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SCIENCE MEDICINES HEALTH

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Prescribing of digoxin for long-term use in atrial fibrillation in France, Germany and the UK during 2000-2014

EMA drug utilisation study using IMS Health and THIN electronic health records

1. PASS information

Title	Prescribing of digoxin for long-term use in atrial fibrillation in France, Germany and the UK during 2000-2014
Protocol version identifier	1.3
Date of last version of the protocol	17 June 2015
EU PAS Register No:	Study not registered
Active substance	Digoxin (ATC code: C01AA05)
Medicinal product(s):	
Product reference:	
Procedure number:	EMA/PRAC/303855
Study initiator	EMA
Research question and objectives	At its meeting 4 – 7 May 2015 the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) adopted a timetable for a review of the scientific literature on the risk of mortality with digoxin in patients with atrial fibrillation. This was due to concerns arising from observational studies with a new signal coming from a recently published study by Freeman JV et al, Circulation, Arrhythmia and Electrophysiology 2014; 8 (1): 49-58. In addition to the literature review, it was agreed to study the use of digoxin in a primary care setting in patients with atrial fibrillation without heart failure. The present study aims to describe the extent of prescription of digoxin in three large EU countries in the period 2000-2012. This is done using the EMA's in-house IMS Health databases (Germany and France) and the THIN database (United Kingdom). It is anticipated that the results will support the PRAC in its review of the signal.
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Marketing authorisation holder

Marketing authorisation holder(s)	Multiple

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List of Abbreviations

ATC: Anatomical Therapeutic Chemical, World Health Organisation classification system for drugs

ATP: adenosine tri-phosphate

AV: atrio-ventricular

BNF: British National Formulary

EMA: European Medicines Agency

EHR: Electronic Health Records

EPITT: European Pharmacovigilance Issues Tracking Tool

EU: European Union

GP: General Practitioner, Family Doctor

ICD: International Classification of Diagnosis

MAH: Marketing Authorisation Holder

PRAC: Pharmacovigilance Risk Assessment Committee

2. Responsible parties

Project lead: Karin Hedenmalm

Epidemiologist: Xavier Kurz

Clinical lead: Kevin Blake

Statistical lead: Jim Slattery and Gianmario Candore

Project sign off: Xavier Kurz

3. Rationale and background

Digoxin is a cardiac glycoside with a long history of use for heart failure and atrial fibrillation or flutter. It is also used for the treatment of paroxysmal supraventricular tachycardia. Digoxin inhibits the sodium-potassium ATP-ase in the myocardium, which causes an increase in intracellular sodium levels that result in a reversal of the action of the sodium-calcium exchanger. The net effect is an increased intracellular calcium concentration, which causes a lengthening of the cardiac action potential, a reduction in heart rate, and an increase in contractility. In addition, digoxin enhances the vagal tone, particularly at the atrioventricular (AV) node. A randomized clinical trial has shown that digoxin may be beneficial in patients with heart failure and sinus rhythm. However, there was a relationship between digoxin concentrations and mortality where higher concentrations were associated with increased mortality.

In May 2015 a signal for digoxin in patients with atrial fibrillation without heart failure was raised by Italy, based on a recently published observational study[1]. During the PRAC meeting 2-7 May, two published meta-analyses were discussed[2],[3].It was decided to conduct a data gathering exercise

[1] Freeman JV, Reynolds, K, Fang M, et al, Digoxin and risk of death in adults with atrial fibrillation: The ATRIA-CVRN study. CIRCEP 2014: 8 (1): 49-58.
[2]Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature, Eur Heart J 2015; May 4.

including a systematic literature review to inform on next steps. Separately EMA proposed to use it's in-house databases to study the use of digoxin for atrial fibrillation in patients without heart failure in the IMS databases. A renewed discussion at PRAC is scheduled to take place at the July 2015 meeting. It is anticipated that information about the extent of use of digoxin in patients with atrial fibrillation and without heart failure will inform PRAC about the size of the potential safety issue.

At the EMA's regular internal 'best-evidence' meeting in May 2015 it was decided to conduct an in-house study using electronic health record databases from IMS Health and THIN.

4. Research question and objectives

The objective of the study is to estimate the extent of use of digoxin in adult patients with atrial fibrillation without heart failure. Yearly point prevalence estimates will be calculated in relation to the total number of patients in the database with at least one consultation with a physician during the year. Results will be stratified by gender and age (less than 75 years or ≥ 75 years). The age stratification was chosen because digoxin is excreted through the kidneys and, as renal function decreases with age, the older age group reflects patients at greater risk of digoxin toxicity. It is not the objective of this study to provide estimates for the total use of cardiac glycosides in the countries included in the study. This is of particular relevance for Germany, where the majority of patients recorded in the IMS database received a cardiac glycoside other than digoxin. Because the study focuses on long-term use, and since intravenous administration of digoxin is mainly carried out in hospitals, data for intravenous use of digoxin have not been analysed.

The study aimed to provide the following data:

- The total number of patients with a digoxin prescription for oral use, and the prevalence of a digoxin prescription for oral use by age group, gender, year and country
- The number of patients with atrial fibrillation with a digoxin prescription for oral use, and the prevalence of a digoxin prescription for oral use in patients with atrial fibrillation
- The number of patients with atrial fibrillation without heart failure with a digoxin prescription for oral use, and the prevalence of a digoxin prescription for oral use in patients with atrial fibrillation without heart failure

5. Research methods in IMS

5.1. Study design

Descriptive study based on an electronic health record (EHR) database.

5.2. Setting and data sources

This analysis includes all patients receiving a prescription of digoxin for oral use, excluding products that contain digoxin in combination with another active substance, recorded in the IMS Disease Analyser in France and Germany. As very few patients received combination products, this did not have an impact on the analysis.

The study period is restricted from 1st January 2000 to 31st December 2014.

The IMS Disease Analyser database includes anonymised patient medical records from France and Germany. In France data are collected through a representative panel of general practitioners (GPs). In Germany data are collected through a representative panel of physicians working outside hospitals

[3] Ouyang A-I, Lv Y-Ni, Zhong H-L, et al, Meta-analysis of digoxin use and risk of mortality in patients with atrial fibrillation, Am J Cardiol 2015; 115: 901-906.

including internists (GPs and specialists in internal medicine) and other specialist physicians[4]; for this analysis only internists (this category of physicians in Germany includes cardiologists) have been considered.

In addition to prescription records, the databases include records of patients diagnoses, test results and demographic and lifestyle characteristics. Coding systems and extent of variables collected for medical terms and lab values differ across countries and completeness of longitudinal records is dictated by the national healthcare delivery system.

The databases used for the analysis have the following characteristics:

- IMS Health Germany database version March 2015 containing patients with data from 1992;
- IMS Health France database version March 2015 containing patients with data from 1997;

5.3. Variables

Digoxin is identified by searching for ATC code (C01A) followed by the substance name. Products that contain digoxin in combination with another active substance are not included.

Patients with atrial fibrillation are identified through the ICD code I48 (atrial fibrillation and flutter). Patients will be considered to have the indication atrial fibrillation if they have received this ICD code prior to and up to one month after the first identified digoxin prescription during the study period.

