RESEARCH

Liver and Thyroid Monitoring in Ambulatory Patients Prescribed Amiodarone in 10 HMOs

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ABSTRACT

BACKGROUND: Amiodarone can cause liver and thyroid toxicity, but little is known about compliance with laboratory tests to evaluate liver and thyroid function among ambulatory patients who are dispensed amiodarone.

OBJECTIVES: The primary objective of this study was to identify the proportion of ambulatory patients who had liver aminotransferase and thyroid function tests during amiodarone therapy. Secondary objectives were to (1) describe factors associated with receipt of laboratory tests and (2) determine the accuracy of administrative data for assessing aminotransferase and thyroid function monitoring.

METHODS: This retrospective cohort study was conducted at 10 health maintenance organizations (HMOs) for the dates of service from January 1, 1999, through June 30, 2001. Participants included 1,055 patients dispensed amiodarone for at least 180 days within this date range; these patients were not necessarily new starts on amiodarone. Administrative claims data were analyzed to assess the percentage of patients with completed alanine/aspartate aminotransferase and thyroid function tests. Depending on the HMO site, electronic or paper medical records were reviewed to evaluate the validity of administrative claims data. Logistic regression models were used to explore factors associated with receipt of laboratory tests.

RESULTS: Both aminotransferase and thyroid function tests were completed in 53.3% of patients within a 210-day follow-up period that included the 180-day period of amiodarone dispensings plus 30 days. Thyroid function, with or without liver function (aminotransferase tests), was assessed in 61.9% of patients, and aminotransferase tests, with or without thyroid function, were assessed in 68.2% of patients. After adjusting for patient characteristics and site, the factor most strongly associated with having both types of laboratory tests evaluated was concomitant therapy with a statin (adjusted odds ratio (OR) 1.55; 95% confidence interval (CI), 1.05-2.29). Other factors associated with having both types of laboratory tests evaluated included the number of outpatient visits in the 6 months before the period of amiodarone dispensings (adjusted OR 1.06; 95% CI, 1.00-1.13 for each additional 5 visits) and living in a neighborhood where a higher median percentage of people had a high school or higher education (adjusted OR 1.09; 95% CI, 1.00-1.18 for every 10% increase in educational level at the block level). There was no association between monitoring and patient illness severity as measured by the number of comorbid conditions. On the basis of an evaluation of a randomly selected subset of 104 patient records, the sensitivity and specificity of automated data were 94.2% and 85.7% for aminotransferase tests and 83.3% and 81.1% for thyroid function tests, respectively.

CONCLUSIONS: Approximately half of ambulatory patients dispensed amiodarone received both recommended laboratory tests for liver and thyroid function. Improved rates of testing for liver aminotransferase and thyroid function are needed for patients who receive amiodarone.

KEYWORDS: Amiodarone, Laboratory monitoring, Thyroid, Aminotransferase, Liver, Patient safety

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The association between amiodarone and liver, thyroid, ocular, cardiac, skin, and pulmonary adverse events has been recognized for more than 20 years.[1-8] Asymptomatic elevation of liver enzymes occurs in 5%-24% of patients prescribed amiodarone, symptomatic liver injury occurs in up to 3%,[4,9] and thyroid dysfunction (including both hyper- and hypothyroidism) occurs in 2% to 24%.[10-12] Nearly all cases of liver and thyroid function abnormalities associated with amiodarone therapy are reversible with prompt recognition and management. If thyroid dysfunction occurs or if liver enzyme elevations exceed 3 times the upper limit of normal, the amiodarone dosage should be reduced or the drug discon-

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TABLE 1 Examples of Aminotransferase and Thyroid Function Monitoring Recommendations for Amiodarone

Author (Year)	Recommended Monitoring Frequency
Aminotransferase(s)	
Wilson and Podrid (1991)[8]	Baseline, then every 3-6 months
Singh (1997)[14]	Baseline, then every 3-6 months
Hilleman et al. (1998)[18]	Baseline, then every 3-6 months
Sanoski et al. (1998)[17]	Every 3-6 months
Product labeling (1999)[16]	On a regular basis in patients on relatively high maintenance doses
Goldschlager et al. (2000)[15]	Baseline, then every 6 months
Pollak and Shafer (2004)[13]	"…Baseline, 1, 3, and 6 months, and then semiannually…"
Amiodarone (drug evaluation) (2005)[9]	"…Prior to initiating therapy…every 6 months thereafter."
Thyroid Function	
Wilson and Podrid (1991)[8]	Baseline, then every 3-6 months
Singh (1997)[14]	Baseline, then every 3-6 months
Hilleman et al.(1998)[18]	Baseline, then every 3-6 months
Sanoski et al. (1998)[17]	Every 3-6 months
Product labeling (1999)[16]	Prior to initiation and periodically thereafter
Goldschlager et al. (2000)[15]	Baseline, then every 6 months
Amiodarone (drug evaluation) (2005)[9]	Baseline, after 2-3 months of therapy and then periodically (once every few months)

tinued.[9,10] In some situations, liver enzyme abnormalities resolve spontaneously despite continuing therapy.[9]

