

Fenoldopam Mesylate for the Prevention of Contrast-Induced Nephropathy

A Randomized Controlled Trial

Gregg W. Stone, MD

Peter A. McCullough, MD, MPH

James A. Tumlin, MD

Norman E. Lepor, MD

Hooman Madyoon, MD

Patrick Murray, MD

Andrew Wang, MD

A. Alan Chu, MD

Gary L. Schaer, MD

Melissa Stevens, MD

Robert L. Wilensky, MD

William W. O'Neill, MD

for the CONTRAST Investigators

CONTRAST-INDUCED NEPHROPATHY, which occurs in 1% to 15% of all patients undergoing invasive angiographic procedures and in as many as 50% of patients with preexisting renal insufficiency or diabetes mellitus, is one of the most common causes of hospital-acquired acute renal failure.¹⁻⁷ The development of contrast-induced nephropathy after diagnostic coronary angiography and percutaneous intervention is associated with prolonged hospitalization, marked increases in morbidity and early and late mortality, and costs.⁴⁻⁸ Other than hydration,^{9,10} most prior studies of measures to prevent contrast-induced nephropathy have either been neutral,¹¹ found deleterious effects,¹²⁻¹⁵ or in the case of N-acetylcysteine, reported conflicting results.¹⁶⁻¹⁹

Context The development of contrast-induced nephropathy in patients undergoing invasive cardiac procedures is associated with a marked increase in cardiovascular morbidity and mortality. Fenoldopam mesylate, a specific agonist of the dopamine-1 receptor, preserves renal blood flow after iodinated contrast administration and has shown promise in ameliorating contrast nephropathy in previous observational and small randomized trials.

Objective To examine the efficacy of fenoldopam mesylate in preventing contrast nephropathy after invasive cardiovascular procedures.

Design Prospective, placebo-controlled, double-blind, multicenter randomized trial with serial serum creatinine levels measured at a central biochemistry laboratory (at baseline and 1, 24, 48, and 72 to 96 hours after study drug administration) and 30-day clinical follow-up.

Patients and Setting Between March 2001 and July 2002, 315 patients with creatinine clearance less than 60 mL/min (1.00 mL/s) at 28 centers in the United States were randomized to receive fenoldopam mesylate (n=157) or placebo (n=158).

Interventions Patients were hydrated and randomized to receive intravenous fenoldopam (0.05 µg/kg/min titrated to 0.10 µg/kg/min) vs matching placebo, starting 1 hour prior to angiography and continuing for 12 hours.

Main Outcome Measure Contrast-induced nephropathy, defined as an increase of 25% or more in serum creatinine level within 96 hours postprocedure.

Results Mean (SD) patient age was 70 (11) years, and 49% had diabetes mellitus. Mean (SD) baseline creatinine clearance was 29.0 (10.0) mL/min (0.48 [0.16] mL/s) (range, 7.5-56.8 mL/min [0.12-0.94 mL/s]), and 157 (108) mL of contrast was administered during the procedures. The primary end point of contrast-induced nephropathy occurred in 33.6% of patients assigned to receive fenoldopam vs 30.1% assigned to receive placebo (relative risk, 1.11; 95% confidence interval, 0.79-1.57; *P* = .61). There were no significant differences in the 30-day rates of death (2.0% vs 3.8%, *P* = .50), dialysis (2.6% vs 1.9%, *P* = .72), or rehospitalization (17.6% vs 19.9%, *P* = .66) in fenoldopam vs placebo randomized patients, respectively.

Conclusion The selective dopamine-1 agonist fenoldopam mesylate does not prevent further renal function deterioration after contrast administration in patients with chronic renal insufficiency.

JAMA. 2003;290:2284-2291

www.jama.com

Author Affiliations and Names of the Investigators, Research Coordinators, and Institutions Participating in the CONTRAST Trial appear at the end of the article.

Financial Disclosures: Drs Stone, McCullough, Tumlin, Madyoon, and Murray have served as

consultants and/or received research grants from Abbott Laboratories, the manufacturer of fenoldopam. **Corresponding Author and Reprints:** Gregg W. Stone, MD, Cardiovascular Research Foundation, 55 E 59th St, Sixth Floor, New York, NY 10022 (e-mail: gstone@crf.org).

Fenoldopam mesylate is a specific dopamine-1 receptor agonist that produces systemic, peripheral, and renal arterial vasodilatation.^{20,21} Approved by the Food and Drug Administration for the treatment of urgent and emergent hypertension, fenoldopam has been shown to increase renal plasma flow in patients with and without chronic renal insufficiency^{21,22} and to prevent the reduction in glomerular filtration rate that occurs in dogs after contrast administration.²³ In humans, fenoldopam preserves or increases renal plasma flow after iodinated contrast, which is otherwise markedly reduced.²⁴ Single and multicenter registry experiences with this agent as a prophylactic measure to reduce contrast-induced nephropathy have been favorable.^{25,26} We therefore performed a large-scale multicenter, prospective, double-blind, placebo-controlled randomized trial to determine the safety and efficacy of fenoldopam mesylate to prevent contrast-induced nephropathy in patients with chronic renal insufficiency undergoing invasive cardiac procedures.