Patients with heart failure are identified through the ICD codes I11.0 (hypertensive heart disease with heart failure), I13.0 (hypertensive heart and renal disease with heart failure), I13.2 (hypertensive heart and renal disease with heart failure and renal failure), I42.0 (dilated cardiomyopathy), I50 (heart failure), and I51.7 (cardiomegaly). Patients with any of these ICD codes during the study period are excluded from the group of patients with atrial fibrillation, and the remaining patients are classified as patients with atrial fibrillation without heart failure.

All patients that have had at least one consultation with their GP/internist during the study period are identified and are considered to represent active patients in the database.

5.4. Study size

This study is a descriptive analysis of EHR data from IMS Health. No sample size or statistical precision calculation is performed.

5.5. Data management

Data extraction and management will be performed in IMS Disease Analyser; any additional analysis will be performed in SAS Enterprise Guide 6.1.

5.6. Data analysis

This analysis is descriptive in nature. In each country the following have been investigated:

- Patients 18 years or older with a prescription of digoxin for oral use by a GP/internist will be identified
- Data will be analysed by age group (below 75 years and ≥ 75 years; in the graphs the total number of patients in all age groups will also be presented for comparison), gender, year and country

[4] A comprehensive bibliography of the studies conducted with IMS Disease Analyser databases, including validation studies in selected therapeutic areas is available at:
http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/Researchers/IMS_bibliography.pdf

- Patients with a diagnosis of atrial fibrillation will be identified in the treatment indication or medical history of the patient
- Patients with a diagnosis of heart failure will be identified in the treatment indication or medical history of the patient
- The denominator for prevalence estimations will use patients who had at least one consultation with a GP/internist in the corresponding time period

5.7. Strengths and limitations of the research methods

- The IMS Disease Analyser maintains data collected through a panel of physicians in each of the study countries. Active patients have been shown to be broadly representative of the population, and are used a proxy for the population denominator in prevalence estimations. Prescription records represent the most complete set of data in IMS Disease Analyser, which strengthen the analyses at prescription level. However, prescriptions of digoxin in hospital and in settings other than GP/internist clinics in Germany and France will be missing.
- Variations in healthcare systems among individual countries
  - Registration of patients with a GP is not a requirement of the national healthcare system in France; however, GPs are increasingly regarded as the primary point of contact for patients and their records can provide substantial information on the patient's medical history managed at primary care level.
  - In Germany the national healthcare insurance system allow patients to visit a physician of choice whenever a medical need emerges, which results in possible information gaps in the patient's medical records maintained by any given physicians, including those contributing data to the German database of IMS Disease Analyser.

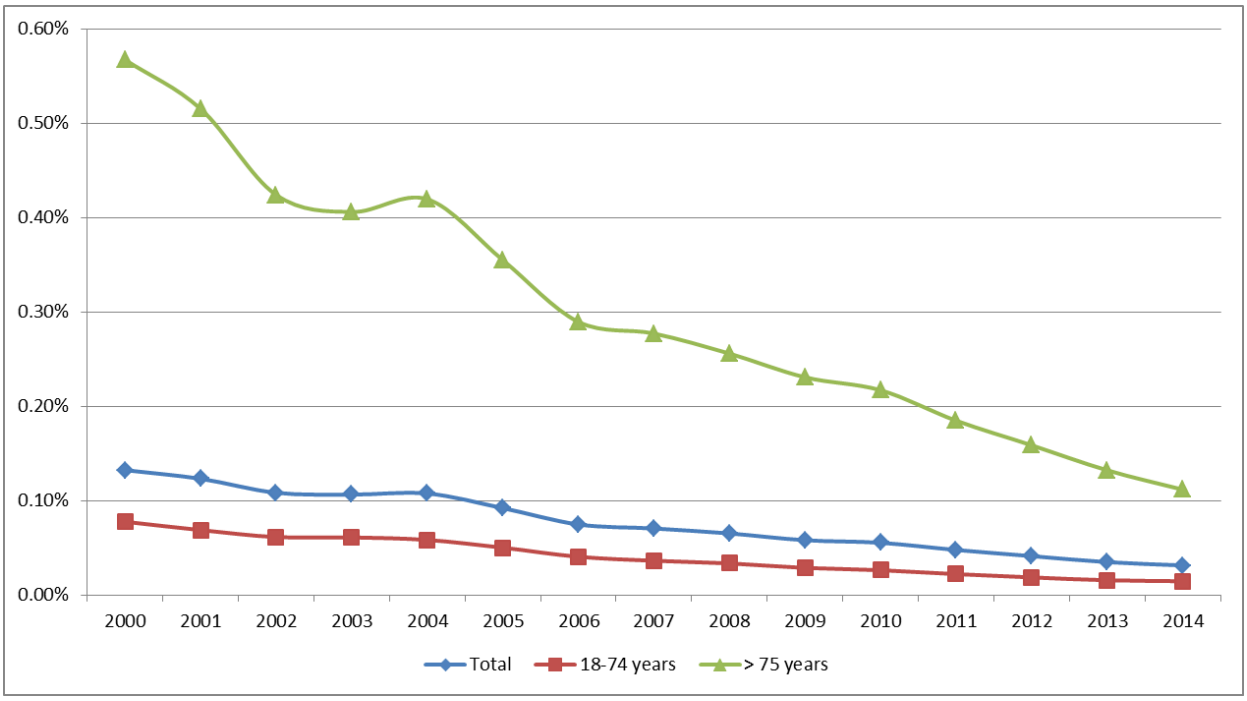
6. Results from IMS France and Germany

6.1. IMS Germany

In IMS Germany, digoxin constituted only a small proportion of the total use of cardiac glycosides (data not shown). Between the years 2000-2014, 2,471 patients were prescribed digoxin by internists, of which 188 patients had an unknown age and 13 were children 0-17 years of age. A total of 441 patients had a recorded diagnosis of atrial fibrillation/flutter (AF) without a recorded diagnosis of heart failure of which 10 patients had an unknown age. The majority of the patients, 418 of 441 (94.8%), had received the AF diagnosis prior to or up to 30 days after start of treatment with digoxin, indicating that digoxin was initiated subsequent to the diagnosis. See also table 1 in section 6.3 of the document.

The proportion of patients with a prescription of digoxin during the years 2000-2014 by age group in relation to all patients that were recorded to have been active in the database is shown in figure 1. In particular, the proportion of patients with a prescription of digoxin decreased constantly from 0.13% to 0.03%. It can also be noted how the proportion of patients with a digoxin prescription was higher in the older age group and that this age group had a much more marked decrease in the use of digoxin (from 0.57% to 0.11%) compared with the younger age group. The split by gender revealed a slightly higher proportion of prescriptions in females (data not shown).

Figure 1. Proportion of patients with a digoxin prescription - Germany



A diagnosis of AF at any time during the years 2000-2014 was identified in 324,201 patients in Germany for a point prevalence of 3.14 per 100 patients that have consulted a GP/internist. The annual proportion of patients with a diagnosis of AF by age group in IMS Germany is shown in figure 2. The trend for a diagnosis of AF slightly decreased in these years from 5,65% to 4,89%. Figure 3 shows the same information but for patients with AF without heart failure, where an increase over time among patients in the oldest age group is noted. The proportion of patients with these diagnoses is higher in the older compared with the younger age group and somewhat higher in male compared with female patients (data not shown).

