



**Prevalence, characteristics and additional stroke risk stratification:
An analysis of the Atrial Fibrillation cohort in the REMEDY study**

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Abstract

Background

Atrial fibrillation (AF) is the most common arrhythmia and may be complicated by embolic stroke. It is also associated with a significant risk of heart failure and mortality. The burden of rheumatic heart disease remains great in the developing world. The prevalence of AF in those with rheumatic heart disease is in the order of 20% with a resultant 17-fold increased risk of embolic stroke.

Over time, many other risk factors for stroke in the AF population have been described. Stroke risk stratification tools such as the CHADS₂ (Congestive heart failure, hypertension, age of 75 or older, diabetes mellitus or stroke/TIA) and CHA₂DS₂VASc (with the addition of a second age category, female gender, and peripheral artery disease) scores have been developed. These are used to assess the need for anticoagulation and have been well validated. These scores have traditionally excluded those patients with valvular AF.

Valvular AF has not been studied extensively in the contemporary era. Oral anticoagulation had previously been advised in all patients with valvular AF. Little is known however about outcomes for stroke and mortality in this cohort of patients. Furthermore, the utilization of the CHADS₂ and CHA₂DS₂VASc scores may provide incremental benefit in prognostication and resultantly, both more diligent prescription of anticoagulation and improved outcomes.

Objectives

The objectives of this study were as follows -

1. To determine the prevalence of AF in the Global Rheumatic Heart Disease Registry (the REMEDY study) and in the Groote Schuur Hospital (GSH) cohort.
2. To assess the demographic, social and clinical characteristics of patients with AF in the REMEDY study and in the GSH cohort.
3. To assess the frequency of CHADS₂ and CHA₂DS₂VASc risk factors in the GSH cohort and to calculate a CHADS₂ and CHA₂DS₂VASc score on each of the patients with AF.

4. To establish whether CHADS₂ and CHA₂DS₂VASc scores further increase the risk of stroke and death in this cohort of patients with valvular AF.

Methods

This is a substudy of the Global Rheumatic Heart Disease Registry (the REMEDY study). We assessed those with AF from the entire cohort for prevalence and outcome data. Patients with ECG or Holter proven AF from the GSH cohort were further risk stratified using the CHADS₂ and CHA₂DS₂Vasc scores. Clinical data was obtained from folder reviews and telephonic interviews. The CHADS₂ and CHA₂DS₂Vasc scores for each patient in the GSH cohort were calculated. Patients were followed up for 2 years and information pertaining to death and stroke were obtained from folder reviews. These were then correlated with the CHADS₂ and CHA₂DS₂Vasc scores.

Results

A total of 2624 REMEDY patients were analysed. Of these, 22% in the total cohort (586 of 2684 patients) and 38.2% in the GSH cohort (187 of 489 patients) had AF. These patients were older (35 years vs. 25 years, $p < 0.0001$), more likely to be female (73.1% vs. 65.6%, $p = 0.001$) and more frequently had a history of congestive heart disease (41.0% vs. 33.3%, $p = 0.001$) when compared to those in sinus rhythm. They also had significantly more strokes (13.8% vs. 5%, $p < 0.0001$) and a poorer NYHA class (NYHA III& IV 30.8% vs. 25.2%, $p = 0.002$).

The cohort with AF had more severely impaired left ventricular (LV) function compared to those in sinus rhythm (Ejection fraction (EF) 57% vs. 61%. $P < 0.0001$). The presence of a larger left atrial (LA) size, spontaneous echo contrast and LA thrombus was much greater in the AF cohort. Of those patients in AF, only 68% had received a prescription for warfarin. The GSH cohort was risk stratified using the CHADS₂ and CHA₂DS₂VASc scores. Twenty-three percent of patients had a CHADS₂ score of 0 and 27.7% of 1. When the same cohort was scored using the CHA₂DS₂VASc score, only 5.4% had a score of 0; this difference was mainly driven by the additional category of female gender. The patients in our cohort were young (median age 28 years) and had few comorbidities. Despite this, patients with AF did

significantly worse than those in sinus rhythm, with a stroke rate of 4.6% and a mortality rate of 13.1% observed at 2 years (compared to a 1.5% stroke rate and 5.5% mortality rate for those in sinus rhythm). The presence of any additional co-morbidities significantly reduced survival in both the short and long term. Greater CHA₂DS₂VASc score categories (CHA₂DS₂VASc 1 and CHA₂DS₂VASc 2 or more) conferred an incrementally higher risk of death.

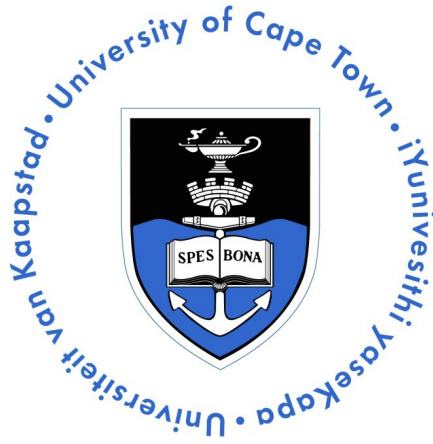
Conclusion

In a contemporary cohort of patients with rheumatic heart disease, AF is common with a prevalence of 22-39%. These patients were older and exhibited features of more advanced disease both clinically and on echo, compared to their sinus rhythm counterparts. The mortality and stroke rates in the AF group were high despite the relatively young age of this cohort. Mortality and stroke increased significantly and incrementally with each greater CHA₂DS₂VASc score category. Given the differences in chronicity between RHD in the developed world (i.e., disease of older people) and RHD in developing countries (i.e., disease of the young), these results cannot be extrapolated to those living in the first world.