As is true of routine laboratory monitoring of many drugs, at this time for amiodarone, it is only assumed that routine monitoring of the aminotransferase liver enzymes (alanine and/or aspartate [ALT/AST] aminotransferases) and thyroid function improves patient outcomes. Despite the lack of direct evidence linking laboratory-value monitoring to outcomes, an agreed-upon and widely recommended strategy to prevent or minimize the adverse effects of amiodarone on liver and thyroid function is to monitor aminotransferase and thyroid function in patients taking maintenance doses of the drug.[9,13-15] The manufacturers recommend in product labeling "regular" or "periodic" monitoring[10,16] of these laboratory tests for all patients prescribed amiodarone. Others (see Table 1) recommend obtaining both ALT/AST and thyroid function tests ([total and/or] free thyroxine [T4] and/or thyroid-stimulating hormone [TSH] at specific frequencies; for example, every 3 or 6 months during therapy.[7-9,13-18]

The extent to which monitoring aminotransferases and thyroid function is conducted as a patient safety measure among patients prescribed amiodarone in ambulatory practice is not well known. The few studies that evaluated liver and thyroid monitoring among patients prescribed amiodarone were conducted at single clinics and/or included fewer than 100 patients.[7,17,19] These small studies all determined that thyroid function and liver enzymes were monitored in low percentages (23%-42%) of patients.[7,17,19] The current study was therefore undertaken to determine the rates of monitoring thyroid function and liver aminotransferases among ambulatory patients dispensed amiodarone therapy across 10 sites. Secondary objectives included determining the accuracy of administrative claims data for aminotransferase and thyroid function monitoring and describing patient factors associated with monitoring. The information provided here can be used as a basis for quality improvement initiatives by individual clinicians as a reminder to monitor individual patients and by organizations to link electronic data to help ensure recommended safety monitoring in patients receiving maintenance amiodarone therapy.

Methods

This retrospective study included members of 10 health maintenance organizations (HMOs) receiving chronic amiodarone therapy, defined as continuing amiodarone dispensings for at least 180 days. Participating HMO sites included members of the HMO Research Network (HMORN) Center for Education and Research in Therapeutics (CERTs). The HMORN CERTs has been described elsewhere.[20] In brief, the HMORN CERTs organizations include staff, groups, networks, independent practice associations, and mixed-model HMOs that serve racially and ethnically diverse populations and provided health care for approximately 7 million people in more than 1,000 locations in the year 2000. The Institutional Review Board of each participating HMO approved this study.

The study sample was drawn from a dataset of 2,020,037 individuals, consisting of approximately 200,000 randomly selected health plan members from practices in each of the

TABLE 2 Sample Selection

Inclusion Criteria	Number of Patients Dropped	Number (%) of Patients Remaining
Patients dispensed amiodarone*	–	2,770 (100)
Patients with at least 6 months membership prior to the first amiodarone dispensing in the study period†	285	2,485 (89.7)
Patients with at least 2 pharmacy claims for amiodarone therapy‡	1,041	1,444 (52.1)
Patients with at least 180 days of continuing amiodarone therapy‡	389	1,055 (38.1)

** Patients who received a dispensing of amiodarone between July 1, 1999, and December 31, 2000.*
† Membership date range included January 1, 1999, through June 30, 2001, disregarding gaps of less than 60 days.
‡ The interval between prescription refills could not be greater than the dispensed days supply plus 1.5 times the dispensed days supply.

10 HMOs. The sampling scheme and demographic distribution of this population have been previously described.[21] The date range of this dataset was claims with dates of service from January 1, 1999, through June 30, 2001. We identified patients who had continuous health plan membership with pharmacy benefits during the study period, disregarding gaps of fewer than 60 days. To be included in this study, patients must have received a dispensing of amiodarone in the 18-month period from July 1, 1999, through December 31, 2000, plus continuing dispensings (with a total days supply) for at least the subsequent 180 days (Table 2). Dispensings for the subsequent 180 days were determined for each patient by the number of amiodarone dispensings to that patient multiplied by the days supply for each dispensing to that patient. Thus, each patient's follow-up period was determined by the patient's individual 180-day period of amiodarone usage. To meet the definition of continuing dispensings, no interval between prescription refills could be greater than the dispensed days supply plus 1.5 times the dispensed days supply. A dispensing gap was ignored if it was less than 1.5 times the dispensed days supply. For example, a patient dispensed a 30-day supply met the criterion of continuing dispensings if no more than 75 days (30 days + [1.5] 30 days) elapsed between the date of one dispensing and the date of the subsequent dispensing. At least 8 of the 10 participating HMOs offered mail-order pharmacy services during part or all of the study period. However, during the study time frame, only 1 or 2 offered a separate mail-order benefit (with a greater days supply).

Because each HMO had its own administrative database platform, the format and content of the claims datasets varied by site. The study dataset was extracted using a standardized work plan distributed to, and run by, research programmers at each site. At some of the sites, claims for laboratory tests provided to hospital inpatients were not included in the study dataset.

