

ACE-inhibitor Therapy at Relatively High Doses and Risk of Renal Worsening in Chronic Heart Failure

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Abstract

Background: Renoprotective effect of angiotensin-converting enzyme (ACE)-inhibitors has been questioned in case of decreased effective circulating volume, like in right or biventricular chronic heart failure.

Objective: To detect clinical predictors of renal worsening in cardiac heart failure (CHF) patient population characterized by two types of ACE-inhibitor dosing regimens.

Methods: According to a retrospective cohort design, we followed 2 groups of patients with CHF — whether right or biventricular —, all in III NYHA class treated with ACE-inhibitors (enalapril or lisinopril), and with left ventricular ejection fraction (LVEF) < 50%, by distinguishing them by ACE-inhibitor dosing: average-low (≤ 10 mg per day) or "high" dose (> 10 mg per day) of enalapril or lisinopril. Aggravated renal failure (ARD) was defined by serum creatinine (Cr) increase > 30% from baseline. Cox proportional hazards model was used to identify the predictors of ARD among the following variables: ACE-inhibitors "high" dose, age, basal LVEF, history of repeated intensive intravenous loop diuretic therapies (IV diur), diabetes, basal Cr, history of hypertension, systolic blood pressure ≤ 100 mm Hg.

Results: 57 patients were recruited, of whom 15 were treated with ACE-inhibitor "high" dose. During a mean follow-up of 718 days, ARD occurred in 17 (29.8%) patients. Only ACE-inhibitor "high" dose (HR: 12.4681 C.I.: 2.1614-71.9239 $p = 0.0050$) and basal Cr (HR: 1.2344 C.I.: 1.0414-1.4632 $p = 0.0157$) were shown to predict ARD. Moreover, ACE-inhibitor "high" doses were shown to fail to predict ARD in both CHF without IV diur and CHF with diabetes.

Conclusions: In III NYHA class CHF, ACE-inhibitor "high" doses and a higher basal Cr predicted ARD. Nephrotoxicity related to ACE-inhibitor "high" doses was increased by IV diur, whereas it was not detected in CHF patients with diabetes. (Arq Bras Cardiol 2011;97(6):507-516)

Keywords: Heart failure, ACE-inhibitors, diuretics, diabetes mellitus.

Introduction

The risk of renal toxicity related to ACE-inhibitors was rather feared when these compounds were introduced as therapeutic agents for hypertension and chronic heart failure (CHF)¹⁻⁴. These concerns were later confuted and/or scaled down by many studies and meta-analyses⁵⁻⁷ highlighting the renoprotective effect of ACE-inhibitors, which arises from their property to induce a reduction in pathologically high glomerular intracapillary pressure, as found in diabetes or primary hypertension.

However, it is also true that combination therapy using high doses of loop diuretics and ACE-inhibitors can entail harmful consequences for glomerular filtration function. This concept is rather clear today^{2,8-11}, but it has a long

time been neglected because of the prevailing notion^{12,13} that the marked pharmacological antagonism of renin-angiotensin-aldosterone system (RAAS) during intensive diuretic therapy is likely to favorably influence both renal function and general hemodynamics in CHF patients, by effectively counterbalancing the RAAS activation, found to consistently stem from the administration of high doses of diuretics¹⁴. Nevertheless, several studies have pointed out that hypotension, as developing during unloading treatment with IV loop diuretics maintained for several days, can produce a more detrimental effect on renal hemodynamics and glomerular filtration, if an ACE-inhibitor therapy is also administered¹⁵⁻¹⁷. This may be caused by an overly marked fall in vasoconstrictor tonic drive of the glomerular efferent arteriole, related to ACE-inhibitor "high" doses (i.e.: > 10 mg of enalapril or equivalent dose of another ACE-inhibitor) and resulting in a noxious blood shift from glomerular capillary toward efferent arteriolar bed. Unfortunately, this worsens the hemodynamic consequences of renal hypoperfusion, diuretic-related, by causing and/or worsening a concurrent drop in glomerular

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filtration rate. Since intensive diuretic therapy is known to be capable of producing impaired renal blood supply and renal worsening from sodium and volume depletion in patients with CHF¹⁸⁻²⁰, the attempt to detect any potential drug interaction between ACE inhibitors and diuretics in our CHF patient population has just been one of the aims of our study. Diabetes would also be expected to predispose patients with CHF to the development of renal worsening²¹. On the other hand, ACE-inhibitor therapy is usually thought to impede or slow down the progression of diabetic nephropathy in patients with diabetes without CHF^{22,23}. Thus, our study has been intended to furnish further data on the effect of ACE inhibitors in patients with CHF and diabetes.

According to several previous studies²⁴⁻²⁶, a higher incidence of significantly worsened renal function is likely to occur in older patients with CHF compared to younger patients regardless of the therapy. Moreover, based on some studies^{25,26}, older patients taking ACE-inhibitors may be more likely to develop renal impairment than older patients who do not take ACE-inhibitors. On the other hand, CHF severity expressed by a low left ventricular ejection fraction (LVEF) would be expected to predispose to renal impairment because of associated poor renal perfusion and neurohormonal activation. Finally, beta-blockers may have beneficial effects on renal function due to property to induce attenuation of renin release coupled to their sympatholytic effects²⁷, even though the risk of reduced renal perfusion because of their negative inotropic effect and/or concurrent possible hypotension is also to be considered.

Accordingly, in our CHF population, we have also investigated the controversial relation between these factors (old age, reduced left ventricular systolic function, beta-blocker therapy) and a possible renal toxicity development during ACE-inhibitor prolonged use at various doses.

