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Population-Level Incidence and Monitoring of Adverse Drug Reactions with Long-term Amiodarone Therapy

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Abstract

Introduction: Amiodarone is associated with significant long-lasting adverse drug reactions (ADRs). Guidelines recommend laboratory monitoring during long-term use. However, data of compliance with laboratory monitoring is lacking.

Aims: The aim of this study was to assess laboratory monitoring of liver and thyroid function during amiodarone prescribing from 1989-2011 in the Tayside, UK, population (approximately 400,000) in relation to National guidelines recommending laboratory monitoring every 6 months. We also report the population-level incidence of abnormal liver and thyroid function in relation to total exposure of amiodarone.

Methods: Utilising well-established record linkage database, a longitudinal retrospective analysis of 1413 patients on long-term amiodarone was carried out, analysing prescribing, biochemical and clinical data.

Results: Forty-six per cent (46%), 28% and 21% of patients underwent liver, thyroid, and combined testing respectively in accordance with guideline recommendations. Thirteen per cent and 17% of patients did not have any ALT or TSH testing, respectively. During follow-up, 117 (9.5%) patients had an ALT 3xULN and 16% patients had an abnormal TSH, (n=125, <0.4mU/l and n=28, >10mU/l). One-hundred and forty patients (10%) required thyroxine replacement therapy and 40 (3%) required on hyperthyroid medication. Total amiodarone exposure increased the likelihood of abnormal biochemical testing 2.5-fold after 4 years therapy for liver and thyroid function (*p<0.0005)*

Conclusion: In this population-based study, adherence to laboratory monitoring guidelines was sub-optimal. There was a positive correlation with total amiodarone exposure and biochemical abnormalities and development of thyroid disease

compared to the general population, highlighting the need for improvement and continued amiodarone monitoring.

Keywords: amiodarone, prescribing, hepatotoxicity, monitoring, thyroid disease, adverse drug reactions

Introduction

Amiodarone is the most prescribed anti-arrhythmic drug worldwide (1), in spite of its high incidence of side effects. Its adverse effects include numerous organ toxicities with liver, thyroid, lungs and eyes being most notably affected (2). The incidence of amiodarone-induced toxicity is reported to be relatively high with thyroid toxicity in 1-22%, hepatic toxicity in 15-50% and pulmonary toxicity in 2-7%(3). Amiodarone's long half-life in conjunction with this high incidence of toxicities makes careful patient monitoring relevant(3) and cost effective(4). As such, guidelines have been developed,(5-8), recommending laboratory monitoring liver and thyroid function at baseline and then testing 6 monthly thereafter.

In the era of these recommendations, implementation of monitoring in the United Kingdom has not been previously reported. The aim of this population based longitudinal study was to assess monitoring in patients on long-term amiodarone in the Tayside population (approximately 400,000) in United Kingdom ~~Tayside~~ between 1989-2011 and to determine the incidence of abnormal liver function tests and thyroid dysfunction in relation to total exposure of amiodarone, using the record-linkage Health Informatics Centre (HIC) dispensed prescription database in Tayside.

Methods

We conducted a retrospective observational population based study of patients who had been prescribed amiodarone using record linked administrative data. Using the unique Scottish patient identification Community Health Index (CHI) number, anonymised prescription data was linked utilising the well-established Health Informatics Centre (HIC) record linkage database in Tayside to demographic and

laboratory results in order to obtain information regarding prescription and monitoring of each patient(9). Indication for amiodarone was derived from Scottish Morbidity Record General / Acute and Inpatient Day Case (SMR01) data regarding primary and co-morbid conditions (identified by ICD-9 codes until 1997 and ICD-10 codes after 1997). All data and access to the extensive clinical NHS Tayside datasets was supplied and organised by HIC. The data was accessed and analysed by a secure remote research portal, “Safehaven®”, after Caldicott approval.

Patient identification

Using the prescription-record linkage database, all patients who were prescribed amiodarone over the 22 years were identified. Long-term was defined as exposure ≥ 6 months (168 days) with regular prescriptions (time between two collected prescriptions ≤3months).

