



ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCE SCHOOL OF MEDICINE
DEPARTMENT OF INTERNAL MEDICINE

**THE PREVALENCE AND DETERMINANTS OF THROMBOEMBOLIC
EVENTS AMONG RHEUMATIC HEART DISEASE PATIENTS WITH
ATRIAL FIBRILLATION AT TASH ADULT CARDIAC OPD FOLLOW-UP
IN ADDIS ABABA ETHIOPIA FROM JUNE 31 2018 TO OCTOBER 31 2024,
A RETROSPECTIVE CHART REVIEW**

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RESIDENT)**

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INTERNIST AND CARDIOLOGIST)**

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A RESEARCH THESIS WILL BE SUBMITTED TO ADDIS ABABA UNIVERSITY
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Title of the research	The prevalence and determinants of thromboembolic events among rheumatic heart disease patients with atrial fibrillation at TASH adult cardiac OPD clinic in Addis Ababa Ethiopia, a retrospective chart review
Duration of the study	FROM JUNE 31 2016 TO OCTOBER 31 2024
Study area	Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia
Total cost	25,940 Ethiopian birr.
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Lists of Abbreviation

AF–atrial fibrillation

APS. Antiphospholipid syndrome

A.R–Aortic regurgitation

A.S. aortic stenosis

DVT. Deep venous thrombosis

Hx.= HISTORY

INR. International normalized ration

No.= number

MS–mitral stenosis

M.R–mitral regurgitation

TASH. Tikur Anbessa specialized hospital

T.R–tricuspid regurgitation

T.S. tricuspid stenosis

P.E. pulmonary thrombosis

P.R. pulmonary regurgitation

P.S. pulmonary stenosis

PAD. Peripheral arterial disease

RHD-Rheumatic heart disease

Abstract

Background: Rheumatic heart disease (RHD) combined with atrial fibrillation (AF) significantly contributes to thromboembolic complications, including ischemic stroke. The coexistence of these conditions increases the risk of cardiovascular issues, underscoring the need for targeted management strategies.

Objective: This study aims to assess the prevalence and determinants of thromboembolic events among patients with RHD and AF at the TASH adult cardiac outpatient clinic in Addis Ababa, Ethiopia, from June 31, 2016, to October 31, 2024.

Methods: This institution-based retrospective chart review included 182 adult patients with RHD and AF who met the inclusion and exclusion criteria. Data were gathered from electronic medical records, and binary logistic regression was employed to analyze the relationship between independent variables and the occurrence of thromboembolic events.

Results: The study population predominantly consisted of female participants (70.9%, 129/182), with a mean age of 40.37 ± 13.01 years. The overall rate of cardioembolic events, which included strokes, was 19.78% (36/182), with stroke occurring in 18.1% (33/182) of the participants. Significant factors associated with cardioembolic events included: disease duration (AOR: 1.07, 95% CI: 1.03–1.13, $P = 0.002$), left atrial size (AOR: 1.14, 95% CI: 1.07–1.24, $P = 0.001$), presence of left atrial thrombus (AOR: 9.83, 95% CI: 1.53–63.21, $P = 0.01$), mitral stenosis (AOR: 1.88, 95% CI: 1.21–17.14, $P = 0.04$), and Subtherapeutic INR levels (<2) (AOR: 4.27, 95% CI: 1.15–15.94, $P = 0.03$).

Conclusion and recommendation: This study highlights the high prevalence of cardioembolic events in patients with RHD and AF, identifying both modifiable and non-modifiable factors that contribute to increased risk. Monitoring left atrial size and INR levels could help reduce the risk of thromboembolic complications. Further research is needed to develop preventive strategies and optimize management to improve patient outcomes.

Keywords: RHD, AF, Cardioembolic Complications, stroke, Ethiopia.

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1. Introduction

1.2 Background

Rheumatic heart disease (RHD) is a life-threatening heart condition that results from damage to heart valves caused by one or several episodes of rheumatic fever, an autoimmune inflammatory reaction to infection with streptococcal bacteria (streptococcal pharyngitis or strep throat).

RHD is the most common form of cardiac disease that affects people of low socioeconomic status, with a worldwide prevalence of 40.5 million individuals (1).

Thromboembolic (ischemic stroke and systemic peripheral embolism) events are one of the complications of rheumatic heart disease patients with AF, with significant morbidity and mortality burden. AF is the most common arrhythmia that is associated with a high risk of stroke (2).

It is estimated that 3–7.5% of all strokes in less developed countries are related to RHD, which represents 144 000–360 000 strokes and 108 000–269 000 stroke-related deaths each year, and 640 000–1.6 million stroke survivors in less developed countries (3). A hospital-based stroke registry in Iran found RHD in almost 45% of patients admitted with Cardioembolic stroke (4), and in India, 29% of cardioembolic strokes are due to RHD (5).

The prevalence of cardioembolic events among RHD patients in Ethiopia is 9.2% and the presence of AF was associated with increased risk cardioembolic events (6). The data regarding the prevalence of thromboembolic complications among RHD patients with AF in Ethiopia is not comprehensive.

1.2 Statement of the Problem

RHD is sufficiently important as a cause of stroke to warrant the attention of research communities, especially in developing countries. However, less importance has been placed on the association of stroke in patients with RHD and AF because most stroke research takes place in high-income countries where RHD is becoming a rare occurrence. In addition to its morbidity, the case-fatality of stroke with RHD ranged from 8.5% to 47.4% in Asia in the last three decades and it was 49.2% in America by 1951(7)

The presence of atrial fibrillation is found to result additional significantly increased burden of stroke among patients with RHD and it was found stroke risk was increased about 18-fold in RHD with AF compared to whereas it was increased just 5-fold in patients with AF alone.

Possibly due to decreased detection of this sequelae stroke, peripheral embolisms were reported more frequently in patients living in upper-middle-income countries compared with those from lower-middle-where the overall prevalence of stroke was stroke 7.1%(8). AF-related cardioembolic strokes are associated with poor functional outcomes, a high risk of permanent severe disability, and high early mortality (9).

