PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Rates and Predictors of Angiotensin-Converting Enzyme Inhibitor Discontinuation Subsequent to Elevated Serum Creatinine: A Retrospective Cohort Study
AUTHORS	Jackevicius, Cynthia; Wong, Joyce; Aroustamian, Irina; Gee, Manyee; Mody, Freny

VERSION 1 - REVIEW

REVIEWER	George Bakris The University of Chicago Medicine, USA
REVIEW RETURNED	06-Apr-2014

GENERAL COMMENTS	This is a well done study in spite of being retrospective and addresses a major issue in the general medical and nephrology community. The limitations are clearly stated by the authors, nevertheless the paper offers an important perspective. The authors should add two more references, one by a noted author that further supports their argument (S. Hirsch, et.al. Am.J Nephrol. 36 (5):430-437, 2012. and P. Ruggenenti and G. Remuzzi. Am J Nephrol. 36 (5):427-429, 2012.). Additionally the authors should note that the relationship between serum creatinine and GFR is curvilinear and thus a 30% increase at a creatinine of 2 would be 2.6 whereas at 1 it would be 1.3.

REVIEWER	Shang-Jyh Hwang Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiuing, Taiwan
REVIEW RETURNED	17-Apr-2014

GENERAL COMMENTS	The authors conducted a retrospective cohort study, and estimated the rates and factors associated with ACEI discontinuation subsequent to SCr elevation after ACEI initiation in three groups of patients (SCr<1.5,1.5-2.0 and>2.0). Predictors were identified using multivariate logistic regression modeling. They found 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. They concluded 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. Comments. 1.This is an interesting study on the issue of whether discontinuation of ACEI is caused primarily due to an elevation of Scr in three different Scr groups and analysis of related factors. The main limitation is the retrospective study based on analyzing electronic claimed dataset. Because of these limitations, the causal - effectiveness relationship cannot be documented, and the time sequence among discontinuation of ACEI, Scr measurement, and/or prescriptions of NSAIDs, diuretics, and beta-blockers was not clearly addressed, and thus we still cannot understand whether the discontinuation is exactly caused by the reason of elevation of Scr or by other causes, even in advance of other drugs prescriptions in prevention of Scr elevation in particular patients. From the whole group data analysis, this important relationship is not documented clearly. 2.The authors should address whether those drugs of NSAIDs, diuretics, and beta-blockers were used concomitantly or separately with ACEI, or ACEI discontinuation before or after the use of these drugs, respectively. 3.The last paragraph of result should be rewritten (page 10, line 22 till page 11, line 10). They mixed up too many data in descriptions, and might make readers confused. There were two numbers of “165”, and which is which is hard to understand. The order in description is also messy and confused. 4.The authors described that they used the Scr data within 10-14 weeks (or 3 months) post ACEI initiation (page 6, line 27), however, in the Result section the median time for a Scr follow-up after ACEI initiation was 3.8 months, which means half of patients might had Scr over 114 days (page 9,line 27), and this is not compatible with the definition addressed in the Method section. 5.Since the authors did not address whether ARB was ever used in these patients, could it possible that the discontinuation of ACEI was replaced by use of ARB? 6.Since they stated that the study patients were hypertensive patients. Of course, they might have co-morbidities of other conditions, but why there were a group of patients with SBP less than 100 mmHg and still taking ACEI with least chance of discontinuation. Again, it is due to mixing up all the conditions in all the study patients, however, the results were not reasonable. 7.From clinical point of view, for the postulated beneficial effect of ACEI on decrease of mortality, slow the progression of eGFR deterioration, but a possible detrimental effect of worsening the renal function, the doctors, especially nephrologists, are interested in whether the decision of continuation or discontinuation of ACEI is correct or wrong. From the retrospective study, it might be hard to answer these questions. In this study, it at least gives us the impression that discontinuation of Scr might not primarily be caused by an elevation of Scr but due to other causes. I would suggest the authors make the finding more clear instead of providing many unnecessary findings.

REVIEWER	Vikas Bhatia Univeristy of Alabama at Birmingham, USA
REVIEW RETURNED	25-Apr-2014

GENERAL COMMENTS	This is a nicely written paper and addresses an important concern. I wanted to make following comments. 1) Please proof read for English. For example the 3rd and the 4th line of the results section in the abstract. 2) I think that the data on the cause of prescription should be provided. This is important as the benefit of ACEI varies from cause to cause (like CHF vs HTN) and thus the threshold to discontinue it. 3) Please add the lack of female patients as one of the limitations of your study as it was based from a VA hospital 4) Do you have follow up till 1 year for all Serum creatinine groups (you presented for Scr >2 group) because that will give a lot of insight into the effect of ACEI on renal function (most of the patients in your study had only mildly abnormal creatinine) 5) Do you have any data on HFrEF patients as those patients have the maximum benefit from ACEI and also at the highest risk of AKI with ACEI 6) Do you have data on which patients had major adverse effects with ACEI warranting discontinuation, if yes, please mention it. 7) Please make the discussion more elaborate and how this study is clinically relevant for day to day practice. 1) Please refer to the above comments. I think this is an important topic but the paper does not address the concern of elevation of SCr wtih ACEI properly. If they address these concerns and make discussion more relevant, this can be a good paper, especially becuase of its public health importance.