Amiodarone laboratory monitoring processes was assessed for the following:

Baseline evaluation (6 months before or one month of the first prescription)

Baseline testing was defined as blood tests 6 months before or one month after commencing amiodarone. The test with closest temporal proximity to the commencement of amiodarone was used to identify patients with abnormal liver or/and thyroid function. Patient with a baseline test 3 times the upper limit of normal (3xULN) were excluded.

Surveillance. Assessment of 6 monthly monitoring

Monitoring requirements were presumed to end once a patient stopped amiodarone medication. Frequency of testing was performed by analysing the number of biochemical tests that were performed during the duration of amiodarone therapy.

Tests performed <30 days apart were not included in analysis. A mean number of days between testing of ≤6months was classed as adequate monitoring.

Case Definitions of Laboratory Adverse Drug Reactions

The upper limit of normal (ULN) of alanine aminotransferase (ALT) was 40 U/L (Biochemistry Service, Ninewells Hospital, Dundee). 3xULN was regarded as an adverse drug reaction (ADR) for ALT.

Normal reference range for Thyroid Stimulating Hormone (TSH) was defined between 0.4 and 4.5 mU/L. Hyperthyroidism was classified as TSH <0.4mU/L and >10mU/L as overt hypothyroidism (10). TSH results from the 3 month period after starting amiodarone were excluded as TSH can transiently increase with amiodarone (11). Patients prescribed thyroxine were excluded from further analysis of biochemical abnormalities. A prescription of thyroxine (after 6 months of starting amiodarone) was deemed an ADR. For comparison, the incidence of thyroid abnormalities during amiodarone therapy was compared to that reported from a large epidemiological study from the same population (The Thyroid Epidemiology, Audit & Research Study, TEARS),(12).

Total amiodarone exposure (dose x duration) was calculated from prescription dose, frequency of dosing and number of prescriptions using SPSS statistical software (version 18, SPSS, Chicago, USA). Total exposure was calculated and grouped into years' on equivalent to 200mg daily (OD) dosing.

Statistical Analysis

Normally distributed logarithmic data was analysed with One-way ANOVA (Analysis of Variance) and post-hoc analysis (using Scheffe's method of multiple comparisons). Correlation of non-normally distributed data was analysed by Spearman's rank

correlation coefficient and non-parametric data was analysed by Chi-squared analysis. Statistical analysis was performed using SPSS statistical software (version 18, SPSS, Chicago, USA).

Results

Patient demographics:

Fig~~ure~~ 1 shows the consort figure that identified 1413 patients on amiodarone for more than 6 months between 03/01/1989 and 15/09/2011 for analysis. The patient demographics are shown in Table 1. The study population was predominantly male (57%) and elderly (mean age 71 years) with 71~~0~~% of patients treated with amiodarone 200mg OD (Table 1).

Amiodarone prescribing

Amiodarone prescribing, grouped into 5-year periods, increased from 186 (13% of the total number of patients in the study) in 1989-1994 to 489 patients (35%) in 2000-2005 (Table 2~~Fig. 2~~). Thereafter, amiodarone prescribing fell to 21% (300 patients). The indication for amiodarone was available in 1169 (83%) patients: 67% for atrial fibrillation; 9% for ventricular tachycardia; 3% for supraventricular tachycardia (unspecified); 3% for atrial fibrillation and ventricular tachycardia combined; and 1% for unspecified tachycardia. In 244 (17%) patients no diagnosis was available. The median daily dose of amiodarone was 200mg and the median total exposure dose was 14,600mg, equivalent to 1.95 years worth of 200mg OD.

Monitoring

Liver dysfunction monitoring: Of the 1413 patients, 180 (13%) patients had no ALT testing. 1233 (87%) had ALT tested at least once between one month of starting amiodarone to discontinuation and 1046 (74%) patients had more than one test. Adequate ALT monitoring occurred in 644 (46%), with ~~644 (46%) of patients were adequately monitored for ALT every 6 months.~~ 305 patients were tested for ALT yearly. The median number of days between testing was 153 days (~5 months) (range 32 days to 7.7 years).