Abbreviations

ACC	American College of Cardiology
AF	Atrial Fibrillation
AFI	Atrial Flutter
AHA	American Heart Association
AR	Aortic Regurgitation
AS	Aortic Stenosis
CHADS ₂ score	Clinical score of combinations of Congestive heart failure, Hypertension, Age, Diabetes mellitus and Stroke/TIA in AF patients to determine risk of future stroke
CHA ₂ DS ₂ VASc score	Clinical score of combinations of Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke, Sex and Vascular Disease in AF patients to determine risk of future stroke
CI	Confidence Intervals
CRF's	Case Report Forms
CVD	Cardiovascular disease
DM	Diabetes Mellitus
ECG	Electrocardiography
EF	Ejection Fraction
ESC	European Society of Cardiology
GSH	Groote Schuur Hospital
HREC	Human Research and Ethics Committee
HTN	Hypertension

IQR	Inter-quartile range
LA	Left atrium
LBBB	Left bundle brunch block
LV	Left ventricle
LVID	Left ventricular internal diameter
Mm	Millimetres
mmHg	Millimetres of mercury
MR	Mitral Regurgitation
MS	Mitral Stenosis
NOACS	Novel oral anticoagulants
NYHA	New York Heart Association
OAC	Oral Anticoagulation Therapy
OR	Odds Ratio
PR	Pulmonary Regurgitation
PS	Pulmonary Stenosis
RBBB	Right bundle branch block
REMEDY	Global Rheumatic Heart Disease Registry
RHD	Rheumatic Heart Disease
SD	Standard Deviation
SR	Sinus Rhythm
SSA	Sub-Saharan Africa
TIA	Transient Ischemic Attack
TR	Tricuspid Regurgitation
TS	Tricuspid Stenosis



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PART A: PROTOCOL

Background

With a prevalence of 0.5% to 1% in the general population,^{1,2} atrial fibrillation (AF) is the most common cardiac arrhythmia. The incidence has risen to 5 million new cases per year.³ Advancing age, essential hypertension, ischemic heart disease, heart failure and diabetes are conditions commonly associated with AF.⁴ Rheumatic heart disease is recognized as a common cause of AF. The prevalence of AF in rheumatic heart disease is around 20%.^{5,6} In more recent years, the literature has reported less frequently on valvular AF, but the problem persists in middle- and low socioeconomic countries where rheumatic heart disease remains prevalent.⁷ Furthermore, RHD in the developing world occurs in a much younger population when compared to the developed world.

The presence of AF is associated with a significant risk of mortality and heart failure. The Framingham, Manitoba, Whitehall and Regional Heart Studies all showed a doubling in mortality when comparing patients with underlying heart disease in AF to those in sinus rhythm.^{8,9,10} In the Manitoba Follow-up study looking at the natural history of AF, the total mortality risk was increased 1.3 fold and the cardiovascular mortality (excluding fatal stroke) showed a relative risk of 1.37.⁹

AF is also the strongest independent predictor for stroke.⁴ It carries a 2 to 7 fold increased risk of ischemic stroke when compared to those patients without AF and one out of every six strokes are due to AF.^{9,10} The stroke risk however is heterogenous. Various risk factors interplay to create a variable risk of stroke and peripheral embolism. Though individuals essentially have identical underlying electrical disturbances in the atrium, the stroke risk in AF varies widely: from <1% to >20% per year.¹¹

Systemic embolism (especially in the form of stroke) is a serious and well-recognized complication of mitral valve disease. In 754 patients with chronic rheumatic heart disease followed up for 5833 patient-years, Szekely et al. showed an incidence of embolism of 1.5% per patient-year – it was however seven times higher in the group with AF compared to those in sinus rhythm (5% per patient year in AF compared to 0.7% per patient year in sinus rhythm).¹²

The Framingham Heart Study analysed their cohort with rheumatic heart disease [RHD] and AF. A 17 fold increased stroke rate was noted when compared to age-matched controls,¹³ resulting in an attributable risk 5 times greater than in those with non-rheumatic AF.¹⁴ It is in light of this that anticoagulation is recommended for those with AF in the presence of valvular heart disease irrespective of other risk factors.

