Rates and Predictors of Angiotensin-Converting Enzyme Inhibitor Discontinuation Subsequent to Elevated Serum Creatinine

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005181
Article Type:	Research
Date Submitted by the Author:	04-Mar-2014
Complete List of Authors:	Jackevicius, Cynthia; Western University of Health Sciences, Wong, Joyce Aroustamian, Irina Gee, Manyee Mody, Freny
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	INTERNAL MEDICINE, Adverse events < THERAPEUTICS, Chronic renal failure < NEPHROLOGY

Rates and Predictors of Angiotensin-Converting Enzyme Inhibitor Discontinuation Subsequent to Elevated Serum Creatinine: A Cohort Study

Cynthia A. Jackevicius, BScPhm, MSc, PharmD[1, 2, 3, 4], Joyce Wong, PharmD[1], Irina Aroustamian, PharmD[1], Manyee Gee, PhD[2], Freny Vaghaiwalla Mody, MD FACC[2,6]

Department of Pharmacy Practice and Administration, Western University of Health Sciences[1], Department of Medicine & Pharmacy, Veteran Affairs Greater Los Angeles Healthcare System[2], Institute of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto[3], Institute for Clinical Evaluative Sciences[4], University Health Network[5],David Geffen School of Medicine, University of California Los Angeles[6]

Corresponding author:

Freny Vaghaiwalla Mody, MD

VA Greater Los Angeles Healthcare System & David Geffen School of Medicine at UCLA

Phone: 310-268-3839 Fax: 310-268-4391 Email: freny.mody@va.gov

Running Title: Predictors of ACEI Discontinuation

Word count: 2602

Key Words: ACE inhibitors, serum creatinine, renal dysfunction, drug utilization, chronic kidney disease

Abstract

Background: Angiotensin-converting enzyme inhibitors (ACEI) are underutilized despite cardiovascular benefits, in part due to concerns of elevations in serum creatinine (SCr). We evaluated rates and predictors of ACEI discontinuation after SCr elevation post-ACEI initiation since limited data are available that examine this issue.

Methods: In this retrospective, cohort study, we estimated the rates and factors associated with ACEI discontinuation subsequent to SCr elevation after ACEI initiation, and for patients with baseline SCr>2mg/dL, the change in SCr associated with chronic use. All patients initiating ACEI from January 1/02 to December 31/04 with 3 months SCr were included, and divided into 3 groups (SCr<1.5,1.5-2.0 and>2.0). Predictors were identified using multivariate logistic regression modeling.

Results: At 3 months follow-up, the mean increase in SCr post-ACEI initiation was 26%, ranging from -0.01 mg/dL to 0.42 mg/dL varying according to level of baseline renal function. ACEI discontinuation was highest in patients with elevated baseline SCr (11.5%) compared with those with SCr>1.5 (5.4%) and those with SCr 1.5-2.0 (7.4%). Patients that were male, or with heart failure were less likely to discontinue ACEI after an elevation of serum creatinine post-ACEI initiation, while those taking NSAIDs, diuretics and beta-blockers were more likely to discontinue ACEI.

Conclusion: Serum creatinine increases <30% on average within 3 months of ACEI initiation, with subsequent discontinuation rates varying by baseline SCr. Elevation in SCr was not associated with ACEI discontinuation rates. Despite an acute increase in SCr, chronic ACEI use was associated with a decrease in SCr in most patients with SCr >2mg/dL.

Article Summary

Strengths and Limitations of this Study

- To date, no studies have evaluated both the acute elevation in serum creatinine post-ACE inhibitor initiation and the predictors of subsequent discontinuation following an elevated serum creatinine.
- This study confirmed the mean increase in serum creatinine after ACE inhibitor initiation is 26%, varying with baseline renal function.
- Factors other than elevation in serum creatinine were associated with ACE inhibitor discontinuation, including, female sex, absence of heart failure, and use of NSAIDs, diuretics or beta-blockers.

Introduction

Current guidelines recommend angiotensin-converting enzyme inhibitors (ACEIs) as the standard of therapy for post-myocardial infarction, chronic heart failure (CHF), and diabetes due to the substantial endothelial, cardiovascular and renal protection.[1-4] Furthermore, ACEIs have also been shown to be a beneficial therapy for hypertension.[5] The renal protective mechanism of ACEIs vary, ranging from improving vascular endothelium function to vasodilatation effects.[6] Despite evidence from numerous trials showing the benefits of improved morbidity and mortality by ACEIs, these drugs are still underutilized.[1-4, 7-10] Clinicians are reluctant to start and continue with adequate dosing of ACEIs primarily due to concerns of elevations in serum creatinine (SCr), particularly in patients with CKD despite evidence that this group of patients benefits from ACEI.[10,11] The most probable cause of an acute elevation in SCr post-ACEI initiation is the decrease in vasoconstriction in the efferent arterioles resulting in pressure reduction in the glomerular apparatus and decreased glomerular filtration rate (GFR).[6] However, homeostasis of hemodynamics occurs with long-term use with gradual return and improvement in GFR.[7] Even with concerns of an acute rise in SCr, ACEIs provide long-term benefits with some data suggesting an improvement in renal function with decrease in SCr with long-term use.[7,11,12] In heart failure (HF) patients, RCTs estimate that between 2.4% and 16% of patients experience an acute increase in SCr of > 0.5mg/dL after ACEI initiation, with improvement with chronic use.[8-9] In a practice-based setting, Bakris and colleagues demonstrated a mean increase in SCr of 30% in a hypertensive population using ACEIs with the increase stabilizing within 2 months after ACEI initiation. This rise in SCr is reversible upon discontinuation and is less likely to occur beyond 4 weeks of initiation.[13,14] HF patients suffer a more pronounced increase in SCr with ACEIs due to a reduction of blood flow to the kidneys from reduced cardiac output, diuretic

use, and vasodilation effect. Although the acute increase in SCr seen in HF patients ranges from 75% to 200% from baseline after ACEI initiation, this elevation was suggested as being acceptable since ACEIs have proven benefits in decreasing mortality in this population.[8,15]

The frequency of the discontinuation rate of ACEI and the determinant factors associated with discontinuation in the real world setting has not been fully characterized. The CONSENSUS II HF trial reported a discontinuation rate of 4.6% with enalapril subsequent to the rise of SCr, while a meta-analysis of randomized controlled trials of HF patients found an ACEI discontinuation rate of 13.8%, of which only 0.4% was attributed to an increase in SCr.[7,16]

To date, no studies have evaluated both the acute elevation in SCr post-ACEI initiation and the predictors of subsequent discontinuation following an elevated SCr. Assessment of these patterns may provide insight into clinician decision making in a real world setting. The objective of our study was to assess the rates and predictors of ACEI discontinuation following an increase in SCr post-ACEI initiation, each according to baseline renal function.

Methods

We conducted a retrospective observational cohort study of all outpatients initiating an ACEI between 2002 and 2004 at the Veterans Affairs Greater Los Angeles Healthcare system (VAGLAHS). The Veterans Health Information System and Technology Architecture (VISTA) database was used to gather patient information (demographics, medication use, allergies, comorbidities, and lab results).

Initiation of ACEI was defined as the dispensing of an outpatient prescription for an ACEI with no previous record of ACEI use in the past 6 months. The following ACEI information was collected: initiation date, discontinuation date, adverse drug reactions (ADR), dosage, dosing frequency and the total daily dose. To determine the prevalence of a change in SCr, SCr was recorded at baseline (within 6 months of ACEI initiation) and 3-months (10-14 weeks) post-initiation. A 0.5mg/dL increase and 30% increase in SCr was considered to be clinically important since several studies have used this as a reference point to define a decrease in renal function.[5-6,14] Discontinuation of ACEI was defined as no refills within 90 days after the last filled prescription which allowed a lenient grace period for patients obtaining late refills. Patients were stratified into three baseline SCr groups (group 1: SCr <1.5mg/dL; group 2: 1.6-2.0mg/dL; and group 3: >2.0mg/dL) for analysis. We assessed above and below 0.5mg/dL and 30% to determine the threshold at which discontinuation occurred and to analyze possible differences in threshold by group. For those patients with a baseline SCr >2mg/dL and continued on an ACEI, SCr was recorded at 1-year to detect any changes post-initiation. Comorbidities (defined by ICD-9 codes: 425-cardiomyopathy, 428-congestive heart failure, 250-diabetes, 410-414-coronary artery disease, 274-gout, 401-hypertension) and concurrent use of NSAIDs, diuretics, and beta-blockers were documented to determine potential factors associated with an

increase in SCr and the discontinuation of ACEIs. Concomitant medication use was defined as having an active prescription within 1 month of the index date of ACEI prescription through the time of discontinuation.

The endpoints of this study were: the proportion of patients with a significant increase in SCr post-ACEI initiation at 3-months follow-up defined as >0.5mg/dL or >30% of baseline by group; the proportion of patients with ACEI discontinued following a rise in SCr by group; the threshold of increase in SCr associated with ACEI discontinuation, stratified by baseline SCr groups; factors (patient characteristics, comorbidities, and concurrent medications) that may be associated with discontinuation of ACEIs; and the change in SCr in patients with baseline SCr >2mg/dL and continued on ACEIs for 1 year.

Continuous baseline characteristics were expressed as the mean +/-SD or median; and categorical baseline characteristics were expressed as a proportion . Chi square test was used to compare the discontinuation rate after detecting a rise in SCr post-ACEI use between groups and to compare the threshold of increase in SCr prior to discontinuation between groups. A multiple logistic regression model was constructed to identify the factors associated with SCr elevation subsequent to ACEI initiation and ACEI discontinuation. The univariate model included patient characteristics (i.e., age, gender), comorbidities (i.e., diabetes, hypertension, coronary artery disease, chronic heart failure, systolic blood pressure (SBP)<100mmHg, gout), concomitant NSAID use, diuretic use (i.e. thiazide, loop, K+ sparing), beta-blocker use, and significant SCr elevation defined as >0.5mg/dL or >30% of baseline. Variables with p <0.2 from the univariate model were placed in a multiple logistic regression model using stepwise selection. Odds ratio with 95% confidence interval were estimated from the regression model. A p-value <0.05 was considered statistically significant. All results were analyzed using SAS [Version 8.2, SAS

Institute, Cary, NC]. This was a non-funded study approved by the institutional review board at VAGLAHS and Western University of Health Sciences.

Results

A total of 3,039 patients were initiated on an ACEI between January 2002 and December 2004 and had a SCr measured within 6 months prior to and 3 months after initiating an ACEI. (Figure 1) The average age was 65.0 years and 97.6% were male with a baseline SCr of 1.28+/- 0.86 mg/dL. Patients were stratified into three groups based on baseline SCr: Group 1 consisted of 2,497 patients with a SCr of <1.5 mg/dL (mean of 1.05+/- 0.19); group 2 had 377 patients with a SCr of 1.5-2.0 mg/dL (mean of 1.67 +/-0.16); and group 3 had 165 patients with a SCr of >2.0 mg/dL (mean of 3.75+/-2.44). (Figure 1) Hypertension (44.2%) and diabetes (28.5%) were the most frequently documented comorbidities, and the most common concomitant medications were diuretics and beta-blockers. (Table 1)

On average, patients had a follow-up SCr available at a median of 3.8 months post-ACEI initiation. The mean changes in SCr at 3 months follow-up were 0.05 +/-0.30 mg/dL, -0.01+/- 0.31 mg/dL, and 0.42 +/-2.20 mg/dL respectively, by group. There was no change in median SCr at 3 months follow-up for all three groups. Counting only those patients with an increase in SCrfor all 3 groups, the average percent increase in SCr prior to ACEI discontinuation was 25.98% +/-41.72 with a median of 13.49%.

At 3 months, the discontinuation rate of ACEI with or without concomitant SCr rise of >0.5mg/dL was highest in group 3 (11.5%), followed by group 2 (7.4%) and group 1 (5.4%) (p< 0.001) (Figure 1). In the multiple logistic regression model the variables significantly associated with a greater likelihood of ACEI discontinuation were the use of NSAIDs, diuretics, and beta-blockers. (Table 2) Of note, a significant increase in SCr (defined as >0.5mg/dl or >30 %) was not associated with ACEI discontinuation. (p=0.498 in the univariate model). A history of CHF, SBP of <100mmHg at baseline and male sex were significantly associated with a reduced

likelihood of ACEI discontinuation.

Changes in SCr were further evaluated based on absolute and percent change. Table 3 depicts the change in SCr subsequent to ACEI discontinuation, at the threshold of 0.5mg/dL and 30% increase in SCr. Group 3 had the highest mean increase in SCr as both absolute and percent change. A majority of the patients who experienced an increase in SCr had a change less than both 30% increase and 0.5mg/dL increase prior to discontinuation. Thus, most ACEI discontinuation did not occur following a clinically significant increase in SCr (>30% or >0.5mg/dL above baseline).

Of the 165 patients with a baseline SCr >2.0mg/dL (mean 3.75+/-2.44), only 50 patients (30.3%) were continued on an ACEI at 1 year. Of the 405 patients who discontinued ACEI, 165 patients discontinued within 90 days of a SCr result. A total of 69 of the 165 (41.8%) patients experienced a decrease in SCr prior to discontinuation (average decrease was 1.04 +/- 1.77) and 76 (46.0%) of the patients experienced an increase (average increase was 1.86+/-0.87) and 20 (12.1%) patients experienced no change from baseline prior to discontinuation. Of the 50 patients who continued on ACEIs, only 35 patients had a follow-up in SCr at 1 year and their mean decrease in SCr was -0.24 +/-0.56 with a median decrease of -0.01mg/dL. Of these 35 patients, one (2.86%) had a larger increase in SCr (from 2.5 to 9.1 mg/dL) as compared with the remaining patients in the group (Figure 2). Excluding this subject as an outlier with a rise in SCr at 1 year that is unlikely due to ACEI, resulted in a mean decrease in SCr at 1 year in group 3 of -0.44+/-1.96 with a median of -0.01mg/dL. While the majority (54.28%) of patients in Group 3 experienced a clinically significant absolute (>0.5 mg/dL) increase in SCr of 0.98+/-1.58 compared with a baseline of 3.75+/-2.44, the 27% relative increase was not above the generally accepted threshold of >30%. Forty percent of this group experienced a decrease in SCr of

1.19+/-2.26 compared to baseline 3.75+/-2.44 and 5.7% had no change in SCr at 1-year follow-up. The average magnitude of decrease in SCr was greater than the average magnitude of increase in SCr with long term use of ACEI (1.19+/-2.26 mg/dL decrease versus 0.98 +/-1.58mg/dL increase, $p<0.001$) in patients with SCr>2 mg/dL.

Discussion

In our study, which had a large hypertensive population, we showed an increase in SCr of approximately 26% post-ACEI initiation. Previous studies have documented similar acute increases in SCr of 30% in hypertensive patients and up to 200% in HF patients.[13,14] It has been suggested that ACEI discontinuation be considered if an increase in SCr exceeds 30% with ACEI use since renal function may be compromised beyond this increase and the benefits of ACEI may not outweigh the risks.[13] Our study showed that the majority of ACEI discontinuation occurred with an increase of less than 30% in SCr, thus suggesting that the threshold of concern for renal deterioration is lower in clinical practice or other factors may be more likely associated with discontinuation.

According to previous trials, a change in SCr of >0.5mg/dL may also be considered clinically significant.[8,9] The majority of the patients that discontinued ACEI in our study experienced a <0.5mg/dL change in SCr. Our study further suggested that on average, SCr was not greatly affected by ACEI since all three groups had no change in median SCr over 3 months. Thus, the discontinuation of ACEI in our population was most likely attributed to drug intolerances, such as, cough, other comorbidities, and concomitant medications, rather than the change in SCr. Only 6% of patients in the lower baseline SCr group suffered from documented cough or nausea leading to the discontinuation of ACEI. The adjusted regression analysis demonstrated that concomitant use of NSAIDs, diuretics, and beta-blockers were factors associated with a higher likelihood of ACEI discontinuation. This may be anticipated since both NSAIDs and diuretics have been documented to decrease renal function and exacerbate SCr elevations when used concomitantly with ACEI.[12] However, this may have led to the discontinuation of ACEI at a lower threshold of SCr increase. If discontinuation of ACEI was

indeed at a lower threshold than that traditionally accepted (SCr rise >0.5 or 30%), improved awareness for clinicians of the short duration of an acute rise in SCr when initiating ACEI, and dose reduction or reassessment of need for concomitant NSAIDs or diuretics may be beneficial strategies. This may confer better clinical outcomes for patients, particularly diabetic patients who would benefit from the nephroprotective actions of ACEI. Contrary to previous findings, beta-blockers were associated with a higher likelihood of discontinuation with concomitant use of ACEI in our study rather than exerting a renoprotective effect with ACEI use.[14] Male sex, CHF history, and SBP of <100mmHg were also associated with a lower chance of ACEI discontinuation. We postulated that patients with CHF and SBP <100mmHg were more likely to be maintained on an ACEI since HF studies have documented benefits of ACEI in decreasing morbidity and mortality.[1,7-8]

In patients with baseline SCr >2 mg/dL, our study showed that SCr can increase, decrease, or remain unchanged with long term ACEI use. Even though the majority of these patients experienced an acute increase in SCr, our results support ACEI use in renal impaired patients since the median change in SCr decreased and in the long term, the magnitude of decrease was much more impressive than the magnitude of increase. Our study is consistent with the prospective findings by Hou et al, that found despite the acute increase in SCr, long term improvement in SCr occurs in many patients with impaired renal function at baseline.[11] The use of ACEI is warranted in this group of patients, along with close monitoring of renal function and electrolytes since benefits were documented in this study as well as in previous studies.[11-12]

Limitations of our study include its retrospective study design with potential for confounding.[20] In addition, the electronic medical records may not be complete and accurate as

is a limitation of any study relying on retrospective documentation. Finally, the sample size of patients with SCr >2 mg/dL was small both pre- and post-follow-up of SCr. However, the large population-based sample increases the generalizability of the findings.

Many clinicians may be reluctant to prescribe ACEIs to all eligible patients due to concerns of an elevation in SCr. Based on this real world study, the magnitude of increase in SCr post-ACEI initiation was lower than the commonly used threshold of 30%. Comorbidities and concomitant medications that may increase SCr or a low threshold of concern for SCr elevations may be more likely associated with ACEI discontinuation rather than a clinically meaningful rise in SCr. The importance of monitoring should be emphasized to detect any drastic increase in SCr >30% and to manage potential adverse drug reactions. Identification of other factors that may increase SCr, such as, NSAID use, diuretic use, and volume depletion should be considered before an ACEI is discontinued. Education may be required to change practice patterns in patients with impaired baseline renal function in order to confer the clinical benefit of chronic ACEI nephroprotection.

Author Contributions:

Jackevicius: Concept/design, data interpretation, critical revision of article, approval of article, statistics

Wong: Design, data analysis/interpretation, drafting article, approval of article, statistics

Aroustamian: Data analysis, critical revision of article, approval of article, statistics

Gee: Data collection/interpretation, critical revision of article, approval of article

Mody: Concept/design, data interpretation, critical revision of article, approval of article

Funding: None.

Data Sharing: No additional data available.

Acknowledgments: None.

