JIMMA UNIVERSITY

INSTITUTE OF HEALTH

DEPARTMENT OF INTERNAL MEDICINE

ASSESSMENT OF ATRIAL FIBRILLATION AND ASSOCIATED CARDIOVASCULAR DISORDERS AMONG ADULT HYPERTHYROIDISM PATIENT AT JIMMA UNIVERSITY FOLLOW UP CLINICS FROM JUNE 2016- AUGUST 2021 G.C

A RESEARCH THESIS TO BE SUBMITTED TO THE DEPARTMENT OF INTERNAL MEDICINE, FACULTY OF MEDICAL SCIENCES FOR PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE SPECIALTY CERTIFICATE IN INTERNAL MEDICINE

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ABSTRACT

Background: The extent of thyroid disorders in Africa remains unknown but the few available studies done in Ethiopia reported the prevalence of autoimmune thyroid disease to be 1.2%. A considerable proportion of hyperthyroidism patients develop specific cardiovascular complications including Atrial fibrillation, heart Failure, pulmonary hypertension, dilated cardiomyopathy as well as ventricular arrhythmias. The heart is particularly sensitive to the change in local T3 levels.

Objective: to find the cardiovascular disorders and assessment of factors associated with development and persistence of Atrial Fibrillation among hyperthyroidism adult patients, who were on follow up at JUMC clinic during June 2016 and August 2021.

Materials and Methods: A retrospective cohort study was done. Data was collected on Oct. 2021GC by a structured questionnaire which included history and physical examination and investigation records. Data analyzed using SPSS version 26. statistical significance taken at p -value less than 0.05. Ethical clearance obtained from JUMC ethical committee.

Result- A total 163 hyperthyroidism patients were included after fulfilling the inclusion criteria for final analysis. The mean Age of patients and duration of symptom was 40.9 years (±11.653) and 12.72 months (±8.8) respectively. Majority of were female 150(92.0%) and most frequent cardiovascular manifestation was SOB in 80 (58.3%), palpitations in 70 (52.1%), and PND in 39 (29.4%) of participants. Resting HR SBP, and DBP at presentation were a mean value of 115.26b/Min (±13.89),116.55(±18.4) and 69.75 (±9.1) respectively. Underlying medical disease found in forty-four patients which includes hypertension 26(16%), cardiac disease in 19(11.7%), DM in three, COPD in two and post TB fibrosis in one patient.

Hyperthyroidism related cardiovascular (CV) complications in newly diagnosed hyperthyroidism patients were found in 30.67% and significantly associated Factors were, AF (p < .001& AOR= 7.3), underlying cardiac disease (P value =002 & AOR=3.25), LA-size (P=.001& AOR=3.36) and baseline FT3 (p =.041& AOR=2.1). Baseline TSH <0.01miu/L was a significant related factor for Hyperthyroidism cardiovascular complication in non-AF patients with p value <.001 and with AOR=.014(CI=.001 - .129).

Similarly, an independent and significant associated factors with AF±HF includes, HF, NYHA class 3 & 4 CHF at DX; p value= .001 and AOR=9.01, Baseline T3 >5PG/ml; with P value .0O2 and AOR= 32.1, Diastolic Dysfunction with p value =.019 (AOR=5.51, 95% CI=1.32-22.99), LA-size >3.8cm; P value .006 and AOR=8.83, T3 or T4 normalization <12mon p value .032 and AOR=.086 ,RHD &/or other VHD; p

value .024 and AOR= 8.8 and HHD P value .01, and AOR 51.5.sinus conversion occurred in only 6/38 (15.7%)

Persistence of thyrotoxic AF occurred in 32/163 (19.2%) of hyperthyroidism patients. Age is the only independent and significantly increased risk of persistence AF with p value of 046.

Conclusion- predictors of AF in hyperthyroidism patient with p value of <0.001 were NYHA class 3 and 4 CHF on presentation, LA-SIZE ≥3.8cm, RHD or other VHD, HHD, baseline FT3 and diastolic Dysfunction. Age was the only significantly associated factor and predictor for persistence of AF.

Keywords- hyperthyroidism, AF, Hyperthyroidism related cardiovascular (CV) complication, AF in hyperthyroidism, Thyrotoxic AF, Persistence of thyrotoxic AF

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I would like to thank Jimma University for giving me the opportunity to undertake and fund this research.

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LIST OF ABBREVIATIONS

AF-Atrial fibrillation

AITD-Autoimmune thyroid disease

ALP-alkaline phosphatase

ALT-Alanine transaminase

ATA - American Thyroid Association

AST- Aspartate transaminase

ATDs- Antithyroid drugs

AV- Atrioventricular

BUN-Blood urea nitrogen

CAD-coronary artery disease

CHF-Congestive heart failure

Cr-Creatinine

DBIL-Direct bilirubin

ECG- Electrocardiogram

FT3-Free triiodothyronine

FT4-Free thyroxine

GD- Graves' disease

GGT -Gamma-glutamyl transpeptidase

IHD- ischemic heart disease,

JUMC- Jimma university Medical Centre

LVEF- Left ventricular ejection fraction

MMI- Methimazole

NHANES- National Health and Nutrition Examination Survey

NYHA- New York Heart Association

PTU - Propylthiouracil

RAI- Radioactive iodine

RBC- Red blood count

SCH - Subclinical hyperthyroidism

SPSS- Statistical Package for Social Sciences

T3- Triiodothyronine

TBIL-Total bilirubin

TFT- Thyroid function test

TgAb-Thyroglobulin antibodies

TH- Thyroid hormone

TMNG- Toxic multinodular goiter

TPOAb-Thyroid peroxidase antibody

TRAb-TSH receptor antibodies

TSH- Thyroid stimulating hormone

Ua- Uric acid

VHD-Valvular heart disease

WHO- World Health Organizatio

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CHAPTER ONE: INTRODUCTION

1.1. Background information

According to 2002 NHANES III, overt hyperthyroidism in USA was detected in 0.5% of the general population while 0.7% of the general population had subclinical hyperthyroidism with an overall prevalence of 1.3%(1).The incidence data for overt hyperthyroidism from large population studies in men and women are comparable, 0.4 per 1000 women and 0.1 per 1000 men, but the age-specific incidence varies considerably(2).

In iodine-sufficient countries Graves' disease accounts for 70–80% of patients with hyperthyroidism, whereas in areas with iodine deficiency, it constitutes ~50%, with the other half attributed to nodular thyroid disease(1). Other important causes of thyrotoxicosis include thyroiditis, iodine-induced and drug-induced thyroid dysfunction, and factitious ingestion of excess thyroid hormones(2)

Only moderate correlation exists between the degree of thyroid hormone elevation and clinical signs and symptoms. Symptoms and signs that result from increased adrenergic stimulation may be more pronounced in younger patients and those with larger goiters(3)

Untreated or partially treated thyrotoxicosis is associated with weight loss, osteoporosis, atrial fibrillation, embolic events, muscle weakness, tremor, neuropsychiatric symptoms, and rarely cardiovascular collapse and death.(3)

Increased thyroid hormone levels most profound effects occur within the cardiovascular system because the heart is particularly sensitive to the change in local tri- iodothyronine (T3) levels (4). CVS effects includes: increase heart rate, venous return, and stroke volume resulting in,(5)increased cardiac output, reduced peripheral vascular resistance, and increased atrial automaticity (6).

Cardiovascular Specific complications including atrial fibrillation, heart failure, pulmonary hypertension(7), and dilated cardiomyopathy as well as ventricular arrhythmias are seen in significant proportion of hyperthyroidism patient. (3).

AF occurrence facilitated by reduced interatrial action potential duration via enhancing spreading of left atrium ectopic activity.(8). Experimental studies have shown that TH excess can provoke paroxysmal AF by increasing triggered activity in pulmonary veins.(9)(10)

Heart failure in hyperthyroidism has many facets, which includes high output failure, tachycardia induced cardiomyopathy, precipitation by AF and precipitation by coexistent organic heart disease (11). About 6% of thyrotoxic individuals develop symptoms of heart failure, (12) even though less than 1% develop dilated cardiomyopathy with impaired left ventricular systolic function. Clear relation for development of HF,`with longstanding disease and exaggerated degrees of sinus tachycardia has already established or more commonly with AF in hyperthyroidism patient.(13)

African countries showed that cardiovascular abnormalities are common. Clinical presentations of patients with hyperthyroidism with prevalence ranging between 8-22%, leading to increased morbidity and mortality in this group of patients(14).

Patients with AF and thyroid disease are clinically distinct from those with AF and no thyroid disease is unknown. Furthermore, effectiveness, duration and initiation of anticoagulation for prevention of AF-related thromboembolic events in patients with thyroid disease has not been adequately studied and is controversial.

All current guidelines recommend TSH levels as the principal guide in the treatment of thyroid diseases because TSH is regarded as the most precise indicator of thyroid function(3,6,15)

Treatment options for Graves' disease include antithyroid drugs, radioactive iodine therapy, and surgery, whereas antithyroid drugs are not generally used long term in toxic nodular goiter, because of the high relapse rate of thyrotoxicosis after discontinuation(6).

β blockers are used in symptomatic thyrotoxicosis, and might be the only treatment needed for thyrotoxicosis not caused by excessive production and release of the thyroid hormones. (5)

In African countries, owing to limited availability of radioisotopes, thyrotoxicosis is treated with antithyroid drugs(ATD) or surgery(1).In Ethiopia also similar pattern of treatment and almost all patient on ATD are using PTU (16)(17,18),despite it not being the first line recommended drug from most current guideline.

Optimal duration of ATD therapy for the titration regimen is 12–18 months. Maximum remission rates (50–55%) are achieved within 12–18 months. Measurement of TSH-R-Ab levels prior to stopping ATD therapy is recommended, as it aids in predicting which patients can be weaned from the medication, with normal levels indicating a greater chance of remission(6).Continued L-T4 treatment following initial ATD therapy does not provide any benefit in terms of the recurrence of hyperthyroidism

1.2 Statement of the problem

AF is one of the most common cardiovascular manifestations of hyperthyroidism and occurs frequently in men than in women. It occurs in 2% to 20% of newly diagnosed hyperthyroid patients, compared to 0.5–9.0% of the general population, whereas ~13% of patients with new-onset AF have biochemical evidence of hyperthyroidism.(19).

In comparison to the general population, <1% in <60 years of age to >8% in those >80 years of age, AF occurs in young age in hyperthyroidism patient and is rarely seen in <40 years of age as compared to ~ 25% of those >60 years of age, (20).

Most patients with overt hyperthyroidism caused by Graves' disease or nodular goitre have greater increase in serum T3 than in serum T4, due to a disproportionate increase in both thyroidal T3 secretion and increased extrathyroidal conversion of T4 to T3.