Figure 2. Proportion of patients with AF – Germany

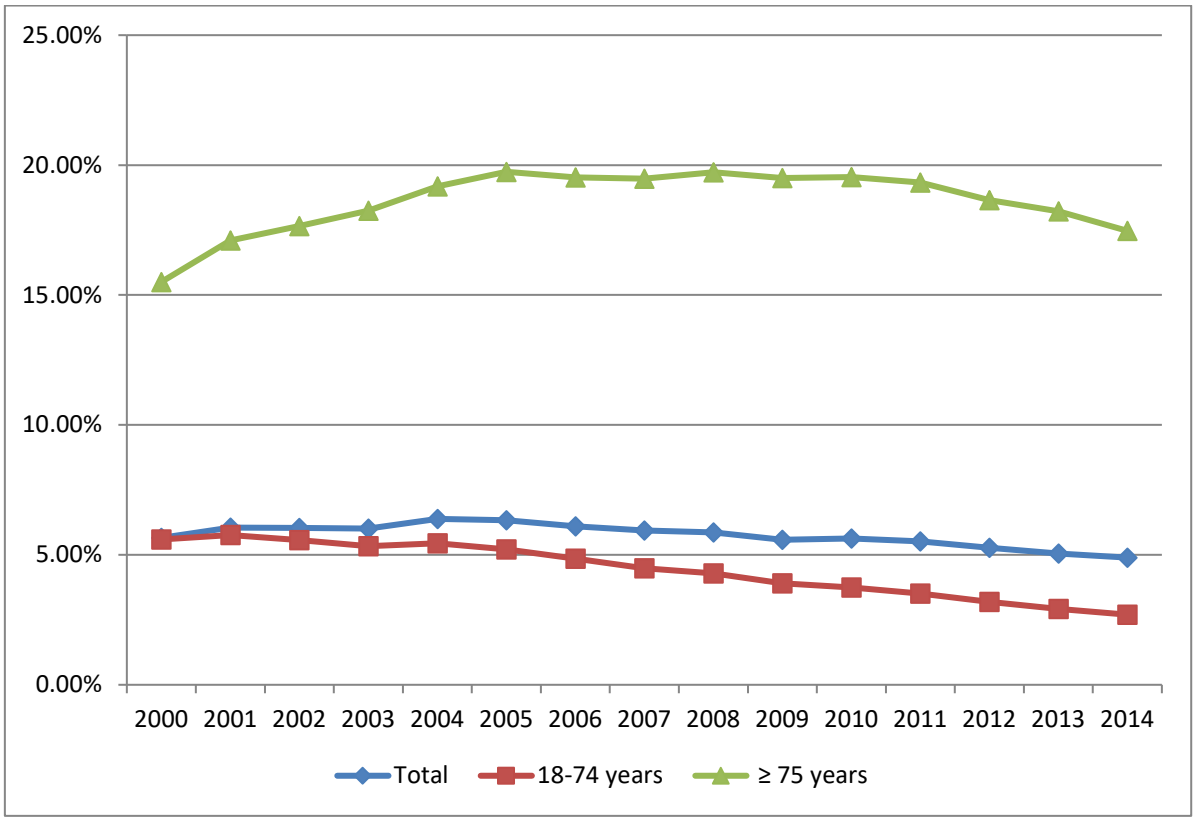
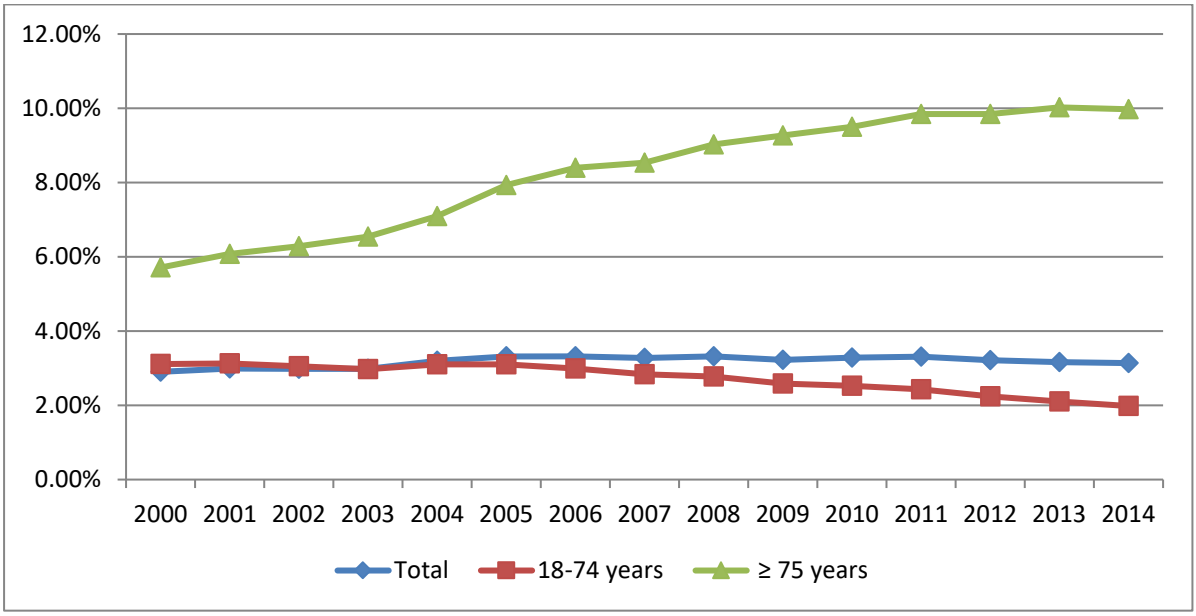


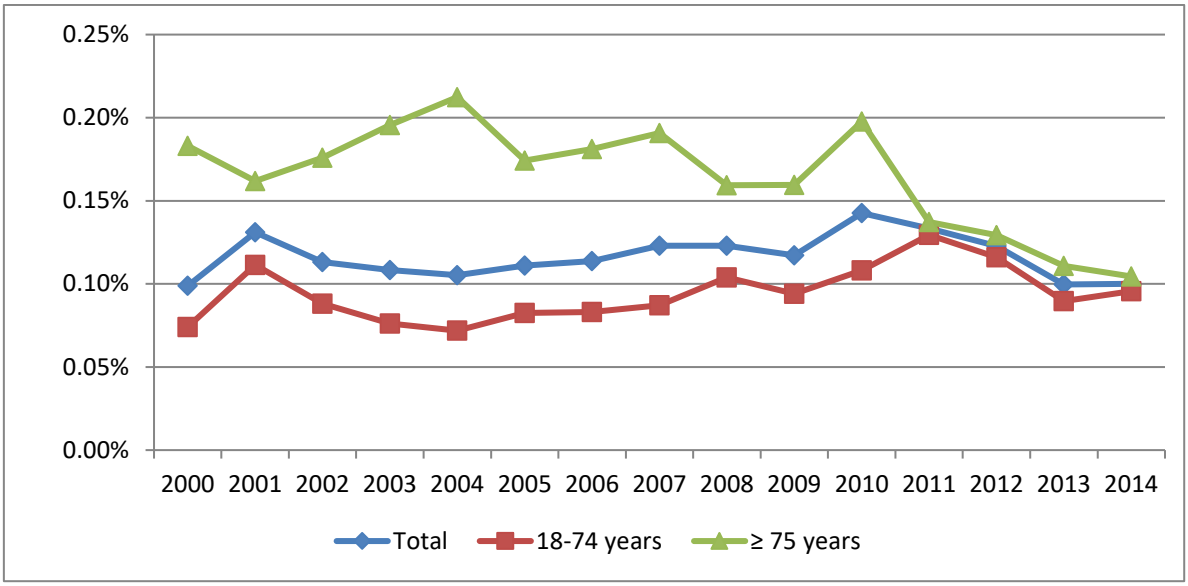
Figure 3. Proportion of patients with AF without heart failure - Germany



