

# Hemodynamic and Clinical Effects of Tezosentan, an Intravenous Dual Endothelin Receptor Antagonist, in Patients Hospitalized for Acute Decompensated Heart Failure

Guillermo Torre-Amione, MD,\* James B. Young, MD,† Wilson S. Colucci, MD,‡ Basil S. Lewis, MD,§ Craig Pratt, MD,\* Gad Cotter, MD,|| Karl Stangl, MD,¶ Uri Elkayam, MD,# John R. Teerlink, MD,\*\* Aline Frey, PHARM.D,†† Maurizio Rainisio, PH.D,†† Isaac Kobrin, MD††

Houston, Texas; Cleveland, Ohio; Boston, Massachusetts; Haifa and Zerifin, Israel; Berlin, Germany; Los Angeles and San Francisco, California; and Allschwil, Switzerland

<b>OBJECTIVES</b>	We sought to investigate the efficacy and safety of tezosentan, a dual endothelin receptor antagonist, in patients hospitalized for acute heart failure (HF).
<b>BACKGROUND</b>	Tezosentan has been previously shown to improve hemodynamics in patients with stable chronic HF.
<b>METHODS</b>	In a double-blind fashion, 292 patients (cardiac index $\leq 2.5$ l/min per $m^2$ and pulmonary capillary wedge pressure (PCWP) $\geq 15$ mm Hg) who were admitted to the hospital and in need of intravenous treatment for acute HF and central hemodynamic monitoring were randomized to 24-h intravenous treatment with tezosentan (50 or 100 mg/h) or placebo. Central hemodynamic variables, the dyspnea score, and safety variables were measured.
<b>RESULTS</b>	After 6 h of treatment, significantly greater increases in the cardiac index and decreases in PCWP were observed with both tezosentan dosages than with placebo (mean treatment effects at 0.38 and 0.37 l/min per $m^2$ with 50 and 100 mg/h and $-3.9$ mm Hg for each dose, respectively; $p < 0.0001$ ). This effect was maintained during the remaining infusion and for $\geq 6$ h after treatment cessation. A tendency for an improved dyspnea score and a decreased risk of clinical worsening was observed after 24 h of treatment with each tezosentan dose. Adverse events, more frequent with tezosentan than with placebo (headache, asymptomatic hypotension, early worsening of renal function, nausea, vomiting), were dose-related.
<b>CONCLUSIONS</b>	Intravenous tezosentan rapidly and effectively improved hemodynamics in these patients. The similar beneficial effects of the two dosages and the increased dose-related adverse events with the higher dosage suggest that the optimal dosing regimen is $< 50$ mg/h. (J Am Coll Cardiol 2003;42:140-7) © 2003 by the American College of Cardiology Foundation

Acute heart failure (HF) is characterized by impairment of left ventricular function, increases in peripheral and pulmonary vascular resistance, systemic desaturation, reductions in perfusion of vital organs and exercise tolerance, and dyspnea (1,2). These hemodynamic disturbances and symptoms can evolve into cardiovascular collapse and ultimately death. The goals of treatment for patients with acute HF are rapid symptom relief and stabilization of the patient, but current knowledge of the pathophysiologic mechanisms leading to the development of acute HF is limited. Therefore, additional treatments with different mechanisms of action are needed.

Plasma endothelin (ET)-1 concentrations are elevated in

patients with chronic HF, correlate with both hemodynamic and symptom severity (3-6), and are strong independent predictors of death in these patients (7). Blockade of the detrimental effects of ET-1 could be effective in improving both hemodynamic and clinical end points in patients with acute HF and those with chronic HF. Tezosentan is a dual ET<sub>A</sub>/ET<sub>B</sub> receptor antagonist designed for parenteral use. It has a short half-life ( $\sim 10$  min) and is eliminated unchanged in the bile without renal excretion (8). The results of two small, short-term studies in patients with symptomatic but stable HF (9,10) indicated that treatment with tezosentan (5 to 100 mg/h up to 6 h) was associated with a dose-related increase in the cardiac index and decreases in systemic and pulmonary pressures and resistances. At all dosages, most of the beneficial effect was achieved within 1 h. No tolerance was evident, and treatment cessation was not associated with a rebound effect (blood pressure [BP] returned to baseline and the increase in the cardiac index was sustained for  $\geq 4$  h) or an increase in the heart rate.