Atrial fibrillation in hyperthyroid human patients is believed to be due to T3 increasing the systolic depolarization and diastolic repolarization, and the decreasing action potential duration, refractory period of the atrial myocardium, and atrial/ventricular nodal refractory period. (21).

The presence of atrial fibrillation at presentation was an independent predictor for the occurrence of CHF. A Taiwan study showed among patients presenting with CHF, 47% had LVEF <50%, predominantly male and had a lower serum T4 level compared to another group. However, LVEF and NYHA functional class improved significantly 3 months after achieving euthyroid status.(12)

An older study found the rate of spontaneous reversion was higher in young men, whereas the presence of congestive cardiac failure adversely affected reversion to sinus rhythm(22). Persistent AF can occur in 35–50% of thyrotoxicosis-related AF patients despite control of hyperthyroidism(23).

Spontaneous reversion of AF within 6 weeks after the return to euthyroid state is an expected outcome in patients <60 years of age who do not have pre-existing heart disease and in whom thyrotoxicosis is of short duration. When AF does not resolve after 3 to 4 months after reaching an euthyroid state, spontaneous reversion to sinus rhythm is unlikely(22).

Main risk factors for the development and persistence of AF in hyperthyroid patients are increasing age, ischemic heart disease, congestive HF, or heart valve disease(22), additionally such patient frequently have a longer duration of hyperthyroidism(24), higher Burch-Warsofsky score ,and higher Cr, UA, ALT, GGT, TBIL, and DBIL levels(25).

In Ethiopia, there is no published study directly assessing the risk factor for persistence of AF or CVS outcomes. Although, a hospital based Study in northwest Ethiopia , largely demonstrated risk factors for persistence and development of AF which is in line with recent studies from China and Taiwan including; long period for resolution of symptoms, long duration of symptom before initiation of ATD and despite treatment with ATD for more than a year, TFTs were normalized in less than one-third of the participants. (18).

Cardioversion may be an option in those who remain in atrial fibrillation after 8-10 weeks of achieving euthyroid state with anticoagulation for at least 3 weeks due to the concern of atrial stunning.(26).

Increase in the risk for thrombosis caused by hypercoagulability is seen in clinical hyperthyroidism. The hypothesis that SCH causes hypercoagulability is not clearly known. The role of the coagulation fibrinolytic system in the pathophysiology of atherosclerosis and arterial thrombosis remains a controversial subject(27)

The risk of ischemic stroke is enhanced by 44% in adults with hyperthyroidism compared to euthyroid controls(28), through a variety of mechanisms including hyperthyroid-induced AF, a possible hypercoagulable state, and/or other autoimmune mechanisms.

However, some in vitro and in vivo studies indicate a hypercoagulability state in hyperthyroidism, but there is insufficient evidence to prove that this state leads to an increased risk of cardiac emboli.(29)in contrary other studies showed overt hyperthyroidism thyrotoxic atrial fibrillation, is clearly associated to cardioembolic stroke(30)(31),

Due to the above controversy, role of anticoagulant therapy is less well defined in AF and hyperthyroidism. However, most recent guideline from AHA and ESC recommends initiation of anticoagulant therapy based on the CHA2DS2-VASc score.

In patients diagnosed with hyperthyroidism, mortality is increased by 20%(32). The excess mortality is attributed to dysrhythmias, cardiac failure, and cerebrovascular disease. The negative impact of thyrotoxicosis on cardiovascular morbidity and mortality remains even at after 25 years treatment for hyperthyroidism.

In a population-based cohort study in Finland, the rate of hospitalization due to cardiovascular disease, including heart failure, atrial fibrillation, hypertension, and cerebrovascular disease, was higher among patients with hyperthyroidism than among the controls. The same group also reported an increased risk of

cardiovascular mortality among subjects with hyperthyroidism compared to the general population even after treatment with radioactive iodine in US.

CHAPTER TWO: LITERATURE REVIEW

2.1. The prevalence of Thyroid Dysfunction:

The extent of thyroid disorders in Africa remains unknown because of under-diagnosis and underreporting but few available studies from Tunisia ,Libya and Ethiopia noted prevalence to be 1.2 to 9.9%(33). According to the UNICEF report in 1993, 78% of the total population of Ethiopia had iodine deficiency(34).

In Ethiopia, Although there is no population-based study regarding the prevalence of thyroid disease, it appears to be not uncommon, from a hospital based study in Addis Ababa done by Mengistu et al is reported to be 1.2% (35). Other Hospital based A cross- sectional study in Jimma on 239 patients in 2018 G.C by Reta et al, aimed to assess the magnitude and pattern of thyroid disorders among patients with anterior neck mass based on clinical decision and serum levels of TFT, among discriminated types of thyroid disorders overt and subclinical hyperthyroidism accounts 14.6% and 17.6% respectively.(36)

2.2. Clinical Manifestations of Hyperthyroidism:

2.2.1. Symptoms

Most patients with overt hyperthyroidism have a dramatic constellation of symptoms characteristically include emotional liability, anxiety, weight loss despite a normal or increased appetite, weakness, tremor, palpitations, heat intolerance and increased perspiration.(3)

While the combination of weight loss and increased appetite is a characteristic finding, due to excessive appetite stimulation. Other symptoms that may be present include hyper defecation, urinary frequency, oligomenorrhea or amenorrhea in women, and gynecomastia and erectile dysfunction in men (37).

Unexplained weight loss, new onset atrial fibrillation, myopathy, menstrual disorders, and gynecomastia are isolated symptoms and signs that should lead to evaluation for hyperthyroidism in patients of any age(5).

Other conditions that should suggest the possibility of hyperthyroidism include osteoporosis, hypercalcemia, heart failure, premature atrial contractions, shortness of breath, and a deterioration in glycaemic control in patients with previously diagnosed diabetes(3).

2.2.2. Physical examination

The physical examination may be notable for hyperactivity, rapid speech and many patients have stare (lid retraction) and lid lag, representing sympathetic hyperactivity.

The skin is typically warm and moist, and the hair may be thin and fine. Tachycardia is common, the pulse is irregularly irregular in patients with atrial fibrillation, systolic hypertension may be present, and the precordium is often hyperdynamic.

Tremor, proximal muscle weakness, and hyperreflexia are other frequent findings. Exophthalmos, periorbital and conjunctival oedema, limitation of eye movement, and infiltrative dermopathy (pretibial myxoedema) occur only in patients with Graves' disease.

Thyroid examination -Thyroid enlargement ranges from minimal to massive in patients with Graves' disease or toxic multinodular goitre. A nonpalpable thyroid or modest thyroid enlargement occurs commonly in older patients with Graves' disease and lymphocytic thyroiditis. The absence of any thyroid enlargement should also suggest struma ovaria single, palpable nodule raises the possibility of an autonomously functioning thyroid adenoma. The thyroid is painful and tender in subacute thyroiditis

2.3. Cardiovascular Outcome of hyperthyroidism

2.3.1. Cardiovascular Outcome of hyperthyroidism patient In Ethiopia

A cross sectional study done by Mulatu and his colleagues, at St. Paul's Hospital on a total of 146 hyperthyroid patients on follow-up in that evaluated for cardiovascular diseases. The mean age was 47.2 years, females accounted for 93.2% of patients. The mean duration of symptoms before presentation was 42 months, 16 (11%) patients had AF and 71 (48.6%) had hypertension. Thyro- cardiac disease was detected in 46.6% of patients. The frequent abnormalities were left ventricular hypertrophy (14.4%), mild diastolic dysfunction (10.9%), moderate to severe mitral regurgitation (8.9%), pulmonary hypertension (8.2%) and dilated cardiomyopathy (4.1%).(17)

2.3.2. New Onset Hyperthyroidism and the Relationship with Atrial Fibrillation-

The prevalence of thyrotoxicosis in patients with AF is 2% to 5%.Although an abnormal TSH level is common in patients with recent-onset AF, only <1% of cases of new-onset AF are caused by overt hyperthyroidism(38–40)

In a British prospective study evaluating the prevalence of cardiovascular abnormalities in 392 patients with overt hyperthyroidism ,AF was present in 29 (7.2%) patients.(9)

Frost et al in a nationwide case control study in Denmark During 20-year period, 40628 patients were followed ± 30 days from the diagnosis of hyperthyroidism to observe for a new onset diagnosis of AF or

atrial flutter. It was found that 8.3% of had a new onset diagnosis of AF or atrial flutter. The adjusted odds ratio of atrial fibrillation was almost doubled in men, and the odds ratio of atrial fibrillation increased by 1.7 per 10-year increment in age. In the presence of IHD, CHF, OR for AF increased 1.8, 3.9, and 2.6-fold respectively.(41)

Sun and colleagues did a retrospective study on 437 hyperthyroid participants who received RAI therapy and from AF group (32 patients) found age and levels of UA, DBIL, and GGT were important risk factors for predicting AF. DBIL levels were predictive of AF, with a specificity of 0.813, a sensitivity of 0.767.(25)

2.3.3. Atrial Fibrillation as a Predictor of Developing Hyperthyroidism:

In a large nationwide cohort study performed in Denmark by Selmer and colleagues, patients who were diagnosed with new onset AF were followed for 13 years. There was a significantly higher incidence of hyperthyroidism being diagnosed particularly in the male ages of 51-60 when compared to the general population of that age without a diagnosis of atrial fibrillation.(42) Another Canadian study was performed testing this association on a smaller scale and failed to show an association(43).

2.3.4. Subclinical hyperthyroidism (SCH) and the association with atrial fibrillation

SCH divided according to its biological severity, into two categories: grade I SCH with lowered but still largely measurable TSH concentration (typically between 0.1 and 0.39 mU/L) and grade II SCH with low or undetectable TSH concentration (typically < 0.1 mU/L). (3)(4). The abnormalities found in patients with SCH are increased HR and prevalence of supraventricular arrhythmias and enhanced left ventricular mass (LVM) (2).