Table 1. Baseline characteristics of cohort (n= 3,039)

Characteristic	Value*	
Age (years, mean+/-SD, median)	65 +/-12, 65	
Gender (n, %)		
Male	2966	97.6%
Ethnicity (n, %)		
African American	414	13.6%
Caucasian	670	22.0%
Hispanic	44	1.45%
Other	341	11.2%
Not documented	1570	51.7%
Baseline serum creatinine (mg/dL, mean+/-SD, median)	Mean+/-SD, Median	
Overall (n=3,039)	Overall: Overall: 1.28 +/- 0.86, 1.10	
Group 1 : < 1.5mg/dL (n=2,497)	Group 1 : < 1.5mg/dL = 1.05 +/-0.19, 1.03	
Group 2 :1.5-2.0 mg/dL (n=377)	Group 2 :1.5-2.0 mg/dL = 1.67 +/-0.16, 1.6	
Group 3 : > 2 mg/dL (n=165)	Group 3 : > 2 mg/dL = 3.75+/-2.44, 2.7	

Co-morbidities (n, %)	n	%
Diabetes Mellitus	866	28.5 %
Hypertension	1343	44.2 %
Chronic Heart Failure	177	5.8 %
Coronary Artery Disease	445	14.6 %
Gout	69	2.3 %
SBP <100 mmHg	88	2.9 %
Concomitant Use of:		
NSAIDs	1053	34.6 %
Diuretics (total)	1771	58.3 %
Loops	773	25.4 %
Thiazides	1264	41.6 %
K- sparing	239	7.9 %
Beta-blockers	1601	52.7 %

*Values are reported as mean +/- SD; median unless otherwise noted

Table 2. Multivariate odds ratios for discontinuation of angiotensin-converting enzyme inhibitors subsequent to elevation of SCr post-ACEI initiation

Co morbidities	Multivariate Odds Ratio (95% CI)	P value
Age	1.00(1.00-1.00)*	0.452
Gender (Male)	0.74 (0.57-0.97)	0.028
Coronary Artery Disease	0.89 (0.79-1.01)	0.061
Chronic Heart Failure	0.79 (0.63-0.99)	0.041
SBP <100mmHg	0.55 (0.40-0.76)	<0.001
Concomitant use of:		
NSAIDs	1.23(1.13-1.34)	<0.001
Diuretics	1.07(0.87-1.31)	<0.001
Thiazides	1.18 (0.98-1.42)	0.084
Loops	0.99 (0.84-1.18)	0.925
Beta-blockers	1.17(1.08-1.27)	<0.001

* Values rounded from 0.999(0.995-1.002)

Table 3. Distribution in magnitude of elevation of serum creatinine in patients who discontinued angiotensin-converting enzyme inhibitors within 90 days post-initiation

Threshold of increase in SCr	Group 1 < 1.5mg/dL n=135	Group 2 1.5-2mg/dL n=28	Group 3 > 2mg/dL n=19	P value
≤ 0.5mg/dL increase	124 (91.85) 0.17 +/-0.11; 0.10	25(89.29) 0.18+/- 0.8; 0.17	8 (42.10) 0.27+/- 0.14; 0.3	<0.001
> 0.5mg/dL increase	11 (8.15) 1.23 +/- 0.99; 0.80	3 (10.71) 0.87 +/-0.25; 0.9	11 (57.90) 2.95 +/- 2.93; 1.7	<0.001
≤ 30% increase	114 (84.45) 14.15%+/- 6.85%; 11.11%	25 (89.29) 10.22%+/- 4.6%; 9.25%	12 (63.15) 12.82%+/-6.64%; 12.99%	0.01
> 30% increase	21 (15.55) 89.25%+/-81.07%; 46.67%	3 (10.71) 45.83% +/- 8.78%; 45%	7 (36.85) 100.32%+/-69.10%; 88.23%	<0.001

*Values are n (%) and mean+/- SD; median

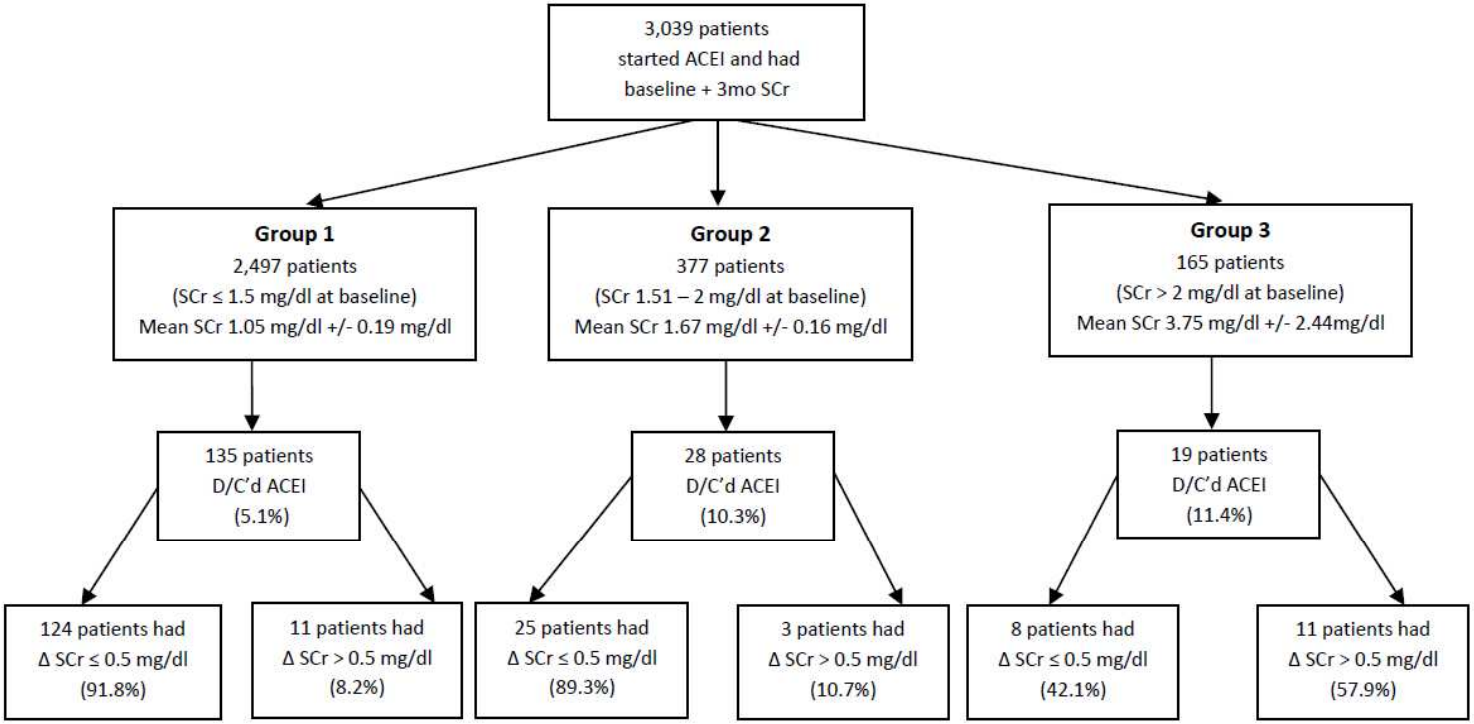
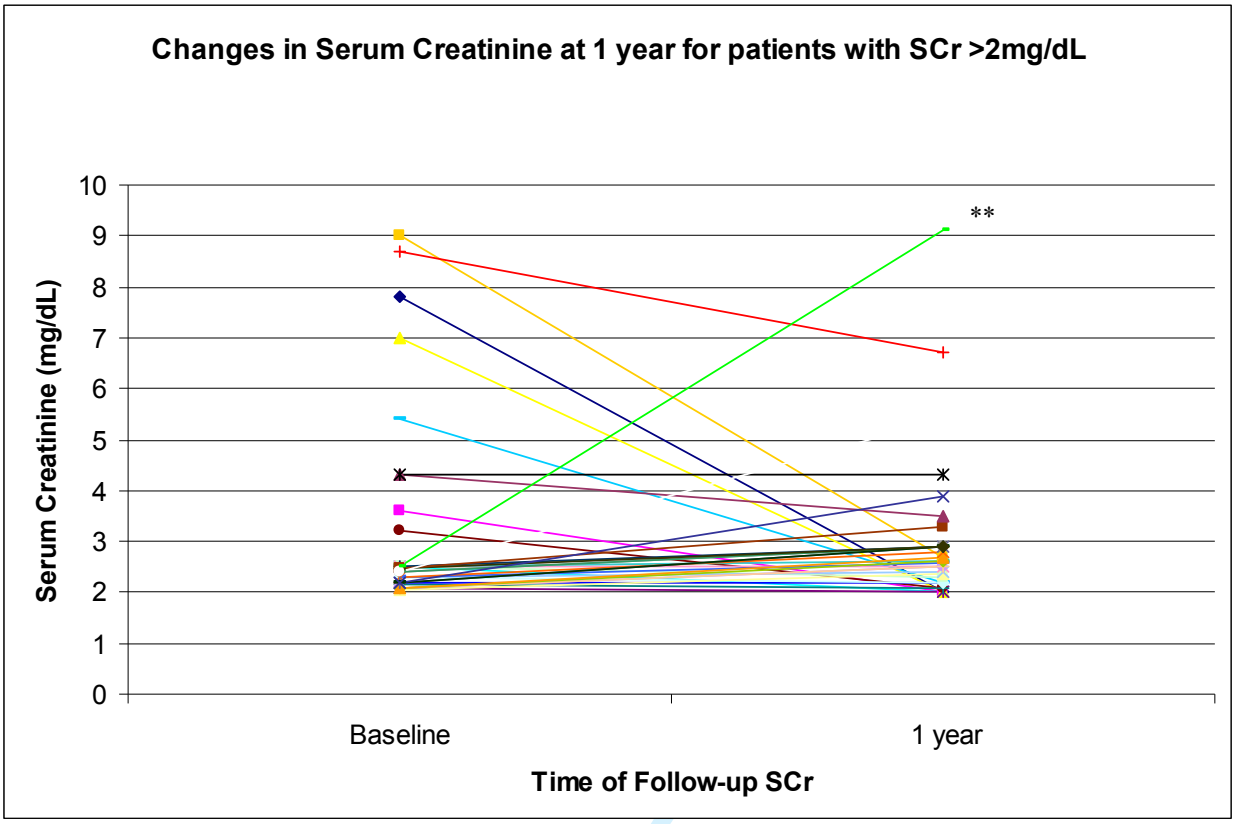


Figure1. Profile of patients included in analysis.
ACEI: Angiotensin-Converting Enzyme Inhibitors; ADR: Adverse Drug Reaction; DIC'd: discontinued; SCr: Serum Creatinine.

Figure 2: Changes in Serum Creatinine at 1 Year for Patients with SCr>2 mg/dL



*The mean change in serum creatinine was -0.24 +/- 0.56 mg/dL with a median of -0.01mg/dL. Excluding outlier (**) resulted in a mean in change serum creatinine of -0.44 +/- 1.96 mg/dL with a median of -0.01mg/dL.

N= 35

References

1. Hung SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web Site. Available at: http://www.acc.org/clinical/guidelines/failure//index.pdf.
2. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA Guidelines for the management of patients with ST-elevation myocardial infarction- Executive Summary. J Am Coll Cardiol 2004;44:671-7.
3. American Diabetes Association. Standards of Medical Care in Diabetes-2014. Diabetes Care 2014;37;S5-S13.
4. Marre M, Leblanc H, Suarez L, et al. Converting enzyme inhibition and kidney function in normotensive diabetic patients with persistent microalbuminuria. BMJ 1987;294:1448-52.
5. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 2003;289:2560-72.
6. Matsuda H, Hayashi K, Arakawa K, et al. Zonal heterogeneity in action of angiotensin-converting enzyme inhibitor on renal microcirculation. J Am Soc Nephrol 1999;10:2272-82.
7. Ahmed A, Kiefe C, Allman R, et al. Survival benefits of angiotensin converting enzyme inhibitors in older heart failure patients with perceived contraindications. J Amer Ger Soc 2002;50:1659-66.

8. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1986;316:1429-35.
9. The SOLVD Investigators. Effects of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1987;325:293-302.
10. Ghali JK, Giles T, Gonzales M, et al. Patterns of physician use of angiotensin converting enzyme inhibitors in the inpatient treatment of congestive heart failure. J. La State Med Soc 1997;149:474-84.
11. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med 2006;354:131-40.
12. Schoolwerth AC, Sica D, Ballerma B, Wilcox C. Renal considerations in angiotensin converting enzyme inhibitor therapy: A statement of healthcare professional from the Council on the Kidney in Cardiovascular Disease and the Council of High Blood Pressure Research of the American Heart Association. Circulation 2001;104:1985-91.
13. Bakris GL, Weir MR. Angiotensin- converting enzyme inhibitor associated elevations in SCr. Is this a cause for concern? Arch Intern Med 2000;168:685-88.
14. Knight E, Glynn R, McIntyre K, et al. 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). Amer Heart J 1999;138:849-55.
15. Ahmed A. Use of angiotensin-converting enzyme inhibitors in patients with heart failure and renal insufficiency: How concerned should we be by the rise in SCr. J Amer Ger Soc 2002;50:1297-1300.

16. Agusti A, Bonet S, Arnau J, et al. Adverse effects of ACE inhibitors in patients with chronic heart failure and/or ventricular dysfunction. Drug Safety 2003;26:895-908.

17. Raebel M, Lyons E, Andrade S, et al. Laboratory monitoring of drugs at initiation of therapy in ambulatory care. J Gen Intern Med 2005;20:1120-26.

18. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003;289:1107-16.

19. Raebel M, Lyons E, Chester E, et al. Randomized trial to improve safety monitoring of ongoing drug therapy in ambulatory patients. Pharmacotherapy 2006;5:626-29.

20. Hess D. Retrospective studies and chart reviews. Respir Care Oct 2004;49:1171-74.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8,18
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8,14-15
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8,18
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9,17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10,17
		(*b*) Report category boundaries when continuous variables were categorized	8-10,14-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Rates and Predictors of Angiotensin-Converting Enzyme Inhibitor Discontinuation Subsequent to Elevated Serum Creatinine: A Retrospective Cohort Study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005181.R1
Article Type:	Research
Date Submitted by the Author:	17-Jun-2014
Complete List of Authors:	Jackevicius, Cynthia; Western University of Health Sciences, Wong, Joyce; Western University of Health Sciences, Aroustamian, Irina; Western University of Health Sciences, Gee, Manyee; VA Greater Los Angeles Healthcare System, Mody, Freny; VA Greater Los Angeles Healthcare System,
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	INTERNAL MEDICINE, Adverse events < THERAPEUTICS, Chronic renal failure < NEPHROLOGY

Rates and Predictors of Angiotensin-Converting Enzyme Inhibitor Discontinuation Subsequent to Elevated Serum Creatinine: A Retrospective Cohort Study

Cynthia A. Jackevicius, BScPhm, MSc, PharmD[1, 2, 3, 4,5], Joyce Wong, PharmD[1], Irina Aroustamian, PharmD[1], Manyee Gee, PhD[2], Freny Vaghaiwalla Mody, MD FACC[2,6]

Department of Pharmacy Practice and Administration, Western University of Health Sciences[1], Department of Medicine & Pharmacy, Veteran Affairs Greater Los Angeles Healthcare System[2], Institute of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto[3], Institute for Clinical Evaluative Sciences[4], Department of Pharmacy, University Health Network[5], Division of Cardiology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles[6]

Corresponding author:

Freny Vaghaiwalla Mody, MD

VA Greater Los Angeles Healthcare System & David Geffen School of Medicine at UCLA

Phone: 310-268-3839 Fax: 310-268-4391 Email: freny.mody@va.gov

Running Title: Predictors of ACEI Discontinuation

Word count: 2714

Key Words: ACE inhibitors, serum creatinine, renal dysfunction, drug utilization, chronic kidney disease

Abstract

Objectives: Angiotensin-converting enzyme inhibitors (ACEI) are underutilized despite cardiovascular benefits, in part due to concerns of known transient elevations in serum creatinine (SCr) after initiation. Our objectives were to evaluate rates and predictors of ACEI discontinuation after SCr elevation post-ACEI initiation since limited data are available that examine this issue.

Setting: Primary and tertiary Veterans healthcare system in Los Angeles, California

Participants: 3,039 outpatients initiating an ACEI with a SCr measured within 6 months prior to and approximately 3 months after initiating an ACEI. Patients were divided into 3 groups (SCr<1.5,1.5-2.0 and>2.0).

Primary and Secondary Outcome Measures: Rates and factors associated with ACEI discontinuation subsequent to SCr elevation after ACEI initiation and for patients with baseline SCr>2mg/dL, the change in SCr associated with chronic use. Predictors were identified using multivariate logistic regression modeling.

Results: At 3 months follow-up, for those with an increase in SCr, the mean increase post-ACEI initiation was 26%, ranging from -0.01 mg/dL to 0.42 mg/dL varying according to level of baseline renal function. ACEI discontinuation was higher in patients with elevated baseline SCr (19/165, 11.5%) compared with those with SCr<1.5 (135/2,497, 5.4%), and those with SCr 1.5-2.0 (28/377, 7.4%). Male patients , and those with heart failure were less likely to discontinue ACEI after an elevation of serum creatinine post-ACEI initiation, while those taking NSAIDs, diuretics and beta-blockers were more likely to discontinue ACEI.

Conclusions: Serum creatinine increases <30% on average within 3 months of ACEI initiation,

with subsequent discontinuation rates varying by baseline SCr. Elevation in SCr was not associated with ACEI discontinuation rates. In patients with SCr>2 mg/dL at baseline, despite an acute increase in SCr after ACEI initiation, chronic ACEI use was associated with a decrease in SCr in most patients.

Article Summary

Strengths and Limitations of this Study

- To date, no studies have evaluated both the acute elevation in serum creatinine post-ACE inhibitor initiation and the predictors of subsequent discontinuation following an elevated serum creatinine.
- This study confirmed the mean increase in serum creatinine after ACE inhibitor initiation is 26%, varying with baseline renal function.
- Factors other than elevation in serum creatinine were associated with ACE inhibitor discontinuation, including, female sex, absence of heart failure, and use of NSAIDs, diuretics or beta-blockers.

Introduction

Current guidelines recommend angiotensin-converting enzyme inhibitors (ACEIs) as the standard of therapy for post-myocardial infarction, chronic heart failure (CHF), and diabetes due to the substantial endothelial, cardiovascular and renal protection.[1-4] Furthermore, ACEIs have also been shown to be a beneficial therapy for hypertension.[5] The renal protective mechanism of ACEIs vary, ranging from improving vascular endothelium function to vasodilatation effects.[6] Despite evidence from numerous trials showing the benefits of improved morbidity and mortality by ACEIs, these drugs are still underutilized.[1-4, 7-10] Clinicians are reluctant to start and continue with adequate dosing of ACEIs primarily due to concerns of elevations in serum creatinine (SCr), particularly in patients with CKD despite evidence that this group of patients benefits from ACEI.[10,11] The most probable cause of an acute elevation in SCr post-ACEI initiation is the decrease in vasoconstriction in the efferent arterioles resulting in pressure reduction in the glomerular apparatus and decreased glomerular filtration rate (GFR).[6] However, homeostasis of hemodynamics occurs with long-term use with gradual return and improvement in GFR.[7] Even with concerns of an acute rise in SCr, ACEIs provide long-term benefits with some data suggesting an improvement in renal function with decrease in SCr with long-term use.[7,11,12]
In heart failure (HF) patients, RCTs estimate that between 2.4% and 16% of patients experience an acute increase in SCr of > 0.5mg/dL after ACEI initiation, with improvement with chronic use. [8-9] In a practice-based setting, Bakris and colleagues demonstrated a mean increase in SCr of 30% in a hypertensive population using ACEIs with the increase stabilizing within 2 months after ACEI initiation. This rise in SCr is proportional to the baseline SCr, such that a 30% increase at a SCr of 2 would be 2.6 while at a SCr of 1, it would be only 1.3, it is reversible upon discontinuation, and it is less likely to occur beyond 4 weeks of initiation.[13,14] HF patients suffer

a more pronounced increase in SCr with ACEIs due to a reduction of blood flow to the kidneys from reduced cardiac output, diuretic use, and vasodilation effect. Although the acute increase in SCr seen in HF patients ranges from 75% to 200% from baseline after ACEI initiation, this elevation was suggested as being acceptable since ACEIs have proven benefits in decreasing mortality in this population.[8,15]

The frequency of the discontinuation rate of ACEI and the determinant factors associated with discontinuation in the real world setting has not been fully characterized. The CONSENSUS II HF trial reported a discontinuation rate of 4.6% with enalapril subsequent to the rise of SCr, while a meta-analysis of randomized controlled trials of HF patients found an ACEI discontinuation rate of 13.8%, of which only 0.4% was attributed to an increase in SCr.[7,16]

To date, no studies have evaluated both the acute elevation in SCr post-ACEI initiation and the predictors of subsequent discontinuation following an elevated SCr. Assessment of these patterns may provide insight into clinician decision making in a real world setting. The objective of our study was to assess the rates and predictors of ACEI discontinuation following an increase in SCr post-ACEI initiation, each according to baseline renal function.

Methods

We conducted a retrospective observational cohort study of all outpatients initiating an ACEI between 2002 and 2004 at the Veterans Affairs Greater Los Angeles Healthcare System (VAGLAHS). The Veterans Health Information System and Technology Architecture (VISTA) database was used to gather patient information (demographics, medication use, allergies, comorbidities, and lab results).