The primary objectives of this trial were to confirm previous preliminary findings and evaluate the hemodynamic effects of two tezosentan doses in patients hospital-

From the \*Methodist DeBakey Heart Center and Baylor College of Medicine, Houston, Texas; †Section on Heart Failure and Cardiac Transplant Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio; ‡Cardiovascular Section, Boston Medical Center, Boston University School of Medicine, Boston, Massachusetts; §Cardiology Department, Lady Davis Carmel Medical Center, Haifa, Israel; ||Cardiology Institute, Assaf-Harofeh Medical Center, Zerifin, Israel; ¶Department of Cardiology, Charite Hospital, Humboldt University, Berlin, Germany; #Division of Cardiology, University of Southern California School of Medicine, Los Angeles, California; \*\*Cardiology, San Francisco Veterans Affairs Medical Center/University of California at San Francisco, San Francisco, California; and ††Actelion Pharmaceuticals Ltd., Allschwil, Switzerland. This study was supported by a grant from Actelion Pharmaceuticals Ltd., Allschwil, Switzerland.

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#### Abbreviations and Acronyms

BP	= blood pressure
CL	= confidence limit
ECG	= electrocardiogram/electrocardiographic
ET	= endothelin
HF	= heart failure
PAP	= pulmonary artery pressure
PCWP	= pulmonary capillary wedge pressure
PVR	= pulmonary vascular resistance
RAP	= right atrial pressure
SVR	= systemic vascular resistance

ized with acute HF and in need of immediate treatment. The impact of tezosentan treatment on dyspnea and death or worsening HF was also explored.

## METHODS

This was a double-blind, randomized, placebo-controlled study of two dosages of tezosentan infused over 24 h, which was approved by the site-specific ethics committees and conducted according to the amended Declaration of Helsinki at 36 centers in Europe, Israel, and the U.S. All patients gave written, informed consent.

**Patients and treatment.** The study population included males and females (surgically sterile, postmenopausal, or using contraceptives) who were  $\geq 18$  years of age with ischemic or non-ischemic heart disease, admitted to the hospital with acute HF, and in need of intravenous treatment (based on the investigator's judgment) for this condition. Entry criteria included a pulmonary capillary wedge pressure (PCWP)  $\geq 15$  mm Hg, a cardiac index  $\leq 2.5$  l/min per  $m^2$ , and the need for continuous hemodynamic monitoring for treatment guidance. Patients with a supine systolic BP  $< 85$  mm Hg, acute coronary syndrome or percutaneous transluminal coronary angioplasty within the last seven days, hemodynamically relevant cardiac arrhythmias, other serious systemic diseases, cardiac or major non-cardiac surgery within the last 30 days, or mechanical ventilatory or circulatory support or chronic/acute dialysis were excluded.

Qualified patients were randomized to 50 or 100 mg/h tezosentan or placebo administered through an intravenous cannula by sequential allocation of randomly ordered, blinded treatment (provided in blocks of three by an independent party). Treatments were identically packaged, and solutions were identically prepared by the pharmacist. Patients were treated for 1 h with tezosentan 25 mg/h or placebo; the infusion rate was doubled to obtain tezosentan at 50 mg/h throughout hour 2. Thereafter, new solutions were administered so that patients received placebo or tezosentan at 50 or 100 mg/h for the next 22 h. The infusion rate could be reduced by half once or twice in case of systolic BP  $< 80$  mm Hg, symptomatic hypotension, or drug-related adverse events. Dosages were chosen based on the results of phase II studies demonstrating that the plateau

of the dose-response curve for the cardiac index was reached with 50 to 100 mg/h; the starting dose (25 mg/h) was chosen to simplify the up-titration.

Oral therapy for HF at any time and parenteral therapy for HF administered up to 2 h (for milrinone, up to 4 h) before randomization were unrestricted. Parenteral treatments were to remain stable, and intravenous diuretics were prohibited during the 2 h before randomization. After the start of study drug, initiation or increase of parenteral treatments (including diuretics up to hour 6) was reserved for patients who continued to deteriorate or showed no response to treatment. Intravenous diuretic treatment was limited to furosemide or, in case of a known allergy, ethacrinic acid in order to standardize use across centers.

**Assessments.** Hemodynamic variables were measured at baseline, at 1, 2, 4, 6, and 24 h after treatment initiation, and at 3 and 6 h after treatment cessation via a Swan-Ganz catheter inserted at least 2 h before the start of infusion. Cardiac output was determined by thermodilution. Systolic and diastolic pulmonary artery pressures (PAP), PCWP, and mean right atrial pressure (RAP) were obtained during expiration. Arterial pressures were measured with a pressure transducer in the arterial line. Heart rate was continuously monitored. The cardiac index and pulmonary and systemic vascular resistances (PVR and SVR, respectively) were calculated using standard formulas.

Patients assessed their dyspnea at 6 and 24 h of infusion using a 7-point scale, ranging from "markedly improved" (1) to "markedly worsened" (7). The eighth rank (worst) was assigned if the patient died or experienced worsening HF during randomized therapy. Time to death or worsening HF (associated with initiation or increase in intravenous inotropic, phosphodiesterase inhibitor, or vasodilator therapy; intravenous diuretic treatment during the first 6 h of randomized treatment; initiation of mechanical circulatory or ventilatory support; or arrhythmias necessitating electrical cardioversion) was evaluated over the 24-h infusion.

