

CHAPTER 4: RESULTS AND DISCUSSION

In this chapter the results of the empirical investigation will be discussed, including the general prescribing patterns of all medicine items in the medicine claims database, as well as the prescribing patterns of warfarin containing products. Another group of results that will be discussed are the prevalence of the co-prescription of drugs that have a potential drug-drug interaction with warfarin. The results discussed relate to the data obtained in the six study years from 1 January 2005 to 31 December 2010. Figure 4.1 illustrates the layout of the process of the empirical investigation.

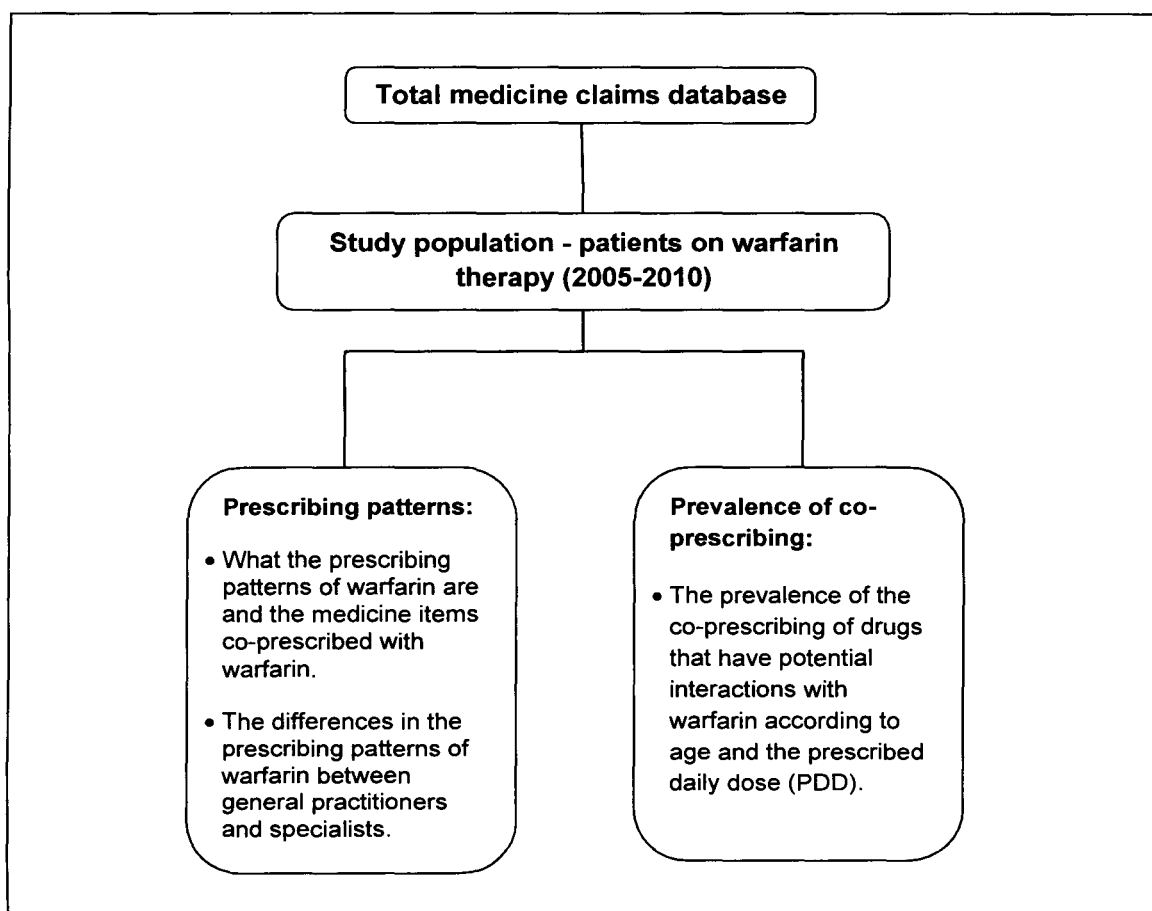


Figure 4.1: Organogram of the empirical investigation

4.1 CLARIFICATION WITH REGARD TO THE INTERPRETATION OF THE RESULTS

- For the purpose of this study, six years were chosen for the study period. The study period ranged from 1 January 2005 to 31 December 2010.
- The medicine products that are listed in the study are the medicine products that were claimed through the medicine claims database of a Pharmaceutical Benefit Management company (PBM). The medicine products are restricted to those available in the private health care sector of South Africa.
- The percentages have been rounded to one decimal and therefore do not always add up precisely to 100% when added together. If the percentage was smaller than one, it was rounded to two decimal places. The averages and d-values were rounded to two decimal places.
- Database refers to the medicine claims database provided by a PBM for analytical purposes.
- The number of patients was determined per year, thus the total number of patients who claimed warfarin therapy over the study period (2005-2010) can include patients who received warfarin prescriptions in more than one year.

4.2 THE GENERAL PRESCRIBING PATTERNS OF MEDICINE ON THE MEDICINE CLAIMS DATABASE

This section includes discussions of the total medicine items available on the database, as well as the warfarin medicine items available on the database.

4.2.1 GENERAL PRESCRIBING PATTERNS

The medicine claims database consisted of a total number of 49 523 818 prescriptions and 118 305 941 medicine items that were claimed during the study period. The total number of prescriptions started off in 2005 with 8 391 836 prescriptions. The lowest number of prescriptions were claimed in 2008 (n=6 775 873). The largest increase (33.2%, n=6 775 873, N=9 023 237) in the number of prescription claimed was seen from 2008 (n=6 775 873) to 2009 (n=9 023 237). The year 2009 is also the year when the largest number of prescriptions was claimed through the medicine claims database. The reason for the fluctuation in claims during the study period is unknown.

Similar changes occur with the number of medicine items claimed on the database compared to that of the number of prescriptions. The lowest number of medicine items claimed also occurs in 2008 (n=16 439 253). The largest increase (31.7%, n=16 439 253, N=21 648 991) also occurs from 2008 to 2009. Similar to the number of prescriptions, the largest number of medicine items claimed on the database was during 2009 (n=21 648 991). The results are summarised in Table 4.1.

Table 4.1: General prescribing patterns (2005-2010)

Year	Total number of prescriptions (n)	%	Total number of medicine items (n)	%
2005	8 391 836	16.9	19 500 774	16.5
2006	8 906 348	18.0	21 113 422	17.8
2007	7 911 096	16.0	19 075 724	16.1
2008	6 775 873	13.7	16 439 253	13.9
2009	9 023 237	18.2	21 648 991	18.3
2010	8 515 428	17.2	20 527 777	17.4
Total	62 938 614	100.0	142 205 711	100.0

Percentages calculated according to the total number of prescriptions or medicine items claimed on the total database for the total study period (2005-2010).

The average number of prescriptions per patient per year steadily increased from 2005 (5.56 ± 6.75) to 2010 (6.98 ± 7.89). However, the d-value of 0.18 indicates that no practically significant change occurred over the six study years. There was also a slight increase in the average number of medicine items per prescription from 2005 (2.32 ± 1.52) to 2010 (2.41 ± 1.67). However, a d-value of 0.05 indicates that no practically significant changes occurred over the six study years. These results are summarised in Table 4.2.

Table 4.2: Average number of prescriptions per patient and number of medicine items per prescription for the total database (2005-2010)

Year	Average number of prescriptions per patient per year	Average number of medicine items per prescription
2005	5.56 ± 6.75	2.32 ± 1.52
2006	5.72 ± 6.96	2.37 ± 1.55
2007	6.71 ± 7.55	2.41 ± 1.59
2008	6.95 ± 7.85	2.43 ± 1.64
2009	6.90 ± 7.88	2.40 ± 1.64
2010	6.98 ± 7.89	2.41 ± 1.67

4.2.2 GENERAL PRESCRIBING PATTERNS OF WARFARIN MEDICINE ITEMS

The database consisted of a total number of 427 238 (0.9%, N=4 952 818) warfarin prescriptions and a total number of 427 744 (0.4%, N=118 305 941) warfarin medicine items claimed during the study period. Warfarin prescriptions started off with 67 268 prescriptions in 2005. Fluctuations occurred in the number of warfarin prescriptions. An increase was observed from 2005 (n=67 268) to 2006 (71 090), followed by a decrease of 5.0% (n=67 534) in 2007. During 2008 (n=61 635) the lowest number of warfarin prescriptions was claimed. The biggest/largest increase (32.6%) was seen from 2008 (n=61 635) to 2009 (n=81 708).

Similar fluctuations occurred within the total number of warfarin medicine items claimed in the database. The lowest number of warfarin medicine items were claimed in 2008 (n=61 689) and the highest number of warfarin medicine items were claimed in 2009 (n=81 853). The largest increase (32.7%) also occurred over these two study years. These results are summarised in Table 4.3.

Table 4.3: General prescribing patterns of warfarin prescriptions and warfarin medicine items for the total database (2005-2010)

Year	Total number of warfarin prescriptions (n)	*%	Total number of warfarin medicine items (n)	*%
2005	67 268	15.7	67 313	15.7
2006	71 090	16.6	71 120	16.6
2007	67 534	15.8	67 570	15.8
2008	61 635	14.4	61 689	14.4
2009	81 708	19.1	81 853	19.1
2010	78 003	18.3	78 199	18.3

*Percentage was calculated according to the total number of warfarin prescriptions or total number of warfarin medicine items claimed on the total database (2005-2010).

Similar changes occur within the average number of warfarin prescriptions as is observed with the average number of prescriptions per patient per year of the total database. The average number of warfarin prescriptions per patient per year steadily increased from 2005 (5.64 ± 4.06) to 2010 (6.38 ± 4.00). The d-value of 0.18, however, indicates that no practically significant change occurred over the six study years. The average number of medicine items per prescription from 2005 (1.00 ± 0.03) to 2010 (1.00 ± 0.05) clearly shows no obvious increase or decrease over the study period and therefore also no statistically significant changes over the six study years. These results are summarised in Table 4.4.

Table 4.4: Average number of warfarin prescriptions per patient per year and warfarin medicine items per prescription for the whole database (2005-2010)

Year	Average number of warfarin prescriptions per patient	Average number of warfarin medicine items per prescription
2005	5.64 ± 4.06	1.00 ± 0.03
2006	5.95 ± 3.99	1.00 ± 0.02
2007	6.45 ± 4.01	1.00 ± 0.02
2008	6.42 ± 3.98	1.00 ± 0.03
2009	6.59 ± 4.08	1.00 ± 0.04
2010	6.38 ± 4.00	1.00 ± 0.05

4.2.3 NUMBER OF PATIENTS FOR THE SIX YEAR STUDY PERIOD

The total number of patients who claimed medication through the database was 7 748 621. Some fluctuations in the number of patients do occur in these two groups of patients. In the total database the year in which the largest number of patients claimed through the database was 2006 (n=1 558 090). These patients represent 20.1% (n=1 558 090, N=7 748 621) of the total number of patients on the total database. During 2008 the smallest number of patients claimed, accounting for 12.6% (n=974 467, N=7 748 621) of the total number of patients. From 2006 through to 2010 the number of patients who claimed through the database decreased by 21.7% (n=1 558 090, N=1 220 289).

The total number of patients who claimed warfarin products during the study period was 68 575. This represents 0.9% (n=68 757, N=7 748 621) of all patients on the database for the six year study period. The fluctuations that occur within the group of patients that claimed warfarin products are similar to that of the total database. However, there are a few differences. The year in which the smallest number of patients claimed warfarin products was 2008 (n=9 606). This represents 14.0% of all the patients who claimed warfarin products through the database. The largest number of patients who claimed warfarin products through the database, however, is in 2009 (n=12 401). This represents 18.1% (n=12 401, N=68 575) of the total number of patients who claimed warfarin products. The largest increase (29.1%) in patients who claimed warfarin products through the database occurs between 2008 (n=9 606) and 2009 (n=12 401). The reasons for these fluctuations are unknown. These results are summarised in Table 4.5.

Table 4.5: Number of patients on the total database (2005-2010)

	Year	Number of patients (n)	**%
Patients who claimed prescriptions on the total database	2005	1 509 621	19.5
	2006	1 558 090	20.1
	2007	1 178 596	15.2
	2008	974 467	12.6
	2009	1 307 528	16.9
	2010	1 220 289	15.7
	Total	7 748 621	100
Patients who claimed warfarin products	2005	11 927	17.4
	2006	11 954	17.4
	2007	10 469	15.3
	2008	9 606	14.0
	2009	12 401	18.1
	2010	12 218	17.8
	Total	68 575	100

**Percentages calculated according to the total number of patients for the specific year in either the total database or for the warfarin products.*

4.3 PRESCRIBING PATTERNS OF THE DIFFERENT WARFARIN PRODUCTS

There are only four warfarin products currently in use in South Africa. These warfarin products include Aspen-warfarin 5 mg tablets®, Cipla-warfarin 1 mg tablets®, Cipla-warfarin 3 mg tablets® and Cipla-warfarin 5 mg tablets®. These are all generic products. No innovator drugs are currently claimed through this PBM.

4.3.1 DIFFERENT TYPES OF WARFARIN PRODUCTS USED IN SOUTH AFRICA

Analyses of the data showed that Aspen-warfarin 5 mg tablets® was the number 1 warfarin product prescribed and dispensed throughout the study period. This product represents 98.8% (n=422 632, N=427 744) of the total number of warfarin products. The warfarin product that is used the least is Cipla-warfarin 3 mg tablets® (0.4%, n=157, N=427 744). The reasons for these values are unknown. These results are summarised in Table 4.6.

Table 4.6: Trade names of warfarin products used

Warfarin products	Number of warfarin medicine items	**%
Aspen-warfarin 5 mg tablets®	422 632	98.80
Cipla-warfarin 1 mg tablets®	1 777	0.42
Cipla-warfarin 3 mg tablets®	157	0.04
Cipla-warfarin 5 mg tablets®	3 178	0.74
	427 744	100

4.3.2 PRESCRIBING PATTERNS OF WARFARIN PRODUCTS ACCORDING TO DIFFERENT PRESCRIBERS

In this study, five groups of prescribing physicians were chosen for the analyses of the prescribing patterns of warfarin according to different types of prescribers. The five groups chosen were cardiologists, paediatric cardiologists, general practitioners, internists and the final group that is categorised as “other”. This group is for prescribing physicians that do not fit in the other four categories.

Table 4.7 indicates that the prescribing physicians that prescribe warfarin the most are general practitioners. General practitioners showed the highest number of warfarin prescriptions (58.27%, n=249 202, N=427 744) compared to other prescribers, while paediatric cardiologists prescribed warfarin the least, representing only 0.02% (n=76, N=427 744) of the total number of warfarin medicine items prescribed. This could be due to the fact that there are more general practitioners in practice than the other prescribing physicians that prescribed warfarin on the database.

