# Appropriate Timelines Monitoring of ACEIs/ARBs Adverse Effects and Laboratory Investigations

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## Abstract

Angiotensin-Converting Enzyme inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) initially used to treat hypertension. They can use to treat diabetes, Chronic Renal Insufficiency (CRI)(RI), Congestive Heart Failure (CHF)(HF), and myocardial infarction (MI). They recorded to have some Adverse Effects (AEs) such as Acute Renal Failure (ARF) due to the lack of appropriate timelines monitoring scheme. The following Systematic Review (SR) will focus on the AEs of the administration of ACEIs/ARBs without appropriate timelines monitoring on adult patients as the specific population under study as per the prevailing literature provides. The data sources include a search for English language literature in the Cochrane database (2015-2019), MEDLINE, and the American Heart Association Journal Database (AHA). The search terms in the above databases included ACEIs /ARBs, adults, clinical trials, laboratory trials, random trails, humans, and timeline monitoring. The study selection included literature with random control trials of patients with the above diseases and how the appropriate monitoring of ACEIs/ARBs had any effects on the angiotensin system in adults. The data extraction is based on eight sources while keeping in mind the data fields used and the quality of the studies conducted. The data synthesis criteria observed a pool of patients larger than 50,000 included in each study that was put under the administration of ACEIs/ARBs for a year while noting the appropriate timelines monitoring of ACEIs/ARBs on the potassium and creatinine and how they affect the patients if they are not properly monitored. The SR of these laboratory studies confirms that under appropriate timelines monitoring of the administration of ACEIs/ARBs, apart from treating the above diseases, have very limited AEs on the renin-angiotensin-aldosterone system of the patients under observation.

**Keywords:** Angiotensin-converting enzyme inhibitors• Angiotensin receptor blockers• Adverse effects

## Introduction

### Rationale

The ACEIs/ARBs use to treat hypertension successfully, Diabetes Mellites (DM), CRI, HF, and MI [1]. ACEs/ARBs presented problems to clinicians and researchers alike due to the need for tight timelines monitoring of patients [2]. RF is one of the AEs that result from the lack of tight timelines monitoring of patients [3]. Other studies suggest the stoppage of usage of the ACEIs/ARBs if the patient notices some symptoms such as coughs, renal insufficiency, hypotension, hyperkalemia and teratogenicity [1]. The SR aims at the best timelines monitoring scheme of ACEIs/ARBs to patients while noting the AEs that they bring on the cardiovascular system. It is, therefore, imperative that the best plans of treatment are recommended that do not worsen the patients' condition. Creatinine and potassium monitoring are suggested as the best way to note ACEIs/ARBs effects.

### Objectives

To examine whether the appropriate timelines monitoring of ACEIs/ARBs had any benefits while at the same time limiting such AEs as RF on adult patients, several randomly controlled laboratory trials on the subject are critically analyzed to better understand the subject [3,4].

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## Methods

### Protocols and Registration

Methods of the analysis and inclusion regarding the proper timelines monitoring of ACEIs/ARBs are extensive as a wide range of studies is examined from various geographical locations worldwide. The inclusion criterion is not, therefore, biased. Other reviewers could consult the Cochrane database (2020) and Medline (2020) to find the studies used in this SR.

### Eligibility Criteria

Types of studies: Randomized Laboratory trials examining the proper timelines monitoring of patients under ACEIs/ARBs while noting the AEs that might result from ACEIs/ARBs on the level of creatinine and potassium. One study considers ACEIs/ARBs effects concerning hyperkalemia [4]. A meta-analysis finds ACEIs/ARBs benefits in treating DM and proper monitoring [5]. Therefore, this SR examines eight research papers that have documented ACEIs/ARBs effects on adult patients and appropriate timelines monitoring.

### Types of Participants

Participants under this SR were adults with hypertension, diabetes, CRI, HF or MI. How a proper timeline monitoring of ACEIs/ARBs of the conditions, as mentioned earlier, had any effect on the improvement of the health of these patients is the thesis of this SR [2].

### Types of intervention

The patients under the laboratory trials were given ACEIs/ARBs over long periods while their creatinine and potassium levels were monitored continuously to observe any changes, be they negative or positive, on their kidneys. For example, Bandak et al. [4] monitored the creatinine and potassium of 69,426 participants and compared the results to 20,186 new users of blockers as a control group. Schmidt et al. [3] on the other hand, used data from 223,814 new users of ACEIs/ARBs and monitored their creatinine and potassium and kept creatinine below 30% and kept potassium below six mmol/L. The study recommended a follow-up period of two weeks after the initiation of ACEIs/

ARBs while suggesting discontinuation of ACEIs/ARBs if the creatinine levels increased above 30% while potassium above 6mmol/L.

