DECLARATION

I, Ashti Juggath, declare that the research report is my own work. It is being submitted for the purpose of completion of the degree of Master in Medicine, Pharmacotherapy, at the University of the Witwatersrand, Johannesburg. It has not been previously submitted for any other degree at this or at any other university

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A. Juggath (Ms)

7th day of February 2008

DEDICATION

This is dedicated to my husband, Bavanethan and my two children, Adiya and Vidur.

ABSTRACT

Angiotensin II inhibitors or Angiotensin Receptor Blockers (ARB's) are the most recent addition to the suite of antihypertensives. They are also one of the most expensive of the drug classes. Since the introduction of the first ARB on the market, the merits of ARB's have been investigated. The mechanism of action and indications are similar to ACE inhibitors thus comparisons have been done between the two classes to ascertain if there are any added benefits in using ARB's.

This study was an analysis of out of hospital chronic medication claims from a managed care organisation in South Africa to view the utilisation pattern of ARB's and to establish if there were any indications for the choice of this specific drug class for the conditions hypertension and heart failure..

A managed care organisation aims to provide clinically appropriate and cost effective medication to its members. It is therefore important to investigate if there are any reasons for a more expensive drug to be used if there is a more cost effective alternative available.

The medication claims for ARB's were investigated, in relation to ACE inhibitors to try and establish if there were any specific reasons for the use of ARB's. From the results obtained, it was evident that ACE inhibitors and ARB's were widely used within the managed care organisation and made up a high percentage of the amount spent on antihypertensive drugs.

The gender utilisation patterns showed that more males used ACE inhibitors and ARB's for both hypertension and heart failure, although there were more females registered for these conditions within the organisation.

The incidence of hypertension and heart failure was more prevalent in the over 45 year old age group and the use of these antihypertensive medications mirrored this.

ARB's were the most expensive class of drugs used for hypertension and heart failure, and there was no reason found to support the specific use of these agents.

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TABLE OF CONTENTS ..... PAGE

CHAPTER

APPENDICES

LIST OF TABLES **PAGE**

LIST OF FIGURES ..... PAGE

NOMENCLATURE/GLOSSARY

ACE Inhibitors	Angiotensin Converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker
WHO ATC	World Health Organisation Anatomical Therapeutic Classification
CIB	Chronic Illness Benefit
CHF	Congestive Heart Failure
CVD	Cardiovascular Disease
Generic Drug	A drug registered as a pharmacological equivalent to its Brand-Name counterpart with the same active ingredient in the same strength and dosage form
ICD -10 Code	International and Statistical Classification of Diseases and Related Health Problems (10th Revision) Code – A World Health Organisation Publication
INN	International Nonproprietary Names (International Standard Nomenclature for Active Ingredients in Drugs – Forms part of the ATC Classification)
MMAP	Maximum Medical Aid Price
Medication Claimant	Refers to an out-of-hospital medication claimant unless otherwise specified
MCO	Managed Care Organisation

CHAPTER 1

INTRODUCTION

1.1 Managed Health Care

"Managed care in its simplest form is just the provision of health care with a corresponding concern for the appropriate use of its resources", (Blackburn and Ito, 1995).

Due to the constantly increasing costs of healthcare, the management and control thereof, has to be maintained.

One of the methods of containing pharmaceutical costs is the use of a drug formulary. The formulary has to consider efficacy and safety in addition to reducing cost (Blackburn and Ito, 1995). The managed care organisation used in this study has a formulary but exceptions from the formulary are allowed when certain criteria are met.

The criterion is based on the disease, the appropriateness of the therapy, the clinical effectiveness and the history of the patient amongst others.

Formularies have been shown to save up to 10% on pharmaceutical costs (Blackburn and Ito, 1995) by using therapeutic substitution, increased generic use and drug utilisation review.

Drug utilisation review (DUR) is the review of doctor prescribing, pharmacist dispensing and the utilisation of the drug by the patient. The goals are to ensure that drugs are used effectively and economically. (Blackburn and Ito, 1995).

1.2 Hypertension

The worldwide estimation of the incidence of hypertension is approximately 1 billion people and hypertension is possibly the cause of 7.1 million deaths per year, (Chobanian, *et al.*, 2003). With an aging population, the prevalence will increase unless there is an implementation of broad and effective preventative measures.

Study investigators recently indicated that if a person has normal blood pressure at age 55 and survived to age 80 to 85, there is a 90% lifetime risk of developing hypertension. (Chobanian, *et al.*, 2003),

In South Africa hypertension is a very costly chronic condition and is related to the development of cardiac disease, which in 1991 accounted for 4 to 5 billion Rands in direct costs. This figure made up 7.5% of the direct health care spending (Southern African Hypertension Society Executive Committee, 2003).

High blood pressure also increases the risk of developing a myocardial infarction, heart failure, stroke and nephropathy. For people between the ages of 40 and 70, each increment of 20mm HG in systolic BP or 10mm Hg in diastolic BP doubles the risk of CVD across the entire BP range from 115/75 to 185/115. (Chobanian, *et al.*, 2003),

The lowering of blood pressure has been shown to decrease the incidence of stroke by a mean of 35 to 40%, a 20 to 25% decrease in myocardial infarction, and more than 50 % in heart failure. (Chobanian, *et al.*, 2003),

1.2.1. Management of Hypertension

The goal of therapy should be the reduction of cardiovascular and renal morbidity and mortality.

Almost all therapeutic guidelines advocate lifestyle modification as the first line of therapy. These methods, which include measures such as weight loss in overweight and obese patients, changes in diet, increases in physical activity and moderation of alcohol consumption, have been shown to assist in the reduction of BP. When there is no advice on lifestyle changes, inadequate drug dosing or inappropriate drug combinations poor BP control may result.

If lifestyle modification has not worked, pharmacological intervention would be necessary, and there are many references with excellent clinical trials to show the various classes of drugs that are effective in reducing BP and preventing or delaying the potential complications that are associated with hypertension.

The different classes of drugs that are used include (Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARB's), beta blockers, calcium channel blockers and thiazide type diuretics.

The South African guideline for the management of hypertension contains recommendations that allow for the treatment of those patients at highest risk, those that can gain maximally from lifestyle modifications and therapy that is most effective. For the compilation of the South African guideline, national and international recommendations, especially those that were strongly evidence based, were used. (Southern African Hypertension Society Executive Committee, 2003)

1.3. Chronic Heart Failure

Chronic heart failure (CHF) is a common chronic cardiovascular syndrome, affecting 1-2% of the adult population in South Africa and more than 10% of these are older than 65 years (South African Medical Association Heart Failure Working Group, 1998).

Even when heart failure is treated, it results in significant morbidity and mortality

In the United States of America, heart failure (HF) is the most common disease related group for Medicare and more money is spent on the diagnosis and treatment of HF than any other diagnosis (Hunt, *et al.*, 2001).It is primarily a disease of the elderly in the USA and 6 to 10% of people over 65 have HF and about 80% of the patients that are admitted to hospital for heart failure are older than 65 (Hunt, *et al.*, 2001).

1.4. The Management of Heart Failure

According to the American College of Cardiology (ACC) clinical guidelines, patients should be routinely managed with a combination of 4 types of drugs - a diuretic, an ACE inhibitor, a beta adrenergic blocker and (usually) digitalis (Hunt, *et al.*,2005). There have been many studies and clinical trials supporting the use of these drugs.

These guidelines do not advocate the use of ARB's except in cases where there has been persistent and troublesome coughing symptoms.

The South African Heart Failure clinical guideline concurs with this and ARB's are also only indicated when the patient does not tolerate ACE inhibitors years (South African Medical Association Heart Failure Working Group, 1998).

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1.5. The Role of ACE Inhibitors and ARB's in the management of hypertension and heart failure

The effects of the renin-angiotensin system on blood pressure have been known for a while now and the blockade of this process by the ACE inhibitors has been effective in the treatment of hypertension. ACE inhibitors have also been of value in decreasing the morbidity and mortality in patients with chronic cardiac failure and post myocardial infarction. (Radecki, 2007)

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II. Angiotensin II is a vasoconstrictor and stimulates the secretion of aldosterone. ACE inhibitors also block the breakdown of bradykinin and stimulate the production of prostaglandin E and prostacyclin which are vasodilators. (DiPiro., *et al*, 1999)

However, this increase in bradykinin levels may also be a cause of some of the major adverse effects of ACE inhibitors, including cough and angioedema.

ARB's are the most recent group of anti-hypertensives that are available and also generally the most expensive as compared to the other classes of antihypertensives. (Table 1.3)

The mechanism of action of this class is direct inhibition of the angiotensin type I receptors (AT1), that mediates the effect of angiotensin II, i.e. vasoconstriction, release of aldosterone, sympathetic activation, secretion of antidiuretic hormone and constriction of the efferent arteriole of the glomerulus thus producing inhibition of the renin-angiotensin system. As ARB's do not affect the angiotensin converting enzyme (ACE), or inhibit kinin catabolism (elevating bradykinin levels), cough and angioedema are generally not experienced as a side effect. (DiPiro, *et al.*, 1999)

Due to this difference from ACE inhibitors, they offer the advantage of the absence of cough as a side effect and generally this is the only indication for their use.

Trials have been conducted to compare the efficacy and safety of the ACE inhibitors and ARB's and a similar pattern of conclusions have resulted. Some of these will be discussed.

In the MAPAVEL (Monitorizacion Ambulatoria Presion Aterial Aprovel)-Study (Coca, *et al.*, 2002) the efficacy of irbesarten (an ARB) and enalapril (an ACE inhibitor) in patients with mild to moderate essential hypertension as assessed by ambulatory blood pressure monitoring was assessed. The blood pressure reduction that was achieved in the two groups was similar but the incidence of adverse effects that were assumed to be related to antihypertensive medication was significantly higher in the enalapril group as compared to the irbesarten group i.e. 24.6% versus 9.2%. Cough occurred in 8.1 % of the enalapril group and only 0.9% of the irbesarten group.

A review of clinical studies (Smith, 2002) conducted on temisarten (an ARB) and enalapril (an ACE inhibitor) concluded that both agents showed equivalent reductions in blood pressure but telmisarten seemed to have a lesser incidence of adverse effects.

A meta-analysis of ARB studies failed to demonstrate the advantages of using ARB's preferentially to ACE inhibitor for congestive heart failure. There were 17 randomised blinded studies included in the analysis where 11 used placebos 4 used ACE inhibitors and 2 had ACE and placebo arms. The ARB's used were losarten, candesarten, valsarten and eposarten. The ACE inhibitors compared were captopril, enalapril and lisinopril. When the ARB's were compared to ACE inhibitors, the odds ratio for all-cause mortality or hospitalisation was 1.09 related to mortality and 0.95 related to hospitalisations. (Klasco, 2007)

There are still ongoing studies to try and ascertain the benefits of using ARB's instead of ACE inhibitors, for example the ONTARGET (Ongoing Telmisarten Alone and in combination with Ramipril Global Endpoint Trial) trial. This is a long term multicentre study where a comparison is being

done with ramipril and temisarten for the protection of patients from cardiovascular disease and death. (Weber, 2006)

The renin- angiotensin system has been implicated in the progression of chronic renal disease in diseases of diabetic or non-diabetic origin. For patients with chronic kidney disease the goal of therapy is to slow down the impairment of renal failure and prevent cardiovascular disease. As most of these patients have hypertension, aggressive blood pressure management is advocated and the treatment regimen usually required consists of 3 or more drugs to reach a target blood pressure reading of less than 130/80mmHg. In these patients ACE inhibitors and ARB's have demonstrated positive effects in retarding the progression of diabetic and non-diabetic renal disease. (Chobanian, *et al.,*2003*)*

The COOPERATE (Concomitant Treatment of Angiotensin II Receptor Blocker and Angiotensin Converting Enzyme Inhibitor in Non-diabetic renal disease) trial (Monita, *et al*, 2003) showed that both ACE inhibitors and ARB's have similar effects on slowing the progression of renal disease when administered separately, but a combination of the two agents had a much better effect than either agent on its own.

