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Effects of Telmisartan Added to Angiotensin-Converting Enzyme Inhibitors on Mortality and Morbidity in Hemodialysis Patients With Chronic Heart Failure

A Double-Blind, Placebo-Controlled Trial

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Objectives The aim of this study was to determine whether telmisartan decreases all-cause and cardiovascular mortality and morbidity in hemodialysis patients with chronic heart failure (CHF) and impaired left ventricular ejection fraction (LVEF) when added to standard therapies with angiotensin-converting enzyme inhibitors.

Background In hemodialysis patients, CHF is responsible for a high mortality rate, but presently very few data are available with regard to this population.

Methods A 3-year randomized, double-blind, placebo-controlled, multicenter trial was performed involving 30 Italian clinics. Hemodialysis patients with CHF (New York Heart Association functional class II to III; LVEF ≤40%) were randomized to telmisartan or placebo in addition to angiotensin-converting enzyme inhibitor therapy. A total of 332 patients were enrolled (165 telmisartan, 167 placebo). Drug dosage was titrated to a target dose of telmisartan of 80 mg or placebo. Mean follow-up period was 35.5 ± 8.5 months (median: 36 months; range: 2 to 40 months). Primary outcomes were: 1) all-cause mortality; 2) cardiovascular mortality; and 3) CHF hospital stay.

Results At 3 years, telmisartan significantly reduced all-cause mortality (35.1% vs. 54.4%; $p < 0.001$), cardiovascular death (30.3% vs. 43.7%; $p < 0.001$), and hospital admission for CHF (33.9% vs. 55.1%; $p < 0.0001$). With Cox proportional hazards analysis, telmisartan was an independent determinant of all-cause mortality (hazard ratio [HR]: 0.51; 95% confidence interval [CI]: 0.32 to 0.82; $p < 0.01$), cardiovascular mortality (HR: 0.42; 95% CI: 0.38 to 0.61; $p < 0.0001$), and hospital stay for deterioration of heart failure (HR: 0.38; 95% CI: 0.19 to 0.51; $p < 0.0001$). Adverse effects, mainly hypotension, occurred in 16.3% of the telmisartan group versus 10.7% in the placebo group.

Conclusions Addition of telmisartan to standard therapies significantly reduces all-cause mortality, cardiovascular death, and heart failure hospital stays in hemodialysis patients with CHF and LVEF ≤40%. (Effects Of Telmisartan Added To Angiotensin Converting Enzyme Inhibitors On Mortality And Morbidity In Haemodialysed Patients With Chronic Heart Failure: A Double-Blind Placebo-Controlled Trial; NCT00490958). (J Am Coll Cardiol 2010;56:1701–8)

Up to 64% of patients with end-stage renal disease (ESRD) have evidence of chronic heart failure (CHF). In hemodialysis patients, CHF is responsible for high rates of mortality and morbidity (1). Although the treatment of patients with CHF in the general population (2–9) is well-established, few data are presently available on patients with CHF on hemodialysis treatment. In fact, it is generally assumed that the effect and the dosage of a given drug, validated in the general population, can be extended to uremic patients. However, this is not necessarily true and should rather be demonstrated in appropriate studies.

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Angiotensin II type 1 receptor blockers (ARB) have been shown to have favorable effects on hemodynamic measure-

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Abbreviations and Acronyms

ACE-I = angiotensin-converting enzyme inhibitor
ARB = angiotensin II type 1 receptor blocker
BB = beta-blocker
CHF = chronic heart failure
CI = confidence interval
ESRD = end-stage renal disease
HR = hazard ratio
LVDd = left ventricular internal diastolic diameter
LVEF = left ventricular ejection fraction
MI = myocardial infarction
NYHA = New York Heart Association
RAAS = renin-angiotensin-aldosterone system

ments, neurohumoral activity, left-ventricular remodelling, mortality, and morbidity when added to angiotensin-converting enzyme inhibitors (ACE-I) in patients with CHF (9–11).

Among ARBs, telmisartan has distinctive angiotensin II type 1 receptor-binding properties: high affinity and slow dissociation; a half-life of approximately 24 h; high plasma protein binding; and a distribution volume of approximately 500 l, indicating additional tissue binding (12).

On these grounds, the aim of the present study was to determine—in a randomized, double-blind, placebo-controlled, multicenter trial—whether a combination of an ARB, namely telmisartan, and standard therapies including ACE-I and beta-blockers (BB) decreases all-cause mortality, cardiovascular mortality, and morbidity in hemodialysis patients with CHF and impaired left ventricular ejection fraction (LVEF).