Initiation of ACEI was defined as the dispensing of an outpatient prescription for an ACEI with no previous record of ACEI use in the past 6 months. The following ACEI information was collected: initiation date, discontinuation date, adverse drug reactions (ADR), dosage, dosing frequency and the total daily dose. To determine the prevalence of a change in SCr, SCr was recorded at baseline (within 6 months of ACEI initiation) and 3-months (10-14 weeks) post-initiation. If SCr data was not available between 10-14 weeks (3 months), the data value of the most proximal assay was recorded. A 0.5mg/dL increase and 30% increase in SCr was considered to be clinically important since several studies have used this as a reference point to define a decrease in renal function.[5-6,14] Discontinuation of ACEI was defined as no refills within 90 days after the last filled prescription which allowed a lenient grace period for patients obtaining late refills. Patients were stratified into three baseline SCr groups (group 1: SCr <1.5mg/dL; group 2: 1.6-2.0mg/dL; and group 3: >2.0mg/dL) for analysis. We assessed above and below 0.5mg/dL and 30% to determine the threshold at which discontinuation occurred and to analyze possible differences in threshold by group. For those patients with a baseline SCr >2mg/dL and continued on an ACEI, SCr was recorded at 1-year to detect any changes post-initiation. Comorbidities (defined by ICD-9 codes: 425-cardiomyopathy, 428-congestive heart failure, 250-diabetes, 410-414-coronary artery disease, 274-gout, 401-hypertension) and

concurrent use of NSAIDs, diuretics, and beta-blockers were documented to determine potential factors associated with an increase in SCr and the discontinuation of ACEIs. Concomitant medication use was defined as having an active prescription within 1 month of the index date of ACEI prescription through the time of discontinuation.

The endpoints of this study were: the proportion of patients with a significant increase in SCr post-ACEI initiation at 3-months follow-up defined as >0.5mg/dL or >30% of baseline by group; the proportion of patients with ACEI discontinued following a rise in SCr by group; the threshold of increase in SCr associated with ACEI discontinuation, stratified by baseline SCr groups; factors (patient characteristics, comorbidities, and concurrent medications) that may be associated with discontinuation of ACEIs; and the change in SCr in patients with baseline SCr >2mg/dL and continued on ACEIs for 1 year.

Continuous baseline characteristics were expressed as the mean +/-SD or median; and categorical baseline characteristics were expressed as a proportion . Chi square test was used to compare the discontinuation rate after detecting a rise in SCr post-ACEI use between groups and to compare the threshold of increase in SCr prior to discontinuation between groups. A multiple logistic regression model was constructed to identify the factors associated with SCr elevation subsequent to ACEI initiation and ACEI discontinuation. The univariate model included patient characteristics (i.e., age, gender), comorbidities (i.e., diabetes, hypertension, coronary artery disease, chronic heart failure, systolic blood pressure (SBP)<100mmHg, gout), concomitant NSAID use, diuretic use (i.e. thiazide, loop, K+ sparing), beta-blocker use, and significant SCr elevation defined as >0.5mg/dL or >30% of baseline. Variables with p <0.2 from the univariate model were placed in a multiple logistic regression model using stepwise selection. Odds ratio with 95% confidence interval were estimated from the regression model. A p-value <0.05 was

considered statistically significant. All results were analyzed using SAS [Version 8.2, SAS Institute, Cary, NC]. This was a non-funded study approved by the institutional review board at VAGLAHS and Western University of Health Sciences.

Results

A total of 3,039 patients were initiated on an ACEI between January 2002 and December 2004 and had a SCr measured within 6 months prior to and 3 months after initiating an ACEI. (Figure 1) The average age was 65.0 years and 97.6% were male with a baseline SCr of 1.28+/- 0.86 mg/dL. Patients were stratified into three groups based on baseline SCr: Group 1 consisted of 2,497 patients with a SCr of <1.5 mg/dL (mean of 1.05+/- 0.19); group 2 had 377 patients with a SCr of 1.5-2.0 mg/dL (mean of 1.67 +/-0.16); and group 3 had 165 patients with a SCr of >2.0 mg/dL (mean of 3.75+/-2.44). (Figure 1) Hypertension (44.2%) and diabetes (28.5%) were the most frequently documented comorbidities, and the most common concomitant medications were diuretics and beta-blockers. (Table 1)

On average, patients had a follow-up SCr available at a median of 3.8 months post-ACEI initiation. The mean changes in SCr at 3 months follow-up most proximal to the 3-month interval were 0.05 +/-0.30 mg/dL, -0.01+/-0.31 mg/dL, and 0.42 +/-2.20 mg/dL respectively, by group ($p>0.05$ vs. baseline for all groups). There was no change in median SCr at 3 months follow-up for all three groups. Counting only those patients with an increase in SCr for all 3 groups, based on an increase from baseline SCr (n=182), the average percent increase in SCr prior to ACEI discontinuation was 25.98% +/-41.72 with a median of 13.49%.

At 3 months, the discontinuation rate of ACEI with or without concomitant SCr rise of >0.5mg/dL was highest in group 3 (11.5%), followed by group 2 (7.4%) and group 1 (5.4%) ($p< 0.001$) (Figure 1). In the multiple logistic regression model the variables significantly associated with a greater likelihood of ACEI discontinuation were the use of NSAIDs, diuretics, and beta-blockers. (Table 2) Of note, a significant increase in SCr (defined as >0.5mg/dl or >30 %) was not associated with ACEI discontinuation. ($p=0.498$ in the univariate model). A history of CHF,

SBP of <100mmHg at baseline and male sex were significantly associated with a reduced likelihood of ACEI discontinuation.

Changes in SCr were further evaluated based on absolute and percent change. Table 3 depicts the change in SCr prior to ACEI discontinuation, at the threshold of 0.5mg/dL and 30% increase in SCr (in 182 patients [5.9%] of all patients initiated on ACEI who had an increase in SCr). Group 3 had the highest mean increase in SCr as both absolute and percent change. A majority of the patients who experienced an increase in SCr had a change less than both 30% increase and 0.5mg/dL increase prior to discontinuation. Thus, most ACEI discontinuation did not occur following a clinically significant increase in SCr (>30% or >0.5mg/dL above baseline).

Of the 165 patients with a baseline SCr >2.0mg/dL (mean 3.75+/-2.44), only 50 patients (30.3%) were continued on an ACEI at 1 year. A total of 69 of the 165 (41.8%) patients experienced a decrease in SCr prior to discontinuation (average decrease was 1.04 +/- 1.77) and 76 (46.0%) of the patients experienced an increase (average increase was 1.86+/-0.87) and 20 (12.1%) patients experienced no change from baseline prior to discontinuation. Of the 50 patients who continued on ACEIs, only 35 patients had a follow-up in SCr at 1 year and their mean decrease in SCr was -0.24 +/-0.56 with a median decrease of -0.01mg/dL. Of these 35 patients, one (2.86%) had a larger increase in SCr (from 2.5 to 9.1 mg/dL) as compared with the remaining patients in the group (Figure 2). Excluding this subject as an outlier with a rise in SCr at 1 year that is unlikely due to ACEI, resulted in a mean decrease in SCr at 1 year in group 3 of -0.44+/-1.96 with a median of -0.01mg/dL. While the majority (54.28%) of patients in Group 3 experienced a clinically significant absolute (>0.5 mg/dL) increase in SCr of 0.98+/-1.58 compared with a baseline of 3.75+/-2.44, the 27% relative increase was not above the generally accepted threshold of >30%. Forty percent of this group experienced a decrease in SCr of

1.19+/-2.26 compared to baseline 3.75+/-2.44 and 5.7% had no change in SCr at 1-year follow-up. The average magnitude of decrease in SCr was greater than the average magnitude of increase in SCr with long term use of ACEI (1.19+/-2.26 mg/dL decrease versus 0.98 +/-1.58mg/dL increase, $p<0.001$) in patients with SCr>2 mg/dL.

Discussion

In our study, which had a large hypertensive population, we showed an increase in SCr of approximately 26% post-ACEI initiation, for those with an increase in SCr. Previous studies have documented similar acute increases in SCr of 30% in hypertensive patients and up to 200% in HF patients.[13,14] It has been suggested that ACEI discontinuation be considered if an increase in SCr exceeds 30% with ACEI use since renal function may be compromised beyond this increase and the benefits of ACEI may not outweigh the risks.[13] Our study showed that the majority of ACEI discontinuation occurred with an increase of less than 30% in SCr, thus suggesting that the threshold of concern for renal deterioration is lower in clinical practice or other factors may be more likely associated with discontinuation.

According to previous trials, a change in SCr of >0.5mg/dL may also be considered clinically significant.[8,9] The majority of the patients that discontinued ACEI in our study experienced a <0.5mg/dL change in SCr. Our study further suggested that on average, SCr was not greatly affected by ACEI since all three groups had no change in median SCr over 3 months. Thus, the discontinuation of ACEI in our population was most likely attributed to drug intolerances, such as, cough, other comorbidities, and concomitant medications, rather than the change in SCr. Only 6% of patients in the lower baseline SCr group suffered from documented cough or nausea leading to the discontinuation of ACEI. The adjusted regression analysis demonstrated that concomitant use of NSAIDs, diuretics, and beta-blockers were factors associated with a higher likelihood of ACEI discontinuation. This may be anticipated since both NSAIDs and diuretics have been documented to decrease renal function and exacerbate SCr elevations when used concomitantly with ACEI.[12] However, this may have led to the discontinuation of ACEI at a lower threshold of SCr increase. If discontinuation of ACEI was

indeed at a lower threshold than that traditionally accepted (SCr rise >0.5 or 30%), improved awareness for clinicians of the short duration of an acute rise in SCr when initiating ACEI, and dose reduction or reassessment of need for concomitant NSAIDs or diuretics may be beneficial strategies. This may confer better clinical outcomes for patients, particularly diabetic patients who would benefit from the nephroprotective actions of ACEI. Contrary to previous findings, beta-blockers were associated with a higher likelihood of discontinuation with concomitant use of ACEI in our study rather than exerting a renoprotective effect with ACEI use.[14] Male sex, CHF history, and SBP of <100mmHg were also associated with a lower chance of ACEI discontinuation. We postulated that patients with CHF and SBP <100mmHg were more likely to be maintained on an ACEI since HF studies have documented benefits of ACEI in decreasing morbidity and mortality.[1,7-8]

In patients with baseline SCr >2 mg/dL, our study showed that SCr can increase, decrease, or remain unchanged with long term ACEI use. Even though the majority of these patients experienced an acute increase in SCr, our results support ACEI use in renal impaired patients since the median change in SCr decreased and in the long term, the magnitude of decrease was much more impressive than the magnitude of increase. Our study is consistent with the prospective findings by Hou et al and retrospective findings by Hirsch et al, who both found that despite the acute increase in SCr, long term improvement in SCr occurs in many patients with impaired renal function at baseline.[11,15,16] The use of ACEI is warranted in this group of patients, along with close monitoring of renal function and electrolytes since benefits were documented in this study as well as in previous studies.[11-12,17--20]

Limitations of our study include its retrospective study design with potential for confounding.[21] Given our VA population, the vast majority of patients were male, limiting

generalizability to female patients. In addition, the electronic medical records may not be complete and accurate as is a limitation of any study relying on retrospective medical chart extraction. Finally, the sample size of patients with SCr >2 mg/dL was small both pre- and post-follow-up of SCr. However, the large population-based sample increases the generalizability of the findings.

Many clinicians may be reluctant to prescribe ACEIs to all eligible patients due to concerns of an elevation in SCr. Based on this real world study, the magnitude of increase in SCr post-ACEI initiation was slightly lower than the commonly used threshold of 30%. We found that, instead of a clinically meaningful rise in SCr, ACEI discontinuation may be more likely associated with either comorbidities, concomitant medications that may increase SCr, or a low threshold of concern for SCr elevations. Identification of other factors that may increase SCr, such as, NSAID use, diuretic use, and volume depletion should be considered before an ACEI is discontinued. The importance of monitoring should be emphasized to detect any drastic increase in SCr >30% and to manage potential adverse drug reactions. Education may be required to change practice patterns in patients with impaired baseline renal function in order to confer the clinical benefit of chronic ACEI nephroprotection.

Author Contributions:

Jackevicius: Concept/design, data interpretation, critical revision of article, approval of article, statistics

Wong: Design, data analysis/interpretation, drafting article, approval of article, statistics

Aroustamian: Data analysis, critical revision of article, approval of article, statistics

Gee: Data collection/interpretation, critical revision of article, approval of article

Mody: Concept/design, data interpretation, critical revision of article, approval of article

Funding: None.

Data Sharing: No additional data available.

Acknowledgments: None.

Table 1. Baseline characteristics of cohort (n= 3,039)

Characteristic	Value*	
Age (years, mean+/-SD, median)	65 +/-12, 65	
Gender (n, %)		
Male	2966	97.6%
Ethnicity (n, %)		
African American	414	13.6%
Caucasian	670	22.0%
Hispanic	44	1.45%
Other	341	11.2%
Not documented	1570	51.7%
Baseline serum creatinine (mg/dL, mean+/-SD, median)	Mean+/-SD, Median	
Overall (n=3,039)	Overall: Overall: 1.28 +/- 0.86, 1.10	
Group 1 : < 1.5mg/dL (n=2,497)	Group 1 : < 1.5mg/dL = 1.05 +/-0.19, 1.03	
Group 2 :1.5-2.0 mg/dL (n=377)	Group 2 :1.5-2.0 mg/dL = 1.67 +/-0.16, 1.6	
Group 3 : > 2 mg/dL (n=165)	Group 3 : > 2 mg/dL = 3.75+/-2.44, 2.7	

Co-morbidities (n, %)	n	%
Diabetes Mellitus	866	28.5 %
Hypertension	1343	44.2 %
Chronic Heart Failure	177	5.8 %
Coronary Artery Disease	445	14.6 %
Gout	69	2.3 %
SBP <100 mmHg	88	2.9 %
Concomitant Use of:		
NSAIDs	1053	34.6 %
Diuretics (total)	1771	58.3 %
Loops	773	25.4 %
Thiazides	1264	41.6 %
K- sparing	239	7.9 %
Beta-blockers	1601	52.7 %

*Values are reported as mean +/- SD; median unless otherwise noted

Table 2. Multivariate odds ratios for discontinuation of angiotensin-converting enzyme inhibitors subsequent to elevation of SCr post-ACEI initiation

Co morbidities	Multivariate Odds Ratio (95% CI)	P value
Age	1.00(1.00-1.00)*	0.452
Gender (Male)	0.74 (0.57-0.97)	0.028
Coronary Artery Disease	0.89 (0.79-1.01)	0.061
Chronic Heart Failure	0.79 (0.63-0.99)	0.041
SBP <100mmHg	0.55 (0.40-0.76)	<0.001
Concomitant use of:		
NSAIDs	1.23(1.13-1.34)	<0.001
Diuretics	1.07(0.87-1.31)	<0.001
Thiazides	1.18 (0.98-1.42)	0.084
Loops	0.99 (0.84-1.18)	0.925
Beta-blockers	1.17(1.08-1.27)	<0.001

* Values rounded from 0.999(0.995-1.002)

Table 3. Distribution in magnitude of elevation of serum creatinine in patients who discontinued angiotensin-converting enzyme inhibitors within 90 days post-initiation

Threshold of increase in SCr	Group 1 < 1.5mg/dL n=135	Group 2 1.5-2mg/dL n=28	Group 3 > 2mg/dL n=19	P value
≤ 0.5mg/dL increase	124 (91.85) 0.17 +/-0.11; 0.10	25(89.29) 0.18+/- 0.8; 0.17	8 (42.10) 0.27+/- 0.14; 0.3	<0.001
> 0.5mg/dL increase	11 (8.15) 1.23 +/- 0.99; 0.80	3 (10.71) 0.87 +/-0.25; 0.9	11 (57.90) 2.95 +/- 2.93; 1.7	<0.001
≤ 30% increase	114 (84.45) 14.15%+/- 6.85%; 11.11%	25 (89.29) 10.22%+/- 4.6%; 9.25%	12 (63.15) 12.82%+/-6.64%; 12.99%	0.01
> 30% increase	21 (15.55) 89.25%+/-81.07%; 46.67%	3 (10.71) 45.83% +/- 8.78%; 45%	7 (36.85) 100.32%+/-69.10%; 88.23%	<0.001

*Values are n (%) and mean+/- SD; median

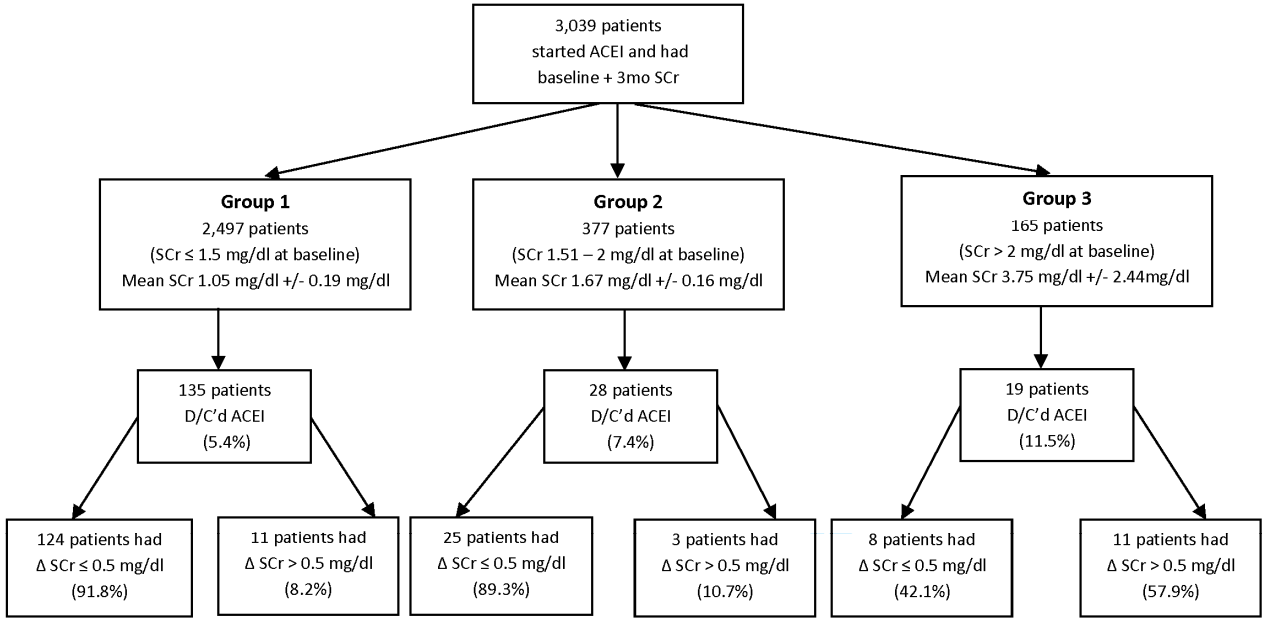
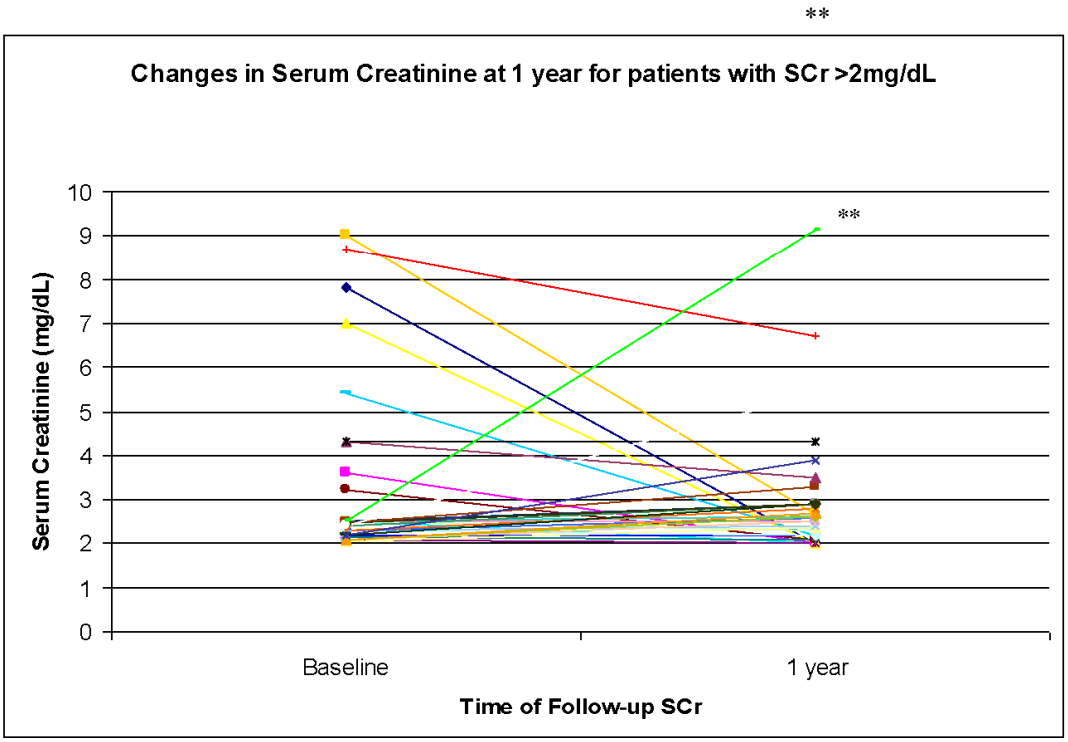


Figure1. Profile of patients included in analysis.
ACEI: Angiotensin-Converting Enzyme Inhibitors; ADR: Adverse Drug Reaction; DIC'd: discontinued; SCr: Serum Creatinine.

