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Utility of Thyroid Stimulating Hormone (TSH) in Atrial Fibrillation

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ABSTRACT

Atrial fibrillation (AF) has become increasingly common in the inpatient setting. Current practices in new onset AF include obtaining laboratory values such as thyroid stimulating hormone (TSH) with reflex thyroxine (T4). We aim to prove that such practices rarely change management and should be limited to patients with additional indicators of hyperthyroidism. From January 2015 to August 2021, a total of 59,470 patients that were 18 years and older were identified with an admission diagnosis of atrial fibrillation using the ICD-10 code I48.92. Patients were excluded if their sex or age were not identified and if they had a previous admission for atrial fibrillation. Out of the 54,968 patients admitted with AF, TSH was ordered in 7,444 (13.54%), free T4 was ordered in 2,669 (4.85%), and both in 2,285 (4.16%). Only 29 (0.013%) of the 2,285 patients who had orders for both TSH and T4 were found to have both low TSH and high T4, indicating an overt hyperthyroid state. Overall, of the 7,444 patients with TSH labs drawn, only 404 (5.43%) were discharged on methimazole or Propylthiouracil (PTU). While we recognize the importance of identifying modifiable risk factors, we propose that TSH levels should not be reflexively ordered during hospitalization for patients with new onset AF without further clinical suspicion of thyroid disease.

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Introduction

Atrial fibrillation (AF) has a worldwide prevalence of 37.5 million cases, which has increased by 33% over the last 20 years. It is projected that it will continue to increase to 60% by 2050 [1]. Incidence increases with age as well as cardiac comorbidities such as obstructive sleep apnea and hypertension [2]. It is known that AF is associated with a substantial increase in morbidity and mortality, in addition to an increased risk of cerebrovascular accidents (CVA), heart failure, and mesenteric ischemia. The risk of CVA alone contributes to a large portion of its morbidity and mortality, since AF increases stroke risk five-fold [3]. For these reasons, guidelines were developed with the primary aim of identifying potential modifiable risk factors for atrial fibrillation. In 2014, the Journal of the American College of Cardiology (JACC) released guidelines that recommended obtaining transthoracic echocardiogram (TTE), serum electrolytes, complete blood count, as well as thyroid, renal, and hepatic function studies in the initial evaluation for patients with new onset AF [4]. These guidelines were developed despite that previous studies have found that less than 1% of AF cases are secondary to hyperthyroidism [5].

Overt hyperthyroidism is a known association with AF. The exact mechanism is unclear, however there have been multiple suggestions. These include an increase in sympathetic tone by triiodothyronine (T3), thereby increasing automaticity in the pulmonary vein cardiomyocytes, as well as decreasing atrial refractory period [6]. In 1994 Sawin et al found that the risk for atrial fibrillation was 28% over a 10 year period in patients who did not take antithyroid medication and had a serum TSH level of 0.1 mU/L or less [7]. In 2017 Baumgartner et al studied the potential risk of developing AF in subclinical hyperthyroidism, subclinical hypothyroidism, and thyroid function within normal limits. They observed that euthyroid individuals with free T4 levels in the high-normal range were associated with an increased risk of incidental AF. However, their study also showed that incidental AF events did not increase across TSH categories within the euthyroid range or in subclinical hypothyroidism [8].

Patients with signs and symptoms of a hyperthyroid state should be screened with a TSH along with a free T3 and T4. The most common symptoms are palpitations, tremors, heat intolerance, weight loss, anxiety, increased frequency of bowel movements, and shortness of breath. On physical exam, pertinent skin findings include warmth, hyperpigmentation, and thinning of hair [9]. Lid lag and stare can occur in all forms of hyperthyroidism, and patients with Graves disease can present with ophthalmopathy. Treatment in this case would include both anti-thyroid medications as well as beta blockers. Rhythm control is generally not recommended in this population, since two thirds of patients spontaneously revert to normal sinus rhythm following restoration of a euthyroid state [10].

Although there is an established relationship between subclinical hyperthyroidism and AF, there have not been any studies proving that early treatment of subclinical hyperthyroidism can prevent development of AF. A previous retrospective study found that only 2% of patients presenting with AF were found to have a low TSH [11]. We thus aim to question the use of routine TSH screening in the initial evaluation of new onset AF. Instead, we suggest a risk driven approach taking into account the full clinical picture

to determine the necessity for thyroid disease screening.

Objective

Our hypothesis is that routine measurement of TSH in new onset AF or AF with rapid ventricular response (RVR) is low yield and in most cases will not change clinical management.