## Types of outcome measures

Creatinine below 30% and potassium below 6mmol/L indicated progress with ACEIs/ARBs therapy while higher levels during the timelines monitoring indicated AEs on their kidneys and hence the termination of ACEIs/ARBs.

## Information Sources

Studies were procured by searching online sources of data include the journal of the **AHA** (2020)[6], American Family Physician (2020)[7], BMJ Open (2020)[8], Libertas Academica (2020)[9], bpac.org website (2020)[10], The Welsh Medicine Resource Center (2020)[11], Cleveland Clinic Journal of Medicine (2020)[12] and the National Health Services database (2020) [13]. All the resources gathered are not more than ten years old to ensure the usage of current sources of information. The initial search of the sources of data to be used in this SR was made on the Cochrane website and care was made in the use of journals that were published not more ten years ago. MEDLINE is another online database that was also used in the identification of the journals in this SR. After the journals were identified in the databases, the mentioned websites were used to further refine the search for the articles. The last search was run on 1st January 2020. A limited search to update the sources was run on 10th January 2020. There were no limits on the type of language used, and different papers were understood after translations were done.

## Search

The following terms were used in the search of the available sources about the SR: ACEIs/ARBs, hyperkalemia, creatinine, potassium, renin-angiotensin, estimated glomerular filtration (e GFR), timelines monitoring, ACEIs/ARBs, Chronic Kidney Disease (CKD), risk score, hypotension, CHF, MI, DM, and RI.

## Study Selection

The suitability of the studies selected was chosen based on an unblinded basis by thoroughly going through the available studies involving the appropriateness of timelines monitoring of ACEIs/ARBs and the AEs that were recorded following their use in a laboratory setting. The journals were also chosen based on the best sources of reliable data.

## Data Collection Process

The Cochrane Consumers and Communication Review Group data extraction template were used to evaluate the data given by the various authors in the journals under SR. The data were further analyzed to come up with a clear basis regarding the claims made in the journals. Errors were, therefore, removed by refining the search for the best journals that observe the best statistical analysis criteria. The data were further critiqued and summarized to provide a clear picture of the studies conducted and the results found in each study. Duplicate studies were removed as the process of data extraction involved the search of many databases. The available journals that are used for this SR were regarded as top-notch and hence there was no need to contact the individual authors or request for data from the original tests conducted. Huge sample sizes were preferred during the extraction of data. On the other hand, treatment comparisons were considered, and the most rigorous ones were considered for data extraction as they included randomized laboratory trials. Moreover, the outcomes of the trials in the journals under SR were compared to come up with unbiased data that could best describe the AEs if any, of ACEIs/ARBs during a proper timelines monitoring of the therapy on patients in a laboratory setting. Authors' names were juxtaposed to avoid duplication of the journals collected and hence have a more diverse set of data for the SR. The description of the study designs was clearly and thoroughly checked and understood so that the best designs were chosen while at the same time removing logical inconsistencies present in the data collection process. Statistically, significant data sets were chosen over those that were a bit bland and unclear. The data set considered under the SR is, therefore, of good quality for understanding the topic of review.

## Data Items

The information that was obtained from each study trial included the participants' characteristics such as sex, gender, age, presence or absence of the diseases such as diabetes, the extent of timelines monitoring of the patients and the model used in the inclusion or exclusion of the participants [3] The type of intervention that the authors used was also considered, including the type of drugs used, the duration of the therapies and the frequency with which the therapies were recommended. The inclusion or exclusion of a placebo was also under consideration as a variable in the data items [4]. The use of another therapy or no intervention in the studies conducted and considered. Finally, the outcomes that were analyzed included the level of improvement of the patients' health. Whether some of the CVD such as MI were dealt with or they persisted under ACEIs/ARBs use and the effect on daily life were considered. Moreover, the unintended consequences of the intervention were also considered in the data items. The length of follow up of the intervention on patients to monitor any changes that were considered during the study was also included in the data items as a variable. ACEIs/ARBs effects on women, especially pregnant ones, were also included as a variable in the data items. The assumption made is that women over the age of fifty were not pregnant during the interventions.