Adverse events were monitored throughout the infusion; hypotension was judged asymptomatic or symptomatic by the investigator. Deaths and serious adverse events were reported up to 28 days after treatment cessation. Routine hematologic studies and multipanel blood chemistry tests, 12-lead electrocardiograms (ECGs), and vital signs were assessed at baseline and at the end of infusion.

**Statistical analysis.** The primary end point (mean change from baseline to hour 6 in the cardiac index) was used to test the null hypothesis that there is no difference between the treatment arms. Secondary end points included changes in other central hemodynamic parameters, the patient's perception of the change in dyspnea, and the time to death or worsening HF. The sample size (77 patients/arm) was estimated using a treatment difference in the cardiac index of 0.3 l/min per  $m^2$  (determined from phase II studies) between any pair of treatments, equal standard deviations (SDs) of 0.5 l/min per  $m^2$ , and Tukey's Studentized Range test (overall two-sided type I error of 0.05, 90% power). The

**Table 1.** Demographics and Baseline Disease Characteristics

	Placebo (n = 94)	Tezosentan	
		50 mg/h (n = 90)	100 mg/h (n = 101)
Demographics			
Age (yrs)	62 ± 12	62 ± 12	60 ± 15
Gender, male/female (%)	72/28	82/18	71/29
Race, white/black/other (%)	78/13/10	80/9/11	78/13/9
Heart failure cause (%)			
Ischemic heart disease	61	68	63
Dilated cardiomyopathy	22	20	24
Other	17	12	13
Ejection fraction* (%)	23 ± 9	24 ± 10	23 ± 10
Number (%) with EF ≥40%	4 (5.6)	7 (9.6)	3 (3.4)
Baseline hemodynamics			
Cardiac index (l/min per m <sup>2</sup> )	1.92 ± 0.37	1.96 ± 0.34	1.91 ± 0.37
PCWP (mm Hg)†	25 ± 7	25 ± 7	24 ± 6
Baseline serum creatinine (μmol/l)	121 ± 49	121 ± 50	109 ± 45
Other relevant diseases (%)			
Previous myocardial infarction	50.0	64.4	52.5
Hypertension	59.6	54.4	44.6
Diabetes	32.9	37.8	34.7
Renal failure	34.0	33.3	22.8
Atrial fibrillation	29.8	24.4	19.8

\*Ejection fraction (EF) measurements within the 12 months before screening were collected as part of the medical history and were available for ≥76% of patients in each group. †Values for pulmonary capillary wedge pressure (PCWP) were not available for all patients (n ≥ 78 per group). Data are presented as the mean value ± SD or percentage of patients, unless otherwise indicated.

estimate assumed that the Student *t* test was used for the three pairwise comparisons, requiring a type I error of 0.017. More than the planned 80 patients per arm were enrolled near the end of recruitment. Efficacy and safety analyses were performed on all randomized patients who received the study drug.

For evaluation of the change in the cardiac index, patients who experienced death or worsening HF were assigned the worst rank (largest percentage decrease in the cardiac index in the relevant population). Patients withdrawn for other reasons during the first 6 h of treatment were included using the last value carried forward. Patients without baseline measurements were excluded. Unplanned analyses were performed for treatment differences in dyspnea scores (Mann-Whitney *U* test) and the time to death or worsening HF (log-rank test) with Kaplan-Meier estimates of the proportions of failures displayed. Other parameters were analyzed descriptively.

## RESULTS

Seven of the 292 randomized patients were not treated, either because of unfulfilled entry criteria (n = 5), withdrawn consent, or a dislodged catheter, and as per protocol, they were omitted from analyses. The remaining 285 patients comprise the efficacy and safety populations. No statistical differences between treatment groups were found regarding baseline characteristics (Table 1). All patients were taking medications for HF at baseline (Table 2), with 41% to 56% given intravenous diuretics and 72% to 76% given oral diuretics (mean 124 to 202 mg and 114 to 124 mg

furosemide equivalents, respectively) during the 24 h before study treatment initiation. During the infusion, oral medications were usually continued, and concomitant intravenous medications were generally similar among treatment groups. One patient receiving 50 mg/h, two receiving 100 mg/h, and two receiving placebo were prematurely discontinued during the first 6 h of treatment, all due to adverse events.