Methods

A retrospective, observational cohort study was designed by recruiting patients with CHF — all of whom treated by ACE-inhibitors at various doses - from two centers (N.R. CI S.M.dP. and C. U. E.d'A.). One investigator in each institute (RDV at E.dA and AC at CI S.M.dP.) reviewed the charts of all patients admitted between June 2006 and June 2008 in the respective outpatients' clinics. Any increase in serum creatinine greater than 30% of its basal value - measured before starting the follow-up period - was defined as aggravated or new-onset renal failure (ARD). Using a cohort design, we analyzed two groups of patients with CHF - whether right or biventricular CHF -, all of whom placed in the III New York Heart Association (NYHA) class and treated with ACE-inhibitors (enalapril or lisinopril). The subdivision of the study population among two groups was made on the basis of the scheduled dose of ACE-inhibitor: average-low (≤ 10 mg per day) or "high" (i.e. > 10 mg per day) dose of enalapril or lisinopril. Patients were recruited as long as they had a history of CHF with clinical picture at enrollment of stable III NYHA class along with echocardiographic left ventricular ejection fraction (LVEF)

$< 50\%$ plus documented presence of ACE-inhibitors in their therapy. Exclusion criteria were myocardial infarction within 30 days, arrhythmia-related syncope, major cardiac surgery, unstable angina, uncontrollable hypertension, cor pulmonale, major neurologic disease or cerebrovascular disease, suspected renal artery stenosis, advanced renal failure (i.e. serum creatinine > 2.2 mg/dl at baseline) and likely noncompliance (e.g.: alcoholism, drug addiction).

Follow-up visits, as usually accomplished at two Institutions involved in our research and checked by our retrospective analysis, included patient's history, physical examination, assessment of medication usage, assessment of adverse effects, alterations in drug dosage, laboratory and echocardiographic data collection. In particular, echoDoppler study of end-expiratory and end-inspiratory venous caval fluctuations¹¹ were periodically done in all followed up CHF III NYHA class patients as customary practice in order to achieve a useful approximate measurement of the patient's hemodynamic status and to monitor his intravascular effective circulating volume. Furthermore, regarding the two groups we had defined on the basis of the ACE-inhibitor dosing, we decided that any possible switch of the original prescribed dose from one to the other group was not to be considered by final statistical analysis (according to the principle of "intention to treat" analysis).

Statistical analysis

Statistical analysis was performed using EPI INFO software (version 3.3 for Windows, from the Center for Disease Control and Prevention, Atlanta, US). Categorical variables were analyzed by Chi-square and Fisher exact tests, while continuous variables were compared using the ANOVA one-way test or Mann-Whitney test for skewed distributions.

Cumulative risk was estimated with Kaplan-Meier analysis. Kaplan-Meier estimator curves were built, and the log-rank test was used to compare the relative risk of ARD between the ACE-inhibitor low and high dose groups. A multivariate Cox proportional hazards model was then fitted by assuming ARD (i.e. a rise in serum creatinine $> 30\%$ from the level found at the enrollment) as endpoint (censored variable). The variables entered into the Cox model were: assumption of a daily oral dose of ACE-inhibitor (enalapril or lisinopril) > 10 mg, age (continuous variable), age < 75 years, history of one or more courses of intensive intravenous diuretic therapy, diabetes, basal LVEF (continuous variable), serum creatinine basal values (continuous variable). The results of the Cox proportional hazards regression analysis yielded estimates of the risks per months (hazards) of ARD, with and without administration of doses > 10 mg per day of enalapril or lisinopril, over time since the enrollment. Based on these estimates, we computed the cumulative risks over treatment horizons between 1 and 3 years, and with ACE-inhibitor assumption ranging between 2.5 and 30 mg per day after the enrollment.

We have also built a number of 2X2 contingency tables, aimed to identify all potential interactions involving high dose ACE-inhibitor regimen. Patients with missing data for any of the abovementioned variables were excluded from the analysis.

Results

We have retrospectively identified and reviewed the records of 112 consecutive patients diagnosed with right or biventricular CHF, all steadily located in III NYHA class as well as characterized by echocardiographic finding of left ventricular ejection fraction (LVEF) < 50% (measured by the Simpson method). Among them, those treated with ACE-inhibitors and fulfilling the other abovementioned criteria for inclusion in the study were 57 (51%), of whom 15 were treated with enalapril or lisinopril daily dose >10 mg.

During a mean follow-up of 718 days, ARD occurred in 17 (29.8%) patients. More exactly, during a mean follow-up of 738 days, 6 (14.3%) of 42 patients in the ACE-inhibitor low dose (≤ 10 mg per day of enalapril or lisinopril) group developed ARD according to the study definition compared with 11 (73.3%) of 15 patients in the ACE-inhibitor high dose (>10 mg per day of enalapril or lisinopril) group during a mean follow-up of 698 days — p (Fisher's exact test) = 0.0001.

No deaths occurred in the recruited cohort of CHF patients through the 2 year follow-up. Twelve hospitalizations were recorded, 9 of which involved patients (6 on the whole) belonging to the high dose ACE-inhibitor group; whereas the 3 hospitalizations computed in low dose ACE-inhibitor group were distributed among 2 patients. All hospitalizations were caused by the need of revising the scheduled therapy due to occurrence of not well tolerated worsening of heart failure signs and/or symptoms, such as increase in peripheral edema or exacerbated breathlessness.

A transition to low ACE-inhibitor dosing regimen occurred in 2/15 (13.3%) of CHF patients originally assigned to the high dose ACE-inhibitor group. The opposite switch towards the ACE-inhibitor high dose group involved 3/42 patients (7% of patients initially treated with a low dose of ACE-inhibitor).

Baseline sex and age distribution and hematochemical and clinical characteristics of the two groups (ACE-inhibitor low and high dose groups) are presented in Table 1. The ANOVA one-way test was applied to compare continuous variables and χ^2 (chi square) or Fisher exact tests were employed for a comparison of dichotomous variables.