Methods

Data were collected in 30 Italian clinics of a dialysis provider network with a prospective database (European Clinical Database), the main purpose of which is the support of quality assurance (13). Participating centers are listed in the Online Appendix. Clinical Trial Ethical Review Committee approval was granted at all participating centers. Each patient provided written informed consent before randomization. The trial was registered with Clinicaltrials.gov (NCT00490958).

We enrolled 351 patients that matched the inclusion criteria: adult hemodialysis patients with CHF; New York Heart Association (NYHA) functional class II and III; ejection fraction ≤40% determined within 6 months; and therapy with ACE-I individually optimized and unchanged for ≥30 days before randomization. The use of other conventional heart failure treatments, including BB and digitalis, was recommended when appropriate. Discontinuation of these agents or the study drug was left to the discretion of the physicians; the reasons for discontinuation were documented, and patients were subsequently observed for outcomes. The recruitment period was from January 1999 to January 2003.

All patients were dialyzed 4×/week. In our population, 92.2% of the patients had an artero-venous fistula. The "dry weight" for all patients was stable for at least 1 month. The arterial pressure values reported in our study refer to the pre-dialysis period. Epoetin therapy was administered when necessary to maintain a mean hemoglobin value of 11.5 ± 0.5 g/dl.

Plasma potassium levels were checked in all patients at the beginning of each dialysis treatment. Possible changes in plasma potassium concentration were controlled by modulating potassium intake and type of hemodialysis and by reducing blood acidosis.

The trial profile is illustrated in Figure 1. During a preliminary "run-in" phase, all patients received telmisartan (20 mg/day) for 2 weeks to determine, before randomization, whether any of the patients had a low tolerance to small doses of the drug. The run-in phase was necessary, because dialysis patients often experience intradialytic hypotension also due to low-dose drugs. Of the 351 enrolled patients, 19 (5.4%) did not complete the first "run-in" phase either because of adverse reactions (7 for symptomatic hypotension, 1 for diarrhea, 1 for flushing) or due to administrative reasons (4 for withdrawal of consent, 6 for change in dialysis center). The final population of 332 ESRD patients was randomized to telmisartan (n = 165) or placebo (n = 167) in addition to ACE-I therapy. Allocation to the telmisartan or the placebo treatment group was conducted randomly by a computer-generated assignment program and communicated through a coordinating telephone center. The assignment code was held at an independent site under control of the Data Safety Monitoring Committee.

The dose of the study drug was doubled, as tolerated, every 2 weeks while aiming for the target dose of 80 mg/day. After randomization, clinical observations and monitoring of blood pressure, serum creatinine, and serum potassium were performed 4×/week before starting each dialysis session. Serial echocardiographic measurements of left ventricular internal diastolic diameter (LVDd) and LVEF were also recorded and were performed on non-dialysis day every 3 months. The mean follow-up period was 35.5 ± 8.5 months (median: 36 months; range: 2 to 40 months).

The primary outcomes for the present analysis were: 1) all-cause mortality; 2) cardiovascular death; and 3) hospital admission for management of worsening CHF. Prespecified secondary outcomes included: acute nonfatal myocardial infarction (MI), combined end point (cardiovascular mortality in addition to acute nonfatal MI), cardiovascular hospital admission, nonfatal stroke, coronary revascularization, and permanent premature treatment withdrawals.

Critical events were classified according to strict definitions. Diagnosis of acute nonfatal MI included the presence of standard myocardial necrosis biomarkers and typical electrocardiograph changes in a clinical setting compatible with MI. Pump failure death was defined as death due to progressive deterioration of heart failure, acute pulmonary edema, or cardiogenic shock. Death was recorded as noncardiovascular if cardiovascular events were excluded as cause of

