EVALUATION OF RENAL SAFETY OF RAAS INHIBITOR THERAPY: A CLINICAL AND PHARMACOVIGILANT STUDY

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by

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Pulau Pinang

Mohammad Ali Khaleel

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ACE	Angiotensin Converting Enzyme Inhibitors
AKI	Acute Kidney Injury
ARBs	Angiotensin II Receptor Inhibitors
ATC	Anatomical Therapeutic Chemical
CKD	Chronic Kidney Disease
DRI	Direct Renin Inhibitors
FDA	FOOD and Drug Administration
FAERS	FDA Adverse Event Reporting System
HUSM	Hospital Universiti Sains Malaysia
IDD	International Drug Dictionary
RAAS	Renin-Angiotensin-Aldosterone System
ROR	Reporting Odds Ratio
PRR	Proportional Reporting Ratio
IC	Information Component
MedDRA	Medical Dictionary for Regulatory Activities
SMQ	Standardized MedDRA Query
SQL	Structured Query Language
ATC	Anatomical Therapeutic Chemical classification system
NHS	National Health Services
NLM	National Library of Medicine
WHO	World Health Organization
ASCII	American Standard Code for Information Interchange
ICU	Intensive Care Unite
ISR	Individual Safety Report

LIST OF APPENDICES

PENILAIAN KESELAMATAN BUAH PINGGANG BAGI TERAPI PERENCAT RAAS: KAJIAN KLINIKAL DAN FARMAKOVIGILANT

ABSTRAK

Selepas memperkenalkan satu pencegah sistem *renin-angiotensin-aldosterone* (RAAS), terdapat risiko fungsi buah pinggang yang berkurangan atau dipanggil hiperkalemia. Oleh itu, ujian-ujian pemantauan bio-kimia untuk kreatinin serum dan potasium dijalankan selepas permulaan terapi dan wajib dijalankan mengikut panduan. Namun demikian, aras pematuhan kepada garis panduan dalam menjalankan ujian-ujian pemantauan dilaporkan rendah di seluruh dunia, dan kadarnya tidak diketahui di Malaysia. Tambahan pula, kreatinin serum meningkat sebanyak ≥30% atau hiperkalemia di Malaysia selepas permulaan pencegah RAAS tidak dapat dikenal pasti. Dengan menggunakan data daripada Hospital Universiti Sains Malaysia (HUSM) daripada 2010 sehingga 2020, kami mengkaji peningkatan kreatinin serum dan kewujudan hiperkalemia, seiring dengan pematuhan kepada ujian-ujian pemantauan. Pematuhan dalam tempoh 15 dan 60 hari ke atas pencegah RAAS adalah 6.7% dan 20.3%, masing-masing. Kadar insiden kreatinin serum meningkat dalam 15 dan 60 hari, iaitu 4.9% dan 6.7%, dan untuk hiperkalemia, 1.6% dan 1.9%, masing-masing. Satu algoritma *machine learning* dibangunkan menggunakan data HUSM untuk meramal peningkatan ≥30% dalam kreatinin serum dalam tempoh 60 hari, dan ia memaparkan metrik prestasi yang kukuh (AUC: 0.945, ketepatan: 0.959, kejituan: 0.737, sensitiviti: 0.583, pengkhususan: 0.985, ketepatan seimbang: 0.784). Model peramal akan membantu pakar-pakar perubatan mengenal pasti pesakit-pesakit yang berisiko tinggi, memastikan pesakit-pesakit itu tidak akan tertinggal sebarang ujian pemantauan, dan memberi peluang kepada pakar-pakar tersebut untuk bersikap

proaktif (daripada bersikap reaktif) terhadap pelan-pelan rawatan pesakit. Untuk kajian yang lebih komprehensif, kami menggunakan *FDA Adverse Event Reporting System* (FAERS), salah satu pangkalan data farmakovigilans terbesar di dunia, mencakupi data daripada Januari 2004 sehingga September 2021. Dalam memastikan data berkualiti, kami menjalankan pembersihan, nyah-duplikasi dan piawaian nama ubat yang rapi, menggunakan RxNorm, dan satu alat khas yang kami cipta untuk tujuan ini, iaitu *International Drug Dictionary* (IDD). IDD dicipta untuk mengenal pasti nama-nama dagangan ubat-ubatan dari seluruh dunia. Set data FAERS yang telah disusun atur, bersama dengan IDD, boleh diperolehi secara percuma, dan ia membekalkan pengkaji dengan alat-alat yang boleh diakses dan pada masa yang sama menjimatkan masa dan usaha. Kami menggunakan *Reporting Odds Ratio* (ROR) dalam FAERS untuk mengkaji kaitan pencegah RAAS dengan AKI dan hiperkalemia. ROR mentah untuk pencegah-pencegah RAAS dan AKI adalah 2.67 (95% CI: 2.61 – 2.72), yang menurun kepada 1.42 (95% CI: 1.39 – 1.46) selepas menyelaraskan pengubah-pengubahnya (*confounders*). Untuk hiperkalemia, ROR mentah adalah 5.65 (95% CI: 5.43-5.88), menurun kepada 2.36 (95% CI: 2.25- 2.48) selepas penyelarasan. Dalam konteks yang sama, penyelarasan sesuatu ubat pencegah-pencegah RAAS membawa kepada kehilangan isyarat-isyarat perkaitan dengan hiperkalemia dan AKI untuk separuh daripada jumlah ubat-ubatan dan melemahkan isyarat-isyarat untuk ubat-ubatan selebihnya. Ini mengutarakan pengaruh signifikan pengubah-pengubah dalam pembangunan AKI atau hiperkalemia berikutan pengendalian terapi pencegah RAAS. Data FAERS juga digunakan untuk penyaringan interaksi ubat-ubatan untuk kes-kes AKI atau hiperkalemia terhasil daripada penggunaan pencegah-pencegah RAAS dengan ubat-ubatan lain. Saringan menggunakan model pengukuran pengecutan Omega (Ω) dan Model *Chi-Square Statistics*. Lisinopril mempamerkan

kecenderungan tertinggi untuk interaksi ubat-ubatan berkenaan AKI (146 interaksi), diikuti dengan Ramipril (79 interaksi), dan Candesartan (69 interaksi). Untuk hiperkalemia, Perindopril menunjukkan kecenderungan tertinggi (79 interaksi), diikuti oleh Candesartan (59 interaksi), dan Ramipril (44 interaksi). Saringan menunjukkan pelbagai pola interaksi dan ini mewajarkan kajian lanjutan untuk tujuan pengesahan.