By using the Cox proportional-hazard regression analysis, the significant univariate predictors of decreased renal function were treatment with ACE-inhibitor high dose, intensive intravenous loop diuretic therapy (one or more courses of infusions), age (continuous variable) and age below 75 years (Table 2). The results of multivariate Cox proportional-hazard analysis, using the occurrence of ARD during follow-up as an endpoint (censored variable), are presented in Table 3. After controlling for all other variables, only treatment with ACE-inhibitor high dose (hazard ratio: 12.4681, C.I.: 2.1614 to 71.9239 $p = 0.0050$) and basal serum creatinine (hazard ratio: 1.2344; C.I.: 1.0414 to 1.4632; $p = 0.0157$) were demonstrated to be associated with increased risk of decreased renal function over the follow-up period. On the basis of the Kaplan-Meier estimator curve, the hazard ratio (HR) for developing renal decreased function was 8,1803 (log rank test $p < 0.0001$) in the ACE-inhibitor high dose group compared with ACE-inhibitor low dose group (Fig. 1).

On testing interaction terms by 2x2 contingency tables to assess effect modification, we found a significant positive

interaction between ACE-inhibitor high dose therapy and loop diuretic intensive therapy: patients taking enalapril or lisinopril at high dose (more than 10 mg and up to 30 mg per day) plus intravenous loop diuretic administration were at increased risk of renal impairment compared with patients of the same ACE-inhibitor high dose group who had not undergone this kind of combination therapy ($p = 0.0862$) (Figure 2). Moreover, in CHF patients without diabetes belonging to the ACE-inhibitor high dose group, an association was detected between use of ACE-inhibitor high doses and increased risk of renal deterioration, but this association was missing in CHF patients of the same ACE-inhibitor high dose group, if they were suffering from diabetes ($p = 0.0077$) (Figure 3). Thus, both intensive intravenous loop diuretic therapy and diabetes were identified as effect modifiers of the relation between ACE-inhibitor high dose and ARD in CHF patients.

Discussion

The results of our study show some relevant differences compared to those achieved by other previous studies^{28,29} regarding the possible association between ACE-inhibitor therapy and development of chronic renal failure. The discrepancy found by comparing our results with those reached by these research studies could be caused by more than one factor.

Firstly, in our study, we chose a rise in serum creatinine > 30% from baseline as a criterion for defining renal damage, which is a more sensitive cut-off compared to those adopted by other authors elsewhere. Instead, the ELITE study²⁸ and the study of Knight et al²⁹ defined renal deterioration as a rise in serum creatinine of > 0.3 and ≥ 0.5 mg/dl respectively, from baseline. Thus, based on the less restrictive inclusion criterion we had adopted, a higher incidence of worsened renal failure was to be expected in our study. Another issue is to be considered, which is the different composition of our case-record: actually, the CHF patients included in our study consistently had a high grade involvement of the right cardiac chambers and consequently were at higher risk of renal failure, due to renal venous congestion, compared to patients enrolled in the previous studies, mostly suffering from left only ventricular insufficiency, i.e. a kind of heart failure less prone to renal failure development, both spontaneous and iatrogenic. The question whether ACE-inhibitors have to be handled more cautiously and administered at lower doses in CHF patients with right or biventricular decompensated heart failure compared to those with left only ventricular failure has not received the relevant consideration and attention it however would deserve. Indeed, in our opinion, renal venous congestion, which is present in right only decompensated heart failure patients, as characterized by systemic venous hypertension, does not benefit from high doses of vasodilator drugs, such ACE-inhibitors. In this setting of patients, pharmacological decongestion achieved through loop diuretics should be combined with a therapeutic policy aimed to preserve glomerular filtration using osmotic agents³⁰⁻³³ in order to maintain a suitable refilling rate and retrieve fluid from extravascular space without inducing any fall in glomerular filtration, intravascular depletion-related.

Our concept of high and low ACE-inhibitor dose should also be highlighted, by emphasizing that it should be

interpreted according to a non-absolute meaning. Actually, in CHF patients already treated with drugs capable of mitigating RAAS activation, such as beta-blockers, aldosterone receptor antagonists or low doses of digoxin, even a dose of 20 mg per day of enalapril or lisinopril could be labeled “high,” especially in case of lack of hypertension or RAAS stimulation. This is just the case of CHF patients with stable hemodynamic and clinical picture, exhibiting a good response to therapy and kept at rest. Moreover, usual treatment of CHF patients located in III NYHA class, as those considered by our study, mostly includes

aldosterone receptor antagonists, whose capacity to improve survival in this clinical setting has been proven³⁴. Therefore, in order to avoid hyperkalemia and its related acidosis and arrhythmias, doses of ACE-inhibitor should be reduced, when coupled to administration of any aldosterone receptor antagonist. Therefore, even a daily dose of 20 mg of enalapril or lisinopril could be defined as “high” when put in this peculiar clinical and pharmacologic scenario.

By comparing the basal features of the two groups (ACE-inhibitor “high” versus ACE-inhibitor “low” dose), an

Table 1 – Baseline hematochemical and clinical characteristics of CHF patients who had been assigned to high and low dose of ACE-inhibitor therapy. The comparisons were accomplished using the ANOVA one-way test for continuous variables and Chi-square or Fisher exact tests for dichotomous variables

Variable	ACE-inhibitor low dose group (n=42)	ACE-inhibitor high dose group (n=15)	p value
Baseline creatinine (mg/dL)	1.4 ± 0.3	1.25 ± 0.4	0.135
Baseline ejection fraction (%)	39 ± 5	41 ± 5	0.189
Age	74.6 ± 3	72.2 ± 4	0.018
Gender (% male)	27(64%)	10(67%)	0.881
Intensive i.v. diuretic therapy (one or more courses)	10(23%)	10(67%)	0.0075
History of hypertension (%)	16(38%)	6(40%)	0.858
Diabetes (%)	6(14.3%)	6(40%)	0.084
SBP <100 mmHg (%)	3(7%)	1(6.6%)	0.4539

ACE - angiotensin-converting enzyme.