Sawin and his group reported a 2.8-fold increased risk of AF in SCH individuals over the age of 60. Later studies reported similar results. The Rotterdam study performed by Heeringa and colleagues, showed a graded response in patients with atrial fibrillation with thyroxine and lower TSH level.(44)(45,46).TSH is also identified as an independent predictor of developing atrial fibrillation with lower limits of normal increasing risk regardless of free T4 levels.(47)

Siu et al, investigated the incidence, clinical characteristics, and outcome of CHF at the initial presentation in patients with primary hyperthyroidism. Studied 591 consecutive patients: CHF was the presenting condition in 34 patients (5.8%) with hyperthyroidism. The presence of atrial fibrillation at presentation was an independent predictor for the occurrence of CHF. Of the 34 patients with CHF, 47% had LVEF <50%,

predominantly male and had a lower serum T4 level in reduced LVEF patients. In these patients, LVEF and NYHA functional class improved significantly 3 months after achieving euthyroid status.(12)

2.3.5. Persistent Atrial Fibrillation and Associated Factors:

Persistent AF occurred in approximately 35–50%of thyrotoxicosis-related AF patients despite control of hyperthyroidism. In Wong et al study, it was observed that out of a total cohort of 1918 patients; 44 (2.3%) had persistent atrial fibrillation. Alternatively from those 133 patients with thyrotoxicosis-related AF, 33.1% had persistent AF , Spontaneous sinus conversion occurred in 89 (66.9%) in which 85 (94%) patients developed sinus conversion before or within 6 months after having achieved euthyroid.(23).

Siu et al. prospectively studied 160 hyperthyroid patients who had atrial fibrillation and they found that, at one year of follow- up, 74 (46%) patients remained in atrial fibrillation(12). Zhou et al. reported the outcome of 83 thyrotoxicosis-related atrial fibrillation who had undergone radioactive iodine treatment. At up to 5 years of follow-up, persistent atrial fibrillation was observed in 27 (32.5%) patients. (48)In Japan, Nakazawa et al. reported persistent atrial fibrillation in 62 out of 163 (38%) and ~1.7% of patients with newly diagnosed hyperthyroidism would develop persistent AF.

2.3.6. Cardioversion in Those with Atrial Fibrillation and Hyperthyroidism:

Although a relationship between the duration of AF and maintenance of sinus rhythm was found (49): a retrospective series done by Nakazawa et al of 106 patients with thyrotoxicosis induced fibrillation but no other heart disease shows high proportion remaining in sinus rhythm, suggests this influence may be less important than the presence or absence of structural heart disease. Further studies are required to identify those who are good candidates for cardioversion when there is a history of thyrotoxicosis induced fibrillation in absence of structural heart disease

2.3.7. Atrial Fibrillation, Thyrotoxicosis, and Emboli:

In a study performed by de Souza and colleagues, in patients with hyperthyroidism and AF. it was found that only age was an accurate predictor of thrombogenic milieu with the remaining risk factors having a low yield (50). This study further delineates that the decision to initiate anticoagulation in patients who have hyperthyroidism and AF may ideally be done on an individual basis.

Staffurth and colleagues studied 262 patients who had a history of thyrotoxicosis and AF. Of those patients, 8% had episodes of arterial embolism.(51).

Yuen and col- leagues reported a case series of 21 patients with thyrotoxicosis and AF from 210 thyrotoxic patients. So, the overall incidence of systemic emboli was 23% (5 of 21 patients). Systemic embolism was noted in 5 patients (24%), all while the patients were still hyperthyroid. The outcomes of the 189 patients who did not have AF were not reported (30)

Barsela and associate reported a case series of 30 patients with AF from among 142 thyrotoxic patients.12 (40%) had documented embolic events. No thyrotoxic patient who remained in sinus rhythm had an embolic event. There was no significant difference in baseline characteristics; however, the presence or absence of heart failure was not specifically categorized.(52)

Hurley and co-authors described their experience over 6 years with 381 patients who had thyrotoxicosis. Among these, 70 developed AF or atrial flutter and 39 reverted to sinus rhythm during antithyroid therapy. In 8 cases of arterial embolism, 6 patients showed evidence of congestive heart failure (which was not further characterized by the authors), including 2 who were found at autopsy to have mitral stenosis(53). The higher thromboembolic risk in these patients may have been due to these underlying, showed risk factors and not necessarily to the hyperthyroid state.

In the most statistically rigorous clinical trial Petersen and co-investigators retrospectively analyzed 610 patients with thyrotoxicosis, 91 of whom had developed AF. The unadjusted risk of stroke in the AF and sinus groups was, respectively, 6.4% and 1.7% in the 1st year, and 13% versus 2.9% over a mean follow-up period of 39 months. A large age disparity was noted: more than 25% of those older than 60 years developed AF. Only the risk of cerebrovascular events was determined; neither arterial-embolic events nor was the presence of heart failure were not included in this study. Age was the only significant independent risk factor.(30)

Bruere Study was done on 8962 Patients with AF, a total of 715 strokes/systemic embolism were recorded, with no significant difference in the rates of these events in patients with a history of thyroid dysfunction vs those without thyroid(51). These data suggest no additional benefit from the inclusion of thyroid dysfunction in thromboembolic prediction models in AF.

Wong et al, in a hospital based retrospective cohort study, among 1918 patients who had a diagnosis of thyrotoxicosis, 133 (6.9%) patients presented with AF. High rate of ischemic stroke was observed among patients with persistent thyrotoxic AF and older age(23). The Author suggested to monitor factors associated with persistent AF beyond 6 month, especially older people to initiate anticoagulation in a timely manner to reduce risk of ischemic stroke.

Research From Taiwan has shown different results about risks of ischemic stroke in hyperthyroidism patient ; (54) Lin and colleagues study found that hyperthyroidism is associated with an increased risk for ischemic stroke among young adults (18 to 44 year): A total of 3176 patients with hyperthyroidism were included and followed for 5 year . From total sample ,0.7% had ischemic strokes (31 [1.0% of the hyperthyroidism patients] and 167 [0.6% of control patients]). The other study done by Chen et al ,Patients with thyrotoxic AF exhibited statistically significant lower risks of all-cause mortality and ischaemic stroke than those with non-thyrotoxic AF, especially thyrotoxic patients with CHA2DS2-VASc scores ≥1.(55)

In a recently published study from ARISTOTLE trial, data shows no difference in clinical outcomes by thyroid disease history; despite differences in baseline characteristics of patients with and without thyroid disease, their clinical outcomes were similar.(29)

2.4. Other Consequences of Hyperthyroidism

Neuropsychiatric and neurologic manifestations - may experience behavioural and personality changes, such as psychosis, agitation, and depression. Less overt manifestations common in less severe thyrotoxicosis include anxiety, restlessness, irritability, and emotional lability. Insomnia is also common.

Symptoms often worsen in patients with pre-existing psychiatric disorders; it might be accompanied by cognitive impairments, particularly impaired concentration, confusion, poor orientation and immediate recall, amnesia, and constructional difficulties.

Patients with severe hyperthyroidism (thyroid storm) can present with an encephalopathy characterized by behavioural and personality changes, such as psychosis, agitation, and depression, often with seizures. These symptoms are typically accompanied by hyperpyrexia and cardiovascular dysfunction.

Other common neurologic manifestations of hyperthyroidism include tremor, hyperreflexia, and myopathy. Less common manifestations include chorea, polyneuropathy, and headache.

Treatment of hyperthyroidism typically leads to improvement in cognitive and behavioural impairments and other neurologic manifestations. Long-term treatment with antiseizure drugs and other neurologic treatments are typically not required.(56)

Patients with Graves' disease may have other neurologic disorder; like myasthenia gravis which occur presumably because of their shared autoimmune pathogenesis.

Genitourinary- Urinary frequency and nocturia are common in hyperthyroidism, although the mechanism is uncertain. Possible causes include primary polydipsia and hypercalciuria(57).

In women high serum luteinizing hormone (LH), a reduced mid-cycle surge in LH secretion, oligomenorrhea, and anovulatory infertility. Amenorrhea can occur with severe hyperthyroidism.

In men, Serum LH concentrations may be slightly high. Extragonadal conversion of testosterone to estradiol is increased, so that serum estradiol concentrations are high. These changes can cause gynecomastia, reduced libido, and erectile dysfunction. Spermatogenesis is often decreased or abnormal.(37)

Bone - bone resorption, resulting in increased porosity of cortical bone and reduced volume of trabecular bone. Serum alkaline phosphatase and osteocalcin concentrations are high, indicative of increased bone turnover. The increase in bone resorption may lead to an increase in serum calcium concentrations, thereby inhibiting parathyroid hormone secretion and the conversion of calcidiol to calcitriol. In addition, the metabolic clearance rate of calcitriol is increased. These changes can result in impaired calcium absorption and an increase in urinary calcium excretion. The net effect is osteoporosis and an increased fracture risk in patients with chronic hyperthyroidism.(58)

Serum lipids -Patients with hyperthyroidism tend to have low serum total and high-density lipoprotein (HDL) cholesterol concentrations and a low total cholesterol/HDL cholesterol ratio.(59)

Respiratory - Dyspnea on exertion may occur for many reasons in hyperthyroidism. Oxygen consumption and carbon dioxide production increase, changes result in hypoxemia and hypercapnia respectively, both of which stimulate ventilation. Reduced exercise capacity may be largely due to respiratory muscle weakness and decreased lung volume(60).

Gastrointestinal - Weight loss is due primarily to hypermetabolism and secondarily to increased gut motility and the associated hyper defecation and malabsorption; rare patients have steatorrhea. Celiac disease is also more prevalent in patients with Graves' disease.

Hematologic -The red blood cell mass is increased in hyperthyroidism, but the plasma volume is increased more, resulting in a normochromic, normocytic anemia. Serum ferritin concentrations may be high.

2.5. Investigation and Diagnosis of Hyperthyroidism

According to ATA and ESE, diagnosis of hyperthyroidism is based upon thyroid function tests, the best initial test is serum TSH. Diagnosis of overt hyperthyroidism is usually straightforward, except for laboratory error or assay interference due to biotin ingestion, all patients with low serum TSH and high free T4 and/or T3 concentrations have primary hyperthyroidism(6)(3).

Causes of hyperthyroidism may be obvious on presentation; a patient with new onset ophthalmopathy, a large non-nodular thyroid, and moderate to severe hyperthyroidism has Graves' disease. However, if the diagnosis is not apparent, depending on available expertise and resources, measurement of thyrotropin receptor antibodies (TRAb), radioactive iodine uptake, or measurement of thyroidal blood flow on USG.

For a nonpregnant radioactive iodine uptake and scan, Toxic multinodular goitre has multiple areas of focal increased and suppressed uptake, toxic adenoma focal increased uptake and Graves' disease shows diffuse increased uptake or to assess the functionality of nodules which may coexist with Graves' disease. Pregnant, hyperthyroid women, measure TRAb or assess thyroidal blood flow on ultrasonography(5)

2.6. Management of Hyperthyroidism

In recent American and European questionnaire-based surveys, surgery represented the first-line treatment in 0.9% and 2.1% of cases, respectively. However, thyroidectomy is an effective treatment when goiter is large, there is coincident primary hyperparathyroidism or suspicion of malignant nodules, the patient wishes to avoid exposure to ATD or RAI, or facilities for RAI treatment are not available(6).