TSH monitoring: 413 (29%) patients on thyroxine were excluded form the analysis, leaving 1000 (71%) patients not prescribed thyroxine: 172 (17%) never had thyroid function testing; 828 (83%) patients had TSH tested at least once and 623 (62%) had more than one TSH test. Of the 1000 patients studied, 277 (28%) patients were adequately monitored at least 6 monthly, 220 (22%) were monitored yearly. The median number of days between testing was 202 days (~7 months) (range 32 days – 8.3 years).

Combined ALT & TSH monitoring: 562 (56%) patients had both ALT and TSH tested. Only 211 patients were adequately monitored (21% of 1000) every 6 months; ~~.~~ 424 (42%) patients had both tests performed yearly.

The 211 patients monitored for both ALT and TSH as per guidelines were grouped into 5-year periods of when they started amiodarone (Table 2~~Fig. 2~~). Monitoring for liver and thyroid toxicity has improved over the last twenty years, from 7.5% of patients in 1989-1994, to 22.3% of patients in 2005-2011 (p<0.001).

Abnormal Laboratory Data

Abnormal ALT

966 (68%) patients had a Bbaseline ALT testing was performed in 966 (68%) patients. P18 patients with a baseline test >3xULN, n=18, and were excluded leaving 1226 patients analysed for abnormal ALT levels. 117 (9.5%) patients developed Aabnormal ALT of 3xULN occurred in 117 (9.5%) patients. 180 (13%) patients did not have ALT monitored.

Total exposure to amiodarone and abnormal ALT

The median total exposure for patients with a result >3xULN was 244,000mg (3.3 years' worth of 200mg OD) ranging from 36,800mg (184 days of 200mg OD) to 2,308,000mg (11,540 days of 200mg daily). The majority of patients were not on amiodarone for longer than 4 years' of 200mg OD equivalent, (Fig. 23). 1048 (74%) 1048 (74%) of the 1413 patients where on ≤4-years' worth of 200mg OD equivalent amiodarone, with the highest number of patients being on amiodarone for 1-years' worth of 200mg OD equivalent (382, 27%) compared to just 20 (1.4%) patients on 10-years' worth of 200mg OD equivalent. There was is a positive correlation between amiodarone exposure and percentage of patients with an abnormal result (p < 0.0005) within each year group, Fig. 23. The correlation between total exposure and percentage of patients with an abnormal result was is strongest in the first 4 years, with a 2.46-fold increase (4.7 to 11.6%) in percentage of patients between the first and fourth year of amiodarone therapy.

Abnormal TSH

1012 (72%) patients had a TSH baseline testing was performed on 1012 (72%) patients;. 33 patients had abnormal TSH at baseline and were removed from further analysis. Of the remaining patients not on thyroxine, 162 (16%) had at least one abnormal TSH, of which 125 (77%) had at least one TSH <0.4mU/L and 45 (28%)

had at least one TSH >10mU/L. The median number of days from starting amiodarone to first abnormal result was 434 (90-6832 days). The median number of days from starting amiodarone to a first suppressed TSH (defined as <0.4mU/L) was 560 days (90-3761 days). The median number of days from starting amiodarone to a high TSH (defined as> 10mU/L) was 609 days (92-4586 days). 172 (17%) patients did not have TFT tested.

Pharmacological intervention for Thyroid abnormalities

140 (10%) patients were started on thyroxine at least 6 months following initiation of amiodarone. The median number of days between starting amiodarone to first thyroxine prescription was 686 days (range 182-6553 days). 40 (3%) patients were prescribed anti-hyperthyroid medication while on amiodarone. The median number of days between starting amiodarone to first anti-hyperthyroid prescription was 951days (range 182-1545 days). The incidence of thyroid abnormalities was, higher than the background population incidence in Tayside as reported in the TEARS study (Table 3~~2~~), with a relative 9.5 and 17.5 fold increase in the incidence of hypothyroidism and hyperthyroidism respectively

Total exposure to amiodarone and abnormal TFT

Fig. 2~~3~~ shows the percentage of patients within each group that had a TSH result <0.4 or >10mU/L, and a positive correlation between years' worth of amiodarone and percentage of patients with an abnormal results ($p < 0.0005$). The correlation between total exposure and percentage of patients with an abnormal result is strongest in the first 4 years, with a 2.5-fold increase (6-15%) in percentage of patients between the first and fourth year of amiodarone therapy.

