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APPENDIX A

Table A1.1: Number of prescriptions per age group for the total database (2005-2010).

Year	Age group	Number of prescriptions (n)	*%
2005	**1**	1 265 278	15.1
	2	1 607 513	19.2
	3	3 034 888	36.2
	4	2 484 157	29.6
	Total	**8 391 836**	**100**
2006	**1**	1 316 352	14.8
	2	1 684 146	18.9
	3	3 284 919	36.9
	4	2 620 931	29.4
	Total	**8 906 348**	**100**
2007	**1**	1 117 175	14.1
	2	1 392 218	17.6
	3	2 940 913	37.2
	4	2 460 790	31.1
	Total	**7 911 096**	**100**
2008	**1**	813 785	12.0
	2	1 057 109	15.6
	3	2 590 083	38.2
	4	2 314 896	34.2
	Total	**6 775 873**	**100**
2009	**1**	1 184 144	13.1
	2	1 602 877	17.8
	3	3 204 818	35.5
	4	3 031 398	33.6
	Total	**9 023 237**	**100**
2010	**1**	1 056 758	12.4
	2	1 519 246	17.8
	3	2 957 617	34.7
	4	2 981 807	35.0
	Total	**8 515 428**	**100**
TOTAL		**49 523 818**	

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

Table A1.2: Number of medicine items claimed per age group for the total database (2005-2010)

Year	Age group	Number of medicine items (n)	*%
2005	**1**	3 047 172	15.6
	2	3 541 730	1.82
	3	6 883 192	35.3
	4	6 028 658	30.9
	Total	**19 500 752**	**100**
2006	**1**	3 223 139	15.3
	2	3 758 460	17.8
	3	7 634 934	36.2
	4	6 496 870	30.8
	Total	**21 113 403**	**100**
2007	**1**	2 731 623	14.3
	2	3 142 969	16.5
	3	6 978 935	36.6
	4	6 222 178	32.6
	Total	**19 075 705**	**100**
2008	**1**	1 946 037	11.8
	2	2 352 355	14.3
	3	6 190 706	37.7
	4	5 950 155	36.2
	Total	**16 439 253**	**100**
2009	**1**	2 776 702	12.8
	2	3 483 990	16.1
	3	7 569 869	35.0
	4	7 818 430	36.1
	Total	**21 648 991**	**100**
2010	**1**	2 431 365	11.8
	2	3 274 509	16.0
	3	7 019 015	34.2
	4	7 802 888	38.0
	Total	**20 527 777**	**100**
TOTAL		**188 305 881**	

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

Table A1.3: Average number of patients per age group for the total database (2005-2010)

Year	Age group	Number of patients (n)	*%	Average number of prescriptions per patient
2005	**1**	409 207	27.1	3.09 ± 3.19
	2	376 572	24.9	4.27 ± 4.86
	3	484 388	32.1	6.27 ± 6.96
	4	239 454	15.9	10.37 ± 9.87
	Total	**1 509 621**	**100**	
2006	**1**	409 518	26.3	3.21 ± 3.31
	2	389 980	25.0	4.32 ± 5.02
	3	511 998	32.9	6.42 ± 7.12
	4	246 594	15.8	10.63 ± 10.19
	Total	**1 558 090**	**100**	
2007	**1**	322 862	27.4	3.46 ± 3.54
	2	274 711	23.3	5.07 ± 5.44
	3	389 654	33.1	7.55 ± 7.61
	4	19 1369	16.2	12.86 ± 10.43
	Total	**1 178 596**	**100**	
2008	**1**	237 612	24.4	3.42 ± 3.61
	2	208 961	21.4	5.06 ± 5.58
	3	345 230	35.4	7.50 ± 7.65
	4	182 694	18.8	12.67 ± 10.85
	Total	**974 497**	**100**	
2009	**1**	326 541	25.0	3.63 ± 3.74
	2	326 468	25.0	4.91 ± 5.48
	3	420 160	32.1	7.63 ± 7.84
	4	234 359	17.9	12.93 ± 10.83
	Total	**1 307 528**	**100**	
2010	**1**	289 332	23.7	3.65 ± 3.75
	2	306 548	25.1	4.96 ± 5.49
	3	388 114	31.8	7.62 ± 7.78
	4	236 295	19.4	12.62 ± 10.70
	Total	**1 220 289**	**100**	
TOTAL		**7 748 621**		

**Percentage was calculated by dividing the number of patients per age group by the total number of the patients for the specific year.*

Table A1.4: Number of prescriptions according to gender for the total database (2005-2010)

Year	Gender	Number of prescriptions (n)	*%
2005	**Female**	5 036 494	60.0
	Male	3 348 219	39.9
	Unspecified	7 123	0.1
	Total	**8 391 836**	**100**
2006	**Female**	5 336 203	59.9
	Male	3 565 331	40.0
	Unspecified	4 814	0.1
	Total	**8 906 348**	**100**
2007	**Female**	4 754 911	60.1
	Male	3 154 367	39.9
	Unspecified	1 818	0.02
	Total	**7 911 096**	**100**
2008	**Female**	4 062 385	60.0
	Male	2 713 488	40.0
	Unspecified	0	0
	Total	**6 775 873**	**100**
2009	**Female**	5 352 713	59.3
	Male	3 670 524	40.7
	Unspecified	0	0
	Total	**9 023 237**	**100**
2010	**Female**	5 032 177	59.1
	Male	3 483 251	40.9
	Unspecified	0	0
	Total	**8 515 428**	**100**
TOTAL		**49 523 818**	