In Addis Ababa, black TASH among stroke patients with associated Valvar heart disease (VHD) accounted for 40% of all heart diseases, and almost half of these also had AF of which none were on treatment (10), RHD was the second commonest risk factors present in 28.8% of strong in the young admitted at black lion hospital and 42.9% of rheumatic heart disease patient had associated AF, all they had mitral stenosis(11), Cardioembolic events were reported in 67 (9.2%) patients, and the presence of AF ($p=0.02$) and sub-therapeutic anticoagulation status was found have significant association (6)

1.3. Rationale of the study

The presence of AF and factors like the prevalence of enlarged atrium, left atrial spontaneous echo contrast, older age, and Subtherapeutic anticoagulation are associated with the occurrence of cardioembolic events among RHD and among other groups of patients without RHD. Which is a complication with significant mortality and morbidity (8)

However, information about this complication in the specific group of patients who are RHD with AF is not comprehensive in Ethiopia and Africa as a whole. Hence this study tries to fill the gap by studying the prevalence of cardioembolic events and it`s determinates in this group of patients.

1.4 Significance of the study

This study will provide the information and serve as a source of knowledge regarding the magnitude of thromboembolic complications in this group of patients and identifying factors that affect its occurrences that can be translated to patient care in cardiology, internal medicine as a whole, and neurology as well with subsequent improvement of patient outcome and quality of life

2. Literature reviews

In cohort population-based, The Framingham study highlighted that chronic AF, with or without RHD, was associated with an 18-fold increased incidence of stroke, which further escalated with the duration of AF (12). A systematic review of 21 observational studies reported that the proportion of RHD in ischemic stroke patients ranged from 3.4% to 23.2% in Asia and 1.8% to 2.0% in Europe and North America over the past three decades (13). Furthermore, in patients with coexisting Valvular heart disease (VHD), AF was associated with a higher risk of thromboembolism when not on anticoagulants, with EHRA Type 1 and Type 2 VHD patients having rates of 4.9% vs. 2.6% and 3.2% vs. 1.9%, respectively (14).

In a retrospective study analyzing the development of AF among rheumatic MS patients, embolic events occurred significantly more often in patients with AF compared to those without AF (11.7% vs. 2.1%). Predictors of embolic events included advanced age, larger left atrial (LA) dimension, lower kidney function, lower cholesterol levels, and severe MS (15). Similarly, a prospective cohort study in China found that 9.1% of rheumatic MS patients with sinus rhythm and 11.9% with AF developed systemic embolism. Previous embolism increased the risk of embolism, while percutaneous balloon mitral Commissurotomy was protective (16). In hospital-based studies conducted in northern India, AF was observed in 24.4% of RHD patients. Complications such as stroke and peripheral thromboembolism were reported in 3.9% and 4.1% of patients, respectively. Variables independently associated with stroke and/or peripheral embolism included advanced age, severe MS, and AF, while severe mitral regurgitation (MR) was linked to a significantly lower risk of stroke and/or embolism (17).

Contrary to these findings, the RE-LY AF registry study, which included patients with AF and/or atrial flutter from 47 countries, revealed that while advanced age, female sex, prior stroke, tobacco use, and lack of anticoagulation were predictors of stroke, moderate-to-severe MS was not an independent risk factor. In this study, 11.6% of patients had RHD, and significant MS was the predominant valve lesion (59.6%). The baseline anticoagulation use rate was higher in RHD patients (60.4% vs. 45.2%), and the one-year stroke rates were 2.8% and 4.1% in patients without and with RHD, respectively (18). Another Indian study demonstrated that AF significantly increased the prevalence of stroke (6.72% vs. 4.1%), systemic thromboembolism (5.97% vs. 3.35%), and combined stroke with thromboembolism (8.58% vs. 5.77%) in RHD patients

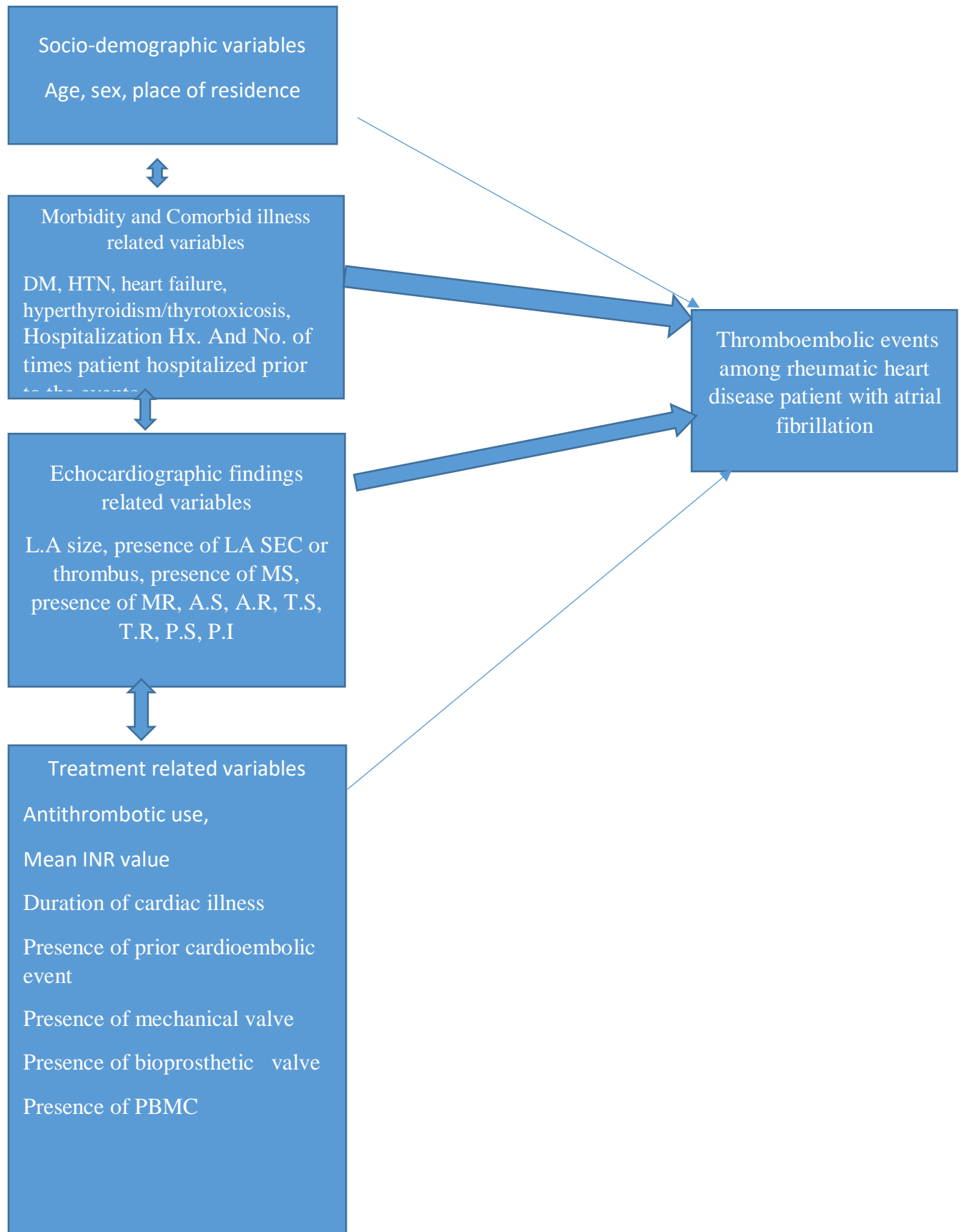
compared to those without AF (19). A case-control study in India further showed that LA spontaneous echo contrast and AF were significantly associated with stroke occurrence in RHD patients (20).