The proportion of patients with a digoxin prescription and a diagnosis of AF in relation to all patients that were recorded to have been active in the database has decreased from 0.02% in 2000 to 0.007% in 2014. The proportion of patients with a digoxin prescription and a diagnosis of AF without a diagnosis of heart failure in relation to all patients that were recorded to have been active in the

database has remained stable at 0.003%. See figure 4 for the proportion of patients that had a digoxin prescription out of all patients with AF without heart failure. There is no trend for a change in the proportion of patients that have a digoxin prescription out of all patients with AF without heart failure, except for patients in the older age group, where use of digoxin has approximately halved in the last years and reached the same level as in the younger age group.

Figure 4. Proportion of patients with digoxin among patients with AF without heart failure – Germany

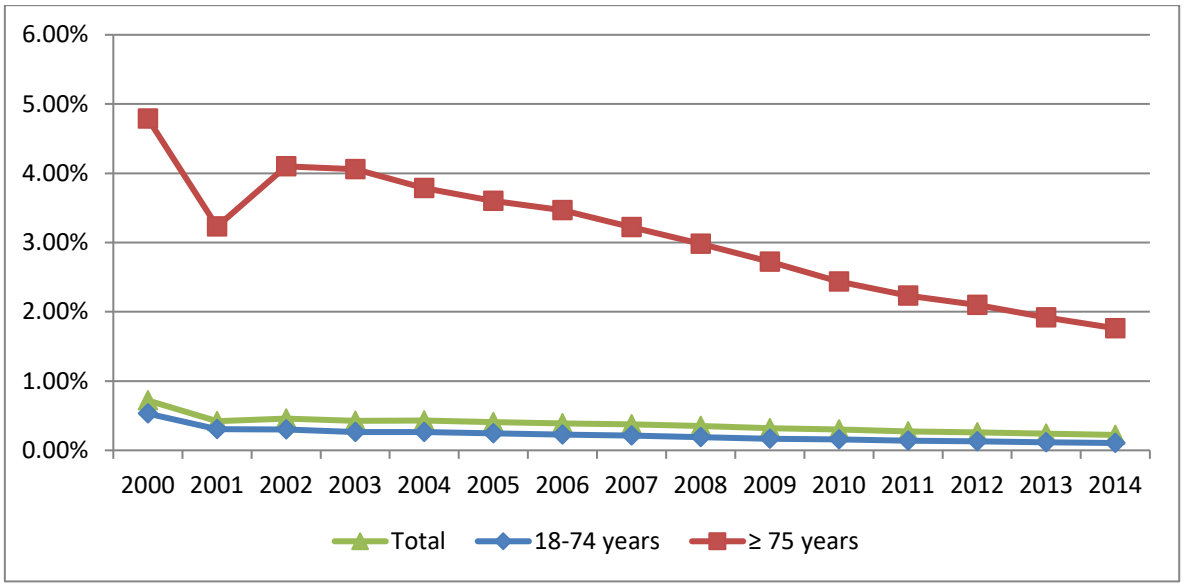


6.2. IMS France

In IMS France, prescribing of digoxin constituted most of the total prescribing of cardiac glycosides to patients (data not shown). During the years 2000-2014, 11,837 patients were prescribed digoxin by GPs of which 142 patients had an unknown age and 74 patients were children 0-17 years of age. A total of 2538 patients had AF without heart failure of which 15 patients had an unknown age and 11 patients were children 0-17 years of age. The majority of the patients (2,385 out of 2,538 patients; 94.0%) had received the AF diagnosis before or up to 30 days after start of treatment with digoxin. See also table 1 in section 6.3 of the document.

The proportion of patients with a prescription of digoxin during the years 2000-2014 split by age group in relation to all patients that were recorded to have been active in the database is shown in figure 5. The proportion of patients with a digoxin prescription in France has decreased from 0.72% to 0.22%. The highest proportion of use is recorded in the oldest age group, where use has decreased from 4.79% to 1.76%. The split by gender revealed a slightly higher proportion of prescriptions in males (data not shown).

Figure 5. Proportion of patients with a digoxin prescription – France



A diagnosis of AF at any time during the years 2000-2014 was identified in 17,109 patients in IMS France for a point prevalence of 0.44 per 100 patients that have consulted a GP. The annual proportion of patients with a diagnosis of AF by age group is shown in figure 6. A higher proportion of patients with AF is recorded in older patients, compared with the younger ones. An increase in the proportion of patients with AF from 0.20% to 0.36% in the total population is noted over the years. The largest increase, from 1.06% to 2.51%, is seen in the oldest age group. The split by gender shows a higher proportion of AF in male compared with female patients (data not shown). Similar trends are noted for AF without heart failure as shown in figure 7.