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

Table A1.5: Number of medicine items claimed per gender for the total database (2005-2010)

Year	Gender	Number of medicine items (n)	*%	Average number of medicine items per prescription
2005	**Female**	11 750 190	60.3	2.33 ± 1.54
	Male	7 734 461	39.7	2.31 ± 1.47
	Unspecified	16 123	0.1	2.26 ± 1.37
	Total	**19 500 774**	**100**	**2.32 ± 1.52**
2006	**Female**	12 699 707	60.1	2.38 ± 1.58
	Male	8 403 158	39.8	2.36 ± 1.50
	Unspecified	10 557	0.1	2.19 ± 1.41
	Total	**21 113 422**	**100**	**2.37 ± 1.55**
2007	**Female**	11 509 346	60.3	2.42 ± 1.62
	Male	7 562 466	39.6	2.40 ± 1.55
	Unspecified	3 912	0.0	2.15 ± 1.47
	Total	**19 075 724**	**100**	**2.43 ± 1.59**
2008	**Female**	9 893 928	60.2	2.44 ± 1.67
	Male	6 545 325	39.8	2.41 ± 1.59
	Unspecified	0	0.0	0
	Total	**16 439 253**	**100**	**2.43 ± 1.64**
2009	**Female**	12 834 715	59.3	2.40 ± 1.67
	Male	8 814 276	40.7	2.40 ± 1.60
	Unspecified	0	0.0	0
	Total	**21 648 991**	**100**	**2.40 ± 1.64**
2010	**Female**	12 103 038	59.0	2.41 ± 1.70
	Male	8 424 739	41.0	2.42 ± 1.64
	Unspecified	0	0.0	0
	Total	**20 527 777**	**100**	**2.41 ± 1.67**
TOTAL		**118 305 941**		

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

Table A1.6: The average number of prescriptions per patient according to gender for the total database (2005-2010)

Year	Gender	Number of patients (n)	*%	Average number of prescriptions per patient
2005	**Female**	842 386	55.8	5.98 ± 7.16
	Male	665 505	44.1	5.03 ± 6.15
	Unspecified	1 730	0.1	4.12 ± 5.21
	Total	**1 509 621**	**100**	**5.56 ± 6.75**
2006	**Female**	868 891	55.8	6.14 ± 7.37
	Male	688 091	44.2	5.18 ± 6.35
	Unspecified	1 108	0.01	4.34 ± 5.78
	Total	**1 558 090**	**100**	**5.72 ± 6.96**
2007	**Female**	654 348	55.5	7.27 ± 7.99
	Male	523 841	44.4	6.02 ± 6.90
	Unspecified	407	0.03	4.47 ± 5.20
	Total	**1 178 596**	**100**	**6.71 ± 7.55**
2008	**Female**	538 254	55.2	7.55 ± 8.32
	Male	436 243	44.8	6.22 ± 7.15
	Unspecified	0	0	0
	Total	**974 497**	**100**	**6.95 ± 7.85**
2009	**Female**	712 305	54.5	7.51 ± 8.38
	Male	595 223	45.5	6.17 ± 7.17
	Unspecified	0	0	0
	Total	**1 307 528**	**100**	**6.90 ± 7.88**
2010	**Female**	661 007	54.2	7.61 ± 8.39
	Male	559 282	45.8	6.23 ± 7.18
	Unspecified	0	0	0
	Total	**1 220 289**	**100**	**6.98 ± 7.89**
TOTAL		**7 748 621**		

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

Table A1.7: The frequency and significance rating of the drugs co-prescribed with warfarin for the total database (2005-2010)

Significance rating	Frequency (n)	*%
1	155 066	43.3
2	30 128	8.4
4	137 144	38.3
5	36 144	10.1
TOTAL	**358 482**	**100.0**

**Percentages calculated according to the total number of drugs co-prescribed with warfarin for the total database (2005-2010).*

Table A1.8: Frequency and significance rating of drugs co-prescribed with warfarin according to age group

Significance rating	*Age group 1*	*Age group 2*	*Age group 3*	*Age group 4*
1	90	1 752	25 502	127 722
2	39	891	5 745	23 453
4	48	1 622	21 090	114 384
5	28	463	5 493	30 160
TOTAL	**205**	**4 728**	**57 830**	**295 719**

Table A1.9: Frequency of the top 10 co-prescribed drugs with a significance rating of 1

Rank	Drug	Frequency (n)	*%
1	Aspirin	48 903	13.6
2	Thyroxine	33 955	9.5
3	Amiodarone	25 060	7.0
4	Simvastatin	19 070	5.3
5	Celecoxib	10 794	3.0
6	Rosuvastatine	6 337	1.8
7	Diclofenac	3 442	1.0
8	Ibuprofen	1 352	0.4
9	Fluvastatin	836	0.2
10	Piroxicam	722	0.2
TOTAL		**150 471**	**42.0**

**Percentages calculated according to the total number of co-prescribed drugs for the total database (2005-2010).*

Table A1.10: Frequency of warfarin co-prescribed drugs with a significance rating of 1