Table 4.7: Prescribing patterns of the different warfarin products according to different prescribers

Prescribing physician	Warfarin products	Number of warfarin medicine items	**%
Cardiologist	Aspen-warfarin 5 mg tablets®	51 960	12.20
	Cipla-warfarin 1 mg tablets®	141	0.03
	Cipla-warfarin 3 mg tablets®	6	0.00
	Cipla-warfarin 5 mg tablets®	271	0.10
	Total	52 378	12.24
Paediatric cardiologist	Aspen-warfarin 5 mg tablets®	76	0.02
	Total	76	0.02
General practitioner	Aspen-warfarin 5 mg tablets®	246 446	57.62
	Cipla-warfarin 1 mg tablets®	831	0.20
	Cipla-warfarin 3 mg tablets®	46	0.01
	Cipla-warfarin 5 mg tablets®	1 879	0.44
	Total	249 202	58.27
Internist	Aspen-warfarin 5 mg tablets®	87 142	20.40
	Cipla-warfarin 1 mg tablets®	638	0.20
	Cipla-warfarin 3 mg tablets®	98	0.02
	Cipla-warfarin 5 mg tablets®	712	0.20
	Total	88 590	20.82
Other	Aspen-warfarin 5 mg tablets®	37 008	8.65
	Cipla-warfarin 1 mg tablets®	167	0.04
	Cipla-warfarin 3 mg tablets®	7	0.00
	Cipla-warfarin 5 mg tablets®	316	0.1
	Total	37 498	8.79
TOTAL	427 744	100	

*Percentage calculated according to the total number of warfarin medicine items for the total database (2005-2010).

4.4 PRESCRIBING PATTERNS OF WARFARIN ACCORDING TO DIFFERENT AGE GROUPS

Warfarin is prescribed differently in different age groups (refer to section 2.2.5.3). In this section attention will be given to the general prescribing patterns of warfarin, the frequency at which warfarin medicine items were claimed through the database, as well as the number of warfarin prescriptions issued to patients over the total study period (2005-2010) in relation to the different age groups chosen for this study (refer to section 3.3.3).

4.4.1 GENERAL PRESCRIBING PATTERNS OF WARFARIN PRESCRIPTIONS ACCORDING TO AGE GROUP

According to the total database, the age group that claimed the most prescriptions in the six study years was age group 3 (consists of patients 39 years to 59 years of age). This age group represents 36.4% (n=18 013 238, N=49 523 818) of the total number of prescriptions claimed through the database from 2005 to 2010. Age group 4 only represents 32.1% (n=15 893 979, N=49 523 818) of the total number of prescriptions claimed (refer to Table A1.1 in Appendix A). The total number of warfarin prescriptions claimed by patients in age group 4 only represents 2.4% (n=377 592, N=15 893 979) of the total number of prescriptions claimed by patients in age group 4 for the total database (2005-2010). Age group 4 represents patients from 59 years of age and older (refer to section 3.3.3).

Age group 1 represents 13.6% (n=6 753 492, N=49 523 818) of the total number of prescriptions claimed in the database from 2005 to 2010 (refer to Table A1.1 in Appendix A). The total number of warfarin prescriptions claimed in this age group only represents 0.001% (n=881, N=49 523 818) of the total number of warfarin prescriptions claimed during the study period. Table 4.8 summarizes these results.

Throughout the study period age group 4 (patients \geq 59 years) showed the highest utilisation/prescriptions for warfarin, representing 76.6% (n=327 592, N=427 238) of the total number of warfarin prescriptions. This can be due to the fact that this group of patients are the so-called "high risk" group for thrombo-embolic disorders (refer to section 2.2.5.3). Some major increases in the number of warfarin prescriptions occur from age group to age group. During each year of the study period (2005 through to 2010) there were large increases in the number of warfarin prescriptions claimed when moving from age group 1 to age group 4.

Age group 1 was issued the least number of warfarin prescriptions in 2005, representing 0.2% of the total number of warfarin prescriptions claimed (refer to Table 4.8). This group is so small because warfarin is only prescribed to patients under the age of 20 for specific reasons, including *inter alia* warfarin therapy for primary or secondary thromboprophylaxis (Bauman *et al.*, 2010:e110; Streif *et al.*, 1999:3007). It is usually only prescribed for children who had undergone the Fontan procedure (Bauman *et al.*, 2010:e110; Streif *et al.*, 1999:3007). These children therefore also run the risk for developing thrombo-embolic disorders (Bauman *et al.*, 2010:e110; Streif *et al.*, 1999:3007) (refer to section 2.2.5.3).

Table 4.8: Number of warfarin prescriptions according to age group

Year	Age group	Number of warfarin prescriptions (n)	%
2005	1	133	0.20
	2	2 495	3.71
	3	14 043	20.88
	4	50 597	75.22
	Total	67 268	100
2006	1	160	0.23
	2	2 356	3.31
	3	14 935	21.01
	4	53 639	75.45
	Total	71 090	100
2007	1	183	0.27
	2	2 084	3.09
	3	13 579	20.11
	4	51 688	76.54
	Total	67 534	100
2008	1	138	0.22
	2	1 725	2.80
	3	11 888	19.29
	4	47 884	77.69
	Total	61 635	100
2009	1	139	0.17
	2	2 547	3.12
	3	16 215	19.85
	4	62 807	76.87
	Total	81 708	100
2010	1	128	0.16
	2	2 249	2.88
	3	14 649	18.78
	4	60 977	78.17
	Total	78 003	100
TOTAL		427 238	

*Percentage calculated according to the total number of patients for the specific year.

4.4.2 NUMBER OF WARFARIN PRESCRIPTIONS PER PATIENT ACCORDING TO AGE

In the total database, the age group with the largest number of patients who claimed prescriptions from 2005 to 2010 was not age group 4, but age group 3. Age group 3 (consisting of patients 39 years to 59 years old) represents 36.6% (n=2 839 544, N=7 748 621) of the total

number of patients who claimed prescriptions in the six year study period. Age group 4 represents only 17.2% (n=1 330 765, N=7 748 621) of the total number of patients. Taking the year 2005 as an example again, a decrease of 50.6% occurs from age group 3 to age group 4 (refer to Table A1.3 in Appendix A).

According to Table A1.3 in Appendix A, the age group with the smallest average number of prescriptions per patient claimed in the total database from 2005 to 2010 is age group 1. This is because this age group has the least number of patients. There is a very small increase in the average number of prescriptions per patient of age group 1 from 2005 (3.09 ± 3.19) to 2010 (3.65 ± 3.75). A d-value of 0.14 indicates that no practically significant change occurred over this period. Age group 4 has the largest average number of prescriptions per patient over the six year study period. An increase in this average also occurs from 2005 (10.37 ± 9.87) to 2010 (12.62 ± 10.70). However a d-value of 0.2 indicates that this change is very small and has no practical significance. The change from age group 1 to age group 4 is quite large. Taking the year 2005 as an example, the averages from age group 1 (3.09 ± 3.19) to age group 4 (10.37 ± 9.87) is quite large and may be practically significant according to a d-value of 0.7.

Age group 4 represents the largest number of patients for whom warfarin prescriptions were claimed over the six study years, representing 72.9% (n=49 986, N=68 575). Age group 3 is the second largest group of patients who claimed warfarin prescriptions over the course of the study. There is a steep increase in the number of patients moving from age group 3 to age group 4. The reason for the large number of patients in age group 4 is explained in section 4.4.1.

The age group with the lowest average number of warfarin prescriptions per patient is age group 1 (2.66 ± 2.52 in 2005) (refer to Table 4.9). This average increases over the course of the study period to 4.07 ± 3.26 in 2010. A d-value of 0.4, however, indicates that a small change has occurred, but the results are practically insignificant (refer to section 3.3.7.4). Age group 4 has the highest average number of warfarin prescriptions per patient. A slight increase also occurs from 2005 (5.97 ± 4.05) to 2010 (6.68 ± 3.97), although the d-value of 0.2 indicates that no practically significant change occurred during the study period. Taking the year 2005 as an example, the increase of the average number of warfarin prescriptions claimed from age group 1 (2.66 ± 2.52) to age group 4 (5.97 ± 4.05) is practically significant and therefore of high importance according to a d-value of 0.8.

Table 4.9: The average number of warfarin prescriptions per patient according to age group

Year	Age group	Number of patients (n)	**%	Average number of warfarin prescriptions per patient
2005	1	50	0.4	2.66 ± 2.52
	2	657	5.5	3.80 ± 3.50
	3	2 744	23.0	5.12 ± 4.06
	4	8 476	71.1	5.97 ± 4.05
	Total	11 927	100	5.64 ± 4.06
2006	1	53	0.4	3.02 ± 3.05
	2	577	4.8	4.08 ± 3.69
	3	2 780	23.3	5.37 ± 4.03
	4	8 544	71.4	6.28 ± 3.93
	Total	11 954	100	5.95 ± 3.99
2007	1	53	0.5	3.45 ± 3.44
	2	462	4.4	4.51 ± 3.72
	3	2 345	22.4	5.79 ± 4.13
	4	7 609	72.7	6.79 ± 3.93
	Total	10 469	100	6.45 ± 4.01
2008	1	36	0.4	3.83 ± 7.76
	2	401	4.2	4.30 ± 3.81
	3	2 064	21.5	5.76 ± 4.04
	4	7 105	74.0	6.74 ± 3.91
	Total	9 606	100	6.42 ± 3.98
2009	1	38	0.3	3.66 ± 3.55
	2	559	4.5	4.56 ± 3.68
	3	2 681	21.6	6.05 ± 4.15
	4	9 123	73.6	6.88 ± 4.02
	Total	12 401	100	6.59 ± 4.08
2010	1	30	0.3	4.07 ± 3.26
	2	532	4.4	4.23 ± 3.55
	3	2 527	20.7	5.80 ± 3.99
	4	9 129	74.7	6.68 ± 3.97
	Total	12 218	100	6.38 ± 4.00
TOTAL		68 575		

**% calculated according to the total number of patients for the specific year.

4.4.3 FREQUENCY OF WARFARIN MEDICINE ITEMS CLAIMED ACCORDING TO AGE GROUPS

The medicine items claimed on the whole database exhibits similar findings to that of total number of prescriptions claimed during the study period. The age group where the most medicine items were claimed is also age group 3, which represents 22.5% (n=42 276 651,

N=188 305 881) of all the medicine items claimed. However, age group 4 is not far behind with 21.4% (n=40 319 179, N=188 305 881) of all the medicine items claimed (refer to Table A1.2 in Appendix A). The total number of warfarin medicine items claimed in age group 4 represents only 0.2% (n=327 984, N=188 305 881) of all the medicine items claimed in the total database.

The age group where the smallest number of medicine items are claimed is age group 1 (consisting of patients 20 years old and younger). This group represents 8.6% (n=16 156 038, N=188 305 881) of the total number of medicine items claimed in the total database (refer to Table A1.1 in Appendix A). The number of patients influences the number of medicine items claimed. Table 4.9 summarizes these results.

The number of warfarin medicine items closely correlated with the number of warfarin prescriptions issued during the study period (refer to Tables 4.8 and 4.10). This was due to the fact that the average number of warfarin medicine items per warfarin prescription is one medicine item per prescription in most of the cases (refer to table 4.4).

The prescribing patterns of warfarin medicine items were similar to that of the warfarin prescriptions. The age group where the most warfarin medicine items were claimed (76.7%, n=327 984, N=427 744) of the total number of warfarin medicine items claimed, was age group 4. As mentioned in above paragraphs, this could be due to the fact that this age group (59 years and older) is the group that has the highest risk of developing thrombo-embolic disorders (refer to section 4.4.1).

Similar findings occurred with age group 1 in warfarin medicine items claimed as with warfarin prescriptions claimed. Age group 1 claimed the smallest number of warfarin medicine items (0.2%, n=882, N=427 744). The reason for this finding has been explained in previous paragraphs (refer to section 4.4.1).

Table 4.10: Average number of warfarin medicine items per warfarin prescription according to age group

Year	Age group	Number of warfarin medicine items	%	Average number of warfarin medicine items per prescription
2005	1	133	0.20	1.00 ± 0.00
	2	2 495	3.71	1.00 ± 0.00
	3	14 059	20.89	1.00 ± 0.03
	4	50 626	75.21	1.00 ± 0.02
	Total	67 313	100	1.00 ± 0.03
2006	1	160	0.22	1.00 ± 0.00
	2	2 356	3.31	1.00 ± 0.00
	3	14 946	21.02	1.00 ± 0.03
	4	53 658	75.45	1.00 ± 0.02
	Total	71 120	100	1.00 ± 0.02
2007	1	183	0.27	1.00 ± 0.00
	2	2 085	3.09	1.00 ± 0.02
	3	13 591	20.11	1.00 ± 0.03
	4	51 711	76.53	1.00 ± 0.02
	Total	67 570	100	1.00 ± 0.02
2008	1	138	0.22	1.00 ± 0.00
	2	1 726	2.80	1.00 ± 0.02
	3	11 896	19.28	1.00 ± 0.03
	4	47 929	77.69	1.00 ± 0.04
	Total	61 689	100	1.00 ± 0.03
2009	1	140	0.17	1.01 ± 0.08
	2	2 556	3.12	1.00 ± 0.06
	3	16 236	19.84	1.00 ± 0.04
	4	62 921	76.87	1.00 ± 0.04
	Total	81 853	100	1.00 ± 0.05
2010	1	128	0.16	1.00 ± 0.00
	2	2 260	2.89	1.00 ± 0.07
	3	14 672	18.76	1.00 ± 0.04
	4	61 139	78.18	1.00 ± 0.05
	Total	78 199	100	1.00 ± 0.05
TOTAL		427 744		

*Percentage calculated according to the total number of warfarin medicine items for the specific year.

4.5 THE PRESCRIBING PATTERNS OF WARFARIN ACCORDING TO GENDER

In this section attention will be given to the general prescribing patterns of warfarin, the frequency at which warfarin medicine items were claimed through the database, as well as the

number of warfarin prescriptions issued to patients over the study period (2005-2010) in relation to gender.

4.5.1 GENERAL PRESCRIBING PATTERNS OF WARFARIN PRESCRIPTIONS ACCORDING TO GENDER

For the purpose of this study, gender was divided into three categories namely female, male and unspecified. The category “unspecified” is for those patients or prescriptions to which no gender has been assigned. This is usually a very small group compared to the other two groups.

The distribution of the number of prescriptions per gender in the total database is slightly different than the number of warfarin prescriptions per gender. The distribution between female and male is closer to 60/40 than 50/50. When viewing the total number of prescriptions per gender from 2005 to 2010, the females represent 59.7% (n=29 574 883, N=49 523 818) of the number of prescriptions claimed and the males represent 40.3% (n=19 935 180, N=49 523 818) of the total (refer to Table A1.4 in Appendix A). The unspecified group represent only 0.05% (n=27 510, N=49 523 818) of the total number of prescriptions per gender in the database from 2005 to 2010.

The distribution of warfarin prescriptions between male and female was close to equal (50/50) over the six year study period. When taking the total number of warfarin prescriptions per gender over the six year study period, the females represented 48.2% (n=205 999, N=427 238) of the number of warfarin prescriptions claimed and the males represent 51.8% (n=221 117, N=427 238) of the total (refer to Table 4.11). As mentioned above, the category “unspecified” is a very small group and represents only 0.03% (n=122, N=427 238) of the total number of warfarin prescriptions claimed.

Table 4.11: Number of warfarin prescriptions according to gender

Year	Gender	Number of warfarin prescriptions (n)	%
2005	Female	32 431	48.2
	Male	34 789	51.7
	Unspecified	48	0.1
	Total	67 268	100
2006	Female	33 970	47.8
	Male	37 081	52.2
	Unspecified	39	0.1
	Total	71 090	100
2007	Female	32 557	48.2
	Male	34 942	51.7
	Unspecified	35	0.1
	Total	67 534	100
2008	Female	29 907	48.5
	Male	31 728	51.5
	Unspecified	0	0
	Total	61 635	100
2009	Female	39 147	47.9
	Male	42 561	52.1
	Unspecified	0	0
	Total	81 708	100
2010	Female	37 987	48.7
	Male	40 016	51.3
	Unspecified	0	0
	Total	78 003	100
TOTAL		427 238	

* Percentage calculated according to the total number of warfarin prescriptions for the specific year.

