CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

This chapter consists of the conclusions that were drawn from the literature review and the empirical investigation of this study. The discussion will also include recommendations for further studies to be conducted in this field. Finally, all limitations regarding this study will be discussed.

5.1 CONCLUSIONS

The aims established in the specific objectives of both the literature review and empirical investigation will be discussed separately in order to assess whether these aims were met in this study.

5.1.1 CONCLUSIONS BASED ON THE LITERATURE REVIEW

The following conclusions can be formulated with regard to the literature review.

- *The first specific objective was to describe the indication and management of warfarin therapy.*

A brief overview was given of the indications for which warfarin is most commonly prescribed. As stipulated by Fitzpatrick and O'Kennedy (2004:11), warfarin is used in the treatment of a wide range of thrombo-embolic disorders. A list consisting of nine indications were formulated from the literature. Some of these indications include the treatment of venous thrombo-embolism and deep vein thrombosis, the treatment and prevention of pulmonary embolism and the treatment of atrial fibrillation with a risk of embolization (Appadu, 2010:252; Appadu, 2010:252) (refer to section 2.2.3).

The management of warfarin therapy is complicated by the fact that there are so many factors that influence warfarin dosing. This is further complicated by the fact that warfarin has a narrow therapeutic index (Gibbon, 2008:612; Jonas & McLeod, 2009:375). The greatest problem experienced with warfarin therapy is the many drug-drug interactions that can occur. This is due to the fact that warfarin is metabolised by many cytochrome P450 enzymes that are responsible

for the metabolism for many other drugs as well (Hirsh *et al.*, 2003:1633; Katzung *et al.*, 2009:596) (refer to section 1.1). Much emphasis was placed on the metabolism of warfarin because this is such an important factor that influences its dosing. A brief overview was provided of the metabolism of warfarin by the cytochrome P450. The metabolism of *S*- and *R*-warfarin was discussed separately because these two isomers are metabolised by different cytochrome P450 enzyme subtypes, which leads to the formation of different metabolites (Anon., 2011; Guo *et al.*, 2006; Kaminsky & Zhang, 1997:67; Miller *et al.*, 2008:2211; Park, 1988). All the metabolic pathways that contribute to the metabolism of warfarin were discussed, as well as a detailed description of all the cytochrome P450 enzyme subtypes that are responsible for its metabolism. A brief discussion was also given on other pathways of metabolism of warfarin (refer to section 2.2.4.4).

Another factor that greatly influences the management of warfarin therapy is warfarin resistance. The literature revealed that as early as 1985 researchers discovered that some rats have already become resistant to warfarin (MacNicoll, 1985). This sparked further research on this topic. It was later discovered that warfarin resistance can be due to either pharmacokinetic or pharmacodynamic mechanisms (Linder, 2001:13). In addition, researchers found that mutations in two key enzymes altered the dose needs of different individuals. Mutations in the CYP2C9 enzyme subtypes could cause the necessity to either increase or decrease warfarin doses due to an altered metabolism of warfarin (Linder, 2001:11; Scott *et al.*, 2008:495; Wells *et al.*, 2010:e259). Mutations in the vitamin K 2,3-epoxide reductase enzyme subunit 1 (VKOR1) are also responsible for a varied warfarin dose response (Linder, 2001:10; Wang *et al.*, 2008:90; Scott *et al.*, 2008:496-497). Methods of estimating the correct warfarin doses for patients with these mutations were also discussed (refer to section 2.2.4.5).

- *The second specific objective was to describe from the literature the process of monitoring patients on warfarin therapy.*

This section started off with a short discussion of all the factors that can influence warfarin therapy and the reason for the importance of its monitoring (refer to section 2.2.5.3). There are two tests that can be performed in order to measure the effect warfarin has on coagulation, namely the prothrombin time (PT), which was used to develop the International Normalised Ratio (INR). The PT is used in a calculation to determine the INR. The PT measures the time it takes for blood to coagulate (Hirsh *et al.*, 2003:636; Leiker *et al.*, 2009:227; Motykie *et al.*, 1999:988). The quality of warfarin treatment is determined by the time in therapeutic range

(TTR). The target INR depends on the condition that is being treated, for example the INR should be between 2 or 3 for patients suffering from atrial fibrillation. An INR below 2 increases the chance of a stroke and an INR above 3 increases the chance for haemorrhage. It is therefore important that the patient's INR is kept in the therapeutic range as long as possible to avoid complications (Habib *et al.,* 2008:129; Hirsh *et al.,* 2003:1641; Nieuwlaat *et al.,* 2010:e128; Wright & Dufull, 2011:1100, 1101).

