ADVERSE DRUG REACTIONS AMONG HOSPITALISED PATIENTS WITH CHRONIC KIDNEY DISEASE IN DUBAI HOSPITAL: WITH REFERENCE TO BLEEDING TENDENCY AMONG HOSPITALISED PATIENTS

by

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Thesis submitted in fulfillment of the requirements for the degree of Doctor of Philosophy

August 2014

ACKNOWLEDGMENTS

First and foremost, my heartfelt gratefulness goes to the God, the One who has no finality for answering my prayers in many ways and blessing me with the abilities that have enabled me to achieve this success.

I would like to express my deepest gratitude to my supervisor Prof. Dr. Syed Azhar Syed Sulaiman for his invaluable guidance, advice and patience. This research would have been impossible without his help, concern, and consistent encouragement.

I would like to thank all the dedicated staff at the Medical Research Committee of Dubai Health Authority and Dubai Hospital. In particular, I would like to acknowledge my field supervisor, Dr. Ali Al Sayed, Director of Pharmaceutical Services Department at the Dubai Health Authority who was responsible for the smooth running of this study and were a part of its success.

Last but certainly not least, I must thank my father, mother, and siblings. Words cannot describe how supportive and understanding they have been during this research period and the write up of this thesis.

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ESRD	End stage renal disease
NHANES	National Health and Nutritional Examination Surveys
UAE	United Arab Emirates
pmp	Per million population
WHO	World Health Organization
WHO-UMC	World Health Organization-Uppsala Monitoring Centre
ACEI/ARBs	Angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers
ADRs	Adverse drug reactions
GIFA	the Gruppo Italiano di Farmacovigilanza nell' Anziano
MDRD	Modification of Diet in Renal Disease
BootCI	bootstrap confidence interval
CI	confidence interval
GFR	Glomerular filtration rate
SE	standard error
OR	odd ratio
BP	blood pressure
IQR	interquartile range
CRP	C-reactive protein

REAKSI ADVERS DRUG DI KALANGAN PESAKIT DIMASUKKAN KE HOSPITAL DENGAN PENYAKIT BUAH PINGGANG KRONIK DI HOSPITAL DUBAI: RUJUKAN PADA KEUPAYAAN PENDARAHAN DI DALAM KALANGAN PESAKIT

ABSTRAK

Penyakit buah pinggang kronik (CKD) terdedah kepada Kesan Advers drug (ADR) kerana mereka biasanya berada dalam regimen pelbagai drug, mempunyai kriteria co-morbid yang berbeza, dan kerana perubahan dalam parameter farmakokinetik dan farmakodinamik. Matlamat keseluruhan tesis ini adalah untuk menilai kesan advers drug dalam kalangan pesakit dimasukkan ke hospital dengan tahap yang sederhana ke CKD yang teruk, dan membangunkan skor risiko ADR untuk mengenal pasti dan mengklasifikasi pesakit CKD yang mempunyai risiko peningkatan ADR semasa di dalam hospital.

Untuk memenuhi objektif tesis, satu kajian secara pemerhatian telah dijalankan di unit buah pinggang Hospital Dubai, Emiriyah Arab Bersatu. Pesakit dengan peringkat CKD 3 hingga 5 (dianggarkan GFR, 10-59 ml/min/1.73 m^2) yang dimasukkan ke unit buah pinggang, antara 1 Januari, 2012, dan 31 Disember, 2012 telah diambil. Bagi setiap pesakit, data dikumpulkan pada kemasukan dengan menggunakan borang yang seragam. Skor risiko ADR telah dibangunkan dengan membina satu siri model regresi logistik. Model patut keseluruhan dan model berjujukan telah dibandingkan dengan menggunakan Kriteria Maklumat Akaike. Nisbah ganjil pembolehubah disimpan dalam model terbaik yang digunakan untuk mengira skor risiko. Tambahan pula, analisis skor kecenderungan telah dijalankan untuk mengkaji hubungan penggunaan antikoagulan dengan hasil yang buruk, dan untuk menguji kesan perlindungan statin terhadap acara-acara utama pendarahan yang disebabkan oleh terapi antikoagulasi.

Antara pesakit dimasukkan ke hospital dengan CKD, sekurang-kurangnya 1 dalam 8 pesakit mengalami ADR semasa penginapan hospital; pesakit CKD yang tidak berada di mana-mana terapi penggantian buah pinggang berada pada risiko yang lebih tinggi untuk mendapatkan ADR; dan, lebih separuh daripada jumlah ADR yang berkaitan dengan pendarahan adalah berkaitan dengan penggunaan antikoagulasi. Pendarahan besar berlaku pada 1 daripada 3 pesakit yang menerima terapi antikoagulasi semasa di hospital, dan pengguna antikoagulan adalah 3 kali lebih berkemungkinan untuk mati berbanding dengan mereka yang tidak menerima terapi antikoagulasi; walau bagaimanapun, statin mempunyai kaitan perlindungan dengan risiko pendarahan antikoagulan berkaitan.

