

# A Study of Prescribing Valsartan in Out-patient Clinics at the Royal Hospital, Muscat, Oman

Zaher Al-Salmi, Fatma Al-Raisi, Ahmed Al-Harbi, Ali Al-Rawahi, Hamed Al-Naamani

## Abstract

**Objectives:** Angiotensin Receptor Blockers such as Valsartan, are a newer class of drugs associated with significant reductions in cardiovascular morbidity and mortality. They are commonly used in hypertension, chronic heart failure, diabetes-related nephropathy and post-myocardial infarction in patients who are intolerant to Angiotensin Converting Enzyme inhibitors (ACEi). A review of medicines used in Royal Hospital (an Omani tertiary health care centre) during 2004 and 2005 showed that Valsartan was one of 20 most expensive drugs used. The main objective of this study was to evaluate the pattern of prescribing valsartan in out-patient clinics.

**Methods:** a retrospective study, applying medicines use evaluation, to describe the pattern of prescribing Valsartan in comparison with international guidelines. The study carried out in the outpatient pharmacy setting, Royal Hospital from 15th May to 30th June 2006. It included 120 adult patients who had been prescribed Valsartan at the outpatient clinics during the study period.

**Results:** among the 120 patients only 109 patients were finally included in the study. Eleven patients who had had duplicated prescriptions were excluded from the study. 78% of the patients

were on Valsartan for its FDA-approved indications while 22% of patients were for other non-approved indications. Half of the patients were initiated on an ACEi before shifting to Valsartan. The other half of the patients was started with Valsartan as a first line choice without any clinical justification.

**Conclusion:** The study showed that half of the patients were initiated on Valsartan without being prescribed an ACEi prior to that, while the recommendation in most of the international guidelines based on indication stated that ARBs are used in patients who are intolerant to ACEi. The study emphasizes the need for further research to highlight the need for developing national guidelines and adhering to these guidelines for rational prescribing.

*From the Department of Pharmacy, Royal Hospital, P.O. Box 1331 Postal Code 111, Muscat, Sultanate of Oman.*

*Received: 12 Oct 2008*

*Accepted: 28 Nov 2008*

*Address correspondence and reprint request to: Dr Zaher Al-Salmi, Department of Pharmacy, Royal Hospital, P.O. Box 1331 Postal Code 111, Muscat, Sultanate of Oman E-mail: alsalmi.zaher@gmail.com*

## Introduction

Like Angiotensin-Converting Enzyme inhibitors (ACEi), Angiotensin-2 Receptor Blockers (ARBs) modulate the activity of the rennin angiotensin system by blocking angiotensin II type 1 receptor.<sup>1</sup> Angiotensin II is a potent vasoconstrictor, and it also stimulates the adrenal cortex to release aldosterone, which increases blood pressure by increasing the retention of sodium and water in the kidney.<sup>1</sup>

ACE inhibitors, and ARBs, have a key role in the treatment of common comorbid conditions in patients with hypertension (HTN). They are associated with significant reductions in cardiovascular (CV) morbidity and mortality whether they are used as first-line therapy or in combination with other agents.<sup>2</sup> Clinical evidence exists to recommend ACE inhibitors in patients with heart failure (HF), myocardial infarction (MI), high coronary heart disease (CHD) risk, diabetes, chronic kidney disease, and recurrent stroke prevention.<sup>3-5</sup> The results of numerous clinical studies have established the reno-protective properties of renin-angiotensin-aldosterone inhibitors, therefore both ACE inhibitors and ARBs provide benefit in patients with diabetes by slowing the

progression of renal disease.<sup>6-10</sup> However, ACE-inhibitors have been used as a first-line agent in many randomized controlled trials comparing them with other antihypertensive drugs, its efficacy in the presence of other co-morbidities and its safety in long-term treatment is well established.<sup>3, 4</sup> Therefore, ARB is clearly indicated when the patient cannot tolerate an ACE inhibitor or when there is a treatment failure. According to the Food and Drug Administration (FDA), Valsartan is approved for the following indications: myocardial infarction, hypertension, and heart failure. International guidelines (NICE, SIGN, ACC/AHA) for treating these diseases stated that ARBs should replace ACE inhibitors when patient can't tolerate them, or in case of poor response.<sup>11-16</sup> Also the guidelines recommended regular monitoring of urea and electrolytes (U&E), where more frequent monitoring should take place in the initiation of therapy (every month), then every three to six months.<sup>11-16</sup>