EVALUATION OF RENAL SAFETY OF RAAS INHIBITOR THERAPY: A CLINICAL AND PHARMACOVIGILANT STUDY

ABSTRACT

After initiating a renin-angiotensin-aldosterone system (RAAS) inhibitor, there is a risk of decreased renal functions or hyperkalaemia. Hence, biochemical monitoring tests for serum creatinine and potassium are warranted after therapy initiation and are mandatory by guidelines. However, adherence to the guidelines for performing these monitoring tests has been reported to be low globally, with unknown rates in Malaysia. Additionally, the prevalence of serum creatinine increase by ≥30% or hyperkalaemia in Malaysia after initiating RAAS inhibitors remains unknown. Using data from Hospital Universiti Sains Malaysia (HUSM) from 2010 to 2020, we studied serum creatinine increase and hyperkalaemia prevalence, along with this monitoring tests adherence. Adherence within 15 and 60 days of RAAS inhibitor initiation was 6.7% and 20.3%, respectively. Incidence rates of serum creatinine increase within 15 and 60 days were 4.9% and 6.7%, and for hyperkalaemia, 1.6% and 1.9%, respectively. An ensembled machine learning algorithm was developed using HUSM data to predict a ≥30% increase in serum creatinine within 60 days, showing robust performance metrics (AUC: 0.945, accuracy: 0.959, precision: 0.737, sensitivity: 0.583, specificity: 0.985, balanced accuracy: 0.784). The predictive model would help physicians to easily highlight patients at high risk, make sure those patients will not miss the monitoring tests, and give physicians a chance to be proactive with patients' treatment plans rather than reactive. For a more comprehensive study, we utilized the FDA Adverse Event Reporting System (FAERS), one of the world's largest pharmacovigilance databases, covering data from January 2004 to September 2021.

To ensure data quality, we conducted thorough cleaning, deduplication, and standardization of drug names using RxNorm, and a unique tool we created for this purpose, the International Drug Dictionary (IDD). The IDD was created to identify different drug trade names from all over the world. The curated FAERS dataset and IDD are now publicly available, providing researchers with readily accessible tools and saving them significant time and effort. We used the Reporting Odds Ratio (ROR) in FAERS to study RAAS inhibitors' association with AKI and hyperkalaemia. The crude ROR for RAAS inhibitors and AKI was 2.67 (95% CI: 2.61 – 2.72), which decreased to 1.42 (95% CI: 1.39 – 1.46) after adjusting for confounders. For hyperkalaemia, the crude ROR was 5.65 (95% CI: 5.43-5.88), decreasing to 2.36 (95% CI: 2.25- 2.48) after adjustment. In the same context, adjusting for individual drugs of RAAS inhibitors led to the loss of association signals with hyperkalaemia and AKI for almost half of the drugs and weakening the signals for the remaining drugs. This highlights the significant influence of confounders in the development of AKI or hyperkalaemia following RAAS inhibitor therapy initiation. FAERS data were also utilized for drug-drug interaction screening for cases of AKI, or hyperkalaemia resulting from the concomitant use of RAAS inhibitors with other drugs. Screening employed the Omega (Ω) shrinkage measure model and Chi-Square Statistics Model. Lisinopril exhibited the highest tendency for AKI-related drug interactions (146 interactions), followed by Ramipril (79 interactions), and Candesartan (69 interactions). For hyperkalaemia, Perindopril showed the highest tendency (79 interactions), followed by Candesartan (59 interactions), and Ramipril (44 interactions). The screening revealed various interaction patterns warranting further research for confirmation.

CHAPTER 1

INTRODUCTION

1.1 Renin Angiotensin Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) is a neuroendocrine system that regulates several biological functions, such as blood pressure and fluid and electrolyte homeostasis. Renin, angiotensin II, and aldosterone are the three primary components of the RAAS, which are present in the brain, heart, vasculature, kidneys, and lungs (Kanugula *et al.*, 2023). The primary function of this system is to increase the blood pressure as a response to renal blood pressure decrease or decreased salt delivery to the distal convoluted tubule. The system increases blood pressure by increasing the vascular tone, sodium reabsorption, and water retention. The RAAS is responsible for managing blood volume and arteriolar tone long-term. The baroreceptor reflex is usually responsible for managing modest and quick adjustments, while the RAAS can alter blood volume on a more persistent basis. Activating intracellular RAAS is one of the fundamental mechanisms responsible for the negative consequences of diabetes (Zamora & Villena, 2019). Moreover, RAAS activity has been strongly associated with the progression of chronic kidney disease (CKD), where angiotensin I-converting enzyme 2 (ACE2) protease enzymatic activity was associated with the eGFR in patients with CKD (Wolke *et al.*, 2017; Yamamoto *et al.*, 2007).

As a result, the RAAS has been a classical target for many drugs treating heart failure, hypertension, diabetes mellitus, CKD, and acute myocardial infarction (S.-M. Huang, Lertora, & Atkinson Jr, 2012; Sica, 2018)

1.2 RAAS inhibitors

The group of drugs known as Renin Angiotensin Aldosterone System (RAAS) inhibitors includes Angiotensin Converting Enzyme inhibitors (ACE inhibitors), Angiotensin II Receptor Blockers (ARBs) and direct renin inhibitors (DRI). These medications are essential in managing conditions like heart failure, myocardial infarction, diabetic microalbuminuria, chronic kidney disease (CKD), and hypertension (Satoskar & Bhandarkar, 2020; Whalen, 2018).

The global antihypertensive drugs market size of about 28.7 billion USD, with a 20% market share of ACE inhibitors (The International Market Analysis Research and Consulting Group (IMARC Group), 2023), reflects the importance of the RAAS inhibitors as a therapeutic group.

ACE inhibitors and ARBs work by blocking the effects of angiotensin II downstream of the enzyme through the RAAS pathway. However, a potential drawback is that they can lead to increased plasma renin activity as they interfere with the feedback mechanism regulated by angiotensin II on production. This "escape phenomenon" may result in the inhibition of RAAS and higher synthesis of angiotensin II via ACE pathways, leading to suboptimal therapeutic outcomes (Touyz, 2013). To overcome these limitations, DRIs like aliskiren have been available for use since 2007, while the first marketed ACE inhibitor (captopril) and ARB (Losartan) were in 1981 and 1995, respectively (U.S. Food and Drug Administration, 2021).