A prospective, multicenter, international, hospital-based registry of patients with symptomatic RHD, remedy study 2-year follow-up of individuals with rheumatic heart disease from 14 low- and middle-income countries in Africa and Asia. Overall, 46 (1.7%) patients had a stroke or TIA and three patients had a non-central nervous system systemic embolism, Patients who were in AF at enrollment were twice as likely to have a stroke as those who were in sinus rhythm (2.4% versus 1.2%, Previous stroke, and older age were independent predictors of stroke/transient ischemic attack or systemic embolism (21).

In a retrospective case of all stroke patients admitted to study TASH over 6 year period from 1990-1996 to assess potential risk factors associated with stroke in the young, which accounted for 28% of 259 patients and RHD was the second commonest risk factor which was prevalent in 29% of the patients, majority of the patient has milder disease, and the type of the involved valve rather than the severity the disease was related to the occurrences of stroke all has mainly mitral valve stenosis, and 42.9 % of RHD patient had established AF (22).

In a retrospective study done in Ethiopia Addis Ababa TASH involving 500 patients chart reviewed from 01 January to 31 June 2016, assessing Prevalence and Predictors of AF and its Embolic Complications in Patients with RHD. It was found 234 (46.8%) had ECG evidence of AF and On multivariable analysis, age ≥ 50 years, LA size greater than 45mm, the presence of MS, and the presence of TR were found to be predictors of AF. Out of the 500 patients, 9.2% had presumed cardioembolic events. Patients with AF were twice more likely to have these events than those with no AF (12.4% versus 6.4%) among those with cardioembolic events 61% had an INR value less than 2 and the presence of AF and an INR value less than 2.0 were related to the occurrence of an acute vascular event (23)

2.2 Conceptual framework



3. Objectives

3.1 General objective

- To assess the prevalence and determinants of thromboembolic events among RHD patients with AF at TASH adult cardiac OPD clinic follow-up in Addis Ababa Ethiopia from June 31, 2016, to October 31, 2024

3.2 Specific objectives

- To determine the prevalence of thromboembolic events among RHD patients with AF;
- To identify factors affecting the occurrence of cardioembolic events among RHD patients with AF

4. Methodology

4.1 Study area

The study was conducted in Tikur Anbessa Specialized Hospital, in Addis Ababa, Ethiopia. The largest teaching hospital in Ethiopia with more than 700 beds provides diagnostic and treatment services (24)

4.2 Study design

An institutional-based retrospective chart (EMR) review study design was used to examine the prevalence and determinates of cardioembolic events among RHD patients with AF.

4.3 Source population

- The source population for this study is all RHD with AF patients who attended Tikur Anbessa Specialized Hospital Adult Cardiac OPD Clinic of Internal Medicine from June 31, 2016, to October 31, 2024

4.4 Inclusion and exclusion criteria

4.4.1 Inclusion criteria

- all patients diagnosed with RHD with AF who have documented echocardiographic and ECG evidence attending Tikur Anbessa Specialized Hospital, adult cardiac OPD clinic from, June 31, 2016, to October 31, 2024, with at least six months of follow-up, will be included in the study;
- Documented cardioembolic event(CNS or systemic) confirmed by imaging(CT scan, MRI, or Doppler study)

4.4.2 Exclusion criteria

- Patients with a diagnosis of malignancy, APS, DVT/P.E or PAD

4.5 Sample size determination and sampling procedure

- Using a single population proportion for the prevalence, using the P value of 9.2%(the prevalence of presumed cardioembolic events in patients with AF and RHD(23)

$$(n = \frac{z^2 p(1-p)}{e^2}, n = \frac{(1.96)^2 * 0.124(0.876)}{0.05^2})$$

$n = 166.9$ approximated to 167 With a 10% nonresponse rate it becomes $183.7 = 184$

- Using a double population proportion formula for the associated factors sample size was calculated by using Fleiss with CC, using a previous case-control study assessing factors associated with stroke in RHD, where prevalence of LA sec is a significant associate factor as well presence of atrial fibrillation (26).

With the following values:-

- Two-sided confidence level of 95%;
- Power 80%;
- Ratio of control to case =1;
- Percent of control exposed= 2.5%;
- Percent of cases with exposure 22.5%;
- Odds ratio= 11.32

The total sample size is 104 with 10% non-response= $114.4 = 115$

The fine sample size will be 184

4.6. Sampling procedure

Simple random sampling using a table of random numbers

4.7. Study variables

- **Dependent variable**;- prevalence of cardioembolic events;
- **Independent variables**
 - ✓ **Socio-demographic**
 - Age
 - Sex
 - ✓ **Comorbidities**
 - Diabetes mellitus;
 - HTN;
 - heart failure
 - hyperthyroidism/thyrotoxicosis

- hospitalization
- No. of hospitalization
- AKI/CKD
- ✓ **echocardiographic**
- LA size;
- LA SEC.
- LA thrombus
- presence of MS;
- Presence of MR;
- Presence of A.S
- Presence of A.R
- Presence of T.S
- Presence of T.R
- Presence of P.S
- Presence of P.R
- ✓ **Treatment-related**
- Antithrombotic use;
- INR
- Duration of cardiac illness
- Presence of a prosthetic valve
- PMBC
- Prior events