**Hemodynamic effects.** The baseline cardiac index was similar in all treatment groups (Table 1), but the change in the cardiac index from baseline to hour 6 of the infusion was significantly greater in both tezosentan groups than in the placebo group (*p* < 0.0001) (Fig. 1). The cardiac index increased to a similar extent in both the 50- and 100-mg/h groups (mean ± SD increases of 0.42 ± 0.53 and 0.41 ± 0.56 l/min per m<sup>2</sup>, respectively) and changed little with placebo (0.04 ± 0.38 l/min per m<sup>2</sup>), which resulted in mean (95% confidence limit [CL]) treatment effects of 0.38 (0.21 to 0.56) and 0.37 (0.20 to 0.54) l/min per m<sup>2</sup>, respectively. About 75% of the maximum observed increase was reached during the first hour of treatment with the 25-mg/h dose, and the maximum was obtained within 4 h. This improvement was sustained over the entire 24-h infusion and persisted for ≥6 h after treatment cessation. Effects were similar with both tezosentan doses.

Other hemodynamic variables were also improved with tezosentan (Fig. 2). Significant decreases in PCWP were obtained by hour 6 with both 50 and 100 mg/h compared with placebo, with mean (95% CL) treatment effects of -3.9 (-6.0 to -1.7) and -3.9 (-6.0 to -1.9) mm Hg,

**Table 2.** Concomitant Medications

	Placebo (n = 94)	Tezosentan	
		50 mg/h (n = 90)	100 mg/h (n = 101)
Baseline (taken within 2 weeks before treatment)			
Loop diuretics	97	97	97
ACE/angiotensin II inhibitor	83	88	93
Nitrates	61	69	64
Digitalis	60	63	65
Beta-blocker	54	57	48
Spirolactone	44	33	37
Anti-arrhythmics	29	22	23
Adrenergic/dopaminergic agents	16	18	25
Phosphodiesterase inhibitors	10	9	14
During the infusion (up to hour 6/hour 6 to end)*			
Loop diuretics	6/35	6/29	7/27
Nitrates	17/19	19/19	15/15
Digitalis	—/1	—/1	1/2
Anti-arrhythmics	2/2	—/2	1/3
Adrenergic/dopaminergic agents	7/17	12/17	14/26
Phosphodiesterase inhibitors	9/14	8/8	10/16

\*Hour 6 equals the time of the 6-h assessment of the cardiac index (primary end point). Data are presented as the percentage of patients.  
 ACE = angiotensin-converting enzyme.

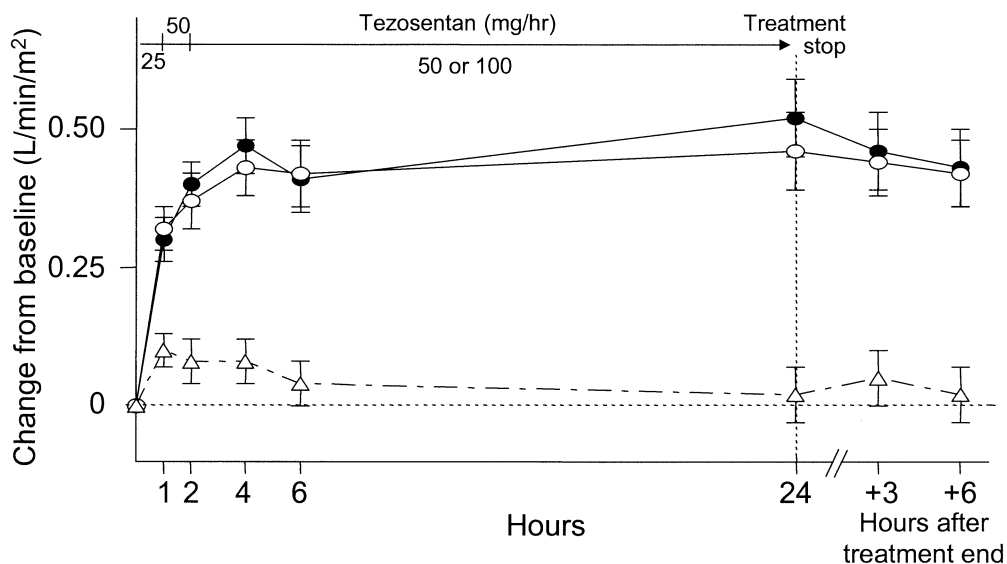
respectively ( $p < 0.0001$ ). Additionally, mean decreases from baseline in other hemodynamic variables were significant with tezosentan and similar with each dose. In contrast, minimal changes were observed with placebo. As with the cardiac index, these beneficial effects were maintained during the entire 24-h infusion and for  $\geq 6$  h after treatment cessation.