DRI drugs, such as aliskiren, work by blocking the action of renin, which reduces the production of angiotensin I and angiotensin II in the body. RAAS inhibitors maintain salts and water homeostasis, blood pressure, and fluid balance through their activities on the heart, kidneys, and blood vessels.

The Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization (WHO) illustrates the three therapeutic groups or classes of RAAS inhibitors in table 1.1.

Table 1.1 Angiotensin Converting Enzyme inhibitors (ACE inhibitors), Angiotensin Receptor Blockers (ARB), and Direct Renin Inhibitor (DRI) as classified by the Anatomical Therapeutic Chemical (ATC) classification system

ATC code	**Drug/Class**
C09AA	ACE inhibitors, plain
C09AA01	Captopril
C09AA02	Enalapril
C09AA03	Lisinopril
C09AA04	Perindopril
C09AA05	Ramipril
C09AA06	Quinapril
C09AA07	Benazepril
C09AA08	Cilazapril
C09AA09	Fosinopril
C09AA10	Trandolapril
C09AA11	Spirapril
C09AA12	Delapril
C09AA13	Moexipril
C09AA14	Temocapril
C09AA15	Zofenopril
C09AA16	Imidapril
C09CA	Angiotensin II receptor blockers (ARBs), plain
C09CA01	Losartan
C09CA02	Eprosartan
C09CA03	Valsartan
C09CA04	Irbesartan
C09CA05	Tasosartan
C09CA06	Candesartan
C09CA07	Telmisartan
C09CA08	Olmesartan medoxomil
C09CA09	Azilsartan medoxomil
C09CA10	Fimasartan
C09XA	Renin-inhibitors
C09XA01	Remikiren
C09XA02	Aliskiren

1.3 RAAS inhibitors renal outcomes

RASS inhibitors have renoprotective properties, with or without diabetes mellitus (F.-Y. Hsu *et al.*, 2017; Leoncini *et al.*, 2020; Navis, Faber, de Zeeuw, & de Jong, 1996) through a reduction in the intraglomerular pressure and through reducing hyperfiltration (H. J. Heerspink *et al.*, 2016; F.-Y. Hsu *et al.*, 2017; Ruggenenti *et al.*, 1999).

Unfortunately, drugs that lower systemic and renal perfusion pressure tend to cause decreased GFR, which manifests as an increase in serum creatinine, and RAAS inhibitors are no exception. ACE inhibitors might have a long-term reduction in GFR, which in most cases does not reflect real damage to the kidney. In fact, the lack or the absence of increased serum creatinine after taking ACE inhibitors can be considered an alarming sign that the drug did not reduce the glomerular filtration pressure, and subsequently, no renal protection will be attained by the drug (Izzo & Weir, 2011).

On the other hand, RAAS inhibitors can also cause a decrease in aldosterone production, which in turn reduces the amount of potassium excreted in the urine and increases the risk of hyperkalaemia (Garlo *et al.*, 2018; Hundemer & Sood, 2021).

Hence, monitoring serum creatinine and potassium levels is warranted for patients who initiate RAAS inhibitor therapy. However, it is not clear if there are differences among RAAS inhibitor drugs in the risks of increasing serum creatinine or potassium after initiating therapy. Understanding RAAS inhibitors' tendency to adverse events can make personalized treatment crucial for patients at risk of elevated creatinine or potassium. Identifying drugs with lower risk aids doctors in balancing benefits and risks for each patient. Armed with this knowledge, doctors can opt for

RAAS inhibitors with potentially lower risk, reducing the need for unnecessary dosage adjustments or discontinuation of effective medication.

1.4 Acute kidney injury

Acute kidney injury (AKI), also referred to as acute renal failure (ARF), is an abrupt or rapid decline in kidney functions that occurs within hours or days, which results in the accumulation of nitrogenous products, with or without a decreased urinary output (Makris & Spanou, 2016). AKIN (Acute Kidney Injury Network), KDIGO (kidney disease: Improving Global Outcomes), and RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) are the most commonly used systems to diagnose AKI.

Worldwide, inpatients have an incidence of AKI ranging from 0.7% to 31%; patients in intensive care units (ICUs) experience an incidence of above 50% (Xu *et al.*, 2023).

AKI has been associated with high mortality, morbidity, and cost of treatment. The mortality rate of AKI patients varies from 20% to 60%, according to the population variation and severity of illness (Srisawat *et al.*, 2015). Moreover, AKI can lead to more severe conditions like CKD or End-Stage Renal Disease (ESRD).

However, regarding the RAAS inhibitors therapy initiation, clinical guidelines consider a threshold of therapy adjustment/discontinuation by an increase in serum creatinine of 30%, rather than a 50% increase as in the AKI definitions, as the consequences of the increase by 30% or even less than that have been linked in the literature to adverse outcomes (Schmidt *et al.*, 2017b; Toshiaki *et al.*, 2019).

1.4.1 AKI Aetiology

AKI is a complex condition linked with many pathophysiologic events of varying severity and cause. AKI's causes are often classified into three main pathophysiologic groups: prerenal AKI, intrinsic AKI, and postrenal AKI. These three groups are illustrated in figure 1.1.