Antara pesakit dimasukkan ke hospital dengan CKD, terdapat kepelbagaian besar dalam risiko untuk ADR. Dengan menggunakan skor risiko ADR, pesakit berisiko tinggi boleh menerima campur tangan yang lebih intensif yang bertujuan untuk mengurangkan hasil buruk berkaitan dadah dan meningkatkan keberkesanan kos terapi CKD. Dengan menggunakan skor ini juga, tahap risiko yang berbeza boleh digunakan untuk pesakit triage untuk keputusan mengenai permulaan terapi penggantian renal. Terapi antikoagulasi pada pesakit dimasukkan ke hospital dengan CKD nyata dikaitkan dengan peningkatan risiko pendarahan dan kematian utama di hospital. Risiko yang lebih tinggi diperhatikan dalam pelbagai kumpulan pesakit dan tidak berkurangan selepas pelarasan bagi faktor lain yang biasa. Keputusan ini menunjukkan bahawa langkah-langkah pencegahan seterusnya untuk mengurangkan bilangan kematian yang disebabkan oleh antikoagulan diperlukan.

ADVERSE DRUG REACTIONS AMONG HOSPITALISED PATIENTS WITH CHRONIC KIDNEY DISEASE IN DUBAI HOSPITAL: WITH REFERENCE TO BLEEDING TENDENCY AMONG HOSPITALISED PATIENTS

ABSTRACT

Chronic kidney disease (CKD) patients are particularly vulnerable to adverse drug reaction (ADR) because they usually are on multiple drug regimens, have different comorbid conditions, and because of alteration in their pharmacokinetics and pharmacodynamic parameters. The overall aim of this thesis was to evaluate and assess adverse drug reactions among hospitalized patients with moderate to severe CKD, and to develop an ADR risk score to identify and stratify CKD patients who are at increased risk of ADRs during hospital stay.

To meet the objective of the thesis, a one year observational prospective study was conducted at the renal unit of Dubai Hospital, the United Arab Emirates. Consecutive patients with CKD stages 3 to 5 (estimated GFR, 10-59 ml/min/1.73 m^2) who were admitted to the renal unit, between January 1, 2012, and December 31, 2012 were recruited. For each patient, data was collected at admission using a standardized form. An ADR risk score was developed by constructing a series of logistic regression models. The overall model fit for sequential models was compared using the Akaike Information Criterion. Odd ratios of the variables retained in the best model were used to compute the risk scores. Furthermore, a propensity score analysis was undertaken to examine the relation of anticoagulant use with adverse outcomes, and to test the

protective effects of statin on the major bleeding events caused by anticoagulation therapy.

Among hospitalised patients with CKD, at least 1 in 8 patients experienced an ADR during hospital stay; patients in ESRD who were not on any renal replacement therapy were at higher risk of developing an ADR; and, more than half of the total ADRs were bleeding events related to anticoagulants use. Major bleeding occurred in 1 of 3 patients who received anticoagulation therapy during hospital stay, and anticoagulant users were 3-times more likely to die when compared with those with no anticoagulation therapy; however, statin had a protective association with the anticoagulant-related bleeding events.

Among hospitalised patients with CKD, there can be considerable heterogeneity in the risk for ADRs. By using the ADR risk score, higher-risk patients could receive more intensive interventions aimed at reducing the drug-related adverse outcomes and improving the cost-effectiveness of CKD therapy. Also, using this score, different risk levels could be used to triage patients for decision regarding the initiation of renal replacement therapy. Anticoagulation therapy in hospitalised patients with CKD was significantly associated with an increased risk of major bleeding and in-hospital mortality. Higher risk was observed in a range of patient groups and was not reduced after adjusting for the common cofounders. These results suggest that further preventive measures to reduce the number of death caused by anticoagulant is warranted.

CHAPTER 1

GENERAL INTRODUCTION

1.1 Prevalence of Chronic Kidney Disease

Chronic kidney disease (CKD) is a major health problem worldwide, with a rising trend in prevalence and incidence, both in developed and developing countries. In the United States, the most recent analysis from National Health and Nutritional Examination Surveys (NHANES) reported that the prevalence of CKD increased from 10% in 1988-1994 to 13.1% in 1999-2004 (Coresh *et al.*, 2007b).

Studies from Australia, and Asia, also, confirm the high prevalence of CKD. The prevalence of CKD in Australia was 11.2 percent (Chadban *et al.*, 2003). In Asia, the prevalence of CKD ranged from 9.07% to 17.8% (Figure 1.1). The prevalence of CKD, in Malaysia was 9.07 percent (Hooi *et al.*, 2013); in China was 10.8 percent (Zhang *et al.*, 2012); in Taiwan was 11.9 percent (Delanaye *et al.*, 2008); in Japan was 12.1 percent (Imai *et al.*, 2009); in Singapore was 12.8 percent (Sabanayagam *et al.*, 2010); in Korea was 13.7 percent (Kim *et al.*, 2009); and in Thailand was 17.8 percent (Ingsathit *et al.*, 2009).