Medicines use review (MUR) showed that Valsartan (Diovan), which is the only ARB available in Royal Hospital (RH) was one of the twenty most expensive drugs used in 2004, and in 2005.<sup>17</sup>

The Royal Hospital serves as the apex tertiary care referral centre for the country, opened in 1987 with 620 bed capacity. The hospital provides facilities for child health, medicine, surgery and obstetrics and gynaecology. It includes the national oncology centre and cardiology centre; it is also the main hospital for the care of complicated HIV patients and other infectious disease cases.<sup>18</sup>

In recent years, Ministry of Health strategy has concentrated on cost effective medications. In view of the subsequent increase in the cost of Valsartan, and the lack of local formulary/protocols to guide the use of such expensive drugs, it appears that there is a need to explore the current status of Valsartan prescribing in Royal Hospital.

### Objectives

The aim of the study was to evaluate the pattern of prescribing Valsartan at the Royal Hospital in adhering to international guidelines. Further objectives included identifying the rationale behind changing from ACEi to Valsartan for the approved indications and to make recommendations to improve the current practice of prescribing Valsartan.

### Methods

#### Outcome measures

Patients treated for HTN, HF, post MI, and diabetes-related nephropathy in the out-patient clinics at the Royal Hospital should be prescribed Valsartan as a second line therapy as an alternative to ACEi if not tolerated or treatment fails

#### Study design

A retrospective study, conducted at the outpatient pharmacy setting, at the Royal Hospital between 15<sup>th</sup> May 2006 and 30<sup>th</sup> June 2006.

#### Inclusion and exclusion criteria

The study included all adult patients who were prescribed Valsartan at the outpatient clinics (n=120) at the Royal Hospital during the study period. Eleven patients who had duplicated prescriptions were excluded from the study.

#### Literature and guideline review

Medline Literature search and review the international guideline concerning the usage of Valsartan was undertaken. Some guidelines reviewed are listed below:

1. American Cardiology College/American Heart Association (ACC/AHA)-2005 Guidelines.<sup>11</sup>

2. British Hypertension Society Guidelines-2004.<sup>12</sup>
3. National Institute for Clinical Excellence (NICE) (hypertension, heart failure)-2006.<sup>13</sup>
4. Scottish Intercollegiate Guideline Network (SIGN)-2001.<sup>14,15,16</sup>

#### Data collection

Data collection proforma was designed to include patient demographics, co-morbidities, indication for Valsartan, reason for stopping ACE inhibitors, adverse drug reactions, U&E monitoring, and treatment cost (Table 1). As the Royal Hospital applies an electronic system, and there were no other source of patient-related medical information; the data was collected by reviewing patients' electronic medical notes. A pilot study was conducted of 20 patients to ascertain the validity of data collection. One of the study's objectives was to estimate the cost of Valsartan and compare it to a standard ACEi used in the study setting. The cost of Valsartan 160mg was compared to Lisinopril 20mg both in standard therapeutic doses. The cost was calculated for 109 patients for one year. The data were then subjected to descriptive statistical analysis using Microsoft Excel program.

**Table 1:** Information included in the data collection form

Information included in the data collection form
• Patients demographics: (age, sex)
• Co-morbidities and concomitant medications
• Indication for Valsartan
• Whether patients were previously on ACEi or not or are on combination
• If yes, what are the reasons behind changing?
• If no, why not?
• Relevant laboratory results
• Adverse drug reactions (ADRs) if any
• The cost of Valsartan/month/patient

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ACEi: Angiotensin-Converting Enzyme inhibitors

### Results

#### Demographics

The study initially included 120 patients but 11 were excluded because these were duplicated prescriptions. Finally, 109 patients were included in the study (prescriptions = 109) during the study period. Of the 109 remaining patients, 54 (49.5%) were male with mean age of 55.8 years (SD=14.2).