Figure 2: Changes in Serum Creatinine at 1 Year for Patients with SCr>2 mg/dL



*The mean change in serum creatinine was -0.24 +/- 0.56 mg/dL with a median of -0.01mg/dL. Excluding outlier (**) resulted in a mean in change serum creatinine of -0.44 +/- 1.96 mg/dL with a median of -0.01mg/dL.

N= 35

Figure Legends

Figure 1:

Title: Profile of patients included in the analysis.

Figure 2:

Title: Change in Serum Creatinine at 1 Year for Patients with SCr>2mg/dL

x-axis: Time of Follow-up SCr

y-axis: Serum Creatinine (,g/dL)

References

1. Hung SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web Site. Available at: http://www.acc.org/clinical/guidelines/failure//index.pdf.
2. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA Guidelines for the management of patients with ST-elevation myocardial infarction- Executive Summary. J Am Coll Cardiol 2004;44:671-7.
3. American Diabetes Association. Standards of Medical Care in Diabetes-2014. Diabetes Care 2014;37;S5-S13.
4. Marre M, Leblanc H, Suarez L, et al. Converting enzyme inhibition and kidney function in normotensive diabetic patients with persistent microalbuminuria. BMJ 1987;294:1448-52.
5. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 2003;289:2560-72.
6. Matsuda H, Hayashi K, Arakawa K, et al. Zonal heterogeneity in action of angiotensin-converting enzyme inhibitor on renal microcirculation. J Am Soc Nephrol 1999;10:2272-82.
7. Ahmed A, Kiefe C, Allman R, et al. Survival benefits of angiotensin converting enzyme inhibitors in older heart failure patients with perceived contraindications. J Amer Ger Soc 2002;50:1659-66.

8. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1986;316:1429-35.
9. The SOLVD Investigators. Effects of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1987;325:293-302.
10. Ghali JK, Giles T, Gonzales M, et al. Patterns of physician use of angiotensin converting enzyme inhibitors in the inpatient treatment of congestive heart failure. J. La State Med Soc 1997;149:474-84.
11. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med 2006;354:131-40.
12. Schoolwerth AC, Sica D, Ballerma B, Wilcox C. Renal considerations in angiotensin converting enzyme inhibitor therapy: A statement of healthcare professional from the Council on the Kidney in Cardiovascular Disease and the Council of High Blood Pressure Research of the American Heart Association. Circulation 2001;104:1985-91.
13. Bakris GL, Weir MR. Angiotensin- converting enzyme inhibitor associated elevations in SCr. Is this a cause for concern? Arch Intern Med 2000;168:685-88.
14. Knight E, Glynn R, McIntyre K, et al. 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). Amer Heart J 1999;138:849-55.
15. Hirsch S, Hirsch J, Udayan B, Rovin BH. Tolerating increases in serum creatining following aggressive treatment of chronic kidney disease, hypertension and proteinuria: pre-renal success. Am J Nephrol 2012;36:430-7.

16. Ruggenenti P, Remuzzi G. Dealing with renin-angiotensin inhibitors, don't mind serum creatinine. Am J Nephrol 2012;36:427-9.

17. Ahmed A. Use of angiotensin-converting enzyme inhibitors in patients with heart failure and renal insufficiency: How concerned should we be by the rise in SCr. J Amer Ger Soc 2002;50:1297-1300.

18. Raebel M, Lyons E, Andrade S, et al. Laboratory monitoring of drugs at initiation of therapy in ambulatory care. J Gen Intern Med 2005;20:1120-26.

19. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003;289:1107-16.

20. Raebel M, Lyons E, Chester E, et al. Randomized trial to improve safety monitoring of ongoing drug therapy in ambulatory patients. Pharmacotherapy 2006;5:626-29.

21. Hess D. Retrospective studies and chart reviews. Respir Care Oct 2004;49:1171-74.

Rates and Predictors of Angiotensin-Converting Enzyme Inhibitor Discontinuation Subsequent to Elevated Serum Creatinine: A Retrospective Cohort Study

Cynthia A. Jackevicius, BScPhm, MSc, PharmD[1, 2, 3, 4,5], Joyce Wong, PharmD[1], Irina Aroustamian, PharmD[1], Manyee Gee, PhD[2], Freny Vaghaiwalla Mody, MD FACC[2,6]

Department of Pharmacy Practice and Administration, Western University of Health Sciences[1], Department of Medicine & Pharmacy, Veteran Affairs Greater Los Angeles Healthcare System[2], Institute of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto[3], Institute for Clinical Evaluative Sciences[4], Department of Pharmacy, University Health Network[5], Division of Cardiology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles[6]

Corresponding author:

Freny Vaghaiwalla Mody, MD

VA Greater Los Angeles Healthcare System & David Geffen School of Medicine at UCLA

Phone: 310-268-3839 Fax: 310-268-4391 Email: freny.mody@va.gov

Running Title: Predictors of ACEI Discontinuation

Word count: 2714~~2602~~

Key Words: ACE inhibitors, serum creatinine, renal dysfunction, drug utilization, chronic kidney disease

Abstract

~~Background~~Objectives: Angiotensin-converting enzyme inhibitors (ACEI) are underutilized despite cardiovascular benefits, in part due to concerns of known transient elevations in serum creatinine (SCr) after initiation. Our objectives were to~~We~~ evaluate~~d~~ rates and predictors of ACEI discontinuation after SCr elevation post-ACEI initiation since limited data are available that examine this issue.

Setting: Primary and tertiary Veterans healthcare system in Los Angeles, California

Participants: 3,039 outpatients initiating an ACEI with a SCr measured within 6 months prior to and approximately 3 months after initiating an ACEI. Patients were divided into 3 groups (SCr<1.5,1.5-2.0 and>2.0).

Primary and Secondary Outcome Measures: Rates and factors associated with ACEI discontinuation subsequent to SCr elevation after ACEI initiation and for patients with baseline SCr>2mg/dL, the change in SCr associated with chronic use. Predictors were identified using multivariate logistic regression modeling.

~~Methods: In this retrospective, cohort study, we estimated the rates and factors associated with ACEI discontinuation subsequent to SCr elevation after ACEI initiation, and for patients with baseline SCr>2mg/dL, the change in SCr associated with chronic use. All patients initiating ACEI from January 1/02 to December 31/04 with 3 months SCr were included, and divided into 3 groups (SCr<1.5,1.5-2.0 and>2.0). Predictors were identified using multivariate logistic regression modeling.~~

Results: At 3 months follow-up, for those with an increase in SCr, the mean increase ~~in SCr~~ post-ACEI initiation was 26%, ranging from -0.01 mg/dL to 0.42 mg/dL varying according to level of baseline renal function. ACEI discontinuation was highe~~rst~~ in patients with elevated baseline SCr

(19/165, 11.5%) compared with those with SCr<~~>1.5 (135/2,497, 5.4%), and those with SCr 1.5-2.0 (28/377, 7.4%). Male ~~P~~patients ~~that were male~~, ~~or~~ and those with heart failure were less likely to discontinue ACEI after an elevation of serum creatinine post-ACEI initiation, while those taking NSAIDs, diuretics and beta-blockers were more likely to discontinue ACEI.

Conclusions: Serum creatinine increases <30% on average within 3 months of ACEI initiation, with subsequent discontinuation rates varying by baseline SCr. Elevation in SCr was not associated with ACEI discontinuation rates. In patients with SCr>2 mg/dL at baseline, ~~D~~despite an acute increase in SCr after ACEI initiation, chronic ACEI use was associated with a decrease in SCr in most patients ~~with SCr >2mg/dL~~.

Article Summary

Strengths and Limitations of this Study

- To date, no studies have evaluated both the acute elevation in serum creatinine post-ACE inhibitor initiation and the predictors of subsequent discontinuation following an elevated serum creatinine.
- This study confirmed the mean increase in serum creatinine after ACE inhibitor initiation is 26%, varying with baseline renal function.
- Factors other than elevation in serum creatinine were associated with ACE inhibitor discontinuation, including, female sex, absence of heart failure, and use of NSAIDs, diuretics or beta-blockers.

Introduction

Current guidelines recommend angiotensin-converting enzyme inhibitors (ACEIs) as the standard of therapy for post-myocardial infarction, chronic heart failure (CHF), and diabetes due to the substantial endothelial, cardiovascular and renal protection.[1-4] Furthermore, ACEIs have also been shown to be a beneficial therapy for hypertension.[5] The renal protective mechanism of ACEIs vary, ranging from improving vascular endothelium function to vasodilatation effects.[6] Despite evidence from numerous trials showing the benefits of improved morbidity and mortality by ACEIs, these drugs are still underutilized.[1-4, 7-10] Clinicians are reluctant to start and continue with adequate dosing of ACEIs primarily due to concerns of elevations in serum creatinine (SCr), particularly in patients with CKD despite evidence that this group of patients benefits from ACEI.[10,11] The most probable cause of an acute elevation in SCr post-ACEI initiation is the decrease in vasoconstriction in the efferent arterioles resulting in pressure reduction in the glomerular apparatus and decreased glomerular filtration rate (GFR).[6] However, homeostasis of hemodynamics occurs with long-term use with gradual return and improvement in GFR.[7] Even with concerns of an acute rise in SCr, ACEIs provide long-term benefits with some data suggesting an improvement in renal function with decrease in SCr with long-term use.[7,11,12]

In heart failure (HF) patients, RCTs estimate that between 2.4% and 16% of patients experience an acute increase in SCr of > 0.5mg/dL after ACEI initiation, with improvement with chronic use. [8-9] In a practice-based setting, Bakris and colleagues demonstrated a mean increase in SCr of 30% in a hypertensive population using ACEIs with the increase stabilizing within 2 months after ACEI initiation. This rise in SCr is proportional to the baseline SCr, such that a 30% increase at a SCr of 2 would be 2.6 while at a SCr of 1, it would be only 1.3, it is reversible upon discontinuation, and it is less likely to occur beyond 4 weeks of initiation.[13,14] HF patients suffer

a more pronounced increase in SCr with ACEIs due to a reduction of blood flow to the kidneys from reduced cardiac output, diuretic use, and vasodilation effect. Although the acute increase in SCr seen in HF patients ranges from 75% to 200% from baseline after ACEI initiation, this elevation was suggested as being acceptable since ACEIs have proven benefits in decreasing mortality in this population.[8,15]

The frequency of the discontinuation rate of ACEI and the determinant factors associated with discontinuation in the real world setting has not been fully characterized. The CONSENSUS II HF trial reported a discontinuation rate of 4.6% with enalapril subsequent to the rise of SCr, while a meta-analysis of randomized controlled trials of HF patients found an ACEI discontinuation rate of 13.8%, of which only 0.4% was attributed to an increase in SCr.[7,16]

To date, no studies have evaluated both the acute elevation in SCr post-ACEI initiation and the predictors of subsequent discontinuation following an elevated SCr. Assessment of these patterns may provide insight into clinician decision making in a real world setting. The objective of our study was to assess the rates and predictors of ACEI discontinuation following an increase in SCr post-ACEI initiation, each according to baseline renal function.

Methods

We conducted a retrospective observational cohort study of all outpatients initiating an ACEI between 2002 and 2004 at the Veterans Affairs Greater Los Angeles Healthcare Ssystem (VAGLAHS). The Veterans Health Information System and Technology Architecture (VISTA) database was used to gather patient information (demographics, medication use, allergies, comorbidities, and lab results).

Initiation of ACEI was defined as the dispensing of an outpatient prescription for an ACEI with no previous record of ACEI use in the past 6 months. The following ACEI information was collected: initiation date, discontinuation date, adverse drug reactions (ADR), dosage, dosing frequency and the total daily dose. To determine the prevalence of a change in SCr, SCr was recorded at baseline (within 6 months of ACEI initiation) and 3-months (10-14 weeks) post-initiation. If SCr data was not available between 10-14 weeks (3 months), the data value of the most proximal assay was recorded. A 0.5mg/dL increase and 30% increase in SCr was considered to be clinically important since several studies have used this as a reference point to define a decrease in renal function.[5-6,14] Discontinuation of ACEI was defined as no refills within 90 days after the last filled prescription which allowed a lenient grace period for patients obtaining late refills. Patients were stratified into three baseline SCr groups (group 1: SCr <1.5mg/dL; group 2: 1.6-2.0mg/dL; and group 3: >2.0mg/dL) for analysis. We assessed above and below 0.5mg/dL and 30% to determine the threshold at which discontinuation occurred and to analyze possible differences in threshold by group. For those patients with a baseline SCr >2mg/dL and continued on an ACEI, SCr was recorded at 1-year to detect any changes post-initiation. Comorbidities (defined by ICD-9 codes: 425-cardiomyopathy, 428-congestive heart failure, 250-diabetes, 410-414-coronary artery disease, 274-gout, 401-hypertension) and

concurrent use of NSAIDs, diuretics, and beta-blockers were documented to determine potential factors associated with an increase in SCr and the discontinuation of ACEIs. Concomitant medication use was defined as having an active prescription within 1 month of the index date of ACEI prescription through the time of discontinuation.

The endpoints of this study were: the proportion of patients with a significant increase in SCr post-ACEI initiation at 3-months follow-up defined as >0.5mg/dL or >30% of baseline by group; the proportion of patients with ACEI discontinued following a rise in SCr by group; the threshold of increase in SCr associated with ACEI discontinuation, stratified by baseline SCr groups; factors (patient characteristics, comorbidities, and concurrent medications) that may be associated with discontinuation of ACEIs; and the change in SCr in patients with baseline SCr >2mg/dL and continued on ACEIs for 1 year.

Continuous baseline characteristics were expressed as the mean +/-SD or median; and categorical baseline characteristics were expressed as a proportion . Chi square test was used to compare the discontinuation rate after detecting a rise in SCr post-ACEI use between groups and to compare the threshold of increase in SCr prior to discontinuation between groups. A multiple logistic regression model was constructed to identify the factors associated with SCr elevation subsequent to ACEI initiation and ACEI discontinuation. The univariate model included patient characteristics (i.e., age, gender), comorbidities (i.e., diabetes, hypertension, coronary artery disease, chronic heart failure, systolic blood pressure (SBP)<100mmHg, gout), concomitant NSAID use, diuretic use (i.e. thiazide, loop, K+ sparing), beta-blocker use, and significant SCr elevation defined as >0.5mg/dL or >30% of baseline. Variables with p <0.2 from the univariate model were placed in a multiple logistic regression model using stepwise selection. Odds ratio with 95% confidence interval were estimated from the regression model. A p-value <0.05 was

considered statistically significant. All results were analyzed using SAS [Version 8.2, SAS Institute, Cary, NC]. This was a non-funded study approved by the institutional review board at VAGLAHS and Western University of Health Sciences.

Results

A total of 3,039 patients were initiated on an ACEI between January 2002 and December 2004 and had a SCr measured within 6 months prior to and 3 months after initiating an ACEI. (Figure 1) The average age was 65.0 years and 97.6% were male with a baseline SCr of 1.28+/- 0.86 mg/dL. Patients were stratified into three groups based on baseline SCr: Group 1 consisted of 2,497 patients with a SCr of <1.5 mg/dL (mean of 1.05+/- 0.19); group 2 had 377 patients with a SCr of 1.5-2.0 mg/dL (mean of 1.67 +/-0.16); and group 3 had 165 patients with a SCr of >2.0 mg/dL (mean of 3.75+/-2.44). (Figure 1) Hypertension (44.2%) and diabetes (28.5%) were the most frequently documented comorbidities, and the most common concomitant medications were diuretics and beta-blockers. (Table 1)

On average, patients had a follow-up SCr available at a median of 3.8 months post-ACEI initiation. The mean changes in SCr at 3 months follow-up most proximal to the 3-month interval were 0.05 +/-0.30 mg/dL, -0.01+/-0.31 mg/dL, and 0.42 +/-2.20 mg/dL respectively, by group (p>0.05 vs. baseline for all groups). There was no change in median SCr at 3 months follow-up for all three groups. Counting only those patients with an increase in SCr for all 3 groups, based on an increase from baseline SCr (n=182), the average percent increase in SCr prior to ACEI discontinuation was 25.98% +/-41.72 with a median of 13.49%.

At 3 months, the discontinuation rate of ACEI with or without concomitant SCr rise of >0.5mg/dL was highest in group 3 (11.5%), followed by group 2 (7.4%) and group 1 (5.4%) (p< 0.001) (Figure 1). In the multiple logistic regression model the variables significantly associated with a greater likelihood of ACEI discontinuation were the use of NSAIDs, diuretics, and beta-blockers. (Table 2) Of note, a significant increase in SCr (defined as >0.5mg/dl or >30 %) was not associated with ACEI discontinuation. (p=0.498 in the univariate model). A history of CHF,

SBP of <100mmHg at baseline and male sex were significantly associated with a reduced likelihood of ACEI discontinuation.

Changes in SCr were further evaluated based on absolute and percent change. Table 3 depicts the change in SCr ~~subsequent to~~prior to ACEI discontinuation, at the threshold of 0.5mg/dL and 30% increase in SCr (in 182 patients [5.9%] of all patients initiated on ACEI who had an increase in SCr). Group 3 had the highest mean increase in SCr as both absolute and percent change. A majority of the patients who experienced an increase in SCr had a change less than both 30% increase and 0.5mg/dL increase prior to discontinuation. Thus, most ACEI discontinuation did not occur following a clinically significant increase in SCr (>30% or >0.5mg/dL above baseline).

Of the 165 patients with a baseline SCr >2.0mg/dL (mean 3.75+/-2.44), only 50 patients (30.3%) were continued on an ACEI at 1 year. ~~Of the 405 patients who discontinued ACEI, 165 patients discontinued within 90 days of a SCr result.~~ A total of 69 of the 165 (41.8%) patients experienced a decrease in SCr prior to discontinuation (average decrease was 1.04 +/- 1.77) and 76 (46.0%) of the patients experienced an increase (average increase was 1.86+/-0.87) and 20 (12.1%) patients experienced no change from baseline prior to discontinuation. Of the 50 patients who continued on ACEIs, only 35 patients had a follow-up in SCr at 1 year and their mean decrease in SCr was -0.24 +/-0.56 with a median decrease of -0.01mg/dL. Of these 35 patients, one (2.86%) had a larger increase in SCr (from 2.5 to 9.1 mg/dL) as compared with the remaining patients in the group (Figure 2). Excluding this subject as an outlier with a rise in SCr at 1 year that is unlikely due to ACEI, resulted in a mean decrease in SCr at 1 year in group 3 of -0.44+/-1.96 with a median of -0.01mg/dL. While the majority (54.28%) of patients in Group 3 experienced a clinically significant absolute (>0.5 mg/dL) increase in SCr of 0.98+/-1.58

compared with a baseline of 3.75+/-2.44, the 27% relative increase was not above the generally accepted threshold of >30%. Forty percent of this group experienced a decrease in SCr of 1.19+/-2.26 compared to baseline 3.75+/-2.44 and 5.7% had no change in SCr at 1-year follow-up. The average magnitude of decrease in SCr was greater than the average magnitude of increase in SCr with long term use of ACEI (1.19+/-2.26 mg/dL decrease versus 0.98 +/-1.58mg/dL increase, $p<0.001$) in patients with SCr>2 mg/dL.

Discussion

In our study, which had a large hypertensive population, we showed an increase in SCr of approximately 26% post-ACEI initiation, for those with an increase in SCr. Previous studies have documented similar acute increases in SCr of 30% in hypertensive patients and up to 200% in HF patients.[13,14] It has been suggested that ACEI discontinuation be considered if an increase in SCr exceeds 30% with ACEI use since renal function may be compromised beyond this increase and the benefits of ACEI may not outweigh the risks.[13] Our study showed that the majority of ACEI discontinuation occurred with an increase of less than 30% in SCr, thus suggesting that the threshold of concern for renal deterioration is lower in clinical practice or other factors may be more likely associated with discontinuation.