The fact that there is so much inter-person variation when it comes to warfarin therapy, the dosing of warfarin is divided into two phases namely the initial phase and the maintenance phase. In the initial phase the INR should be tested regularly in order to find a stable dose response. The initial warfarin dose is usually 5 mg per day. When the maintenance phase is reached (for patients on chronic therapy) the INR can be tested less frequently (Asnis *et al.,* 2007:213; Hirsh *et al.,* 2003:1637).

Dose adjustments to achieve the desired INR proved to be difficult. This led to the develop warfarin dosing nomograms in order to estimate the required dose for an individual patient, taking into account all the factors that can influence warfarin dose such as genetic polymorphisms, age, gender, body mass index (BMI), etc. (Asnis *et al.,* 2007: 213, 216; Cho *et al.,* 2011:1372, 1374; Jonas & McLeod, 2009:383; Monkman *et al.,* 2009:275, 278; Wells *et al.,* 2010:e259; White, 2010:194, 195).

In order to improve patient compliance with warfarin therapy two programs were developed to make warfarin treatment monitoring easier for the patients, namely patient self-testing (PST) and patient self-management (PSM) (Ansell *et al.,* 2005:38; Ansell & Hughes, 1996:1098-1099). This section continues to discuss the obstacles with PST and PSM and further discusses the difference in the warfarin doses between different age groups (refer to section 2.2.5.3).

- *The third specific objective was to investigate the pharmacokinetic and pharmacodynamic characteristics of warfarin that may lead to drug-drug interactions with warfarin.*

This section started with a few definitions of drug-drug interactions (DDI). One of these definitions is provided by Tatro (2011:xvii), who stated that a DDI can be "the phenomenon that occurs when the effects or pharmacokinetics of a drug are altered by prior administration or co-administration of a second drug." The mechanism of drug interactions can be divided into two groups namely pharmacokinetic and pharmacodynamic interactions (Brunton, 2012). A schematic representation was given to summarise all the mechanisms of interaction that can be

divided into these two groups (refer to Figure 2.11). The most important mechanisms of interactions that pertain to the metabolism of warfarin are enzyme induction and inhibition, protein binding and additive or synergistic interactions. All of these mechanisms were discussed shortly in this section (refer to section 2.2.6).

- *The fourth specific objective was to describe the factors that may influence the appropriate prescription of warfarin therapy.*

Genetic factors play a major role in the dose of warfarin treatment. Various genetic polymorphisms in the genes encoding CYP2C9 and VKORC1 cause enormous inter-person variations in individuals on warfarin therapy. Pharmacogenetics inspired the research into dosing algorithms that incorporate genetic factors, as well as clinical factors that may influence warfarin treatment. Positive results concluded that these dosing algorithms are very accurate in predicting the correct warfarin dose (Cho *et al.,* 2011:1372, 1374; Finkelman *et al.,* 2011:612; Wells *et al.,* 2010:e259) (refer to sections 2.2.4.5 and 2.2.5.3).

The literature identified five clinical factors that may influence warfarin treatment. These factors include age, BMI, the nutritional status of the patient, various chronic illnesses, and finally, drug interactions (Jonas & McLeod, 2009:383; White, 2010:195-197). All these factors and their influence on warfarin therapy were shortly discussed in this section (refer to section 2.2.5.3).

5.1.2 CONCLUSIONS BASED ON THE EMPIRICAL INVESTIGATION

The following conclusions can be formulated with regard to the empirical investigation.

- *The first specific objective was to investigate the prescribing patterns of warfarin in a part of the private health care sector of South Africa.*

This section first illustrated the general prescribing patterns of all medicine items on the total database from 2005 to 2010 (refer to section 4.2.1). The general prescribing patterns of all medicine items were presented as total number of prescriptions and total number of medicine items claimed through the medicine claims database for the six year study period. The total number of prescriptions claimed were 49 523 818 and the total number of medicine items claimed were 118 305 941 (refer to Table 4.1). The average number of prescriptions per patient and the average number of medicine items per prescription per year were also presented. The highest average number of prescriptions claimed per patient per year (6.98 ± 7.89) was 2010.

The highest average number of medicine items claimed per prescription (2.41 ± 1.67) was also 2010 (refer to Table 4.2).