The definition for valvular AF is however ambiguous. It is widely recognized that mitral stenosis is associated with an increased risk of thromboembolism.^{15,16} Of these patients with embolic phenomena in mitral stenosis, around 80% were in AF.¹⁷ There are conflicting theories and results as to whether or not mitral regurgitation increases the risk of thromboembolism. No studies have shown aortic stenosis, aortic regurgitation or tricuspid regurgitation as a risk factor independent of AF for thromboembolism. This is thought to be on the basis that blood flow in the left atrium is not reduced.¹⁸

Mechanical valves show a definite increased risk of thromboembolic events of 4% per year if not on anticoagulation. Systemic embolism reduces to 0.7-1% per year on warfarin.¹⁹ Based on this information, a definition for valvular AF has been proposed: MARM-AF (Mechanical and Rheumatic AF). This specifies the disease entity, recognizing that only those patients with AF and specifically mitral stenosis and prosthetic valves are at increased risk of stroke – and thus clarifying management issues with regards to anticoagulation.¹⁸ This has been given consideration in the most recent ESC guidelines.²⁰ Those with other valve lesions would be risk stratified using the scoring methods (as per non-valvular AF) referred to later in this text. No randomized trials looked at anticoagulation specifically in mitral stenosis, but observational retrospective studies showed a 4-15 fold reduction in events in those who received anticoagulation.^{21,22}

Observational data in the 1970's demonstrated the occurrence of embolic events in patients with AF due to heart disease other than mitral valve disease. Since then, the vast majority of studies on AF focused on those patients with non-valvular AF. Many risk factors for stroke

have been identified among patients with AF. The individual stroke risk depends on a combination of these risk factors.

Risk factors that have consistently emerged as major independent predictors for stroke are: a history of previous stroke or TIA (RR 2.5), age (RR 1.5/decade), hypertension (RR 2.0) and diabetes (RR1.8).^{23,24} The Loire Valley AF project demonstrated the impact of age on stroke risk.²⁵ A history of heart failure and female gender were also predictors in some other studies.^{26,27} Observational data showed an odds ratio of 1.81 for peripheral arterial disease predicting stroke.²⁶

Over the years, many stroke risk prediction scores have been developed and divide patients into low-, moderate- or high-risk groups. Those with the highest risk for stroke were then eligible to receive oral anticoagulation (OAC) therapy. Numerous studies have shown that even those patients at moderate risk for stroke, do benefit from oral anticoagulation therapy, with dose-adjusted warfarin reducing the incidence of stroke in those with AF by more than 60% when compared to placebo.²⁸ Since OAC use is however associated with an increased risk of bleeding, especially intracranial bleeds, occurring at a rate of 2-5 per 1000 patients annually,²⁹ there has thus been a greater move to better risk stratify and identify those patients truly at low risk for stroke. In this low-risk patient group, the risks of oral anticoagulation likely outweigh the risk of thromboembolism.^{30,31}

The CHADS₂ score was derived from a combination of risk factors established in the AF Investigators (AFI)³² and the Stroke Prevention in Atrial Fibrillation (SPAF) cohorts.³³ It allocated one point for each of the following – Congestive heart failure, Hypertension, Age 75 or older, Diabetes mellitus, except 2 points for Stroke/TIA (Addendum 6, Table 1 in the Appendix- Section D). Low risk patients were defined as those having a score of 0, moderate risk was a score of 1-2 and high risk, a score of >2. A strong correlation between the CHADS₂ score and adjusted stroke rate emerged. Stroke rate per 100 patient years increases by a factor of 1.5 with each increase in score of 1 point.³²

There were a few limitations using the above model: having had a previous stroke or TIA only presumed a moderate risk (CHADS₂ of 2), even though it was clear from previous studies that these patients were at highest risk of stroke recurrence. The risk score classification was revised, and now low risk = a score of 0, moderate risk = a score of 1 and high risk a score of 2 or greater. This score has since been validated in numerous other studies.^{25,30,34}

But even those patients with moderate scores, i.e. CHADS₂ scores of 1, had a significantly higher stroke rate compared to those with a CHADS₂ score of 0; it thus classified many patients as having intermediate risk for stroke, even though some of them might be at truly low risk, with the risk of oral anticoagulation therefore outweighing the benefit and resulting in more people being anticoagulated than was justifiable. Conversely, among 25 286 Asian patients with a CHADS₂ score of 0, the annual stroke rate ranged from 1.15% to 4.47%³⁵. The same group of patients (CHADS₂ 0) was reclassified using the CHA₂DS₂VASc score- their scores now ranged from 0 to 3. There was a clear need to further risk stratify and identify those who are clearly at low risk for stroke and therefore not requiring potentially harmful anticoagulation.

The CHA₂DS₂VASC score aimed to address this need. – It utilizes the following variables: Congestive heart failure or LV dysfunction, Hypertension, Age 75 or older (2), Diabetes mellitus, Stroke/TIA(2), Vascular disease, Age 65-74, Female gender (Addendum 6, Table 2 in the Appendix- Section D) to calculate a score. A score of 0=low risk, 1=intermediate risk and 2 or more=a high risk of stroke.