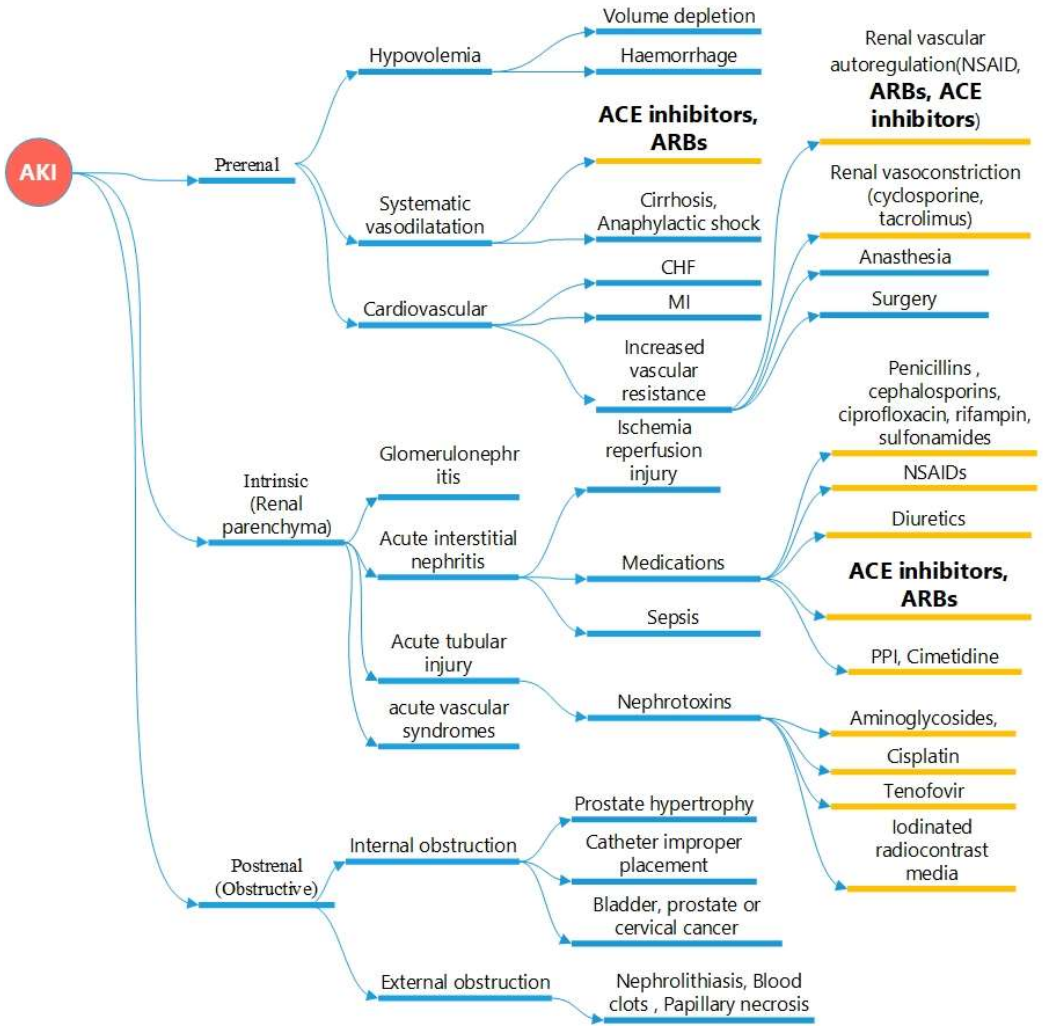

Figure 1-1 Common Causes of AKI

CHF: Congestive heart failure, MI: Myocardial infarction, PPI: Proton pump inhibitor, NSAIDs: Non-steroidal anti-inflammatory drugs, References: (Makris & Spanou, 2016; Waikar, Murray, & Singh, 2018).

1.5 RAAS inhibitors associated AKI

RAAS inhibitors have been linked to an increased risk of AKI, although it was considered debatable, at least in RAAS inhibitors monotherapy. In the absence of apparent clinical trials linking the RAAS inhibitors to AKI, the evidence in literature came from observational studies (Mansfield *et al.*, 2016; Mark *et al.*, 2020; Scheen & Delanaye, 2022; S.-Y. Yang *et al.*, 2021). None of the landmark clinical trials showed any increase in the risks of AKI with ACE inhibitors or ARBs (Tomson & Tomlinson, 2019). Most observational studies lacked the patients' level information, such as indications, comorbidities, and concomitantly administered drugs (Scheen & Delanaye, 2022). Confounding by indication is prevalent among RAAS inhibitor users because they often have underlying medical conditions that increase their risk of developing AKI, independent of the RAAS inhibitors. These conditions are frequently overlooked in retrospective analyses, compounded by the challenge of identifying an appropriate comparison group. A borderline elevated risk of acute kidney injury was shown to be associated with preoperative use of RAAS inhibitors, according to a meta-analysis of retrospective studies including patients undergoing cardiovascular surgery (OR 1.17; p =0.04) (Yacoub *et al.*, 2013). However, up to the best of our knowledge, no previous study has compared all RAAS inhibitors' associated risks of AKI or hyperkalaemia.

1.6 Hyperkalaemia

Elevation in serum potassium levels is called hyperkalaemia. There is no universal consensus on the serum potassium level, after which we can consider the case as having hyperkalaemia. Some references state that a serum potassium level over 5.0 mmol/L (McMurray *et al.*, 2012; Weinstein *et al.*, 2021; Zhang, He, & Wu, 2022)

is the diagnostic criterion for the clinical condition known as hyperkalaemia, while others consider 5.2 (Vijayakumar, Butler, & Bakris, 2019) or 5.5 mmol/L (Schroeder *et al.*, 2020) as the cut of point. However, the units of serum potassium levels can be expressed as milliequivalents per liter (mEq/L) or millimoles per litre (mmol/L) with no difference in the value. According to recent research, the prevalence of hyperkalaemia ranges from 2.6 to 2.7 percent in the general population, whereas it ranges from 8.9 to 9.3 percent in patients with CKD and heart failure (Mu *et al.*, 2020).

The adverse effects of hyperkalaemia might vary from minor abnormalities in an electrocardiogram to sudden cardiac arrest. The influence that potassium has on how cardiac functions are the most important contributor to morbidity and death(Segura & Ruilope, 2008). In a recent matched cohort study in China (J. Zhang *et al.*, 2022), researchers found that in the hyperkalaemia cohort, all-cause mortality was 5.39 times greater than in the non-hyperkalaemia cohort. Research highlights a significant economic burden associated with hyperkalaemia. Studies have shown that patients with hyperkalaemia incur considerably higher healthcare costs than those without the condition (Betts *et al.*, 2018; Haas *et al.*, 2020; Mu *et al.*, 2020; J. Zhang *et al.*, 2022). For instance, one study found a $7,208 increase in 30-day costs and a $19,348 increase in year-long costs for patients with hyperkalaemia (Neuenschwander *et al.*, 2023). These findings suggest that effective management of hyperkalaemia, especially in high-risk populations, can substantially impact patient well-being and healthcare resource utilization.