Drug	Frequency (n)	*%
Aluminium	118	0.07
Amiodarone	25 060	16.16
Aspirin	48 903	31.54
Azithromycin	126	0.08
Celecoxib	10 794	6.96
Cimetidine	193	0.12
Clarithromycin	214	0.14
Cyclophosphamide	58	0.04
Danazol	1	0.00
Diclofenac	3 442	2.22
Doxycycline	173	0.11
Econazole	37	0.02
Erythromycin	44	0.03
Fenofibrate	208	0.13
Fluconazole	72	0.05
Fluorouracil	11	0.01
Flurbiprofen	108	0.07
Fluvastatin	836	0.54
Gatifloxacin	22	0.01
Gemfibrozil	28	0.02
Ibuprofen	1 352	0.87
Indomethacin	400	0.26
Itraconazole	66	0.04
Ketoconazole	189	0.12
Ketoprofen	353	0.23
Ketorolac	75	0.05
Liothyronine	222	0.14
Lovastatin	84	0.05
Magnesium	65	0.04
Mefenamic acid	59	0.04
Metronidazole	156	0.10
Miconazole	60	0.04
Minocycline	42	0.03
Moxifloxacin	256	0.17
Naproxen	250	0.16
Oxytretracycline	11	0.01
Phenobarbitone	422	0.27

**Percentages calculated according to the total number of co-prescribed drugs with a significance rating of 1.*

Table A1.10: Frequency of warfarin co-prescribed drugs with a significance rating of 1 (continued)

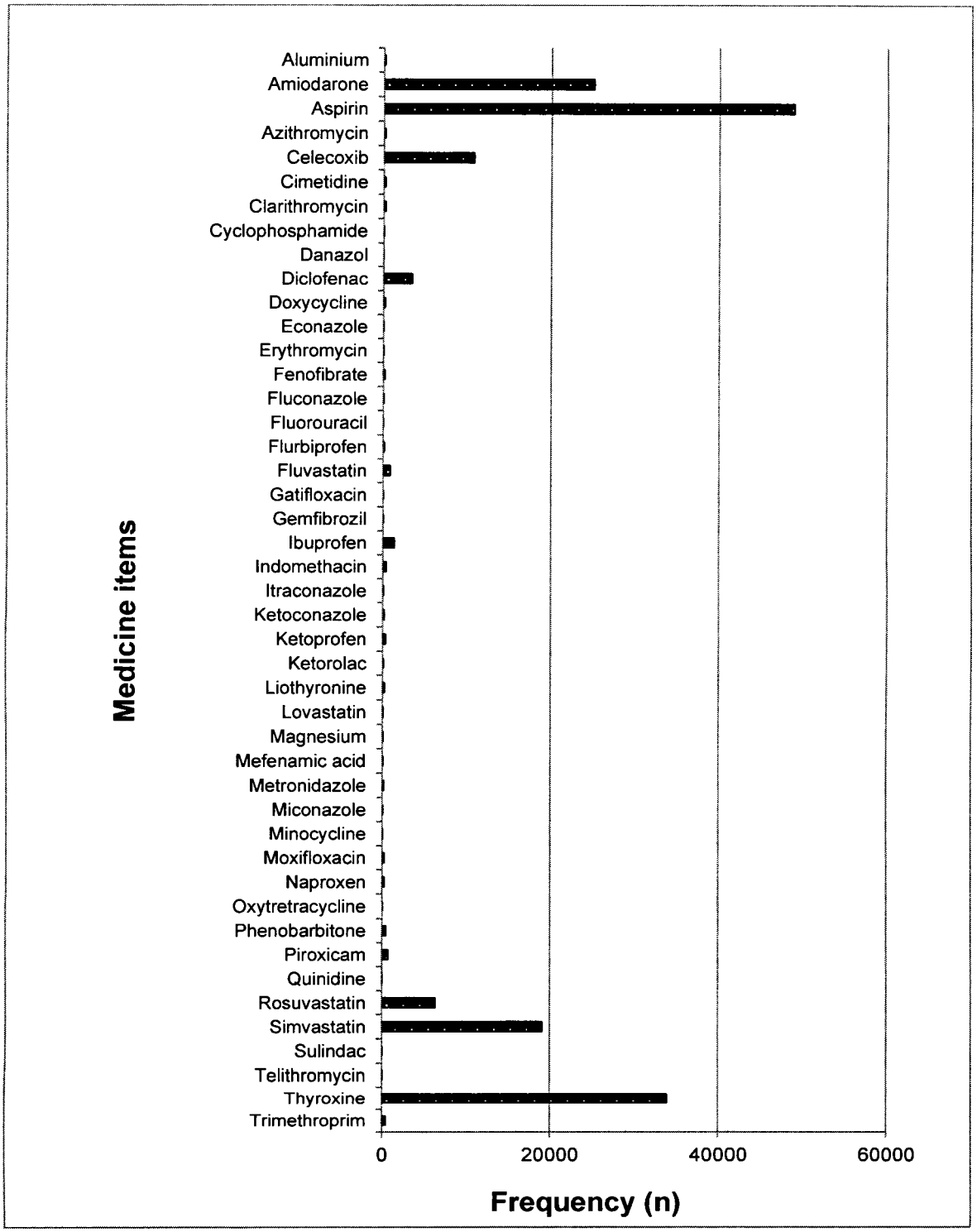
Drug	Frequency (n)	*%
Piroxicam	722	0.47
Quinidine	22	0.01
Rosuvastatin	6 337	4.09
Simvastatin	19 070	12.30
Sulindac	5	0.00
Telithromycin	27	0.02
Thyroxine	33 955	21.90
Trimethroprim	419	0.27
TOTAL	**155 067**	**100.00**