Figure 6. Proportion of patients with AF – France

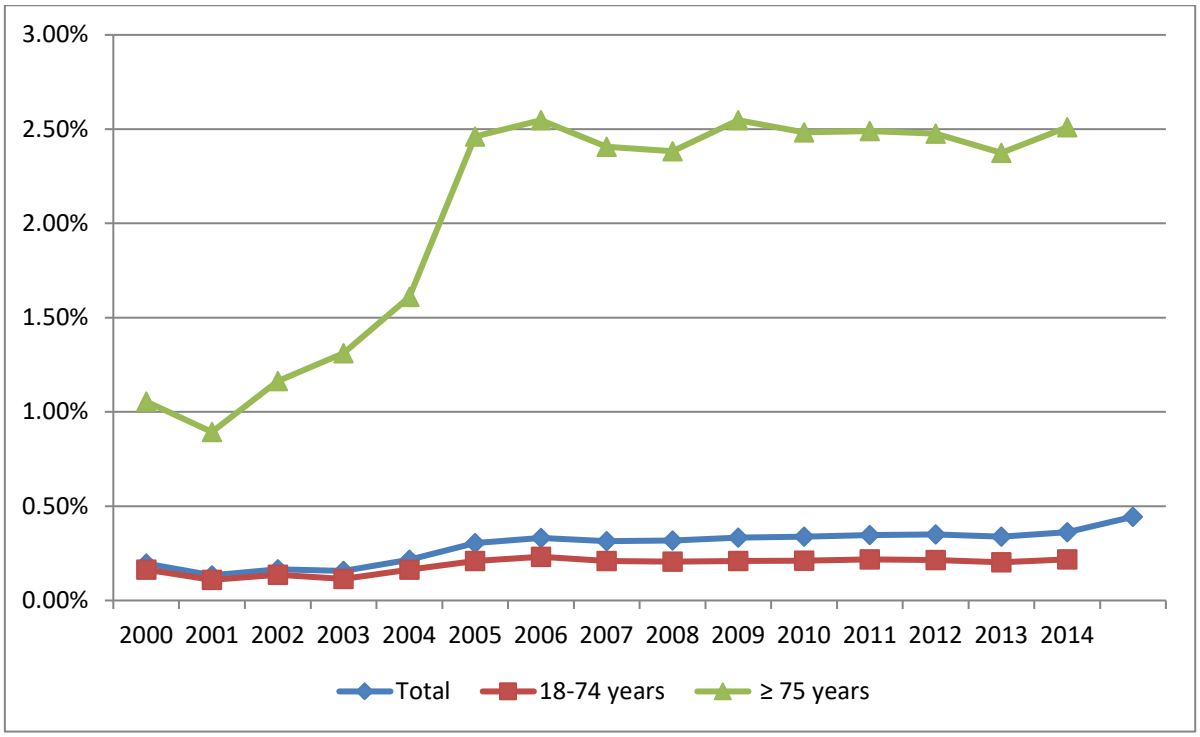
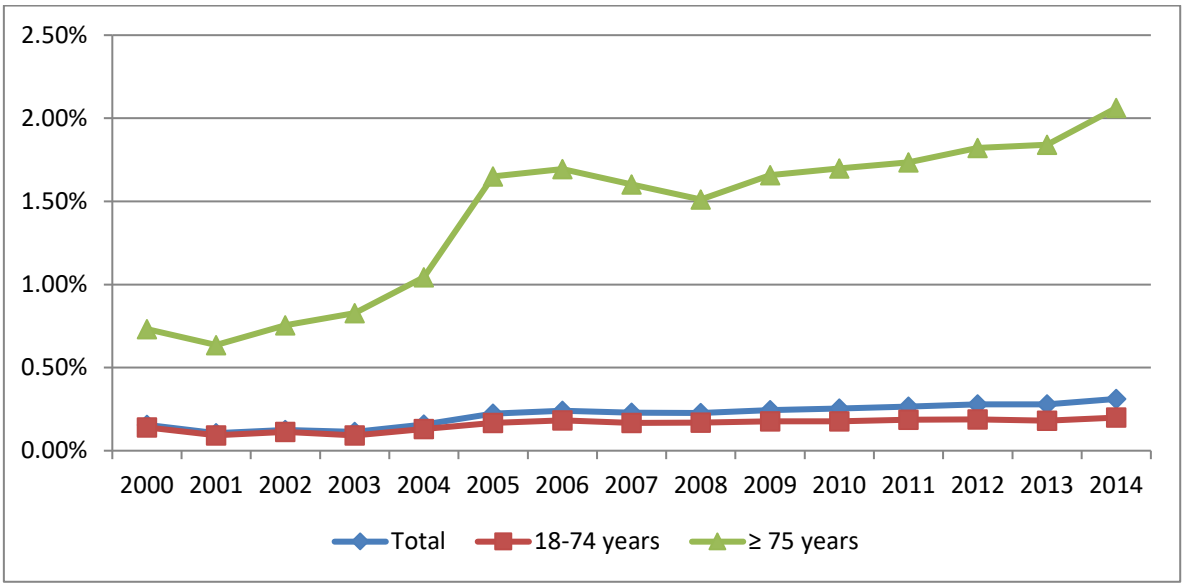
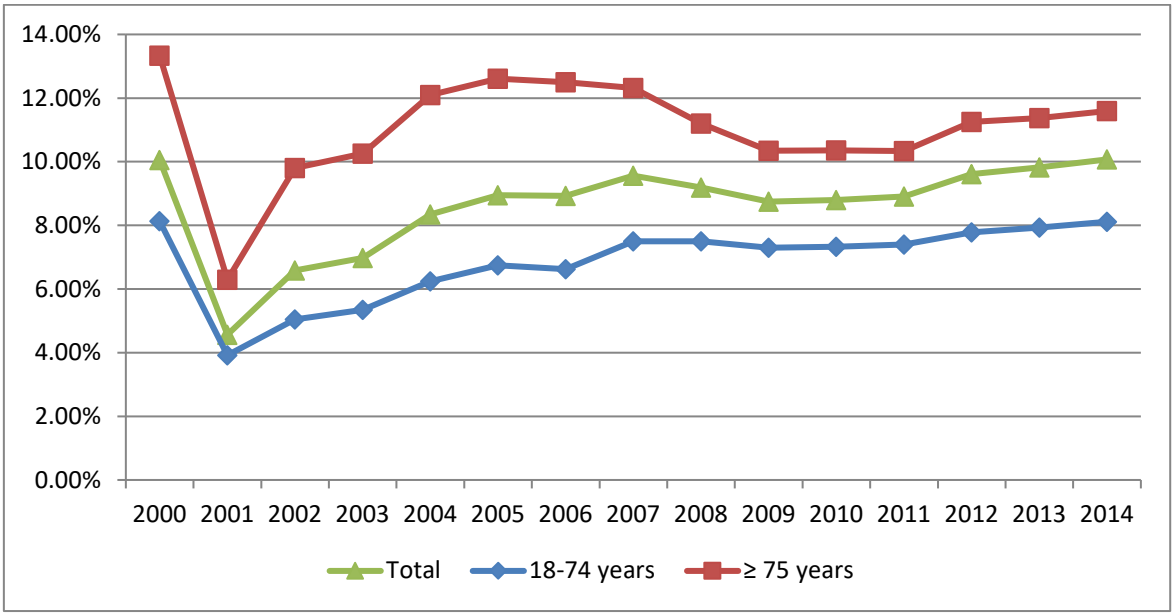


Figure 7. Proportion of patients with AF without heart failure – France



The proportion of patients with a digoxin prescription and a diagnosis of AF in relation to all patients that were recorded to have been active in the database has fluctuated between a low of 0.10% in 2014 and a high of 0.18% in 2006 with 0.14% at the beginning of the study period in 2000. Similarly, the proportion of patients with a digoxin prescription and a diagnosis of AF without heart failure in relation to all patients that were recorded to have been active in the database has fluctuated between a low of 0.06% in 2001 and 2014 and a high of 0.09% at the beginning of the period in 2000. See figure 8 for the proportion of patients that had a digoxin prescription out of all patients with AF without heart failure. Except for the first years of the study period, this proportion has remained relatively stable.

Figure 8. Proportion of patients with digoxin among patients with AF without heart failure – France



6.3. Comparison between IMS Germany and IMS France

For a comparison between the use of digoxin in IMS Germany and IMS France, please see table 1.

