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An investigation of the concomitant use of angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs and diuretics

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Abstract. – OBJECTIVE: To determine in retrospective data the prevalence at hospital discharge of co-prescribing angiotensin-converting enzyme inhibitors (ACE-I) and non-steroidal anti-inflammatory drugs (NSAIDs) and ACE-I/NSAIDs and diuretics and to identify factors associated with the co-prescription. Secondary, we evaluated the extent of serum creatinine and potassium monitoring in patients treated with ACE-I and these associations and determined the prevalence of values above the upper normal limit (UNL) in monitored patients.

PATIENTS AND METHODS: Hospitalized patients with ACE-I in their therapy at discharge were included in 3 groups as follows: ACE-I, DT (double therapy with ACE-I and NSAIDs) and TT (triple therapy with ACE-I, NSAIDs and diuretics) groups. We evaluated differences on demographic characteristics, co-morbidities, medications, laboratory monitoring and quantified the patients with serum creatinine and potassium levels above the UNL using descriptive statistics. Logistic regression analysis with backward elimination was performed to identify significant predictors of combination therapy.

RESULTS: Of 9960 admitted patients, 1214 were prescribed ACE-I, 40 were prescribed ACE-I/NSAIDs and 22 were prescribed ACE-I/NSAIDs/diuretics (3.13% and 1.72%, respectively, of the patients prescribed with ACE-I). Serum creatinine and potassium were monitored for the great majority of patients from all groups. The highest percentage of hyperkalemia was found in the DT group (10% of the patients) and of serum creatinine above UNL in the TT group (45.45%). The logistic regression final model showed that younger patients and monitoring for potassium were significantly associated with combination therapy.

CONCLUSIONS: The prevalence of patients receiving DT/TT was relatively low and their monitoring during hospitalization was high. Factors associated with the combinations were younger patients and patients not tested for serum potassium.

Key Words:
Angiotensin-converting enzyme inhibitors, Acute kidney injury, Hyperkalemia, Creatinine.

Introduction

Randomized controlled trials have demonstrated that angiotensin-converting enzyme inhibitors (ACE-I) reduce the rates of death, myocardial infarction, stroke and heart failure complications among patients with heart failure[1], left ventricular dysfunction[2-4], previous vascular disease alone[5-7] or high risk diabetes mellitus[8]. In addition, real practice data showed the important role of ACE-I in the management of blood pressure[9], heart disease (improving mortality[10], all-cause mortality in systolic heart failure with chronic kidney disease[11], total mortality or heart failure hospitalization in heart failure with preserved ejection fraction[12]), ischemic stroke[13] (improving short term outcomes) and coronary artery disease[14] (improving 6-months mortality).

Patients benefit from these positive effects of ACE-I, but there are still concerns and challenges that need to be addressed regarding their adverse drug reactions (ADRs) and especially related to

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renal failure and hyperkalemia. Worsening renal function and hyperkalemia were found to be the main reasons for ACE-I treatment discontinuation in patients hospitalized for acute heart failure[15]. Moreover, patients on lisinopril and with hyperkalemia were found to have an increased risk of death (HR = 1.49, $p = 0.02$)[16]. Deterioration of the renal function consecutive to ACE-I utilization can range from renal failure requiring treatment discontinuation[17] to dialysis-dependent renal failure[18]. Although biochemical disturbances associated with these adverse outcomes in ACE-I treated patients usually occur within the first 3 weeks of treatment, and monitoring of serum creatinine and potassium levels is recommended before treatment initiation and after, during this timeframe, the presence of other drugs in patient's treatment can worsen the renal disturbance and hyperkalemia at any point in patient's chronic therapy.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used (40-60% as lifetime prevalence in the general population[19,20]) in chronic and acute inflammatory diseases and so are diuretics in the hypertensive patients. NSAIDs and diuretics used together with ACE-I represent a risk factor for developing acute renal failure (ARF) and hyperkalemia[21-24], as each of these drugs has the potential to affect renal function. ACE-I cause a haemodynamic reduction in glomerular filtration rate with concomitant rise in serum creatinine due to efferent arteriolar vasodilatation. NSAIDs cause inhibition of prostacyclin synthesis leading to renal afferent arteriolar vasoconstriction. Diuretics' use can lead to hypovolaemia[25] and affect the serum potassium levels.

To prevent these serious ADRs, the Summaries of Product Characteristics of ACE-I specify that patients should be monitored for serum creatinine and potassium before and within 3 weeks from starting the therapy with ACE-I, and periodically thereafter if ACE-I and NSAIDs are in use together, with/without diuretics. Therefore, we arbitrarily assumed that hospitalizations from any cause facilitate the monitoring of ACE-I treated patients for serum creatinine and potassium levels, whether patients are before, at the beginning or on long established treatment with ACE-I+NSAIDs with/without diuretics.

