

Effects of Tezosentan on Symptoms and Clinical Outcomes in Patients With Acute Heart Failure

The VERITAS Randomized Controlled Trials

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ACUTE HEART FAILURE IS A COMMON cause of emergency admission to hospital.¹⁻³ The principal symptom, dyspnea, is thought to be caused by an increase in pulmonary capillary wedge pressure (PCWP), often associated with a decrease in stroke volume and cardiac index and increase in systemic vascular resistance.¹⁻³ The immediate aims of treatment are to relieve dyspnea and to improve and stabilize the patient's hemodynamic and clinical state.¹⁻⁵ Additional goals are prevention of death and readmission, both of which occur frequently.¹⁻⁵

Context Plasma concentrations of the vasoconstrictor peptide endothelin-1 are increased in patients with heart failure, and higher concentrations are associated with worse outcomes. Tezosentan is an intravenous short-acting endothelin receptor antagonist that has favorable hemodynamic actions in heart failure.

Objective To determine if tezosentan improves outcomes in patients with acute heart failure.

Design, Setting, and Participants The Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies, 2 independent, identical, and concurrent randomized, double-blind, placebo-controlled, parallel-group trials conducted from April 2003 through January 2005 at sites in Australia, Europe, Israel, and North America. Patients admitted within the previous 24 hours with persisting dyspnea and a respiratory rate of 24/min or greater were eligible provided they fulfilled 2 of 4 criteria: (1) elevated plasma concentrations of B-type or N-terminal pro-B-type natriuretic peptide, (2) clinical pulmonary edema, (3) radiologic pulmonary congestion or edema, or (4) left ventricular systolic dysfunction.

Intervention Infusion of tezosentan (5 mg/h for 30 minutes, followed by 1 mg/h for 24 to 72 hours [n=730]) or placebo (n=718).

Main Outcome Measures The coprimary end points were change in dyspnea (measured at 3, 6, and 24 hours using a visual analog scale from 0-100) over 24 hours (as area under the curve) in the individual trials and incidence of death or worsening heart failure at 7 days in both trials combined.

Results Of the 1435 patients who received treatment as assigned, 855 (60%) were men; mean age was 70 years. Mean left ventricular ejection fraction (measured in 779 patients [54%]) was 29% (SD, 11%). Baseline dyspnea scores were similar in the 2 treatment groups. Tezosentan did not improve dyspnea more than placebo in either trial, with a mean treatment difference of -12 (95% confidence interval [CI], -105 to 81) mm·h ($P=.80$) in the first trial and -25 (95% CI, -119 to 69) mm·h ($P=.60$) in the second. The incidence of death or worsening heart failure at 7 days in the combined trials was 26% in each treatment group (odds ratio, 0.99; 95% confidence interval, 0.82-1.21; $P=.95$).

Conclusion The endothelin receptor antagonist tezosentan did not improve symptoms or clinical outcomes in patients with acute heart failure.

Trial Registration clinicaltrials.gov Identifiers: NCT00525707 (VERITAS-1) and NCT00524433 (VERITAS-2).

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Currently, patients with acute heart failure are treated with drugs that have a diuretic, vasodilator, or inotropic action (or some combination of these ac-

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tions), though the evidence base for any treatment in acute heart failure is weak.¹⁻⁵

The endothelins are peptides with a powerful vasoconstrictor action as well as other effects that could be harmful in heart failure.⁶⁻⁸ Higher plasma endothelin concentrations also predict worse clinical outcomes in patients with heart failure.⁶⁻⁸ Tezosentan is a short-acting endothelin A-type and B-type receptor antagonist developed for intravenous use.⁹⁻¹³ It is a potent vasodilator that reduces systemic vascular resistance and PCWP and increases cardiac output in a dose-dependent manner.⁹⁻¹³

The Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies (VERITAS) were designed to test the hypothesis that tezosentan would have a favorable effect on symptoms and clinical outcomes in patients with acute heart failure.¹⁴

METHODS

The VERITAS program consisted of 2 independent, identical, and concurrent studies (VERITAS-1 and VERITAS-2) conducted from April 2003 through January 2005, the design of which has been described in detail.¹⁴ The study was approved by the ethics committee/independent review board of each participating hospital.

The steering committee, a group of advisors, and the sponsor designed the trials and also met periodically to assess the progress of the study, address operational issues, and, at the end of the study, interpret the results. The independent data and safety monitoring board (DSMB)¹⁴ met periodically to review safety data and, after interim analysis, to review efficacy data. The DSMB was empowered to recommend early termination of the study program for futility (see below) or if major concerns arose about the safety of tezosentan. Analysis of data for the DSMB was carried out by an independent statistical group.

Study Design

VERITAS-1 and VERITAS-2 were randomized, double-blind, placebo-controlled, parallel-group studies (FIGURE 1). Patients were eligible if they

were 18 years or older and met the inclusion and exclusion criteria. The key inclusion criteria were admission to hospital with acute heart failure within the previous 24 hours and persistence of dyspnea at rest. The patient's report of dyspnea had to be supported by a respiratory rate of at least 24/min. The investigator's clinical diagnosis of heart failure had to be supported by at least 2 of 4 criteria: (1) elevated concentration of B-type natriuretic peptide (BNP) or N-terminal pro-BNP, (2) pulmonary edema on physical examination, (3) radiologic pulmonary congestion or edema, or (4) left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] <40% or wall motion index ≤ 1.2). If the patient had a pulmonary artery catheter, the cardiac index (measured as L/min per m²) had to be 2.5 and the PCWP 20 mm Hg or greater.

The patient must also have received at least 1 dose of an intravenous diuretic 24 hours or less and 2 hours or more prior to initiation of the study drug (or an infusion of diuretic at a constant rate for ≥ 2 hours). If other intravenous treatments were initiated before the start of study drug, their dose had to be stable for 2 hours or more for vasodilators, sympathomimetics, or calcium sensitizers or for 4 hours for phosphodiesterase inhibitors and nesiritide.

The exclusion criteria have been described in detail and included cardiogenic shock within 48 hours, ST-segment elevation myocardial infarction, ongoing ischemia or administration of a thrombolytic agent, hypotension (systolic blood pressure <100 mm Hg in patients not receiving a vasodilator or <120 mm Hg in those receiving a vasodilator), anemia (hemoglobin concentration <10 g/dL, hematocrit <30%), or renal dysfunction (creatinine concentration >2.5 mg/dL [to convert to $\mu\text{mol/L}$, multiply by 88.4]).¹⁴ Information on race/ethnicity was collected for each patient by means of an investigator check box.