Cardioversion may be an option in those who remain in atrial fibrillation after 8-10 weeks of remaining in a euthyroid state with anticoagulation for at least 3 weeks due to the concern of atrial stunning.(26). Role of anticoagulant therapy is less well defined in AF and hyperthyroidism, however most recent guideline from AHA and ESC prefer initiation of anticoagulant therapy based on the CHA2DS2-VASc score.

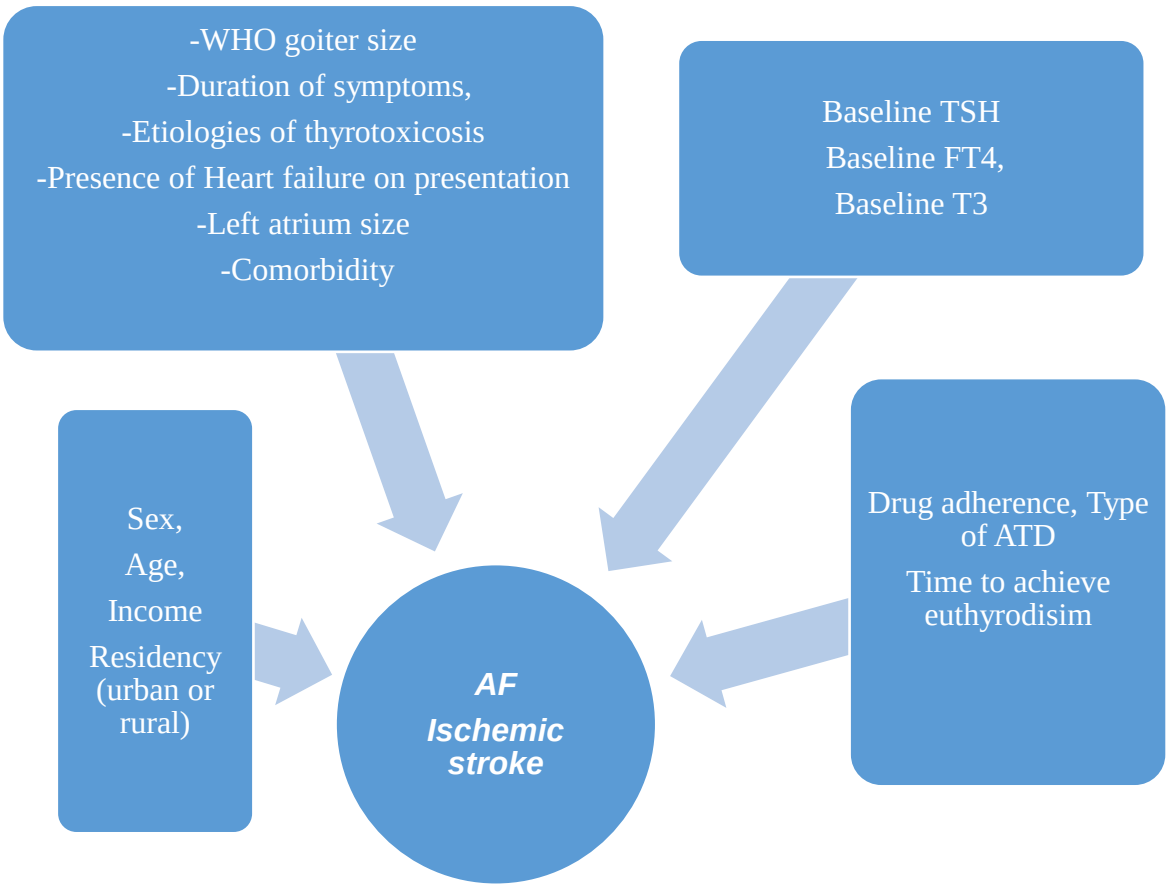
2.7. Mortality of overt Hyperthyroidism

In a meta-analysis by Brandt et al, the mortality of subjects with overt hyperthyroidism was increased by 20% compared with the controls although there was pronounced heterogeneity in the studies included(32).

Register-based Dutch follow-up study of 239,768 individual were associated with increased mortality, for both overt hyperthyroidism (HR=1.12) and subclinical hyperthyroidism (HR=1.09) (24). However, in earlier British Study by Parle et al(40), has shown a significant increases in mortality due to circulatory disease with radioiodine treated patient, is no longer evident during T4 therapy(61).

Timely intervention to decrease mortality and prevention of circulatory disease is important, as evidenced by excess mortality was noted with increasing duration of decreased or elevated serum TSH (24).

2.8Conceptual Framework



CHAPTER THREE: OBJECTIVES

3.1. Objective:

To assess AF and associated cardiovascular disorders among adult patients with hyperthyroidism who were on follow up at JUMC clinic from June 2016 to August 2021.

3.2. Specific Objectives:

3.2.1. To find cardiac disorders among patients with hyperthyroidism.

3.2.2. To find factors associated with development of persistence AF and ischemic stroke among adult patients with hyperthyroidism.

CHAPTER FOUR: MATERIALS AND METHODS

4.1. Study Area and Period

The study was conducted at JUMC referral clinic, in Jimma town, which is in Oromia region, southwest of Ethiopia. JUMC is one of the teaching hospitals in the country which serves as a referral hospital for southwestern Ethiopia. The Jimma zone is part of southwestern Ethiopia and has a total population of 2,773,730 according to projection of figures from the Central static Agency in 2005(Census 2007). Among the different service units in JUMC, chronic illness clinic is worth mentioning, the clinic settled in the new building on ground plus two levels to the North of the internal medicine department. Hyperthyroidism patients are usually seen in Endocrine and general chronic referral clinic which run every Tuesday and Monday respectively and serve about 15-25 patients daily on average. The activities are carried out by one Endocrinologist, three to four residents who rotate every month and nurses.

The study was conducted at JUMC chronic follow up referral clinic on a scheduled date on October 1st to 30th 2021GC.

4.2 Source, Sample and Study population

Source population-All patients visiting JUMC Adult endocrine chronic medical referral clinic from June 2016 G.C to August 2021.G.C.

Sample population -All patients with diagnosis of hyperthyroidism visiting JUMC Adult endocrine chronic medical referral clinic from June 2016 G.C to August 2021. G.C.

Study Population-All adult patients and who fulfill the inclusion from June 2016 G.C to August 2021.G.C.

4.3. Study design

A retrospective cross-sectional study will be employed

4.4. Sample Size and Technique

Sample size was determined purposively, and non-Probability Sampling (Convenient Sampling) Technique used

4.5. Sampling: Procedure

4.5.1 Inclusion criteria

1-Age -greater than eighteen

2-Sex -both Male and Female

3-Diagnosed as having hyperthyroidism according to ATA-2016 and European endocrinology society-2018 Guideline

4.5.2. Exclusion criteria

1- recorded biochemical evidence of hyperthyroidism is unavailable and unable to be determined during the study period.

2- patient medical record incomplete and unable to reach them during the study period for interview and examination

3- patients diagnosed for hypothyroidism and had been on levothyroxine

Initially, All Adult patients (N=194) that have hyperthyroidism from June 2016 G.C to August 2021.G.C. included for medical record review. Afterward, medical records were assessed for eligibility, among them thirty-one patients were excluded. The reason for exclusion, incomplete medical records (N= 10), no ECG record (N=11), no record of thyroid hormone analysis (N=6), pregnant patients (3) and one patient Died immediately after admission to the MICU. Finally, a total of 163 patients who fulfilled the inclusion criteria were included in the final analysis.

4.6. Data Collection

Record review used as an instrument and data collection format (structured questionnaire) used as a tool.

4.7. Measurements

I.7.1 Variables

Dependent Variables

Diagnosed AF according to AHA 2021 guideline with 12 lead surface ECG**,** Persistence AF ***and*** cardiovascular complication

Independent variables

Personal information

Sex, Age, Residency (urban or rural)

Clinical- Spectrum/range of manifestation

Duration of symptoms, Presence of Heart failure, NYHA-class (on presentation) and) Comorbidity

Laboratory

Baseline (TSH, FT4, T3)

Imaging

Echocardiographic finding (LA and LV size, PAAP, EF, structural abnormality, systolic or/and diastolic dysfunction)

Treatment

Type of Drugs used as ATD and rate control, Drug adherence and Definitive treatment (Thyroidectomy and RIT)

4.7.2: Data collection procedure

Patients diagnosed with hyperthyroidism and on follow up were collected based on their chart number from the logbook then their charts retrieved from card room. The information copied to data collection format by reviewing the patients' chart.

The data collection format included the socio-demographic characteristics of the patients, clinical characteristics of the patients, complication and intervention done.

Data collected by two nurses working at chronic clinic and one physician who supervised the data collection procedures. The data collection done by reviewing each patient register chart with supervision of the whole activity by the investigator. The necessary data on associated factors obtained by careful review of the chart.

4.8. Data quality control

Measures undertaken to ensure quality of data including Pre-testing of the data collection instrument three months ahead of data collection at chronic clinic of on five percent of the sample population patients (charts).

Training on data collection for data collectors given before data collection was started and supervision of the data collection process, data storage and management done by principal investigator.

4.9. Data processing and analysis

Collected data checked, entered and analyzed using SPSS windows version 26. Descriptive analysis carried out using frequency, distributions, central tendency and dispersion measures. Presence of statistical association between dependent and independent variables assessed using chi-square and logistic regression. Association with p- value of < 0.05 considered to be statistically significant. Results presented in text, tabulation and figurative presentations from which conclusions and recommendations been made. In addition, results compared with other studies and discussed.

4.10. Ethical consideration

Ethical clearance obtained from Jimma University College of public health and medical sciences Ethical review committee. An official letter obtained from department of internal medicine and given to responsible body at chronic illness clinic. Information obtained from the records kept confidential by not recording participants name and their phone number on questionnaires. Besides, the questionnaires were putted in closed cabinet in the internal medicine department till publication of the study. Also, this subject matter kept confidential if next research needed.

4.11. Operational definitions

- Adherence status - defined according to Morisky's, which has 8 items medication adherence questionnaires. High adherence considered if the patient score 0/8, medium adherence if score is 1-2 out of 8 and low adherence if score is >2 out of 8

- AF is a supraventricular tachyarrhythmia with uncoordinated atrial activation and consequently ineffective atrial contraction. Characteristics on an ECG include irregular R-R intervals ,absence of distinct repeating P waves, and 3) irregular atrial activity(62).
- Comorbidity - Long standing disease conditions which includes DM, CKD, CLD, HTN, VHD, IHD
- Euthyroid range is considered when - TSH =0.4–5.0 mU/L and normal value for FT4 = 10.4–19.6 Pmol/l, T3 = 0.92–2.3 nmol/l and
- GD is an autoimmune disorder in which TRAb stimulate the TSH receptor, increasing thyroid hormone production.
- HF with reduced EF (HFrEF)- Clinical diagnosis of HF and LVEF < 40%.
- Hyperthyroidism- is a form of thyrotoxicosis due to inappropriately high synthesis and secretion of thyroid hormone(s) by the thyroid and suppressed TSH levels and elevated FT3 and/or estimated FT4 levels (1).
- Illiterate – can't read and write and haven't attend formal education
- Income –estimated average amount of cash money an individual earns monthly in terms of Ethiopian currency. For those without monthly salary their raw materials will be estimated in terms of Ethiopian birr.
- New York Heart Association (NYHA) functional classification:

  Class I: No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF

  Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.

  Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.

  Class IV: Unable to perform any activity without symptoms of HF, or symptoms at rest.
- Paroxysmal AF defined as AF episodes lasting no longer than 7 days with spontaneous conversion.
- permanent AF - persistent AF also includes cases of long-standing AF (e.g.,> 1 year), usually leading, in which cardioversion has failed or has been fore gone
- Persistent AF as AF with at least one episode >7 days, or the need for cardioversion.
- Subclinical hyperthyroidism (SCH) defined by biological criteria regardless of the presence of clinical signs of hyperthyroidism. SCH is biologically determined by a concentration of TSH below the normal with concentrations of FT4 and FT3 within the normal range (1).
- Thyrotoxicosis - refers to a clinical state that results from inappropriately high thyroid hormone action in tissues.

- Thyrotoxicosis- TSH level < 0.4 mU/L.
- TMNG is simply a late-stage of goiter that has been round for a while and has a chance to grow and become lumpy or nodules
- TSH, FT4 and T3 normalization: when TSH, FT4 and T3 are within the euthyroid range.
- TSH-induced hyperthyroidism- is an exceedingly rare cause of overt hyperthyroidism, due to either a TSH-secreting pituitary adenoma or partial resistance to the feedback effect of T4 and T3 on TSH secretion
- WHO goiter size

  Grade 0: The goiter is not palpable or visible even when the neck is extended

  Grade 1: The goiter is detected on palpation and/or visible when the neck is extended;

  Grade 2: Goiter is visible when neck is in the normal position;

  Grade 3: Large goiter visible from distance

CHAPTER -FIVE RESULT DISCUSSION AND CONCLUSION

5.1 Result

5.1.1 Sociodemographic

Initially, 193 patient medical records were assessed for eligibility among them thirty patients were excluded because they had incomplete medical records (N= 10), has no ECG record (N=9), had no record of thyroid hormone analysis (N=6), were pregnant patients (3), patient died immediately after admission to the MICU (N=1), A total 163 patients were included in the final analysis. The mean age of the patients was 40.92 years (±1.653), the majority of participants' age range from 40-60 years.

Majority of the patients were female 150 (92.0%), married (81.5%) and followers of Islam139 (85.3%) by Religion, came from urban areas 84 (54%), and ability to read and write of the participants 82(52.8%). Most participants were housewives 42.9%. Additionally, their monthly income is low in 100(61.3%) of them, according to WHO monthly income categories. Socio demographic characteristics of the participant is not associated with AF or Non-AF group, hyperthyroidism cardiovascular complication on analysis done by chi square and univariate analysis, see table 1 below.

Table 1 Socio-demographic characteristic of the patient and their association with presenting AF VS non-AF group and rhythm pattern from ECG taken on follow-up

Variable	Categories	Total Count/%	Across ECG Rhythm distribution- P value / df	AF vs. NON AF 1st ECG p value, OR(CI)
ages	<20	6/3.7%	.865/4	.684,
(yrs.)	20-40	63/38.7		1.16(.55-2.45)
	40-60	82/50.3%		
	.>60	12/7.4%		
sex	male	13/8.0%		.983,
	female	150/92%		1.013
marital	single	22.7%	0.244	.143, .495(.194-1.3).
status	married	74.8%		
	divorced	1.2%		
	widowed	1.2%		
occupatio	student	4.9%	0.143	.560, 1.054(.883-1.3)
n	farmer	18.4%		
	employee	15.3%		
	merchant	3.7%		
	employed	12.9%		
	daily labor	1.8%		
	housewife	42.9%		
Residenc	rural	75/46.0%		.793, .881(.341-2.3)
e	urban	88(54%)		
monthly	low	100/61.3%	0.167	.052,1.923(.993-3.7)
income	low middle	55/33.7%		
	high middle	8/4.9%		

5.1.2Clinical characteristics, comorbidity, and complication

The Mean duration of symptom was 12.72(±8.8) which is associated with increased risk of AF on univariate analysis but not statically significant with multivariable regression analysis. Similarly,

the mean months of follow up was 23.38 (± 15.1, median20) which had no statistical difference in distribution related to Cardiovascular (CV) complication or ECG rhythm pattern, with P value of 0.697 and 0.297, respectively.

Major cardiovascular manifestation was SOB in 80 (58.3%) and Palpitations in 70 (52.1%) of participant patients followed by PND in 39 (29.4%).

According to Framingham criteria HF was diagnosed in 50/163 (30.6%) patients, most of them had NYHA-class 3 in 10 (6.1%) and NYHA-class 4 in 38 (23.3%) of patients and the other two had NYHA class1 and 2 HF on presentation.

Among NYHA class 3 and 4 48 patients twenty-seven of them have AF at presentation. NYHA class 3 and 4 HF at presentation were associated independently and significantly with univariate and multivariable regression with presence of AF.

NYHA improvement is significantly poor in AF patients after treatment with ATD and other HF Guideline directed treatment compared to non-AF hyperthyroidism HF patients. However, HF at presentation and NYHA class at presentation are not indicators for persistence of AF, similarly improvement in NYHA class has no significant difference between types of AF by pairwise comparison. See (Table 3&4).

Majority of patients were tachycardic on presentation with mean value of 115.26 beat/Min (±13.89 & median=115) and hypertension diagnosed in 20.2% of patient according to AHA2021 HTN guideline, on first diagnosis with mean value for SBP and DBP were 116.55(±18.4) and 69.75 (±9.1), respectively.

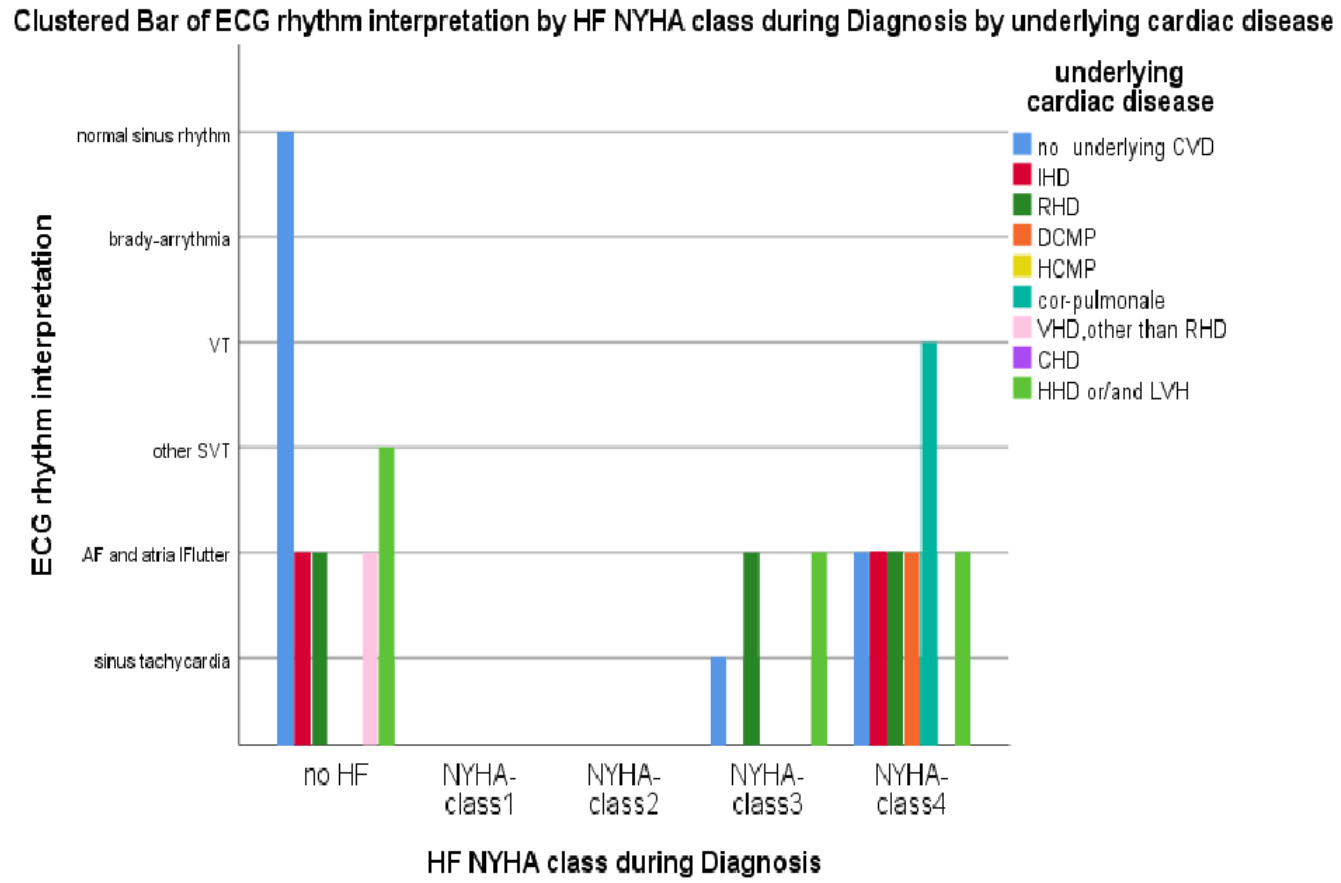
The Goiter size category is documented based on WHO goiter size, Grade 1 in 80(49.1%), and 2 in 45(27.6%), followed by Grade three and zero.

Despite an absence of immunochemical study in JUMC, based on clinical phenotype and US imaging findings TMNG and Graves' disease are the two most common etiologies each of them accounts in 87(53.4%) and 69(42.3%) of patients, respectively. The other unusual causes are toxic adenoma (N=6) and thyroiditis (N=1).

Both the etiology and WHO goiter size have no relationship with CV complication of hyperthyroidism with p value of 0.726 and 0.421, respectively.

Underlying medical disease found in fifty-four patients which includes history of hypertension in 26(16%), cardiac disease in 19(11.7%), DM (N=1), COPD (N=2) and post TB fibrosis (N=1) patients. See fig 1 below for clustered bar illustration of underlying cardiac disease and ECG rhythm interpretation.

