MANAGEMENT OF TYPE 2 DIABETES MELLITUS

A PHARMACOEPIDEMIODEMICAL REVIEW

ANUSOOYA SAUGUR

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MANAGEMENT OF TYPE 2 DIABETES MELLITUS
- A PHARMACOEPIDEMIOLOGICAL REVIEW

By

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DECLARATION

I, Anusooya Saugur (206080380), hereby declare that the dissertation for Magister Pharmaciae is my own work and that it has not been previously submitted for assessment or completion of any postgraduate qualification to another university or for another qualification.

Anusooya Saugur
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ABSTRACT

Type 2 diabetes mellitus (DM) is a progressive disease characterised by hyperglycaemia caused by defects in insulin secretion and insulin action. In early stages of type 2 DM, dietary and lifestyle changes are often sufficient to control blood glucose levels. However, over time, many patients experience β cell dysfunction and require insulin therapy, either alone or in combination with oral agents. There are guidelines available to structure the management of this disease state, including both the use of oral hypoglycaemic agents and or insulin. Besides health complications, there are economic burdens associated with the management of type 2 diabetes mellitus.

The aim of this study was to determine the management of type 2 DM in a South African sample group of patients drawn from a large medical aid database. The objectives of the study were: to establish the prevalence of type 2 DM relative to age, examine the nature of chronic comorbid disease states, establish trends in the prescribing of insulin relative to other oral hypoglycaemic agents, investigate cost implications, and determine trends in the use of blood and urine monitoring materials by patients. The study was quantitative and retrospective and descriptive statistics were used in the analysis.

DM was found to be most prevalent amongst patients between 50 and 59 years old. Results also demonstrated that 83% of DM patients also suffered from other chronic comorbid diseases, with cardiovascular diseases, especially hypertension and hypercholesterolaemia being the most prominent. This study also revealed that DM is predominantly managed with oral hypoglycaemic agents.

Changes in drug prescribing, for chronic disease states such as DM may have medical, social and economic implications both for individual patients and for society and it is envisaged that the results of this study can be used to influence future management of DM.

Keywords: Pharmacoepidemiology, management, type 2 diabetes mellitus.
CHAPTER ONE

INTRODUCTION
1.1 INTRODUCTION

The World Health Organisation (WHO) (2003: 8) defines pharmacoepidemiology as “the study of the use and effects/side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population, thereby improving health complications”.

A pharmacoepidemiological review can either be drug- or utilisation-oriented. In the former, drugs (individual or groups) are analysed in terms of safety and effectiveness. Whereas for utilisation-oriented reviews, the focus is to intervene in drug therapy in order to ameliorate its quality. Pharmacoepidemiological reviews also focus on the pattern, quality, determinants and outcomes of drug use. Furthermore, these studies extend over long periods of time for large patient populations (WHO, 2003).

This dissertation focused on a drug utilisation study that was conducted on all data of the diabetic patients who were registered on the medical aid database between 1 January 2008 and 8 December 2010. The diabetic medication records were obtained from a medical aid administrator. The records were of patients who were diagnosed with diabetes mellitus (DM) with/without other chronic comorbid disease states and represented people resident in South Africa (SA). This chapter provides an outline of the background to the study; problem statement; aim and objectives; and division of the chapters.

1.2 BACKGROUND TO THE STUDY

The WHO estimated the world prevalence of DM to be 171 million people in 2000. Furthermore, it was estimated that by 2030, the global prevalence will increase to 366 million. According to the WHO in 2000, 814 000 people were affected by this chronic condition in South Africa. It is further estimated that by 2030, approximately one million South Africans will be affected by diabetes. Table 1.1 outlines the prevalence of DM around the world in 2000 (WHO, 2010).
Table 1.1: World prevalence of diabetes mellitus in 2000

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>POPULATION</th>
<th>PREVALENCE (% OF TOTAL POPULATION)</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>1 015 920 000</td>
<td>31 705 000 (3,1)</td>
</tr>
<tr>
<td>United States of America</td>
<td>282 170 000</td>
<td>17 702 000 (6,3)</td>
</tr>
<tr>
<td>United Kingdom (Great Britain &amp; Northern Ireland)</td>
<td>58 890 000</td>
<td>1 765 000 (3,0)</td>
</tr>
<tr>
<td>South Africa</td>
<td>44 000 000</td>
<td>814 000 (1,9)</td>
</tr>
<tr>
<td>Canada</td>
<td>30 770 000</td>
<td>2 006 000 (6,5)</td>
</tr>
<tr>
<td>Australia</td>
<td>19 150 000</td>
<td>941 000 (4,9)</td>
</tr>
<tr>
<td>New Zealand</td>
<td>3 860 000</td>
<td>179 000 (4,6)</td>
</tr>
<tr>
<td>Mauritius</td>
<td>1 190 000</td>
<td>111 000 (9,3)</td>
</tr>
</tbody>
</table>

(Adapted from WHO, 2010 and World Bank, 2010a)

From Table 1.1, it can be observed that DM is a chronic condition that affects many people worldwide. According to Isley, Reasner and Triplitt (2008), the increasing number of patients affected by DM is partly due to the westernisation of lifestyle, which includes practising unhealthy eating habits. Other contributing factors suggested, included: a lack of exercise and having a body mass index (BMI) above 30kg/m², which is considered to be obese (Isley et al., 2008).

Besides health complications associated with DM, economic problems often arise. These problems can be in terms of the management of the disease state itself and also in the treatment of complications that may occur. These financial issues are directly related to the increased number of people diagnosed with DM (Guidelines and Protocols Advisory Committee, 2005).
1.3 PROBLEM STATEMENT

In 2000, it was estimated that in a population of 44 million, 814 000 (1.9%) South Africans were already affected by DM. The World Health Organisation (2010) has estimated that in 2030, DM will affect about one million South Africans. The management of this chronic disease state is becoming problematic. South Africans are at risk of an increase in mortality and morbidity associated with the increase in prevalence of DM.

There are various implications associated with the management of DM, including both economic implications, as well as health complications (Guidelines and Protocols Advisory Committee, 2005). The major health problems of DM are categorised into microvascular and macrovascular complications (Bate & Jerums, 2003).

1.4 AIM AND OBJECTIVES

The aim of this study was to determine and describe the management of type 2 DM in a sample group of DM patients taken from a large South African medical aid company database; and more specifically to focus on the use of insulin in these patients.

The specific research objectives were to:

1. establish the prevalence of type 2 DM relative to age, gender and ethnicity, in the study population;

2. examine the prevalence and nature of chronic comorbid disease states, especially those that can be related to micro and macrovascular complications in diabetic patients;

3. establish the extent, profile and trends in the prescribing of insulin, relative to oral hypoglycaemic agents, over a three year period;
investigate the cost implications of the patterns of hypoglycaemic drug use;

5. examine the extent and trends of use of blood and urine glucose monitoring materials by patients, relative to their use of insulin and other hypoglycaemic agents; and

6. use prescribing indices, such as prescribed daily doses (PDD) and defined daily doses (DDD), to compare the observed patterns of prescribing with relevant recommended guidelines and protocols.

1.5 DIVISION OF CHAPTERS

This study is divided into five chapters. These are as follows: chapter one: introduction; chapter two: an overview of the management of type 2 DM; chapter three: research methodology; chapter four: results and discussion; and lastly chapter five: conclusion, limitations and recommendations.

Chapter one introduces the research and provides a brief summary of the background to the study and the problem statement. In addition, the aim and objectives of the study are described.

An overview of the management of type 2 DM is thoroughly discussed in chapter two. The purpose of this chapter is to provide a literature review on DM, its management, background on insulin and includes similar previous studies performed.

The design and methodology used to carry out the study are described in chapter three. The methodology includes the explanation of the data collection and analysis.

In chapter four, the results of the study are discussed. Some of the findings of the study are either tabulated or depicted in graphs.
Lastly, the conclusion and the limitations of the study are discussed in chapter five. Additionally, some recommendations with regards to the study are also made in this chapter.
CHAPTER TWO

AN OVERVIEW OF THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS
In order to understand and describe the treatment of type 2 DM within the context of existing knowledge and literature, a comprehensive literature review was conducted. Consideration was given to the following aspects of DM and its management: description of type 2 DM; overview of the epidemiology; death statistics; overview of the aetiology; clinical findings; risk factors; comorbid diseases; management; insulin use; and pharmacoepidemiological reviews.

The definition, types, complications and international classification of DM were included when describing type 2 DM. Subsequently, the prevalence of type 2 DM was discussed with regards to the age, ethnicity and gender of patients according to the different studies performed worldwide. Death statistics pertaining to type 2 DM in South Africa were discussed after the epidemiology. The possible disease-related and drug-related causes of type 2 DM were discussed in the aetiology sub-section of the literature review.

Then, a description of the clinical findings of type 2 DM was provided. The clinical findings were described in comparison to normal values in an individual who does not suffer from type 2 DM. The risk factors that predispose a patient to the development of type 2 DM were included in this literature review. After describing the risk factors, an in-depth description about the existence of comorbid disease states associated with type 2 DM, was provided. The core of the literature review - the management of type 2 DM, was then systematically discussed in detail. Subsequently, insulin was discussed: a background on insulin was provided, as well as its use and complications in type 2 DM. Lastly, two pharmacoepidemiological reviews pertaining to this area of research were described in terms of the methodology and the findings of the studies.

The section that follows provides an explanation of type 2 DM.
2.1 TYPE 2 DIABETES MELLITUS

2.1.1 Definition of diabetes mellitus and types of diabetes mellitus

Diabetes mellitus is defined by the American Diabetes Association (ADA) (2010: S62) as “a group of metabolic diseases characterised by hyperglycaemia, resulting from defects in insulin secretion, insulin action, or both”. Diabetes mellitus can be categorised into four different types, (Karam & Nolte, 2006; Mbanya & Ramiaya, 2006) which are described in Table 2.1.

Table 2.1: Types of diabetes mellitus

<table>
<thead>
<tr>
<th>TYPE OF DIABETES MELLITUS</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1: Insulin-dependent diabetes</td>
<td>It occurs when there is an insulin deficiency (complete or severe), associated with the autoimmune destruction of beta cells (β-cells) of the pancreas.</td>
</tr>
<tr>
<td>Type 2: Non-insulin dependent diabetes</td>
<td>This type is described as a combination of “absent or inadequate pancreatic insulin secretion”, together with “tissue resistance to the action of insulin” (Karam &amp; Nolte, 2006).</td>
</tr>
<tr>
<td>Type 3: Other specific types of diabetes</td>
<td>This type of diabetes may occur as a result of genetic syndromes, pancreatic disorders and drugs (Mbanya &amp; Ramiaya, 2006). This will be described further in section 2.3.</td>
</tr>
<tr>
<td>Type 4: Gestational diabetes</td>
<td>This condition is described as either the initial development or the detection of glucose intolerance during pregnancy (Bhattacharyyya, 2001; Mbanya &amp; Ramiaya, 2006). Glucose intolerance may develop during pregnancy because of the high levels of ‘anti-insulin’ hormones that are released from the placenta, especially during the third trimester. Most often, glucose tolerance normalises after six weeks, but in some patients, it may continue and manifest as type 2 DM (Bhattacharyyya, 2001).</td>
</tr>
</tbody>
</table>

Type 1 and Type 2 DM are the major classifications of diabetes conditions that are encountered in Sub-Saharan Africa (Mbanya & Ramiaya, 2006). There are
specific characteristics which differentiate these two types of DM. Table 2.2 contrasts these characteristics.

**Table 2.2: Main distinguishing characteristics of type 1 and type 2 diabetes mellitus**

<table>
<thead>
<tr>
<th>TYPE 1 DM</th>
<th>TYPE 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually develops at an early stage in life</td>
<td>Usually develops later on in life</td>
</tr>
<tr>
<td>Children usually affected, but may occur at any stage in life</td>
<td></td>
</tr>
<tr>
<td>Condition remains the same throughout life</td>
<td>With time, condition worsens</td>
</tr>
<tr>
<td>Ketosis more likely to occur</td>
<td>Ketosis not likely to occur</td>
</tr>
<tr>
<td>Genetic predisposition plays a minor role</td>
<td>Genetic predisposition plays a major role</td>
</tr>
<tr>
<td>Treatment with insulin is necessary</td>
<td>Treatment with insulin is not necessary, but may be helpful</td>
</tr>
<tr>
<td>Patients are usually thin</td>
<td>Patients are often obese; but can be either normal weight or underweight</td>
</tr>
</tbody>
</table>

(Adapted from Bhattacharyya, 2001; Chisholm & Shaw, 2003; Mbanya & Ramiaya, 2006)

**2.1.2 Complications of diabetes mellitus**

Both types 1 and 2 DM are associated with complications (Mbanya & Ramiaya, 2006). The ADA (2010: S62) reports that there is “long-term damage, dysfunction and failure of different organs; especially the eyes, kidneys, nerves, heart and blood vessels”, linked to the chronically increased blood glucose levels evident in diabetics. These complications form part of the major factors accounting for the increased morbidity and mortality rates on a global level; and they may be broadly classified into the following two categories: macrovascular and microvascular (ADA, 2010; Brown, 2010). As the names describe, macrovascular complications involve the large arteries, whereas microvascular complications include those affecting the smaller blood vessels and capillaries.
Table 2.3 contrasts examples of the two different types of complications of DM.

<table>
<thead>
<tr>
<th>MACROVASCULAR COMPLICATIONS</th>
<th>MICROVASCULAR COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Amputation</td>
</tr>
<tr>
<td>Angina</td>
<td>Autonomic Neuropathy</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>Diabetic Retinopathy</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>Erectile Dysfunction</td>
</tr>
<tr>
<td>Transient Ischaemic Heart Attack</td>
<td>Micro-/Macro-albuminuria</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td></td>
<td>Peripheral Neuropathy</td>
</tr>
</tbody>
</table>

(Adapted from Bate & Jerums, 2003)

In 2006, Mbanya and Ramiaya reported on studies performed on the South African prevalence of diabetes complications. In a study performed by Gill, Huddle and Rolfe in 1995 in a secondary care clinic, 42% of 64 patients were found to suffer from neuropathy. In another study performed by Bawa, Bradshaw, Levitt, Maphumolo and Zwarenstein in 1997, 37% of 300 patients in a primary care clinic, were reported to have suffered from nephropathy. In 1997, in a study conducted by Becker, Joannou, Kalk, Mahanlal, Mahomed and Ntsepo, retinopathy was found to be prevalent amongst 37% of the 507 patients who were attending a secondary care clinic.

One of the primary goals of therapy in the management of type 2 DM is the prevention and management of the aforementioned complications (Table 2.3). The other goals of therapy will be discussed in section 2.7.

Mbanya and Ramiaya (2006) suggested that non-communicable diseases added considerable burden to disease and death amongst adults. Furthermore,
these researchers estimated that DM, being one of the non-communicable diseases, would be one of the leading causes of death by 2020.

2.1.3 International Classification of Diseases and diabetes mellitus

The International Classification of Diseases (ICD) is a standard diagnostic classification used internationally. The WHO member states started using the ICD-10 system in 1994 (WHO, 2011a).

The ICD-10 system classifies the different disease states according to chapters and then blocks within the chapters. Diabetes mellitus forms part of Chapter IV which is endocrine, nutritional and metabolic diseases (E00-E90). The ICD-10 codes for DM are E10-E14 (WHO, 2011b). The main ICD-10 codes are E10 and E11 which represent type 1 and type 2 DM, respectively. Other ICD-10 codes are E12 and E13, which represent malnutrition-related DM and other specified DM, respectively. Additionally, there are other subdivisions which are added to the E10-E14 categories, which are described in Table 2.4 (adapted from WHO, 2011b). For instance, an ICD-10 code of E11.9 stands for type 2 DM without complications.

Table 2.4: Subdivisions of E10-E14 ICD 10 Codes

<table>
<thead>
<tr>
<th>SUBDIVISION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>.0</td>
<td>With coma</td>
</tr>
<tr>
<td>.1</td>
<td>With ketoacidosis</td>
</tr>
<tr>
<td>.2+</td>
<td>With renal complications</td>
</tr>
<tr>
<td>.3+</td>
<td>With ophthalmic complications</td>
</tr>
<tr>
<td>.4+</td>
<td>With neurological complications</td>
</tr>
<tr>
<td>.5</td>
<td>With peripheral circulatory complications</td>
</tr>
<tr>
<td>.6</td>
<td>With other specified complications</td>
</tr>
<tr>
<td>.7</td>
<td>With multiple complications</td>
</tr>
<tr>
<td>.8</td>
<td>With unspecified complications</td>
</tr>
<tr>
<td>.9</td>
<td>Without complications</td>
</tr>
</tbody>
</table>

(WHO, 2011c)
OVERVIEW OF THE EPIDEMIOLOGY OF DIABETES MELLITUS

Epidemiology is described as “the study of the distribution of diseases and determinants of disease in populations” (Martin, 2007). Dawson and Trapp (2004: 1) describe epidemiology as “the study … of the patterns of health or disease and the factors that influence these patterns”.

It was reported that by 2030, 366 million people will be affected by DM globally; as compared to 171 million people who were found to be affected in 2000 (Green, King, Roglic, Sicree & Wild, 2004). However, the global prevalence for DM differs among researchers. According to WHO (2002), the global prevalence of this non-communicable disease was 177 million people in 2000 and 194 million people in 2003; 66% of whom resided in developing countries, in both 2000 and 2003. Moreover, Mbanya and Ramiaya (2006) identified epidemiological studies which demonstrated an increase in diabetes incidence and prevalence in Africa. Incidence is defined as “the number of new cases of a disease which came into existence within a certain period of time per specified unit of population” (Timmreck, 2002: 134). Prevalence is defined as “the proportion of people who have a given disease or condition at a specified point in time” (Dawson & Trapp, 2004: 411). The rising prevalence of DM has been attributed to numerous causes, including:

- increasing population size;
- aging population;
- movement of people from rural to urban areas; and
- rising prevalence figures for obesity and lack of physical exercise (Green et al., 2004; Mbanya & Ramiaya, 2006).

The following sub-sections (2.2.1-2.2.3) focus on the prevalence of type 2 DM, relative to age, ethnicity and gender.

2.2.1 Age

In 2010, 8-10% of the South African population was believed to have been affected by DM (Brown, 2010). The international prevalence of DM amongst all
age groups was estimated to be 2.8% in 2000 (Rheeder, 2006). This prevalence estimate is expected to rise to 4.4% by 2030 (Green et al., 2004; Rheeder, 2006).

According to the International Diabetes Federation (IDF) (2010), the prevalence of DM was estimated to be 4.5% for 44 million South Africans, aged 20 to 79 years (World Bank, 2010a). The IDF (2010) Diabetes Atlas further estimated that by 2030, the prevalence figure would increase to 5.6% for South Africans in the abovementioned age group. In 2003, South Africa was classified as one of the top five countries to be affected by DM in Sub-Saharan Africa (Mbanya & Ramiaya, 2006).

The prevalence of DM worldwide is expected to be on the rise in people who are older than 65 years of age (Green et al., 2004; Rheeder, 2006). According to Mbanya and Ramiaya (2006), age is considered to be one of the major risk factors for DM in Africa.

Table 2.5 illustrates the estimated global prevalence of DM amongst all adult age groups for the year 2000 and 2030. It is evident that the age group, 45-64 years, was most commonly affected by DM in 2000. The same global trend is expected for the year, 2030.

<table>
<thead>
<tr>
<th>AGE GROUP (YEARS)</th>
<th>ESTIMATED NUMBER OF PEOPLE AFFECTED BY DM GLOBALLY IN 2000 (MILLIONS)</th>
<th>ESTIMATED NUMBER OF PEOPLE AFFECTED BY DM GLOBALLY IN 2030 (MILLIONS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-44</td>
<td>34</td>
<td>60</td>
</tr>
<tr>
<td>45-64</td>
<td>82</td>
<td>178</td>
</tr>
<tr>
<td>65+</td>
<td>56</td>
<td>132</td>
</tr>
</tbody>
</table>

(Adapted from Green et al., 2004)
Tables 2.6 and 2.7 depict the prevalence of DM, according to the specified age groups, in different regions of South Africa in 1993-1995 (Table 2.6) and in SA during 2003 (Table 2.7).

**Table 2.6: Diabetes mellitus prevalence (%) in South Africa**

<table>
<thead>
<tr>
<th>REGION</th>
<th>YEAR</th>
<th>AGE GROUP (YEARS)</th>
<th>POPULATION SIZE</th>
<th>DIABETES PREVALENCE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cape Town</td>
<td>1993</td>
<td>&gt; 30</td>
<td>729</td>
<td>6,3</td>
</tr>
<tr>
<td>Durban</td>
<td>1993</td>
<td>&gt; 15</td>
<td>479</td>
<td>4,2</td>
</tr>
<tr>
<td>Mangaung (Free State)</td>
<td>1995</td>
<td>≥ 25</td>
<td>758</td>
<td>6,0</td>
</tr>
</tbody>
</table>

(Adapted from Mbanya & Ramiaya, 2006)

**Table 2.7: Estimated prevalence (%) of diabetes mellitus in South Africa, according to age groups, in 2003**

<table>
<thead>
<tr>
<th>NUMBER OF PEOPLE WITH DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population (thousands)</td>
</tr>
<tr>
<td>Population Prevalence (%)</td>
</tr>
<tr>
<td>Age group (years)</td>
</tr>
<tr>
<td>20-39 years</td>
</tr>
<tr>
<td>40-59 years</td>
</tr>
<tr>
<td>60-79 years</td>
</tr>
</tbody>
</table>

(Adapted from Mbanya & Ramiaya, 2006)

In Table 2.7, the estimated prevalence of DM in different age groups in both developing and developed countries, (in 2000) is summarised. World Bank (2008) defined developing countries as countries of low-income or middle-income economies and includes countries such as: China, India and South Africa. Developed countries are countries of high income; and examples include countries such as: Australia, France and New Zealand (World Bank, 2010b).

Table 2.8 outlines the diabetes prevalence rates in developed and developing countries for the various age categories. From Table 2.8, it can be observed
that in developed countries, the age group: 65+ years, was most commonly affected by DM in the year 2000. Furthermore, the same prevalence trend was estimated for the year 2030 for the same age group. This particular prevalence trend, relating to developed countries, was also discussed by Mbanya and Ramiaya (2006).

Table 2.8: Estimated diabetes mellitus prevalence in various age groups in developing and developed countries

<table>
<thead>
<tr>
<th>AGE GROUP (YEARS)</th>
<th>ESTIMATED NUMBER OF PEOPLE AFFECTED BY DIABETES IN 2000 (MILLIONS)</th>
<th>ESTIMATED NUMBER OF PEOPLE AFFECTED BY DIABETES IN 2030 (MILLIONS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEVELOPING COUNTIES</td>
<td>DEVELOPED COUNTRIES</td>
</tr>
<tr>
<td>20-44</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>45-64</td>
<td>60</td>
<td>24</td>
</tr>
<tr>
<td>65+</td>
<td>28</td>
<td>26</td>
</tr>
</tbody>
</table>

(Adapted from Green et al., 2004)

In contrast to what was identified in developed countries, the most prevalent age group that was evident in developing countries was the 45-64 year age group. Comparing the global prevalence trends identified in Table 2.8 to the findings of Mbanya and Ramiaya (2006), it was also found that DM was most prevalent in the 45-64 years age group, in developing countries, according to Mbanya and Ramiaya (2006).

2.2.2 Ethnicity

In the United States of America (USA), type 2 DM occurs most commonly amongst people of Indian, Japanese and Mexican origin (Bhattacharyya, 2001). In the United Kingdom (UK), people of Asian origin are most frequently affected (Bhattacharyya, 2001). This would appear to be similar in SA, where the prevalence of DM in the Indian community in Durban in 1994, was found to be 13% (Rheeder, 2006). Furthermore, in 2006, Mbanya and Ramiya reported the
highest prevalence of DM in SA to be amongst people of Indian origin, suggesting that 12-13% of the Indian community in SA had diabetes.

The other ethnic groups that were reported to be mostly affected were Africans, followed by Caucasians (Mbanya & Ramia, 2006). Charlton, Levitt and Lombard (1997) found the prevalence to be 28.7% in an elderly coloured community in Cape Town. Ethnicity was considered to be one of the other major risk factors for DM in Africa (Mbanya & Ramia, 2006).

### 2.2.3 Gender

Tables 2.9 and 2.10 compare the estimated prevalence of DM, according to gender in SA and globally, respectively.

**Table 2.9: Estimated prevalence of diabetes mellitus in South Africa (in 2003) according to gender**

<table>
<thead>
<tr>
<th>Population (thousands)</th>
<th>DM Prevalence (%)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 741</td>
<td>3.4</td>
<td>322.7</td>
<td>518.5</td>
<td>841.2</td>
</tr>
</tbody>
</table>

(Adapted from Mbanya & Ramia, 2006)

**Table 2.10: Estimated global diabetes prevalence percentages, by age and gender, during 2000**

<table>
<thead>
<tr>
<th>AGE GROUP (YEARS)</th>
<th>FEMALE (%)</th>
<th>MALE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-29</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>45-49</td>
<td>5.6</td>
<td>5.8</td>
</tr>
<tr>
<td>65-70</td>
<td>12.2</td>
<td>12.0</td>
</tr>
<tr>
<td>75-79</td>
<td>14.0</td>
<td>13.0</td>
</tr>
</tbody>
</table>

(Adapted from Green et al., 2004)
From the data presented in Table 2.10, the global prevalence of diabetes for males and females was considered to be similar. In contrast to the findings of Mbanya and Ramiaya (2006), Green et al., (2004) found that DM was more prevalent in males under the age of 60 years, and women older than 65 years of age.

Bhattacharyya (2001) found that in the USA, females were more frequently diagnosed with type 2 DM than their male counterparts. Conversely, in the UK, it was evident that males were more commonly affected. This is also the case in South Africa where DM is considered to be more prevalent amongst males (Rheeder, 2006).

### 2.3 DEATH STATISTICS IN SOUTH AFRICA AND DIABETES MELLITUS

According to Statistics South Africa (2008), DM was ranked as the sixth leading cause of death due to natural causes during 2007 and 2008. Of the 603 094 deaths recorded in South Africa in 2007, 20 198 (3,3%) deaths were due to DM (Statistics South Africa, 2008). In 2008, of the 592 073 recorded deaths, 19 558 (3,3%) were due to DM (Statistics South Africa, 2008).

Furthermore, for the age group 50-64 years, DM was ranked as the second most prominent cause of death, responsible for 6 413 (6,0%) deaths out of a total of 106 046 reported deaths. In the age group, 65 years and plus, DM was ranked as the third most common cause of death, responsible for 10 413 (7,1%) recorded deaths. It is noteworthy to mention that for categories under the age of 50 years DM was not ranked amongst the ten most prominent causes of natural death in South Africa (Statistics South Africa, 2008).

As previously mentioned, in 2008, the total number of reported deaths due to DM was 19 558. Insulin-dependent DM, accounted for 1,1% (208 deaths) of these, whereas non-insulin-dependent DM accounted for 5,1% (1 005 deaths) of them. However, for the remaining 93,8% of the deaths (n = 19558) due to DM, the type of diabetes was unspecified.
2.4 OVERVIEW OF THE AETIOLOGY OF TYPE 2 DIABETES MELLITUS

Aetiology is defined as “the cause of a specific disease” (Martin, 2007). Insulin resistance and an insufficient insulin secretion response are considered to be the causes of type 2 DM (Bhattacharyya, 2001). However, the specific aetiologies of insulin resistance and secretion in type 2 DM are relatively unclear (Mbanya & Ramiaya, 2006).

Insulin resistance is defined as a “diminution in the response of the body's tissues to insulin, so that higher concentrations of serum insulin are required to maintain normal circulating glucose levels” (Martin, 2007).

In a normal individual, after food is digested, it is released into the blood stream in the form of amino acids, glucose and fatty acids (Dale, Moore, Rang & Ritter, 2003). The abovementioned breakdown products stimulate the pancreatic beta (β) cells to release insulin (Dale et al., 2003). The latter is released at different rates, depending on the stimuli; the most common one being the concentration of glucose (Karam & Nolte, 2006). Both the rate at which blood glucose changes and the total concentration of glucose play a role in the β cells’ response (Dale et al., 2003).

Insulin is normally released at a stable basal rate and additionally, according to blood glucose changes (Dale et al., 2003). The stable basal rate is due to stored insulin that is being released; whereas a delayed rate is due to the continuous release of stored insulin, as well as synthesis (Dale et al., 2003). In a DM patient, these responses are compromised and thus, contribute to the decreased β cell function. This is because the cells in the liver, skeletal muscle and adipose/fat tissue become less sensitive to insulin and ultimately become insulin resistant (Isley et al., 2008; IDF, 2011c). When insulin resistance occurs, glucose can no longer be absorbed in the cells, since insulin is the hormone that enables glucose absorption (IDF, 2011c). Consequently, the glucose molecules remain in the blood stream, which prompts the pancreas to produce more insulin in order to absorb the glucose molecules (IDF, 2011c). The constant demand for more insulin production eventually puts a lot of strain on
the β cells of the pancreas and eventually leads to their decreased functioning (IDF, 2011c). When the β cells are no longer able to produce insulin, the person becomes hyperglycaemic characterised by an increased plasma glucose level (IDF, 2011c).

At this stage, the patient is diagnosed with type 2 DM (IDF, 2011c). Bartels, Bradberry, Cerveny, Cziraky, Hawkins and Talbert (2002) described decreased pancreatic β-cell function as one of the main features of type 2 DM, and the progression of the disease is related to the deteriorating β-cell function.