METHODS

Study Population

The CONTRAST trial was a randomized, multicenter, double-blind, placebo-controlled, phase 3 study of an intravenous infusion of fenoldopam mesylate in patients at risk for developing contrast-induced nephropathy undergoing diagnostic and/or interventional cardiology procedures. Consecutive eligible patients 18 years of age or older with a creatinine clearance of less than 60 mL/min (1.00 mL/s) (calculated by the Cockcroft-Gault formula²⁷) and not undergoing dialysis were considered for enrollment at academic and community-based institutions. The principal exclusion criteria included known severe allergy to contrast media that could not be premedicated; known allergy to fenoldopam or its infusion components such as metabisulfite or sulfites; acute renal failure or unstable renal function; systolic blood pressure less than 100 mm Hg; acute myocardial infarction or decompensated heart or respiratory fail-

ure; contraindication to dopaminergic agents (eg, history of increased intraocular pressure or glaucoma); current use of mannitol or dopamine; planned addition, discontinuation, or dose adjustment of trimethoprim, cimetidine, metoclopramide, bromocriptine, levodopa, nonsteroidal anti-inflammatory drugs, or catechol-*O*-methyltransferase inhibitors during the study; exposure to iodinated contrast within the previous 10 days; other serious medical conditions likely to interfere with data collection or follow-up; and participation in other investigational protocols within 30 days. The study was approved by the institutional review board at each participating center, and consecutive, eligible patients signed informed, written consent.

Protocol

After patient eligibility was confirmed and consent obtained, a 0.45% normal saline infusion was started at 1.5 mL/kg/h (or 1.0 mL/kg/h if heart failure was present) for 2 to 12 hours prior to study drug administration. Patients were then randomized 1:1 to receive fenoldopam or matching placebo, stratified by the presence or absence of pharmacologically treated diabetes. Two concealed randomization schedules (for diabetic and nondiabetic patients), each in blocks of 6, were prepared by the sponsor and maintained by a research pharmacist at each site. When informed an eligible patient had been enrolled, the research pharmacist allocated the patient to the next sequential randomization number. The study drug infusion was then prepared by the research pharmacist and initiated by the nursing staff 1 hour (± 30 minutes) prior to catheterization at 0.05 μ g/kg/min and increased in 20 minutes to 0.10 μ g/kg/min if tolerated. The infusion was then maintained during angiography and percutaneous intervention and continued for 12 hours postprocedure. Formal recommendations were in place to downtitrate the study drug for mild hypotension or tachycardia without symptoms and to discontinue the drug for severe hemodynamic disturbance or symptoms. Each 1 mL of placebo contained matching amounts of

all excipient components (ie, sodium metabisulfite [1 mg], citric acid anhydrous [3.44 mg], sodium citrate dihydrate [0.61 mg], and propylene glycol [518 mg]) in a sterile aqueous solution. All caregivers, trial participants, patients, and committee members were blinded to the group assignment, with the exception of (1) the research pharmacist, who had no patient care responsibilities and who did not interact with other study participants and (2) select personnel from the sponsor for purposes of performing drug accountability.

All in-hospital volume inputs and outputs were carefully collected and recorded. Volume losses such as blood, urine output, vomiting, diarrhea, excessive diaphoresis, and the like were replaced in accordance with standard medical practices. Blood samples were scheduled to be drawn and sent to a central biochemistry laboratory for serum creatinine measurements after the prestudy drug hydration period (but before study drug administration) and at 24 hours (or at the time of discharge, if earlier), 48 to 60 hours, and 72 to 96 hours following the completion of study drug administration. If patients were discharged in less than 96 hours, research nurses traveled to the patients' homes and obtained blood samples at the designated times.

Data Collection and Management

Clinical data were prospectively collected by dedicated research nurses, and 100% of case report form data were verified on-site by independent study monitors. Data were double-key entered into a computerized database. An independent data and safety monitoring board periodically assessed safety throughout the study.

Study End Points and Statistical Analysis

The primary efficacy end point was the development of contrast-induced nephropathy, defined as an increase in serum creatinine level of 25% or more from baseline to the maximum value obtained within the 24- to 96-hour period following completion of study drug

administration. Additional efficacy end points included measurements of contrast-induced nephropathy defined as 2 consecutive increases in serum creatinine level of 25% or more, and an increase in serum creatinine level of 0.5 mg/dL (44.2 μ mol/L) or more. Pre-specified clinical end points included

the duration of the index hospitalization and the 30-day rates of death, dialysis, and rehospitalization.

The sample size was selected to demonstrate a reduction in the primary end point of contrast-induced nephropathy from 30% in the control group to 15% in the treatment group. Using a χ^2

test for 2×2 tables and a 2-sided α of .05, 268 randomized patients afforded the study 80% power. Recruitment of approximately 300 patients was thus planned to accommodate incomplete data ascertainment or follow-up.

The primary end point was analyzed by Cochran-Mantel-Haenszel methodology, using diabetic status as the stratification variable. Other categorical variables were compared by the Fisher exact test. Continuous variables are presented as mean (SD) and were compared with 1-way analysis of variance, or for outcomes measures, by the nonparametric Wilcoxon rank sum test. The influence of baseline subgroup demographic, laboratory, and procedural variables on the primary end point were evaluated, and interaction effects were examined by Breslow-Day tests for homogeneity.

Unless otherwise stated, all analyses were by intention to treat (ie, all available data were analyzed from all randomized patients according to their initial treatment assignment, regardless of the actual medication, dose, and duration administered). All *P* values are 2-sided.

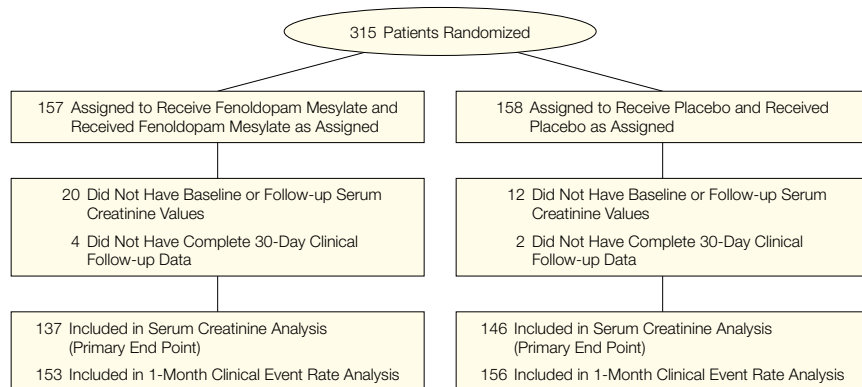
An independent data and safety monitoring board met after approximately 150 patients were enrolled to consider premature termination of the trial if the primary end point had been met with an α of .0001, recommending that the trial continue to completion. Thus, final *P* values of <.0499 were required for statistical significance of the primary end point. SAS version 6.12 (SAS Institute Inc, Cary, NC) was used for the data analysis.