4.8. Operational definition

- Cardioembolic events (cardioembolic stroke and peripheral arterial embolism)
 - **Cardioembolic stroke**; - stroke attributable to arterial occlusion from an embolus that presumably arose in the heart (2021 AHA/ASA guideline for prevention of stroke in patients with stroke and TIA);
 - **Peripheral arterial embolism**; - obstruction in a peripheral artery due to embolus, typically originating from a distant site, which impedes blood flow to the affected region (WHO ICD-11)

- **Diabetes mellitus:** - 2024 American diabetes association guideline: -
 - 1. Fasting Plasma Glucose (FPG): A level of 126 mg/dL or higher after fasting;
 - 2. Oral Glucose Tolerance Test (OGTT): A 2-hour blood glucose level of 200 mg/dL or more after ingesting a glucose solution;
 - 3. Hemoglobin A1c: A result of 6.5% or greater, reflecting chronic hyperglycemia;
 - 4. Random Plasma Glucose Test: A result of 200 mg/dL or higher in individuals showing symptoms of hyperglycemia.
- **Hypertension;** - the presence of a diagnosis of hypertension;
- **Heart failure:** - HF is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood(2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure);
- **Hyperthyroidism** is a state of thyroid hormone excess, thyrotoxicosis is clinical manifestations from high thyroid hormone levels, regardless of source (American Thyroid Association (ATA, 2016)
- **Hospitalization:** Refers to the formal admission of a patient to a hospital or medical facility for inpatient care, typically involving at least one overnight stay, for medical observation, diagnosis, treatment, or surgical/non-surgical intervention
- **No. hospitalization.** The total count of distinct hospital admission
- **AKI/CKD.** Presence of diagnosis of AKI/CKD
- **LA size** based on American Society of Echocardiography minor dimension measurements of LA
 1. Normal LA Diameter: Less than 40 mm.
 2. Enlarged LA Diameter:
 - Mildly enlarged: 40-44 mm;
 - Moderately enlarged: 45-49 mm;
 - Severely enlarged: 50 mm or greater
- **LA SEC.** is a dynamic, swirling pattern of echogenicity (smoke-like appearance) seen in the left atrium on Transesophageal echocardiography or transthoracic echocardiography(ASE, 2010 Chamber Quantification & 2018 Contrast Guidelines)
- **L.A thrombus.:** is a solid, well-defined mass in the left atrium or left atrial appendage, typically adherent to the atrial wall, visualized on TEE or TTE(ASE Guidelines)

- **Mitral stenosis;** -, defined by mitral valve area less than or equals to 2cm²(brawunwalds heart disease 12th edition)
 - Mild, moderate, and severe based on the echocardiography report of the patient
- **Mitral regurgitation.** American Society of Echocardiography (ASE) criteria
 - Mild, moderate, and severe based on the echocardiography report of the patient
- **Aortic stenosis;** - characterized by the narrowing of the aortic valve opening, which leads to an obstruction of blood flow from the left ventricle to the aorta
 - Mild, moderate, and severe based on the echocardiography report of the patient
- **Aortic regurgitation;** - is a condition where there is a retrograde flow of blood from the aorta into the left ventricle during diastole due to the failure of the aortic valve to close properly.
 - Mild, moderate, and severe based on the echocardiography report of the patient
- **Tricuspid stenosis;** - is a condition characterized by the narrowing of the tricuspid valve orifice, which impedes the normal flow of blood from the right atrium to the right ventricle during diastole.
 - Mild, moderate, and severe based on the echocardiography report of the patient
- **Tricuspid regurgitation;** - is a condition in which the tricuspid valve does not close properly during systole, allowing blood to flow backward from the right ventricle into the right atrium. This leads to volume overload in the right atrium and ventricle.
 - Mild, moderate, and severe based on the echocardiography report of the patient
- **Pulmonic stenosis;** -is a condition in which there is a narrowing of the pulmonic valve, which impedes blood flow from the right ventricle to the pulmonary artery during systole
 - Mild, moderate, and severe based on the echocardiography report of the patient
- **Pulmonic regurgitation;** - is a condition in which the pulmonic valve does not close properly during diastole, resulting in the backflow (regurgitation) of blood from the pulmonary artery into the right ventricle
 - Mild, moderate, and severe based on the echocardiography report of the patient
- **Prosthetic valve.** The presence of mechanical or bioprosthetic valve;
- **Percutaneous balloon Commissurotomy** is a catheter-based procedure to relieve stenosis of the mitral valve (or other valves) by inflating a balloon to separate fused

commissures, improving valve leaflet mobility and increasing valve area(ACC/AHA, VHD Guidelines))

- **Antithrombotic use:** - the use of anticoagulant or antiplatelet;
- **Therapeutic INR:** - INR value of 2-3 for native valve or aortic MV and 2.5-3.5 for mechanical mitral valve (2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease
- **Duration of illness.** the time period from diagnosis of the disease until the current time
- **Prior cardioembolic event.** Presence stroke or Peripheral embolism more than once

4.9 Data collection instrument

A structured checklist was used to collect data from patients' medical record charts (EMR). The checklist contains three parts. The first part is used to assess the sociodemographic characteristics of the patients. The second and third part is used to determine the presence of independent variables.

4.10. Data collection procedure

Two data collectors were employed for data collection by using the structured checklist and a formal orientation was given to the data collectors by the investigator. The primary investigator will superintend the process of data collection for accuracy.

4.11 Data Quality Assurance

To ensure the quality of data, an orientation was given to the data collectors then the checklist was pretested on 18 participants to check for inconsistencies and errors. Participants involved in the pretest will be excluded from later data collection. Inconsistencies and errors were corrected accordingly.

4.12 Data management and analysis

First, the collected data will be checked for completeness and consistency. Then were coded and entered using the software SPSS v30.0.0. Data analysis was done using the same software. Descriptive statistics is presented using frequency tables, graphs, and charts.

A binary logistic regression model was used to assess the associations between the independent variable and prevalence of thromboembolic events among RHD patients with AF. Univariate

analysis was performed to calculate the unadjusted odd ratio (OR) and screen out potentially significant independent variable at 25% level of significance ($P= 0.25$) to be included in the multivariable binary logistic regression model. Odds ratio, p-value and 95% CI for odds ratio will be used for testing significance and for result interpretation. Variables with a P value of less or equal to 0.05 were considered statistically associated with the outcome variable

4.13 Ethical consideration

Ethical clearance was obtained from Department review board of internal medicine, Addis Ababa University, College of Health Sciences. A formal letter of permission was submitted to the College of Health Sciences, School of Medicine, and Department of Internal Medicine before starting the study. Written or verbal consent was not required as the study only uses secondary data. The collected data was kept confidential and was used for study purposes only.