Study Treatment

After obtaining written informed consent, patients were randomized 24 hours or less

from admission to receive an infusion of either placebo or tezosentan, 5 mg/h for 30 minutes, followed by 1 mg/h for at least 24 (and up to 72) hours. Patients in the placebo group received an identical volume of saline infusion (104 mL for the first 24 hours). Patients and study investigators were blinded to study assignment.

Primary End Points

The primary end point of each individual VERITAS study was the change from baseline in dyspnea over the first 24 hours of treatment, measured at 3, 6, and 24 hours as the area under the curve. Dyspnea was assessed by each patient using a visual analog scale (VAS) consisting of a 10-cm vertical line with the phrase "I am not breathless at all" at the bottom of the scale and "I am the most breathless I have ever been" at the top. The VAS was scored from 0 to 100, but the patient was unaware of the numerical value of his or her response.

The primary efficacy end point of the combined studies was the incidence of death or worsening heart failure at 7 days. Worsening heart failure could occur during the index admission or after discharge. Worsening heart failure occurring during initial hospital admission was defined either as the development of pulmonary edema, cardiogenic shock, or other evidence of worsening heart failure or as lack of improvement in the patient's heart failure with treatment (treatment failure). Both definitions required at least 1 of the following: (1) initiation of new intravenous therapy, (2) reinstatement of prior intravenous therapy, (3) increase in current intravenous therapy for heart failure, (4) implementation of mechanical circulatory (eg, intra-aortic balloon pump) or ventilatory (including continuous positive airway pressure) support, or (5) use of ultrafiltration, hemofiltration, or hemodialysis. Worsening heart failure occurring after the index admission was defined either as an unplanned visit to an emergency department because of worsening heart failure (pulmonary edema, cardiogenic shock, or other evidence of worsening heart failure) or as unplanned admission because of worsening heart failure. Both

definitions required at least 1 of the following: (1) administration of intravenous treatment for heart failure, including diuretic, vasodilator, or inotropic agents; (2) implementation of mechanical, circulatory, or ventilatory support;

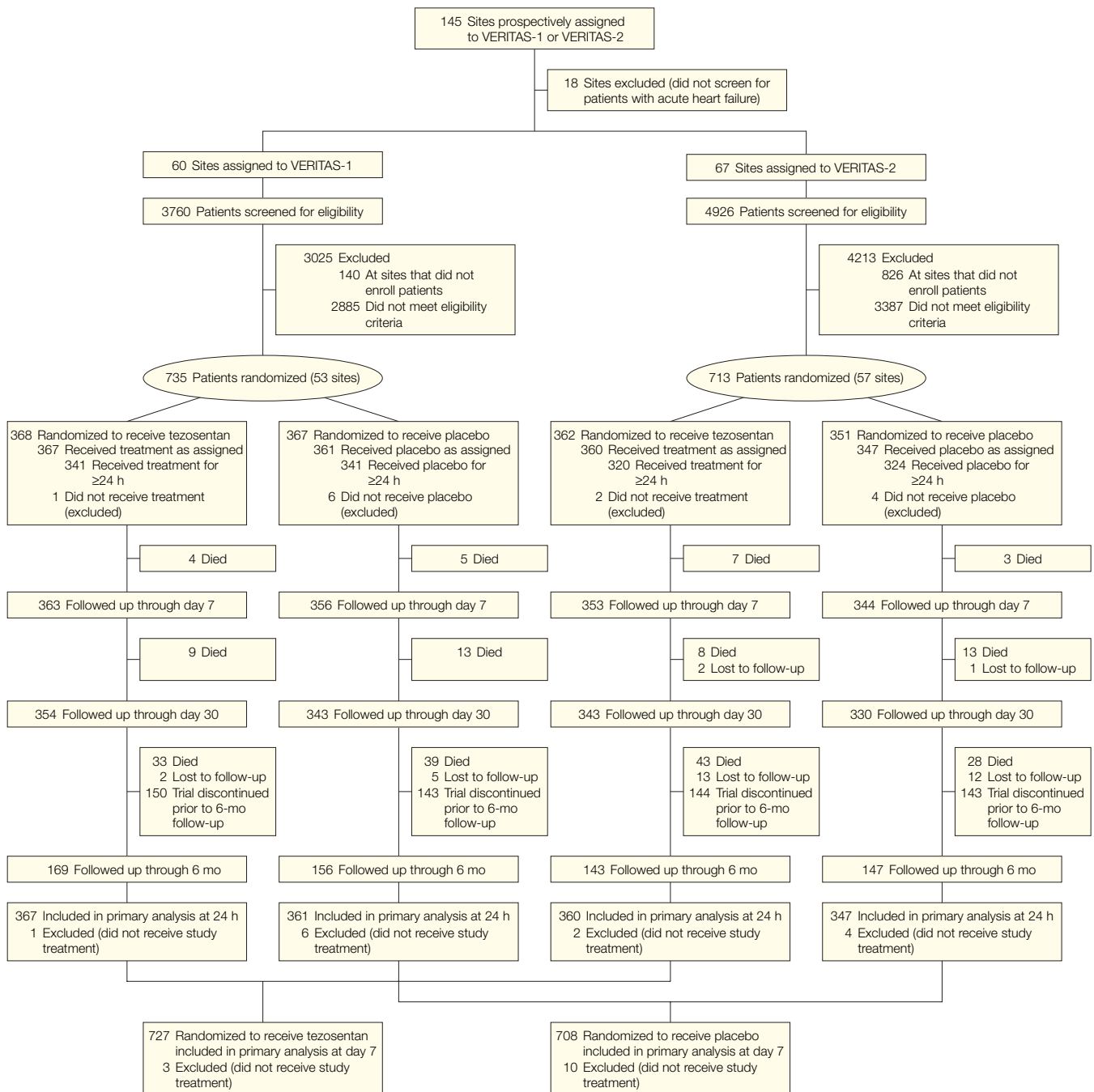
or (3) use of ultrafiltration, hemofiltration, or hemodialysis.

Main Secondary Objectives

The main secondary objectives were to determine whether tezosentan re-

duced the incidence of death or major cardiovascular events at 30 days, improved hemodynamic measures over the first 24 hours (in the subset of patients with a pulmonary artery catheter in place for clinical indications), reduced the

Figure 1. Disposition of Patients in VERITAS-1 and VERITAS-2



VERITAS indicates Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies.

length of initial hospital admission and days in hospital up to 30 days, and influenced 6-month mortality.¹⁴

Statistical Analyses

The primary outcome in the individual studies, area under the curve of

the change of the dyspnea score from baseline over the first 24 hours of treatment, was analyzed as a normally distributed variable (with an expected standard deviation of 600 mm·h). The null hypothesis was tested by means of the *t* test against an alternative of a

mean difference of at least 150 mm·h for the active group compared with placebo.