Discussion

The study provides an insight into the effect of amiodarone exposure and the attendant risks of ADRs. The results of this study show that a significant proportion of patients in the community are on amiodarone for considerably longer than one year and, importantly, the risk of LFT and TFT abnormalities increases with total exposure to amiodarone. Throughout the 22 years in Tayside that this project analysed, the majority of patients failed to have adequate monitoring in accordance with guidelines. Although monitoring improved significantly over the study period, it remained suboptimal with only 22.3% of patients being monitored adequately with comprehensive monitoring for both hepatic and thyroid dysfunction in the last 5-years of the study. Baseline testing was performed in only 68% of patients for ALT and 72% for TSH. As the prevalence of incidental abnormal ALT can be as high as 7.3%,(13), this highlights the need for more stringent baseline testing.

In contrast to previous studies mostly in the USA, demonstrating poor monitoring, this is the largest and longest study investigating amiodarone monitoring in a public healthcare service. Raebel *et al,*(14), reported monitoring in 53.3% of 1055 patients over 10 Health Maintenance Organisations over a 6-month period. Bickford *et al,(15),* found monitoring rates of 35% and 20% for ALT and TSH respectively,(16). However, of 227 initially identified patients, only 45 patients were analysed. A further study assessing guideline development for monitoring of high risk medications, including amiodarone, found that 60% and 48% had LFT and TFT monitoring, respectively over a 13-month period,(17). Other studies have demonstrated low monitoring rates, from 23-42%, however their cohorts were of less than 100 patients,(18, 19). There are differences in the monitoring rates between Tayside and the USA, possibly related to differences in healthcare systems, but notably our study spans a 22-year era before and after guideline development and reports relatively contemporary data compared to previous studies.

The median total exposure of amiodarone in our study was 1.95 years worth of 200mg OD. While previous papers have suggested that toxicity is less likely on amiodarone doses of 200mg daily,(5), our study found that total cumulative exposure of amiodarone is important, even at doses

equivalent to 200mg OD. It is worth noting that most studies reported on the effects of limited amiodarone exposure, over a relatively short time period, in contrast to ours. A prospective study of 125 patients over 5 years found than doses greater than 2.5mg/kg had a greater than 6% risk of deranged LFT's,(20), however we found that at 4-years of amiodarone at 200mg OD, the risk of having an abnormal ALT test and TSH was increased 2.5 fold, to a prevalence of 11.6%.

Our study highlights that there is a need to monitor patients for toxicity even with relatively low doses. Indeed, 9.5% of patients in Tayside had at least one ALT result >3xULN and 17% of patients had abnormal TSH results. Goldschlager *et al* reported an incidence of 15-30% for ALT >2xULN,(16), compared with 12.3% of patients in our study. One possible explanation for the difference is underreporting, as that 12% of patients in Tayside never had ALT tested. Similarly with TSH, where 17% of thyroxine naïve patients never had TSH tested. A recent large cross sectional study investigating the prevalence of prescribing and monitoring in primary care in the UK found that 42.2% of patients did not have TFT monitoring within 6 months of their start date. The prevalence noted was higher than observed in our study; however reliability of the data (derived from the intra-class correlation coefficient) was low (0.47),(21).

The clinical significance of biochemical abnormalities associated with amiodarone use is not clear. Raeder *et al* found that 52% of 217 patients developed ADRs after an average of 11.8 month of treatment, with 8.3% of patients discontinuing amiodarone. Only 19% of patients had clinically significant adverse effects, with clinical hepatitis accounting for 0.5%,(22). Although this suggests that most patients develop only mild transaminitis, the longterm consequences of mild transaminitis with continued use of amiodarone are unknown and most of the studies reporting a low incidence of severe reactions, such as hepatitis, cirrhosis or death are in short term studies,(22-24). In addition, the risk of clinically significant hepatitis being missed remains.