## Risk of Bias in Individual Studies

Bandak et al. [4] did a randomized laboratory test on a Swedish cohort that is representative of the adult population. The researchers in this study went further by conducting the trial over a period of three years and ensuring that there was a follow-up ACEIs/ARBs effects on the participants.

926 participants who died during the study were eliminated to remove bias from the study results. The use of double-blind to both the patients and the healthcare workers was also used to assess the risk of bias in the studies under review. Moreover, whether the data collectors and the assessors of the resulting outcomes were blinded was also considered in the analysis of the studies to reduce the risk of bias. The follow-up mechanism and its effectiveness were also considered in selecting the best studies in a bid to avoid bias in individual studies. Heterogeneity of the studies could, therefore, be assessed based on the methods used by the researchers in the timelines monitoring of ACEIs/ARBs to avoid bias in the size of the effects of the therapies on participants. The early stoppage of the trials was also considered to avoid the risk of bias in the studies under review. The paper by Bicket, [1] was chosen because the author reported no conflict of interest due to no funding from anyone or organization. The paper by Schmidt et al. [3] was chosen since the authors conducted the largest study on the effects of the ACEIs/ARBs therapy in the UK and that it was inclusive of all participants despite their demographics, health insurance status and hospital affiliation. Moreover, the paper by Ramos-Nino et al. [5] was chosen due to the lack of conflict of interest that the authors report and that the analysis ACEIs/ARBs effects and their timelines monitoring were taken from a huge set of data such as the HOPE, MICRO-HOPE and UKDPS meta-analysis show.

## Summary Measures

The relative risk of such AEs as RI, coughs, hypotension, hyperkalemia, and teratogenicity while monitoring ACEIs/ARBs to patients, were the primary measures of treatment effect. A meta-analysis of the outcomes was performed by considering the relative risks using randomized data samples. Quantitative analysis, on the other hand, considered whether the participants required the intervention of the ACEIs/ARBs or not while focusing on the results given in the follow-up. The primary outcome measure was the levels of creatinine and potassium in the body of the patients under study. A measurement of over 30% in the levels of creatinine and over 6mmol/L potassium levels was regarded as a signal for the stop of the therapy.

## Planned Methods of Analysis

The Breslow-Day test was adopted to measure the consistency of the data provided in all the studies under consideration of the effects of ACEIs/ARBs to participants and the need for appropriate monitoring [14]. The merit of this formulation is that the availability of a few studies is not a hindrance to SR since inconsistency of the data is an absolute variable. The measure of heterogeneity

has a consistency level that is fairly certain to find and hence recommended for the SR. The Quality of Life measurement of the available outcome data was done based on absolute terms such as coughs on the side of participants while ignoring any standard deviations such as how many coughs were recorded as normal since that would be ridiculous. In some cases, the standard means and variance of the dosages given to the patients and the means and variance of the level of potassium and creatinine were considered to come up with a better understanding of the therapy given. The change of the administration of the ACEIs/ARBs within participants was noted while the differences between participants were also noted and at the same time, the duration of monitoring of the patients was also considered in the method of analysis. Other interventions apart from the administration and timelines monitoring of participants were considered such as the use of either ACEIs/ARBs.