4.14 Data dissemination

The final result of the research is be submitted to Addis Ababa University School of Medicine. The results will be presented during the defense. The copies of the results will be available to the Internal Medicine Department and Publication in scientific journals will be attempted.

5. Results

5.1 Sociodemographic and Comorbidities

The study included a total of 182 participants, with a predominance of females, who comprised 70.9% (129 out of 182) of the group. The mean age of the participants was 40.37 years, with a standard deviation of ± 13.01 years. Most participants, 62.6% (114 out of 182), live outside of Addis Ababa, while 37.4% (68 out of 182) live within the city. In terms of age distribution, 31.3% (57 out of 182) were in the 30-39 age group, and 24.7% (45 out of 182) were over 50 years old. Regarding morbidity and comorbidities, 91.2% (166 out of 182) of the participants had heart failure, with 34.1% (62 out of 182) having been hospitalized due to this condition. Among the total of 62 hospital admissions, 45 patients experienced one admission episode, 13 had two admission episodes, and 10 had three or more episodes. Additionally, 19.2% (35 out of 182) of participants had kidney disease, 6.6% (12 out of 182) had hypertension, and 2.2% (4 out of 182) had diabetes. The mean duration of the disease was 9.28 years, with a standard deviation of ± 5.5 years. The majority of participants, 45.1% (82 out of 182), had lived with the disease for 6-10 years.

Table 1: Sociodemographic Characteristics and Comorbidities of the Study Population

Variables		Count	Percentage
Sex	Female	129	70.9
	Male	53	29.1
Age group	17-29	38	20.9
	30-39	57	31.3
	40-49	42	23.1
	≥ 50	45	24.7
Residency	Addis Ababa	68	37.4
	Outside Addis Ababa	114	62.6
Morbidity and Comorbidities			
Hypertension	Yes	12	6.6
Diabetes	Yes	4	2.2
Heart Failure	Yes	166	91.2
Kidney disease	Yes	35	19.2
HF hospitalization	Yes	62	34.1
Duration of disease			
	≤ 5	44	24.2

	6-10	82	45.1
	≥11	56	30.8

5.2 Echocardiographic Findings in Study Participants

The echocardiographic findings revealed that the average left atrial (LA) size was 52.37 ± 13.92 mm. Among the participants, 47.8% (87 out of 182) had severely enlarged left atria (greater than 50 mm), while 23.6% (43 out of 182) exhibited moderately enlarged left atria (ranging from 45 to 49 mm). A significant portion of the population had mitral stenosis, with 89.6% (129 out of 144) experiencing severe stenosis. Mitral regurgitation was seen in 75.3% (137 out of 182) of the participants, with 43.1% (59 out of 137) classified as having severe regurgitation. Aortic regurgitation was observed in 42.9% (78 out of 182) of participants, predominantly of mild severity (62.8%, or 49 out of 78). Additionally, 61.5% (112 out of 182) of the participants had tricuspid regurgitation, with 60.7% (68 out of 112) showing severe regurgitation. There were two patients with moderate pulmonic regurgitation, and no cases of pulmonic stenosis were reported.

Table 2: Echocardiographic Findings, Including LA Size, Valve Abnormalities, and Severity in Study Participants

Variables	Number	Percentage
Left atrial size		
Normal	18	9.9
Mildly (40-44 mm)	34	18.7
Moderately (45-49 mm)	43	23.6
Severely (>50 mm)	87	47.8
Mitral stenosis	144	79.1
Mild	9	6.3
Moderate	6	4.2
Sever	129	89.6
Mitral regurgitations	137	75.3
Mild	37	27.0
Moderate	41	29.9
Sever	59	43.1
Aortic stenosis	20	11.0
Mild	8	40.0
Moderate	9	45.0
Sever	3	15.0
Aortic registration	78	42.9
Mild	49	62.8
Moderate	23	29.5

Sever	6	7.7
Tricuspid stenosis	13	7.1
Mild	1	7.7
Moderate	3	23.1
Sever	9	69.2
Tricuspid regurgitation	112	61.5
Mild	19	17.0
Moderate	25	22.3
Sever	68	60.7
Presence of LA thrombus	14	7.7
Presence of LA sec	8	4.39

5.3 Cardioembolic Prevalence, Surgical Procedures, and Antithrombotic Management

A total of 19.78% (36 out of 182) of the study participants experienced cardioembolic events, with a 95% confidence interval of 14.3% to 26.3%. Stroke occurred in 18.1% (33 out of 182) of participants, including one patient who had two episodes. Limb ischemia was observed in 1.6% (3 out of 182) of participants, and no other sites of ischemia were documented. Prosthetic valve replacement was performed in 7.1% (13 out of 182) of participants, with 12 of these being mechanical valves and 01 bioprosthetic. Among those who underwent prosthetic valve replacement, 61.5% (8 out of 13) had the procedure performed following a stroke. Similarly, 66.7% (14 out of 21) of patients who received PBMC procedures also did so after experiencing a stroke. The majority of participants, 91.8% (146 out of 159), were treated with warfarin. Over a period of six months, 70.3% (128 out of 182) achieved documented therapeutic targets. Among these, 63.3% (81 out of 128) were within the therapeutic range, while 31.3% (40 out of 128) had subtherapeutic levels.

Table 3 Surgical Procedures, Antithrombotic Management, and Therapeutic Target Achievement in Study Participants

Variables	Number	Percentage
Surgical procedures		
Prosthetic valve	13	7.1
PBMC	21	11.5
Anticoagulant and antiplatelet	159	87.4
Warfarin	146	91.8
Rivaroxaban	2	6.9
Aspirin	11	1.3
Not taking any antithrombotic	23	12.6
Documented INR value(6months)	128	70.3
Therapeutic	81	63.3
Subtherapeutic	40	31.3
Supratherapeutic	7	5.5
Not determined	18	

5.4 Factors Associated with Cardioembolic Events

In the unadjusted analysis, factors with a P-value less than 0.25 were considered for inclusion in the multivariable analysis. The following factors met the criteria: duration of disease (P = 0.001), left atrial (LA) size (P = 0.01), presence of hypertension (P = 0.23), presence of LA thrombus (P = 0.006), presence of mitral stenosis (P = 0.029), mitral regurgitation (P = 0.21), and subtherapeutic INR levels (P = 0.06).