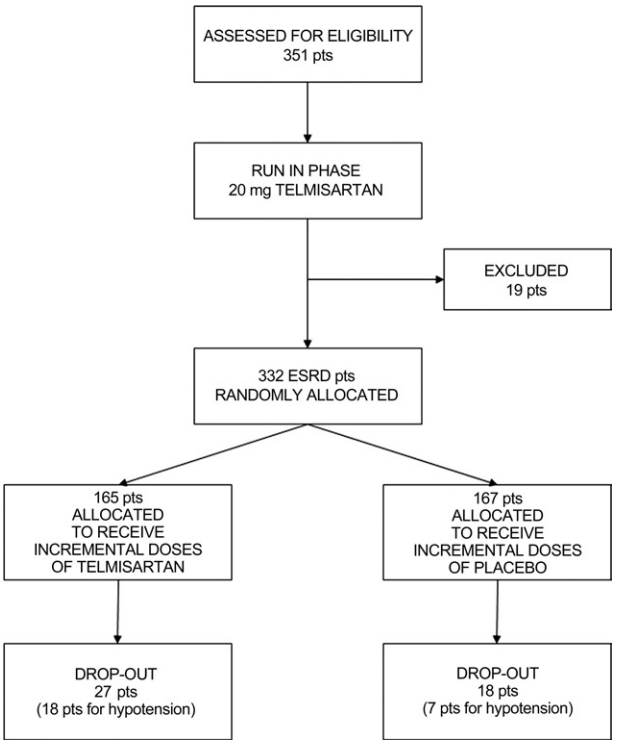

Figure 1 **Trial Profile**

Of the 351 eligible patients (pts), 19 were excluded during the run-in phase. The remaining 332 patients were randomly allocated to receive telmisartan or placebo. ESRD = end-stage renal disease.

death. Death was classified as due to unknown cause when there was insufficient evidence to confirm the cardiovascular or noncardiovascular cause.

A CHF hospital admission was defined as admission to hospital necessitated by heart failure and primarily for its treatment or when heart failure was a major component of the hospital admission of the patient. A patient admitted to a hospital for CHF decompensation had to have documented signs and symptoms of worsening heart failure requiring intravenous drug administration and a supplementary hemodialysis treatment.

Statistical analysis. An annual event rate of 20% for the primary end point (all-cause mortality) was expected in patients with ESRD, on the basis of previous reports. As a consequence, a total sample of at least 240 patients (120/group) was required to detect a 10% decrease of the event rate in the group of patients taking telmisartan with a 2-tailed test with a significance level of 5%, a power level of 90%, a drop-out rate of 5%, and a total follow-up period of 36 months. However, in our study protocol nearly 100 more patients were enrolled than the calculated sample size. This higher number of patients enrolled was decided because of the possible event of transfers of these patients to other centers or protocol violation.

Data are presented as mean ± SD. Descriptive statistics procedures were used to analyze the distribution of each variable. Samples were tested for normal distribution with the Box-Bartlett homogeneity test, skew analysis (that measures the asymmetry of the distribution) and kurtosis analysis (that shows the extent to which observations cluster around a central point). In this study, continuous variables showed a normal distribution. The analysis was carried out on an intention-to-treat basis and included all randomized patients. Patient groups were compared by paired and unpaired Student *t* test for continuous variables and the chi-square test for categorical variables. Multivariable Cox proportional hazard regression models were performed to weigh the independent effects of potential determinants on a dependent variable. The following variables were included into the analysis: clinical data (age, sex, pre-dialysis systolic blood pressure, heart rate, diabetes mellitus, previous MI), standard echocardiographic indexes (LVEF), and laboratory measurements (hemoglobin, albumin, parathormone). The 0.05 probability level was adopted to indicate the significance of the association between predictive variables and events. The risk associated with a given variable was expressed by a hazard ratio (HR) with corresponding 95% confidence intervals (CIs). In the multivariable analysis, an automatic backward stepwise procedure was adopted. The cumulative probability of freedom from cardiac events was calculated with Kaplan-Meier life-table analysis and compared between groups with the log-rank test.

The software packages were SPSS for Windows release 12.0 (SPSS, Inc., Chicago, Illinois) and Clinical Trial Simulator (CTS) (IcebergSim version 3.06 beta, Practihc Coordinating Office, Oslo, Norway).

Patient characteristics and treatment. Clinical features of the 351 patients enrolled in the study, including details of their background medical treatment, are shown in Table 1. At the time of randomization, overall, approximately two-thirds of patients (66.5%) were NYHA functional class II, and one-third (33.5%) were NYHA functional class III.

The 2 groups (telmisartan or placebo) were comparable for all the clinical variables considered. No significant differences were evidenced at baseline in LV internal diastolic diameter and LVEF.