## Risk of Bias Across Studies

The effects of ACEIs/ARBs were noted across the studies while noting the population under study. Bandak et al. [4] used a population of 19,524 participants. while Schmidt et al. [3] used 223,814 participants in the UK under primary care for a period of 10 years from 2004 to 2014 presenting a huge population for considerations. A huge data set is advantageous because it avoids the biases from small trials that might provide wrong results. Regression asymmetry test and correlation tests were used in the analysis of the statistical data, such as the levels of potassium and creatinine of participants and the critical levels reached before the termination of the interventions [15]. The differences in study quality were also kept in mind in the analysis of the available studies. The internal consistency of the studies was also analyzed to come up with the correct conclusions regarding the timelines monitoring of ACEIs/ARBs and their AEs on the participant. For example, Bandak et al. [4] consider the base level for potassium to be 5.5 mmol/L, while Bicket, [1] considers the base level to be 5.7 mmol/L. Additionally, Bandak et al. [4] while comparing the methods and the results used, ensured that 76% of the participants had their potassium levels noted before the study began. The authors also used a control group that would be given blockers instead of the ACEIs/ARBs therapy and also monitored their potassium levels before the intervention using blockers. The authors noticed that the level of potassium in the participants was unusually high and yet they did not have kidney disease and hence refined their study using glomerular filtration to only notice that those patients with kidney disease truly had a higher level of potassium in their system than those without. The authors predicted the risk of hyperkalemia on patients on ACEIs/ARBs therapy and after a one-year study was proven right. The authors further refined their results by comparing them to a US-based Geisinger Health System and were also proven right. The authors have therefore adopted the hyperkalemia susceptibility score to come up with a measure of how potassium level in patients with either DM or HF could be best observed to mitigate AEs on patients under ACEIs/ARBs by close monitoring while maybe omitting other AEs begun. The variables are, therefore, present and consistent in the methods and results sections. Schmidt et al. [3] on the other hand, used potassium levels of 6mml/L, creatinine levels of 30%, and two weeks after treatment for monitoring, as the baselines under which the ACEIs/ARBs therapy should be conducted. In the results, however, the authors noticed that 10% of patients were not monitored two months after treatment. Moreover, 28% of the patients are the only ones who met the targeted two weeks after treatment monitoring, while 47% were monitored before treatment and two weeks after. Moreover, the authors admit that there were some limitations to the study, such as the lack of blood data of patients in the hospital database and that due to the lack of data pertaining to the level of creatinine in the blood of patients, the authors might have underestimated the relationship between creatinine levels and patient symptoms.

## Additional Analysis

Sensitivity analysis was used in the examination of the studies to determine whether the data collectors, data analysts, patients, and health workers were blinded to the laboratory monitoring ACEIs/ARBs AEs. The time needed before monitoring of the patients was also addressed in the sensitivity analysis. On the other hand, the type of patients under the study was also noted as regards the ailments that they had before the initiation of the study. The individual AEs were also analyzed taking note of the levels of creatinine and potassium

from the blood before and after the beginning of the laboratory studies. One unpublished study was considered regarding the right prescription of ACEIs/ARBs to the patients as an additional analysis. Regressions to the mean and subgroup analysis were also conducted to validate the thoroughness of the results presented by the researchers [15]. Subgroup analysis was used to compare the summary of the authors in the studies with the actual result that they found in the trials. Meta-regression, on the other hand, was used to compare the validity of the outcomes presented by the authors with the population of the study. However, regression was used cautiously to avoid oversimplifications of the findings presented.

# Results

## Study Selection

A total of eight studies were considered under SR of the AEs of prescribing ACEIs/ARBs and their timelines monitoring. There were two trials under consideration in this SR. After inquiring the databases of Cochrane, MEDLINE, PubMed, and the AHA a total of 875 accurate citations were retrieved. After removing the duplicates, 502 remained. Of these, 450 were discarded since, after a thorough reading of their respective abstracts, they did not stand up to the particular criteria pertaining to large sample size and randomized trials that are excellent for a research paper. Twenty studies were ignored due to the presence of the language barrier as they were missing English translations. The remaining 32 studies were carefully examined and read through fully. It appeared that after a careful analysis of the remaining studies, 24 of them did not meet the inclusion criteria. Four articles met the inclusion criteria and were added to the review. An additional four studies were included in the review after thoroughly crossing-checking other papers that cited them while at the same time checking the papers that the studies cited too.

## Study Characteristics

**Methods:** The two studies that monitored the effects of ACEIs/ARBs on participants were both in English. Bandak et al. [4] monitored the risk of hyperkalemia on 69,426 participants under ACEIs/ARBs for a period of three years while taking note of the GFR of both potassium and creatinine of the participants. 946 participants who died during the study were excluded from the final results. The study was conducted over a period of three years with a follow up one year later, but the results used are for the first year of the study. The Schmidt et al. [3] paper, on the other hand, included 223,914 participants from the UK for a set period of 10 years from 2010 to 2014 while only presenting results after a 12-month period of monitoring patients under ACEIs/ARBs therapy. Both studies considered adults with cardiovascular conditions such as DM, HF, MI, and hypertension.