Similarly the DETAIL (Diabetics Exposed to Telmisarten And Enalapril) study compared the effects of telmisarten(an ARB) and enalapril(an ACE inhibitor) in patients with type 2 diabetes and early nephropathy. The outcome of this trial showed that one agent was not superior over the other in providing long term renoprotection. (Barnett, *et al*.,2004)

The ELITE- Evaluation of Losarten In The Elderly (Pitt, *et al*., 1997) study compared captopril (an ACE inhibitor) and losarten (an ARB) in patients with congestive heart failure in 125 centres in the Americas, Europe and South Africa. The findings of the study showed that there was no significant difference between the 2 age groups in the primary endpoint which was the worsening of renal dysfunction but there was a significant decrease in the all-cause mortality in the losarten group as compared to the captopril group i.e. 4.8% with losarten and 8.7% with captopril.

In the elderly the tolerability profile of the medication used is very important and as a large number of the patients that have hypertension or heart failure fall into this category, studies were conducted to determine if there

were significant differences in the adverse effects of ARB's and ACE'S. A trial conducted by Karlberg *et al*., (1999), showed differences between telmisarten (an ARB) and enalapril (an ACE inhibitor) but the efficacy was similar. There was also a difference in the number of patients that discontinued therapy within the two groups. 11.5% of the patients that used enalapril discontinued therapy whilst only 7.9% of the patients in the telmisarten group continued therapy.

The following table illustrates the differences of some of the main adverse effects:

Table 1.1: Differences in Adverse Effects between Telmisarten and Enalapril

	Telmisarten	**Enalapril**
Cough	6.50%	15.80%
Diarrhoea	4.30%	2.20%
Vertigo	0.70%	3.60%

Seventy one percent of all the patients enrolled in the trial experienced at least one adverse event. However, 37% of the patients taking enalapril and 25% of the patients taking telmisarten had treatment related adverse effects.

The long term tolerability of valsarten (an ARB) and lisinopril (an ace inhibitor) was compared in elderly hypertensive patients (Bremner, *et al*., 1997). Patients in both treatment groups experienced adverse effects; however there was a greater incidence of cough in the group using lisinopril than in the group using valsarten- 18% versus 11%. The authors (Bremner, *et al*., 1997), concluded that although the long term efficacy was the same the incidence of side effects of valsarten was lower.

Thus the ARB's would appear to be a drug more suitable for use in elderly patients as there is improved tolerability. Safety and efficacy though cannot be justifiably determined by short term trials and furthermore there has been variability in the anti-hypertensive effects of the different ARB's.

From the findings of specifically designed prospective studies, cough occurs in 7-15% of the general population on ACE inhibitors (Klasco,2007) and according to the guidelines set out by the South African Hypertension

society this is the only compelling indication where ARB's should be used instead of ACE inhibitors.

The Angiotensin II Antagonists that are available on the South African market are:

Table1.2. Angiotensin receptor blockers available in South Africa in 2003

Trade Names	Ingredient	Strength	Price*
Atacand®	Candersarten	8mg	R254.98
Atacand®	Candersarten	16mg	R287.64
Aprovel®	Irbesarten	75mg	R274.00
Aprovel®	Irbesarten	150mg	R274.00
Aprovel®	Irbesarten	300mg	R274.00
Cozaar®	Losarten	50mg	R279.41
Diovan®	Valsarten	80mg	R288.65
Diovan®	Valsarten	160mg	R288.65
Micardis®	Telmisarten	40mg	R275.03
Micardis®	Telmisarten	80mg	R275.03
Teveten®	Eprosarten	600mg	R262.90

*Prices from 2003

Choice of ACE Inhibitor:

The following table indicates equivalent ACE inhibitors & their strengths

Table 1.3. ACE inhibitors available in South Africa in 2003

Trade Names	Ingredient	Strength	Price*(MMAP)
Mavik®	Trandolapril	0.5mg	R174.99
Mavik®	Trandolapril	1mg	R205.36
Zestomax®, Zestril®, Prinivil®	Lisinopril	5mg	R78.20
Zestomax®, Zestril®, Prinivil®	Lisinopril	10mg	R103.30
Zestomax®, Zestril®, Prinivil®	Lisinopril	20mg	R173.40
Hr-enalapril®, Renitec®, Pharmapress®	Enalapril	5mg	R50.00
Hr-enalapril®, Renitec®, Pharmapress®	Enalapril	10mg	R75.00
Hr-enalapril®, Renitec®, Pharmapress®	Enalapril	20mg	R156.20
Accupril®	Quinapril	5mg	R126.77
Accupril®	Quinapril	10mg	R177.56
Accupril®	Quinapril	20mg	R268.46
Accupril®	Quinapril	40mg	R268.46
Cibace®	Benazepril	10mg	R143.35
Monopril®	Fosinopril	10mg	R168.73
Monopril®	Fosinopril	20mg	R289.15
Ramace®	Ramipril	1.25mg	R140.82
Ramace®	Ramipril	2.5mg	R183.79
Ramace®	Ramipril	5mg	R260.28
Tritace®	Ramipril	1.25mg	R160.15
Tritace®	Ramipril	2.5mg	R205.36
Tritace®	Ramipril	5mg	R299.15
Tritace®	Ramipril	10mg	R326.50
Coversyl®	Perindopril	4mg	R216.92

*Prices from 2003.

MMAP denotes the maximum medical aid price. This is a price that is set by a company that is the custodian of the drug prices in South Africa. The price is based on the generic prices of the generic drugs available in the

relevant drug class and is often used as a guide for generic manufacturers to position the pricing of new generics on the market

1.7. Aims

ARB's are very widely used in the private sector and this study will investigate the frequency of their use for the conditions hypertension and heart failure in relation to ACE inhibitors for the same conditions and try to ascertain if there are any obvious trends in the pattern of the use of these two different classes within a specific managed care organisation.

The cost comparison of the two agents was also an important parameter to consider, as in managed care organisations, the intent is to "provide the patient with the best possible treatment at the best price." Due to the high incidence of hypertension in our society, hypertension is a condition has huge cost implication for the medical aids. Thus if it is found that the amount spent within the managed care organisation on ARB's is much higher than that for ACE inhibitors, the criteria for the approval of this class of drugs should be reviewed as well as the reason for their prescription.

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CHAPTER 2

METHODOLOGY

2.1. Aims

- To investigate the frequency of the use of Angiotensin receptor blockers for the conditions hypertension and heart failure in relation to ACE inhibitors for the same conditions within a specific managed care organisation
- To ascertain if there are any obvious trends in the pattern of use of these two different classes

2.2. Objectives

- To establish the incidence of chronic hypertension and chronic heart failure within the organisation
- To determine the frequency of use of ACE inhibitors and ARB's within the chronic claimants for hypertension and heart failure
- To observe prescribing patterns of ACE inhibitors and ARB's for hypertension and heart failure
- To ascertain if there were specific reasons or population groups for the use of ACE inhibitors and ARB's for hypertension and heart failure
- To look at the cost implications of using ACE inhibitors and ARB's for hypertension and heart failure

All the data was based on chronic medication claims.

2.3. Study Design

The study is based on the out of hospital chronic medicine claims received for ACE inhibitors and ARB's within the managed care organisation from which the data is being utilised. The claims were identified by the ICD 10 codes for the conditions hypertension and heart failure, for the patients registered on the chronic illness benefit (CIB).The drug classes were isolated by the relevant WHO ATC codes.

Reasons to try to identify specific reasons for the use of ARB's as compared to ACE inhibitors such as age, gender, prescriber preference or related diseases were looked at.

There are many limitations as this is a retrospective study and all the patient data is not available e.g. the actual reasons for the use of the

specific drugs, the clinical information, patient history and the incidence of side effects.

One of the important factors in terms of total cost to the scheme is hospitalisation but these costs could not be accurately quantified. Therefore the cost reflected is based only that of the chronic out of hospital medication claimed.

2.4. Study procedure/Methods:

Background

The data was obtained from a South African managed healthcare organisation that serves as an administrator for medical aids and a medical aid scheme.

Generic substitution or the use of a drug formulary is not enforced, however for items that are not on the formulary, a co-payment is generally enforced.

Patients can consult a general practitioner or specialist of their choice and they can obtain the prescribed medication from a pharmacy or dispensing doctor.

All patients requesting chronic medication benefits for hypertension and heart failure are required to have a chronic application form completed by their doctor to confirm their diagnosis and the medication required.

Chronic medication benefit applications need to go through a drug utilization review (DUR) by clinical pharmacists at the company. This process checks for suitability, safety and cost effectiveness of therapy. Once this is completed, the successful applicants are electronically enrolled on the Chronic Illness Benefit (CIB) Programme confirming authorization for chronic medication benefits on the Pharmacy Benefit Management (PBM) system. An ICD 10 (International and Statistical Classification of Diseases and Related Health Problems – 10th Revision) code is then allocated to the patient's membership number, and this is in accordance with the diagnosis that was confirmed by the treating doctor. All medication relevant to the confirmed diagnosis is linked to the appropriate ICD 10 code.

Patient and provider reports that reflect medication prescribing trends and claiming patterns at member level can be created from the data on the PBM system. These reports were used to analyze the use of ARB's and ACE inhibitors of the patients registered on the CIB programme.

The medication claimants for the year are identified by the number of claims received in total, claims per unique member number, claims per ICD 10 code and claims per WHO ATC drug class grouping.

Thus the numbers would differ in some cases as one member may submit more than one chronic claim per month, have more than one ICD 10 condition and have more than one product that is claimed.

2.5. Inclusion criteria for selection of the sample population:

- Patients of all races and both genders were considered in the study.
- Patients were all adults, i.e. over the age of 18 years old.
- Patients that were enrolled on the CIB Programme for hypertension and heart failure during 2003
- Patients would have been prescribed ARB's or ACE inhibitors for hypertension or heart failure in the year 2003

2.6. Exclusion criteria for selection of the sample population:

- Patients who were not enrolled on the CIB Programme but claimed for these medication classes from the acute or in hospital benefit
- Patients enrolled on the CIB Programme for hypertension at any other time than the period January 2003 to December 2003

2.7. Aspects of the patient population analysed

2.7.1. Chronic patient population

Total patients that claimed for chronic medication in the year 2003.

This will be used as a reference to determine the incidence of hypertension in the organisation.

2.7.2. Sample Population: Chronic medication patients that claimed for hypertension and heart failure

Members that were enrolled on the Chronic Illness Benefit (CIB) Programme for chronic medication benefits for the conditions hypertension and heart failure according to the medication claims records, for the period January 2003 to December 2003.

These members were identified by virtue of the ICD 10 codes that are allocated to the patients on the chronic application form and linked when the chronic medication claims are submitted. This was used to determine the fraction of patients that claimed for hypertension, and the fraction that claimed for heart failure to assess the incidence of these conditions in the total chronic patient population. The ICD 10 code I10 was used for hypertension and the code I50 was used for heart failure.

The prescribed medication and medication claiming patterns were observed for a period of 12 months from the date of enrolment on CIB for a hypertension and heart failure.

The members were categorized by age and gender to observe trends in the prescribing patterns of the medication classes investigated

2.7.3. Chronic medication claims for drug classes used in hypertension and heart failure

The medication claimants were identified by the claims received per unique member ID, claims per ICD 10 code and the claims per WHO ATC groups.

The numbers would differ in some cases as one member may submit more than one chronic claim per month, have more than one ICD 10 condition and have more than one NAPPI code claimed.

2.7.4. Prescriber Patterns of ACE inhibitors and ARB's

This analysis was done to assess if there is an inclination by specialists or GPs to use either class of drug.

Grouping, by prescribing medical practitioner to differentiate patients managed by a specialist physician or cardiologist from those managed by a general practitioner was done. Board of Healthcare Funders (BHF) practice numbers reflected against patients' membership numbers will be used to identify treating medical practitioners.

2.7.5. Frequency of use of ACE Inhibitors and ARB's

The number of claims received for ACE inhibitors and ARB's to the overall medication claims received for hypertension and heart failure was compared.

2.7.6. Financial implications of ACE Inhibitors and ARB's

The total and the average cost of the claims for ACE inhibitors were compared to the total and average cost of the ARB's for the respective conditions.

2.7.7 Special populations that used ACE inhibitors or ARB's-Co-morbidities

Claims for selected co-morbid conditions were extracted from the database for the patients that claimed for ACE inhibitors and ARB's to establish if there are any conditions where either class is more favoured by prescribers.

2.8. Data Analysis

The data was extracted from the chronic medication claims from the managed care organisation for the stated time period with the appropriate ICD 10 codes using Microsoft Access® and a database of the claims created. From this database, the specific ICD 10 codes were analysed and queries done to link the drug classes by the WHO ATC codes, the age and gender of the members isolated, the co-morbid conditions identified and the costs quantified.

