EVALUATION OF CLINICALLY IMPORTANT DRUG INTERACTIONS INVOLVING ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AMONG CARDIAC PATIENTS

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by

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DEDICATION

To

My precious mother Sadia, my father, my sisters Salma,

Sara, Samah and my brothers

who give me inspiration, unconditional

sacrifices, love and Dawat

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LIST OF ABBREVIATIONS

ACE	Angiotensin-Converting Enzyme
ACEIs	Angiotensin-Converting Enzyme Inhibitors
ACS	Acute Coronary Syndromes
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ARF	Acute Renal Failure
AT1	Angiotensin Receptors Blocker Type 1
BMI	Body Mass Index
BNF	British National Formulary
BP	Blood Pressure
bid	Twice a day
CAD	Coronary Artery Disease
CI	Confidence Interval
CONSENSUS II	Cooperative New Scandinavian Enalapril Survival Study II
CT scan	Computed Tomography Scans
COX	Cyclooxygenase
COX-2	Cyclooxygenase Inhibitors Second Isoform
DBP	Diastolic Blood Pressure
DDIs	Drug-Drug Interactions
DI	Drug Interaction
DIPS	Drug Interactions Probability Scale
dL	Deciliter
ECHO	Echocardiography

ECG	Electrocardiogram
E.g.	For example
ET	Exercise Stress Test
GFR	Glomerular Filtration Rate
HF	Heart Failure
HOPE	The Heart Outcomes Prevention Evaluation Study
hr	hour
i.e	it est (this is, these are)
IV	Intravenous
JNC	The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure
K^+	Potassium Ion
KCl	Potassium Chloride
kg	Kilogram
L	Liter
LVH	Left Ventricular Hypertrophy
MAP	Mean Arterial Pressure
mEq	milliequivalent
mg	Milligram
MI	Myocardial Infarction
min	Minute
ml	Milliliter
mmHg	Millimeter of mercury
mmol	Millimole
MRI	Magnetic Resonance Imaging

m^2	Meter square
NO	Nitric Oxide
NSAIDs	Non Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
OR	Odds Ratio
PVD	Peripheral Vascular Diseases
RALES	The Randomized Aldactone Evaluation Study
RAS	Renin-Angiotensin-System
REIN	Ramipril Efficacy In Nephropathy Study
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOLVD	Studies of Left Ventricular Dysfunction
SPSS	Statistical Package for Social Sciences Software
tds	Three times a day
WHO	World Health Organization
µmol	Micromole
&	And

PENILAIAN TERHADAP INTERAKSI DRUG PENTING YANG MELIBATKAN PERENCAT PENUKAR ENZIM ANGIOTENSIN DIKALANGAN PESAKIT JANTUNG

ABSTRAK

Perencat penukar enzim angiotensin (ACEIs) telah digunakan secara meluas untuk merawat hipertensi dan penyakit kardiovaskular yang lain. Interaksi ubat-ACEI adalah merupakan masalah kesihatan yang signifikan dan perlu penyelidikan lanjut. Penyelidikan ini dijalankan bertujuan untuk menilai kesan interaksi ubat-ACEIs termasuk hiperkalemia, nefrotoksisiti, hipotensi ortostatik dan penurunan keberkesanan ACEIs. Satu kajian prospektif kohort telah dijalankan untuk mengenalpasti insidens, kebarangkalian, keterukan kesan-kesan tersebut dan faktor-faktor risiko yang terlibat. Persampelan mudah dilakukan ke atas 500 orang pesakit jantung dewasa yang telah menerima rawatan ubat ACEIs bersama dengan ubat-ubatan lain di wad perubatan dan kardiologi, Hospital Pulau Pinang dari Januari hingga Ogos 2006. Data ciri-ciri demografi, tanda-tanda vital, komobiditi, terapi ubat terkini, dan ujian-ujian makmal telah dikumpulkan. Penilaian susulan keadaan pesakit dipantau untuk menilai sekiranya terdapat kesan dan/atau simptom yang berkaitan interaksi ubat dengan agen ACEIs. Hiperkalemia ditakrif berdasarkan paras kalium serum melebihi 5 mmoL/L dan nefrotoksisiti dinilai sekiranya paras urea serum melebihi 8.3 mmol/L dan kreatinin serum melebihi 130μmol/L. Sementara itu, purata tekanan arteri (*MAP*) yang kurang daripada 80 mmHg diguna sebagai definisi hipotensi ortostatik. Penurunan kesan ACEIs didefinisikan sebagai kegagalan untuk mencapai matlamat terapi ACEIs dan penilaiannya dibuat menggunakan terminologi status hasil farmakoterapi. Skala Kebarangkalian Interaksi Ubat (*Drug Interaction*