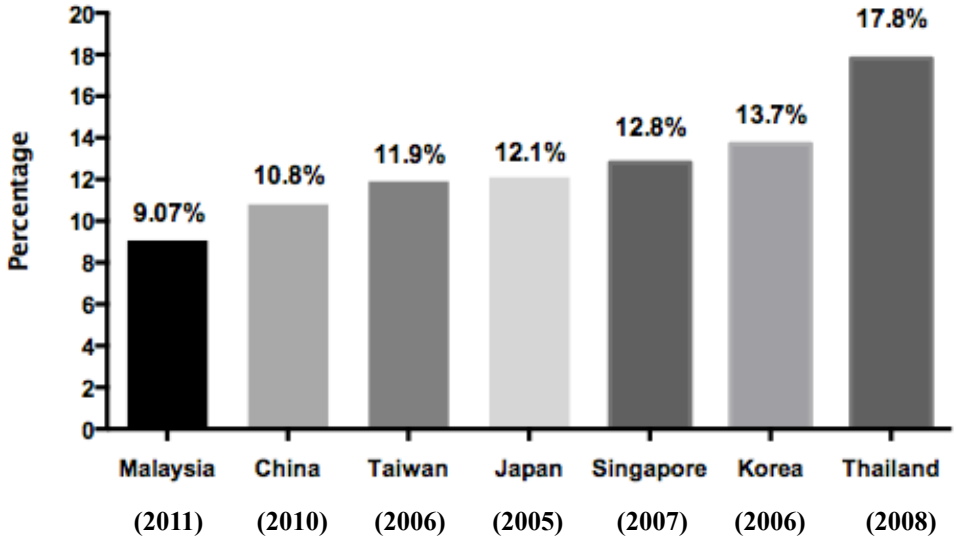


Figure 1.1. Prevalence of CKD in Asia

However, there are scarce data on the epidemiology of CKD in the Middle East, particularly among the Arab countries, and most of the available data is about end stage renal disease (ESRD). Due to the absence of national renal registries in these countries data that do exist are based on small studies, and because of their sample size and design considerations data from these studies have limited generalizability (Table 1.1). Furthermore, the epidemiology of ESRD itself in this region is also underreported (Farag *et al.*, 2012, Hassanien *et al.*, 2012).

Table 1.1. Available data on the epidemiology of CKD and ESRD in the Arab countries

Country	Incidence of CKD, pmp	Prevalence of CKD, pmp	Incidence of ESRD, pmp	Prevalence of ESRD, pmp
Egypt	–	–	74	375
Jordan	–	–	111	312
Kuwait	366	–	78	81
Lebanon	–	–	-	243
Oman	–	–	100	-
Saudi Arabia	–	–	136	434
Qatar	–	–	122	480
UAE	–	–	74	-

Abbreviations: CKD, chronic kidney disease; ESRD, end stage renal disease; UAE, United Arab Emirates; pmp, per million population. (Abboud, 2006, Farag *et al.*, 2012)

Diabetes mellitus, hypertension and obesity are the key risk factors for CKD (Coresh *et al.*, 2007b, Haroun *et al.*, 2003). Noticeably, some of these countries such as United Arab Emirates (UAE), Saudi Arabia, Bahrain, and Kuwait, have been identified by World Health Organization (WHO) as having 'very high prevalence of diabetes' (10.2-17.9% range) [Table 1.2]. Extrapolations based on the epidemiology of these factors may provide some insight into the epidemiology of CKD. In 2008, according to the WHO, the UAE, had an estimated prevalence of diabetes mellitus of 10.2%, hypertension of 27.5%, and obesity of 32.7% in its adult population. Diabetes mellitus was the main cause of ESRD among 23.3% of individuals (Farag *et al.*, 2012).

Table 1.2. WHO estimated prevalence (%) of metabolic risk factors in 2008

Country	Prevalence of diabetes mellitus,%	Prevalence of hypertension,%	Prevalence of obesity,%	Total population
Bahrain	11.0	37.1	32.9	1,261,835
Kuwait	11.9	29.1	42.0	2,736,732
Saudi Arabia	17.9	33.1	33.0	27,448,086
UAE	10.2	27.5	32.7	7,511,690

Abbreviations: UAE, United Arab Emirates.

1.2 Chronic Kidney Disease in the United Arab Emirates

Chronic kidney disease is an epidemic in the UAE, and with an increasing diabetes and hypertension burden, and growing elderly population CKD is expected to increase further. Currently, there is no national or regional renal registry, but developing strategies for prevention and management of CKD by the Health Ministry of UAE has been a priority, although there is a tremendous challenge ahead (Awwad, 2010).

May 2009, the Health Ministry of UAE, as part of their commitment to raise awareness regarding CKD prevention, organised a public health screening campaign which aimed to identify hypertension and diabetes mellitus in the population of Abu Dhabi, the capital of UAE. Data collection was performed by a team of nephrology staff who screened people for diabetes mellitus and hypertension at selected places like shopping centers. Screening was performed over 6 hours period daily. In that campaign, more than 3000 people were screened. The detection of either hypertension, or diabetes mellitus or both was done by measuring blood glucose levels and by self report. Results revealed that 8% had high blood glucose levels; 11% were taking antihypertensive medications; 3% were classified as overweight; and 0.8% reported family history of CKD. The screening campaign helped target key risk factors for CKD and strengthened the kidney care measures by improving early detection and prevention of CKD progression among the population. The results of the screening campaign were published in the local press (Awwad, 2010).