All the subsets were then imported into Microsoft Excel® to tabulate the data and display it graphically.
The data was represented in terms of number of members registered on the chronic illness benefit and the percentage of members where applicable or the number of prescriptions claimed for the drugs and percentages thereof.

2.9. Ethics

Ethics approval was granted for this study (please refer to Appendix B).
The data only contained unique member numbers and there were no names of the members divulged in the data extract.
The providers were also anonymous. The providers were identified by the BHF practice numbers only and the identities not revealed.

CHAPTER 3

RESULTS

The results were obtained from an analysis of the out of hospital chronic claims for prescriptions for hypertension and heart failure within the managed care organisation.

In the first part, the demographics of these conditions were investigated to give an overall view of the incidence of the diseases.

Thereafter, the utilisation pattern of the drugs for hypertension and heart failure is shown, with specific emphasis on ACE inhibitors and ARB's.

In the last section of the results, the respective costs of the conditions were illustrated.

3.1 Incidence of hypertension and heart failure

Table 3.1. Members that claimed for chronic medication in 2003

Total chronic members	364793	
Members that claimed for hypertension	83109	22.8%
Members that claimed for heart failure	2694	0.7%
Members that claimed for other chronic conditions	278990	76.5%

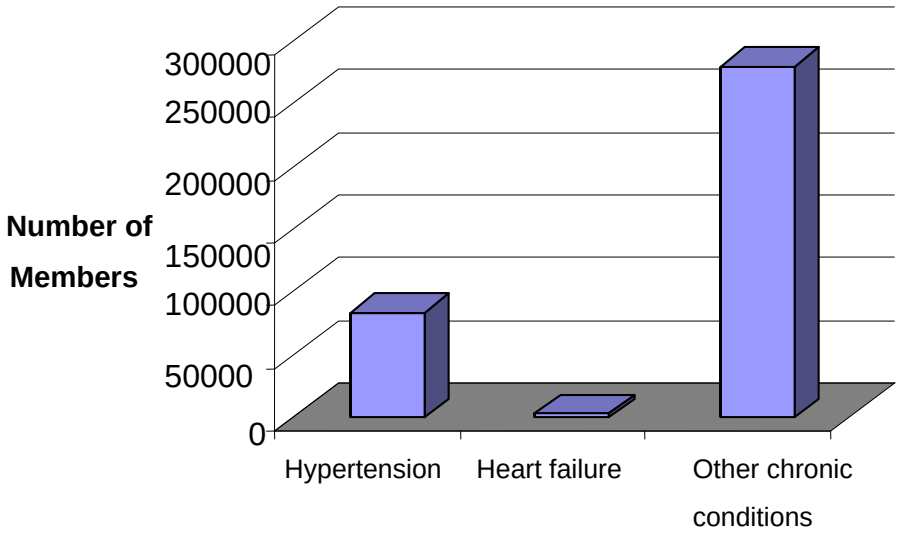

Figure 3.1 Incidence of hypertension and heart failure

The incidence of hypertension and heart failure in the organisation is depicted by the total number of chronic medication claims that were received as compared to the number of hypertension and heart failure medication claims received in the year 2003.The number of members that submitted claims for hypertension medication in the year 2003 comprised of 22.78% of the chronic claimants.

Heart failure claims accounted for 0.74% of all the chronic claims, which amounted to 2694 members.

Table 3.2. Age bands for the incidence of hypertension within the managed care organisation

Disease Group	Age Band	Sum of Members (%)
Hypertension	<30	821 (1%)
	30-44	9352 (11%)
	45-65	49391 (60%)
	>65	23545 (28%)
	Total	83109

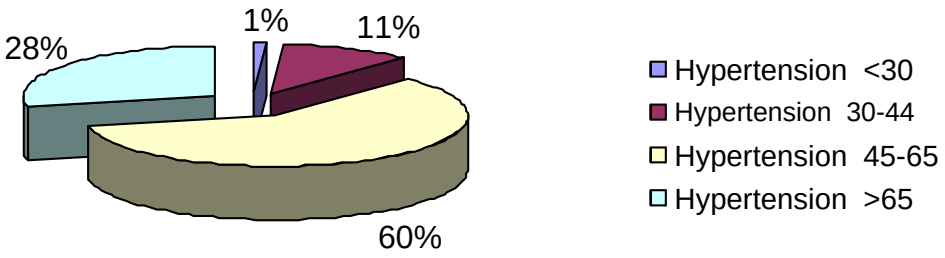

Figure 3.2. Age bands for the incidence of hypertension within the managed care organisation

The age distribution of the members that claimed for hypertension showed that the majority of the patients were in the 45 to 65 year old age group (60%) followed by the over 65 year old patients (28%).

Table 3.3. Age bands for the incidence of heart failure within the managed care organisation

Disease Group	Age Band	Sum of Members
Heart Failure	<30	32 (1%)
	30-44	89 (3%)
	45-65	946 (35%)
	>65	1627 (61%)
	Total	2694

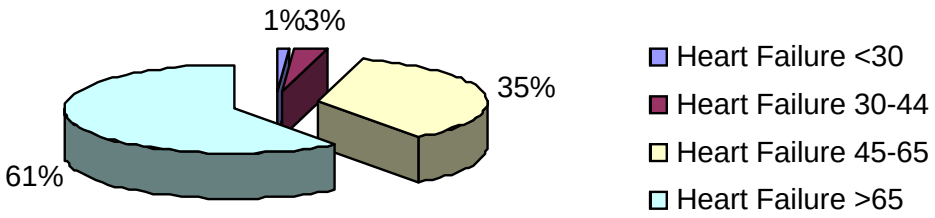

Figure 3.3. Age bands for the incidence of heart failure within the managed care organisation

The greatest prevalence of members that submitted medication claims for heart failure was in the over 65 year old age group (61%) and the second highest was the 45 to 65 year old group (35%).

Table 3.4. Gender distribution of hypertension and heart failure

	Female		Male		Total
Hypertension	43901	52.82%	39208	47.18%	83109
Heart Failure	1471	54.60%	1223	45.40%	2694
Total	45372		40431		85803

Gender distribution of members for hypertension and heart failure showed very similar trends. For both conditions, females comprised of the greater numbers i.e. 52.82% and 54.6% for hypertension and heart failure respectively.
Male members thus constituted the balance i.e. 47.18% and 45.4%.

3.2. Drug Classes Claimed for Hypertension

Table 3.5. Comparison of drug classes claimed for hypertension

Drug Class	Number of claimants	% of Claimants
ACE inhibitors, plain	22597	17.3%
ACE inhibitors, combinations	15733	12.1%
Beta blocking agents	15368	11.8%
Selective calcium channel blockers with mainly vascular effects	11913	9.1%
ARB's, plain	10316	7.9%
ARB's in combination	9790	7.5%
Low-ceiling diuretics, excl. thiazides	8023	6.2%
Diuretics and potassium-sparing agents in combination	6258	4.8%
Beta blocking agents and thiazides	5680	4.4%
Antithrombotic agents	5175	4.0%
High-ceiling diuretics	3020	2.3%
Beta blocking agents and other diuretics	2927	2.2%
Selective calcium channel blockers with direct cardiac effects	2629	2.0%
Potassium	2124	1.6%
Antiadrenergic agents, peripherally acting	1769	1.4%
Low-ceiling diuretics, thiazides	1662	1.3%
Antiadrenergic agents, centrally acting	1552	1.2%
Antihypertensives and diuretics in combination	970	0.7%
Other analgesics and antipyretics	922	0.7%
Potassium-sparing agents	875	0.7%
Beta blocking agents, thiazides and other diuretics	323	0.2%
Arteriolar smooth muscle, agents acting on	131	0.1%
Vasodilators used in cardiac diseases	99	0.1%
Other drugs incorrectly authorised	405	0.3%
Total	130261	

Of the total number of claims received for hypertension, ACE inhibitors plain constituted 17.3% and ACE inhibitors in combination with diuretics made up 12.1%.

ARB's make up 15.4% of the claims, of which ARB's, plain constitute 7.9% and ARB's in combination with diuretics 7.5%.

These figures in Table 3.5 represent all the claims received and include members that are on more than one class of drug as part of their treatment regimen. This is

the reason that the total number of claimants (130261) is higher than the total number of hypertensive members on the medical scheme or the member could have submitted more than one claim per month or the same member could have claimed for more than one medication class per month.

The component “other drugs” were incorrectly authorised included cholesterol lowering agents, vitamins, anti-diabetic agents and many other drug classes that were not used for hypertension. The incorrect ICD 10 code was assigned to these medicines when the claims were captured.

Similar errors were made when the class “other analgesics and antipyretics” were authorised for hypertension.

Table 3.6. Comparison of the drug classes claimed for heart failure

Drug Class	Number of claimants	% of Claimants
High-ceiling diuretics	1412	22.6%
Potassium	876	14.0%
Cardiac glycosides	828	13.3%
Antithrombotic agents	629	10.1%
ACE inhibitors, plain	501	8.0%
Potassium-sparing agents	478	7.7%
Beta blocking agents	463	7.4%
Vasodilators used in cardiac diseases	149	2.4%
Selective calcium channel blockers with direct cardiac effects	144	2.3%
Diuretics and potassium-sparing agents in combination	135	2.1%
Other analgesics and antipyretics	116	1.9%
ARB's, plain	86	1.4%
Antiarrhythmics	83	1.3%
ACE inhibitors, combinations	75	1.2%
Low-ceiling diuretics, excl. thiazides	63	1%
Selective calcium channel blockers with mainly vascular effects	52	0.8%
Low-ceiling diuretics, thiazides	39	0.6%
ARB's, combinations	34	0.6%
Beta blocking agents and thiazides	14	0.2%
Antiadrenergic agents, peripherally acting	12	0.12%
Beta blocking agents and other diuretics	10	0.2%
Other drugs incorrectly authorised	39	0.6%
Total	6238	

As for the number of claimants for hypertension, the number of total claimants for heart failure is higher that than the number of members that have heart failure due to the fact that members could be on more than one drug for heart failure or the member could have submitted more than one claim per month.

The highest number of claims received for medication classes used for heart failure was 22.6% for high ceiling diuretics. 9.2% of the claims were for ACE inhibitors of which 8.0% were ACE inhibitors, plain and 1.2% were ACE inhibitors in combination with diuretics. For ARB claims, 1.4% were ARB's plain and 0.6% were ARB's with diuretics.

3.3. ACE inhibitors and ARB's as Monotherapy

In order to show the trends of use of the individual agents, it was important for the use of these agents to be reflected when they were used alone so that the effect of the class was observed and not a combined effect with other classes.

Table 3.7. Members that used ACE inhibitors or ARB's as monotherapy for hypertension

Class of Drug	Number of Members on Monotherapy	% of Total Hypertension members
ACE inhibitors	**11236**	**13.52%**
ARB's	**5303**	**6.38%**

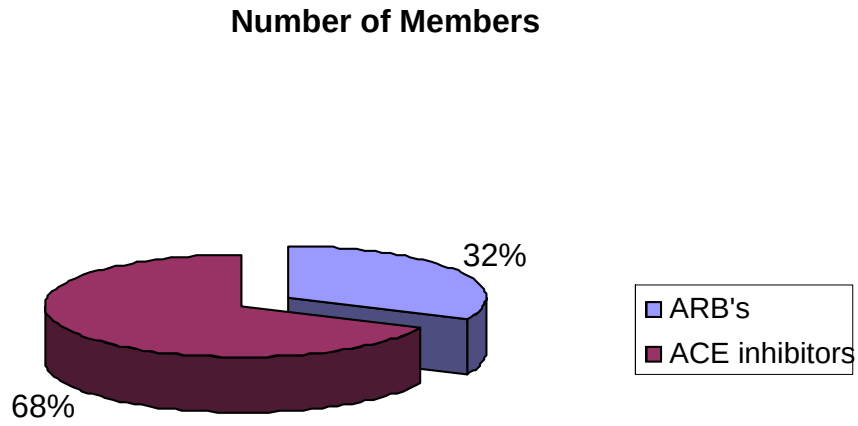

Figure 3.4. Members that used ACE inhibitors or ARB's as monotherapy for hypertension

ACE inhibitors as monotherapy showed much higher usage than ARB's as monotherapy for hypertension, 11236 members versus 5303. This comprised 6.38% and 13.52% of the total number of members on antihypertensives for ARB's and ACE inhibitors respectively.