The general prescribing patterns of warfarin medicine items were presented next (refer to section 4.2.2). The total number of warfarin prescriptions and the total number of warfarin medicine items were 427 238 and 427 744 respectively (refer to Table 4.3). The average number of warfarin prescriptions per patient and the average number of warfarin medicine items per prescription per year was also identified (refer to Table 4.4). The number of patients who claimed warfarin prescriptions on the medicines claims database was also analysed and the results showed that a total of 68 575 patients claimed warfarin prescriptions in the six year study period (refer to section 4.2.3). This represents 0.9% of the total number of patients on the database (refer to Table 4.5).

The results revealed that only four types of warfarin products were claimed through the medicine claims database in the six year study period. These products include Aspen-warfarin 5 mg tablets®, Cipla-warfarin 1 mg tablets®, Cipla-warfarin 3 mg tablets® and Cipla-warfarin 5 mg tablets® (refer to section 4.3). The results revealed that the warfarin product that was prescribed the most was Aspen-warfarin 5 mg tablets® with a frequency of 422 632 (n=427 744, 98.8%) (refer to section 4.3.2).

The different prescribing patterns of warfarin medicine items were also analysed according to the prescribing physician. The results revealed that general practitioners prescribed the most warfarin medicine items in the six year study period (n=249 202, N=427 744, 58.3%). Paediatric cardiologists prescribed the lowest frequency of warfarin medicine items (n=76, N=427 744, 0.02%).

The age group that claimed the most warfarin prescriptions in the study period was age group 4 (n=327 592, N=427 238, 76.6%) (refer to section 4.4.1). This age group consists of patients 59 years and older. The age group that claimed the lowest frequency of warfarin prescriptions was age group 1 (n=881, N=427 238, 0.2%). This age group consists of patients 20 years and younger. The age group with the largest number of patients who received warfarin prescriptions was age group 4 (refer to section 4.2.2). This age group consisted of 72.9% (n=49 986, N=68 575) of all the patients who claimed warfarin prescriptions in the study period. The age group with the lowest number of patients is age group 1 (n=260, N=68 575, 0.4%). The average number of warfarin prescriptions per patient according to age group was also presented (refer to Table.9). The highest frequency of warfarin medicine items claimed in the study period belongs

to age group 4 (refer to section 4.4.3). The age group claimed 76.7% (n=327 984, N=427 744) of all the warfarin medicine items in the medicine claims database. Age group 1 (concits of patients 20 years and younger) only claimed 0.2% (n=882, N=427 744) of the total number of warfarin medicine items claimed. The average number of warfarin medicine items per prescription was also analysed (refer to Table 4.10). From these results it can be assumed that warfarin is not underutilised in age group 4.

The number of warfarin prescriptions claimed according to gender was distributed almost evenly between females and males. Females claimed 48.2% (n=205 999, N=427 238) of the total number of warfarin prescriptions in the six year study period whereas males claimed 51.8% (n=221 117, N=427 238) (refer to section 4.5.1). The number of patients who claimed warfarin prescriptions according to gender was also distributed evenly. Females represented 49.9% (n=34 238, N=68 575) of the total number of patients who claimed warfarin prescriptions and males represent 50.0% (n=34 315, N=68 757). The average number of warfarin prescriptions claimed per patient was also identified (refer to Table 4.12). The number of warfarin medicine items claimed through the medicine claims database follows the same trend. Females claimed 48.2% (n=206 232, N=427 744) of the total number of warfarin medicine items in the six year study period and males claimed 51.8% (n=221 390, N=427 744). The average number of warfarin medicine items claimed per prescription according to gender for the six year study period was also analysed (refer to Table 4.13). The results show that there is no difference in warfarin use between females and males.

The average prescribed daily dose (PDD) of warfarin per prescription was also analysed (refer to section 4.6). The average PDD of warfarin according to the prescribing physician revealed that general practitioners prescribed the highest average PDD for warfarin (7.01 mg ± 9.86 mg). The lowest average PDD of warfarin were prescribed by paediatric cardiologists (4.61 mg ± 1.29 mg). The d-values for the average PDD of warfarin for the different prescribing physicians were also identified (refer to section 4.6.1). The range of PDD of warfarin that was prescribed the most by the prescribing physicians was 5.00 mg to 9.99 mg (refer to Graph 4.1). The average PDD of warfarin between females and males was almost similar (6.60 mg ± 9.06 mg, 6.74 mg ± 8.41 mg) (refer to section 4.6.2). A d-value of 0.02 indicates that there are no practical difference between the average PDD of warfarin between females and males. The range of PDD of warfarin that was prescribed the most according to gender was 5.00 mg to 9.99 mg (refer to Graph 4.2). The highest PDD of warfarin prescribed according to age group was for age group 2 (7.42 mg ± 7.42 mg) (refer to section 4.6.3). The d-values for the in PDD of warfarin

between the different age groups are summarised in Table 4.16. The range of PDD of warfarin that was prescribed the most according to age group was 5.00 mg to 9.99 mg (refer to Graph 4.3). From the results it can be assumed that general practitioners prescribe the most warfarin medicine items because they may receive the most patients needing warfarin therapy.