Methods

Study Design and Population

We conducted a retrospective study of patients who were admitted to HCA healthcare hospitals from January 2015 to August 2021, aged 18 to 89 based on a confirmed admission diagnosis of AF using the ICD code I48.91. A total of 59,470 patients were identified. Of these, 54,968 patients remained for further analysis after the following exclusion criteria were applied: having a prior hospital admission to an HCA facility with documented AF, unknown race, or unknown sex.

Data Processing and Analysis

For each patient included above, our data analysts used logistic regression to determine the following three research questions. First, what is the likelihood that TSH was ordered during the hospitalization? Then, what is the likelihood that these patients have low TSH (<0.5 mlU/L), and high T4 (>12 ug/dL) or T3 (>5.5 ug/dL) indicating a diagnosis of overt hyperthyroidism? And finally, what is the likelihood that methimazole or propylthiouracil were prescribed on discharge? These research questions were further controlled by age, sex, race, and comorbidities such as: sleep apnea, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM) and hypertension (HTN) using common ICD-10 codes as shown in Table 1.

Table 1: ICD-10 Codes used for common comorbidities

- Sleep Apnea Codes: G4733, G4730, R0681, G4731, G4739, 32723, G4737
- CAD- Code I2510
- COPD- Codes J449, J441
- DM- Codes E119, E1122, E1165, E1140, E1151, E1142, E11649, E1121, E11621, E118, E1169, E11319, E1143,E1152, E11622, E1110, E11628, E1022, E109, E1139, E1065, E11610, E1136, E1141, E099, E10319, E1040, E1159, E139,E1129, E1051, E10649, E1010, E1021, E1042, E108, E0965, E1043, E1144, E1149, E11641, E1340, E1342, E0922, E09649, E1069, E11311, E11618, E11620, E1322, E1365, E10621, E10622, E10628, E113219, E1321, E1310
- HTN - Code I10

Results

We analyzed a total of 54,968 patients after our exclusion criteria was applied. During hospitalization 1,538 (2.8%) expired or were discharged to hospice, while the remaining were either discharged, transferred to another facility, or left against medical advice. Features of the population including comorbidities are noted in Table 2. The most commonly identified comorbidities were HTN (43.3%), and CAD (30.2%) and OSA (13.2%).

Of the 54,968 patients admitted with AF, a TSH lab was ordered in 32,438 patients (59.01%) while it was only performed in 7,465 (13.58%), free T4 was ordered in 2,692 (4.90%), and both in 2,285 (4.16%). Only 21.53 % of TSH labs ordered were performed. This was likely due to a variety of factors including patients expiring, being transferred to a different facility or leaving against medical advice prior to lab draws, patients refusing lab draws, or inability to draw or process labs. Also, some labs may have been ordered as an outpatient lab for a follow up appointment outside of our facility. Further extrapolations regarding likelihood of receiving TSH labs based on demographics and comorbidities are shown in Table 2.

Out of the patients who received both TSH and T4, only 29 (0.013%) were found to have both low TSH and high T4 indicative of an overt hyperthyroid state. Additionally, 456 patients (19.96%) that received both a TSH and T4 lab had low TSH and normal T4 or T3, indicating possible subclinical hyperthyroidism. There were 202 patients with low TSH who did not receive additional testing for T3 or T4. Overall, 115 (1.41%) patients with TSH labs were discharged on methimazole or PTU. While 42 of those 115 (36.52%) patients discharged on methimazole or PTU received a refill for a pre-existing prescription.

Table 2: Likelihood of receiving TSH labs based on demographics and comorbidities

- Females were 1.07 times more likely to get TSH drawn than males ($p < 0.001$, Exp(B) = 1.066, 95 % confidence interval (CI) [1.029,1.105])
- Patients that identified as 'other' in race were 1.11 times more likely to have a TSH ordered than the 'white' race population ($p < 0.001$, Exp(B) = 1.111, 95% C.I. [1.038, 1.189])
- Patients with CAD were 0.842 times as likely to receive a TSH order ($p < 0.001$, Exp(B) = 0.842, 95% C.I. [0.811,0.875]) than patients without CAD
- Patients HTN were 0.763 times as likely to receive a TSH order ($p < 0.001$, Exp(B) = 0.763, 95% C.I. [0.737,0.790]) thank patients without HTN

Overall, patients with TSH orders were 2.684 times more likely to be prescribed methimazole or PTU at discharge ($p < 0.001$, Exp(B) = 2.684, 95% C.I. [2.092, 3.443]) than patients that did not have a TSH order, when all other variables in the model were held constant. Further extrapolations regarding likelihood of receiving a prescription of PTU or methimazole on discharge based on demographics and comorbidities are shown in Table 3.