The multivariable analysis revealed several factors significantly associated with the risk of cardioembolic events, all with P-values less than 0.05. Duration of disease was found to significantly increase the odds of cardioembolic events; each additional year of disease duration increased the likelihood of such events by 7% (adjusted odds ratio [AOR]: 1.07, 95% confidence interval [CI]: 1.03–1.13, P = 0.002). LA size also had a significant association, with each millimeter increase in size raising the odds of cardioembolic events by 14% (AOR: 1.14, 95% CI: 1.07–1.24, P = 0.001). The presence of an LA thrombus was linked to a dramatic increase in the odds of experiencing a cardioembolic event, presenting an almost 10-fold higher risk (AOR: 9.83, 95% CI: 1.53–63.21, P = 0.01). Additionally, mitral stenosis was associated with an 88% increase in the odds of cardioembolic events (AOR: 1.88, 95% CI: 1.21–17.14, P = 0.04). Lastly, patients with subtherapeutic INR levels (below 2) faced a 4.27-fold increased risk of cardioembolic events (AOR: 4.27, 95% CI: 1.15–15.94, P = 0.03).

Table 4: Univariable and Multivariable Analysis of Factors Associated with the Risk of Cardioembolic Events

Variables	COR (95%CI)	P-value	AOR (95%CI)	P-value
Duration of disease (year)	1.14(1.06,1.229)	0.001	1.07(1.03,1.13)	0.002
Left atrium size (millimeter)	1.07(1.04,1.09)	0.01	1.14(1.07,1.24)	0.001
Presences of HTN*	2.13 (0.61,7.60)	0.23	3.01(0.55,16.65)	0.33
Presences LA thrombus*	4.79 (1.56,14.71)	0.006	9.83(1.53,63.21)	0.01
Presences mitral stenosis*	5.16 (1.18,22.56)	0.029	1.88(1.21 17.14)	0.04
Presences Mitral regurgitation*	0.82(0.36,1.87)	0.21	0.77(0.71,2.87)	0.19
Subtherapeutic INR (<2)	3.2(0.97, 10.17)	0.06	4.27(1.145,15.94)	0.03

*COR: crude odd ration, AOR: Adjusted odd ratio, * the comparative groups in the absence of the indicated variables*

Discussion

Cardioembolic events, including stroke, pose a significant risk for patients with cardiovascular diseases. In this study, 19.78% of participants experienced cardioembolic events, with stroke being

the most common manifestation. Our analysis indicated that longer disease duration, larger left atrial (LA) size, the presence of an LA thrombus, mitral stenosis, and subtherapeutic international normalized ratio (INR) levels were significantly associated with an increased risk of these events.

When comparing cardioembolic event rates across different studies, our findings reveal a notably higher incidence. Among our cohort, 19.78% (36 out of 182) of participants experienced cardioembolic events, considerably higher than rates reported in various other studies. For instance, a study from India found that only 3.9% of patients with rheumatic heart disease (RHD) experienced stroke or peripheral embolism. Another Indian study observed a stroke prevalence of 6.72% among RHD patients, while research conducted in Addis Ababa, Ethiopia, reported a 9.2% rate of presumed cardioembolic events in patients with RHD and atrial fibrillation (AF). The differences in cardioembolic event rates may be attributed to variations in patient demographics, disease severity, and comorbidities. Factors such as LA enlargement, the presence of AF, inadequate anticoagulation therapy, and disparities in healthcare likely contribute to these discrepancies.

Our study, focusing on patients with RHD and AF, found a high incidence of cardioembolic events, consistent with previous research. The Framingham study linked chronic AF to an 18-fold increase in the risk of stroke, with this risk escalating alongside the duration of AF. A systematic review of 21 studies reported that the prevalence of RHD among ischemic stroke patients in Asia ranged from 3.4% to 23.2%, aligning with our findings. These results highlight the significant role of AF, particularly in conjunction with RHD, in increasing stroke risk.

In our study, we found that the duration of atrial fibrillation (AF) significantly contributes to the occurrence of cardioembolic events. Consistent with findings from the Framingham study, we observed that patients with a longer duration of AF experienced a higher incidence of stroke and other embolic events. An Ethiopian study further supports this, indicating that patients with prolonged AF were twice as likely to experience cardioembolic events. Therefore, the duration of the disease plays a critical role in increasing stroke risk among patients with AF and rheumatic heart disease (RHD).

We also identified an increased left atrial (LA) size as a key predictor of cardioembolic events. This aligns with a prospective cohort study conducted in China, which demonstrated that larger LA sizes were significantly associated with an elevated risk of systemic embolism in patients with

rheumatic mitral stenosis (MS), particularly those with AF. Furthermore, the Ethiopian study similarly identified an LA size greater than 40 mm as a significant predictor of cardioembolic events. These findings underscore the importance of monitoring LA size as part of risk stratification for patients with AF and RHD, since an enlarged atrium increases the likelihood of thrombus formation and subsequent embolization.

The presence of an LA thrombus was another important factor linked to a greater risk of cardioembolic events in our study. This finding is consistent with a study conducted in India, which showed that LA spontaneous echo contrast and thrombus were significantly associated with the occurrence of stroke in patients with RHD and AF. These results highlight the critical need for early detection of LA thrombus and appropriate anticoagulation therapy to reduce thromboembolic complications.

Mitral stenosis (MS) emerged as a significant factor in the development of cardioembolic events in our study. The association between MS and embolic events is well-documented, as the hemodynamic disturbances caused by the narrowed mitral valve promote thrombus formation in the left atrium. For instance, a study from northern India found that severe MS and the presence of AF were independently associated with an increased risk of stroke and systemic embolism. Similarly, the Ethiopian study also identified MS as a predictor of cardioembolic events, emphasizing its role in elevating stroke risk in patients with RHD. The hemodynamic consequences of MS, especially when combined with AF, lead to blood stasis, significantly raising the risk of thromboembolism. Therefore, patients with both MS and AF should be closely monitored for potential thromboembolic complications.