Figure 1 clustered bar graph of ECG rhythm distribution by HF NYHA Class during diagnosis by underlying heart disease



Echocardiography examination performed in 59/163(36.2%) of participants, which is done for patients diagnosed with hyperthyroidism and had clinical signs or/and symptoms for cardiovascular complication which includes thirty AF patients.

Systolic dysfunction and Diastolic dysfunction found in 18(11%) and 27(16.6%) of patients, respectively. Estimated PAP was normal in 26 patients; the remaining patients diagnosed with Pulmonary arterial

hypertension (PTH), which was severe in 4(2.4%), Moderate 7(4.3%) and Mild in 22(13.5%) patients (See Table2).

Table 2 imaging and treatment descriptive statistics

Variables	Category	Freq/ %	Category	Freq/ %	Category	Freq/ %
1st ECG	no AF	125/ 76.7	AF	38/ 23.3		
Types of ECG rhythm &AF (Follow up ECG)	Persistence	32/ 19.7	VT	1/ .6	other SVT	8/ 4.9
	Restored Al	6/ 3.7	ST	98/ 60.1	sinus rhythm	24/ 14.7
Baseline Thyroid Hormone level	TSH (m IU/L		FT4 ng/dl/ P mol/L		FT3 pg./ml	
	0.1-0.4	7/ 4.3	<7 / <90	8/ 4.9	<5	51/ 31.3
	undetectabl or <0.1	156/ 95.7	≥7/ ≥9o	155/ 95.1	≥5	112/ 68.7
Echocardiography						
Structural DX	Normal	7/ 4.3	HHD & LVHH	18/ 11.0	IHD	5/ 3.1
	CAMP	13/ 8.0	RHD & OTHERVHD	16/ 9.8		
Ventricular Dysfunction	Normal	15/ 9.2	Systolic dysfunction	16/ 9.8	Diastolic dysfunction	27/ 16.6
Estimated PAP	Normal	26/ 16.0	Mild PHT	22/ 13.5	Moderate PHT	7/ 4.3
Treatment						
Drugs	PTU	160/ 98.2	Carbimazole	3/ 1.8	BB	160/ 98.2
Drug Adherence	Low	11/ 6.7	Medium	108/ 66.3	excellent	44/ 27.0
CHADs2vas2c score	Score ≥2	35/ 21.5	score ≥3	3/ 1.8	Surgery	10/ 6.1%

Diastolic and systolic dysfunction associated with increased risk of AF with univariate regression. However only diastolic dysfunction had repeated the significant increased risk of AF on multivariable regression with p value of .002 and AOR 9.19(CI=2.29-36.84). (See Table 3)

Table 3 – univariate, multivariable and linear regression for AF hyperthyroidism patients

Variable	Univariate analysis			multivariate Analysis	
Independent variable	B	P-value	95% C.I (COR)	P-value	AOR(95% C.I)
LA-size >3.8cm	**3.31**	**<.001**	**9.6-77.4(27.3)**	**.006**	**8.825 (1.893-41.1**
NYHA class 3&4 at DX	**3.34**	**<.001**	**10.7-73.96(28.1)**	**.001**	**9.008(2.414-33.6**
Diastolic Dysfunction	**2.34**	**<.001**	**4.18-25.6(10.35)**	**.019**	**5.505 (1.318-22.9**
Baseline -T3 >5PG	**1.98**	**<.001**	**2.1-24.95(7.3)**	**.002**	**32.165 (3.39-305.**
T3or T4 normalization<12mon	**-2.5**	**.014**	**.826-3.7(1.7)**	**.032**	**.086(.009 - .808)**
Underlying-RHD &VHD	**3.58**	**<.001**	**7.6-168.1 (35.9)**	**.024**	**8.8(1.34-58.97)**
HF at presentation	**3.051**	**<.001**	**8.5-52.4(21.13)**	**.005**	**6.4(0.558-75.1)**
Underlying- corpulmonale	3.3	.001	4.2-181.3(27.5)	.308	3.04 (.36-25.9)
HHD	1.07	.004	1.004-8.4 (2.9)	.01	51.5 (7.97 -42.38)
>9month duration-SX	1.17	.002	1.52-6.86(3.3)	.497	1.807(.328-9.963)
DCMP	3.6	.053	6.1-21.6(3.6)	.47	10.7 (.3-11.1)
Systolic dysfunction	2.44	.001	.038-.202(.087)	.450	
Underlying HTN	1.74	.471	561-3.495 (1.4)	.981	
ECG rate >130/min	1.42	.026	. 1.2-14.5(4,4)	.556	
Linear regression					
	Standardized Coefficients-B		**T**	**P value**	**95.0%CI**
NYHA class 3 &4 CHF	.442		9.558	<.001	.618-.940
HHD	.378		6.941	<.001	.303-.545
LAZISE≥3.8CM	.312		6.670	<.001	.387-.712
baseline FT3	.201		3.043	.003	.079-.371
Diastolic Dysfunction	.168		2.194	.030	.016-.307
RHD &VHD	.094		2.170	.032	.008-.163
Anova	Df		Mean Square	F	Sig.
Regression	6		3.040	59.917	.000h

Predictors: (Constant), NYHA class at first presentation, underlying Cardiac HHD AND RHD, LA size baseline FT3, and diastolic Dysfunction

PAP, diastolic and systolic dysfunction detected on echocardiography is not significantly different in patients with persistent atrial fibrillation and spontaneous reversal of atrial fibrillation.

The mean LA (left atrium) diameter for persistence AF and spontaneously restored (paroxysmal AF) was 4.13± 0.6cm and 3.95± 0.43cm, respectively. LA diameter >3.8cm is found more in the AF group compared with non-AF group with p value of .006 and AOR=8.83 (95% CI= 1.89-41.15). However, LA diameter was not statically different in patients having persistent atrial fibrillation from those who have spontaneous reversed atrial fibrillations by pairwise comparison.

Structural heart disease found on Echocardiography (N=52); HHD or LVH in 18 (11.0%), RHD and other causes of VHD in 16 (9.8%), dilated cardiomyopathy in 13(8.0%), and IHD in 5 (3.1%) patients.

Hyperthyroidism related cardiovascular (CV) complication including HF, systolic and diastolic dysfunction, Pulmonary hypertension, newly diagnosed DCMP and exacerbation of underlying cardiac disease. Identified significantly associated Factors with CV complication were, AF (p < .001& AOR= 7.3), underlying cardiac disease (P value =002 & AOR=3.25), LA-size (P=.001& AOR=3.36) and baseline FT3 (p =.041& AOR=2.1). However, LA-size and baseline FT3 were the two predictors for Hyperthyroidism CV complication on linear regression with standardized B coefficient .369 (p value .001) and standardized B coefficient .332 (p value .041), respectively.

AF with or without HF at presentation diagnosed in 38(23.3%) patients among them 32(19.6%) have persistent AF.

Identified factor which were associated independently and significantly with AF in a representative sample of hyperthyroidism patients includes: HF at presentation; p value of 0.005 and AOR=6.75 (CI=1.78-25.69)), NYHA class 3 & 4 CHF at DX; p value .001 and AOR9.008(CI=2.414-33.617) , Diastolic Dysfunction ;p value .019 and AOR 5.505 (1.318-22.998), LA-size >3.8cm; P value .006 and AOR 8.825 (1.893-41.152), Baseline -T3 >5PG/ml; P value .002 and AOR 32.165 (3.39-305.067) , RHD &/or other VHD; p value .024 and AOR= 8.8 (CI=1.3-58.9), HHD; P value .01 and AOR 51.5 (7.97 -42.38)) and T3or T4 normalization in < 12 month; p value .032 and AOR=.086(CI=.009 - .808),

NYHA class 3 and 4 CHF on presentation, LA-SIZE ≥3.8cm, RHD &VHD and HHD, baseline FT3 and diastolic Dysfunction were predictors of AF in hyperthyroidism patients with p value of <0.001.

Although it needs Holter ECG monitoring to differentiate sinus conversion or paroxysmal AF despite that limitation, six patients demonstrated sinus rhythm on subsequent follow up ECG and patient reporting of

clinical improvement associated with AF taken as restored AF. Moreover, normal levels of FT3 and FT4 were achieved in less than 6 months in 4/6 patients and at 12 months in the remaining two patients.

Persistence thyrotoxic AF in 32 (19.2%) of patients. During this period other rhythms found other than persisted AF were normal sinus rhythm and sinus tachycardia in 122(74.7%), other SVT in eight and VT in one patient.

Factors associated with AF are similar distribution along types of AF (persistence, transient or permanent) except age.

Table 4-pairwise analysis for types of AF

Dependent-variable persistence AF	Bi_ variant		Multi-variable regression	Hodges-Lehman Median Difference
Independent variable	P Value	AOR (95%CI)	P-value,AOR (95%CI)	P-value/Estimate(95%CI)
AGE	**.046**	**1.89(1.79-2.9)**	**.046,1.89(1.79-1.9)**	**.029/10 (1-2)**
LA-size	**.001**	**8.3(2.32-29.5)**	**.507, 2.1 (.38-7.2)**	**.551/-.2(-.8 -40)**
T3/4.normalization	**.053**	**.23(.04-1.02)**	**.846,.83(.13-5.3)**	**.511-1.528**
Duration of symptom	**.314**	**1.2(.132-5.3)**	**0.521**	**.47/2.5(-4-6)**
DBP	.357	1.1(.94-1.19)		.132/1.0(-10-1)
VHD and RHD	.67	.67(.10-4.34)		.063/2.0(.00-5)
HHD	.317	.37(.05-2.6)		.115
HTN	.429	.46 (.07-3.1)		.598
ECG rate >130/min	.373	4(.19-84.2)		
HF at presentation	.797	1.3(.198-8.2)		
Diastolic dysfunction	.888	.88(.15-5.05)		
baseline FT3(1)	.947	1.08(.09-12.9)		

AF tends to persistence with increasing age, which increased the risk of persistence AF ,with p value of 046 AOR =1.890(.794=.998) with multivariate regression and it is also the only predictor of persistence of AF by linear Regression. However, factors like longer duration of symptom, LA-size >3.8cm, HF at presentation and Diastolic dysfunction on echocardiography higher in persistence AF patients but they are not statically significant. Pair wise comparison across spontaneous and persistence AF by Kruskal-Wallis

Test and Mann-Whitney U Test used according to data distribution, age show significant difference along types of AF with P value of .029 and Estimate 10.0(CI=1-20) by Independent-Samples Hodges-Lehmann Median Difference

In non-AF hyperthyroidism patient CV complication occurred in Sixteen (9.8%) patient, who have presented with HF in 10/16 patients with or without other associated cardiovascular complication including pulmonary hypertension (N=8), diastolic dysfunction (N=11) and newly diagnosed dilated cardiomyopathy (N=7) and LVH/HHD (N=9).