Our primary objectives were (1) to determine the prevalence at hospital discharge of concomitant use of ACE inhibitors with NSAIDS and/or diuretics and (2) to identify factors associated with the prescription of these combinations. The secondary objectives were to evaluate the extent of serum creatinine and potassium monitoring in patients treated with ACE-I and these associations and to determine the prevalence of values above the upper normal limit (UNL) in monitored patients.

Patients and Methods

Database

Our retrospective analysis used data collected between January 1st, 2013 and June 30th, 2014 in a large academic hospital from Cluj-Napoca, Romania. Data on all inpatient admissions during our study period were considered for the analyses. For each patient, we had access to demographic information, diagnostics, investigations (laboratory and clinical), interventions, treatment during hospitalization period provided by the hospital and prescription details at discharge. Diagnostics are coded with International Classification of Diseases (ICD)-10[26] and medications are registered as both generic and brand names.

Study Population and Exposure Assessment

The addressability of the hospital units is Cluj County mainly but also other counties in Transylvania region. Of all patients admitted to the hospital, we extracted the ones that had been prescribed ACE-I at discharge. We included patients with ACE-I but no NSAIDs or diuretics in the ACE-I group, patients with ACE-I/NSAIDs in double therapy (DT) group and patients with ACE-I/NSAIDs/diuretics in the triple therapy (TT) group. Concurrent use of ACE-I, NSAIDs and diuretics was deemed when these medicines were prescribed at the discharge moment, even on more than one form, but for overlapping period of time. We included in the analysis the latest laboratory values determined before discharge. All ACE-I, NSAIDs and diuretics licensed in Romania during the study period were comprised in the analysis (see Appendix 1 for the complete list).

Statistical Analysis

Descriptive statistics for patients in the 3 groups were conducted to evaluate differences related to demographic characteristics (age, sex), co-morbid conditions, medications, and laboratory monitoring. Co-morbid conditions were determined using the Elixhauser modified by Quan al-

gorithm[27]. We quantified the number of patients with serum creatinine and potassium levels above the UNL.

Given the small number of patients treated with DT and TT, our final analysis combined the two groups to identify factors associated with such therapies. We performed a logistic regression analysis with backward elimination to identify significant predictors of combination therapy.

Ethics

We performed an observational study on anonymous data which under Romanian legislation does not need to be approved by an Ethic Committee.

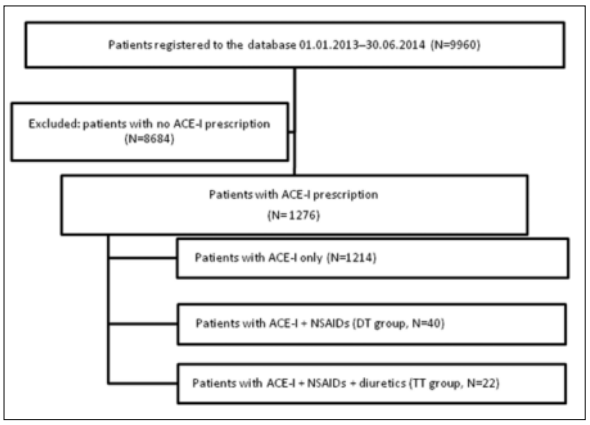

Figure 1. Flow diagram of the total patient cohort. N: number of patients in a given group; ACE-I: angiotensin-converting enzyme inhibitors; NSAIDs: non-steroidal anti-inflammatory drugs; DT: double therapy; TT: triple therapy.

Results

Patients and Prevalence of Target Drug Associations

Of the total number of unique patients (N = 9960) admitted during the study period, 1276 patients had prescriptions for an ACE-I at discharge and hence were eligible to be included in this analysis. 1214 patients were prescribed ACE-I, 40 patients were prescribed ACE-I associated with NSAIDs (a prevalence of 3.13% of the patients prescribed with ACE-I) and 22 patients (1.72% of the patients prescribed with ACE-I) were prescribed ACE-I associated with NSAIDs and diuretics (Figure).

Patients prescribed DT and TT were younger than those prescribed only ACE-I. Although women represented the majority of patients in all three groups, there were differences from one group to another (Table I). The diagnostic of congestive heart failure was the one present in all 3 groups, in higher percentage in the DT group.

Table I. Demographic characteristics.