Subtherapeutic international normalized ratio (INR) levels were strongly associated with an increased risk of cardioembolic events in our study, confirming findings from other research. Suboptimal anticoagulation therapy is a well-established risk factor for thromboembolic events in patients with AF and RHD, as it does not adequately prevent thrombus formation in the left atrium. A study from the RE-LY AF registry, which included patients from 47 countries, indicated that inadequate anticoagulation was a significant risk factor for stroke in patients with RHD. Additionally, the Ethiopian study found that patients with INR values below 2.0 were at significantly higher risk of embolic complications. These findings emphasize the critical importance of maintaining therapeutic INR levels in patients with AF and RHD to reduce the risk

of stroke and systemic embolism. Furthermore, the Ethiopian study underscored the necessity of vigilant anticoagulation management to prevent acute vascular events, highlighting the global relevance of this issue in the care of patients with AF and RHD.

Strength and limitations

Our study possesses several notable strengths that enhance its scientific value. Firstly, it includes a substantial cohort of patients with atrial fibrillation (AF) and rheumatic heart disease (RHD), providing a robust dataset for examining cardioembolic risk factors. The integration of sociodemographic data, comorbidities, and imaging findings allows for a comprehensive analysis of the factors influencing cardioembolic events. Furthermore, the use of multivariate analysis enabled us to control for potential confounders, ensuring that the identified predictors—such as left atrial (LA) size and subtherapeutic international normalized ratio (INR) levels—are independent contributors to these events.

However, our study also has certain limitations. Its retrospective design restricts our ability to establish causality between the identified risk factors and cardioembolic events. Since the study was conducted at a referral center, the findings may be subject to referral bias; patients with more severe conditions or complications are more likely to be referred, which could over represent the most severe cases. Additionally, reliance on medical records for sociodemographic, comorbidity, and imaging data may have introduced issues regarding data completeness and accuracy. The convenience sampling approach might also have led to selection bias.

6. Conclusion and recommendations

Cardioembolic events, primarily strokes, affected 19.78% of participants. We identified both modifiable risk factors (such as subtherapeutic INR, the presence of LA thrombus, and inadequate

anticoagulation) and non-modifiable risk factors (including disease duration, LA size, and mitral stenosis). Based on the findings, we recommend optimizing anticoagulation therapy to consistently maintain therapeutic INR levels, thereby reducing the risk of thromboembolic events, particularly in patients with AF and RHD. Regular imaging should be employed to monitor LA size and detect thrombus presence, facilitating timely interventions when necessary. In patients with mitral stenosis, vigilant monitoring and management are critical to prevent complications such as stroke. Additionally, early identification and management of cardiovascular conditions, especially in individuals with longer disease durations, can help mitigate the risk of cardioembolic events. Lastly, a personalized care approach that considers both modifiable and non-modifiable risk factors should be adopted to effectively prevent cardioembolic events in patients with cardiovascular diseases.

Reference

1. Roth GA, Mensah GA, Johnson Com et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update from the GBD 2019 Study. *J Am Coll Cardiol*. 2020 Dec 22;76(25):2982-3021. doi: 10.1016/j.jacc.2020.11.010.
2. Caplan LR, Hier DB, D'Cruz I. Cerebral embolism in the Michael Reese stroke Registry. *Stroke*. 1983 Jul-Aug;14(4):530-6. doi: 10.1161/01.str.14.4.530. PMID: 6658927.

3. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group streptococcal diseases. *Lancet Infect Dis*. 2005 Nov;5(11):685-94. doi: 10.1016/S1473-3099(05)70267-X. PMID: 16253886.
4. Ghandehari K, Izadi-Mood Z. Khorasan stroke registry: analysis of 1392 stroke patients. *Arch Iran Med*. 2007 Jul;10(3):327-34. PMID: 17604469.
5. Chockalingam A, Gnanavelu G, Elangovan S,
6. Chockalingam V. Clinical spectrum of chronic RHD in India. *J Heart Valve Dis*. 2003 Sep;12(5):577-81. PMID: 14565709.
7. Yadeta D, Semeredin N, Mekonnen GE. Prevalence and Predictors of AF and Its Embolic Complications in Patients With RHD at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. *Ethiop J Health Dev*. 2019;33.
8. Wang D, Liu M, Lin S, Hao Z, et al. Stroke and RHD: a systematic review of observational studies. *Clin Neurol Neurosurg*. 2013 Sep;115(9):1575-82. doi: 10.1016/j.clineuro.2013.06.017. Epub 2013 Jul 25. PMID: 23890677.
9. Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, et al. Characteristics, complications, and gaps in evidence-based interventions in RHD: the Global RHD Registry (the REMEDY study). *Eur Heart J*. 2015 May 7;36(18):1115-22a.
10. Eriksson SE, Olsson JE. Survival and recurrent strokes in patients with different subtypes of stroke: a fourteen-year follow-up study. *Cerebrovasc Dis*. 2001;12(3):171-80. doi: 10.1159/000047700. PMID: 11641580
11. Zenebe G, Alemayehu M, Asmera J. Characteristics and outcomes of stroke at Tikur Anbessa Teaching Hospital, Ethiopia. *Ethiop Med J*. 2005 Oct;43(4):251-9. PMID: 16523645
12. Bekele Alemayehu, Bekele Alemayehu, and Kebede Oli. Stroke admission to Tikur Anbessa Teaching Hospital: With emphasis on stroke in the young. *Ethiopian Journal of Health Development*, 16(3), 309–315. Addis Ababa, Ethiopia.
13. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic AF and risk of stroke: the Framingham study. *Neurology*. 1978 Oct;28(10):973-7. doi: 10.1212/wnl.28.10.973. PMID: 570666.