Besides the abovementioned primary aetiologies, DM may also be secondary to a disease or drug. Drugs may cause DM in genetically-predisposed patients (Bhattacharyya, 2001). Tables 2.11 and 2.12 summarise some of the disease-related and drug-related origins of DM, respectively.
### Table 2.11: Disease-related origin of diabetes mellitus

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine disease</strong></td>
<td></td>
</tr>
<tr>
<td>Acromegaly</td>
<td>The main characteristics of acromegaly are: increased levels of growth hormone and insulin-like growth factor 1. Furthermore, the disease is linked to cardiovascular, respiratory, endocrine, metabolic and compression symptoms (Both, Cordes, Omran, Reisch &amp; Wuster, 2010).</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>It occurs as a result of a “functional adrenocorticotropic hormone-producing adenoma of the anterior pituitary gland” (Ciric, Couldwell, Delashaw, Fleseriu &amp; Liu, 2007). Cushing’s syndrome may also be caused by other tumours or hyperplasia of the adrenal gland. The constant presence of excessive glucocorticoids is the main trait of this endocrine disease (Chrousos, 2006).</td>
</tr>
<tr>
<td><strong>Genetic syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>Down’s syndrome</td>
<td>Cano-Pérez, Cerda-Esteva, Chillaron-Jordan, Corretger, Flores-Le-Roux &amp; Goday-Arno, (2009) described Down’s Syndrome as being the most frequently occurring chromosomal disorder where there is a deficiency in mental skills. Three copies of chromosome 21 in each body cell cause this chromosomal disorder. There are normally two copies of chromosome 21 (Potter, 2008).</td>
</tr>
<tr>
<td>Turner’s syndrome</td>
<td>Turner’s syndrome is a common chromosomal disorder in females where the X-chromosome is completely or partially missing (monosomy). This monosomy may occur “with or without cell line mosaicism” (Gawlik &amp; Malecka-Tendera, 2008). There are usually two X-chromosomes (Martin, 2007). The foremost clinical characteristics are: the short height of the females and failure of the ovaries to develop (Gawlik &amp; Malecka-Tendera, 2008).</td>
</tr>
<tr>
<td>Klinefelter’s syndrome</td>
<td>Klinefelter’s syndrome affects “sexual differentiation in men with two or more chromosomes” and can manifest at any stage in life. The principal feature of this syndrome is that the level of testosterone is usually half of the normal level (Brenner, De Morentin &amp; Dodiuk-Gad, 2004).</td>
</tr>
</tbody>
</table>

(Adapted from Bhattacharyya, 2001)
### Table 2.12: Drug-related origin of diabetes mellitus

<table>
<thead>
<tr>
<th><strong>DRUG</strong></th>
<th><strong>PHARMACOLOGICAL CLASS</strong></th>
<th><strong>MECHANISM(S) OF ACTION</strong></th>
</tr>
</thead>
</table>
| **Alpha interferon** | Immunostimulants (Rossiter, 2009) | Alpha interferon binds to specific receptors on the cell membrane, which induces intracellular signals, that do the following:  
• prevent the following viral processes: penetration, translation, transcription, protein processing, maturation and release;  
• enhance the expression of major histocompatibility complex antigens;  
• increase the phagocytic activity of macrophages; and  
• increase the proliferation and survival of cytotoxic T cells (Safrin, 2006). |
| **Beta-agonists** | Sympathomimetics                | β-agonists bind to and activate either β₁ or β₂ adrenoceptors or both, which activates adenylyl cyclase and increases the conversion of adenosine triphosphate into cAMP. In the liver, the activation of β adrenoceptors results in an increased synthesis of cAMP, which consequently causes the activation of glycogen phosphorylase (Hoffman, 2006). |
| **Diazoxide**     | Vasodilators                    | As a vasodilator, diazoxide relaxes the smooth muscle of arterioles which consequently results in a decrease in the systemic vascular resistance. The fore-mentioned effects result in compensatory mechanisms involving baroreceptors, the sympathetic nervous system, rennin, angiotensin and aldosterone. Insulin release from the pancreas is inhibited by diazoxide (Benowitz, 2006). |
| **Glucocorticoids** | Corticosteroids for systemic use | Once the glucocorticoids have entered the cell, they bind to intracellular receptors in the cytoplasm. After glucocorticoids bind to the specific receptors, dimers formation takes place. The dimers then relocate to the nucleus where binding occurs in the deoxyribonucleic acid (DNA). The initiation or the prevention of genes then occurs (Dale et al., 2003). Activation of these receptors regulates the transcription of genes. Furthermore, these receptors are responsible for sex hormones and thyroid hormones. |
Table 2.12: Drug-related origin of Diabetes Mellitus (continued)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PHARMACOLOGICAL CLASS</th>
<th>MECHANISM(S) OF ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinic acid (Niacin)</td>
<td>Vitamins</td>
<td>The secretion of very-low-density-lipoproteins (VLDL) is inhibited by niacin. Consecutively, the production of low-density-lipoproteins (LDL) is also reduced. Furthermore, there is a reduction in triglyceride levels as a result of an increase in the clearance of VLDL. Niacin is also responsible for the inhibition of adipose tissue. There is a possible decrease in the transfer of free fatty acids to the liver (Kane &amp; Malloy, 2006).</td>
</tr>
</tbody>
</table>
| Thiazide diuretics    | Diuretics             | Thiazide diuretics block the Na⁺/Cl⁻ transporter; thus inhibiting the reabsorption of sodium chloride from the epithelial cells of the distal convoluted tubule. Hyperglycaemia may occur with the use of thiazide diuretics, as a result of the following:  
  • decreased insulin release from the pancreas, and  
  • a reduction in the use of glucose in tissues (Ives, 2006). |

(Adapted from Bhattacharyya, 2001)
Figure 2.1 summarises the possible aetiologies of type 2 DM. Diabetes mellitus is directly or indirectly caused by genetic factors and/or environmental factors. These factors can lead to obesity, which predispose a person to the development of DM. This may be because of the relative insulin deficiency and/or insulin resistance that have been linked to obesity.

![Diagram showing possible causes of type 2 diabetes mellitus]

Figure 2.1: Possible causes of type 2 diabetes mellitus
(Adapted from Bhattacharyya, 2001)

Irrespective of the possible causes of type 2 DM, the clinical symptoms of this non-transmittable disease remain typical. These clinical symptoms eventually link to the clinical findings for the diagnosis of type 2 DM. Section 2.5 describes of the clinical findings leading to the diagnosis of DM.

2.5 CLINICAL FINDINGS FOR THE DIAGNOSIS OF DIABETES MELLITUS

Blood and urine glucose levels are the primary clinical factors used in the diagnosis of DM. Although DM may also be diagnosed from diabetes-associated complications, it has been observed that type 2 DM patients may not present with any symptoms, until many years after onset (Mbanya & Ramiaya,
2006). These symptoms include polyuria and polydipsia, in addition to the clinical findings for the diagnosis of type 2 DM (Bhattacharyya, 2001).

According to the SEMDSA guidelines (2009), the diagnosis of DM is based upon the following criteria:

• In the presence of symptoms of diabetes:
  ➢ random plasma glucose > 11.1 mmol/l, or
  ➢ fasting plasma glucose (FPG) > 7.0 mmol/l, or
  ➢ 2 hour plasma glucose (2 PG) > 11.1 mmol/l during oral glucose tolerance test (OGTT).

• In the absence of symptoms of diabetes:
  ➢ FPG should be performed on two separate days or an OGTT should be conducted.
  ➢ An OGTT is a test performed for the diagnosis and screening of DM and pre-DM. The requirements prior to performing this test are for the patient to fast overnight and not to take any medications or smoke. However, the patient may drink water. The patient is given 75 grams of glucose orally; and the plasma glucose levels are measured at the time that the glucose is given and 2 hours later. The glucose solution should be consumed within 5 minutes or less and the concentration of the glucose solution should not exceed 25g/100ml (Schatz & Winter, 2003).
  ➢ During an OGTT, the ability of a person’s cell uptake and metabolism of glucose, are measured. The levels of glucose in the blood and urine are monitored once the oral dose of glucose has been given. If the test shows that the person’s blood glucose rises and stays above the normal range, it is an indication that the person’s insulin secretion is insufficient to cope with the absorbed glucose (Handford & Nowak, 2004).
2.6 RISK FACTORS

There are risk factors which predispose individuals to the development of type 2 DM. The following section discusses these risks. Patients at risk of developing type 2 DM may display no symptoms; however, they may have impaired glucose tolerance (IGT), which is defined as “a blood glucose level higher than normal, but less than that required for diagnosis of DM” (Bhattacharyya, 2001: 6). Blood glucose tests are used to confirm IGT (Bhattacharyya, 2001) (Refer to section 2.5 for blood glucose levels).

Predisposing risk factors for DM may be classified into two main categories, namely: modifiable and non-modifiable. The modifiable risk factors include the lifestyle, environmental and medical factors. A genetic predisposition is a major non-modifiable risk factor for type 2 DM (Bhattacharyya, 2001).

A lack of physical exercise and the consumption of rich foods (refined carbohydrate and fatty foods) may contribute to the development of type 2 DM. A lack of physical exercise can lead to obesity, which is considered to precipitate type 2 DM (Bhattacharyya, 2001). Chehade and Mooradian (2000) suggest that central obesity is one of the major risk factors associated with the development of DM. Furthermore, Rheeder (2006) argued that the increased global prevalence of obesity is linked to the increased prevalence of DM. Mbanya and Ramiaya (2006) identified a link between a lack of exercise, obesity and DM. Additionally, these researchers debated whether the lack of physical activity was linked to the sedentary lifestyle associated with urbanisation. In particular, in Sub-Saharan Africa, a lack of exercise is considered to be a significant risk factor for DM (Mbanya & Ramiaya, 2006).

The human and financial costs associated with DM, are considered to be high. Alberti, Shaw and Zimmet (2001) reported that both developing and developed countries are facing considerable healthcare problems as a result of the increased prevalence of DM around the globe. The healthcare problems, that Alberti et al., (2001) described, include obesity, hypertension (HT) and dyslipidaemia.
2.7 TYPE 2 DIABETES MELLITUS AND COMORBID DISEASE STATES

Statistics South Africa (2007) reported that amongst 21 915 deaths that were attributable to DM, 53.6% were also due to cardiovascular disease; 36.8% due to hypertensive disease; 14.6% due to stroke; and 9.9% due to ischaemic heart disease.

Patients who suffer from type 2 DM are often also diagnosed with hypertension and dyslipidaemia. This collection of comorbid disease states is termed insulin resistance syndrome or metabolic syndrome (Isley et al., 2008). The following section describes the metabolic syndrome. Sections 2.7.2-2.7.4 provide a brief overview of hypertension, dyslipidaemia and coronary artery disease, respectively.

2.7.1 Metabolic Syndrome

Metabolic syndrome, which is also known as Syndrome X and most recently termed “Insulin Resistance Syndrome”, is characterised by the presence of type 2 DM or glucose intolerance, together with a collection of cardiovascular risk factors, including central obesity, hypertension, dyslipidaemia and atherosclerotic heart disease (Alberti et al., 2001; Bhattacharyya, 2001; Chisholm & Shaw, 2003). In Syndrome X, there is a combination of hyperinsulinaemia and insulin resistance, which affect the other comorbid disease states.

The new IDF (2011b) definition of the metabolic syndrome is characterised by the presence of central obesity. IDF (2011b) defines central obesity as a waist circumference of greater than or equal to:

- ninety-four centimetres (cm) for European men,
- ninety cm for Chinese and South Asian men, or
- eighty cm for Chinese, European and South Asian women.
Waist circumference for males and females from Ethnic South and Central America; Sub-Saharan Africa; and the Eastern Mediterranean and Middle East, must be recorded with reference to the European males and females, since there are insufficient data for these ethnic groups (IDF, 2011b). It is important to understand that waist circumference must be compared to the ethnic group of the patient and not to the country of residence of the patient (IDF, 2011b).

In addition to central obesity, two of the following factors need to be present to determine whether a patient has metabolic syndrome or not:

- an increased level of triglycerides (TG) \( \geq 1.7 \text{ mmol/l} \) or therapy for the increased TG level;
- a decreased level of high-density-lipoproteins (HDL) level \(< 1.03 \text{ mmol/l in men and } < 1.29 \text{ mmol/l in women}\) or therapy for the reduced HDL level;
- an elevated blood pressure (BP) \([\text{systolic BP } \geq 130 \text{ mmHg or diastolic } \geq 85 \text{ mmHg}]\) or treatment for increased BP; and
- an elevated fasting plasma glucose level (FPG) \( \geq 5.6 \text{ mmol/l} \) or a patient already diagnosed with type 2 DM.

Central obesity and insulin resistance are considered to be the major contributing causes of the metabolic syndrome in patients (IDF, 2011b).

According to Pogach (2009), comorbid disease states can be considered as possible contraindications for the use of insulin or oral hypoglycaemic agents in particular patients. The latter would either have modified metabolism, appetite, weakness or cognitive function.

Type 2 diabetics are at risk of developing complications because of Syndrome X (Isley et al., 2008). Furthermore, Syndrome X is considered to pose a greater cardiovascular risk over the addition of the risks associated with each disease state involved in the metabolic syndrome (IDF, 2011c).
2.7.2 Hypertension

Hypertension is diagnosed when a patient’s BP is found to be elevated when measured on numerous occasions (Benowitz, 2006). In HT, there is an increased arterial blood pressure and the values of systolic BP and diastolic BP are higher than the normal values (Saseen and Maclaughlin, 2008). The normal systolic BP is $< 120\text{mmHg}$ (Age $\geq 18$ years) and the normal diastolic BP is $< 80\text{mmHg}$ (Age $\geq 18$ years) (Maclaughlin & Saseen, 2008).

Amongst all cardiovascular disease states, HT is considered to be the most common one (Benowitz, 2006). If HT is left untreated, it causes blood vessel damage and eventually results in failure of the kidneys, coronary disease, heart failure and stroke (Benowitz, 2006).

With regards to type 2 DM and HT, it has been reported that HT is often present as a comorbid disease state in patients with DM, affecting about 20-60% of DM patients (Dobesh, 2006). Type 2 DM patients who also suffer from HT are more likely to suffer from a cardiovascular disease (CVD). It has been reported that 75% of diabetic cardiovascular complications occur in patients suffering from these two diseases (Dobesh, 2006). Some of the diabetic cardiovascular complications are peripheral vascular disease and stroke (Dobesh, 2006).

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II-receptor blockers (ARB’s) are the agents of choice for the first line treatment of HT in the presence of type 2 DM in patients (Bakris et al., 2003; K/DOQI, 2004; ADA, 2005). Dobesh (2006) reported that certain beta-blockers are preferred as add-on therapy for the management of HT in patients with DM, since they have glycaemic and metabolic effects. ADA (2005) recommended the use of calcium-channel blockers, beta-blockers or diuretics for blood pressure control in hypertensive diabetic patients with either albuminuria or nephropathy.
2.7.3 Dyslipidaemia

Dyslipidaemia is also known as either hyperlipidaemia or hypercholesterolaemia. In dyslipidaemia, there is a high level of TG observed, as well as a high level of LDL (Talbert, 2008). A low level of HDL is also evident as part of dyslipidaemia (Talbert, 2008). Moreover, the total cholesterol level is higher than the normal value of less than 5mmol/L (Talbert, 2008).

Dyslipidaemia is considered to be of one of the major contributing factors for CVD in DM patients (Mooradian, 2009). One of the reasons for this could be because dyslipidaemia eventually results in atherosclerosis. Diabetic patients are at a high risk of developing atherosclerosis because of the changes in their plasma lipid levels (Mooradian, 2009). Dyslipidaemia can be of different origins and diabetic patients can develop any kind of dyslipidaemia. However, dyslipidaemia due to insulin resistance and insulin deficiency remain the most common types of dyslipidaemias in DM patients (Mooradian, 2009). A high plasma TG concentration, low HDL and high LDL cholesterol concentrations are the identifiable characteristics of dyslipidaemia due to insulin resistance and deficiency (Mooradian, 2009).

Mooradian (2009) reported the following findings of the Framingham Heart Study:

- an increased total plasma cholesterol level was found in 13% of males and 24% of females who had suffered from DM, as compared to 14% of males and 21% of females who did not suffer from DM;
- an increased LDL cholesterol level was present in 9% of males and 15% of females affected by DM; relative to their non-diabetic counterparts (11% of males; 16% of females) (no significant difference);
- a high TG plasma level was noticeable in 19% of diabetic males and 17% of diabetic females when compared to the non-diabetic males and females: 9% and 8%, respectively (significant difference); and
a low HDL cholesterol level was found in 21% of diabetic males and 25% of diabetic females, as opposed to 12% of males and 10% of females who were not diabetic.

In conclusion, both diabetic males and females were found to exhibit increased triglyceride and LDL levels as well as a lower HDL cholesterol level, when compared to non-diabetic patients (Mooradian, 2009). The increased risk of CVD in patients suffering from DM may be attributable to the high TG level and low HDL cholesterol level (Mooradian, 2009). Furthermore, it is reported that the abovementioned risk factors, as well as an increased LDL cholesterol level, could contribute to the early development of atherosclerosis in DM patients (Mooradian, 2009).

In terms of the management of dyslipidaemia and DM, there are some key recommendations that need to be made. These include lifestyle modifications, in terms of caloric restriction in the diet and an increased level of physical exercise (Mooradian, 2009). It is also important for a diabetic patient to aim for glycaemic control, as this may contribute to the management of the accompanying dyslipidaemia (Mooradian, 2009). However, it has been reported that achieving proper glycaemic control does not always assist in decreasing abnormal plasma lipid levels (Mooradian, 2009).

Lastly, DM patients who are considered to be high risk patients for CVD should be initiated on statin therapy, regardless of their plasma cholesterol levels (Mooradian, 2009). Some DM patients eventually require other medications to manage dyslipidaemia, due to the complex nature of the co-existing diseases (Mooradian, 2009).

2.7.4 Coronary Artery Disease

Coronary artery disease (CAD) is defined as the “atherosclerosis of the coronary arteries, which may cause angina pectoris and lead to myocardial infarction” (Martin, 2007). Avogaro, Negut, Ramondo, Scognamiglio and Tiengo (2006) described one of the findings of the Framingham study, namely that
diabetes is one of the major risk factors in the development of a CAD. In conjunction with DM, CAD was considered to be a worldwide health issue (Berry, Tardif & Bourassa, 2007).

It has been reported that 55% of DM patients suffered from CAD, as compared to 2-4% of CAD found in the general population (Berry et al., 2007). In 2006, Avogaro et al. reported that 75% of diabetic patients had died as a result of CAD. When comparing diabetic with non-diabetic patients, it was found that diabetic patients were more likely to develop heart failure, myocardial infarction and death due to cardiac problems, relative to their non-diabetic counterparts (Avogaro et al., 2006). Classical symptoms of CAD are often not recognised at first, as they are not evident. As a result, CAD is often diagnosed in its progressive stage (Avogaro et al., 2006).

Patients who suffer from both DM and CAD are encouraged to perform aerobic exercise, as well as eating a balanced diet in order to lose weight (Berry et al., 2007). This is deemed a noteworthy non-pharmacological management plan, since these patients are highly likely to develop a CAD (Berry et al., 2007). In terms of the pharmacological management of CAD and DM, the prophylactic use of aspirin (an antiplatelet) is encouraged (Berry et al., 2007). Patients who require aspirin prophylaxis are those who are aged forty years or older, with other risk factors, with or without the presence of DM, for ten years (Berry et al., 2007). If a patient is allergic to aspirin, clopidogrel should be used as an alternative antiplatelet agent.

In conclusion, DM, together with all of the abovementioned comorbid disease states, must be managed adequately to achieve therapeutic outcomes (Mooradian, 2009).

### 2.8 MANAGEMENT OF TYPE 2 DIABETES MELLITUS

In order to ensure effective management of DM, the goals of therapy need to be established. The primary goals of therapy, as identified by Isley et al. (2008), include:
• improving the quality of life of diabetic patients;
• achieving near to normal blood glucose levels – i.e. optimal glycaemic control; and
• decreasing the incidence of death amongst diabetic patients.

Additional goals of therapy, as described in the Standard Treatment Guidelines and Essential Medicines List of South Africa (National Department of Health, 2008), include the following:
• prevention of hyper- and hypo-glycaemic coma, which are acute complications of type 2 DM;
• management of chronic comorbid disease states that are prevalent in type 2 DM; and
• prevention of diabetic complications.

In order to achieve the abovementioned goals of therapy, a management plan for diabetic patients should be developed and implemented. The management of type 2 DM consists of both pharmacological and non-pharmacological treatment. This combination aims at achieving identified glycaemic targets in diabetic patients. In order to manage this chronic condition, many countries have developed management guidelines. Table 2.13 outlines the glycaemic targets, as depicted by the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) (2009):

<table>
<thead>
<tr>
<th>GLYCOSYLATED HAEMOGLOBIN LEVEL (HBA1C)</th>
<th>PRE-PRANDIAL PLASMA GLUCOSE LEVEL (MMOL/L)</th>
<th>POSTPRANDIAL PLASMA GLUCOSE LEVEL (MMOL/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7%</td>
<td>4-7</td>
<td>5-8</td>
</tr>
</tbody>
</table>

(Adapted from SEMDSA, 2009)

Glycaemic targets are achieved with the use of pharmacological agents. On the other hand, the use of non-pharmacological approaches contributes to the
prevention of macrovascular complications that are associated with type 2 DM.
For the prevention or delay of diabetes-related complications, the ADA and the American Association of Clinical Endocrinologists have issued guidelines that place emphasis on the importance of achieving and maintaining glycaemic levels to as close as possible to the normal non-diabetic level (American Association of Clinical Endocrinologists Diabetes Mellitus Clinical Practice Guidelines Task Force, 2007; ADA, 2009). It is noteworthy to mention that there are acute complications associated with DM. The following acute diabetic metabolic complications were found to be most prevalent in Sub-Saharan African diabetic patients:
- diabetic ketoacidosis;
- hyperosmolar non-ketotic coma; and
- hypoglycaemia (Mbanya & Ramiaya, 2006).

Mbanya and Ramiaya (2006) stated that diabetic ketoacidosis is strongly linked to a high death rate in developing countries. Furthermore, it is seen to occur frequently as a diabetic emergency (Mbanya & Ramiaya, 2006). Other targets described in the SEMDSA guidelines (2009) include: body mass index (BMI), waist, lipid and blood pressure targets. These targets are listed in Table 2.14.

Table 2.14: Other targets to be achieved by the diabetes mellitus patient

<table>
<thead>
<tr>
<th>TARGET</th>
<th>TARGET LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Less than 25kg/m²</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>&lt; 94 cm in men</td>
</tr>
<tr>
<td></td>
<td>&lt; 90 cm in men of South Asian origin</td>
</tr>
<tr>
<td></td>
<td>&lt; 80 cm in women</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Systolic Pressure: &lt; 130 mmHg</td>
</tr>
<tr>
<td></td>
<td>Diastolic Pressure: &lt; 80 mmHg</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>&lt; 4.5 mmol/l</td>
</tr>
<tr>
<td>Low-density-lipoprotein (LDL) cholesterol</td>
<td>&lt; 2.5 mmol/l</td>
</tr>
<tr>
<td></td>
<td>&lt; 1.8 mmol/l if patient suffers from cardiovascular, cerebrovascular, or peripheral vascular disease</td>
</tr>
<tr>
<td>High-density-lipoprotein (HDL) cholesterol</td>
<td>&gt; 1.0 mmol/l in men</td>
</tr>
<tr>
<td></td>
<td>&gt; 1.2 mmol/l in women</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt; 1.7 mmol/l</td>
</tr>
</tbody>
</table>

(Adapted from SEMDSA, 2009)
The following sections (2.8.1 - 2.8.2) discuss the various non-pharmacological and pharmacological treatments (respectively) that may be implemented in the management of type 2 DM.

### 2.8.1 Non-pharmacological management approaches

The non-pharmacological management of type 2 DM entails dietary changes and an exercise programme. These lifestyle modifications should be tailored to the patient’s lifestyle. Furthermore, these lifestyle changes should be financially feasible and should not infringe on the patient’s culture and beliefs (Isley et al., 2008). The patient should also be advised on smoking cessation and on moderate alcohol use.

#### 2.8.1.1 Dietary Changes

The recommended dietary changes include: eating balanced meals; which contain moderate amounts of carbohydrates; and minimal saturated fats (Isley et al., 2008). These dietary changes are aimed at limiting the amount of calories being consumed; thus promoting weight loss (Isley et al., 2008).

However, the glycaemic index (GI) is the most commonly known physiological classification of food (Brand-Miller, Foster-Powell & Holt, 2002). According to the GI, food is categorised based on its postprandial glycaemic effect (Brand-Miller et al., 2002). When comparing foods per gram of carbohydrate, a high peak is observed in the postprandial blood glucose level with foods with a high GI, as well as a higher total blood glucose response (Brand-Miller et al., 2002). This occurs during the first two hours after consuming food (Brand-Miller et al., 2002). This is observed in comparison with foods with a low GI, where the opposite glucose response occurs. Brand-Miller and colleagues (2002) reported that the GI is a more suitable nutritional model than carbohydrates being chemically classified. Previously, carbohydrates were categorised according to simple or complex, and sugar or starch (Brand-Miller et al., 2002).
Diet remains a debatable matter for diabetic patients, specifically pertaining to the GI foods (ADA, 2002). According to the ADA (2002), a low-GI diet could result in a decreased postprandial hyperglycaemia. However, the ADA (2002) emphasises that the sole use of low-GI diet cannot be used as the main management plan due to a lack of supporting evidence. On the contrary, the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes (2000) suggested substituting a low-GI diet for a high-GI diet.

In 2003, Brand-Miller *et al.* carried out a meta-analysis of randomised controlled trials. This meta-analysis compared the use of low- and high-GI diets in the management of type 1 and 2 diabetes. It was concluded that a low-GI diet, compared to a normal or a high-GI diet, contributed towards better glycaemic control. Additionally, it was suggested that the benefit of a low-GI diet is significant and similar to the advantages of using new pharmacological treatments (Brand-Miller *et al.*, 2003).

### 2.8.1.2 Exercise

According to the SEMDSA guidelines (2009), weight loss is recommended for overweight and obese diabetic patients. Weight loss can be achieved with regular exercise. The recommended exercise plan is “30-45 minutes of moderate-intensity aerobic physical activity” (SEMDSA, 2009: 1), at least three times a week. This exercising schedule can assist in achieving and maintaining an ideal BMI, which lies in the range of 18.5 - 25kg/m². The pace of exercise should be increased incrementally and a realistic weight loss goal should be established. Some examples of moderate-intensity aerobic physical activities, include:

- brisk walking;
- badminton;
- basketball;
- cycling;
- dancing;
- swimming;
• table tennis; and
• volley ball (Bauman et al., 2007).

In addition to lifestyle modifications, the SEMDSA guidelines provide an in-depth approach to the glycaemic management of type 2 DM, which will be discussed in section 2.8.3.

### 2.8.2 Pharmacological treatments

The pharmacological management of type 2 DM entails the use of oral hypoglycaemic agents and insulin; either as monotherapy, or in combination. The primary objective of pharmacological treatment(s) is to achieve adequate glycaemic control in the diabetic patient. Other aspects that are considered in the pharmacological management of type 2 DM are: costs implications, side-effect profiles of medications and how fast glycaemic control needs to be achieved. It has been suggested that the management of type 2 DM consists not only of glycaemic control, but also involves the consideration of cardiovascular risk factors (Chehade & Mooradian, 2000).

The oral hypoglycaemic agents are categorised according to their different mechanisms of action. Table 2.15 summarises the different types of oral hypoglycaemic agents currently used in South Africa, in terms of their mechanisms of action, trade names, dosage forms and strengths available.
Table 2.15: Various oral hypoglycaemic agents used in South Africa

<table>
<thead>
<tr>
<th>CLASS</th>
<th>MECHANISM/S OF ACTION</th>
<th>EXAMPLES</th>
<th>TRADE NAMES</th>
<th>DOSAGE FORMS</th>
<th>STRENGTHS AVAILABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Proposed mechanisms of action: Decrease gluconeogenesis in the kidney and liver; slow down glucose absorption from the gastrointestinal tract and increase the conversion of glucose to lactate by enterocytes; directly stimulate tissue glycolysis with an increase in glucose removal from blood; and reduce plasma glucagon levels. (Karam &amp; Nolte, 2006)</td>
<td>Metformin#</td>
<td>Accord Metformin®, Arrow Metformin®, Austell-Metformin®, Bigsens®, Glucophage®, Mylan-Metformin®, Metforal®, Metoreg®, Metphage®, Sandoz Metformin®</td>
<td>Tablets film-coated tablets</td>
<td>500mg 850mg</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Directly decrease lipolysis and increase fat synthesis; decrease blood glucose; improve lipid metabolism; and increase endothelial functions.</td>
<td>Pioglitazone</td>
<td>Actos®, Cipla-Pioglitazone®</td>
<td>Tablet</td>
<td>15mg 30mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rosiglitazone</td>
<td>Avandia®</td>
<td>Tablet</td>
<td>2mg 4mg</td>
</tr>
</tbody>
</table>
### Table 2.15: Various oral hypoglycaemic agents used in South Africa (continued)

<table>
<thead>
<tr>
<th>CLASS</th>
<th>MECHANISM/S OF ACTION</th>
<th>EXAMPLES</th>
<th>TRADE NAMES</th>
<th>DOSAGE FORMS</th>
<th>STRENGTHS AVAILABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas</td>
<td>Increase insulin release from the β cells of the pancreas; reduce serum glucagon levels; and close potassium channels in extrapancreatic tissues.</td>
<td>Glibenclamide#</td>
<td>Bio-Glibenclamide®, Daonil®, Diacare®, Glycomin®, Sandoz Glibenclamide®</td>
<td>Tablet</td>
<td>5mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gliclazide#</td>
<td>Adco-Glucomed®, Arrow Gliclazide®, Austell-Gliclazide®, Diaglucide®, Diamicron®, Glycron®, Glygard®, Mylan-Gliclazide®, Sandoz-Gliclazide®, Sandoz-Gliclazide®</td>
<td>Tablet Modified-release tablet</td>
<td>80mg, 40mg, 30mg</td>
</tr>
</tbody>
</table>

# Oral hypoglycaemic agents which form part of the South African Essential Medicines List (National Department of Health, 2008)
### Table 2.15: Various oral hypoglycaemic agents used in South Africa (continued)

<table>
<thead>
<tr>
<th>CLASS</th>
<th>MECHANISM OF ACTION</th>
<th>EXAMPLES</th>
<th>TRADE NAMES</th>
<th>DOSAGE FORMS</th>
<th>STRENGTHS AVAILABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas (continued)</td>
<td></td>
<td>Glimepiride</td>
<td>Amaryl®&lt;sup&gt;®&lt;/sup&gt;, Euglim&lt;sup&gt;®&lt;/sup&gt;, Glamaryl&lt;sup&gt;®&lt;/sup&gt;, Mylan-Glimepiride&lt;sup&gt;®&lt;/sup&gt;, Sandoz Glimepiride&lt;sup&gt;®&lt;/sup&gt;, Sulphonur&lt;sup&gt;®&lt;/sup&gt;, Zydus-Glimerpiride&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Tablet</td>
<td>1mg, 2mg, 4mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glipizide</td>
<td>Minidiab&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td>5mg</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Trigger release of insulin from β cells by binding to potassium channels.</td>
<td>Nateglinide</td>
<td>Starlix&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td>120mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repaglinide</td>
<td>NovoNorm&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td>0.5mg, 1mg, 2mg</td>
</tr>
<tr>
<td>Alpha Glucosidase Inhibitors</td>
<td>Reduce starch and disaccharide digestion and absorption from the gastrointestinal tract after a meal.</td>
<td>Acarbose</td>
<td>Glucobay&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td>50mg, 100mg</td>
</tr>
</tbody>
</table>

(Adapted from Karam & Nolte, 2006; Rossiter, 2009; Snyman, 2010)

# Oral hypoglycaemic agents which form part of the South African Essential Medicines List (National Department of Health, 2008)
The agents listed in Table 2.15 are often used in combination; as well as in conjunction with insulin, to reach glycaemic targets, that were described in Table 2.14. The pharmacological management of type 2 DM is usually complemented by non-pharmacological options so that the goals of therapy are attained. The different types of insulin used in the pharmacological management of type 2 DM will be discussed in section 2.9.