Probability Scale DIPS) digunakan untuk menilai kebarangkalian hubungan di antara interaksi ubat dengan kesan buruk. Ujian '*Mann-Whitney'* dan ujian *t* yang tidak bersandar digunakan untuk membandingkan nilai purata sekiranya perlu. '*Binary Logistic Statistic'* digunakan untuk analisis univariat manakala '*backward stepwise logistic regression'* digunakan untuk analisis multivariat. Keputusan kajian menunjukkan insidens kesan buruk tersebut adalah hiperkalemia, 9.8%; nefrotoksisiti, 8.4%;hipotensi ortostatik, 8.2%; dan penurunan efikasi ACEIs, 1.6%. Kebarangkalian hubungan keempat-empat kesan buruk tersebut dengan interaksi ubat-ACEIs adalah berjulat diantara perkadaran mungkin dengan paling mungkin. Keterukan kesan buruk berada di antara perkadaran major dengan minor untuk hiperkalemia, manakala untuk lain-lain kesan buruk berada di antara sederhana dengan minor. Usia yang lanjut (≥ 60 tahun), penyakit hepar dan ginjal, dan jumlah ubat-ubatan merupakan faktor-faktor risiko yang meningkatkan risiko untuk hiperkalemia. Tabiat merokok, penyakit hepar dan jumlah ubat-ubatan merupakan penentu yang menyumbang kepada peningkatan risiko nefrotoksisiti. Penyakit hepar dikenalpasti sebagai penyebab yang singnifikan untuk hipotensi ortostatik. Kajian ini telah mengenalpasti interaksi ubat ACEIs di kalangan pesakit jantung yang signifikan secara klinikal. Penyakit hepar didapati sebagai faktor penting yang mengaruhkan hiperkalemia, nefrotoksisiti dan hipotensi ortostatik. Perhatian khusus disarankan untuk pesakit yang menerima bersama ubat yang dapat berinteraksi dengan ACEIs.

EVALUATION OF CLINICALLY IMPORTANT DRUG INTERACTIONS INVOLVING ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AMONG CARDIAC PATIENTS

ABSTRACT

Angiotensin-converting enzyme inhibitors (ACEIs) are widely used for the treatment of hypertension and other cardiovascular diseases. ACEIs-drug interaction is a significant health problem that needs further investigations. This research aimed to evaluate adverse events of ACEIs-drug interactions including hyperkalemia, nephrotoxicity, orthostatic hypotension and reduced efficacy of ACEIs. A prospective cohort study was conducted to identify the incidence, probability and severity of such events and also to determine the associated risk factors. Using convenient sampling, 500 adult cardiac patients admitted to medical and cardiology wards at Penang Hospital, who received ACEIs concomitantly with interacting drugs, were recruited from January to August 2006. Data on demographic characteristics, vital signs, comorbid conditions, current drug therapies, and laboratory investigations were collected. Patient's follow-up evaluation was done for any signs and/or symptoms of adverse events associated with ACEIs-drug interactions. Hyperkalemia was defined as potassium level above 5.0 mmol/L and nephrotoxicity as serum urea and creatinine above 8.3 mmol/L and 130 μmol/L, respectively. Mean arterial pressure (MAP) of less than 80 mmHg was used to define orthostatic hypotension. Reduced efficacy of ACEIs was defined as the failure to achieve the goal of ACEIs therapy and its evaluation was made using Pharmacotherapy Outcomes Status Terminology. Drug Interactions Probability Scale (DIPS) was used to assess the likelihood of association between the drug interactions

and the events. Mann-Whitney test and independent *t*-test were used to compare means wherever applicable. Binary logistic statistics were used for univariate analyses, whereas, backward stepwise logistic regression was used for multivariate analyses. This study showed that the incidences of the events were: hyperkalemia, 9.8%; nephrotoxicity, 8.4%; orthostatic hypotension, 8.2%; and reduced efficacy of ACEIs, 1.6%. Probability of association of the four events with ACEIs-drug interactions ranged between probable and possible rating. The Severity was found between major and minor rating for hyperkalemia, whereas, it was rated between moderate and minor for other events. Advanced age (≥ 60 years), renal and hepatic disease and number of medications were risk factors associated with increased risk of hyperkalemia. Smoking habit, hepatic disease and number of medications were predictors that contributed to high risk of nephrotoxicity. Hepatic disease was considered as a significant predictor for orthostatic hypotension. This study has identified clinically important ACEIs-drug interaction events among cardiac patients. Hepatic disease was found as an important factor that predicts hyperkalemia, nephrotoxicity and orthostatic hypotension. Special attention for patients who are prescribed ACEIs with interacting drugs is strongly recommended.

CHAPTER 1

INTRODUCTION

1.1 Background

A drug interaction is an interference of a drug with the effect of another drug, food or drugs in clinical laboratory tests or diseases. Drug-drug interactions (DDIs) are considered as a situation in which the effects of one drug are altered by prior or concurrent administration of another drug (Gennaro *et al*., 2000). DDIs are important subsets of adverse drug events. There is focusing attention on the prevention of DDIs to reduce errors in the administration of prescribed medications. However, adverse drug reactions (ADRs) including drug interactions are defined according to World Health Organization (WHO) (1972, cited by Linda and Colleen,1991) as a noxious and unintended response that occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of a disease, or for the modification of physiological functions.

1.1.1 Mechanisms of drug interactions

Mechanisms of drug interactions are classified as pharmacokinetic and pharmacodynamic interactions.

1.1.1 (a) Pharmacokinetic interaction

It occurs when the precipitant (interacting) drug alters the absorption, distribution, metabolism or elimination of object drug leading to change of plasma concentration of the later drug (Gennaro *et al*., 2000).