1.3 Nephrology Care in Dubai Hospital

The renal unit of the Dubai Hospital, a 625-bed general medical/surgical hospital in Dubai, the United Arab Emirates, provides a full range of services for adult patients with renal diseases, including the diagnosis and management of acute kidney failure, CKD and nephritic/nephrotic syndrome. The unit cares for renal transplant patients starting from as early as 10 days after the transplant, provides regular dialysis therapy as haemodialysis or peritoneal dialysis, and provides extra-corporeal blood purification to patients with intoxication or autoimmune diseases (Dubai Health Authority).

Laboratory tests are usually aimed at urea, creatinine, electrolytes, and urinalysis, which are frequently the key tests when searching for a diagnosis. More specialised tests can be ordered to discover or link certain systemic diseases to kidney failure such as hepatitis B or hepatitis C, lupus serologies, paraproteinemias (amyloidosis or multiple myeloma) or various other systemic diseases that lead to kidney failure. Other tests often performed by nephrologists are, renal biopsy to obtain a tissue diagnosis of a disorder when the exact nature or stage remains uncertain; Ultrasound scanning of the urinary tract and occasional examinations of the renal blood vessels; CT scanning when mass lesions are suspected (Dubai Health Authority).

1.4 Pharmaceutical Services in Dubai Hospital

In western countries, the hospital pharmacist has changed its traditional role of dispensing and supply of medication to a more patient-centered pharmaceutical care activity (Leufkens *et al.*, 1997). However, this role is not fully applicable to hospital pharmacists in UAE. The main activities for hospital pharmacists in UAE are preparing and dispensing of medications (Dameh, 2009). For example in Dubai Hospital, the pharmacy department provides comprehensive pharmacy services to all units of the hospital, including all ambulatory care clinics, where patients are treated with medications. However, pharmacist services are mainly restricted to purchasing, stocking and dispensing of the medication products and limited time, if any, is spent on assessment of patient needs for pharmaceutical care.

Pharmacy education in UAE is based on a product-oriented approval with a focus on basic pharmaceutical sciences. This is in contrast with western countries, where pharmacy education focuses on pharmaceutical sciences, but there is also an emphasis on patient-centered pharmaceutical care aspects. Similarly, in other Middle Eastern countries, the changing role of pharmacists in the health care system is impacting on hospital pharmacy practice and education, and changes are being introduced. For example, during this few years some pharmacy schools in UAE have opened a postgraduate clinical pharmacy program.

1.5 Pharmacovigilance in the Middle East

According to World Health Organization-Uppsala Monitoring Centre, pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any drug-related problem" (WHO-UMC). While most studies on the drug safety are conducted in western countries, few data are available from the Middle East (Olsson *et al.*, 2010). Drug safety data from developed countries cannot be extrapolated to that of developing countries, since the incidence, nature and severity of adverse drug reactions may differ because of different ethnic and genetic backgrounds (Eliasson, 2006).

In a meta-analysis study, McDowell and coauthors (2006) investigated the adverse reactions to cardiovascular drugs for different ethnic groups. The authors demonstrated that compared to Caucasian patients, having African ethnicity conferred a three-fold risk of angioedema from ACEI (angiotensin-converting enzyme inhibitor), and higher risk of intracranial haemorrhage from the thrombolytic therapy. In their study, the authors reported that African and East Asian patients had a higher risk of cough when using ACEIs (McDowell *et al.*, 2006). In addition, other influences such as environmental factors, alcohol, smoking, and diet might alter the risk of adverse drug reactions in a given population (Pirmohamed and Park, 2001).

More recently, the status of pharmacovigilance in the Middle East was surveyed using the translated Uppsala Monitoring Centre Assessment of Country Pharmacovigilance Situation questionnaire. The author indicated that out of eleven participating countries, six countries had an official pharmacovigilance program (Egypt, Iraq, Jordan, Oman, Kingdom of Saudi Arabia and the United Arab Emirates), while five (Bahrain, Kuwait, Palestine, Qatar and Yemen) reported no drug safety related program or centre (Wilbur, 2013).

The program of medication safety has been recently introduced in the UAE, hence scarce data on pharmacovigilance and ADRs are available from this country. In 2008, the UAE government launched the National Pharmacovigilance Centre (NPC), where all suspected ADRs and medication errors must be reported in an official form (Wilbur, 2013). These forms will then be used to issue safety warnings, provide professional education and training, conduct drug regulatory activities, and develop national drug therapeutic guidelines (Wilbur, 2013).

1.6 Problem Statement

In Dubai, clinical pharmacists spend limited time on clinical services. Barriers to the implementation of clinical pharmacy services have been the lack of specific clinical training for pharmacists, the limited pharmacy personnel, and the fear of poor acceptance from physicians (Dameh, 2009).

An important step towards implementing clinical pharmacy services is to target patients who are at high risk for adverse reactions to drugs, because they are more likely to benefit. Chronic kidney disease patients are among these, because of multiple comorbidities, multiple medication use (Manley *et al.*, 2003), and altered pharmacokinetics and pharmacodynamics parameters (Verbeeck and Musuamba, 2009).