According to previous trials, a change in SCr of >0.5mg/dL may also be considered clinically significant.[8,9] The majority of the patients that discontinued ACEI in our study experienced a <0.5mg/dL change in SCr. Our study further suggested that on average, SCr was not greatly affected by ACEI since all three groups had no change in median SCr over 3 months. Thus, the discontinuation of ACEI in our population was most likely attributed to drug intolerances, such as, cough, other comorbidities, and concomitant medications, rather than the change in SCr. Only 6% of patients in the lower baseline SCr group suffered from documented cough or nausea leading to the discontinuation of ACEI. The adjusted regression analysis demonstrated that concomitant use of NSAIDs, diuretics, and beta-blockers were factors associated with a higher likelihood of ACEI discontinuation. This may be anticipated since both NSAIDs and diuretics have been documented to decrease renal function and exacerbate SCr elevations when used concomitantly with ACEI.[12] However, this may have led to the discontinuation of ACEI at a lower threshold of SCr increase. If discontinuation of ACEI was

indeed at a lower threshold than that traditionally accepted (SCr rise >0.5 or 30%), improved awareness for clinicians of the short duration of an acute rise in SCr when initiating ACEI, and dose reduction or reassessment of need for concomitant NSAIDs or diuretics may be beneficial strategies. This may confer better clinical outcomes for patients, particularly diabetic patients who would benefit from the nephroprotective actions of ACEI. Contrary to previous findings, beta-blockers were associated with a higher likelihood of discontinuation with concomitant use of ACEI in our study rather than exerting a renoprotective effect with ACEI use.[14] Male sex, CHF history, and SBP of <100mmHg were also associated with a lower chance of ACEI discontinuation. We postulated that patients with CHF and SBP <100mmHg were more likely to be maintained on an ACEI since HF studies have documented benefits of ACEI in decreasing morbidity and mortality.[1,7-8]

In patients with baseline SCr >2 mg/dL, our study showed that SCr can increase, decrease, or remain unchanged with long term ACEI use. Even though the majority of these patients experienced an acute increase in SCr, our results support ACEI use in renal impaired patients since the median change in SCr decreased and in the long term, the magnitude of decrease was much more impressive than the magnitude of increase. Our study is consistent with the prospective findings by Hou et al and retrospective findings by Hirsch et al, who both ~~that~~ found that despite the acute increase in SCr, long term improvement in SCr occurs in many patients with impaired renal function at baseline.[11,15,16] The use of ACEI is warranted in this group of patients, along with close monitoring of renal function and electrolytes since benefits were documented in this study as well as in previous studies.[11-12,17--20]

Limitations of our study include its retrospective study design with potential for confounding.[20,21] Given our VA population, the vast majority of patients were male, limiting

generalizability to female patients. In addition, the electronic medical records may not be complete and accurate as is a limitation of any study relying on retrospective ~~documentation~~ medical chart extraction. Finally, the sample size of patients with SCr >2 mg/dL was small both pre- and post-follow-up of SCr. However, the large population-based sample increases the generalizability of the findings.

Many clinicians may be reluctant to prescribe ACEIs to all eligible patients due to concerns of an elevation in SCr. Based on this real world study, the magnitude of increase in SCr post-ACEI initiation was slightly lower than the commonly used threshold of 30%. We found that, instead of a clinically meaningful rise in SCr, ~~C~~ACEI discontinuation may be more likely associated with either comorbidities, ~~and~~ concomitant medications that may increase SCr, or a low threshold of concern for SCr elevations ~~may be more likely associated with ACEI discontinuation rather than a clinically meaningful rise in SCr~~. Identification of other factors that may increase SCr, such as, NSAID use, diuretic use, and volume depletion should be considered before an ACEI is discontinued. The importance of monitoring should be emphasized to detect any drastic increase in SCr >30% and to manage potential adverse drug reactions. ~~Identification of other factors that may increase SCr, such as, NSAID use, diuretic use, and volume depletion should be considered before an ACEI is discontinued.~~ Education may be required to change practice patterns in patients with impaired baseline renal function in order to confer the clinical benefit of chronic ACEI nephroprotection.

Author Contributions:

Jackevicius: Concept/design, data interpretation, critical revision of article, approval of article, statistics

Wong: Design, data analysis/interpretation, drafting article, approval of article, statistics

Aroustamian: Data analysis, critical revision of article, approval of article, statistics

Gee: Data collection/interpretation, critical revision of article, approval of article

Mody: Concept/design, data interpretation, critical revision of article, approval of article

Funding: None.

Data Sharing: No additional data available.

Acknowledgments: None.

Table 1. Baseline characteristics of cohort (n= 3,039)

Characteristic	Value*	
Age (years, mean+/-SD, median)	65 +/-12, 65	
Gender (n, %)		
Male	2966	97.6%
Ethnicity (n, %)		
African American	414	13.6%
Caucasian	670	22.0%
Hispanic	44	1.45%
Other	341	11.2%
Not documented	1570	51.7%
Baseline serum creatinine (mg/dL, mean+/-SD, median)	Mean+/-SD, Median	
Overall (n=3,039)	Overall: Overall: 1.28 +/- 0.86, 1.10	
Group 1 : < 1.5mg/dL (n=2,497)	Group 1 : < 1.5mg/dL = 1.05 +/-0.19, 1.03	
Group 2 :1.5-2.0 mg/dL (n=377)	Group 2 :1.5-2.0 mg/dL = 1.67 +/-0.16, 1.6	
Group 3 : > 2 mg/dL (n=165)	Group 3 : > 2 mg/dL = 3.75+/-2.44, 2.7	

Co-morbidities (n, %)	n	%
Diabetes Mellitus	866	28.5 %
Hypertension	1343	44.2 %
Chronic Heart Failure	177	5.8 %
Coronary Artery Disease	445	14.6 %
Gout	69	2.3 %
SBP <100 mmHg	88	2.9 %
Concomitant Use of:		
NSAIDs	1053	34.6 %
Diuretics (total)	1771	58.3 %
Loops	773	25.4 %
Thiazides	1264	41.6 %
K- sparing	239	7.9 %
Beta-blockers	1601	52.7 %

*Values are reported as mean +/- SD; median unless otherwise noted

Table 2. Multivariate odds ratios for discontinuation of angiotensin-converting enzyme inhibitors subsequent to elevation of SCr post-ACEI initiation

Co morbidities	Multivariate Odds Ratio (95% CI)	P value
Age	1.00(1.00-1.00)*	0.452
Gender (Male)	0.74 (0.57-0.97)	0.028
Coronary Artery Disease	0.89 (0.79-1.01)	0.061
Chronic Heart Failure	0.79 (0.63-0.99)	0.041
SBP <100mmHg	0.55 (0.40-0.76)	<0.001
Concomitant use of:		
NSAIDs	1.23(1.13-1.34)	<0.001
Diuretics	1.07(0.87-1.31)	<0.001
Thiazides	1.18 (0.98-1.42)	0.084
Loops	0.99 (0.84-1.18)	0.925
Beta-blockers	1.17(1.08-1.27)	<0.001

* Values rounded from 0.999(0.995-1.002)

Table 3. Distribution in magnitude of elevation of serum creatinine in patients who discontinued angiotensin-converting enzyme inhibitors within 90 days post-initiation

Threshold of increase in SCr	Group 1 < 1.5mg/dL n=135	Group 2 1.5-2mg/dL n=28	Group 3 > 2mg/dL n=19	P value
≤ 0.5mg/dL increase	124 (91.85) 0.17 +/-0.11; 0.10	25(89.29) 0.18+/- 0.8; 0.17	8 (42.10) 0.27+/- 0.14; 0.3	<0.001
> 0.5mg/dL increase	11 (8.15) 1.23 +/- 0.99; 0.80	3 (10.71) 0.87 +/-0.25; 0.9	11 (57.90) 2.95 +/- 2.93; 1.7	<0.001
≤ 30% increase	114 (84.45) 14.15%+/- 6.85%; 11.11%	25 (89.29) 10.22%+/- 4.6%; 9.25%	12 (63.15) 12.82%+/-6.64%; 12.99%	0.01
> 30% increase	21 (15.55) 89.25%+/-81.07%; 46.67%	3 (10.71) 45.83% +/- 8.78%; 45%	7 (36.85) 100.32%+/-69.10%; 88.23%	<0.001

*Values are n (%) and mean+/- SD; median

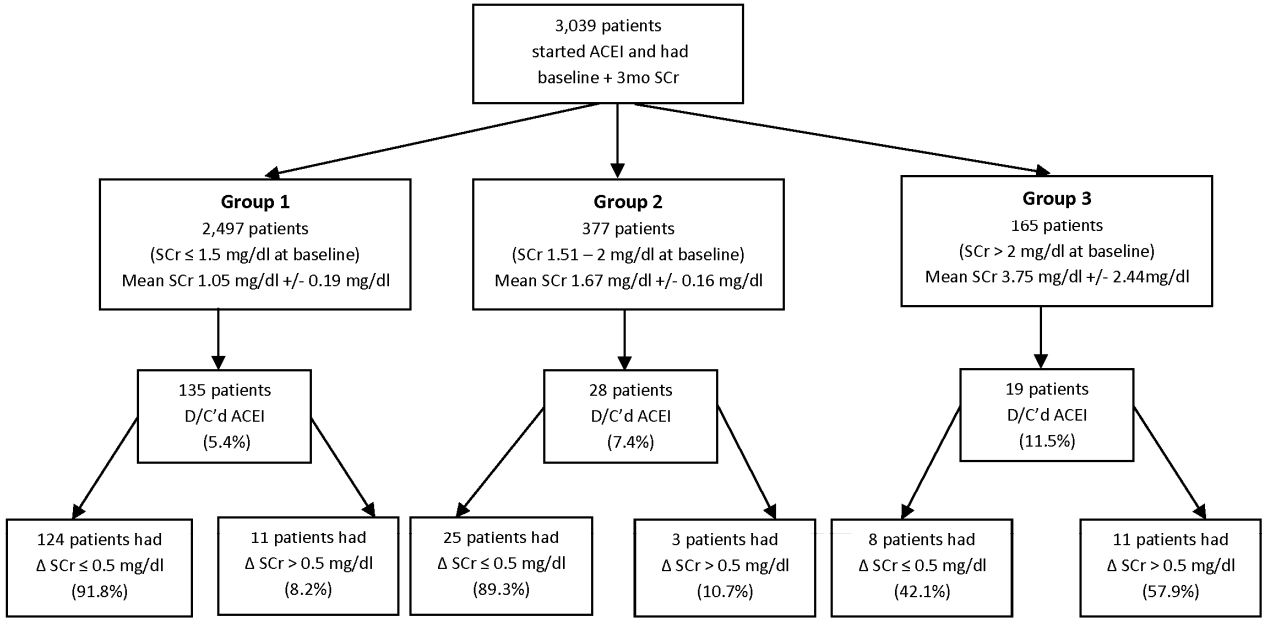
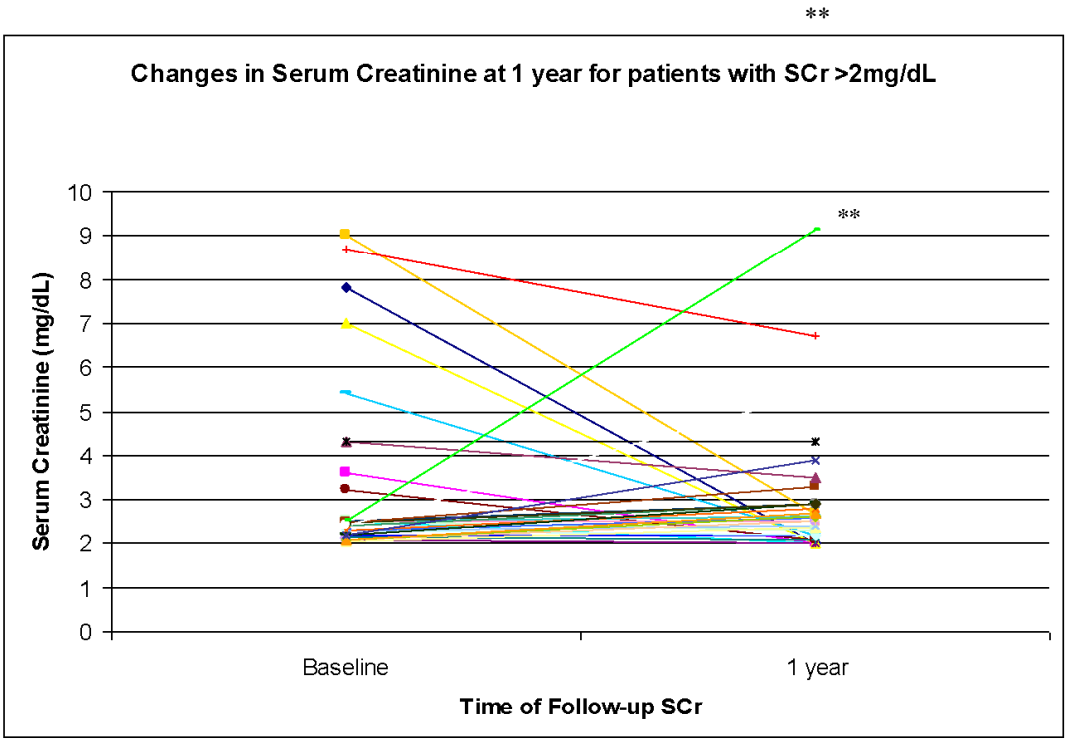


Figure1. Profile of patients included in analysis.
ACEI: Angiotensin-Converting Enzyme Inhibitors; ADR: Adverse Drug Reaction; DIC'd: discontinued; SCr: Serum Creatinine.

Figure 2: Changes in Serum Creatinine at 1 Year for Patients with SCr>2 mg/dL



*The mean change in serum creatinine was -0.24 +/- 0.56 mg/dL with a median of -0.01mg/dL. Excluding outlier (**) resulted in a mean in change serum creatinine of -0.44 +/- 1.96 mg/dL with a median of -0.01mg/dL.

N= 35

Figure Legends

Figure 1:

Title: Profile of patients included in the analysis.

Figure 2:

Title: Change in Serum Creatinine at 1 Year for Patients with SCr>2mg/dL

x-axis: Time of Follow-up SCr

y-axis: Serum Creatinine (,g/dL)

References

1. Hung SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web Site. Available at: http://www.acc.org/clinical/guidelines/failure//index.pdf.
2. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA Guidelines for the management of patients with ST-elevation myocardial infarction- Executive Summary. J Am Coll Cardiol 2004;44:671-7.
3. American Diabetes Association. Standards of Medical Care in Diabetes-2014. Diabetes Care 2014;37;S5-S13.
4. Marre M, Leblanc H, Suarez L, et al. Converting enzyme inhibition and kidney function in normotensive diabetic patients with persistent microalbuminuria. BMJ 1987;294:1448-52.
5. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 2003;289:2560-72.
6. Matsuda H, Hayashi K, Arakawa K, et al. Zonal heterogeneity in action of angiotensin-converting enzyme inhibitor on renal microcirculation. J Am Soc Nephrol 1999;10:2272-82.
7. Ahmed A, Kiefe C, Allman R, et al. Survival benefits of angiotensin converting enzyme inhibitors in older heart failure patients with perceived contraindications. J Amer Ger Soc 2002;50:1659-66.

8. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1986;316:1429-35.
9. The SOLVD Investigators. Effects of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1987;325:293-302.
10. Ghali JK, Giles T, Gonzales M, et al. Patterns of physician use of angiotensin converting enzyme inhibitors in the inpatient treatment of congestive heart failure. J. La State Med Soc 1997;149:474-84.
11. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med 2006;354:131-40.
12. Schoolwerth AC, Sica D, Ballerma B, Wilcox C. Renal considerations in angiotensin converting enzyme inhibitor therapy: A statement of healthcare professional from the Council on the Kidney in Cardiovascular Disease and the Council of High Blood Pressure Research of the American Heart Association. Circulation 2001;104:1985-91.
13. Bakris GL, Weir MR. Angiotensin- converting enzyme inhibitor associated elevations in SCr. Is this a cause for concern? Arch Intern Med 2000;168:685-88.
14. Knight E, Glynn R, McIntyre K, et al. 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). Amer Heart J 1999;138:849-55.
15. Hirsch S, Hirsch J, Udayan B, Rovin BH. Tolerating increases in serum creatining following aggressive treatment of chronic kidney disease, hypertension and proteinuria: pre-renal success. Am J Nephrol 2012;36:430-7.

16. Ruggenenti P, Remuzzi G. Dealing with renin-angiotensin inhibitors, don't mind serum creatinine. Am J Nephrol 2012;36:427-9.

~~15.~~17. Ahmed A. Use of angiotensin-converting enzyme inhibitors in patients with heart failure and renal insufficiency: How concerned should we be by the rise in SCr. J Amer Ger Soc 2002;50:1297-1300.

~~16. Agusti A, Bonet S, Arnau J, et al. Adverse effects of ACE inhibitors in patients with chronic heart failure and/or ventricular dysfunction. Drug Safety 2003;26:895-908.~~

~~17.~~18. Raebel M, Lyons E, Andrade S, et al. Laboratory monitoring of drugs at initiation of therapy in ambulatory care. J Gen Intern Med 2005;20:1120-26.

~~18.~~19. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003;289:1107-16.

~~19.~~20. Raebel M, Lyons E, Chester E, et al. Randomized trial to improve safety monitoring of ongoing drug therapy in ambulatory patients. Pharmacotherapy 2006;5:626-29.

~~20.~~21. Hess D. Retrospective studies and chart reviews. Respir Care Oct 2004;49:1171-74.

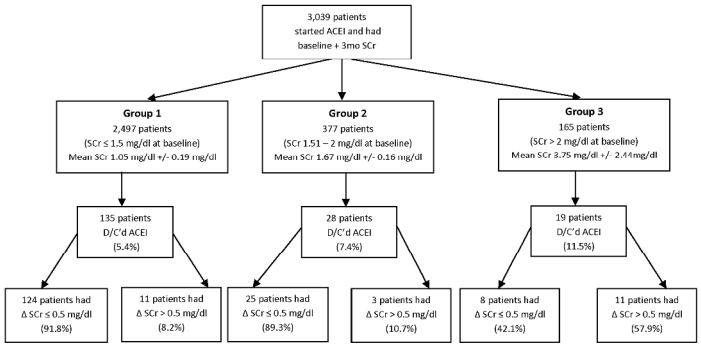
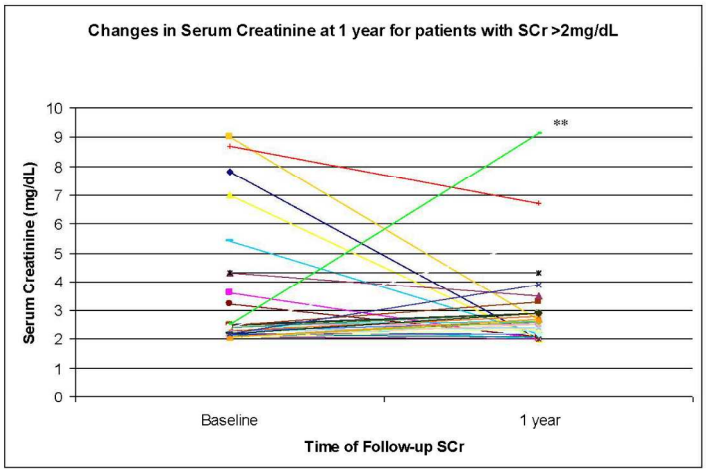


Figure1. Profile of patients included in analysis.
ACEI: Angiotensin-Converting Enzyme Inhibitors; ADR: Adverse Drug Reaction; DIC'd: discontinued; SCr: Serum Creatinine.

279x215mm (300 x 300 DPI)

Figure 2: Changes in Serum Creatinine at 1 Year for Patients with SCr>2 mg/dL



*The mean change in serum creatinine was -0.24 +/- 0.56 mg/dL with a median of -0.01mg/dL. Excluding outlier (**) resulted in a mean in change serum creatinine of -0.44 +/- 1.96 mg/dL with a median of -0.01mg/dL.