**Percentages calculated according to the total number of co-prescribed drugs with a significance rating of 1.*

Table 1.11: Frequency of warfarin co-prescribed drugs with a significance rating of 2

Drug	Frequency (n)	*%
Azathioprine	426	1.41
Betamethasone	590	2.00
Budesonide	4 085	13.56
Carbamazepine	3 369	11.18
Chloramphenicol	52	0.17
Cholestyramine	182	0.60
Ciprofloxacin	302	1.00
Disulfiram	1	0.00
Fludrocortisone	158	0.52
Griseovulfin	13	0.04
Hydrocortisone	374	1.24
Levofloxacin	290	0.96
Methylprednisone	559	1.86
Nalidixic acid	96	0.32
Nevirapine	95	0.32
Norfloxacin	112	0.37
Ofloxacin	21	0.07
Paracetamol	8 488	28.17
Phenytoin	2 277	7.56
Prednisone	5 872	19.49
Ranitidine	730	2.42
Rifampicin	17	0.06
Tramadol	1 191	3.95
Trazodone	443	1.47
Triamcinolone	385	1.28
TOTAL	**30 128**	**100.00**

**Percentages calculated according to the total number of warfarin co-prescribed drugs with a significance rating of 2.*



Graph A1.1: Frequency of warfarin co-prescribed drugs with a significance rating of 1

Table A1.12: Frequency of the top 10 warfarin co-prescribed drugs with a significance rating of 2

Drug	Frequency (n)	*%
Paracetamol	8 488	2.37
Prednisone	5 872	1.64
Budesonide	4 085	1.14
Carbamazepine	3 369	0.94
Phenytoin	2 277	0.64
Tramadol	1 191	0.33
Ranitidine	730	0.20
Betamethasone	590	0.16
Methylprednisone	559	0.16
Trazodone	443	0.12
TOTAL	**27 604**	**7.7**

**Percentage calculated according to the total number of warfarin co-prescribed drugs for the total database (2005-2010).*

Table A1.13: Frequency of warfarin co-prescribed drugs with a significance rating of 4 and 5

Drug	Frequency (n)	*%
Atenolol	22 534	6.29
Furosemide	58 180	16.23
Hydrochlorothiazide	34 660	9.67
Indapamide	21 737	6.06
Lopinavir/Ritonavir	33	0.01
Spironolactone	36 144	10.08
TOTAL	**173 288**	**48.34**

**Percentage calculated according to the total number of warfarin co-prescribed drugs with a significance rating of 4 and 5.*

Table A1.14: The top 10 drugs co-prescribed with warfarin

Drug	Frequency (n)	*%
Aspirin	48 903	13.64
Thyroxine	33 955	9.47
Amiodarone	25 056	6.99
Simvastatin	19 070	5.32
Celecoxib	10 794	3.01
Paracetamol	8 488	2.37
Rosuvastatin	6 337	1.77
Prednisone	5 872	1.64
Budesonide	4 085	1.14
Diclofenac	3 442	0.96
TOTAL	**166 006**	**46.31**

**Percentages calculated according to the total number of warfarin co-prescribed drugs for the whole database (2005-2010).*

Table A1.15: The top 5 drugs co-prescribed with warfarin

Drug	Frequency (n)	*%
Aspirin	48 903	13.64
Thyroxine	33 954	9.47
Amiodarone	25 056	6.99
Simvastatin	19 070	5.32
Celecoxib	10 794	3.01
TOTAL	**137 782**	**38.43**

**Percentages calculated according to the total number of warfarin co-prescribed drugs for the total database (2005-2010).*

Table A1.16: The frequency of different aspirin doses

Aspirin dose (mg)	Frequency (n)	*%
0.00-99.99	28 357	58.00
100.00-149.99	14 885	30.44
150.00-299.99	4 530	9.26
300.00<	1 131	2.31
TOTAL	**48 903**	**100.00**

**Percentages calculated according to the total number of aspirin products claimed through the database (2005-2010).*

Table A1.17: Comparison of the frequencies of different warfarin doses and high risk aspirin doses

	Warfarin doses (mg)	Frequency (n)	*%
Aspirin doses (mg) 150.00-299.99	10.00-29.99	2 885	6.00
	30.00-49.99	455	0.93
	50.00-69.99	0	0.00
	70.00-99.99	0	0.00
	100<	2	0.00
	TOTAL	**3 342**	**6.93**
Aspirin doses (mg) 300.00<	10.00-29.99	217	1.38
	30.00-49.99	95	0.24
	50.00-69.99	8	0.02
	70.00-99.99	49	0.10
	100<	190	0.39
	TOTAL	**1 038**	**2.13**