Moreover, pharmacokinetic drug interactions are often manageable and their risk can be reduced by dosage adjustments (Bergk *et al*., 2004).

1.1.1(b) Pharmacodynamic interaction

This type of interaction occurs when the drug has similar or opposite pharmacological effects to the object drug when administered concurrently, leading to a change in pharmacological effect by additive (synergistic) effect or opposite (antagonistic) effect without change in drug plasma concentration (Gennaro e*t al.*, 2000). Notably, pharmacodynamic interactions are exclusively relevant to the elderly patients because the elderly patients have reduced homeostatic mechanisms (Seymour and Routledge, 1998).

1.1.2 Causes of drug interactions

In accordance with the suggestion of Moini (2005), there are many causes of drug interactions including multiple pharmacological effects, non-prescription drug use, patients' non-compliance and drug abuse.

1.1.3 Risk factors for drug interactions

Patient-related risk factors for drug interactions include age, sex, genetic factors, predisposing diseases and lifestyle such as smoking and alcohol consumption (Bergk *et al*., 2004). A study by Bjerrum *et al.* (2003) demonstrated that one third of the study population had received two or more drugs. Of these only 15% were exposed to drugs with potential interaction and the risk of interaction increased with age. Moreover, they observed that most interactions were found in patients treated with cardiovascular drugs such as diuretics, angiotensin-convering enzyme inhibitors

(ACEIs), digoxin, beta blockers and calcium channel blockers with non steroidal anti-inflammatory drugs (NSAIDs), antidiabetics, potassium-sparing diuretics and anticoagulants.

Patients taking multiple drugs usually have multiple diseases. Therefore, their ability to metabolize the drugs can be affected as a result of target organs that are more sensitive to the effects of the drug (Leipzig and Edelberg, 2001). Hence, adverse drug reactions are higher in geriatric patients who receive large number of drugs (Egger *et al*., 2003a). A study conducted in Colorado by Page II and Ruscin (2006) documented that a higher number of admission medications (≥ 5) was strongly associated with adverse drug events in hospitalized elderly patients. Similarly, a study carried-out by Straubhaar *et al.* (2006) showed that the number of medications and the number of potential DDIs per patient significantly increased during hospital stay.

Despite accumulating evidences that using multiple drugs to treat many diseases of the elderly decreases morbidity and mortality, the potential for clinically significant drug interactions greatly increased (Delafuente, 2003). A retrospective study performed in Thailand found that the rate of potential drug interactions was directly proportional to the patient's age and the number of the drugs they received (Janchawee *et al*., 2005).

1.1.4 Epidemiology of drug interactions

Most published studies used different methods and criteria to define and distinguish between clinically significant and clinically non-significant drug-drug interactions. Therefore, it is difficult to obtain an accurate estimate of the incidence of drug interactions (Boxtel *et al*., 2001).

Harvard Medical Practice Study I, carried-out by Brennan *et al.* (2004) found that the incidence rate of adverse drug events in hospitalized patients was 3.7% of hospital inpations. Whereas, Bates and colleagues (1993) noted that the incidence of adverse drug events was about six per 100 admissions. In a population-based study conducted in Utah and Colorado, 0.63% was the incidence of preventable adverse drug events among elderly inpatients (Thomas and Brennan, 2000).

A previous study showed that more than one-half of hospitalized patients who were exposed daily to eight drugs were receiving potentially interacting drugs (Bente *et al*., 2005). Whilst, potentially serious drug interactions were found in 1.4% of the prescriptions and 7.4% of the patients who had been prescribed concurrently two or more drugs (Grönroos *et al*., 1997). Björkman *et al.* (2002) documented that potential DDIs were widespread among elderly patients who received combination of many drugs and 50% of the potential DDIs would lead to adverse drug reactions and another 50% could reduce therapeutic efficacy.

Egger *et al*. (2003b) showed in a study conducted at the University Hospital Basel that 53.8% of potential drug interactions at discharge resulted from change of medications during hospital stay. Moreover, the same study showed that 12.2% of

DDIs were classified as major severity and majority of these (63%) were due to combination of ACE inhibitors with potassium-sparing diuretics or potassium supplementation.

The incidence of DDIs in hospitalized patients ranged between 15-16.6% (Passarelli *et al*., 2005; Pirmohamed *et al*., 2004). A study conducted in a community and general hospital in Los Angeles found that 47% of the study population had been at high risk for drug interactions, particularly patients who had received 3 or more medications and/or patients older than 50 years of age (Goldberg *et al*., 1996). In Brazil, Cruciol-Souza and Thomson, (2006), by using a computer program found that almost 50% of the prescriptions reported at least one DDI.

A retrospective study noted that the incidence of potential adverse interactions in emergency department was 3.8% (Heininger-Rothbucher *et al*., 2001). Conversely, other reports found that the frequency of drug interactions requiring emergency department visits ranged from 0.054 to 4% (Raschetti *et al*., 1999; Becker *et al*., 2006). A review of nineteen DDIs studies found a wide variation of reported potential drug interactions of clinical significance ranging from 1% to 23.2% (Jankel and Speedie, 1990). The review showed that the rates of potential drug interactions in hospital patients ranged from 2.2% to 30%. However, the variation in the reported incidence rates for all potential drug interactions ranged from 2.2% to 70.3% (Jankel and Speedie, 1990).

