Amiodarone Pharmacovigilance Through an Intelligent Electronic Health Record Application

Olivia R. Newgaard, BA; Rajeev Chaudhry, MBBS, MPH; Jenny A. Schutte, RN; Richard Arndt, PharmD, MHA; Jennifer R. Rich, MPH; Andrew D. Calvin, MD, MPH; Richard D. Hanna, MD

ABSTRACT

Background: Amiodarone is the most effective and commonly used antiarrhythmic medication. Given its risk of toxicity, routine monitoring is recommended but is challenging to ensure in clinical practice.

Methods: We created an intelligent application, built within our electronic health record, that identified every living patient with an active outpatient prescription by a clinician in our health system. The application was designed to identify patients with lapses in recommended monitoring and facilitate scheduling of overdue testing.

Results: The percentage of patients with overdue monitoring tests decreased with use of the application, with greatest improvement in pulmonary function testing.

Discussion: Implementing a program to monitor and mitigate adverse reactions to amiodarone by using programable features of an electronic health record is feasible.

BACKGROUND

Amiodarone is uniquely effective in treating ventricular and supraventricular cardiac arrhythmias and is the most widely used antiarrhythmic drug.[1] However, amiodarone also is associated with serious and potentially life-threatening adverse drug reactions, particularly with prolonged therapy.[1-6] To mitigate these risks, consensus guidelines recommend routine follow-up testing for liver-, thyroid-, and lung-related toxicities.[1-6] In clinical practice, it is often challenging to ensure that this testing is completed, and studies have shown that formal monitoring programs improve compliance with these guidelines.[1-6] Barriers to creating monitoring programs include the task's perceived complexity and additional costs.[6] The electronic health record (EHR) used by our institution (Epic; Epic Systems Corporation) has features that facilitate the creation of patient registries. The cardiology department at Mayo Clinic Health System in Northwest Wisconsin (MCHS NW WI) worked with our Cohort Knowledge Information Solution build team to design and implement an amiodarone monitoring application within our EHR. Here, we report our initial experience with the creation and implementation of this application.

METHODS

Project approval was secured in the fourth quarter of 2020. Programming of the application was completed by our institutional registry programmers during the first half of 2021, and pilot testing began in July 2021. Refinements and modifications were made throughout the rest of the year, and the product was fully functional in January 2022. Patient data were collected for this study from January 2022 through August 2022.

Every night, the application updated the list of living patients with an active outpatient prescription for amiodarone prescribed by a MCHS NW WI clinician. The application was populated with data of interest for each patient, according to the guidelines for recommended testing in patients treated with amiodarone (Table 1). Notable data incorporated were the most recent results

• • •

Author Affiliations: Medical College of Wisconsin, Wausau, Wisconsin (Newgaard); Division of Community Internal Medicine, Geriatrics, and Palliative Medicine and Department of Artificial Intelligence and Informatics, Mayo Clinic, Rochester, Minnesota (Chaudhry); Department of Nursing (Schutte), Pharmacy Services (Arndt), Research and Innovation (Rich), and Cardiology (Calvin, Hanna), Mayo Clinic Health System – Northwest Wisconsin Region, Eau Claire, Wisconsin.

Corresponding Author: Richard D. Hanna, MD, Cardiology, Mayo Clinic Health System – Northwest Wisconsin Region, 1400 Bellinger St, Eau Claire, WI 54703; phone 715.838.6320; email hanna.richard@mayo.edu; ORCID ID 0000-0002-5148-6683

of serum thyrotropin (TSH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) measurements, chest radiography, and pulmonary function testing (PFT). Other data fields were imported into the registry, such as primary care physician, date of most recent cardiology visit, and prescribing clinician.[1,3] Additional data columns in the application, when clicked on, could organize the list, bringing the patients most in need of intervention to the top. Tests that were more than 2 months beyond their due date were defined as overdue. Another column showed the total number of overdue results for a given patient; clicking on that column brought patients with the most overdue results to the top, which was an effective way for the amiodarone monitoring program coordinator (AMPC) to focus on those most in need of attention.

Because the application was integrated in the EHR, additional patient information was readily available to the AMPC by simply opening the patient record from within the application, which facilitated an individualized approach to addressing overdue testing. Notifications of overdue testing requests were sent as electronic messages if patients were active users of integrated patient portals or as telephone calls if they were not. Amiodarone-specific message templates were created to make this communication more efficient. Patients enrolled in hospice care were not directly contacted, although assistance with medication questions was offered to the patient's clinicians. After patients agreed to have amiodarone-specific monitoring testing, the AMPC marked the necessary orders as pending for the cardiologist to sign.