N= 35

2

215x279mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8,18
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8,14-15
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8,18
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9,17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10,17
		(*b*) Report category boundaries when continuous variables were categorized	8-10,14-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Rates and Predictors of Angiotensin-Converting Enzyme Inhibitor Discontinuation Subsequent to Elevated Serum Creatinine: A Retrospective Cohort Study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005181.R2
Article Type:	Research
Date Submitted by the Author:	15-Jul-2014
Complete List of Authors:	Jackevicius, Cynthia; Western University of Health Sciences, Wong, Joyce; Western University of Health Sciences, Aroustamian, Irina; Western University of Health Sciences, Gee, Manyee; VA Greater Los Angeles Healthcare System, Mody, Freny; VA Greater Los Angeles Healthcare System,
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	INTERNAL MEDICINE, Adverse events < THERAPEUTICS, Chronic renal failure < NEPHROLOGY

Rates and Predictors of Angiotensin-Converting Enzyme Inhibitor Discontinuation Subsequent to Elevated Serum Creatinine: A Retrospective Cohort Study

Cynthia A. Jackevicius, BScPhm, MSc, PharmD[1, 2, 3, 4,5], Joyce Wong, PharmD[1], Irina Aroustamian, PharmD[1], Manyee Gee, PhD[2], Freny Vaghaiwalla Mody, MD FACC[2,6]

Department of Pharmacy Practice and Administration, Western University of Health Sciences[1], Department of Medicine & Pharmacy, Veteran Affairs Greater Los Angeles Healthcare System[2], Institute of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto[3], Institute for Clinical Evaluative Sciences[4], Department of Pharmacy, University Health Network[5], Division of Cardiology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles[6]

Corresponding author:

Freny Vaghaiwalla Mody, MD

VA Greater Los Angeles Healthcare System & David Geffen School of Medicine at UCLA

Phone: 310-268-3839 Fax: 310-268-4391 Email: freny.mody@va.gov

Running Title: Predictors of ACEI Discontinuation

Word count: 2753

Key Words: ACE inhibitors, serum creatinine, renal dysfunction, drug utilization, chronic kidney disease

Abstract

Objectives: Angiotensin-converting enzyme inhibitors (ACEI) are underutilized despite cardiovascular benefits, in part due to concerns of known transient elevations in serum creatinine (SCr) after initiation. Our objectives were to evaluate rates and predictors of ACEI discontinuation after SCr elevation post-ACEI initiation since limited data are available that examine this issue.

Setting: Primary and tertiary Veterans healthcare system in Los Angeles, California

Participants: 3,039 outpatients initiating an ACEI with a SCr measured within 6 months prior to and approximately 3 months after initiating an ACEI. Patients were divided into 3 groups (SCr<1.5,1.5-2.0 and>2.0).

Primary and Secondary Outcome Measures: Rates and factors associated with ACEI discontinuation subsequent to SCr elevation after ACEI initiation and for patients with baseline SCr>2mg/dL, the change in SCr associated with chronic use. Predictors were identified using multivariate logistic regression modeling.

Results: At 3 months follow-up, for those with an increase in SCr, the mean increase post-ACEI initiation was 26%, ranging from -0.01 mg/dL to 0.42 mg/dL varying according to level of baseline renal function. ACEI discontinuation was higher in patients with elevated baseline SCr (19/165, 11.5%) compared with those with SCr<1.5 (135/2,497, 5.4%), and those with SCr 1.5-2.0 (28/377, 7.4%). Male patients , and those with heart failure were less likely to discontinue ACEI after an elevation of serum creatinine post-ACEI initiation, while those taking NSAIDs, diuretics and beta-blockers were more likely to discontinue ACEI.

Conclusions: Serum creatinine increases <30% on average within 3 months of ACEI initiation,

with subsequent discontinuation rates varying by baseline SCr. Elevation in SCr was not associated with ACEI discontinuation rates. In patients with SCr>2 mg/dL at baseline, despite an acute increase in SCr after ACEI initiation, chronic ACEI use was associated with a decrease in SCr in most patients.

Article Summary

Strengths and Limitations of this Study

- To date, no studies have evaluated both the acute elevation in serum creatinine post-ACE inhibitor initiation and the predictors of subsequent discontinuation following an elevated serum creatinine.
- This study confirmed the mean increase in serum creatinine after ACE inhibitor initiation is 26%, varying with baseline renal function.
- Factors other than elevation in serum creatinine were associated with ACE inhibitor discontinuation, including, female sex, absence of heart failure, and use of NSAIDs, diuretics or beta-blockers.

Introduction

Current guidelines recommend angiotensin-converting enzyme inhibitors (ACEIs) as the standard of therapy for post-myocardial infarction, chronic heart failure (CHF), and diabetes due to the substantial endothelial, cardiovascular and renal protection.[1-4] Furthermore, ACEIs have also been shown to be a beneficial therapy for hypertension.[5] The renal protective mechanism of ACEIs vary, ranging from improving vascular endothelium function to vasodilatation effects.[6] Despite evidence from numerous trials showing the benefits of improved morbidity and mortality by ACEIs, these drugs are still underutilized.[1-4, 7-10] Clinicians are reluctant to start and continue with adequate dosing of ACEIs primarily due to concerns of elevations in serum creatinine (SCr), particularly in patients with CKD despite evidence that this group of patients benefits from ACEI.[10,11] The most probable cause of an acute elevation in SCr post-ACEI initiation is the decrease in vasoconstriction in the efferent arterioles resulting in pressure reduction in the glomerular apparatus and decreased glomerular filtration rate (GFR).[6] However, homeostasis of hemodynamics occurs with long-term use with gradual return and improvement in GFR.[7] Even with concerns of an acute rise in SCr, ACEIs provide long-term benefits with some data suggesting an improvement in renal function with decrease in SCr with long-term use.[7,11,12]
In heart failure (HF) patients, RCTs estimate that between 2.4% and 16% of patients experience an acute increase in SCr of > 0.5mg/dL after ACEI initiation, with improvement with chronic use. [8-9] In a practice-based setting, Bakris and colleagues demonstrated a mean increase in SCr of 30% in a hypertensive population using ACEIs with the increase stabilizing within 2 months after ACEI initiation. This rise in SCr is proportional to the baseline SCr, such that a 30% increase at a SCr of 2 would be 2.6 while at a SCr of 1, it would be only 1.3, it is reversible upon discontinuation, and it is less likely to occur beyond 4 weeks of initiation.[13,14] HF patients suffer

a more pronounced increase in SCr with ACEIs due to a reduction of blood flow to the kidneys from reduced cardiac output, diuretic use, and vasodilation effect. Although the acute increase in SCr seen in HF patients ranges from 75% to 200% from baseline after ACEI initiation, this elevation was suggested as being acceptable since ACEIs have proven benefits in decreasing mortality in this population.[8,15]

The frequency of the discontinuation rate of ACEI and the determinant factors associated with discontinuation in the real world setting has not been fully characterized. The CONSENSUS II HF trial reported a discontinuation rate of 4.6% with enalapril subsequent to the rise of SCr, while a meta-analysis of randomized controlled trials of HF patients found an ACEI discontinuation rate of 13.8%, of which only 0.4% was attributed to an increase in SCr.[7,16]

To date, no studies have evaluated both the acute elevation in SCr post-ACEI initiation and the predictors of subsequent discontinuation following an elevated SCr. Assessment of these patterns may provide insight into clinician decision making in a real world setting. The objective of our study was to assess the rates and predictors of ACEI discontinuation following an increase in SCr post-ACEI initiation, each according to baseline renal function.

Methods

We conducted a retrospective observational cohort study of all outpatients initiating an ACEI between 2002 and 2004 at the Veterans Affairs Greater Los Angeles Healthcare System (VAGLAHS). The Veterans Health Information System and Technology Architecture (VISTA) database was used to gather patient information (demographics, medication use, allergies, comorbidities, and lab results).

Initiation of ACEI was defined as the dispensing of an outpatient prescription for an ACEI with no previous record of ACEI use in the past 6 months. The following ACEI information was collected: initiation date, discontinuation date, adverse drug reactions (ADR), dosage, dosing frequency and the total daily dose. To determine the prevalence of a change in SCr, SCr was recorded at baseline (within 6 months of ACEI initiation) and 3-months (10-14 weeks) post-initiation. If SCr data was not available between 10-14 weeks (3 months), the data value of the most proximal assay was recorded. A 0.5mg/dL increase and 30% increase in SCr was considered to be clinically important since several studies have used this as a reference point to define a decrease in renal function.[5-6,14] Discontinuation of ACEI was defined as no refills within 90 days after the last filled prescription which allowed a lenient grace period for patients obtaining late refills. Patients were stratified into three baseline SCr groups (group 1: SCr <1.5mg/dL; group 2: 1.6-2.0mg/dL; and group 3: >2.0mg/dL) for analysis. We assessed above and below 0.5mg/dL and 30% to determine the threshold at which discontinuation occurred and to analyze possible differences in threshold by group. For those patients with a baseline SCr >2mg/dL and continued on an ACEI, SCr was recorded at 1-year to detect any changes post-initiation. Comorbidities (defined by ICD-9 codes: 425-cardiomyopathy, 428-congestive heart failure, 250-diabetes, 410-414-coronary artery disease, 274-gout, 401-hypertension) and

concurrent use of NSAIDs, diuretics, and beta-blockers were documented to determine potential factors associated with an increase in SCr and the discontinuation of ACEIs. Concomitant medication use was defined as having an active prescription within 1 month of the index date of ACEI prescription through the time of discontinuation.

The endpoints of this study were: the proportion of patients with a significant increase in SCr post-ACEI initiation at 3-months follow-up defined as >0.5mg/dL or >30% of baseline by group; the proportion of patients with ACEI discontinued following a rise in SCr by group; the threshold of increase in SCr associated with ACEI discontinuation, stratified by baseline SCr groups; factors (patient characteristics, comorbidities, and concurrent medications) that may be associated with discontinuation of ACEIs; and the change in SCr in patients with baseline SCr >2mg/dL and continued on ACEIs for 1 year.

Continuous baseline characteristics were expressed as the mean +/-SD or median; and categorical baseline characteristics were expressed as a proportion . Chi square test was used to compare the discontinuation rate after detecting a rise in SCr post-ACEI use between groups and to compare the threshold of increase in SCr prior to discontinuation between groups. A multiple logistic regression model was constructed to identify the factors associated with SCr elevation subsequent to ACEI initiation and ACEI discontinuation. The univariate model included patient characteristics (i.e., age, gender), comorbidities (i.e., diabetes, hypertension, coronary artery disease, chronic heart failure, systolic blood pressure (SBP)<100mmHg, gout), concomitant NSAID use, diuretic use (i.e. thiazide, loop, K+ sparing), beta-blocker use, and significant SCr elevation defined as >0.5mg/dL or >30% of baseline. Variables with p <0.2 from the univariate model were placed in a multiple logistic regression model using stepwise selection. Odds ratio with 95% confidence interval were estimated from the regression model. A p-value <0.05 was

considered statistically significant. All results were analyzed using SAS [Version 8.2, SAS Institute, Cary, NC]. This was a non-funded study approved by the institutional review board at VAGLAHS and Western University of Health Sciences.

Results

A total of 3,039 patients were initiated on an ACEI between January 2002 and December 2004 and had a SCr measured within 6 months prior to and 3 months after initiating an ACEI. (Figure 1) The average age was 65.0 years and 97.6% were male with a baseline SCr of 1.28+/- 0.86 mg/dL. Patients were stratified into three groups based on baseline SCr: Group 1 consisted of 2,497 patients with a SCr of <1.5 mg/dL (mean of 1.05+/- 0.19); group 2 had 377 patients with a SCr of 1.5-2.0 mg/dL (mean of 1.67 +/-0.16); and group 3 had 165 patients with a SCr of >2.0 mg/dL (mean of 3.75+/-2.44). (Figure 1) Hypertension (44.2%) and diabetes (28.5%) were the most frequently documented comorbidities, and the most common concomitant medications were diuretics and beta-blockers. (Table 1)

On average, patients had a follow-up SCr available at a median of 3.8 months post-ACEI initiation. The mean changes in SCr at 3 months follow-up most proximal to the 3-month interval were 0.05 +/-0.30 mg/dL, -0.01+/-0.31 mg/dL, and 0.42 +/-2.20 mg/dL respectively, by group ($p>0.05$ vs. baseline for all groups). There was no change in median SCr at 3 months follow-up for all three groups. Counting only those patients with an increase in SCr for all 3 groups, based on an increase from baseline SCr (n=182), the average percent increase in SCr prior to ACEI discontinuation was 25.98% +/-41.72 with a median of 13.49%.

At 3 months, the discontinuation rate of ACEI with or without concomitant SCr rise of >0.5mg/dL was highest in group 3 (11.5%), followed by group 2 (7.4%) and group 1 (5.4%) ($p< 0.001$) (Figure 1). In the multiple logistic regression model the variables significantly associated with a greater likelihood of ACEI discontinuation were the use of NSAIDs, diuretics, and beta-blockers. (Table 2) Of note, a significant increase in SCr (defined as >0.5mg/dl or >30 %) was not associated with ACEI discontinuation. ($p=0.498$ in the univariate model). A history of CHF,

SBP of <100mmHg at baseline and male sex were significantly associated with a reduced likelihood of ACEI discontinuation.

Changes in SCr were further evaluated based on absolute and percent change. Table 3 depicts the change in SCr prior to ACEI discontinuation, at the threshold of 0.5mg/dL and 30% increase in SCr (in 182 patients [5.9%] of all patients initiated on ACEI who had an increase in SCr). Group 3 had the highest mean increase in SCr as both absolute and percent change. A majority of the patients who experienced an increase in SCr had a change less than both 30% increase and 0.5mg/dL increase prior to discontinuation. Thus, most ACEI discontinuation did not occur following a clinically significant increase in SCr (>30% or >0.5mg/dL above baseline).

Of the 165 patients with a baseline SCr >2.0mg/dL (mean 3.75+/-2.44), only 50 patients (30.3%) were continued on an ACEI at 1 year. A total of 69 of the 165 (41.8%) patients experienced a decrease in SCr prior to discontinuation (average decrease was 1.04 +/- 1.77) and 76 (46.0%) of the patients experienced an increase (average increase was 1.86+/-0.87) and 20 (12.1%) patients experienced no change from baseline prior to discontinuation. Of the 50 patients who continued on ACEIs, only 35 patients had a follow-up in SCr at 1 year and their mean decrease in SCr was -0.24 +/-0.56 with a median decrease of -0.01mg/dL. Of these 35 patients, one (2.86%) had a larger increase in SCr (from 2.5 to 9.1 mg/dL) as compared with the remaining patients in the group (Figure 2). Excluding this subject as an outlier with a rise in SCr at 1 year that is unlikely due to ACEI, resulted in a mean decrease in SCr at 1 year in group 3 of -0.44+/-1.96 with a median of -0.01mg/dL. While the majority (54.28%) of patients in Group 3 experienced a clinically significant absolute (>0.5 mg/dL) increase in SCr of 0.98+/-1.58 compared with a baseline of 3.75+/-2.44, the 27% relative increase was not above the generally accepted threshold of >30%. Forty percent of this group experienced a decrease in SCr of

1.19+/-2.26 compared to baseline 3.75+/-2.44 and 5.7% had no change in SCr at 1-year follow-up. The average magnitude of decrease in SCr was greater than the average magnitude of increase in SCr with long term use of ACEI (1.19+/-2.26 mg/dL decrease versus 0.98 +/-1.58mg/dL increase, $p<0.001$) in patients with SCr>2 mg/dL.

Discussion

In our study, which had a large hypertensive population, we showed an increase in SCr of approximately 26% post-ACEI initiation, for those with an increase in SCr. Previous studies have documented similar acute increases in SCr of 30% in hypertensive patients and up to 200% in HF patients.[13,14] It has been suggested that ACEI discontinuation be considered if an increase in SCr exceeds 30% with ACEI use since renal function may be compromised beyond this increase and the benefits of ACEI may not outweigh the risks.[13] Our study showed that the majority of ACEI discontinuation occurred with an increase of less than 30% in SCr, thus suggesting that the threshold of concern for renal deterioration is lower in clinical practice or other factors may be more likely associated with discontinuation.

According to previous trials, a change in SCr of >0.5mg/dL may also be considered clinically significant.[8,9] The majority of the patients that discontinued ACEI in our study experienced a <0.5mg/dL change in SCr. Our study further suggested that on average, SCr was not greatly affected by ACEI since all three groups had no change in median SCr over 3 months. Thus, the discontinuation of ACEI in our population was most likely attributed to drug intolerances, such as, cough, other comorbidities, and concomitant medications, rather than the change in SCr. Only 6% of patients in the lower baseline SCr group suffered from documented cough or nausea leading to the discontinuation of ACEI. The adjusted regression analysis demonstrated that concomitant use of NSAIDs, diuretics, and beta-blockers were factors associated with a higher likelihood of ACEI discontinuation. This may be anticipated since both NSAIDs and diuretics have been documented to decrease renal function and exacerbate SCr elevations when used concomitantly with ACEI.[12] However, this may have led to the discontinuation of ACEI at a lower threshold of SCr increase. If discontinuation of ACEI was

indeed at a lower threshold than that traditionally accepted (SCr rise >0.5 or 30%), improved awareness for clinicians of the short duration of an acute rise in SCr when initiating ACEI, and dose reduction or reassessment of need for concomitant NSAIDs or diuretics may be beneficial strategies. This may confer better clinical outcomes for patients, particularly diabetic patients who would benefit from the nephroprotective actions of ACEI. Contrary to previous findings, beta-blockers were associated with a higher likelihood of discontinuation with concomitant use of ACEI in our study rather than exerting a renoprotective effect with ACEI use.[14] Male sex, CHF history, and SBP of <100mmHg were also associated with a lower chance of ACEI discontinuation. We postulated that patients with CHF and SBP <100mmHg were more likely to be maintained on an ACEI since HF studies have documented benefits of ACEI in decreasing morbidity and mortality.[1,7-8]

In patients with baseline SCr >2 mg/dL, our study showed that SCr can increase, decrease, or remain unchanged with long term ACEI use. Even though the majority of these patients experienced an acute increase in SCr, our results support ACEI use in renal impaired patients since the median change in SCr decreased and in the long term, the magnitude of decrease was much more impressive than the magnitude of increase. Our study is consistent with the prospective findings by Hou et al and retrospective findings by Hirsch et al, who both found that despite the acute increase in SCr, long term improvement in SCr occurs in many patients with impaired renal function at baseline.[11,15,16] The use of ACEI is warranted in this group of patients, along with close monitoring of renal function and electrolytes since benefits were documented in this study as well as in previous studies.[11-12,17--20]

Limitations of our study include its retrospective study design with potential for confounding.[21] Given our VA population, the vast majority of patients were male, limiting

generalizability to female patients. In addition, the electronic medical records may not be complete and accurate as is a limitation of any study relying on retrospective medical chart extraction. We did not have data on the peak creatinine, nor comprehensive assessment of all adverse events given our data extraction methods. Finally, the sample size of patients with SCr >2 mg/dL was small both pre- and post-follow-up of SCr, particularly at 1-year follow-up. Exploration of the reasons for ACEI discontinuation long-term in this group would be beneficial. However, the large population-based sample increases the generalizability of the findings.

Many clinicians may be reluctant to prescribe ACEIs to all eligible patients due to concerns of an elevation in SCr. Based on this real world study, the magnitude of increase in SCr post-ACEI initiation was slightly lower than the commonly used threshold of 30%. We found that, instead of a clinically meaningful rise in SCr, ACEI discontinuation may be more likely associated with either comorbidities, concomitant medications that may increase SCr, or a low threshold of concern for SCr elevations. Identification of other factors that may increase SCr, such as, NSAID use, diuretic use, and volume depletion should be considered before an ACEI is discontinued. The importance of monitoring should be emphasized to detect any drastic increase in SCr >30% and to manage potential adverse drug reactions. Education may be required to change practice patterns in patients with impaired baseline renal function in order to confer the clinical benefit of chronic ACEI nephroprotection.

Author Contributions:

Jackevicius: Concept/design, data interpretation, critical revision of article, approval of article, statistics

Wong: Design, data analysis/interpretation, drafting article, approval of article, statistics

Aroustamian: Data analysis, critical revision of article, approval of article, statistics

Gee: Data collection/interpretation, critical revision of article, approval of article

Mody: Concept/design, data interpretation, critical revision of article, approval of article

Funding: None.

Data Sharing: No additional data available.

Acknowledgments: None.