Baseline TSH <0.01miu/L associated with Hyperthyroidism cardiovascular complication with p value <.001 and with AOR= .014 (.001- .129) and is the only predictor in non-AF patients. Baseline FT4 and TSH showed similar distribution among patients with AF and non-AF Patients with p value of 0.864and 0.246, respectively.

Underlying HHD is associated with increased CV related complication in non-AF group but is not statically significant with p value .189 and AOR= 5.2(CI .44-61.2) on multivariate analysis.

Thromboembolic disease or associated imaging findings are seen exclusively in persistence AF which are echo contrast (N=2) and LV thrombus (N=1) and ischemic stroke (N=1) which.

Ischemic stroke seen in only one patient 60 years old male patient and has multiple comorbidities, who had also persistent thyrotoxic AF.

Among 163 of the patients included in this study, 160 (98.2%) of them were taking propylthiouracil (PTU) and the remaining 3(1.8%) were on Carbimazole as antithyroid drug (AED), it might be due to methimazole or carbimazole are not easily available locally and expensive.

Similarly, almost all patients were taking rate controller either BB 161(98.8%) or CCB 2(1.2%) as rate controller medication. On the other hand, Surgery (thyroidectomy) as definitive treatment is done only for 11(6.1%) of patients. Majority of Patients adherence for ATD were medium and low based on Morisky score.

Anticoagulant was prescribed only for 03 patients among AF patients despite some of them having an indication based on CHADS2 VASC 2 score.

128 (78.5%) and 53 (32.5%) of patients has not achieved normalization of TSH and FT4/FT3, respectively.in addition to majority of patient not achieved normalization of TSH and FT4/FT3, normalized after 6-12 month of treatment only in 29 (17.8 %) and 12(7.4%) patients, respectively.

AF patient less achieving T3 or T4 normalization in less than 12 months compared to non-AF patients with B value of -2.3 and p value of .032 (AOR=.086 &CI=.009 - .808) but not significant along types of AF (see fig2 and 3).

Figure 2 pie chart for normalization of TSH in hyperthyroidism patient

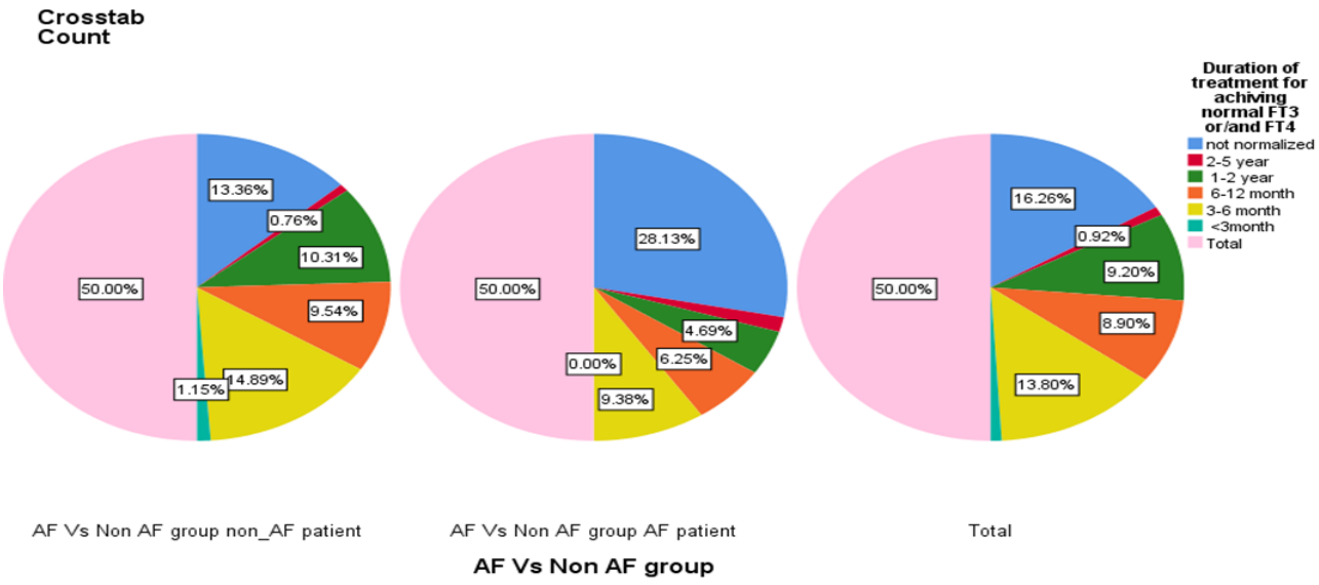
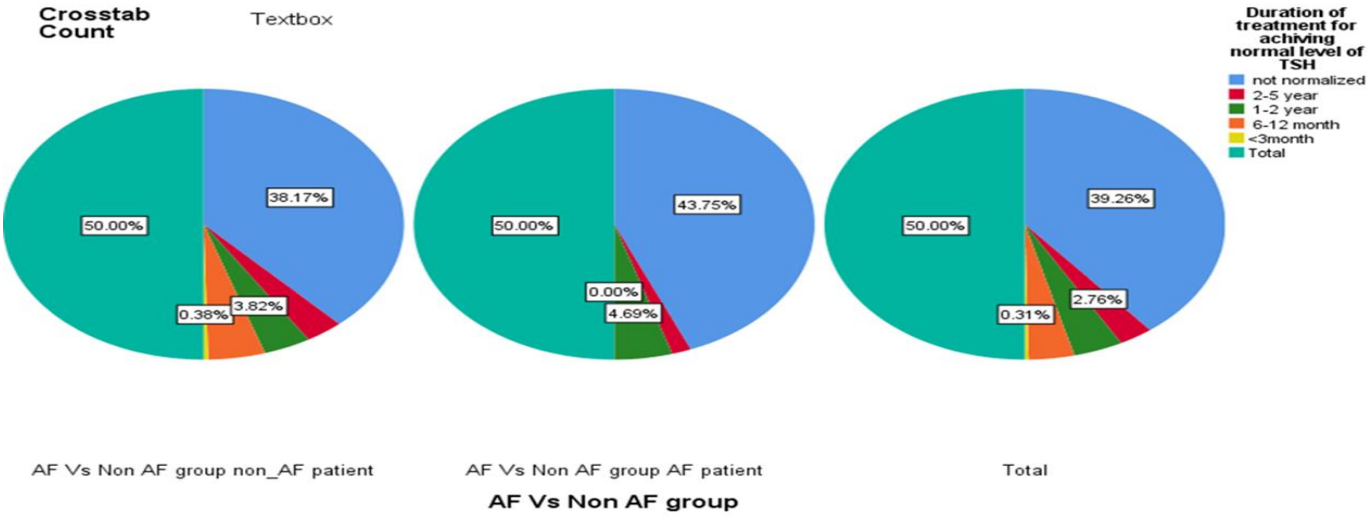


Figure 3 pie chart for normalization of T3/4 in hyperthyroidism patient



5.2 Discussion

The mean Age of patients was (40.92±11.653),which was younger as compared to a population based study done in Jimma in which the mean age was 63.3 ± 11.9 (63). Additionally, the prevalence of AF in our study young hyperthyroidism patient was higher (N=32,19.8 %) as compared to above study (4.3% (27/634)). Similarly AF incidence was higher in hyperthyroidism young patients Compared to the general population in other western study(64),The higher incidence of AF in young hyperthyroidism patients might be due to higher prevalence of hyperthyroidism in younger age group compared to the general population in which AF is often caused by structural heart disease mainly attributed to Ischemic heart disease and other degenerative heart disease.

In our study thyro-cardiac in disease was found in 31.9% of participants among them AF was found in 23.3%. the prevalence of AF and thyro-cardiac disease is higher in our study as compared to a study done in north west Ethiopia in which AF was found in 5.245%, CHF in 0.96% and CHF + AF in 7.62% of patients (18). Similarly, another Ethiopian study which was done in Addis Ababa showed; AF in 11% which is lower than stated prevalence of AF in our study, but the same study found higher prevalence of thyro-cardiac disease (46.6%) compared with our study (31 %) (17).

The prevalence of AF seems higher in Ethiopia as its seen from our study and Addis Ababa study which are described above (17) which is also seen in our study as compared to western study in which AF found only in 7.2% of patients. The increasing prevalence can be explained by; a high prevalence of CVD in our study patients(41)., long duration of symptom before treatment of hyperthyroidism and, failure to achieve euthyroidism in early phase of diagnosis and treatment, as all mentioned factors are identified risk factors for development of AF.

A Population based Danish study showed AF is more common in overt hyperthyroidism with increasing age, male gender, and underlying cardiovascular disease, especially CAD, congestive heart failure, and valvular heart diseases (41). This study also found comparable results except male in gender and age which were not significantly affecting the occurrence of AF in our study similar with a Chinese study done in 2010GC (54).

The risk of AF increases significantly with Underlying HTN, ECG rate >130/min, and duration of symptom >9 month on univariate regression but not repeated a significant association on multivariate regression. (See table 3).

Predictors of AF in a representative sample of patients with hyperthyroidism found these independent variables are NYHA class 3 & 4 at DX, diastolic dysfunction, LA-size >3.8cm, Baseline T3 >5PG/ml and underlying CVD.

Underlying CVD (VHD including RHD & HHD) were demonstrated as a predictor of AF by Bar-Sela et al, studies like our study, rheumatic or hypertensive heart disease were significantly associated with the presence of AF.

Interestingly in these retrospective cohort study in a patient with overt thyroid dysfunction increasing serum T3 concentration >5pg/ml is increasing risk of AF 8.3× (CI 41.18-58.59) in hyperthyroidism patient with p value of 0.033 and an independent predictor for presence of AF (p value=0.03). This association is consistent with a recent animal study showed T3 increases systolic depolarization and diastolic repolarization, and decreases the action potential duration, refractory period of the atrial myocardium, and atrial/ventricular nodal refractory period which result AF in hyperthyroidism patients(21).

Ischemic stroke occurred only in one 60 years old male patient, who had multiple comorbidities before being diagnosed with hyperthyroidism which includes, HTN, DM and IHD. A study by Bruere et al, similarly showed hyperthyroidism is not an independent risk factor for stroke/systemic embolism in atrial fibrillation(51), Similarly, In a recently published study from ARISTOTLE trial, data shows no difference in cardio embolism by thyroid disease history; despite differences in baseline characteristics of patients with and without thyroid disease, their clinical outcomes were similar.(29)

The Mean follow up of the patient was 23.38 month (±15.1) and median of 20 months. Over this period of follow up, spontaneous sinus conversion occurred in only 6/38(15.7%) patients over a period of 6month to 12 months, which is small number of patients achieving sinus rhythm as compared to a Taiwan study in 85(94%) of patients achieving sinus rhythm (23).