REVIEWER	Jordan L. Rosenstock Lenox Hill Hospital USA
REVIEW RETURNED	28-Apr-2014

GENERAL COMMENTS	The main thrust of this paper, that ACEI discontinuation in the first 3 months seemed unconnected to changes in serum creatinine in the population studied, is an interesting and worthwhile observation. The paper is also reasonably well written and organized. However, I did have a number of concerns. First, though this is a minor point, the authors describe what sounds like a mean increase in serum creatinine of 26% after ACEI initiation in both the Abstract and Discussion. Yet in the Results, this increase seems to be only in patients who actually had an elevation in serum creatinine "prior to ACEI discontinuation" which is a much more specific group. This needs to be more clear. More fundamentally, I had some methodological concerns. It seems that only 2 creatinines were used: baseline and ninety days. How did we know that the ninety day creatinine wasn't measured well after the ACEI was stopped due to a rise in serum creatinine and the creatinine had by 90 days returned close to baseline? Wouldn't a peak creatinine be more a more useful measure? I would have liked to see if serum potassium increase preceded ACEI discontinuation. Also, there is a brief mention in the Discussion of a 6% incidence of cough in the "lower creatinine" group; I would have been interested in seeing if that also was associated with dc

	(or at least be given the incidence of cough in the CKD groups). As a frequent prescriber of ACEI in CKD patients, I was most impressed with the fact that almost 70% of patients in group 3 were no longer on ACEI at one year, despite only 11.5% discontinuation at 3 months. I would in fact be more interested in exploring why those patients stopped, which may be beyond the scope of this study. But the fact that the overwhelming majority were no longer on ACEI after one year highlights the fact that drawing inferences from the small number of patients in group 3 who continued the ACEI at one year may not be wise. In fact, the dramatic improvement in many patients shown in figure 2 highlights that this may be an atypical population. It seems strange to start an ACEI with creatinines above 4 which many had done, according to fig 2, and this suggests that those numbers may not be a true baseline. To conclude that the data support long term ACEI use in CKD patients seems a stretch. Regarding the final paragraph on page 10 -- it seems that sentences 2 and 3 should be removed as they make the paragraph difficult to follow. Aside from that, as I stated earlier, I would be interested to hear more about the 115 patients who stopped the ACEI instead of the 50 who continued. And I might want to hear more about group 2 as well. Page 10, line 8-- I believe should be "prior to" and not "subsequent to ACEI discontinuation". Though as I argued above I'm not sure how to tell which came first. I'm not sure that both the medians and means are needed. Were mean creatinine changes also not significantly different in paragraph 2 of results?

VERSION 1 – AUTHOR RESPONSE

Reviewer Name George Bakris
Institution and Country The University of Chicago Medicine, USA
Please state any competing interests or state ‘None declared’: None

This is a well done study in spite of being retrospective and addresses a major issue in the general medical and nephrology community. The limitations are clearly stated by the authors, nevertheless the paper offers an important perspective.

Reply: Thank you for your comments on the importance of our study.

The authors should add two more references, one by a noted author that further supports their argument (S. Hirsch, et.al. Am.J Nephrol. 36 (5):430-437, 2012. and P. Ruggenenti and G. Remuzzi. Am J Nephrol. 36 (5):427-429, 2012.). Additionally the authors should note that the relationship between serum creatinine and GFR is curvilinear and thus a 30% increase at a creatinine of 2 would be 2.6 whereas at 1 it would be 1.3.

Reply: As suggested, we have added the two recommended references. We have clarified in the introduction section that the relationship between serum creatinine and GFR is a relative rather than absolute proportional change, as follows:
“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 “

Reviewer Name Shang-Jyh Hwang
Institution and Country Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiuing, Taiwan
Please state any competing interests or state 'None declared': None declared

The authors conducted a retrospective cohort study, and estimated the rates and factors associated with ACEI discontinuation subsequent to SCr elevation after ACEI initiation in three groups of patients (SCr<1.5,1.5-2.0 and>2.0). Predictors were identified using multivariate logistic regression modeling. They found 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. They concluded 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.