- *The second specific objective was to investigate the prevalence of co-prescribing of potentially interacting drugs with warfarin in South Africa over a six year period, 2005-2010).*

The results showed that a total number of 358 482 drugs were co-prescribed with warfarin in the six year study period (refer to section 4.7.1). The drugs that were co-prescribed with warfarin could be assigned one of four significance ratings (SR) (refer to section 2.3.3) namely, 1, 2, 4, and 5. Drugs with a significance rating of 1 (n=155 066, N=358 482, 43.3%) and 4 (n=137 144, N=358 481, 38.3%) were prescribed the most.

The age group that was prescribed the highest frequency of potentially interacting drugs was age group 4 (n=295 719). The drug with a SR of 1 that was co-prescribed the most with warfarin was aspirin (n=48 903, N=358 482, 13.6%) (refer to section 4.2.7). Paracetamol (n=8 488, N=358 482, 2.37%) was the drug with a SR of 2 that was co-prescribed the most with warfarin. A total number of 30 128 (N=358 481, 8.4%) of drugs with a SR of 2 was co-prescribed with warfarin (refer to section 4.7.3). There were only five different drugs with a SR of 4 and one drug with a SR of 5 that was co-prescribed with warfarin (refer to section 4.7.4), therefore these drugs were discussed together. From these six drugs furosemide (n=22 534, N=358 482, 16.23%) was co-prescribed the most. These two groups of co-prescribed drugs comprised of 48.4% (n=173 288, N=358 481) of the total number of drugs co-prescribed with warfarin for the six year study period. The top 10 drugs that were co-prescribed were identified (refer to section 4.7.5). From these ten drugs the top 5 drugs co-prescribed with warfarin were extracted. The top 5 co-prescribed drugs include aspirin, thyroxine, amiodarone, simvastatin and celecoxib (refer to Graph 4.11). The top 5 drugs represented 38.43% (n=137 782, N=358 482) of the total number of co-prescribed drugs. The drug that was co-prescribed the most with warfarin in the six year study period was aspirin (n=48 903, N=358 482, 13.64%). These five drugs were discussed separately (refer to sections 4.7.5.1 to 4.7.5.5).

- *The third specific objective was to assess whether warfarin treatment is changed when prescribed together with potentially interacting drugs.*

Only the doses of the top 5 drugs co-prescribed with warfarin were analysed and compared to the doses of warfarin that were co-prescribed (refer to sections 4.7.5.1 to 4.7.5.5). Analyses in the co-prescribing of aspirin with warfarin led to the selection of two ranges of high risk aspirin doses namely, 150.00 mg to 299.99 mg and 300.00 mg and more (refer to section 4.7.5.1). These two high risk aspirin doses were also co-prescribed the least with warfarin (n=4 530, N=48 903, 9.26%; n=1 131, N=48 903, 2.31%) (refer to Graph 4.12). The warfarin dose range that was co-prescribed the most with the two high risk aspirin dose ranges was 10.00 mg to 29.99 mg (n=2 885, N=48 903, 6.00%). It was concluded from the literature that aspirin can augment the effect of warfarin (Baxter, 2008:385; Hansten & Horn, 2011:221; Tatro, 2011:175). The range of high risk aspirin dose that was co-prescribed the most with this range of warfarin dose was 150.00 mg to 299.99 mg (n=3 342, N=48 903, 6.93%) (refer to Graph 4.13). The age group that received the highest frequency of the high risk aspirin dose ranges was age group 4 (n=3 571, N= 48 903, 7.30%; n=904, N=48 903, 1.85%) (refer to Graph 4.15). This age group consists of patients 59 years and older. It can therefore be concluded that high aspirin doses are commonly co-prescribed with warfarin.

All the dose ranges of thyroxine was analysed against the doses of warfarin (refer to section 4.7.5.2). The thyroxine dose range that was co-prescribed the most was 0.02499 mg and less (n=20 614, N=33 954, 60.71%) (refer to Graph 4.16). The warfarin dose range that was co-prescribed the most with thyroxine was 10.00 mg to 29.99 mg (n=24 918, N=33 954, 73.39%) (refer to Graph 4.17). The age group that was co-prescribed the highest frequency of thyroxine was age group 4 (n=28 663, N=33 954, 84.42%) (refer to Graph 4.18). The literature stipulated that as the thyroid metabolic rate fluctuates, so does the warfarin dose requirements (Baxter, 2008:455; Hansten & Horn, 2011:1754). It can therefore be concluded that high thyroxine doses are commonly co-prescribed with warfarin.