4.5.2 NUMBER OF PATIENTS WHO CLAIMED WARFARIN PRESCRIPTIONS ACCORDING TO GENDER

In the total database there is a slight increase in the average number of prescriptions (females, males and unspecified) claimed from 2005 (5.56 ± 6.75) to 2010 (6.98 ± 7.89) (refer to Table A1.6 in Appendix A). However, this does not imply a practically significant change according to a d-value of 0.1. There is also no significant change between female and male patients when it comes to the average number of prescriptions per patient claimed through the whole database from 2005 to 2010.

According to Table 4.12, the distribution of female patients to male patients who claimed warfarin prescriptions in the study period is close to 50/50. The female patients represent 49.9% (n=34 238, N=68 575) and the male patients represent 50.0% (n=34 315, N=68 757) of the total number of patients who claimed warfarin prescriptions in the six year study period (refer to Table 4.12). The group of patients categorised as “unspecified” represent only 0.03% (n=22, N=68 575) of the total.

The distribution of females to males in the number of patients who claimed prescriptions in the study period in the total database is slightly different. The ratio of females to males shifts up to 55/45 respectively. The female patients represent 55.2% (n=4 277 191, N=7 748 621) and the male patients represent 44.8% (n=3 468 185, N=7 748 621) of the total number of patients who claimed prescriptions in the study period (refer to Table A1.6 in Appendix A). The “unspecified” group of patients represent only 0.04% (n=3 245, N=7 748 621) of the total number of patients who claimed prescriptions in the whole database from 2005 to 2010.

In 2005, the total average number of warfarin prescriptions (females, males and unspecified) claimed per patient was 5.64 ± 4.06 . This average slightly increases from 2005 to 2010 (6.38 ± 4.00) (refer to Table 4.12). A d-value of 0.2 indicates that the change that occurs is very small and not practically significant. There is also no significant change in the average numbers of warfarin prescriptions claimed per patient in the study period.

Table 4.12: Average number of warfarin prescriptions per patient according to gender

Year	Gender	Number of patients (n)	%	Average number of warfarin prescriptions per patient
2005	Female	5 972	50.07	5.43 ± 3.99
	Male	5 946	49.85	5.85 ± 4.13
	Unspecified	9	0.08	5.33 ± 4.36
	Total	11 927	100	5.64 ± 4.06
2006	Female	5 933	49.63	5.73 ± 3.93
	Male	6 015	50.32	6.16 ± 4.02
	Unspecified	6	0.05	6.50 ± 3.08
	Total	11 954	100	5.95 ± 3.99
2007	Female	5 264	50.28	6.18 ± 3.99
	Male	5 198	49.65	6.72 ± 4.02
	Unspecified	7	0.07	5.00 ± 1.63
	Total	10 469	100	6.45 ± 4.01
2008	Female	4 812	50.09	6.22 ± 3.96
	Male	4 794	49.91	6.62 ± 4.00
	Unspecified	0	0	0.00
	Total	9 606	100	6.42 ± 3.98
2009	Female	6 193	49.94	6.32 ± 4.01
	Male	6 208	50.06	6.86 ± 4.12
	Unspecified	0	0	0.00
	Total	12 401	100	6.59 ± 4.08
2010	Female	6 064	49.63	6.26 ± 4.00
	Male	6 154	50.37	6.50 ± 3.99
	Unspecified	0	0	0.00
	Total	12 218	100	6.38 ± 4.00
TOTAL		68 575		

*Percentage calculated according to the total number of patients for the specific year.

4.5.3 FREQUENCY OF WARFARIN MEDICINE ITEMS CLAIMED ACCORDING TO GENDER

The distribution of the number of medicine items claimed between females and males differ from the warfarin medicine items claimed. In the total database the distribution is closer to 60/40 for females and males respectively. In the total database (2005-2010), the females represent 59.8% (n=70 736 924, N=118 305 941) of the total number of medicine items claimed and the males represent 40.1% (n=47 484 425, N=118 305 941) (refer to Table A1.5 in Appendix A). The “unspecified” group only represents 0.03% of the total.

There is a slight change in the average number of medicine items per prescription in the total database from 2005 (2.32 ± 1.52) to 2010 (2.41 ± 1.67). A d-value of 0.1 indicates that this change has no practical significance (refer to section 3.3.7.4). The average number of medicine items per prescription between females and males show similar results to that of the average number of warfarin medicine items per prescription. There is also no practically significant change when it comes to these results (refer to Table A1.5 in Appendix A).

The distribution of warfarin medicine items between females and males is very similar to the distribution of warfarin prescriptions. The distribution of warfarin medicine items between females and males is close to 50/50. When taking the total number of all the warfarin medicine items claimed by patients, the females represent 48.2% ($n=206\ 232$, $N=427\ 744$) of the total number of warfarin medicine items claimed and the males represent 51.8% ($n=221\ 390$, $N=427\ 744$) of the total (refer to Table 4.13). The unspecified group represents only 0.03% ($n=122$, $N=427\ 744$) of the total number of warfarin medicine items claimed from 2005 to 2010.

There is no change in the average number of warfarin medicine items per prescription in all categories of gender over the six study years. It is therefore quite obvious that there is no practically significant change in the average number of warfarin medicine items over the course of the study period (refer to Table 4.13). The average number of warfarin medicine items per prescription between females and males does not show any significant change either.

Table 4.13: Number of warfarin medicine items according to gender

Year	Gender	Number of warfarin medicine items (n)	**%	Average number of warfarin medicine items per prescription
2005	Female	32 452	48.21	1.00 ± 0.03
	Male	34 813	51.72	1.00 ± 0.03
	Unspecified	48	0.07	1.00 ± 0.00
	Total	67 313	100	1.00 ± 0.03
2006	Female	33 983	47.78	1.00 ± 0.03
	Male	37 098	52.16	1.00 ± 0.02
	Unspecified	39	0.05	1.00 ± 0.00
	Total	71 120	100	1.03 ± 0.02
2007	Female	32 577	48.21	1.00 ± 0.02
	Male	34 958	51.74	1.00 ± 0.02
	Unspecified	35	0.05	1.00 ± 0.00
	Total	67 570	100	1.00 ± 0.02
2008	Female	29 936	48.53	1.00 ± 0.03
	Male	31 753	51.47	1.00 ± 0.03
	Unspecified	0	0.00	0
	Total	61 689	100	1.00 ± 0.03
2009	Female	39 220	47.92	1.00 ± 0.04
	Male	42 633	52.08	1.00 ± 0.04
	Unspecified	0	0.00	0
	Total	81 853	100	1.00 ± 0.04
2010	Female	38 064	48.68	1.00 ± 0.04
	Male	40 135	51.32	1.00 ± 0.06
	Unspecified	0	0.00	0
	Total	78 199	100	1.00 ± 0.05
TOTAL		427 744		1.00 ± 0.04

**Percentages calculated according to the total number of warfarin medicine items for the specific year.*

4.6 PRESCRIBING PATTERNS OF WARFARIN ACCORDING TO THE PRESCRIBED DAILY DOSE

The prescribed daily dose (PDD) illustrates the average amount of a drug that is prescribed to a patient per day. The exact doses of warfarin that was prescribed can be calculated according to the equation in section 3.3.5.2, therefore this measurement was used.

In this section the prescribing patterns of warfarin according to PDD will be discussed in relation to the different prescribers, warfarin medicine items, gender and age groups.

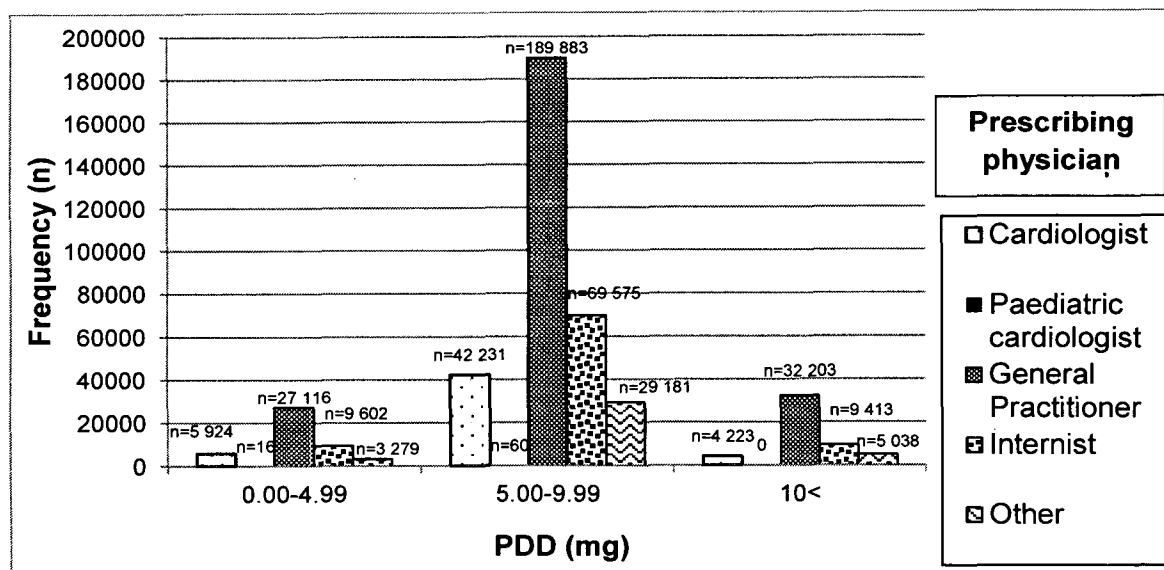
4.6.1 THE PDD OF WARFARIN ACCORDING TO PRESCRIBERS

The highest average PDD of warfarin medicine items was prescribed by general practitioners (7.01 mg ± 9.86 mg). Paediatric cardiologists (4.61 mg ± 1.29 mg) prescribed the lowest PDD of warfarin. The average PDD prescribed by cardiologists for warfarin was 5.97 mg ± 6.02 mg. A d-value 0.1 indicates that there is no practical difference between the average PDD of warfarin medicine items between general practitioners and cardiologists. The average PDD of warfarin medicine items of internists (6.15 mg ± 5.73 mg) and other prescribing physicians (6.61 mg ± 9.67 mg) was similar. A d-value of 0.03 indicates that there is no practical difference between the average PDD of warfarin medicine items between internists and general practitioners. These results are summarised in Table 4.14.

Table 4.14: Average PDD of warfarin according to prescribing physician

Prescribing physician	Number of warfarin medicine items (n)	**%	Average PDD (in mg) for warfarin medicine items
Cardiologist	52 378	12.42	5.97 ± 6.02
Paediatric cardiologist	76	0.02	4.61 ± 1.29
General practitioner	249 202	58.26	7.01 ± 9.86
Internist	88 590	20.71	6.15 ± 5.73
Other	37 498	8.76	6.61 ± 9.67
TOTAL	427 744	100	6.67 ± 8.73

The range PDD that the prescribing physicians prescribed most frequently was between 5.00 mg to 9.99 mg. A PDD of 10 mg and more was prescribed the least. Graph 4.1 shows the range of PDD of warfarin medicine items according to each prescribing physician.



Graph 4.1: The PDD of warfarin according to prescribing physicians

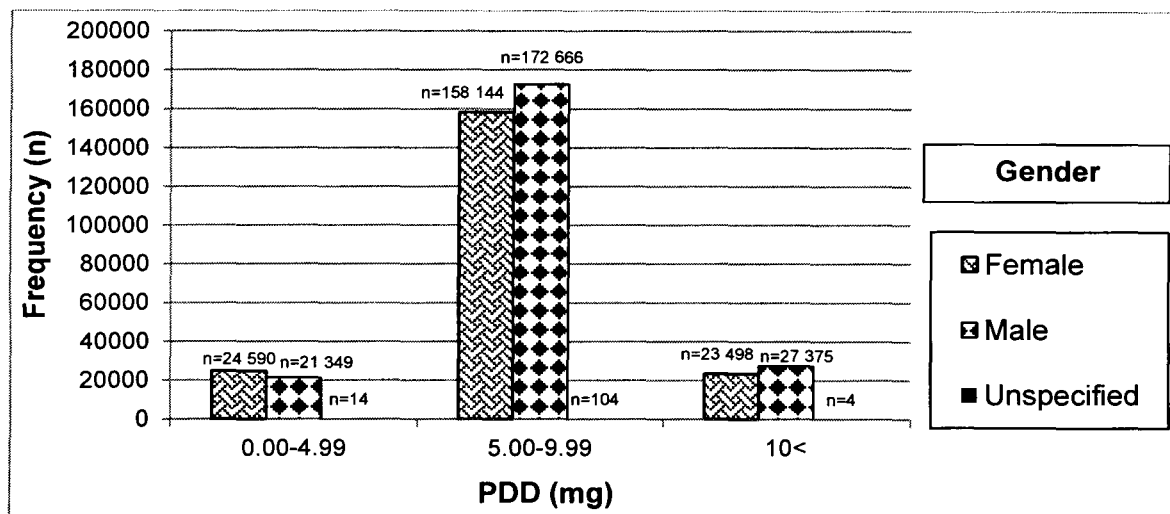
4.6.2 PDD OF WARFARIN ACCORDING TO GENDER

The average PDD of warfarin between females and males are similar ($6.60 \text{ mg} \pm 9.06 \text{ mg}$, $6.74 \text{ mg} \pm 8.41 \text{ mg}$). A d-value of 0.02 indicates that there is no practical significant difference between the average PDD of warfarin between females and males. The average PDD of warfarin for the unspecified group ($5.32 \text{ mg} \pm 1.68 \text{ mg}$) is slightly lower. A d-value of 0.14 and 0.16 indicates that there is no practically significant difference for the average PDD of warfarin between females and the unspecified group and males and the unspecified groups respectively. Table 4.15 shows these results.

Table 4.15: Average PDD of warfarin according to gender for the whole database (2005-2010)

Gender	Number of warfarin medicine items (n)	%	Average PDD (in mg) for warfarin medicine items
Female	206 232	48.21	6.60 ± 9.06
Male	221 390	51.80	6.74 ± 8.41
Unspecified	122	0.03	5.32 ± 1.68
TOTAL	427 744	100	6.67 ± 8.73

The range of PDD for warfarin that was prescribed the most for all gender groups was between 5.00 mg to 9.99 mg. The range PDD for warfarin that was prescribed the least was 10 mg and more, except for males where the range PDD that was prescribed the least was between 0.00 mg to 4.99 mg. Graph 4.2 summarises these results.



Graph 4.2: PDD of warfarin according to gender

4.6.3 PDD OF WARFARIN ACCORDING TO AGE GROUP

The average PDD of warfarin for age group 1 (7.24 mg ± 8.76 mg), age group 2 (7.42 mg ± 7.42 mg), and age group 3 (7.23 mg ± 8.21 mg) are similar. Age group 4 has a slightly lower average PDD for warfarin compared to the rest of the age groups. Age group 2 (7.42 mg ± 7.42 mg) showed the highest average PDD for warfarin for all the age groups (refer to Table 4.16). Table 4.15 expresses the d-value of age group 1 to age group 3 compared to age group 4.