Table 3.8. Members that used ACE inhibitors or ARB's as monotherapy for heart failure

Class of Drug	Number of Members	% of Total Heart Failure Members
ARB's	**11**	**0.41%**
ACE inhibitors	**57**	**2.12%**

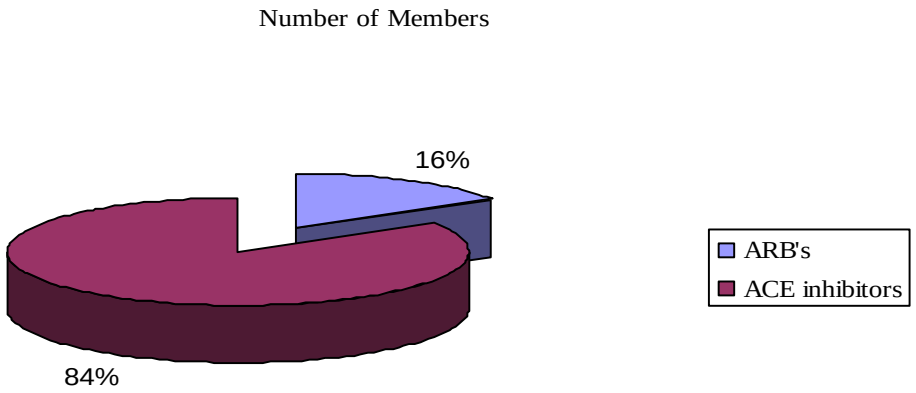

Figure 3.5. Members that used ACE inhibitors or ARB's as monotherapy for heart failure

In order to show the trends of use of the individual agents, it was important for the use of these agents to be reflected when they were used alone so that the effect of the class was observed and not a combined effect with other classes.
ACE inhibitors as monotherapy showed much higher usage than ARB's –
57 members versus 11 members for heart failure.
Again, comparing this number in relation to the total number of members that have heart failure, ACE inhibitors accounted for 2.12% and ARB's for 0.41%.

Table 3.9 Use of ACE inhibitor and ARB's in hypertension by age bands

Drug Category	Age Band	Sum of Members	%
ACE inhibitors	< 30	168	1.50%
ACE inhibitors	30 - 44	1544	13.74%
ACE inhibitors	45 - 65	6789	60.42%
ACE inhibitors	> 65	2735	24.34%
ARB's	< 30	94	1.77%
ARB's	30 - 44	954	17.99%
ARB's	45 - 65	3334	62.87%
ARB's	> 65	921	17.37%

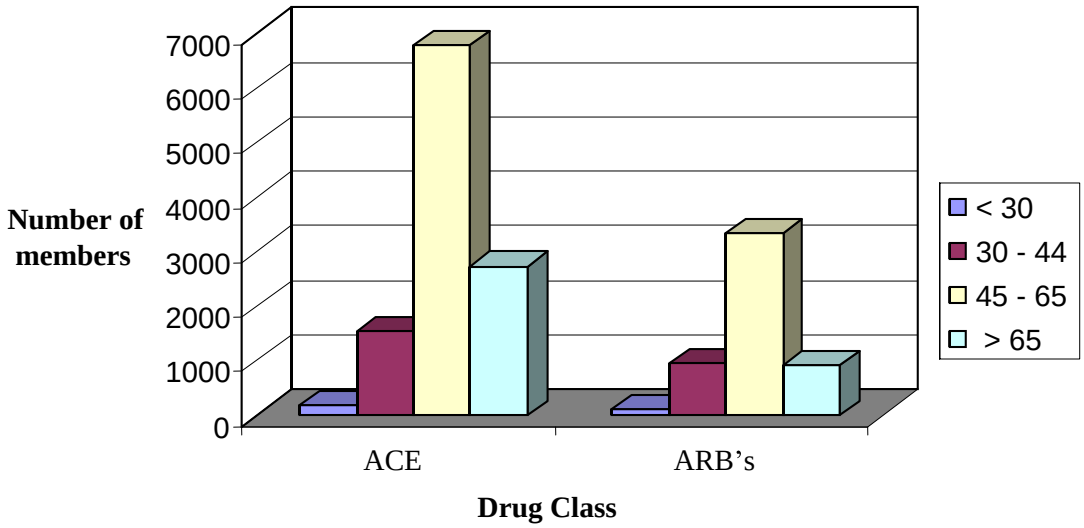

Figure 3.6. Age bands for ACE inhibitor and ARB use in hypertension

The age distribution of the members that claimed for both ACE inhibitors and ARB's as chronic is shown by the above graph.

The group of members that had the most claims was in the 45 to 65 age i.e. 62.87% for ARB's and 60.42% for ACE inhibitors. For ACE inhibitors, the second largest group was the over 65 year old group- 24.34% whereas for ARB's this was the 30-44 year old group- 17.99%.

Table 3.10. Age bands for ACE inhibitor and ARB use in heart failure

Drug Category	Age Band	Sum of Members	%
ACE inhibitors	<30	4	7%
ACE inhibitors	> 65	32	56%
ACE inhibitors	30 - 44	3	5%
ACE inhibitors	45 - 65	18	32%
ARB's	45 - 65	5	45%
ARB's	> 65	6	55%

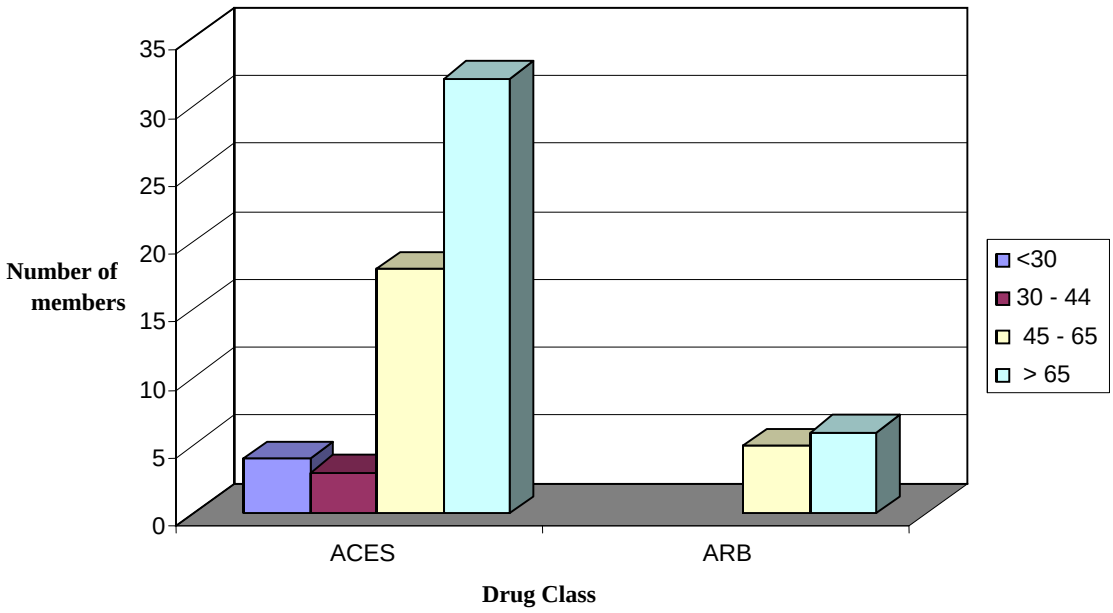

Figure 3.7 Age bands for ACE inhibitor and ARB use in heart failure

For heart failure the pattern of use differs as compared to hypertension. The most prevalent age group that utilises ARB's are those members greater than 65 years old. This is in keeping with the population that is most affected by heart failure as shown in Table 3.3.

There are more patients that use ACE inhibitors for heart failure than those that use ARB's. For this drug group a similar trend is observed and this could be due again to the fact that heart failure is more prevalent amongst this age group i.e. greater than 65 years old.

Table 3.11. Gender distribution for members using ACE inhibitors or ARB's for hypertension

Drug Category	Gender	Members	%
ACE inhibitors	F	4784	42.58%
ACE inhibitors	M	6452	57.42%
ARB's	F	2229	42.03%
ARB's	M	3074	57.97%

There is a difference amongst the use of ARB's between the different genders. 3074(57.97%) males used ARB's and 2229(42.03%) were females.

For ARB's, there are more males members that use ACE's as compared to female, i.e. 57.42% of the members were male and 42.58% were female.

Table 3.12. Gender distribution for members using ACE inhibitors or ARB's for heart failure

Drug Category	Gender	Members	%
ACE inhibitors	**F**	21	36.84%
ACE inhibitors	**M**	36	63.16%
ARB's	**F**	4	36.36%
ARB's	**M**	7	63.64%

The gender distribution of ARB and ACE inhibitor use amongst the members in the organisation showed a higher incidence of males within both drug classes.
For ACE inhibitors 63.16% of the members were male and 36.84% were female, ARB use produced a similar pattern with males constituting 63.64% of the members and females 36.36%.

3.4. Prescriber patterns for ACE inhibitors or ARB's in hypertension and heart failure

Table 3.13.Prescriber patterns for members using ACE inhibitors or ARB's for hypertension

Prescriber Type	ARB's	%	ACE inhibitors	%
General Practitioner	5145	71.17%	10872	71.73%
Physician or cardiologist	884	12.23%	1476	9.74%
Other	1200	16.60%	2808	18.53%
	7229		**15156**	

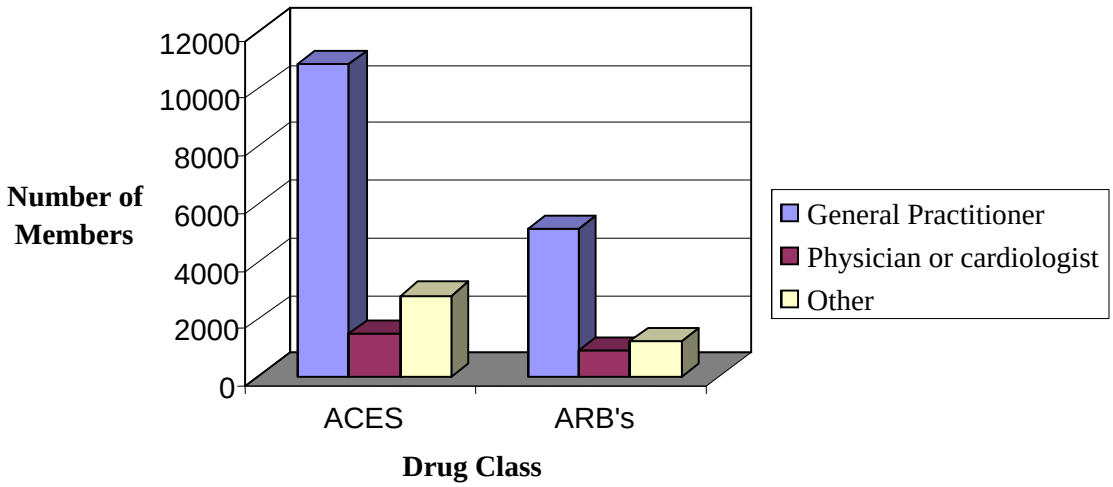

Figure 3.8 Prescriber patterns for members ACE Inhibitors or ARB's for hypertension

"Other" comprised all other specialities except those that are listed and included a vast array of disciplines including surgeons, dermatologists, neurologists etc.

The component "other" could be attributed to data capturing errors if more than one prescription from more than one prescriber was received at the same time or the member could have requested a repeat prescription from a specialist that they were consulting for another diagnosis. The most prominent discipline of providers that wrote prescriptions for ACE inhibitors and ARB's were general practitioners i.e. 71.73% and 71.17% respectively, Cardiologists and physicians combined provided 9.74% of the ACE inhibitor prescriptions 12.23% of the ARB prescriptions.