Recommended laboratory monitoring for liver aminotransferases was defined as the presence of an automated administrative claim/record of a laboratory test for ALT or AST within each patient's study evaluation period. Similarly, recommended laboratory monitoring for thyroid function was defined as the presence of an administrative record of any laboratory test for TSH, triiodothyronine (T3; total and/or free), and/or T4 (total and/or free); claims for thyrotropin-releasing hormone (TRH) were also determined; none were identified for study patients) within each patient's study evaluation period. The patient's study evaluation period for the laboratory monitoring was the same for both ALT/AST and thyroid function; that is, the 180-day period of ongoing amiodarone therapy plus a 30-day "grace period," so monitoring within 210 days was considered to be monitoring within the recommended time period. Laboratory test dates were the dates the tests were performed or the results were reported. Codes for laboratory tests were evaluated according to standard coding methods such as the Current Procedural Terminology codes or organization-specific codes and included codes for both single tests and for test panels that included one or more of the aminotransferase or thyroid function tests, including general health panel laboratory tests that include ALT, AST, and TSH (Table 3).

To assess the accuracy of the administrative claims data, we examined a random sample of medical records of study patients from the 10 sites. For purposes of this study, the medical record was considered the "gold standard," meaning that the medical record served as the basis of comparison and was assumed to be more accurate. The laboratory monitoring information contained within the medical records (i.e., the presence of laboratory test results and the dates the laboratory tests were reported) was considered the gold standard. Abstractors were instructed to review all information in the medical record for the time frame of interest (e.g., laboratory printouts, progress notes, information from outside consults, etc.) to ensure abstraction of ALT/AST or thyroid function testing.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the administrative claims data were determined in comparison with the data abstracted from the medical records. Sensitivity was defined as the proportion of patients who had an aminotransferase or thyroid function test performed that was documented in the medical record and who also had an administrative claims code for the

test. Specificity was the proportion of patients who did not have an aminotransferase or thyroid function test documented in the medical record and who also did not have a claims code for the test. The PPV was the proportion of patients who had a laboratory test conducted according to administrative data that were true positives according to the medical record. The NPV was the proportion of patients who did not have a laboratory test conducted according to administrative data that were true negatives according to the medical record.

HMO administrative claims and enrollment files were used to identify patient age on the date of first drug dispensing, gender, chronic diseases, hospitalizations (during the 6 months before and during the study period), outpatient visits, and concomitant drug therapy with a statin, a thiazolidinedione, or an anticonvulsant. These drugs were chosen because ALT/AST monitoring is also recommended when patients receive chronic therapy with any of them and patients who were receiving chronic therapy with any of these 3 drug classes could have received ALT/AST monitoring for that chronic therapy independent of amiodarone therapy monitoring.[22,23] The number of chronic diseases for each patient was determined using a calculation derived from medication information contained in the Chronic Disease Score method of Clark et al. that we refer to as CDsum.[24] With CDsum, the total number of chronic diseases is calculated on the basis of medications dispensed. For example, a patient dispensed only insulin and albuterol would be identified as having 2 chronic diseases. To evaluate characteristics that predicted lack of monitoring, hospitalizations and outpatient visits that occurred within 6 months prior to each study patient's period of continued dispensings of amiodarone were identified. Outpatient visits comprise clinic appointments, visits to the clinic laboratory, and emergency department visits. Geocoding (a standardized technique to identify the coordinates of a location when the address is known) was used to provide surrogate patient-level measures of socioeconomic status (SES). For this surrogate measure of SES, the residential street address was combined with census block-level data from the 2000 U.S. Census to construct proxies of patient race, education, and household income (poverty level).[25]

Descriptive statistics were computed to characterize patients, drug dispensings, and laboratory monitoring. Proportions of patients dispensed amiodarone who received laboratory monitoring and those who did not were tabulated overall and stratified by site, age group, sex, CDsum, outpatient visits, hospitalizations within the 6 months prior to the laboratory monitoring/ongoing amiodarone therapy period, the 3 SES variables, and concomitant drug therapy. The numbers of patients receiving concomitant therapy with amiodarone plus an anticonvulsant (n = 30) or a thiazolidinedione (n = 14) were very small and, therefore, we did not further evaluate these concomitant drugs. Statistical significance of differences was tested using the Chi-square test or Wilcoxon rank sum test.

TABLE 3 Current Procedural Terminology (CPT) Codes for Aminotransferase and Thyroid Function Tests*

Laboratory Test Type	CPT Code	Description
ALT	80050	General health panel
	80053	Comprehensive metabolic panel (2000, 2001)
	80058	Liver function panel (1999)
	80076	Liver function panel (2000, 2001)
	84460	ALT
AST	80050	General health panel
	80053	Comprehensive metabolic panel (2000, 2001)
	80054	Comprehensive metabolic panel (1999)
	80058	Liver function panel (1999)
	80076	Liver function panel (2000, 2001)
	84450	AST
TSH	80050	General health panel
	80418	Combined rapid anterior pituitary evaluation panel, includes TSH
	80439	Two hour, panel must include TSH
	84443	TSH
T4	84436	Thyroxine, total
	84439	Thyroxine, free
T3	84480	Triiodothyronine, total
	84481	Triiodothyronine, free
T3 and/or T4	80091	Total thyroxine and T3 and T4 uptake (1999)
	80092	T3, T4, and TSH (1999)
	84479	Assay of thyroid T3 or T4

** Any organization-specific codes were mapped to these standard codes at each participating HMO site.*
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HMO = health maintenance organization; TSH = thyroid stimulating hormone.