Moreover, Patients with CKD display a wide range of abnormalities in the homeostatic pathway that may account for their increased risk for both thrombotic events and bleeding (Jalal *et al.,* 2010). The early stages of CKD are mainly associated with the prothrombotic tendency (Jalal *et al.,* 2010), whereas in its more advanced stages, beside the procoagulant state, platelets can become dysfunctional due to uremic-related toxin exposure leading to an increased bleeding tendency (Jalal *et al.,* 2010, Boccardo *et al.,* 2004). The increased risk of thromboembolic diseases among CKD patients commonly requires anticoagulation therapy (Dager and Kiser, 2010). Therefore, this thesis reports the results of the studies performed by a clinical pharmacist providing pharmaceutical care on the renal unit of a Dubai Hospital.

1.7 General Objectives

The overall aim of this thesis is to evaluate adverse drug reaction (ADR) among hospitalised patients with moderate to severe CKD.

1.7.1 Specific Objectives

The specific aims of this thesis are as the following:

(1) To determine the incidence and patterns of ADR among hospitalised patients with CKD stages 3 to 5.

(2) To assess the type, causality, severity and preventability of each identified ADR.

(3) To identify which drug category causes the most adverse reactions.

(4) To develop an ADR risk assessment score by using routinely obtained baseline data from hospitalised patients with CKD stages 3 to 5.

(5) To explore the relationship between anticoagulants use and (a) major bleeding events, (b) in-hospital mortality, (c) length of hospital stay, and (d) readmission at 30 days.

(6) To study the association among subgroup of patients with anticoagulants use and the occurrence of major bleeding events.

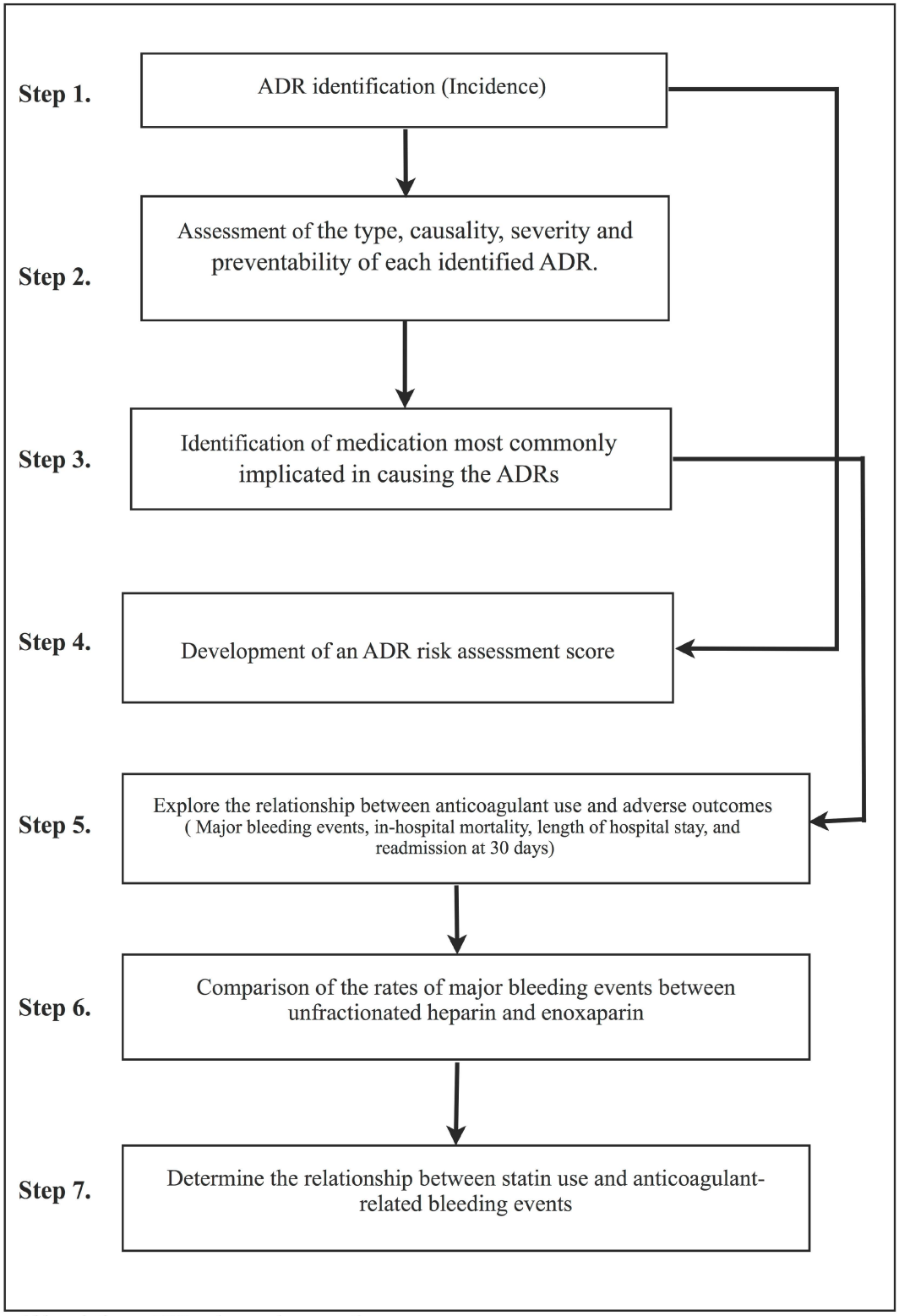
(7) To compare the risk of major bleeding associated with the use of UFH versus enoxaparin.