Comments.
1.This is an interesting study on the issue of whether discontinuation of ACEI is caused primarily due to an elevation of Scr in three different Scr groups and analysis of related factors. The main limitation is the retrospective study based on analyzing electronic claimed dataset. Because of these limitations, the causal -effectiveness relationship cannot be documented, and the time sequence among discontinuation of ACEI, Scr measurement, and/or prescriptions of NSAIDs, diuretics, and beta-blockers was not clearly addressed, and thus we still cannot understand whether the discontinuation is exactly caused by the reason of elevation of Scr or by other causes, even in advance of other drugs prescriptions in prevention of Scr elevation in particular patients. From the whole group data analysis, this important relationship is not documented clearly.

Reply: Thank you for your comment. By addressing the comments below, we hope that the relationship is more clearly documented.

2.The authors should address whether those drugs of NSAIDs, diuretics, and beta-blockers were used concomitantly or separately with ACEI, or ACEI discontinuation before or after the use of these drugs, respectively.

Reply: The drugs were used concomitantly. In the methods, results and discussion sections, we have indicated concomitant. Concomitant time period is defined in the methods section.

3.The last paragraph of result should be rewritten (page 10, line 22 till page 11, line 10). They mixed up too many data in descriptions, and might make readers confused. There were two numbers of "165", and which is which is hard to understand. The order in description is also messy and confused.

Reply: We have revised the last paragraph of the results section to improve clarity of the results by removing the second sentence. This clarifies the two numbers of "165" now referring to the same group with SCr>2.

4.The authors described that they used the Scr data within 10-14 weeks (or 3 months) post ACEI initiation (page 6, line 27), however, in the Result section the median time for a Scr follow-up after ACEI initiation was 3.8 months, which means half of patients might had Scr over 114 days (page

9,line 27), and this is not compatible with the definition addressed in the Method section.

Reply: We have clarified that it was the SCr closest to 10-14 weeks in the methods, as follows: “If SCr data was not available between 10-14 weeks (3 months), the data value of the most proximal assay was recorded.”

5.Since the authors did not address whether ARB was ever used in these patients, could it possible that the discontinuation of ACEI was replaced by use of ARB?

Reply: We did not address whether ARBs replaced use of ACEI for side effects, such as, cough, however, it was not the primary purpose, and beyond the scope of our study. This would be an interesting question to explore in a separate study.

6.Since they stated that the study patients were hypertensive patients. Of course, they might have co-morbidities of other conditions, but why there were a group of patients with SBP less than 100 mmHg and still taking ACEI with least chance of discontinuation. Again, it is due to mixing up all the conditions in all the study patients, however, the results were not reasonable.

Reply: The purpose of our study was to determine general patterns of ACEI use, regardless of indication. Our study population was not solely hypertensive patients. Some patients in our study had a documented history of heart failure, and it is likely these patients who would have been more likely to have lower systolic blood pressures. In Table 1, we report that 44.2% of patients had hypertension. Hopefully referring to Table 1 clarifies our population.

7.From clinical point of view, for the postulated beneficial effect of ACEI on decrease of mortality, slow the progression of eGFR deterioration, but a possible detrimental effect of worsening the renal function, the doctors, especially nephrologists, are interested in whether the decision of continuation or discontinuation of ACEI is correct or wrong. From the retrospective study, it might be hard to answer these questions. In this study, it at least gives us the impression that discontinuation of Scr might not primarily be caused by an elevation of Scr but due to other causes. I would suggest the authors make the finding more clear instead of providing many unnecessary findings.

Reply: We agree with the reviewer that it is difficult to answer these questions from our retrospective study which can only imply associated risk factors rather than a causal relationship.

For the second recommendation, we have revised the conclusion to clarify this point, as follows:
From: “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.”

To: “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.”

Reviewer Name Vikas Bhatia
Institution and Country Univeristy of Alabama at Birmingham, USA
Please state any competing interests or state ‘None declared’: None

This is a nicely written paper and addresses an important concern. I wanted to make following comments.
1) Please proof read for English. For example the 3rd and the 4th line of the results section in the

abstract.

Reply: We have revised the results section of the abstract to clarify the wording.

2) I think that the data on the cause of prescription should be provided. This is important as the benefit of ACEI varies from cause to cause (like CHF vs HTN) and thus the threshold to discontinue it.

Reply: We concur that citing the indication for ACEI prescription would be helpful, however, our data are based on electronic medical record extraction (not chart review) and providers are not required to enter indication when prescribing. Therefore, we do not have the exact indication for the ACEI prescription in our records. It is also possible that in some patients, ACEI may have multiple overlapping indications, such as, hypertension, heart failure, diabetic nephroprotection.