Table 3: Likelihood of being prescribed methimazole or PTU based on demographics and comorbidities

- Female patients were 2.198 times more likely to be prescribed methimazole or PTU at discharge ($p<0.001$, Exp(B) = 2.198, 95% C.I. [1.782, 2.710] than male patients
- Black patients ($p<0.001$, Exp(B) =2.016, 95% C.I. [1.549, 2.622]) and race 'other' patients ($p=0.002$, Exp(B) =1.652, 95% C.I. [1.211, 2.254]) were 2.016 and 1.652 times more likely to be prescribed methimazole or PTU at discharge ($p=0.019$, Exp(B) = 0.747, 95% C.I. [0.586, 0.954]) as white patients.
- Patients with sleep apnea were 0.516 times as likely to go home with these medications ($p<0.001$, Exp(B) = 0.516, 95% C.I. [0.356, 0.748]) than patients without a diagnosis of sleep apnea
- Patients with DM were 0.747 times as likely to be prescribed methimazole or PTU at discharge ($p=0.019$, Exp(B) = 0.747, 95% C.I. [0.586, 0.954]) as patients without DM

Discussion

Our study involved a final population size of 54,968 patients thus the power was adequate. We excluded patients with a known previous admission for AF in order to focus on common practices in new onset AF. Our population group mainly identified as 'white' (84.5%) and thus we may argue that these findings could best be generalized to the caucasion population. The mean age in our population was 70 years. However, this would likely be

higher if patients older than 89 were included in the study given that incidence of AF increases with age [12]. Patients over the age of 89 are all considered 90 years of age to preserve their confidentiality and thus were excluded from our study, this was an inevitable limitation to our study. We identified that the most common comorbidities were HTN (43.3%), and CAD (30.2%). Interestingly, the comorbidity of sleep apnea was surprisingly low (13.2%) in our patient population, despite its association with AF.

TSH was ordered in 13.58% of our patients as a component of their workup during their hospitalization for AF. Only 115 (1.41%) of the patients with TSH labs were discharged on methimazole or PTU, putting into question the utility of routinely obtaining TSH as part of a workup for AF [13].

Given that the data for this study was obtained throughout the entire HCA database over a period of 6.5 years with relatively minimal exclusion criteria, the authors believe that this study has good generalizability with respect to a typical hospitalized patient population in the United States. Additionally, today's TSH tests are generally regarded to be both accurate and sensitive which speaks to the validity of these results with regards to accurately identifying overt and subclinical hyperthyroidism.

One noted limitation to our study is data extraction through ICD-10 codes. In our attempt to limit this data to new onset atrial fibrillation, we used a prior hospitalization with AF as an exclusion criteria. However, this data was only pulled from HCA facilities and some of the patients may have been admitted to non-affiliated hospitals in the past. Overall, it is reasonable to assume that some patients included in our study may have prior diagnosis of AF. Unfortunately, a feasible way to resolve this limitation in a future study would be through individual patient confirmation of possible atrial fibrillation at another facility, which would be logistically difficult and prone to recall bias. The second limitation is that a very low percentage of TSH labs ordered were performed which presents a major limitation to our study. This was possibly due to some of the reasons mentioned in our results section including difficult lab draws, patients being transferred or expiring prior to lab draws, or labs being ordered on discharge and being performed at an outpatient facility. A third limitation is that it was not identified whether patients were referred to an endocrinologist upon discharge. Some hospitalists may not feel comfortable initiating antithyroid medications and instead opt for endocrinology referrals. This could be addressed in a future study by focusing on endocrinology referrals in addition to methimazole and PTU prescriptions at discharge for those patients that screen positive for hyperthyroidism.

With the rising costs of healthcare in the United States, it is a part of our role as a physician to be cognizant of, and exclude, potential extraneous tests during our evaluation. The cost of ordering a TSH alone may not be extremely significant, but when you consider the additional costs associated with incidental TSH abnormalities that cost can rise substantially. While we recognize the importance of identifying disease modifiable risk factors, we propose that TSH levels should not be reflexively ordered in the hospital on patients with new onset AF without additional signs or symptoms of hyperthyroidism. Further randomized control trials comparing the management and outcomes of patients with and without reflex TSH labs ordered during hospitalization would provide further data to support or oppose this recommendation.

Conclusion

Our retrospective study based on ICD-10 code 148.91 for atrial fibrillation suggests that routine measurement of TSH in patients with atrial fibrillation is likely a low yield practice. Only 115 (1.41%) of our patients that had a TSH performed during their hospitalization for atrial fibrillation were discharged on methimazole or propylthiouracil. Overall we propose moving away from routine TSH testing in atrial fibrillation and recommend a more risk driven approach based on historical and exam findings suggestive of hyperthyroidism to guide further testing.

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