Table 4.16: The d-values for the average PDD of age groups 1, 2, and 3 compared to age group 4

Age group	Average PDD (in mg) of warfarin medicine items	d-value
1	7.24 ± 8.76	0.08
2	7.42 ± 7.42	0.10
3	7.23 ± 8.21	0.08
4	6.50 ± 8.90	*0.02
TOTAL	6.67 ± 8.73	

*The d-value of age group 4 compared to the total average of PDD of warfarin for the total database (2005-2010).

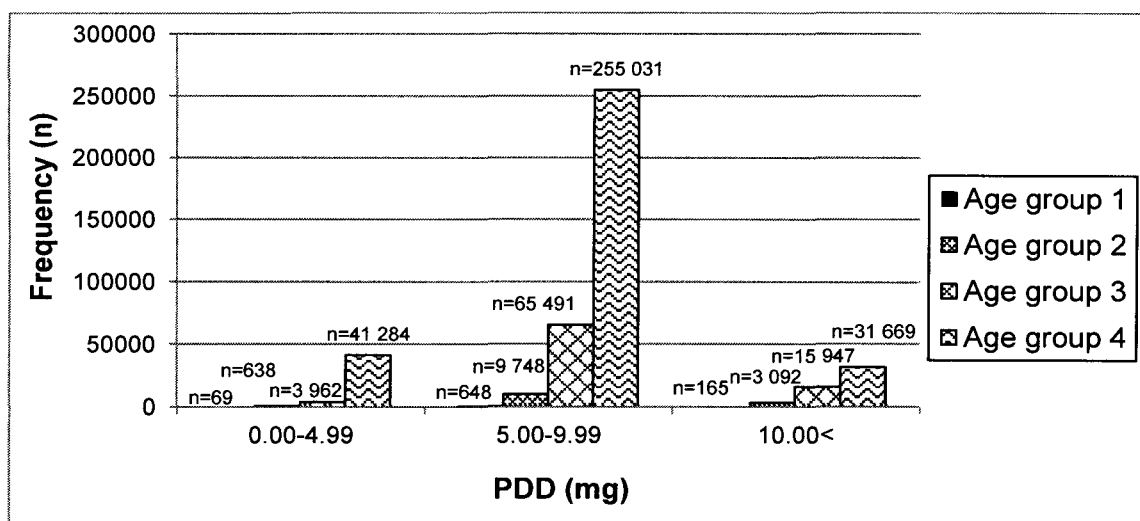
The d-values show that there is no practical significant difference in the average PDD of warfarin between the different age groups.

Table 4.17: Average PDD of warfarin according to age group

Age group	Number of warfarin medicine items (n)	*%	Average PDD (in mg) of warfarin medicine items
1	882	0.21	7.24 ± 8.76
2	13 478	3.15	7.42 ± 7.42
3	85 400	20.00	7.23 ± 8.21
4	327 984	76.70	6.50 ± 8.90
TOTAL	427 744	100	6.67 ± 8.73

*Percentage calculated according to the total number of warfarin medicine items for the whole database (2005-2010).

The range PDD that was prescribed the most for age group 1 to age group 4 was 5.00 mg to 9.99 mg. The range of PDD that was prescribed the least was 0.00 mg to 4.99 mg except for age group 4, for which this range was 10 mg and more.



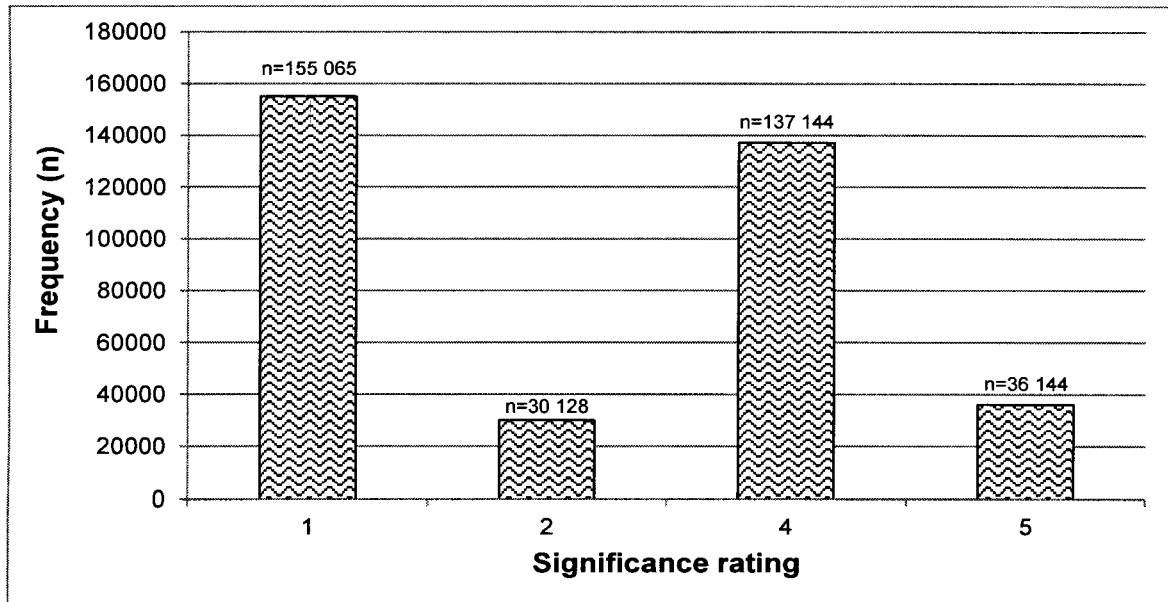
Graph 4.3: The PDD of warfarin according to age group for the total database (2005-2010)

4.7 DRUGS CO-PRESCRIBED WITH WARFARIN ACCORDING TO THE DATABASE AND THE SIGNIFICANCE RATINGS OF THESE DRUGS

In this section all the drugs that were co-prescribed with warfarin according to the total database (2005-2010) are discussed. These drugs will be divided into groups according to the significance rating (refer to section 2.3.3) of the potential drug-drug interaction with warfarin for each drug.

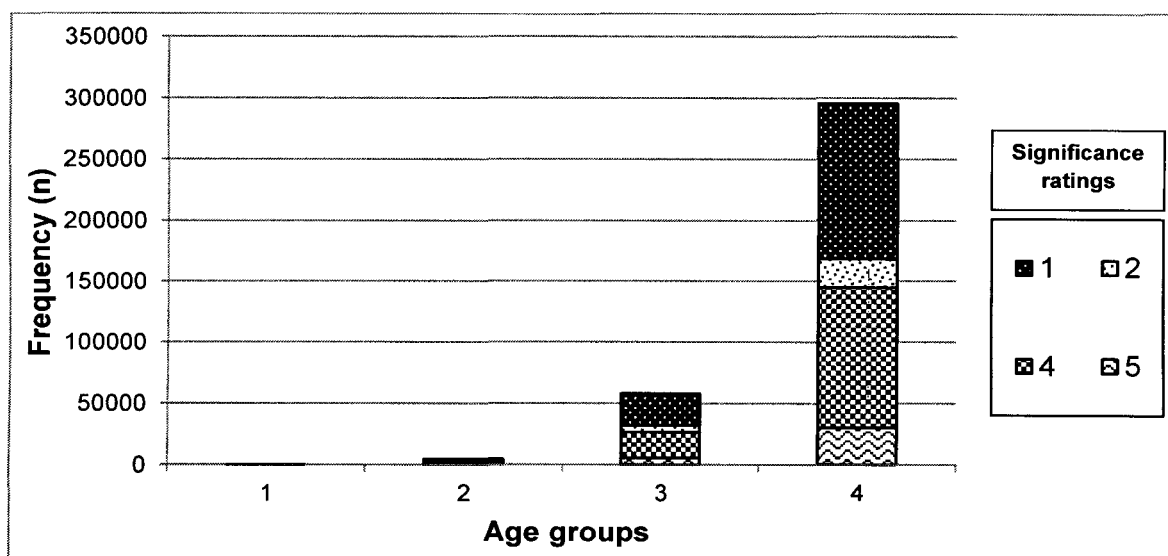
4.7.1 GENERAL PRESCRIBING PATTERNS OF CO-PRESCRIBED DRUGS

According to Tatro (2011), potential drug-drug interactions (PDDI) can be assigned one of five (1-5) significance ratings (SR) according to the severity and documentation level of these PDDIs. However, the data indicated that the drugs co-prescribed with warfarin only comprised four of the five SR's namely 1, 2, 4, and 5. There were no PDDIs with a SR of 3. The data showed that drugs with a SR of 1 (n=155 065, N=358 482, 43.3%) were prescribed the most with warfarin. Drugs with a significance rating of 2 (n=30 128, N=358 482, 8.4%) were prescribed the least (refer to Table A1.7). These results are summarised in Graph 4.4.



Graph 4.4: Number of and significance ratings of drugs co-prescribed with warfarin

The highest frequency of drugs co-prescribed with warfarin that could potentially interact with warfarin belonged to age group 4 (n=295 719). The lowest frequency of co-prescribed drugs belonged to age group 1 (n=205) (refer to Table A1.8). This follows the same trend as the number of warfarin prescriptions per person per age group and the number of warfarin medicine items per age group (refer to section 4.4.1 and 4.4.3). These results are illustrated in Graph 4.5.



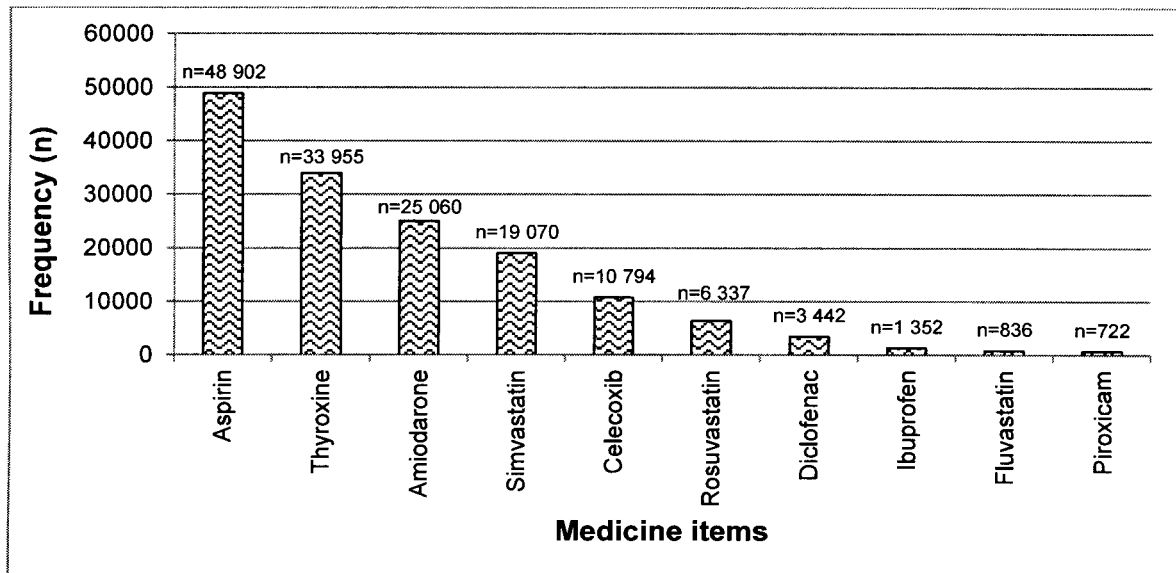
Graph 4.5: The frequency and significance ratings of drugs co-prescribed with warfarin according to age group

4.7.2 CO-PRESCRIBED DRUGS WITH A SIGNIFICANCE RATING OF 1

The following are drugs co-prescribed with warfarin with a SR of 1 (refer to Graph A1.1). These are drugs with a PDDI that may cause life threatening effects and permanent damage (refer to section 2.3.3). In an effort to analyse which drugs were co-prescribed with warfarin most frequently, the following are the top 10 drugs with a SR of 1 that were co-prescribed (refer to Graph 4.6, also refer to Table A1.10).

The drug that was prescribed the most with warfarin with a SR of 1 was aspirin (n=48 902, N=358 482, 13.6%). This can be cause for concern as aspirin in combination with warfarin could increase the risk of haemorrhaging 2.5-fold (Baxter, 2008:385). The effect aspirin has on the gastric mucosa can also increase the risk for gastric haemorrhaging when administered with warfarin. Aspirin can also increase prothrombin time, which increases the risk for

haemorrhaging (Hansten & Horn, 2011, Baxter, 2008:385, Tatro, 2011) (refer to Table A1.14). Piroxicam (n=722, N=358 482, 0.2%) was co-prescribed the least in the top 10. These results are illustrated in Graph 4.6.

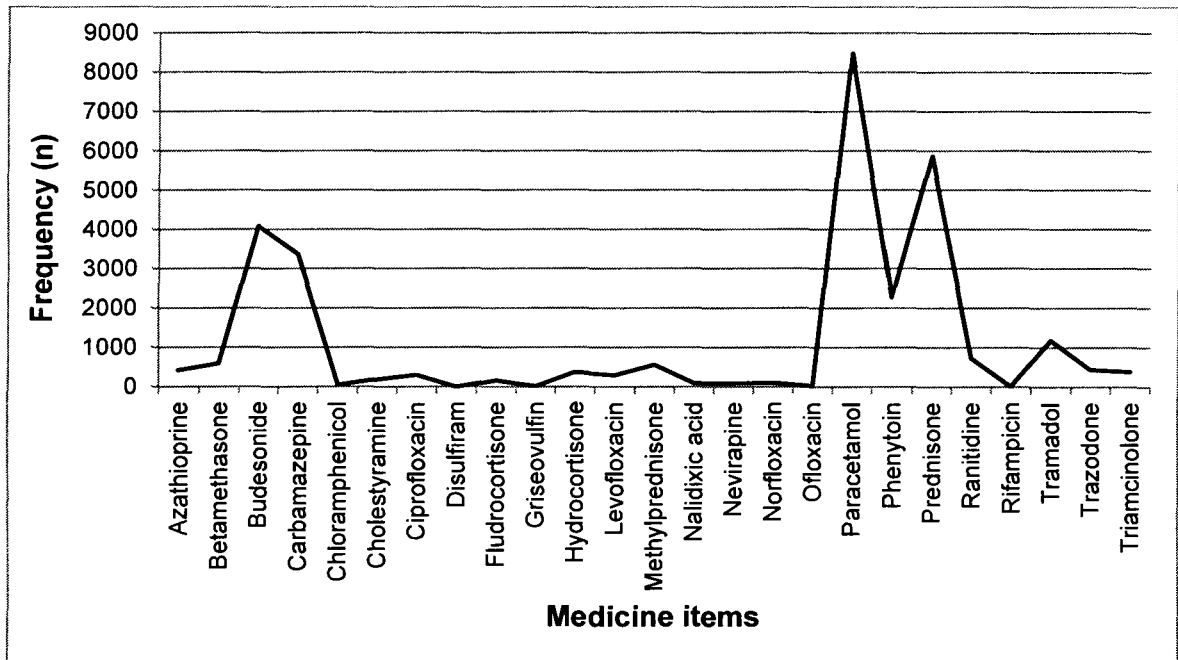


Graph 4.6: The top 10 drugs co-prescribed with warfarin with a significance rating of 1

