after the development of an ARF defined as "R" of RIFLE score, to a placebo or fenoldopam (Corlopam - Cephalon, Roma, Italy) continuous infusion. Starting dose will be 0.1  $\mu$ /kg/min (ranging from 0.025 to 0.3  $\mu$ g/kg/min, according to mean arterial pressure). Since the renal protective effect of fenoldopam seems to be related to the dose, it will be suggested to administer at least 0.1  $\mu$ g/kg/min.

The infusion will be maintained for 96 hours or until the patient's ICU discharge. Transfer out of the ICU will be performed with SpO<sub>2</sub>  $\geq 94\%$  at an FiO<sub>2</sub>  $\leq 0.5$  by face-mask, adequate cardiac stability with no hemodynamically significant arrhythmias, chest tube drainage less than 50 ml/h,

urine output greater than 0.5 ml/kg/h, no intravenous inotropic or vasopressor therapy aside from dopamine 5  $\mu$ g/kg/min, and no seizure activity. Criteria for hospital discharge will be hemodynamic as well as respiratory recovery, the presence of clean and dry incisions, afebrile condition, normal bowel movement, and independent ambulation and regular oral nutrition.

Preoperative data will be collected according to the clinical score to predict ARF suggested by Thakar et al. (15) (Table 2), the Continuous Improvement in Cardiac Surgery Study score (CICSS) by Chertow et al. (16) (Table 3), the Simplified model to predict postoperative dialysis by Mehta et al. (17) (Table

**Table 3** - The Continuous Improvement in Cardiac Surgery Study score (CICSS) by Chertow et al. (16).

	Points
Valvular surgery	3
Estimated creatinine clearance ml/min	
$\geq 100$	0
80-99	2
60-79	3
40-59	5
< 40	9
Intra aortic ballon pump prior to surgery	5
Prior heart surgery	3
NYHA* functional class 4	2
Peripheral vascular disease	2
Left ventricular ejection fraction < 0.35	2
Pulmonary rales	2
Chronic obstructive pulmonary disease	2
Systolic blood pressure	
120-139	0
140-159	0
< 120 and valvular surgery	2
< 120 and CABG†	0
$\geq 160$ and valvular surgery	0
$\geq 160$ and CABG†	3
Abbreviations	
* New York Heart Association	
† Coronary Artery Bypass Graft	

**Table 4** - The Simplified model to predict postoperative dialysis by Mehta et al. (18).

	Score
Last serum creatinine (mg/dl)	
0.5	5
1.0	10
1.5	15
2.0	20
2.5	25
3.0	30
3.5	35
4.0 and higher	40
Age	
< 55	0
55-59	1
60-64	2
65-69	3
70-74	4
75-79	5
80-84	6
85-89	7
90-94	8
95-99	9
> 100	10
Surgery	
CABG* only	0
Abbreviations	
* Coronary Artery Bypass Graft	
† New York Heart Association	

**Table 5** - A simplified predictive index for renal replacement therapy after cardiac surgery suggested by Wijeyesundera et al. (18).

Variable	Points
Estimated glomerular filtration rate 31-60 mL/min	1
Estimated glomerular filtration rate ≤ 30 mL/min	2
Diabetes mellitus requiring medication	1
Left ventricular ejection fraction ≤ 40	1
Previous cardiac surgery	1
Procedures other than isolated coronary artery bypass graft or isolated atrial septal defect repair	1
Non elective procedure	1
Preoperative intra-aortic balloon pump	1

4), and the Simplified Renal Index score by Wijeyesundera et al. (18) (Table 5). Telephone-based interviews will be performed at 1 month and 1 year after the procedure.

### Study endpoints

The primary endpoint will be the rate of RRT (continuous venous-venous hemofiltration or hemodialysis, according to center guidelines and protocols). The theoretical need for RRT will be documented as well as defined as the presence of one of the following parameters and symptoms: serum creatinine > 6 mg/dl during hospital stay; clinical presentation of uremia, including altered mental status, itching and/or severe nausea and vomiting; hypoxia (oxygen saturation < 90% with  $\text{FiO}_2 > 40\%$  unresponsive to diuretics); wedge pressure > 25 mmHg; hyperkalemia (> 6.5 mmol/l or > 6.0 after treatment with cation-exchange resins); metabolic acidosis with bicarbonate levels ≤ 10 mEq/l in spite of endovenous bicarbonates administration. Secondary endpoints will be represented by: mortality (in-hospital mortality and telephone follow-up), time on mechanical ventilation (hours), length of ICU and hospital stay (days), peak serum creatinine (mg/dl) and the rate of ARF (following the RIFLE score definition).