**Clinical assessments.** A small improvement in the patient's perception of dyspnea was observed after 6 h with tezosentan ( $p = 0.46$ ), which was larger after 24 h of treatment ( $p = 0.07$ ) (Fig. 3). Because hemodynamic effects were similar between the two tezosentan doses and the study was not powered with respect to clinical outcomes, a

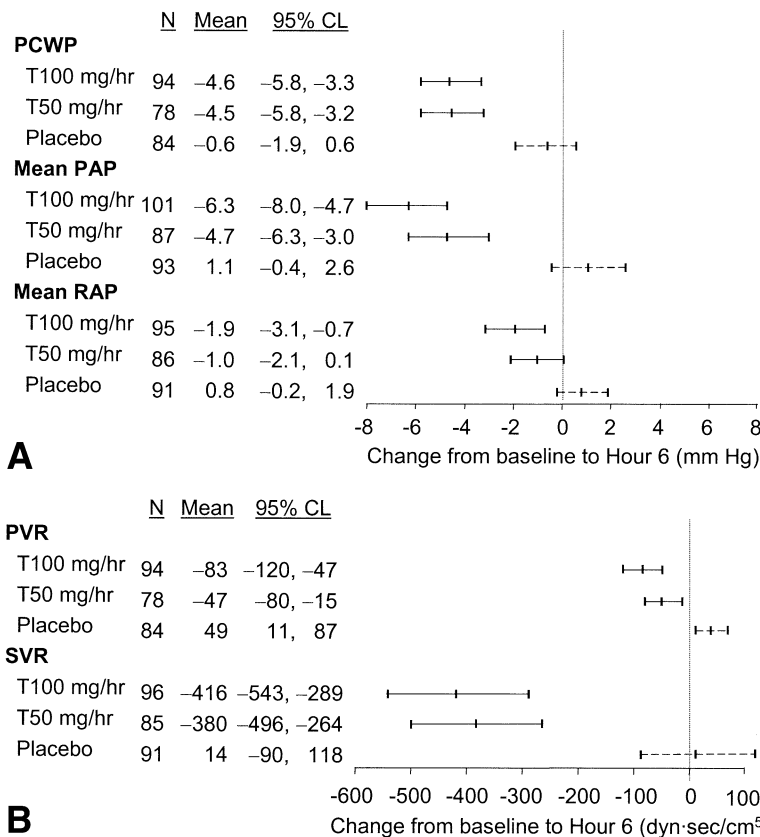
post hoc analysis was performed with the two dose groups combined. In this pooled analysis, dyspnea was improved in a significantly greater proportion of patients receiving tezosentan ( $n = 191$ ) than those receiving placebo ( $n = 94$ ) after 24 h of infusion ( $p = 0.048$ ).

During the infusion, death or worsening HF occurred in fewer patients receiving tezosentan (8.9% in each group) than those receiving placebo (16.0%), which is reflected in the time-to-event analysis (Fig. 4). When the similar tezosentan arms were pooled (post hoc analysis), a trend was seen, but the results did not reach statistical significance.

**Safety assessments.** The continuous 24-h infusion of tezosentan was generally well tolerated, but the overall



**Figure 1.** Cardiac index: change from baseline to 6 h after treatment cessation (mean  $\pm$  SE). **Triangles** = placebo group ( $n = 94$ ); **open circles** = 50 mg/h tezosentan ( $n = 90$ ); **solid circles** = 100 mg/h tezosentan ( $n = 101$ ).



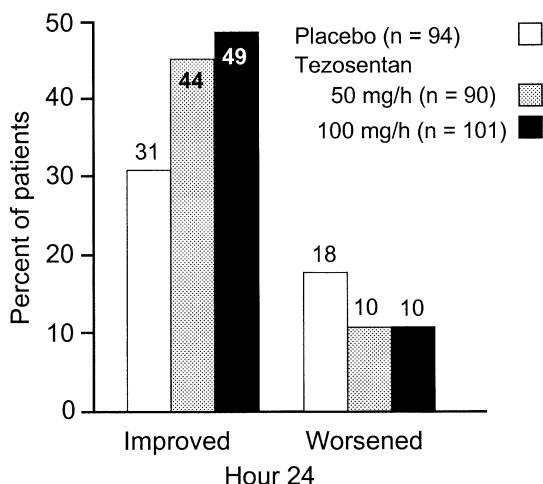
**Figure 2.** Change from baseline to hour 6 of infusion in (A) pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (PAP), and mean right atrial pressure (RAP) and (B) pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) (means, 95% confidence limit [CL]). Confidence limits not crossing zero represent a significant change from baseline at  $p < 0.05$ . **Dashed lines** = placebo; **solid lines** = tezoesentan (T).

incidence of adverse events during treatment was higher with tezoesentan than with placebo, due to higher incidences of headache and hypotension (Table 3). Most cases of headache were mild; moderate to severe headache occurred in five and seven patients receiving tezoesentan at 50 and 100 mg/h, respectively, and did not occur with placebo. Hypotension appeared to be dose-related, but most cases were asymptomatic. Symptomatic hypotension occurred in three