2.9 INSULIN USE IN TYPE 2 DIABETES MELLITUS PATIENTS

Insulin is “a small protein molecule” (Karam & Nolte, 2006), which consists of two chains, A and B, made up of a total of 51 amino acids. When glucose is ingested, the pancreatic β-cells secrete insulin, at concentrations greater than low basal levels. Once insulin is secreted, it subsequently affects its target cells by:

- encouraging fat and glucose storage; and
- influencing cell growth and metabolic functions of the liver, adipose and muscle tissues (Karam & Nolte, 2006).

2.9.1 Background on insulin

In 1921, at the University of Toronto, doctors Banting and Best, were successful in producing a pancreatic extract, which possessed anti-diabetic properties. This pancreatic extract was to be called ‘insulin’ at a later stage (Basavaraj, Bharath, Deveswaran, Furtado & Sindhu, 2011). On the 3rd May 1922, the discovery of insulin was officially announced at one of the meetings of the Association of American Physicians (Ainsberg & Cooper, 2010). At that particular gathering, a paper entitled “The Effect Produced on Diabetes by Extract of Pancreas” was presented. The authors of the paper were: Banting, Best, Collip, Campbell, Fletcher, Macleod and Noble (Ainsberg & Cooper, 2010). The aforementioned paper provided a description of all of the work that had been done with regards to the discovery of insulin (Ainsberg & Cooper, 2010).
Nordisk Insulin Laboratorium was founded in 1923, by Dr Krogh and Professor Hagedorn and it was the first manufacturing plant to produce Scandinavian insulin (Ainsberg & Cooper, 2010). In 1925, Novo Terapeutisk Laboratorium was established. The latter initiated the production of insulin and a special syringe for its injection (Ainsberg & Cooper, 2010).

Basavaraj et al. (2011) reported that Nordisk Insulin Laboratories’ researchers, Dr Hagedorn and Dr Norman, made the discovery of combining protamine, extracted from the sperm of American trout, with insulin. This discovery resulted in a prolonged effect of insulin (Ainsberg & Cooper, 2010; Basavaraj et al., 2011). The innovation led to a new, longer-acting insulin which was introduced in 1936 (Basavaraj et al., 2011).

A further discovery was the addition of zinc to the protamine insulin preparation, by Scott and Fisher at the University of Toronto (Basavaraj et al., 2011). The final insulin preparation had a slower action (Ainsberg & Cooper, 2010) and the zinc enhanced its stability (Basavaraj et al., 2011). In 1936, this led to the introduction of protamine zinc insulin (Ainsberg & Cooper, 2010; Basavaraj et al., 2011).

Neutral protamine Hagedorn, also known as NPH, was produced as the first crystalline protamine-isophane insulin (Basavaraj et al., 2011). This insulin was a formulation developed by Nordisk laboratories in 1946 (Basavaraj et al., 2011). Basavaraj et al. (2011) reported that NPH and fast-acting insulin produced a stable mixture.

It is to be noted that previously in 1948, beef and pork pancreas were used to produce insulin (Ainsberg & Cooper, 2010): 226.8 g of purified insulin was manufactured from 2540 kg of beef and pork pancreas (Ainsberg & Cooper, 2010). Patients self-injecting with this type of insulin eventually developed insulin resistance after a while (Ainsberg & Cooper, 2010). These patients later benefited from the introduction of sulphated insulin (Ainsberg & Cooper, 2010). Sulphated insulin was designed by a small research team at Connaught, in the late 1950’s to early 1960’s (Ainsberg & Cooper, 2010).
According to Basavaraj et al. (2011), lente insulin formulations were manufactured with different ratios of amorphous and crystalline zinc insulin, in the mid 1950’s.

Synthetic human insulin was manufactured by Genentech (a small biotechnology company) in 1978 (Ainsberg & Cooper, 2010; Basavaraj et al., 2011). Recombinant deoxyribonucleic acid (DNA) techniques were used in the manufacture of synthetic human insulin (Ainsberg & Cooper, 2010; Basavaraj et al., 2011). Eli Lilly was responsible for the development and testing of this specific insulin type (Ainsberg & Cooper, 2010). In 1982, the Food and Drug Administration (FDA) approved this insulin (Ainsberg & Cooper, 2010). In 1983, synthetic human insulin was sold as Humulin® (Ainsberg & Cooper, 2010).

The innovation of manufacturing insulin using recombinant DNA technology has ensured that there is a constant supply of insulin (Basavaraj et al., 2011). Furthermore, it has helped in terms of overcoming a few of the therapeutic limitations of the original insulin molecule (Basavaraj et al., 2011).

### 2.9.2 The United Kingdom Prospective Diabetes Study

The Diabetes Trial Unit (2011a) described the United Kingdom Prospective Diabetes Study (UKPDS) as “a landmark randomised, multicentre trial of glycaemic therapies in 5 102 patients with newly diagnosed type 2 diabetes”. The UKPDS was carried out from 1977 to 1997, i.e. over twenty years in twenty-three clinical sites in the UK (DTU, 2011a). The study’s conclusive findings were that complications resulting from type 2 DM, could be decreased with improved glycaemic control and/or blood pressure control (DTU, 2011a). These complications were considered as being unavoidable in the past (DTU, 2011a).

The findings of the UKPDS were as follows (DTU, 2011b):

- The use of a sulphonylurea or insulin therapy to reduce glucose exposure was found to decrease “any diabetes-related endpoint” risks by 12% and
microvascular disease by 25%. Decreasing glucose exposure resulted in to HbA1C 7.0%, compared to 7.9% over a median of 10.0 years. With regards to the reduction in the incidence of microvascular disease, there was a 16% decrease in myocardial infarction rates.

- Both sulphonylureas and insulin were found to increase the occurrence of hypoglycaemia and the development of weight gain. However, these did not impact negatively on the quality of life of the patients.
- Blood pressure that was well controlled with an ACE inhibitor or a beta-blocker was found to reduce micro and macrovascular diseases in 1 148 hypertensive patients. An improved blood pressure refers to a reading of 142/82 mmHg, relative to 152/87 mmHg over a median of 8.4 years.
- In terms of the financial implications, it was deduced that it was more cost-effective to reduce the complications of DM; when compared with the costs associated with the use of extra medications that may be required to treat the complications.

2.9.3 Insulin use

According to the UKPDS (1998b), the secretion of insulin in type 2 DM patients is a progressive defect. The study showed that newly diagnosed type 2 DM patients had a 50% insulin secretion deficiency; and after a period of six years, post-diagnosis, this value increased to 75% (UKPDS, 1998b). In the UKPDS Study, type 2 DM was managed in the conventional way with the use of oral hypoglycaemic agents, followed by the use of insulin. Many researchers have argued that most type 2 DM patients will eventually need the addition of insulin therapy to oral hypoglycaemic medications, so that glycaemic control may be achieved (De Witt & Hirsch, 2003; Grégoire, Moisan, Pérez, Sirois & Poirier, 2009; Pogach 2009). Furthermore, other studies have suggested that there is a significant improvement in the glycaemic control of type 2 DM, when insulin is added early to the oral therapy (Gerich, Riddle & Rosenstock, 2003; Riddle, 2004; Austin et al., 2006). This finding was also confirmed by UKPDS study, which suggested that if insulin therapy was added to oral therapy within the first six years of treatment, strict glycaemic control could be maintained (Burden, Cull, Holman, Paisey & Wright, 2002).
Despite the evidence supporting the positive benefits from the use of insulin in type 2 diabetics, it is often used as a last resort in the pharmacological management (as described in the abovementioned guidelines - refer to sections 2.7.3 and 2.7.4). Most often, insulin is used when oral hypoglycaemic agents are no longer effective (Hirsch, 2005). Conversely, Hirsch (2005) argued that the new concept for insulin therapy uses the HbA1c level to determine glycaemic control and to start insulin therapy if there has been an increased level of blood glucose. Additionally, Hirsch (2005) suggested that this could explain why insulin therapy is usually started later, as the β-cells have decreased progressively in functionality. Patients are more likely to be on insulin therapy, if they are receiving subspecialty care from endocrinologists (Pogach, 2009). According to Davidson (2005), insulin is required by type 2 DM patients, who are not being managed successfully on oral hypoglycaemic medications. In addition, Davidson (2005) stated that appropriate insulin use, together with patient concordance, is most likely to control type 2 DM patients effectively.

Mbanya and Ramiaya (2006) defined the use of insulin in Sub-Saharan Africa as being underutilised. It was further explained that a small number of type 2 diabetic patients required insulin when they were in a hyperglycaemic state. Bhattacharyya (2001) implied that type 2 diabetics may eventually need insulin in order to control hyperglycaemia, but they do not depend on the use of insulin in order to survive.

According to Hirsch (2005), there is no standard regimen yet for an insulin therapy in the strict management of type 2 DM. Patients are usually started on either a basal or a prandial insulin (Bastyr et al., 2000; Gerich et al., 2003). Having mentioned this though, basal and prandial insulin may be used in conjunction with each other. The concomitant administration of the basal and prandial insulins occurs if the HbA1c is greater than 10,0% at the time of insulin initiation; and if the patient was started on maximal doses of oral hypoglycaemic agents initially (Hirsch, 2005). The management of type 2 DM with insulin should be designed specifically for each patient, according to his/her individual needs (Chehade & Mooradian, 2000). However, Davidson (2005) argued that the initial insulin regimen that is commenced in a type 2 DM patient is not
important. It is further debated that the most important aspect of management is to increase insulin therapy until satisfactory results are obtained and to then maintain that regimen (Davidson, 2005). Exogenous insulin and insulin analogues are used in the last stages of the disease progress, when there is a decline in the ability to secrete insulin (Chehade & Mooradian, 2000).

### 2.9.4 Available insulin preparations

The main features which distinguish one insulin preparation from another include the following (Karam & Nolte, 2006):
- the sequence of the amino acids;
- the techniques which were used for the recombination of the insulin analogue;
- concentration;
- solubility; and
- pharmacokinetic properties, like the time of onset and the duration of insulin activity (Chehade & Mooradian, 2000).

There are different insulin preparations available on the market. These are outlined in Table 2.16, which provides examples of the various types of insulin preparations available on the South African market. It is noteworthy to mention that these insulin injections are administered subcutaneously. Some preparations are already pre-mixed, whereas others require the use of syringes and needles (Karam & Nolte, 2006).
Table 2.16: Types of insulin preparations available in SA

<table>
<thead>
<tr>
<th>INSULIN CATEGORY</th>
<th>GENERIC NAME</th>
<th>TRADE NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-fast acting / rapid-acting</td>
<td>insulin glulisine</td>
<td>Apidra®</td>
</tr>
<tr>
<td></td>
<td>insulin lispro</td>
<td>Humalog®</td>
</tr>
<tr>
<td></td>
<td>insulin aspart</td>
<td>NovoRapid®</td>
</tr>
<tr>
<td>Fast-acting</td>
<td>soluble insulin</td>
<td>Humulin R®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biosulin R®</td>
</tr>
<tr>
<td>Intermediate- to long-acting</td>
<td>isophane insulin</td>
<td>Humulin N®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biosulin N®</td>
</tr>
<tr>
<td></td>
<td>insulin glargine</td>
<td>Lantus®</td>
</tr>
<tr>
<td></td>
<td>insulin detemir</td>
<td>Levemir®</td>
</tr>
<tr>
<td></td>
<td>isophane insulin</td>
<td>Protaphane HM®</td>
</tr>
<tr>
<td>Biphasic</td>
<td>30% soluble, 70% isophane</td>
<td>Actraphane HM®</td>
</tr>
<tr>
<td></td>
<td>30% soluble, 70% isophane</td>
<td>Biosulin 30/70®</td>
</tr>
<tr>
<td></td>
<td>25% lispro, 75% lispro protamine</td>
<td>Humalog Mix25®</td>
</tr>
<tr>
<td></td>
<td>30% aspart, 70% protamine</td>
<td>NovoMix 30®</td>
</tr>
<tr>
<td></td>
<td>aspart</td>
<td></td>
</tr>
</tbody>
</table>

(Adapted from Rossiter, 2009 & Snyman, 2010)

2.9.4.1 Insulin Colour Code

With the intent of standardising insulin across the globe, the IDF (2011a) introduced insulin colour coding. Each category of insulin preparation, namely fast-acting insulin, regular and NPH insulin mixtures as well as long-acting insulin, has its own colour code on the product's label (IDF, 2011a). Each insulin preparation type has the same colour code, irrespective of the manufacturer; hence enhancing standardisation across the world (IDF, 2011a). For instance, brown is indicative of 30/70 insulin mixtures.

The objective of introducing insulin colour coding for the different insulin preparations - that are available on the market worldwide - is to facilitate insulin use in diabetic patients. By introducing the insulin colour codes, the IDF aimed at minimising misunderstandings and doubts regarding the purchase of insulin from a different supplier or overseas. At present, insulin colour codes are only available for human insulin preparations. There is currently a team working towards the development of insulin colour codes for insulin analogues too (IDF,
Table 2.17 outlines the various insulin preparations and their accompanying colour codes.

Table 2.17: Insulin Colour Codes

<table>
<thead>
<tr>
<th>PREPARATION TYPE</th>
<th>PRODUCT</th>
<th>COLOUR NAME</th>
<th>PANTONE COLOUR NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast acting insulin</td>
<td>Hoeschst Pump Insulin</td>
<td>Blue</td>
<td>072C</td>
</tr>
<tr>
<td></td>
<td>Regular</td>
<td>Yellow</td>
<td>123C</td>
</tr>
<tr>
<td></td>
<td>Regular Buffered</td>
<td>Red</td>
<td>185C</td>
</tr>
<tr>
<td>Insulin Mixtures</td>
<td>10/90</td>
<td>Blue-Green</td>
<td>328C</td>
</tr>
<tr>
<td>(Regular/NPH)</td>
<td>15/85</td>
<td>Olive</td>
<td>104C</td>
</tr>
<tr>
<td></td>
<td>20/80</td>
<td>Magenta</td>
<td>Magenta C</td>
</tr>
<tr>
<td></td>
<td>25/75</td>
<td>Turquoise</td>
<td>313C</td>
</tr>
<tr>
<td></td>
<td>30/70</td>
<td>Brown</td>
<td>471C</td>
</tr>
<tr>
<td></td>
<td>40/60</td>
<td>Violet</td>
<td>253C</td>
</tr>
<tr>
<td></td>
<td>50/50</td>
<td>Grey</td>
<td>445C</td>
</tr>
<tr>
<td>Long acting insulin</td>
<td>Lente</td>
<td>Turquoise</td>
<td>312C</td>
</tr>
<tr>
<td></td>
<td>NPH</td>
<td>Light Green</td>
<td>375C</td>
</tr>
<tr>
<td></td>
<td>Semilente</td>
<td>Light Blue</td>
<td>545C</td>
</tr>
<tr>
<td></td>
<td>Ultralente</td>
<td>Dark Green</td>
<td>363C</td>
</tr>
</tbody>
</table>

(Adapted from IDF, 2011a)

2.9.4.2 Pharmacokinetic properties of insulin preparations

Different insulin preparations are used as insulin therapy in order to mimic the normal physiological insulin response as closely as possible (IDF, 2005). As previously mentioned, the pharmacokinetic properties, namely the time of onset and the duration of insulin activity, distinguish one insulin preparation type from another (Karam & Nolte, 2006). Another pharmacokinetic property that differs from one insulin preparation to another is the time taken to peak (IDF, 2005). Table 2.18 depicts the different pharmacokinetic properties of the different insulin preparations available.
Either a short- or rapid-acting insulin preparation is used to mimic bolus insulin in the type 2 DM patient after consuming a meal (IDF, 2005). Basal insulin is replicated by the use of either an intermediate- or a long-acting insulin preparation (IDF, 2005). The different preparations are used according to their time of onset, as well as the duration of insulin activity. The pharmacokinetic properties will differ slightly in a patient from day to day; as well as from patient to patient (IDF, 2005).

Table 2.18: Pharmacokinetic properties of insulin preparations

<table>
<thead>
<tr>
<th>INSULIN PREPARATION (EXAMPLES)</th>
<th>TIME OF ONSET (HOURS)</th>
<th>TIME TAKEN TO PEAK (HOURS)</th>
<th>DURATION OF INSULIN ACTIVITY (HOURS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro Aspart</td>
<td>&lt; 0.25</td>
<td>0.75-2.5</td>
<td>3.5-4.5</td>
</tr>
<tr>
<td><strong>Short</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soluble Regular</td>
<td>0.5-1</td>
<td>2-4</td>
<td>6-8</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>1-2</td>
<td>6-12</td>
<td>18-24</td>
</tr>
<tr>
<td>Lente</td>
<td>1-3</td>
<td>6-12</td>
<td>18-24</td>
</tr>
<tr>
<td><strong>Long acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultralente</td>
<td>4-6</td>
<td>8-20</td>
<td>≥24</td>
</tr>
<tr>
<td>Glargine</td>
<td>3-4</td>
<td>3-24</td>
<td>≥24</td>
</tr>
<tr>
<td>Detemir</td>
<td>1-2</td>
<td>3-8</td>
<td>12-24 (depending on dose)</td>
</tr>
</tbody>
</table>

(Adapted from IDF, 2005)

2.9.5 Factors affecting insulin use

There are various factors that affect the use of insulin in type 2 DM patients. Some of these factors are:

- the extent to which the patient is prepared to inject him-/herself and the frequency thereof;
- age;
- ability to inject;
- daily diet and exercise routines;
- patient's aptitude to perform daily blood glucose monitoring; and
- ability to achieve individual glycaemic targets (IDF, 2005).

2.9.6 Disadvantages and risks of insulin use

It has been suggested that there is an unwillingness to start insulin therapy, from both the healthcare professionals and patients, who are concerned about the possibility of weight gain and the perceived danger of intense hypoglycaemia that are associated with insulin use (Kleinebreil et al., 2005; Vivian, 2007).

Chehade & Mooradian (2000) reported that one of the disadvantages of using agents which increase the availability of insulin, like insulin itself, is the associated weight gain. The treatment of DM with insulin in overweight patients was found to be associated with a 6.5 kg increase in body weight, according to the findings of the UKPDS (UKPDS, 1998a; UKPDS, 1998b). Thus, the initiation of insulin in obese type 2 DM patients should be based on a risk/benefit judgement, with regards to the importance of managing type 2 DM and weight gain (Chehade & Mooradian, 2000).

The UKPDS (1998b) reported a link between the use of insulin and insulin secretatogues, and hypoglycaemia. The same study found that every year, the incidence rate for hypoglycaemic events, related to the use of insulin, was 1.8%. Chehade and Mooradian (2000) implied that hypoglycaemia could have occurred because of meals taken at inconsistent times; the administration of higher than required dosages of insulin; or exercise, which was not planned. The abovementioned concerns could result in insulin use being delayed or absent in the treatment of type 2 DM (Kleinebreil et al., 2005; Vivian, 2007). As a result, poor glycaemic control may be evident in diabetic patients (Kleinebreil et al., 2005 & Vivian, 2007). According to Gerich et al. (2003), it is common for an insulin delay, or a poor adjustment in the management of type 2 DM patients. Consequently, there are poor clinical outcomes, as a result of inadequate glycaemic control (Gerich et al., 2003).
The use of insulin in elderly diabetic patients (66 years and above) is considered to pose a risk (Pogach, 2009). Budnitz, Kegler, Richards and Shehab (2007) reported that insulin is considered to be the second most common medication linked to patients requiring emergency department treatment; or being admitted to the hospital in the US. Whilst in Canada, the combination of insulin use and oral hypoglycaemic agents has been affiliated with motor vehicle accidents (Hemmelgarn, Lévesque & Suissa, 2006).

In light of the aforementioned risks and disadvantages that have been related to insulin use, it can be deduced that glucose monitoring forms an integral part of the management of DM, especially after the commencement of insulin. Pogach (2009) recommended that an increase in the number of deaths, hypoglycaemic episodes, as well as other side effects, should be monitored when evaluating glycaemic control after starting insulin.

### 2.9.7 Barriers to initiating insulin therapy

The use of insulin is often limited by the barriers that patients and health care professionals face (Meece, 2008). Health care professionals may have concerns with regards to insulin therapy. Some of these concerns are described by Meece (2008) as: a patient’s lack of adherence to insulin regimen, due to perceived complexity of regimen, associated weight gain, hypoglycaemia and scarcity of material and human resources. One of the other barriers challenging health care professionals is the time-consuming teaching process that is necessary to educate the patient (Meece, 2008). It has been argued that the initiation of insulin therapy should never pose as a risk to the patient (IDF, 2005). Moreover, starting insulin therapy should not be expressed in such a way that the patient is being reprimanded for not being able to adhere to previous recommendations (IDF, 2005). Patients should be encouraged in order to create a positive outlook on his/her condition at the start of insulin therapy (IDF, 2005).

The barriers that the diabetic patient faces, regarding insulin therapy, are discussed in the following sections (Sections 2.9.7.1-2.9.7.7).
2.9.7.1 Fear of needles

Patients may have a fear of needles because they link insulin injections with others that they may have received previously, for purposes other than that of receiving insulin therapy (Meece, 2008; Sease, 2011). Needles used for insulin injections are manufactured with the following properties: small diameter; sharpened by a laser and coated with silicone. These needles are manufactured in such a way that needle entry into the skin is improved and injections become as painless as possible (Graff & McClanahad, 1998). This fear of needles, which may be experienced by some diabetic patients, may be resolved by the use of pen aids which assist in covering the needle (Meece, 2008; Sease, 2011). Meece (2008) recommended that patients be referred for counselling if there is a genuine needle phobia. IDF (2005) argued that the fear of needles is common, but that needle phobia is unusual.

2.9.7.2 Sense of failure in the patient and stigmatisation

One of the other barriers to insulin therapy is a feeling of a sense of failure in the diabetic patient. Insulin is often prescribed in the management of this progressive disease as a result of its nature (Meece, 2008; Sease, 2011). However, some patients may view initiation of insulin therapy as a personal failure (Meece, 2008; Sease, 2011). Insulin therapy may have a stigma attached to it and consequently cause embarrassment for the patient in society (Meece, 2008). This stigmatisation may be an obstacle to insulin use.

2.9.7.3 Fear of gaining weight

Metformin should be continued when insulin is initiated, since metformin is known to support weight loss in diabetic patients (Buse et al., 2006; ADA, 2007). The fear of weight gain associated with insulin initiation should be counteracted with patient education about exercising and a balanced diet (Sease, 2011). Thus, when insulin is started, the likelihood of gaining weight is
minimised, since the anabolic effects of insulin are decreased (Meece, 2008; Sease, 2011).

2.9.7.4 Fear of hypoglycaemic episode

The fear of a hypoglycaemic episode is one of the many hindrances to insulin use. With good patient education about the proper use of insulin, this barrier can be overcome. The patient should be made aware of the symptoms of hypoglycaemia and what steps to take if experiencing any of those symptoms (Sease, 2011). Furthermore, providing education on how to prevent a hypoglycaemic episode can overcome this barrier (Sease, 2011). It is to be noted that newer insulin preparations are less likely to cause a hypoglycaemic episode, when compared with the older preparations on the market (Marcus, 2008; Meece, 2008; Sease, 2011). This is accounted for by the fact that the actions of endogenous insulin are imitated by insulin analogues in terms of their time-action profiles (Marcus, 2008; Meece, 2008; Sease, 2011).

The fear of a hypoglycaemic episode can be reduced by patient education about: insulin dosing and the amount of carbohydrate consumed; insulin preparation’s time-action profile; having a knowledge of when to inject insulin with regards to timing when eating meals and exercising; and lastly drug interactions with insulin, especially alcohol use (Meece, 2008).

2.9.7.5 Fear of complications

Some patients have a fear of complications associated with insulin use. This is often due to the fact that they know other patients who were initiated on insulin therapy, at a later stage of their condition; and shortly thereafter, had suffered from a complication of DM (Meece 2008, Sease, 2011). Patients immediately associate insulin use with diabetic complications (Sease, 2011), which is an incorrect perception of insulin. Diabetic complications actually arise from uncontrolled DM over a long period of time (Meece, 2008; Sease, 2011). As a matter of fact, insulin use provides more stringent blood glucose level control
and hence, prevents the development of complications associated with DM (Marcus, 2008; Meece 2008, Sease, 2011).

### 2.9.7.6 Perceived complexity of insulin regimen

Some patients are resistant to insulin therapy as they perceive the insulin regimen to be complex in nature and thus, may find it difficult to adhere to (Marcus, 2008; Meece, 2008). Additionally, insulin regimens have been regarded by some patients as being ‘time-consuming’ (Meece, 2008). However, this perception can be challenged by informing the patients of the newer available insulin preparations, as these are less complicated in nature (Meece, 2008). The newer insulin preparations allow for better integration into the patient’s lifestyle as well (Sease, 2011).

### 2.9.7.7 Cost implications

As with any other commodity, insulin use is associated with a cost implication. The patient needs to be able to purchase the insulin therapy consistently on a monthly basis. For patients who do not have medical aids, insulin therapy can become a barrier to its actual use because it becomes expensive (Meece, 2008; Sease, 2011). Meece (2008) reported that in the US, it is more cost-effective to use insulin, as compared to the concomitant use of three oral hypoglycaemic agents.

Besides the barriers to insulin therapy, there are also some side effects which are affiliated with the use of insulin. Section 2.9.8 provides an overview of these side effects.

### 2.9.8 Side effects of insulin therapy

There are several side effects associated with the start of insulin therapy. These side effects include: a potential allergic reaction, hypoglycaemic episode, weight gain, lipohypertrophy, lipoatrophy and insulin oedema (IDF, 2005).
2.9.8.1 Potential allergic reaction and hypoglycaemic episode

A potential allergic reaction may take place in the form of swelling and reddening at the injection site (IDF, 2005). A systemic reaction may also occur (IDF, 2005). These allergic reactions, local or systemic in nature, may be caused by the preservatives that are present in the insulin preparations or by the insulin itself (IDF, 2005). According to the IDF (2005), any diabetic patient that is on insulin therapy is at risk of developing a hypoglycaemic episode.

2.9.8.2 Weight gain

Insulin use has often been linked to weight gain. Weight gain occurs as a result of insulin’s action in the body. When it is administered, it reduces the breakdown of fat and enhances the formation of fat in the body (IDF, 2005). Weight gain has been most often observed in those diabetic patients who were started on insulin or whose insulin therapy was increased (IDF, 2005). Another reason that could be attributed to the weight gain is if the patient is injecting more insulin doses than required (IDF, 2005).

2.9.8.3 Lipohypertrophy and Lipoatrophy

Martin (2007) defined lipohypertrophy as “a local build-up of fat tissue near the site of repeated insulin injections…and tends to alter the rate of absorption of further injections into the body.” Lipoatrophy, on the other hand, is defined as “an immune reaction to insulin injections close to the site of injection, resulting in localised hollowing of the fat tissue” (Martin, 2007). Lipohypertrophy and lipoatrophy can be reduced by the rotation of insulin injection sites (ADA, 2004).

2.9.8.4 Insulin oedema

Insulin oedema is observed most frequently when insulin therapy is either commenced or increased (IDF, 2005). Patients who are at high risk of developing oedema in the aforementioned clinical circumstances are those
patients who are severely underweight; or who have had extensive phases of poor glycaemic control (IDF, 2005).

2.9.9 Starting insulin therapy

Insulin therapy is usually started in a type 2 DM patient when glycaemic targets are no longer attained with maximal doses of oral hypoglycaemic agents (IDF, 2005). When initiating insulin therapy, the dose will depend on the age, weight and glycaemic targets of the type 2 DM patient (IDF, 2005). The starting dose of insulin is 10 units of intermediate-acting insulin, injected once a day, subcutaneously. This dose of insulin should be started whilst still continuing oral hypoglycaemic agents at the maximum tolerated doses (IDF, 2005). It is recommended that the 10 units of insulin be administered, either in the morning or before going to sleep - once daily. The morning or evening administration will vary from patient to patient as the hyperglycaemic time is different for each patient (IDF, 2005).

2.9.9.1 Insulin devices and innovations in insulin drug delivery

Routes of insulin delivery have advanced progressively since 1922, when patients were using a whetstone-sharpened steel needle to inject insulin (Ainsberg & Cooper, 2010). Currently, there are several insulin devices available to patients who require insulin therapy. These insulin devices are: disposable syringes and needles, prefilled pens, reusable pens, dosers, jet injectors and insulin pumps (Marcus, 2008; Ainsberg & Cooper, 2010). There are other administration routes of insulin that are being researched. These include: transdermal, oral, pulmonary and intranasal routes of administration, as well as pancreatic transplants (Ainsberg & Cooper, 2010; Basavaraj et al., 2011). The latest innovation in insulin drug delivery is the development of inhaled insulin which will be discussed in section 2.10.10.4.
2.9.9.2 Syringe and needle

The syringe and the needle are used in administering insulin subcutaneously. They are used for one injection only and thereafter disposed of (IDF, 2005). The patient normally draws up the number of units to be administered.