Ten percent of our study population required thyroxine treatment, while 3% developed overt hyperthyroidism, similar to a 612 patient sub-study of the SAFE-Trial, where 7% of study patients on amiodarone were prescribed levothyroxine with 5% of patients developed overt hyperthyroidism,(10). Nevertheless, the close monitoring of study subjects in the clinical trial program in contrast to the real world setting where 17% of patients on amiodarone never had

thyroid testing, resulting in cases thyroid dysfunction being possibly missed, suggests that there is a potential risk of underestimating thyroid dysfunction. Indeed, comparison with epidemiological data in Tayside,(13), indicates that the incidence of hypothyroidism and hyperthyroidism during amiodarone treatment is increased by 9.5 and 17.5 fold respectively (table 32) when compared to that of the background incidence,(12). The results also show that biochemical abnormalities indicative of hyperthyroidism while on amiodarone are more common than hypothyroidism, but clinically significant disease requiring pharmacological intervention is much lower.

Our results demonstrate a direct correlation between length of exposure to amiodarone and abnormal biochemical results. Previous studies have shown small correlations with duration of treatment and ADRs,(22, 24). More recently, a large 12-year study of 930 patients found that duration of treatment was the only independent predictor of adverse effect (OR 1.21 per year, p=0.016),(25). A previous meta-analysis of adverse effects of low dose amiodarone found the odds for hepatotoxicity was similar to that of the control group at 12 months,(2). Indeed, our data shows that ALT abnormalities do not commonly develop in the first year of 200mg daily amiodarone (4.7%), but importantly increases thereafter, with the number of patients with an abnormal ALT result increased 2.5-fold over the following 4-years' worth of 200mg OD equivalent dosing.

Previous studies have found that thyroid toxicity typically occurs in the first 24 months,(16). However, our study found that thyroid function abnormalities occurred later with the median number of days from starting amiodarone to biochemical hyperthyroidism and hypothyroidism being 560 days (90-3761 days) and 609 days (92-4586 days) respectively. Yet, despite the small sample sizes in the increasing exposure years, our study shows that there is a continued increase in the incidence of thyroid toxicity in this reduced cohort.

Limitations

Being a retrospective linkage study, there were several limitations including lack of access to clinical data to correlate biochemical abnormalities. This may have resulted in over-estimating

ADRs as we were unable to identify other potential causes. We were also not able to determine the incidence of other amiodarone ADRs or the clinicians' decision to continue or discontinue amiodarone, and reasons for poor monitoring. We included only incident thyroid disease by selecting patients diagnosed after 6-months on amiodarone, however, we were unable to exclude previous resolved thyroid disease. After 4-years' worth of 200mg OD dosing exposure equivalent, the relationship with biochemical abnormalities was unpredictable, possibly because of the small number of patients with prolonged exposure, resulting in fewer person years follow-up, which may also limit the comparison of incidence of thyroid abnormalities using the TEARS data.

Conclusion

This retrospective study, which we believe to be the largest and longest follow up study of amiodarone monitoring in a public healthcare service, has identified the increasing risk of developing ADRs with continued exposure to amiodarone. Although the majority of these will be of minimal significance, there remains a risk of clinical significant ADRs being missed through poor adherence to monitoring guidance, highlighting the need for improved surveillance. While monitoring practice has improved in accordance with current guidelines, there is still a shortfall in achieving safe standards, which is of particular concern, as amiodarone remains the most widely prescribed anti-arrhythmic drug worldwide. Consideration of strategies to improve monitoring in patients who are prescribed amiodarone such as the introduction of a shared care protocol between primary and secondary care or computerised prescribing prompts, which have shown to be effective,(26), may reduce amiodarone-toxicity through education and active intervention.