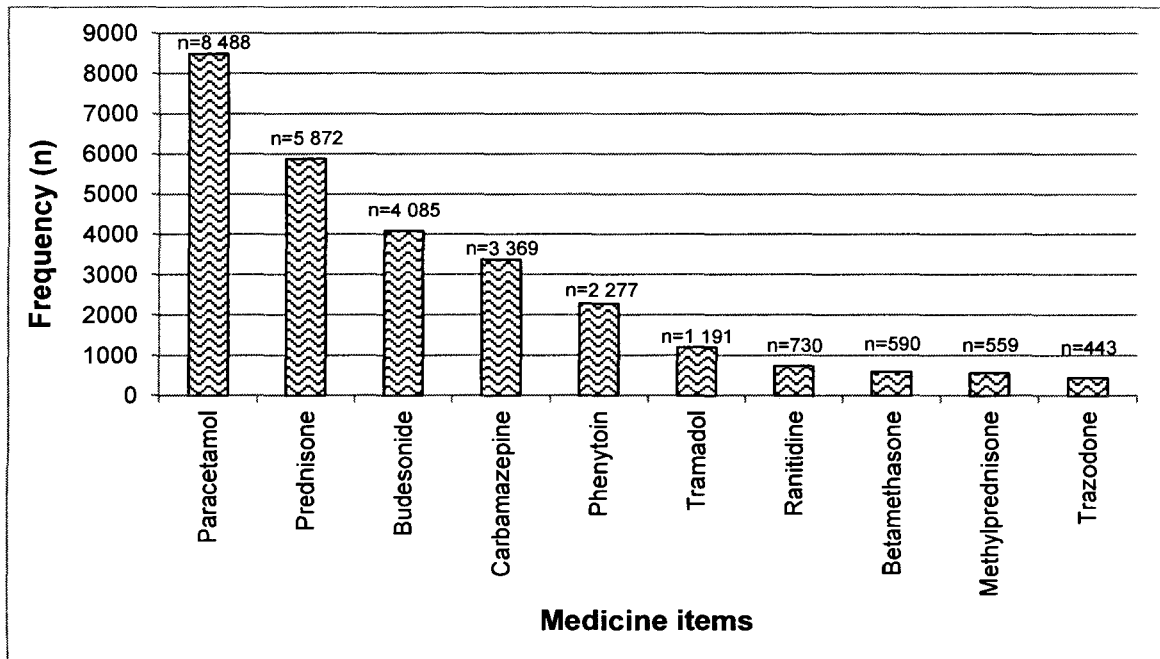
4.7.3 CO-PRESCRIBED DRUGS WITH A SIGNIFICANCE RATING OF 2

In this section drugs with a SR of 2 that were co-prescribed with warfarin are discussed. The PDDI of these drugs can cause a deteriorated clinical state and hospital admission may be necessary (Tatro, 2011: xiv). The need for therapy may be increased (refer to section 2.3.3). Graph 4.7 illustrates the frequencies of these drugs (also refer to Table A1.11).

Paracetamol (n=8 488, N=358 482, 2.37%) was co-prescribed the most with warfarin. It is reported that paracetamol may cause an increase in the anti-thrombic effects of warfarin (Tatro, 2011:70). However, the INR was only increased by a factor of 1 in some individuals (Baxter, 2008:438). Hansten and Horn (2011), states that this increased anti-thrombic effect is only achieved after continuous dosing with paracetamol. The drug that was co-prescribed the least in this group was Trazodone (n=443, N=358 482, 0.12%). These results are illustrated in Graph 4.8.



Graph 4.7: Frequency of warfarin co-prescribed drugs with a significance rating of 2

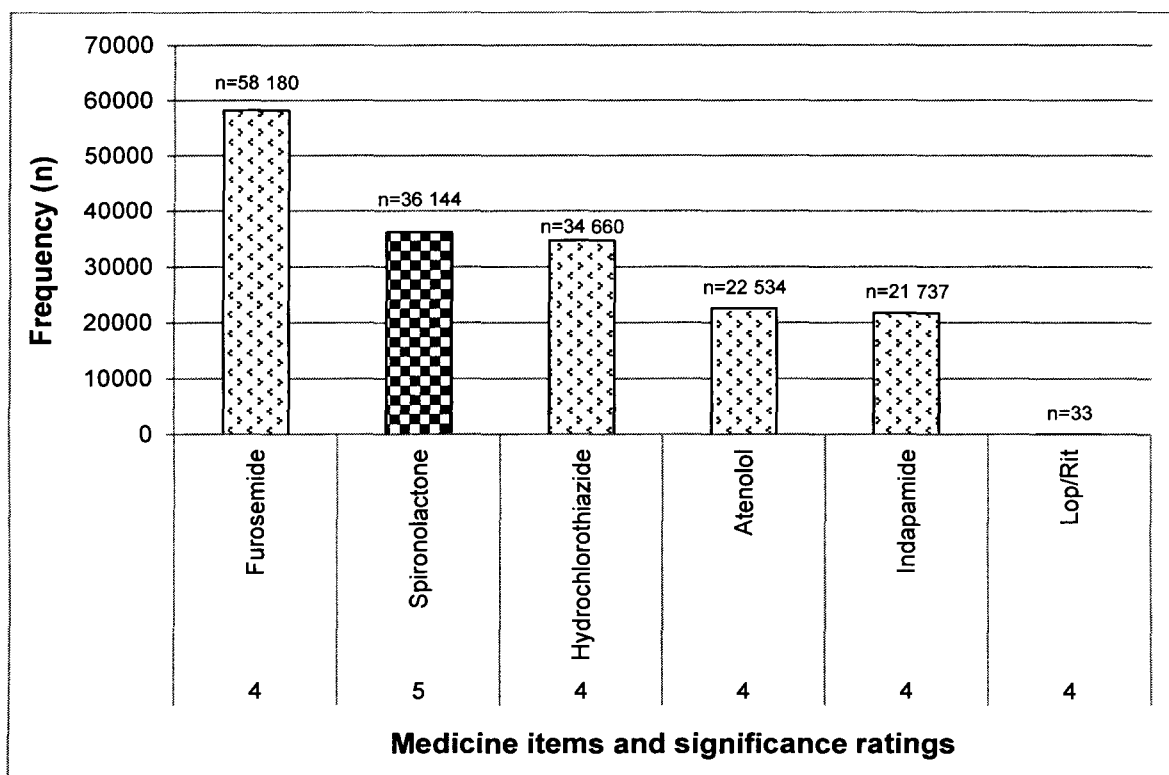


Graph 4.8: The top 10 drugs co-prescribed with warfarin with a significance rating of 2

4.7.4 CO-PRESCRIBED DRUGS WITH A SIGNIFICANCE RATING OF 4 AND 5

In this section the drugs with a SR of 4 and 5 were combined. This is because of the few drug items that were co-prescribed with warfarin that fit into these categories. Only four drug items with a SR of 4 was co-prescribed with warfarin namely atenolol, furosemide, hydrochlorothiazide, indapamide and the lopinavir/ritonavir combination. Spironolactone was the only drug with a SR of 5 that was co-prescribed with warfarin. This group of drugs can cause a deteriorated clinical status, hospital admission and therapy may be needed or may cause only effects that are mild in nature that may only bother the patient, but for this reason they can sometimes go unnoticed (refer to section 2.3.3).

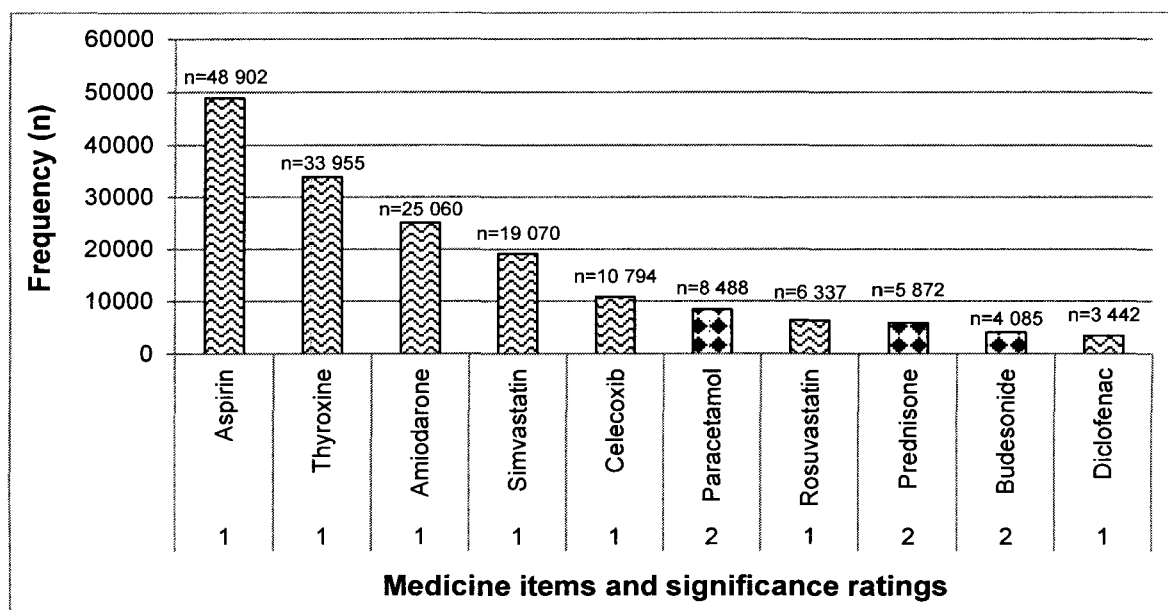
In this combined group the drug that was co-prescribed the most with warfarin was furosemide (n=58 180, N=358 482, 16.23%). This is not a great cause for concern as loop diuretics do not as a rule interact with anticoagulants, but can theoretically increase the effects of anticoagulants due to the displacement of these drugs from their protein binding sites (Baxter, 2008:403; Hansten & Horn, 2011:1115; Tatro, 2011:114). The drug that was prescribed the least in this group was the lopinavir/ritonavir combination (n=33, N=358 482, 0.01%) (refer to Table A1.13). Graph 4.9 illustrates these results.



Graph 4.9: Frequencies of warfarin co-prescribed drugs with a significance rating of 4 and 5

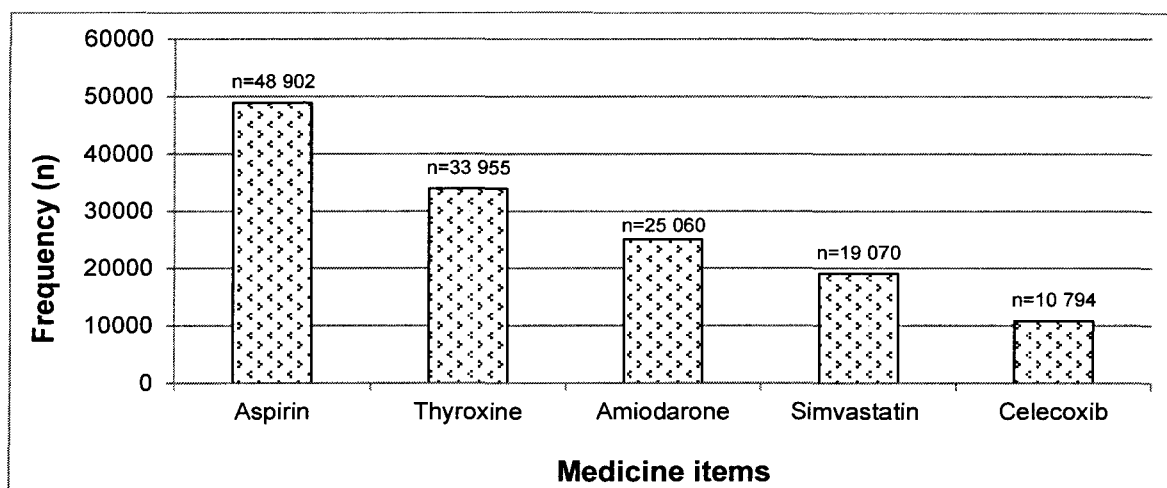
4.7.5 TOP 5 DRUGS CO-PRESCRIBED WITH WARFARIN

In this section the top five drugs that were co-prescribed with warfarin according to the database will be discussed. Drugs with a SR of 1 and 2 were selected because these drugs can potentially cause the most harm when they are co-prescribed with warfarin. In order to select the top five drugs the top ten drugs with a SR of 1 and 2 were first identified. The top ten drugs revealed that the majority of drugs had a SR of 1. In total there were seven drugs with a SR of 1 and only three drugs with a SR of 2. Graph 4.10 illustrates these results (refer to Table A1.19).



Graph 4.10: The top 10 drugs co-prescribed with warfarin

From the top ten drugs, the top five drugs that were co-prescribed with warfarin according to the database was extracted. The top five drugs in descending order that were co-prescribed with warfarin was aspirin (n=48 902, 13.6%), thyroxine (n=33 954, 9.5%), amiodarone (n=25 060, 7.0%), simvastatin (n=19 070, 5.3%) and celecoxib (n=10 794, 3.0%). A study done in Scotland (Snaith *et al.*, 2008:207) found that the drugs that were most frequently co-prescribed with warfarin were antibiotics, anti-inflammatory drugs and other antithrombic drugs such as fibrinolytics. In 1992 a study done in Ireland (Johnson & Dack, 1992:119) showed that the majority of drugs that were co-prescribed with warfarin were non-steroidal anti-inflammatory drugs and similar to this study, aspirin (refer to section 1.1). The results from the database is illustrated in Graph 4.11 (refer to Table A1.15).



Graph 4.11: The top 5 drugs co-prescribed with warfarin

These five drugs represent 38.43% (n=137 782, N=358 482) of the total number of drugs that were co-prescribed with warfarin according to the database. Aspirin was co-prescribed the most (n=48 902, N=358 482, 13.64%). Celecoxib (n=10 794, N=358 482, 3.01%) was co-prescribed the least with warfarin in the top five. These drugs will be discussed individually in the sections that follow.

4.7.5.1 Aspirin

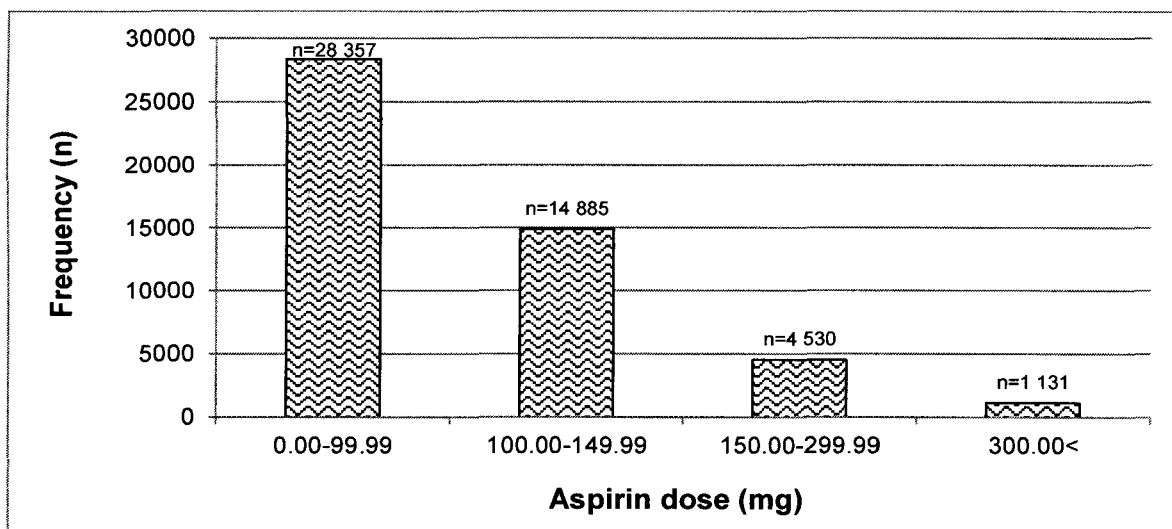
The South African Medicines Formulary (SAMF:102) recommends aspirin doses of 75 mg to 150 mg when used as an antiplatelet. When used as an analgesic or antipyretic, the recommended dose is 300 mg to 900 mg every four to six hours, not exceeding 4 g per day. Inflammatory diseases could require up to 5.4 g per day in divided doses. An aspirin dose of up to 7.8 g per day in divided doses could be necessary for acute rheumatic fever (SAMF, 2005:102, 417, 418).