2.9.9.3 Pens

Insulin pens are presented as pre-filled and re-usable pens (Marcus, 2008). Pre-filled pens are easy to use (IDF, 2005). The main advantage of using insulin pens is that there is a decreased dosage error (IDF, 2005). Furthermore, pens make it convenient for a diabetic patient who needs to inject regularly (IDF, 2005). However, this insulin device may be problematic for elderly patients as they may struggle with loading a new cartridge into an insulin pen (IDF, 2005). In order to minimise this problem, disposable pre-loaded insulin pens are now available for use, particularly for elderly diabetic patients (IDF, 2005).

2.9.9.4 Insulin pumps

Insulin pumps work by delivering insulin regularly (every minute) of the day, subcutaneously (IDF, 2005). This insulin device is demanding as the patient needs to be completely committed to utilising the insulin pump (IDF, 2005). The insulin pump works according to a programme that automatically programs the pump to release a slow, continuous level of basal insulin (IDF, 2005). In order to cater for the specific insulin requirements of a patient, the basal insulin can be released at different rates in a day (IDF, 2005). If a patient just had a meal or is experiencing a high blood glucose level, the insulin pump can be used to administer bolus insulin (IDF, 2005). It is noteworthy to mention that the insulin pump is a costly therapy (IDF, 2005).

2.9.9.5 Inhaled insulin

Exubera® is an inhaled insulin preparation that was developed by Pfizer Inc. In 2006, Exubera®, the first inhaled insulin powder was approved for the US and
European markets (Marcus, 2008; Basavaraj et al., 2011). It is used for the delivery of bolus doses of rapid acting insulin prior to a meal (IDF, 2005; Marcus, 2008). However, despite the use of inhaled insulin, the patient would still have to administer basal insulin subcutaneously (IDF, 2005). Exubera® was withdrawn from the US market as it was not used by many patients, since the doses were higher and there were associated side-effects with the inhaled insulin powder. The side-effects reported were: increased occurrence of cough as well as a small decrease in the forced expiratory volume [non-progressive] (Marcus, 2008). A second inhaled insulin formulation was developed, but it has also been discontinued. The rationale was that insulin analogues were more convenient and clinically important than inhaled insulin formulations (Marcus, 2008).

The treatment of type 2 DM remains an innovative area with new advances in technology in this modern era. Perhaps in the future there will be other routes of insulin administration.

Sections 2.10 and 2.11 describe the South African and international guidelines describing the management of type 2 DM, respectively. These sections were included in order to determine the extent to which prescribing guidelines and treatment protocols in South Africa have taken international trends into consideration.

2.10 SOUTH AFRICAN GUIDELINES

At present, there are two guidelines that are used in the health care systems in SA; namely: the SEMDSA Guidelines and the EML Standard Treatment Guidelines. The latter is used mostly in the public sector and the former is used in both the private and public sectors. These guidelines are aimed at reducing morbidity and mortality in type 2 DM patients. The following section provides a discussion of the abovementioned South African guidelines.
2.10.1 SEMDSA Guidelines for Diagnosis and Management of type 2 diabetes mellitus for Primary Health Care – 2009

The SEMDSA guidelines (2009) focus specifically on the following aspects:

- criteria for diagnosis of DM;
- glycaemic targets for control (for non-pregnant adults);
- BMI, waist, lipid and blood pressure goals;
- key processes of care (patient education, children, lifestyle, self-monitoring of blood glucose);
- glycaemic management of type 2 DM in non-pregnant adults;
- blood pressure treatment recommendations;
- lipid treatment recommendations; and the
- use of antiplatelet agents.

One of the key processes of care is self-monitoring of blood glucose (SMBG). The aim of SMBG is to reach and maintain glycaemic control in the diabetic patient. SEMDSA Guidelines (2009) recommend that patients, who are self-injecting insulin on multiple occasions on a daily basis, should perform SMBG three or more times per day. For those patients who are only injecting insulin once a day; or who are using once daily insulin in conjunction with oral hypoglycaemic agents, the SEMDSA Guidelines (2009) suggest that SMBG be conducted once daily. According to the SEMDSA Guidelines (2009), patients using oral hypoglycaemic agents (without insulin) need only perform SMBG tests, when additional pharmacological management is being assessed, or when a hypoglycaemic episode needs to be confirmed. Thus, SMBG was not encouraged for routine use (SEMDSA, 2009).

Figure 2.2 illustrates the steps involved in the pharmacological management of type 2 DM, as per the SEMDSA guidelines.
The previous SEMDSA guidelines for the diagnosis and management of type 2 DM for primary health care were issued in 2002. The main difference between the SEMDSA Guidelines of 2002 and 2009, is the changes to insulin therapy in the management of type 2 DM. Table 2.19 compares and contrasts these main differences in insulin therapy.
Table 2.19: Main differences in the SEMDSA guidelines of 2002 and 2009

<table>
<thead>
<tr>
<th>SEMDSA GUIDELINES 2002</th>
<th>SEMDSA GUIDELINES 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication for insulin therapy:</strong></td>
<td>1. As first line therapy if patient suffers from severe uncontrollable diabetes together with catabolism. The following criteria are used to evaluate the patient:</td>
</tr>
<tr>
<td>When glycaemic targets are not being achieved by patient, even though patient is adherent to hypoglycaemic therapy and there are no considerable factors causing stress.</td>
<td>• fasting plasma glucose level greater than 14 mmol/l;</td>
</tr>
<tr>
<td></td>
<td>• random glucose levels &gt; 16.7 mmol/l regularly;</td>
</tr>
<tr>
<td></td>
<td>• HbA1c level greater than 10% or;</td>
</tr>
<tr>
<td></td>
<td>• the presence of ketonuria or;</td>
</tr>
<tr>
<td></td>
<td>• symptomatic diabetes with considerable weight loss, presence of glucose in the urine and increased thirst.</td>
</tr>
<tr>
<td></td>
<td>2. In conjunction with oral hypoglycaemic agents, either as a second-line or third-line treatment.</td>
</tr>
<tr>
<td><strong>Insulin Therapy:</strong></td>
<td>1. Either basal insulin:</td>
</tr>
<tr>
<td>• Either intermediate or long acting insulin at bedtime either in combination with oral hypoglycaemic agents or on its own.</td>
<td>• 10 units of intermediate acting (NPH) or long-acting insulin at bedtime;</td>
</tr>
<tr>
<td>• The abovementioned insulin type was to be titrated against the reading taken just before breakfast.</td>
<td>• titrating by 2 units every 3 to 7 days until the fasting glucose is within glycaemic target.</td>
</tr>
<tr>
<td>• Initial insulin dose: 0.2 – 0.3 units/kg.</td>
<td>2. Continue metformin and sulphonylurea therapy:</td>
</tr>
<tr>
<td>• A twice daily dose of a biphasic insulin preparation was to be used for a patient requiring more than 30 units daily.</td>
<td>• use insulin glargine or insulin detemir if nocturnal hypoglycaemia is problematic with NPH / lente insulin.</td>
</tr>
<tr>
<td>• Two thirds of the dose would be intermediate acting and one third of the dose would be short-acting.</td>
<td>3. Biphasic insulin:</td>
</tr>
<tr>
<td></td>
<td>• minimum total dose: 0.4 units/kg;</td>
</tr>
<tr>
<td></td>
<td>• two thirds of total dose initially administered before breakfast, titrate the morning dose according to the pre-supper glucose levels;</td>
</tr>
<tr>
<td></td>
<td>• one third of total dose before supper; titrate the evening dose according to the pre-breakfast glucose levels;</td>
</tr>
<tr>
<td></td>
<td>• metformin therapy should be continued, but sulphonylurea therapy should be stopped.</td>
</tr>
<tr>
<td></td>
<td>➢ If basal or biphasic insulin therapy fails, then multiple daily injections should be considered.</td>
</tr>
<tr>
<td></td>
<td>• If glycaemic targets are still not being achieved, patient should be referred to a specialist at any stage.</td>
</tr>
</tbody>
</table>

(Adapted from SEMDSA Guidelines 2002 and 2009)
2.10.2 Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008)

The Standard Treatment Guidelines provide information on:

- non-drug treatment: general measures - diet and lifestyle; and

Figure 2.3 provides the steps in the management of type 2 DM as stipulated in the EML.

![Diagram of diabetes management steps]

**Figure 2.3: Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008)**

From Figure 2.3, it can be observed that insulin therapy is used as a last resort in the management of DM according to the Standard Treatment Guidelines (National Department of Health, 2008). Insulin is only used when the combination of two or more oral hypoglycaemic agents have failed to assist the DM patient to reach glycaemic targets (National Department of Health, 2008). According to these guidelines, the sulphonylurea should be stopped as soon as insulin therapy is started, but metformin can be continued to be given
simultaneously (National Department of Health, 2008). The Standard Treatment Guidelines (National Department of Health, 2008) state that insulin therapy can either be used as add-on therapy to oral hypoglycaemic agents or it can be used as a substitution monotherapy. An intermediate or long-acting insulin is recommended as add-on therapy, whereas a biphasic insulin is recommended for substitution therapy.

The previous South African Standard Treatment Guidelines were published in 2003. The main difference between the previous and the new guidelines, is the recommendation of aspirin for all type 2 DM patients, unless there is a contraindication, and in the dosage adjustments for insulin therapy (National Department of Health, 2003). It should be emphasised that, like the 2008 guideline, the use of insulin was recommended in the 2003 version as a last resort, when the use of combination oral hypoglycaemic agents was no longer providing efficacy.

Upon comparison of the 2003 and 2008 Standard Treatment Guidelines, the following similarities were identified:

- ten units of insulin in the evening before bedtime were recommended as add on therapy;
- if glycaemic targets were not being achieved, the ten units add-on therapy must be gradually increased to twenty units;
- two thirds of the total daily dose to be given thirty minutes before breakfast and one third of the total daily dose thirty minutes prior to supper;
- an increase of four units every week was recommended in the insulin therapy for patients using biphasic regimen;
- the first increase was to be added to the dose that was normally administered in the morning; and that the second increase be added to the dose that was given in the evening; and
- if more than thirty units of insulin were required, then the patient would need to be referred (National Department of Health, 2003 & 2008).
In contrast, the following differences were noticed between the 2003 and 2008 guidelines:

- the 2003 guidelines recommended that for patients using biphasic insulin regimens, there should be an increase of 0.6 units every day and an increase of four units every week (National Department of Health, 2003); and
- the 2008 guidelines only recommended an increase of four units every week (National Department of Health, 2008).

It is evident from both South African guidelines that the use of insulin remains the last resort in the pharmacological management of type 2 DM. According to the UKPDS, metformin has been associated with a decreased incidence of macrovascular and microvascular complications (Karam & Nolte, 2006). It is promising to note that in both guidelines, metformin is prescribed as the first-line oral therapeutic agent.

2.11 INTERNATIONAL GUIDELINES

Due to the increased prevalence of type 2 DM on a global level (Chaturvedi, 2002; Chisholm & Shaw, 2003; International Diabetes Federation and World Health Organization, 2006), most countries have developed their own guidelines and protocols for the management of this chronic disease state.

This section highlights some of the differences in the guidelines that are used in other countries, relative to those that are used in South Africa. For example, the New Zealand and United Kingdom guidelines are precise with regards to the use of insulin in type 2 diabetic patients. This contrasts with the South African guidelines, which recommend insulin therapy as the last resort, but provide no specific details for its use. Section 2.8 described the use of insulin in the management of type 2 DM.
2.11.1 Canada

Relative to South Africa, which has a glycaemic management plan according to HBA$_{1C}$ levels that are greater than 7%, Canada’s management plan is in accordance to a HBA$_{1C}$ level of less than, or more than 9%.

In the Canadian protocol, if HBA$_{1C}$ level is more than 9% after the combined use of two oral hypoglycaemic agents from different classes, basal and/or pre-prandial insulin is recommended. This differs from the SEMDSA guidelines which recommend the use of basal insulin as a second-line option, if HBA$_{1C}$ level is more than 8.5%, after the use of metformin for three months.

Moreover, in Canada, if the glycaemic target is not being reached, it is suggested that a drug from another oral hypoglycaemic class be added, or that insulin be used. However, in South Africa, the next step in the guideline suggests only the addition of another drug which was not previously selected.

Lastly, the protocol in Canada recommends that if the desired outcome is not being achieved with insulin therapy, the insulin regimen should be increased or an oral hypoglycaemic agent should be added. This contrasts to the South African guideline, which on the other hand, suggests the initiation of biphasic insulin.

2.11.2 New Zealand

In New Zealand, insulin therapy is recommended if the target HBA$_{1C}$ level is still not being reached on maximised oral hypoglycaemic therapy and lifestyle modification. The guideline further suggests that oral hypoglycaemic agents should still be used in conjunction with insulin and lifestyle changes.

The insulin therapy regimen is outlined as follows:
- intermediate-acting insulin is to be used initially;
• intermediate-acting insulin, 6 - 10 units at bedtime, to be added if fasting glucose level is higher than 6mmol/l; the dose may be increased by 1 - 2 units every three to four days until the target level is reached;
• if the fasting glucose level is within the target range, but the daytime glucose level is still not within the target range, an intermediate-acting insulin should be added (6 -10 units at breakfast) and to be increased by 1 - 2 units every three to four days, until target level is achieved; and
• if target HBA\textsubscript{1C} level is still not being achieved, the patient should be referred to a specialist, since twice daily insulin administration or even more injections, will be required.

This detailed insulin therapy in the New Zealand guideline contrasts with the South African guideline in the sense that the latter does not recommend particular doses for the glycaemic management with insulin therapy.

2.11.3 United Kingdom

The use of insulin in the United Kingdom’s guideline is prescribed in combination with an oral hypoglycaemic agent; or as monotherapy.

In a combination regimen, recommended insulin use, includes:
• basal insulin therapy with the continuation of either metformin and a sulphonylurea or acarbose;
• pre-mixed insulin therapy or mealtime and basal insulin regimen in conjunction with metformin and sulphonylureas; and
• insulin therapy with the use of pioglitazone (under specific conditions).

For insulin monotherapy:
• start with human isophane protamine insulin (NPH) at night or as a twice daily dose when necessary;
• long-acting insulin glargine may be used as an alternative; or
• biphasic human insulin (pre-mixed) regimen may be administered as a twice daily dose.
In the UK’s guideline, the use of exenatide in very specific clinical conditions is recommended. Exenatide is a glucagon-like-polypeptide 1 (GLP-1) synthetic analogue. It is administered subcutaneously. The possible mechanisms of action are: increased glucose-mediated insulin secretion, decreased glucagon release after a meal and reduced gastric emptying (Karam & Nolte, 2006).

This particular agent is available, but it is not recommended in the South African guideline yet. Exenatide is available as Byetta® 5 µg and 10 µg disposable pens in SA (Snyman, 2010). It is indicated as add-on therapy for DM 2 patients who are poorly controlled with lifestyle modifications and oral hypoglycaemic combinations (Snyman, 2010). Exenatide is administered sixty minutes before the two main meals of the day, six hours or more in between the two meals (Snyman, 2010). It is usually started as a twice daily dose of 5 µg subcutaneously, for one month and may be increased to a twice daily dose of 10 µg subcutaneously (Snyman, 2010).

The United Kingdom’s guideline also provides a comprehensive description regarding insulin therapy, similar to that of the New Zealand one; but different from the Canadian and South African guidelines, which provide a general overview. The abovementioned guidelines illustrate that protocols differ from country to country.

2.12 PHARMACOEPIDEMIOLOGICAL REVIEWS AND DRUG UTILISATION RESEARCH

The WHO (2003: 8) defines pharmacoepidemiology as “the study of the use, effects and side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population, thereby improving health outcomes.” Sections 2.12.1 to 2.12.3 provide an overview of pharmacoepidemiological studies and drug utilisation research, describe terminologies used for such reviews and identify similar studies that have been conducted overseas.
2.12.1 Overview of pharmacoepidemiological review and drug utilisation research

The WHO (2003: 8) defined epidemiology as “the study of the distribution and determinants of health-related states and events in the population, and the application of this study to control of health problems”. Pharmacoepidemiological reviews and drug utilisation research form part of epidemiology.

A pharmacoepidemiological review can either be drug- or utilisation-oriented. In the former, drugs (individual or groups) are analysed in terms of safety and effectiveness. Whereas for utilisation-oriented reviews, the focus is to intervene in drug therapy in order to improve its quality. Pharmacoepidemiological reviews also focus on the pattern, quality, determinants and outcomes of drug use. Furthermore, these studies extend over long periods of time for large patient populations (WHO, 2003).

Drug utilisation research (DUR) is defined as “the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences” (WHO, 2003: 8). The main aim is to evaluate the rationale of therapy (WHO, 2003). Auditing of drug therapy is the method employed to achieve the afore-stipulated aim of DUR (WHO, 2003). Thus, DUR forms part of pharmacoepidemiology as it provides information about drug exposure in terms of its nature, extent and determinants (WHO, 2003).

2.12.2 Purpose of drug utilisation research

The purpose of DUR is to conduct a comprehensive investigation into the use of drug and prescribing patterns (WHO, 2003). The purposes of DUR have been divided into different characteristics with respect to drugs, and are discussed as follows: in terms of the pattern of use, quality of use, determinants and outcomes of use.
• Pattern of use
One of the aims of DUR is to determine the pattern of use of medications. The profiles of the drugs, as well as the extent to which they are being used, are determined (WHO, 2003). Patterns in drug use and the costs involved are considered over a period of time in DUR (WHO, 2003).

• Quality of use
In a DUR where the quality of use of drugs is being assessed, an audit of drugs is conducted (WHO, 2003). In such a DUR, local prescribing guidelines or formularies are used as a standard to compare the actual prescribing of drugs (WHO, 2003). The drug aspects which are used to determine the quality of use are: choice, cost, dosage and interactions with other medications (WHO, 2003).

• Determinants of use
User, prescriber and drug characteristics form part of the determinants of use of medications. Drug utilisation review is often carried out to provide information about these determinants (WHO, 2003).

• Outcomes of use
The outcomes of use are evaluated in terms of health outcomes, including the benefits, as well as the side effects of therapy. The financial aspect of therapy is also considered to be part of the outcomes of use (WHO, 2003).

2.12.3 Types of drug utilisation research

The two main types of DUR are descriptive and analytical studies. These are discussed as follows:

• Descriptive studies
In descriptive studies, the focus is to provide a description of DUR patterns (WHO, 2003). Moreover, these types of studies involve placing the emphasis on problems requiring more comprehensive studies (WHO, 2003).
Analytical studies
In contrast to descriptive studies, analytical studies are aimed at finding the relationship between the DUR data and statistics on disease, treatment outcomes and quality care (WHO, 2003). Furthermore, analytical studies investigate the rationale of drug therapy (WHO, 2003).

In addition to the two types of DUR described above, DUR can be further categorised into three other types of studies, namely: cross-sectional, longitudinal and continuous longitudinal studies. These are discussed below:

- Cross-sectional studies
In DUR cross-sectional studies, the data provide a brief overview of the drug use over a specified period of time (WHO, 2003). The results that are obtained are usually compared to similar studies that are carried out elsewhere over the same period of time (WHO, 2003). The focus of the study can be based on either of the following: drug, problem, indication, prescriber or patient (WHO, 2003). Furthermore, in cross-sectional studies, drug use can be measured or another criterion can be used to assess drug use with respect to prescribing guidelines (WHO, 2003).

- Longitudinal studies
The aim of longitudinal studies is to obtain general trends about medications, without emphasising the prescribing patterns of individualised practitioners or practices (WHO, 2003). Data for longitudinal studies are often obtained from a database, or from a sample of pharmacies or medical practices (WHO, 2003). Furthermore, data can be obtained from cross-sectional surveys that have been repeated (WHO, 2003). It can be noted that in longitudinal studies, the data collection process is continuous and thus, patients and prescribers are always changing (WHO, 2003). This type of study contrasts with cross-sectional studies where data focus on one specific period of time only.

- Continuous longitudinal studies
Continuous longitudinal studies make use of claim databases to carry out DUR. These databases are useful tools, as they can provide information that will
support therapy and changes to health outcomes, as well as explaining side effects. They also allow for the observation of data relating to individual patients, as each patient may be identified with an anonymous number (WHO, 2003). Continuous longitudinal studies examine the entire medical information for each individual patient in a database, as well as the drug prescribing patterns for each patient (WHO, 2003).

### 2.12.4 Terminologies used in pharmacoepidemiological reviews

In pharmacoepidemiological reviews, there are specific terminologies that are often used to explain certain concepts in the research or study, with respect to disease(s) and/or drug(s). The following terms are most frequently used in pharmacoepidemiological reviews: anatomical therapeutic chemical classification system, international classification of diseases, defined daily dose and prescribed daily dose.

- **Anatomical Therapeutic Chemical Classification System**

The Anatomical Therapeutic Chemical (ATC) Classification System is an international system that was developed by researchers in Norway. WHO (2003: 33) defined a drug classification system as a “common language for describing the drug assortment in a country or region and is a prerequisite for national and international comparisons of drug utilisation data, which have to be collected and aggregated in a uniform way”. In the ATC Classification System, drugs are divided into different groups with respect to the organ or system on which they act. Thereafter, the grouping is done based on their chemical, pharmacological and therapeutic properties (WHO, 2003).

The ATC Classification System uses five different levels to group drugs (WHO, 2003). The first level categorises drugs into one of the fourteen main groups (WHO, 2003). Thereafter, drugs are sub-divided into therapeutic/pharmacological subgroups, which form the second and third levels of the ATC Classification System (WHO, 2003). Drugs are then further categorised according to the therapeutic/pharmacological/chemical subgroup, which
constitutes the fourth level of grouping (WHO, 2003). Lastly, drugs are classified according to their chemical substance (WHO, 2003). Metformin will be used as an example to illustrate the ATC Classification System. The ATC code for metformin is A10BA02. A represents the main anatomical group, i.e. the first level and represents the alimentary tract and metabolism (Rossiter, 2009). A10 represents drugs used in diabetes [second level, main therapeutic group] (Rossiter, 2009). A10B is representative of blood glucose lowering drugs [third level, therapeutic/pharmacological subgroup] (Rossiter, 2009). A10BA represents biguanides [fourth level, therapeutic/pharmacological/chemical subgroup] (Rossiter, 2009). A10BA02 is metformin, which is the fifth level of classification, i.e. the subgroup for chemical substance (Rossiter, 2009).

- **International Classification of Diseases**

A standard diagnostic classification system that is used internationally is the international classification of diseases (ICD) (WHO, 2011a). The ICD classification and ICD-10 codes, specifically pertaining to DM, were discussed in section 2.1.3.

- **Defined Daily Dose**

The defined daily dose (DDD) is a unit of measure used in DUR studies (WHO, 2003). It is described as “the assumed average maintenance dose per day for a drug used for its major indication in adults” (WHO, 2003: 38). The average of two or more commonly used doses is used to calculate the DDD. Consequently, DDD may be a dose which is rarely prescribed, since it is an average dose (WHO, 2003).

- **Prescribed Daily Dose**

The prescribed daily dose (PDD) is defined as “the average daily dose prescribed, as obtained from a representative sample of prescriptions” (WHO, 2003: 39). Pharmacy, medical records or prescription studies can be used to
determine the PDD (WHO, 2003). One of the key aspects of evaluating the PDD is to take into consideration the diagnosis of the patient(s) in the study (WHO, 2003). Furthermore, if a drug is indicated for different uses, the PDD and the diagnosis need to be linked when evaluating the PDD (WHO, 2003). Other important information which can be used when evaluating the PDD are age and gender (WHO, 2003).

It should be remembered that the PDD does not automatically equate to the DDD in a study (WHO, 2003). In an event where there is a significant difference between the PDD and the DDD, this difference needs to be accounted for when evaluating and interpreting results, more specifically those pertaining to morbidity (WHO, 2003). Since different countries have different PDDs, it is deemed essential to take that into consideration when comparing PDDs from one country to another (WHO, 2003).

The PDD does not inevitably reflect the actual drug utilisation of drugs because some prescriptions are not always dispensed and not all of the patients administer all of the medications that were dispensed to them (WHO, 2003).

2.12.5 Summary of pharmacoepidemiological studies already concluded

Section 2.12.5 describes two pharmacoepidemiological studies involving type 2 DM patients and insulin use. After a thorough discussion on type 2 DM, pharmacoepidemiology and insulin, this section provides details about other pharmacoepidemiological studies that have been carried out.

2.12.5.1 Study researching the beneficial effects of insulin compared to sulphonylureas on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients

The abovementioned study was carried out in Sweden as a multicentre randomised clinical trial, by Alvarsson et al. (2003). The aim of the study was to
provide a comparison on the effects of a sulphonylurea against insulin therapy in terms of the insulin secretion deterioration in type 2 DM patients (Alvarsson et al., 2003). The objectives of the study were to investigate:

- whether therapy with insulin or glibenclamide was linked to the improved functioning of the β-cells, after the diagnosis of type 2 DM; and
- metabolic control with each of the two treatment options (glibenclamide and insulin).

The study population consisted of diabetic males and females aged between thirty-five and seventy years, (limits included) who were diagnosed less than two years before they were approached to participate in the study (Alvarsson et al., 2003). The inclusion and exclusion criteria are discussed below.

The inclusion criterion was: at screening, fasting blood glucose levels between 7,0 mmol/l and 12,0 mmol/l on one occasion, when the patient was on diet only for a minimum of a month (Alvarsson et al., 2003). The exclusion criteria were for patients who had:

- latent autoimmune diabetes in adults;
- been receiving drug treatment for more than six months;
- a plasma C-peptide concentration of less than 0,2nmol/l;
- prominent ketonuria;
- a BMI greater than 35kg/m²;
- a plasma creatinine level that was greater than 150 µmol/l;
- severe retinopathy;
- advanced heart disease;
- other potentially life-threatening disease; and
- islet cell antibodies (ICAs).

The study was carried out in six Swedish diabetic clinics (Alvarsson et al., 2003). Fifty-six patients were found to be eligible for the randomisation (Alvarsson et al., 2003). Of these fifty-six patients, five patients tested positive to ICA’s and thus, were removed from the study [56 - 5 = 51]. The remaining fifty-one patients were then used in the study. Twenty-eight patients were
randomised with glibenclamide and twenty-three with insulin therapy (Alvarsson et al., 2003). The study sample was found to be thirty-nine patients, since ten patients left the study early* and two patients, who were randomised on glibenclamide, were excluded since they tested positive for antibodies [51 - 12 = 39] (Alvarsson et al., 2003).

* Two insulin-randomised patients passed away; three insulin-randomised and three glibenclamide-randomised patients left because of personal reasons; and two glibenclamide-randomised patients left because they needed insulin therapy after one year

The quality of life of the patients was assessed on an annual basis using the SF-36 questionnaire (Alvarsson et al., 2003). This particular questionnaire measured the following:

1. physical functioning;
2. physical role;
3. body ache;
4. general well-being;
5. vitality;
6. social functioning;
7. emotional role; and
8. mental well-being.

In summary, over a period of two years, in a population of 39 patients, the trial monitored their β-cell function, glycaemic control and quality of life. Table 2.20 summarises the findings of the trial.
Table 2.20: Results of Swedish Multicentre Randomised Clinical Trial

<table>
<thead>
<tr>
<th>Effect on</th>
<th>Insulin-randomised group</th>
<th>Glibenclamide-randomised group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>After one year: 20,6 ± 2,0 IU/day</td>
<td>After one year: 2,4 ± 0,4 mg/day</td>
</tr>
<tr>
<td></td>
<td>After two years: 22,3 ± 2,2 IU/day (no significant change)</td>
<td>After two years: 3,0 ± 0,5 mg/day (significant increase; ( P = 0,03 ))</td>
</tr>
<tr>
<td><strong>Other drug treatments</strong></td>
<td>At start of trial: used by one patient</td>
<td>At start of trial: used by seven patients</td>
</tr>
<tr>
<td>(β-antagonists, lipid-lowering agents, ACE-</td>
<td>After two years: six patients</td>
<td>After two years: ten patients</td>
</tr>
<tr>
<td>inhibitors; or ARBs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body weight</strong></td>
<td>After two years: increase from 80,3 ± 2,4 to 83,0 ± 2,4 kg (( P &lt; 0,01 ))</td>
<td>After two years: increase from 86,4 ± 2,7 to 88,1 ± 3,0 kg (( P = 0,02 ))</td>
</tr>
<tr>
<td></td>
<td>Both the insulin and glibenclamide-randomised groups did not experience a significant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>weight increase.</td>
<td></td>
</tr>
<tr>
<td><strong>Lipid levels</strong></td>
<td>Lipid levels remained the same for this group</td>
<td>Significant increase in HDL cholesterol levels from 0,15 ± 0,30 mmol/l (( P = 0,03 ))</td>
</tr>
<tr>
<td><strong>Glucagon-stimulated C-peptide response</strong></td>
<td>After one year: increased</td>
<td>After one year: decreased</td>
</tr>
<tr>
<td><strong>Fasting insulin levels after treatment</strong></td>
<td>After two years: higher</td>
<td>After two years: lower</td>
</tr>
<tr>
<td><strong>withdrawal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c levels</strong></td>
<td>After one year: decreased (( P = 0,01 ))</td>
<td>After one year: decreased (( P = 0,01 ))</td>
</tr>
<tr>
<td></td>
<td>After two years: Lower, compared to baseline (( P &lt; 0,005 ))</td>
<td>After two years: increased (( P &lt; 0,01 ))</td>
</tr>
<tr>
<td></td>
<td>The difference between the two groups was considered to be significant: ( P = 0,02 )</td>
<td></td>
</tr>
<tr>
<td><strong>Quality of life</strong></td>
<td>After the 2 years, no change in the quality of life was observed in either of the groups.</td>
<td></td>
</tr>
</tbody>
</table>

(Alvarsson et al., 2003)
In summary, the trial found that the parameters of β-cell functioning were conserved better in the insulin-randomised group than the glibenclamide-randomised group (Alvarsson et al., 2003). Additionally, it was observed that patients in the insulin group responded to an increase in fasting blood glucose level in terms of fasting insulin (Alvarsson et al., 2003).

The trial concluded that the use of insulin in the early stages of type 2 DM, as compared to the use of a glibenclamide, extended insulin secretion in the body and promoted metabolic control (Alvarsson et al., 2003).