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Conflicts of interests (related to this work)

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Both Dr Choy and Dr Rankin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Table 1. Baseline characteristics

		n (%) patients
Gender	Male	811 (57.4%)
	Female	602 (42.6%)
Age	Mean (SD)	71.3 (11.3)
Dose/day	200mg	1003 (71.00)
	<200mg	366 (26.0)
	>200mg	44 (3.1)
Indication for starting amiodarone	AF	952 (67.4)
	VT	125 (8.8)
	SVT	39 (2.8)
	AF & VT	45 (3.2)
	Unspecified tachycardia	8 (0.6)
	No diagnosis	244 (17.3)
Duration of Therapy	Median (days)	852
	Minimum (days)	168
	Maximum (days)	8,079

Table 2: Prescribing of amiodarone & biochemical monitoring in accordance with guidelines, split in 5-year groups. There is a significant increase in prescribing over the last 22-years from 7.5% to 22.3% of patients being monitored in accordance with guidelines. (χ^2=33.1, df=3, p<0.001)

Years	Total No. of patients	No. of patients with 1 ALT & TSH test	No. of patients monitored in accordance with guidelines (%)
1989-1994	186	56	14 (7.5)
1994-2000	438	150	43 (9.8)
2000-2005	489	225	87 (17.8)
2005-2011	300	131	67 (22.3)

Table 32. Incidence of thyroid pharmacological intervention compared to the TEARS study

Patient characteristics			Hypothyroidism				Hyperthyroidism			
Age	n/patients	Person years follow-up	TEARS incidence rate (per 1000/year)	Predicted incidence (per 1000/year)	Actual incidence (per 1000/year)	Relative increase	TEARS incidence rate (per 1000/year)	Predicted incidence (per 1000/year)	Actual incidence (per 1000/year)	Relative increase
Female										
60-69	113	444	9.06	4.03	7	1.74	1.12	0.50	1	2.01
70-79	242	1002	8.84	8.86	32	3.61	1.29	1.29	11	8.51
80+	201	598	9.72	5.81	23	3.96	1.05	0.62	2	3.19
Male										
60-69	251	897	1.78	1.60	21	13.15	0.27	0.24	12	49.5
70-79	295	973	2.69	2.62	32	12.23	0.29	0.28	5	17.7
80+	124	316	4.85	1.53	11	7.17	0.45	0.14	0	-
All cases	1413	4959	2.97	14.73	140	9.5	0.46	2.28	40	17.5

Figure Legends:

Fig.1. Consort diagram depicting flow of study participants

~~Fig. 2: Prescribing of amiodarone & biochemical monitoring in accordance with guidelines, split in 5-year groups. There is a significant increase in prescribing over the last 22-years from 7.5% to 22.3% of patients being monitored in accordance with guidelines. (χ^2=33.1, df=3, p<0.001)~~

Fig 2~~3~~. Incidence~~Relationship~~ of liver and thyroid abnormalities ~~and~~ for each year~~s~~ of amiodarone exposure, defined as equivalent exposure to 200mg/day per year