Drug interaction studies demonstrated five to seven-fold difference in the effect between participants. These significant variations might be due to different doses,

routes of administration, formulations and sequences of drug administration, genetics and other modifiers of drug elimination or response such as food, environment and disease (Horn and Hansten, 2004b).

1.1.5 Evaluation and recognition of drug interactions

The assessment of clinical relevance of a potential DDI requires the knowledge of how often a potential DDI indeed clinically manifests (Egger *et al*., 2003b). A study conducted at University of Erlangen showed that 18% of hospitalized patients experienced probable or definite adverse drug reactions that could have been detected from abnormal laboratory tests (Tegeder *et al*., 1999). Nevertheless, only about one-third were detected and treated by physicians (Tegeder *et al*., 1999). In contrast, a study suggested that computerized algorithms may support physicians but never replace the comprehensive clinical evaluation of the individual case (Bergk *et al*., 2004). Furthermore, another report showed a limited use of computerized drug database in monitoring elderly patients (Egger *et al*., 2003a). Notably, a prospective case series study was conducted to evaluate a computer alert system used to detect adverse events. They found that only one patient presented with serious potential consequences of positive alert; an elderly patient with renal insufficiency and hyperkalemia due to receiving ACEIs and potassium chloride (Raschke *et al*., 1998).

According to Linda and Colleen (1991), the recognition of adverse drug reactions or interactions requires physician's review of patient's clinical course, observation of relevant characteristics of patient and drug reaction outcome. However, for the assessment of the probability of association of the drug and drug reactions, patient's

current medications, significant medical problems and risk factors for drug interactions should be evaluated (Linda and Colleen, 1991).

1.1.6 Management of drug interactions

The identification of patients at risk and an accurate management of their drug therapy are important challenges for health care professionals to avoid serious clinical consequences caused by adverse drug reactions (Indermitte, 2006). Moreover, a complete medication history of prescribed and non-prescribed drugs taken by patients is an essential consideration to avoid or minimize drug interactions risks (Moini, 2005).

Management of DDIs can be through proper dosage adjustment of the interacting drugs or prescription of non-interacting combination drugs. The interaction can be managed by close laboratory or clinical monitoring for evidence of interaction (Hansten, 2003). However, drug interactions sometimes might be predictable, depending on the knowledge of pharmacological properties of the drugs and understanding of pharmacokinetic and pharmacodynamic principles of the combination drugs (Moini, 2005).

1.2 ACE inhibitors

1.2.1 Renin system

The renin-angiotensin-system (RAS) plays a major role in the development and progression of cardiovascular diseases. Angiotensin-converting enzyme (ACE) is an enzyme involved in the metabolism of many small peptides including the conversion

of angiotensin I, an inactive octapeptide into angiotensin II (Lopez-Sendon *et al*., 2004). RAS has a pivotal role in blood pressure regulation. Reducing sodium delivery at macula densa, decrease renal perfusion pressure, and sympathetic activation, all these lead to stimulation of renin secretion by the juxtaglomerular cell (Brown and Vaughan, 1998).

ACE also known as kininase II, is the enzyme that catalyses the degradation of bradykinin and other potent vasodilator peptides (Lopez-Sendon *et al*., 2004). Kinins exert vasoactive effects by releasing various autocoids from endothelium. Activation of endothelial bradykinin receptors increases the formation of local vasodilators nitric oxide (NO), which is known as endothelium-derived relaxation factor, epoprostenol known as (prostacyclin, prostaglandin I_2) and platelet-activating factor (Verme-Gibboney, 1997). In addition, ACE controls the balance between the vasodilatory and natriuretic effect of bradykinin as well as vasoconstrictive and salt-retentive properties of angiotensin II. ACE inhibitors alter this balance by decreasing the formation of angiotensin II and the breakdown of bradykinin (Brown and Vaughan, 1998).

Angiotensin II is the main effector molecule of RAS that can act either as systemic hormone (endocrine) or as a locally generated factor (paracrine, autocrine) (Unger, 2002). Moreover, angiotensin II is a hormone circulating in the blood and has crucial roles in cardiovascular systems. Its key function is to constrict blood vessels leading to elevation of the blood pressure and increasing the work required for the heart to pump blood into systemic circulation. This effect is critical for weakened heart muscle in case of heart attack or heart failure (Sweitzer, 2003).

Angiotensin II has a significant role in the pathophysiology of heart failure. However, there is a controversy that another enzyme in addition to ACE could contribute to local production of angiotensin II in the heart. This is known as chymase, a chymotrypsin-like serine protease that is synthesized and stored in the cardiac mast cells and is not affected by ACE inhibitors. Chymase exerts its action on the heart after the mast cells are stimulated to degranulate in chronic inflammatory states (Kokkonen *et al*., 2003).

It is worthwhile to note that, angiotensin II plays a negative role in growth promotion by increasing the size and thickness of several cardiovascular structures. High level of angiotensin II in the blood leads to thickening of the heart which is known as hypertrophy and it is recognized as a sign of high risk of death caused by heart disease (Sweitzer, 2003). Moreover, elevation of angiotensin II level in the walls of blood vessels triggers it to become thicker and stiffer. In addition to the constriction, the arteries become predisposed to cholesterol deposits and blockages which can lead to heart attacks and strokes (Sweitzer, 2003).