2.12.5.2 Initiation of insulin therapy in elderly patients taking oral hypoglycaemic agents

In 2009, a study was performed in Canada, by Grégoire et al. where they investigated the commencement of insulin therapy in elderly patients, who were also on oral hypoglycaemic agents. It was a population-based inception cohort study, which used the Quebec health insurance board’s database, as well as Quebec’s registry of admissions.

The population of the study was the general population of the health insurance plan, which included all of the permanent residents of Quebec (Grégoire et al., 2009). The database contained both medical services and hospital admissions records (Grégoire et al., 2009). Patients who were sixty-five years of age or older, not living in an institution and all of those people who did not meet the eligibility criteria for a private drug insurance, were covered in Quebec’s public drug plan (Grégoire et al., 2009). In 2006, in a population of 7.5 million people, 3.2 million were using the public drug plan (Grégoire et al., 2009). Each patient was allocated a unique coded health number which was used to link the databases and the registry for each patient (Grégoire et al., 2009). The database from the health insurance plan contained the following information:

- patient demographics, including age, gender and residence area;
- physician services, including date, diagnosis and physician’s speciality; and
• prescription drugs dispensed, including drug identification, date dispensed and number of days supplied (Grégoire et al., 2009).

The hospital data were extracted from another database. The data that were extracted pertained to the dates and the primary diagnosis (Grégoire et al., 2009). Prior to conducting the analyses, certain inclusion and exclusion criteria were applied to the database, in order to ensure that only the new users of oral hypoglycaemic agents were included (Grégoire et al., 2009). These criteria are discussed below:

• The inclusion criterion was for patients who received a minimum of one script for an oral hypoglycaemic agent between 1 January 1998 and 24 December 2004.

• The exclusion criteria were as follows, with respect to patients who:
  ➢ had previously received an oral hypoglycaemic agent in the one year timeframe before the index date (the index date is considered to be the date on which the first claim was made for any oral hypoglycaemic agent during the time period defined in the inclusion criterion);
  ➢ were aged less than 66 years of age (patients aged 66 years or older were considered to be elderly patients);
  ➢ were dispensed insulin in the one year timeframe before the index date or any day within seven days post index date;
  ➢ did not meet the eligibility criteria for the Quebec drug plan for the one year timeframe prior to the index date; and
  ➢ had either acarbose, thiazolidinedione or combination therapy with metformin or an insulin secretatogue as initial therapy [because there are only a small number of patients on such therapies and also because the Quebec province does not reimburse the use of thiazolidinediones as third line treatment] (Grégoire et al., 2009).

The patients who met the inclusion criterion (without contravening any exclusion criteria) were then monitored from the start of oral hypoglycaemic management,
until 31 December 2004 (Grégoire et al., 2009). Grégoire et al. (2009) followed up with the patients until: they had started insulin therapy; were no longer eligible for the drug therapy; or had passed away. Insulin therapy was considered to have been started if patients had received a minimum of one script for insulin, which was definitely dispensed and if that patient had already been using oral hypoglycaemic agents (Grégoire et al., 2009). Once the study had started, data such as the age, gender, oral hypoglycaemic agent(s) dispensed, year and residence area (rural or urban), were evaluated (Grégoire et al., 2009). This was obtained in order to correlate this data with the initiation of insulin therapy (Grégoire et al., 2009).

Grégoire et al. (2009) used the Kaplan-Meier method to calculate the incidence rate for the initiation of insulin therapy. The study sample was found to be 69,674 patients, who were all included in the analyses (Grégoire et al., 2009).

Some of the following findings were reported by Grégoire and his team (2009):

- 66.3% of the study sample were using metformin as the initial oral hypoglycaemic treatment; whereas only
- 29.3% of the study sample were using an insulin secretatogue;
- insulin therapy was initiated at rate of 9.7 cases per 1000 patient-years ('patient-years' refers to the interim between the index date and the date on which the first insulin prescription was recorded); and
- 2.8% of 1955 patients, who were initially on oral hypoglycaemic agents, started using insulin during a follow-up of 2.9 median years.

Patients who were deemed more likely to receive insulin therapy had to meet the following criteria:

- initially treated with an insulin secretatogue;
- under the care of either an endocrinologist or intern;
- used high doses of oral hypoglycaemic agent initially;
- used oral corticosteroids;
- used glucometer strips;
- was hospitalised in the year preceding the initiation of oral hypoglycaemic agent(s); and
- those who were using sixteen or more medications (Grégoire et al., 2009).

In conclusion, Grégoire et al. (2009) reported the rate at which insulin was initiated, to be 9.7 cases per 1000 patient-years. The implication thereof is that in one year approximately 10 patients would be initiated on insulin therapy for every 1000 new patients using oral hypoglycaemic agents. Grégoire et al. (2009) mentioned a few limitations of their study. These include:

- the medications were analysed based on the number of scripts that had been dispensed, but this kind of analysis did not necessarily reflect actual drug usage of the patients;
- new patients, who were using oral hypoglycaemic agents and started on insulin, could not be assessed in terms of the following: whether they had a high BMI, the degree of the progression of DM, and if they had adequate glycaemic control; and
- the commencement of insulin therapy was considered to reflect the secondary failure of oral hypoglycaemic agents, where currently, insulin is being recommended as initial therapy in type 2 DM patients with high glucose plasma levels.

This chapter discussed type 2 DM and the pharmacological management thereof, namely oral hypoglycaemic agents and insulin. This chapter included a detailed description of the definition; types; complications and ICD-10 classification of type 2 DM. This chapter also provided an overview of the epidemiology and aetiology of type 2 DM. The clinical findings for the diagnosis and the risk factors of type 2 DM were also considered. The death statistics in SA that were associated with type 2 DM were also examined. Another aspect in the management of type 2 DM was then addressed: type 2 DM and other comorbid disease states, namely: the metabolic syndrome, hypertension, dyslipidaemia and coronary artery disease. The non-pharmacological
management of type 2 DM was also considered. Insulin was thoroughly discussed, from a brief history of insulin to the different types of insulin preparations available and the side effects associated with its use. This was followed by an investigation of the South African and international guidelines pertaining to the management of type 2 DM. This section was then concluded by a discussion of the pharmacoepidemiological reviews and drug utilisation reviews that involved type 2 DM patients.
CHAPTER 3

RESEARCH METHODOLOGY
This chapter describes the study design and methodology used to conduct this pharmacoepidemiological review. The ethical considerations are also discussed.

### 3.1 INTRODUCTION

This pharmacoepidemiological study was a retrospective drug utilisation review. The study was quantitative in nature, since the drugs prescribed and the extent, to which the guidelines were being adhered to, was assessed from a statistical perspective.

### 3.2 STUDY DESIGN

A quantitative approach to drug utilisation review was used to determine the use of insulin in the management of patients diagnosed with type 2 DM. A quantitative study is defined by Leedy (1997: 104) as “an inquiry into a social or human problem, based on testing a theory composed of variables, measured with numbers and analysed with statistical procedures, in order to determine whether the predictive generalisations of the theory hold true”. The WHO (2003: 8) defined drug utilisation research as “the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences”.

Bilker et al. (2003: 1494) suggested that “retrospective drug utilisation review programmes are structured ongoing initiatives that interpret patterns of drug use in relation to predetermined criteria and attempt to minimise inappropriate prescribing”. The drug utilisation review was retrospective in nature because the data were obtained from a medical aid company and it was used to compare prescribing patterns to the SEMDSA guidelines (2009).

### 3.3 LITERATURE REVIEW

Since this study aimed at investigating the management of type 2 DM, a comprehensive literature review based on type 2 DM, was conducted from
February 2010 to November 2011. The purpose of the literature review was to gain an understanding of; as well as to obtain background and contextual knowledge; regarding type 2 DM. In addition, it provided information about the methodologies employed by other researchers in studies of a similar nature. A range of reference sources was consulted during the literature review, namely: text books, journal articles (local and international), and internet websites of diabetes organisations. Search engines EBSCOhost®, Science Direct® and Google™ Scholar were used to search for relevant journal articles.

3.4 DATA COLLECTION

The method that was used to obtain data from the medical aid company is discussed in this section as well as the format in which the information was provided by the medical aid company.

3.4.1 Data request

The medical aid company, from which the database was obtained, serves a substantial proportion of the private health sector of South Africa. The database consisted of records that were captured in community pharmacies across the country. A request letter for data was sent to the medical aid company. All criteria were described in the request letter, which is attached as Appendix B. The medical aid company accepted the request and provided a database with records pertaining to all diabetic patients. The records in the database extended over a three year period: from 1 January 2008 to 8 December 2010. Lastly, the gender and ethnicity of the patients were requested in the database, but were not provided.

3.4.2 Data format

The database was obtained on the 26 November 2010 as two comma-separated value (.csv) files. One of the files contained all of the diabetic medications and the other file contained all information pertaining to the comorbidities of the diabetic patients. The two files were imported into Microsoft
Excel® 2007. The entire database consisted of 50 529 patients, each having one or more patient records. "Column headings" for the file containing all of the medications used in the management of type 2 DM, are depicted below:

Table 3.1: Column headings and descriptions for the database containing the oral hypoglycaemic agents and insulin preparations

<table>
<thead>
<tr>
<th>COLUMN HEADING</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANON_NO</td>
<td>An anonymous number allocated to each patient.</td>
</tr>
<tr>
<td>AGE_AT</td>
<td>The age of the patient at the time of dispensing, in number of years.</td>
</tr>
<tr>
<td>PLAN_CODE</td>
<td>The code for the medical aid scheme type/plan the patient uses.</td>
</tr>
<tr>
<td>SERVICE_DATE</td>
<td>The date on which the script was dispensed. Format of date: dd/mm/yyyy.</td>
</tr>
<tr>
<td>SPECIALIST_CATEGORY</td>
<td>This refers to the status of the medical practitioner who prescribed the script. For example: General Practitioner (GP) or specialist.</td>
</tr>
<tr>
<td>ATC_CODE</td>
<td>The Anatomical Therapeutic Chemical Classification of the medication.</td>
</tr>
<tr>
<td>NAPPI_CD</td>
<td>The National Pharmaceutical Product Index (NAPPI) code of the medication. A NAPPI code is unique to each medication on the market and assists in claims. For example, the NAPPI code of Glucophage® 1000mg (active ingredient: metformin) is 703909001.</td>
</tr>
<tr>
<td>PRODUCT_NAME</td>
<td>The trade name of every product dispensed.</td>
</tr>
<tr>
<td>STRENGTH</td>
<td>The strength of the medication dispensed.</td>
</tr>
<tr>
<td>STRENGTH_UOM</td>
<td>The units corresponding to the strength of the medication (IU/1ml, U/1ml, or mg).</td>
</tr>
<tr>
<td>QUANTITY</td>
<td>The amount of medication(s) dispensed.</td>
</tr>
<tr>
<td>DOSAGE_FORM</td>
<td>The formulation of the medication (injections, tablets or slow release tablets) issued.</td>
</tr>
<tr>
<td>PRIMARY_ICD</td>
<td>The ICD-10 codes of the diagnosis of the patient's condition. For example: the primary ICD and the line ICD of a patient suffering from type 2 DM was E119.</td>
</tr>
<tr>
<td>LINE_ICD</td>
<td></td>
</tr>
<tr>
<td>AMTCLAIMED</td>
<td>The amount claimed from the medical aid company for the medication(s) dispensed.</td>
</tr>
</tbody>
</table>
Additional “column headings” that were found in the file with the comorbidities are shown in Table 3.2.

Table 3.2: Column headings and descriptions for chronic comorbidities database

<table>
<thead>
<tr>
<th>COLUMN HEADING</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTG_CODE</td>
<td>The category code of the chronic disease state.</td>
</tr>
<tr>
<td>DISEASE_CHAPTER_DESCR</td>
<td>The general category description of the chronic disease state. For example: cardiovascular disease.</td>
</tr>
<tr>
<td>CTG_DESCR</td>
<td>The specific category description of the chronic disease state. For example: Essential Hypertension.</td>
</tr>
</tbody>
</table>

3.5 DATA VERIFICATION

The database, obtained from the medical aid company, was verified to confirm that the information supplied met the criteria stipulated in the request letter.

The DM csv file was divided into three different Microsoft Excel® 2007 files and each was verified individually. The number of patient records for DM1, DM2 and DM3 files were as follows: 1000 001, 1000 001 and 14 005 (total of 2 014 007 records. Patient records were merged and the unique patient number was used to determine the total number of patients. It was found that the total number of diabetic patients in the database was 50 529 patients (DM1 file: 43 007; DM2 file: 41 591; DM3: 2 621).

The comorbid disease csv file, which was the file containing information pertaining to the chronic comorbid disease state(s) of the diabetic patients, was also broken down into three different Microsoft Excel © 2007 files, which were individually analysed. The total number of patient records was 2 399 595 records (comorbid disease 1 file: 1 000 001; comorbid disease 2 file: 1000 001; comorbid disease 3 file: 399 593). Therefore, the total number of patient records, inclusive of DM and comorbidity data, were 4 413 602 patient records.
The data was verified with respect to the ICD-10 codes and age, as described in sections 3.5.1 and 3.5.2, respectively.

### 3.5.1 ICD-10 Codes

Upon observation of the database, it was noted that there were inconsistencies in the ICD-10 codes and the classification of patients with respect to types 1 and 2 DM. Thus, complex sort criteria were used to filter the files in order to differentiate type 2 DM from type 1 DM. It was observed that the total number of diabetic patients in the study population (N) was 50,529. However of these, 10,899 patients were type 1 diabetic patients and 39,630 patients were type 2 DM. The type 1 patients were excluded from further analysis and stored in a separate file. Thus, the study sample (n) was 39,630 patients.

The comorbidity files were merged with the abovementioned study sample by ensuring that the comorbidity patient records corresponded to the matching DM patient records. The total number of records for the 39,630 patients was 3,112,701.

### 3.5.2 Age

Whilst verifying the data in the age column, it was observed that 586 patients were recorded as having had an age of “0” years. All of these patients were excluded from further age analyses, i.e. age group distribution for the study sample; and age group and insulin analysis. For these analyses, the study sample was taken as 39,044 patients (39,630 - 586 patients). However, since these patients only formed 1.5% of the total study sample and due to the fact that these patients had useful information regarding anti-diabetic medications, they were included in all of the other analyses.

### 3.6 DATA ANALYSES

With the use of both Microsoft Excel® 2007 and Statistica®, various data analyses were performed for the study sample (39,630 patients) and the results
are presented and discussed in Chapter 4. Sections 3.6.1 and 3.6.2 describe the steps involved in the analysis of patient demographics and ICD-10 codes, respectively. The other additional analyses, including statistical and quantitative analyses, are described in sections 3.6.3 and 3.6.4.

### 3.6.1 Patient demographics

The patient demographics that were evaluated in this study were restricted to the age of the type 2 DM patients. As described in section 3.7.2, the patients who had an age of “0” years recorded in the database were excluded from all further age-related analyses. The age of the patients varied considerably and thus, age category groups were allocated to the patients and analyses were carried out with respect to these age categories. These age categories were used to describe the demographics of the study sample and to determine insulin use relative to age.

The age categories (in years) that were used were based on those described by Bradshaw, Levitt, Norman and Pieterse (2007) in their research entitled “Estimating the burden of disease attributable to diabetes in South Africa in 2000”. The age groups (in years) used by Bradshaw were: <30; 30-44; 45-59; 60-69; 70-79; and >79.

For the purposes of the study, the age category 45-59 was further broken down into two categories, namely 45-49 and 50-59 because of an expected prevalence in those age groups. Thus, the age categories (in years) used in this study were as follows :< 30; 30-44; 45-49; 50-59; 60-69; 70-79; and >79.

### 3.6.2 ICD-10 Codes

As mentioned previously, there were some discrepancies in the allocated ICD-10 codes. For example, some patients who were on oral hypoglycaemic medication had been allocated a type 1 code. The ICD-10 code for type 1 DM is E109 and that for type 2 DM is E119. Complex sort criteria, based on the nature
of the medication, were used to filter the database in order to distinguish between the two types of diabetes. All patients using oral hypoglycaemic agents were allocated a type 2 DM ICD-10 code of E119. If they were not using oral hypoglycaemic agents, then the nature of insulin being administered was used as the criterion to determine which type of DM was most likely to have been diagnosed.

3.6.3 Study sample analyses

Besides the demographic description analyses that have already been described, Microsoft Excel® 2007 and Statistica® were used to further analyse the study sample with respect to: comorbid disease states medication use; insulin use; prescriber category; cost implications and prescribed and defined daily doses. The manner in which each of these analyses was conducted is explained in the sections which follow (3.6.3.1-3.6.3.7).

3.6.3.1 Characteristics of the entire study population

In order to assess the study sample with regards to the age distribution, the study sample (39 630 patients) was investigated with respect to the different age groups described in section 3.5.1. Thereafter, the relationship between the prevalence of type 2 DM and age was investigated.

3.6.3.2 Comorbid disease states analyses

The prevalence and importance of comorbid disease states in type 2 DM patients was discussed in section 2.7. Therefore, it was relevant to assess the patient database in order to identify and describe the existence of comorbid disease states. The following analyses were conducted:

- Number of comorbid disease states(s) per type 2 DM patient

Of the 39 630 patients in the database, 33 034 (83.4%) of them were identified as having comorbid disease states. The number of comorbid disease states per
patient was analysed. The number of comorbid disease states per patient ranged from one to eight. Since the number of patients, who were diagnosed with between five and eight comorbid disease states, was small for the purposes of this analysis, these patients’ categories were grouped together.

- Nature of comorbid disease states
The nature of the comorbid disease states was analysed and described in the following manner. The category of the comorbid disease state was determined by analysing the “Disease_Chapter_Descr” heading in the database. As explained earlier in the report, this column contained the general category description of the chronic comorbid disease state. It is noteworthy to mention that since a patient may suffer from more than one comorbid disease state category, the total number of incidences of comorbid disease (n = 44 241) was greater than the number of patients in the study sample (33 034 diabetic patients with one or more comorbidities).

It was found that there were ambiguous comorbid disease state categories in the disease category. Examples of these ambiguous categories were: “default-unknown” and “NONE”. To prevent any confusion, these ambiguous categories were combined as a category “unknown”. In the database, “default-unknown” was described as “DFLT-Default-Unknown CTG”; and “NONE” was described as “UNLC-Unallocated CTG code”. “Miscellaneous” was one of the findings in this analysis, however it is not representative of a disease state category as such since it is described as “578-Encounter for other Administrative Reasons” in the database.

In the comorbidity analysis, the cardiovascular disease state category was found to be the most prevalent with DM. This category encompassed the following cardiovascular disease states:
  - aortic stenosis;
  - arrhythmias;
  - cardiomyopathies;
  - conduction stenosis;
congestive heart failure;
- coronary artery disease;
- essential hypertension;
- hypercholesterolaemia;
- mitral regurgitation;
- mitral stenosis;
- other cardiovascular symptoms;
- other circulatory disorders;
- other diseases of the arteries;
- other disorders of pulmonary circulation;
- pulmonary embolism;
- rheumatic fever;
- thrombophlebitis; and
- varicose veins of lower extremities.

In order to obtain a clearer picture of the other frequently diagnosed comorbid disease state categories co-existing with DM (besides for cardiovascular disease states), another graph was drawn (excluding the cardiovascular disease category).

- Overview of the most prevalent comorbid disease states in type 2 DM patients

The specific category description of the chronic disease state was used to perform this analysis. The number of comorbid disease states for this particular evaluation was 44 241. This was greater than the number of patients suffering from a comorbidity (33 034) and this can be attributable to the fact that one patient may have been affected by more than one comorbid disease state.

3.6.3.3 Medication use analyses

The database contained numerous data about medication use. Analyses that were performed to determine medication use in the study sample are listed below:
- Number of medications prescribed per patient;
The number of medications prescribed for each patient was evaluated. The study sample was used and the size was 39,630 patients.

- Category distribution of all medications prescribed to the study sample
The “Product Name” field was used to determine the category distribution of all the medications prescribed to the study sample. The four terms used in this analysis were: oral hypoglycaemic agents, insulin, testing materials and other chronic disease state treatments. These terms will be discussed in the following paragraphs.

- Oral hypoglycaemic agents and insulin
Oral hypoglycaemic agents referred to all of the oral hypoglycaemic agents that were dispensed to patients in the database. Insulin included all of the insulin preparations that were dispensed to patients in the database for the management of type 2 DM. Biphasic insulin analogues, biphasic insulins, intermediate-to-long acting insulins and long-acting insulins were all preparations categorised as ‘insulin’.

- Testing materials
The testing materials were the blood and urine glucose monitoring materials that were dispensed to the patients. Although they are not medications as such, they were recorded under “product name”.

- Other chronic comorbid disease state treatments
Other chronic comorbid disease state treatments referred to any drug/s that was/were dispensed for the management of one or more comorbid disease states. These included all of the other medications besides oral hypoglycaemic agents, insulin and/or testing materials.

Thus, medications dispensed to the diabetic patients were categorised according to the abovementioned groups.
Overview of the nature and numbers of oral hypoglycaemic agents dispensed

Since oral hypoglycaemic agents were of relevance to the study, a breakdown was conducted of the different oral hypoglycaemic agents that were used. Using complex sort filters, all of the oral hypoglycaemic agents were converted from the trade name to the generic name (according to Table 2.15) and analysed accordingly. The total number of records for oral hypoglycaemic agents was 56,033 records. The number of records per medication was noted and expressed as a percentage of the total number of oral hypoglycaemic agent records.

3.6.3.4 Insulin use analyses

Insulin was the main focus of this DUR study and hence, in-depth insulin analyses were carried out with respect to the different insulin preparations. The following analyses were performed and discussed: insulin use and oral hypoglycaemic agents; insulin use and other comorbid disease state treatments; insulin use and age categories; and overview of insulin preparations dispensed and number of records. The methodology linked to the aforementioned analyses are summarised below:

- Insulin use and oral hypoglycaemic agents
  Statistical analyses as described in section 3.8.4 were carried out to determine the relationship between insulin use and oral hypoglycaemic agents. The statistical significance as well as the practical significance in effect size was calculated.

- Insulin use and other comorbid disease state treatments
  Analyses were conducted to determine the relationship between insulin use and the treatment of comorbid disease states. Both the statistical significance and the practical significance in effect size were calculated.
Insulin use and age categories
The relationship between insulin use, relative to the age of the patients, was also statistically analysed. Again, statistical significance and practical significance in effect size were determined.

Overview of insulin preparations dispensed and number of records
Biphasic insulin analogues, biphasic insulins, intermediate-to-long acting insulins and long-acting insulins were investigated with regard to the number of records dispensed. Each type of insulin category was analysed separately. The total number of records for each type of preparation was calculated and thereafter, the number of records of different formulations or products within each preparation category, were analysed.

3.6.3.5 Prescriber category analysis

The prescriber category analysis consisted of three analyses, namely: the number of prescribers per patient, category distribution of prescribers, and prescriber category for medications prescribed in study sample.

Number of prescribers per patient
The database was then analysed regarding the prescriber category. The database had a field entitled “specialist” and this was used to identify the type of prescriber of the script. Since the term “specialist” was confusing, as a prescriber could also be a specialist; the term “specialist” was changed to “prescriber category” to be able to differentiate.

The number of prescribers per patient was then analysed. The number of prescribers ranged from one to five prescribers. For analysis purposes, three-to-five prescribers were grouped together. There were 38 824 prescribers who were analysed. This number is greater than the study sample. This may be due to the fact that one patient may have been under the care of more than one prescriber. Thus, n referred to the total number of prescribers rather than the total number of patients.
• Category distribution of prescribers
Once the number of prescribers per patient was calculated, prescribers were then assessed according to their different areas of specialisation. The smaller groups of prescribers were clustered and termed “others”.

• Prescriber category for medications prescribed in study sample
The medications, including oral hypoglycaemic agents, insulin, testing materials and other chronic comorbid disease state treatments, were evaluated in terms of the prescribers who were prescribing the most medications most frequently. This was aimed at gaining insight into the prescribing patterns of the different categories of prescribers. In the analysis, 88 719 medication records were examined and n referred to the total number of medications, rather the total number of patients.

3.6.3.6 Cost implications overview
The cost implications of the diabetic medications were analysed with the average, minimum and maximum cost per treatment calculated for the oral hypoglycaemic agents and for the different insulin preparations. Each drug and its different strengths were analysed individually.

3.6.3.7 Prescribed daily doses (PDDs) and defined daily doses (DDDs)
Prescribed daily doses and defined daily doses form the mainstay of DUR. The average number of tablets per day, mode number of tablets per day and DDD, were calculated for oral hypoglycaemic agents. The average numbers of units, mode number of units per day and described daily dose were calculated for the different insulin preparations. In addition to PDD and DDD, the unit ranges used per day, for the insulin, were calculated for each preparation. The unit ranges that were used, included: 0-50 units; 51-100 units; 101-150 units; and > 150 units.
3.6.3.8 Statistical and quantitative analyses used for study sample

Microsoft Excel® 2007 and Statistica® were used to calculate mean, minimum and maximum values. Statistica® was also used to calculate the *p*-value and Cramér’s *V* value.

The *p*-value of an analysis is calculated in order to determine whether a result is statistically significant. Statsoft (2011) defines statistical significance of a result as “the probability that the observed relationship or a difference in a sample occurred by pure chance and that in the population from which the sample was drawn, no such relationship or difference exist”. In essence, statistical significance indicates the degree to which the result being analysed is an accurate representation of the population. When the *p*-value of an analysis is 0.05, it is indicative that there is a 5% probability that the relation between the variables being assessed in the sample happened by chance (Statsoft, 2011). When the *p*-value of an analysis is 0.05, that analysis is considered to be borderline statistically significant (Statsoft, 2011). Statistical significance occurs when the *p*-value of a result ≤ 0.01 (Statsoft, 2011). A result is considered to be “highly” significant when the *p*-value ≤ 0.001 or ≤ 0.005 (Statsoft, 2011).

Cramér’s *V* value is an effect size measure and indicates the level of practical importance of the finding. The following table illustrates the different Cramér’s *V* values and their interpretation:

<table>
<thead>
<tr>
<th>CRAMÉR’S V VALUE</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00 – 0.09</td>
<td>Negligible association</td>
</tr>
<tr>
<td>0.10 – 0.19</td>
<td>Weak association</td>
</tr>
<tr>
<td>0.20 – 0.39</td>
<td>Moderate association</td>
</tr>
<tr>
<td>0.40 – 0.59</td>
<td>Relatively strong association</td>
</tr>
<tr>
<td>0.60 – 0.79</td>
<td>Strong association</td>
</tr>
<tr>
<td>0.80 – 1.00</td>
<td>Very strong association</td>
</tr>
</tbody>
</table>

(Adapted from Lea & Parker, 1997)
The afore-described $p$- and Cramér's V values and interpretations were used during the analysis and discussion of the results of the study. The findings of the study are later described in chapter four.

### 3.7 ETHICAL APPROVAL FOR THE STUDY

A research proposal was drafted and submitted to the Department Research Technology and Innovation (DRTI) committee of the NMMU Pharmacy Department. Once the proposal was approved by the DRTI, it was then submitted to the NMMU Faculty of Health Sciences Research, Technology and Innovation (FRTI) committee for ethical approval. The FRTI committee granted ethical approval for the conduction of the research (H10HEAPH008). Appendix A is a copy of the ethics approval letter for the study.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association, 2008).

One of the ethical concerns raised was the inclusion of participants under the age of eighteen years in the study. This study was a review of a database in which all diabetic patients, including those who were under the age of eighteen years, were included. Since the patients in the database were not in any way identifiable or influenced or affected by this study, it was considered ethical to include them in the study.

### 3.8 CONFIDENTIALITY

The main ethical consideration in this study was the confidentiality of the patients and their respective drug therapies. The names or personal details of the patients were not made available to the researcher and can therefore not be disclosed in any manner in reports ensuing from the study. Individual patients were identified according to a numbering system allocated by the medical aid company. Furthermore, no patients were contacted or interviewed for the purpose of research. Since the study was retrospective in nature, no changes were made or recommended for the patients’ drug therapies. The identity and
confidentially of all subjects included in the study has therefore been and
remains protected. Lastly, no prescribers were contacted or identified during the
study.

3.9 LIMITATIONS OF THE STUDY

Before consideration is given to the results of the study (chapter four) it is
necessary to acknowledge the following limitations:

- The database, provided by the medical aid company, was inconsistent in
the classification of the diabetic patients into types, according to the ICD-
10 codes. The most common problem noted was that several type 2 DM
patients, who received both oral hypoglycaemic agents and insulin, were
classified with the ICD-10 code for type 1 DM. It was therefore, very
difficult at times to determine if the patients who had received insulin only,
had been classified correctly as type 1 diabetics. Consequently, although
filters were used in an attempt to separate type 1 and type 2 patients,
many of these who were on insulin only, had to be manually screened,
according to the type of insulin that they were receiving, which was both
time-consuming and may have resulted in some patients being incorrectly
classified.

- Although gender and ethnicity had been requested from the medical aid
company, these were not provided in the database and therefore could not
be considered. These patient demographics may have contributed to
obtaining more information in terms of type 2 DM prevalence with regards
to gender and ethnicity of the patients.

- Some patient records lacked all of the information and therefore had to be
excluded from the analysis.

- Caution needs to be exercised when generalising the results, since the
database was drawn from only one medical aid company which was being
used by private patients only. Furthermore, the general population of the
medical aid company was used as the study population. Thus, the results
of this study may not be representative of the trends and patterns in the
population of SA as it reflects patterns in private practice only; without considering the public sector trends in SA.
CHAPTER 4

RESULTS AND DISCUSSION: THE PHARMACOTHERAPEUTIC MANAGEMENT OF TYPE 2 DIABETIC PATIENTS
The main findings will be discussed in this section under the following headings:

- Demographics of the study sample.
- Epidemiological analysis of comorbid disease states in type 2 DM patients.
- Conclusion.

4.1 DEMOGRAPHICS OF THE STUDY SAMPLE

This section describes the size and age distribution of the study sample. Although the gender and ethnicity of data were requested from the medical aid, these were unfortunately not provided, so a comprehensive demographic description of the study sample was not possible.

