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Changes in Serum Creatinine and Potassium after Initiation of Perindopril Post Acute Coronary Syndrome (ACS)

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***Abstract*— *Background**: While Angiotensin Converting Enzyme inhibitors (ACEi) are important in preventing cardiac remodeling post acute coronary syndrome (ACS), it also acutely increases serum creatinine and reduces glomerular filtration rate (GFR). Current guidelines advocates monitoring serum creatinine and potassium 2 weeks post initiation and accepts up to 30% increase in creatinine from baseline. We aim to assess the increase in serum creatinine and potassium after the initiation of perindopril in post ACS patients and to identify patient characteristics associated with different levels of creatinine increase. **Methodology**: This is a retrospective observational, cross-sectional study analyzing data collected from the patient electronic records. 143 patients with complete data were available for analysis. **Results**: Mean baseline creatinine was 91.5 ± 18.9mcmol/l increasing significantly to 95.7 ± 21.6mcmol/l ($p<0.001$). Logistic regression analysis predicted older age, increasing BMI and lower baseline creatinine to have a significantly higher chance of developing creatinine increases ≥10%. Adjusted odds ratio was 1.042 (95% confidence interval (CI) 1.00- 1.08), 1.103 (95% CI 1.02 - 1.20) and 0.959 (95% CI 0.94 - 0.98) respectively. **Conclusion**: Acute increases in serum creatinine and potassium can be seen 2 weeks into the treatment. However, ACEi induced renal impairment is rare. Further studies need to be done to risk stratify patients to recommend a more robust and cost effective monitoring protocol in our resource limited setting.*

***Keywords*—** *Acute coronary syndrome; angiotensin converting enzyme inhibitor; creatinine; perindopril; potassium*.

I. INTRODUCTION

Angiotensin Converting Enzyme inhibitors (ACEi) are a mainstay in the treatment of hypertension, heart failure, diabetic microalbuminuria or proteinuric renal diseases and for secondary prevention in coronary artery diseases (CAD) [1]. Among the ACEi, perindopril has marked restorative effects on endothelial function, thus slowing the rate of progression of heart failure [2]. Evidence from landmark trials (EUROPA and PREAMI), supported its role in prevention of cardiac remodelling [2],[3].

However, treatment with perindopril, also results in acute increases in serum creatinine and reduced glomerular filtration rate (GFR), through its vasodilatory effect on the efferent arterioles resulting in lower intraglomerular filtration rate. The potential impact on renal function should be evaluated by comparing pre initiation and post initiation levels of serum creatinine. Reduction of dose or even discontinuation is recommended if the rise of serum creatinine remains at least 30% above baseline within 2 months of initiation [4]. The Malaysian Clinical Practice Guidelines of Chronic Kidney Disease (CKD) 2018, in line with NICE Guidelines and United Kingdom Renal Association (UKRA) suggests a baseline assessment and follow up monitoring within 2 weeks of perindopril initiation [4]-[6].

Despite various clinical guidelines across the world recommending strict monitoring of renal function post initiation of ACEi, poor adherence to these guidelines has been reported in the United Kingdom (UK) [7], United States of America (USA) [8] and Netherlands [9]. Postulated explanations include the lack of evidence of clinical importance and cost effectiveness, considering the rarity of ACEi induced renal impairment in clinical trials. Also lacking are consistent monitoring guidelines tailored to different risk profiles [8]. In a recent UK general practice-based cohort study, only 9% of the population had guideline recommended ideal baseline and a follow up testing within 2 weeks of initiation of ACEi. The proportion of patients with a creatinine increase of ≥30% amongst those who had guideline recommended renal function monitoring was only 1.2%, while 0.4% developed a potassium level of >6mmol/l [7].

In the past, the work of Bakris and Weir assured us that a rise in serum creatinine up to 30% from baseline post initiation of ACEi was safe and would occur within the first 2 weeks and would stabilize within 2-4 weeks [10]. Nonetheless, there is new evidence of long term cardiorenal adverse outcomes even in creatinine increases of <30% from baseline. Schmidt *et al* showed a dose-response correlation between the levels of creatinine increase with end stage renal disease, myocardial infarction, heart failure and all cause mortality [11]. Therefore, this study aims to assess the increase in serum creatinine and potassium after the initiation of perindopril in patients post ACS in the local population and to assess relationship between patient characteristics with different levels of creatinine increase.