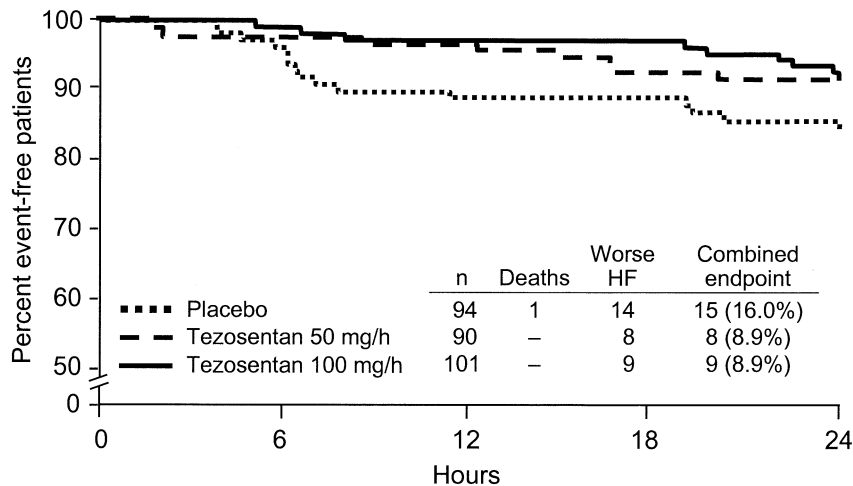
patients receiving placebo, in three patients receiving 50 mg/h tezoesentan, and in five patients receiving 100 mg/h tezoesentan. However, hypotension was the most common reason for premature treatment discontinuation (Table 4). No other adverse event had a higher incidence with tezoesentan than with placebo, but apparent dose-related trends were observed in nausea and vomiting.

The occurrence of renal failure appeared related to tezoesentan treatment (Table 3) and was therefore evaluated in greater detail. When adverse event reports (renal failure/impairment) and marked increases in serum creatinine ( $>154 \mu\text{mol/l}$  with  $>75\%$  increase) were combined, the incidence was similar in all three treatment groups (Table 4). However, renal failure appeared to occur earlier among patients receiving tezoesentan (during treatment or within 48 h after) and later in patients receiving placebo. The proportions of these patients receiving dialysis and who recovered were similar among the three groups. Many who experienced renal failure during the study had a history of chronic renal failure (50%, 71%, and 78% receiving placebo and low and high tezoesentan doses, respectively). Overall, mean ( $\pm$ SD) serum creatinine concentrations changed little ( $-7 \pm 23$ ,  $8 \pm 41$ , and  $4 \pm 31 \mu\text{mol/l}$ , respectively).

Only two of the 21 deaths during the 28-day follow-up (Table 4) occurred during or within 48 h after the infusion. One patient died during placebo infusion (ventricular fibril-



**Figure 3.** Percent of patients with markedly or moderately improved (scores 1 to 2) or worsened (scores 6 to 8) dyspnea after 24-h infusion.



**Figure 4.** Kaplan-Meier plot of time to the combined end point of death or worsening heart failure (HF) during 24-h infusion.

lation secondary to progressive respiratory failure and worsening HF), and one patient died of cardiac arrest 44 h after the 50-mg/h tezosentan infusion was stopped. A post hoc analysis of the time to death, cardiac failure, pulmonary edema, or cardiogenic shock assessed over the 28-day follow-up suggested that the reduction in these events obtained with the lower tezosentan dose was not lost over time (Fig. 5). After six months, the incidence of death was similar among the treatment groups (Table 4). Except for increased serum creatinine, no clinically relevant differences among treatment groups were observed in hematologic or clinical chemistry parameters. There were no differences in mean changes in ECG parameters or the incidence of treatment-emergent ECG changes, and there was no evidence for a pro-arrhythmic effect. Changes in heart rate

were minor in all groups (Table 4). Decreases in BP were larger with tezosentan than with placebo and appeared to be dose-related.

## DISCUSSION

Initial investigations have characterized the effects of short-term (6 h) intravenous treatment with tezosentan in patients with stable HF (9), but this is the first report of 24-h use in patients admitted to the hospital specifically for treatment of acute HF. The study evaluated the effects of tezosentan on both hemodynamic function and HF symptoms, as rapid improvements in both are needed in this patient population.

Hemodynamics were rapidly and significantly improved with both tezosentan doses; the cardiac index was significantly increased and PCWP significantly decreased compared with placebo. This confirms previous findings on the cardiac index and verifies the trend seen in PCWP in the smaller study (9). In addition, significant decreases from baseline were observed in mean PAP, RAP, PVR, and SVR with tezosentan, which were not observed with placebo. These beneficial hemodynamic effects were rapid in onset, sustained during infusion, and maintained for  $\geq 6$  h after treatment cessation. The magnitude of the hemodynamic effect was similar for both the 50- and 100-mg/h dosages, and most of the observed increase in the cardiac index was obtained during the first hour at the 25-mg/h starting dose. These findings suggest that both dosages were at the plateau of the dose-response curve, and a benefit might be attained at doses of 25 mg/h or less.