Associations between patient characteristics and laboratory monitoring were assessed using logistic regression modeling. Characteristics considered in univariate regression models included site, age group (in 5-year increments), sex, CDsum, outpatient visits, hospitalization in the 6 months prior to the laboratory monitoring/ongoing amiodarone therapy period, the 3 SES variables, and the presence or absence of concomitant therapy with a statin. We developed a generalized estimating equations (GEE) logistic regression model with HMO site as a cluster variable. The GEE model initially included those variables with $P < 0.10$ in the univariate regression models: age group, outpatient visits, poverty, education, and concomitant therapy with a statin. CDsum was not included in the GEE model because it correlated with outpatient visits (Spearman correlation coefficient = 0.39). Customary residual and influential statistics were examined to assess model fit and evaluate outliers. Analyses were conducted using SAS Version 9.1 (SAS Institute Inc., Cary, NC). The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

TABLE 4 Characteristics of Patients Dispensed Amiodarone

Characteristic	Total Patients (n = 1,055)	Aminotransferase and Thyroid Function Monitoring*		
		Yes (n = 562; 53.3%)	No (n = 493; 46.7%)	*P* Value†
Gender (%)				
Female	411 (39.0)	226 (40.2)	185 (37.5)	
Male	644 (61.0)	336 (59.8)	308 (62.5)	0.372
Median age in years (5th-95th percentiles)‡	73 (51-87)	74 (54-87)	73 (51-88)	0.115
Median number of amiodarone dispensings in the 180-day period of continuing therapy§	4 (2, 7)	4 (2, 7)	4 (2, 7)	0.02
Median number of chronic diseases (5th, 95th percentiles)‖	5 (2, 7)	5 (2, 7)	5 (2, 7)	0.138
Any hospitalization(s) during the 6 months prior to the laboratory monitoring/ongoing amiodarone therapy period (%)	416 (39.4)	232 (41.3)	184 (37.3)	0.184
Any hospitalization(s) during the laboratory monitoring/ongoing amiodarone therapy period (%)	230 (21.8)	131 (23.3)	99 (20.1)	0.205
Median number of outpatient visits (5th, 95th percentiles)¶	11 (2, 33)	13 (3, 32)	10 (1, 33)	<0.001
Socioeconomic status#				
Race (median % white; 5th, 95th percentiles)#	88 (36, 99)	87 (40, 99)	88 (29, 99)	0.930
Education (median % with high school education or better; 5th, 95th percentiles)#	88 (36, 99)	89 (67, 99)	88 (65, 98)	0.009
Poverty (median % below the federal poverty level; 5th, 95th percentiles)#	6 (1, 25)	6 (0, 23)	6 (1, 28)	0.124
Concomitant therapy with a statin (%)**	438 (41.5)	261 (46.4)	177 (35.9)	<0.001

** The numbers and percentages reported in this table reflect patients who received both ALT or AST and TSH or T4, i.e., both aminotransferase and thyroid function monitoring. The percentage of patients who received TSH or T4 (with or without ALT or AST) was 61.9%. The percentage of patients who received ALT or AST (with or without TSH or T4) was 68.2%.*

† Chi-square test or Wilcoxon rank sum test.

‡ The median age for females was 76 (57-88) compared with 72 (50-86) years for males (P <0.001).

§ The distribution of amiodarone dispensings by numbers of study patients is: ≤2 dispensings = 201 (19%) patients; 3 dispensings = 276 (26%) patients, 4 dispensings = 208 (20%) patients; 5 dispensings = 131 (12%) patients; ≥6 dispensings = 239 (23%) patients.

‖ As calculated from CDsum, the total number of chronic diseases calculated from the medications dispensed.

¶ During the 6 months prior to the laboratory monitoring/ongoing amiodarone therapy period evaluated.

 # Among patients in this study, in each block where the patients lived, the median percentage of individuals of white race was 88%, the median percentage of individuals with a high school education or higher was 88%, and the median percentage of individuals living below the federal poverty level was 6%.