II. METHODOLOGY

This is a retrospective, observational, cross-sectional study conducted by analysing data collected from the patient electronic records from January 2018 to June 2019 in one of

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the tertiary hospital in Johor, Malaysia. We identified patients who were discharged from the Coronary Care Unit (CCU) within the study period via their electronic database. We utilised the CERNER Powerchart system to extract demographic details, laboratory investigations including serum creatinine and potassium at baseline and 2 weeks after treatment initiation and all relevant clinical information with a structured data collection form. This comprehensive system contains electronic health records for all patients undergoing investigations and receiving treatment in this hospital.

Patients were included if they are more than 18 years of age, had a diagnosis of either ST-elevation Myocardial Infarction (STEMI), Non ST-elevation Myocardial Infarction (NSTEMI) or Unstable Angina (USA), newly initiated on perindopril prior to discharge from the CCU and lived in the Johor Bahru district. We excluded patients with incomplete data, who have contraindications to perindopril, are pregnant, already on ACE inhibitors prior to admission and those with a preinitiation serum creatinine of >150mcmol/l. Convenience sampling method was used, in which at least 130 cases were required to achieve a power of 90% to detect a 10% difference in the change of serum creatinine post perindopril initiation.

The primary outcome was to assess the changes in serum creatinine and potassium from baseline, 2 weeks after initiation of perindopril. The secondary outcomes included the analysis of demographic data, determining the proportion of patients with increased serum creatinine ≥30% from baseline and serum potassium ≥5.6mmol/l 2 weeks after initiation of perindopril, determining the proportion of patients with serum creatinine increase of <10% and ≥10% as well as assessing the relationship between comorbidities and the risks of developing different levels of creatinine increase.

The statistical analysis was executed using IBM Statistical Package for Social Science (SPSS) software for Windows, version 21 (IBM Corp., Armonk, N.Y., USA). Descriptive data was expressed as mean with standard deviation (SD) for a normally distributed data and frequency and percentages for categorical data. The Chi-square test was used with p <0.05 is considered as statistically significant. Using a logistic regression model, we examined patient characteristics associated with creatinine monitoring of 2 weeks into treatment. Ethic approval was obtained from the Medical Research Ethical Committee (MREC), Ministry of Health (MOH) Malaysia.

III. RESULTS

A total admission to CCU during the study period was 788 patients, of which 162 patients met the inclusion criteria. After screening, 19 patients met the exclusion criteria, leaving 143 patients with complete data for analysis. Descriptive analysis for patients initiated on ACE inhibitors with creatinine monitoring 2 weeks post initiation is depicted in Table 1. Mean baseline creatinine was 91.5 ± 18.9mcmol/l and this increased significantly to 95.7 ± 21.6mcmol/l (p <0.001) 2 weeks post initiation of ACE inhibitor. The mean potassium level also increased after initiation of perindopril from 3.8 ± 0.5mmol/l to 4.0 ± 0.9mmol/l (p =0.01). Only 3 patients (2.1%) had an increase in serum creatinine of ≥30% from baseline. None of our patients had an increase in serum potassium ≥5.6mmol/l.

Our patients were predominantly male, of Malay race and had a history of smoking cigarettes. Most of our patients were overweight (44%). All patients had acute coronary syndrome with 76.9% being diagnosed with ST elevation myocardial infarction and given intravenous streptokinase on presentation. 70.6% of our patients had concurrent beta blockers and 4.9% had concurrent diuretics prescribed to them on discharge.