Table 3.14: Prescriber trends for ACE Inhibitors or ARB's for heart failure

Prescriber Type	ARB's	%	ACE inhibitors	%
General Practitioner	9	52.94%	25	54.55%
Physician or cardiologist	5	29.41%	25	32.47%
Other	3	17.7%	10	12.99%
Total	**17**		**70**	

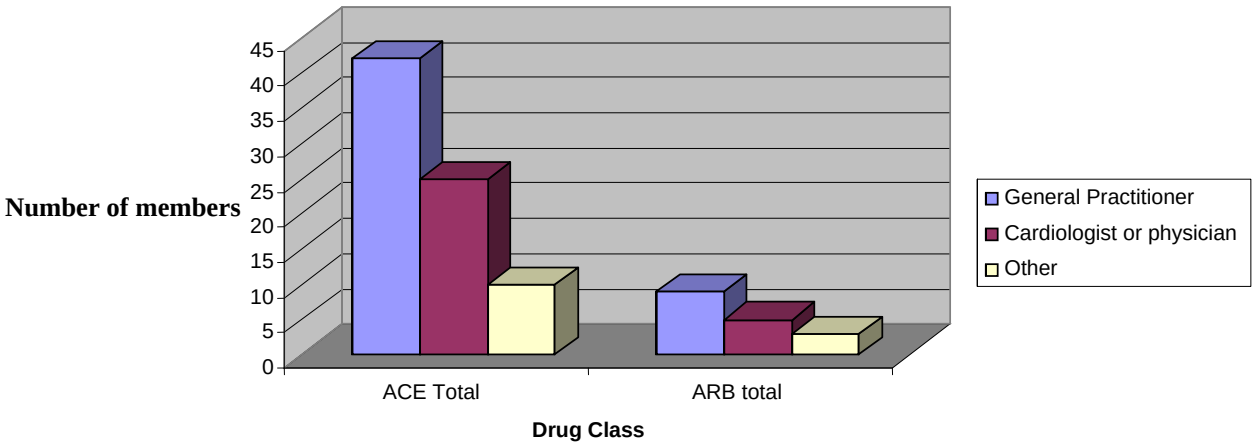

Figure 3.9. Prescriber trends for ACE inhibitors or ARB's for heart failure

Again, the largest discipline of providers that wrote prescriptions for ARB's and ACE inhibitors in heart failure were general practitioners i.e. 52.94 and 54.55% respectively. However, the percentages were not as high as hypertension. Cardiologists and physicians combined provided 29.41% of the ARB prescriptions and 32.47% of the ACE inhibitor prescriptions. The "other" category consisted of 17.65% for ARB prescriptions and 12.99% of ACE inhibitor prescriptions.

3.5. Possible Factors for the prescription of ACE inhibitors or ARB's

Table 3.15. Co-Morbidities in patients using ARB's or ACE inhibitors for hypertension

Co-morbidities	ACE inhibitor	%	ARB's	%
Other/None	9386	82.20%	4621	86.10%
E10-Insulin Dependent Diabetes Mellitus	353	3.09%	98	1.83%
E11- Non-insulin dependent diabetes mellitus	1092	9.56%	344	6.40%
J43- Emphysema	9	0.08%	2	0.04%
J44 – Chronic Obstructive Pulmonary disease	152	1.33%	58	1.10%
J45 – Asthma	427	3.74%	244	4.60%

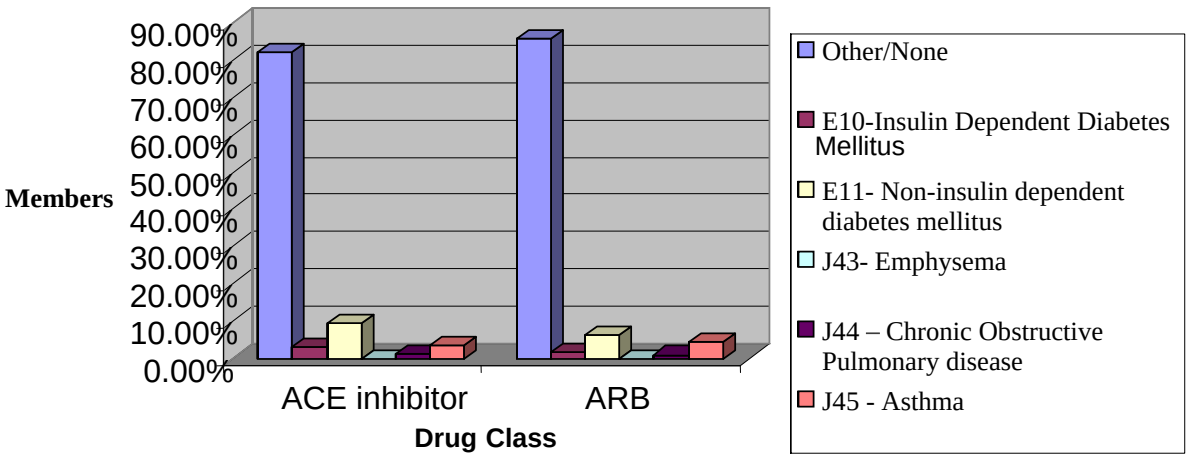

Figure 3.10 Co-Morbidities in claimants using ACE inhibitors or ARB's for hypertension

Selected co-morbidities were studied to ascertain if there was a preference for

ARB's in certain co-morbid conditions. ACE inhibitor use was greater for all co-morbidities.

The total number of claimants is higher than the number of members as the same member could have claimed for more than one condition.

Of the total member distribution, most claimants had other conditions as compared to the specific ones selected or no co-morbid conditions. This was 86.1% of patients on ARB's and 82.2% on ACE inhibitors.

1.83% of the members on ARB's and 3.09% of the claimants on ACE inhibitors had insulin dependent diabetes mellitus.

6.41% of the members on ARB's and 9.56% of the patients on ACE inhibitors had no-insulin dependent diabetes mellitus.

1.08% that used ARB's and 1.33% that used ACE inhibitors had COPD and 4.55% that used ARB's and 3.74% that used ACE inhibitors had asthma.

Table 3.16 Co-Morbidities in patients using ACE Inhibitors and ARB's for heart failure

Co-morbidities	ACE inhibitor	%	ARB's	%
Other/None	51	89.47	9	81.82
E10-Insulin Dependent Diabetes Mellitus	1	1.75	1	9.09
E11- Non-insulin dependent diabetes mellitus	3	5.26	0	0
J44 – Chronic Obstructive Pulmonary disease	2	3.5	0	0
J45 – Asthma	0	0	1	9.09

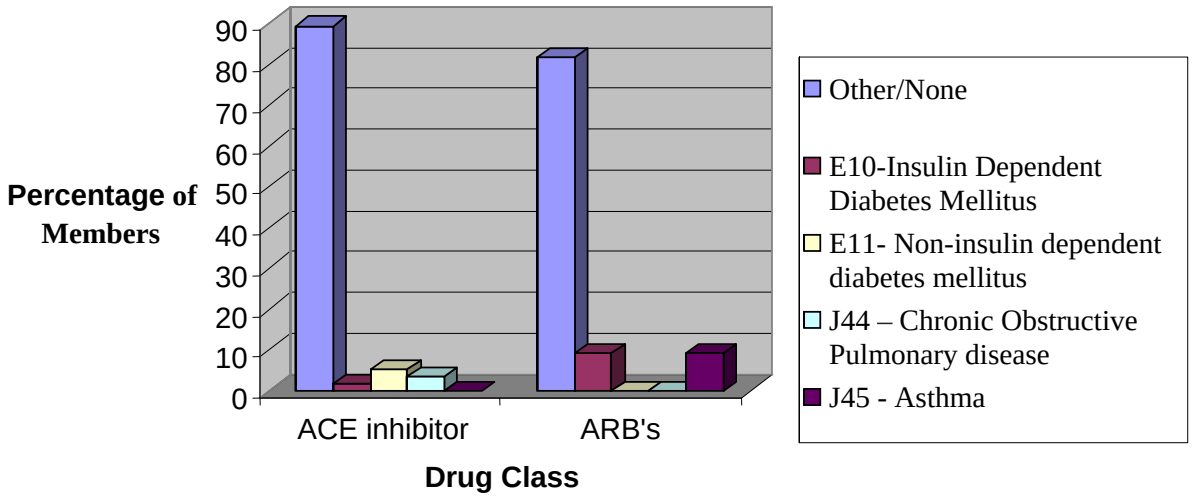

Figure 3.11 Co-Morbidities in patients using ACE Inhibitors or ARB's for heart failure

Of the members that used ACE inhibitors for hypertension, 1.75% had insulin dependent diabetes mellitus and 5.26% had non insulin dependent diabetes mellitus as co-morbid conditions.

In the group comprising of the members that used ARB's for heart failure, there was a low percentage of members that had insulin dependent diabetes mellitus, i.e. 9.09% and 9.09% had asthma. This amounts to only one member that had either condition.

3.6. Amount spent on hypertension and heart Failure

Table 3.17 Amount spent on chronic medication (Rands)

Total amount spent	703,336,252	
Amount spent on hypertension	141,489,306	20.10%
Amount spent on heart failure	4,699,092	0.70%
Amount spent on other conditions	557,147,854	79.20%

Hypertension accounts for 20.12% of the spend on chronic medication claims by the managed care organisation for the period January to December 2003. Heart failure makes up 0.67 % of the total claimed amount on chronic medication for the same period.

Table 3.18 Amount spent on different drug classes for hypertension: 2003

Drug Class	Amount Spent (R)	% of Amount Spent
ACE inhibitors, plain	23,197,179	16.40%
ACE inhibitors, combinations	22,709,478	16.05%
Selective calcium channel blockers with mainly vascular effects	19,644,444	13.88%
ARB's, plain	16,736,974	11.83%
ARB's, combinations	15,975,487	11.29%
Beta blocking agents	13,315,470	9.41%
Beta blocking agents and thiazides	5,101,571	3.61%
Low-ceiling diuretics, excl. thiazides	4,550,092	3.22%
Selective calcium channel blockers with direct cardiac effects	3,562,005	2.52%
Antiadrenergic agents, peripherally acting	3,022,933	2.14%
High-ceiling diuretics	2,577,962	1.82%
Beta blocking agents and other diuretics	2,507,317	1.77%
Antiadrenergic agents, centrally acting	1,565,454	1.11%
Diuretics and potassium-sparing agents in combination	1,545,717	1.09%
Antihypertensives and diuretics in combination	1,232,117	0.87%
Potassium	1,116,731	0.79%
Antithrombotic agents	791,744	0.56%
Beta blocking agents, thiazides and other diuretics	628,291	0.44%
Potassium-sparing agents,low ceiling diuretics, thiazides	826,171	0.58%
Antiarrhythmics	160,165	0.11%
Arteriolar smooth muscle, agents	153,209	0.11%
Vasodilators used in cardiac diseases	95,593	0.07%
Other drugs incorrectly authorised	473,202	0.33%
Antihypertensives and diuretics in combination	1,232,117	0.87%
Potassium	1,116,731	0.79%
Antithrombotic agents	791,744	0.56%
Beta blocking agents, thiazides and other diuretics	628,291	0.44%
Potassium-sparing agents,low ceiling diuretics, thiazides	826,171	0.58%
Antiarrhythmics	160,165	0.11%
Arteriolar smooth muscle, agents	153,209	0.11%
Vasodilators used in cardiac diseases	95,593	0.07%
Other drugs incorrectly authorised	473,202	0.33%

The largest portion of the cost of hypertension was on ACE inhibitors, where the combinations with ACE inhibitors made up 16.05% and plain ACE inhibitors made up 16.4%. This is 32.45% of the amount spent in total. ARB's as a group constitute 23.12% of the total antihypertensive cost.

Table 3.19 Amount spent on different drug classes for heart failure

Drug Class	Spent	% of Spent
High-ceiling diuretics	1,458,814	31.04%
ACE inhibitors, plain	524,772	11.17%
Beta blocking agents	512,049	10.90%
Potassium	461,181	9.81%
Potassium-sparing agents	253,245	5.39%
Antiarrhythmics	219,670	4.67%
Selective calcium channel blockers with direct cardiac effects	214,322	4.56%
Antithrombotic agents	193,976	4.13%
Vasodilators used in cardiac diseases	155,948	3.32%
ARB's, plain	153,285	3.26%
ACE inhibitors , combinations	105,587	2.25%
Selective calcium channel blockers with mainly vascular effects	92,199	1.96%
Cardiac glycosides	73,714	1.57%
ARB's, combinations	66,481	1.41%
Selective calcium channel blockers with direct cardiac effects	62,189	1.32%
Diuretics and potassium-sparing agents in combination	32,473	0.69%
Antiadrenergic agents, peripherally acting	26,862	0.57%
Low-ceiling diuretics, excl. thiazides	21,600	0.46%
Beta blocking agents and thiazides	12,342	0.26%
Beta blocking agents and other diuretics	10,627	0.23%
Low-ceiling diuretics, thiazides	6,897	0.15%
Other drugs incorrectly authorised	40858.89	0.00%

The amount spent on chronic medication for heart failure in the year 2003 by drug class corresponds closely with the number of prescriptions for the different classes as shown is Table 3.6.High ceiling diuretics comprise 31.04% of the total

spent, ACE inhibitors make up 13.41%- 11.17% are ACE inhibitors plain and 2.25% are ACE inhibitor combinations and ARB's constitute only 9.84% of the total amount spent, make up 25.46%.