**Percentages calculated according to the total number of aspirin products claimed through the database (2005-2010).*

Table A1.18: Frequency of high risk aspirin doses according to age group

	Age groups	Frequency (n)	*%
Aspirin doses (mg) 150.00-299.99	1	0	0.00
	2	89	0.18
	3	870	1.78
	4	3 571	7.30
	TOTAL	**4 530**	**9.26**
Aspirin doses (mg) 300.00<	1	1	0.00
	2	12	0.02
	3	214	0.44
	4	904	1.85
	TOTAL	**1 131**	**2.31**

**Percentages calculated according to the total number of aspirin products claimed through the database (2005-2010).*

Table A1.19: Summary of the effects of aspirin when co-prescribed with warfarin

Significance rating	1
Drug	Aspirin
Classification	Cyclooxygenase-1 (COX-1) inhibitor (Brunton, 2012; Hersh *et al.,* 2007:2486).
Effect	Increased anticoagulation. In combination with aspirin may increase gastric haemorrhaging (Tatro, 2011:175). Aspirin can in small doses (100 mg to 150 mg) inhibit the function of platelets, leading to an increased risk for haemorrhaging or minor bleeding. A hypoprothrombineamic effect could be caused by large aspirin doses of 3 g per day and higher (Hansten & Horn, 2011:221). Hypoprothrombinaemic responses concur with increased PTs. Prolonged bleeding times have also been documented (Baxter, 2008:385).
Mechanism	Aspirin and warfarin are both highly protein bound (~99%). The possibility exists that aspirin displaces warfarin from its protein binding sight, therefore increasing the free fraction of warfarin in the blood, which leads to an increased anticoagulant effect (Hersh *et al.,* 2007:2485; Hansten & Horn, 2011:221). The inhibition of platelets by aspirin could also add to warfarin's increase anticoagulant effect (Baxter, 2008:386; Hansten & Horn, 2011:221). The irritation caused by aspirin on the gastric mucosa can also increase the risk for gastric haemorrhaging (Baxter, 2008:386).
Management	INR should be monitored as frequently as possible. Warfarin dose should be adjusted accordingly if aspirin is initiated or discontinued. Unfamiliar bleeding should be reported immediately (Tatro, 2011:175). Aspirin use in conjunction with warfarin should be avoided unless for an intended increase in anticoagulation. If aspirin is added to warfarin treatment for reasons other than anticoagulation, then alternatives should be strongly considered (Hansten & Horn, 2011:221, 222). Patients should be notified of all over-the-counter medication that contains aspirin (Baxter, 2008:386).

Table A1.20: The frequency of different thyroxine doses

Thyroxine dose (mg)	Frequency (n)	*%
<0.0249	20 614	60.71
0.0250-0.0499	1 515	4.46
0.0500-0.0999	10 223	30.11
0.10000-0.1499	470	1.38
0.1500-0.2999	636	1.87
0.300<	496	1.46
TOTAL	**33 954**	**100.00**

**Percentages calculated according to the total number of thyroxine products claimed through the database (2005-2010).*

Table A1.21: Comparison of the frequencies of different warfarin doses and thyroxine doses

	Warfarin doses (mg)	Frequency (n)	*%
Thyroxine doses (mg) <0.0249	0.00-9.99	4 899	14.43
	10.00-29.99	15 534	45.75
	30.00-49.99	170	0.50
	50.00-69.99	4	0.01
	70.00-99.99	1	0.00
	100<	6	0.02
	TOTAL	**20 614**	**60.71**
Thyroxine doses (mg) 0.0250-0.0499	0.00-9.99	294	0.87
	10.00-29.99	860	2.53
	30.00-49.99	360	1.06
	50.00-69.99	1	0.00
	70.00-99.99	0	0.00
	100<	0	0.00
	TOTAL	**1 515**	**4.46**
Thyroxine doses (mg) 0.0500-0.0999	0.00-9.99	2 290	6.74
	10.00-29.99	7 823	23.04
	30.00-49.99	106	0.31
	50.00-69.99	3	0.01
	70.00-99.99	0	0.00
	100<	1	0.00
	TOTAL	**10 223**	**30.11**

**Percentages calculated according to the total number of thyroxine products claimed through the database (2005-2010).*

Table A1.21: Comparison of the frequencies of different warfarin doses and thyroxine doses (continued)

	Warfarin doses (mg)	Frequency (n)	*%
Thyroxine doses (mg) 0.1000-0.1499	0.00-9.99	110	0.32
	10.00-29.99	335	0.99
	30.00-49.99	23	0.07
	50.00-69.99	1	0.00
	70.00-99.99	0	0.00
	100<	1	0.00
	TOTAL	**470**	**1.38**
Thyroxine doses (mg) 0.1500-0.2999	0.00-9.99	147	0.43
	10.00-29.99	334	0.98
	30.00-49.99	41	0.12
	50.00-69.99	12	0.04
	70.00-99.99	8	0.02
	100<	94	0.28
	TOTAL	**636**	**1.87**
Thyroxine doses (mg) 0.3000<	0.00-9.99	286	0.84
	10.00-29.99	32	0.09
	30.00-49.99	115	0.34
	50.00-69.99	0	0.00
	70.00-99.99	6	0.02
	100<	57	0.17
	TOTAL	**496**	**1.46**