RESULTS

Patient Population and Baseline Characteristics

Between March 2001 and July 2002, 315 patients at 28 centers in the United States were randomized to receive fenoldopam mesylate (*n* = 157) or placebo (*n* = 158) (FIGURE 1). Baseline demographic features were well matched between the 2 groups, except for a slightly higher incidence of hypertension in those assigned to re-

Figure 1. Randomization Flow and Follow-up Process



The number of patients eligible for randomization was not tracked during the course of enrollment.

Table 1. Baseline Clinical Features

	Fenoldopam Mesylate (<i>n</i> = 157)	Placebo (<i>n</i> = 158)
Demographic		
Age, y		
Mean (SD)	69.0 (11.1)	70.2 (10.4)
Range	38.9-93.3	44.3-89.5
Weight, kg		
Mean (SD)	83.7 (18.5)	84.5 (16.6)
Range	49.0-150.0	52.6-144.0
Male sex, No. (%)	108 (68.8)	100 (63.3)
Medical history, No. (%)		
Diabetes mellitus	77 (49.0)	76 (48.1)
Insulin dependent	45 (28.7)	45 (28.5)
Hypertension	142 (90.4)	128 (81.0)
Hypercholesterolemia	121 (77.1)	128 (81.0)
Prior myocardial infarction	83 (52.9)	72 (45.6)
Prior congestive heart failure	77 (49.0)	73 (46.2)
Prior coronary bypass surgery	51 (32.5)	54 (34.2)
Prior percutaneous intervention	60 (38.2)	57 (36.1)
Peripheral vascular disease	50 (31.8)	61 (38.6)
Unstable angina	87 (55.4)	86 (54.4)
Clinical, mean (SD)		
Systolic arterial pressure, mm Hg	139 (21)	145 (22)
Diastolic arterial pressure, mm Hg	70 (13)	72 (12)
Heart rate, beats/min	68 (13)	69 (12)
Serum creatinine, mg/dL	1.82 (0.71)	1.81 (0.83)
Creatinine clearance, mL/min	29.0 (9.8)	29.1 (10.3)

SI conversion factors: To convert serum creatinine to μ mol/L, multiply by 88.4; creatinine clearance to mL/s, multiply by 0.0167.

ceive fenoldopam ($P=.02$) (TABLE 1). The study cohort was elderly and characterized by a high frequency of diabetes mellitus, prior myocardial infarction, and congestive heart failure. The mean creatinine clearance was 29 mL/min (0.48 mL/s), ranging from 7.5 to 56.8 mL/min (0.12-0.94 mL/s).

Hydration, Drug Administration, and Procedural Data

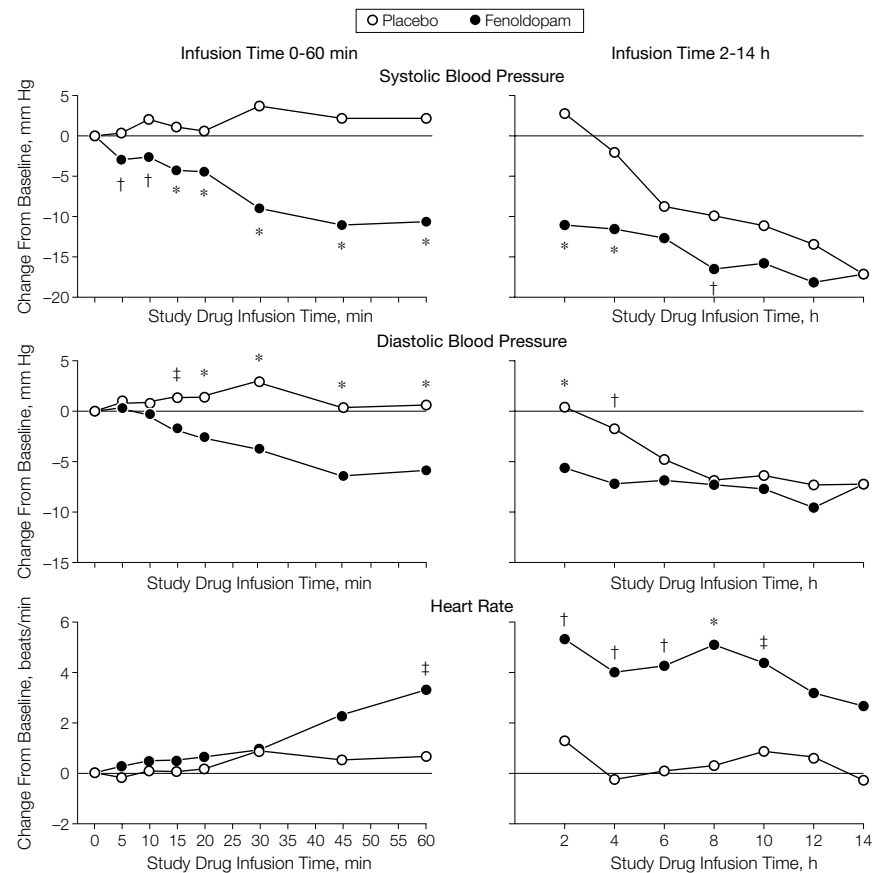
After consent and prior to catheterization, patients assigned to receive fenoldopam were intravenously hydrated with 692 (468) mL of fluid over 8.2 (4.9) hours, compared with placebo patients who received 666 (391) mL over 7.5 (4.3) hours (data are mean [SD]; $P=.60$ for amount and $P=.15$ for duration). The total amount of hydration received after the catheterization through the day postprocedure was 2829 (1223) mL in the fenoldopam group and 2832 (1095) mL in the placebo group (data are mean [SD]; $P=.98$). All 315 randomized patients received study drug. Fenoldopam administration resulted in a mild to moderate decrease in blood pressure and increase in heart rate during the infusion period (FIGURE 2). Premature study drug discontinuation or intolerance of the maximal dose occurred more frequently with fenoldopam than placebo (TABLE 2), most commonly for mild hypotension or tachycardia.

