Original Investigation

Effect of Fenoldopam on Use of Renal Replacement Therapy Among Patients With Acute Kidney Injury After Cardiac Surgery
A Randomized Clinical Trial

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IMPORTANCE No effective pharmaceutical agents have yet been identified to treat acute kidney injury after cardiac surgery.

OBJECTIVE To determine whether fenoldopam reduces the need for renal replacement therapy in critically ill cardiac surgery patients with acute kidney injury.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, double-blind, placebo-controlled, parallel-group study from March 2008 to April 2013 in 19 cardiovascular intensive care units in Italy. We randomly assigned 667 patients admitted to intensive care units after cardiac surgery with early acute kidney injury (≥50% increase of serum creatinine level from baseline or oliguria for ≥6 hours) to receive fenoldopam (338 patients) or placebo (329 patients). We used a computer-generated permuted block randomization sequence for treatment allocation. All patients completed their follow-up 30 days after surgery, and data were analyzed according to the intention-to-treat principle.

INTERVENTIONS Continuous infusion of fenoldopam or placebo for up to 4 days with a starting dose of 0.1 μg/kg/min (range, 0.025-0.3 μg/kg/min).

MAIN OUTCOMES AND MEASURES The primary end point was the rate of renal replacement therapy. Secondary end points included mortality (intensive care unit and 30-day mortality) and the rate of hypotension during study drug infusion.

RESULTS The study was stopped for futility as recommended by the safety committee after a planned interim analysis. Sixty-nine of 338 patients (20%) allocated to the fenoldopam group and 60 of 329 patients (18%) allocated to the placebo group received renal replacement therapy ($P = .47$). Mortality at 30 days was 78 of 338 (23%) in the fenoldopam group and 74 of 329 (22%) in the placebo group ($P = .86$). Hypotension occurred in 85 (26%) patients in the fenoldopam group and in 49 (15%) patients in the placebo group ($P = .001$).

CONCLUSIONS AND RELEVANCE Among patients with acute kidney injury after cardiac surgery, fenoldopam infusion, compared with placebo, did not reduce the need for renal replacement therapy or risk of 30-day mortality but was associated with an increased rate of hypotension.

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More than 1 million patients undergo cardiac surgery every year in the United States and Europe alone.[1] One of its most common complications is acute kidney injury (AKI), which is associated with morbidity and mortality.[2] Moreover, AKI requiring renal replacement therapy (RRT) (dialysis) affects approximately 5% of patients admitted to the intensive care unit (ICU), is associated with a mortality rate of up to 60%,[3] and markedly increases the cost of care.

The pathophysiology of AKI after cardiac surgery is complex. However, renal and especially medullary ischemia is a major mechanism of renal injury in this setting. Fenoldopam mesylate is a selective dopamine receptor D_1 agonist, which induces vasodilation of the renal, mesenteric, peripheral, and coronary arteries.[4] Unlike dopamine, fenoldopam has no significant affinity for D_2 receptors; thus, theoretically, it can induce greater vasodilation in the renal medulla than in the cortex.[5] Because of these hemodynamic effects, fenoldopam has been widely promoted for the prevention and therapy of AKI in the United States and many other countries with apparent favorable results in cardiac surgery[6] and in other settings.[7] Meta-analyses of randomized trials reported a reduction in the incidence and progression of AKI[8] together with decreased use of RRT and mortality.[8] However, the absence of a definitive trial leaves clinicians uncertain as to whether fenoldopam should be prescribed after cardiac surgery to prevent deterioration in renal function. To date, few interventions[9] and no pharmacological agents are proven to be efficacious in treating perioperative AKI. Recent literature[10,11] on treatment of cardiac surgery-associated AKI suggests that further studies with adequate statistical power are needed for fenoldopam.

Accordingly, we conducted an investigator-initiated, double-blind, randomized, placebo-controlled, multicenter trial to test whether fenoldopam infusion reduces the need for RRT, mortality rates, or both among critically ill cardiac surgery patients with AKI.

Methods

We performed a multicenter, prospective, randomized (1:1), double-blind, placebo-controlled, parallel-group study in 19 Italian hospitals in the period from March 2008 to April 2013 after local ethics committee approval. Patients aged 18 years or older signed written consent the day before surgery and were randomized while in the ICU after cardiac surgery if they had AKI, defined by the R (risk) criteria of the RIFLE (Risk, Injury, Failure, Loss, End Stage) classification[12] (≥50% postoperative increase in serum creatinine or oliguria, defined as urinary output <0.5 mL/kg/h for ≥6 hours).

Exclusion criteria included previous allergy to fenoldopam, glaucoma, fenoldopam administration within the previous 30 days, use of preoperative RRT (for these patients we did not request preoperative consent), expected ICU stay less than 24 hours after randomization, RRT already started or about to start, do-not-resuscitate orders, and participation in other randomized studies within the previous 30 days (these patients had signed written consent preoperatively but were not randomized even if they developed AKI) (**Figure 1**).

The study protocol (in Supplement 1)[13] and details of planned statistical analyses[14] have been published. Our report accords with the CONSORT 2010 statement.

Randomization and Treatment

Patients scheduled for cardiac surgery were assessed by a member of the local research team to explain the study protocol and obtain signed informed consent preoperatively. We used a computer-generated permuted block (up to a size of 20 and a 1:1 allocation) randomization sequence. Randomization was stratified by center. Treatment allocation was prepared by an independent operator not otherwise involved in the trial and was concealed by opaque, sealed envelopes that were sequentially numbered. Race/ethnicity was determined by clinicians and collected because there is an association between ethnicity and serum creatinine levels.