(8) To determine the relationship between statin use and risk of anticoagulant-related bleeding events.

(9) To examine the association among subgroup of patients with statin use and the occurrence of major bleeding events.

1.8 Framework of Thesis

Figure 1.2. outlines the different steps of the thesis work. During the first three steps (Chapter 2), ADR was identified among hospitalised patients with CKD stages 3 to 5 (estimated glomerular filtration rate, 10–59 ml/min/1.73 m^2) who were admitted between January 1, 2012, and December 31, 2012, to the renal unit of Dubai Hospital. Later, the identified ADRs was assessed for their causality, type, severity and preventability. Medication most commonly related to causing ADRs was then identified. In the fourth step (Chapter 3), factors associated with ADRs were identified by using demographic, clinical and laboratory variables of patients with CKD stages 3 to 5. An ADR risk score was developed by constructing a series of logistic regression models. The overall model performance for sequential models was evaluated using Akaike Information Criterion for goodness of fit. Odd ratios for the variables retained in the best model were used to compute the risk scores. During the last three steps (Chapter 4), the incidence of adverse outcomes of anticoagulants (in-hospital mortality, the occurrence of major bleeding, length of hospital stay, and readmission at 30 days) in hospitalised patients with CKD was determined. Later, the risk of major bleeding events in the use of unfractionated heparin versus adjusted therapeutic doses of enoxaparin was compared. Finally, the association of statin use with reduced risk of anticoagulant-related bleeding events was studied. Propensity score methodology was applied in the last three steps of the thesis; that helped design observational studies in a way that is comparable to the way randomised studies are designed.



Abbreviations: ADR, adverse drug reaction.

Figure 1.2. Framework of thesis

CHAPTER 2

ADVERSE DRUG REACTIONS AMONG HOSPITALISED PATIENTS WITH MODERATE TO SEVERE CHRONIC KIDNEY DISEASE

2.1 INTRODUCTION

2.1.1 Terminology of Drug Safety

There is a large diversity of terms in medical publications for the unwanted effects that follow the use of drugs…more than a century ago it was known as 'the side effects of the drug' - translated from Louis Lewin, Die Nebenwirkungen der Arzneimittel (1881).

The term 'unwanted effect' is an alternate for 'adverse effect'; and, the terms 'adverse effect' and 'adverse reaction' refer to the same situation, but an adverse effect is noticed from the point of the drug, whereas an adverse reaction is noticed from the point of the patient. The drug causes an 'effect', whereas the patient has a 'reaction'. However, the term 'adverse drug effect (or reaction)' must be differentiated from the term 'adverse event (or experience)'. An adverse drug reaction is an undesirable outcome that can be referred, with some degree of causality, to an effect of a drug, whereas an adverse event is an adverse outcome that happens while a patient is receiving a drug or at subsequent time but that may or may not be referred to an effect of a drug. All adverse drug reaction are adverse events, but not all adverse events are adverse drug reaction. This differentiation is important in the clinical field, in which not all adverse events are necessarily drug induced (Aronson and Ferner, 2005).

This can be further explained in Figure 2.1, a Venn diagram that shows the relation between adverse events, adverse drug reactions, and medication errors. For example, adverse drug event, as defined by Bates and colleague (1995), is "an injury resulting from medical intervention related to a drug", would involve adverse drug reactions, whether caused by medication errors or not, and harm caused by medication errors that are not adverse drug reactions (i.e. the areas marked 2, 3 and 4 in Figure 2.1).