4.1.1 Number of patients

The database of diabetic patients, obtained from the medical aid company (sections 3.3 – 3.4) was analysed. It was found that the total number of diabetic patients in the database was 50 529 however 21.6% (10 899) of these patients had a diagnosis of type 1 DM and were therefore, excluded from the study sample (Figure 4.1). The final study sample included 39 630 type 2 DM patients.

![Figure 4.1: Distribution of type 1 and type 2 diabetic patients in the database (n = 50 529)](image)
4.1.2 Age distribution of the study sample

The study sample was analysed according to the selected age categories, which were previously described in section 3.4.2. The age category distribution of the study sample is outlined in Figure 4.2.

![Figure 4.2: Age distribution of type 2 diabetic patients (n = 39 551*)](image)

* Total sample size was 39 630 patients; but 79 patients had their ages captured as "0" and thus were excluded from the age analysis.

From Figure 4.2, it can be observed that the age groups most commonly affected by type 2 DM, were the 50 to 59 year and 60 to 69 year age groups, comprising 29.7% and 26.1% of the study sample, respectively (n = 39 551).

The prevalence of DM in the study sample corresponds to the global trends of DM; where it is more frequently diagnosed in people who are older than 65 years of age (Green et al., 2004; Rheeder, 2006). A similar trend was observed in a South African study (n = 200), where 28.7% of patients, who were of mixed origin, aged 65 years and older were found to have type 2 DM (SEMDSA, 2011). The findings are also in accordance with the evidence reported in 2000,
by Green et al. (2004), who identified the age group, 45 to 64 years, to be most commonly affected by DM.

In a South African study, Bradshaw et al. (2007), identified DM as being most prevalent in male patients over the age of 80 years and in female patients, aged 60 to 69 years. However, no gender descriptions were provided in the study database, so a similar age and gender analysis was not possible.

4.2 COMORBID DISEASE STATES IN TYPE 2 DIABETES MELLITUS PATIENTS

As discussed in the literature review (section 2.7), other comorbid disease states - particularly those associated with insulin resistance syndrome - are often present in type 2 DM patients. The majority of DM patients in the sample (83.4%) had been diagnosed with and were being treated for at least one other disease state. Only 16.6% (6 596 patients) were not being treated for another disease state - that is that they had no diagnosed comorbidities. Figure 4.3 illustrates the extent to which the diabetic population was affected by one or more comorbid disease state(s).

![Figure 4.3: Presence of comorbid disease states in type 2 DM patients (n = 39 630)](image_url)
The comorbid disease states were further analysed according to the:
- number of comorbid disease states per diabetic patient;
- nature of comorbid disease states; and
- most prevalent comorbid disease states identified in the study sample.

4.2.1 Number of comorbid disease state(s) per patient

As alluded to in section 4.2, in addition to DM, 83,4% of the patients in the study sample had been diagnosed with at least one other disease state. The number of comorbid disease states per diabetic patient was investigated and is outlined in Figure 4.4. The majority of patients with comorbidities (73,7%) only had one co-existing disease state, whilst 20,5% had been diagnosed with two comorbid disease states and 4,5% were found to have three comorbid disease states.

It is noteworthy to mention that although only 0,3% of the DM patients had more than five comorbid disease states, the highest number identified was eight (0,01%). The average number of comorbid disease state per type 2 DM patient was found to be 1,34.

Figure 4.4: Number of comorbid disease states per type 2 DM patient

\(n = 33\,034^*\)

* Total sample size: 39 630, but 6 596 diabetic patients had no co-existing disease states
4.2.2 Nature of comorbid disease states

Isley et al. (2008) reported that patients with type 2 DM were often diagnosed with other comorbid disease states and developed metabolic or insulin resistance syndrome. Morbidity statistics in South Africa published in 2007, revealed that death in type 2 DM patients was often as a result of cardiovascular disease (53.6%), with 36.8% due to hypertensive disease and 14.6% as a result of a stroke (Statistics South Africa, 2007). These figures suggest that there are often comorbidities associated with DM. Therefore, a further analysis was conducted to investigate the nature of the comorbid disease state(s). Figure 4.5 summarises the categories of comorbid disease states that were diagnosed in the study sample.

![Figure 4.5: Categories and prevalence of comorbid disease states](n = 44241*)
* NOTE: One patient may suffer from more than one comorbid disease state category, thus, $n$ is greater than the number of patients in the study sample (33,034 diabetic patients with one or more comorbidities), and refers to the number of comorbid disease state cases, rather than the number of patients.

According to Figure 4.5, 71.2% of the comorbid disease state cases, that were found to be accompanying DM, were classified as cardiovascular diseases. In order to obtain a better understanding of the nature of the disease states coexisting with DM, further analyses were conducted. Excluding the cardiovascular diseases, the other comorbid disease states were grouped into broader categories, which are depicted in Figure 4.6.
Figure 4.6: Distribution of comorbid disease states (excluding cardiovascular), according to category [n = 44 241]

# Unknown refers to the comorbid disease states for which patients were being treated, but for which no diagnosis was indicated. This was discussed in section 3.8.3.2 in the research methodology.

The most prevalent comorbid disease state categories (following cardiovascular disease states) that were seen in the diabetic study sample: were endocrine (4.7%), miscellaneous (5.2%) and respiratory (4.7%) in nature. The
‘miscellaneous’ disease category was used to group the following ICD-10 descriptions: ‘encounter for other administrative reasons’; and ‘other general signs, symptoms and conditions’. Section 4.2.3 provides a summary of the individual disease states that were found to be most frequently diagnosed in the study sample.

### 4.2.3 Overview of the most prevalent comorbib disease states in type 2 diabetic patients

In order to provide an in-depth understanding of the comorbid disease states that accompanied DM, an analysis was conducted to identify the ten most prominent comorbid disease states. The results are presented in Figure 4.7.

![Figure 4.7: Ten most prominent comorbid disease states (with ICD-10 codes) associated with DM (n = 44 241)](image)

The three most prevalent comorbid disease states that were identified were all cardiovascular diseases, namely: essential hypertension (40,1%), hypercholesterolaemia (23,5%) and coronary artery disease (5,0%). This is consistent with the finding that cardiovascular diseases as a group, accounted for 71,2% of all coexisting disease states in the diabetic study sample. This was
also in accordance with the literature previously cited, which suggested that insulin resistant syndrome was highly prevalent in type 2 DM and that the cause of death in type 2 DM patients was often of a cardiovascular nature (Alberti et al., 2001; Bhattacharyya, 2001; Chisholm & Shaw, 2003; Avogaro et al., 2006). Other comorbid disease states that were found to occur in the diabetic study sample, included: psychiatric (2.4%), ophthalmologic (2.0%), neurological (1.9%), musculoskeletal (1.6%) and obstetrical and gynaecological (1.3%) disorders.

Disease states of a neurological nature, affected 1.9% of the study sample and were considered to be relevant because some of the microvascular complications of type 2 DM include: diabetic - , autonomic - and peripheral neuropathies (Bate & Jerums, 2003). Moreover, diabetic retinopathy, another microvascular complication of type 2 DM (Bate & Jerums, 2003) may have accounted for the occurrence of ophthalmologic comorbid disease states present in the study sample. Obstetrical and gynaecological comorbid disease states may have been related to vaginal thrush that may have occurred in the diabetic women. Comorbid disease states of a psychiatric nature may possibly be linked to the presence of depression in type 2 DM patients. Osteomyelitis, another microvascular complication of type 2 DM, could explain the occurrence of musculoskeletal comorbid disease states (Bate & Jerums, 2003).

### 4.3 PHARMACOEPIDEMIOLOGICAL ANALYSIS OF MEDICATION USE IN TYPE 2 DIABETES MELLITUS PATIENTS

A pharmacoepidemiological analysis was conducted to evaluate the medications that were being used by the study sample of type 2 diabetic patients. As was observed in section 4.2, the majority of patients also had one or more comorbid disease states. Thus, the analysis focused on both the use of diabetic medications, as well as the other medications that were being prescribed for the management of the coexisting disease state(s). These findings are presented in the following order: number of medications prescribed per patient (section 4.3.1) and the nature and category distribution of prescribed medications (section 4.3.2).
4.3.1 Number of medications prescribed per patient

The total number of medications that were prescribed per patient for both the management of the DM and the coexisting disease state/s is outlined in Figure 4.8. Figure 4.8 shows that the number of medications concurrently prescribed, per patient, ranged from a minimum of one, to a maximum of thirty-seven. The concurrent use of thirty-seven medications could raise an issue of polypharmacy.

The modal number of medications per patient, was four (11.7%) and only 5.5% of the patients were receiving a single medication. In other words, 94.5% of the type 2 diabetic patients had been prescribed at least two or more medications. This is to be expected, since the majority of patients (73.7%) had been diagnosed with at least one other disease state, in addition to type 2 DM.

![Figure 4.8: Distribution of the number of medications prescribed per patient (n = 39360)](image-url)
### 4.3.2 Nature of the prescribed medications

In order to gain a better perspective about the nature of the medications that were dispensed to the diabetic patients, they were categorised according to the following classes: oral hypoglycaemic agents, insulins, testing materials and agents used in the management of comorbid disease states. As discussed in section 2.8, the management of type 2 DM also incorporates regular blood glucose monitoring, therefore the testing materials were also included in the pharmacoepidemiological analysis of medication use in type 2 DM. Figure 4.9 shows the percentage distribution of patient medication, according to the aforementioned categories.

![Bar chart showing percentage distribution of medications](image)

**Figure 4.9: Distribution of all medications prescribed according to category classification**

(n = 39 630)
According to Figure 4.9, it is evident that 38.0% of all of the medications that were prescribed to the study sample were oral hypoglycaemic agents. This is consistent with the fact that oral hypoglycaemic agents are recommended as first-, second- and third-line treatments in the pharmacological management of type 2 DM (previously discussed in section 2.10). This finding is therefore in agreement with the prescribing guidelines in SA, namely the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009), as well as the Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (National Department of Health, 2008).

According to the aforementioned South African guidelines, metformin, glibenclamide, gliclazide and pioglitazone are the most frequently recommended oral hypoglycaemic agents.

In addition to the oral hypoglycaemic agents, other chronic disease state treatments were included in this analysis. The category - “other chronic disease state treatments”, included all medications that were being used for the management of the comorbid disease state(s). It is evident that more than a third (35.9%) of the total number of medications that were prescribed for the diabetic patients, were being used to treat other chronic comorbid disease states. This is consistent with the finding that 83.4% of the study sample had at least one comorbidity.

It was also observed that the proportion of the total number of medications that were used for the management of comorbid disease states (35.9%), was similar to the number of oral hypoglycaemic agents dispensed (38.0%). This finding is considered to be relevant since the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009) provide recommendations for the pharmacological management of HT and hyperlipidaemia. Additionally, the SEMDSA guidelines recommend the use of antiplatelet agents in type 2 DM patients. In comparison, the Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008) recommend simvastatin therapy in all type 2 DM patients. Therefore, it was predictable that 35.9% of medications were being used for the management of comorbid disease state(s), in the type 2 DM patients.
The insulin category encompasses the different insulin preparations (available on the South African market) that are used in the management of type 2 DM. These insulin preparations could be intermediate-, long-acting or biphasic insulin preparations. It was found that insulin constituted 10,7% of the total medications that were prescribed. Insulin use (10,7%) was found to be approximately one third of the trend observed for oral hypoglycaemic agents (38,0%).

Testing materials represented blood and urine monitoring materials, which were being used by the study sample. Testing materials were dispensed as medications, thus, they were also analysed as part of medication use. Figure 4.9 showed that 15,4% of the medications that were dispensed, were testing materials. Testing materials were more likely to have been used by type 2 DM patients who were on insulin treatment, relative to those patients using oral hypoglycaemic agent(s). As described in section 2.10.1, SMBG is necessary in patients injecting insulin and only necessary for special cases in patients on oral hypoglycaemic agents. Since only 10,7% of patients in the database were using insulin, it is to be expected that only 15,4% of the patients were using testing materials. This finding is in accordance with the SMBG recommendation as per the SEMDSA for Diagnosis and Management of type 2 DM for Primary Health Care (2009) guidelines (discussed in section 2.10.1).

The abovementioned findings with regards the distribution of medications used compared similarly to the results of a study conducted in Norway by Holmen and Midthjell (1994). In this Norwegian study, it was found that amongst the 2 242 diabetic patients (who were 20 years of age or older), 39% were taking oral hypoglycaemic agents, compared to 38,0% in this study. These results indicate that the use of oral hypoglycaemic agents was preferred to insulin. In contrast, regarding insulin use, it was observed in the Norwegian study, that 20% of the diabetic patients were administering insulin, versus 10,7% in this study. Furthermore, the study performed in Norway revealed a comparable pattern with the antidiabetic medications (41%) and the other chronic disease state treatments (35,9%) in this study. Since oral hypoglycaemic agents were more commonly used by type 2 diabetic patients as compared to insulin, an overview
of the oral hypoglycaemic agents dispensed, was performed. This is discussed in section 4.4.

4.4 OVERVIEW OF ORAL HYPOGLYCAEMIC AGENTS DISPENSED

This section reviews the oral hypoglycaemic agents that were dispensed to the patients in the study sample. The nature of the agents dispensed to the patients and an analysis of the PDD and DDD for each oral hypoglycaemic agent will be provided. A summary of all of the oral hypoglycaemic agents that were dispensed is provided in Table 4.1.

Table 4.1: A summary of oral hypoglycaemic agents dispensed
(n = 56 033)

<table>
<thead>
<tr>
<th>MEDICATION GROUP</th>
<th>NUMBER OF MEDICATIONS DISPENSED</th>
<th>PERCENTAGE OF TOTAL NUMBER OF MEDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>31 365</td>
<td>56,0%</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>601</td>
<td>1,1%</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>20 970</td>
<td>37,4%</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>83</td>
<td>0,2%</td>
</tr>
<tr>
<td>Alpha Glucosidase Inhibitors</td>
<td>43</td>
<td>0,08%</td>
</tr>
<tr>
<td>Biguanides + Sulphonylureas</td>
<td>2 971</td>
<td>5,3%</td>
</tr>
<tr>
<td><strong>Total number of oral hypoglycaemic agents</strong></td>
<td><strong>56 033</strong></td>
<td><strong>100,0%</strong></td>
</tr>
</tbody>
</table>

Biguanides was found to be the most frequently prescribed medication group amongst the oral hypoglycaemic agents (56,0%). Furthermore, the study concluded that sulphonylureas were the second most popular oral hypoglycaemic agents. These findings were predictable since the Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008) recommend biguanides and sulphonylureas as first- and second-line agents in the pharmacological management of type 2 DM, respectively.

The SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009) recommend, as second-line therapy, that
sulphonylureas be used on their own or added to metformin if glycaemic targets are not being achieved with metformin alone. In this study, it was noted that the combination use of biguanides and sulphonylureas was 5.3%, after monotherapy with biguanides and sulphonylureas. This observation of the combination use of biguanides and sulphonylureas after monotherapy with either metformin or sulphonylureas, was in line with The SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009).

According to Table 4.1, thiazolidinediones use was 1.1% out of 56 033 medications. This small percentage, as compared to the use of biguanides, was considered to be predictable, since the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009) recommend the use of a thiazolidinedione as a third-line agent in the pharmacological management of type 2 DM.

Table 4.2 provides a detailed analysis of the oral hypoglycaemic agents dispensed. The oral hypoglycaemic agents were categorised according to the medication group and thereafter according to the different strengths within the group.

**Table 4.2: Details of oral hypoglycaemic agents dispensed (n = 56 033)**

<table>
<thead>
<tr>
<th>MEDICATION NAME</th>
<th>NUMBER OF MEDICATIONS DISPENSED</th>
<th>PERCENTAGE OF NUMBER OF MEDICATIONS IN CATEGORY</th>
<th>PERCENTAGE OF TOTAL NUMBER OF MEDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biguanides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin 500mg</td>
<td>13 950</td>
<td>44.5%</td>
<td>24.9%</td>
</tr>
<tr>
<td>Metformin 850mg</td>
<td>11 689</td>
<td>37.3%</td>
<td>20.9%</td>
</tr>
<tr>
<td>Metformin 1000mg</td>
<td>5 726</td>
<td>18.3%</td>
<td>10.2%</td>
</tr>
<tr>
<td><strong>Total Number of Medications</strong></td>
<td><strong>31 365</strong></td>
<td><strong>100%</strong></td>
<td><strong>56.0%</strong></td>
</tr>
</tbody>
</table>
### Table 4.2: Details of oral hypoglycaemic agents dispensed (continued)

<table>
<thead>
<tr>
<th>MEDICATION NAME</th>
<th>NUMBER OF MEDICATIONS DISPENSED</th>
<th>PERCENTAGE OF NUMBER OF MEDICATIONS IN CATEGORY</th>
<th>PERCENTAGE OF TOTAL NUMBER OF MEDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone 15mg</td>
<td>145</td>
<td>24,1%</td>
<td>0,3%</td>
</tr>
<tr>
<td>Pioglitazone 30mg</td>
<td>361</td>
<td>60,1%</td>
<td>0,6%</td>
</tr>
<tr>
<td>Rosiglitazone 2mg</td>
<td>12</td>
<td>2,0%</td>
<td>0,02%</td>
</tr>
<tr>
<td>Rosiglitazone 4mg</td>
<td>83</td>
<td>13,8%</td>
<td>0,2%</td>
</tr>
<tr>
<td><strong>Total Number of Medications</strong></td>
<td>601</td>
<td>100%</td>
<td>1,1%</td>
</tr>
<tr>
<td><strong>Sulphonylureas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glibenclamide 5mg</td>
<td>4 045</td>
<td>19,3%</td>
<td>7,2%</td>
</tr>
<tr>
<td>Gliclazide 30mg</td>
<td>6 156</td>
<td>29,4%</td>
<td>11,0%</td>
</tr>
<tr>
<td>Gliclazide 40mg</td>
<td>7</td>
<td>0,03%</td>
<td>0,01%</td>
</tr>
<tr>
<td>Gliclazide 80mg</td>
<td>7 592</td>
<td>36,2%</td>
<td>13,6%</td>
</tr>
<tr>
<td>Glimepiride 1mg</td>
<td>809</td>
<td>3,9%</td>
<td>1,4%</td>
</tr>
<tr>
<td>Glimepiride 2mg</td>
<td>1 275</td>
<td>6,1%</td>
<td>2,3%</td>
</tr>
<tr>
<td>Glimepiride 3mg</td>
<td>10</td>
<td>0,05%</td>
<td>0,02</td>
</tr>
<tr>
<td>Glimepiride 4mg</td>
<td>1 008</td>
<td>4,8%</td>
<td>1,8%</td>
</tr>
<tr>
<td>Glipizide 5mg</td>
<td>60</td>
<td>0,3%</td>
<td>0,1%</td>
</tr>
<tr>
<td>Chlorpropamide 250mg</td>
<td>8</td>
<td>0,04%</td>
<td>0,01%</td>
</tr>
<tr>
<td><strong>Total Number of Medications</strong></td>
<td>20 970</td>
<td>100%</td>
<td>37,4%</td>
</tr>
<tr>
<td><strong>Meglitinides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide 120mg</td>
<td>4</td>
<td>4,8%</td>
<td>0,01%</td>
</tr>
<tr>
<td>Repaglinide 0,5mg</td>
<td>22</td>
<td>26,5%</td>
<td>0,04%</td>
</tr>
<tr>
<td>Repaglinide 1mg</td>
<td>41</td>
<td>49,4%</td>
<td>0,07%</td>
</tr>
<tr>
<td>Repaglinide 2mg</td>
<td>16</td>
<td>19,3%</td>
<td>0,03%</td>
</tr>
<tr>
<td><strong>Total Number of Medications</strong></td>
<td>83</td>
<td>100%</td>
<td>0,2%</td>
</tr>
<tr>
<td><strong>Alpha Glucosidase Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose 50mg</td>
<td>27</td>
<td>62,8%</td>
<td>0,05%</td>
</tr>
<tr>
<td>Acarbose 100mg</td>
<td>16</td>
<td>37,2%</td>
<td>0,03%</td>
</tr>
<tr>
<td><strong>Total Number of Medications</strong></td>
<td>43</td>
<td>100%</td>
<td>0,08%</td>
</tr>
</tbody>
</table>
In the Biguanides medication group, Metformin 500mg tablet was established to be the oral hypoglycaemic agent that was the most frequently dispensed in that group: 44,5% of 31365 biguanides. Metformin 500mg being the most used oral hypoglycaemic agent, was in accordance with the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009) and the Standard Treatment Guidelines and Essential Medicines List for Primary
Health Care (2008). These guidelines were previously discussed in sections 2.11.1 and 2.11.2.

Furthermore, it was noted that Gliclazide 80mg was the most commonly prescribed Sulphonylurea agent: 36.2% of 20970 Sulphonylureas. This pattern is identifiable when considering the Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008). The latter recommends either Glibenclamide or Gliclazide as a second-line pharmacological treatment for type 2 DM. It can be deduced from these observations that the Sulphonylurea of choice was Gliclazide.

When observing the combination use of Biguanides and Sulphonylureas, Metformin + Glibenclamide 500/5mg was found to be the most commonly used combination agent (45.7% of 2 971 medications). As described earlier in the discussion, with reference to the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009), it is understandable that this pattern was observed for the combination use of Biguanides and Sulphonylureas.

Lastly, when taking the Thiazolidinediones medication group into consideration, it was observed that Pioglitazone 30mg was used 60.1% out of 601 medications in that group. According to the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009), Pioglitazone is recommended to be added to therapy when glycaemic targets are not being achieved with the use of Sulphonylureas and Biguanides.

When comparing the different medication groups to the two guidelines, namely the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009) and the Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008), it was predictable to find that Biguanides, Sulphonylureas, combination thereof, and Thiazolidinediones were the most commonly prescribed oral hypoglycaemic agents. The other oral hypoglycaemic agents, namely: Meglitinides and Alpha Glucosidase Inhibitors, were used to a lesser extent in this study. The
abovementioned trends in oral hypoglycaemic use indicates that both the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009) and the Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008) were used when prescribing oral hypoglycaemic agents for the management of type 2 DM.

4.5 EPIDEMIOLOGICAL ANALYSIS OF INSULIN USE IN TYPE 2 DIABETES MELLITUS PATIENTS

As was identified earlier in the discussion, insulin use was found to constitute 10,7% of the total number of medications used in the study sample. In order to identify patterns of insulin prescribing and to compare these with recommended guidelines, the use of insulin alone; and in combination with oral hypoglycaemic agents; and agents used in the management of comorbidities, was analysed.

4.5.1 Overview of insulin preparations dispensed

The aim of this section is to provide an overview of the insulin preparations that were dispensed to the study sample. Table 4.3 provides a summary of the categories of insulin preparations that were dispensed.

<table>
<thead>
<tr>
<th>INSULIN PREPARATION CATEGORY</th>
<th>NUMBER OF INSULIN PREPARATIONS DISPENSED</th>
<th>PERCENTAGE OF TOTAL NUMBER OF INSULIN PREPARATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic Insulin Analogues</td>
<td>5 802</td>
<td>57,2%</td>
</tr>
<tr>
<td>Biphasic Insulins</td>
<td>1 652</td>
<td>16,3%</td>
</tr>
<tr>
<td>Intermediate-to-Long Acting</td>
<td>1 269</td>
<td>12,5%</td>
</tr>
<tr>
<td>Long-Acting Insulins</td>
<td>1 422</td>
<td>14,0%</td>
</tr>
<tr>
<td><strong>Total number of insulin preparations</strong></td>
<td><strong>10 145</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

It is evident from Table 4.3 that the two most frequently prescribed types of insulin were: biphasic insulin analogues (57,2%) and biphasic insulins (16,3%).
This identified trend may be attributed to the fact that the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009) recommend the addition of biphasic insulin preparations, after treatment with oral hypoglycaemic agents has been initiated, if deemed necessary. In addition, the Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008) recommend the use of biphasic insulin as substitution therapy for oral hypoglycaemic agents in the management of type 2 DM. The difference between biphasic insulin analogues and biphasic insulins stem from their pharmacokinetic properties. Most biphasic insulin analogues have an onset of action of fifteen minutes, whereas biphasic insulins have an onset of action of thirty minutes. It should also be noted that intermediate-to-long acting and long-acting insulins are used to a lesser extent compared to biphasic insulin preparations. The Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008) suggest the use of intermediate or long-acting insulins as add-on therapy to oral hypoglycaemic agents for the management of type 2 DM.

Table 4.4: Details of insulin preparations dispensed

<table>
<thead>
<tr>
<th>INSULIN PREPARATION CATEGORY AND TRADE NAMES IN EACH CATEGORY</th>
<th>NUMBER OF INSULIN PREPARATIONS DISPENSED</th>
<th>PERCENTAGE OF NUMBER OF INSULIN PREPARATIONS IN CATEGORY</th>
<th>PERCENTAGE OF TOTAL NUMBER OF INSULIN PREPARATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic insulin analogues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humalog mix25 cartridge 3ml® 182</td>
<td>3,1%</td>
<td>1,8%</td>
<td></td>
</tr>
<tr>
<td>Humalog mix25 kwikpen® 594</td>
<td>10,2%</td>
<td>5,9%</td>
<td></td>
</tr>
<tr>
<td>Humalog mix25 penset 3ml® 729</td>
<td>12,6%</td>
<td>7,2%</td>
<td></td>
</tr>
<tr>
<td>Humalog mix25 vial 10ml® 13</td>
<td>0,2%</td>
<td>0,1%</td>
<td></td>
</tr>
<tr>
<td>Humalog mix50 cartridge 3ml® 42</td>
<td>0,7%</td>
<td>0,4%</td>
<td></td>
</tr>
<tr>
<td>Novomix30 flexpen 3ml® 4 079</td>
<td>70,3%</td>
<td>40,2%</td>
<td></td>
</tr>
<tr>
<td>Novomix30 penfill 3ml® 163</td>
<td>2,8%</td>
<td>1,6%</td>
<td></td>
</tr>
<tr>
<td>Total number of insulin preparations 5 802</td>
<td>100%</td>
<td>57,2%</td>
<td></td>
</tr>
</tbody>
</table>
Table 4.4: Details of insulin preparations dispensed (continued)

<table>
<thead>
<tr>
<th>INSULIN PREPARATION CATEGORY AND TRADE NAMES IN EACH CATEGORY</th>
<th>NUMBER OF INSULIN PREPARATIONS DISPENSED</th>
<th>PERCENTAGE OF NUMBER OF INSULIN PREPARATIONS IN CATEGORY</th>
<th>PERCENTAGE OF TOTAL NUMBER OF INSULIN PREPARATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actraphane hm (ge) penset 3ml®</td>
<td>1 076</td>
<td>65,1%</td>
<td>10,6%</td>
</tr>
<tr>
<td>Actraphane hm(ge) penfill 3ml®</td>
<td>26</td>
<td>1,6%</td>
<td>0,3%</td>
</tr>
<tr>
<td>Actraphane hm(ge) vial 10ml®</td>
<td>152</td>
<td>9,2%</td>
<td>1,5%</td>
</tr>
<tr>
<td>Humulin 30/70 cartridge 3ml®</td>
<td>62</td>
<td>3,8%</td>
<td>0,6%</td>
</tr>
<tr>
<td>Humulin 30/70 disposable pen 3ml®</td>
<td>207</td>
<td>12,5%</td>
<td>2,0%</td>
</tr>
<tr>
<td>Humulin 30/70 vial 10ml®</td>
<td>38</td>
<td>2,3%</td>
<td>0,4%</td>
</tr>
<tr>
<td>Insuman Comb 30/70 cartridge 3ml®</td>
<td>91</td>
<td>5,5%</td>
<td>0,9%</td>
</tr>
<tr>
<td><strong>Total number of insulin preparations</strong></td>
<td><strong>1 652</strong></td>
<td><strong>100%</strong></td>
<td><strong>16,3%</strong></td>
</tr>
<tr>
<td>Intermediate-to-long acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin N cartridge 3ml®</td>
<td>21</td>
<td>1,7%</td>
<td>0,2%</td>
</tr>
<tr>
<td>Humulin N disposable 3ml®</td>
<td>261</td>
<td>20,6%</td>
<td>2,6%</td>
</tr>
<tr>
<td>Humulin N vial 10ml®</td>
<td>12</td>
<td>0,9%</td>
<td>0,1%</td>
</tr>
<tr>
<td>Protaphane flexpen 3ml®</td>
<td>936</td>
<td>73,8%</td>
<td>9,2%</td>
</tr>
<tr>
<td>Protaphane hm(ge) penfill 3ml®</td>
<td>16</td>
<td>1,3%</td>
<td>0,2%</td>
</tr>
<tr>
<td>Protaphane hm(ge) vial 10ml®</td>
<td>23</td>
<td>1,8%</td>
<td>0,2%</td>
</tr>
<tr>
<td><strong>Total number of insulin preparations</strong></td>
<td><strong>1 269</strong></td>
<td><strong>100%</strong></td>
<td><strong>12,5%</strong></td>
</tr>
<tr>
<td>Long-acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levemir prefilled cartridge 3ml®</td>
<td>24</td>
<td>1,7%</td>
<td>0,2%</td>
</tr>
<tr>
<td>Lantus I Optiset pen®</td>
<td>294</td>
<td>20,7%</td>
<td>2,9%</td>
</tr>
<tr>
<td>Levemir flexpen prefilled 3ml®</td>
<td>463</td>
<td>32,6%</td>
<td>4,6%</td>
</tr>
<tr>
<td>Lantus Optiset disposable pen®</td>
<td>641</td>
<td>45,1%</td>
<td>6,3%</td>
</tr>
<tr>
<td><strong>Total number of insulin preparations</strong></td>
<td><strong>1 422</strong></td>
<td><strong>100%</strong></td>
<td><strong>14,0%</strong></td>
</tr>
</tbody>
</table>

Table 4.4 provides more details with regards to the different insulin preparations dispensed to the study sample.

Amongst the biphasic insulin analogues category, the Novomix30 flexpen (3ml) was found to be the most popular preparation (70,3%) in the 5 802 biphasic insulin analogues. This pattern was to be expected because Novomix30 flexpen (3ml) has the longest onset of action time, time to peak and duration when compared to the other biphasic insulin analogues (Rossiter, 2009), thus making it a suitable biphasic insulin preparation. Similarly, Actraphane hm (ge) Penet
(3ml) was observed to be the most commonly used biphasic insulin (65,1% of 1 652 biphasic insulins). Actraphane has a longer duration of action, as well as a longer time to peak, when compared to other biphasic insulins (Rossiter, 2009), hence making it an ideal choice.