### Statistical analysis and sample size calculation

An independent clinician investigator with extensive experience in designing, conducting and analysing clinical trials, not involved in patient management, will be responsible for the statistical analysis. Data will be stored electronically and analysed by means of the Epi Info 2002 (CDC), SPSS 11.0 (SPSS), and STATA 9.0 (STATA) softwares, when appropriate. All data analysis will be carried out according to a pre-established intention-to-treat analysis plan. Dichotomous data (including the primary outcome) will be compared by using a two-

tailed chi<sup>2</sup>test with the Yates correction or Fisher's exact test when appropriate. Continuous measurements will be compared using the Mann-Whitney U test. Two-sided significance tests will be used throughout. Data will be presented as medians (25<sup>th</sup> and 75<sup>th</sup> percentiles) or as means ( $\pm$  standard deviation - SD). Regarding the primary endpoint sample size, with an expected need for RRT of 5% in the treatment group vs 10% in the control group (7, 8), aiming for a 0.05 alpha and 0.80 power, a total of 870 patients will have to be enrolled (435 patients per group). This number will be increased by 15% (leading to a total of 1000 patients) in order to take into account potential protocol deviations. All 1000 patients will be analysed according to the intention-to-treat principle, beginning immediately after randomization. Two interim analyses will be carried out during the course of this study, after randomizing 250 and 500 patients.

#### ***Monitoring of the study***

Monitors will verify adherence to required clinical trial procedures and confirm accurate collection of data and will follow the Good Clinical Practice (GCP) guidelines. Study monitoring and follow-up, from the initial set-up to final reporting, will be fulfilled according to current National and International requirements.

#### ***Ethical issues***

The drug is safe and has been used as an antihypertensive drug in clinical practice for more than 15 years. We might probably observe more hypotensive episodes in the treatment group but once being aware of this potential side effect it shouldn't be problematic to detect and manage these episodes in the ICU. No interference with the subject privacy is planned. Data will be stored in an electronic database without indicating the name of the patients (a numeric code will be used).

## **RESULTS**

During the present study we will expect that fenoldopam would reduce the need for RRT in patients at risk for ARF after cardiac surgery and allow a faster recovery and a better outcome. Our trial should work out clear recommendations regarding fenoldopam administration in a cardiosurgical setting to improve outcomes and reduce hospital costs. Improved survival of critically ill patients undergoing cardiac surgery would be the most relevant implication of this study. Reduction in cost per patient will be striking, since acute renal failure and renal replacement therapy prolong intensive care and hospital stay.

## **DISCUSSION**

Nephroprotection in patients with or at risk of ARF is a topical matter in cardiac anesthesia. Many studies (9-12) and meta-analyses (7, 8) appeared in literature suggesting a protective effect by fenoldopam in patients undergoing cardiac procedures. Roasio et al showed that an infusion of 0.1  $\mu\text{g}/\text{kg}/\text{min}$  of fenoldopam administered for 48 hours in patients with acute renal injury after cardiac surgery reduced the need for RRT in a single-center case-matched study. However, literature is not unanimous and data from large, multicentre, randomized trials powered enough to detect a difference in clinical relevant outcomes are lacking. We will conduct a large multicentre randomized study comparing fenoldopam to a placebo in patients undergoing cardiac procedures who will develop an ARF to address the question whether the administration of this drug might influence patients' outcome after cardiac surgery. 30.000 cardiac surgical interventions are performed in Italy every year (and 1.000.000 in the world). Since acute renal

failure develops in 2-10% of this population, up to 3000 patients in Italy (100.000 in the world) could benefit from the results of this study every year. This will be the first multicentre randomized controlled trial comparing the effects of fenoldopam to placebo after cardiac surgery.

This study is powered enough to highlight potential advantages deriving from fenoldopam administration in patients that are at high risk for postoperative acute renal dysfunction.

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