This score was developed in 2010 and was better at predicting those patients who were truly at low risk for developing thromboembolism. It added 3 more factors – the 65-74 year old age group, female gender and vascular disease (in the form of a prior MI, peripheral arterial disease or aortic plaque). In the initial validation study, it only classified 9% as low risk (with no thromboembolic events occurring in this group). The same cohort classified according to the CHADS₂ score had an event rate of 1.4%³⁰. The added benefit of the CHA₂DS₂VASC score was also seen in a Danish cohort of 19 444 patients who had CHADS₂ scores of 0. Their stroke rates ranged from 0.8% to 3.2% per year. The 28 132 patients who had a

CHADS₂ score of 1 had stroke rates of up to 8.18% at 1 year³¹. The CHA₂DS₂VASC score was particularly helpful in further delineating those patients with a CHADS₂ score of 0 and 1 - if the CHA₂DS₂VASC score was 0 in males or 1 in females (with female sex being the only risk factor), no oral anticoagulation was required. All other patients would therefore require oral anticoagulation³⁰. This is now the recommended risk scheme of choice by most guidelines societies^{20,36}.

Neither of the 2 risk scores is foolproof, with c-statistics in the order of 0.69.³⁵ It also does not include more complex parameters such as renal impairment or AF burden, both of which have been shown to be associated with an increased risk of stroke.^{37,38} However, both of these stroke-risk prediction scores have been widely used in studies to compare the newer oral anticoagulation drugs (NOACS) to the established treatment option (Vitamin K antagonists) in patients with non-valvular AF. These drugs trials have previously excluded patients with valvular AF.

Oral anticoagulation is advised in all patients with valvular AF. This group of patients has however not been studied in the contemporary era and little is known about the outcomes of stroke and mortality in valvular AF. Furthermore, the utilization of the CHADS₂ and CHA₂DS₂VASC scores for the prediction of stroke in these patients has not been assessed and these scores may well be of incremental benefit in prognostication. This awareness of a more defined stroke and mortality risk in valvular AF patients will hopefully result in the more diligent prescription and monitoring of adequate anticoagulation.

Hypothesis

Patients with rheumatic heart disease and atrial fibrillation have a significantly higher morbidity and mortality compared to those in sinus rhythm. The presence of other risk factors as described by the CHADS₂ and CHA₂DS₂VASc scores significantly lead to an incremental increase in stroke and mortality risk.

Study Aims

This is a substudy of the Global Rheumatic Heart Disease Registry (the REMEDY study).

It aims to:

1. Determine the prevalence of AF in the adult cohort of patients with rheumatic valvular heart disease (RVHD).
2. Characterize the clinical and demographic profile of the patients with AF and RVHD.
3. Assess the frequency of CHADS₂ (Congestive heart failure, Hypertension, Age 75 or older, Diabetes Mellitus, Stroke/TIA(2)) and CHA₂DS₂VASc (Congestive heart failure, Hypertension, Age 75 or older (2), Diabetes mellitus, Stroke/TIA(2), Vascular disease, Age 65-74, Sex/gender- female) in the Groote Schuur Hospital (GSH) cohort of AF patients with RVHD.
4. Characterize the outcomes in the form of stroke and death in this cohort of AF patients.
5. Assess whether there is an incremental increase in stroke risk and death with increasing CHADS₂ and CHA₂DS₂VASc scores.

Study Objectives

The objectives of the study are to:

1. Determine the prevalence of AF in the REMEDY study and in the GSH cohort.
2. Assess the demographic, social and clinical characteristics of patients with AF in the REMEDY study and in the GSH cohort.
3. Assess the frequency of CHADS₂ and CHA₂DS₂VASc risk factors in the GSH cohort and to calculate a CHADS₂ and CHA₂DS₂VASc score on each of the patients with AF.
4. Establish whether CHADS₂ and CHA₂DS₂VASc scores further increase the risk of stroke and death in this cohort of patients with valvular AF.

Study Setting and design

This cohort comprises patients already enrolled in the REMEDY study. REMEDY is a multi-center, international prospective registry collecting contemporary demographic and clinical data in patients with rheumatic heart disease. In total, 25 sites enrolled 3343 patients in Africa, the Middle East, Asia and South America with proven rheumatic heart disease. The design and rationale as well as the baseline findings for this study have been published previously^{39,40}.

Patients with AF from the entire cohort will be assessed for prevalence and outcome data. In this cohort, the diagnosis of AF is made on clinical examination, and/or ECG and Holter monitoring. At the Groote Schuur Hospital site, only the patients with AF on ECG or Holter will be analysed and further risk stratified using the CHADS₂ and CHA₂DS₂VASc scores. Groote Schuur Hospital is a tertiary center and one of two cardiology referral units in the Western Cape, South Africa.

Patient Recruitment

Inclusion criteria:

- Patients with rheumatic heart disease who have ECG and/or Holter proven AF.
- Patients with another concomitant reason for oral anticoagulation (e.g., mechanical prosthetic valves) use will not be excluded from the study.

No distinction has been made between the various types of AF (paroxysmal vs. persistent vs. permanent).

Exclusion from AF analysis:

- Atrial flutter patients /other atrial arrhythmias

Data Collection:

A standardised data collection form capturing all relevant demographic, clinical, ECG and echo data from medical charts and patient interview will be used. (Baseline CRF –

Addendum 2 – Section D). The ECG's and Holter traces for each of the GSH patients would be reviewed by a cardiologist and the diagnosis of AF verified.