N-acetylcysteine was administered prior to the procedure in 49.6% of patients in the fenoldopam group and 54.1% of patients in the placebo group ($P=.48$). Percutaneous coronary intervention was performed in approximately one third of patients, whereas two thirds had diagnostic procedures only. A total of 157 (108) mL of contrast was administered per procedure. Low-osmolar contrast was administered to all patients, 90% of which was nonionic. Iodixanol was used in 10.4% of patients in the fenoldopam group and 8.5% of patients in the placebo group ($P=.70$).

Contrast-Induced Nephropathy

Serum creatinine levels at both baseline and during the 96-hour postdrug

Figure 2. Changes in Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate During Study Drug Infusions



Levels of significance: * indicates statistically significant vs placebo at the .001 level; †, statistically significant vs placebo at the .01 level; ‡, statistically significant vs placebo at the .05 level.

Table 2. Study Drug Administration and Procedural Results*

	Fenoldopam Mesylate (n = 157)	Placebo (n = 158)	P Value
Procedure type†			
Coronary angiography	155 (98.7)	156 (98.7)	>.99
Bypass graft angiography	25 (15.9)	29 (18.4)	.65
Left ventriculography	50 (31.8)	51 (32.3)	>.99
Aortography	14 (8.9)	15 (9.5)	>.99
Renal arteriography	18 (11.5)	20 (12.7)	.86
Percutaneous coronary intervention	54 (34.4)	55 (34.8)	>.99
Other procedure	25 (15.9)	30 (19.0)	.55
Use of contrast			
Contrast amount, mean (SD), mL	153 (107)	162 (110)	.44
Range, mL	25-600	15-640	
Nonionic contrast	137 (89.5)	140 (89.7)	>.99
Study drug administration			
Prematurely discontinued	21 (13.4)	11 (7.0)	.06
Maximum dose tolerated for entire study	116 (73.9)	139 (88.0)	.002
Total study drug duration, mean (SD), h	13.0 (4.1)	13.8 (2.7)	.03

*Data presented as No. (%) unless otherwise indicated.

†More than 1 procedure type possible per patient.

administration period were available and analyzed at the central biochemistry laboratory in 283 (90%) of 315 randomized patients (Figure 1). By 48 hours, contrast nephropathy had developed in 19.9% of patients assigned

to receive fenoldopam vs 15.9% assigned to receive placebo ($P=.45$). Within 96 hours, the primary end point of contrast-induced nephropathy had been reached in 33.6% of patients in the fenoldopam group vs 30.1% of patients in the placebo group (relative risk [RR], 1.11; 95% confidence interval [CI], 0.79-1.57; $P=.61$). The incidence of contrast-induced nephropathy was also similar in both groups when defined by an absolute increase in serum creatinine level (TABLE 3). There were no significant interactions between treatment group and diabetic status, hypertension, baseline renal function, N-acetylcysteine use, or amount of hydration or contrast use (TABLE 4; Breslow-Day test for homogeneity $>.30$ for all tested variables).

30-Day Outcomes

The index hospitalization length of stay was comparable in both groups (median [interquartile range] 3.0 [2.0, 6.5] and 3.0 [1.0, 6.0] days) for the fenoldopam and control groups, respectively, $P=.21$). Repeat invasive procedures requiring contrast administration and bypass surgery were similarly distributed in both groups. Within 30 days, 18.8% of patients were rehospitalized, 2.3% required dialysis, 2.6% had a myocardial infarction, and 2.9% of patients died. The 30-day composite rate of death, myocardial infarction, or dialysis was increased in patients developing vs not developing contrast-induced nephropathy (12.2% vs 4.1%, $P=.02$). Major adverse event rates, however, occurred with comparable frequency in both treatment groups (Table 3).

COMMENT

The principal finding of this prospective, randomized, double-blind trial, the largest such study to date of any preventive measure for contrast-induced nephropathy, is that the specific dopamine-1 agonist fenoldopam mesylate is ineffective in preventing further renal function deterioration in patients with chronic renal insufficiency receiving iodinated contrast. The lack of efficacy of fenoldopam was independent of dia-

Table 3. Primary and Secondary End Points

	Fenoldopam Mesylate	Placebo	P Value
Renal function deterioration within 96 hours			
No. of patients	137	146	
Serum creatinine increase by $\geq 25\%$, No. (%)	46 (33.6)	44 (30.1)	.61
2 Consecutive 25% increases in serum creatinine, No. (%) [*]	20 (20.4)	18 (16.5)	.48
Serum creatinine increase by ≥ 0.5 mg/dL, No. (%)	39 (28.5)	35 (24.0)	.42
Maximum serum creatinine change, mean (SD), mg/dL [†]	0.32 (0.53)	0.26 (0.45)	.86
Clinical end points, No. (%)			
No. of patients	153	156	
Repeat angiography and/or angioplasty	16 (10.5)	16 (10.3)	$>.99$
Coronary artery bypass graft surgery	15 (9.7) [‡]	15 (9.6)	$>.99$
30-Day adverse events, No. (%)			
Death	3 (2.0)	6 (3.8)	.50
Dialysis	4 (2.6) [‡]	3 (1.9)	.72
Myocardial infarction	5 (3.3)	3 (1.9)	.50
Rehospitalization	27 (17.6)	31 (19.9)	.66
Composite of death, dialysis, myocardial infarction, or rehospitalization	36 (23.4) [‡]	36 (23.1)	$>.99$

SI conversion factor: To convert serum creatinine to $\mu\text{mol/L}$, multiply by 88.4.