The primary outcome in the 2 studies combined, incidence of death or worsening heart failure, was analyzed as a binomial variable. The null hy-

Table 1. Clinical Characteristics of Patients in VERITAS-1 and VERITAS-2

Characteristic	No. (%)			
	VERITAS-1		VERITAS-2	
	Tezosentan (n = 367)	Placebo (n = 361)	Tezosentan (n = 360)	Placebo (n = 347)
Age, mean (SD), y	70 (13)	70 (12)	70 (11)	70 (13)
Sex				
Men	220 (60)	222 (61)	222 (62)	191 (55)
Women	147 (40)	139 (39)	138 (38)	156 (45)
Race				
White	327 (89)	318 (88)	301 (84)	288 (83)
Black	31 (8)	30 (8)	22 (6)	28 (8)
Other	10 (2)	13 (4)	37 (10)	31 (9)
Criteria for inclusion				
Pulmonary congestion				
Clinical examination	327 (89)	329 (91)	323 (90)	305 (88)
Radiography	297 (81)	302 (84)	297 (83)	289 (83)
Left ventricular systolic dysfunction	167 (46)	158 (44)	182 (51)	170 (49)
Plasma concentration of BNP or NT pro-BNP >3× ULN	96 (26)	91 (25)	54 (15)	46 (13)
Cause of heart failure				
Ischemic	269 (73)	257 (71)	234 (65)	210 (61)
Hypertensive	97 (26)	115 (32)	126 (35)	122 (35)
Idiopathic	44 (12)	42 (12)	48 (13)	64 (18)
Valvular	13 (4)	20 (6)	15 (4)	11 (3)
Other	21 (6)	20 (6)	27 (8)	32 (9)
History of chronic heart failure	281 (77)	282 (78)	250 (69)	232 (67)
Physiological measurements, mean (SD)				
Blood pressure, mm Hg				
Systolic	131 (22)	130 (23)	132 (23)	132 (23)
Diastolic	72 (13)	72 (15)	72 (14)	72 (14)
Heart rate, beats per min	81 (17)	82 (18)	82 (18)	84 (17)
Respiratory rate, breaths per min	26.2 (3.8)	26.3 (3.6)	26.2 (4.9)	26.3 (4.3)
LVEF, %	20 (10)	30 (12)	28 (10)	30 (12)
No. with LVEF measurement	195	193	195	196
Laboratory assessments, mean (SD)				
Serum sodium, mEq/L	139 (4)	139 (4)	139 (7)	139 (4)
BUN, mg/dL	28.3 (18.0)	27.4 (25.1)	27.2 (12.9)	25.1 (12.9)
Creatinine, mg/dL	1.4 (0.46)	1.3 (0.45)	1.3 (0.43)	1.3 (0.42)
Hemoglobin, g/dL	1.3 (0.19)	1.3 (0.20)	1.3 (0.18)	1.3 (0.19)
Medical history				
Hypertension	299 (82)	291 (81)	277 (77)	272 (78)
Myocardial infarction	204 (56)	205 (57)	176 (49)	165 (48)
Diabetes mellitus	165 (45)	166 (46)	191 (53)	162 (47)
Renal impairment	142 (39)	131 (36)	128 (36)	120 (35)
Atrial fibrillation	129 (35)	135 (37)	135 (38)	127 (37)
CABG	84 (23)	87 (24)	74 (21)	63 (18)
Angina pectoris	86 (23)	84 (23)	51 (14)	45 (13)
Stroke	63 (17)	49 (14)	64 (18)	60 (17)

(continued)

Table 1. Clinical Characteristics of Patients in VERITAS-1 and VERITAS-2 (cont)

Characteristic	No. (%)			
	VERITAS-1		VERITAS-2	
	Tezosentan (n = 367)	Placebo (n = 361)	Tezosentan n = 360)	Placebo (n = 347)
Medical treatment (oral)				
Aspirin	236 (64)	237 (66)	213 (59)	190 (55)
ACE inhibitor	197 (54)	202 (56)	179 (50)	185 (53)
β -Blocker	177 (48)	169 (47)	164 (46)	161 (46)
Lipid-lowering drug	168 (46)	156 (43)	135 (38)	131 (38)
Loop diuretic ^a	121 (33)	111 (31)	93 (26)	94 (27)
Digoxin	76 (21)	74 (21)	87 (24)	78 (23)
Spironolactone	63 (17)	64 (18)	62 (17)	76 (22)
Calcium antagonist	57 (16)	45 (13)	47 (13)	57 (16)
Amiodarone	45 (12)	52 (14)	43 (12)	27 (8)
Angiotensin receptor blocker	39 (11)	37 (10)	36 (10)	34 (10)
Medical treatment (intravenous)				
Nitrate	61 (17)	57 (16)	50 (14)	53 (15)
Nitroprusside	0	1 (0.3)	3 (0.8)	3 (0.9)
Dobutamine	8 (2)	6 (2)	5 (1)	7 (2)
Dopamine	7 (2)	8 (2)	9 (3)	5 (1)
Nesiritide	4 (1)	9 (3)	4 (1)	4 (1)
Milrinone	1 (0.3)	0	0	1 (0.3)
Furosemide-equivalent dose of intravenous diuretic, mean (SD), mg ^b	112 (93)	113 (113)	108 (111)	98 (81)

Abbreviations: ACE, angiotensin-converting enzyme; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; NT pro-BNP, N-terminal pro-BNP; ULN, upper limit of normal; VERITAS, Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies. SI conversion factors: To convert serum sodium values to mmol/L, multiply by 1.0; BUN values to mmol/L, by 0.357; creatinine values to μ mol/L, by 88.4; hemoglobin values to g/L, by 10.0.

^aPatients taking an oral loop diuretic at time of randomization (43% were receiving an intravenous loop diuretic at that time); per protocol, 99% of patients had received an intravenous loop diuretic ≤ 24 and ≥ 2 hours prior to study drug initiation.

^bAdministered within 24 hours prior to initiation of study treatment. Furosemide (20 mg) = bumetanide (1 mg), ethacrynic acid (25 mg), torasemide (10 mg), and pirtanide (6 mg).

pothesis was tested using the Fisher exact test against the alternative of a risk reduction of 25% when the active group was compared with placebo (which was expected to have an event rate of 35%).

The overall type I error of .05 in the VERITAS program was split, with .0008 attributed to the analysis of the individual studies (.04 to each) and .0492 (or .0092 using a more restrictive overall type I error of .01) to the combined studies. The intent was to submit the VERITAS program for registration with the US Food and Drug Administration for marketing approval if the end point of death or worsening heart failure reached a significance level of less than .01 in the analysis of the combined studies or if the dyspnea end point was significant at less than .04 in the analysis of each individual study (VERITAS-1 and VERITAS-2) or if the end point of death or worsening heart failure was significant at an overall α of .05. Based

on the above conditions and a 90% power for each of the coprimary end point analyses, the required sample size was estimated to be 1760 patients (440 in each group of the 2 studies). Analysis was by intention-to-treat.