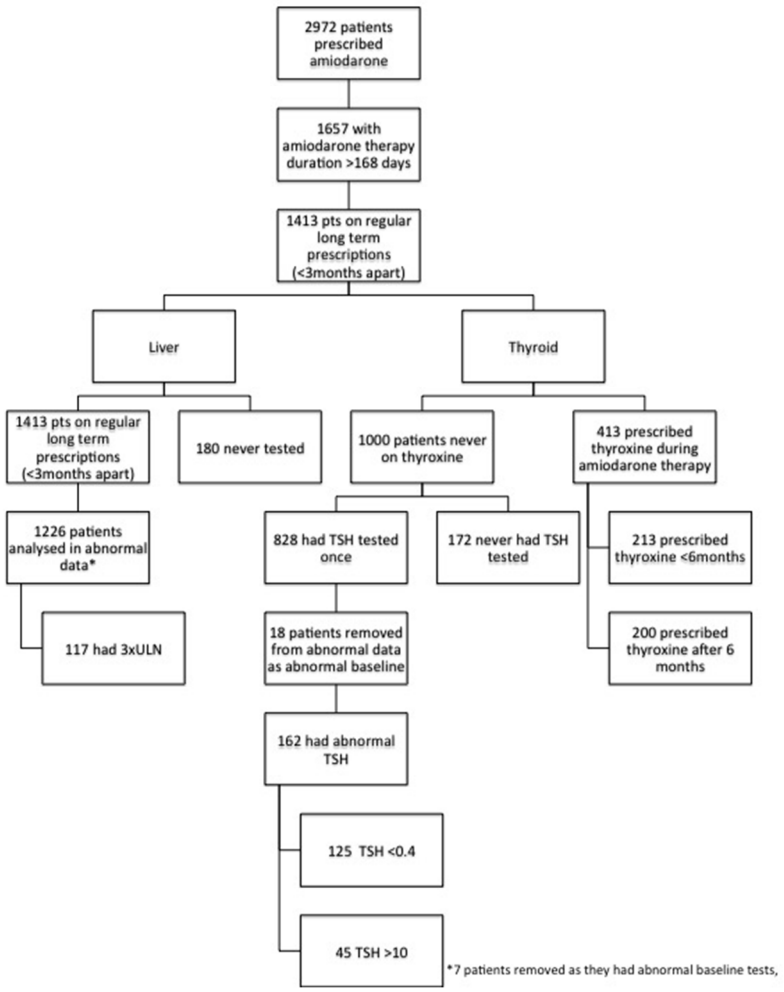

Fig.1. Consort diagram depicting flow of study participants

254x254mm (72 x 72 DPI)

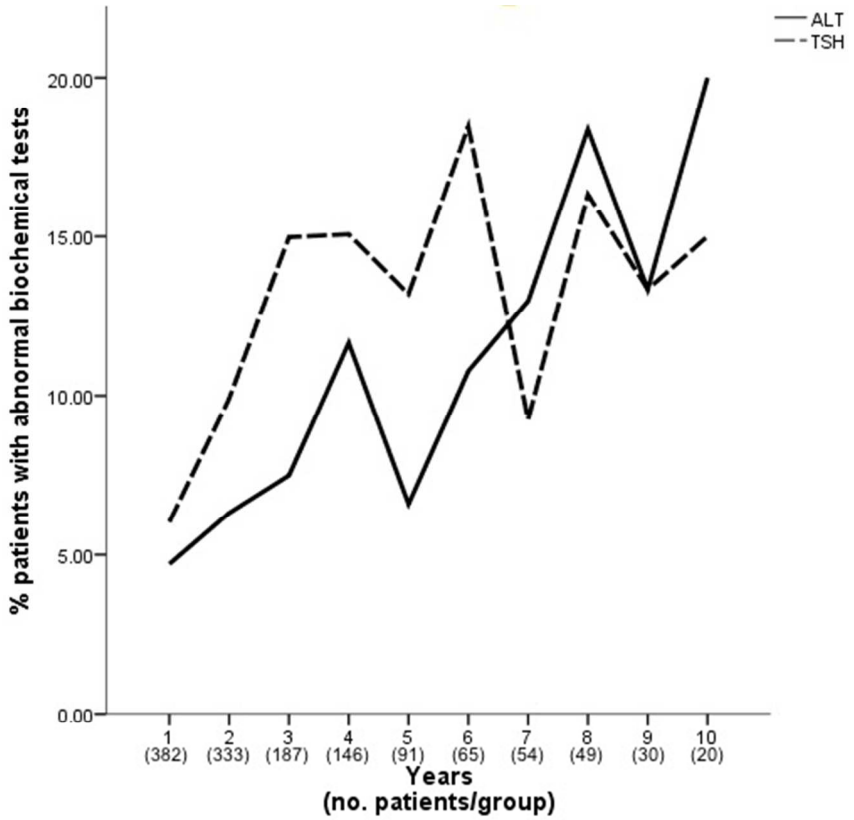

Fig 2. Incidence of liver and thyroid abnormalities for each year of amiodarone exposure, defined as equivalent exposure to 200mg/day per year

210x172mm (72 x 72 DPI)