Table 3.20 Amount spent on ACE inhibitors and ARB's used as monotherapy for hypertension

Drug Class	Number of members	Total amount paid per member per year	Average amount paid per member per year	% of total hypertension Cost
ARB's	5303	8,601,875	1,622	6.08%
ACE inhibitors	11236	10936107.19	973	7.73%

This table depicts the average cost of members that were prescribed ARB's and ACE inhibitors as monotherapy for hypertension. ARB's were shown to have a higher average cost per member per year, which was R1 622 and the average cost of ACE inhibitors per member per year was R973. The table also illustrates the total cost of these drug classes over the year.

Table 3.21 Amount spent on ACE inhibitors and ARB's used as monotherapy for heart failure

Drug Class	Number of members	Total amount paid per member per year	Average amount paid per member per year	% of total heart failure Cost
ARB's	11	18591.09	1690.09	0.40%
ACE inhibitors	57	64312.1	1128.28	1.37%

For hypertension, the average cost of an ARB prescription was higher than an ACE inhibitor prescription for members on monotherapy that had heart failure. For

ARB’s, the average cost was R1690 and for ACE inhibitors the average cost was found to be R1128.

Chapter 4

Discussion

4.1. Incidence of hypertension and heart failure

The incidence of hypertension within the managed care organisation is 22.7% (83 109 members), which is similar to the prevalence in South Africa at 23.9%. This estimate was provided by the first Demographic and Health Survey (SADHS) that was conducted in South Africa in 1998 and is the crude rate with hypertension criteria being defined by using the South African and ISH/WHO cut off points of >=140/90 (Steyn,*et al*.,2005). Of the 65 possible conditions on the chronic medication list that the managed healthcare organisation paid for in 2003, this is a high percentage.

The worldwide trend of hypertension incidence is 50 million in the United States of America and approximately 1 billion people worldwide (Chobanian, *et al*., 2003),

With an aging population, the prevalence will further increase if major preventative measures are not implemented.

Heart failure claims are not as high as for hypertension within the organisation, only 0.74% of the membership, but this is still 2 694 members and this incidence is lower than the South African prevalence which was quoted as 1-2% in 1998.(South African Medical Association Heart Failure Working Group, 1998).

The USA statistics were reported to be 1.5% of the population (Boyle and Hobbs, 2004).

4.2. Age bands for the incidence of hypertension and heart failure within the organisation

Age distribution of hypertensive patients within the chronic claimants found the majority of the patients in the 45 to 65 year old age group(60%) followed by the over 65 year old patients(28%).

A study conducted by the Centre for Disease Control in the United States in 2002 found the incidence of hypertension to be the most prevalent in people over 60 years (65.2%). However, the highest prevalence of people on treatment for hypertension was in the age group of 40-59(40.5%) which is similar to the most prevalent age group in the managed care organisation (Glover, *et al.*, 2005).

The overall incidence of heart failure in the organisation by age showed the highest number in the age group as over 65 year olds (61%). The South African Medical Association Heart failure working group states that more than 10% of the adult population that has heart failure is over 65. (South African Medical Association Heart Failure Working Group, 1998). In the USA, about 80% of patients admitted to hospital with heart failure are older than 65 years old. (Hunt, *et al*.,2005)

4.3 Gender distribution of hypertension and heart failure

Gender distribution of members for hypertension and heart failure showed very similar trends. For both conditions, females comprised of the greater numbers i.e. 52.8% and 54.6% for hypertension and heart failure respectively.

Male members thus constituted the balance i.e. 47.18% and 45.4%.

The CDC survey showed that 45.2% of women and 56.1% of men were on treatment for hypertension. (Glover, *et al.*, 2005)

4.4. Comparison of the drug classes claimed for hypertension

Of the total number of claims received for hypertension, ACE inhibitors make up 29.4% of the total. This includes ACE inhibitors plain and ACE inhibitors in combination with diuretics, clearly demonstrating that this is the most preferred class of drug used for hypertension as shown in Table 3.5.

ARB’s make up 15.4% of the claims and this similarly consists of ARB’s, plain and ARB’s in combination with diuretics. Therefore, ACE inhibitors and ARB’s make up 44.8% of all antihypertensive claims.

It is possible that all of these members are probably not on first line therapy, according to the South African and international guidelines.

These figures represent all the claims received and include members that are on more than one class of drug as part of their treatment regime.

The results of the SAHS survey which was conducted in 1998 (Steyn,*et a*l.,2005) show that diuretics accounted for 43% of all the antihypertensive agents used and ACE inhibitors made up 18.7% of the antihypertensives, which is quite different to the results obtained from the managed care organisation. In the year of the survey, (1998), ARB's were still a novel class of drugs and did not feature in the survey. The sample used in the survey included the private and public sectors.

For hypertension, most studies cite that ARB's should only be used if there is an ACE inhibitor induced cough (Southern African Hypertension Society Executive Committee, 2000). The guidelines were published in the SAMJ, March 2004, which are adapted from the WHO/ISH(World Health Organisation/International Society for Hypertension), and advocate the use of ARB's if the patients experience ACE-inhibitor induced cough or have left ventricular failure diabetes mellitus with albuminuria and renal disease. JNC VII (Chobanian A.V. *et al*, 2003), also stipulates that ARB's should only be used if patients have intolerance to ACE inhibitors or have the patient has diabetes mellitus with albuminuria and renal disease.

From these studies it could be inferred that these are some of the reasons for the prescription of the ARB's on the claims received by the managed care organisation. Research indicates that cough only manifests as a side effect in 7-15% of the general population in specially designed prospective studies of cough. (Klasco, 2007).

A study conducted on the economic implications of evidence based prescribing in hypertension found that adherence to the guidelines would have resulted in considerable savings (Fischer and Avorn, 2004). However, the findings from this study was that most practitioners did not adhere to evidence based recommendations and the assumptions made by the investigators was that the use of the newer agents was due in parts to vigorous marketing. This assumption could be extrapolated to the results obtained from the managed care organisation as well.

The authorisation criteria at the managed care organisation for approving ARB's for treatment in 2003 were not very strict. The only questions that were asked were if the member was using the medicinal agent as first line treatment. Members were only approved if the primary treatment plan was not effective.

4.5. Comparison of the drug classes Claimed for heart failure in 2003

The breakdown of the prescriptions for chronic medication received for heart failure in 2003 resulted in 22.6% for high ceiling diuretics, 9.2% for all ACE inhibitors and only 2% for all ARB's.

These figures were based on all the medication claims received for any of the drug classes of used for heart failure, as shown in Table 3.6.

The South African guidelines for heart failure stipulate that ARB's should only be used if there is ACE inhibitor intolerance (South African Medical Association heart failure working group, 1998)

4.6. Members that used ACE inhibitors or ARB's as monotherapy

In order to show the trends of use of the individual agents, it was important for the use of these agents to be reflected when they were used alone so that the effect of the class was observed and not a combined effect with other classes

4.7 ACE inhibitors or ARB's as monotherapy for hypertension

ACE inhibitors as monotherapy showed much higher usage than ARB's – 11236 members versus 5303 members for hypertension.

In relation to the total number of members registered for hypertension, this use is 6.4% and 13.5% for ARB's and ACE inhibitors respectively.

The MAPAVEL (Monitorizacion Ambulatoria presion Arterial APROVEL) study showed equivalent efficacy with enalapril and irbesarten in controlling blood pressure with mild to moderate hypertension (Coca, *et al.*, 2002). Therefore the specific reasons for the use of ARB's are questionable.

4.8. ACE inhibitors or ARB's as monotherapy for heart failure

ACE inhibitors as monotherapy showed much higher usage than ARB's as monotherapy, 57 members versus 11 members for heart failure. Findings from a meta analysis of ARB studies failed to demonstrate that ARB's were superior to ACE inhibitors in patients with congestive heart failure. This meta analysis included 17 randomized blinded studies. (Klasco,2007)

Again, the inclination to use ARB's has to be established.

ACE inhibitors accounted for 2.1% and ARB's for 0.4% of the total number of members registered for heart failure.

Although this is very low, it is not a surprising finding as a wide range of drugs are used for heart failure, with diuretics being the mainstay of treatment. Digoxin is also almost on all prescriptions (Hunt, *et al*, 2005).

4.9. Age bands for ACE inhibitor and ARB use in hypertension

Both classes showed similar results for the 45-65 year age band which was the most prevalent. For ACE inhibitors, the second largest group was the over 65 year old group, whereas for ARB's this was the 30-44 year old group.

These numbers would correlate to the general trend of age distribution of hypertensive patients and the member distribution, which was the majority of the patients in the 45 to 65 year old age group (60%) followed by the over 65 year old patients (28%). In terms of age specification for the use of ARB's, the elderly are at an advantage due to the decreased side effect profile of the ARB's (Messerli, *et al*, 2001) but the largest group of patients are in the 45 to 65 year old age group not the over 65 year old group.

In terms of the age specification for the use of ARB's, the elderly are at an advantage due to the decreased side effect profile of ARB's (Messerli, *et al*, 2001).

There is however, no preference shown for ARB's in the elderly members of the organisation i.e. the percentage of members over 65 using ARB 's is 18% and the percentage using ACE inhibitors is 24.34%.

4.10 Age bands for ACE inhibitor and ARB use for heart failure

For heart failure the pattern of use differs as compared to hypertension. The most prevalent age group that utilises ACE inhibitors and ARB's are those members greater than 65 years old as depicted in Table 3.10 and Figure 3.7.

This could be attributed to the fact that heart failure is more prevalent amongst this age group i.e. greater than 65 years old as shown in the overall incidence of heart failure in the organisation by age where the largest group was in the over 65 year olds (61%) in Table 3.3 and Figure 3.3.

In addition to this, the ARB's are beneficial for the elderly population as they have an improved side effect profile (Messerli, *et al*, 2001).

The ELITE study (Pitt, 1999), favour ARB use compared to ACE inhibitor use because of improved tolerance of the ARB's. In this study, 33 patients on captopril(an ACE inhibitor) and 2 patients on losarten(an ARB) discontinued therapy due to side effects. These side effects included cough, angio-oedema, hyperkalaemia, perturberance of taste and rash. All the patients in the study were over 65 years old.

4.11 Gender distribution for ACE inhibitor and ARB use for hypertension

Gender distribution of members for hypertension and heart failure showed very similar trends. For both conditions, females comprised of the greater numbers i.e. 52.8% and 54.6% for hypertension and heart failure respectively.

Male members thus constituted the balance i.e. 47.18% and 45.4%.

There is a definite difference amongst the use of ARB's and ACE inhibitors between the different genders for hypertension.

Both classes showed a higher number of males 57.97% and 57.42% for ARB's and ACE inhibitors respectively.

In a study by Ajayi and Adigun in 2000, a 3:1 preponderance of female patients that experienced cough was found. Other studies also found that cough affects females 2 to 3 times more often than males. (Klasco,2007) The number of females that used ARB's was lower than that of males

within the organisation so there can be no correlation made with these studies.

4.12 Gender distribution for ACE inhibitor and ARB use for heart failure

A similar pattern of use was shown for the use of ARB's and ACE inhibitors for heart failure as shown in Table 3.12. More male members, 36(63.16%), used ACE inhibitors, as compared to 21 female members (63.16%).

Seven (63.64%) of the members that used ARB's for heart failure were male and four (36.36%) were female.

Supporting literature on differences in heart failure treatment for men and women was not found.

4.13 Prescriber patterns for ACE inhibitor and ARB use for hypertension

The discipline of providers that wrote most of the prescriptions for ARB's and ACE inhibitors were general practitioners, about 71% for both classes. Cardiologists, physicians and other specialists made up the balance of the prescribers, as per Table 3.13 and Figure 3.8.

This is quite interesting as if ARB's are being reserved for the more "complicated" cases of hypertension and are not being used as first line agents, it is possible that general practitioners are treating the more "complicated" cases or not adhering to the guidelines. It would be assumed that these patients, especially since they are part of a private healthcare benefit would consult a specialist.

The ARB's are one of the more expensive classes of antihypertensives so although the patient is not incurring the cost of a specialist consultation by visiting the GP, the monthly prescription has a greater cost implication to the scheme.