Interim analyses of the coprimary end points were planned to be performed after 50% and 75% of patients had been randomized. The DSMB could recommend discontinuation of the study (for futility) if it was evident at interim analysis that neither of the objectives of the program could be fulfilled. Termination would be advised if the conditional power (calculated using the method of stochastic curtailing) fell below 10% for both death or worsening heart failure at 7 days (at $\alpha = .05$) and dyspnea (at $\alpha = .04$ for each study).¹⁴ These conditions were fulfilled at the second interim analysis, and randomization was stopped on November 6, 2004. Analyses were per-

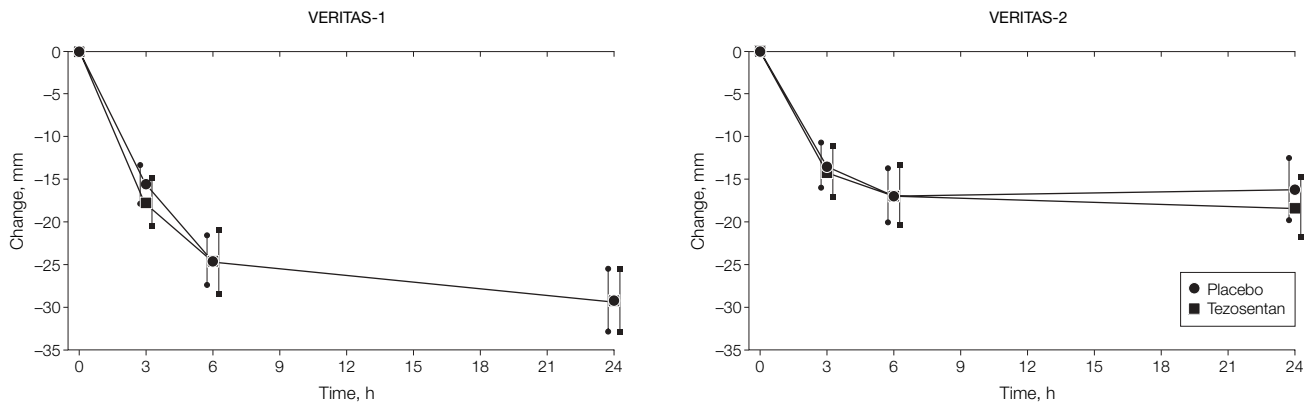
formed using SAS version 8.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Between April 11, 2003, and January 20, 2005, 1448 patients were randomized and evaluated at 110 sites in Australia, Europe, Israel, and North America: 735 patients at 53 sites in VERITAS-1 and 713 at 57 sites in VERITAS-2. Due to early termination of the trials for futility, only 82% of the planned number of patients (1760) was enrolled. Flow of patients through the trials is summarized in Figure 1.

Baseline Characteristics

The treatment groups were well balanced in all respects. Of the 1435 patients who received treatment as assigned, 855 (60%) were men; the mean age of patients was 70 years. Heart failure was present before admission in 1045 (73%), and 750 (52%) had a prior history of myocardial

Figure 2. Change in Dyspnea in VERITAS-1 and VERITAS-2

Change in dyspnea shown as the area under the curve. VERITAS indicates Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies. Error bars indicate 95% confidence intervals.

infarction; 1139 (79%) had a history of hypertension, and the mean systolic blood pressure at baseline was 132 mm Hg (TABLE 1). Left ventricular ejection fraction was measured in 779 patients (54%); the mean (SD) LVEF was 29% (11%). Investigators performed invasive hemodynamic monitoring in 84 patients (6%). The mean (95% confidence interval [CI]) cardiac index was 2.06 (1.97 to 2.18); PCWP, 26 (25 to 27) mm Hg; and systemic vascular resistance, 1777 (1630 to 1926) dyne·s/cm⁵.

Criteria for Study Enrollment

The majority of the 1435 patients had qualified for enrollment by having clinical (1284 [90%]) and radiographic (1185 [83%]) evidence of pulmonary congestion or edema. Fewer were enrolled on the basis of documented left ventricular systolic dysfunction (677 [47%]) or an elevated concentration of BNP (262 [18%]) or N-terminal pro-BNP (32 [2%]).

Treatment at Baseline

As planned, all patients received an intravenous diuretic. An angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was used at the time of randomization in 909 (63%), a β -blocker in 671 (47%), and spironolactone in 265 (19%). Very few patients received other intravenous vasoactive agents at baseline or during

infusion of study drug: 221 (15%) received nitrates at baseline (20% during study drug infusion), 26 (1.8%) received dobutamine (3.3%), 7 (0.5%) received nitroprusside (1.1%), 21 (1.5%) received nesiritide (2.9%), 29 (2.0%) received dopamine (4.5%), and 2 (0.1%) received milrinone (0.6%).

Study Drug Administration

Study drug was received as assigned by 727 of 730 (99.6%) patients assigned to receive tezosentan and 708 of 718 (98.6%) assigned to receive placebo (Figure 1). The median time from admission to the start of study drug was 11 hours. At least 24 hours of treatment was received by 661 of 727 (91%) patients given tezosentan and 665 of 708 (94%) given placebo.

Change in Dyspnea

The mean (95% CI) VAS score for dyspnea at baseline was 66.5 (64.2 to 68.8) in the tezosentan group and 63.7 (61.5 to 65.9) in the placebo group at baseline in VERITAS-1; the corresponding scores in VERITAS-2 were 60.3 (57.7 to 62.9) and 59.4 (56.7 to 62.0), respectively, where a higher score indicated greater dyspnea. The level of dyspnea decreased rapidly in both treatment groups after randomization (FIGURE 2). The coprimary end point of the area under the curve of the change in dyspnea from baseline was similar in each treatment

group in both VERITAS-1 and VERITAS-2. In VERITAS-1, the mean (95% CI) change was -562 (-628 to -497) mm·h in the tezosentan group and -550 (-617 to -483) in the placebo group (difference between treatments, -12 [-105 to 81] mm·h; $P=.80$). In VERITAS-2, the corresponding change in the tezosentan group was -367 (-432 to -302) mm·h and in the placebo group was -342 (-410 to -274) (difference between treatments, -25 [-119 to 69] mm·h; $P=.60$).