Table 1. Overview of adult patients with a digoxin prescription in Germany and France during 2000-2014

	Germany	**France**
No. of adult patients with a digoxin prescription (% of all active patients)	2,270 (0.02%)	11,621 (0.43%)
No. of adult patients with a digoxin prescription and AF (% of all active patients)	1,154 (0.01%)	3,583 (0.13%)
No. of adult patients with a digoxin prescription and AF without heart failure (% of all active patients)	431 (0.005%)	2,512 (0.09%)
No. of adult patients with a digoxin prescription without AF and without heart failure	498	6,105

6.4. THIN UK

6.4.1. Methods in analysis of THIN

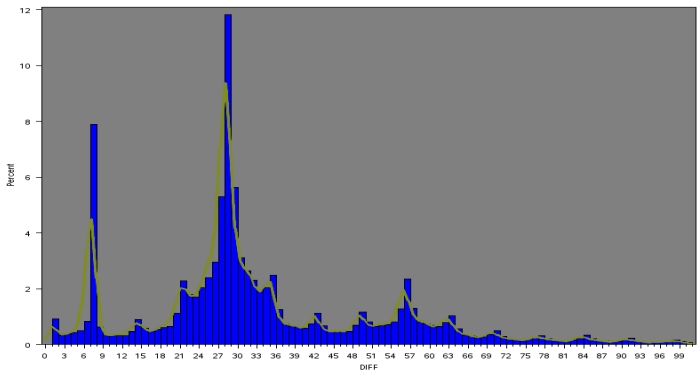
The analysis of THIN is based on the January 2014 dataset. A ten year period from 2004 to 2013 was examined. Identification of atrial fibrillation and heart failure was based on the code list given in annex 1. Indication for prescriptions is not formally coded in THIN and hence assessment of indication must be based on searches of prior medical history. In this study any patient with any previous code related to AF or HF was considered to be a prevalent case. Digoxin was identified by a search for 'digoxin' in the text field describing the medicinal products followed by manual examination of all fields in the product dictionary for the ATC codes returned by the search. Denominators for prevalences were all valid patients enrolled with THIN practices at the beginning of the year under consideration.

6.4.2. Exposure to digoxin

During the years 2004-2013, a total of 91859 patients were prescribed digoxin by general practitioners. 177 (0.19%) of these patients were aged under 18 at all prescription dates. When recorded, the commonest dosing regimen in THIN patients was 1 tablet per day and the prescribed strengths were:

Dose mcg	Frequency	Percentage
50.00	31284	0.5
62.50	1587920	24.5
125.00	3441385	53.0
250.00	1430035	22.0
500.00	2906	0.0

Intervals between prescriptions generally centred around 1 month but weekly and 2 monthly prescriptions were also observed. The histogram shows the distribution of observed intervals in days between consecutive prescriptions less than 100 days apart.

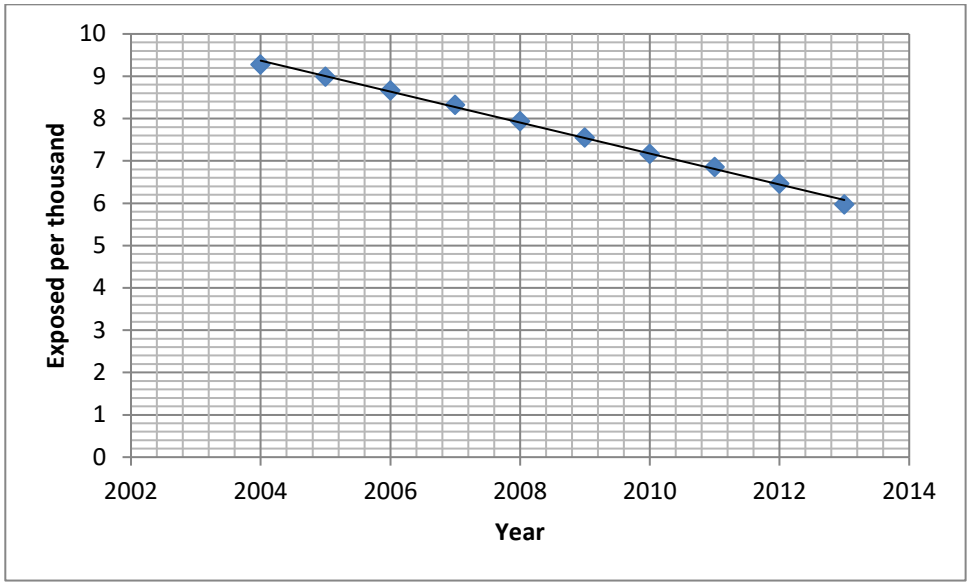


The numbers of patients receiving digoxin by year are shown in Table 1. The numbers of prescriptions is counted as the number of different dates on which prescriptions were issued. The average annual number of prescriptions varies between 8.3 and 9.7 over the years. The number of patients receiving digoxin fell from 9.3 per thousand in 2004 to 6.0 per thousand in 2013. (Fig 1)

Table 1

Year prescription	Patients	Prescriptions	Denominator 1 Jan
2004	38003	314329	4094640
2005	37317	315881	4150986
2006	36511	316288	4211761
2007	35363	316916	4245184
2008	33909	311092	4271032
2009	32293	300911	4275299
2010	30037	285467	4188258
2011	28159	271646	4106280
2012	26240	255617	4057955
2013	23681	227537	3965435

Fig 1. Exposure to digoxin in THIN UK practices (All patients)

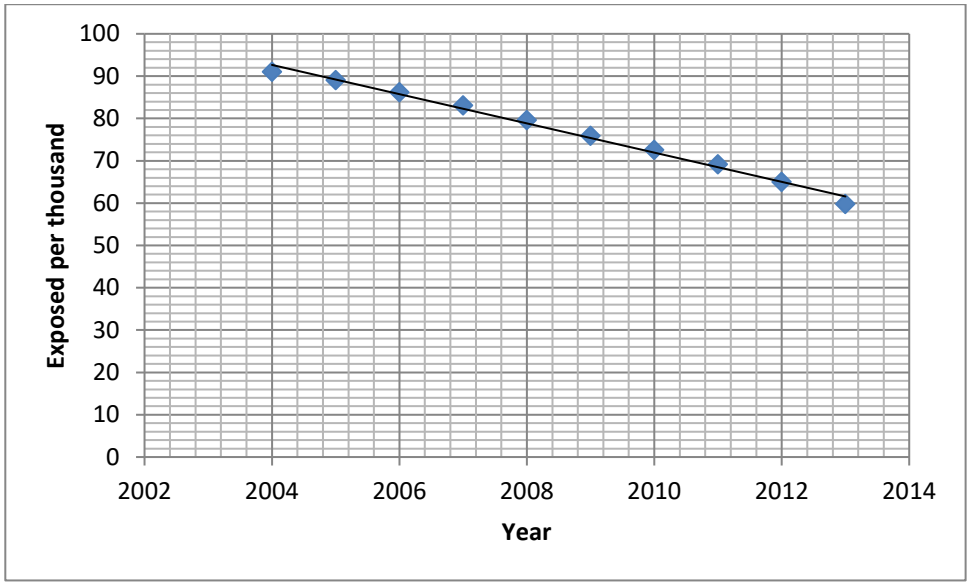


Seventy percent of patients receiving digoxin were aged 75 or over. Table 2 shows the counts of these patients and prescriptions and the start of year populations in THIN. Fig 2 shows the corresponding annual exposure rates.

Table 2 Patients aged 75 and over prescribed digoxin

Year prescription	Patients	Prescriptions	Denominator 1 Jan
2004	26149	221914	287335
2005	25846	224763	290258
2006	25402	227269	294869
2007	24816	230317	298751
2008	23922	228258	300718
2009	22896	223152	301742
2010	21458	212975	295831

Year prescription	Patients	Prescriptions	Denominator 1 Jan
2011	20243	203013	292633
2012	18871	191770	290567
2013	16997	170416	284348



6.4.3. Prevalence of atrial fibrillation and heart failure

The patients with prior records of atrial fibrillation and heart failure in THIN practices are shown in Table 3. The recorded level of atrial fibrillation has risen over the period from 2004 to 2013 but recorded heart failure has fallen from 9.7 to 9.0 per 1000.

