Meta-Analysis of Observed Mortality Data from All-Controlled, Double-Blind, Multiple-Dose Studies of *Losartan* in Heart Failure

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Clinical studies of heart failure utilizing losartan, an angiotensin-II receptor antagonist, found that this drug is well tolerated and demonstrates hemodynamic, neurohormonal, and symptomatic improvement. To assess all-cause mortality in heart failure patients treated with losartan, a meta-analysis including 1,896 patients was performed on 6 controlled, double-blind, multiple-dose studies, regardless of sample size or duration of follow-up. A combination of logarithmic (log) odds ratios with a continuity correction was utilized for the meta-analysis. Treatment groups were comparable with regard to demographic characteristics, heart failure characteristics, and concomitant cardiovascular therapies. Concomitant use of open-label angiotensin-converting enzyme (ACE) inhibitors was not allowed in any study. The mean left ventricular ejection fraction obtained in individual studies ranged from 23% to 31%. Seven hundred forty patients were randomized to control therapy and 1,154 patients were randomized to losartan therapy. There were 36 deaths (3.12%) in the losartan groups compared with 47 in the control groups (6.35%) during the double-blind periods. The odds of dying in the losartan groups were 0.51 times (0.31 to 0.81) that of dying in the control groups ($p = 0.004$). In this analysis, treatment with losartan provided a beneficial effect upon survival. However, because the number of deaths in these studies is relatively small and the follow-up relatively short, a large confirmatory study is needed to assess the mortality benefit of losartan compared with an ACE inhibitor.
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Losartan (Cozaar, Merck Research Laboratories, West Point, Pennsylvania) is a specific angiotensin-II (A-II) receptor antagonist.[1] In the myocardium vessels A-II may be produced by non–angiotensin-converting enzyme (ACE) dependent pathways, such as chymase.[2,3] A-II receptor antagonists therefore may have an advantage in blocking the effects of A-II compared with ACE inhibitors.[4,5] In patients with heart failure, losartan is associated with hemodynamic, symptomatic, and neurohormonal improvements, and is well tolerated.[6–8] In the Evaluation of Losartan in the Elderly (ELITE) study, the largest clinical study of an A-II receptor antagonist in patients with heart failure, an unexpected reduction in mortality was observed among patients randomized to losartan compared with captopril.[9] Because mortality was neither a primary nor a secondary end point in the ELITE study, this unexpected observation may well have been due to chance alone. Consequently, to put this result in perspective, a retrospective meta-analysis of all observed mortality data from all-controlled, double-blind, multiple-dose studies of losartan was performed.

METHODS

Selection of studies: A total of 8 clinical studies in the losartan heart failure program were available. Two of the 8 clinical studies in heart failure patients did not qualify for inclusion into the meta-analysis. One was a pharmacokinetic study, and the other was a single-dose study. No patients died during the course of these 2 studies. The remaining 6 studies were multicenter, randomized, double-blind studies, and had parallel treatment groups (Table I). These 6 studies were included in the meta-analysis, regardless of sample size, type of control (placebo or active), and duration of follow-up. The duration of the double-blind treatment period was 12 weeks in 4 of the studies; in the other 2 it was 8 weeks[10] and 48 weeks, respectively.[11] One of the 6 studies was a hemodynamic (HM), multiple-dose study.[6] In this study, patients received placebo or losartan in 1 of the following doses: 2.5, 10, 25, or 50 mg/day for a 12-week period. Hemodynamic assessment was performed on the day after catheter placement and for 24 hours after ingestion of the test medication. These measurements were repeated after 12 weeks of therapy. Two phase II, exercise pilot studies (Phase II-US and Phase II-S) were designed to examine the hypothesis that replacement of ACE inhibitor therapy with losartan would not cause deterioration of exercise tolerance.[8,9] The effects of losartan

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*A list of the study group investigators appears in the Appendix.