**Percentages calculated according to the total number of thyroxine products claimed through the database (2005-2010).*

Table A1.22: Frequency of thyroxine doses according to age group

	Age group	Frequency (n)	*%
Thyroxine doses (mg) <0.0249	1	0	0.00
	2	187	0.55
	3	3 240	9.54
	4	17 187	50.62
	TOTAL	**20 614**	**60.71**
Thyroxine doses (mg) 0.0250-0.0499	1	0	0.00
	2	17	0.05
	3	174	0.51
	4	1 324	4.00
	TOTAL	**1 515**	**4.46**

**Percentages calculated according to the total number of thyroxine products claimed through the database (2005-2010).*

Table A1.22: Frequency of thyroxine doses according to age group (continued)

	Age group	Frequency (n)	*%
Thyroxine doses (mg) 0.0500-0.0999	1	1	0.00
	2	94	0.28
	3	1 348	3.97
	4	8 780	25.86
	TOTAL	**10 223**	**30.11**
Thyroxine doses (mg) 0.1000-0.1499	1	0	0.00
	2	19	0.06
	3	97	0.29
	4	354	1.04
	TOTAL	**470**	**1.38**
Thyroxine doses (mg) 0.1500-0.2999	1	0	0.00
	2	3	0.01
	3	101	0.30
	4	532	1.57
	TOTAL	**636**	**1.87**
Thyroxine doses (mg) 0.3000<	1	0	0.00
	2	1	0.00
	3	9	0.03
	4	486	1.43
	TOTAL	**496**	**1.46**

**Percentages calculated according to the total number of thyroxine products claimed through the database (2005-2010).*

Table A1.23: Summary of the effects of thyroxine when co-prescribed with warfarin

Significance rating	1
Drug	Thyroxine
Classification	Thyroid hormone replacement (replacement of T_4) in hypothyroidism (Brunton, 2012).
Effect	In patients with hypothyroidism, the warfarin dose was decreased following an increased response to warfarin after initiation of thyroxine. This may increase the risk for haemorrhaging (Tatro, 2011:188). Warfarin sensitivity can increase with an increase in the dose of thyroxine. Patients with hyperthyroidism have an increased sensitivity toward warfarin (Baxter, 2008:455).
Mechanism	It is speculated that thyroxine enhances warfarin affinity towards receptors in the liver, which could add onto the decreased production of clotting factors (Baxter, 2008:455; Rouby *et al.,* 2004:17). With hypothyroidism the metabolism of vitamin K-dependent clotting factors are slowed down, decreasing the onset of anticoagulation of warfarin (Rouby *et al.,* 2004:17). The opposite is true in hyperthyroidism or the administration of thyroxine (Tatro, 2011:188).
Management	Warfarin dosing should be adjusted accordingly following thyroid hormone therapy. Warfarin doses my need to be decreased when thyroxine is initiated or increased when thyroxine is discontinued (Tatro, 2011:188). Extra precautions are usually unnecessary when a patient already stabilized on thyroxine is initiated on warfarin therapy (Hansten & Horn, 2011:1754). Some drugs such as amiodarone can cause thyrotoxicosis, which also can lead to the necessity of decreasing the warfarin dose (Baxter, 2008:456).

Table A1.24: Frequency of different amiodarone doses

Amiodarone dose (mg)	Frequency (n)	*%
0.00-99.99	652	2.60
100.00-299.99	22 386	89.34
300.00-499.99	1 301	5.19
500.00-699.99	397	1.58
700.00<	320	1.28
TOTAL	**25 056**	**100.00**

**Percentages calculated according to the total number of amiodarone products claimed through the database (2005-2010).*

Table A1.25: Comparison of the frequencies of different warfarin doses and high risk amiodarone doses

	Warfarin doses (mg)	Frequency (n)	*%
Amiodarone doses (mg) 300.00-499.99	0.00-9.99	510	2.04
	10.00-29.99	734	2.93
	30.00-49.99	56	0.22
	50.00-69.99	0	0.00
	70.00-99.99	1	0.00
	100<	0	0.00
	TOTAL	**1 301**	**5.19**
Amiodarone doses (mg) 500.00-699.99	0.00-9.99	49	0.20
	10.00-29.99	116	0.46
	30.00-49.99	232	0.93
	50.00-69.99	0	0.00
	70.00-99.99	0	0.00
	100<	0	0.00
	TOTAL	**397**	**1.58**
Amiodarone doses (mg) 700.00<	0.00-9.99	12	0.05
	10.00-29.99	115	0.46
	30.00-49.99	32	0.13
	50.00-69.99	5	0.02
	70.00-99.99	33	0.13
	100<	123	0.49
	TOTAL	**320**	**1.28**

**Percentages calculated according to the total number of amiodarone products claimed through the database (2005-2010).*

Table A1.26: Frequency of high risk amiodarone doses according to age group

	Age group	Frequency (n)	*%
Amiodarone doses (mg) 300.00-499.99	1	1	0.00
	2	9	0.04
	3	212	0.85
	4	1 079	4.31
	TOTAL	**1 301**	**5.19**
Amiodarone doses (mg) 500.00-699.99	1	0	0.00
	2	1	0.00
	3	45	0.18
	4	351	1.40
	TOTAL	**397**	**1.58**
Amiodarone doses (mg) 700.00<	1	0	0.00
	2	0	0.00
	3	27	0.11
	4	293	1.17
	TOTAL	**320**	**1.28**