An additional form capturing data pertaining to CHADS₂ / CHA₂DS₂VASc risk factors will be filled using data from medical records or telephonic interviews. (Addendum 3)

- Congestive heart failure is defined as symptoms or clinical signs of heart failure.
- Hypertension was defined by patient self-report, antihypertensive medications on prescription charts, and/or documented blood pressures of >140/90 mmHg.
- Age: Two age categories were defined:
 1. Age 75 or older: In the CHADS₂ score this scored one point; in the CHA₂DS₂VASc score, this scored 2 points
 2. Age 65-74: This age category did not apply to the CHADS₂ score but scored 1 point in the CHA₂DS₂VASc score
- Diabetes mellitus was defined as self-reported, antiglycaemic medication (oral anti-glycaemics and insulin), random glucose of 11mmol/l or fasting glucose of 6.7mmol/l
- Stroke/TIA was defined on the basis of self-reported symptoms or signs of a stroke or TIA or objective clinical or CT scan evidence of a stroke.
- Vascular disease included those with a history of previous myocardial infarction or significant coronary disease on coronary angiography, peripheral vascular disease by symptoms, clinical signs or Doppler as well as proven aortic plaque on imaging (CT or MRI)

The CHADS₂ and CHA₂DS₂VASc scores for each patient with AF in the GSH cohort will be calculated and for each score, 3 categories will be considered: Low risk - score of 0, intermediate risk – score of 1 and high risk, score of 2 or more.

Patients will be followed up and information pertaining to the outcomes of death and most importantly stroke will be captured from medical records and patient interviews in accordance with the REMEDY protocol. (Follow-up and Outcomes CRF's – Addenda 4&5 – Section D). These outcomes will be correlated with the CHADS₂ and CHA₂DS₂VASc scores.

Statistics

The prevalence of AF in the entire cohort of REMEDY patients and well as in the local Groote Schuur Hospital cohort will be calculated using the total REMEDY enrollments. (n=3343) and the total Groote Schuur enrolments (n=489) as denominators. These will be presented as percentages and as per 1000 population with 95% confidence intervals. Continuous variables will be expressed as means with standard deviations, or medians with interquartile ranges as appropriate. Categorical variables will be expressed as frequencies and percentages. Linear regression models will assess the relationship between the variables. Cox regression models will be used to assess the risk of stroke/thromboembolism using CHA₂DS₂VASc score. Kaplan-Meier estimates of event –free survival at 2 years will be obtained, relating it to the CHA₂DS₂VASc score categories of 0, 1 and 2 or more.

Ethics

Ethics approval has been granted for the REMEDY study. An ethics application for this substudy of REMEDY has been granted by the University of Cape Town Human Research Ethics Committee (HREC 127/2016 – Addendum 7 – Section D). The study will conform to the principles outlined in the Helsinki Declaration (2008).

Budget

This study is partially funded by a Discovery Foundation Grant.

Outputs / Dissemination of results

This forms the basis of my M.Phil dissertation and will be submitted to a peer-reviewed journal for publication.

REFERENCES

1. Go AS, Hylek EM, Phillips KA et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; **285**: 2370-2375.
2. Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995; **155**: 469-473.
3. Chugh SS, Harmceller R, Narayan K, Singh D, Rienstra M, Benjamin EJ et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014; **129**: 837-847
4. Stevenson WG, Stevenson LW, Middlekauff HR, et al. Improving survival for patients with atrial fibrillation and advanced heart failure [published erratum appears in *J Am Coll Cardiol* 1997; **30**: 1902] *J Am Coll Cardiol* 1996; **28**: 1458-1463.
5. Bentivoglio LG, Uricchio JF, Waldo A et al. An electrocardiographic analysis of sixty five cases of mitral regurgitation. *Circulation* 1958; **18**: 572.
6. Probst P, Goldschlager N, Selzer A. Left atrial size and the risk of stroke and death. The Framingham Heart Study. *Circulation* 1995; **92**: 835.
7. Sliwa K, et al. Spectrum of Heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. *Lancet* 2008; **371**: 915-922
8. Kannel WB, Abbott RD, Savage DD et al. Coronary heart disease and atrial fibrillation: the Framingham Study. *Am Heart J* 1983; **106**: 389-396.
9. Krahn AD, Manfreda J, Tate RB et al. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-up Study. *Am J Med* 1995; **98**: 476-84.
10. Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation [published erratum appears in *Lancet* 1987; **1**: 878]. *Lancet* 1987; **1**: 526-529.
11. Olesen JB, Lip GY, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: a nationwide cohort study. *Br Med J* 2011; **342**: d124
12. Szekely P. Systemic Embolism and Anticoagulant Prophylaxis in Rheumatic Heart Disease. *BMJ* 1964; **1**: 1209-1212.