After patients developed AKI as defined, they were randomized to receive placebo (saline) or fenoldopam (Corlopam; Teva Italia) by continuous infusion. Fenoldopam and placebo were identical in shape, color, appearance, and size. The participants and ICU staff were blinded to treatment allocation throughout the entire study.

The study drug was administered as a continuous intravenous infusion for a total of 96 hours or until ICU discharge or death. The starting dose was 0.1 μg/kg/min (range, 0.025-0.3 μg/kg/min). Dose increases to 0.2 μg/kg/min and 0.3 μg/kg/min, reductions (for hypotension) to 0.05 μg/kg/min and 0.025 μg/kg/min, or discontinuations (for hypotension in spite of dose reduction) were allowed, and the dose was recorded hourly. Hypotension was defined by the clinician at the bedside.

Patient Evaluation and Follow-up

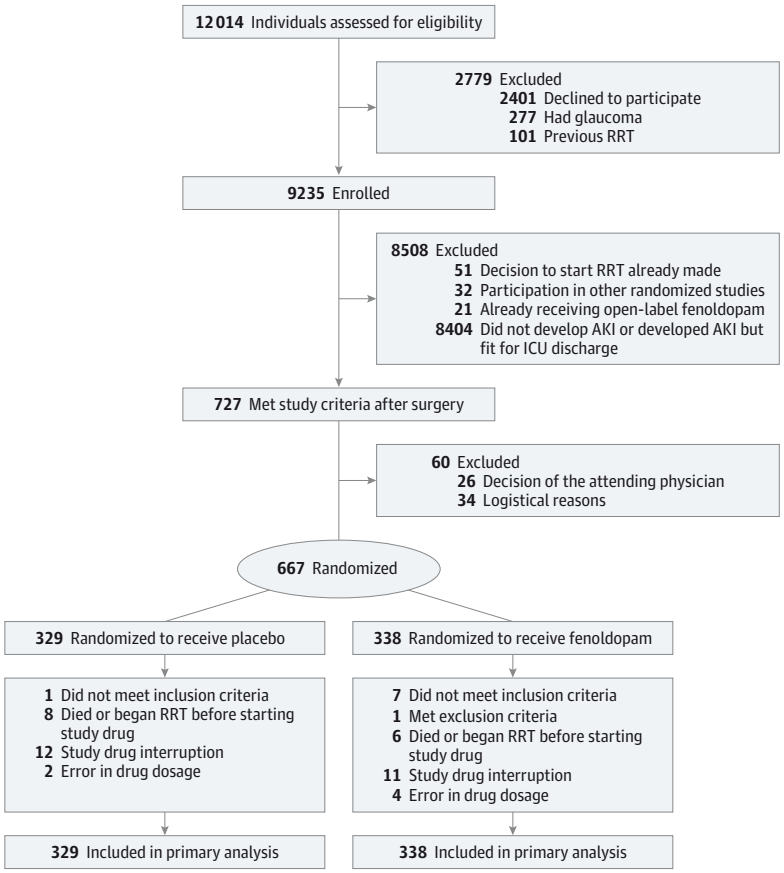
Initiation of RRT in the ICU (continuous venovenous hemofiltration or hemodialysis, according to center guidelines and protocols) was at discretion of the attending physicians because of the lack of guidelines or consensus statements to define widely accepted criteria for initiation. However, we collected the number of patients who reached predefined criteria for RRT (eTable 1 in Supplement 2) but did not receive RRT. We also used standardized criteria for ICU discharge to the postoperative cardiac surgery ward (peripheral capillary oxygen saturation ≥94% with a fraction of inspired oxygen ≤0.5 by face mask, adequate hemodynamic stability, absence of clinically 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, and no seizure activity). From the main ward, patients were then transferred to rehabilitation centers following local standards.

End Points

The primary end point was the rate of RRT administration in the ICU. Secondary end points included mortality (ICU mortality and mortality 30 days after surgery), time receiving mechanical ventilation (hours), length of ICU and hospital stay (days), peak serum creatinine level (mg/dL), and the incidence of AKI (according to the RIFLE score I and F definitions).[12]

Independent monitors verified adherence to required clinical trial procedures and confirmed accurate collection of data

Figure 1. Assessment, Randomization, and Follow-up of Study Patients



AKI indicates acute kidney injury; ICU, intensive care unit; RRT, renal replacement therapy (dialysis).

according to good clinical practice guidelines following current national and international requirements.[15]

Statistical Analysis and Sample Size

Following published literature,[8,16] we hypothesized a need for RRT of 5% in the treatment group vs 10% in the control group (50% relative risk reduction) and estimated that 870 patients would have to be enrolled (435 patients per group) in the trial to achieve an 80% power at an α of .05. This number was increased by 15% (leading to a total of 1000 patients) to take into account possible loss to follow-up or withdrawal of consent.

The first 2 planned interim analyses were conducted at 250 and 500 patients, and the safety committee recommended continued enrolment for this superiority trial. The third, planned interim analysis was anticipated (from 750 to 667 patients) as requested by the major ethics committee for the trial because of the overall high mortality rate. After such additional interim analysis, the study was stopped for futility as suggested by the independent safety committee. This decision was strengthened by the higher-than-expected rate of RRT (18% instead of the anticipated 10% in the placebo group), which increased the power to detect the hypothesized 50% relative risk reduction. Data analysis followed the method suggested by Reboussin et al[17] as applied in the dedicated software PASS (PASS version 08.0.11, NCSS) and based on previous work by Lan and DeMets[18] with continuity correction. Adjustments for multiple interim analyses are detailed in eTable 2 in Supplement 2.