Table 2 - Univariate predictors of decreased renal function in CHF population of the study

Clinical variable	Hazard Ratio	95% CI	p
ACE-inhibitor high dose	8.6809	3.1764 - 23.7241	<0.0001
Intensive intravenous diuretics (one or more courses of infusion)	3.2847	1.2512 - 8.6227	0.0163
Diabetes	2.1937	0.8146 - 5.9072	0.1220
Age <75 years	3.1439	1.1925 - 8.2887	0.0212
Age (continuous variable)	0.8647	0.7727 - 0.9675	0.0117
Serum basal creatinine (mg/dl)	1.0697	0.9395 - 1.2180	0.3114
LVEF%	0.9943	0.9022 - 1.0958	0.9091

ACE - angiotensin-converting enzyme; .LVEF - left ventricular ejection fraction.

Table 3 - Multivariate predictors of decreased renal function in CHF population of the study

Covariate	b	SE	p	Exp(b)	95% CI of Exp(b)
ACE-inhibitor high dose	2.5232	0.8987	0.0050	12.4681	2.1614 a 71.9239
age (continuous variable)	0.003006	0.09106	0.9737	1.0030	0.8398 a 1.1979
age <75 years	0.4766	0.8819	0.5889	1.6106	0.2885 a 8.9912
Serum basal creatinine (mg/l)	0.2106	0.08720	0.0157	1.2344	1.0414 a 1.4632
diabetes	0.3119	0.6839	0.6483	1.3661	0.3600 a 5.1837
intensive intravenous diuretics (one or more courses of infusion)	0.1556	0.7235	0.8297	1.1684	0.2850 a 4.7896
LVEF%	-0.1295	0.07119	0.0689	0.8785	0.7647 a 1.0094

ACE - angiotensin-converting enzyme; .LVEF - left ventricular ejection fraction.

unequal distribution of age and pharmacological approaches is evident. These basal differences, pertaining to the observational design of study, influence the results of Cox proportional hazards regression univariate analysis. Actually, some predictors of worsened renal failure developed over the follow-up, as detected by Cox univariate analysis, may represent a simple reflection of this basal heterogeneous distribution of age and pharmacologic schemes between the two groups. For instance, according to univariate analysis (Table 2), intensive intravenous loop diuretic administration is associated with increased risk of developing renal damage over the follow-up period, but this association may simply be caused by a selection bias in our study originating from a more frequent use of high doses of ACE-inhibitor by patients who have undergone the intravenous loop diuretic regimen (see Table 1). A selection bias also accounts for the univariate finding of less incidence of renal worsening in patients older than 75 years: actually, the patients taking high doses of ACE-inhibitor had a significantly lower age compared to ACE-inhibitor low dose group (Table 1).

Furthermore, another issue worthy of debate is that among the studies³⁵⁻³⁷ which have faced the problem of dosage of the ACE-inhibitor therapy in CHF patients, the enrolled cohorts were consistently characterized by preliminary

selection of the study population, aimed to exclude any CHF patient with overt renal failure at baseline, according to an overly strict enrollment criterion. Therefore, there was the selection of a kind of patient more likely to not feel the effects of ACE-inhibitor high doses, that instead are usually believed to be capable of provoking harmful renal changes just in CHF patients already suffering from renal failure. On the contrary, in our study design, we did not state the need to exclude the CHF patients found to have mild to moderate chronic renal disease at enrollment, provided that their serum creatinine did not exceed the cut-off of 2.2 mg/dl, which overtly conflicts with the criteria³⁶ adopted in the majority of the studies investigating the comparison between high and low doses of ACE-inhibitors in CHF clinical setting.

As far as we know, the highest doses of ACE-inhibitor have never been blamed for genesis of progressive renal damage; instead, a potential for renal toxicity of the ACE-inhibitors in CHF patients, without distinction of doses, is highlighted by a study of Knight et al²⁹, in which the ACE-inhibitor enalapril is associated to a 33% increase in the risk of developing renal worsening over a two-year follow-up, by using an univariate Cox model.

In our study, by means of Cox proportional hazards multivariate regression, basal serum creatinine was also

