

11. Cubeddu LX, Seamon MJ. Statin withdrawal: clinical implications and molecular mechanisms. *Pharmacotherapy* 261288–1296.
12. Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J, Cai J, Yang R, Han J, Huang Y, He S. Effects of ARBs and ACEIs on virus infection, inflammatory status and clinical outcomes in COVID-19 patients with hypertension: a single center retrospective study. *Hypertension* 7651–58.
13. Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiol* 5825–830.
14. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, Liu YM, Zhao YC, Huang X, Lin L, Xia M, Chen MM, Cheng X, Zhang X, Guo D, Peng Y, Ji YX, Chen J, She ZG, Wang Y, Xu Q, Tan R, Wang H, Lin J, Luo P, Fu S, Cai H, Ye P, Xiao B, Mao W, Liu L, Yan Y, Liu M, Chen M, Zhang XJ, Wang X, Touyz RM, Xia J, Zhang BH, Huaeg X, Yuan Y, Rohit L, Liu PP, Li H. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res* 1261671–1681.
15. Lam KW, Chow KW, Vo J, Hou W, Li H, Richman PS, Mallipattu SK, Skopicki HA, Singer AJ, Duong TQ. Continued in-hospital ACE inhibitor and ARB use in hypertensive COVID-19 patients is associated with positive clinical outcomes. *J Infect Dis* 2221256–1264.
16. Gustafson D, Raju S, Wu R, et al. Overcoming barriers: the endothelium as a linchpin of coronavirus disease 2019 pathogenesis? *Arterioscler Thromb Vasc Biol* 401818–1829.
17. Fedson DS. Treating the host response to emerging virus diseases: lesson learned from sepsis, pneumonia, influenza and Ebola. *Ann Transl Med* 4421.
18. Koh KK, Sakuma I, Shimada K, Hayashi T, Quon MJ. Combining potent statin therapy with other drugs to optimize simultaneous cardiovascular and metabolic benefits while minimizing adverse events. *Korean Circ J* 47432–439.
19. Fedson DS. A practical treatment for patients with Ebola virus disease. *J Infect Dis* 211661–662.
20. Fedson DS, Opal SM, Rordam OM. Hiding in plain sight; an approach to treating patients with severe COVID-19 infection. *mBio* 11. e00398-20.
21. Pirofski L-a, Casadevall A. Pathogenesis of COVID-19 from the perspective of the damage-response framework. *mBio* 11. e01175-20.
22. Parihar SP, Guler R, Brombacher F. Statins: a viable candidate for host-directed therapy against infectious diseases. *Nat Rev Immunol* 19104–117.
23. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *N Engl J Med* NEJMoa2021436.
24. Angus DC. Optimizing the trade-off between learning and doing in a pandemic. *JAMA* <https://doi.org/10.1001/jama.2020.4984>.  
<https://doi.org/10.1016/j.amjcard.2020.09.050>

### Implementation of a Novel Order Set to Improve Baseline Pulmonary, Hepatic, and Thyroid Function Testing at Time of Inpatient Amiodarone Initiation

Amiodarone is a chemically-unique class III antiarrhythmic drug and is commonly-prescribed by internists and cardiologists alike.<sup>1</sup> In addition to its



Accept

The use of amiodarone can result in a variety of long-term toxicities. Baseline and every 6 months to annual monitoring of liver function, thyroid, and pulmonary systems is recommended by the Heart Rhythm Society and major cardiovascular organizational guidelines. Specific recommendations can be found at: Goldschlager N, et al. *Heart Rhythm* 2007;4:1250–1259.