Data were stored electronically and analyzed by Stata version 13.0 (StataCorp). All 667 randomized patients completed their follow-up 30 days after surgery for major outcomes (RRT and survival). Missing data for baseline characteristics and secondary outcomes were less than 10% if not otherwise stated in tables. We did not apply any imputation for missing data. All data analysis was carried out according to a preestablished intention-to-treat analysis plan,[13,14] including those few patients who were later discovered not to have satisfied the inclusion criteria (the serum creatinine increase from baseline was slightly <50% at randomization in 8 patients and 1 patient was later discovered to have recently received fenoldopam) or those who did not properly receive the study drug (they died or had RRT before receiving the study drug, or they had study drug interruption or the wrong dose per physician decision or mistake). We continued to collect all data about these patients even in the presence of a protocol deviation. We also performed per-protocol analyses as reported in eTables 3, 4, and 5 in Supplement 2.

Dichotomous data (including the primary outcome) were compared by 2-tailed χ^2 test with the Yates correction or Fisher exact test when appropriate. Continuous measurements were compared using the Mann-Whitney *U* test. Two-sided significance tests were used throughout. Data are presented as me-

dians (interquartile ranges [IQRs]) or as means (SDs). Means and standard deviations were used when the variables were normally distributed, while medians and IQRs were used with nonnormally distributed variables. Differences between the fenoldopam and placebo groups were assessed using univariate and multivariate regression analysis. For the univariate analysis, the cutoff level for significance was set at $P < .05$. Risk difference was assessed for categorical variables. Mean or percentile differences were calculated for continuous variables where appropriate. Multivariate regression analyses were performed for RRT and for the composite end point, RRT and/or death. A logistic regression model using stepwise selection was used. The prerandomization clinical data and centers were entered into the model if they had a univariate P value <.10. Treatment group (fenoldopam vs placebo) was forced into the multivariate model. In the multivariate analyses, clinical factors or potential confounding variables were expressed as odds ratio with 95% confidence intervals. In all the subgroup analyses, the heterogeneity was estimated by the χ^2 test for heterogeneity and the I^2 statistic.

All P values reported are 2-sided. The outcome parameters and the method of statistical analysis, including the subgroup analyses, were defined before unblinding, with the exception of the post hoc subgroup analyses that are described in eFigures 1, 2, and 3 in Supplement 2.

Results

From March 2008 to April 2013, 9235 patients signed the written consent in 19 centers. A total of 667 (7.2%) patients developed early postoperative AKI according to trial criteria and were randomized (338 to the fenoldopam group and 329 to placebo) and analyzed according to the intention-to-treat principle (Figure 1). All patients completed their follow-up 30 days after surgery.

The 2 groups of patients had similar characteristics at baseline (**Table 1** and **Table 2**). Mean age was 70 years, 423 (64%) were men, and 290 (48%) fulfilled the criteria for New York Heart Association (NYHA) class III or IV. Patients were randomized when reaching the AKI criteria at a median of 32 hours (IQR, 26-52 hours) after the beginning of surgery, with serum creatinine increasing from a mean (SD) of 1.1 (0.40) mg/dL to 2.0 (0.69) mg/dL in the fenoldopam group and from a mean (SD) of 1.1 (0.41) mg/dL to 2.0 (0.72) mg/dL in the placebo group.

Study Treatment

Study drug was administered at a mean dose of 0.12 µg/kg/min (fenoldopam) and 0.13 µg/kg/min (placebo) for a total of 62 (31.3) hours and 65 (30.3) hours, respectively (**Table 3**), with 653 of 667 patients effectively receiving it. Six patients in the fenoldopam group and 8 patients in the placebo group died or the decision to start RRT was made after the decision to randomize and before starting the study drug (Figure 1).

Study Outcomes

Acute kidney injury (Table 3) progressed to treatment with RRT in 69 of 338 patients (20%) in the fenoldopam group and 60 of 329 patients (18%) in the placebo group ($P = .47$). In addition, predefined criteria for RRT were reached by 25 patients (9 in the fenoldopam group and 16 in the placebo group), with an overall risk to develop severe AKI (Table 3) of 78 of 338 patients (23%) in the fenoldopam group vs 76 of 329 patients (23%) in the placebo group ($P = .99$). Serum creatinine values in the 2 groups were similar during the study period (**Figure 2**) and after excluding patients requiring RRT. Indications and treatment variables for RRT are reported in **Table 4**.

Intensive care unit mortality was 58 of 338 patients (17%) in the fenoldopam group and 58 of 329 patients (18%) in the placebo group ($P = .87$), while 30-day mortality was 78 of 338 (23%) in the fenoldopam group and 74 of 329 (22%) in the placebo group ($P = .86$).

Planned subgroup analyses and per-protocol analyses (eFigure 1 and eTables 3, 4, and 5 in Supplement 2) showed no difference in the rate of RRT in the treatment and control groups (all $P > .05$, test for interaction = .99). The rate of RRT according to center is reported in eFigure 2 (all $P > .05$, test for interaction = .48). Exploratory analyses including only centers using study drug at high doses did not show any difference (eFigure 3 with all $P > .05$, test for interaction = .91).

Factors associated with use of RRT are listed in eTable 6 in Supplement 2, and factors associated with the composite end point, RRT and/or death, are in eTable 7 in Supplement 2.