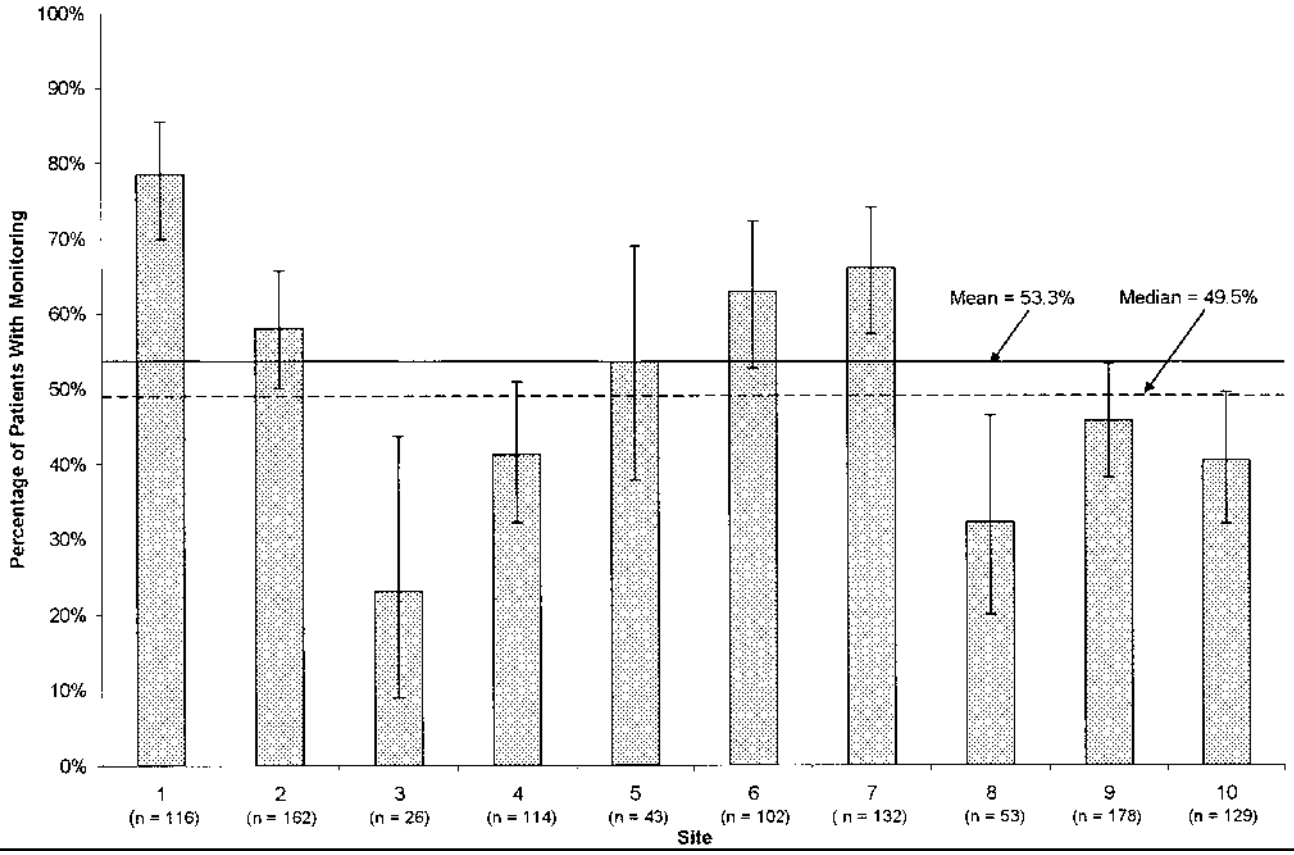
*** Statins include atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin.*

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TSH = thyroid stimulating hormone; T4 (thyroxine).

Results

We identified 1,055 patients who met the study eligibility criteria for chronic amiodarone therapy (Tables 2 and 4). Both thyroid function and liver aminotransferases were monitored in 53.3% of patients (95% confidence interval [CI], 50.2%-56.3%). The 10 participating HMO sites had significant variability in monitoring, with a range across sites from 23.1% to 78.4% of patients monitored (Figure 1). Liver aminotransferases were monitored in 68.2% of patients (95% CI, 65.3%-71.1%), and thyroid function tests were monitored in 61.9% of patients (95% CI, 58.9%-64.8%). Among all patients with thyroid tests evaluated, thyroid function monitoring comprised 97.2% TSH tests and 2.8% T4 tests. Patients with and without monitoring did not differ in age, sex, estimated number of chronic diseases, hospitalization, or poverty level (Table 4). When patient characteristics and site were controlled, only 3 factors were associated with monitoring: concomitant therapy with a statin (crude odds ratio (OR), 1.55; 95% CI, 1.21-1.98; adjusted OR, 1.55; 95% CI, 1.05-2.30), number of outpatient visits in the 6 months before the period of ongoing amiodarone dispensings (crude OR, 1.07; 95% CI, 1.01-1.14; adjusted OR, 1.06; 95% CI, 1.00-1.13 for each additional 5 visits), and living in a neighborhood where a higher median percentage of people had a high school or higher education (crude OR, 1.15; 95% CI, 1.02-1.28; adjusted OR, 1.09; 95% CI, 1.00-

FIGURE 1 *Liver Aminotransferase and Thyroid Function Test Monitoring by HMO Site*



HMO=health maintenance organization.

1.18 for every 10% increase in educational level at the block level) (scaled deviance = 1.370). There were no overly influential or outlying observations. The effect of clustering by site was small (exchangeable working correlation = 0.056).

Medical records of 104 study patients prescribed chronic amiodarone therapy were abstracted. The sensitivity, specificity, PPV, and NPV of the administrative claims in comparison with the abstracted medical records for ALT/AST and thyroid function monitoring were good to excellent as shown in Table 5.

Discussion

We found that only about one half (53.3%) of patients receiving ongoing therapy with amiodarone had laboratory tests conducted to assess liver injury and thyroid function during an approximately 7-month period. The laboratory test findings from administrative claims data in our study were validated with medical record review. We demonstrated that administrative claims records at these sites were sufficiently sensitive and specific to be useful in determining whether laboratory testing was conducted.