^{*}Denominator = 98 for the fenoldopam group and 109 for the placebo group.

[†]From baseline value to the peak value within 96 hours after study drug administration.

[‡]Denominator = 154 (1 patient lost to 30-day follow-up required dialysis and 1 required bypass surgery before hospital discharge).

Table 4. Subgroup Analysis for the Primary Study End Point of Contrast-Induced Nephropathy

	No./Total (%)		Relative Risk (95% Confidence Interval)	P Value
	Fenoldopam Mesylate	Placebo		
All patients	46/137 (33.6)	44/146 (30.1)	1.11 (0.79-1.57)	.61
Diabetic status				
No diabetes	23/68 (33.8)	22/73 (30.1)	1.12 (0.69-1.82)	.72
Diabetes (all)	23/69 (33.3)	22/73 (30.1)	1.11 (0.68-1.79)	.72
Diabetes (insulin requiring)	13/38 (34.2)	13/42 (31.0)	1.11 (0.59-2.08)	.81
Hypertension				
Yes	40/122 (32.8)	37/120 (30.8)	1.06 (0.74-1.54)	.78
No	6/15 (40.0)	7/26 (26.9)	1.49 (0.41-3.60)	.49
Baseline serum creatinine value				
≤ 2.0 mg/dL	40/107 (37.4)	35/108 (32.4)	1.15 (0.80-1.66)	.48
> 2.0 mg/dL	6/30 (20.0)	9/38 (23.7)	0.84 (0.34-2.11)	.78
N-acetylcysteine use before procedure				
Yes	24/68 (35.3)	21/79 (26.6)	1.33 (0.82-2.16)	.28
No	22/69 (31.9)	23/67 (34.3)	0.93 (0.58-1.50)	.86
Contrast amount				
≤ 150 mL	26/84 (31.0)	21/82 (25.6)	1.21 (0.74-1.97)	.49
> 150 mL	20/52 (38.5)	23/62 (37.1)	1.04 (0.65-1.66)	$>.99$
Precontrast hydration				
< 475 mL	18/49 (36.7)	12/45 (26.7)	1.38 (0.75-2.53)	.38
475-950 mL	13/44 (29.5)	14/47 (29.8)	0.99 (0.53-1.87)	$>.99$
> 950 mL	15/44 (34.1)	18/54 (33.3)	1.02 (0.59-1.79)	$>.99$
Study drug tolerated for 12 h after catheterization	27/91 (29.7)	31/105 (29.5)	1.00 (0.65-1.55)	$>.99$
Study drug prematurely discontinued	19/46 (41.3)	13/41 (31.7)	1.30 (0.74-2.29)	.38

SI conversion factor: To convert serum creatinine to $\mu\text{mol/L}$, multiply by 88.4.

betic status, baseline renal function, N-acetylcysteine use, hydration status, and amount of contrast administered.

The pathophysiology of contrast-induced nephropathy, although incompletely understood, is characterized by acute tubular necrosis, possibly as a result of iodinated contrast-induced reductions in renal blood flow as well as oxygen free radical-mediated direct tubular toxicity.^{23,28,29} Atheroembolism and apoptosis have also been implicated as contributing factors.^{30,31} Attempts to diminish contrast-induced nephropathy with free radical scavengers such as N-acetylcysteine have had mixed results.¹⁶⁻¹⁹ Reductions in renal blood flow after contrast identify patients prone to contrast-induced nephropathy,²⁴ and thus numerous vasodilators have been studied to prevent further renal deterioration after contrast administration, with little success.¹¹⁻¹⁵ However, the reduction in renal blood flow after contrast affects the renal medulla disproportionately, with intense vasoconstriction resulting in medullary ischemia.³² Previously studied vasodilators that increase renal plasma flow, including dopamine and endothelin B receptor antagonists, may shunt blood to the renal cortex at the expense of further reducing medullary perfusion, thereby exacerbating regional hypoxia.^{33,34} This finding might explain why previously studied vasodilators have actually worsened the incidence of contrast-induced nephropathy.¹¹⁻¹⁵

Fenoldopam mesylate, a specific dopamine-1 receptor agonist, is a unique vasodilator that selectively increases both renal cortical and outer medullary blood flow while decreasing systemic vascular resistance.^{20,35,36} In an anesthetized canine model, Bakris et al demonstrated that the reduction in renal blood flow and glomerular filtration rate that occurs after contrast is completely blocked by prior fenoldopam administration.²³ Prior observational registry experiences and case-controlled studies in humans at risk for contrast-induced nephropathy undergoing coronary and peripheral procedures have reported marked reductions in further renal func-

tion deterioration with prophylactic fenoldopam use.^{25,26} In a previous 4-center, placebo-controlled, double-blind, prospective, randomized trial in 45 patients with chronic renal insufficiency (creatinine level, 2.0-5.0 mg/dL [176.8-442.0 μ mol/L]) receiving iodinated contrast, the primary end point of renal plasma flow at 1 hour increased 16% above baseline with 0.1 μ g/kg/min of fenoldopam vs decreasing 33% with placebo ($P < .05$).²⁴ A reduction in renal blood flow was strongly correlated with contrast-induced nephropathy ($P < .001$), and contrast-induced nephropathy occurred within 72 hours in 41% of patients assigned to receive placebo vs 21% of patients assigned to receive fenoldopam ($P = .15$). As a result of these studies, fenoldopam has become widely used in recent years for contrast-induced nephropathy prophylaxis. In a recently reported open-label randomized trial, however, in which 123 patients with chronic renal insufficiency undergoing cardiovascular procedures were randomized to receive saline hydration, fenoldopam, or N-acetylcysteine, no differences in contrast-induced nephropathy within 48 hours were noted with either active treatment, questioning the utility of both. As only 15% of control patients developed contrast-induced nephropathy, however, this trial was markedly underpowered to find differences with either therapy.³⁷