Safety and Toxicity

In the fenoldopam group, there was a statistically significant ($P = .003$) difference in arterial blood pressure compared with the placebo group (mean [SD], 124 [20.4] mm Hg vs 120 [18.5] mm Hg) 1 hour after starting the study drug (Table 3). Moreover, the number of patients experiencing hypotension during study drug infusion was 85 (26%) in the fenoldopam group vs 49 (15%) in the placebo group ($P = .001$) (Table 3).

Discussion

In this multicenter, double-blind, randomized clinical trial (RCT) among cardiac surgery patients with early renal dysfunction, we found that fenoldopam was not effective in attenuating the course of AKI from an early stage to initiation of RRT. There were also no significant differences in mortality rates or in any other secondary outcomes. The effect on RRT rate did not differ significantly in predefined subgroups. Fenoldopam induced greater hypotension than placebo. The study was stopped early for futility, as recommended by the study safety committee, based on a planned interim analysis.

Relationship to Previous Studies, Meta-analyses, and Consensus Statements

Our results are not in agreement with previous small RCTs,[23-27] subgroup analyses of middle-sized RCTs,[6,28] and meta-analyses[8,16] that suggested that fenoldopam is an effective nephroprotective agent. In fact, fenoldopam was considered to be one of the few drugs with a potential beneficial effect on renal function in critically ill patients with or at risk for AKI.[29-31]

Table 1. Patient Characteristics: Baseline and Intraoperative

	Placebo (n = 329)	Fenoldopam (n = 338)
Baseline		
Age, mean (SD), y	70 (9.4)	70 (8.2)
Female sex, No. (%)	128 (39)	111 (33)
Weight, mean (SD), kg	74 (14.3)	74 (14.6)
Height, mean (SD), cm	165 (9.0)	166 (8.5)
White race, No. (%)	323 (99)	336 (99)
Elective surgery, No. (%)	292 (90)	308 (92)
Reoperative surgery, No. (%)	68 (21)	57 (17)
Predictive scores, median (IQR)		
CICSS[19,a,b]	7 (5-9)	7 (4-9)
Thakar et al[20,a,c]	2 (1-4)	2 (1-4)
Mehta et al[21,d]	14 (12-18)	14 (12-18)
Wijeysundera et al[22,e]	2 (1-2)	2 (1-2)
Endocarditis, No. (%)[f]	17 (5.3)	10 (3.0)
Myocardial infarction, No. (%)[f]	40 (12)	32 (9.6)
Hypotension, No. (%)[f]	51 (16)	39 (12)
Hypertension, No. (%)[f]	78 (24)	92 (28)
Atrial fibrillation, No. (%)[f]	118 (37)	128 (38)
Left ventricular ejection fraction, mean (SD), %	52 (11.6)	52 (11.7)
NYHA classification, No. (%)		
I	31 (11)	43 (14)
II	113 (39)	131 (42)
III	124 (42)	112 (36)
IV	25 (8.5)	29 (9.2)
Pulmonary hypertension, No. (%)[f]	35 (11)	34 (10)
Chronic lung disease, No. (%)[f]	79 (25)	75 (23)
Peripheral vascular disease, No. (%)[f]	39 (12)	48 (15)
Diabetes under medical treatment, No. (%)	66 (21)	76 (23)
Obesity, No. (%)[f]	73 (22)	73 (22)
IABP, preoperative, No. (%)	10 (3.2)	15 (4.6)
Total bilirubin, preoperative, mean (SD), mg/dL	0.9 (0.62)	0.8 (0.50)
Intraoperative		
Cardiopulmonary bypass time, median (IQR), min	117 (86-161)	120 (90-161.5)
Aortic cross-clamp time, median (IQR), min	80 (56-114.5)	82 (60-111)
CABG surgery, No. (%)	139 (43)	148 (45)
Mitral valve surgery, No. (%)	142 (44)	153 (46)
For insufficiency	131 (41)	131 (41)
Aortic valve surgery, No. (%)	133 (41)	127 (38)
Tricuspid valve surgery, No. (%)	54 (17)	64 (19)
Ascending aorta surgery, No. (%)	49 (15)	37 (11)
Other cardiac surgery, No. (%)	77 (24)	85 (26)
Transfusion, intraoperative, No. (%)	193 (60)	168 (52)
Hematocrit, minimum intraoperative, mean (SD), %	23.3 (3.46)	23.7 (3.78)

Abbreviations: AKI, acute kidney injury; CABG, coronary artery bypass graft; IABP, intra-aortic balloon pump; ICU, intensive care unit; IQR, interquartile range; NYHA, New York Heart Association.

SI conversion factor: To convert bilirubin to µmol/L, multiply by 17.104.

[a] Missing values between 10% and 15%.

[b] The Continuous Improvement in Cardiac Surgery Study score.[19] Score range, 0-32: low risk, 0-5; medium, 6-10; high, 11-15; very high, ≥16.

[c] The clinical score to predict AKI after cardiac surgery.[20] Score range, 0-17: low risk, 0-2; medium, 3-5; high, 6-8; very high, >8.

[d] The simplified model to predict postoperative dialysis.[21] This score identifies as predictors of risk serum creatinine, age, surgery type (CABG plus valve or valve only vs CABG only), diabetes, recent myocardial infarction, race, chronic lung disease, reoperation, NYHA class, and cardiogenic shock. Score range, 0-83. Risk of postoperative dialysis is expressed as continuous, ranging from 0% to >85%.