3) Please add the lack of female patients as one of the limitations of your study as it was based from a VA hospital

Reply: We have revised our limitations section to add a sentence on the lack of female patients as a limitation, as follows: “Given our VA population, the vast majority of patients were male, limiting generalizability to female patients. “

4) Do you have follow up till 1 year for all Serum creatinine groups (you presented for Scr >2 group) because that will give a lot of insight into the effect of ACEI on renal function (most of the patients in your study had only mildly abnormal creatinine)

Reply: We do not have 1-year follow-up data on patients with SCr<2 in our available dataset.

5) Do you have any data on HFrEF patients as those patients have the maximum benefit from ACEI and also at the highest risk of AKI with ACEI

Reply: We do not have ejection fraction available for the patients in order to determine whether patients have reduced or preserved ejection fraction heart failure. Electronic medical record extraction of EF from earlier reports has been shown to be inconsistent and potentially unreliable, possibly leading to spurious conclusions.

6) Do you have data on which patients had major adverse effects with ACEI warranting discontinuation, if yes, please mention it.

Reply: We have available data recorded under allergies for patients who had documented cough or nausea due to ACEI. We have reported this information in the discussion section of the paper. We do not have other adverse effects available, besides cough, nausea and changes in serum creatinine.

7) Please make the discussion more elaborate and how this study is clinically relevant for day to day practice.
Reply: We have revised the last paragraph of the discussion section to clarify how this is clinically relevant for practice. The last paragraph now reads as follows:
“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."

We have also modified part of the conclusion in the abstract to clarify the conclusion in patients in the highest SCr. Group, from: "Despite an acute increase in SCr, chronic ACEI use was associated with a decrease in SCr in most patients with SCr >2mg/dL.
To: "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.

1) Please refer to the above comments. I think this is an important topic but the paper does not address the concern of elevation of SCr wtih ACEI properly. If they address these concerns and make discussion more relevant, this can be a good paper, especially becuase of its public health importance.

Reply: Thank you for your comments about the importance of this topic which was the incentive to generate the data to reinforce the continuation (rather than discontinuation) of ACEI to confer long-term clinical benefit despite a transient rise in SCr acutely. However, the conclusions were stated to remain focused on data that was indicated in the results from medical record extraction. Future studies with detailed information from chart review would be needed to conclusively answer questions about the exact temporal changes in SCr with ACEI.

Reviewer Name Jordan L. Rosenstock
Institution and Country Lenox Hill Hospital
USA
Please state any competing interests or state 'None declared': none declared

The main thrust of this paper, that ACEI discontinuation in the first 3 months seemed unconnected to changes in serum creatinine in the population studied, is an interesting and worthwhile observation. The paper is also reasonably well written and organized.

Reply: Thank you for your comments.

However, I did have a number of concerns.
First, though this is a minor point, the authors describe what sounds like a mean increase in serum creatinine of 26% after ACEI initiation in both the Abstract and Discussion. Yet in the Results, this increase seems to be only in patients who actually had an elevation in serum creatinine "prior to ACEI discontinuation" which is a much more specific group. This needs to be more clear.

Reply: We have clarified this point in the abstract and discussion sections by adding "for those with an increase in SCr". We have also added in the results the number of patients this represents (data that was originally and still is quantified in Table 2): "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%."

More fundamentally, I had some methodological concerns. It seems that only 2 creatinines were used: baseline and ninety days. How did we know that the ninety day creatinine wasn't measured well after the ACEI was stopped due to a rise in serum creatinine and the creatinine had by 90 days returned close to baseline? Wouldn't a peak creatinine be more a more useful measure?

Reply: We concur with this limitation. Unfortunately, we do not have peak creatinine available in our dataset but would like to note that the 90-day SCr is indicative of a trend of creatinine change based on baseline serum creatinine group.

I would have liked to see if serum potassium increase preceded ACEI discontinuation. Also, there is a brief mention in the Discussion of a 6% incidence of cough in the "lower creatinine" group; I would have been interested in seeing if that also was associated with dc (or at least be given the incidence of cough in the CKD groups).

Reply: We do not have information on serum potassium in our dataset as this was not in the original objectives for our study. We examined whether cough was associated with ACEI discontinuation in the univariate analysis and found it was not associated, likely due to the low incidence of cough reported.