Aspirin could be a cause of great concern when co-prescribed with warfarin. Aspirin doses larger than 3 g per day can cause major increases in the risk for haemorrhaging. The prothrombin time (PT) is also markedly prolonged when these large doses of aspirin is co-administered with warfarin (Baxter, 2008:385; Tatro, 2011:175). The risk for gastrointestinal haemorrhaging increases with an aspirin dose of 500 mg per day. Extreme haemorrhaging episodes can be experienced in patients with prosthetic heart valves following the co-administration of 500 mg per day aspirin with warfarin (Hansten & Horn, 2011:221). Smaller

doses of aspirin (100 mg to 150 mg per day) may increase the risk of minor bleeding. Aspirin as low as 75 mg per day is also related to minor bleeding events, but are commonly administered with warfarin when the benefit outweighs the risk (Hansten & Horn, 2011:221; Tatro, 2011:175).

Aspirin and warfarin are commonly used together because they act at different sites of the blood coagulation cascade (refer to sections 2.2.5.1 and 2.4.4). This combination is used as prophylaxis in a wide variety of thrombo-embolic and atherothrombotic disorders. It is estimated that almost 1 000 000 patients in North America may receive this combination (Donadini & Douketis, 2010:208).

According to the literature, patients receiving low-dose aspirin (100 mg or less) are at low risk for major haemorrhaging (Hansten & Horn, 2011; Tatro, 2011:175). Higher aspirin doses (150 mg or more) increase this risk. After minor adaptation of these parameters the following graph can be generated:

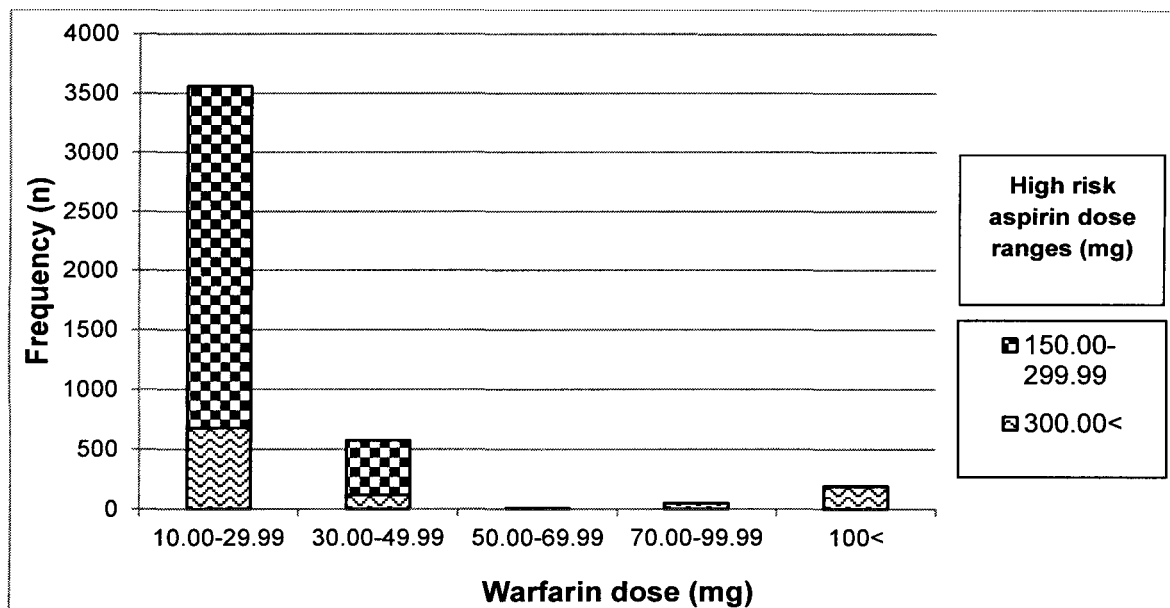


Graph 4.12: The frequency of different ranges of aspirin doses

It is clearly illustrated in Graph 4.12 that the range of doses that was most frequently co-prescribed with warfarin was between 0.00 mg and 99.99 mg. This group represents 58.00% (n=28 357, N=48 903) of the total number of aspirin products prescribed (refer to Table A1.16).

The total risk when aspirin is co-prescribed with warfarin cannot be completely evaluated by just analysing the doses of aspirin. Warfarin doses in combination with aspirin must also be

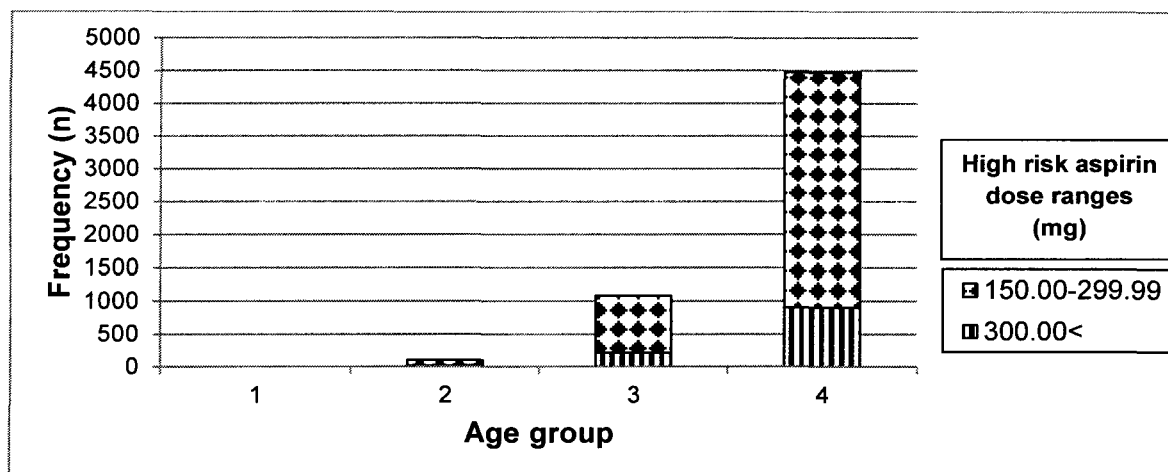
analysed. The frequencies of different warfarin doses are compared to the frequencies of the two high risk groups of aspirin doses in Graph 4.13.



Graph 4.13: Comparison of the frequencies of different warfarin doses and high risk aspirin dose ranges

The range of high risk aspirin doses that accumulated the most warfarin prescriptions was between 150.00 mg and 299.99 mg ($n=3\ 342$, $N=48\ 903$, 6.93%). The range of warfarin doses that was prescribed the most in this group was between 10.00 mg and 29.99 mg ($n=2\ 885$, $N=48\ 903$, 6.00%). So, even though a low warfarin dose was prescribed, a high aspirin dose was co-prescribed that could markedly increase the risk of major haemorrhaging (Hansten & Horn, 2011:221).

The age group that received the highest frequency of co-prescribed aspirin in doses ranging from 150.00 mg to 299.99 mg and 300.00 mg and more was age group 4 ($n=3\ 571$, $N=48\ 903$, 7.30%; $n=904$, $N=48\ 903$, 1.85%). These results are illustrated in Graph 4.14 (refer to Table A1.18).



Graph 4.14: High risk aspirin doses according to age group

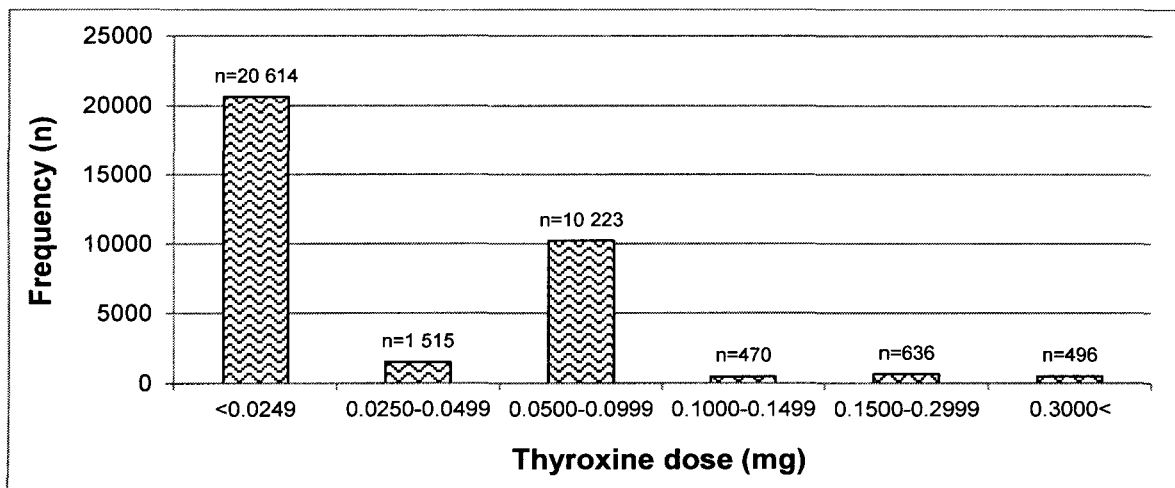
The effects of aspirin when co-prescribed with warfarin are summarised in Table A1.19.

4.7.5.2 Thyroxine

The normal initial dose for thyroxine is 0.05 mg (50 µg) daily with an increase of 0.05 mg every two to three weeks. The maintenance dose is usually 0.1 mg to 0.15 mg per day. In elderly patients, patients with cardiac disease or patients with chronic hypothyroidism the average initial dose is usually 0.025 mg per day with an increase of 0.025 mg every three to four weeks (SAMF, 2005:256).

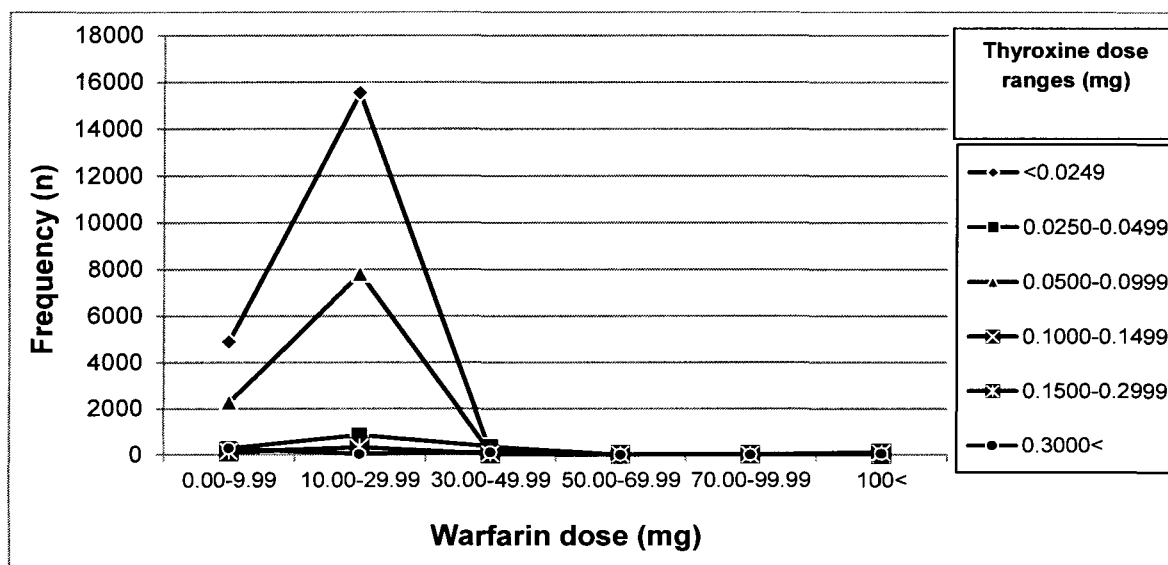
The interaction between warfarin and thyroxine is not purely a drug-drug interaction, but rather a drug-disease interaction (Squizzato *et al.*, 2012:520). As the thyroid metabolic rate fluctuates, so does the warfarin dose requirements to maintain a stable INR. The response to warfarin can increase when thyroxine is administered. It is believed that an increase in thyroid hormones increases the rate at which vitamin K-dependent clotting factors are metabolised, therefore an increased response to warfarin is experienced (Baxter, 2008:455; Hansten & Horn, 2011:1754). Patients with hyperthyroidism have an increased response to warfarin and therefore need lower warfarin doses to maintain the desired INR (Baxter, 2008:455). Patients stabilised on warfarin therapy who are initiated on thyroid hormone replacement usually experience an increase in the effects of warfarin. However, patients stabilised on thyroid hormones and who are initiated on warfarin therapy often do not encounter this problem (Hansten & Horn, 2011:1754).

The range of thyroxine doses most frequently prescribed according to the database was 0.0249 mg and smaller (n=20 614, N=33 954, 60.71%). The second most common dose range of thyroxine prescribed is 0.0500 mg to 0.0999 mg (n=10 223, N=33 954, 30.11%). The dose range that was prescribed the least was 0.10 mg to 0.1499 mg (n=470, N=33 954, 1.38%). These results are summarised in Graph 4.15 (refer to Table A1.20).



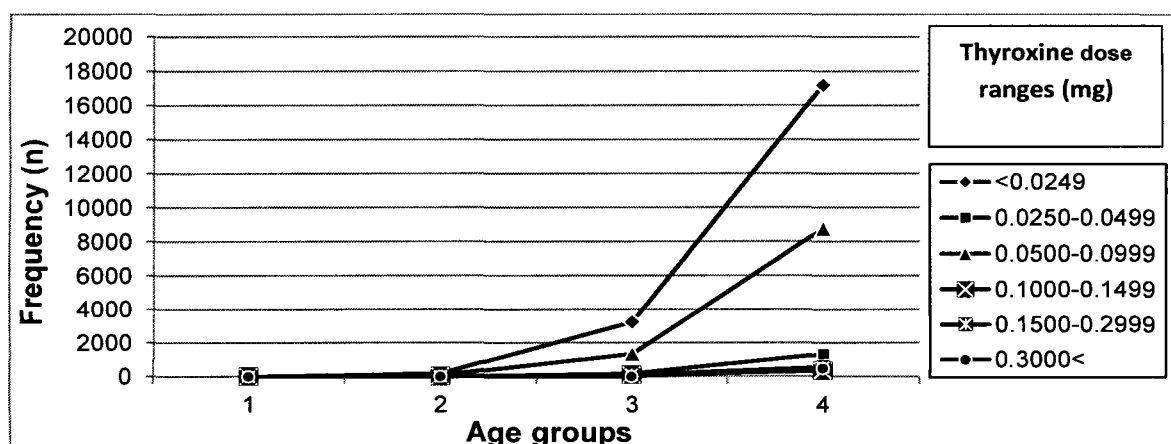
Graph 4.15: The frequency of different thyroxine doses

Due to the fact that warfarin sensitivity can increase with any dose of thyroxine (Baxter, 2008:455; Hansten & Horn, 2011:1754), one can assume that no matter what thyroxine dose is prescribed with warfarin, there will always be some risk for haemorrhaging, therefore all thyroxine dose ranges must be analysed with all dose ranges of warfarin. The warfarin dose range that was prescribed the most with thyroxine was 10.00 mg to 29.99 mg (n=24 918, N=33 954, 73.39%). The warfarin dose range that was prescribed the least with thyroxine was 70.00 mg to 99.99 mg (n=15, N=33 954, 0.04%). These results are illustrated in Graph 4.16 (refer to Table A1.21).