[e] The simplified renal index scoring scheme for estimating risk of postoperative renal replacement therapy.[22] Score range, 0-9: low risk, ≤1; intermediate, 2-3; high, ≥4.

[f] Comorbidities were documented in the medical history. Hypotension was defined as systolic blood pressure (SBP) <120 mm Hg before surgery. Hypertension was defined as SBP >160 mm Hg before surgery. Atrial fibrillation was documented as paroxysmal or permanent. Pulmonary hypertension was defined as pulmonary artery pressure >60 mm Hg. Obesity was defined as body mass index ≥30 (calculated as weight in kilograms divided by height in meters squared).

Cardiac surgery appeared to be the best setting to test the putative beneficial renal effects of fenoldopam, both because of previously published small RCTs[23-27] and meta-analyses[8,16] and because of pathophysiological principles. Although the etiology of AKI in cardiac surgery is multifactorial,[19] the reduction in cardiac output that is frequently observed in patients undergoing cardiac surgery may play a major role by decreasing renal perfusion through a reduction in renal blood flow and through the activation of the sympathetic nervous system and the renin-angiotensin system.[32] In this setting, a selective renal vasodilator appeared a logical and promising intervention.

Moreover, dopamine receptors are widely expressed in the kidney. D_1 receptors are expressed in the medial layer of renal vessels and induce a dose-dependent vasodilation of renal capacitance vessels. Fenoldopam activates adenylate cyclase, causing arterial vasodilatation and natriuresis by inhibiting so-

Table 2. Patient Characteristics: Renal Function and ICU (at Randomization)

	Placebo (n = 329)	Fenoldopam (n = 338)
Renal Function		
Creatinine level		
Preoperative, by quartile, No. (%)		
First (<0.084 mg/dL)	84 (26)	81 (24)
Second (0.85-1.00 mg/dL)	88 (27)	88 (26)
Third (1.01-1.29 mg/dL)	74 (23)	80 (24)
Fourth (>1.29 mg/dL)	78 (24)	85 (25)
At randomization, mean (SD), mg/dL	2.0 (0.72)	2.0 (0.69)
Peak in ICU, mean (SD), mg/dL	2.4 (1.05)	2.5 (1.03)
Creatinine ≥1.5 mg/dL, No. (%)		
Preoperative	43 (16)	50 (15)
At randomization	247 (76)	258 (77)
eGFR, No. (%), mL/min/1.73 m^2		
Chronic kidney disease stage 3-5 (eGFR <60)	118 (36)	123 (37)
≥90	38 (12)	47 (14)
60-89	167 (52)	163 (49)
45-59	58 (18)	58 (17)
30-44	47 (23)	46 (37)
≤29	13 (4.1)	19 (5.7)
ICU		
Blood pressure, mean (SD), mm Hg		
Systolic	122 (20.5)	123 (20.7)
Mean arterial pressure	79 (13.5)	80 (12.5)
Diastolic	59 (11.6)	59 (11.8)
Inotropic drugs, No. (%)[a]	218 (75)	241 (81)
Diuretic drugs, No. (%)[a]	246 (85)	246 (82)
Mechanical ventilation, No. (%)	120 (40)	134 (41)
IV fluids in last 6 h before randomization, median (IQR), mL	620 (400-920)	610 (360-1000)
Transfusions in ICU, No. (%)[a]	198 (69)	196 (68)
Main cause of AKI, No. (%)		
Low cardiac output syndrome	142 (46)	158 (49)
Renal hypoperfusion	70 (23)	70 (22)
Major cardiac surgery	48 (15)	42 (13)
Hypovolemia	16 (5.1)	20 (6.1)
Nephrotoxic drugs	13 (4.2)	12 (3.7)
Other cause	12 (3.7)	15 (4.6)
Microembolization	6 (1.9)	5 (1.5)
Septic shock	4 (1.3)	4 (1.2)
Time from beginning of surgery to randomization, median (IQR), h	32.5 (25.5-52.0)	32.5 (26.0-51.4)
Met R criteria of RIFLE, No. (%)[12b]		
Oliguria[a]	55 (20)	67 (23)
Creatinine	264 (83)	265 (80)

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; RRT, renal replacement therapy.

SI conversion factor: To convert creatinine to μmol/L, multiply by 88.4.

[a] Missing values between 10% and 15%.

[b] RIFLE is a classification scheme for AKI devised by the Acute Dialysis Quality Initiative Group. Acronym indicates the 5 stages of the classification: risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage kidney disease. The patient is classified according to serum creatinine (SCr) level and urine output (UO) separately and can fulfill criteria for classification stages through changes in each or both SCr and UO, whichever is worst. Changes are intended from baseline values (preoperative data in our study). The criteria for each stage are as follows: Stage R: SCr ×1.5 (or GFR decrease >25%) or UO <0.5 mL/kg/h for 6 h. Stage I: SCr ×2 (or GFR decrease >50%) or UO <0.5 mL/kg/h for 12 h. Stage F: SCr ×3 (or GFR decrease >75%) or UO <0.3 mL/kg/h for 24 h or anuria for 12 h. Stage L: persistent AKI (need for RRT for >4 wk). Stage E: end-stage renal disease (need for RRT for >3 mo). Note that the F stage is achievable even if the increase in SCr is <3 times the baseline value as long as the new SCr is >4.0 mg/dL with an acute increase of ≥0.5 mg/dL. The designation RIFLE-F_C should be used in this case to denote "acute-on-chronic" disease.

dium-potassium ATPase-dependent processes at the proximal convoluted tubule and in the thick part of the ascending loop of Henle.[33] Fenoldopam,[34] 0.1 μg/kg/min, significantly increases renal blood flow in hemodynamically stable patients with preserved renal function undergoing cardiac surgery.