1.6.1 Drug-induced hyperkalaemia

One of the common causes of hyperkalaemia is the drug-induced form. By reducing renal potassium excretion or preventing extrarenal disposal, many drugs have

the potential to induce hyperkalaemia. A retrospective study found that more than sixty percent of patients who were not receiving dialysis and had blood potassium levels of 6.5 mEq/L or above on admission or during their hospital stay were taking at least one medicine known to induce or aggravate hyperkalaemia (Noize *et al.*, 2011). In the same study, ACE inhibitors were the predominating drug known to cause hyperkalaemia for the patients (47.1 percent). Having CKD, consuming a high amount of potassium (Weinstein *et al.*, 2021), being an older person, or taking another medication that imposes hyperkalaemia (Palmer *et al.*, 2021); are all factors that would increase the risk of developing drug-induced hyperkalaemia. Figure 1.2 shows the most known drugs to cause hyperkalaemia.

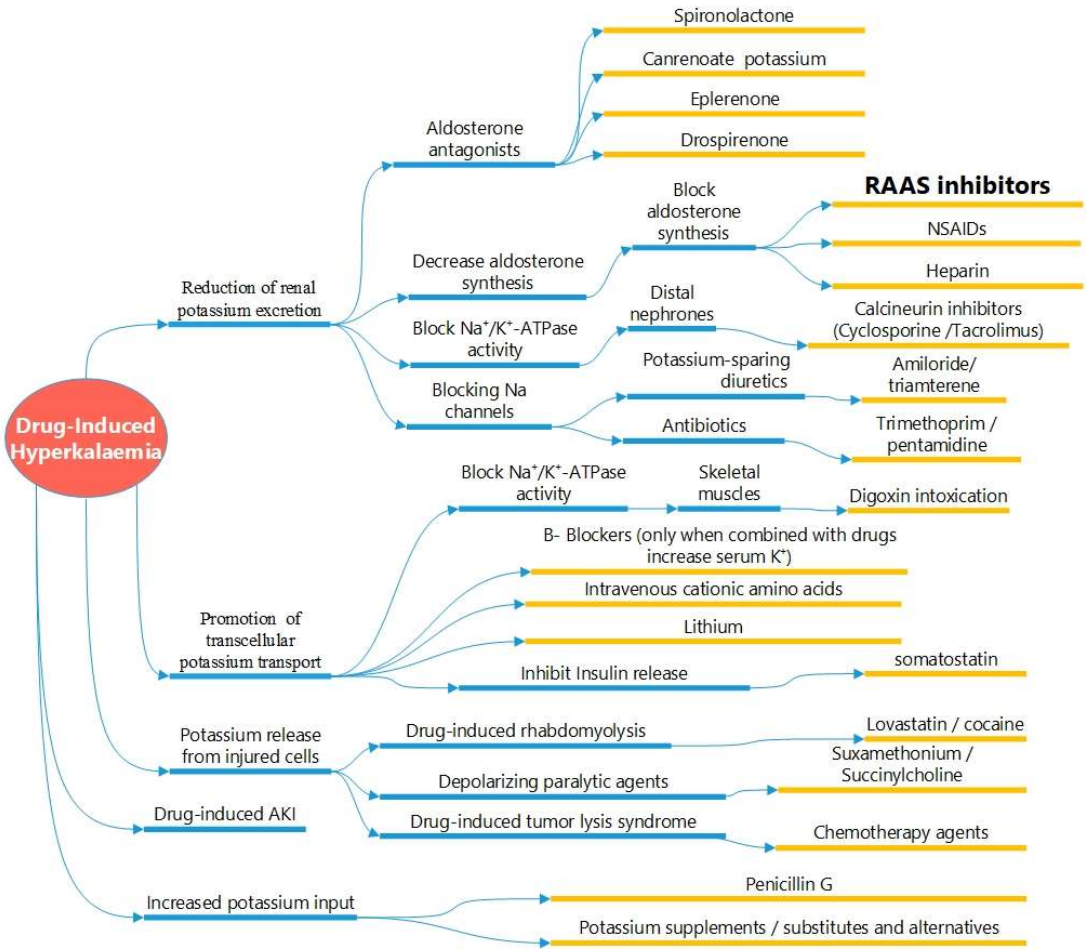

Figure 1-2 Most common drugs causing hyperkalaemia (Ben Salem *et al.*, 2014; Dunn, Benton, Orozco-Torrentera, & Adamson, 2015; Gilbert & Weiner, 2018; Noize *et al.*, 2011; Perazella, 2000)

1.7 Renal injuries and hyperkalaemia in Malaysia

Literature regarding kidney injuries in Malaysia is scarce. However, another study that was carried out on 26,663 ICU patients in Malaysia found that during the first 24 hours of admission, 24.2 percent had developed AKI (Ralib *et al.*, 2018). Another study found that chronic kidney disease was 15.48 percent in Malaysia (Saminathan *et al.*, 2020). According to the findings of these studies, kidney injuries are serious challenges facing Malaysia's public health.

Regarding hyperkalaemia, according to a study published in the Medical Journal of Malaysia in 2021, 66.5% of patients referred to the emergency department with hyperkalaemia had background medical illnesses, particularly chronic kidney disease (CKD). The prevalence of hyperkalaemia was not stated in that study (Ismail *et al.*, 2021). However, another study published in the Journal of Clinical and Diagnostic Research in 2019 reported that the prevalence of hyperkalaemia in patients with CKD in Malaysia was 31.5 % when hyperkalaemia was defined as potassium ≥ 5.5 mEq/L. This study also found that the prevalence of hyperkalaemia increased with decreasing estimated glomerular filtration rate (eGFR) and was associated with factors such as age, sex, and the use of certain medications (Sarafidis *et al.*, 2012).

1.8 Predictive modeling of the increased serum creatinine after initiating RAAS inhibitors therapy

Predictive modeling in healthcare represents a significant advancement in patient care and disease management. Its application in predicting AKI has been recently growing very fast, especially for models employing machine learning

algorithms (Yu, Ji, Huang, & Feng, 2023; X. Zhang *et al.*, 2022). Elevated serum creatinine is a crucial indicator of kidney function deterioration and requires careful monitoring. Traditionally, monitoring tests are conducted after drug initiation, and physicians react to the results by either continuing, adjusting, or discontinuing medications, which tend to be reactive rather than proactive. This approach risks delayed responses when timely intervention is crucial, potentially leading to higher risks of missed adverse events (i.e., AKI), postponed optimal treatments, and suboptimal patient outcomes. In this context, developing and implementing a predictive model to detect early changes in serum creatinine levels in patients starting RAAS inhibitors could revolutionize patient management. Utilizing patients' demographics, laboratory data, current medications, and comorbidities, such a model aims to predict and identify patients at risk of significant renal function changes, enabling timely and more effective and timely clinical interventions.