Table 1. Baseline characteristics of cohort (n= 3,039)

Characteristic	Value*	
Age (years, mean+/-SD, median)	65 +/-12, 65	
Gender (n, %)		
Male	2966	97.6%
Ethnicity (n, %)		
African American	414	13.6%
Caucasian	670	22.0%
Hispanic	44	1.45%
Other	341	11.2%
Not documented	1570	51.7%
Baseline serum creatinine (mg/dL, mean+/-SD, median)	Mean+/-SD, Median	
Overall (n=3,039)	Overall: Overall: 1.28 +/- 0.86, 1.10	
Group 1 : < 1.5mg/dL (n=2,497)	Group 1 : < 1.5mg/dL = 1.05 +/-0.19, 1.03	
Group 2 :1.5-2.0 mg/dL (n=377)	Group 2 :1.5-2.0 mg/dL = 1.67 +/-0.16, 1.6	
Group 3 : > 2 mg/dL (n=165)	Group 3 : > 2 mg/dL = 3.75+/-2.44, 2.7	

Co-morbidities (n, %)	n	%
Diabetes Mellitus	866	28.5 %
Hypertension	1343	44.2 %
Chronic Heart Failure	177	5.8 %
Coronary Artery Disease	445	14.6 %
Gout	69	2.3 %
SBP <100 mmHg	88	2.9 %
Concomitant Use of:		
NSAIDs	1053	34.6 %
Diuretics (total)	1771	58.3 %
Loops	773	25.4 %
Thiazides	1264	41.6 %
K- sparing	239	7.9 %
Beta-blockers	1601	52.7 %

*Values are reported as mean +/- SD; median unless otherwise noted

Table 2. Multivariate odds ratios for discontinuation of angiotensin-converting enzyme inhibitors subsequent to elevation of SCr post-ACEI initiation

Co morbidities	Multivariate Odds Ratio (95% CI)	P value
Age	1.00(1.00-1.00)*	0.452
Gender (Male)	0.74 (0.57-0.97)	0.028
Coronary Artery Disease	0.89 (0.79-1.01)	0.061
Chronic Heart Failure	0.79 (0.63-0.99)	0.041
SBP <100mmHg	0.55 (0.40-0.76)	<0.001
Concomitant use of:		
NSAIDs	1.23(1.13-1.34)	<0.001
Diuretics	1.07(0.87-1.31)	<0.001
Thiazides	1.18 (0.98-1.42)	0.084
Loops	0.99 (0.84-1.18)	0.925
Beta-blockers	1.17(1.08-1.27)	<0.001

* Values rounded from 0.999(0.995-1.002)

Table 3. Distribution in magnitude of elevation of serum creatinine in patients who discontinued angiotensin-converting enzyme inhibitors within 90 days post-initiation

Threshold of increase in SCr	Group 1 < 1.5mg/dL n=135	Group 2 1.5-2mg/dL n=28	Group 3 > 2mg/dL n=19	P value
≤ 0.5mg/dL increase	124 (91.85) 0.17 +/-0.11; 0.10	25(89.29) 0.18+/- 0.8; 0.17	8 (42.10) 0.27+/- 0.14; 0.3	<0.001
> 0.5mg/dL increase	11 (8.15) 1.23 +/- 0.99; 0.80	3 (10.71) 0.87 +/-0.25; 0.9	11 (57.90) 2.95 +/- 2.93; 1.7	<0.001
≤ 30% increase	114 (84.45) 14.15%+/- 6.85%; 11.11%	25 (89.29) 10.22%+/- 4.6%; 9.25%	12 (63.15) 12.82%+/-6.64%; 12.99%	0.01
> 30% increase	21 (15.55) 89.25%+/-81.07%; 46.67%	3 (10.71) 45.83% +/- 8.78%; 45%	7 (36.85) 100.32%+/-69.10%; 88.23%	<0.001

*Values are n (%) and mean+/- SD; medi

References

1. Hung SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation** and Management of Heart Failure). American College of Cardiology Web Site. Available at: http://www.acc.org/clinical/guidelines/failure//index.pdf.
2. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA Guidelines for the management of patients with ST-elevation myocardial infarction- Executive Summary. J Am Coll Cardiol 2004;44:671-7.
3. American Diabetes Association. Standards of Medical Care in Diabetes-2014. Diabetes Care 2014;37;S5-S13.
4. Marre M, Leblanc H, Suarez L, et al. Converting enzyme inhibition and kidney function in normotensive diabetic patients with persistent microalbuminuria. BMJ 1987;294:1448-52.
5. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 2003;289:2560-72.
6. Matsuda H, Hayashi K, Arakawa K, et al. Zonal heterogeneity in action of angiotensin-converting enzyme inhibitor on renal microcirculation. J Am Soc Nephrol 1999;10:2272-82.
7. Ahmed A, Kiefe C, Allman R, et al. Survival benefits of angiotensin converting enzyme inhibitors in older heart failure patients with perceived contraindications. J Amer Ger Soc 2002;50:1659-66.

8. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1986;316:1429-35.
9. The SOLVD Investigators. Effects of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1987;325:293-302.
10. Ghali JK, Giles T, Gonzales M, et al. Patterns of physician use of angiotensin converting enzyme inhibitors in the inpatient treatment of congestive heart failure. J. La State Med Soc 1997;149:474-84.
11. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med 2006;354:131-40.
12. Schoolwerth AC, Sica D, Ballerma B, et al. Renal considerations in angiotensin converting enzyme inhibitor therapy: A statement of healthcare professional from the Council on the Kidney in Cardiovascular Disease and the Council of High Blood Pressure Research of the American Heart Association. Circulation 2001;104:1985-91.
13. Bakris GL, Weir MR. Angiotensin- converting enzyme inhibitor associated elevations in SCr. Is this a cause for concern? Arch Intern Med 2000;168:685-88.
14. Knight E, Glynn R, McIntyre K, et al. 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). Amer Heart J 1999;138:849-55.

15. Hirsch S, Hirsch J, Udayan B et al. Tolerating increases in serum creatining following aggressive treatment of chronic kidney disease, hypertension and proteinuria: pre-renal success. Am J Nephrol 2012;36:430-7.

16. Ruggenenti P, Remuzzi G. Dealing with renin-angiotensin inhibitors, don't mind serum creatinine. Am J Nephrol 2012;36:427-9.

17. Ahmed A. Use of angiotensin-converting enzyme inhibitors in patients with heart failure and renal insufficiency: How concerned should we be by the rise in SCr. J Amer Ger Soc 2002;50:1297-1300.

18. Raebel M, Lyons E, Andrade S, et al. Laboratory monitoring of drugs at initiation of therapy in ambulatory care. J Gen Intern Med 2005;20:1120-26.

19. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003;289:1107-16.

20. Raebel M, Lyons E, Chester E, et al. Randomized trial to improve safety monitoring of ongoing drug therapy in ambulatory patients. Pharmacotherapy 2006;5:626-29.

21. Hess D. Retrospective studies and chart reviews. Respir Care Oct 2004;49:1171-74.

Figure Legends

Figure 1:

Title: Profile of patients included in the analysis.

Figure 2:

Title: Change in Serum Creatinine at 1 Year for Patients with SCr>2mg/dL

x-axis: Time of Follow-up SCr

y-axis: Serum Creatinine (,g/dL

Rates and Predictors of Angiotensin-Converting Enzyme Inhibitor Discontinuation Subsequent to Elevated Serum Creatinine: A Retrospective Cohort Study

Cynthia A. Jackevicius, BScPhm, MSc, PharmD[1, 2, 3, 4,5], Joyce Wong, PharmD[1], Irina Aroustamian, PharmD[1], Manyee Gee, PhD[2], Freny Vaghaiwalla Mody, MD FACC[2,6]

Department of Pharmacy Practice and Administration, Western University of Health Sciences[1], Department of Medicine & Pharmacy, Veteran Affairs Greater Los Angeles Healthcare System[2], Institute of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto[3], Institute for Clinical Evaluative Sciences[4], Department of Pharmacy, University Health Network[5], Division of Cardiology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles[6]

Corresponding author:

Freny Vaghaiwalla Mody, MD

VA Greater Los Angeles Healthcare System & David Geffen School of Medicine at UCLA

Phone: 310-268-3839 Fax: 310-268-4391 Email: freny.mody@va.gov

Running Title: Predictors of ACEI Discontinuation

Word count: 27534~~14~~

Key Words: ACE inhibitors, serum creatinine, renal dysfunction, drug utilization, chronic kidney disease

Abstract

Objectives: Angiotensin-converting enzyme inhibitors (ACEI) are underutilized despite cardiovascular benefits, in part due to concerns of known transient elevations in serum creatinine (SCr) after initiation. Our objectives were to evaluate rates and predictors of ACEI discontinuation after SCr elevation post-ACEI initiation since limited data are available that examine this issue.

Setting: Primary and tertiary Veterans healthcare system in Los Angeles, California

Participants: 3,039 outpatients initiating an ACEI with a SCr measured within 6 months prior to and approximately 3 months after initiating an ACEI. Patients were divided into 3 groups (SCr<1.5,1.5-2.0 and>2.0).

Primary and Secondary Outcome Measures: Rates and factors associated with ACEI discontinuation subsequent to SCr elevation after ACEI initiation and for patients with baseline SCr>2mg/dL, the change in SCr associated with chronic use. Predictors were identified using multivariate logistic regression modeling.

Results: At 3 months follow-up, for those with an increase in SCr, the mean increase post-ACEI initiation was 26%, ranging from -0.01 mg/dL to 0.42 mg/dL varying according to level of baseline renal function. ACEI discontinuation was higher in patients with elevated baseline SCr (19/165, 11.5%) compared with those with SCr<1.5 (135/2,497, 5.4%), and those with SCr 1.5-2.0 (28/377, 7.4%). Male patients , and those with heart failure were less likely to discontinue ACEI after an elevation of serum creatinine post-ACEI initiation, while those taking NSAIDs, diuretics and beta-blockers were more likely to discontinue ACEI.

Conclusions: Serum creatinine increases <30% on average within 3 months of ACEI initiation,

with subsequent discontinuation rates varying by baseline SCr. Elevation in SCr was not associated with ACEI discontinuation rates. In patients with SCr>2 mg/dL at baseline, despite an acute increase in SCr after ACEI initiation, chronic ACEI use was associated with a decrease in SCr in most patients.

Article Summary

Strengths and Limitations of this Study

- To date, no studies have evaluated both the acute elevation in serum creatinine post-ACE inhibitor initiation and the predictors of subsequent discontinuation following an elevated serum creatinine.
- This study confirmed the mean increase in serum creatinine after ACE inhibitor initiation is 26%, varying with baseline renal function.
- Factors other than elevation in serum creatinine were associated with ACE inhibitor discontinuation, including, female sex, absence of heart failure, and use of NSAIDs, diuretics or beta-blockers.

Introduction

Current guidelines recommend angiotensin-converting enzyme inhibitors (ACEIs) as the standard of therapy for post-myocardial infarction, chronic heart failure (CHF), and diabetes due to the substantial endothelial, cardiovascular and renal protection.[1-4] Furthermore, ACEIs have also been shown to be a beneficial therapy for hypertension.[5] The renal protective mechanism of ACEIs vary, ranging from improving vascular endothelium function to vasodilatation effects.[6] Despite evidence from numerous trials showing the benefits of improved morbidity and mortality by ACEIs, these drugs are still underutilized.[1-4, 7-10] Clinicians are reluctant to start and continue with adequate dosing of ACEIs primarily due to concerns of elevations in serum creatinine (SCr), particularly in patients with CKD despite evidence that this group of patients benefits from ACEI.[10,11] The most probable cause of an acute elevation in SCr post-ACEI initiation is the decrease in vasoconstriction in the efferent arterioles resulting in pressure reduction in the glomerular apparatus and decreased glomerular filtration rate (GFR).[6] However, homeostasis of hemodynamics occurs with long-term use with gradual return and improvement in GFR.[7] Even with concerns of an acute rise in SCr, ACEIs provide long-term benefits with some data suggesting an improvement in renal function with decrease in SCr with long-term use.[7,11,12]
In heart failure (HF) patients, RCTs estimate that between 2.4% and 16% of patients experience an acute increase in SCr of > 0.5mg/dL after ACEI initiation, with improvement with chronic use. [8-9] In a practice-based setting, Bakris and colleagues demonstrated a mean increase in SCr of 30% in a hypertensive population using ACEIs with the increase stabilizing within 2 months after ACEI initiation. This rise in SCr is proportional to the baseline SCr, such that a 30% increase at a SCr of 2 would be 2.6 while at a SCr of 1, it would be only 1.3, it is reversible upon discontinuation, and it is less likely to occur beyond 4 weeks of initiation.[13,14] HF patients suffer

a more pronounced increase in SCr with ACEIs due to a reduction of blood flow to the kidneys from reduced cardiac output, diuretic use, and vasodilation effect. Although the acute increase in SCr seen in HF patients ranges from 75% to 200% from baseline after ACEI initiation, this elevation was suggested as being acceptable since ACEIs have proven benefits in decreasing mortality in this population.[8,15]

The frequency of the discontinuation rate of ACEI and the determinant factors associated with discontinuation in the real world setting has not been fully characterized. The CONSENSUS II HF trial reported a discontinuation rate of 4.6% with enalapril subsequent to the rise of SCr, while a meta-analysis of randomized controlled trials of HF patients found an ACEI discontinuation rate of 13.8%, of which only 0.4% was attributed to an increase in SCr.[7,16]

To date, no studies have evaluated both the acute elevation in SCr post-ACEI initiation and the predictors of subsequent discontinuation following an elevated SCr. Assessment of these patterns may provide insight into clinician decision making in a real world setting. The objective of our study was to assess the rates and predictors of ACEI discontinuation following an increase in SCr post-ACEI initiation, each according to baseline renal function.

Methods

We conducted a retrospective observational cohort study of all outpatients initiating an ACEI between 2002 and 2004 at the Veterans Affairs Greater Los Angeles Healthcare System (VAGLAHS). The Veterans Health Information System and Technology Architecture (VISTA) database was used to gather patient information (demographics, medication use, allergies, comorbidities, and lab results).

Initiation of ACEI was defined as the dispensing of an outpatient prescription for an ACEI with no previous record of ACEI use in the past 6 months. The following ACEI information was collected: initiation date, discontinuation date, adverse drug reactions (ADR), dosage, dosing frequency and the total daily dose. To determine the prevalence of a change in SCr, SCr was recorded at baseline (within 6 months of ACEI initiation) and 3-months (10-14 weeks) post-initiation. If SCr data was not available between 10-14 weeks (3 months), the data value of the most proximal assay was recorded. A 0.5mg/dL increase and 30% increase in SCr was considered to be clinically important since several studies have used this as a reference point to define a decrease in renal function.[5-6,14] Discontinuation of ACEI was defined as no refills within 90 days after the last filled prescription which allowed a lenient grace period for patients obtaining late refills. Patients were stratified into three baseline SCr groups (group 1: SCr <1.5mg/dL; group 2: 1.6-2.0mg/dL; and group 3: >2.0mg/dL) for analysis. We assessed above and below 0.5mg/dL and 30% to determine the threshold at which discontinuation occurred and to analyze possible differences in threshold by group. For those patients with a baseline SCr >2mg/dL and continued on an ACEI, SCr was recorded at 1-year to detect any changes post-initiation. Comorbidities (defined by ICD-9 codes: 425-cardiomyopathy, 428-congestive heart failure, 250-diabetes, 410-414-coronary artery disease, 274-gout, 401-hypertension) and

concurrent use of NSAIDs, diuretics, and beta-blockers were documented to determine potential factors associated with an increase in SCr and the discontinuation of ACEIs. Concomitant medication use was defined as having an active prescription within 1 month of the index date of ACEI prescription through the time of discontinuation.

The endpoints of this study were: the proportion of patients with a significant increase in SCr post-ACEI initiation at 3-months follow-up defined as >0.5mg/dL or >30% of baseline by group; the proportion of patients with ACEI discontinued following a rise in SCr by group; the threshold of increase in SCr associated with ACEI discontinuation, stratified by baseline SCr groups; factors (patient characteristics, comorbidities, and concurrent medications) that may be associated with discontinuation of ACEIs; and the change in SCr in patients with baseline SCr >2mg/dL and continued on ACEIs for 1 year.

Continuous baseline characteristics were expressed as the mean +/-SD or median; and categorical baseline characteristics were expressed as a proportion . Chi square test was used to compare the discontinuation rate after detecting a rise in SCr post-ACEI use between groups and to compare the threshold of increase in SCr prior to discontinuation between groups. A multiple logistic regression model was constructed to identify the factors associated with SCr elevation subsequent to ACEI initiation and ACEI discontinuation. The univariate model included patient characteristics (i.e., age, gender), comorbidities (i.e., diabetes, hypertension, coronary artery disease, chronic heart failure, systolic blood pressure (SBP)<100mmHg, gout), concomitant NSAID use, diuretic use (i.e. thiazide, loop, K+ sparing), beta-blocker use, and significant SCr elevation defined as >0.5mg/dL or >30% of baseline. Variables with p <0.2 from the univariate model were placed in a multiple logistic regression model using stepwise selection. Odds ratio with 95% confidence interval were estimated from the regression model. A p-value <0.05 was

considered statistically significant. All results were analyzed using SAS [Version 8.2, SAS Institute, Cary, NC]. This was a non-funded study approved by the institutional review board at VAGLAHS and Western University of Health Sciences.

Results

A total of 3,039 patients were initiated on an ACEI between January 2002 and December 2004 and had a SCr measured within 6 months prior to and 3 months after initiating an ACEI. (Figure 1) The average age was 65.0 years and 97.6% were male with a baseline SCr of 1.28+/- 0.86 mg/dL. Patients were stratified into three groups based on baseline SCr: Group 1 consisted of 2,497 patients with a SCr of <1.5 mg/dL (mean of 1.05+/- 0.19); group 2 had 377 patients with a SCr of 1.5-2.0 mg/dL (mean of 1.67 +/-0.16); and group 3 had 165 patients with a SCr of >2.0 mg/dL (mean of 3.75+/-2.44). (Figure 1) Hypertension (44.2%) and diabetes (28.5%) were the most frequently documented comorbidities, and the most common concomitant medications were diuretics and beta-blockers. (Table 1)

On average, patients had a follow-up SCr available at a median of 3.8 months post-ACEI initiation. The mean changes in SCr at 3 months follow-up most proximal to the 3-month interval were 0.05 +/-0.30 mg/dL, -0.01+/-0.31 mg/dL, and 0.42 +/-2.20 mg/dL respectively, by group ($p>0.05$ vs. baseline for all groups). There was no change in median SCr at 3 months follow-up for all three groups. Counting only those patients with an increase in SCr for all 3 groups, based on an increase from baseline SCr (n=182), the average percent increase in SCr prior to ACEI discontinuation was 25.98% +/-41.72 with a median of 13.49%.

At 3 months, the discontinuation rate of ACEI with or without concomitant SCr rise of >0.5mg/dL was highest in group 3 (11.5%), followed by group 2 (7.4%) and group 1 (5.4%) ($p< 0.001$) (Figure 1). In the multiple logistic regression model the variables significantly associated with a greater likelihood of ACEI discontinuation were the use of NSAIDs, diuretics, and beta-blockers. (Table 2) Of note, a significant increase in SCr (defined as >0.5mg/dl or >30 %) was not associated with ACEI discontinuation. ($p=0.498$ in the univariate model). A history of CHF,

SBP of <100mmHg at baseline and male sex were significantly associated with a reduced likelihood of ACEI discontinuation.

Changes in SCr were further evaluated based on absolute and percent change. Table 3 depicts the change in SCr prior to ACEI discontinuation, at the threshold of 0.5mg/dL and 30% increase in SCr (in 182 patients [5.9%] of all patients initiated on ACEI who had an increase in SCr). Group 3 had the highest mean increase in SCr as both absolute and percent change. A majority of the patients who experienced an increase in SCr had a change less than both 30% increase and 0.5mg/dL increase prior to discontinuation. Thus, most ACEI discontinuation did not occur following a clinically significant increase in SCr (>30% or >0.5mg/dL above baseline).

Of the 165 patients with a baseline SCr >2.0mg/dL (mean 3.75+/-2.44), only 50 patients (30.3%) were continued on an ACEI at 1 year. A total of 69 of the 165 (41.8%) patients experienced a decrease in SCr prior to discontinuation (average decrease was 1.04 +/- 1.77) and 76 (46.0%) of the patients experienced an increase (average increase was 1.86+/-0.87) and 20 (12.1%) patients experienced no change from baseline prior to discontinuation. Of the 50 patients who continued on ACEIs, only 35 patients had a follow-up in SCr at 1 year and their mean decrease in SCr was -0.24 +/-0.56 with a median decrease of -0.01mg/dL. Of these 35 patients, one (2.86%) had a larger increase in SCr (from 2.5 to 9.1 mg/dL) as compared with the remaining patients in the group (Figure 2). Excluding this subject as an outlier with a rise in SCr at 1 year that is unlikely due to ACEI, resulted in a mean decrease in SCr at 1 year in group 3 of -0.44+/-1.96 with a median of -0.01mg/dL. While the majority (54.28%) of patients in Group 3 experienced a clinically significant absolute (>0.5 mg/dL) increase in SCr of 0.98+/-1.58 compared with a baseline of 3.75+/-2.44, the 27% relative increase was not above the generally accepted threshold of >30%. Forty percent of this group experienced a decrease in SCr of

1.19+/-2.26 compared to baseline 3.75+/-2.44 and 5.7% had no change in SCr at 1-year follow-up. The average magnitude of decrease in SCr was greater than the average magnitude of increase in SCr with long term use of ACEI (1.19+/-2.26 mg/dL decrease versus 0.98 +/-1.58mg/dL increase, $p<0.001$) in patients with SCr>2 mg/dL.