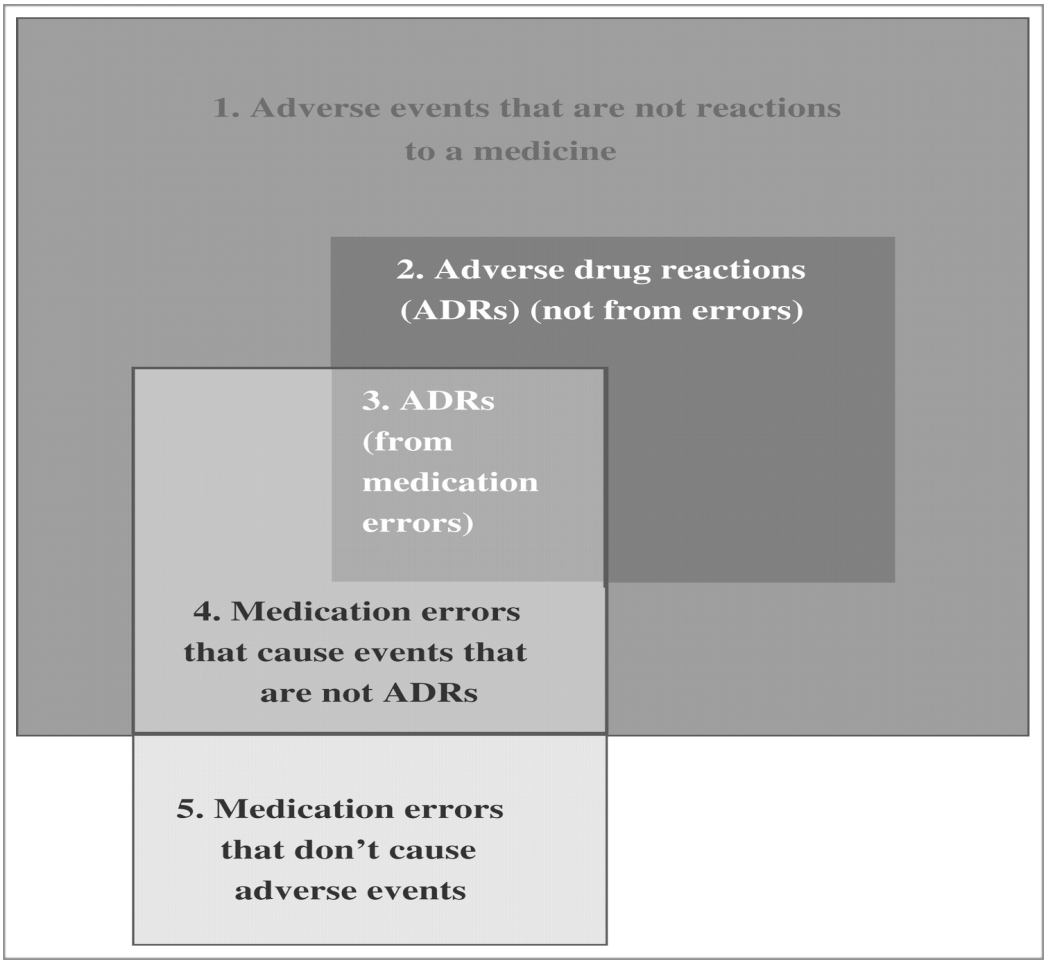


Figure 2.1. A Venn diagram representing the relation between adverse events, adverse drug reactions, and medication errors. Figure adapted from (Aronson and Ferner, 2005)

2.1.2 Adverse Drug Reactions

2.1.2.1 Definition

Almost thirty years ago an adverse drug reaction (ADR) has been defined by the World Health Organization (1975) as: "Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for modification of physiological functions." This definition has been commonly used in ADR studies but has been criticised in the way that ADR can occur at doses other than those described in the definition, for example after a test dose (Aronson and Ferner, 2005). Furthermore, the use of the word noxious excludes ADR that may be minor, and thus may undermine the current ADR surveillance systems (Edwards and Aronson, 2000, Laurence and Carpenter, 1998).

Alternatively, Edwards and Aronson defined an ADR as: "An appreciably harmful or unpleasant reaction, resulting from the use of a medicinal product, which predicts hazards from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (Edwards and Aronson, 2000). This definition excludes ADRs that require no intervention and has been used more frequently in ADR studies (Davies *et al*., 2009, Pirmohamed *et al*., 2004). In this thesis the definition developed by Edwards and Aronson was used to identify an ADR.

2.1.2.2 Types of ADRs

Based on a system developed by Rawlin and Thompson, ADRs can be classified into two types; type A and B. Type A are those reactions directly related to the pharmacological effect of a drug, so-called augmented adverse reactions, and, type B are reactions caused by a hypersensitive response of the body to the presence of a drug, so-called bizarre adverse reactions. Characteristic for type A adverse reactions is common occurrence (>1%), a dose effect relationship and predictability. An example of a type A adverse reaction is hypoglycemia caused by antidiabetic medications. Characteristics of type B adverse reactions are the rare occurrence (<1%), acute in nature and with unexpected onset and severity. An example of a type B adverse drug reaction is the increased destruction of peripheral blood cells caused by the immune system involving drug-related antibodies (Rawlins and Thompson, 1991).

2.1.2.3 Causality Assessment of ADRs

It is essential to detect ADRs and to establish a causal relationship between drugs and their adverse reaction. Many causality assessment methods have been proposed to assess the relationship between a causative drug and an adverse reaction in a given patient. These methods fall into three broad groups: expert judgement, comprehensive algorithms and probabilistic methods or Bayesian approaches (Agbabiaka *et al.*, 2008).

Expert judgements are individual assessments that rely on an expert opinion in the area using no standardised tool to achieve a conclusion regarding drug-related causality (Arimone *et al.*, 2005, Wiholm, 1984). Algorithms are sets of questions with associated scores for computing the likelihood of a causality (Naranjo *et al.*, 1981a, Venulet *et al.*, 1986, WHO-UMC). Probabilistic methods or Bayesian approaches make use of specific information in an ADR case to transform the prior estimate of probability into a posterior estimate of probability of drug causality relationship. The prior probability is computed from epidemiological information and the posterior probability combines the epidemiological information with the clinical evidence in the ADR case to reach decision regarding the estimate of causation (Lane, 1986, Lane *et al.*, 1987).