**Percentages calculated according to the total number of amiodarone products claimed through the database (2005-2010).*

Table A1.27: Summary of the effects of amiodarone when co-prescribed with warfarin

Significance rating	1
Drug	Amiodarone
Classification	Amiodarone is an anti-arrhythmic drug that is a structural analogue of thyroid hormones (Brunton, 2012).
Effect	The effects of warfarin are augmented by the concomitant use of amiodarone. This increases the risk for haemorrhaging. The PT is also extended by the co-administration of amiodarone. The INR is also increased. Warfarin clearance can also be decreased (Tatro, 2011:90). Amiodarone also increases the incidence of hypoprthrombineamia and haemorrhaging. Amioradone also increases the sensitivity of warfarin because it is a structural analogue of thyroxine (Hansten & Horn, 2011:101). These effects can be seen six to 16 weeks after amiodarone has been withdrawn (Baxter, 2008:363). Amiodarone can also cause thyrotoxicosis (Woeber & Warner, 1999:49).
Mechanism	Amiodarone is a potent inhibitor of CYP2C9, thus inhibits the metabolism of *S*-warfarin (Habib *et al.*, 2008:132; Tatro, 2011:90). Amiodarone can cause hyperthyroidism, which in turn can cause an enhanced sensitivity towards warfarin (Hansten & Horn, 2011). Amiodarone may also inhibit CYP3A4 and CYP1A2 (Baxter, 2008:363).
Management	The INR should be monitored closely after initiation of amiodarone. The warfarin dose should be reduced in the following way: 100 mg per day of amiodarone, reduce warfarin dose by 25%; 200 mg per day of amiodarone, reduce warfarin dose by 30%; 300 mg per day of amiodarone, reduce warfarin by 35%; 400 mg per day of amiodarone, reduce warfarin dose by 40% (Tatro, 2011:90). The INR should be closely monitored for at least two months after amiodarone therapy has been discontinued (Hansten & Horn, 2011:102).

Table A1.28: The frequency of different simvastatin doses

Simvastatin dose (mg)	Frequency (n)	*%
0.00-9.99	314	1.65
10.00-19.99	4 067	21.33
20.00-39.99	9 836	51.58
40.00-79.99	4 496	23.58
80.00<	357	1.87
TOTAL	**19 070**	**100.00**

**Percentages calculated according to the total number of simvastatin products claimed through the database (2005-2010).*

Table A1.29: Comparison of the frequencies of different warfarin doses and simvastatin doses

	Warfarin doses (mg)	Frequency (n)	*%
Simvastatin doses (mg) 0.00-9.99	0.00-9.99	115	0.60
	10.00-29.99	199	1.05
	30.00-49.99	0	0
	50.00-69.99	0	0
	TOTAL	**314**	**1.65**
Simvastatin doses (mg) 10.00-19.99	0.00-9.99	1 363	7.15
	10.00-29.99	2 646	13.88
	30.00-49.99	56	0.29
	50.00-69.99	2	0.01
	TOTAL	**4 067**	**21.33**
Simvastatin doses (mg) 20.00-39.99	0.00-9.99	2 541	13.32
	10.00-29.99	7 089	37.17
	30.00-49.99	206	1.08
	50.00-69.99	0	0.00
	TOTAL	**9 836**	**51.58**
Simvastatin doses (mg) 40.00-79.99	0.00-9.99	948	4.97
	10.00-29.99	3 344	17.53
	30.00-49.99	194	1.01
	50.00-69.99	10	0.05
	TOTAL	**4 496**	**23.58**
Simvastatin doses (mg) 80.00<	0.00-9.99	23	0.12
	10.00-29.99	205	1.07
	30.00-49.99	58	0.30
	50.00-69.99	71	0.37
	TOTAL	**357**	**1.87**

**Percentages calculated according to the total number of simvastatin products claimed through the database (2005-2010).*

Table A1.30: Frequency of simvastatin doses according to age group

	Warfarin doses (mg)		Frequency (n)	*%
Simvastatin doses (mg) 0.00-9.99	**Age groups**	**1**	0	0.00
		2	1	0.01
		3	53	0.28
		4	260	1.36
	TOTAL		**314**	**1.65**
Simvastatin doses (mg) 10.00-19.99	**Age groups**	**1**	0	0.00
		2	39	0.20
		3	552	2.89
		4	3 476	18.23
	TOTAL		**4 067**	**21.33**
Simvastatin doses (mg) 20.00-39.99	**Age groups**	**1**	0	0.00
		2	34	0.18
		3	1 423	7.46
		4	8 379	43.94
	TOTAL		**9 836**	**51.58**
Simvastatin doses (mg) 40.00-79.99	**Age groups**	**1**	0	0.00
		2	6	0.03
		3	720	3.78
		4	3 770	19.77
	TOTAL		**4 496**	**23.58**
Simvastatin doses (mg) 80.00<	**Age groups**	**1**	0	0.00
		2	14	0.07
		3	72	0.38
		4	271	1.42
	TOTAL		**357**	**1.87**

**Percentages calculated according to the total number of simvastatin products claimed through the database (2005-2010).*

Table A1.31: Summary of the effects of simvastatin when co-prescribed with warfarin