Persistence of thyrotoxic AF occurred in 32/38 (84.3%) and 19.2% of newly diagnosed AF patients and of total hyperthyroidism patients respectively. which is much higher compared to a Japan study 62 out of 16 (38%) newly diagnosed AF patients and 1.6 % of newly diagnosed hyperthyroidism patient developed persistent AF (65)

Even though, Age was not affecting the development of AF in hyperthyroidism patients (N=163) in our study, it is found to be as the only significant factor with persistence of AF in separate analysis of AF patients (N=38). In a patient once developed AF tends to persist with p value of .046 AOR =1.890(1.79-1.998) in greater than 40 years old patients. Similarly, by pairwise comparison with paroxysmal AF and age showed significant difference among types of AF with P value of .029. Estimate 10(CI =1-20) by Independent-Samples Hodges-Lehmann Median Difference.

The above finding of our study is comparable with other study done by Hurley et al., in which being young was one of the important factors for reversion of atrial fibrillation(53).However, other important factors from above study and Yamamoto et al. are not significantly associated with reversion of AF in our study which were, recent onset of AF, absence of other heart disease and onset of induced hypothyroidism.

5.3 Conclusion

This study found AF in 38 (23.3%) of hyperthyroidism patients, among them its Persistence in 32(19.2%). All six patients restoring sinus rhythm were not in euthyroid state but were achieving normal value for T3 and T4 level which is normalized in less than 6 months in 4 of patients and in <12 months in two of them.

Clinical characteristics and imaging finding which were associated significantly with AF in a representative sample of patients with hyperthyroidism including HF, NYHA class 3 & 4 CHF at DX, Diastolic Dysfunction LA-size >3.8cm, Baseline -T3 >5PG/ml, T3or T4 normalization<12mon and underlying CVD (RHD &/or other VHD, HHD).

Predictors of AF in hyperthyroidism patients with p value of <0.001 were NYHA class 3and 4 CHF on presentation, LA-SIZE ≥3.8cm, RHD &VHD and HHD, baseline FT3 and diastolic Dysfunction.

Factors associated with AF are similarly distributed among types of AF except age, which is the only independent and significant factors associated persistence of AF (p value=0.049 and AOR-1.89)

5.4 Recommendation

1. Recommendation for community

Health education about early symptom of hyperthyroidism should be given to seek medical care as early as possible and to avoid CV complication.

2. Recommendation for clinicians

It’s important to meticulously search for identified Risk factors for AF during work up at diagnosis and follow up.

Goal directed treatment to achieve normalization of T3 or/and t4 concentration in < 6 month is desirable.

Regular individualized joint follows up by Endocrinologist and cardiologist with clear aim should be considered for AF with hyperthyroidism patients.

We should consider using other alternative ATD or definitive treatment for unresponsive patients with usual ATD, especially for hyperthyroidism patients with considerable risk for cardiovascular complication.

It’s better to consider surgical management as definitive treatment in our setup during early period of diagnosis to get the benefit of euthyroid state in restoring AF

3. Recommendation for Hospital administration

It’s advisable to work on available alternative treatment modalities for definitive treatment as radioiodine therapy.

It’s important to make sure ATD with proven efficacy with affordable price to be available in governmental pharmacy especially for low-income population.

We recommend increasing the number of days in which thyroid hormone analysis is done in JUMC and to work on the capacity of immunohistochemical laboratories to classify etiology of Hyperthyroidism accurately.

4. Recommendation for researchers

Further prospective study to identify additional factors with hyperthyroidism related cardiovascular complication

5. Recommendation for government.

The FMOH can include hyperthyroidism as preventable NCD and act accordingly mainly to prevent avoidable CV complication of hyperthyroidism

5.5 Limitations

Limitation

- Main limitations of this study were its retrospective nature
- Echocardiography was done only for 59 patients and all patients with AF had no echocardiography,
- AF patients might be misclassified as we used resting 12 lead ECG record on diagnosis and subsequent follow up to classify them as persistent or paroxysmal.
- Etiology of hyperthyroidism is classified based on clinical phenotype which is not recommended way of identifying the etiology of hyperthyroidism

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ANNEX 1: DATA COLLECTION INSTRUMENT

Questionnaire

Topic- ASSESMENT OF AF AND OTHER CARDIOVASCULAR DISORDERS AMONG ADULT HYPERTHYROIDISM PATIENT AT JIMMA UNIVERSITY FOLLOW UP CLINICS FROM JUNE 2016- AUGUST 2021 G.C

Instructions: Dear data collector, the aim of this study is to examine factors associated with persistence AF and ischemic stroke in hyperthyroidism patient. The results of the study will help us to know possible factors associated with persistent atrial fibrillation and ischemic stroke in hyperthyroidism. Furthermore, the findings of this study could be useful in planning health promotion and disease control programs for patient who comes with AF and hyperthyroidism. So, you are kindly requested to revise each chart thoroughly, interview the respective clients carefully and record on the designed check list

General information

Questionnaire Code ……. MRN number /Card Number----------

Part one: Socio-demographic and economic characteristics of the participant or attendant

1. Age ……(years)

2. Sex: 1. Male 2. Female

3. Ethnicity: 1. Oromo 2. Amhara 3. Kaffa/Dawuro 4. Gurage 5. Tigre 6. Other (specify)…….

4. Religion: 1. Muslim 2. Orthodox 3. Protestant 4. Wakefata 5. Other (specify)……

5. Marital status: 1. Single 2. Married 3. Divorced 4. Widowed

6. Residence: 1. Rural 2. Urban

7. Estimated distance from hospital _____ (km) OR _____(minutes)

8. Education: 1. No formal education, 2. Able to read and write, 3. Primary (grade 1-8) 4. Secondary (grade 9-12), 5. University/college and above

9. Occupation 1. Student 2. Farmer 3. Government employee 4. Merchant (business man/woman) 5. Unemployed 6. Daily labor 7. House wife 8. Other (Specify)……

10. Average monthly income in ETB (converted from 2020 World Bank category): 1. <3,100(low) 2. 3100 - 12,100(low middle) 3. 12,101 - 37, 600 (high middle) 4. >37,600(high)

Part two: Clinical characteristics of the participants

11. Duration of Thyrotoxicosis diagnosis in months …….

12. Duration of symptoms before diagnosis in months …….

13. Follow up in the clinic (in Years) ……

14. WHO goiter size 1. Grade 0: The goiter is not palpable/visible even when the neck is extended2. Grade 1: The goiter is detected on palpation and/or visible when the neck is extended 3. Grade 2: Goiter is visible when neck is in the normal position

4. Grade 3: Large goiter visible from distance.

15. Does the patient have HF on first presentation based on Framingham criteria A) yes B) No?

16. Etiologies of thyrotoxicosis 1. GD 2. TMNG 3. Thyroiditis 4. Toxic adenoma 5. Other specify

17. Does the patient have any of this Underlying medical condition before or at diagnosis of hyperthyroidism?

1.Cardiac disease, 2. HTN 3 .DM 4Alcohol history 5. COPD, 6. Smoking, 7 Khat chewing

8. Other (specify)…….

18. If the underlying medical condition was Cardiac disease, which one of the following is identified?

1.IHD 2. RHD 3. DCMP 4. HCMP 5. Other (specify)…….....

19. Does the patient have any Complications of Thyrotoxicosis? 1. Yes 2. No

20. If the response is yes to Q no 19, which complication has been identified? 1. CHF 2. AF 3. CHF+AF 4. Thyroid storm 5. Thromboembolism 6. other please specify

21. If the patient has been diagnosed with HF, what was the NYHA class during diagnosis? 1. NYHA Class I 2. NYHA Class II 3. NYHA Class III 4. NYHA Class IV

22. If the patient has been diagnosed with HF, what is the current NYHA class? 1. NYHA Class I 2. NYHA Class II 3. NYHA Class III 4. NYHA Class IV

23. Duration of Atrial fibrillation (AF) diagnosis (if any) …….

24. ECG (please keep a copy of the ECG) 1.HR……. 2. Other findings ……

25. Did the patient have history of stroke or TIA? 1. Yes 2. No

26. If yes is to question 25 , when it is diagnosed, Type and territory of stroke ----------

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27. Base line TSH 1. < 0.4 2) undetectable

28. Baseline FT4 1. <7 ng/dl or < 90 pmol/liter 2. > 7 ng/dl or >90 pmol/liter

29. Baseline FT3 1. > 5 pg./ml 2. <5 pg./ml

30. ECHO finding (conclusion and Left Atrium size) ……

Part three: Treatment

31. Time on ATDs (in Years) ……

32. Which ATD is being used? 1)PTU 2) carbimazole 3) Methimazole

33. Experienced drug side effect

1.GI intolerance 2. Rash 3. Arthralgia 4. Hepatitis

5. Agranulocytosis

34. Does the patient take any drug for rate control? 1.yes 2 No

35. If the answer is yes for Q No 34 Which drugs is used for rate control?

1. B-blocker 2. CCB 3. Digoxin 4. Other(specify)……

36. After diagnosis of hyperthyroidism: time since normalization of TFTs (if its normalized)

1. < 3 month 2. 3 -6 month 3. > 1 years 4. >2 years

37. Does the patient take any anticoagulant? 1. Yes 2. No

38. If yes to question 37, what was the indication for anticoagulation?

1. Mitral stenosis 2. CHA2DS2-VASc score≥2 3. Thrombus 4. Prostatic valve 5. Other (specify----------

39. Which anticoagulant is he/she is taking and for how many years ?----------
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40. If your answer is no Q 37 but do you think the patient have indication for anticoagulation?
1. Yes 2. No

41. If yes to question no 40, which indication does he / she have?

1. Mitral stenosis 2. CHA2DS2-VASc score≥2 3. Thrombus 4. Prostatic valve 5. Other (specify----------
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Part 4. Assessment of adherence

42 Based on Morinsky score Adherence is 1. High =0 2. Medium=1-2 3. Low =3-8

43 What was the reason for Drug discontinuation? (Multiple answer possible)

1. Forget fullness 2. Inconvenient work schedule 3. Unaffordability (cost) 4. Don't believe in the medication 5. Fear of side effect 6. Irregular or poor drug supply 7. Lack of awareness about the treatment's objective 8. Lack of awareness about the disease 9. Long distance from treatment setting 10. Other (specify) _____

Thank you very much!

…… ……..

Name and signature of data collector Name and signature of principal investigator