The results of our study differ from those of several previous small RCTs that showed a preserved creatinine clearance in elective coronary revascularization patients,[25] a decrease in postoperative serum creatinine level in patients who had a serum creatinine level greater than 1.5 mg/dL before cardiac surgery,[26] and a lower incidence of AKI after complex cardiac operations.[27] More importantly, our findings also differ from the results of a double-blind, single-center RCT[24] with 193 patients and a subgroup analysis of a multicenter RCT,[6] respectively, in which fenoldopam had been used in the cardiac surgery setting to prevent AKI[24] and its progression.[6]

Implication of Study Findings

Fenoldopam is available in Europe and the United States. It was approved by the US Food and Drug Administration (FDA) in 1997

Table 3. Outcomes, End Points, and Adverse Events

	Placebo (n = 329)	Fenoldopam (n = 338)	Mean, Risk, or Percentile Difference (95% CI)	*P* Value
End points, No. (%)				
RRT in ICU	60 (18)	69 (20)	−2.17 (−8.16 to 3.81)	.47
Mortality in ICU	58 (18)	58 (17)	0.47 (−5.28 to 6.22)	.87
Mortality at 30 d[a]	74 (22)	78 (23)	−0.58 (−6.95 to 5.78)	.86
RRT according to standardized criteria	76 (23)	78 (23)	0.0002 (−0.06 to 0.06)	.99
RRT and/or mortality in ICU	92 (28)	98 (29)	−0.01 (−0.8 to 0.06)	.77
ICU				
Study drug administration				
Mean dose, µg/kg/min	0.13 (0.06)	0.12 (0.06)	0.01 (−0.004 to 0.02)	.006
Administration time, h	62 (31.3)	65 (30.3)	−2.74 (−7.42 to 1.94)	.25
Pressure 1 h after randomization, mm Hg				
Systolic blood pressure	124 (20.4)	120 (18.5)	4.54 (1.55 to 7.53)	.003
Mean arterial pressure	79 (12.9)	77 (11.9)	2.75 (0.63 to 4.87)	.01
Diastolic blood pressure	59 (11.2)	57 (10.9)	1.81 (0.09 to 3.51)	.04
Inotropic drugs 1 h after randomization, No. (%)	206 (71)	230 (77)	−6.16 (−13.21 to 0.89)	.09
Diuretic drugs first day after randomization, No. (%)	236 (82)	230 (79)	3.46 (−2.98 to 9.90)	.29
Hypotension during study drug infusion, No. (%)[b]	49 (15)	85 (26)	−10.39 (−16.55 to 4.24)	.001
Mechanical ventilation time, median (IQR), h	24 (15-72)	27 (17-70)	−1.00 (−4.75 to 2.00)	.50
Time in ICU after randomization, median (IQR), d	4 (2-7)	4 (2-6)	0.00 (0.00 to 0.00)	.74
IABP, No. (%)	52 (16)	66 (20)	−3.63 (−9.44 to 2.17)	.22
Catecholamine drugs for >48 h, No. (%)	178 (56)	189 (58)	−1.82 (−9.46 to 5.82)	.64
Sepsis, No. (%)	37 (12)	37 (11)	0.21 (−4.71 to 5.14)	.93
Tracheostomy, No. (%)	34 (11)	27 (8.4)	2.40 (−2.16 to 6.98)	.30
Hypoacusia, No. (%)	2 (0.7)	5 (1.6)	−0.90 (−2.52 to 0.71)	.27
Unblinding, No. (%)	0	0		
Adverse reactions, No. (%)	0	0		
RIFLE criteria, No. (%)[c]				
Injury (increased creatinine ×2)	189 (59)	177 (53)	5.88 (−1.70 to 13.47)	.13
Failure (increased creatinine ×3 or ≥4.0 mg/dL)	63 (20)	57 (17)	2.56 (−3.37 to 8.48)	.39
Surgical Ward				
In-hospital complications after ICU discharge, No. (%)[d]	59 (23)	59 (22)	1.05 (−6.17 to 8.28)	.77
Cardiac	22 (8.7)	23 (8.8)	−0.01 (−4.89 to 4.86)	.99
Pulmonary	14 (5.6)	17 (6.5)	−0.90 (−5.01 to 3.19)	.66
Renal[e]	4 (1.6)	7 (2.7)	−1.07 (−3.56 to 1.40)	.39
Infectious	10 (4.0)	10 (3.8)	0.16 (−3.17 to 3.50)	.92
Hemorrhagic	5 (2.0)	2 (0.8)	1.22 (−0.79 to 3.24)	.23
Multiorgan failure	3 (1.2)	3 (1.1)	0.05 (−1.80 to 1.90)	.95
Neurologic	3 (1.2)	3 (1.1)	−0.05 (−1.80 to 1.90)	.95
Sternal wound infection	3 (1.2)	2 (0.8)	0.43 (−1.27 to 2.13)	.62
Other	2 (0.8)	2 (0.8)	−0.03 (−1.48 to 1.50)	.96
Time in hospital after surgery, median (IQR), d				
Overall population[d]	15 (10-28)	15 (11-24)	0.00 (−1.00 to 2.00)	.71
Survivors group only[d]	14 (11-23.5)	15 (11-22)	1.00 (−1.00 to 2.00)	.44
Time in hospital after randomization, median (IQR), d	13 (9-25)	13 (9-22)	0.00 (−1.00 to 2.00)	.82
Urea at hospital discharge, mg/mL[d]	75 (56.6)	79 (64.7)	−4.17 (−15.94 to 7.59)	.48
30-d follow-up				
New hospitalization, No. (%)[d]	57 (25)	43 (19)	6.67 (−0.95 to 14.29)	.09
Hypoacusia, No. (%)[d]	11 (5.2)	7 (3.2)	2.06 (−1.71 to 5.83)	.28
Last creatinine, mg/mL[d]	1.3 (0.66)	1.4 (0.68)	−0.11 (−0.27 to 0.04)	.16

Abbreviations: IABP, intra-aortic balloon pump; ICU, intensive care unit; IQR, interquartile range; RRT, renal replacement therapy.