Our finding that many patients prescribed amiodarone do not have recommended laboratory monitoring is important. However, the percentage of patients with laboratory monitoring in our study is actually higher than the 23% to 42% of patients documented as monitored in the small number of other published abstracts and studies.[7,17,19]

Stelfox et al. found that increases in comorbidity were associated with a lower likelihood of monitoring.[7] We found no association between monitoring and the surrogate measure we used to determine the number of comorbid conditions, that is, CDsum, but these differing findings may not be directly comparable because Stelfox used a different measure of comorbidity than that used in our study (Charlson Comorbidity Index in the Stelfox et al. study and CDsum in the present study).[7] Similar to Stelfox et al., we found no association between monitoring and patients' age or sex.[7]

In our study, the factor most strongly associated with a higher rate of monitoring was concomitant therapy with a statin, a drug for which ALT/AST monitoring is also recommended; patients treated with a statin had a 55% greater likelihood of receiving monitoring of both liver enzymes and thyroid function. We found

TABLE 5 *Accuracy of Administrative Claims Data in Comparison to the Medical Record* for Assessing Prevalence of Liver Aminotransferase and Thyroid Function Test Monitoring*

Measure of Validity*(n = 104 Medical Records)	% (Range Across Sites)	
	Alanine/Aspartate Aminotransferase	Thyroid Function Tests†
Sensitivity (%)	94.2 (77.8-100)	83.3 (42.9-100)
Specificity (%)	85.7 (50.0-100)	81.1 (50.0-100)
Positive predictive value (%)	92.9 (71.4-100)	88.7 (66.7-100)
Negative predictive value (%)	88.2 (33.3-100)	73.2 (33.3-100)

** The research design defined the medical record as the benchmark for determination of monitoring of amiodarone side effects via laboratory tests. For example, sensitivity was defined as the proportion of patients who had an aminotransferase (or thyroid function) test conducted that was documented in the medical record, who also had an administrative claims code for the test. Specificity was the proportion of patients who did not have an aminotransferase (or thyroid function) test documented in the medical record who also did not have a claims code for the test. The positive predictive value was the proportion of patients who had the laboratory test conducted, according to administrative data, who were true positives according to the medical record. The negative predictive value was the proportion of patients who did not have the laboratory test conducted, according to administrative data, who were true negatives according to the medical record.*

† Thyroid function tests = thyroid-stimulating hormone (TSH), thyroxine (T4), or triiodothyronine (T3).

little association between monitoring rates and socioeconomic factors. These data should be interpreted with caution because we were limited by the lack of patient-level data. Although we found significant differences in educational level of those monitored compared with those who were not monitored, the absolute differences were very small.

The incidence of amiodarone-associated adverse events is dependent on both dose and duration of therapy, with risk believed primarily to exist with daily dosages exceeding 400 mg and durations of therapy exceeding 10 to 12 months[4,9,26] Most adverse effects are mild, but toxicity of sufficient severity to require discontinuing amiodarone has been reported in up to one fourth of patients.[9,10] Liver injury with amiodarone includes, very rarely, acute hepatitis (only 13 cases reported through 2002) and liver failure (<5 reported cases),[9,10,27-29] but the liver injury seen most often is symptomatic (<3% of patients) or asymptomatic (up to 24% of patients), sometimes transient, abnormal elevation of ALT and/or AST.[7,10] Because both clinical liver disease and fatalities have occurred with amiodarone use,[28,29] patients receiving amiodarone are recommended to have routine ALT/AST monitoring. Persistent elevations in liver enzymes alert clinicians to weigh the risks and benefits of amiodarone dosage reduction or discontinuation—often weighing the risk of sudden cardiac death against the risk of liver toxicity. An elevation of ALT/AST of 2 to 3 times the upper limit of normal, or a doubling of the ALT/AST in a patient with an elevated baseline value, is cited as the level above which amiodarone dosage reduction can be appropriate.[10,19] Withdrawal of the drug does not guarantee prompt reversal of organ toxicity, however, because tissue concentrations of amiodarone persist for weeks to months following drug withdrawal; during long-term oral administration, the mean half-life following cessation of therapy is 40 to 49 days.[9,30]

Both hyper- and hypothyroidism are associated with amiodarone therapy and can develop in normal thyroid glands as well as in glands with preexisting abnormalities.[10] The amiodarone molecule contains large amounts of inorganic iodine (a 600 mg per day amiodarone dosage provides 225 mg of iodide) and amiodarone-induced thyrotoxicosis occurs due to either iodine-induced excessive thyroid hormone synthesis or to a thyroid destructive process caused by the drug or iodine.[10] Amiodarone inhibits peripheral conversion of T4 to T3 with resulting increases in both serum T4 and reverse T3 accompanied by a reduction in serum T3.[10] The majority of patients remain euthyroid despite these biochemical changes, and it is important to specifically evaluate serum TSH levels to determine whether thyroid dysfunction is present. We found that the vast majority (97.2%) of the thyroid function tests obtained in patients in our study were TSH tests.

Hyperthyroidism occurs in about 2% of amiodarone-treated patients, with a higher incidence in patients with prior inadequate dietary iodine.[9] Hyperthyroidism can be especially hazardous in the patient population prescribed amiodarone because of the possibility of arrhythmia breakthrough or aggravation.[31,32] Hyperthyroidism associated with amiodarone therapy has occurred anywhere from 1 to 73 months after initiation of therapy and with amiodarone dosages ranging from 200 to 600 mg per day; thus, ongoing monitoring is important.