Protaphane flexpen (3ml) was found to be the most commonly used intermediate-to-long acting insulin (73,8% of 1 269 intermediate-to-long acting insulins). When Protaphane and Humulin N are compared in terms of their pharmacokinetic properties, it is evident that Protaphane has a longer onset of action, time to peak and duration of action (Rossiter, 2009). These properties make Protaphane an appropriate and more favourable intermediate-to-long acting insulin.

According to Table 4.4, the Lantus Optiset disposable pen was found to be the most popular insulin preparation in the category: long-acting insulins (45,1% of 1 422 long-acting insulins). Upon contrasting the pharmacokinetics of the various long-acting insulins, it was found that there are no noticeable differences amongst the preparations to justify the preferred use of Lantus Optiset. Perhaps the choice of Lantus Optiset was based on the cost implications, which will be discussed later in section 4.7.

4.5.2 Prescribing of insulin with oral hypoglycaemic agents

As described in section 2.10, insulin is used for the management of type 2 DM, with or without the use of oral hypoglycaemic agents. The use of insulin in this regard has been reported to make a significant improvement in the glycaemic control (Burden et al., 2002; Gerich et al., 2003; Riddle, 2004; Austin et al., 2006).

An analysis was carried out to determine the prescribing patterns of insulin and oral hypoglycaemic agents. It was identified that 88,9% of the type 2 DM patients (n = 39 629) were prescribed oral hypoglycaemic agents. Of these 35 229 patients, 19,2% were also on insulin therapy. Thus, only 80,8% of patients (n = 35 229) were on oral hypoglycaemic agents alone. The remainder of the study sample, who were not on oral hypoglycaemic agents, were
analysed. It was observed that 71.9% of these 4 400 patients, who were not using oral hypoglycaemic agents, were using insulin. These patients on insulin monotherapy constituted 8.0% (n = 39 629) of the study sample. The rest of the type 2 DM patients (100% - [88.9% + 8.0%] = 3.1%) were not on any oral hypoglycaemic agents nor insulin therapy.

It was highly significant to observe that most patients were being managed on oral hypoglycaemic agents only, as compared to patients who were being managed with a combination of oral hypoglycaemic agents and insulin therapy (Chi-square = 5785.5; df=1; p = 0.0000). Furthermore, the above mentioned finding was considered to be of medium practical significance in effect size (Cramér's V = 0.38).

4.5.3 Insulin use and other disease state treatments

In order to investigate the use of insulin in the management of type 2 DM in the presence of other comorbid disease states, an analysis of insulin use and other disease state treatments was carried out.

Upon comparison of comorbid disease state treatments and insulin use, it was found that 84.1% of the study sample (n = 39 629) was being treated for comorbid disease state(s). Amongst these patients, it was determined that 24.5% (n = 33 332) were also using prescribed insulin. It was significant to conclude that only approximately one quarter of patients with comorbidities were managed with insulin (Chi-square = 32.2; df=1; p = 0.0000). However, this analysis was considered to be of small practical significance in effect size, since Cramér's V was found to be 0.03.

4.5.4 Insulin use and age categories

In order to obtain a better understanding of the use of insulin in the study sample, insulin use, relative to patient age, was analysed. From table 4.5, it can observed that 48.3% of patients under the age of 30 years (n = 582) were using insulin. Similarly, in the age category 30-44 years, 29.0% of patients (n = 5 895)
were on insulin. It is to be noted that insulin was used the least in the age group older than 79 years of age (16,0%). It was deemed significant that insulin was used to a lesser extent as the age groups of the patients increased (Chi-square = 350, 6; df = 6; p = 0,0000). However, this analysis was considered to be of small practical significance (Cramér’s V = 0,099). The minimal use of insulin in the elderly group was to be expected since there have been several risks that have been associated with the use of insulin in the elderly, namely hyper- and hypoglycaemia (Lawrence et al., 2006). Furthermore, there are other factors which affect the use of insulin in the elderly type 2 diabetic patients. These factors are: comorbid disease state(s), side effects of medications used and the process of aging (Lawrence et al., 2006).

The patterns of insulin use in the different age categories were considered to be more applicable to type 1 DM rather than type 2 DM. Literature states that type 1 DM is more prevalent in younger patients (Bhattacharyya, 2001; Chisholm & Shaw, 2003; Mbanya & Ramiaya, 2006) and requires the use of insulin. Although the data were screened for type 2 DM patients, it would seem that the age category of less than 30 years, together with the pattern of insulin use identified, may reflect that there could have been a few type 1 DM patients (1,5%; n = 39 629) that were incorrectly captured as type 2 DM patients.

Table 4.5: Insulin use in the different age categories

<table>
<thead>
<tr>
<th>AGE CATEGORY (YEARS)</th>
<th>PERCENTAGE OF PATIENTS IN AGE CATEGORY WHO WERE ON INSULIN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>48,3</td>
</tr>
<tr>
<td>30 – 44</td>
<td>29,0</td>
</tr>
<tr>
<td>45 – 49</td>
<td>25,5</td>
</tr>
<tr>
<td>50 – 59</td>
<td>25,8</td>
</tr>
<tr>
<td>60 – 69</td>
<td>24,1</td>
</tr>
<tr>
<td>70 – 79</td>
<td>20,4</td>
</tr>
<tr>
<td>&gt; 79</td>
<td>16,0</td>
</tr>
</tbody>
</table>
4.6 EPIDEMIOLOGICAL ANALYSIS OF PRESCRIBER CATEGORY IN TYPE 2 DIABETIC MELLITUS PATIENTS

In order to obtain a better understanding of the medication prescribing patterns, an epidemiological analysis of the various prescribers, who had been prescribing the medications for the study sample, was carried out. The number of prescribers per patient was determined for the total sample of prescriber category records. Figure 4.10 illustrates the number of prescribers per patient. According to Figure 4.10, it can be seen that 62,9% of the study sample was under the care of one prescriber and that 33,1% of the study sample was being treated by two prescribers. On average, the number of prescribers per patient was found to be 1,4.

![Figure 4.10: Number of prescribers per patient (n = 38 824##)](image)

## One patient may be under the care of two prescribers, thus, n is greater than the number of patients in the study sample (33 034 diabetic patients with one or more prescribers); and refers to the total number of prescribers rather than the number of patients.

Figure 4.11 explains the distribution of the categories of prescribers. It is identifiable that the prescribers who were prescribing the majority of medications for the patients in this study, were ‘general practitioners’ (GP), who accounted for 61,4% of the total number of prescribers. It can also be noted that the second largest group were ‘specialists’ (32,4%).
Figure 4.11: Category distribution of prescribers (n = 54850)

*Others include other prescribers that are discussed in Table 4.6.

**Although pharmacists are not prescribers, it is likely that they were selling schedule 0-1 medications, as well as, and testing materials.

With reference to Figure 4.11, it is to be noted that, according to the database, one patient may have had more than one specialist category record. For instance, a patient may be recorded as being managed by a GP in one record, but the next record (for that same patient) could have indicated that he/she had subsequently been referred for management by a specialist. In addition, it is plausible that the prescription was initiated by a specialist and thereafter maintained by a GP. Since the results of the study covered a three year period, it was not possible to identify who had initiated the prescription.

In order to obtain a better understanding of the distribution of the prescriber category, an additional prescriber category distribution analysis was carried out, excluding general practitioners, specialists and pharmacists. Table 4.6 depicts the aforementioned analysis of the “others” prescriber category.
Table 4.6: Prescriber category for “others”

<table>
<thead>
<tr>
<th>PRESCRIBER CATEGORY</th>
<th>PERCENTAGE OF TOTAL SAMPLE OF PRESCRIBER CATEGORY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>1,37</td>
</tr>
<tr>
<td>Dental</td>
<td>0,44</td>
</tr>
<tr>
<td>Miscellaneous specialist</td>
<td>0,36</td>
</tr>
<tr>
<td>Pathology</td>
<td>0,04</td>
</tr>
<tr>
<td>Radiology</td>
<td>0,04</td>
</tr>
<tr>
<td>Psychology</td>
<td>0,01</td>
</tr>
<tr>
<td>Support Services</td>
<td>0,08</td>
</tr>
<tr>
<td>Optometry</td>
<td>0,01</td>
</tr>
<tr>
<td>Anaesthetist</td>
<td>0,15</td>
</tr>
<tr>
<td>Manipulatory</td>
<td>0,01</td>
</tr>
<tr>
<td>Alternative</td>
<td>0,01</td>
</tr>
<tr>
<td>Other</td>
<td>0,01</td>
</tr>
</tbody>
</table>

“Hospital” was found to be the highest prescriber category in the “others” prescriber group. This could be linked to type 2 DM patients being hospitalised because of poor glycaemic control, leading to diabetic complications.

The Medicines and Related Substances Act 1965 (Act 101 of 1965) as amended [section 22 A - Control of Medicines and Scheduled Substances] describes an authorised prescriber as “a medical practitioner, dentist, veterinarian practitioner, nurse or other person registered under the Health Professions Act, 1974”. Taking the above description of an authorised prescriber into consideration, it is suggested that the “dental” category refers to dentists. In conclusion, excluding “hospital” and “dental” prescriber categories, it is proposed that these “prescribers” have been either incorrectly captured or the incorrect codes have been used. Since these categories are not prescribers, they have been considered irrelevant to the study.

A further analysis, giving consideration to the nature of medication and prescriber category, was conducted. The four prescriber categories that were observed were GP, Specialist, Hospital and Pharmacist categories. The outcomes of this analysis are presented in Figure 4.12.
Figure 4.12: Prescriber category for medications prescribed in study sample (n = 88 719**)

**One patient may have more than one medication category, thus, n is greater than the number of patients in the study sample (33 034 diabetic patients with one or more medication categories); and refers to the total number of medications rather than the number of patients.

Figure 4.12 shows that GPs prescribed 73,0% of oral hypoglycaemic agents, whereas specialists prescribed 25,9% of oral hypoglycaemic agents. However, with respect to insulin, it was observed that 61,4% of insulin prescriptions were generated by GPs, versus 31,3% by specialists. With respect to the medication for comorbidities, 68,9% of the prescriptions were written by GPs and 29,7% by specialists.

When considering the prescribing patterns of oral hypoglycaemic agents and comorbid disease state treatments, it is plausible to suggest that most patients visit GPs for the management of type 2 DM, as well as for other comorbid disease state(s). Out of all the medication categories that specialists prescribed, insulin was prescribed to the greatest extent. This is understandable since...
specialists often manage type 2 DM patients who are not being adequately managed and who require a more stringent approach to maintaining adequate glycaemic control. This accounts for the higher prescribing rate of insulin by the specialists.

4.7 OVERVIEW OF THE COST IMPLICATIONS OF HYPOGLYCAEMIC DRUG USE

As mentioned in section 2.8.2, cost is one of the factors which impact on the management of DM and since one of the purposes of a pharmacoepidemiological study is to support rational and cost-effective use of drugs, it is important to consider costs in this study. The cost implications and their relationship with prescribing patterns of hypoglycaemic drug use, were analysed for both the oral agents as, well as for the insulins.

Table 4.7 provides the average, minimum and maximum cost per treatment for oral hypoglycaemic agents. All oral hypoglycaemic agents present in the database were analysed accordingly. When investigating the Biguanides group, the Metformin 500mg tablet was found to be the least expensive Biguanide (R40.48) when considering the average cost per treatment. It was predictable to find that the Metformin 500mg tablet was the most affordable tablet since in Table 4.2, the Metformin 500mg tablet was found to be the most commonly used Biguanide oral hypoglycaemic agent. However, the Thiazolidinediones’ prescribing patterns and cost implications did not correspond to that of the Biguanides. It was observed that the Pioglitazone 15mg tablet was the most affordable average cost per treatment for the Thiazolidinediones. This contrasts with the previous finding that identified the Pioglitazone 30mg tablet as being the most frequently prescribed thiazolidinedione (refer to Table 4.2). Similarly, it can be observed from Tables 4.2 and 4.7 that although the Gliclazide 40mg tablet provided the most affordable average cost per treatment, it was the Gliclazide 80mg tablet that was identified as the most frequently used Sulphonylurea. This discrepancy could be accounted for by the possibility of the smaller dosage strengths having been used to double the required dosage requirements, because of the cost implications involved.
With regards to the combination preparations of Biguanides and Sulphonylureas, the average cost per treatment of Metformin + Glibenclamide 250mg/1,25mg tablet was R 67,47, which was the least expensive combination oral hypoglycaemic agent. This finding contrasted with the Metformin + Glibenclamide 500mg/5mg tablet, which was found earlier to be the most popular combination oral hypoglycaemic agent (Table 4.2). Furthermore, the Metformin + Glibenclamide 500mg/5mg tablet was found to be the most expensive oral hypoglycaemic combination treatment, as it was R 168,28.

Table 4.7: Average, minimum and maximum cost per treatment for oral hypoglycaemic agents

<table>
<thead>
<tr>
<th>NAME OF ORAL HYPOGLYCAEMIC TABLET AND STRENGTH</th>
<th>AVERAGE COST PER TREATMENT</th>
<th>MINIMUM COST PER TREATMENT</th>
<th>MAXIMUM COST PER TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biguanides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin 500mg</td>
<td>R 40,48</td>
<td>R 6,39</td>
<td>R 344,34</td>
</tr>
<tr>
<td>Metformin 850mg</td>
<td>R 62,42</td>
<td>R 13,12</td>
<td>R 441,99</td>
</tr>
<tr>
<td>Metformin 1000mg</td>
<td>R 68,87</td>
<td>R 15,90</td>
<td>R 438,41</td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone 15mg</td>
<td>R 119,69</td>
<td>R 73,89</td>
<td>R 333,99</td>
</tr>
<tr>
<td>Pioglitazone 30mg</td>
<td>R 175,49</td>
<td>R 60,83</td>
<td>R 563,60</td>
</tr>
<tr>
<td>Rosiglitazone 2mg</td>
<td>R 189,99</td>
<td>R 128,94</td>
<td>R 399,35</td>
</tr>
<tr>
<td>Rosiglitazone 4mg</td>
<td>R 303,60</td>
<td>R 122,63</td>
<td>R 597,19</td>
</tr>
<tr>
<td><strong>Sulphonylureas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glibenclamide 5mg</td>
<td>R 53,12</td>
<td>R 3,38</td>
<td>R 781,56</td>
</tr>
<tr>
<td>Gliclazide 30mg</td>
<td>R 127,26</td>
<td>R 25,14</td>
<td>R 987,24</td>
</tr>
<tr>
<td>Gliclazide 40mg</td>
<td>R 24,43</td>
<td>R 13,54</td>
<td>R 58,82</td>
</tr>
<tr>
<td>Gliclazide 80mg</td>
<td>R 73,96</td>
<td>R 9,67</td>
<td>R 761,61</td>
</tr>
<tr>
<td>Glimepiride 1mg</td>
<td>R 86,50</td>
<td>R 24,50</td>
<td>R 334,14</td>
</tr>
<tr>
<td>Glimepiride 2mg</td>
<td>R 160,53</td>
<td>R 39,67</td>
<td>R 801,24</td>
</tr>
<tr>
<td>Glimepiride 3mg</td>
<td>R 198,39</td>
<td>R 179,70</td>
<td>R 216,07</td>
</tr>
<tr>
<td>Glimepiride 4mg</td>
<td>R 271,42</td>
<td>R 50,00</td>
<td>R 1456,26</td>
</tr>
<tr>
<td>Glipizide 5mg</td>
<td>R 156,71</td>
<td>R 39,94</td>
<td>R 452,60</td>
</tr>
<tr>
<td>Chlorpropamide 250mg</td>
<td>R 44,90</td>
<td>R 16,46</td>
<td>R 105,04</td>
</tr>
<tr>
<td><strong>Meglitinides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide 120mg</td>
<td>R 294,01</td>
<td>R 238,52</td>
<td>R 407,37</td>
</tr>
<tr>
<td>Repaglinide 0,5mg</td>
<td>R 89,36</td>
<td>R 58,25</td>
<td>R 119,45</td>
</tr>
<tr>
<td>Repaglinide 1mg</td>
<td>R 150,99</td>
<td>R 56,78</td>
<td>R 239,60</td>
</tr>
<tr>
<td>Repaglinide 2mg</td>
<td>R 287,45</td>
<td>R 101,06</td>
<td>R 505,32</td>
</tr>
<tr>
<td><strong>Alpha Glucosidase Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose 50mg</td>
<td>R 184,87</td>
<td>R 46,59</td>
<td>R 253,06</td>
</tr>
<tr>
<td>Acarbose 100mg</td>
<td>R 256,14</td>
<td>R 102,40</td>
<td>R 324,64</td>
</tr>
</tbody>
</table>
Table 4.7: Average, minimum and maximum cost per treatment for oral hypoglycaemic agents (continued)

<table>
<thead>
<tr>
<th>NAME OF ORAL HYPOGLYCAEMIC TABLET AND STRENGTH</th>
<th>AVERAGE COST PER TREATMENT</th>
<th>MINIMUM COST PER TREATMENT</th>
<th>MAXIMUM COST PER TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biphasic insulin analogues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin + glibenclamide 250mg/1,25mg</td>
<td>R 67,47</td>
<td>R 18,20</td>
<td>R 205,06</td>
</tr>
<tr>
<td>Metformin + glibenclamide 500mg/2,5mg</td>
<td>R 151,53</td>
<td>R 58,30</td>
<td>R 672,12</td>
</tr>
<tr>
<td>Metformin + glibenclamide 500mg/5mg</td>
<td>R 168,28</td>
<td>R 41,21</td>
<td>R 514,44</td>
</tr>
</tbody>
</table>

Similar to the oral hypoglycaemic agents, the different insulin analogues were analysed for cost implications. The insulin preparations were tabulated according to the type of preparations, namely: biphasic insulin analogues, biphasic insulins, long-acting insulin analogues and intermediate to long-acting insulins. Table 4.8 depicts the cost per treatment of the insulin preparations.

Table 4.8: Average, minimum and maximum monthly cost per treatment for insulin preparations

<table>
<thead>
<tr>
<th>NAME OF INSULIN PREPARATION</th>
<th>AVERAGE COST PER TREATMENT</th>
<th>MINIMUM COST PER TREATMENT</th>
<th>MAXIMUM COST PER TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biphasic insulin analogues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humalog mix25 cartridge 3ml®</td>
<td>R 681,22</td>
<td>R 89,41</td>
<td>R 2916,06</td>
</tr>
<tr>
<td>Humalog mix25 kwikpen®</td>
<td>R 612,91</td>
<td>R 0,00</td>
<td>R 1790,84</td>
</tr>
<tr>
<td>Humalog mix25 penset 3ml®</td>
<td>R 652,58</td>
<td>R 138,65</td>
<td>R 2455,45</td>
</tr>
<tr>
<td>Humalog mix25 vial 10ml®</td>
<td>R 961,58</td>
<td>R 286,21</td>
<td>R 1483,35</td>
</tr>
<tr>
<td>Humalog mix50 cartridge 3ml®</td>
<td>R 799,38</td>
<td>R 129,50</td>
<td>R 2410,19</td>
</tr>
<tr>
<td>Novomix30 flexpen 3ml®</td>
<td>R 640,94</td>
<td>R 0,00</td>
<td>R 15393,76</td>
</tr>
<tr>
<td>Novomix30 penfill 3ml®</td>
<td>R 669,41</td>
<td>R 112,38</td>
<td>R 1821,02</td>
</tr>
<tr>
<td><strong>Biphasic insulins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actraphane hm (ge) penset 3ml®</td>
<td>R 663,03</td>
<td>R 102,36</td>
<td>R 2 943,45</td>
</tr>
<tr>
<td>Actraphane hm (ge) penfill 3ml®</td>
<td>R 494,16</td>
<td>R 223,22</td>
<td>R 850,30</td>
</tr>
<tr>
<td>Actraphane hm (ge) vial 10ml®</td>
<td>R 476,45</td>
<td>R 0,00</td>
<td>R 1 256,28</td>
</tr>
<tr>
<td>Humulin 30/70 cartridge 3ml®</td>
<td>R 582,28</td>
<td>R 249,17</td>
<td>R 1 184,31</td>
</tr>
<tr>
<td>Humulin 30/70 disposable Pen 3ml®</td>
<td>R 500,43</td>
<td>R 99,24</td>
<td>R 1 754,68</td>
</tr>
<tr>
<td>Humulin 30/70 vial 10ml®</td>
<td>R 456,75</td>
<td>R 85,27</td>
<td>R 934,32</td>
</tr>
<tr>
<td>Insuman Comb 30/70 cartridge 3ml®</td>
<td>R 491,80</td>
<td>R 159,07</td>
<td>R 1 383,44</td>
</tr>
</tbody>
</table>
From Table 4.8 it can be observed that the most expensive biphasic insulin analogue was the Humalog Mix25 vial 10ml® (average cost per treatment = R 961,58). The two least expensive biphasic insulin analogues were: Humalog Mix25 kwikpen® (average cost per treatment = R 612,91) and Novomix30 flexpen 3ml® (average cost per treatment = R 640,94). As described earlier in Table 4.4, the Novomix30 flexpen 3ml® was found to be the most frequently used biphasic insulin analogue. Therefore, it was to be expected that the Novomix30 flexpen 3ml was the second most affordable biphasic insulin analogue preparation.

From Table 4.8 it can be noted that the least expensive insulin preparation was the Humulin 30/70 vial 10ml (average cost per treatment = R 456,75). The average cost per treatment for the Actraphane Hm (Ge) penset 3ml®, the most expensive insulin preparation, was found to be R 663,03. In this study, the Actraphane Hm (Ge) penset 3ml® was the most frequently prescribed biphasic insulin (Table 4.4). It was not expected that the Actraphane Hm (Ge) penset 3ml® would be the most expensive biphasic insulin preparation since it was the most frequently dispensed preparation in that category. It is possible to attribute this discrepancy to the suggestion that this particular biphasic insulin preparation results in satisfactory glycaemic control. Hence, making the

Table 4.8: Average, minimum and maximum monthly cost per treatment for insulin preparations (continued)

<table>
<thead>
<tr>
<th>NAME OF INSULIN PREPARATION</th>
<th>AVERAGE COST PER TREATMENT</th>
<th>MINIMUM COST PER TREATMENT</th>
<th>MAXIMUM COST PER TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate-to-long acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin N cartridge 3ml®</td>
<td>R 397,51</td>
<td>R 95,00</td>
<td>R 593,12</td>
</tr>
<tr>
<td>Humulin N disposable 3ml®</td>
<td>R 427,94</td>
<td>R 0,00</td>
<td>R 1 518,72</td>
</tr>
<tr>
<td>Humulin N vial 10ml®</td>
<td>R 438,86</td>
<td>R 248,37</td>
<td>R 772,44</td>
</tr>
<tr>
<td>Protaphane flexpen 3ml®</td>
<td>R 519,39</td>
<td>R 109,02</td>
<td>R 1 442,37</td>
</tr>
<tr>
<td>Protaphane hm(ge) penfill 3ml®</td>
<td>R 561,39</td>
<td>R 215,35</td>
<td>R 830,61</td>
</tr>
<tr>
<td>Protaphane hm(ge) vial 10ml®</td>
<td>R 532,66</td>
<td>R 220,51</td>
<td>R 1 499,49</td>
</tr>
<tr>
<td>Long-acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lantus I optiset penset®</td>
<td>R 613,88</td>
<td>R 137,74</td>
<td>R 1 895,01</td>
</tr>
<tr>
<td>Lantus optiset disposable pen®</td>
<td>R 581,47</td>
<td>R 108,11</td>
<td>R 2 205,32</td>
</tr>
<tr>
<td>Levemir flexpen prefilled 3ml®</td>
<td>R 595,01</td>
<td>R 132,40</td>
<td>R 3 506,75</td>
</tr>
<tr>
<td>Levemir prefilled cartridge 3ml®</td>
<td>R 654,93</td>
<td>R 467,40</td>
<td>R 1 153,79</td>
</tr>
</tbody>
</table>
Actraphane Hm (Ge) penset 3ml® a suitable agent of choice in the management of type 2 DM.

As observed from Table 4.8, the average cost per treatment for the Humulin N cartridge 3ml® and the Protaphane hm(ge) penfill 3ml® were R 397.51 and R 561.39, respectively. The Humulin N cartridge 3ml® was considered to be the least expensive intermediate-to-long acting insulin preparation and the Protaphane hm(ge) penfill 3ml® the most expensive one. The average cost of the Protaphane flexpen 3ml®-the most commonly used intermediate-to-long acting insulin preparation - was R 519.39. Although the Protaphane flexpen 3ml® was not the least expensive preparation in the insulin category, it is possible that it was the agent of choice based on its pharmacokinetic properties and to a lesser extent, on the cost implications.

Lastly, it was evident from Table 4.8 that the most expensive long-acting insulin analogue was the Levemir prefilled cartridge 3ml®. The average cost per treatment of that specific insulin preparation was R 654.93. The least expensive long-acting insulin was found to be the Lantus Optiset Disposable Pen® (average cost per treatment = R 581.47). The Lantus Optiset Disposable Pen® was also found to be the most often prescribed long-acting insulin preparation. Hence, it can be concluded that the prescribing pattern of the Lantus Optiset Disposable Pen® could be related to the fact that it was the cheapest agent amongst all of the long-acting insulins.

4.8 PRESCRIBED DAILY DOSE AND DEFINED DAILY DOSE FOR HYPOGLYCAEMIC AGENTS

Prescribed daily dose (PDD) and defined daily dose (DDD) remain the mainstay of a drug utilisation review study, because they are used as units of measure in order to establish patterns and determinants of use of medications (WHO, 2003) [section 2.12]. As discussed by Truter (2008), the DDD is used as a unit to measure and compare drug treatment. Hence, DDD provides an estimation of the use of drug treatment; however it does not automatically reveal the actual or recommended dose. Since this study was of a DUR nature, the PDD and
DDD had to be investigated for both oral hypoglycaemic agents and insulin preparations. However, it is to be noted that the DDD of prescription records only provides a rough estimation of use and not the actual use of medication (Truter, 2008).

Table 4.9 provides an overview of the average and mode number of tablets per day, as well as the defined daily dose for the oral hypoglycaemic agents. It can be seen that some of the mode number of tablets per day, which was used as the PDD and DDD, corresponded with each other. This could be indicative of prescribers having prescribed according to the recommended protocols, namely the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009) and the Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008), for these specific oral hypoglycaemic agents.

Table 4.9: Average number of tablets per day, mode number of tablets per day and defined daily dose for the oral hypoglycaemic agents

<table>
<thead>
<tr>
<th>NAME OF ORAL HYPOGLYCAEMIC TABLET AND STRENGTH</th>
<th>AVERAGE NUMBER OF TABLETS PER DAY</th>
<th>MODE NUMBER OF TABLETS PER DAY (PDD)</th>
<th>DDD (TABLETS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biguanides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin 500mg</td>
<td>2,4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Metformin 850mg</td>
<td>2,2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Metformin 1000mg</td>
<td>2,0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone 15mg</td>
<td>1,12</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pioglitazone 30mg</td>
<td>1,1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rosiglitazone 2mg</td>
<td>1,3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rosiglitazone 4mg</td>
<td>1,3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Sulphonylureas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glibenclamide 5mg</td>
<td>2,2</td>
<td>2</td>
<td>0,5</td>
</tr>
<tr>
<td>Gliclazide 30mg</td>
<td>2,0</td>
<td>2</td>
<td>1 – 4</td>
</tr>
<tr>
<td>Gliclazide 40mg</td>
<td>1,7</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Gliclazide 80mg</td>
<td>2,4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Glimepiride 1mg</td>
<td>1,1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Glimepiride 2mg</td>
<td>1,1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Glimepiride 3mg</td>
<td>1,0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 4.9: Average number of tablets per day, mode number of tablets per day and defined daily dose for the oral hypoglycaemic agents (continued)

<table>
<thead>
<tr>
<th>NAME OF ORAL HYPOGLYCAEMIC TABLET AND STRENGTH</th>
<th>AVERAGE NUMBER OF TABLETS PER DAY</th>
<th>MODE NUMBER OF TABLETS PER DAY (PDD)</th>
<th>DDD (TABLETS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glimepiride 4mg</td>
<td>1,1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Glipizide 5mg</td>
<td>1,9</td>
<td>2</td>
<td>0,5</td>
</tr>
<tr>
<td>Chlorpropamide 250mg</td>
<td>1,7</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Meglitinides**

<table>
<thead>
<tr>
<th>Name</th>
<th>Average Number of Tablets Per Day</th>
<th>Mode Number of Tablets Per Day (PDD)</th>
<th>DDD (Tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nateglinide 120mg</td>
<td>2,1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Repaglinide 0,5mg</td>
<td>2,7</td>
<td>3</td>
<td>Individualised dose</td>
</tr>
<tr>
<td>Repaglinide 1mg</td>
<td>2,4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Repaglinide 2mg</td>
<td>3,1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

**Alpha Glucosidase Inhibitors**

<table>
<thead>
<tr>
<th>Name</th>
<th>Average Number of Tablets Per Day</th>
<th>Mode Number of Tablets Per Day (PDD)</th>
<th>DDD (Tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose 50mg</td>
<td>2,5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Acarbose 100mg</td>
<td>2,5</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

**Biguanides + Sulphonylureas**

<table>
<thead>
<tr>
<th>Name</th>
<th>Average Number of Tablets Per Day</th>
<th>Mode Number of Tablets Per Day (PDD)</th>
<th>DDD (Tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + glibenclamide 250mg/1,25mg</td>
<td>1,8</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Metformin + glibenclamide 500mg/2,5mg</td>
<td>2,1</td>
<td>2</td>
<td>1 – 2</td>
</tr>
<tr>
<td>Metformin + glibenclamide 500mg/5mg</td>
<td>2,3</td>
<td>2</td>
<td>1 – 2</td>
</tr>
</tbody>
</table>

Discrepancies in the PDD and DDD could be because the management of type 2 DM is often individualised according to glycaemic levels being targeted. Grimmsmann and Himmel (2011) argued that a discrepancy in PDD and DDD may be due to the degree of severity of the disease in the patient. These researchers also suggest that the doctor’s choice of therapeutic agents may also be another reason explaining the difference in PDD and DDD.
Table 4.10: Average number of units, mode number of units per day and described daily dose of insulin preparations

<table>
<thead>
<tr>
<th>PRODUCT NAME</th>
<th>AVERAGE NUMBER OF UNITS PER DAY</th>
<th>MODE NUMBER OF UNITS PER DAY (PDD)</th>
<th>DDD (UNITS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic insulin analogues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humalog Mix25 cartridge 3ml®</td>
<td>65,9</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Humalog Mix25 kwikpen®</td>
<td>62,6</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Humalog Mix25 penset 3ml®</td>
<td>61,2</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Humalog Mix25 vial 10ml®</td>
<td>233,3</td>
<td>166,7</td>
<td>40</td>
</tr>
<tr>
<td>Humalog Mix50 cartridge 3ml®</td>
<td>79,1</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Novomix30 flexpen 3ml®</td>
<td>60,6</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Novomix30 penfill 3ml®</td>
<td>63,7</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Biphasic insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actraphane Hm(Ge) penfill 3ml®</td>
<td>53,5</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Actraphane Hm(Ge) penset 3ml®</td>
<td>63,4</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Actraphane Hm(Ge) vial 10ml®</td>
<td>107,5</td>
<td>33,3</td>
<td></td>
</tr>
<tr>
<td>Humulin 30/70 cartridge 3ml®</td>
<td>66,9</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Humulin 30/70 disposable pen 3ml®</td>
<td>59,8</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Humulin 30/70 vial 10ml®</td>
<td>86,0</td>
<td>33,3</td>
<td></td>
</tr>
<tr>
<td>Insuman Comb 30/70 cartridge 3ml®</td>
<td>65,7</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Intermediate-to-long acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin N cartridge 3ml®</td>
<td>41,9</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Humulin N disposable pen 3ml®</td>
<td>51,3</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Humulin N vial 10ml®</td>
<td>52,8</td>
<td>33,3</td>
<td></td>
</tr>
<tr>
<td>Protaphane flexpen 3ml®</td>
<td>49,0</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Protaphane hm(ge) penfill 3ml®</td>
<td>54,4</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Protaphane hm(ge) vial 10ml®</td>
<td>147,8</td>
<td>33,3</td>
<td></td>
</tr>
<tr>
<td>Long-acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lantus I Optiset penset®</td>
<td>46,7</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Lantus Optiset disposable pen®</td>
<td>46,6</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Levemir flexpen prefilled 3ml®</td>
<td>47,3</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Levemir prefilled cartridge 3ml®</td>
<td>55,8</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

(DDD adapted from WHO, 2011d).