**Participants:** Bandak et al. [4] included 69,426 participants who were mostly white with either of the following conditions: DM, cerebrovascular disease, HF, Coronary Artery Disease (CAD), and Peripheral Vascular Disease (PAD). The participants were also enquired of their use of such drugs as diuretics, blockers, and other antihypertension drugs. Half of the population under consideration was women, while the average age of the participants was 55 years. The recorded levels of potassium in the blood before the onset of therapy averaged 4.1mmol/L. Those participants with albuminuria, 20% of them had values ranging between 30 and 299mg/g while 5% had values above 300mg/g. On the other hand, Schmidt et al. [3] examined 223,814 patients with a median age of 60 years. Smoking and alcohol intake among the participants were also noted before the study was conducted. The Body Mass Index (BMI) criteria used categorized patients under underweight up to obese. The severity of CKD on patients was also noted and graded into four stages. The authors also noted the presence or absence of diseases such as HF, MI, hypertension, arrhythmia, and PAD. The baseline potassium level used was 5mmol/L.

**Intervention:** Bandak et al. [4] used a baseline 5-5.5mmol/L of potassium in the blood while GFR of less than 60ml/min per $1.73m^2$ was used to further refine the results of the study in a comparison between patients with and without kidney disease. Schmidt et al. [3] on the other hand, used the potassium level of more than 6mmol/L as a benchmark for the two weeks follow up laboratory monitoring of the effects of the ACEIs/ARBs to the renal system.

Authors at bpacnz, 2018 recommend a more detailed prescription regime to be used in the monitoring of any AEs of ACEIs/ARBs (Table 1)[10].

**Outcomes:** Bandak et al. [4] noted a marked correlation between the use of ACEIs/ARBs and the risk of hyperkalemia. The authors did a one year follow up of the participants to come up with the best measure of the effects of poor timelines monitoring of the effects of ACEIs/ARBs on the human renal system. The geographical origin of the included data was Sweden. Bicket [1] on the other hand, it recorded a decrease in both fatal and non-fatal MI, reinfarction, angina, stroke, end-stage renal disease, and HF. Moreover, the author suggested some of the AEs of the poor monitoring of ACEIs/ARBs as being RI, hypotension, cough, hyperkalemia and teratogenicity. The author goes on to list some of the ACEIs such as Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, and Trandolapril. The author suggests instances of mortality in the poor usage of ACEIs/ARBs due to the poor timelines monitoring of patients. Schmidt M et al. [3] on the other hand, recorded the susceptibility of AEs on the renal system of patients who had more than 6mmol/L and 30% potassium and creatinine levels, respectively. The authors noted the poor timelines monitoring of patients under the use of ACEIs/ARBs, which contributed to AEs such as hyperkalemia. The authors note that 76% of the participants had a baseline test follow up less than 12 months before the initiation of the treatments, while 52% had the tests less than three months while 34% had the tests less than one month before the treatment begun. On the other hand, the authors noted that during the follow-up tests, 29% were monitored less than two were after treatment, while 51% were monitored less than a month, and 62% were monitored less than two months after initiating treatment. The authors suggest a more rigorous approach of two weeks after treatment as the baseline for monitoring the effects of ACEIs/ARBs. The geographical origin of the included data was UK. Ramos-Nino et al. [5] on the other hand, show that ACEIs/ARBs are very effective in limiting the onset of diabetes while at the same time reducing complications associated with diabetes. The geographical origin of the included data was the USA. Momoniat T et al. [2] on the other hand, suggests that a proper monitoring regime is needed when prescribing ACEIs/ARBs to prevent the prevalence of RF. Without a proper monitoring regime, some of the AEs that the authors mention is hyperkalemia, RI, HF, DM, endogenous potassium load, hypertension, Addison disease, advanced age, and lower BMI. Wemerec on the other hand, suggests that ACEIs/ARBs are beneficial in the treatment of kidney but that an improper timeline monitoring of the therapy could result in hyperkalemia. The study was conducted in Wales and hence provides an alternative view of ACEIs/ARBs AEs from another demographic view. The study considered a cohort of patients less than 55 years. The authors further mention teratogenicity, urticaria, angioedema, dry coughs, RF and hypotension as some of the AEs of poor timelines monitoring of ACEIs/ARBs. The authors further suggest that the combined use of ACEIs and ARBs was more prone to extremely AEs than the use of either drug in the treatment of renal dysfunction but a combined use of the two therapies could be beneficial in the treatment of HF [16] Moreover, the authors from bpacnz [10] noted that hypertension, HF, MI and diabetic nephropathy as some of the conditions suitable for the prescription of ACEIs. When used for heart failure and hypertension, the authors noted no morbidity or mortality as AEs of the use of ACEIs/ARBs. The authors, however, do not quote any studies that they base their suggestions upon. Taking the Blood Pressure ( BP) of patients regularly, noting symptoms of hypotension and testing the level of creatinine and electrolytes are some of the best timelines monitoring of the ACEIs/ARBs therapy on patients to mitigate AEs. The authors considered New Zealand as the point of the study. The authors from (NHS, 2017) provided some recommendations concerning drug monitoring of ACEIs/ARBs, such as the prior testing of BP, eGFR, and Urea and Electrolytes (U&Es) before the onset of using ACEIs/ARBs. The potassium level baseline is put at 5mmol/L and that patients are to avoid the use of ACEIs/ARBs if they record that level. The paper recommends a range of 1- 4 weeks of monitoring patients after doses depending on the severity of any vascular disease, renal impairment, and DM. The authors' further detail the specific periods needed for both monitorings until stabilization and ongoing monitoring for such conditions as HF, hypertension, CKD, and post-MI. For each of these conditions, the authors provide a detailed time and dosage of monitoring BPs, eGFR, and U&Es. This