Limitations

A potential limitation to our study was that we primarily used health plan administrative claims data to determine whether laboratory tests were completed, and some would argue that the medical record is the more accurate source of this information. However, the sensitivity and specificity of the claims data were shown to be good to excellent for documenting completion of

these tests. Also, it is possible that not all medication dispensing or laboratory testing was captured by the HMO data systems. For example, 21.8% of the patients in this study were hospitalized during the study period. The patients who were dispensed amiodarone therapy and who were hospitalized during the study follow-up period may have received laboratory tests for aminotransferase and/or thyroid function during the hospitalization that were not captured in the data available to us because laboratory tests completed during hospitalizations were contained in the dataset for only some of the participating sites. Therefore, our measured rates of laboratory monitoring may underreport actual rates of monitoring. However, if the laboratory testing information was not available in the dataset, as evidenced by the good negative predictive value (Table 5), the laboratory testing information was also not available in the medical record and therefore not available to the prescriber to use in managing the ambulatory medical care of the patient.

Aside from the missing data for laboratory monitoring that may have occurred during a hospital stay in the follow-up period, the administrative claims data used in this study are sufficiently accurate to be useful to assess laboratory monitoring. As is true of all studies where prescriber intent is not directly determined, we could not separate laboratory tests conducted for the purpose of assessing the potential toxicity of amiodarone from laboratory tests conducted for other reasons that had nothing to do with amiodarone therapy. Further, we did not have information on amiodarone dosage and could not evaluate whether monitoring was associated with higher daily drug dosages or if dosages were adjusted based on laboratory results. Although we do not know the percentage of abnormal test results among patients in this study, we believe it would be similar to previously published percentages.[4,9-12] In a randomized intervention trial conducted during 2003 at one of the sites that participated in the current study, 15% of patients who were prescribed amiodarone and who received thyroid and/or aminotransferase laboratory testing as a result of the study intervention had abnormal test results.[33]

There is the possibility that some patients were misclassified as continuing on amiodarone therapy. On the basis of the study definition of continuing dispensings, patients with as few as 2 dispensings of amiodarone in the 180-day dispensing period were included (Table 4). For example, a study patient with only 2 dispensings could have had dispensings of amiodarone for a 90-day supply on day 1 and day 91, and discontinued therapy for some reason on day 92.

We found variation in monitoring by HMO site (Figure 1). These HMOs differ in potentially critical patient and system factors, including geographic location, race and ethnicity of members, availability of an electronic medical record, and types and extent of clinical pharmacy programs, patient safety programs, and receipt of care from multispecialty clinics. This project was not designed to explore why one participating HMO had better rates of monitoring of ALT/AST and thyroid function than did another. However, it may be useful to understand, for example, how the characteristics of the HMO where 23.1% of patients dispensed amiodarone had ALT/AST and thyroid monitoring differed from the HMO where 78.4% of patients received monitoring (Figure 1). Knowledge of organizational characteristics and programs would augment our ability to implement decision support systems or other systematic mechanisms to assist in ensuring recommended safety monitoring in patients receiving amiodarone. It is also important to recognize that these data were collected 5 to 6 years ago, and the rates of monitoring for adverse effects associated with amiodarone therapy may be different today, although monitoring recommendations do not differ from those published 5 to 6 years ago.

Conclusions

The percentage of ambulatory patients who are prescribed amiodarone and who receive monitoring of liver enzymes and thyroid function needs improvement. Automated, administrative claims data can be appropriate to evaluate the prevalence of aminotransferase and thyroid function monitoring, but this source of information has limitations that should be recognized.

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DISCLOSURES

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REFERENCES

1. Harris L, McKenna WJ, Rowland E, Krikler DM. Side effects and possible contraindications of amiodarone use. *Am Heart J.* 2005;106:916-23.

2. Pollak PT. Oral amiodarone: historical overview and development. *Pharmacother.* 1998;18(6 pt 2):121S-126S.

3. Mechlis S, Lubin E, Laor J, et al. Amiodarone-induced thyroid gland dysfunction. *Am J Cardiol.* 1987;59:833-35.

4. Lewis JH, Ranard RC, Caruso A, et al. Amiodarone hepatotoxicity: prevalence and clinicopathologic correlations among 104 patients. *Hepatology.* 1989;9:679-85.

5. Martino E, Safran M, Aghini-Lombardi F, et al. Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy. *Ann Intern Med.* 1984;101:28-34.

6. Trip MD, Wiersinga W, Plomp TA. Incidence, predictability, and pathogenesis of amiodarone-induced thyrotoxicosis and hypothyroidism. *Am J Med.* 1991;91:507-11.

7. Stelfox HT, Ahmed SB, Fiskio J, Bates DW. Monitoring amiodarone's toxicities: Recommendations, evidence, and clinical practice. *Clin Pharmacol Ther.* 2004;75:110-22.

8. Wilson JS, Podrid PJ. Side effects from amiodarone. *Am Heart J.* 1991; 121:158-71.

9. Anonymous. Amiodarone (drug evaluation). Klasco RK. DRUGDEX System (electronic version); 2005. Greenwood Village, CO: Thomson Micromedex; 2005.