13. Wolf PA, Dawber TR, Thomas HE Jr et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978; **28**: 973-977.
14. Wolf PA, Abbott RD, Kannel WB. Atrial Fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; **22**(8) 983-988.
15. Rowe JC, Bland EF, Sprague HB, White PD. The course of mitral stenosis without surgery: ten-and twenty year perspectives. *Ann Intern Med* 1960;**52**:741-749.
16. Caplan LR, D’Cruz I, Hier DB, Reddy H, Shah S. Atrial size, atrial fibrillation, and stroke. *Ann Neurol* 1986;**19**:158-161.
17. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. *Br H J* 1962; **24**: 349-357
18. De Caterina R, Camm AJ. What is ‘valvular’ atrial fibrillation? A reappraisal. *European Heart Journal* 2014;**35**: 3328-3335.
19. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation* 1994;**89**: 635-641.
20. Kirchhof P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal* 2016 ; **37**: 2893-2962
21. Laupacis A, Albers G, Dunn M, Feinberg W. Antithrombotic therapy in Atrial Fibrillation. *Chest* 1992;**102**: 4265-4335.
22. Abernathy WS, Willis PW 3rd. Thromboembolic complications of rheumatic heart disease. *Cardiovasc Clin* 1973;**5**: 131-175.
23. National Institute for Health and Care Excellence. Atrial Fibrillation: the management of atrial fibrillation. <http://guidance.nice.org.uk/CG180>. Published June 2014. Accessed June 18,2014.
24. Hart RG, Pearce LA, McBride R, et al. the Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. *Stroke* 1999;**30**: 1223-1229.
25. Olesen JB, Fauchier L, Lane DA, Taillandier S, Lip GY. Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest* 2012; 141(1):147-153.
26. Pisters R, Lane DA, Marin F, et al. Stroke and thromboembolism in atrial fibrillation. *Circ J.* 2012; 76:2289-2304.
27. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischemic

- stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *European Heart Journal* 2012; 33: 1500-1510.
28. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic treatment to prevent stroke in patients who have non-valvular AF. *Ann Intern Med* 2007;**146**: 857-867.
 29. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in non- valvular atrial fibrillation: an individual patient meta-analysis. *J Am Med Assoc* 2002;**288**: 2441-2448.
 30. Lip GY, Nieuwlaat R, Pisters R et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest* 2010; 137:263-272.
 31. Olesen JB, Torp-Pedersen C, Hansen ML, et al. The value of the CHA₂DS₂VASC score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS₂ score 0-1: a nationwide cohort study. *Thromb Haemost* 202;**107**:1172-1179.
 32. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomised controlled trials. *Arch Intern Med* 1994; **154**: 1449-1457.
 33. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991; **84**: 527-539.
 34. Lip G. Can we predict stroke in Atrial Fibrillation? *Clinical Cardiology* 2012; 35 (S1): 21-27
 35. Chao TF, Liu CJ, Tuan TC et al. Comparisons of CHADS₂ and CHA₂DS₂-Vasc scores for stroke risk stratification. *Heart Rhythm* 2016;**13**: 46-53
 36. January CT, Wann LS, Alpert JS, et al. American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology* 2014; 64(21):e1-e76.
 37. Olesen JB, Lip GY, Kamper AL, Hammel K, Kober L, Lane DA, Lindhardssen J, Gislason GH, Torp-Pedersen C. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Eng J Med* 2012; **367**:625-635.
 38. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilckler CM, Claton QD, Ziegler PD. The relationship between daily tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TREDIDS Study. *Circ Arrhythm Electrophysiol*

2009;2: 474-480.

39. Karthikeyan G, Zuhlke L, et al. Rationale and design of a Global Rheumatic Heart Disease Registry: the REMEDY Study. *American Heart Journal* 2012 163 (4) 535-540

40. Zuhlke L, Engel M, et al. Characteristics, complications , and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *European Heart Journal* 2015; 36 (18):1115-1122.



*Prevalence, characteristics and additional stroke risk stratification: An analysis of the
Atrial Fibrillation cohort in the REMEDY study*

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PART B: LITERATURE REVIEW

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and remains a major contributor of cardio-embolic stroke and peripheral emboli. Although non-valvular AF becomes increasingly prevalent with advancing age, AF associated with valvular pathology affects a much younger age group. In this group, the presence of AF increases the risk of stroke up to 17-fold.^{1,2,3}

In recent years, most stroke risk prediction tools focused on patients with non-valvular AF. Models such as the CHADS₂ (Assigning one point for the variables of congestive heart failure, hypertension, age of 75 years or older, diabetes mellitus and 2 points for stroke or TIA) and CHA₂DS₂VASc (with the addition of a second age category – 64-74 scores one point, over 75 scores 2, as well as one point for female sex and peripheral artery disease) risk scores are commonly being used in clinical practice both to predict stroke risk as well as assessing the need for anticoagulation in non-valvular AF.

The prevention of stroke with the use of anticoagulation treatment for AF has been evaluated in many randomized controlled trials and meta-analyses.⁴⁻¹⁷ Several guidelines have been developed in an attempt to standardize evidence-based practice and best ensure minimal risk of thrombo-embolism and bleeding in patients on anticoagulation therapy for AF.^{18,19,20}

In the developing world, rheumatic heart disease remains common. AF in this group occurs in a much younger population but bears the same devastating consequences of increased stroke risk, morbidity and mortality. This group with valvular atrial fibrillation has not been extensively studied in the contemporary era. When RHD (and its related AF) does occur in the developed world, the patients tend to be older.

This chapter will review:

- The magnitude of the problem of AF
- Stroke risk prediction in valvular AF
- The changing definition of valvular AF
- Stroke risk prediction in non-valvular AF
- The utility of the risk prediction tools available for non-valvular AF, and
- How these risk prediction tools interplay with those who have valvular AF.