All patients were taking ACE-I—enalapril or ramipril in 84% of patients, mean daily dose of 18.6 mg and of 8.9 mg, respectively, similar to that reached in a previous trial (14) and without significant differences in either group. Furthermore, 60.3% of telmisartan patients and 61.6% of placebo patients were receiving carvedilol, the only BB used, as previously described (15), at a similar mean dose in the 2 groups (mean 46 mg/day). The mean daily dose of the study drug was 75.2 mg in the telmisartan group and a putative 78.3 mg in the placebo group. The target dose of 80 mg/day was reached in 76% of the telmisartan group.

No patient had an implantable defibrillator or a biventricular pacemaker.

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Table 1 Baseline Characteristics of the Study Population

	Telmisartan (n = 165)	Placebo (n = 167)	p Value
Age, yrs	62.7 ± 14.2	62.8 ± 14.6	NS
Male, n	88.0	91.0	NS
Time on dialysis, months	93.6 ± 16.4	94.3 ± 15.8	NS
Body surface area, m^2	1.87 ± 0.12	1.89 ± 0.11	NS
Delta body weight, kg	2.8 ± 0.8	2.7 ± 0.8	NS
Diabetic	28.4	29.6	NS
Previous MI	57.3	56.5	NS
Smoking current	12.7	11.3	NS
Smoking previous	26.5	27.4	NS
HR, beats/min	67.1 ± 8.8	68.5 ± 8.4	NS
Pre-dialysis SBP, mm Hg	124.5 ± 8.3	126.3 ± 7.9	NS
Pre-dialysis DBP, mm Hg	82.6 ± 6.2	79.4 ± 6.7	NS
LVDd, cm/m^2	3.7 ± 0.5	3.6 ± 0.6	NS
LVEF	30.4 ± 7.5	29.2 ± 7.8	NS
NYHA functional class I	0	0	NS
NYHA functional class II	32.4	34.6	NS
NYHA functional class III	67.6	65.4	NS
NYHA functional class IV	0	0	NS
Hemoglobin, g/dl	11.3 ± 0.7	11.5 ± 0.6	NS
Albumin, g/dl	3.94 ± 0.64	3.89 ± 0.52	NS
PTH, ng/l	251.5 ± 33.6	240.3 ± 38.4	NS
Current treatment			
ACE-I	100.0	100.0	NS
Digitalis	53.2	49.8	NS
Beta-blockers	60.3	61.6	NS
Nitrates	48.4	47.6	NS
Statin	67.5	68.4	NS
Amiodarone	19.6	18.7	NS
Aspirin	63.5	64.2	NS
Other antiplatelet agents	32.4	33.1	NS

Values are mean ± SD or percentages.

ACI-I = angiotensin-converting enzyme inhibitors; DBP = diastolic blood pressure; LVDd = left ventricular internal diastolic diameter; MI = myocardial infarction; NYHA = New York Heart Association functional class; PTH = parathormone; SBP = systolic blood pressure.

Results

Mortality. During the 3-year follow-up, telmisartan significantly reduced all-cause mortality (n = 58, 35.1% vs. n = 91, 54.4%; $p < 0.001$). Furthermore, there were significantly fewer cardiovascular deaths in the telmisartan group (n = 50, 30.3% vs. n = 73, 43.7%; $p < 0.001$). In particular, the number of pump failure deaths and sudden cardiac deaths was significantly reduced in patients receiving telmisartan (n = 34, 20.6% vs. n = 52, 31.1%; $p < 0.0005$ for pump failure mortality; and n = 12, 7% vs. n = 18, 10.8% $p < 0.01$ for sudden cardiac death), whereas the number of nonfatal MIs, unknown causes of death, and noncardiovascular deaths did not significantly differ between the 2 groups. According to Cox proportional hazards regression analysis, after adjustment for clinical, echocardiographic, and laboratory variables, the use of telmisartan seemed to be a strong independent predictor for reduction in both all-cause mortality (HR: 0.51; 95% CI: 0.32 to 0.82; $p < 0.005$) and cardiovascular mortality (HR: 0.42; 95% CI: 0.38 to 0.61; $p < 0.0001$) (Table 2).

The cumulative 3-year mean survival time was 30.6 months in the telmisartan group and 24.2 months in the placebo group (log-rank: 13.7; $p < 0.001$) (Fig. 2). In addition, patients receiving telmisartan showed increased 3-year survival time free of cardiovascular deaths compared with patients receiving placebo (32.3 months vs. 21.4 months, respectively; log-rank: 18.2; $p < 0.0001$) (Fig. 3A).