There was no difference between tezosentan and placebo in key unplanned subgroups (FIGURE 3). The response in patients with baseline VAS scores for dyspnea above and below the median (65 mm) was similar. Similarly, a preplanned exploratory analysis of the change in rate of respiration (area under the curve analysis) showed no difference between tezosentan and placebo; in VERITAS-1 and VERITAS-2 combined, the mean (95% CI) change in the tezosentan group was -32 (-50 to -15) breaths/min·h and in the placebo group was -26 (-43 to -9) (difference between treatments, -6.4 [-31 to 18]; $P=.61$).

The mean (95% CI) change in the area under the curve for dyspnea change did not differ between treatment groups in the subset of 84 patients monitored hemodynamically (treatment difference, -5 [-328 to 318]; $P=.97$), and the

treatment difference did not differ significantly between patients who were and were not monitored hemodynamically ($P = .89$ for interaction).

Death or Worsening Heart Failure Up to 7 Days

The incidence of the coprimary end point of death or worsening heart failure up to 7 days from randomization in VERITAS-1 and VERITAS-2 combined is shown in TABLE 2. In both treatment groups, 26% of patients experienced this composite outcome (odds ratio, 0.99; 95% CI, 0.82 to 1.21; $P = .95$). The effect of tezosentan compared with placebo was similar across a range of unplanned subgroups, including those defined by sex, age, etiology, LVEF, comorbidity, baseline blood pressure, and renal function and concomitant treatment.

Secondary and Exploratory End Points

The secondary end point of the incidence of death or worsening heart failure up to 30 days was 32% in the tezosentan group and 33% in the placebo group (Table 2). The incidence of the composite outcome of death or a major cardiovascular event at 7 days and 30 days is summarized in Table 2.

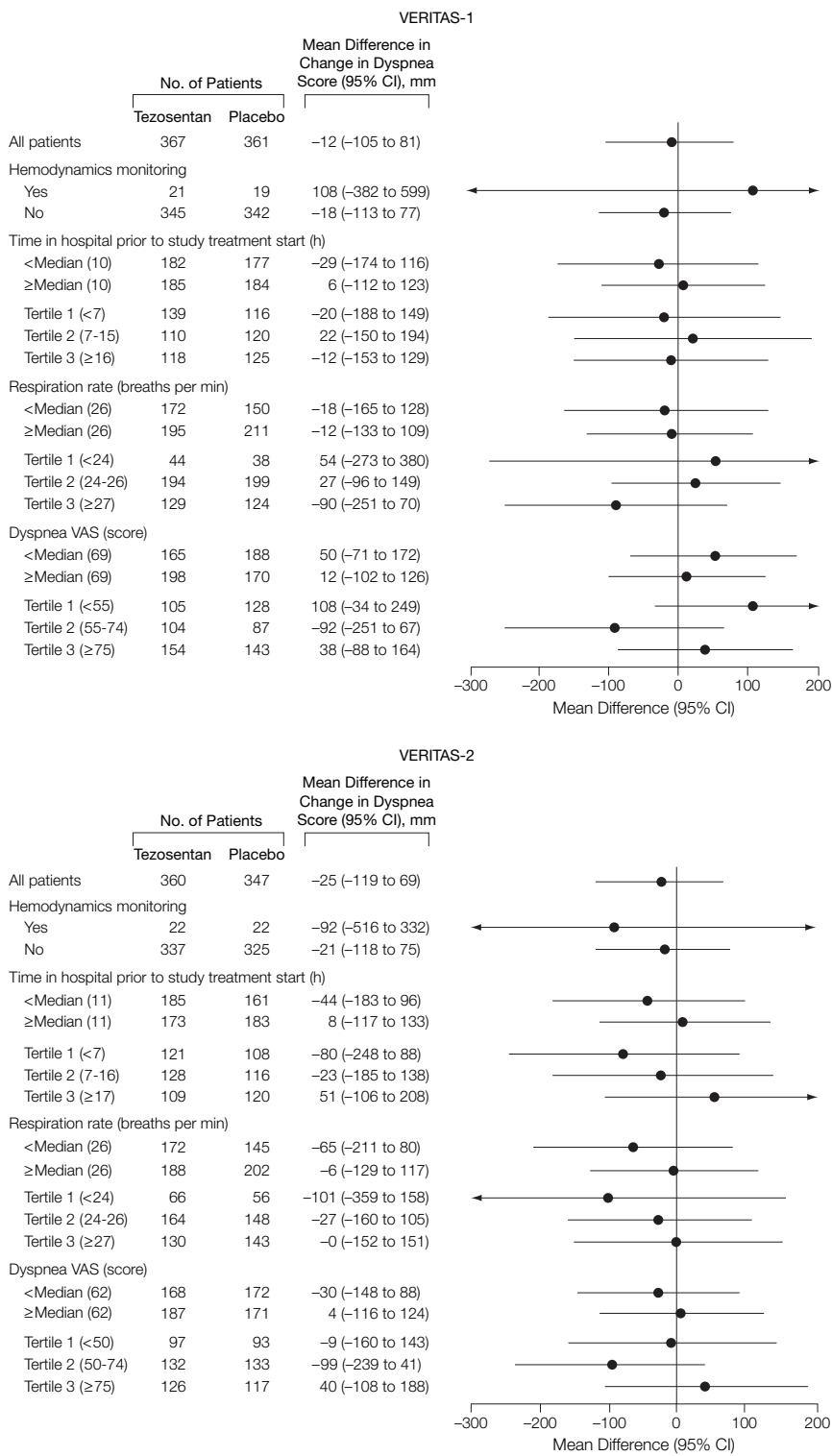
The mean (SD) number of days spent in hospital during the index admission after randomization was 9 (7) in both treatment groups and from randomization to day 30 was 11 (8) in each treatment group.

The number of deaths at 6 months was 104 (14.3%) in the tezosentan group and 101 (14.3%) in the placebo group (hazard ratio, 1.01; 95% CI, 0.77 to 1.33).

Changes in Hemodynamic Measurements

Changes in key hemodynamic measurements at 3, 6, and 24 hours from start of study drug were secondary end points and are summarized in TABLE 3. Greater decreases in PCWP, right atrial pressure, and pulmonary and systemic vascular resistance and a trend to a greater increase in cardiac index were observed in the tezosentan group.

Figure 3. Change in Dyspnea Over 24 Hours in Key Subgroups of VERITAS-1 and VERITAS-2



Change in dyspnea shown as placebo-corrected area under the curve. CI indicates confidence interval; VAS, visual analog scale; VERITAS, Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies. Error bars indicate 95% confidence intervals.