The Bayesian concepts have been successfully used in detection of rare and severe ADR cases, for example in haematologic dyscrasia associated with ticlopidine therapy (Paradiso-Hardy *et al.*, 2000), and Guillain-Barre Syndrome due to zimeldine therapy (Naranjo *et al.*, 1990). However, the complexity of the Bayesian approaches makes it unsuitable for routine clinical use. In addition when this approach was compared with the Naranjo algorithm it was found that assessments of ADR using both methods were significantly correlated ($r = 0.45$, $P<0.0001$) (Lanctôt and Naranjo, 1995)

It is clinically important that all suspected ADRs should be objectively assessed and presented using a suitable causality assessment tool. There is still no method widely accepted for the causality assessment of ADRs (Agbabiaka *et al.*, 2008), however, among the above mentioned methods, the Naranjo algorithm (Naranjo *et al.*, 1981a) is the most frequently used for causality assessment of ADRs in the literature and clinical practice as it offers a simple methodology. The algorithm classifies ADRs into definite (score, 9-12 points), probable (score, 5-8 points), possible (score, 1-4 points), or doubtful (score, 0 point) (Table 2.1).

2.1. Adverse drug reaction causality assessment[a], Naranjo algorithm[b]

Question	Yes	No	Do Not Know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administrated?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administrated?	+1	0	0
Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
Are there alternative causes (other than the drug) that could solely have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

[a]The total number of points calculated from this table define the category an adverse drug reaction belongs to. The categories are defined as follows: definite (score, 9-12 points), probable (score, 5-8 points), possible (score, 1- 4 points), or doubtful (score, ≤0 point).
[b](Naranjo *et al.*, 1981a)

2.1.2.4 Severity Assessment of ADRs

The term severity is often used to explain the intensity of a medical event, as in grading ‘mild’, ‘moderate’ and ‘severe’. Severity assessment categorises the ADRs as mild, moderate, or severe based on the steps taken for the management of the ADRs. According to WHO criteria; a serious ADR is classified as one which is fatal, life threatening, requires or prolongs hospitalisation, and/or results in significant persistent disability or incapacity (WHO-UMC).

In 1963, in a study of evaluating the hazards of hospitalization, Schimmel referred to any untoward events or complication of therapy as ‘episodes’. In the study, an episode was classified as minor, if it was short and subsided without specific therapy; as moderate, if it required significant therapy, or if it prolonged hospital stay by a day or more; and as major if it was life-threatening or fatal.

In 1992, Hatwig and Siegel developed a simple scale for assessing the severity of ADRs. The scale was originally adapted from a severity-indexed scale already being used to review significant medication-administration errors (Hartwig *et al.*, 1991) and the concepts are similar to those of Schimmel (1963), with length of stay, therapy required, and prognosis being the main focus of severity assessment. The scale classifies ADRs into seven levels according to their severity. Levels 1&2 fall under mild category whereas levels 3 & 4 fall under moderate and levels 5, 6 & 7 fall under severe category (Table 2.2).

Table 2.2. Adverse drug reaction severity assessment, Hartwig and Siegel scale[a]

Level	Description	Scale
1	An ADR occurs but requires no change in treatment with the suspected drug.	Mild
2	The ADR requires that the suspected drug be withheld, discontinued, or otherwise changed. No antidote or other treatment is required, and there is no increase in length of stay.	Mild
3	The ADR requires that the suspected drug be withheld, discontinued, or otherwise changed, and/or an antidote or other treatment is required, and there is no increase in length of stay.	Moderate
4	a) Any level 3 ADR that increases length of stay by at least one day, or (b) The ADR is the reason for admission.	Moderate
5	Any level 4 ADR that requires intensive medical care.	Severe
6	Did the reaction reappear when a placebo was given?	Severe
7a	The adverse reaction causes permanent harm to the patient.	Severe
7b	The adverse reaction either directly or indirectly leads to the death of the patient.	Severe

Abbreviations: ADR, adverse drug reaction.
[a](Davies *et al.*, 2009, Hartwig *et al.*, 1992)

2.1.2.5 Preventability Assessment of ADRs

At a first glimpse, one can simply classify which ADRs are preventable by their type and conclude that a type A reaction is predictable and hence, is preventable whereas a Type B reaction is not predictable and is therefore, not preventable (Rawlins and Thompson, 1991). However, in clinical practice type A ADRs might not be always preventable, sometime there are few clinical alternatives but to use the drug in the patient. Type B reactions can also be prevented if previous allergy to an ADR is noticed before administration. This is emphasised on the importance of using a structured method for assessing the preventability of ADRs.

In 1990, Hallas and colleagues developed criteria or definitions to assess preventability of an ADR. The criteria are shown in Table 2.3.

Table 2.3. Adverse drug reaction preventability assessment, Hallas *et al*. criteria[a]

Criteria	
The ADR was due to a drug treatment procedure inconsistent with current knowledge of good medical practice	Definitely preventable
The ADR could have been avoided by an effort exceeding the obligatory demand of current knowledge of good medical practice	Possibly preventable
The ADR could not have been avoided by any reasonable means	Non-preventable

Abbreviations: ADR, adverse drug reaction.
[a](Hallas *et al.*, 1990)