In the current large-scale, placebo-controlled, double-blind, randomized trial using a central core laboratory to measure serum creatinine, fenoldopam mesylate was ineffective at preventing the development of contrast-induced nephropathy or its clinical sequelae in patients with baseline renal insufficiency undergoing invasive cardiac procedures. Contrast-induced nephropathy, defined as a serum creatinine level increase of 25% or more within 24 to 96 hours postdrug administration (the typical time course for its development³⁸), developed in 30.1% of patients treated with placebo (identical to the postulated control rate) vs 33.6% of patients treated with fenoldo-

pam. Given the 95% CI around this 11% hazard, the treatment effect of fenoldopam could range from a 21% decrease to a 57% increase in contrast-induced nephropathy relative to placebo. Even using a stricter definition of contrast-induced nephropathy, a 0.5 mg/dL (44.2 μ mol/L) or more increase in serum creatinine, nephropathy developed in 28.5% of patients in the fenoldopam group vs 24.0% in the control group, a 12% RR increase. Moreover, no subgroups were identified in which a significant signal for fenoldopam benefit was present. Thus, even with the most optimistic projections, it is unlikely that the utility of fenoldopam would outweigh its cost, inconvenience, and adverse effects.

It is unlikely that a different dose or infusion duration of fenoldopam would prove effective. The 0.1 μ g/kg/min target dose in the current study results in significant increases in renal blood flow, and higher doses are likely to be poorly tolerated because of systemic hypotension.^{2,24,39} Moreover, even the current dose of fenoldopam produced hypotension and tachycardia sufficient to warrant its interruption or discontinuation in a significant proportion of patients (Figure 2 and Table 3). Indeed, a nonsignificant trend toward harm was present if premature study drug discontinuation was required. Lower doses of fenoldopam, on the contrary, would be unlikely to increase renal plasma flow sufficiently to be protective.^{2,24,39} The duration that renal blood flow is reduced after iodinated contrast in unprotected patients is unknown, although it may persist well beyond 4 hours.²⁴ An infusion of fenoldopam longer than 12 hours postprocedure, however, is not a practical consideration.

Patients with baseline renal insufficiency ranging from mild to severe were enrolled in this study. There was no interaction, however, between fenoldopam and baseline renal function, suggesting a possible treatment effect in mild vs more severe renal insufficiency. A previously noted disproportionate benefit of fenoldopam in dia-

betic patients at risk for contrast-induced nephropathy²⁴ also did not materialize. The degree of hydration used in the current trial was similar or greater than in prior studies,⁹⁻¹⁹ and there were no differences in the amount or duration of hydration between the 2 groups, nor was fenoldopam relatively more or less effective depending on the degree of hydration. Finally, no interaction between fenoldopam and N-acetylcysteine use was evident.

A recent randomized trial reported a marked reduction in contrast-induced nephropathy in diabetic patients undergoing coronary and peripheral invasive procedures treated with the iso-osmotic nonionic contrast agent iodixanol compared with the low osmolar nonionic agent iohexol (3% vs 26%, $P=.002$).⁴⁰ Although iodixanol was used in only 10% of patients in the current trial, contrast-induced nephropathy, using the same definition (serum creatinine increase of ≥ 0.5 mg/dL [$44.2 \mu\text{mol/L}$]) occurred in 33.3% of patients treated with iodixanol compared with 25.3% of those treated with other contrast agents ($P=.39$). Although unlikely, the small number of patients receiving iodixanol in the current study precludes ruling out a beneficial treatment effect with fenoldopam.

Limitations

The primary study end point of contrast-induced nephropathy could not be determined in approximately 10% of patients in whom serial creatinine measurements were not available. Most of these patients were asymptomatic as outpatients and declined returning to the clinic for blood draws. Moreover, the baseline characteristics were similar in patients with vs without follow-up creatinine assessment, and the principal results were unchanged in sensitivity analyses when these patients were imputed either as developing or not developing contrast-induced nephropathy. Second, while the current study size effectively rules out fenoldopam having utility for the prevention of contrast-induced nephropathy in the study population as a whole, it is possible that sub-

groups might have been identified that could benefit had more patients been enrolled. Third, either a greater amount or duration of hydration might have improved the tolerability of fenoldopam; however, even when the study drug was not prematurely discontinued, the point estimate for efficacy was entirely neutral (Table 4). Fourth, the mechanism of renal failure after contrast administration in patients undergoing invasive cardiac procedures is complex, and in selected cases may be due to non-dye-related etiologies such as atheroembolism or procedural-related hemodynamic disturbances, situations that fenoldopam would not be expected to favorably affect.

Conclusions and Clinical Implications

Based on the current study, fenoldopam mesylate should not be used as a prophylactic measure to prevent further renal function deterioration in patients at risk for contrast-induced nephropathy. The negative findings from this investigation, in concert with prior disappointing studies of other vasodilators, suggest that disturbances in intrarenal hemodynamics may not represent the critical pathophysiologic insult that produces contrast-induced nephropathy. The outcomes and implications of this study also reaffirm the importance of completing adequately powered, prospective, double-blind randomized controlled trials before active therapies are adopted into widespread use.