analysis, therefore, provides a good description of timelines monitoring of the AEs of ACEIs/ARBs while at the same time comparing the results with the other studies mentioned [13].

## Risk of Bias within Studies

Bandak et al. [4] only measured instances of hyperkalemia as an AE of ACEIs/ARBs. Bicket [1] on the other hand, did a meta-analysis of ACEIs/ARBs effects in the treatment of such conditions as DM while quoting studies that only encompassed 1,123 patients. Even though the author quoted the other four trials, this number is minimal to provide any good conclusions. Schmidt et al. [3] on the other hand, it did not have past data on creatinine levels of the patients. Ramos-Nino et al. [5] on the other hand, quotes studies that they use to base their conclusions upon without providing the criteria of selection of such studies. The authors of bpacnz [10] make a general assumption of the increase in the levels of potassium as a result of the use of ACEIs without quoting any study or trial. Additionally, the authors from Wemerec [16] make conclusions from other sources without indicating the criteria used in the selection of the data and evidence.

## Results of individual studies

Bandak et al. [4] noted a marked correlation between the use of ACEIs/ARBs and the risk of hyperkalemia. Bicket [1] on the other hand, recorded the decrease in both fatal and non-fatal MI, reinfarction, angina, stroke, end-stage renal disease, and HF. Moreover, the authors suggested some of the AEs of the poor monitoring of ACEIs/ARBs as being RI, hypotension, cough, hyperkalemia and teratogenicity. The author suggests instances of mortality in the poor usage of ACEIs/ARBs due to the poor timelines monitoring of patients. On the other hand, it recorded the susceptibility of AEs on the renal system of patients who had more than 6mmol/L and 30% potassium and creatinine levels, respectively. The authors noted the poor timelines monitoring of patients under the use of ACEIs/ARBs, which contributed to AEs such as hyperkalemia. The authors note that 76% of the participants had a baseline test follow up less than 12 months before the initiation of the treatments, while 52% had the tests less than three months while 34% had the tests less than one month before the treatment begun. The authors noted that during the follow-up tests, 29% were monitored less than two were after treatment, while 51% were monitored less than a month, and 62% were monitored less than two months after initiating treatment. The authors suggest a more rigorous approach of two weeks after treatment as the baseline for monitoring the effects of ACEIs/ARBs [3]. ACEIs/ARBs are very effective in limiting the onset of diabetes while at the same time reducing complications associated with diabetes [5]. Momoniat T at al. [2] suggest that without a proper monitoring regime, some of the AEs that the authors mention are hyperkalemia, RI, HF, DM, endogenous potassium load, hypertension, Addison disease, advanced age, and lower BMI. Wemerec [16] additionally, suggests that ACEIs/ARBs are beneficial in the treatment of kidney but that an improper timeline monitoring of the therapy could result in hyperkalemia. The authors further mention teratogenicity, urticaria, angioedema, dry coughs, RF and hypotension as some of the AEs of poor timelines monitoring of ACEIs/ARBs. The authors further suggest that the combined use of ACEIs/ARBs was more prone to extremely AEs than the use of either drug in the treatment of renal dysfunction, while a combined use of the two therapies could be beneficial in the treatment of heart failure. Moreover, the authors from bpacnz [10] noted that hypertension, HF, MI, and diabetic nephropathy as some of the conditions suitable for the prescription of ACEIs. When used for HF and hypertension, the authors noted no morbidity or mortality as AEs of the use of ACEIs/ARBs. Taking the BP of patients regularly, noting symptoms of hypotension, and testing the level of creatinine and electrolytes are some of the best timelines monitoring of the ACEIs/ARBs therapy on patients to mitigate AEs. The authors from (NHS, 20170 provided some recommendations concerning drug monitoring of ACEIs/ARBs such as the prior testing of BPs, eGFR, and U&Es before the onset of using ACEIs/ARBs. The potassium level baseline is put at 5mmol/L and that patients are to avoid the use of ACEIs/ARBs if they record that level. The paper recommends a range of 1-4 weeks of monitoring patients after doses depending on the severity of any vascular disease, renal impairment, and DM in the patients. The authors further detail the specific periods of time needed for both monitorings until stabilization and ongoing monitoring for such conditions as