In an investigation into the prescribing patterns for ACE inhibitors, the overall prescribing patterns were found to be not always in adherence to evidence from the literature (Doyle, *et al*, 1998)

Another study in Bahrain followed the prescribing patterns of physicians and general practitioners (Sequira, *et al*, 2002). The conclusion of this study was that both groups had instances where they did not adhere to the guidelines.

4.13 Prescriber patterns for ACE inhibitor and ARB use for heart failure

Prescriptions by general practitioners were also more prevalent in the heart failure population for ARB's and ACE inhibitors (52.94% and 54.55%) respectively, see Table 3.14 and Figure 3.9. The reason for this could be that due to the complexity of the condition, specialists are consulted more frequently when a patient has heart failure.

Other studies on prescribing trends for heart failure were not found at the time of compiling this report

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4.14 Co-Morbidities in patients using ACE inhibitors or ARB's for hypertension

The co-morbidities were chosen on the basis of the compelling indication to use ARB's over ACE inhibitors i.e., mcroalbuminuria and one of the common side effects of ARB's i.e., cough.

The respiratory chronic conditions were chosen to determine if their presence would influence prescribing patterns and show a preference for ARB's.

Of the total member distribution, most patients had other or no co-morbid conditions as compared to the specific ones reported on- 86.1% of patients on ARB's and 82.2% on ACE inhibitors.

Thus a higher percentage of patients on ACE inhibitors had co-morbidities than patients on ARB's, Table 3.17 details the incidences of the co-morbid conditions.

Of the co-morbid conditions selected to report on, non-insulin dependent diabetes mellitus was the most common with 6.4% of the members on ARB's and 9.56% of the members on ACE inhibitors having this diagnosis listed.

Most studies cite both ACE inhibitors and ARB's as being beneficial in patients with the progression of renal disease in type 2 diabetes mellitus. One of these was the DETAIL (Diabetics exposed to Telmisarten and Enalapril) study where patients on either class of drug showed no

statistically significant differences in glomerular filtration rate. (Barnett, *et al.,* 2004)

Asthmatics made up the second highest group, with 4.6% on ARB's and 3.74% on ACE inhibitors. For members that had non-insulin diabetes mellitus, 1.83% were on ARB's and 3.09% were on ACE inhibitors.

In the Netherlands, a study conducted showed that ARB's were found to be the agents of first choice in patients with asthma and COPD. ACE inhibitor use increased in hypertensive patients with diabetes, proteinuria or renal insufficiency (Greving, *et al*, 2004).

4.14 Co-Morbidities in patients using ACE inhibitors or ARB's for heart failure.

Within the group of members that used ACE inhibitors for heart failure, 89.47% had either other or no co-morbidities compared to those selected. 1.75% had insulin dependent diabetes mellitus and 5.26% had non insulin dependent diabetes mellitus.

Two (3.5%) of the members had COPD.

For asthma and insulin dependent diabetes mellitus, the percentage reported was. 9.09% of each condition for members using ARB's, which is only one member that had either condition.

Thus from these numbers it is difficult to conclude that the co-morbidities contribute to the selection of either class for treatment.

4.15 Amount Spent on chronic conditions and drug classes

Hypertension medication claims account for 20.12% of the amount spent of on all chronic medication which is a large proportion as there to put this in context, in 2003, there were 65 chronic conditions that were covered by this managed care organisation.

Heart failure makes up 0.67 % of the total claimed amount on chronic medication.

There are also many generic drugs that are used and their use is encouraged as it enables the condition to be more cost effective for the members and the organisation so this could also assist in the reduction of the cost of the condition.

Unfortunately this is just the cost of the chronic medication and the hospital related admissions are not quantified so the cost of these conditions to the organisation cannot be assessed by these figures alone.

4.16 Comparison of the amount spent on ACE Inhibitors and ARB's vs other anti-hypertensives

Together, ACE inhibitors and ARB's made up 55.5% of the total cost of anti-hypertensives. This is a major portion of the total cost of all the medication classes. It can be assumed that these are also high cost drugs as the proportion of these classes used for hypertension is 44.8%. The conclusions of a study conducted to analyse the cost effectiveness of the hypertensive guidelines in South Africa showed that if the use of thiazides replace the more expensive classes of antihypertensives, the cost effectiveness ratios for primary prevention will be further reduced compared to no treatment. (Gaziano, *et al*.,2005) In the organisation, as blood pressure readings were not available, it could not be ascertained if the medication was being used for prevention or treatment of hypertension.

4.17 Comparison of the amount spent on ACE Inhibitors and ARB's vs other medication for heart failure

The amount spent on chronic medication for heart failure in the year 2003 by drug class corresponds very closely with the number of prescriptions for the different classes. ARB's constitute only 9.84% of the total amount spent,

ACE's make up 25.46% whereas all the other classes of drugs used for heart failure provide the balance which is 64.7%.

The argument used for the proportion of drugs used thus will be the same for the amount spent.

4.18 Average costs of ARB's vs ACE inhibitors as monotherapy for hypertension and heart failure

ARB's were shown to have a higher average cost per member per year than ACE inhibitors for hypertension, which was R1 622 and the average cost of ACE inhibitors per member per year was R973. Table 3.21 illustrates the total cost of these drug classes over the year. However due to there being significantly more patients on ACE inhibitors than ARB's, the total cost and thus the proportion of the hypertension spend was greater.

For heart failure, the average cost of an ARB prescription for the year was higher than an annual ACE inhibitor prescription for members on monotherapy that had heart failure. For ARB's, the average cost was R1690 and for ACE inhibitors the average cost was found to be R1128.The average cost for hypertension and heart failure may differ due to the cost of the different agents being used or there may be variable doses of the different agents.

The finding that ARB's incur more cost to the scheme is not surprising as Tables 1.2. and 1.3 in Chapter 1 details the prices of the agents and ARB's are generally more expensive than ACE inhibitors. In addition, ACE inhibitors have been on the market for a longer period than ARB's there are more generics available for ACE inhibitors which would contribute to a lower price of these agents.

In an analysis done that compared the cost of antihypertensive agents as monotherapy for 5 years showed that losarten cost 1 279.88 Euros and enalapril cost 607.45 Euros over the same time period.(Stafilas, *et al,* 2003).

CHAPTER 5

LIMITATIONS

The data used was based on only out of hospital chronic medication claims. The exact history of the patient, the blood pressure reading on initiation and during treatment was not monitored and the admission rate per patient was also not determined.

The hospital admissions that were related to the conditions would have been important information to have as it would have assisted in determining the efficacy of the drug classes.

The ICD 10 coding of the conditions and the drug to condition link were not always accurate. This presented a problem when reporting on the classes of drugs that were used for the conditions as there were some inappropriate classes authorised or incorrect conditions captured.

The reasons for authorising the specific drug class were not accessible in the data extracted. This was important to ascertain the specific reasons for the use of ARB's which could not be established e.g. if the member experienced an ACE inhibitor related cough or any other side effect or if the member's blood pressure was not adequately controlled on the ACE inhibitor.

With regards to the data on the co-morbid conditions, these conditions are just some of the indications where these drugs could be used.

For diabetes with proteinuria, the use of ACE's or ARB's is a compelling indication. However since the ICD 10 capture or submission is often not at a 5^{th} level of coding, it cannot be determined if there is diabetes with or without proteinuria. Thus adherence to the guidelines cannot be confirmed by this.

There can only be assumptions made that this is the reason for their use.

In terms of the provider information, there were also some incorrect details of provider BHF numbers captured which may have reflected the mix of providers inaccurately.

CHAPTER 6

SUMMARY

ARB's are regularly used in the private sector and this study investigated the frequency of their use for the conditions hypertension and heart failure as compared to ACE inhibitors for these conditions, and to try to ascertain if there are any obvious trends in the pattern of the use of these two different classes within a specific managed care organisation.

As shown by the results, hypertension is very costly to the managed care organisation where the data for this study were obtained. It is also a very prevalent condition amongst the patient population studied.

Of all the medication classes that were claimed for hypertension and heart failure, ACE inhibitors and ARB's were very popular. Within the group of hypertension claimants, ACE inhibitors were the more common class both as monotherapy and in combination with other agents and this was followed by ARB's.

For heart failure claims, both classes only represented a small proportion of the drug classes used as diuretics are the mainstay of therapy.

With regards to the prescribing doctors for these chronic conditions, general practitioners were shown to have written more prescriptions than specialists.

The age prevalence of the utilization of ACE inhibitors and ARB's followed the general trends in the organization for hypertension and heart failure.

Although there was a higher number of males that used ACE inhibitors and ARB's, there is no indication for the preferential use of either class in hypertension or heart failure.

The co-morbidities were chosen to ascertain if ARB's showed a higher usage in certain conditions. The number of members with co-morbid conditions was fairly low and the use of ACE inhibitors was higher for all the reported conditions.

ACE inhibitors and ARB's are generally more expensive than most other antihypertensive agents and this was illustrated by the high average cost of these drugs for the year. ARB's also have a higher average cost than ACE inhibitors. This is also partly due to the situation in 2003 where there were no

generic equivalents for ARB’s available as they were fairly new on the market and the patents had not expired as yet for these agents.

CHAPTER 7

CONCLUSION AND RECOMMENDATIONS

7.1 CONCLUSION

Hypertension and heart failure are conditions were shown to have a substantial cost implication for the managed care organisation in terms of the amount that is spent on chronic medication.

From the analysis of the out of hospital chronic medication claims from the managed care organisation, no conclusive findings were made about the specific reasons for the use of ARB's over ACE inhibitors.

The use of ARB's is advocated for diabetic patients with microalbuminuria, however no preference for the class was shown in the members with diabetes as a co-morbid condition.

Similarly, there was no propensity for the increased use of ARB's in the elderly as the ARB's have an improved side effect profile in the elderly.

Therefore, the criteria for the approval of these drugs has to be well defined and there should be strict criteria before authorising ARB's. This will assist to contain the costs of the condition to the organisation and will be in line with the national and international guidelines for the treatment choices in hypertension.

From popular information and opinion amongst MCO's and from personal experience on working on many chronic hypertension and heart failure applications, ARB's seem to be more widely used than they should be and not according to the criteria set out in the guidelines. The results have shown that ARB's are very widely used and there was no evidence to prove that the use was according to the guidelines. The actual reasons for prescribing ARB's could unfortunately not be established and the use of ARB's was not higher than ACE inhibitors. However, considering that they were still a relatively new class of drugs, the use was still high.

This study has to be conducted again with data from subsequent years with the recommendations below to continue the pursuit of a more cost effective model for hypertension and heart failure management in the

private care sector of South Africa without compromising the care of the patients.

7.2 RECOMMENDATIONS

Both hypertension and heart failure are PMB conditions and thus the managed care organisation is compelled to pay for these conditions so there will always be a need to decrease the amount that is spent on these conditions.

Cost effectiveness is always a factor for the competitive industry of managed care and this has to be accomplished without compromising the health of the patient.

One of the most popular and effective measures of containing the cost of chronic medication in managed care is the drug utilization review (DUR) interventions and the use of formularies by the medical schemes. The use of generic or therapeutic substitution is also looked at during DUR.

One of the many follow up studies that should be done is to duplicate this study for the following years and extrapolate it to include all classes of anti-hypertensives to evaluate the cost, prescribing habits, demographic distribution of the claimants and the different reasons for the use of the different agents in the conditions. A comparison of the costs and effectiveness of the different agents has to be established.

If there are prescribers identified who constantly prescribe more expensive agents, interactions with them could set up to ascertain the reasons for the prescriptions and useful interventions suggested to try to reduce the cost.

An improved form of recording the reason for the use of certain drug classes needs to be achieved. It was difficult to determine the reasons for the use of these drugs as the exact explanation for the choice of drug class was not captured.

If the patients were switched to ACE inhibitors from ARB's due to an ACE inhibitor induced cough for example, the percentage could be established and checked if this correlated to the trials done. Other reasons that would be important to note are the conditions in which ARB's are the preferential drug e.g. in proteinuria, asthma or other respiratory conditions where cough may already be a factor e.g. chronic bronchitis.

If possible, treatment compliance also should be monitored and drugs should not just be switched if the non responsiveness to treatment was due to non compliance.

The members should be educated on compliance issues and counselled about side effects as an extra benefit of the managed care organisation.