No results found for: TSH, AST, ALT, BILITOT, BILIDIR, ALKPHOS, ALB

- Hepatic function panel  
Routine, Normal, ONE TIME LAB, First occurrence tomorrow at 0600, Blood, Venous P
- TSH Reflexive  
Routine, Normal, ONE TIME LAB, First occurrence tomorrow at 0600, Blood, Venous P
- Pulmonary Function Tests, Adult  
Routine, ONE TIME, First occurrence today at 0831  
Please call the PFT Lab, 924-5219, to schedule. Tests to include: Complete PFTs - CPT will depend on what is actually performed
- AFib
  - amiodarone (PACERONE) tablet 400 mg  
400 mg, Oral, 2 TIMES DAILY, 14 doses, with the First Dose today at 0900, Last dose on Sun 6/14 at 2100 Remove
  - Followed by
  - amiodarone (PACERONE) tablet 200 mg  
200 mg, Oral, DAILY, First Dose on Mon 6/15 at 0900, Until Discontinued Remove
- VTach
  - amiodarone (PACERONE) tablet 400 mg  
400 mg, Oral, 3 TIMES DAILY, 21 doses, with the First Dose today at 0900, Last dose on Sun 6/14 at 2100 Remove
  - Followed by
  - amiodarone (PACERONE) tablet 400 mg  
400 mg, Oral, DAILY, 7 doses, with the First Dose on Mon 6/15 at 0900, Last dose on Sun 6/21 at 0900 Remove
- Maintenance Dose - specify start date at the end of loading period
  - amiodarone (PACERONE) tablet 200 mg  
200 mg, Oral, DAILY, First Dose today at 0900, Until Discontinued

Next Required

Accept

Figure 1. Oral amiodarone initiation order set. Searches for available thyroid, hepatic, and pulmonary function testing over the past six months, and provides orders for each. Also provides dosing and duration for common amiodarone indications.

known blockade of myocardial outward potassium channels and resultant class III properties, amiodarone is pharmacologically complex and exhibits class I, II, and IV effects as well. Thus, it is a common choice in the management of both supraventricular and ventricular arrhythmias, especially in patients with underlying structural heart disease.<sup>1,2</sup>

Unfortunately, the lipophilic properties of amiodarone potentiate adverse systemic effects when the drug is administered chronically, including pulmonary, thyroid, and hepatic toxicity.<sup>1-4</sup> Though current guidelines recommend a baseline evaluation before initiating chronic oral amiodarone therapy, including pulmonary, thyroid, and liver function tests,<sup>4,5</sup> adherence to these guidelines is poor.<sup>6</sup> Given our sense that our institution was not meeting baseline testing guidelines for inpatients initiated on chronic oral amiodarone therapy, we developed a multidisciplinary team to construct and implement a guideline-based amiodarone initiation order set.

We retrospectively reviewed electronic medical record (EMR) data at our institution from May 2018 to May 2019 and identified all patients (n=610) initiated and later discharged on oral amiodarone therapy. Of these patients, we recorded the percentage of patients who had been ordered individual and composite baseline pulmonary, thyroid, and hepatic function testing before hospital discharge. As a multidisciplinary team, we then created a novel amiodarone oral loading initiation order set designed to automatically generate (1) appropriate amiodarone dosing and duration by indication (atrial fibrillation, ventricular tachycardia, and maintenance dosing), (2) most recent thyroid and hepatic function laboratory data available by date, and (3) option for pulmonary, thyroid, and hepatic function testing ordering with recommendation to pursue if no available results within the last 6 months (Figure 1). The integration of this order set into our EMR was coupled with an internal advertising campaign led by a

resident physician team. Finally, ordering data for patients discharged from May 2019 to March 2020 (n=495) were reviewed in a similar fashion to baseline data.

We found that in the 12 months before implementation of this order set, 610 patients were discharged who had been newly prescribed oral amiodarone during their admission. Of these patients, 24.4%, 12.3%, and 23.3% received pulmonary, thyroid, and hepatic function testing, respectively, before hospital discharge. A total of 46.4% of patients received at least 1 of the aforementioned tests. Overall, 1.5% of patients received all recommended testing. Following the implementation of our order set, we used an interrupted time-series analysis and found no significant change in the percentage of eligible patients receiving orders for baseline testing before to hospital discharge (26.3% TFT, net change 9.4%,  $p=0.168$ , 12.3% LFT, net change 5.9%,  $p=0.150$ , 15.8% PFT, net change  $-0.3%$ ,  $p=0.956$ , Figure 2).