Table 3. Prevalent Atrial Fibrillation and Heart Failure in THIN patients 2004-2013

	AF				AF per 1000		HF per 1000
	No		Yes				
	HF		HF		No HF	ALL	
	No	Yes	No	Yes			
2004	4001663	26999	53101	12877	13.0	16.1	9.7
2005	4054272	26369	57138	13207	13.8	16.9	9.5
2006	4111233	25782	61218	13528	14.5	17.7	9.3
2007	4141861	25087	64538	13698	15.2	18.4	9.1
2008	4165461	24557	67264	13750	15.7	19.0	9.0
2009	4168314	24164	69041	13780	16.1	19.4	8.9
2010	4080182	23455	71019	13602	17.0	20.2	8.8
2011	3997563	23104	71934	13679	17.5	20.8	9.0
2012	3949476	22844	71945	13690	17.7	21.1	9.0
2013	3858150	22185	71597	13503	18.1	21.5	9.0

The prevalences of both atrial fibrillation and heart failure increase with age and are higher in men than women. Table 4 shows figures for 2013.

Table 4 Prevalent Atrial Fibrillation in 2013 by Age Group and Sex

		AF				AF per 1000		HF per 1000
		No		Yes				
		HF		HF		No HF	ALL	
		No	Yes	No	Yes			
AgeGp	sex							
0 -17	M	417789	168	26	1	0.1	0.1	0.4
	F	400195	127	16	0	0.0	0.0	0.3
18-74	M	1382010	7352	20971	3137	14.8	17.1	7.4
	F	1404707	3907	11180	1200	7.9	8.7	3.6
75+	M	100130	4575	18672	4558	145.9	181.6	71.4
	F	153319	6056	20732	4607	112.2	137.2	57.7

6.4.4. Atrial fibrillation with and without heart failure in patients exposed to digoxin

Table 5 shows the counts of patients prescribed digoxin each year by whether they had prior records of atrial fibrillation and heart failure.

Table 5 Patients receiving digoxin by year, atrial fibrillation, heart failure, age group and sex

				2004		2005		2006		2007		2008		2009		2010		2011		2012		2013	
AF	**HF**	**Age Grp**	**Sex**	**PAT**	**PRSC**	**PAT**	**PRSC**	**PAT**	**PRSC**	**PAT**	**PRSC**	**PAT**	**PRSC**	**PAT**	**PRSC**	**PAT**	**PRSC**	**PAT**	**PRSC**	**PAT**	**PRSC**	**PAT**	**PRSC**
No	**No**	**0 -17**	**M**	34	161	31	175	31	151	27	154	19	109	20	103	16	111	14	108	15	114	16	107
No	**No**	**0 -17**	**F**	25	120	17	92	16	64	21	109	18	85	11	65	7	60	12	67	13	69	11	57
No	**No**	**18-74**	**M**	1307	7914	1072	6598	919	5662	841	5464	770	4829	712	4466	613	4216	537	3749	477	3446	409	2900
No	**No**	**18-74**	**F**	942	6229	802	5421	683	4515	549	3689	507	3460	445	2975	401	2846	397	2828	322	2389	315	2243
No	**No**	**75+**	**M**	1885	13591	1645	11924	1363	10114	1214	8728	1083	7974	1008	7873	928	7528	820	6899	794	6462	689	5311
No	**No**	**75+**	**F**	3700	28814	3212	24349	2803	21450	2512	20488	2309	19168	2172	18766	2049	17784	1842	15810	1654	14150	1391	11494
No	**Yes**	**0 -17**	**M**	5	29	5	29	3	20	4	24	2	16	3	27	4	26	4	39	4	27	2	15
No	**Yes**	**0 -17**	**F**	7	42	6	39	4	36	4	35	5	35	4	30	3	21	2	18	2	16	1	4
No	**Yes**	**18-74**	**M**	480	3696	418	3284	342	2963	303	2415	270	2019	241	1774	213	1636	210	1828	194	1629	163	1492
No	**Yes**	**18-74**	**F**	254	2034	212	1649	191	1386	160	1106	139	1032	137	1054	118	1026	110	942	86	718	89	721
No	**Yes**	**75+**	**M**	571	4697	464	4050	402	3211	366	3020	342	3089	306	2786	267	2453	253	2524	205	2245	187	1853
No	**Yes**	**75+**	**F**	917	8411	779	7159	658	6033	558	5353	471	4907	405	4296	365	3891	317	3269	261	2745	211	2379
Yes	**No**	**0 -17**	**M**	2	5	4	28	3	23	3	14	0	0	0	0	0	0	0	0	0	0	0	0
Yes	**No**	**0 -17**	**F**	2	17	2	14	1	7	1	9	1	13	1	13	0	0	0	0	1	9	1	6
Yes	**No**	**18-74**	**M**	4660	34229	4687	35199	4659	35426	4525	35011	4306	34106	4080	32064	3720	29569	3422	27762	3178	25506	2845	22506
Yes	**No**	**18-74**	**F**	2914	23454	2950	24168	2955	24206	2858	24141	2740	22929	2569	21214	2354	19832	2164	18723	2042	17561	1873	16072
Yes	**No**	**75+**	**M**	4932	39933	5153	42847	5406	46798	5428	49038	5395	50279	5224	48715	4926	46939	4701	45228	4444	43236	4043	38015
Yes	**No**	**75+**	**F**	7793	72289	8253	78214	8539	83510	8669	87022	8562	87633	8312	86890	7837	82765	7356	78719	6880	74652	6224	67557
Yes	**Yes**	**0 -17**	**M**	1	7	1	6	1	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Yes	**Yes**	**0 -17**	**F**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Yes	**Yes**	**18-74**	**M**	1514	12367	1540	12655	1553	12808	1534	12717	1460	12382	1390	11925	1279	11209	1232	11085	1179	10645	1128	9983
Yes	**Yes**	**18-74**	**F**	824	7024	772	6710	769	6634	727	6541	720	6679	683	6381	638	5918	578	5460	551	5243	476	4330
Yes	**Yes**	**75+**	**M**	2014	17098	2066	18110	2074	18971	2016	18971	1937	18282	1906	18666	1790	18093	1725	17725	1623	17453	1526	15720
Yes	**Yes**	**75+**	**F**	3220	32168	3226	33161	3136	32296	3043	32867	2853	32066	2664	30828	2509	29544	2463	28863	2315	27302	2081	24772
Total				**38003**	**314329**	**37317**	**315881**	**36511**	**316288**	**35363**	**316916**	**33909**	**311092**	**32293**	**300911**	**30037**	**285467**	**28159**	**271646**	**26240**	**255617**	**23681**	**227537**

The total numbers and percentages of patients receiving digoxin with records of AF and HF are shown in Table 6. The majority of these patient, rising to 63% in 2013, had AF without any recorded HF. Twelve percent in that year had no record of either AF or HF, which may suggest some under recording of the medical conditions.