1.9 Recommendations for monitoring tests

As mentioned earlier, RAAS inhibitors tend to increase serum creatinine and potassium levels after therapy initiation; as a result, monitoring tests are warranted after RAAS therapy initiation in both literature (George L. Bakris & Agarwal, 2018; G. L. Bakris & Weir, 2000) and national and international guidelines (NHS-SPS, 2021; NICE, 2022,b; M. A. Weber *et al.*, 2014). The National Health Service Specialist Pharmacy Service (NHS-SPS) recommends that for heart failure patients, RAAS inhibitor therapy initiation or dose adjustment to monitor serum creatinine, sodium, and potassium within two weeks, followed by monthly monitoring for three months. For hypertensive patients, the NHS-SPS recommends monitoring within seven days for serum creatinine, sodium, and potassium; for CKD or post-myocardial infarction,

it is recommended to monitor within two weeks. The National Institute for Healthcare and Care Excellence (NICE) recommends that for hypertension cases, measurements for serum creatinine and electrolytes be performed before and within one to two weeks of starting ACE inhibitors or ARBs therapy and within one to two weeks of any dose increment. The NICE also states that if the estimated glomerular filtration rate (eGFR) decreases by 25% or the serum creatinine increases by 30%, investigate the cause, make dose adjustments, or discontinue the medication. For potassium levels, the NICE recommends that if the serum potassium is 5.0 mmol/L or more, investigate the cause, reduce the medication dose, and recheck within 5 to 7 days, while if it is above 6.0 mmol/L, discontinue the medication. For heart failure patients using ACE inhibitors, the NICE have similar recommendations to that of testing intervals, but different thresholds. Most guidelines recommend discontinuing or adjusting the dose of ACE inhibitors or ARBs if serum creatinine exceeds a 30% increase compared to the baseline or if hyperkalaemia occurs post-initiating the therapy.

According to the local Malaysian guidelines, after initiating ACE inhibitors, serum creatinine, and potassium should be checked within two weeks; if there is a persistent increase in serum creatinine of more than 30% or if a sustained increase in serum potassium of greater than 5.6mmol/L occurs for more than two months, then the dosage should be lowered or stopped (Ministry of Health Malaysia, 2018).

1.9.1 Adherence to the monitoring tests

Evaluating adherence to clinical guidelines serves as a method for assessing the quality of healthcare services (Kötter, Blozik, & Scherer, 2012). The adherence to monitoring tests, in general, is reported to be low in the literature. A UK cohort study found that only one-tenth of the patients completed the monitoring for serum

potassium and creatinine after initiating ACE inhibitors or ARBs (Schmidt *et al.*, 2017,a). In another Canadian study involving two centers, one center had 25.6%, and the other had a 32% adherence rate to the monitoring tests (Parikh *et al.*, 2020).

However, it is unclear how much these guidelines are followed in the local clinical practice settings. To the best of our knowledge, this is the first study in Malaysia to measure adherence to monitoring tests required by the guidelines.

1.10 Pharmacovigilance & FAERS: Monitoring Drug Safety

The development of new medications is a rigorous process involving extensive pre-clinical and clinical trials. However, these controlled settings often involve limited patient populations and relatively short durations of drug exposure. Consequently, some rare or unexpected adverse drug reactions may not be identified until after a medication reaches the broader market.

Pharmacovigilance bridges this gap by actively monitoring the safety of medications after they are approved for use. This crucial practice encompasses systematically collecting, analyzing, and evaluating data on adverse drug reactions. Pharmacovigilance plays a vital role in protecting public health by continuously monitoring drug safety in the real world. Pharmacovigilance can be defined as "The Science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem" (WHO, 2019).

A cornerstone of pharmacovigilance is the use of spontaneous adverse event reporting systems. These systems facilitate the voluntary reporting of suspected adverse drug reactions by healthcare professionals, patients, and consumers. This real-world data provides valuable insights into the safety profile of medications beyond the data collected during clinical trials.

In the United States, the FDA Adverse Event Reporting System (FAERS) serves as the primary platform for spontaneous ADR reporting. This database, maintained by the Food and Drug Administration (FDA), allows healthcare providers and the public to submit reports of suspected adverse drug reactions associated with any medication or vaccine. The wealth of data within FAERS offers a unique opportunity to explore medication safety comprehensively. By leveraging this rich resource, researchers can contribute significantly to the field of pharmacovigilance. Researchers can analyze trends, identify potential safety signals, and explore the real-world safety profile of specific medications by utilizing FAERS data.

1.11 A comprehensive study involving all drugs of the RAAS inhibitors associated with AKI or hyperkalaemia

To improve the comprehensiveness of our research, a large database is needed in terms of the spectrum of RAAS inhibitors included in the study and the available drugs for adverse drug-drug interactions.

The FDA Adverse Event Reporting System (FAERS) database is one of the most comprehensive databases in the world, documenting adverse drug reactions spontaneously reported to the FDA. It provides valuable insights into drug reactions on a large scale and has the benefit of capturing a broad variety of adverse effects across diverse populations.

However, the FAERS database is not without limitations. The nature of its open and spontaneous reporting system means that it cannot be solely relied upon to make clinical recommendations. It lacks granularity in critical areas such as current and historical laboratory analyses, comorbidities, medication history, and detailed patient demographics. Additionally, the incidence rate of adverse events cannot be calculated

from any spontaneous adverse event reporting database, as the actual count of patients who were given the drug is unknown, and also due to under-reporting trends of the adverse events due to the nature of the spontaneous adverse events reporting running model, where, unlike controlled clinical trials, spontaneous reporting relies on healthcare professionals and patients to submit reports voluntarily. This dependence on individual initiative can lead to under-reporting. Moreover, reporters to such databases usually focus on severe events, where milder cases of hyperkalaemia might be overlooked or not reported, which can also lead to under-reporting.

To overcome the limitations inherent in spontaneous reporting systems like FAERS, a combined approach that leverages its strengths alongside a complementary analysis of patient data from hospital records can be employed. This comprehensive strategy would provide a more nuanced understanding of the renal safety profile of RASS inhibitors.