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TABLE I Losartan in Heart Failure: Study Descriptions

Study	Short Description of Study	Primary End Point	No. of Patients Enrolled		Losartan/Control Dose(s), (mg)	Duration Baseline/ Double-blind (wks)	Start/Completion of Study
			Losartan	Control			
HM	Hemodynamics, multiple dose	Hemodynamic effects	125	29	Losartan/Placebo 2.5, 10, 25, 50	12 wks double-blind	Dec. 1991/Oct. 1992
Phase II-US	Exercise, Pilot, US	Exercise	78	38	Losartan 50 Losartan 25 Enalapril 20	12 wks double-blind	June 1992/Oct. 1993
Phase II-S	Exercise, Pilot, NYHA III/IV, Scandinavian	Exercise	108	58	Losartan 50 Losartan 25 Enalapril 20	8 wks double-blind	Nov. 1992/July 1993
Phase III-US	Pivotal Exercise, US	Exercise	237	114	Losartan/Placebo 12.5→ 25→ 50	12 wks double-blind	Feb. 1994/Oct. 1995
Phase III-Int'l	Pivotal Exercise, International	Exercise	254	131	Losartan/Placebo 12.5→ 25→ 50	12 wks double-blind	June 1994/Jan. 1996
ELITE	Safety Evaluation in Elderly, Pivotal, US & International	Safety (Renal dysfunction)	352	370	Losartan 12.5→25→ 50 Captopril 18.75→ 37.5→ 75→ 150	48 wks double-blind	May 1994/June 1996

NYHA = New York Heart Association.

50 mg/day and losartan 25 mg/day were compared with those of enalapril 10 mg twice daily. In both studies treatment with the test medication started immediately after discontinuation of therapy with any previous ACE inhibitor. Two phase III exercise trials were similar in that they enrolled patients who had never received ACE inhibitors or who had discontinued ACE inhibitors, for at least 6 weeks in the United States study (Phase III-US) and 12 weeks in the international study (Phase III-Int'l). In both studies patients were randomized to losartan or matching placebo in a 2:1 ratio. Losartan was administered in increasing doses from 12.5 to 25 mg and 50 mg as tolerated. Exercise capacity (maximal treadmill exercise time) was the primary end point. ELITE was a long-term (48 weeks) captopril-controlled trial conducted in elderly patients who had never received ACE inhibitors.[11] Mortality was a predefined efficacy end point in ELITE; in all other studies mortality was captured as part of the safety evaluation. The incidence of death was obtained directly from case report forms.

Statistical analysis: A method based on a combination of logarithmic (log) odds ratios (OR) with a continuity correction[12] was used to perform this meta-analysis of mortality data from 6 different trials. In 5 of the 6 studies, a higher proportion of patients were allocated to losartan; thus, the Peto method for obtaining pooled effect estimates yielded biased results when applied to such unbalanced data.[13] Heterogeneity testing was performed to establish if differences between the study designs had a significant impact on their outcomes. Intention-to-treat analysis was used; all randomized patients were included in the statistical analysis, regardless of withdrawal for any reason during the double-blind period or not satisfying the protocol criteria. In the ELITE trial, all deaths that occurred up to day 336 were counted unless patients remained on therapy longer, in which case deaths were counted up to the last day of therapy. In all other studies, deaths that occurred in the double-blind period or deaths within 14 days of discontinuation from the double-blind period were counted. One patient who received losartan (HM) and who was included in all analyses was reported to have been resuscitated after cardiac arrest on day 12 after discontinuation from study therapy and later died on day 30. In addition to the overall meta-analysis, analyses of different groupings of studies were conducted according to: the control agent (placebo or ACE inhibitor), the patient population (received or did not receive ACE inhibitors), patients switched from ACE inhibitors, and duration of follow-up (short-term studies).

RESULTS

Baseline demographics and heart failure characteristics of patients enrolled in the losartan heart failure studies are presented in Table II. More men than women participated in all studies. The mean age of patients was ~60 years, except for the ELITE trial, where age was >70 years. The studies were dominated by white patients, whereas the percentage of Hispanics was approximately 30% in 1 trial (Phase III-Int'l). More than half of all patients had coronary (ischemic) heart disease as the etiology of heart failure. For most patients, heart failure had been diagnosed within the last 5 years.