Hospital admissions. Significantly fewer patients receiving telmisartan were admitted to the hospital for CHF: 56 (33.9%) patients in the telmisartan group versus 92 (55.1%) patients in the placebo group ($p < 0.0001$). By contrast, the number of hospital admissions for acute nonfatal MI, combined end point, revascularization, and stroke did not significantly differ between the 2 groups. Cox regression analysis showed that—after adjustment for clinical, echocardiographic, and laboratory variables—treatment with telmisartan was independently associated with reduction of hospital admission for worsening of heart failure (HR: 0.38; 95% CI: 0.19 to 0.51; $p < 0.0001$).

After Kaplan-Meier analyses, the telmisartan group showed increased 3-year mean survival time free of CHF hospital admissions compared with patients receiving placebo (33.3 vs. 20.6 months, respectively; log-rank: 19.3; $p < 0.0001$) (Fig. 3B).

The beneficial effects of telmisartan were also evidenced in patients treated with the combination of ACE-I and BB.

Clinical and echocardiographic analysis. At the time of the last examination, more patients treated with telmisartan compared with placebo showed an improvement in NYHA functional class (37.4% vs. 32.6%) ($p < 0.001$), and fewer showed a deterioration (6.9% vs. 11.2%) ($p < 0.001$).

Excluding the drop-out patients, a significant reduction from baseline of both systolic (118.3 ± 7.2 mm Hg vs. 125.3 ± 7.3 mm Hg; $p = 0.006$) and diastolic (78.2 ± 5.4 mm Hg vs. 83.7 ± 7.1 mm Hg; $p = 0.004$) blood pressure was observed in the telmisartan group during the first year of treatment. Conversely, no significant decrease of either systolic or diastolic blood pressure was observed during the following 2 years.

As for heart rate, no significant differences from baseline were observed at the end of the follow-up in either group (67.1 ± 8.8 beats/min vs. 65.7 ± 7.9 beats/min in telmisartan group; 68.5 ± 8.4 beats/min vs. 69.3 ± 8.1 beats/min in the placebo group).

As for the echocardiographic evaluation, in the telmisartan group a significant decrease in LVDd as well as an increase in LVEF were observed. In particular, such improvement in left ventricle systolic function began within 6 months, reached a plateau within 2 years, and persisted for 3 years in telmisartan compared with placebo patients, irrespective of age, sex, etiology, NYHA functional classification, and co-treatment therapy.

Final echocardiographic changes between the 2 groups were: LVDd: −0.12 ± 0.6 in telmisartan versus −0.04 ± 0.3 (cm/m^2) in placebo ($p < 0.0001$); LVEF: +5.8 ± 6.7% in telmisartan versus +3.1 ± 4.4% in placebo ($p < 0.0001$).

Table 2 Cox Proportional Hazards Regression Analysis

	Telmisartan (n = 165)	Placebo (n = 167)	HR (95% CI)	p Value
End points				
All-cause mortality	58	91	0.51 (0.32–0.82)	0.004
Hospital admission for CHF	56	92	0.38 (0.19–0.51)	0.00007
All cardiovascular deaths	50	73	0.42 (0.38–0.61)	0.00009
Nonfatal MI	4	5	0.81 (0.61–1.2)	0.5
Nonfatal stroke	2	4	0.72 (0.55–1.1)	0.4
Exploratory analyses				
Pump failure deaths	34	52	0.45 (0.25–0.66)	0.0004
Sudden cardiac death	12	18	0.53 (0.33–0.68)	0.008
Other cardiovascular deaths	4	3	0.85 (0.62–1.1)	0.22
Noncardiovascular deaths	7	15	0.65 (0.43–0.9)	0.02
Unknown cause of death	1	3	0.82 (0.55–1)	0.8
Permanent treatment withdrawals	26	16	1.3 (1.1–1.6)	0.008

Cox proportional hazards regression analysis showing the independent effects of treatment with telmisartan in the study population, after adjustment for clinical, echocardiographic, and laboratory variables.
CHF = chronic heart failure; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

Drop-out. The study drug was discontinued (Table 3) because of adverse effects in 27 (16.3%) patients in the telmisartan group and in 18 (10.7%) of the placebo group ($p < 0.01$). We observed, among the drop-out patients, hypotension in 18 patients (66.6%) and in 7 patients (40%) of the respective groups. Among patients with hypotension, 13 of 18 in the telmisartan group and 4 of 7 in the placebo group were taking a combination of both ACE-I and BB.