Half of the prescriptions (n=55) included in the study were prescribed from the cardiology clinics (50.5%), followed by 38

prescriptions (34.9%) from internal medicine clinics and 16 prescriptions (14.7%) from the nephrology clinics.

**Indication of Valsartan in studied patients**

The patients had an average of 5.9 medications per prescription (SD=2.5) with a maximum of 12 medications per prescription and a minimum of one medication. A total of 127 medications were used to treat the different co-morbidities of the patients included in this study (Table 2). Most of the patients were prescribed Valsartan for its FDA-approved indication (92%, n=100). There were 62% (n =78) on Valsartan for hypertension, and 17% (n = 22) were prescribed Valsartan for heart failure (see Table 2).

Of the 109 patients, 59 (54%) were previously initiated on an ACEi. Of the 59 patients, 11 (19%) patients were prescribed valsartan in combination with an ACEi for proteinuria, and in 48 (81%) patients ACEi was stopped due to different reasons. Of the 48 patients, ACEi was stopped in 10 (21%) because the patients developed side effects (mainly cough) and were changed to Valsartan. In three (6%) patients the reason behind stopping ACEi was given as ineffectiveness of ACEi, while in 35 (73%) there was no explanation why ACEi was stopped and Valsartan initiated.

On the other hand, of the 109 patients, 50 (46%) patients were commenced on Valsartan and were not on any ACEi previously. Among those who were not on an ACEi earlier, the explanation that was given in one (2%) patient was not being the first choice (i.e. patient was treated with Valsartan for isolated systolic hypertension (ISH)).<sup>19</sup> The other 49 (98%) patients had no clear documentation to justify the use of Valsartan as a first line choice.

**Table 2:** Indication of Valsartan in studied patients

Indication	Numbers	Percent
Hypertension	78	62
Heart failure	22	17
Proteinurea	12	9
DM-related nephropathy	13	10
ISH	1	1
No indication	1	1
TOTAL	127	100

DM=Diabetes Mellitus; ISH= Isolated Systolic Hypertension

**Laboratory monitoring (Urea and Electrolyte)**

Although the drug evaluated in this study had laboratory testing recommended in clinical guidelines, we observed a wide variation in testing rates. 42% (n=46) of the patients were having U&E done regularly (every 3-6 months). Laboratory monitoring was done

once a year in 36% (n=39) of the patients , and 22% (n =24) of the patients rarely had U&E tested.

**Adverse drug reactions (ADR) associated with Valsartan**

The present study revealed that only 18 (16.5%) patients had ADR while in 91 (83.5%) patients there was no documented ADR in the medical notes. A number of patients (21%, n =10) developed cough, which was the main documented side effect. There were five (4.6%) patients experiencing hyperkalaemia (serum potassium levels > 5 mmol/l), one (0.9%) patient suffered from abdominal pain, and two (1.8%) patients were complaining of headache. Apart from cough, the ADRs detected in this study were not reported by the treating teams as an ADR, but were identified during the study period while reviewing the electronic notes and laboratory results.

**Cost**

Estimated average cost per prescription of Valsartan (160mg/day) was Omani rials (OR) 9.30/month/patient (1 OR= \$ 2.6), was compared with average cost per prescription of Lisinopril (20mg/day), which was OR 0.80/month/patient. Total cost of Valsartan for 109 patients in one year was OR 16000, compared to OR 1,000 for Lisinopril.

**Discussion**

The FDA approved indications for Valsartan are myocardial infarction, hypertension, and heart failure. International guidelines clearly state that ARBs should replace ACE inhibitors when patients cannot tolerate them, or in case of poor response.<sup>11-16</sup> The results revealed that more than half of the patients included in this study (54%, n=59) were initially on an ACEi prior to commencing Valsartan, and 50 (46%) patients were initiated on Valsartan as a first line therapy. Of the 59 patients, 11(19%) patients were prescribed Valsartan in combination with an ACEi for proteinuria, and 48 (81%) patients were shifted to Valsartan after discontinuation of their ACEi. Cough in 10 patients, and ineffectiveness in 3 patients was documented as the reason for changing to Valsartan. However, no clear explanation was given for changing 35 patients' medication to Valsartan.

Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines,<sup>20</sup> recommend the use of ACEi and ARBs for diabetic kidney disease and nondiabetic kidney disease, as they lower blood pressure (BP), reduce proteinuria by 35-40%, slow progression of kidney disease and are likely to reduce CVD risk, although, there is weak evidence that combined therapy is preferred.<sup>21</sup> One large study of nondiabetic kidney disease,<sup>21</sup> showed that combined therapy was more effective than either alone in slowing the decline in glomerular filtration rate (GFR). However, additional studies

are required to support the combination as most of the guidelines recommend using one class rather than using both.<sup>21</sup>

A number of patients developed side effects with the ACEi. Cough was the main documented side effect (9%, n =10). The Heart Outcomes Prevention Evaluation (HOPE)<sup>22</sup> study reported that cough affected 14.3% of the patient and 4% required discontinuation of ACEi.<sup>21</sup> In the present study changing to Valsartan because of cough was justified although there might be other reasons for cough which must be ruled out before labeling it as a side effect of ACEi.

The medical notes showed that in three (6%) patients ACEi was ineffective thus it was stopped and changed to Valsartan. Meta-analysis<sup>23</sup> of ARB studies showed that there is no superiority of ARBs over ACEi in patients with heart failure. VALIANT trial<sup>24</sup> concluded that Valsartan was well tolerated and was as effective as Captopril in patients with acute MI complicated with HF or left ventricle systolic dysfunction.<sup>24</sup> All this evidence shows that there is no superiority of ARBs over ACEi in terms of efficacy. Although in clinical practice, treatment failure can occur where individual patients failed to respond to a specific drug. However; there were only three (6%) patients where ineffectiveness was reported. Of the 48 patients who were on ACEi previously, no clear explanation was given for changing 35 patients' (73%) medication to Valsartan. Of the 109 patients, there were 49 (45%) patients initiated on Valsartan without giving any reasons for not trying an ACEi as a first line measure

There is an ongoing argument among health care professionals which relates to the ineffectiveness of generic ACEi in comparison with the brand Valsartan. It is obvious that there is a big difference in the direct cost of the two drugs, and it seems that the reporting system to the Directorate General of Drug Supply of ineffectiveness/intolerance of the available generic drugs was not activated and not implemented in daily practice. The Oman National Formulary (ONF) was published in 2003 and has not been reviewed or updated since then. In the Royal Hospital, the clinical pharmacy service started ten years ago. Most of the staff hold an MSc in clinical pharmacy. The service provides pharmaceutical cover for most critical areas. However, the role of the clinical pharmacy section is still neglected by the Drug and Therapeutic Committee.

Living in an era of Evidence Based Medicine (EBM), in which clinical guidelines are available in all specialties worldwide, a question has arisen: Do we need our own national guidelines or can we rely on the available international guidelines?

This study demonstrates the need to develop our own national guidelines, to update the ONF, and to activate the Drug and Therapeutic Committees to ensure the standardization of safe,

cost-effective prescribing of medications.

#### **Limitation of the study**

This study does not include any major clinical trials or guidelines that were published after June 2006. Also the Valsartan brand was changed in 2008 to the generic brand, thus changing costs estimated in the study. However, the need for national guidelines, periodically updated formulary, an active Drug and Therapeutic committee is essential for long-term health care strategy planning to ensure safe and cost-effective medications.

#### **Conclusion**

This study was conducted at the Royal Hospital, Muscat, Oman, to evaluate the pattern of prescribing Valsartan because of increased consumption over a significant period. The study also concludes that irrational prescribing of Valsartan was mainly because of lack of national guidelines, or lack of adherence to the international guidelines. Prescribing according to guidelines and rational drug use will save our resources. Developing our national guidelines was one of the main goals of this study.

#### **Acknowledgments**

The authors owe their gratitude and thanks to pharmacist Jehan Al-Fannah, Head of Clinical Pharmacy service at Royal Hospital, for all her support throughout the study period.

The authors report no conflict of interest and no funding has been received in this work.

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