The presence of systolic left ventricular dysfunction was confirmed by measurement of left ventricular (LV) ejection fraction (EF); mean LVEF of individual double-blind studies ranged from 23% to 31%. There were no significant differences between treatment groups in any of the demographic or heart failure characteristics. The treatment groups were also similar in respect to secondary diagnoses in all studies. Concomitant use of an open-label ACE inhibitor was not allowed in any study, and the ELITE trial did not allow enrollment of patients previously treated with an ACE inhibitor. In the Phase III-Int'l trial any ACE

TABLE II Losartan in Heart Failure: Baseline Demographics and Heart Failure Characteristics

Study	HM		Phase II-US		Phase II-S		Phase III-US		Phase III-Int'l		ELITE	
Therapy	Losartan (n = 125)	Placebo (n = 29)	Losartan (n = 78)	Enalapril (n = 38)	Losartan (n = 108)	Enalapril (n = 58)	Losartan (n = 237)	Placebo (n = 114)	Losartan (n = 254)	Placebo (n = 131)	Losartan (n = 352)	Captopril (n = 370)
Age (yrs, mean)	61	61	57	60	65	64	65	65	60	61	74	73
Range	(28–77)	(34–80)	(25–83)	(33–81)	(32–82)	(42–78)	(20–90)	(37–89)	(28–85)	(27–86)	(64–93)	(64–91)
Men (%)	85	97	78	76	74	84	66	70	68	74	66	67
Racial Origin (%)												
White	82	86	68	76	100	98	83	82	58	62	91	88
Hispanic	0	0	4	8	0	0	1	4	32	28	4	4
Black	7	7	26	13	0	0	15	12	5	5	5	5
Other	11	7	3	3	0	2	1	2	5	6	1	3
Etiology (%)												
Coronary HD)	64	72	47	47	72	64	53	54	50	46	60	60
IDC	30	17	37	50	23	29	25	32	22	22	40	40
Systemic hypertension	2	3	6	0	1	2	7	6	17	19		
Valvular HD	4	3	4	3	4	3	5	2	4	3		
Other	1	3	5	0	0	2	10	6	7	10		
HF Diagnosis ≤5 years, %	75	72	74	63	78	78	81	83	79	82	79	79
NYHA (%)												
Class II	66	72	54	34	NA	NA	33	37	46	55	66	64
Class III	32	21	44	66	82	90	65	61	52	42	33	34
Class IV	1	7	3	0	19	10	2	2	2	3	1	2
LVEF (%)												
Mean (SD)	25, 8	23, 8	26, 10	24, 8	24, 6	23, 6	29, 9	29, 9	28, 8	28, 8	31, 7	30, 8
CTR			0.5	0.5	NA	NA	0.56	0.55	0.57	0.57	NA	NA
ACE-Naïve (%)	59.2	48.3	0	0	14.8	10.3	29.5	36.8	81.5	80.2	96.3	96.7
Time of D/C of ACE Before DB	14 d (c = 3 d)		14 d		1 d		6 wks		12 wks		NA	

C = captopril; CTR = cardiac thoracic ratio; D/C = discontinued; DB = double-blind; HF = heart failure; IDC = idiopathic dilated cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

inhibitor (if previously used) had to be discontinued at least 12 weeks before enrollment; however, most patients (81%) never received an ACE inhibitor. Thus, patients in this trial may be considered ACE inhibitor-free. In addition, there was no significant difference between treatment groups in the prior use of ACEs. Most patients in the HM, Phase II-US, Phase II-S, and Phase III-US trials had received ACE inhibitors. Thus, patients from these trials are grouped together and considered ACE inhibitor experienced. With regards to other prior and concomitant therapy, diuretics were used slightly more in patients treated with losartan (90%) than in patients given placebo (83%) in the Phase III-US trial, and calcium channel blockers were used more ($p < 0.05$) in patients who underwent losartan therapy (29%) than patients who received placebo (18%) in the Phase III-Int'l trial; this difference in distribution was mainly due to a significantly greater use of diltiazem in the losartan group (11%) than in the placebo group (4%). No major difference was observed between treatment groups in the distribution of other concomitant therapies, such as hydralazine, anticoagulants, antiarrhythmics, or β blockers.