Table 2. Primary (Death or Worsening Heart Failure) and Secondary (Death or Major Cardiovascular Event) End Points Up to Day 7 and Day 30

	No. (%)			
	Day 7		Day 30	
	Tezosentan (n = 727)	Placebo (n = 708)	Tezosentan (n = 727)	Placebo (n = 708)
Death or Worsening Heart Failure				
Patients with an event ^a	191 (26.3)	187 (26.4)	232 (31.9)	235 (33.2)
Events ^b				
Death	11 (1.5)	8 (1.1)	28 (3.9)	34 (4.8)
Cardiogenic shock	3 (0.4)	5 (0.7)	2 (0.3)	4 (0.6)
Pulmonary edema	47 (6.5)	39 (5.5)	61 (8.4)	55 (7.8)
Other evidence of worsening heart failure	83 (11.4)	92 (13.0)	96 (13.2)	104 (14.7)
Treatment failure	47 (6.5)	43 (6.1)	42 (5.8)	37 (5.2)
Heart transplant	0	0	1 (0.1)	0
Lost to follow-up	0	0	2 (0.3)	1 (0.1)
Death or Major Cardiovascular Event				
Patients with an event ^c	205 (28.2)	201 (28.4)	249 (34.3)	251 (35.5)
Events (other than death or worsening heart failure) ^d				
Myocardial infarction	15 (2.1)	11 (1.6)	19 (2.6)	15 (2.1)
Atrial fibrillation	5 (0.7)	2 (0.3)	6 (0.8)	3 (0.4)
Stroke	4 (0.6)	1 (0.1)	7 (1.0)	5 (0.7)
Myocardial ischemia	4 (0.6)	0	4 (0.6)	0
Ventricular tachycardia	3 (0.4)	1 (0.1)	4 (0.6)	1 (0.1)
Cardiac arrest	3 (0.4)	0	4 (0.6)	0
Ventricular fibrillation	2 (0.3)	4 (0.6)	3 (0.4)	5 (0.7)

^aComparison between treatment groups (Fisher exact test): $P = .95$ at day 7 and $P = .61$ at day 30.

^bRanked by severity; each patient counted once (as the most serious event); separate analyses for days 7 and 30, ie, a patient in cardiogenic shock on day 6 who died on day 8 was categorized as having cardiogenic shock in the day 7 analysis and as a death in the day 30 analysis. Patients who had received a heart transplant or were lost to follow-up were counted as treatment failure.

^cComparison between treatment groups (Fisher exact test): $P = .95$ at day 7 and $P = .66$ at day 30.

^dEach patient could have more than 1 event.

By 24 hours, the mean (SD) decrease in systolic blood pressure was 14.6 (18.3) mm Hg in the tezosentan group and -8.5 (21.1) mm Hg in the placebo group, a statistically significant difference of -6.1 (95% CI, -8.2 to -4.1) mm Hg ($P < .0001$). The mean (SD) decrease in diastolic blood pressure was -9.7 (13.7) mm Hg in the tezosentan group and -4.4 (14.3) mm Hg in the placebo group, a statistically significant difference of -5.3 (95% CI, -6.7 to -3.8) mm Hg ($P < .0001$).

Safety and Adverse Effects

Of 727 tezosentan-treated and 708 placebo-treated patients, 103 (14.2%) and 68 (9.6%), respectively, stopped the study drug because of an adverse effect ($P = .008$). This difference was mainly due to hypotension (leading to discontinuation in 60 [8.3%] in the tezosentan group and 33 [4.7%] in the placebo-treated group, $P = .003$), which was the most common adverse effect associated with discontinuation. Overall, hypotension up to 5 days after study drug initiation was reported as an adverse effect in 165 of tezosentan-treated patients (22.7%) and 103 placebo-treated pa-

Table 3. Hemodynamic Changes From Baseline at 3, 6, and 24 Hours in Patients Who Underwent Pulmonary Artery Catheterization

Measure	Baseline, Mean (95% CI)	Change From Baseline					
		3 h		6 h		24 h	
		Mean (95% CI)	P Value ^a	Mean (95% CI)	P Value ^a	Mean (95% CI)	P Value ^a
Cardiac index ^b							
Placebo (n = 41)	2.01 (1.86 to 2.15)	0.18 (0.00 to 0.36)	.07	0.18 (-0.02 to 0.39)	.19	0.15 (-0.08 to 0.39)	.39
Tezosentan (n = 43)	2.14 (1.98 to 2.30)	0.31 (0.17 to 0.45)		0.25 (0.11 to 0.40)		0.15 (-0.01 to 0.31)	
PCWP, mm Hg							
Placebo (n = 41)	25.6 (23.9 to 27.3)	-1.5 (-3.0 to 0.0)	.02	-1.9 (-4.0 to 0.1)	.01	-2.9 (-5.6 to -0.1)	.24
Tezosentan (n = 43)	26.3 (24.5 to 28.1)	-4.6 (-6.3 to -2.9)		-5.2 (-7.1 to -3.2)		-4.1 (-6.8 to -1.4)	
mPAP, mm Hg							
Placebo (n = 40)	35.4 (32.3 to 38.5)	-0.7 (-3.1 to 1.6)	.003	-0.9 (-3.5 to 1.7)	.005	-0.8 (-4.4 to 2.7)	.07
Tezosentan (n = 42)	36.7 (34.1 to 39.3)	-5.0 (-7.2 to -2.8)		-5.6 (-8.1 to -3.0)		-4.4 (-8.0 to -0.7)	
SVR, dyne·s/cm ⁵							
Placebo (n = 41)	1813 (1590 to 2037)	-157 (-361 to 47)	.02	-54 (-253 to 145)	.02	137 (-148 to 421)	.04
Tezosentan (n = 41)	1742 (1538 to 1946)	-371 (-524 to -218)		-306 (-475 to -137)		-101 (-365 to 163)	
PVR, dyne·s/cm ⁵							
Placebo (n = 40)	243 (174 to 313)	9 (-44 to 61)	.06	-21 (-32 to 75)	.03	127 (27 to 228)	.07
Tezosentan (n = 41)	232 (190 to 273)	-39 (-79 to 1)		-38 (-82 to 6)		53 (-36 to 142)	
RAP, mm Hg							
Placebo (n = 41)	15.9 (13.5 to 18.3)	0.8 (-0.6 to 2.2)	.02	-0.2 (-2.1 to 1.6)	.27	0.7 (-1.9 to 3.3)	.33
Tezosentan (n = 42)	14.6 (12.8 to 16.5)	-2.0 (-3.2 to -0.7)		-1.0 (-2.7 to 0.7)		0.0 (-2.4 to 2.4)	

Abbreviations: CI, confidence interval; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVR, systemic vascular resistance. All values are means (standard error of mean).

^aFrom Mann-Whitney U test.