SI conversion factor: To convert creatinine to µmol/L, multiply by 88.4.

[a] Mortality at 30 d follows the definition of operative mortality outlined by the Society of Thoracic Surgeons: all deaths occurring during the acute episode of care in which the operation was performed (this includes patients transferred to other acute care facilities), even if after 30 d, and those deaths occurring after discharge from the hospital but within 30 d of the procedure unless the cause of death is clearly unrelated to the operation.

[b] Hypotension during study drug infusion was defined as systolic blood pressure <90 mm Hg.

[c] Scoring system to evaluate risk, injury, failure, loss, and end-stage kidney injury.

[d] Missing values between 10% and 15%.

[e] Renal complications intended as new worsening of renal function.

and indicated for in-hospital, short-term management of severe hypertension. Fenoldopam has not gained FDA approval for renal indications, although it has been widely used off-label in the United States for kidney protection in various settings.[8,16] Our trial demonstrates that fenoldopam is not effective for the treatment of AKI in cardiac surgery and, in addition, suggests that it might not be effective for other patients with early AKI. These findings are in keeping with those of treatment with dopamine and suggest that either dopaminergic stimulation is inadequate in this setting or that the mechanism for AKI after cardiac surgery does not involve renal vasoconstriction or both.

Strengths and Limitations

This trial was randomized and double-blind in design with allocation concealment, thus reducing the risk of selection bias. It focused on patient-centered, objectively verifiable, and clinically relevant outcomes, thus reducing ascertainment bias. The intervention had biological plausibility and was supported by a series of single-center studies with promising results and by meta-analyses, thus justifying the initial trial hypothesis. Our results appear likely to carry external validity because patients were recruited in university and nonuniversity hospitals with the use of pragmatic inclusion criteria and few exclusion criteria. The results are also likely to have high reproducibility, as the trial protocol was simple, with routine practice maintained throughout, except for fenoldopam or placebo infusion.

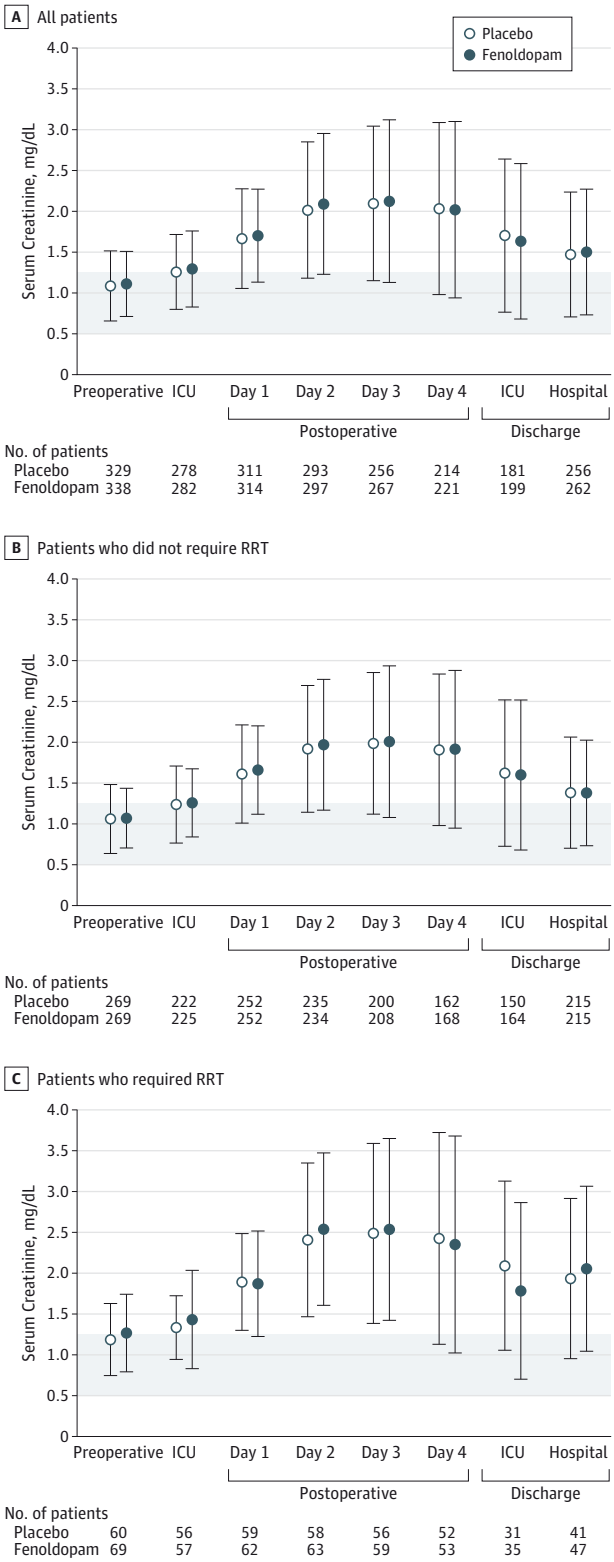
Cardiac surgery–related AKI is characterized by an abrupt deterioration in kidney function after cardiac surgery as evidenced by a reduction in the glomerular filtration rate. Importantly, this deterioration is not always detected in the first 24 to 48 hours using conventional monitoring by serum creatinine levels, especially because of cardiopulmonary bypass dilution effects. Furthermore, several patients have isolated AKI not requiring ICU care. As a consequence, the low (7.2%) incidence of AKI reported in this study population does not correspond to the overall incidence of postoperative AKI after cardiac surgery, and the same selection bias applies to the apparently high incidence (19%) of RRT in our patients with AKI.