Total mortality: A total of 1,894 patients were enrolled in the 6 controlled, double-blind, multiple-dose studies; 1,154 patients were randomized to receive losartan and 740 patients were randomized to control groups (274 patients received placebo, 96 patients received enalapril, and 370 patients received captopril). There were a total of 47 deaths (6.35%) in the control groups compared with 36 (3.12%) in the losartan groups during double-blind therapy (mean follow-up time of 25.4 weeks; $p = 0.004$).

There were differences between the 6 studies with respect to design, dosage of losartan, patient characteristics, control groups, sample size, and length of follow-up. The follow-up was 8 weeks in 1 study, 12 weeks in 4 studies, and 48 weeks in 1 study. However, the test for heterogeneity showed that there was insufficient evidence to reject the null hypothesis of homogeneity among the trial results (chi-square 6.79, 5 degrees of freedom; $p = 0.237$).

The individual OR of mortality and the respective 95% confidence intervals (CI) for all 6 studies are included in Table III and illustrated in Figure 1, which shows that 2 earlier studies (HM and Phase II-US) differed from the remaining 4 studies (Phase II-S, Phase III-US, Phase III-Int'l, and ELITE). It should, however, be noted that the trend in favor of losartan is consistent among the larger (phase III) studies.

All of the 95% CI of OR for the individual studies contained the OR value of 1.0 (there was no significant difference) with the exception of 2 trials, the Phase III-Int'l (0.05 to 0.62) and the ELITE (0.3 to 0.99) trials. For both of these trials, a significant reduction was observed in the odds of dying in the

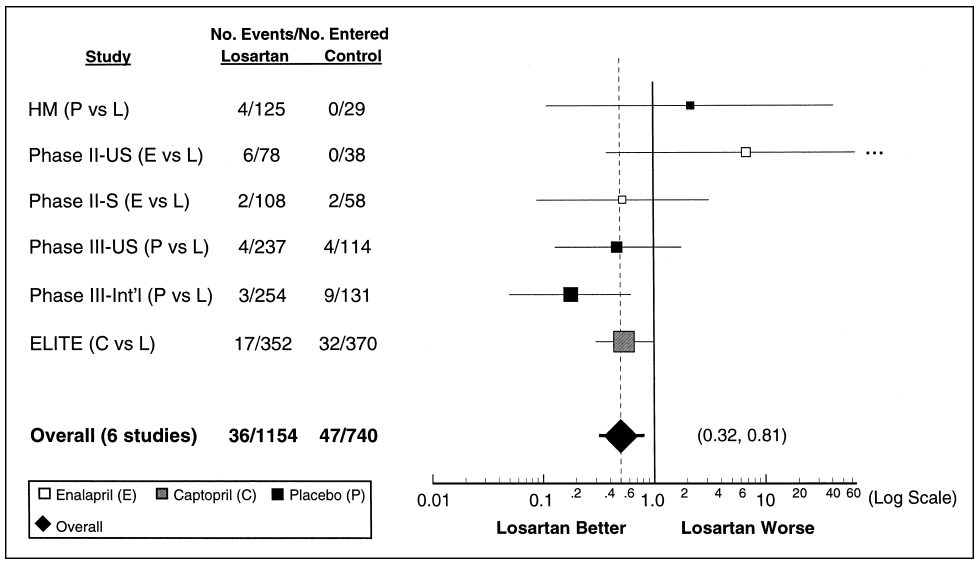

FIGURE 1. Losartan in heart failure: observed mortality data from 6 controlled, double-blind, multiple-dose studies according to a meta-analysis based on combination of log OR with a continuity correction. OR (95% CI) are shown separately for each study and overall. The size of each square is in a rank order according to the number of deaths observed in each study. The odds of dying in the control group is 1.98 times the odds of dying in the losartan group (95% CI 1.24 to 3.17).