Author Affiliations: Department of Cardiology, Cardiovascular Research Foundation and Lenox Hill Heart and Vascular Institute, New York, NY (Dr Stone); Department of Cardiology, William Beaumont Hospital, Royal Oak, Mich (Drs McCullough, Stevens, and O'Neill); Department of Nephrology, Emory University School of Medicine, Atlanta, Ga (Dr Tumlin); Department of Cardiology, Cedars-Sinai Medical Center, Los Angeles, Calif (Dr Lepor); Department of Cardiology, St Joseph's Medical Center, Stockton, Calif (Dr Madyoon); Department of Cardiology, University of Chicago, Chicago, Ill (Dr Murray); Department of Cardiology, Duke University Medical Center, Durham, NC (Dr Wang); Department of Cardiology, Saint Francis Medical Center, Peoria, Ill (Dr Chu); Department of Cardiology, Rush-Presbyterian-St Luke's Medical Center, Chicago, Ill (Dr Schaer); and Department of Cardiology, Hospital of the University of Pennsylvania, Philadelphia (Dr Wilensky).

Author Contributions: As principal investigator, Dr Stone had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Stone, McCullough, Tumlin, Lepor, Madyoon, Murray, Wang, O'Neill.

Acquisition of data: Stone, McCullough, Lepor, Wang, Chu, Schaer, Stevens, Wilensky, O'Neill.

Analysis and interpretation of data: Stone, McCullough, Lepor, Madyoon, Murray, O'Neill.

Drafting of the manuscript: Stone, McCullough, Lepor, Murray, O'Neill.

Critical revision of the manuscript for important intellectual content: Stone, McCullough, Tumlin, Lepor, Madyoon, Murray, Wang, Chu, Schaer, Stevens, Wilensky, O'Neill.

Statistical expertise: Stone, Tumlin, Madyoon.

Obtained funding: Stone, O'Neill.

Administrative, technical, or material support: Lepor, Murray, Schaer, Stevens, Wilensky, O'Neill.

Study supervision: Stone, McCullough, Murray.

CONTRAST Study Organization: Executive Committee: Gregg W. Stone (co-principal investigator), William W. O'Neill (co-principal investigator), Norman Lepor, Hooman Madyoon, Peter A. McCullough, Patrick Murray, James Tumlin; **Site Monitoring:** Abbott Laboratories, Abbott Park, Ill, Karen Zylberman, Project Manager; **Data Management:** Kendle International, Cincinnati, Ohio; **Biostatistical Analysis:** Terry Boodhoo, Abbott Laboratories, Abbott Park, Ill; **Central Biochemistry Laboratory:** Covance Central Laboratory Services, Inc, Indianapolis, Ind; **Clinical Sites** (*The principal investigator is listed first and study coordinator[s] listed second*): Arizona (Phoenix): Arizona Heart Institute, Georges Nseir, Gail Ferrell; California (Los Angeles): Cedars Sinai Medical Center, Raj Makkar, Kelly Davis, Honore Voorman; (Stockton): St. Joseph's Medical Center, Hooman Madyoon, Theresa Weaver; Connecticut (Hartford): Hartford Hospital, Raymond McKay, Deborah Murphy; District of Columbia (Washington): Washington Hospital Center, Ron Waksman, Daniella Claus; Florida (Ocala): Munroe Regional Medical Center, Robert Feldman, Keith Tighe, Debby Audrain; (Orlando): Florida Hospital, Bruce Stein, Abigail S. Rivera Roldan; Georgia (Atlanta): Piedmont Hospital, Harold Carlson, Kyle Reid; Illinois (Chicago): Rush-Presbyterian-St Luke's Medical Center, Gary Schaer, Josette Bax; University of Chicago Hospitals, John Lopez, Peggy Bennett; (Evanston): St Francis Medical Center, Shahriar Dadkhah, Amy Fisch; (Peoria): Heart-Care Midwest, Alan Chu, Jennifer Deeb; Indiana (Beech Grove): St. Francis Hospital and Health Centers, George Revtyak, Shelly Napier; (Indianapolis): St. Vincent Hospital, James Hermiller, Lynn Burkett; Iowa (Davenport): Genesis Medical Center, Eric Dippel, Monica Youngblut; Kentucky (Lexington): Central Baptist Hospital, Thomas Ferguson, Jeannie Gadd; Maryland (Baltimore): Johns Hopkins Hospital, Jeffrey Brinker, Karin Turyna; Massachusetts (Burlington): Lahey Clinic Medical Center, Manish Chauhan, Deanna Niemann; Michigan (Ann Arbor): St. Joseph Mercy Hospital, James Bengtson, Terry Peyton; (Royal Oak): William Beaumont Hospital, Melissa Stevens, Ann Colar, Barbara Higgins; New York (Manhasset): North Shore University Hospital, Stanley Katz, Lynne Clausen; (New York City): Lenox Hill Heart and Vascular Institute, Gregg W. Stone, Lena Langer; North Carolina (Durham): Duke University Medical Center, Andrew Wang, Cynthia Pierce; (Raleigh): Wake Medical, J. Tift Mann III, Michael Arrowood; Ohio (Cincinnati): The Christ Hospital, John J. Young, Kelly Moorman; Pennsylvania (Philadelphia): Hospital of the University of Pennsylvania, Robert Wilensky, Sharon Bradley; Thomas Jefferson University, Michael Savage, Kathleen Keefe McAllister; Texas (San Antonio): University Hospital, Janet Hays, Mary Stigent.

Funding/Support: This study was funded by Abbott Laboratories, Abbott Park, Ill.

Role of the Sponsor: Abbott Laboratories, the manufacturer of the drug studied in the article, was involved with the principal investigators and steering committee in study design, conduct of the study, and in data analysis and interpretation; Abbott also supplied the placebo used in the study. Manuscript preparation was performed completely independently of the sponsor, however, though the sponsor had the right for a nonbinding review prior to submission.