14. Wang D, Liu M, Lin S et al. Stroke and RHD: a systematic review of observational studies. *Clin Neurol Neurosurg*. 2013 Sep;115(9):1575-82. doi: 10.1016/j.clineuro.2013.06.017. Epub 2013 Jul 25. PMID: 23890677.
15. Melgaard L, Jensen M, Overvad TF, et al. Thromboembolic and bleeding outcomes in patients with AF and valvular heart disease: A descriptive nationwide cohort study. *Int J Clin Pract*. 2020 Oct;74(10):e13589. doi: 10.1111/ijcp.13589. Epub 2020 Jul 7. PMID: 32574395.
16. Kim HJ, Cho GY, Kim YJ et al. Development of AF in patients with rheumatic mitral valve disease in sinus rhythm. *Int J Cardiovasc Imaging*. 2015 Apr;31(4):735-42. doi: 10.1007/s10554-015-0613-2. Epub 2015 Feb 10. PMID: 25665684.
17. Chiang CW, Lo SK, Ko YS, Cheng NJ, Lin PJ, Chang CH. Predictors of systemic embolism in patients with mitral stenosis. A prospective study. *Ann Intern Med*. 1998 Jun 1;128(11):885-9. doi: 10.7326/0003-4819-128-11-199806010-00001. PMID: 9634425.
18. Negi PC, Mahajan K, Rana V, Sondhi S et al. Clinical Characteristics, Complications, and Treatment Practices in Patients With RHD: 6-Year Results From HP-RHD Registry. *Glob Heart*. 2018 Dec;13(4):267-274.e2. doi: 10.1016/j.gheart.2018.06.001. Epub 2018 Sep 6. PMID: 30197242.
19. Benz AP, Healey JS, Chin A, et al. Stroke risk prediction in patients with AF with and without RHD. *Cardiovasc Res*. 2022 Jan 7;118(1):295-304. doi: 10.1093/cvr/cvaa344. PMID: 33386845.
20. Negi PC, Sondhi S, Rana V et al. Prevalence, risk determinants, and consequences of AF in rheumatic heart disease: 6 years hospital based-Himachal Pradesh-Rheumatic Fever/Rheumatic Heart Disease (HP-RF/RHD) Registry. *Indian Heart J*. 2018 Dec;70 Suppl 3(Suppl 3):S68-S73. doi: 10.1016/j.ihj.2018.05.013. Epub 2018 May 19. PMID: 30595324; PMCID: PMC6309149.
21. Gupta A, Bhatia R, Sharma G, Prasad K, Singh MB, Vibha D. Predictors of Ischemic stroke in RHD. *J stroke Cerebrovasc Dis*. 2015 Dec;24(12):2810-5. doi: 10.1016/j.jstrokecerebrovasdis.2015.08.014. Epub 2015 Sep 26. PMID: 26409719
22. Zühlke L, Engel ME, Karthikeyan G, et al. Characteristics, complications, and gaps in evidence-based interventions in RHD: the Global RHD Registry (the REMEDY study). *Eur Heart J*. 2015 May 7;36(18):1115-22a. doi: 10.1093/eurheartj/ehu449. Epub 2014 Nov 25. PMID: 25425448; PMCID: PMC4422972.

23. Stroke Admission to Tikur Anbessa Teaching Hospital: With Emphasis on Stroke in the Young. *Ethiopian Journal of Health Development*.
24. Yadeta D, Semeredin N, Mekonnen GE. Prevalence and Predictors of AF and Its Embolic Complications in Patients With RHD at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. *Ethiop J Health Dev*. 2019;33.
25. Kahr PC, Hillis LD. Infective endocarditis in patients with RHD. *J Am Coll Cardiol*. 2016 May 3;67(17):2027-38. doi: 10.1016/j.jacc.2016.02.022.

Annex

Addis Ababa University College of Health Science
School of Medicine, Department of Internal Medicine

Checklist

Date: (DD/MM/YYYY) ____/____/____.

Section 1: Sociodemographic factors. Put a ✓ on the choice that applies.

1.1. Sex. Male female

1.2. Age in years---

1.3. Place of residence: Addis Ababa Out of Addis Ababa

Section 2.

2.1 morbidity and Comorbid illness related variables

2.1.1 Presence of diabetes mellitus. Yes No.

2.1.2 Presence of HTN. Yes No.

2.1.3 History of heart failure Yes. No.

2.1.4 Heart failure hospitalization Yes. No

2.1.5 If yes, for heart failure hospitalization, No. of hospitalization.....

2.1.6. Hospitalization for other indication (not including cardioembolic events). Yes. No.

2.1.7. If yes, number of hospitalization.....

2.1.8 Presence AKI or CKD yes No.

2.1.9 Presence of hyperthyroidism/thyrotoxicosis. Yes NO

2.2. Echocardiographic findings related variables

2.2.1 L.A size. In absolute number-----

- a. Mildly enlarged: 40-44 mm.
- b. Moderately enlarged: 45-49 mm.
- c. Severely enlarged: 50 mm or greater

2.2.1. Presence of LA SEC. YES NO.

2.2.2. L.A thrombus. Yes. NO

2.2.2. Presence of MS. Yes. NO

If yes,
Mild
Moderate
Severe

2.2.3. Presence of MR. Yes. No.

If yes,
Mild
Moderate
Severe

2.2.3. Presence of T.R. Yes. No.

If yes,
Mild
Moderate
Severe

2.2.4. Presence of T.S. Yes. No.

If yes
Mild
Moderate
Severe

2.2.4. Presence of A.R Yes. NO

If yes,
Mild
Moderate
Severe

2.2.5. Presence of A.S Yes. NO

If yes,
Mild
Moderate
Severe

2.2.6. Presence of P.S yes. No.

If yes,

Mild

Moderate

Severe

2.2.6. Presence of P.R. Yes. No.

If, yes

Mild

Moderate

Severe

Section 3. Treatment related variables

3.1. Total duration of illness in years _____

3.2. Presence of bioprosthetic valves yes . No

If yes,

Before cardioembolic event

After cardioembolic event

3.3. Presence of Mechanical Yes. NO.

If yes,

Before cardioembolic event

After cardioembolic event

3.3. PBMC done, yes no

If, yes,

Before cardioembolic event

After cardioembolic event

3.4. What type of anti-thrombotic did the patient receive if any

- a) UFH
- b) Warfarin
- c) Low molecular weight heparin
- d) Rivaroxaban

- e) Other
- f) Not taking any antithrombotic medication

3.5. Mean INR value of last 06 months (prior to cardioembolic event). In absolute no. _____

Subtherapeutic	<input type="checkbox"/>	therapeutic	<input type="checkbox"/>
Supratherapeutic	<input type="checkbox"/>	not determined	<input type="checkbox"/>

Section 4. Type of cardioembolic event

- 4.1. Stroke , if yes, No of event _____
- 4.2. Limb ischemia if yes, No. of events _____
- 4.3. Mesenteric ischemia if yes, No. of events _____
- 4.4 other site, _____ and No. of events _____