Our study has some limitations. The study was interrupted for futility, and fewer patients were randomized than planned. However, this is the largest multicenter RCT of fenoldopam. In addition, the case for the futility of the intervention was clear and subject to the recommendations of the safety committee.

Hypotension was more frequent in the fenoldopam group, suggesting that the drug may have been administered at too high a dose. It is possible that fenoldopam caused harm (eTable 8 in Supplement 2). However, our study had insufficient power to detect such harm. It is also possible that hypotension may have allowed clinicians to guess which treatment patients were allocated to receive. However, hypotension is very common after cardiac surgery, making such post hoc treatment identification unlikely. We did not collect information on the intensity or duration of hypotension. Such hypotension may have attenuated any beneficial effects that the drug may have on renal function.

Our subgroup analyses failed to identify differences. However, our subgroups were small, and a type II error cannot be excluded. The reported incidence of severe AKI requiring RRT

Figure 2. Serum Creatinine Values by Treatment Group



Scores are reported as mean (SD). Serum creatinine values are similar between treatment groups at each time point, and they significantly differ from baseline with an analysis-of-variance test. To convert creatinine to µmol/L, multiply by 88.4. Shaded area indicates normal range of serum creatinine values, 0.5-1.25 mg/dL.

Table 4. Indications and Treatment Variables for RRT

Variable	Placebo (n = 329)	Fenoldopam (n = 338)	Mean, Risk, or Percentile Difference (95% CI)	P Value
Most relevant indication, No./ Total No. (%)[a]				
Oliguria	28/51 (55)	25/59 (42)	0.53 (0.43 to 0.63)	.50
High serum creatinine or urea level[a]	11/51 (22)	12/59 (20)		
Fluid overload	7/51 (14)	14/59 (24)		
Immunomodulation (sepsis)	1/51 (2.0)	4/59 (6.8)		
Metabolic acidosis[a]	3/51 (5.9)	2/59 (3.4)		
Hyperkalemia[a]	1/51 (2.0)	2/59 (3.4)		
Creatinine at RRT start, mean (SD), mg/mL	3.1 (1.39)	3.3 (1.32)	−0.18 (−0.70 to 0.32)	.47
Urea at RRT start, mean (SD), mg/mL	140 (79.9)	146 (84.8)	−5.48 (−40.18 to 29.21)	.75
Diuresis 6 h before CVVH application, median (IQR), mL/h	30 (13.3 to 73.3)	37 (16.7 to 136.7)	−1.66 (−13.33 to 12.00)	.85
Time receiving RRT, median (IQR), h	63 (35.5 to 189)	58 (34 to 178)	4.67 (−21.75 to 30.33)	.72

Abbreviations: CVVH, continuous venovenous hemofiltration; IQR, interquartile range; RRT, renal replacement therapy.

SI conversion factor: To convert creatinine to μmol/L, multiply by 88.4.

[a] Most relevant indication is a multimodal variable; risk difference for this variable is a cumulative measure. High creatinine was defined as a prerandomization level >6 mg/dL. Hyperkalemia was defined as a prerandomization level >6.5 mmol/L. Metabolic acidosis was defined as bicarbonate level ≤10 mEq/L.

was high; however, this was a high-risk population (patients were on average 70 years old and half were NYHA class III or IV) with a complicated postoperative course after cardiac surgery (ongoing AKI in patients not fit for ICU discharge), and the rate of RRT was high in all centers (eFigure 2 in Supplement 2), indicating that illness severity played an important role in this population. The high surgical risk of these patients, the long time on cardiopulmonary bypass and aortic cross-clamping, the need to receive support with catecholamine, and the development of low cardiac output syndrome all likely contributed to the high incidence of RRT and consequent mortality. The initiation of dialysis was left to the judgment of the attending physician because of the lack of widely accepted criteria or guidelines for initiating RRT. However, RRT initiation is unlikely to have been subject to bias because of the double-blind design of the trial. Furthermore, we found no differences between fenoldopam and placebo when using standardized criteria for RRT or the RIFLE criteria for AKI progression, both of which are independent of clinical decisions (Table 2).

Our findings differ from those of several small previous studies. However, the limitations of single-center randomized trials[35] and meta-analyses are well known and may account for the difference in outcome between our study and previous trials or meta-analyses and thus explain the discrepancy between the hypothesized effect and actual results of this multicenter RCT.

Conclusions

Among patients with AKI after cardiac surgery, fenoldopam infusion, compared with placebo, did not reduce the need for RRT or risk of 30-day mortality but was associated with an increased rate of hypotension. Given the cost of fenoldopam, the lack of effectiveness, and the increased incidence of hypotension, the use of this agent for renal protection in these patients is not justified.

ARTICLE INFORMATION

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