TABLE III Losartan in Heart Failure: Meta-Analysis* of Observed Mortality in Multiple-Dose, Randomized, Double-Blind, Controlled Studies (mortality OR [95% CI])

	No. of Dead/No. of Enrolled (%)			95% CI		
Study	Losartan	Control	OR	Lower	Upper	p Value
HM	4/125 (3.2)	0/29 (0.0)	2.19	0.11	41.72	0.603
Phase II-US	6/78 (7.7)	0/38 (0.0)	6.90	0.38	125.83	0.192
Phase II-S	2/108 (1.9)	2/58 (3.4)	0.53	0.09	3.15	0.486
Phase III-US	4/237 (1.7)	4/114 (3.5)	0.47	0.13	1.78	0.269
Phase III-Int'l	3/254 (1.2)	9/131 (6.9)	0.18	0.05	0.62	0.007
ELITE	17/352 (4.8)	32/370 (8.6)	0.54	0.30	0.99	0.046
Overall	36/1154 (3.1)	47/740 (6.4)	0.50	0.32	0.81	0.004

*Based on a combination of log ORs.
Test for heterogeneity: chi-square = 6.79 (5 d.f.), p value = 0.237.

losartan group compared with the respective control group. These 2 trials were the 2 largest among the 6 studies considered. In 2 other studies, HM and Phase II-US, a higher proportion of deaths were observed in the losartan-treated groups. However, these were not only the smallest studies in this collection; they also had the smallest control groups (i.e., 29 and 38 patients for the HM and the Phase II-US, respectively) among the 6 studies. Of the 4 patients who died in the HM study, 2 patients were treated with the 2.5-mg dose and the other 2 with the 10 mg dose of losartan, both now considered to be subtherapeutic dosages.

Table III provides the overall OR for mortality. The odds of dying in the losartan group were 0.5 times the odds of dying in the control group. The 95% CI for the overall OR with respect to mortality is 0.32 to 0.81. Thus, the odds of dying in the losartan group were significantly lower than the odds of dying in the control group. It is noteworthy that although 3 of 6 studies had active ACE inhibitor controls, an overall survival benefit was observed. Therefore, this analysis is conservative as an evaluation of the beneficial effects of losartan on mortality.

Table IV and Figure 2 display the results from an analysis of different groupings of the studies. The OR corresponding to ACE inhibitor switch group are not displayed in Figure 2 because it is the smallest group and the individual OR for Phase II-US and Phase II-S trials are displayed in Figure 1. The OR (95% CI) observed in the different groupings of studies also tend to support the beneficial effect of losartan on mortality compared with controls. The group that switched from ACE inhibitors was the only group with an OR >1 (i.e., 1.07 [95% CI 0.23 to 4.89]). The OR for the placebo-controlled studies and ACE inhibitor controlled studies were 0.34 (95% CI 0.14 to 0.8) and 0.6 (95% CI 0.34 to 1.04), respectively. The OR for the short-term studies (≤12 weeks) (i.e., all studies except ELITE) was 0.45 (95% CI 0.21 to 0.95). The OR for the studies in patients who never received and received ACE inhibitors were 0.44 (95% CI 0.26 to 0.76) and 0.76 (95% CI 0.3 to 1.96), respectively (Figure 2).