Search Strategy

A comprehensive literature search was performed using the following databases: MEDLINE, Google Scholar, Clinical Key, Clinical Evidence and Pubmed. The keywords that were used for the search were: atrial fibrillation, valvular atrial fibrillation, rheumatic atrial fibrillation, CHADS₂, CHA₂DS₂VASc score, Anticoagulation for atrial fibrillation in CHADS₂. This search yielded 72 references: 5 Guidelines, 43 observational/cohort studies, 5 review articles, 4 meta-analyses, 2 editorials, 10 trials and 3 case series.

Magnitude of the problem

AF is the most common cardiac arrhythmia and has a prevalence of about 0.5% - 1% in the general population.^{21,22} The incidence continues to rise with 5 million new cases reported per year. This is thought largely to be due to increased surveillance, better detection methods with more modern and accessible technologies, and improved survival.^{23,24} Prevalence increases with age, approaching 8% in those patients in the ninth decade.^{1,25,26} It is well known that advancing age, essential hypertension, ischemic heart disease, heart failure, diabetes and valvular heart disease are conditions commonly associated with AF.²⁷

Rheumatic heart disease (RHD) was previously recognized as a common cause of AF. In a cohort of 500 patients with mitral valve disease, Fleming et al found 57% of these patients (average age 50) to be in AF.² Wipf et al. reported AF prevalence rates in a surgical series of

rheumatic heart disease of up to 75%.²⁸ Diker et al. found a 39% prevalence of AF in a cohort of 1110 patients with rheumatic heart disease. Of those with pure mitral stenosis (854 patients), 403 (47%) had AF, accounting for 29% of the total cohort. Patients with the combined lesions of mitral stenosis and regurgitation and tricuspid regurgitation lesions had even higher rates of AF (70%) in this cohort.³

Though other studies showed slightly lower rates, the prevalence of AF in rheumatic heart disease is consistently about 20%.^{29,30} Although more recent literature reports less frequently on valvular AF, the problem persists in middle- and low socio-economic countries where rheumatic heart disease remains prevalent.³¹

The presence of AF is associated with a significant risk of mortality and heart failure. The Framingham, Manitoba, Whitehall and Regional Heart Studies all showed a doubling in mortality when comparing patients with underlying heart disease in AF to those in sinus rhythm.^{32,33,25} In the Manitoba Follow-up study looking at the natural history of AF, the total mortality risk was increased 1.3 fold and the cardiovascular mortality (excluding fatal stroke) showed a relative risk of 1.37.³³ It is also the strongest independent predictor for stroke.⁴

Patients with AF have a 2 to 7 fold increased risk of ischemic stroke compared to those without AF and one out of every six strokes are due to AF.^{1,4,25,33} The stroke risk is heterogenous – a number of mechanisms relating to Virchow's triad of thrombogenesis are at play: 1. Flow disturbance due to stasis in the left atrium (abnormal blood flow), 2. Structural heart and/or vascular disease (representing the abnormal 'vessel wall'), 3. Abnormal coagulation both in the form of reduced platelet survival and increased platelet stickiness. (this has been studied extensively in recent years).^{34,35,36} Numerous risk factors interplay to create a variable risk of stroke and peripheral embolism. Although individuals essentially have identical underlying electrical disturbances in the atrium, the stroke risk in AF varies widely: from <1% to >20% per year.³⁷

Stroke risk prediction in Valvular Atrial Fibrillation

Systemic embolism is a serious and well-recognized complication of mitral valve disease. Strokes account for more than 60% of these embolic events.^{38,2} Szekely et al. showed an incidence of embolism of 1.5% per patient-year when following up 754 patients with chronic rheumatic heart disease for 5833 patient-years. This was seven times higher in the group with AF compared to those in sinus rhythm (5% per patient year in AF compared to 0.7% per patient year in sinus rhythm).³⁹

A comprehensive study of 839 cases showed a four-fold increase in the incidence of embolic phenomena in those patients with AF compared to those in sinus rhythm. In both groups, there was an increase in events with increasing age.⁴⁰

Fleming et al in 1971 showed that in a cohort of 500 inpatients in Cambridge UK, 57% of patients were found to be in AF. Of those in AF, 35% presented with embolic phenomena. The incidence of embolic events once again increased with age. The severity of the mitral valve disease did not influence the incidence of embolic events.²

In the Framingham Heart Study, patients with (RHD) and AF had a 17 fold increased stroke rate compared to age-matched controls⁴¹, with an attributable risk 5 times greater than those with non-rheumatic AF.¹ It is in light of this that anticoagulation is recommended for those with AF in the presence of valvular heart disease irrespective of other risk factors.