Graph 4.16: Comparison of the frequencies of different warfarin doses and different thyroxine dose ranges

The age group that was co-prescribed the highest frequency of thyroxine was age group 4 (n=28 663, N=33 954, 84.42%). The thyroxine dose range that was co-prescribed the most in this age group was 0.0249 mg and smaller (n=17 187, N=33 954, 50.62%). The age group that was co-prescribed the lowest frequency of thyroxine was age group 1 (n=1, N=33 954, 0.00%). These results are illustrated in Graph 4.17 (refer to Table A1.22). The effects of thyroxine when co-prescribed with warfarin are summarised in Table A1.23.



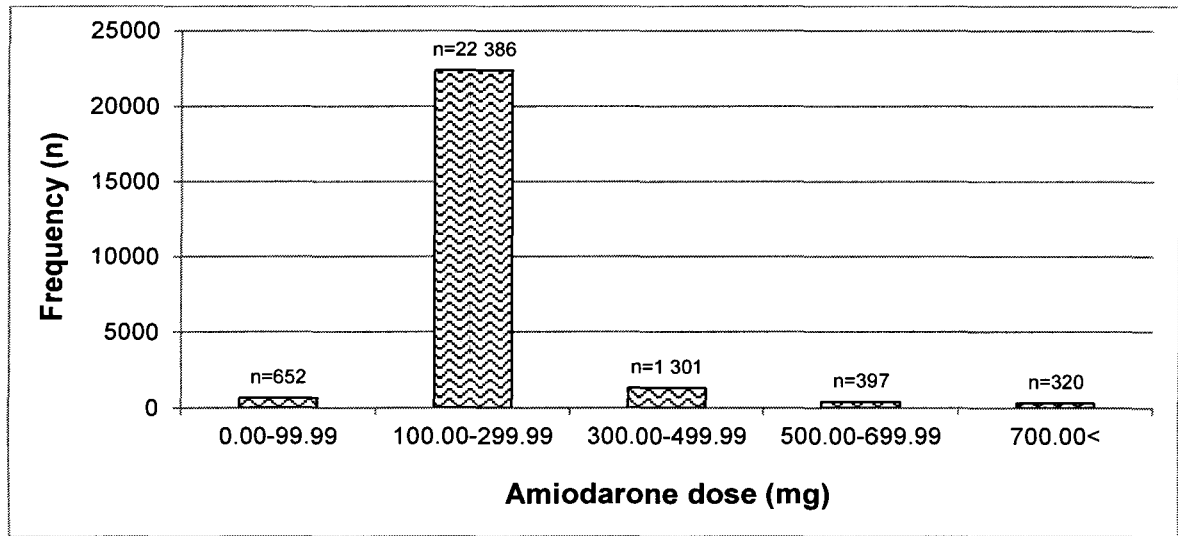
Graph 4.17: Dose ranges of thyroxine according to age group

4.7.5.3 Amiodarone

Amiodarone is indicated for the prophylaxis and treatment of supraventricular and ventricular arrhythmias (SAMF, 2005:127). The average initial dose of amiodarone is usually 200 mg three times a day with a decrease in 200 mg a day every week. The rapid control of life threatening ventricular arrhythmias requires a dose as high as 1600 mg per day (400 mg three to four times a day) (SAMF, 2005:128).

Amiodarone augments the anticoagulation effects of warfarin. The risk for haemorrhage is further increased by a prolonged PT (Tatro, 2011:90). These effects are not immediate and are sometimes only noticed two months after warfarin patients are initiated on amiodarone therapy (Baxter, 2008:363; Habib *et al.*, 2008:133). Amiodarone doses of 100 mg to 400 mg can lead to a decreased warfarin clearance time, which adds to the reason to decrease the warfarin doses of patients receiving amiodarone therapy (Hansten & Horn, 2011:101; Tatro, 2011:90). This could be due to the fact that amiodarone competes with warfarin as a substrate for CYP2C9 (Habib, 2008:132). The reduction in warfarin doses depends on the amiodarone dose (Baxter, 2008:363). As the amiodarone dose is increased, the warfarin dose must be decreased (refer to Table A1.27). Another mechanism for interaction that increases the effects of warfarin is the thyrotoxicosis that is caused with amiodarone (Baxter, 2008:363). Thyrotoxicosis initially causes hyperthyroidism, which can lead to an increased response to warfarin (Baxter, 2008:455; Hansten & Horn, 2011:101, 1754). This is followed by hypothyroidism that can decrease the sensitivity to warfarin, thus rendering the need for warfarin dose adjustments (Baxter, 2008:455; Hansten & Horn, 2011:101, 1754).

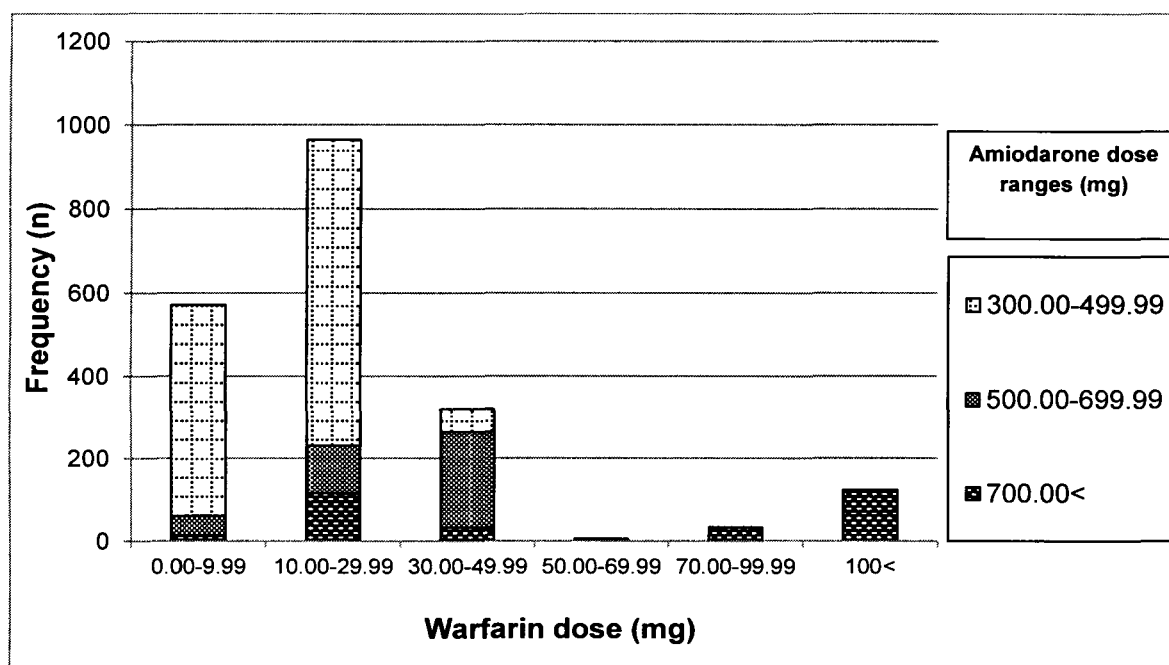
The range of amiodarone doses that was co-prescribed most frequently with warfarin was 100.00 mg to 299.99 mg (n=22 386, N=25 056, 89.34%). The range of amiodarone doses that was co-prescribed the least was 700.00 mg and higher (N=320, N=25 056, 1.28%). These results are illustrated in Graph 4.18 (refer to Table A1.24).



Graph 4.18: The frequency of different amiodarone doses

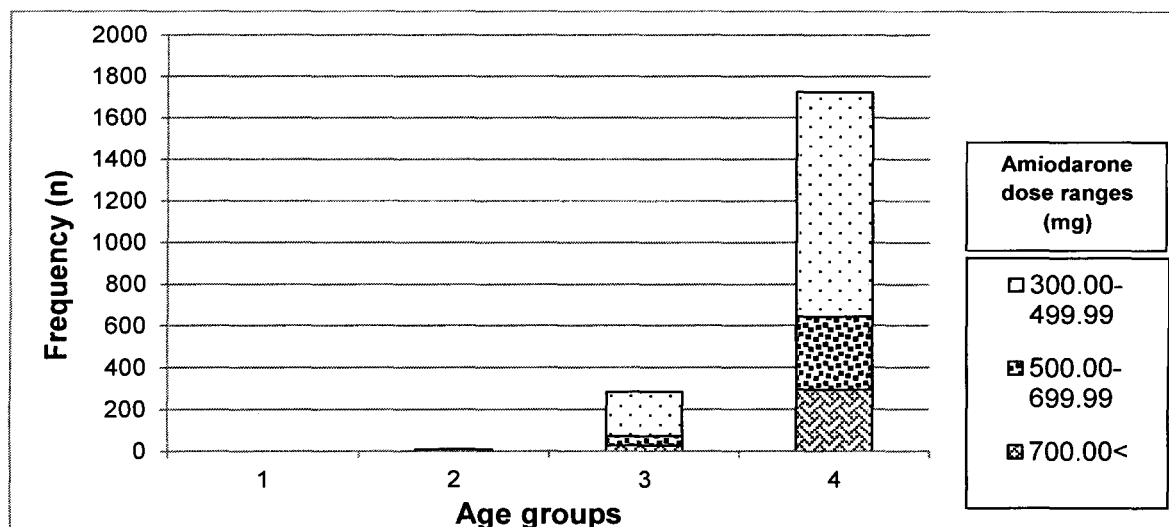
The largest decrease in warfarin doses is necessary with amiodarone doses 300 mg and higher. Large amiodarone doses like these usually require a reduction of 35% to 65% of the warfarin dose (Baxter, 2008:363; Tatro, 2011:90). It can therefore be assumed that high risk amiodarone doses when co-prescribed with warfarin is 300 mg and higher.

The warfarin dose range that was prescribed the most with high risk amiodarone doses was 10.00 mg to 29.99 mg (n=965, N=25 056, 3.85%). The warfarin dose range that was co-prescribed the least was 50.00 mg to 69.99 mg (n=5, N=25 056, 0.02%). The high risk amiodarone dose range that was co-prescribed the most with warfarin was 300.00 mg to 499.99 mg (n=1 301, N=25 056, 5.19%). The high risk amiodarone dose range that was co-prescribed the least was 700.00 mg and higher (n=320, N=25 056, 1.28%). These results are illustrated in Graph 4.19 (refer to Table A1.25).



Graph 4.19: Comparison of the frequencies of different warfarin doses and high risk amiodarone dose ranges

The age group that was co-prescribed with the most high risk amiodarone doses was age group 4 (n=1 723, N=25 056, 6.88%). The age group that was co-prescribed the least high risk amiodarone doses was age group 1 (n=1, N=25 056, 0.00%). These results are illustrated in Graph 4.20 (refer to Table A1.26). Refer to Table A1.27 for the effects of amiodarone when co-prescribed with warfarin.



Graph 4.20: High risk amiodarone doses according to age group

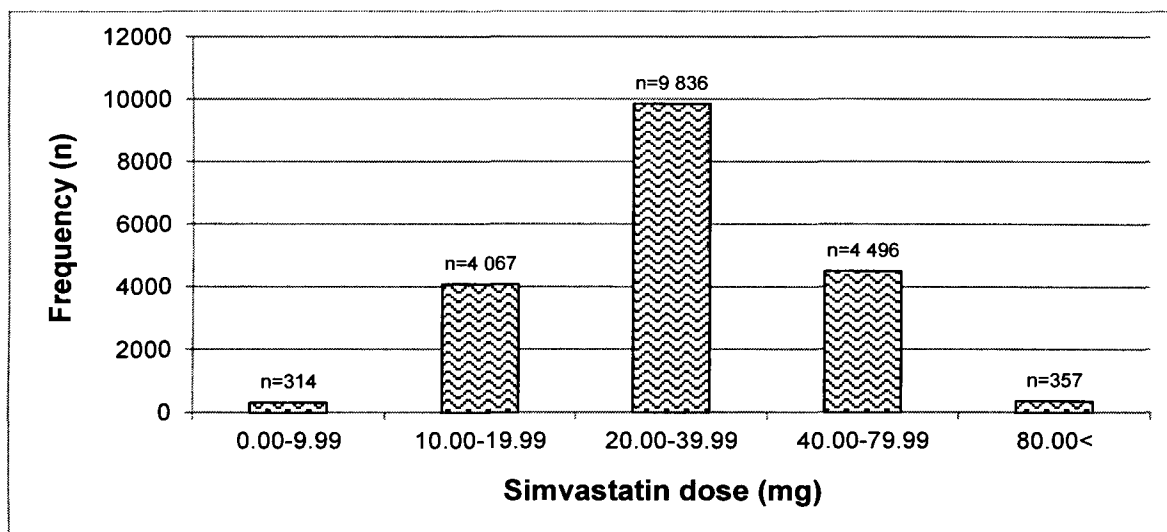
4.7.5.4 Simvastatin

The normal initial dose of simvastatin is 10 mg at night. This dose should be adjusted every four weeks if necessary. A maximum dose of 80 mg should not be exceeded. A dose of up to 20 mg per day may be sufficient (SAMF, 2005:166).