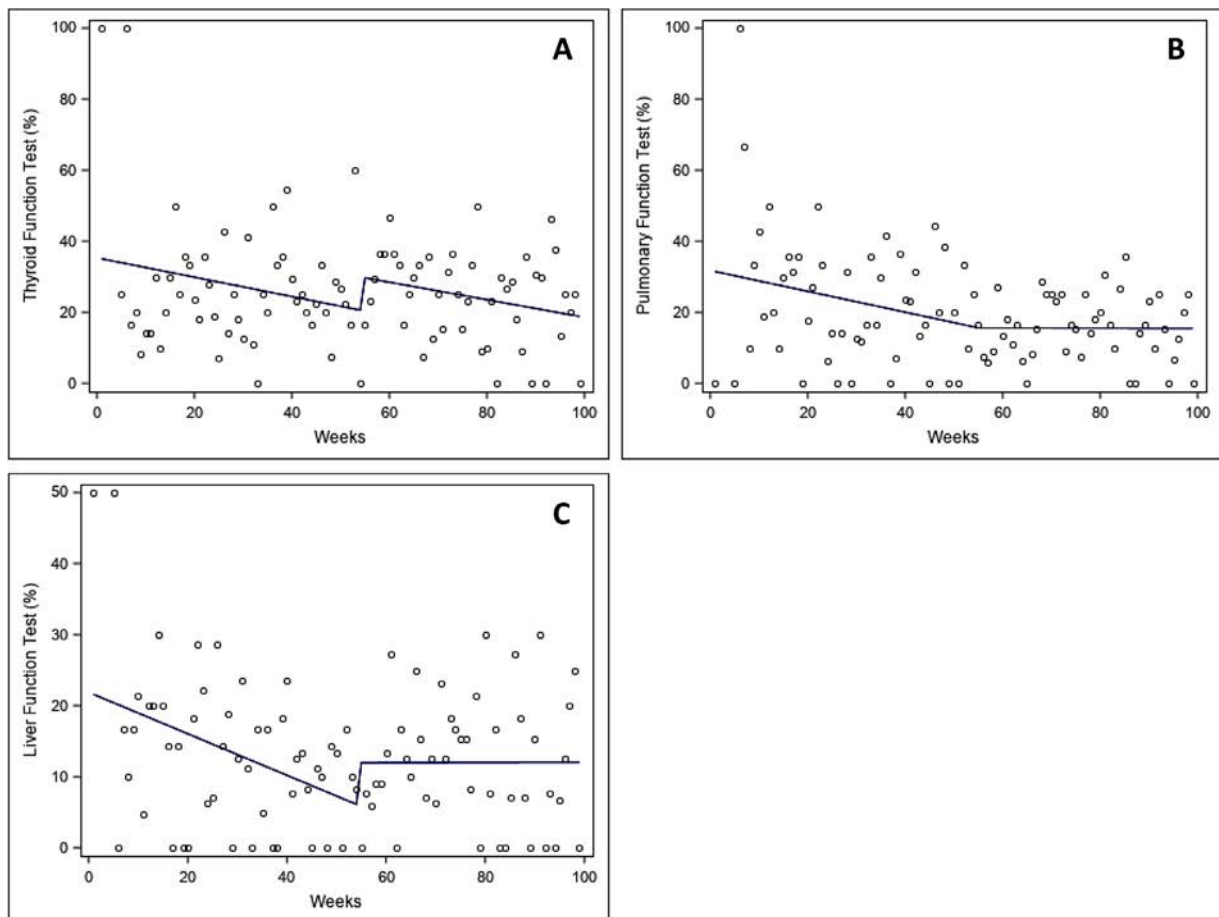


Figure 2. Change in thyroid (A), pulmonary (B), and liver (C) function testing over time.

We also found the order set was utilized in only 8.2% of eligible patients.