According to the WHO (2011d), the DDD of all the insulin preparations is 40 units. Based on this DDD, the PDD of this study was compared and contrasted. Table 4.10 clearly depicts that the majority of the insulin preparations analysed in this DUR, have a PDD of 50 units. The PDD is close to the recommended DDD of 40 units for insulin preparations. When comparing and contrasting the PDDs of biphasic insulin analogues with the DDD, it was observed that the
Humalog Mix25 vial 10ml\textsuperscript{®} had a PDD of 166.7 units. This PDD was considered to be unusual since the rest of the biphasic insulin analogues had a PDD of 50 units. It is possible that some patients were using this specific biphasic insulin analogue to achieve stricter glycaemic control relative to other patients and hence, required more than the modal 50 units.

It was observed that the Actraphane Hm(Ge) vial 10ml\textsuperscript{®} and the Humulin 30/70 vial 10ml\textsuperscript{®} had a PDD of 33.3 units amongst the biphasic insulins. The PDDs of these biphasic insulin preparations was found to be smaller than the rest of the biphasic insulins (50 units). A similar pattern was observed amongst the intermediate-to-long acting insulins, where the Humulin N vial 10ml\textsuperscript{®} and the Protaphane hm(ge) vial 10ml\textsuperscript{®} had a PDD of 33.3 units compared to the 50 units of the other preparations in the same insulin category.

Tables 4.11 – 4.14 depict the range of units used per day for the following: biphasic insulin analogues, biphasic insulins, long-acting insulins and intermediate-to-long acting insulins, respectively.
Table 4.11: Range of units used per day for biphasic insulin analogues

<table>
<thead>
<tr>
<th>NAME OF PREPARATION</th>
<th>HUMALOG MIX 25 CARTRIDGE 3ML®</th>
<th>HUMALOG MIX25 KwikPen®</th>
<th>HUMALOG MIX25 PENSET 3ML®</th>
<th>HUMALOG MIX50 CARTRIDGE 3ML®</th>
<th>NOVOMIX30 PENFILL 3ML®</th>
<th>NOVOMIX30 FLEXPEN 3ML®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units range (per day)</td>
<td>Number of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-50</td>
<td>125</td>
<td>437</td>
<td>560</td>
<td>3</td>
<td>23</td>
<td>110</td>
</tr>
<tr>
<td>51-100</td>
<td>51</td>
<td>139</td>
<td>146</td>
<td>2</td>
<td>14</td>
<td>49</td>
</tr>
<tr>
<td>101-150</td>
<td>4</td>
<td>17</td>
<td>21</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>&gt;150</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>182</td>
<td>594</td>
<td>729</td>
<td>13</td>
<td>42</td>
<td>163</td>
</tr>
</tbody>
</table>

Table 4.12: Range of units used per day for biphasic insulins

<table>
<thead>
<tr>
<th>NAME OF PREPARATION</th>
<th>INSUMAN COMB 30/70 CARTRIDGE 3ML®</th>
<th>ACTRAPHANE HM(GE) VIAL 10ML®</th>
<th>ACTRAPHANE HM(GE) PENFILL 3ML®</th>
<th>ACTRAPHANE HM(GE) PENSET 3ML®</th>
<th>HUMULIN 30/70 VIAL 10ML®</th>
<th>HUMULIN 30/70 DISPOSABLE PEN 3ML®</th>
<th>HUMULIN 30/70 CARTRIDGE 3ML®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units range (per day)</td>
<td>Number of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-50</td>
<td>66</td>
<td>61</td>
<td>21</td>
<td>770</td>
<td>15</td>
<td>164</td>
<td>43</td>
</tr>
<tr>
<td>51-100</td>
<td>19</td>
<td>74</td>
<td>5</td>
<td>278</td>
<td>21</td>
<td>38</td>
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<tr>
<td>101-150</td>
<td>4</td>
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<td>22</td>
<td>1</td>
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<td>0</td>
<td>6</td>
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<tr>
<td>TOTAL</td>
<td>91</td>
<td>152</td>
<td>26</td>
<td>1076</td>
<td>38</td>
<td>207</td>
<td>62</td>
</tr>
</tbody>
</table>
Table 4.13: Range of units used per day for intermediate-to-long acting insulin

<table>
<thead>
<tr>
<th>NAME OF PREPARATION</th>
<th>HUMULIN N CARTRIDGE 3ML®</th>
<th>HUMULIN N DISPOSABLE 3ML®</th>
<th>HUMULIN N VIAL 10ML®</th>
<th>PROTAPHAN E HM(GE) PENFILL 3ML®</th>
<th>PROTAPHAN E FLEXPEN 3ML®</th>
<th>PROTAPHAN E HM(GE) VIAL 10ML®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units range (per day)</td>
<td>Number of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-50</td>
<td>20</td>
<td>233</td>
<td>6</td>
<td>11</td>
<td>883</td>
<td>12</td>
</tr>
<tr>
<td>51-100</td>
<td>1</td>
<td>25</td>
<td>6</td>
<td>5</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>101-150</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>5</td>
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</tr>
<tr>
<td>&gt;150</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>21</td>
<td>261</td>
<td>12</td>
<td>16</td>
<td>936</td>
<td>23</td>
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</tbody>
</table>

Table 4.14: Range of units used per day for long-acting insulin

<table>
<thead>
<tr>
<th>NAME OF PREPARATION</th>
<th>LANTUS I OPTISET PENSET®</th>
<th>LANTUS OPTISET DISPOSABLE PEN®</th>
<th>LEVEMIR FLEXPEN PREFILLED 3ML®</th>
<th>LEVEMIR PREFILLED CARTRIDGE 3ML®</th>
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<td>TOTAL</td>
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<td>641</td>
<td>463</td>
<td>24</td>
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</table>
4.9 CONCLUSION

The management of type 2 DM was critically evaluated in this chapter. The main focus was directed towards the use of insulin in the management of type 2 DM, with or without the use of oral hypoglycaemic agents. Furthermore, the prevalence of comorbid disease states was assessed in the type 2 DM patients. In the past, the management of type 2 DM was solely restricted to the use of oral hypoglycaemic agents and insulin was considered as a last option. Nowadays, insulin use is encouraged in the early phases of diagnosis for better management of type 2 DM. In this study, it was found that the management of type 2 DM was still being managed mostly by oral hypoglycaemic agents and to a lesser extent by insulin therapy. Nevertheless, it was rewarding to observe that metformin was the most frequently prescribed oral hypoglycaemic agent as it is the first line pharmacological management of type 2 DM according to the prescribing guidelines. Another interesting finding of the study was that the majority of diabetic patients suffered from at least one or more comorbid disease state(s), which was indicative of the insulin resistance syndrome. Whilst comparing insulin therapy versus oral hypoglycaemic agents, it was observed that insulin therapy was more expensive.
CHAPTER FIVE

CONCLUSION AND RECOMMENDATIONS
5.1 STUDY IN REVIEW

The prevalence of DM is increasing worldwide (Clouse & Lustman, 2004). Mortality rates due to DM are on the rise, despite pharmaceutical advances and the implementation of management guidelines (Brunton et al., 2005). It was estimated that in 2000, 171 million people worldwide were suffering from DM and this is expected to increase to approximately 366 million people by 2030. However, the prevalence is higher in developing countries. For example, of the 194 million people who were reported to have had DM in 2003, 66% resided in developing countries (WHO, 2002).

It has been estimated that in South Africa, 8-10% of the population is affected by DM (Brown, 2010). In 2007, morbidity statistics revealed that 21 915 deaths were diabetes-related (Statistics South Africa, 2007). The causes of death in diabetic patients, included: cardiovascular disease (53.6%); hypertension (36.8%); stroke (14.6%); and ischaemic heart disease (9.9%).

Type 2 diabetics are at risk of developing macrovascular complications because of Syndrome X (Isley et al., 2008) [section 2.7.1]. Hypertension, in particular, is often present as a comorbid disease state in diabetic patients, affecting 20-60% of patients (Dobesh, 2006). The combination of DM and hypertension also increases the risk of cardiovascular disease (CVD). In fact, 75% of diabetic cardiovascular complications have been reported to occur in patients who suffer from DM and CVD (Dobesh, 2006). Another major factor contributing to CVD in diabetic patients is dyslipidaemia. Diabetic patients have a greater risk of developing atherosclerosis due to the changes in their plasma lipid levels (Mooradian, 2009). It has been estimated that 55% of diabetics suffer from coronary artery disease (CAD), as compared to a 2-4% prevalence of CAD in the general population (Berry et al., 2007).

The pharmacological management of type 2 DM involves the use of oral hypoglycaemic agents and insulin, alone or in combination. The primary objective of pharmacological treatment is to achieve glycaemic control. Traditionally, type 2 DM was conventionally managed with oral hypoglycaemic agents, however, in the last fifteen years, insulin has been increasingly used.
Many researchers argue that most type 2 DM patients will eventually require the addition of insulin therapy to their existing oral hypoglycaemic regimens in order to achieve adequate glycaemic control (De Witt & Hirsch, 2003; Grégoire et al., 2009; Pogach, 2009). Several studies have demonstrated a significant improvement in the glycaemic control of type 2 diabetic patients, when insulin was added to oral therapy at an early stage of treatment (Gerich et al., 2003; Riddle, 2004; Austin et al., 2006). This finding was also confirmed by the UKPDS study, which suggested that if insulin therapy was added to oral therapy within the first six years of treatment, strict glycaemic control could be maintained (Burden et al., 2002) [section 2.9.3].

5.2 SUMMARY OF MAIN FINDINGS

The results of the analyses performed in this study were described in chapter four. The main findings of the study are summarised in this section. The results chapter aimed at analysing the management of type 2 DM in a sample group of DM patients, taken from the database of a South African medical aid company, and more specifically, assessing the use of insulin in these patients.

The findings relating to the following objectives of the study are reviewed in this section:

1. To establish the prevalence of type 2 DM relative to age, gender and ethnicity, in the study population.

2. To examine the prevalence and nature of chronic comorbid disease states, especially those that can be related to micro and macrovascular complications in diabetic patients.

3. To establish the extent, profile and trends in the prescribing of insulin, relative to oral hypoglycaemic agents, over a three year period.

4. To investigate the cost implications of the patterns of hypoglycaemic drug use.
5. To examine the extent and trends of use of blood and urine glucose monitoring materials by patients, relative to their use of insulin and other hypoglycaemic agents.

6. Using prescribing indices, such as PDDS and DDDS, to compare the observed patterns of prescribing with relevant recommended guidelines and protocols.

5.2.1 Characteristics of the study population

The study sample was evaluated to determine the age distribution. Type 2 DM was found to be most prevalent in the age groups: 50 to 59 years and 60 to 69 years (29.7% and 26.1% of the study sample, respectively). These age prevalence trends corresponded to international trends in terms of the prevalence of type 2 DM (section 4.1.2). Thus, it can be suggested that type 2 DM gets diagnosed at a later stage in life, due to the nature of the disease state.

5.2.2 Epidemiological analysis of comorbid disease states in type 2 diabetes mellitus patients

The distribution trends and descriptive statistics, pertaining to the comorbid disease states in type 2 DM patients, established the following:

- It was noted that 83.0% of the study sample was suffering from at least one co-existing comorbid disease state.
- Of the patients who had identified with one or more comorbidities, the highest percentage (73.7%) had only had one comorbid disease. The most prevalent class of comorbid diseases, that was present in the study sample, was cardiovascular diseases.
- The three most commonly diagnosed comorbid disease states in the sample group were identified as: essential hypertension (40.1%), hypercholesterolaemia (23.5%), and coronary artery disease (5.0%).
The chronic comorbid disease state trends that were observed supported the view that type 2 DM forms part of a complex syndrome, namely: the insulin resistance syndrome. Furthermore, it also indicates that type 2 DM patients may suffer from chronic comorbid disease state(s) because of the macrovascular complications associated with type 2 DM. The comorbid disease state(s) that have been associated with type 2 DM are inter-linked with regards to the quality of life of the patient and adherence to drug therapy.

5.2.3 Epidemiological analysis of medication use in type 2 diabetes mellitus patients

The following patterns were observed with regards to medication use:

- 94,5% of the patients in the sample had been prescribed at least two or more medications.
- Of the medications that were prescribed, 38,0% were oral hypoglycaemic agents and 10,7% were insulin preparations.

Hence, it can be said that there are more patients who were managed with oral hypoglycaemic agents, relative to insulin. This indicates that the patients in the study sample had been managed according to the two South African guidelines, namely: the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009) and The Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008).

5.2.4 Overview of oral hypoglycaemics dispensed and number of records

It was evident that the Metformin 500mg tablet was the oral hypoglycaemic agent that was most frequently dispensed (24,9%; n = 56 033). Taking the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009) and the Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008) into consideration, it is predictable to have identified the Metformin 500mg tablet as being the most commonly used oral hypoglycaemic agent in the study.
5.2.5 Epidemiological analysis of insulin use in type 2 diabetes mellitus patients

The relationship between the use of insulin and oral hypoglycaemic agents was evaluated. The following observation was made: 88.9% of the diabetic patients (n = 39 629) were taking oral hypoglycaemic agents. Of these patients (n = 35 229), 19.2% were using insulin therapy concurrently. Only 80.8% of these patients (n = 35 229) were on oral hypoglycaemic agents alone. Thus, it was statistically significant to find that monotherapy with oral hypoglycaemic agents was higher than the combination use of oral hypoglycaemic agents and insulin (Chi-square = 5785.5; df = 1; p = 0.0000). The abovementioned finding was considered to have had a medium practical significance, since Cramér’s value was 0.38.

The relationship between insulin use and the co-administration of other comorbid disease state treatment(s) was carried out. It was found that 84.1% of the study sample (n = 39 629) were using treatments for comorbid disease state(s). Furthermore, of these patients, 24.5% (n = 33 332) were also administering insulin. It was significant to conclude that approximately one quarter of the patients with comorbidities were managed with insulin (Chi-square = 32.2; df = 1; p = 0.0000). However, this finding was considered to be of small practical significance in effect size. (Cramér’s V = 0.03).

The relationship between insulin and age categories was carried out and it was observed that 48.3% of patients who were under the age of 30 years (n = 582), were using insulin. Also, in the age category: 30 to 44 years, 29.0% of patients (n = 5 895) were on insulin therapy. It is noteworthy to mention that insulin was being used the least in patients over 79 years of age, (16.0% in that age group [n = 1 503]). The trends observed for the use of insulin in the age categories of 30 years of age or less and 30 to 44 years of age, were more indicative of patterns for insulin use in type 1 DM, rather than those expected in type 2 DM patients. It was deemed significant that insulin was used to a lesser extent as the age groups of the patients increased (Chi-square = 350.6; df = 6; p =
0,0000). This analysis was considered to be of small practical significance, since Cramér's V was found to be 0,099.

Furthermore, the following main observations were made with regards to the most commonly used insulin preparations:

- The two highest categories used were: biphasic insulin analogues (57,2%) and biphasic insulins (16,3%). The most commonly prescribed biphasic insulin analogue was Novomix30 Flexpen 3ml (70,3%; n = 5802). Actraphane hm(ge) Penset 3ml was found to be the most frequently used biphasic insulin preparation (65,1%; n = 1652). The aforementioned patterns can be explained by the fact that the SEMDSA Guidelines for Diagnosis and Management of type 2 DM for Primary Health Care (2009) and The Standard Treatment Guidelines and Essential Medicines List for Primary Health Care (2008), recommend the use of biphasic insulin preparations after therapy with oral hypoglycaemic agents has been initiated. The difference between biphasic insulin analogues and biphasic insulins is that most biphasic insulin analogues have a quicker onset of action time (15 minutes) versus biphasic insulins, which ordinarily have an onset time of 30 minutes. Protaphane Flexpen 3ml was the most popular amongst the prescribers in terms of the intermediate-to-long acting insulin preparations (73,8%; n= 1 269).

5.2.6 Epidemiological analysis of prescriber category in type 2 diabetic mellitus patients

- It was evident that the prescribers, who were prescribing the majority of medications for the type 2 DM patients in this study, were GPs, who accounted for 61,4% of the total number of prescribers. After GPs, specialists were found to constitute the second highest percentage (32,4%, n = 38 824).

- It was seen that GPs prescribed 73,0% of the oral hypoglycaemics, whereas specialists prescribed 25,9% of oral hypoglycaemics. However,
with respect to insulin, it was observed that 61,4% of insulin prescriptions were generated by GPs and 31,3% by specialists. With regards to the medication prescribed for the comorbidities, 68,9% of the prescriptions were written by GPs and 29,7% by specialists.

5.2.7 Overview of the cost implications of hypoglycaemic drug use

The average, minimum and maximum cost per treatment for oral hypoglycaemic agents and the different categories of insulin preparations, were calculated. Tables 4.8 - 4.12 of outlined these particular findings of the study. The Metformin 500mg tablet was found to be the least expensive oral hypoglycaemic agent in the Biguanides group (R 40,48) when considering the average cost per treatment. This result was to be expected, since (as per Table 4.2), the Metformin 500mg tablet was found to be the most commonly prescribed Biguanide. Additionally, the Pioglitazone 15mg tablet was found to provide the most affordable average cost per treatment in the Thiazolidinediones group. This finding was surprising because the Pioglitazone 30mg tablet was identified as being the most frequently used Thiazolidinedione oral hypoglycaemic agent (Table 4.2). Similarly, despite the Gliclazide 40mg tablet having been identified as the most affordable average cost per treatment amongst the Sulphonylureas, it was in fact, the Gliclazide 80mg tablet that was most commonly prescribed in the study sample. These discrepancies could be attributed to the possibility of the use of smaller dosage strengths to double the required dosage requirements because of cost implications involved. It is also possible that higher dosage strengths were used and halved for the required dosage requirements because of the unavailability of the medication's required dosage strength.

5.2.8 Prescribed daily doses and defined daily doses for hypoglycaemic agents and insulin preparations

The prescribed daily doses (PDDs) and defined daily doses (DDD) for oral hypoglycaemic agents and insulin preparations, were investigated. It was observed that the PDDs of most of the oral hypoglycaemic agents
corresponded to their respective DDDs. With regards to insulin preparations, most of the insulin preparations had a PDD = 1.25 DDD, that is the DDD was 40 units and most of the preparations had a PDD of 50 units. These discrepancies in the PDDs and DDDs may be linked to the following two main plausible causes: the management of type 2 DM is individualised according to each patient; and each prescriber has his/her own preferred choice of therapy, based on his/her experience.

5.3 RECOMMENDATIONS

This pharmacoepidemiological evaluation has yielded useful information pertaining to the research topic and makes it possible to make the following recommendations:

- The management of type 2 DM should be holistic in nature. At present, type 2 DM is managed on its own and if a patient suffers from another comorbid disease state, that disease state is treated independently.

- Pharmacists should play an active role in the management of type 2 DM. Due to the fact that they are the healthcare professionals who are most frequently in contact with the patients, they can assist in the management plan. Pharmacists can be the communication intermediary between the patients and the prescribers, and hence can assist in determining the best treatment plan for type 2 DM patients.

- Prescribers should be encouraged to prescribe testing materials as per existing guidelines. This may encourage better glycaemic control and thus, improve the management of type 2 DM.

- Similar studies should be carried out for patients in the public sector to be able to determine general patterns for the population of SA.
• Pharmacists should provide training to pharmacy personnel for the correct recording of data so as to avoid inconsistencies in ICD-10 codes and/or capturing of data.

• Community pharmacists should be more involved in diabetes education, and perhaps have a diabetic clinic in their pharmacies. This could increase the emphasis and awareness regarding the management of type 2 DM.

• In future, this study could be expanded to include a patient-questionnaire component, so as to address patient concerns about the use of insulin therapy in type 2 DM.

5.4 CONCLUDING STATEMENT

Research has shown that the addition of insulin to oral hypoglycaemic medications assists in achieving glycaemic control (De Witt & Hirsch, 2003; Grégoire et al., 2009; Pogach, 2009). It is important to recognise that insulin can be used alone, or in combination, for the management of type 2 DM. The primary aim of this study was to investigate the management of type 2 DM, focusing more specifically on the use of insulin. From the study’s results, it was concluded that the management of type 2 DM with oral hypoglycaemic agents, remains the mainstay of therapy. It was observed that insulin was used to a lesser extent compared to the use of oral hypoglycaemic agents.


[Accessed 28 February 2010].


Bhattacharyya, A. 2001. Aetiology and Pathology of Type 2 Diabetes Mellitus. Hospital Pharmacist, [Online], 8, pp. 5-9. Available at:
[Accessed 9 June 2010].


Diabetes Trial Unit (DTU), 2011b. *United Kingdom Prospective Diabetes Study Results*, [Online], Available at: http://www.dtu.ox.ac.uk/ukpds_trial/results.php [Accessed 24 October 2011].


Available at: www.cmaj.ca/cgi/content/full/180/13/1287 [Accessed 28 March 2011].


APPENDIX A

ETHICS APPROVAL
Copy to: 
Supervisor: Ms L Kritiotis
Co-supervisors: Ms S Burton

Ref: 206080330
Contact person: Ms N Ahmed

31 May 2010
Ms A Saugur
22 Tielan Road
Summerstrand
Port Elizabeth
6001

FINAL RESEARCH/PROJECT PROPOSAL: MPharm

Please be advised that your final research proposal was approved by the Faculty Research, Technology and Innovation Committee subject to the following amendments/recommendations being made to the satisfaction of your Supervisor:

COMMENTS/RECOMMENDATIONS

1) That the student clarify why she does not need consent;
2) There must be some additions to the ethics application form on p. 3;
3) That the candidate clarifies why participants could be under 18 year on p. 3 (f) of the ethics application form;
4) That the candidate acknowledges, how representative members are of a particular medical aid;
5) Describing patterns could be different depending on the medical aids;
6) Candidate to indicate in a sentence "this is the general population of a medical aid";
7) "The student should not identify the medical aid.

Ethics approval has been granted by the FRTI committee and no further REC-H approval is required. FRTI committee number is H1019EAPC108.

Please be informed that this is a summary of deliberations that you must unpack with your Supervisor.

Kind regards

OFFICE OF THE DEAN
FACULTY OF HEALTH SCIENCES
APPENDIX B
REQUEST LETTER FOR DATABASE FROM MEDICAL AID
REQUEST LETTER FOR DATABASE FROM MEDICAL AID

DETAILS OF DATA REQUEST:

A) CRITERIA FOR THE RESEARCH POPULATION

All data pertaining to all of the diabetic patients (ICD-10 codes: E10.9, E11.9 and E14) currently registered on the Discovery Health database.

FORMAT OF DATA REQUEST

i) Data to be provided on CD (researcher prepared to cover costs).

ii) Data will be analysed using the Microsoft® Windows 2007 Professional Package (Access® and Excel®). If it is not possible to provide data in Access® and Excel® format; data may be ASCII delimited (with a comma as a delimiter).

iii) Each record to include data as indicated in Column A to Column V (see below).

iv) Each new drug prescribed for a particular patient must represent a different record/row.

v) The data should be for the period: 2005 to current.

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</tr>
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<td>COLUMN I</td>
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TITLE OF THE PROJECT

MANAGEMENT OF TYPE 2 DIABETES MELLITUS – A PHARMACOEPIDEMIOLOGICAL REVIEW

SUMMARY (including motivation for the study)

Diabetes mellitus is a prevalent chronic disease. The WHO predicts that within the next 20 years diabetes will become one of the world’s main ‘disablers and killers’. Diabetes results in or is a substantial contributor to significant morbidity, including metabolic complications, retinopathy, neuropathy, nephropathy, peripheral vascular disease, ulcerations and amputations, cardiovascular disease, stroke, digestive disorders, infection, oral complications, depression and anxiety disorders. There is a growing body of evidence to suggest that intensive treatment and optimisation of glycaemic control reduces the incidence of microvascular complications such as retinopathy, neuropathy and nephropathy, and possibly even macrovascular complications. Studies have shown that type 2 diabetes is a progressive disease and over time, almost all patients experience β cell dysfunction and will require insulin therapy, either alone or in combination with oral agents, for satisfactory glycaemic control. Patients with type 2 diabetes are frequently reluctant to begin insulin use and in
many instances delay the commencement of insulin therapy for fairly lengthy periods of time, leading to chronically elevated blood glucose levels, and raising the risk of long-term complications – a phenomenon which has been termed ‘psychological insulin resistance’ (PIR). Amongst others, one of the explanations provided for PIR is the subtle negative messages received from healthcare providers toward insulin use.

Changes in drug prescribing and use over time, for chronic disease states such as type 2 diabetes may have medical, social and economic implications both for individual patients and for society. This study will investigate the patterns and trends in the use of insulin in the treatment of type 2 diabetes, in the private healthcare sector, in South Africa.

OBJECTIVES OF THE STUDY

The objectives of this study will be, with respect to type 2 diabetes:

1. establish the prevalence of type 2 diabetes relative to age, gender and ethnicity, in the study population,
2. examine the prevalence and nature of comorbid disease states, especially those that can be related to micro and macrovascular complications in diabetic patients,
3. establish the extent, profile and trends in the prescribing of insulin, relative to other oral hypoglycaemic agents, over a five year period,
4. investigate the cost implications of the patterns of hypoglycaemic drug use,
5. relative to their use of insulin and other hypoglycaemic agents, examine the extent and trends of use of blood and urine glucose monitoring materials by patients,
6. using prescribing indices such as prescribed daily doses (PDD) and defined daily doses (DDD), compare the observed patterns of insulin prescribing with relevant recommended guidelines and protocols,
7. determine the extent to which prescribing guidelines and treatment protocols in South Africa take into account evidence and international trends in this regard.

POTENTIAL UTILISATION OF RESULTS

Using a quantitative approach to investigate the patterns and trends in the treatment of type 2 diabetes over a five year period, this study aims to facilitate discussion on evidence-based, rational drug use, from a medical and economic perspective. The study will also highlight potential areas of intervention with the aim of rationalising hypoglycaemic drug prescribing and use and optimising the quality of life of patients.
The results of this research will be submitted in the fulfilment of the requirements for the degree of Magister Pharmaciae in the Faculty of Health Sciences at Nelson Mandela Metropolitan University (NMMU). The final printed version of the dissertation will be made available through the NMMU library services and a copy will be made available to Discovery Health. An article will be prepared for publication in an accredited journal and the results may be presented at a national or international conference.

RESEARCHERS:

Principal Researcher: Anusooya Saugur (MPharm student)
Primary Responsible Person: Susan Burton (Supervisor)
Co-Investigator: Lia Kritiotis (Supervisor)

Susan Burton
Lecturer Pharmacy Practice
Nelson Mandela Metropolitan University
Email: susan.burton@nmmu.ac.za
Tel: 041-5044212 / 0733556849
APPENDIX C

GLOSSARY
ACE Angiotensin Converting Enzyme
ARB Angiotensin II-Receptor Blockers
ATC Anatomical Therapeutic Chemical Classification System
β Beta
BMI Body Mass Index
BP Blood Pressure
CAD Coronary Artery Disease
CVD Cardiovascular Disease
cm Centimetre
DM Diabetes Mellitus
DDD Defined Daily Dose
DUR Drug Utilisation Review
FPG Fasting Plasma Glucose
GI Glycaemic Index
HbA₁c Glycosylated Haemoglobin
HDL High-Density-Lipoproteins
HT Hypertension
ICD International Classification of Diseases
IDF International Diabetes Federation
IGT Impaired Glucose Tolerance
kg Kilogram
l Litre
LDL Low-Density-Lipoproteins
m Metre
mg Milligram
MI Myocardial Infarction
NAPPI National Pharmaceutical Pricing Index
PDD Prescribed Daily Dose
SEMDSA Society For Endocrinology, Metabolism And Diabetes of South Africa
TG Triglycerides
UK United Kingdom
<table>
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<td>Very-Low-Density-Lipoproteins</td>
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