1.12 Spontaneous adverse drug reporting systems: A Crucial Tool

Understanding drug risks and safety profiles requires continuous drug monitoring, surveillance, and assessment of associated adverse drug reactions. One of the essential sources of real-world adverse drug reaction information is the spontaneous adverse drug reaction reporting system, which is an inexpensive and widely used tool for detecting new, rare, and severe adverse drug reactions (Nour & Plourde, 2019). It is common in both developed and developing countries to have an official body or authority dedicated to organizing the activities of spontaneous adverse drug reporting in that country and overseeing the analysis of these reports. The United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is one of the world's largest spontaneous adverse drug reporting systems.

1.13 Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS)

Over two million reports of drug or biologic product-related adverse events and medication errors are received annually by FDA through FAERS, making it an invaluable source of adverse drug reactions mining globally. Moreover, FAERS is open to the public and not limited to the United States, as 28% of reports are from outside the US (M. A. Khaleel *et al.*, 2022). FAERS commenced on September 10, 2012, succeeding the Adverse Event Reporting System (Legacy AERS or LAERS), which has been publicly available since 2004. To provide a clean dataset of FAERS, two critical steps must be adequately addressed: case report deduplication and standardizing drug names.

Unstructured drug name input and uncontrolled case duplication in the FAERS database (Hauben, Reich, De Micco, & Kim, 2007; Poluzzi, Raschi, Piccinni, & De Ponti, 2012) are two of the major known challenges to using the FAERS database. Drug names in FAERS may have misspellings, typographical errors, different formats, and naming conventions of the drug's active component, strength, dosage form, route of administration, or even the name of the drug's manufacturer. Therefore, the same drug entity can be found in the database in various formats, making it impossible to aggregate all these different drug name formats into a single drug entity without recognizing all these formats as one drug name, which requires performing appropriate data wrangling and cleaning, followed by mapping and standardizing drug names to a reference drug nomenclature vocabulary. Researchers also face difficulty extracting the active ingredient identities from various multinational brand names, as the FAERS database receives reports from all over the world (M. A. Khaleel *et al.*, 2022). To solve

this specific problem of international drug trade names, we need a machine-readable source of international drug names to automate the drug identification process.

Due to the uncontrolled inputs of reports from various sources (such as healthcare professionals, patients, or manufacturing companies), case report duplication is a known issue in spontaneous adverse event reporting databases (G. Niklas Norén, Orre, Bate, & Edwards, 2007), and FAERS is no exception. This would make some case reports to be reported multiple times from different sources. Moreover, some case reports could have multiple entries from follow-up reports of the same initial instance, another source of the duplication of case reports.

All these concerns would impact the integrity and accuracy of the data analysis conducted on the database if they were not adequately managed and reduced to a minimum. Therefore, time-consuming and multi-step raw data processing should be undertaken first. This would require knowledgeable people to query the database to finally obtain a clean, normalized, and standardized dataset, making it suitable for usage by any researcher. Most researchers lack the knowledge and technical expertise to handle such a burden before starting FAERS data mining. To the best of the researcher's knowledge, the most recent clean dataset from the FAERS database that is open to the public goes up to June 2015 (Banda *et al.*, 2016). Since then, the FAERS database has been expanded to include millions of new case reports, in addition to the introduction of numerous new drugs into the market.

1.14 RxNorm

RxNorm is a standard clinical drug vocabulary that includes other source vocabularies and the RxNorm source vocabulary (Nelson *et al.*, 2011). These source vocabularies encompass drug-related information and terminologies in different

healthcare systems or applications. Here are just an examples of some of source vocabularies:

- The National Drug File (NDF), overseen by the U.S. Food and Drug Administration (FDA), which furnishes standardized terminology for drugs available in the United States.

- The Anatomical Therapeutic Chemical Classification System (ATC), developed and maintained by the World Health Organization Collaborating Center for Drug Statistics Methodology, categorizes drugs into five levels.

- The Veterans Health Administration National Drug File (VANDF), curated by the U.S. Department of Veterans Affairs, encompasses data on clinical drugs, drug classes, ingredients, and National Drug Code (NDC) Directory codes.

- DRUGBANK, a database supported by the Canadian Institutes of Research, Alberta Innovates - Health Solutions, and The Metabolomics Innovation Centre (TMIC), provides comprehensive information on FDA-approved small molecule and biotech drugs, nutraceuticals, experimental drugs, and non-redundant protein sequences associated with these drugs.

The RxNorm was created by the United States National Library of Medicine (NLM) to fill the gap of needing a standardized system for identifying and naming medications. RxNorm is used to improve communications between different healthcare systems, pharmacies, and electronic health records in the United States, as each system has its nomenclature. RxNorm also provides relationships between drug names, which would help normalize drug names to the targeted active ingredient level.

RxNorm is open to the public after proper user registration. All these factors make the RxNorm the best choice to standardize the drug names in FAERS to the active ingredient level.

1.15 International Drug Dictionary (IDD)

A drug dataset containing international brand names is essential for identifying international drug names in the FAERS database in the cleaning process. This dataset is invaluable for those studying various international drug brands or seeking to map multiple trade names with their active ingredients in one step. However, many websites on the internet offer free access for a single drug search to identify international drug trade names but not for a list of drugs to be searched and identified. Up to the best of our knowledge, no such a tool or software is freely available for users, so creating such a dataset or software would greatly enhance the researchers involved in identifying drug brand names from international origin, especially when hundreds or thousands of drugs are needed to be identified and linked to its active ingredients.

1.16 Weber effect

In 1984, Weber suggested that reporting to spontaneous adverse events systems follows a specific pattern, in which the reports peak in the second year of marketing that specific drug, followed by a decline in reporting over the years (J. C. P. Weber, 1987). This phenomenon might be explained by the increased emphasis of medical professionals on a newly developed medication, suggesting that the quantity of newly identified signals may rise and gradually decrease over time. The presence of the Weber effect is considered as a reporting bias (Arora, Jalali, & Vohora, 2017; Satake *et al.*, 2021). Moreover, the increased media attention due to regulatory authority

letters to medical professionals or resulting from excessive advertising campaigns may increase the reporting of adverse events more than expected in a phenomenon called "notoriety bias" (Poluzzi *et al.*, 2012).