Our results demonstrate that implementation of a novel, evidence-based order set for inpatient oral amiodarone loading did not have a significant impact on ordering of recommended baseline screening tests. This was unexpected, as the implementation of standardized order sets has consistently been shown to improve quality of care whereas reducing healthcare costs, medical error, and length of stay.<sup>7</sup> One potential explanation for the order set's inefficacy is poor utilization, which may be attributable to alert fatigue. For example, it has been observed that 44% to 96% of EMR alerts are overridden,<sup>8</sup> which may be due to some combination of both cognitive overload and desensitization.<sup>9</sup> There is also a paucity of data describing the intervention- and practice-specific features which predict success of EMR alerts and clinical decision support systems, which may explain the high degree of variability in their reported effectiveness.<sup>10</sup>

With regard to amiodarone drug monitoring specifically, one intervention which does have an increasing body of supporting evidence is the development of multidisciplinary amiodarone monitoring clinics (AMCs). A comprehensive review of such programs suggested improved adherence to amiodarone monitoring guidelines.<sup>11</sup> Similarly, the pharmacy literature on postintervention strategies for concomitant amiodarone and warfarin management has yielded encouraging results.<sup>12</sup> One can speculate that amiodarone is often prescribed across a wide range of medical and surgical practices in both the inpatient and outpatient settings, where the primary prescriber may not follow the patient long-term. This raises support for longitudinal outpatient amiodarone management in multidisciplinary AMCs.

In conclusion, we developed and implemented a novel order set in an attempt to improve ordering of baseline screening for inpatients started on oral amiodarone therapy. However, the order set did not have a significant impact and was poorly-utilized. These results may suggest growing EMR alert fatigue in clinicians, and there may be a larger role for dedicated AMCs to protect patients from potential toxicities.

### Disclosures

The authors declare no conflict of interest.

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1. PVassallo, RGTrohman. Prescribing amiodarone: an evidence-based review of clinical indications. *J Am Med Assoc*2982007 1312–1322.
2. GADan, AMartinez-Rubio, SAgewall, GBor-iani, MBorgrefe, FGaita, Ivan Gelder, BGor-enek, JCKaski, KKjeldsen, GYLip, BMerkely, KOkumura, JPPiccini, TPotpara, BKPoulsen, MSaba, ISavelieva, JLTamargo, CWolpert. Antiarrhythmic drugs-clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). *Europace*202018731–732.
3. RMColunga, MCiacciarelli, APolidoro, LLuliano. Adverse reactions of amiodarone. *J Geriatr Cardiol*162019552–566.
4. LASiddoway. Amiodarone: guidelines for use and monitoring. *Am Fam Phys*682003 2189–2196.
5. NGoldschlager, AEEpstein, GNaccarelli, BOIshansky, BSingh. Practical guidelines for clinicians who treat patients with amiodarone. Practice guidelines subcommittee, North American society of pacing and electrophysiology. *Arch Intern Med*1602000 1741–1748.
6. CLBickford, APSpencer. Adherence to the NASPE guideline for amiodarone monitoring at a medical university. *J Manag Care Pharm*122006254–259.
7. DJBallard, GOGola, NSFleming, DHeck, JGunderson, RMehta, RKhetan, JDKerr, et al. The Impact of Standardized Order Sets on Quality and Financial Outcomes. *KHenriksenJBBattlesMAKeysAdvances in Patient Safety: New Directions and Alternative Approaches (Vol. 2: Culture and Redesign)*2008Agency for Healthcare Research and Quality (US)Rockville (MD).
8. Hvan der Sijs, JAarts, AVulto, MBerg. Overriding of drug safety alerts in computerized physician order entry. *J Am Med Inform Assoc*132006138–147.
9. JSAncker, AEdwards, SNosal, DHausler, EMauer, RKAushal. Effects of workload, work complexity, and repeated alerts on alert fatigue in a clinical decision support system. *BMC Med Inform Decis Mak*172017. Article No. 36: 1-9.
10. RBackman, SBayliss, DMoore, ILitchfield. Clinical reminder alert fatigue in healthcare: a systematic literature review protocol using qualitative evidence. *Syst Rev*62017. Article No. 255: 1-6.
11. DLDixon, SPDunn, MSKelly, TRMcLlarky, REBrown. Effectiveness of pharmacist-led amiodarone monitoring services on improving adherence to amiodarone monitoring recommendations: a systematic review. *Pharmacotherapy*362016230–236.
12. SCherian, RAMarshi. Establishing standards of care for amiodarone monitoring in an outpatient setting. *Am J Pharmacy Benefits*92017108–115.

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