1.2.2 Role of ACE inhibitors in cardiovascular diseases

The cardioprotective actions of ACE inhibitors occur by increasing the oxygen supply to tissue oxygen demand during various cardiovascular stresses. The beneficial cardiovascular effects of ACE inhibitors in addition to its hemodynamic action are related to an improvement of the cardiovascular kinin/nitric oxide (NO) pathway (Magen and Viskoper, 2000).

ACE inhibitors attenuate the formation of angiotensin II by competitively blocking the conversion of angiotensin I to angiotensin II, thereby, reducing the circulation and local levels of angiotensin II. Also it reduces aldosterone and vasopressin secretion and decreases sympathetic nerve activity (Lopez-Sendon *et al*., 2004). However, a study suggested that the most important vascular effect of ACE inhibitors is related to accumulation of endogenous bradykinin rather than due to reduced generation of angiotensin II (Hornig *et al*., 1997). This occurs by ACE inhibitors' enhancement effect on flow-dependent, endothelium-mediated dilation by a bradykinin-dependent mechanism (Hornig *et al*., 1997). Furthermore, ACE inhibitors decrease the total peripheral vascular resistances, promote natriuresis and cause little change in heart rate. Also it has little effect on cardiac output or capillary wedge pressure in normotensive and hypertensive patients without chronic heart failure (Lopez-Sendon *et al*., 2004).

Activation of RAS may exert many adverse effects on the cardiovascular system such as arterial hypertension, chronic renal failure and atherosclerosis (Grote *et al*., 2004). More evidences indicate that the RAS not only plays a role in development of cardiac remodeling and heart failure, but also it has a role in initiation and progression of aspects of cardiovascular disease including atherosclerosis (Schmidt-Ott *et al.*, 2000). Similarly, an experimental study documented a pathogenic role for the RAS in early stages of atherosclerosis. Therefore, the RAS play an important role in both initiation and acceleration of atherosclerotic process and ACE inhibitors may have benefit in treatment of this disease (Warnholtz *et al*., 1999).

ACE inhibitors are a cornerstone therapy for heart failure patients with left ventricular systolic dysfunction. However, diuretics are essential for controlling volume overload, but they do not confer mortality reduction benefits like the first-line therapies of ACE inhibition and beta blockade (Bicket, 2002), except spironolactone which can reduce mortality from progressive heart failure (Pitt *et al*., 1999). The Heart Outcomes Prevention Evaluation (HOPE) study showed that the use of long-acting ACE inhibitors in patients with normal left ventricular function and no evidence of heart failure who are at high risk for cardiovascular disease could reduce rates of mortality, myocardial infarction, stroke, coronary revascularization, cardiac arrest and heart failure. Moreover, ACEIs may reduce the risk of diabetes and relevant complications (The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, 2000). However, evidences suggested that ACE inhibitors should be initiated early and continued for years in patients with heart failure and/or left ventricular dysfunction following myocardial infarction (Bonarjee and Dickstein, 2001).

1.2.3 Role of ACE inhibitors in renal diseases

Clinical evidences suggested that the use of drugs that block RAS are beneficial for patients with renal insufficiency (Bakris and Weir, 2000). Moreover, as cited by Bakris and Weir (2000) in accordance with the Sixth Report of The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI, 1997), that ACEIs are specifically indicated for use in patients with renal insufficiency [i.e. serum creatinine 133-265 μmol/L (1.5-3.0 mg/dL)] (Bakris and Weir, 2000). However, when ACEIs are used with antihypertensive therapy, they demonstrate therapeutic benefits and provide renoprotective effects that

The intrinsic renal autoregulation mechanism is adjusted by two mechanisms, angiotensin II and the sympathetic hormones. The decline or fall of renal perfusion pressure in case of hypovolemia or chronic heart failure, leads to activation of sympathetic nervous system and secretion of renin from juxtaglomerular cells of afferent arterioles. This further leads to production of angiotensin II at the level of renal glomerulus which causes vasoconstriction of postglomerular efferent more than preglomerular afferent arterioles. This imbalance of effect on the efferent arteriolar circulation restores glomerular capillary pressure and maintains glomerular filtration despite reduced perfusion pressure. At this juncture, filtration fraction (glomerular filtration rate (GFR)/renal plasma flow) increases, which sustains proximal tubular sodium reabsorption (Schoolwerth *et al*., 2001). Inhibition of these two hormones by using ACEIs or NSAIDs leads to reduction of the blood flow and pressure within the glomeruli which causes decrease glomerular filtration rate and a rise in serum creatinine with resultant functional renal insufficiency (Packer, 1988). The progression of renal insufficiency in chronic heart failure patients receiving ACEIs becomes acute in the presence of concomitant NSAIDs therapy and the risk of renal

The investigators of Ramipril Efficacy In Nephropathy (REIN) study reported that prolongation of ACEIs use for the treatment of patients with chronic proteinuric nephropathies significantly delayed the acceleration of end stage renal failure (Ruggenenti et al., 1999). Likewise, a study performed in China showed that the use of benazepril with conventional antihypertensive treatment, for non-diabetic patients with advanced renal insufficiency granted the elevation of renal protection (Hou *et al*., 2006). Although ACEIs therapy reduces the rate of progressive renal injury in renal disease and also improves renal blood flow and sodium excretion rate in chronic heart failure, its use is associated with functional renal insufficiency and/or hyperkalemia (Schoolwerth *et al*., 2001).