^bCalculated as L/min per m².

tients (14.5%) ($P < .001$). At 72 hours, the mean increase in serum urea concentration in the tezosentan group was 1.7 (5.0) mmol/L; in the placebo group, it was 1.5 (6.2) mmol/L (mean difference, 0.2; 95% CI, -0.4 to 0.8; $P = .58$). For the same time point, the mean increase in serum creatinine concentration was 0.09 (0.35) mg/dL in the tezosentan group and 0.07 (0.32) mg/dL in the placebo group (mean difference, 0.02; 95% CI, -0.02 to 0.05; $P = .39$).

COMMENT

In VERITAS, low-dose tezosentan did not improve dyspnea in patients studied early after an unplanned admission to hospital with acute heart failure, nor did it improve their subsequent risk of death or nonfatal cardiovascular events. The dose of tezosentan used in VERITAS was chosen on the basis of a careful placebo-controlled dose-ranging study that showed this dose to reduce PCWP and systemic vascular resistance as well as plasma concentrations of BNP.¹³ These hemodynamic actions were confirmed in VERITAS by the reduction in blood pressure and, in a subset of patients, PCWP.

Why did tezosentan fail to improve dyspnea in VERITAS, despite evidence of improved hemodynamics? The reduction in PCWP in the small subset of VERITAS patients with a pulmonary artery catheter was of a similar magnitude to that produced by tezosentan in past studies.^{9,12,13} More importantly, it was also similar to the change in PCWP observed in trials of levosimendan and nesiritide, in which both of those drugs reduced dyspnea in invasively monitored patients.^{15,16} It is possible, however, that the hemodynamic effect of the dose of tezosentan used was less in the nonmonitored patients in VERITAS. Tezosentan also reduced dyspnea and PCWP more than placebo in patients monitored invasively in the Randomized Intravenous Tezosentan 2 (RITZ-2) study ($n = 292$). Inclusion required a low cardiac index (≤ 2.5) and an increased PCWP (≥ 15 mm Hg). Although a larger dose of tezosentan (50 or 100 mg/h) was infused in RITZ-2 than in VERITAS (1

mg/h), the effect of tezosentan on PCWP in RITZ-2 (placebo-corrected mean reduction, 4.1 mm Hg) was similar to that in the subset of patients that underwent invasive hemodynamic monitoring in VERITAS (placebo-corrected mean reduction, 3.3 mm Hg).¹⁷

One proposed explanation for the apparent discrepancy between VERITAS and these prior trials is that knowledge of hemodynamic changes in some way influenced the assessment of dyspnea.¹⁸ In 1 trial of nesiritide that did not require invasive hemodynamic monitoring, neither dose of nesiritide improved dyspnea more than usual therapy.¹⁶ Furthermore, in the larger RITZ-1 trial, in which patients ($n = 669$) did not undergo invasive hemodynamic monitoring, treatment with tezosentan (50 mg/h) did not improve dyspnea.¹⁹ Similarly, in a large placebo-controlled trial of levosimendan that did not require hemodynamic monitoring, there was no apparent improvement in dyspnea.²⁰ In another trial, Vasodilation in the Management of Acute Congestive Heart Failure (VMAC), nesiritide (but not glyceryl trinitrate) improved dyspnea at 3 hours, but a Food and Drug Administration review concluded that this difference was driven by the subset of patients monitored hemodynamically.^{21,22}

The results of 3 additional trials, however, seem to refute the hypothesis that knowledge of hemodynamic changes may influence the assessment of dyspnea, though comparison of studies with and without monitoring is only available for nesiritide, tezosentan, and levosimendan. In the Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE) trial, levosimendan was reported to improve dyspnea compared with placebo, but further details on the proportion of patients monitored invasively, and the change in dyspnea in these compared with nonmonitored patients, have not yet been presented.²³ In addition, 2 recent, large, placebo-controlled trials showed that the arginine vasopressin antagonist tolvaptan improved patient-reported dyspnea, apparently without investigator knowledge of hemodynamics.²⁴

An alternative explanation is that the potentially beneficial effect on breathlessness of reducing PCWP with tezosentan may have been offset by another, detrimental, action of endothelin blockade, for example, induction of pulmonary venous-arterial shunting leading to desaturation.

We do not think other factors explain the difference in findings between VERITAS and the "positive" trials of nesiritide and levosimendan. The patients in VERITAS were generally similar although somewhat older, and a higher proportion had preserved LVEF. However, the effect of tezosentan was similar in all subgroups, including those defined by age and LVEF. The subgroup that underwent hemodynamic monitoring in VERITAS had the same baseline PCWP as patients in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE).²⁵

The VAS has been shown to be a more sensitive and reproducible measure of change in dyspnea than the Likert and Borg scales, albeit in a setting other than acute heart failure.²⁶ It is of concern, however, that assessment of the key symptom in acute heart failure, dyspnea, has been so poorly studied. It is also a major methodological limitation of trials in acute heart failure that the large improvement in dyspnea in the placebo group (ie, in response to usual care) makes it very difficult to detect any additional effect of new treatments with the most commonly used instruments, ie, the VAS and Likert scales. In the recent tolvaptan studies, a patient-reported score for dyspnea was used, and this did detect a difference between active treatment and placebo.²⁴ Understanding whether the efficacy differs among these different instruments for assessing breathlessness will be important for the conduct of future trials in this area.

Tezosentan also had no effect on the primary mortality/morbidity composite outcome (or any of the secondary outcomes), though even with this end point we had 80% power to detect a 25% relative risk reduction. Although

disappointing and contrary to expectations based on the potential pathophysiological role of endothelin-1 in heart failure, our findings are consistent with earlier trials in chronic heart failure.²⁷⁻³⁰ In those trials, long-term treatment with oral endothelin receptor antagonists had no effect on left ventricular remodeling or clinical outcomes.²⁷⁻³⁰ Conceptually, however, short-term intravenous administration of a drug might have less prospect of showing a longer-term effect on morbidity and mortality outcomes, emphasizing the difficulty in evaluating new treatment for acute heart failure. Despite its hemodynamic actions, milrinone did not reduce morbidity and mortality in Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), and nesiritide does not reduce morbidity or mortality in acute heart failure.³¹⁻³³ Of course, it is also possible that a beneficial effect of tezosentan in one subgroup of patients may have been offset by harm in another, eg, patients with a low baseline blood pressure. VERITAS did not, however, have the statistical power for such an analysis, which in any case could only be hypothesis-generating.

In summary, tezosentan, a treatment with “favorable” hemodynamic actions, failed to improve breathlessness or reduce fatal and nonfatal cardiovascular events in patients following an emergency admission to hospital with acute heart failure. So far, it has proved impossible to identify a therapeutic role for endothelin antagonists in patients with acute or chronic heart failure.