**Table 1.** Authors at bpacnz, 2018 recommend a more detailed prescription regime to be used in the monitoring of any AEs of ACEIs/ARBs.

| Drug | Starting dose in hypertension | Maintenance dose in hypertension | Starting dose in heart failure | Maintenance dose in heart failure |
|---|---|---|---|---|
| Cilazapril | 0.5-1.0 mg once daily | 2.5-5 mg once daily | 0.5 mg once daily | 5 mg once daily |
| Enalapril | 5 mg once daily | 20 mg once daily | 2.5 mg once daily | 10 mg twice daily |
| Lisinopril | 2.5-10 mg once daily | 20 mg once daily | 2.5 mg once daily | 20 mg once daily |
| Perindopril | 2-4 mg once daily | 4-8 mg once daily | 2 mg once daily | 4 mg once daily |
| Quinapril | 2.5-10 mg once daily | 20-40 mg once daily | 2.5 mg once daily | 10 mg once daily |

HF, hypertension, CKD, and post-MI. For each of these conditions, the authors provide a detailed time and dosage of monitoring BPs, eGFR and U&Es of the patients [13].

### Synthesis of Results

The results presented concerning the AEs of an improper timelines monitoring of ACEIs/ARBs were noted to be fairly consistent across the board. Some of the AEs include MI, RF, hypotension, and DM. The authors therefore generally recommend the proper timelines monitoring of patients and the stop of the usage of the drugs if the AEs are detected. There was no disparity in the levels of creatinine and potassium in the blood of participants as they did not go off the mark but coalesced to around 30% and 6mmol/L respectively.

### Risk of Bias Across Studies

The studies were conducted in fairly rich developed countries and hence ignored data from other countries, especially those with a population of black or brown people. The studies are therefore biased since the effects of ACEIs/ARBs are not known from Africa, Asia, or Latin America. This is an oversight by the authors.

### Additional Analyses

The authors had the baseline range of the level of potassium above, which the AEs are bound to set in during the administration of ACEIs/ARBs as 5, 5.5, and 6mmol/L [3,4]. This is the area that had some inconsistency in the analysis of the data presented by the authors. On the other hand, additionally, the authors presented some varying prices of the ACEIs used by the patients, but they were not that far off the mark as the healthcare systems in different countries vary [5,10].

## Discussion

### Summary of evidence

In general, the evidence presented by the authors is sufficient to illustrate that ACEIs/ARBs should be administered under strict timelines monitoring regime. The use of ACEIs/ARBs in DM and hypertension among other conditions is beneficial up to a point and that without proper monitoring of the potassium and creatinine level of patients, some AEs such as RF and MI among others are bound to occur [1]. The authors present a consensus on the level of potassium as around 6mmol/L while that of creatinine at 30% in the blood to summon the termination of the intervention [3].

## Limitations

Bicket [1], Ramos-Nino et al. [5], bpacnz [10], Wemerec [16] and Momoniat T [2] all present meta-analyses that have discrepancies in the number of participants that were used across trials as some were as low as 1,123 while in other instances the number of participants considered was missing altogether. None of the trials quoted came from outside the developed countries such as the UK, Sweden, the USA and New Zealand.

## Conclusion

The need for proper timelines monitoring in the administration of ACEIs/ARBs is therefore recommended to reduce the AEs of the use of these drugs while at the same time harnessing the benefits. Healthcare workers are therefore advised to help their patients in the observation of this regime. On the other hand, the trials conducted in this respect are still very few and hence the need for future researchers to delve more into the uses of ACEIs/ARBs. Moreover, researchers need to go to other countries that the studies have not been conducted and prove or disprove the results presented.

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