A retrospective cohort study performed in an acute care setting found that the therapeutic benefits of ACEIs for patients with elevated serum creatinine levels had greater increase in survival for patients who had insufficient renal function than patients who had normal renal function (Frances *et al*., 2000). In addition, they suggested that moderate renal insufficiency could not be considered a contraindication to the use of ACEIs therapy for patients who have poor left ventricular ejection fraction following myocardial infarction (Frances *et al.*, 2000).

1.2.4 Pharmacokinetics and pharmacodynamics of ACE inhibitors

ACEIs are increasingly recognized as having an important role in the treatment of hypertension and/or other cardiac, renal and vascular diseases. ACEIs are available as ester prodrugs to improve gastrointestinal absorption of the active metabolites of most of ACEIs (Edling *et al*., 1995). They are mostly eliminated via renal excretion and some are eliminated by renal and hepatic mechanisms. Thus, the dose of ACEIs must be adjusted for patients with renal or hepatic dysfunction, because their active metabolites may accumulate in these patients with prolonged use (Verme-Gibboney, 1997).

ACEIs are classified into three groups according to the chemical structure of their active moiety. Sulfhydryl containing ACE inhibitors include captopril, fentiapril, pivalopril, zofenopril, benazepril and alacepril. While, fosinopril is the only ACE inhibitor drug containing phosphinyl group active moiety. Carboxyl moiety containing ACE inhibitor drugs include enalapril, cilazapril, spirapril, lisinopril, quinapril, ramipril, trandolapril, moexipril and perindopril (Brown and Vaughan, 1998; Lopez-Sendon *et al*., 2004).

It is noteworthy that the doses of ACE inhibitors prescribed in clinical practice are considerably lower than the target doses used in randomized clinical trials. However, a study suggested that it might be that the higher doses were not achieved because of uncertainty about who was responsible for titrating the doses, the hospital clinicians or the general practitioners. However, there were possibilities that the doses differed for different indications (Kvan and Reikvam, 2004).

The oral bioavailability of ACEIs drugs ranges from 13-95%. However, the concurrent administration of food adversely affects the oral absorption of ACEIs (Harrold, 2006). The three most lipophilic compounds are trandolapril, quinapril and benazepril. Whereas, the least hydrophilic compounds are lisinopril, enalapril and captopril. Table1.1 demonstrates the pharmacokinetic parameters and standard dosages of ACEIs. Renal elimination is the most important route of elimination of these drugs. Some of the drugs are renally/hepatically eliminated, whereas others are eliminated via renal/fecal route. Moreover, all ACEIs have similar duration of action, onset of action and dosing interval, except captopril that has a more rapid onset of action and shorter duration (Harrold, 2006). Hence, it requires more frequent dosing than other ACEIs. Additionally, perindopril has longer elimination half-life time than others ACEIs.

Table 1.1 Pharmacokinetic parameters of ACE inhibitors

Drug name generic/brand	Standard dosage* (mg)	Onset of action (hr)	Duration of action (hr)	Elimination* half-life (hr)	Route of elimination
Captopril Capoten®	25-100 t.d.s	0.25-0.50	6-12	2	Renal
Benazepril Lotensin®	2.5-20 b.i.d	1	24	11	Renal/hepatic
Fosinopril Monopril®	10-40 daily	1	24	12	Renal/hepatic
Enalapril Vasotec®	2.5-20 b.i.d	1	24	12	Renal
Lisinopril Zestril®	2.5-10 daily	1	24	12	Renal
Quinapril Accupril®	10-40 daily	1	24	2-4	Renal /fecal
Ramipril Altace®	2.5-10 daily	1	24	8-14	Renal/fecal
Trandolapril Mavik®	1-4 daily	0.5-1.0	24	16-24	Renal/fecal
Moexipril Univasc®	7.5-30 daily	1	24	16-24	Renal/fecal
Perindopril Aceon®	4-8 daily	1	24	>24	Renal

(Harrold, 2006; *Lopez-Sendon *et al*., 2004)

1.3 ACE inhibitors-drug interactions

Drug-drug interactions are one of the causes of adverse drug reactions in hospitalized patients. Numerous DDIs have been reported, but only a few of them are clinically significant and merit attention.

Concurrent use of ACEIs with some drugs may lead to drug interactions. However, majority of DDIs involving ACEIs are not well understood, but they seemed to occur through a combination of both pharmacodynamic and pharmacokinetic mechanisms (Anderson and Nawarskas, 2001). Concurrent use of antacids with ACEIs may reduce the availability of the ACEIs. Potassium-sparing diuretics and potassium supplements or low salt substances with high potassium contents may induce hyperkalemia (Lopez-Sendon *et al*., 2004). Moreover, increased risk of hyperkalemia due to coadministration of trimethoprim-sulfamethoxazole with ACEIs in the presence of renal impairment or diabetes mellitus has been reported (Hansten and Horn, 2005).