The amiodarone dose range that was co-prescribed the most was 100.00 mg to 299.99 mg (n=22 386, N=25 056, 89.34%) (refer to section 4.7.5.3). Three high risk amiodarone dose ranges were identified namely 300.00 mg to 499.99 mg, 500.00 mg to 699.99 mg, and 700.00 mg and higher. The warfarin dose range that was co-prescribed the most with the three groups of high risk amiodarone dose ranges was 10.00 mg to 29.99 mg (n=965, N=25 056, 3.85%). From the three high risk amiodarone dose ranges the one dose range that was prescribed the most with warfarin was 300.00 mg to 499.99 mg (n=1 301, N=25 056, 5.19%) (refer to Graph 4.20). The age group that was co-prescribed the highest frequency of these amiodarone dose ranges was age group 4 (n=1 723, N=25 056, 6.88%) (refer to Graph 4.21). The literature states

that amiodarone increases the anticoagulant effects of warfarin (Tatro, 2011:90). It can therefore be concluded that high amiodarone doses are commonly co-prescribed with warfarin.

The co-prescribed simvastatin dose range with the highest frequency was 20.00 mg to 39.99 mg (n=9 836, N=19 070, 51.58%) (refer to section 4.7.5.4). The warfarin dose range that was co-prescribed most frequently with simvastatin was 10.00 mg to 29.99 mg (n=13 483, N=19 070, 70.70%) (refer to Graph 4.23). The age group that received the highest frequency of co-prescribed simvastatin was age group 4 (n=16 156, N=19 070, 84.72%) (refer to Graph 4.24). The literature stated that simvastatin could potentially increase the risk for haemorrhaging when co-prescribed with warfarin (Baxter, 2008:450; Hansten & Horn, 2011:1710; Tatro, 2011:135). It can therefore be concluded that high simvastatin doses are commonly co-prescribed with warfarin.

Celecoxib was the fifth most frequent drug that was co-prescribed with warfarin (refer to section 4.7.5.5). The celecoxib dose range that was co-prescribed the most was 100.00 mg to 299.99 mg (n=8 814, N=10 794, 81.66%) (refer to Graph 4.25). The warfarin dose range that was prescribed the most with celecoxib was 10.00 mg to 29.99 mg (n=7 046, N=10 794, 65.28%) (refer to Graph 4.26). The age group that received the highest frequency of co-prescribed celecoxib was age group 4 (n=9 206, N=10 794, 85.29%) (refer to Graph 4.27). The literature revealed that there is a potential for an increased anticoagulant effect when celecoxib is co-administered with warfarin (Baxter, 2008:429; Dentali *et al.,* 2006:1242). It can therefore be concluded that high celecoxib doses are commonly co-prescribed with warfarin.

5.2 RECOMMENDATIONS

The following are recommendations proposed for future studies:

- To investigate the level of patient compliance with warfarin therapy using different point of care systems;
- To investigate alternative anticoagulant therapies;
- To obtain clinical data such as INR values of individual patients to investigate the time in therapeutic range comparing warfarin therapy alone and warfarin therapy with potentially interacting co-prescribed drugs.
- To assess whether complications do arise when high doses of potentially interacting drugs are co-prescribed with warfarin.

5.3 LIMITATIONS

The following are limitations that were encountered in this study that could influence its applicability:

- The data obtained only represented a section of the private health care sector of South Africa, which made the generalisation of the results to the total health care sector of South Africa difficult.
- Certain patients were not classified in a gender and were known as "unspecified".
- It was not possible to obtain from the data the duration of warfarin therapy for a particular patient.
- No clinical data (INR values or PT values) were available to assess whether the required warfarin dose is prescribed to maintain the desired INR or whether warfarin dose adjustments are required when potentially interacting drugs were co-prescribed.
- The initial warfarin dose for a particular patient was unknown; therefore it was difficult to analyse whether or not the warfarin dose was adjusted when a potentially interacting drug was co-prescribed.

5.4 CHAPTER SUMMARY

The conclusions made from the objectives of the literature review and empirical investigation was discussed in this chapter. Recommendations for further studies and limitations encountered in this study were also discussed.