A new episode visit type entitled amiodarone monitoring was created, which enabled linking of all the AMPC's activity for a given patient to one location in the EHR. Programmers also created an Amiodarone Episode Smart Form that allowed for (1) manually enrolling or removing patients from the application; (2) documenting the reason for amiodarone discontinuation, such as therapy completed or adverse effect; (3) manually entering PFT results that predated our EHR (before 2017); and (4) manually assigning a patient's clinic region when it could not be autopopulated accurately. Patients were assigned to a region within our health system according to the practice location of the prescribing clinician. Importantly, the assigned region determined which workgroup would address a particular cohort of patients. At first, a considerable number of patients (nearly 1,000) could not be assigned a region because of a lack of specificity regarding the clinician's location in the EHR (eg, trainees). By interrogating additional data fields within the EHR, however, such as the primary hospital in which a clinician practiced, the number of patients with an unknown region in the health system was reduced to less than 80.

Programmers also facilitated several other application enhancements and process improvements. For instance, the AMPC found it helpful to write comments in a fixed column that documented previous work or information, such as "patient refused testing" or "[clinician] reports amiodarone will only be continued for 3 months." In addition, a process was developed for entering laboratory and chest radiography results from outside institutions.

Table 1. Guideline-Recommended Testing for Patients Using Amiodarone[1]

Organ System	Testing	Timing
Liver	ALT or AST	Baseline and every 6 months
Thyroid	TSH	Baseline and every 6 months
Lungs	Chest radiography Pulmonary function tests with DLCO	Baseline and every 12 months Baseline (repeat if clinical suspicion cion of pulmonary toxicity)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLCO, diffusing capacity of lung for carbon monoxide; TSH, thyrotropin.

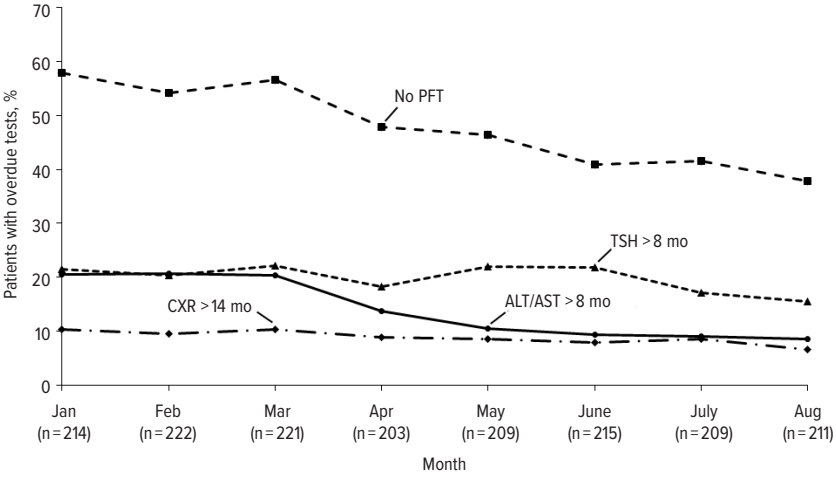
To determine whether time was significantly associated with a decrease in the number of overdue measures, a repeated measures logistic regression model was executed for each of the 4 outcomes. For all modeling, a significance level of .05 was used. Analysis was conducted in R version 4.1.2 (R Foundation for Statistical Computing).

RESULTS

Use of the application immediately identified 6 patients who had no testing for several years and were no longer followed up in the cardiology department. We contacted the primary care clinicians, and all were receptive to having the patient seen in the cardiology department to review testing and discuss whether continuing amiodarone had a favorable risk/benefit ratio. Next, the AMPC focused on patients with the most overdue tests. The number of patients overdue for all recommended testing decreased from 19 of 180 patients (10.6%) in July 2021 to 3 of 222 patients (1.4%) in February 2022. During the same time frame, the percentage of patients with 2 or more overdue tests decreased from 45.6% (82/180) to 34.7% (77/222).

The Figure shows the change in percentage of patients with overdue testing for several measures during the first 8 months of 2022. Efforts to address overdue tests often had a several-week time delay, and appreciable improvement in the measures was first noted after 4 months. The regression models confirmed that time was significantly associated with a decrease in overdue testing over the 8-month observation period for AST and ALT measurements, chest radiography, and PFT (all $P < .05$) but not for serum TSH measurement ($P = .12$). The greatest improvement was in PFT; the percentage of patients with overdue testing decreased by 20 points (57.9% to 37.9%) during the 8-month period. Indeed, at the end of 8 months' follow-up, patients had a 78% decrease in the odds of overdue status for PFT, compared with the start of 2022 (odds ratio, 0.22; 95% CI, 0.09-0.53; $P < .001$).

Figure. Patients Overdue for Recommended Testing



Graph shows the percentage of patients overdue for thyrotropin measurement by more than 8 months (TSH >8 mo) chest radiography by more than 14 months (CXR >14 mo), and alanine aminotransferase and aspartate aminotransferase measurement by more than 8 months (ALT/AST >8 mo) and patients having no pulmonary function testing (No PFT), per month. Data were collected from the application from January through August 2022. The number of patients per month is also shown.

Table 2. Summary of Full-time Equivalent Time Devoted to Creation of the Application in 2021

Task	Time spent, h
Programming	
Understanding needs of the practice	26
Developing the application in EHR	45
Demonstrating use to practice and functionalities of use	11
Total programming time	82
Amiodarone monitoring program coordinator time	65
Total FTE time programming and refining the application	147

Abbreviations: EHR, electronic health record; FTE, full-time equivalent.