Haloperidol may increase the risk of hypersensitivity to ACEIs (Lopez-Sendon *et al*., 2004). High incidence of acute renal failure (ARF) was found in patients without renal artery stenosis who received ACEIs combined with diuretics (Bridoux *et al*., 1992). Furthermore, according to Hansten and Horn (1999, cited by, Anderson and Nawarsk, 2001), concomitant use of aspirin with ACEIs probably antagonizes ACEIs effects, but this interaction may become less prominent with lower aspirin doses. Some evidences suggested that salicylate might reduce the effectiveness of ACEIs in congestive heart failure patients (Lopez-Sendon *et al*., 2004). Similarly, Hansten and Horn, (2005) noted that aspirin can inhibit both the antihypertensive effect of ACEIs

and other favorable hemodynamic effects in CHF patients. However, the inhibitory effect of aspirin is probably dose-related.

Moreover, use of ACEIs with α-blockers such as doxazosin, prazosin and terazosin can augment the first-dose syncope (Lopez-Sendon *et al*., 2004). Further, use of loop diuretics with ACEIs may potentiate acute hypotension in the presence of volume depletion. Concurrent use of ACEIs with lithium and digoxin may lead to elevation of plasma levels of lithium and digoxin (Lopez-Sendon *et al*., 2004). NSAIDs and cyclosporine with ACEIs may increase urea or creatinine levels excessively. Furthermore, coadministration of diuretics with ACEIs increases sensitivity to vasodilator effects of ACEIs (Lopez-Sendon *et al*., 2004).

The evaluation of drug interactions requires the knowledge of the onset of the event and if the interaction is a known interactive property of the object and precipitant drugs (Limon, 2000). There is also the need for recognition of any other cause of the event, rather than the drug interaction. The recognition of the clinical significance of the interaction event, evaluation of the clinical changes and management of the interaction are important issues (Limon, 2000).

The likelihood of the relevance or association of the drug interaction event with the drug therapy is classified as definite, probable, possible or doubtful (Linda and Colleen, 1991). The probability classification is based on the temporal relationship between the drug administration and the reaction, whether the reaction is a known consequence of the drug, if the reaction were resolved on discontinuation of the drug to determine its association with a reaction and if the patient's clinical state could

explain the reaction. Clinical decision sometimes is important to determine probability. The Naranjo algorithm is a method for scoring reaction characteristics and is frequently used in clinical practice (Linda and Colleen, 1991; Naranjo *et al*., 1981).

A study showed that the prevalence of hyperkalemia during a two-year period of ACEIs use was 11% (Reardon and MacPherson, 1998). However, a previous study found that about 20.5% of the patients exposed to potential DDIs might experience hyperkalemia (Straubhaar *et al*., 2006). A case-control study of chronic heart failure patients showed that hyperkalemia was reported in about 8.5% of hospitalized patients (Ramadan *et al*., 2005). While, the result of a study conducted by Egger *et al*. (2003b) reported that the rate of hyperkalemia due to combination of ACEIs with potassium-sparing diuretics was 5.2%.

A study performed among elderly patients with congestive heart failure found that the rate of renovascular disease due to ACEIs' use was 33.7% (MacDowall *et al*., 1998). Whereas, a prospective study showed that the incidence rate of treatment-related acute renal failure (ARF) in elderly was 1.4% (Kohli *et al*., 2000).

A study in geriatric patients found that the prevalence of orthostatic hypotension due to lisinopril use was 60% (Poon and Braun, 2005). Similarly, another study found that the prevalence of orthostatic hypotension among elderly patients was 30% (Luukinen *et al.*, 1999). The incidence of drug-induced orthostatic hypotension was 1.3% and mostly occurred in elderly patients (Montastruc *et al*., 1997). Another study showed that the incidence of orthostatic hypotension in hypertensive patients

was 27% while in normotensive patients the incidence was 22% (Masuo *et al*., 1996). Egger and colleagues (2003b) documented that the incidence of hypotension due to potential DDIs of combination of ACEIs with diuretics was 13.2%. The same investigators reported that combination of aspirin with ACEIs decreased antihypertensive effect of ACEIs in 10% of the patients, which was considered as moderately severe interaction. Moreover, decrease and normalization of blood pressure (BP) by antihypertensive drugs such as β-blockers, ACEIs and calcium antagonists lead to decreased incidence of orthostatic hypotension in hypertensive elderly patients (Masuo *et al*., 1996).

1.4 Literature review

This study highlights on four outcomes of ACEIs-drug interactions with interacting drugs among cardiac patients. Interacting drugs are: aspirin, thiazide and loop diuretics, spironolactone, potassium chloride (KCl) and α-blockers such as prazosin and doxazosin. The adverse outcomes are: hyperkalemia, nephrotoxicity, orthostatic hypotension and reduced efficacy of ACEIs. Results of this study documented the incidences, possible risk factors as well as the probability and severity of such events.