The magnitude of the hemodynamic improvements obtained with tezosentan in this study was at least as large if not larger than that reported for new vasodilators, such as nesiritide (B-natriuretic peptide) (11) and other ET receptor antagonists (12,13) in patients with severe chronic HF. However, dosages, treatment durations, patient populations, and concomitant therapies were different, making comparisons difficult. Selective ET<sub>A</sub> and dual ET<sub>A</sub>/ET<sub>B</sub>

**Table 3.** Summary of Adverse Events During Randomized Treatment

Adverse Event	Placebo (n = 94)	Tezosentan	
		50 mg/h (n = 90)	100 mg/h (n = 101)
Patients with $\geq 1$ adverse event	47 (50.0)	63 (70.0)	71 (70.3)
Total number of events	97	105	143
Headache	3 (3.2)	25 (27.8)	23 (22.8)
Hypotension*	6 (6.4)	15 (16.7)	25 (24.8)
0-6 h	4	8	9
>6-24 h	2	7	16
Cardiac failure	22 (23.4)	8 (8.9)	18 (17.8)
Vomiting	3 (3.2)	2 (2.2)	9 (8.9)
Nausea	2 (2.1)	3 (3.3)	8 (7.9)
Hypokalemia	3 (3.2)	1 (1.1)	3 (3.0)
Renal failure	0	2 (2.2)	5 (5.0)
Treatment failure	8 (8.5)	1 (1.1)	4 (4.0)
Insomnia	3 (3.2)	1 (1.1)	3 (3.0)
Dyspnea	3 (3.2)	2 (2.2)	2 (2.0)
Pulmonary edema	3 (3.2)	3 (3.3)	0
Pyrexia	3 (3.2)	0	1 (1.0)
Other†	26 (27.7)	30 (33.3)	33 (32.7)

\*Reports of hypotension have been further categorized by the time of occurrence during the infusion. †Adverse events occurring in  $\leq 3.0\%$  of patients in any treatment group. Data are presented as the number (%) of patients.

**Table 4.** Summary of Safety Data

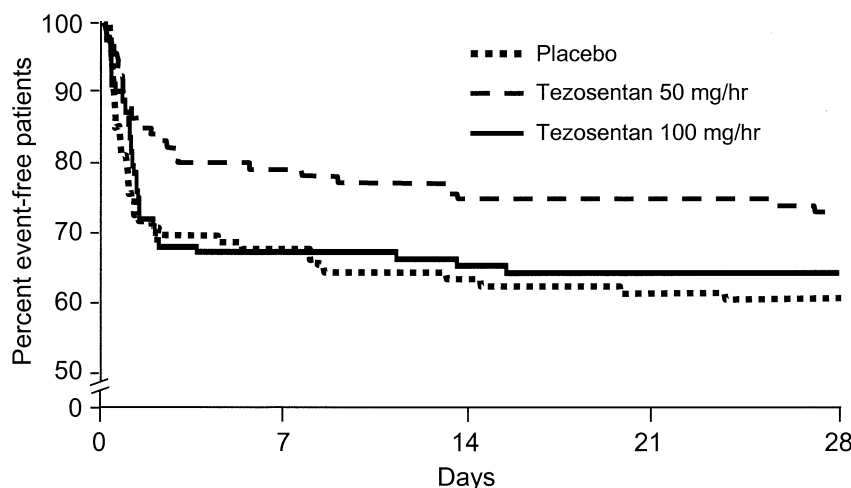
	Placebo (n = 94)	Tezosentan	
		50 mg/h (n = 90)	100 mg/h (n = 101)
Overall incidence			
Premature discontinuation			
Due to any adverse event	2 (2.1)	6 (6.7)	10 (9.9)
Due to hypotension	1	5	6
Deaths up to 28 days	5 (5.3)	7 (7.8)	9 (8.9)
Deaths up to 24 weeks	16 (17.0)	14 (15.6)	20 (19.8)
Renal failure*	8 (8.5)	7 (7.8)	10 (9.9)
During infusion	1	2	7
During 48 h after infusion	1	4	2
48 h to 28 days after infusion	6	1	1
Received hemodialysis	3	4	5
Recovered from acute renal failure	4	4	6
Death from renal failure	3	1	3
Change from baseline to end of infusion			
Heart rate (beats/min)	0.5 ± 12.2	-0.6 ± 10.1	-1.8 ± 9.9
Systolic blood pressure (mm Hg)	-7.8 ± 20.0	-13.6 ± 15.2	-16.3 ± 17.1
Diastolic blood pressure (mm Hg)	-3.6 ± 15.6	-9.4 ± 12.1	-12.9 ± 12.5

\*Includes marked increases in serum creatinine and adverse events of renal failure and renal impairment during treatment and up to 28 days after treatment cessation. Data are presented as the number (%) of patients or mean value ± SD.

receptor antagonists have been shown to reduce pulmonary and arterial pressures, but significant improvement has so far been reported only with dual receptor antagonists, such as tezosentan. The relative effects of dual versus selective ET receptor antagonism in chronic HF have yet to be fully elucidated.