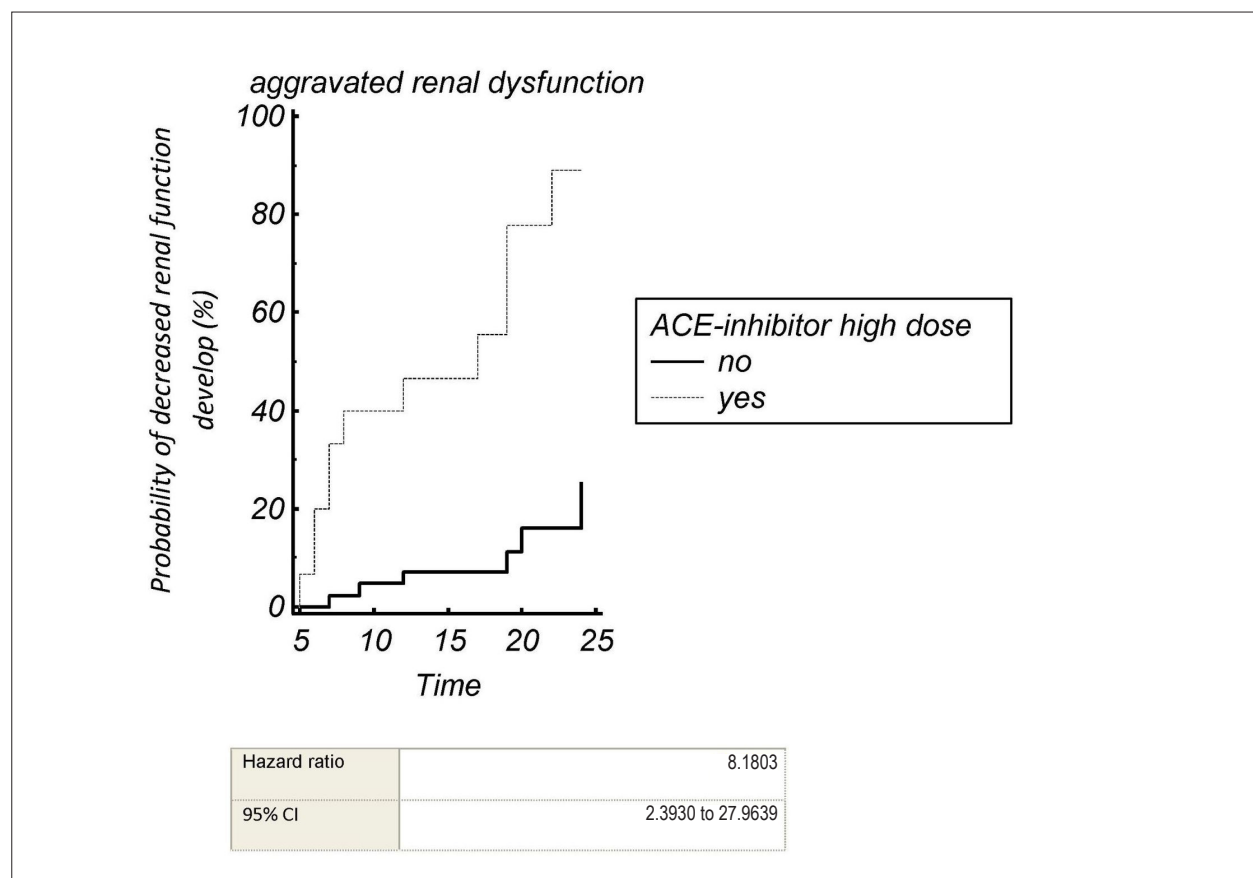


Fig. 1 – Kaplan-Meier estimator curve for the probability of developing decreased renal function during the follow-up period. The hazard ratio (HR) for developing decreased renal function was 8,1803 (logrank test $p < 0.0001$) in the ACE-inhibitor high dose group compared with ACE-inhibitor low dose group.

identified as a predictor of renal deterioration. The risk in the course of time was calculated to rise by 23.4% per mg/deciliter of increase in serum creatinine (Table 3). This finding prompts us to infer that a high basal serum creatinine is a marker of increased risk of renal impairment in the subsequent follow-up and may give rise to an unfavorable renal outcome, irrespective of the therapy. Besides, this observation agrees with other reports in the literature³⁸.

In our study, by using 2x2 contingency tables, we found that ACE-inhibitor “high” dose did not increase the risk of renal deterioration in CHF patients with diabetes, while increasing the risk of diuretic-associated renal impairment in CHF patients (Figures 2 and 3). In other words, in the ACE-inhibitor “high” dose group, the effect of maximal ACE-inhibition as a risk factor for worsening renal function in CHF patients was found to be mitigated in CHF patients

with diabetes compared to those without diabetes (Figure 3), probably because ACE-inhibitors usually exert a very important renoprotective effect in all diabetic patients, including diabetic patients with CHF. This finding is supported by many studies demonstrating the renal protective effect of ACE-inhibition in patients with diabetes^{5,21,22}. Furthermore, in our study, intensive intravenous diuretic therapy was a univariate, but not a multivariate predictor of the development of renal impairment, which is a more pronounced effect in the ACE-inhibitor “high” dose group. The relation between unloading therapy with loop diuretics and renal impairment is frequently reported in the literature, but the results from this study, based on a little case record, only partially confirm this risk, since our multivariate analysis failed to identify unloading intensive diuretic treatment as a significant predictor of renal worsening in our CHF patient