1.4.1 Hyperkalemia

Hyperkalemia is defined as a serious and potentially life-threatening electrolyte disorder, following a number of underlying abnormalities in potassium homeostasis (Perazella and Mahnensmith, 1997). Hyperkalemia may develop as a complication of therapy with ACEIs in patient with one or more of three factors impairing potassium excretion such as decreased delivery of sodium to the distal nephron, aldosterone

In chronic heart failure patients, reduction in effective circulatory blood volume leads to increase production of renin. This increases activity of angiotensin II, and aldosterone promote sodium-water retention that may lead to secondary aldosteronism and worsen oedema or hyponatremia and hypokalemia (Saito *et al*., 2005). Spironolactone, an aldosterone antagonist has been used as a diuretic or antihypertensive agent. When it is used for chronic heart failure patient, it prevents the onset of secondary aldosteronism by inhibition of sodium reabsorption and potassium excretion in the renal distal tubule and it prevents hypokalemia (Saito *et al*., 2005).

ACEIs lead to lowering the blood pressure by inhibition of angiotensin II and consequently aldosterone secretion. ACEIs and spironolactone with potent diuretics such as furosemide are commonly used clinically for chronic heart failure patients. However, use of ACEIs with spironolactone singly may be associated with

$^{+}$ ACEIs with spironolactone did not depend on spironolactone dose and might lead to arrhythmia and cardiac arrest (Saito *et al*., 2005). On the other hand, a retrospective study among ambulatory patients showed that 72.3% of the patients at risk of hyperkalemia associated with spironolactone therapy had serum potassium and creatinine evaluated within the study period (Raebel *et al*., 2007).

Azotemic patients on ACEIs develop elevation of serum potassium by two ways. One is when the patient is receiving more than one medication capable of causing elevation of potassium level (Chiu *et al*., 1997), and the other one is the abnormal systemic hemodynamic as in chronic heart failure patients may cause severe renal vasoconstriction, thus, decrease glomerular filtration rate and tubular flow. In this situation elevation of potassium is due to combination of multiple factors (Garcia *et al*., 2001). Also there are many factors that may contribute to potassium balance in renal failure such as urinary flow, fecal excretion and cellular uptake (Garcia *et al*., 2001).

ACEIs play a role in keeping serum potassium levels within normal range, by improving insulin sensitivity and changes in intra-cellular potassium distribution (Garcia *et al*., 2001). Likewise, another study suggested that insulin and β_2-adrenergic receptors enhanced cellular potassium uptake via increased activity of the sodium-potassium-adenosine triphosphatase pump. Consequently, insulin-dependent diabetic patients and patients receiving β-blockers are considered to be at high risk for hyperkalemia (Obialo *et al*., 2002).

Schepkens *et al*. (2001) study demonstrated that the morbidity and mortality from hyperkalemia in certain high-risk patients due to concomitant use of ACE inhibitors with spironolactone may outweigh the potential long-term benefits. This result may be an evidence for rising incidence of hyperkalemia corresponding to increased prescription of spironolactone as potential option in the treatment of heart failure patients (Georges *et al*., 2000). It is worthwhile to note that, RALES reported that the use of spironolactone in the treatment of cardiac patients reduced the risk of death and hospitalization for all cardiac causes among patients with heart failure due to left ventricular systolic dysfunction and using standard therapy including ACE inhibitors. The study documented that spironolactone improved symptoms of heart failure and had cardioprotective effects (Pitt *et al*., 1999). In addition, a retrospective study conducted in Brazil observed that concomitant use of ACEIs with spironolactone for decompensated heart failure patients was associated with severe hyperkalemia. Renal impairment and the functional class of CHF were found as significant predictors of hyperkalemia in these patients (Cruz *et al*., 2003).

A study performed to evaluate the usage of spironolactone for severe heart failure patients suggested that spironolactone should not be recommended for all patients. This coincided with their result that less than 20% of their patients were taking spironolactone. This is regardless of clinical evidence which shows that it can decrease mortality and hospitalization rates in patients with severe heart failure (Trujillo *et al*., 2004). Notably, the important features of patients who develop hyperkalemia due to the use of spironolactone with ACEIs include advanced age and concurrent use of other drugs responsible for elevation of serum potassium such as potassium-sparing diuretics, potassium supplements, NSAIDs or cyclooxygenase

Population-based time series study conducted in Ontario suggested that the rate of prescription of spironolactone for elderly patients on ACE inhibitors therapy increased greatly after publication of RALES (Juurlink *et al*., 2004). Moreover, they observed increases in rates of hospitalization for hyperkalemia associated with increase in morbidity and mortality rate (Juurlink *et al*., 2004).

A case series study observed that there are certain factors that lead to the development of severe hyperkalemia in patients with heart failure treated with spironolactone and ACE inhibitors or AT1 receptor blockers; advanced age, dose of spironolactone more than 25 mg/day, insufficient renal function and diabetes mellitus type-2. The investigators suggested that undetected hyperkalemia may be the possible cause for sudden death in some heart failure patients (Wrenger *et al*., 2003). Whereas, a study carried out among heart failure outpatients using spironolactone found that elderly patients with decreased left ventricular ejection fraction (≤ 20%) and higher NYHA class were considered to be at higher risk for hyperkalemia (Svensson *et al*., 2004).

A case-control study performed in Buffalo showed that the risk of hyperkalemia in chronic heart failure patient was not only related to concomitant use of spironolactone with ACE inhibitors but other risk factors independently associated with hyperkalemia such as diabetes mellitus and impaired renal function (Ramadan *et al*., 2005).