10. Pacerone tablets (Upsher-Smith). *Physician's Desk Reference* (electronic version); 2003. Greenwood Village, CO: Thomson Micromedex; 2003.

11. Harjai KJ, Licata AA. Effects of amiodarone on thyroid function. *Ann Intern Med.* 1997;126:63-73.

12. Gittoes NJL, Franklyn JA. Drug-induced thyroid disorders. *Drug Saf.* 1995;13:46-55.

13. Pollak PT, Shafer SL. Use of population modeling to define rational monitoring of amiodarone hepatic effects. *Clin Pharmacol Ther.* 2004;75:342-51.

14. Singh BN. Amiodarone: the expanding antiarrhythmic role and how to follow a patient on chronic therapy. *Clin Cardiol.* 1997;20:608-18.

15. Goldschlager N, Epstein AE, Naccarelli G, Olshansky B, Singh B, for the Practice Guidelines Subcommittee, North American Society of Pacing and Electrophysiology. Practical guidelines for clinicians who treat patients with amiodarone [special article]. *Arch Intern Med.* 2000;160:1741-48.

16. Cordarone (Wyeth Laboratories). *Physician's Desk Reference.* 54th ed. Montvale, NJ: Medical Economics Company, Inc.; 1999:3283-86.

17. Sanoski CA, Schoen MD, Gonzalez RC, Avitall B, Bauman JL. Rationale, development, and clinical outcomes of a multidisciplinary amiodarone clinic. *Pharmacotherapy.* 1998;18 (6 pt 2):146S-151S.

18. Hilleman D, Miller MA, Parker R, Doering P, Pieper JA. Optimal management of amiodarone therapy: efficacy and side effects. *Pharmacotherapy.* 1998; 18(6 pt 2):138S-145S.

19. Just VL, Williams RE. Improving the safety of amiodarone in the congestive heart failure population: baseline assessment of compliance with national guidelines in a large CHF clinic [abstract]. *Value Health.* 2002;5:126. Abstract HP3.

20. Chan KA, Davis RL, Gunter MJ, et al. The HMO Research Network. In: Strom BL, ed. *Pharmacoepidemiology.* 4th ed. Chichester, UK: John Wiley & Sons, Ltd.; 2005:261-69.

21. Chan KA, for the HMO Research Network CERTs Patient Safety Study Investigators. Development of a multipurpose dataset to evaluate potential medication errors in ambulatory settings. In: Henriksen K, Battles JB, Marks ES, Lewin DI, eds. *Advances in Patient Safety: From Research to Implementation.* Rockville, MD: Agency for Healthcare Research and Quality; 2005.

22. McEvoy GK, ed. *AHFS Drug Information (2004).* Bethesda, MD: American Society of Health-System Pharmacists, Inc.; 2004.

23. Klasco RK. DRUGDEX System (electronic version); 2006. Greenwood Village, CO: Thomson Micromedex. Available at: http://www.thomsonhc.com. Accessed: October 12, 2005.

24. Clark DO, Von Korff M, Saunders K, Baluch WM, Simon GE. A chronic disease score with empirically derived weights. *Med Care.* 1995;33:783-95.

25. Kreiger N, Chen JT, Waterman PD, Soobader MJ, Subramanian SV, Carson R. Geocoding and monitoring US socioeconomic inequalities in mortality and cancer incidence: does choice of area-based measure and geographic level matter? The Public Health Disparities Geocoding Project. *Am J Epidemiol.* 2002;156:471-82.

26. Vorperian VR, Havighurst TC, Miller S, et al. Adverse effects of low dose amiodarone: a meta-analysis. *J Am Coll Cardiol.* 1997;30:791-98.

27. Bravo AER, Drewe J, Schlienger RG, Krahenbuhl S, Pargger H, Ummenhofer W. Hepatotoxicity during rapid intravenous loading with amiodarone: Description of three cases and review of the literature. *Crit Care Med.* 2005;33:128-34.

28. Gilinsky NH, Briscoe GW, Kuo CS. Fatal amiodarone hepatotoxicity. *Am J Gastroenterol.* 1988;83:161-63.

29. Chang CC, Petrelli M, Tomashefski JF, et al. Severe intrahepatic cholestasis caused by amiodarone toxicity after withdrawal of the drug. A case report and review of the literature. *Arch Pathol Lab Med.* 1999;123:251-56.

30. Staubli M, Bircher J, Galeazzi RL, et al. Serum concentrations of amiodarone during long term therapy. Relation to dose, efficacy and toxicity. *Eur J Clin Pharmacol.* 1983;24:485-94.

31. Hermida JS, Tcheng E, Jarry G, et al. Radioiodine ablation of the thyroid to prevent recurrence of amiodarone-induced thyrotoxicosis in patients with resistant tachyarrhythmias. *Europace.* 2004;6:169-74.

32. Bogazzi F, Bartalena L, Cosci C, et al. Treatment of type II amiodarone-induced thyrotoxicosis by either iopanoic acid or glucocorticoids: a prospective, randomized study. *J Clin Endocrinol Metab.* 2003;88:1999-2002.

33. Raebel MA, Chester EA, Newsom EE, et al. Randomized trial to improve laboratory safety monitoring of drug therapy in ambulatory patients. *Pharmacotherapy.* 2006;26:619-26.