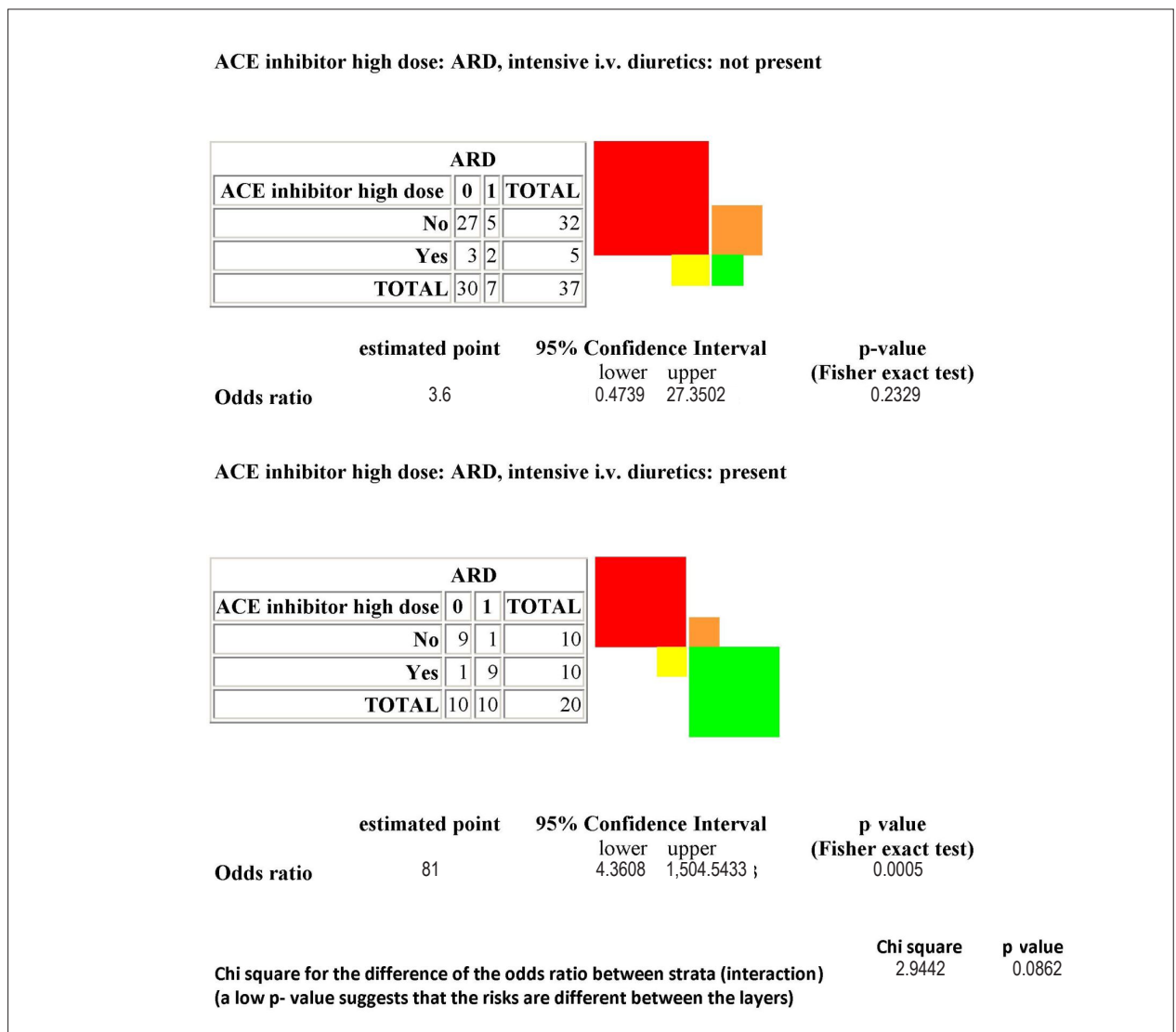


Fig. 2 – No: administration of enalapril or lisinopril dose ≤ 10 mg per day; Yes: presence of ACE-inhibitor high dose (>10 mg of enalapril or lisinopril per day); 0: no evidence of aggravated renal dysfunction (ARD); 1: presence of ARD.

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population. On the other hand, the detrimental effect on renal function of intravenous loop diuretics, as pointed out by some authors^{9,18-20}, could also be potentially explained by the selection bias¹⁴. In other words, CHF patients with more severe per se clinical picture and at increased risk for cardiac and renal impairment might have been more likely to receive repeated infusional treatments with intravenous loop diuretics.

Study limitations

The study has some limitations that must be considered. The most important limitation is that this study is based on a retrospective design ("retrospective cohort study"), so as to not allow us to follow the natural history of worsening renal function after its development and subsequent changes in the ACE-inhibitor dose. Thus, it would require to be further validated by a specifically targeted, controlled randomized

trial. Besides this, we do not have a direct measurement of renal function such as glomerular filtration rate. However, in most clinical settings, serum creatinine is still the usual indirect measurement of renal function. Another limitation is that there were some variations of the ACE-inhibitor dosage during the follow-up in both high and low dose group. These changes entailed that few patients (2/15 equal to 13.3% of patients originally assigned to the high dose group) were getting a reduction in daily dosing so as to vary their real place from high to low dose group. Even though more rarely (3/42 pts; 7%), the opposite shift, i.e. the transition from low to high dose of ACE-inhibitor, was also demonstrated. The count of the cases of alteration in original dosing was carried out, whereas none of these changes in ACE-inhibitor dose grouping was considered by final statistical analysis according to the principle of intention to treat. Therefore, the CHF patients who were shown to vary the original dose of ACE-inhibitor, were analyzed as