Characteristic	ACE-I (N = 1214)	DT (N = 40)	TT (N = 22)
Age, years (mean ± SD)	67.89 ± 11.66	62.07 ± 11.06	62.59 ± 9.69
Sex, female, n (%)	731 (60.21)	21 (52.50)	18 (81.82)
Comorbid conditions, n (%)			
Myocardial infarction	3 (0.25)	–	–
Congestive heart failure	128 (10.54)	6 (15.00)	2 (9.09)
Peripheral Vascular Disease	18 (1.48)	–	–
Cerebrovascular Disease	42 (3.46)	1 (2.50)	–
Connective Tissue Disease/Rheumatic Disease	12 (0.99)	–	1 (4.55)
Diabetes without complications	12 (0.99)	–	–
Diabetes with complications	2 (0.16)	–	–
Renal Disease	10 (0.82)	–	–
Medications, n (%)			
Beta–blocker	53 (4.37)	2 (5.00)	–
ARB	2 (0.16)	–	–
Statin	128 (10.54)	1 (2.5)	3 (13.64)
CCB	20 (1.65)	–	1 (4.55)
Patients with serum laboratory values higher than UNL, n (%)			
Glucose	353 (29.08)	11 (27.50)	8 (36.36)
Sodium	50 (4.12)	2 (5.00)	1 (4.55)
Urea	409 (33.69)	11 (27.50)	4 (18.18)

ACE-I: angiotensin-converting enzyme inhibitors; DT: double therapy; TT: triple therapy; N: number of patients in a given group; SD: standard deviation; n: number of patients in a given category; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; UNL: upper normal limit; Glucose UNL: 110 mg/dL; Sodium UNL: 145 mmol/L; Urea UNL: 45 mg/dL.

Only 1 patient from the TT group had a Connective Tissue Disease/Rheumatic Disease and none from the DT group. Other cardiovascular medications were mostly encountered in the ACE-I group, but little present in the patients in the DT and TT groups (Table I).

Serum Creatinine and Potassium Monitoring

Serum creatinine and potassium were monitored for the great majority of patients from all groups, with the highest figures in the ACE-I group. The highest percentage of hyperkalemia was found in the DT group (10% of the patients) and of serum creatinine above UNL in the TT group (45.45%) (Table II).

Logistic Regression

In unadjusted analyses, younger patients were more likely to be prescribed a combination therapy. In addition, combination therapy was associated with laboratory testing for glucose, sodium, creatinine and potassium during hospitalization (Table III). In the adjusted analysis, age (p = 0.0008, OR = 0.96 [0.94-0.98]) and laboratory testing for serum potassium levels (not tested *vs* tested with normal values, p=0.0004, OR=3.67 [1.91-7.04]) remained statistically significant as factors associated with combination therapy prescribed at discharge.

Discussion

Strategies to enhance greater evidence-based use of ACE-I through the analysis of the existing observational data was identified by Crowley et al[28] as top research priority for ACE-I and angiotensin II receptor blockers for treatment of ischemic heart disease. To our knowledge, this is the first study investigating under Romanian real life conditions, the use of ACE-I associated with NSAIDs and diuretics following this trend of using existing observational data.

We considered that an analysis of the real life data on these combinations would be useful as, although patients are at higher risk of renal disturbances within the first 3 weeks of therapy with ACE-I, ARF was reported between 4 days and 2 years after starting therapy with ACE-I/NSAID or ACE-I/NSAID/diuretic[22,29,30].

Our results showed that 3.13% of the patients prescribed with ACE-I had also been prescribed NSAIDs and 1.72% of the patients prescribed with ACE-I and NSAIDs had also been prescribed diuretics. According to the literature, 1.85% of the patients who had been prescribed ACE-I and NSAIDs developed ARF. The importance of these small percentages comes from the perspective of the seriousness of the possible outcome, ARF being most of the times reversible after discontinuation of treatment but could also lead to permanent renal damage and even death[22,28,29,31,32]. It was recently showed by Lapi et al[24] that the patients on triple therapy have 31% higher rates of developing ARF and in another case-control study[28] that adding an NSAID to the therapy with ACE-I increases the chances of hospitalization due to ARF by 2.2 folds. In our study the indicators for renal damage that could be taken into account would be the serum creatinine and potassium levels. These were monitored for a great part of the patients in all 3 groups of ACE-I users, but unexpectedly lower in the DT and TT groups and thereby we can conclude that no special consideration was given to the risk of taking NSAIDs and diuretics together with ACE-I. This is consistent with the findings of Bootsma et al[33],

Table II. Patients on ACE-I therapy with serum creatinine and potassium monitored.