TABLE I. Characteristics of patients initiated on ACE inhibitors

	N=143	%
Mean Age	52.4 ± 10.1	
Age		
<30	3	2.1
30-39	18	12.6
40-49	35	24.5
50-59	48	33.6
60-69	34	23.8
≥70	5	3.5
Gender		
Male	127	88.8
Female	16	11.2
Race		
Malay	93	65.0
Chinese	26	18.2
Indian	20	14.0
Others	4	2.8
BMI		
Underweight <18.5	2	1.4
Normal 18.5-24.9	33	23.1
Overweight 25-29.9	63	44.1
Obese ≥ 30	45	31.5
Comorbids		
DM	69	48.3
HPT	61	42.7
HF	4	2.8
Baseline eGFR (ml/min/1.73m2)		
≥90	56	39.2
60-89	73	51.0
45-59	13	9.1
30-44	1	0.7
Diagnosis		
STEMI	110	76.9
NSTEMI	13	9.1
USA	20	14.0
Smoking status		
Never	41	28.7
Ever	102	71.3
Concurrent BP lowering agents		
Beta blocker	101	70.6
Calcium channel blocker	7	4.9
Diuretic	7	4.9
Others	1	0.7
Increase in serum creatinine		
<10%	95	66.4
10-19%	30	21.0
20-29%	15	10.5
≥30%	3	2.1

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The majority of our patients had a creatinine increase of <10% (66.4%). A higher creatinine increase was seen amongst the female gender with (p=0.003). Although not statistically significant, for our population, parameters associated with higher creatinine increase were Indian ethinicity and higher BMI (Table 2). Patients who never smoked had a significantly higher tendency to exhibit higher creatinine changes (p=0.05).

Comparison of mean baseline creatinine between those who ever smoked and never smoked revealed a significantly lower baseline amongst never smokers of 88mcmol/l compared to 93mcmol/l in ever smokers (p = 0.006).

TABLE II. Comparison of clinical characteristics of patients with creatinine increase <10% and ≥10% from baseline

	<10% n= 95 (%)	**≥10% n = 48 (%)**	***p*-value**
Age*	51.49 ± 9.92	54.10 ± 10.51	<0.001
Age			0.29
<40	13 (65)	7 (35)	
40-49	26 (74.3)	9 (25.7)	
50-59	34 (70.8)	14 (29.2)	
≥60	22 (55.0)	18 (14.0)	
Gender			0.003
Male	90 (70.9)	37 (29.1)	
Female	5 (31.3)	11 (68.8)	
Race			0.67
Malay	64 (68.8)	29 (31.2)	
Chinese	17 (65.4)	9 (34.6)	
Indian	11 (55.0)	9 (45.0)	
Others	3 (75.0)	1 (25.0)	
BMI			0.56
<25	25 (73.5)	9 (26.5)	
25-29.9	42 (65.6)	22 (34.4)	
≥ 30	28 (62.2)	17 (37.8)	
Baseline creatinine*	95.39 ± 18.41	83.75±17.53	<0.001
Smoking status			0.05
Never	22 (53.7)	19 (46.3)	
Ever	73 (71.6)	29 (28.4)	
Diagnosis			0.83
STEMI	72 (65.5)	38 (34.5)	
NSTEMI & USA	23 (69.7)	10 (30.3)	
Comorbids			
DM	46 (66.7)	23 (33.3)	1.0
HPT	39 (63.9)	22 (36.1)	0.6
HF	4 (100)	0	0.3

Results are given as numbers with (%), BMI = body mass index, STEMI = ST elevation myocardial infarction, NSTEMI = non-ST elevation myocardial infarction, USA = unstable angina, DM = diabetes mellitus, HPT = hypertension, HF = heart failure.
*expressed mean ± standard deviation

TABLE III. Binary Logistic Regression method forward of risk factors associated with creatinine increase of >10% post perindopril initiation

Variables	Regression coefficient (b)	Wald	Adjusted OR (95% CI)	*p*-value
Age	0.014	4.241	1.042 (1.00 - 1.08)	0.039
BMI	0.098	5.458	1.103 (1.02 - 1.20)	0.019
Baseline creatinine	-0.041	12.811	0.959 (0.94 - 0.98)	<0.001

Logistic regression analysis was used to predict the factors with a likelihood of creatinine rise by at least 10%. The predictor variables that met all assumptions and fit the model were age, BMI and baseline creatinine (Table 3). The overall model was significant at p <0.001 according to the Model chi-square statistic. It explained 19.9% of variance (Nagelkerke R^2) and correctly predicted 73.4% of cases. The rise in serum creatinine is higher with older age and increased BMI. On the other hand, patients with lower baseline creatinine had a significantly higher chance of developing creatinine increases of ≥10%.