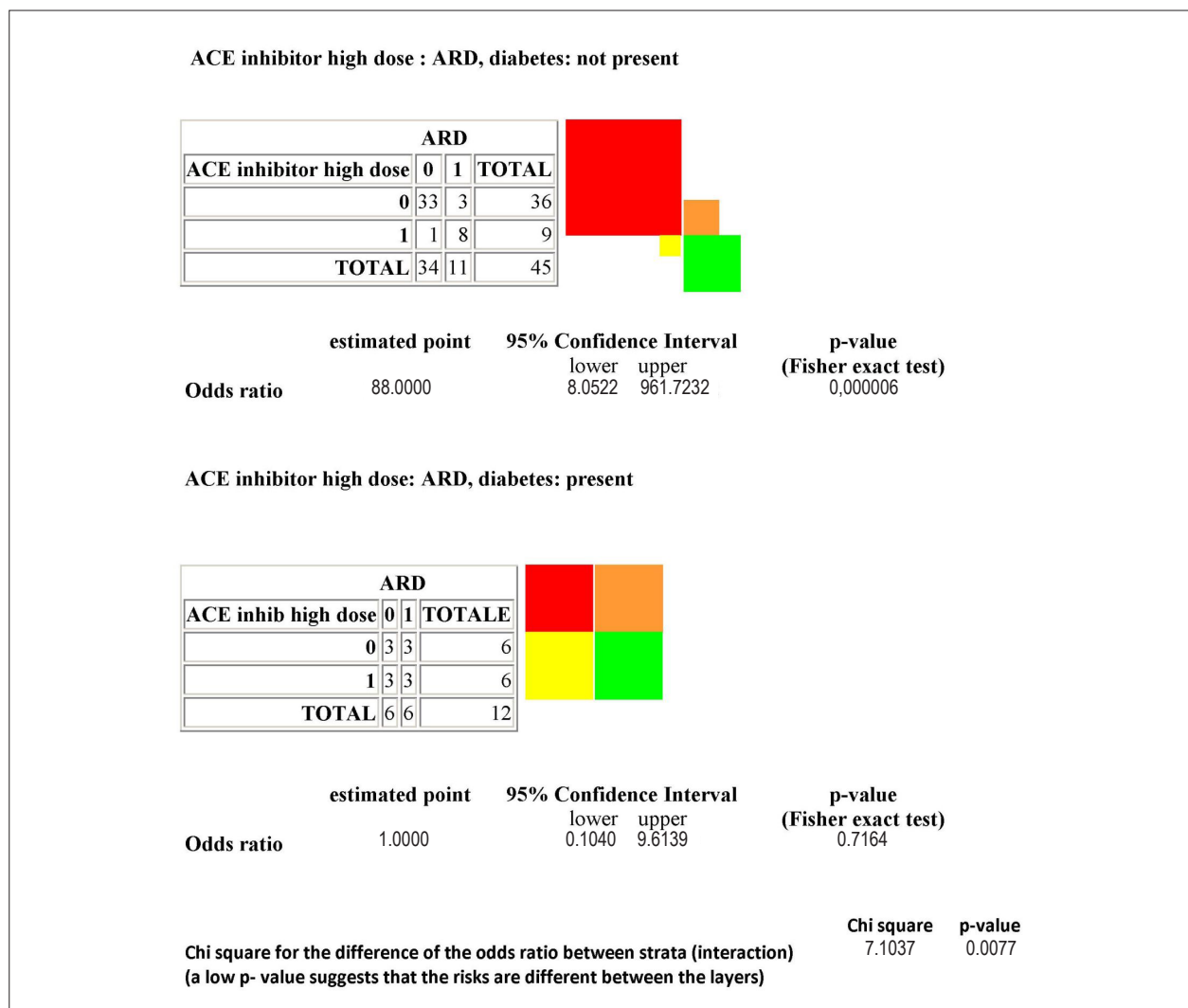


Fig. 3 – No: administration of enalapril or lisinopril dose ≤ 10 mg per day; Yes: presence of ACE-inhibitor high dose (>10 mg of enalapril or lisinopril per day); 0: no evidence of aggravated renal dysfunction (ARD); 1: presence of ARD.

belonging to initial high or low ACE-inhibitor regimen, as assigned at enrollment. Finally, the rough measurement of the volemic status consisting in echographic estimate of respiratory changes in caval diameters might perhaps have biased our results by failing to timely detect any drop in blood effective circulating volume not so pronounced as to be identified by ultrasonography. It is known that a loss of venous return and cardiac preload, related to even mildly impaired intravascular volume, is able to elicit reflex splanchnic vasoconstriction³⁹, thereby reducing renal flow and glomerular filtration rate in CHF patients, especially in the presence of splanchnic and renal venous congestion⁴⁰. Instead, direct measurement of volemic status by central venous pressure invasive monitoring during hemodynamic instability periods⁸, perhaps would allow us to better modulate the ACE-inhibitor doses, by reducing or stopping them in the presence of timely diagnosed volume depletion. Thus poorly conducted monitoring of the volemic status -by caval echography- rather than use of ACE-inhibitor high doses might have prompted an erroneously oversized ACE-inhibitor and diuretic long lasting therapy, so propitiating transition from initial condition of cardiac overload to relative hypovolemic status inducing insidious subacute renotubular injury⁸.

Conclusions

Despite the well-documented decrease in mortality rate caused by ACE inhibitor use in patients with CHF, our study highlights that high doses of ACE-inhibitor increase the risk of glomerular filtration's impairment in these patients, as measured by rise in serum creatinine level. Moreover, even

a higher serum creatinine at admission has been shown to be associated with increased risk of renal worsening over a two year follow-up period. The "nephrotoxic" risk related to ACE-inhibitor "high" doses is significantly greater in CHF patients of any age concomitantly prescribed intensive intravenous loop diuretic regimens. Therefore, patients with advanced CHF should not be denied the benefit associated with ACE inhibitors but require close clinical monitoring of renal function, especially in case any intensive diuretic therapy should be planned to relieve symptoms or signs of marked fluid retention.

Conversely, ACE inhibitor therapy, even administered at high doses, seems to reduce the risk of renal impairment, diabetes-related.

These findings could be used to implement treatment guidelines for monitoring ACE inhibitor therapy in patients with CHF and they may also yield valuable insights for further investigation concerning some still not well understood pathophysiologic and renoprotective mechanisms.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

References

1. Packer M, Lee WH, Medina N, Yushak M, Kessler PD. Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic heart failure. *Ann Intern Med.* 1987;106(3):346-54.
2. Cleland JG, Gillen G, Dargie HJ. The effects of frusemide and angiotensin-converting enzyme inhibitors and their combination on cardiac and renal haemodynamics in heart failure. *Eur Heart J.* 1988;9(2):132-41.
3. Devoy MA, Tomson CR, Edmunds ME, Feehally J, Walls J. Deterioration in renal function associated with angiotensin converting enzyme inhibitor therapy is not always reversible. *J Intern Med.* 1992;232(6):493-8.
4. Kostis JB, Shelton B, Gosselin G, Coulet C, Hood WB Jr, Kohn RM, et al. Adverse effects of enalapril in the Studies of Left Ventricular Dysfunction (SOLVD). SOLVD Investigators. *Am Heart J.* 1996;131(2):350-5.
5. Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulindependent diabetes mellitus: a 7-year follow-up study. *Arch Intern Med.* 1996;156(3):286-9.
6. Giatras I, Lau J, Levey AS. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a metaanalysis of randomized trials. Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. *Ann Intern Med.* 1997;127(5):337-45.
7. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med.* 2000;160(5):685-93.
8. MacFadyen RJ, Ng Kam Chuen MJ, Davis RC. Loop diuretic therapy in left ventricular systolic dysfunction: has familiarity bred contempt for a critical but potentially nephrotoxic cardio renal therapy? *Eur J Heart Fail.* 2010;12(7):649-52.
9. Brandimarte F, Mureddu GF, Boccanelli A, Cacciatore G, Brandimarte C, Fedele F, et al. Diuretic therapy in heart failure: current controversies and new approaches for fluid removal. *J Cardiovasc Med (Hagerstown).* 2010;11(8):563-70.
10. De Vecchis R, Ciccarelli A, Pucciarelli A. Unloading therapy by intravenous diuretic in chronic heart failure: a double-edged weapon? *J Cardiovasc Med (Hagerstown).* 2010; 11(8):571-4.
11. Cioffi G, Tarantini L, Pulignano G, Del Sindaco D, De Feo S, Opasich C, et al. Prevalence, predictors and prognostic value of acute impairment in renal function during intensive unloading therapy in a community population hospitalized for decompensated heart failure *J Cardiovasc Med (Hagerstown).* 2007;8(6):419-27.
12. Ikram H, Chan W, Espiner EA, Nicholls MG. Haemodynamic and hormone responses to acute and chronic frusemide therapy in congestive heart failure *Clin Sci (Lond).* 1980;59(6):443-9.
13. Wilcox CS, Mitch WE, Kelly RA, Friedman PA, Souney PF, Rayment CM, et al. Factors affecting potassium balance during frusemide administration. *Clin Sci (Lond).* 1984;67(2):195-203.