As a frequent prescriber of ACEI in CKD patients, I was most impressed with the fact that almost 70% of patients in group 3 were no longer on ACEI at one year, despite only 11.5% discontinuation at 3 months. I would in fact be more interested in exploring why those patients stopped, which may be beyond the scope of this study. But the fact that the overwhelming majority were no longer on ACEI after one year highlights the fact that drawing inferences from the small number of patients in group 3 who continued the ACEI at one year may not be wise. In fact, the dramatic improvement in many patients shown in figure 2 highlights that this may be an atypical population. It seems strange to start an ACEI with creatinines above 4 which many had done, according to fig 2, and this suggests that those numbers may not be a true baseline. To conclude that the data support long term ACEI use in CKD patients seems a stretch.

Reply: Thank you for your comments. We have revised the discussion section to note that our findings are consistent with prior prospective and retrospective findings, as suggested by Dr. Bakris' comments above.

Regarding the final paragraph on page 10 -- it seems that sentences 2 and 3 should be removed as they make the paragraph difficult to follow. Aside from that, as I stated earlier, I would be interested to hear more about the 115 patients who stopped the ACEI instead of the 50 who continued. And I might want to hear more about group 2 as well.

Reply: We have revised the final paragraph on page 10 by removing sentence 2. We believe it reads more clearly without sentence 2.

We do not have more information to provide on groups 2 and 3 as requested, due to limitations by methodology of electronic medical record extraction.

Page 10, line 8-- I believe should be "prior to" and not "subsequent to ACEI discontinuation". Though as I argued above I'm not sure how to tell which came first.

Reply: We have changed this sentence as suggested. Thank you for noticing this inconsistency in wording.

I'm not sure that both the medians and means are needed. Were mean creatinine changes also not significantly different in paragraph 2 of results?

Reply: None of the serum creatinine increases were statistically significantly increased, however, for

the highest serum creatinine group, the increase was marginally significant with a p=0.06. We have added “p>0.05 vs. baseline for all groups “ to this sentence in the results section.

VERSION 2 – REVIEW

REVIEWER	Shang-Jyh Hwang Kaohsiung Medical University, Kaohsiung, Taiwan
REVIEW RETURNED	03-Jul-2014

- The reviewer completed the checklist but made no further comments.

REVIEWER	Vikas Bhatia University of Alabama at Birmingham
REVIEW RETURNED	07-Jul-2014

GENERAL COMMENTS	This edited version addresses some of my questions are others were limited by lack of data. In my opinion this paper is of moderate importance and de-emphasized the point of prescribing ACEI for the right indications (though they don't have the data for that, which would have made it more interesting). Also it shows the safety of ACEI in kidney disease real world patients.

REVIEWER	Jordan L. Rosenstock Lenox Hill Hospital, New York, USA
REVIEW RETURNED	11-Jul-2014

GENERAL COMMENTS	I think that in the discussion, the authors should address more explicitly the significant limitations of the methodology. These include the lack of peak creatinine (as the 90 day creatinine might have reflected a return to baseline off the ACEI), lack of data on adverse events such as hyperkalemia and cough that could have led to ACEI dicontinuation, and the significant shortcomings of the one year data as I outlined in my review. That being said, I think if these issues are addressed in the discussion, the paper is a worthwhile hypothesis generator about ACEI discontinuation.

VERSION 2 – AUTHOR RESPONSE

The reviewer(s) have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

Reply: Thank you.

Reviewer(s)' Comments to Author:

Reviewer Name Shang-Jyh Hwang
Institution and Country Kaohsiung Medical University, Kaohsiung, Taiwan
Please state any competing interests or state ‘None declared’: None declared

No further comments

Reply: Thank you.

Reviewer Name Vikas Bhatia
Institution and Country University of Alabama at Birmingham
Please state any competing interests or state ‘None declared’: None

This edited version addresses some of my questions are others were limited by lack of data. In my opinion this paper is of moderate importance and de-emphasized the point of prescribing ACEI for the right indications (though they don't have the data for that, which would have made it more interesting). Also it shows the safety of ACEI in kidney disease real world patients.

Reply: Thank you.

Reviewer Name Jordan L. Rosenstock
Institution and Country Lenox Hill Hospital, New York, USA
Please state any competing interests or state ‘None declared’: none declared

I think that in the discussion, the authors should address more explicitly the significant limitations of the methodology. These include the lack of peak creatinine (as the 90 day creatinine might have reflected a return to baseline off the ACEI), lack of data on adverse events such as hyperkalemia and cough that could have led to ACEI dicontinuation, and the significant shortcomings of the one year data as I outlined in my review. That being said, I think if these issues are addressed in the discussion, the paper is a worthwhile hypothesis generator about ACEI discontinuation.

Reply: Thank you for the comment. We have revised the limitations section as suggested by the reviewer, as follows: “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.”