IV. Discussion

The significance of acutely reduced eGFR after starting ACE inhibitors have been brought to light by Bakris & Weir who also illustrated the rise in creatinine being higher for those with volume depletion, heart failure and bilateral renal artery stenosis [11]. Similarly, our results also show a significant rise in mean creatinine and potassium 2 weeks into treatment, depicting its efficacy.

Acute increases of serum creatinine post ACE inhibitor treatment have shown to be associated with major clinical events, even with serum creatinine increases of <30% [13]. Looking at our population, the large majority had creatinine increases well below 30% from baseline. Further outcome studies need to be carried out to look into long term major clinical events in this group.

Despite guideline driven recommendation of repeating renal function within 2 weeks of initiation of ACE inhibitors, we find that this practice is not cost effective especially in developing countries with limited resources. Consistent with population-based studies in developed countries like UK, Netherlands and Canada, only 2.1% of our population had a creatinine increase of ≥30% while none of them had a potassium increase ≥5.6mmol/l [8]. This raises the question of routine repetition of renal function post ACE inhibitors without considering the resources available.

All patients in this study had coronary artery disease and therefore ACE inhibitors were initiated to prevent cardiac remodeling. The results are not reflective of the general population as these were the more stable cases with lower Thrombolysis in Myocardial Infarction (TIMI) Score. Patients with high TIMI Score and those who did not respond to the initial treatment were transferred to the state cardiology unit in a different hospital for intervention. Future studies should include patients with a broader range of diagnoses and comorbids for risk stratification and to provide a more robust monitoring protocol for patients started on ACE inhibitors both for hypertension and cardioprotection.

Obesity is a risk factor for chronic kidney disease, independent to metabolic syndrome. Abnormal activation of renin-angiotensin system (RAS) is one of the postulated pathophysiology [15]. Addition of ACE inhibitors should therefore confer nephroprotective effect through RAS blockade as mentioned in the REIN trial [16]. However, all our patients sustained acute coronary syndrome with possible extensive atherosclerosis. Addition of ACE inhibitors in the setting of renal artery narrowing could reduce the glomerular

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filtration rate. Hence, obesity in this subset of patients is a risk for higher creatinine increase.

Older age group was consistently reported to be associated with increased likelihood of acute increases in serum creatinine [12],[13]. Age-related reduction in muscle mass contributes to declining GFR in the elderly due to reduced urinary excretion of creatinine [17]. Addition of ACE inhibitors further reduces GFR by relative efferent vasodilatation explaining older age as a risk factor for a higher rise in serum creatinine.

Interestingly, a significant proportion of patients who never smoked had a higher rise in serum creatinine. This rise is within guideline accepted range. Smoking induces arteriosclerosis and myointimal hyperplasia of the renal arteries and intrarenal arteries and arterioles which eventually results in the production of angiotensin II, resulting in vasoconstriction [18],[19]. Treatment with ACE inhibitors causes a deleterious effect by inhibiting the excess production of angiotensin II [18]. Hence, we postulate that due to the damage sustained from smoking, these patients are unable to produce the intended response by ACE inhibitors. Therefore, non-smokers would exhibit a higher rise, albeit within limits, depicting the efficacy of the treatment.

Consistent with a recent study, lower baseline creatinine showed a greater increase in serum creatinine post ACE inhibitors [13]. In our study population, this can be explained by an association to smoking status. Patients who never smoked and had greater creatinine rise had a lower baseline creatinine, compared to those who ever did. Besides that, our data set does not include patients with eGFR less then 30ml/min/1.73m^2 as it is yet an uncommon practice to initiate ACE inhibitors at lower GFR.

V. Conclusion

Acute increases in serum creatinine and potassium can be seen 2 weeks into treatment. However, ACE inhibitor induced renal impairment is rare. In patients with post ACS, risk of acute rise in serum creatinine is higher with older age and increased BMI. Limitations include small sample size and restricted comorbids and not involving serial monitoring of serum creatinine and potassium. Further studies should be more inclusive to represent the local population. This is vital to devise risk stratification algorithms and to recommend a more robust and cost-effective monitoring protocol in our resource limited setting.

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