Table 6

AF	HF	Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
No	**No**	N	7893	6779	5815	5164	4706	4368	4014	3622	3275	2831
		%	20.8	18.2	15.9	14.6	13.9	13.5	13.4	12.9	12.5	12.0
No	**Yes**	N	2234	1884	1600	1395	1229	1096	970	896	752	653
		%	5.9	5.0	4.4	3.9	3.6	3.4	3.2	3.2	2.9	2.8
Yes	**No**	N	20303	21049	21563	21484	21004	20186	18837	17643	16545	14986
		%	53.4	56.4	59.1	60.8	61.9	62.5	62.7	62.7	63.1	63.3
Yes	**Yes**	N	7573	7605	7533	7320	6970	6643	6216	5998	5668	5211
		%	19.9	20.4	20.6	20.7	20.6	20.6	20.7	21.3	21.6	22.0

7. Conclusions

7.1. Use of digoxin in Germany and France

The use of digoxin in Germany was very small, and the majority of patients that received a prescription for a cardiac glycoside in IMS Germany did not receive digoxin. In France, a greater proportion of patients received digoxin including a majority of patients that received a prescription for a cardiac glycoside. In both countries the use of digoxin decreased during 2000-2014, although patients with digoxin that had a diagnosis of AF without heart failure did not show the same decreasing trend. In 2014, three out of 100,000 active patients and 80 out of 100,000 active patients, respectively, had a prescription for digoxin and a diagnosis of AF without heart failure in Germany and France.

Around half of the patients that received a prescription for digoxin in Germany had a recorded diagnosis of AF vs. ca 30% in France, whereas a similar proportion of patients around 20% had a recorded diagnosis of AF without heart failure. Half of the patients that received a prescription for digoxin in France vs. ca 20% in Germany did not have a recorded diagnosis of AF and also not of heart failure, indicating that they had a different treatment indication or that the treatment indication was not accurately recorded.

A diagnosis of AF was more common among patients in the older age group and in male patients compared with the younger age group and female patients. A higher proportion of patients in Germany compared with France had a diagnosis of AF.

7.2. Use of digoxin in the UK

Although use of digoxin decreased over the period 2004 to 2013 it remains considerably higher than in Germany or France. The fairly high average numbers of prescriptions per year suggest that most patients are on long term treatment regimens.

In 2013 more than 80% of patients receiving digoxin had a diagnosis of atrial fibrillation and 60% had AF without any code indicating heart failure.

ANNEX 1 Read codes for Atrial Fibrillation and Heart Failure

medcode	Description	Category
14AN.00	H/O: ATRIAL FIBRILLATION	AF
14AR.00	HISTORY OF ATRIAL FLUTTER	AF
14V1.00	H/O: CARDIAC PACEMAKER IN SITU	AF
14V1.11	H/O: CARDIAC PACEMAKER	AF
212R.00	ATRIAL FIBRILLATION RESOLVED	AF
3264.00	ECG: ATRIAL ECTOPICS	AF
3272.00	ECG: ATRIAL FIBRILLATION	AF
3273.00	ECG: ATRIAL FLUTTER	AF
662S.00	ATRIAL FIBRILLATION MONITORING	AF
6A9..00	ATRIAL FIBRILLATION ANNUAL REVIEW	AF
793M100	PERC TRANSLUMINAL ABLATION OF ATRIAL WALL FOR ATRIAL FLUTTER	AF
793M300	PERC TRANSLUM ABLAT CONDUCT SYS HEART FOR ATRIAL FLUTTER NEC	AF
8CMW200	ATRIAL FIBRILLATION CARE PATHWAY	AF
8HTy.00	REFERRAL TO ATRIAL FIBRILLATION CLINIC	AF
8OAD.00	PROVISION OF WRITTEN INFORMATION ABOUT ATRIAL FIBRILLATION	AF
9N2b.00	SEEN BY CARDIAC PACEMAKER TECHNICIAN	AF
9Os..00	ATRIAL FIBRILLATION MONITORING ADMINISTRATION	AF
9Os0.00	ATRIAL FIBRILLATION MONITORING FIRST LETTER	AF
9Os1.00	ATRIAL FIBRILLATION MONITORING SECOND LETTER	AF
9Os2.00	ATRIAL FIBRILLATION MONITORING THIRD LETTER	AF
9Os3.00	ATRIAL FIBRILLATION MONITORING VERBAL INVITE	AF
9Os4.00	ATRIAL FIBRILLATION MONITORING TELEPHONE INVITE	AF
G573.00	ATRIAL FIBRILLATION AND FLUTTER	AF
G573000	ATRIAL FIBRILLATION	AF
G573100	ATRIAL FLUTTER	AF
G573200	PAROXYSMAL ATRIAL FIBRILLATION	AF
G573300	NON-RHEUMATIC ATRIAL FIBRILLATION	AF
G573400	PERMANENT ATRIAL FIBRILLATION	AF
G573500	PERSISTENT ATRIAL FIBRILLATION	AF
G573600	PAROXYSMAL ATRIAL FLUTTER	AF
G573z00	ATRIAL FIBRILLATION AND FLUTTER NOS	AF
G57y500	WANDERING ATRIAL PACEMAKER	AF
8A54.00	CARDIAC OUTPUT MONITORING	HF
8A54000	MONITORING CARDIAC OUTPUT USING CONTINUOUS OESOPHAG DOPPLER	HF
8A54100	MONITORING OF CARDIAC OUTPUT USING PULSE CONTOUR ANALYSIS	HF
8A54400	MONITORING OF CARDIAC OUTPUT USING ECHOCARDIOGRAPHY	HF
8B29.00	CARDIAC FAILURE THERAPY	HF
G58..00	HEART FAILURE	HF
G58..11	CARDIAC FAILURE	HF
G580.00	CONGESTIVE HEART FAILURE	HF
G580.11	CONGESTIVE CARDIAC FAILURE	HF
G580.12	RIGHT HEART FAILURE	HF
G580.13	RIGHT VENTRICULAR FAILURE	HF
G580.14	BIVENTRICULAR FAILURE	HF

medcode	Description	Category
G580000	ACUTE CONGESTIVE HEART FAILURE	HF
G580100	CHRONIC CONGESTIVE HEART FAILURE	HF
G580200	DECOMPENSATED CARDIAC FAILURE	HF
G580300	COMPENSATED CARDIAC FAILURE	HF
G580400	CONGESTIVE HEART FAILURE DUE TO VALVULAR DISEASE	HF
G58z.00	HEART FAILURE NOS	HF
G58z.11	WEAK HEART	HF
G58z.12	CARDIAC FAILURE NOS	HF
G5y3.11	DILATATION - CARDIAC	HF
G5y3000	ATRIAL DILATATION	HF
G5y3100	VENTRICULAR DILATATION	HF
G5y3200	CARDIAC DILATATION NOS	HF
G5y3300	ATRIAL HYPERTROPHY	HF
G5y3400	VENTRICULAR HYPERTROPHY	HF
G5y3411	LEFT VENTRICULAR HYPERTROPHY	HF
G5y3500	CARDIAC HYPERTROPHY NOS	HF
G5y3600	RIGHT VENTRICULAR DILATATION	HF
G5y4z00	POST CARDIAC OPERATION HEART FAILURE NOS	HF
G5yy900	LEFT VENTRICULAR SYSTOLIC DYSFUNCTION	HF
G5yyA00	LEFT VENTRICULAR DIASTOLIC DYSFUNCTION	HF
G5yyB00	RIGHT VENTRICULAR DIASTOLIC DYSFUNCTION	HF
G5yyC00	DIASTOLIC DYSFUNCTION	HF
G5yyD00	LEFT VENTRICULAR CARDIAC DYSFUNCTION	HF