An increase in plasma potassium leading to discontinuation of the drug was observed in 5 cases (3%) in the telmisartan group compared with 2 cases (1%) in the placebo group. Thirteen patients (4 in the telmisartan and 9 in the placebo group) were excluded from the study due to protocol violation or other nonmedical reasons.

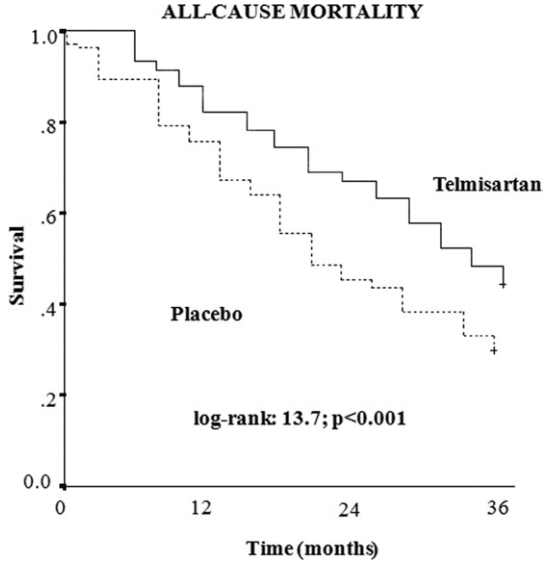

Figure 2 Kaplan-Meier Life-Table Analysis for All-Cause Mortality

The cumulative 3-year mean survival time was 30.6 months in the telmisartan group **(solid line)** and 24.2 months in the placebo group **(dotted line)**.

Discussion

The results of our trial demonstrate that the addition of telmisartan (titrated up to 80 mg, as tolerated) to standard heart failure medications, including ACE-I and often BB, in hemodialysis patients with CHF and LVEF ≤40% decreases the risk of all-cause and cardiovascular death as well as hospital stay for CHF decompensation.

Such beneficial effects of telmisartan were evident within 6 months from the beginning of the treatment and persisted for the entire treatment period.

To the best of our knowledge, our results are the first to provide evidence that the addition of an ARB, namely telmisartan, to regimens including various combination of ACE-I, digitalis, and BB is feasible and beneficial in ESRD patients with CHF receiving dialysis treatment.

The patient population analyzed in the present study is representative in terms of demography and comorbidity of the "real world" of CHF hemodialyzed patients (Table 1). Although the mean age in the cohort is not so advanced (62.9 ± 14.7 years), the female sex is well-represented (46.1%). All patients present a moderate-to-severe reduction in LVEF (mean 30%). In addition, ischemic etiology of CHF was confirmed in more than 55% in both arms of the study (positive clinical history for MI). A higher prevalence of diabetes (approximately 30%) has been found in our population compared with the entire population in the European Clinical Database (18.6%) (16) or in the Italian Hemodialysis Registry (13.8%) (17). Furthermore, all ESRD patients were on a 4×/week hemodialysis treatment, which is the standard medication administered to our CHF subjects.

Another significant feature is that the blood pressure values of patients were mainly under control at enrollment.

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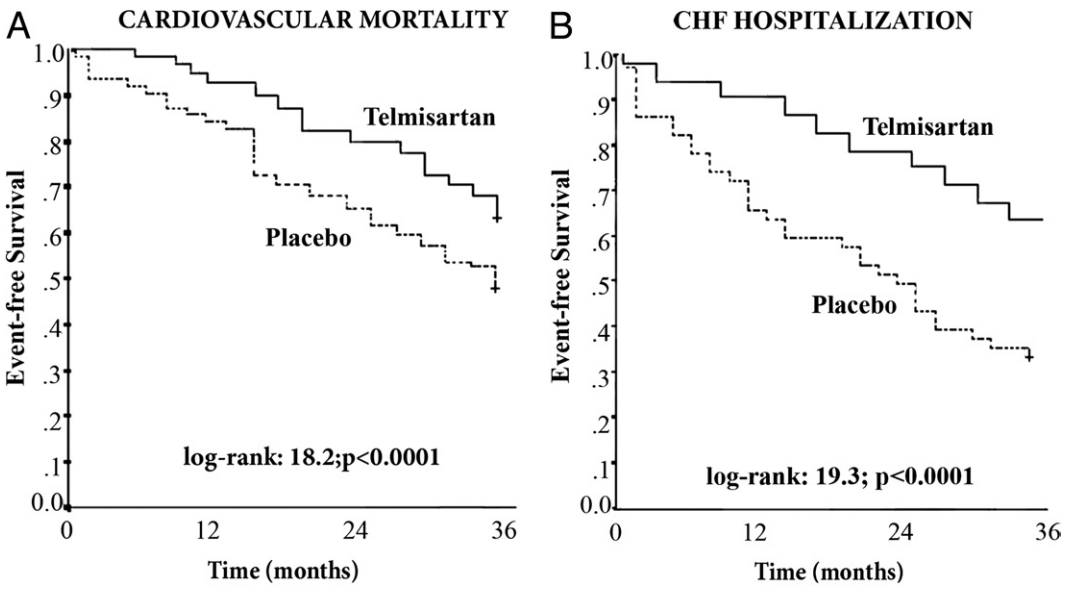