Significance rating	1
Drug	Simvastatin
Classification	Hydroxymethylglutaryl coenzyme A reductase inhibitor (HMG-CoA reductase inhibitor) (Brunton, 2012; Westergren *et al.,* 2007:1292).
Effect	An enhanced anticoagulation effect (Hansten & Horn, 2011:1709; Tatro, 2011:135). This leads to an increased risk for haemorrhaging (Baxter, 2004:450). Warfarin metabolism may be reduced (Westergren *et al.,* 2007:1292).
Mechanism	The metabolism of *R*- and *S*-warfarin is reduced due to the inhibition of CYP2C9 and CYP3A4 by simvastatin (Baxter, 2008:452; Sconce *et al.,* 2006:1424; Tatro, 2011:135). Another possibility could be that simvastatin is also highly protein-bound and therefore displaces warfarin from its protein-binding site, thus increasing the free fraction of warfarin in the blood (Hansten & Horn, 2011:1710).
Management	INR should be monitored closely after initiation or discontinuation of simvastatin (Sconce *et al.,* 2006:1424; Tatro, 2011:135). Simvastatin dose adjustments can also be made (Baxter, 2008:452).

Table A1.32: The frequency of different celecoxib doses

Thyroxine dose (mg)	Frequency (n)	*%
0.00-99.99	833	7.72
100.00-299.99	8 814	81.66
300.00-499.99	790	7.32
500.00<	357	3.31
TOTAL	**10 794**	**100.00**

**Percentages calculated according to the total number of celecoxib products claimed through the database (2005-2010).*

Table A1.33: Comparison of the frequencies of different warfarin doses and celecoxib doses

	Warfarin doses (mg)	Frequency (n)	*%
Celecoxib doses (mg) 0.00-99.99	0.00-9.99	128	1.19
	10.00-29.99	629	5.83
	30.00-49.99	73	0.68
	50.00-69.99	1	0.01
	70.00-99.99	0	0.00
	100.00<	2	0.02
	TOTAL	**833**	**7.72**
Celecoxib doses (mg) 100.00-299.99	0.00-9.99	2 794	25.88
	10.00-29.99	5 787	53.61
	30.00-49.99	141	1.31
	50.00-69.99	9	0.08
	70.00-99.99	4	0.04
	100.00<	79	0.73
	TOTAL	**8 814**	**81.66**
Celecoxib doses (mg) 300.00-499.99	0.00-9.99	263	2.44
	10.00-29.99	460	4.26
	30.00-49.99	61	0.57
	50.00-69.99	2	0.02
	70.00-99.99	0	0.00
	100.00<	4	0.04
	TOTAL	**790**	**7.32**
Celecoxib doses (mg) 500.00<	0.00-9.99	110	1.02
	10.00-29.99	170	1.57
	30.00-49.99	22	0.20
	50.00-69.99	7	0.06
	70.00-99.99	16	0.15.
	100.00<	32	0.30
	TOTAL	**357**	**3.31**

**Percentages calculated according to the total number of celecoxib products claimed through the database (2005-2010).*

Table A1.34: Frequency of celecoxib doses according to age group

	Warfarin doses (mg)		Frequency (n)	*%
Celecoxib doses (mg) 0.00-99.99	Age groups	1	0	0.00
		2	4	0.04
		3	411	3.81
		4	418	3.87
	TOTAL		**833**	**7.72**
Celecoxib doses (mg) 100.00-299.99	Age groups	1	5	0.05
		2	50	0.46
		3	848	7.86
		4	7 911	73.29
	TOTAL		**8 814**	**81.66**
Celecoxib doses (mg) 300.00-499.99	Age groups	1	0	0.00
		2	9	0.08
		3	208	1.93
		4	573	5.31
	TOTAL		**790**	**7.32**
Celecoxib doses (mg) 500.00<	Age groups	1	0	0.00
		2	0	0.00
		3	53	0.49
		4	304	2.82
	TOTAL		**357**	**3.31**

**Percentages calculated according to the total number of celecoxib products claimed through the database (2005-2010.*

Table A1.35: Summary of the effects of celecoxib when co-prescribed with warfarin

Significance rating	1
Drug	Celecoxib
Classification	Cyclooxygenase-2 inhibitor (COX-2 inhibitor) (Brunton, 2012; Malhi *et al.,* 2004:107).
Effect	Increases the anticoagulant effects of warfarin (Tatro, 2011:157). Can cause an increase in INR (Hansten & Horn, 2011:379). The risk of haemorrhaging increases, especially in the elderly. Can also increase the risk for upper gastrointestinal haemorrhaging (Baxter, 2008:428). It is speculated that celecoxib could cause "gastrointestinal toxicity and bleeding" and the risk of this may be increased by the co-administration of warfarin (Baxter, 2008:429).
Mechanism	The mechanism of the interaction is considered to be unknown (Hansten & Horn, 2011:379; Tatro, 2011:157). Some possibilities could be that both celecoxib and warfarin are metabolised by CYP2C9 and therefore an interaction may occur (Baxter, 2011; Dentali *et al.,* 2006:1242). There is also a possibility that celecoxib can displace warfarin from its protein-binding site (Dentali *et al.,* 2006:1242).
Management	INR should be monitored, especially when celecoxib is initiated or discontinued (Baxter, 2008:429; Tatro, 2011:157).