1.17 Pharmacovigilant

The World Health Organization (WHO) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems" (World Health Organization. Quality & Safety of Medicines, 2006). This field is critically important in ensuring the safety and efficacy of medications once they have entered the market. While clinical trials provide essential data on a drug's safety and efficacy, they are limited by their relatively small sample sizes, controlled environments, and specific patient populations. Pharmacovigilance extends the monitoring of drugs into the real world, where a broader and more diverse population may experience different side effects or drug interactions not observed during clinical trials.

The importance of pharmacovigilance cannot be overstated. It serves as an ongoing safety net that catches adverse drug reactions that were not evident during the initial phases of drug development. Through rigorous monitoring, reporting, and analysis, pharmacovigilance systems can identify previously unknown medication risks, improving patient safety. When a potential risk is identified, regulatory authorities can take action, such as updating drug labels with new warnings, restricting use, or even withdrawing the drug from the market if necessary.

1.18 Problem Statement

Kidney disease (acute or chronic) is a major global and local burden in Malaysia, and drug-induced nephrotoxicity is considered one of the main streams of kidney disease (Sales & Foresto, 2020).

RAAS inhibitors can cause an increase in serum creatinine and potassium after initiating therapy for some patients, which, if persisted, requires dose adjustment or drug discontinuation as stated by both local and international guidelines. The prevalence of this increase is not fixed in literature and is controversial, ranging from 1.7% to 10.5% for increased serum creatinine (Pitt *et al.*, 1997; Schmidt *et al.*, 2017b) and from 0.4% to 2.1% (Jun *et al.*, 2021; Schmidt *et al.*, 2017,a). However, it is still unclear what causes some individuals' serum creatinine levels to rise while others' levels remain stable. More research is needed to clarify this discrepancy and identify the elements generating the differing reactions.

Guidelines require monitoring tests of serum creatinine potassium before and after starting the therapy. However, it has been reported in the literature that patients' adherence to the monitoring tests for serum creatinine and potassium after initiating the therapy is low, and up to the best of the researcher's knowledge, the local Malaysian patients' adherence to the biochemical monitoring tests in general, and to specifically the monitoring tests after initiating RAAS inhibitors have never been investigated before. Failure to monitor adherence to biochemical tests could result in missed opportunities to improve healthcare systems. If low adherence rates to these tests are found, more patients risk having elevated serum creatinine levels or hyperkalaemia without timely intervention from healthcare providers. Consequently, the higher the non-adherence to these monitoring tests, the more actions are required from healthcare

providers to ensure patients undergo the necessary tests. Most research evaluating the renal safety profile of RAAS inhibitors focused on the overall ACE inhibitors or ARBs rather than on individual RAAS inhibitors, and relatively few studies were conducted among the Asian population. An extensive database is needed to include the maximum number of the RAAS inhibitor drugs in the study. Hence, one of the largest pharmacovigilant databases, the FAERS database, is used. Leveraging the FAERS database enhances the feasibility and broadens the screening scope for drug-drug interactions between RAAS inhibitors and concomitant medications linked to KI or hyperkalaemia. Unfortunately, the FAERS database is not ready for use in the form it is released with, so an intensive technical and time-consuming process is required prior to analyzing the FAERS database.

Moreover, curing the FAERS database requires an international drug brand name vocabulary to recognize the brand names coming from outside the United States. Up to the best knowledge of the searcher, the latest free publicly available version of the cleaned FAERS dataset was up to June 2015 (Banda *et al.*, 2016); since then, millions of new reports have entered the FAERS database, and many newly developed drugs have also entered the database. So, for a researcher to investigate drugs in FAERS, it would be better to have an updated version of the clean, usable FAERS dataset.

Curing the FAERS database in full and making it available to the public would not only enhance this project's comprehensive coverage of the topic but also extend its benefits to serve as a valuable resource for any researcher interested in exploring the FAERS database. Providing free public access to a clean version of the FAERS database would save researchers much of the tedious and time-consuming process of cleaning the FAERS database, which requires a certain level of data-wrangling and

database querying expertise that might be beyond the capabilities of most researchers interested in the field. Moreover, it would enhance the availability of this data and participate in the collaborative research community.

Many predictive models are available to predict AKI in different clinical scenarios. However, to the best of our knowledge, no modeling has predicted the increase in serum creatinine by 30% or more after initiating RAAS inhibitors. Such predictive modeling would serve as a tool for clinicians to identify high-risk patients. This proactive identification allows for early intervention, such as adjusting medication dosages or exploring alternative therapies, thereby reducing the risk of kidney damage and other complications associated with elevated creatinine levels. Furthermore, this tool's integration into clinical workflows promises to enhance patient care by providing real-time, data-driven insights, making it an invaluable asset in managing patients initiating RAAS inhibitors.

Exploring the reporting trends of RAAS inhibitors associated with AKI or hyperkalaemia would help us understand the timing of these adverse events and whether the incidence of AKI or hyperkalaemia is increasing, decreasing, or remaining stable over time. Such temporal patterns are crucial for ongoing drug safety monitoring. Moreover, studying the Reporting Odds Ratio (ROR) of all RAAS inhibitors associated with AKI or hyperkalaemia, would enable us to rank all RAAS inhibitors according to their ROR. Adjusting the ROR of RAAS inhibitors associated with AKI or hyperkalaemia for possible confounders will enhance our understanding of how various risk factors contribute to the development of AKI or hyperkalaemia.

Up to the best of the researcher's knowledge, there is no previous research done to investigate the reporting trends and the Reporting Odds Ratio (ROR) of the individual drugs of RAAS inhibitors associated with AKI or hyperkalaemia from a pharmacovigilant prospective.

1.18.1 Rational of the study

Globally, there exists a necessity for the early detection of drug induced increased serum creatinine or serum potassium beyond acceptable limits by the guidelines.

Adherence to the guidelines that mandate performing the monitoring tests after initiating RAAS inhibitors has been reported to be low globally, and no previous investigations have been conducted locally in Malaysia.

Moreover, the proportion of patients suffering from increased serum creatinine or hyperkalaemia is inconsistent among literature globally and has never been investigated locally in Malaysia.

By establishing predictive modeling for the increased serum creatinine after initiating RAAS inhibitors, physicians would have the chance to emphasize performing monitoring tests for high-risk patients developing increased serum creatinine, giving a clearer medical vision for all possible scenarios and alternative treatments.

By Curating the FAERS database and making it publicly available for the research community, we will save interested researchers in FAERS the resources (time and skills) needed to cure the database. Furthermore, creating an international drug