DISCUSSION

The meta-analysis method based on a combination of log ORs with a continuity correction was selected for this analysis. The OR is an approximation of the relative risk when event rates are low. To evaluate the robustness of the meta-analysis results, the data were also reanalyzed by Peto's modification of the Mantel-Haenszel method.[14] A significant mortality benefit was once again observed in favor of losartan and similar estimates of the overall ORs were observed. However, because the Peto method is more sensitive to heterogeneity between the study results, it resulted in a statistically significant heterogeneity between the studies, possibly due to the results of the Phase II-US and the Phase III-Int'l studies, which were in sharp contrast to one another. In Phase II-US, a total of 116

TABLE IV Losartan in Heart Failure: Meta-Analysis* of Observed Mortality in Multiple-Dose, Randomized, Double-Blind, Controlled Studies (mortality OR [95% CI]) Grouping of Studies

Grouping (studies)	No. of Dead/No. of Enrolled (%)		Odds Ratio	95% Confidence Interval		p Value
	Losartan	Control		Lower	Upper	
Placebo controlled (HM, PE-US, & PE-INT)	11/616 (1.8)	13/274 (4.7)	0.34	0.14	0.80	0.014
ACE controlled (Phase II-US, Phase II-S & ELITE)	25/538 (4.6)	34/466 (7.3)	0.60	0.34	1.04	0.069
ACE free (Phase III-Int'l & ELITE)	20/606 (3.3)	41/501 (8.2)	0.44	0.26	0.76	0.003
ACE experienced (HM, Phase II-US, Phase II-S, & Phase III-US)	16/548 (2.9)	6/239 (2.5)	0.76	0.30	1.96	0.571
Short term (≤12 wks) (HM, Phase II-US, Phase II-S, Phase III-US, & Phase III-Int'l)	19/802 (2.4)	15/370 (4.1)	0.45	0.21	0.95	0.037
ACE switched (Phase II-US & Phase II-S)	8/186 (4.3)	2/96 (2.1)	1.07	0.23	4.89	0.929
Overall	36/1154 (3.1)	47/740 (6.4)	0.50	0.32	0.81	0.004

*Based on a combination of log ORs.

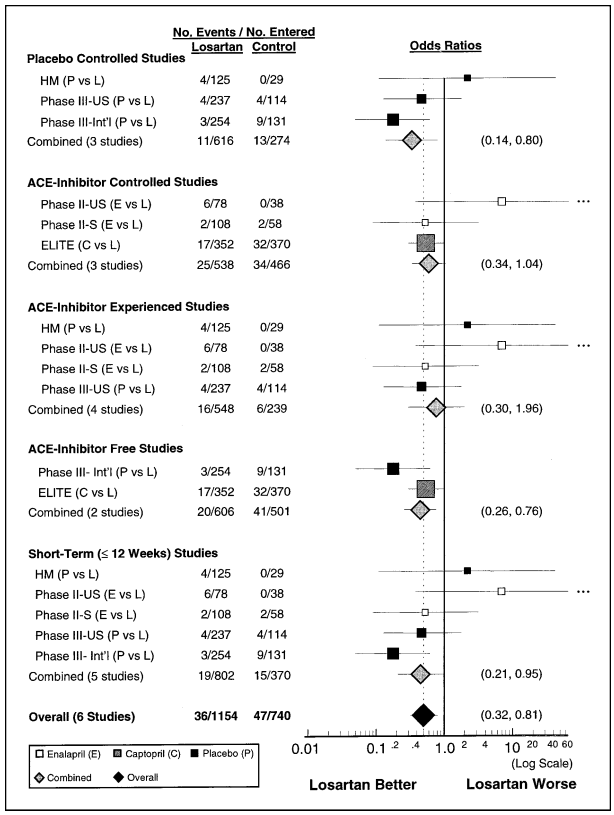

FIGURE 2. Losartan in heart failure: meta-analysis conducted as described in Figure 1. OR (95% CI) are displayed for groups of studies: placebo-controlled, ACE-inhibitor controlled, ACE-inhibitor experienced, ACE-inhibitor free, and short term (≤12 weeks) studies.

patients were switched from ACE inhibitor therapy with the randomized treatment (i.e., losartan 25 mg/day, losartan 50 mg/day, and enalapril 10 mg twice daily). In Phase III-Int'l, a total of 381 patients, all of whom discontinued any ACE inhibitor at least 12 weeks before enrollment, were randomized to losartan or matching placebo in a 2:1 ratio. However, most patients (81%) randomized in the Phase III-Int'l trial were never treated with ACE inhibitors. The results of this trial strongly favored losartan.