REFERENCES

1. Lasser EC, Lyon SG, Berry CC. Reports on contrast medial reactions: analysis of data from reports to the US Food and Drug Administration [published correction appears in *Radiology*. 1997;204:876]. *Radiology*. 1997;203:605-610.
2. Berns AS. Nephrotoxicity of contrast media. *Kidney Int*. 1989;36:730-740.
3. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both: a prospective controlled study. *N Engl J Med*. 1989;320:143-149.
4. Gruberg L, Mintz GS, Mehran R, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol*. 2000;36:1542-1548.
5. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*. 1997;103:368-375.
6. Hou SH, Bushinsky DA, Wish JB, et al. Hospital acquired renal insufficiency: a prospective study. *Am J Med*. 1983;74:243-248.
7. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality: a cohort analysis. *JAMA*. 1996;275:1489-1494.
8. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;105:2259-2264.
9. Trivedi HS, Moore H, Nasr S, Aggarwal K, Agrawal A, Goel P, Hewett J. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. *Nephron*. 2003;93:C29-C34.
10. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med*. 1994;331:1416-1420.
11. Hall KA, Wong RW, Hunter GC, et al. Contrast-induced nephrotoxicity: the effects of vasodilator therapy. *J Surg Res*. 1992;53:317-320.
12. Chertow GM, Sayegh MH, Allgren RL, et al. Is the administration of dopamine associated with adverse or favorable outcomes in acute renal failure? *Am J Med*. 1996;101:49-53.
13. Wang A, Holcslaw T, Bashore TM, et al. Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. *Kidney Int*. 2000;57:1675-1680.
14. Kurnik BR, Allgren RL, Genter FC, et al. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis*. 1998;31:674-680.
15. Abizaid AS, Clark CE, Mintz GS, et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. *Am J Cardiol*. 1999;83:260-263.
16. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med*. 2000;343:180-184.
17. Kay J, Chow WH, Chan TM, et al. A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. *JAMA*. 2003;289:553-558.
18. Bocalandro F, Amhad M, Smalling RW, Sdringola S. Oral acetylcysteine does not protect renal function from moderate to high doses of intravenous radiographic contrast. *Catheter Cardiovasc Interv*. 2003;58:336-341.
19. Durham JD, Caputo C, Dokko J, et al. A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. *Kidney Int*. 2002;62:2202-2207.
20. Singer I, Epstein M. Potential of dopamine A-1 agonists in the management of acute renal failure. *Am J Kidney Dis*. 1998;31:743-755.
21. Mathur VS, Swan SK, Lambrecht LJ, et al. The effects of fenoldopam, a selective dopamine receptor agonist, on systemic and renal hemodynamics in normotensive subjects. *Crit Care Med*. 1999;27:1832-1837.
22. Murphy MB, McCoy CE, Weber RR, et al. Augmentation of renal blood flow and sodium excretion in hypertensive patients during blood pressure reduction by intravenous administration of the dopamine 1 agonist fenoldopam. *Circulation*. 1987;76:1312-1318.
23. Bakris GL, Lass NA, Glock D. Renal hemodynamics in radiocontrast medium-induced renal dysfunction: a role for dopamine-1 receptors. *Kidney Int*. 1999;56:206-210.
24. Tumlin JA, Wang A, Murray PT, Mathur VS. Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. *Am Heart J*. 2002;143:894-903.
25. Madyoon H. Clinical experience with the use of fenoldopam for prevention of radiocontrast nephropathy in high-risk patients. *Rev Cardiovasc Med*. 2001;2(suppl 1):S26-S30.
26. Kini AS, Mitre CA, Kamran M, et al. Changing trends in incidence and predictors of radiographic contrast nephropathy after percutaneous coronary intervention with use of fenoldopam. *Am J Cardiol*. 2002;89:999-1002.
27. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.
28. Deray G, Baumelou B, Martinez F, Brillet G, Jacobs C. Renal vasoconstriction after low and high osmolar contrast agents in ischemic and nonischemic canine kidney. *Clin Nephrol*. 1991;36:93-96.
29. Katholi RE, Woods TW, Taylor GJ, et al. Oxygen free radicals and contrast nephropathy. *Am J Kidney Dis*. 1998;32:64-71.
30. McCullough PA, Manley HJ. Prediction and prevention of contrast nephropathy. *J Interv Cardiol*. 2001;14:547-558.
31. Hizoh I, Haller C. Radiocontrast-induced renal tubular cell apoptosis: hypertonic versus oxidative stress. *Invest Radiol*. 2002;37:428-434.
32. Liss P, Nygren A, Olsson U, et al. Effects of contrast media and mannitol on renal medullary blood flow and red cell aggregation in the rat kidney. *Kidney Int*. 1996;49:1268-1275.
33. Brodsky S, Abassi Z, Wessale J, Ramadan R, Winaver J, Hoffman A. Effects of A-192621.1, a specific endothelin-B antagonist, on intrarenal hemodynamic responses to endothelin-1. *J Cardiovasc Pharmacol*. 2000;36(5 suppl 1):S311-S313.
34. Neiberger RE, Passmore JC. Effects of dopamine on canine intrarenal blood flow distribution during hemorrhage. *Kidney Int*. 1979;15:219-226.
35. Shusterman NH, Elliott WJ, White WB. Fenoldopam, but not nitroprusside, improves renal function in severely hypertensive patients with impaired renal function. *Am J Med*. 1993;95:161-168.
36. Kien ND, Moore PG, Jaffe RS. Cardiovascular function during induced hypotension by fenoldopam or sodium nitroprusside in anesthetized dogs. *Anesth Analg*. 1992;74:72-78.
37. Allaqaband S, Tumuluri R, Malik AM, et al. Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. *Catheter Cardiovasc Interv*. 2002;57:279-283.
38. Gutierrez N, Diaz A, Timmis GC, O'Neill WW, Stevens MA, McCullough PA. Determinants of serum creatinine trajectory in acute contrast nephropathy. *J Interv Cardiol*. 2002;15:349-354.
39. O'Connell DP, Ragsdale NV, Boyd DG, et al. Differential human renal tubular responses to dopamine type 1 receptor stimulation are determined by blood pressure status. *Hypertension*. 1997;29:115-122.
40. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med*. 2003;348:491-499.