Figure 3 Kaplan-Meier Life-Table Analysis for Cardiovascular Mortality and CHF Hospital Stay

Cumulative 3-year survival time free of cardiovascular deaths **(A)** and hospital admissions **(B)** in patients treated with telmisartan **(solid line)** or placebo **(dotted line)**. CHF = chronic heart failure.

This point is particularly important to evaluate this treatment in daily practice, especially with regard to adverse effects such as hypotension. In our study, drop-out percentage for hypotension (16.3% in the telmisartan group vs. 10.7% in the placebo group) was significantly lower than that reported in dialysis guidelines (18). This might be because the telmisartan target dose was reached during an up-titration phase, similar to the one used in BB therapy.

However, most drop-out patients were taking a combination of ACE-I and BB at the start of the trial. The combination of telmisartan with both ACE-I and BB in this subgroup of patients was associated with a significant increase in hypotension leading to discontinuation of the drug.

All enrolled patients, at the recruitment stage, were already being treated in accordance with the K-DOQI recommendations (19) for CHF hemodialysis patients. All subjects were receiving an ACE-I, and more than 60% also had a BB in both arms in their therapeutic schedule. The ability of these drugs to reduce both mortality and morbidity in the general CHF population has already been demonstrated. In the case of hemodialysis patients with CHF, only BB (15,20) has shown similar effects. Therefore, the significant reduction in global mortality, which was based on a substantial decrement in cardiovascular death after the addition of telmisartan, seems to have introduced an additional and not a substitute advantage. These observations reinforce the need of a multi-treatment for all CHF patients with low LVEF, if the goal is to achieve the lowest possible morbidity and mortality rates.

Table 3 Adverse Events in Overall Study Population

	Telmisartan (n = 165)	Placebo (n = 167)	p Value
Total adverse events	27 (16.3)	18 (10.7)	<0.01
Hypotension	18 (66.6)	7 (38.9)	<0.005
Increase in plasma potassium	5 (18.6)	2 (11.1)	NS
Diarrhea	4 (14.8)	3 (16.7)	NS
Dizziness	0	2 (11.1)	NS
Back pain	0	2 (11.1)	NS
Sore throat	0	2 (11.1)	NS

Values given are n (%).

Very few data exist from trials with ARB on hemodyalized patients, and most trials have been conducted on a small cohort of hypertensive patients, often in an open-label fashion (21,22). Fewer data are available for hemodyalized patients with CHF.

Although a comparison of our data with those reported from other trials using an ARB in non-CHF or nonuremic patients might be difficult, some observations are needed. In the Val-HeFT (Valsartan Heart Failure Trial) and CHARM (Candesartan in Heart Failure to Affect Reduction in Morbidity and Mortality) study, all-cause mortality did not decrease (benefits included only a decrease of hospital stays in the first study and also of cardiovascular mortality in the second). All-cause mortality significantly decreased only in the subgroup of the patients of the CHARM study with ejection fraction <40% (23).

Conversely, in our cohort, characterized by high mortality and morbidity rate, the addition of telmisartan to conven-

tional heart failure therapy produced a significant reduction of each single pre-specified cardiovascular end point (all-cause mortality, cardiovascular mortality, hospital stay for CHF). Moreover, the beneficial effects were linked up to a standard dosage of telmisartan (80 mg, if tolerated). Conversely, in other ARB trials the beneficial effects were obtained at a higher dose than standard practice: 100 mg losartan in the LIFE (Losartan Intervention For End-point reduction in hypertension) study (24), 32 mg candesartan in the CHARM trial (11), and 320 mg valsartan in the ValHeFT (10).