These drug classes also need to be investigated in other conditions e.g. post a myocardial infarction and stroke. There have been beneficial effects shown with ACE inhibitors after a myocardial infarction but not ARB's as yet. (Dickestein, *et al*.,2002)

If the study is done on more updated data, the DRG (Disease Related Group) data will benefit as well. This will enable the hospital events to be recorded and the actual cost of the disease to the scheme and possibly the potential savings if a more effective agent is used regardless of the cost.

As ICD 10 capture became mandatory from July 2005, the DRG's would be more accurately recorded and the cost effectiveness could be more realistic and valuable.

Another further study that can be done to add value is the prevalence of the use of ACE inhibitors and ARB's together. Beneficial effects have been shown in some cases of diabetes mellitus with proteinuria. This is a relatively new indication and thus new information is always of assistance in the managed care setting.

REFERENCES

1. Barnett, A.H, Bain, S.C, Bouter P *et al. 2004.* Angiotensin receptor blockade versus converting enzyme inhibition in type 2 diabetes and nephropathy. The Diabetics Exposed to Telmisarten and Enalapril Study Group. *New England Journal of Medicine*. vol 351.pp 1952-1961.

2. Berkin, L and Ball, S. 2002. Modern approaches to heart failure treatment. *Prescriber*. No 19. pp 63-75.

3. Blackburn, S. and Ito, S, M.(eds).1995. A pharmacist's guide to principles and practices of managed care pharmacy. Virginia. *The Foundation for Managed Care Pharmacy. (FMCP)*. pp 1-59.

4. Boyle, A. and Hobbs, R. 2004. "Heart failure". <http//.www .clevelandclinicmeded.com/diseasemanagement/cardiology/heartfailure/heartfailure/> (Accessed on 20 December 2005).

5. Bremner, A.D., Mehring G.H, and Meilenbrok, S. 1997. Long term systemic tolerability of valsarten compared with lisinopril in elderly hypertensive patients. *Advances in therapy*. Vol 14. no.5. pp 245-253.

6. Chobanian A.V, Bakris G.L, Black H.R, et al.2003. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Journal of the American medical Association(JAMA)*. Vol. 289. no.19. pp 2560-2571.

7. Coca, A., Calvo C., Garcia-Puig, J et al. 2002. A multicenter, randomized, double-blind comparison of the efficacy and safety of irbesartan and enalapril in adults with mild to moderate essential hypertension, as assessed by ambulatory blood pressure monitoring: The MAPAVEL study. *Clinical Therapeutics*. Vol. 24. no.1. pp 126-138.

8. DiPiro, J. T., Talbert, R.L., Yee, G.C., *et al*. 1999. *Pharmacotherapy, a pathophysiological approach*. Mcgraw Hill/Appleton and Lange.4th edition. pp.135-177.

9. Doyle, J.C.,Mottram, D.R. and Stubbs H.. 1998. Prescribing of ACE inhibitors for cardiovascular disorders in general practice. *Journal of Clinical Pharmacy and Therapeutics.* Vol 23. no.2. pp133-136. <http://www.ingentaconnect.com/contect/bsc/jcpt/1998/0000002/art00044> (Accessed on 19 November 2007).

10 Dickenstein, K and Kjekhus, J (The OPTIMAAL Steering committee, for the OPTIMAAL study group).2002. Effects of losarten and captopril on mortality and morbidity in high risk patients after myocardial infarction: The OPTIMAAL randomised trial. *The Lancet.* vol 360. no 9335. pp752-760.

11. Dunlap, M.E., Peterson, R.C. 2002. ACE inhibitors vs ARB's: Is one better than the other for heart failure? Cl*eveland Clinic Journal of Medicine*. Vol. 69. no 5. pp 433-438 <http://www.ccjm.org/pdffiles/dunlap502.pdf> (Accessed on 20 December 2005).

12. Fischer, M.A. and Avorn, J. 2004. Economic implications of evidence-based prescribing for hypertension. *Journal of the American medical Association(JAMA)*. Vol 291. no. 15. pp1850 <http://jama.ama-assn.org/cgi/content/full/291/15/1850> (Accessed on 29 April 2004).

13. Gaziano, T.A. and Steyn, K. 2005. Cost effectiveness analysis of hypertensive guidelines in South Africa. <http://www.procor.org/discussion/displaying.asp?ref=239&cat=ProCOR+Dialogue> (Accessed on 23 November 2007).

14. Glover, M.J., Greenlund, K.J., et al. 2005. Racial/Ethnic disparities in prevalence, treatment and control of hypertension- United States 1999-2002. <http:www.cdc.gov/mmwr/preview/mmwrhtml/mm5401a3.htm> (Accessed on 23 November 2007).

15. Greving, J.P., Denig, P., Van der Veen, W.J., *et al*.(2004)Does comorbidity explain trends in prescribing of newer antihypertensive agents? *Journal of Hypertension.* vol 22. no 11.pp 2209-2215.

16. HOPE(Heart Outcomes Prevention Evaluation) Study Investigators. 2000. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE sub study. *The Lancet*. vol. 355. no.9200. pp 253-259.

17. Hunt, S.A, Baker, D.W, Chin, M.H, *et al*.2001.ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines(committee to revise 1995 guideline for evaluation and management of heart failure) <http://www.acc.org/clinical/guidelines/failure/hf_index.htm> (Accessed on 10 January 2006).

18. Hunt S.A., Abraham, W.T, Chin, M.H.. *et al.* 2005. ACC/AHA 2005 Guideline update for the diagnosis and management of chronic heart failure in the adult-summary article. <http://www.acc.org/clinical/guidelines/failure/hf_index.htm> (Accessed on 10 January 2006)

19. Kaplan, N.M. 1999. Angiotensin ii receptor antagonists in the treatment of hypertension. http://www.aafp.org/afp/9909115ap/1185.html (Accessed on 17 October 2007).

20. Karlberg B.E., Lins, L-E. and Hermansson, K. 1999.Efficacy and safety of telmisartan, a selective at1 receptor antagonist, compared with enalapril in elderly patients with primary hypertension. *Journal of Hypertension*. Vol. 17:293-302. <http://www.medscape.com/viewarticle/4076894>(Accessed on 20/01/2005).

21. Klasco R.K.(Ed):Drugdex® system. Thompson healthcare, Greenwood village, Colorado (Edition expires12/2007).

22. Messerli, F.H. ,Okereke, C.E., ,2001. Efficacy and safety of angiotensin ii receptors blockers in elderly patients with mild to moderate hypertension. *American Journal of Geriatric Cardiology*, 10(1), 42-49 <http://www.medscape.com/viewarticle/4076894>(Accessed on 20/01/2005).

23. Miller, A, E, Cziraky, M and Spinler, S.A. 2006. ACE inhibitors versus ARB's: A comparison of practice guidelines and treatment selection. <http://www.formularyjournal.com/formualry/article/articleDetail.jsp?id=335323> (Accessed on 08 July 2007).

24. Monita, H., Nakao, N., Yoshimura, A,M *et al.* 2003 Combination treatment of an angiotensin ii receptor blocker and ace inhibitor in non-diabetic renal disease(COOPERATE):A Randomised Controlled Trial. *The Lancet*. Vol. 361. pp 117-124

25. Prescribing information, Diovan®.2000. Norvartis pharmaceuticals, Canada.

26. Stafilas, P.C, Sarafidis, A.P, Lasaridis, A.N , et *al.* 2004. An economic evaluation of the 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of mild-to-moderate hypertension in Greece. <http:// www. nature.com/ajh/journal/v18/n9/full/ajh2005204a.html> (Accessed on 20 November 2007).

27. Pitt, B, Martinez, F ,Segal, R., et al.1997. Randomised trial of losarten versus captopril in patients with heart failure(evaluation of losarten in the elderly study,(ELITE) *The Lancet*. Vol. 349. pp 747-752.

28 Radecki,T.E. 2007. ACE inhibitors. <http://www.modern-psychiatry/com/ace_inhibitors.htm> (Accessed on 15 January 2008).

29. Radecki,T.E.2007. Angiot ii r blockers. <http://www.modern-psychiatry /com/angiot_ii_blockers.htm> (Accessed on 15 January 2008).

30. Sequira, R.P., Jassim, K.A, Damanhori, A.H. *et al*.2002. Prescribing pattern of antihypertensive drugs by family physicians and general practitioners in the primary care setting in Bahrain. <http://www.ion.chanels.org/showabstract.php?pmid=12421390> (Accessed on 20 November 2007).

31. Smith, D.H.,2002. Treatment of hypertension with an angiotensin ii receptor antagonist compared with an angiotensin converting enzyme inhibitor: A review of clinical studies of telmisarten and enalapril. *Clinical Therapeutics*. Vol. 24. no10. pp 1484-1501.

32. Snyman, J(editor). 2006. MIMS Desk Reference. Vol.41. Johnnic Publishing limited. pp 231-236 332-335, 691-695, 782-786.

33. Southern African Hypertension Society Executive Committee. 2000. Hypertension clinical guideline 2000. *South African Medical Journal(SAMJ)* vol. 91. no. 2. pp 163-171.

34. Southern African Hypertension Society Guideline Working Group 2000 and 2003. 2001. Hypertension guideline 2003 update. *South African Medical Journal (SAMJ)* .vol. 94. no. 3. pp 209-225.

35. South African Medical Association Heart Failure Working Group. 1998. Heart failure clinical guideline. *South African Medical Journal.(SAMJ).* Vol 88. no. 9. pp 1133-1156.

36. Steyn, K, Fourie, J. and Temple, N. 2005. Chronic diseases of lifestyle in South Africa since 1995-2005. <http://www.mrc.ac.za/chronic/cdl/chapter8/pdf> (Accessed on 3 March 2006).

37. Weber, M.A.2006. Hypertension treatment and implications of recent cardiovascular outcome trials. *Journal of Hypertension*. vol 24. no.2. pp S37-S44.

38. World Health Organisation. 1996. International and statistical classification of diseases and related health problems, vol.1. 10th Revision England: WHO Publications. pp. 311-388.

39. World Health Organisation 2003. Anatomical therapeutic classification(ATC).

40. Young, J.B.(1999) ARB's or ACE inhibitors in heart failure: one better or use both? <http://www.theheart.org/article/119691.do> (Accessed on 27 November 2007).

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APPLICATION NUMBER 9102060N
STATUS (DEG 69) (MM044) PZZ

2004-04-20

Dear Ms Juggath

Approval of protocol entitled Utilization pattern of angiotension II inhibitors within South African managed care organisation

I should like to advise you that the protocol and title that you have submitted for the degree of Master Of Science In Medicine (Part-Time).(Coursework) have been approved by the Postgraduate Committee at its recent meeting. Please remember that any amendment to this title has to be endorsed by your Head of Department and formally approved by the Postgraduate Committee.

Prof AGS Gous has/have been appointed as your supervisor/s. Please maintain regular contact with your supervisor who must be kept advised of your progress.

Please note that approval by the Postgraduate Committee is always given subject to permission from the relevant Ethics Committee, and a copy of your clearance certificate should be lodged with the Faculty Office as soon as possible, if this has not already been done.

Yours sincerely

S Benn (Mrs)
Faculty Registrar
Faculty of Health Sciences

Telephone 717-2075/2076

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Juggath

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M040822**
PROJECT	Utilization Pattern of angiotensin II Inhibitors Within a South African Managed Care Organization
INVESTIGATORS	Ms A Juggath
DEPARTMENT	School of Therapeutic Sciences
DATE CONSIDERED	04.08.27
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 04.08.30 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof A Gous

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Discovery

Discovery Health
P O Box 786722
Sandton
2146

To Whom It May Concern:
Committee for Research on Human Subjects (Medical)
University of the Witwatersrand
P O Wits
2050

02 July 2004

Dear Sir/Madam

Non-disclosure Agreement – Research Report

The purpose of this letter is to confirm that Discovery Health will provide **Ashti Juggath, student number 9102060N,** with details contained in our medical records to complete her research report for the degree M.Sc(Med)(Part Time)(Coursework).

The information contained in these medical records supplied by Discovery Health to Ashti Juggath, will not divulge patient and/or heath care provider names and /or addresses in the interest of patient and health care provider confidentiality.
The patients will be identified by member numbers and the health care providers will be identified by BHF (Board of Health Care Funders) codes.

Should you have any ethical concerns with regard to patient confidentiality in the medical records provided by Discovery Health, please do not hesitate to contact me.

Thank you,

Yours faithfully

Dr S D Cornejo
Divisional Manager
Clinical Risk Management
Discovery Health