Discussion

In our study, which had a large hypertensive population, we showed an increase in SCr of approximately 26% post-ACEI initiation, for those with an increase in SCr. Previous studies have documented similar acute increases in SCr of 30% in hypertensive patients and up to 200% in HF patients.[13,14] It has been suggested that ACEI discontinuation be considered if an increase in SCr exceeds 30% with ACEI use since renal function may be compromised beyond this increase and the benefits of ACEI may not outweigh the risks.[13] Our study showed that the majority of ACEI discontinuation occurred with an increase of less than 30% in SCr, thus suggesting that the threshold of concern for renal deterioration is lower in clinical practice or other factors may be more likely associated with discontinuation.

According to previous trials, a change in SCr of >0.5mg/dL may also be considered clinically significant.[8,9] The majority of the patients that discontinued ACEI in our study experienced a <0.5mg/dL change in SCr. Our study further suggested that on average, SCr was not greatly affected by ACEI since all three groups had no change in median SCr over 3 months. Thus, the discontinuation of ACEI in our population was most likely attributed to drug intolerances, such as, cough, other comorbidities, and concomitant medications, rather than the change in SCr. Only 6% of patients in the lower baseline SCr group suffered from documented cough or nausea leading to the discontinuation of ACEI. The adjusted regression analysis demonstrated that concomitant use of NSAIDs, diuretics, and beta-blockers were factors associated with a higher likelihood of ACEI discontinuation. This may be anticipated since both NSAIDs and diuretics have been documented to decrease renal function and exacerbate SCr elevations when used concomitantly with ACEI.[12] However, this may have led to the discontinuation of ACEI at a lower threshold of SCr increase. If discontinuation of ACEI was

indeed at a lower threshold than that traditionally accepted (SCr rise >0.5 or 30%), improved awareness for clinicians of the short duration of an acute rise in SCr when initiating ACEI, and dose reduction or reassessment of need for concomitant NSAIDs or diuretics may be beneficial strategies. This may confer better clinical outcomes for patients, particularly diabetic patients who would benefit from the nephroprotective actions of ACEI. Contrary to previous findings, beta-blockers were associated with a higher likelihood of discontinuation with concomitant use of ACEI in our study rather than exerting a renoprotective effect with ACEI use.[14] Male sex, CHF history, and SBP of <100mmHg were also associated with a lower chance of ACEI discontinuation. We postulated that patients with CHF and SBP <100mmHg were more likely to be maintained on an ACEI since HF studies have documented benefits of ACEI in decreasing morbidity and mortality.[1,7-8]

In patients with baseline SCr >2 mg/dL, our study showed that SCr can increase, decrease, or remain unchanged with long term ACEI use. Even though the majority of these patients experienced an acute increase in SCr, our results support ACEI use in renal impaired patients since the median change in SCr decreased and in the long term, the magnitude of decrease was much more impressive than the magnitude of increase. Our study is consistent with the prospective findings by Hou et al and retrospective findings by Hirsch et al, who both found that despite the acute increase in SCr, long term improvement in SCr occurs in many patients with impaired renal function at baseline.[11,15,16] The use of ACEI is warranted in this group of patients, along with close monitoring of renal function and electrolytes since benefits were documented in this study as well as in previous studies.[11-12,17--20]

Limitations of our study include its retrospective study design with potential for confounding.[21] Given our VA population, the vast majority of patients were male, limiting

generalizability to female patients. In addition, the electronic medical records may not be complete and accurate as is a limitation of any study relying on retrospective medical chart extraction. We did not have data on the peak creatinine, nor comprehensive assessment of all adverse events given our data extraction methods. Finally, the sample size of patients with SCr >2 mg/dL was small both pre- and post-follow-up of SCr, particularly at 1-year follow-up. Exploration of the reasons for ACEI discontinuation long-term in this group would be beneficial. However, the large population-based sample increases the generalizability of the findings.

Many clinicians may be reluctant to prescribe ACEIs to all eligible patients due to concerns of an elevation in SCr. Based on this real world study, the magnitude of increase in SCr post-ACEI initiation was slightly lower than the commonly used threshold of 30%. We found that, instead of a clinically meaningful rise in SCr, ACEI discontinuation may be more likely associated with either comorbidities, concomitant medications that may increase SCr, or a low threshold of concern for SCr elevations. Identification of other factors that may increase SCr, such as, NSAID use, diuretic use, and volume depletion should be considered before an ACEI is discontinued. The importance of monitoring should be emphasized to detect any drastic increase in SCr >30% and to manage potential adverse drug reactions. Education may be required to change practice patterns in patients with impaired baseline renal function in order to confer the clinical benefit of chronic ACEI nephroprotection.

Author Contributions:

Jackevicius: Concept/design, data interpretation, critical revision of article, approval of article, statistics

Wong: Design, data analysis/interpretation, drafting article, approval of article, statistics

Aroustamian: Data analysis, critical revision of article, approval of article, statistics

Gee: Data collection/interpretation, critical revision of article, approval of article

Mody: Concept/design, data interpretation, critical revision of article, approval of article

Funding: None.

Data Sharing: No additional data available.

Acknowledgments: None.

Table 1. Baseline characteristics of cohort (n= 3,039)

Characteristic	Value*	
Age (years, mean+/-SD, median)	65 +/-12, 65	
Gender (n, %)		
Male	2966	97.6%
Ethnicity (n, %)		
African American	414	13.6%
Caucasian	670	22.0%
Hispanic	44	1.45%
Other	341	11.2%
Not documented	1570	51.7%
Baseline serum creatinine (mg/dL, mean+/-SD, median)	Mean+/-SD, Median	
Overall (n=3,039)	Overall: Overall: 1.28 +/- 0.86, 1.10	
Group 1 : < 1.5mg/dL (n=2,497)	Group 1 : < 1.5mg/dL = 1.05 +/-0.19, 1.03	
Group 2 :1.5-2.0 mg/dL (n=377)	Group 2 :1.5-2.0 mg/dL = 1.67 +/-0.16, 1.6	
Group 3 : > 2 mg/dL (n=165)	Group 3 : > 2 mg/dL = 3.75+/-2.44, 2.7	

Co-morbidities (n, %)	n	%
Diabetes Mellitus	866	28.5 %
Hypertension	1343	44.2 %
Chronic Heart Failure	177	5.8 %
Coronary Artery Disease	445	14.6 %
Gout	69	2.3 %
SBP <100 mmHg	88	2.9 %
Concomitant Use of:		
NSAIDs	1053	34.6 %
Diuretics (total)	1771	58.3 %
Loops	773	25.4 %
Thiazides	1264	41.6 %
K- sparing	239	7.9 %
Beta-blockers	1601	52.7 %

*Values are reported as mean +/- SD; median unless otherwise noted

Table 2. Multivariate odds ratios for discontinuation of angiotensin-converting enzyme inhibitors subsequent to elevation of SCr post-ACEI initiation

Co morbidities	Multivariate Odds Ratio (95% CI)	P value
Age	1.00(1.00-1.00)*	0.452
Gender (Male)	0.74 (0.57-0.97)	0.028
Coronary Artery Disease	0.89 (0.79-1.01)	0.061
Chronic Heart Failure	0.79 (0.63-0.99)	0.041
SBP <100mmHg	0.55 (0.40-0.76)	<0.001
Concomitant use of:		
NSAIDs	1.23(1.13-1.34)	<0.001
Diuretics	1.07(0.87-1.31)	<0.001
Thiazides	1.18 (0.98-1.42)	0.084
Loops	0.99 (0.84-1.18)	0.925
Beta-blockers	1.17(1.08-1.27)	<0.001

* Values rounded from 0.999(0.995-1.002)

Table 3. Distribution in magnitude of elevation of serum creatinine in patients who discontinued angiotensin-converting enzyme inhibitors within 90 days post-initiation

Threshold of increase in SCr	Group 1 < 1.5mg/dL n=135	Group 2 1.5-2mg/dL n=28	Group 3 > 2mg/dL n=19	P value
≤ 0.5mg/dL increase	124 (91.85) 0.17 +/-0.11; 0.10	25(89.29) 0.18+/- 0.8; 0.17	8 (42.10) 0.27+/- 0.14; 0.3	<0.001
> 0.5mg/dL increase	11 (8.15) 1.23 +/- 0.99; 0.80	3 (10.71) 0.87 +/-0.25; 0.9	11 (57.90) 2.95 +/- 2.93; 1.7	<0.001
≤ 30% increase	114 (84.45) 14.15%+/- 6.85%; 11.11%	25 (89.29) 10.22%+/- 4.6%; 9.25%	12 (63.15) 12.82%+/-6.64%; 12.99%	0.01
> 30% increase	21 (15.55) 89.25%+/-81.07%; 46.67%	3 (10.71) 45.83% +/- 8.78%; 45%	7 (36.85) 100.32%+/-69.10%; 88.23%	<0.001

*Values are n (%) and mean+/- SD; median

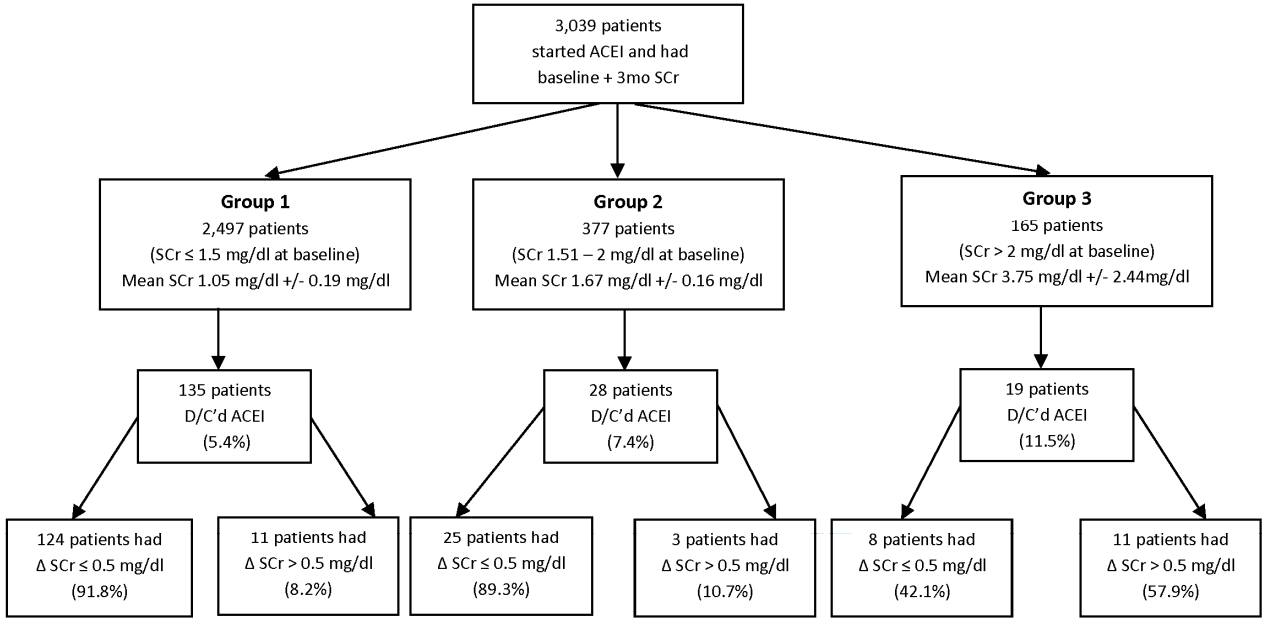
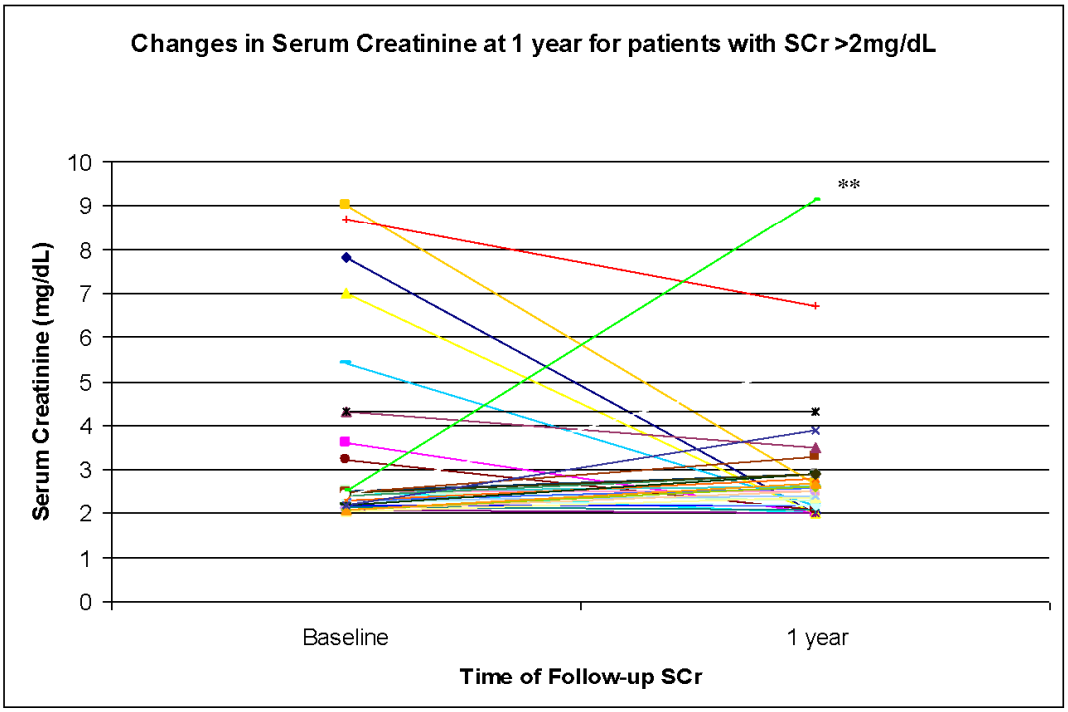


Figure1. Profile of patients included in analysis.
ACEI: Angiotensin-Converting Enzyme Inhibitors; ADR: Adverse Drug Reaction; DIC'd: discontinued; SCr: Serum Creatinine.

Figure 2: Changes in Serum Creatinine at 1 Year for Patients with SCr>2 mg/dL



*The mean change in serum creatinine was -0.24 +/- 0.56 mg/dL with a median of -0.01mg/dL. Excluding outlier (**) resulted in a mean in change serum creatinine of -0.44 +/- 1.96 mg/dL with a median of -0.01mg/dL.

N= 35

Figure Legends

Figure 1:

Title: Profile of patients included in the analysis.

Figure 2:

Title: Change in Serum Creatinine at 1 Year for Patients with SCr>2mg/dL

x-axis: Time of Follow-up SCr

y-axis: Serum Creatinine (,g/dL)

References

1. Hung SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web Site. Available at: http://www.acc.org/clinical/guidelines/failure//index.pdf.
2. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA Guidelines for the management of patients with ST-elevation myocardial infarction- Executive Summary. J Am Coll Cardiol 2004;44:671-7.
3. American Diabetes Association. Standards of Medical Care in Diabetes-2014. Diabetes Care 2014;37;S5-S13.
4. Marre M, Leblanc H, Suarez L, et al. Converting enzyme inhibition and kidney function in normotensive diabetic patients with persistent microalbuminuria. BMJ 1987;294:1448-52.
5. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 2003;289:2560-72.
6. Matsuda H, Hayashi K, Arakawa K, et al. Zonal heterogeneity in action of angiotensin-converting enzyme inhibitor on renal microcirculation. J Am Soc Nephrol 1999;10:2272-82.
7. Ahmed A, Kiefe C, Allman R, et al. Survival benefits of angiotensin converting enzyme inhibitors in older heart failure patients with perceived contraindications. J Amer Ger Soc 2002;50:1659-66.

8. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1986;316:1429-35.
9. The SOLVD Investigators. Effects of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1987;325:293-302.
10. Ghali JK, Giles T, Gonzales M, et al. Patterns of physician use of angiotensin converting enzyme inhibitors in the inpatient treatment of congestive heart failure. J. La State Med Soc 1997;149:474-84.
11. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med 2006;354:131-40.
12. Schoolwerth AC, Sica D, Ballerma B, Wilcox C. Renal considerations in angiotensin converting enzyme inhibitor therapy: A statement of healthcare professional from the Council on the Kidney in Cardiovascular Disease and the Council of High Blood Pressure Research of the American Heart Association. Circulation 2001;104:1985-91.
13. Bakris GL, Weir MR. Angiotensin- converting enzyme inhibitor associated elevations in SCr. Is this a cause for concern? Arch Intern Med 2000;168:685-88.
14. Knight E, Glynn R, McIntyre K, et al. 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). Amer Heart J 1999;138:849-55.
15. Hirsch S, Hirsch J, Udayan B, Rovin BH. Tolerating increases in serum creatining following aggressive treatment of chronic kidney disease, hypertension and proteinuria: pre-renal success. Am J Nephrol 2012;36:430-7.

16. Ruggenenti P, Remuzzi G. Dealing with renin-angiotensin inhibitors, don't mind serum creatinine. Am J Nephrol 2012;36:427-9.

17. Ahmed A. Use of angiotensin-converting enzyme inhibitors in patients with heart failure and renal insufficiency: How concerned should we be by the rise in SCr. J Amer Ger Soc 2002;50:1297-1300.

18. Raebel M, Lyons E, Andrade S, et al. Laboratory monitoring of drugs at initiation of therapy in ambulatory care. J Gen Intern Med 2005;20:1120-26.

19. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003;289:1107-16.

20. Raebel M, Lyons E, Chester E, et al. Randomized trial to improve safety monitoring of ongoing drug therapy in ambulatory patients. Pharmacotherapy 2006;5:626-29.

21. Hess D. Retrospective studies and chart reviews. Respir Care Oct 2004;49:1171-74.

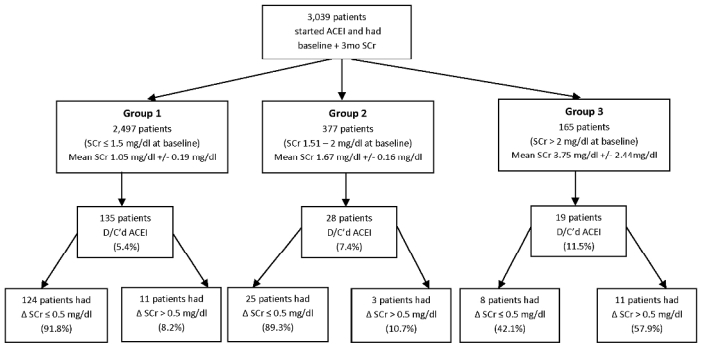
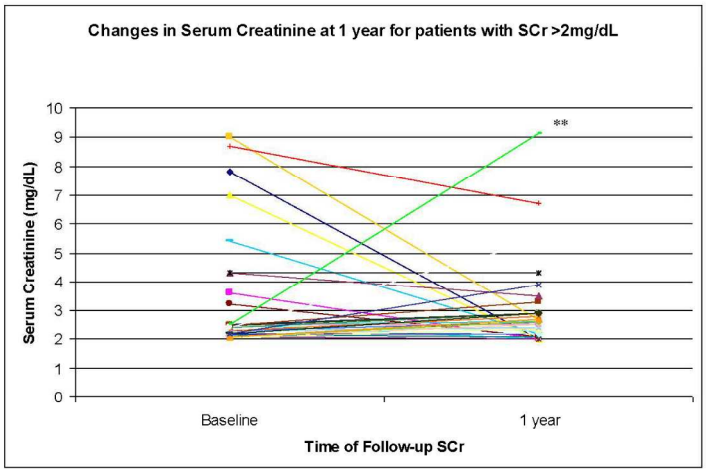


Figure1. Profile of patients included in analysis.
ACEI: Angiotensin-Converting Enzyme Inhibitors; ADR: Adverse Drug Reaction; DIC'd: discontinued; SCr: Serum Creatinine.

279x215mm (300 x 300 DPI)

Figure 2: Changes in Serum Creatinine at 1 Year for Patients with SCr>2 mg/dL



*The mean change in serum creatinine was -0.24 +/- 0.56 mg/dL with a median of -0.01mg/dL. Excluding outlier (**) resulted in a mean in change serum creatinine of -0.44 +/- 1.96 mg/dL with a median of -0.01mg/dL.

N= 35

2

215x279mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8,18
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8,14-15
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8,18
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9,17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10,17
		(*b*) Report category boundaries when continuous variables were categorized	8-10,14-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.