The ELITE II (Losartan Heart Failure Survival Study) (25) and Val-HeFT trials increased the possibility of a negative outcome in CHF patients when losartan and valsartan, respectively, were combined with a BB. Our results, in line with the CHARM-Added study, seem to relieve such fears. Evidence that more than 60% of our patients and more than 50% of the CHARM-Added (14) population were beta-blocked compared with a relatively low 33% in the Val-HeFT study (10) considerably reassures us about a possible danger due to this triple association (ACE-I, ARB, and BB) in CHF patients.

We strongly believe that an effective antagonization of the activated renin-angiotensin-aldosterone system (RAAS) cannot be reached by ACE-I therapy alone in hemodialyzed patients.

The addition of an ARB to standard therapy leads to a stronger antagonization of the activated RAAS, according to our experience with hemodialyzed patients with CHF. This is due to the different pharmacokinetics between ACE-I and ARBs in hemodialysis. The ACE-I are strongly removed by dialysis, whereas sartans—telmisartan among these—are not affected by this removal.

It is not surprising that limited data are available to support the use of ACE-I in ESRD patients receiving dialysis (26). No article has been published thus far addressing the efficacy of ACE-I for established CHF in dialysis patients. Despite this lack of data, the guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative work group suggest that BB and ACE-I should be used in all ESRD patients receiving dialysis with CHF (19). These guidelines are based on limited data from the ESRD population and are extended from data obtained from the general population. In fact, although BB efficacy has been specifically tested in hemodialyzed patients with CHF—albeit in small trials (15,20)—ACE-I efficacy is not univocally accepted for this particular population.

Because the current therapeutic approach to CHF in the general population mainly aimed at achieving maximal RAAS and sympathetic system inhibition, it is obviously based on the use of ACE-I and BB in association. But ACE-I are largely removed by dialysis, and the dosing revealed to be effective to improve the outcome in non-uremic patients with CHF is hardly attainable in dialysis (27,28).

The improvement of the LVEF and the favorable left ventricular remodelling in the arm treated with telmisartan in our population support that evidence. The improvement of LVEF certainly contributes significantly to the improvement of the outcome, as seen in a previous study in a CHF population (29). The plateau reached within 2 years might be the consequence of the peculiar characteristics of our study population.

The combination therapy with ACE-I and telmisartan affects also the NYHA functional class with significant improvement and less damage.

It is possible that the lower blood pressure values reached in the telmisartan-treated group might also play a role in the improvement of morbidity and mortality, because optimal blood pressure values are not well-established for hemodialyzed patients (30).

All things considered, the association of ACE-I and ARBs should always be used together with BB in the therapy of hemodialyzed patients with CHF and should not be limited to patients that still suffer from the symptoms despite the use of ACE-I and BB, as CHF guidelines suggest in non-ESRD patients.

Study limitations. Although the sample size of the current study is relatively small, it should be underlined that our population represents a highly selected group of dialysis patients with heart failure in advanced NYHA functional class, exhibiting a very high mortality and morbidity rate (despite routine medications and optimization of the dialysis regimen), as shown in the placebo group. In addition, the high mortality rate exhibited by these patients per se reduces the sample size needed to achieve statistical significance.

Another controversial aspect is that in our population the Kaplan-Meier plots separate early, whereas neurohormonal antagonism usually takes months to show a difference. We do not have a definite answer to this aspect. We could assume that in this specific population the beneficial effects of telmisartan were in a first phase essentially due to a hemodynamic improvement and were also neurohormonal only after.

As for primary end points, our multivariable analyses were substantially exploratory, both for multiplicity of comparisons and high correlation among different end points. As a result, some comparisons could be underpowered, due to the low number of events.

Finally, the risk of hypotension might limit the applicability of our study to all patients receiving dialysis. An up-titration phase of telmisartan, similar to the one used in BB therapy, might increase the feasibility of this therapy.

Conclusions

Our findings demonstrate that the ARB telmisartan significantly reduces all-cause mortality, cardiovascular death, and hospital admission for decompensated heart failure in hemodialysis patients with CHF and LVEF ≤40% when

added to standard therapies including ACE-I and BB. Although further larger trials in hemodialyzed patients with CHF are desirable, our experience could offer clinicians an opportunity to make additional improvements in the poor prognosis of ESRD patients with CHF.

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Key Words: chronic heart failure ■ dialysis ■ mortality ■ telmisartan.

APPENDIX

For the participating centers and researchers presently in charge, please see the online version of this article.