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REFERENCES

- Nieminen MS, Harjola VP. Definition and epidemiology of acute heart failure syndromes. *Am J Cardiol*. 2005;96(6A):5G-10G.
- Zannad F, Adamopoulos C, Mebazaa A, Gheorghide M. The challenge of acute decompensated heart failure. *Heart Fail Rev*. 2006;11(2):135-139.
- Gheorghide M, Zannad F, Sopko G, et al; International Working Group on Acute Heart Failure Syndromes. Acute heart failure syndromes: current state and framework for future research. *Circulation*. 2005;112(25):3958-3968.
- Sharma M, Teerlink JR. A rational approach for the treatment of acute heart failure: current strategies and future options. *Curr Opin Cardiol*. 2004;19(3):254-263.
- Nieminen MS, Bohm M, Cowie MR, et al; ESC Committee for Practice Guideline (CPG). Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26(4):384-416.
- McMurray JJ, Ray SG, Abdullh I, Dargie HJ, Morton JJ. Plasma endothelin in chronic heart failure. *Circulation*. 1992;85(4):1374-1379.
- Van Beneden R, Gurme O, Selvais PL, et al. Superiority of big endothelin-1 and endothelin-1 over natriuretic peptides in predicting survival in severe congestive heart failure: a 7-year follow-up study. *J Card Fail*. 2004;10(6):490-495.
- Masson S, Latini R, Anand IS, et al; Val-HeFT investigators. The prognostic value of big endothelin-1 in more than 2,300 patients with heart failure enrolled in the Valsartan Heart Failure Trial (Val-HeFT). *J Card Fail*. 2006;12(5):375-380.
- Torre-Amione G, Young JB, Durand J, et al. Hemodynamic effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients with class III to IV congestive heart failure. *Circulation*. 2001;103(7):973-980.
- Kaluski E, Kobrin I, Zimlichman R, et al. RITZ-5: Randomized Intravenous Tezosentan (an endothelin A/B antagonist) for the treatment of pulmonary edema: a prospective, multicenter, double-blind, placebo-controlled study. *J Am Coll Cardiol*. 2003;41(2):204-210.
- O'Connor CM, Gattis WA, Adams KF Jr, et al; Randomized Intravenous Tezosentan Study-4 Investigators. Tezosentan in patients with acute heart failure and acute coronary syndromes: results of the Randomized Intravenous Tezosentan Study (RITZ-4). *J Am Coll Cardiol*. 2003;41(9):1452-1457.
- Torre-Amione G, Young JB, Colucci WS. Hemodynamic and clinical effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2003;42(1):140-147.
- Cotter G, Kaluski E, Stangl K, et al. The hemodynamic and neurohormonal effects of low doses of tezosentan (an endothelin A/B receptor antagonist) in patients with acute heart failure. *Eur J Heart Fail*. 2004;6(5):601-609.
- Teerlink JR, McMurray JJ, Bourge RC, et al; VERITAS Investigators. Tezosentan in patients with acute heart failure: design of the Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Study (VERITAS). *Am Heart J*. 2005;150(1):46-53.
- Slawsky MT, Colucci WS, Gottlieb SS, et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. *Circulation*. 2000;102(18):2222-2227.
- Colucci WS, Elkayam U, Horton DP, et al; Nesiritide Study Group. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. *N Engl J Med*. 2000;343(4):246-253.
- Louis A, Cleland JG, Crabbe S, et al. Clinical trials update: CAPRICORN, COPERNICUS, MIRACLE, STAF, RITZ-2, RECOVER and RENAISSANCE and cachexia and cholesterol in heart failure: Highlights of the Scientific Sessions of the American College of Cardiology, 2001. *Eur J Heart Fail*. 2001;3(3):381-387.
- Teerlink JR. Dyspnea as an end point in clinical trials of therapies for acute decompensated heart failure. *Am Heart J*. 2003;145(2)(suppl):S26-S33.
- Teerlink JR, Massie BM, Cleland JGF, Tzivoni D; for the RITZ-1 Investigators. A double-blind, parallel-group, multi-center, placebo-controlled study to investigate the efficacy and safety of tezosentan in reducing symptoms in patients with acute decompensated heart failure [abstract]. *Circulation*. 2001;104:526.
- Moiseyev VS, Poder P, Andrejevs N, et al; RUSSLAN Study Investigators. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction: a randomized, placebo-controlled, double-blind study (RUSSLAN). *Eur Heart J*. 2002;23(18):1422-1432.
- Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287(12):1531-1540.
- US Food and Drug Administration. NDA 20-920 Natrecor (nesiritide). http://www.fda.gov/ohrms/dockets/ac/01/briefing/3749b2_02_02-FDA-Medical%20Review.pdf. Accessibility verified October 12, 2007.
- Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. *Eur J Heart Fail*. 2006;8(1):105-110.
- Gheorghide M, Konstam MA, Burnett JC Jr, et al; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST clinical status trials. *JAMA*. 2007;297(12):1332-1343.
- Binanay C, Califf RM, Hasselblad V, et al; ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA*. 2005;294(13):1625-1633.
- Grant S, Aitchison T, Henderson E, et al. A comparison of the reproducibility and the sensitivity to change of visual analogue scales, Borg scales, and Likert scales in normal subjects during submaximal exercise. *Chest*. 1999;116(5):1208-1217.
- Anand I, McMurray J, Cohn JN, et al; EARTH Investigators. Long-term effects of darusentan on left-ventricular remodeling and clinical outcomes in the EndothelinA Receptor Antagonist Trial in Heart Failure (EARTH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364(9431):347-354.
- Packer M, McMurray J, Massie BM, et al. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. *J Card Fail*. 2005;11(1):12-20.
- Coletta A, Thackray S, Nikitin N, Cleland JG. Clinical trials update: highlights of the scientific sessions of the American College of Cardiology 2002: LIFE, DANAMI 2, MADIT-2, MIRACLE-ICD, OVERTURE, OCTAVE, ENABLE 1 & 2, CHRISTMAS, AFFIRM, RACE, WIZARD, AZACS, REMATCH, BNP trial and HARDBALL. *Eur J Heart Fail*. 2002;4(3):381-388.
- Prasad SK, Dargie HJ, Smith GC, et al. Comparison of the dual receptor endothelin antagonist enrasentan with enalapril in asymptomatic left ventricular systolic dysfunction: a cardiovascular magnetic resonance study. *Heart*. 2006;92(6):798-803.
- Cuffe MS, Califf RM, Adams KF Jr, et al; Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287(12):1541-1547.
- Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation*. 2005;111(12):1487-1491.
- Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA*. 2005;293(15):1900-1905.