14. Kazory A, Ross EA. Contemporary trends in the pharmacological and extracorporeal management of heart failure: a nephrologic perspective. *Circulation*. 2008;117(7):975-83.
15. Bridoux F, Hazzan M, Pallot JL, Fleury D, Lemaitre V, Kleinknecht D, et al. Acute renal failure after the use of angiotensin-converting-enzyme inhibitors in patients without renal artery stenosis. *Nephrol Dial Transplant*. 1992;7(2):100-4.
16. Mandal AK, Markert RJ, Saklayen MG, Mankus RA, Yokokawa K. Diuretics potentiate angiotensin converting enzyme inhibitor-induced acute renal failure. *Clin Nephrol*. 1994;42(3):170-4.
17. Wynckel A, Ebikili B, Melin JP, Randoux C, Lavaud S, Chanard J. Long-term follow-up of acute renal failure caused by angiotensin converting enzyme inhibitors. *Am J Hypertens*. 1998;11(9):1080-6.
18. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. *Am J Cardiol*. 2006;97(12):1759-64.
19. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. *Eur J Heart Fail*.
20. Peacock WF, Costanzo MR, De Marco T, Lopatin M, Wynne J, Mills RM, et al; ADHERE Scientific Advisory Committee and Investigators. Impact of intravenous loop diuretics on outcomes of patients hospitalized with acute decompensated heart failure: insights from the ADHERE registry. *Cardiology*. 2009;113(1):12-9.
21. Stein G, Fünfstück R, Schiel R. Diabetes mellitus and dialysis. *Minerva Urol Nefrol*. 2004;56(3):289-303.
22. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med*. 1993;329(20):1456-62.
23. Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet*. 2005;366(9502):2026-33.
24. Fliser D, Franek E, Joest M, Block S, Mutschler E, Ritz E. Renal function in the elderly: impact of hypertension and cardiac function. *Kidney Int*. 1997;51(4):1196-204.
25. Schwartz D, Komowski R, Schwartz IF, Dotan I, Weinreb B, Averbuch M, et al. Prediction of renal impairment in elderly patients with congestive heart failure treated with captopril. *Cardiovasc Drugs Ther*. 1996;10(1):75-9.
26. MacDowall P, Kalra PA, O'Donoghue DJ, Waldek S, Mamtara H, Brown K. Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. *Lancet*. 1998;352(9121):13-6.
27. Barone FC, Nelson AH, Ohlstein EH, Willette RN, Sealey JE, Laragh JH, et al. Chronic carvedilol reduces mortality and renal damage in hypertensive stroke-prone rats. *J Pharmacol Exp Ther*. 1996;279(2):948-55.
28. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet*. 1997;349(9054):747-52.
29. Knight EL, Glynn RJ, McIntyre KM, Mogun H, Avorn J. Predictors of decreased renal function in patients with heart failure during angiotensin-converting enzyme inhibitor therapy: results from the studies of left ventricular dysfunction (SOLVD). *Am Heart J*. 1999;138(5 Pt 1):849-55.
30. Paterna S, Di Pasquale P, Parrinello G, Fornaciari E, Di Gaudio F, Fasullo S, et al. Changes in brain natriuretic peptide levels and bioelectrical impedance measurements after treatment with high-dose furosemide and hypertonic saline solution versus high-dose furosemide alone in refractory congestive heart failure: a double-blind study. *J Am Coll Cardiol*. 2005;45(12):1997-2003.
31. Issa VS, Bacal F, Mangini S, Carneiro RM, Azevedo CH, Chizzola PR, et al. Hypertonic saline solution for renal failure prevention in patients with decompensated heart failure. *Arq Bras Cardiol*. 2007;89(4):251-5.
32. De Vecchis R, Ciccarelli A, Ariano C, Pucciarelli A, Cioppa C, Giasi A, et al. Renoprotective effect of small volumes of hypertonic saline solution in chronic heart failure patients with marked fluid retention: results of a case-control study. *Herz*. 2011;36(1):12-7.
33. Redfors B, Swärd K, Sellgren J, Ricksten SE. Effects of mannitol alone and mannitol plus furosemide on renal oxygen consumption, blood flow and glomerular filtration after cardiac surgery. *Intensive Care Med*. 2009;35(1):15-22.
34. Pitt B, Zannad F, Remme W, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341(10):709-17.
35. Rydén L, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Packer M, et al. Efficacy and safety of high-dose lisinopril in chronic heart failure patients at high cardiovascular risk, including those with diabetes mellitus. Results from the ATLAS trial. *Eur Heart J*. 2000;21(23):1967-78.
36. Roffman DS. High-versus low-dose ACE inhibitor therapy in chronic heart failure. *Ann Pharmacother*. 2004;38(5):831-8.
37. Thomas S, Geltman E. What is the optimal angiotensin-converting enzyme inhibitor dose in heart failure? *Congest Heart Fail*. 2006;12(4):213-8.
38. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J*. 2004;147(2):331-8.
39. Abboud FM, Eckberg DL, Johannsen UJ, Mark AL. Carotid and cardiopulmonary baroreceptor control of splanchnic and forearm vascular resistance during venous pooling in man. *J Physiol*. 1979;286:173-84.
40. Tang WH, Mullens W. Cardiorenal syndrome in decompensated heart failure. *Heart*. 2010;96(4):255-60.