It is speculated that simvastatin when co-prescribed with warfarin could increase the PT and INR, therefore increasing the risk for haemorrhaging. Single cases have been reported where patients stabilised on warfarin were initiated on simvastatin, and had bleeding episodes (Baxter, 2008:450; Hansten & Horn, 2011:1710; Tatro, 2011:135). There are some cases where 20 mg simvastatin per day had no significant effect on warfarin anticoagulation (Tatro, 2011:135). However, there are studies that contradict this. Westergren *et al.* (2007:1292) found that the effects of warfarin were increased by 10% to 30% after simvastatin was introduced. There are disputes whether or not simvastatin does have an effect on warfarin therapy or not. However, according to theory it could. After discovering that the levels of some of the metabolites of warfarin are decreased after initiation with simvastatin, it was theorised that simvastatin may inhibit the metabolism of warfarin by inhibition of CYP2C9 and CYP3A4 enzyme subtypes (Baxter, 2008:450; Tatro, 2011:135). Another theory is that plasma vitamin K levels are altered by fluctuating triglyceride levels, which could lead to an increase of warfarin sensitivity (Sconce

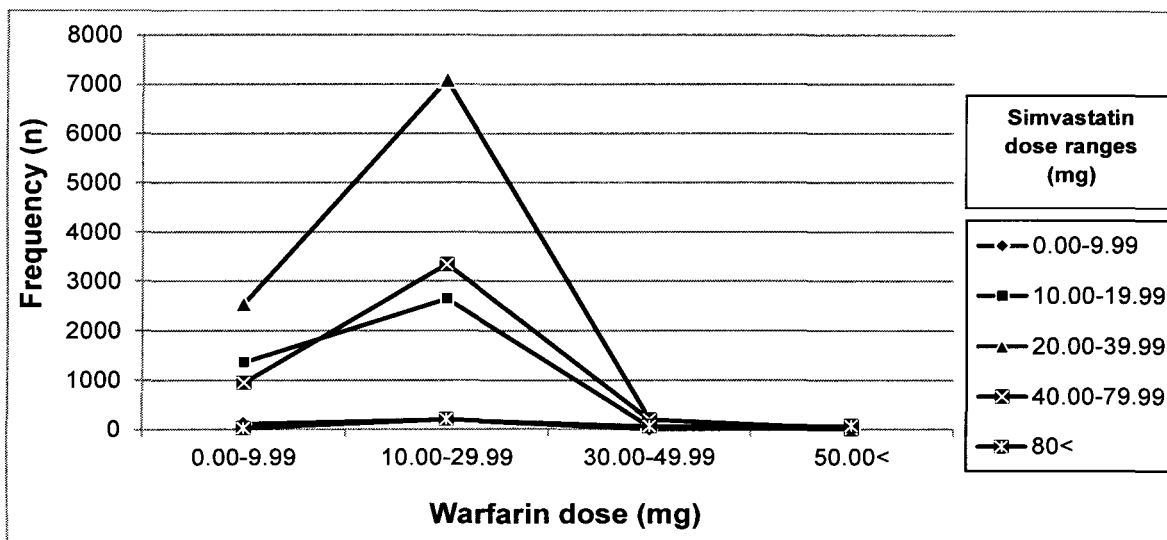
et al., 2006:1423). It can therefore be assumed that for any dose of simvastatin, there could potentially be an interaction with warfarin.

The range of simvastatin doses that were co-prescribed the most with warfarin was 20.00 mg to 39.99 mg (n=9 836, N=19 070, 51.58%). The range of simvastatin doses that were co-prescribed the least was 0.00 mg to 9.99 mg (n=314, N=19 070, 1.65%). These results are illustrated in Graph 4.21 (refer to Table A1.28).



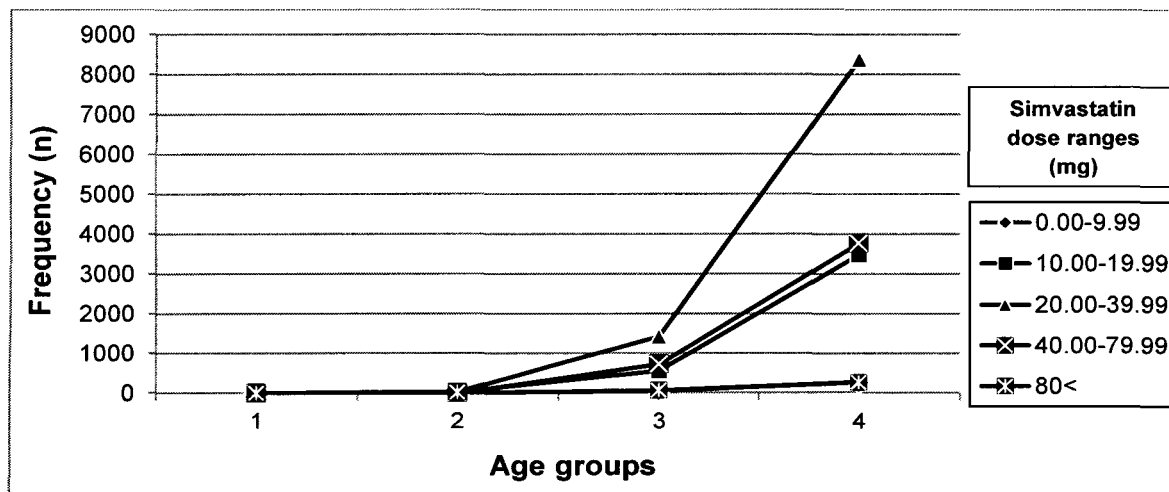
Graph 4.21: The frequency of different simvastatin doses

The range of warfarin doses that was prescribed most frequently with simvastatin was 10.00 mg to 29.99 mg (n=13 483, N=19 070, 70.70%). The range of warfarin doses that were co-prescribed the least was 50.00 mg and more (n=83, N=19 070, 0.44%). These results are illustrated in Graph 4.22 (refer to Table A1.29).



Graph 4.22: Comparison of the frequencies of different warfarin doses and simvastatin dose ranges.

The age group that were co-prescribed the most simvastatin was age group 4 (n=16 156, N=19 070, 84.72%). Age group 1 had no prescriptions for simvastatin together with warfarin, however, simvastatin was co-prescribed in age group 2 (n=94, N=19 070, 0.49%). These results are illustrated in Graph 4.23 (refer to Table A1.30).



Graph 4.23: Simvastatin doses according to age group

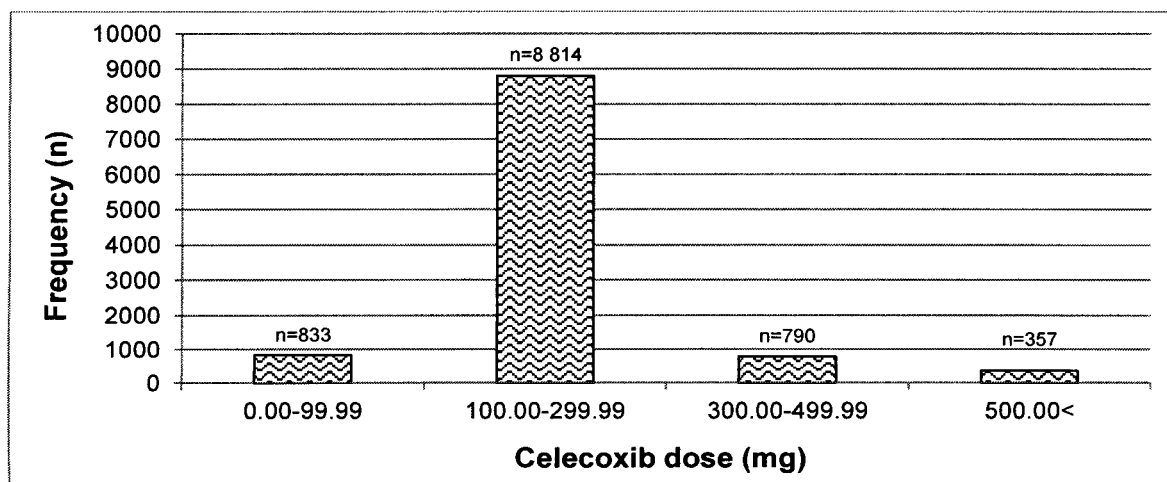
Refer to Table A1.31 for the effects of simvastatin when co-prescribed with warfarin.

4.7.5.5 Celecoxib

Celecoxib is usually indicated for the therapy of pain associated with osteoarthritis or rheumatoid arthritis in doses of 100 mg to 200 mg. In the treatment of pain due to post-dental surgery, doses of up to 400 mg can be administered (SAMF, 2005:375).

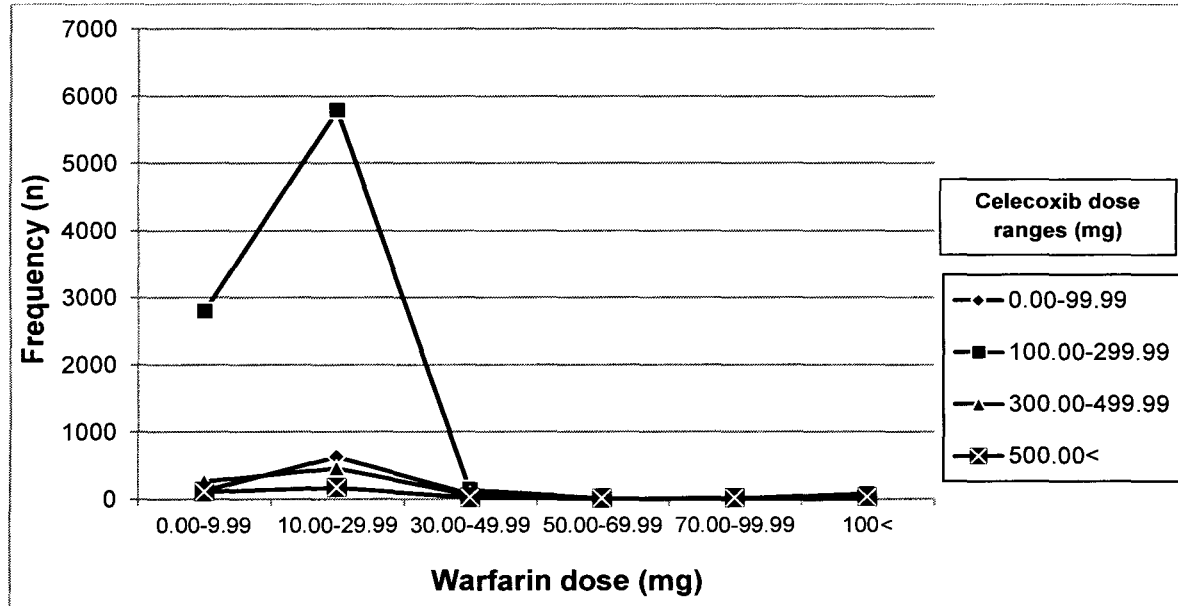
In cases concerning elderly patients the INR was increased after celecoxib 200 mg per day was administered. Some cases of gastrointestinal haemorrhaging were also reported (Baxter, 2008, 428; Tatro, 2011:157). There are reports that celecoxib has no effect on the effect of warfarin, INR or PT (Hansten & Horn, 2011:379; Malhi *et al.*, 2004:107). Even with these conflicting views there is still a chance that celecoxib may interact with warfarin. Celecoxib is a cyclooxygenase-2 (COX-2) inhibitor that inhibits platelet aggregation. This effect coupled with warfarin's anticoagulant effect may increase the chances for haemorrhaging. Other possible mechanisms for interaction include protein-binding displacement and competition for metabolism by the CYP2C9 enzyme subtype (Baxter, 2008:429; Dentali *et al.*, 2006:1242). Considering these aspects celecoxib could potentially interact with warfarin at any dose.

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%). The dose range that was co-prescribed the least was 500.00 mg and more (n=357, N=10 794, 3.31%). These results are illustrated in Graph 4.24 (refer to Table A1.32).



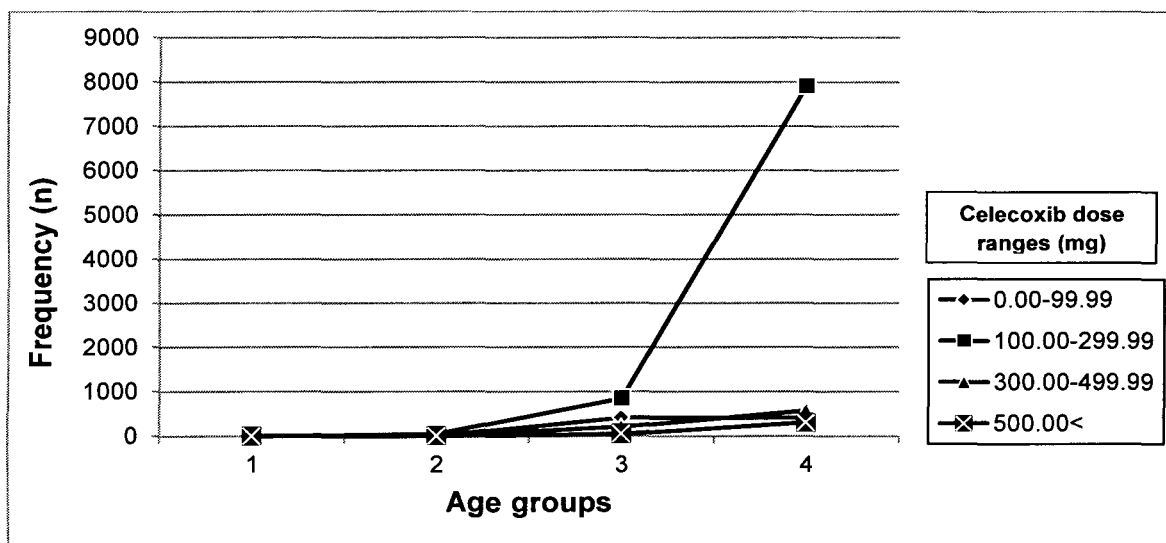
Graph 4.24: The frequency of different celecoxib doses

The range of warfarin doses that was prescribed most frequently with celecoxib was 10.00 mg to 29.99 mg (n=7 046, N=10 794, 65.28%). The doses range that was co-prescribed the least was 50.00 mg to 69.99 mg (n=19, N=10794, 0.18%). These results are illustrated in Graph 4.25 (refer to Table A1.33).



Graph 4.25: Comparison of the frequencies of different warfarin doses and celecoxib dose ranges

The age group that was co-prescribed the highest frequency of celecoxib was age group 4 (n=9 206, N=10 794, 85.29%). The age group that was co-prescribed the lowest frequency of celecoxib was age group 1 (n=5, N=10 794, 0.05%). These results are illustrated in Graph 4.26 (refer to Table A1.34).



Graph 4.26: Celecoxib doses according to age group

Refer to Table A1.35 for the effects of celecoxib when co-prescribed with warfarin.

4.8 CHAPTER SUMMARY

In this chapter the discussion started off with the analysis of the general prescribing patterns of all medicine items on the total database for the six year study period. Along with this the general prescribing patterns of all warfarin containing products claimed through the medicines claims database were also discussed. The results showed that only four warfarin products were claimed through the database namely Aspen-warfarin 5 mg tablets®, Cipla-warfarin 5 mg tablets®, Cipla-warfarin 3 mg tablets® and Cipla-warfarin 1 mg tablets® (refer to Table 4.6).

Analysis of the prescribing patterns of warfarin medicine items according to prescribing physician revealed that general practitioners prescribed the highest frequencies of warfarin medicine items per prescription per patient. General practitioners on average also prescribed the highest PDD of warfarin medicine items compared to the other prescribing physicians (refer to Table 4.7, Table 4.13 and Graph 4.1). According to the prescribing patterns of warfarin medicine items according to the age group, the age group that had the most patients, that received the most warfarin prescriptions and that received the most warfarin medicine items per

prescriptions was age group 4 (consisting of patients 59 years and older) (refer to Table 4.8, Table 4.9 and Table 4.10).

The age group that received the highest PDD was age group 2 (refer to Table 4.16). The number of warfarin patients, warfarin prescriptions claimed and warfarin medicine items claimed per prescription were equally distributed between females and males (refer to Table 4.11, Table 4.12 and Table 4.13).

According to the results the drugs that were co-prescribed with warfarin had PDDIs with a SR of 1, 2, 4 and 5. There were no drugs that may have a PDDI with warfarin with a SR of 3 (refer to Graph 4.4). Age group 4 received the highest frequency of co-prescribed drugs with warfarin (refer to Graph 4.5). The top 5 drugs that were co-prescribed with warfarin were aspirin, thyroxine, amiodarone, simvastatin and celecoxib. The top 5 drugs that were co-prescribed with warfarin all had PDDIs with a SR of 1 (refer to Graph 4.11). These drugs were discussed individually.

In Chapter 5 the conclusions pertaining to the results of the literature review and the empirical investigation are discussed. Recommendations for future studies and the limitations of this study are also discussed.