Although fairly well tolerated, both dosages of tezosentan were associated with increased incidences of headache, hypotension, early worsening of renal function, and, with the higher dosage, nausea and vomiting. Renal dysfunction occurred primarily in patients who had a history of chronic renal failure, although the time of occurrence appeared to differ depending on the treatment. Tezosentan may unmask patients prone to develop this complication, resulting in an earlier appearance of renal dysfunction with tezosentan than with placebo. As modest increases in serum creatinine have

been associated with increased mortality (14), the earlier appearance of renal dysfunction in tezosentan-treated patients is an important observation, particularly in the higher-dose group. Although the number of deaths up to 28 days was higher in the 100-mg/h dose group, death due to renal failure was similar to that with placebo, and deaths at six months were similar in all groups. However, the study was not powered to determine treatment effect on this parameter, and larger studies are needed to exclude any potential long-term detrimental effect. The mechanism for the earlier appearance of renal dysfunction is unknown but may be related to an excessive dilatory effect on efferent arterioles of renal glomeruli, similar to the effect observed with angiotensin-converting enzyme inhibitors. In a rat model of HF, short-term administration of tezosentan reduced renal vascular resistance and increased glomerular



**Figure 5.** Kaplan-Meier plot of time to death, cardiac failure, pulmonary edema, or cardiogenic shock during treatment and up to 28 days after the end of treatment.

filtration (15), suggesting that ET receptor blockade might improve renal function in chronic HF patients.

The beneficial hemodynamic effects with tezosentan were accompanied by trends toward improvement in clinical end points after 24 h of treatment. Because both dosages showed similar effects and the study was powered with respect to the hemodynamic end points, exploratory post hoc analyses of clinical end points were performed with the two tezosentan groups combined. With the larger number of patients, the improvement in dyspnea with tezosentan was significant, and the lower risk of death or worsening HF approached significance. Assessment of clinical benefit may have been biased by the observed hemodynamic effect, and further investigation is needed. However, these results suggest that in addition to providing immediate hemodynamic benefit, tezosentan treatment might improve symptoms and have an impact on clinical outcomes. Another post hoc analysis over the 28-day follow-up period indicated that the clinical benefits obtained with the lower tezosentan dose were not associated with a worsened short-term outcome, unlike with milrinone (16,17), flosequinan (16,17), and the higher tezosentan dose. As with other agents, a beneficial hemodynamic effect does not always translate into improved prognosis. Other mechanisms, specifically neurohormonal and inflammatory modulation, might be more closely related than hemodynamics to a patient's outcome.

Levels of ET-1 have been shown to correlate with prognosis in patients with severe HF (7), and appropriate blockade of the ET system may prove beneficial, both in the short and long term. The rapid onset and sustained beneficial hemodynamic effects observed during and after the 24-h infusion of tezosentan in patients hospitalized with acute HF indicate that blockade of the adverse effects of ET may become an important treatment option for these patients. Hence, it is possible that the ideal treatment for acute HF would be a drug with neurohormonal modulatory effects which does not induce extensive vasodilation. Therefore, efficacy and safety data from this study suggest that the optimal dosing regimen for tezosentan is lower than 50 mg/h, and this is being evaluated in a large, prospective trial.

**Reprint requests and correspondence:** Dr. Guillermo Torre-Amione, Baylor College of Medicine Section of Cardiology, Texas Medical Center, One Baylor Plaza, Houston, Texas 77030. E-mail: gtorre@bcm.tmc.edu.

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## APPENDIX

**Steering Committee:** Wilson S. Colucci, Basil S. Lewis, Guillermo Torre-Amione, James B. Young.

**Participating Investigators:** *Austria:* Richard Pacher; *Germany:* Gert Baumann, Bernhard Mox, Hans-Georg Olbrich, Olaf Roediger, Karl Stangl; *Netherlands:* P. A. R. Milliano, A. J. A. M. Withagen; *Israel:* Gad Cotter, Edo Kaluski, Basil S. Lewis, Alon Marmor, Leonardo Reisin, Zvi Vered; *Switzerland:* Augusto Gallino, T. Moccetti, Paul Mohacsi; *United States:* Sonjai Bhatia, Biykem Bozkurt, William Dec, Reynolds Delgado, Leo Egbujiobi, Uri Elkayam, Jalal Ghali, Michael Givertz, Lee Goldberg, Peter Hanley, Denise Hermann, Michael Kesselbrenner, Rafael Levites, Asim Nisar, Mara T. Slawsky, David O. Taylor, Guillermo Torre-Amione, Hector Ventura, Lynne Waggoner, James B. Young, Lawrence Zisman.