Although there were differences in the 6 studies with respect to design, dosage of losartan, patient characteristics, controls, sample size, and duration of double-blind follow-up, the studies were similar enough for inclusion into a single meta-analysis. Of 1,154 patients randomized to losartan, 36 (3.1%) died, whereas of the 740 patients randomized to control groups, 47 (6.4%) died (mean follow-up time of 25.4 weeks; $p = 0.004$). Thus, the meta-analysis found that the overall odds of dying in the losartan group were significantly lower than the odds of dying in the control group. This analysis should be considered conservative because in 3 of the 6 studies ACE inhibitors, with a confirmed mortality benefit,[15,16] were used as the control. Moreover, it should be noted that the rates of death observed in patients in our losartan groups varied from 1.8% to 4.6% (follow-up 2 to 11 months), which is less than those reported with ACE inhibitors in previous meta-analyses of randomized trials of heart failure patients.[15,16] This comparison is true even after exclusion of the larger and/or long-term trials such as Studies of Left Ventricular Dysfunction (SOLVD)[17,18] and Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),[19] respectively, with rates of death of 5.7% in the meta-analysis by Garg and Yusuf[15] and 6.4% in the meta-analysis by Nony et al[16] after follow-up times of 3 to 6 months.

The magnitude of the benefit of losartan on mortality in patients with heart failure and its possible advantage over ACE inhibitors needs to be determined in studies where mortality is a prespecified primary end point. Prospective randomized trials such as ELITE II,[20] and Valsartan Heart Failure Trial (VAL-HEFT),[21] and Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) are currently exploring the effectiveness of A-II receptor antagonists alone and in combination

with ACE inhibitors, on mortality in patients with heart failure due to systolic left ventricular dysfunction. It is likely that other trials with A-II receptor antagonists in patients with heart failure will be initiated in the near future. One should in the interim be cautious in extrapolating the data from this meta-analysis to all A-II receptor antagonists. The differences between A-II receptor antagonists have only begun to be explored. Losartan is an active pro-drug with an active metabolite. It has uricosuric effects[22,23] that have not been seen with other A-II receptor antagonists.[24] In experimental models it has been found to have antiarrhythmic properties and to block thromboxane A-II and prostaglandin H II receptors independent of its effects as an A-II receptor antagonist.[25,26] Studies such as this make it imperative to carefully investigate each of the available A-II receptor antagonists in large-scale prospective randomized trials and not to assume a class effect at this time.

The ELITE study resulted in an unexpected benefit on mortality in heart failure patients treated with losartan. A similar benefit was also observed in the combined group of patients from all other controlled, double-blind, multiple-dose studies. Thus, the latter did not invalidate the benefit observed in the ELITE study, although the other studies had relatively few events, being of smaller size and shorter duration (mean follow-up time of 11.4 weeks). In conclusion, the meta-analysis of data from 6 randomized heart failure studies shows an observed reduction in mortality in patients treated with losartan. However, there was some evidence of heterogeneity between the studies, and the analysis was based on a relatively small number of deaths observed over a relatively short time period, which reaffirms the need for a large confirmatory trial, especially to assess the mortality benefit of losartan as compared with an ACE inhibitor.

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APPENDIX

Losartan Heart Failure Mortality Meta-analysis Study Group: *Merck Research Laboratories, West Point, PA:* Bettye S. Briggs, RN, Robert Segal, MD, Paul I. Chang, MD, Joseph P. Arena, PhD, Steve E. M. Caffe, MD, Balasamy Thiyagarajan, PhD, Joseph F. Heyse, PhD, Geraldine Mantell, MD.

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