	ACE-I (N = 1214)	DT (N = 40)	TT (N=22)	*p* value
Patients with laboratory values monitored, n (%)				
Potassium	1129 (93.00)	30 (75.00)	18 (81.82)	< 0.0001
Creatinine	1159 (95.47)	35 (87.50)	20 (90.91)	0.045
Patients with laboratory values higher than UNL, n (%)				
Potassium	72 (5.93)	4 (10.00)	1 (4.55)	0.54
Creatinine	259 (21.33)	6 (15.00)	10 (45.45)	0.01

ACE-I: angiotensin-converting enzyme inhibitors; DT: double therapy; TT: triple therapy; N: number of patients in a given group; n: number of patients in a given category; Potassium UNL: 5.1 mmol/L; Creatinine UNL: 1.2 mg/dL; p-value was calculated using chi-square analysis for differences between ACE-I group and DT/TT groups.

Table III. Factors associated with the prescription of DT and TT.

Explanatory variable	DT/TT	
	Unadjusted OR	95% CI
Age	**0.96**	**0.94-0.98**
Sex (ref=male)	1.12	0.66-1.9
Congestive heart failure	1.26	0.58-2.7
Cerebrovascular Disease	0.46	0.06-3.38
Connective Tissue Disease/Rheumatic Disease	1.64	0.21-12.83
Beta-blocker	0.73	0.17-3.07
Statin	0.58	0.21-1.64
CCB	0.98	0.13-7.41
Glucose tested		
High vs normal	1.2	0.68-2.14
Not tested vs normal	**3.03**	**1.28-7.13**
Sodium tested		
High vs normal	1.44	0.43-4.79
Not tested vs normal	**3.95**	**2.08-7.48**
Urea tested		
High vs normal	0.69	0.37-1.26
Not tested vs normal	2.30	0.98-5.36
Creatinine tested		
High vs normal	1.43	0.78-2.59
Not tested vs normal	**2.94**	**1.26-6.87**
Potassium tested		
High vs normal	1.70	0.66-4.44
Not tested vs normal	**4.05**	**2.13-7.70**

DT/TT: group including patients with either double or triple therapy; OR: odds ratio; CI: confidence interval; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; Normal: serum levels in the normal range; High: serum levels above the upper normal limit; Values with statistically significant associations are written in bold.

that serum creatinine monitoring is less often performed in the high risk patients. Potassium monitoring was less frequent than creatinine monitoring in the DT and TT groups and with lower number of hyperkalemia cases. DT group had the highest percentage of hyperkalemic patients and TT group had the highest percentage of serum creatinine above UNL.

The findings above could suggest that the monitoring of the serum creatinine and potassium was done extensively, but the abnormal results of the serum creatinine and potassium levels were not followed by the precaution of not prescribing the combinations that could lead to renal damage. This could be due to the fact that serum creatinine and potassium level rise could have been only mild. For patients on ACE-I a rise in serum creatinine of less than 30% from the initial value is considered acceptable[34] and for potassium a level ≤ 5.5 mmol/L it is accepted[15,16]. In this case, if patients were monitored regularly and the benefit/risk ratio was considered positive, the physicians might have decided to keep the combinations in patients' therapy. However, when we accounted for multiple variables in our adjusted logistic regression analysis, this showed that younger patients and patients not tested for serum potassium were more likely to have the combination therapy prescribed at discharge. Like this, 2 of the precautions required in case of associating ACE-I with NSAIDs and/or diuretics (older age and serum potassium monitoring) were taken into account when prescribing the combinations.

Another explanation could be that patients were monitored for serum creatinine and potassium as routine procedure and prescribers were not aware of the renal risk posed by the combinations and so they kept the combinations in patients' therapy.

Strengths and Limitations

The strength of our study comes from using the real life data collected for a varied population and bringing new information on the prescribing and monitoring habits of the ACE-I users in our region.

The limitations of our study were mainly due to the retrospective nature and availability of data in the database. Data regarding the treatment during hospitalization might have not been complete, as often patients are using medications provided independently from community pharmacies, due to hospital lack of funding. As a consequence we do not know how many patients were on ACE-I therapy during hospital stay and for this reason we performed the analyses on the discharge prescriptions, which represent the most accurate way to evaluate patients' therapy in our database. The use of some medications (especially NSAIDs, which may have been purchased without prescription) might be underestimated.

The effect of the drug combinations and also the reason for prescribing the double or triple therapy to patients with elevated serum creatinine and potassium levels could not be determined as per the retrospective design of the study. Also, it would have been interesting to determine how many patients were discontinued with one of the drugs due to high creatinine/potassium levels and not prescribed the combinations at discharge, but database limitations did not allowed us to.

Conclusions

The prevalence of patients receiving double or triple combination of potentially interacting ACE-I, NSAIDs and diuretics was relatively low and the monitoring of these patients during hospitalization was high. Still, an important percentage of patients were prescribed triple therapy even though the serum creatinine levels were above the UNL. Further studies are needed to determine the exact values of creatinine for which the combinations are prescribed and to improve physicians' knowledge on specific risks posed by these potential DDIs.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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