Table 2 summarizes the time spent creating and refining the application throughout 2021—a total of 147 hours. Routine management of the patient cohort in 2022 occupied an average of 18.5 hours per month of AMPC time.

DISCUSSION

To our knowledge, this is the first description of the design and initial implementation of a medication-specific application in the Epic EHR to ensure monitoring of patients receiving antiarrhythmic drug therapy.[6] Our experience demonstrates that the implementation of such a program is feasible and is associated with clinically meaningful improvements in adherence to recommended guidelines. Improvements were apparent early in the project's implementation.

Baseline PFT showed the most opportunity for improvement and the greatest decrease in patients with overdue testing during the study period compared with other monitoring tests. We identified several reasons for such high percentages of patients without PFT during the beginning months. First, amiodarone is often started during acute illness when the performance of PFT will not result in accurate data; thus, the "baseline" function is more appropriately obtained after full recovery from the acute illness. In addition, PFT (as well as other follow-up and testing) often was delayed by logistics due to the COVID-19 pandemic. Because the pandemic peak was waning during the project in 2022, it most likely was easier for patients to successfully make appointments to complete their tests. Efforts are ongoing to further improve all metrics. The data from the application have provided useful feedback to clinicians regarding lapses in follow-up that must be addressed.

Barriers related to efficiently implementing applications of this type could be overcome with a focus on intelligent application development by EHR vendors and the incorporation of machine learning tools. The benefits for the development and automation of complex medication management monitoring systems include improved patient safety, improved medication management outcomes, and reduced administrative burden. Given that resources were scarce during this project, the application was designed to be as efficient as possible, without overburdening already strained clinicians with automatic (often erroneous) system-generated messages. The AMPC role proved invaluable for offloading clerical tasks, such as finding tests completed at outside facilities, determining which alerts truly required action, and marking appropriate orders as pending for overdue testing. Programming the registry to allow 2 months for routine testing to be completed in the course of routine care before triggering action by the AMPC saved considerable duplication of effort. Because this project had no outside funding, allocating resources such as AMPC time was a considerable challenge, and we anticipate this would also be a barrier for other institutions. The benefit to patient care, however, is also quite evident, and we believe that among the many initiatives that can be pursued with an EHR, pharmacovigilance programs of this sort will have an excellent return on investment. We anticipate that the programming and clerical burden will improve incrementally as the processes are standardized to incorporate other high-risk medications and as EHR vendors enhance registry capabilities.

Considering the success of this pilot project, we hope to expand use of this EHR intelligent application throughout the institution. Furthermore, the application was purposefully

designed so that other heart rhythm medications may be added, thereby allowing for efficient expansion of future pharmacovigilance efforts.

Acknowledgments: The authors wish to thank Lorraine D. Rongstad and Susanne C. Degen for administrative support and Amber M. Bolles, MA, Ambulatory Documentations Systems for programming support. The Scientific Publications staff at Mayo Clinic provided editorial consultation, proofreading, and administrative and clerical support.

Funding/Support: This project was supported through a a 2020 Mayo Clinic Midwest Clinical Practice Committee Project Innovation Grant.

Financial Disclosures: None declared.

REFERENCES

1. Epstein AE, Olshansky B, Naccarelli GV, Kennedy JI, Jr., Murphy EJ, Goldschlager N. Practical management guide for clinicians who treat patients with amiodarone. *Am J Med.* 2016;129(5):468-475. doi:10.1016/j.amjmed.2015.08.039

2. Graham MR, Wright MA, Manley HJ. Effectiveness of an amiodarone protocol and management clinic in improving adherence to amiodarone monitoring guidelines. *J Pharm Technol.* 2004;20(1):5-10. doi:10.1177/875512250402000103

3. Johnson SG, Canty K, Billups S, Schimmer J. Adherence to amiodarone monitoring recommendations before and after implementation of a centralized pharmacy service: a cohort study. *J Pharm Pract*. 2010;23(6):536-539. doi:10.1177/0897190009358770

4. Snider M, Kalbfleisch S, Carnes CA. Initial experience with antiarrhythmic medication monitoring by clinical pharmacists in an outpatient setting: a retrospective review. *Clin Ther.* 2009;31(6):1209-1218. doi:10.1016/j.clinthera.2009.06.014

5. Spence MM, Polzin JK, Weisberger CL, Martin JP, Rho JP, Willick GH. Evaluation of a pharmacist-managed amiodarone monitoring program. *J Manag Care Pharm.* 2011;17(7):513-522. doi:10.18553/jmcp.2011.17.7.513

6. Tafreshi J, Chui MA, Riley AB. Implementation of an amiodarone ambulatory care clinic. *Am J Health Syst Pharm*. 2009;66(22):1997-2001. doi:10.2146/ajhp080555

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

Visit www.wmjonline.org to learn more.