The changing definition of valvular AF

The definition for valvular AF is ambiguous. It is widely recognized that mitral stenosis is associated with an increased risk of thromboembolism.^{42,43} However, it remains unclear whether or not the pathogenesis is the identical to that of non-valvular AF. In those patients with

mitral stenosis who have an embolic event, +/- 80% are in atrial fibrillation.⁴⁴ If a previous event has occurred, there is a very high recurrence rate of 15-40 events per 100 patient months.^{45,46}

There are conflicting theories and results as to whether or not mitral regurgitation increases the risk of thromboembolism. A retrospective study showed that thromboembolism rates were similar when compared to those with no mitral regurgitation.⁴⁷ Due to the higher blood flow patterns in the atria, it was actually thought by some to be protective. In mitral valve prolapse, some series showed an increase in the rate of thromboembolism but this was not reproduced in the later Framingham study.⁴⁸ No studies have shown aortic stenosis, aortic regurgitation or tricuspid regurgitation as a risk factor independent of atrial fibrillation for thromboembolism. This is thought to be on the basis that blood flow in the left atrium is not reduced.⁴⁶ Mechanical valves show a definite increased risk of thromboembolic events of 4% per year if not on anticoagulation. Systemic embolism reduces to 0.7-1% per year on warfarin.⁴⁹

Based on this information, a more descriptive definition for valvular AF has been proposed: MARM-AF (Mechanical and Rheumatic AF). This specifies the disease entity more clearly, and recognizes that only those patients with AF and specifically mitral stenosis and prosthetic valves are at increased risk of stroke – thus clarifying management issues with regards to anticoagulation.⁴⁶ This has been given consideration in the most recent ESC guidelines.¹⁹ Those with other valve lesions would be risk stratified using the scoring methods referred to later in this text.

No randomized trials looked at anticoagulation specifically in mitral stenosis, but observational retrospective studies showed a 4-15 fold reduction in events in those who received anticoagulation.^{45,50} Numerous observational studies in valvular AF suggested long term anticoagulation as a method of preventing systemic emboli.^{51,52,38} Roy et al. reviewed 254 patients with AF to assess the incidence of embolic events relative to the type of cardiovascular disease and anticoagulant use. Thirty-two events occurred during an 833 patient year follow-up. Thirty events occurred in the 549 patient years with no

anticoagulation therapy (5.46 per 100 patient years) and only two events occurred in those on anticoagulation, during a 284 patient year period (0.7 per 100 patient years), demonstrating an 8-fold increase in frequency. This observation was regardless of the presence of mitral disease or whether the AF was chronic or paroxysmal. This suggested that anticoagulation in AF patients should not be limited only to those with mitral valve disease⁵³ and that other risk factors may contribute to the stroke risk as well.

Stroke risk prediction in Non-valvular Atrial Fibrillation

Observational data in the 1970's suggested the occurrence of embolic events in patients with AF due to heart disease other than mitral valve disease. A necropsy study of 333 patients with AF showed embolism to occur in 41 % of patients with mitral valve disease, 35% of those with ischemic heart disease and 17% of those with 'other' heart disease.⁵⁴

Since then, the vast majority of studies on AF focused on those patients with non-valvular AF. Many risk factors for stroke have been identified among patients with AF. The individual stroke risk depends on a combination of these risk factors. Risk factors that have consistently emerged as major independent predictors for stroke are: a history of previous stroke or TIA (RR 2.5), age (RR 1.5/decade), hypertension (RR 2.0) and diabetes (RR1.8).^{18,55} The Loire Valley AF project demonstrated the impact of age on stroke risk.⁵⁶ A history of heart failure and female gender were also predictors in some other studies.^{57,58} Observational data showed an odds ratio of 1.81 for peripheral arterial disease predicting stroke.⁵⁶

Over the years, many stroke risk prediction scores have been developed. These are used to categorize patients into a low-, moderate- or high-risk groups with the aim of anticoagulating those patients at highest risk for stroke. Numerous studies have shown that even those patients at moderate risk for stroke, do benefit from oral anticoagulation therapy, with dose-adjusted warfarin reducing the incidence of stroke in those with AF by more than 60% when compared to placebo.⁵⁹ Since it's use is however associated with an increased risk on bleeding, especially intracranial bleeds, occurring at a rate of 2-5 per 1000 patients

annually.⁶⁰ There has thus been a greater move to better risk stratify and identify those patients truly at low risk for stroke who would not require oral anticoagulation.^{61,62}

The utility of the risk prediction tools in non-valvular AF

CHADS₂ score – Congestive heart failure, Hypertension, Age 75 or older, Diabetes mellitus, Stroke/TIA (2) (Addendum 6, Table 1 in the Appendix- Section D)

For each risk factor that the patient has, they score one point except for stroke or TIA which scores 2 points. The CHADS₂ score was derived from a combination of risk factors established in the AF Investigators (AFI)⁴ and the Stroke Prevention in Atrial Fibrillation (SPAF)¹⁵ studies and has been in use since 2001. The initial validation of the CHADS₂ score was in the National Registry of Atrial Fibrillation (NRAF)⁶³ in 1733 patients who had non-valvular AF and not taking oral anticoagulation at discharge. In this cohort, low risk patients were defined as those having a score of 0, moderate risk was a score of 1-2 and high risk, a score of >2. A strong correlation between the CHADS₂ score and adjusted stroke rate emerged. Stroke rate per 100 patient years increases by a factor of 1.5 with each increase in score of 1 point. The c statistic for the score was 0.82 (but later studies showed a lower c statistic).⁵¹

There were a few limitations using the above model: having had a previous stroke or TIA only presumed a moderate risk (CHADS₂ of 2), even though it was clear from previous studies that these patients were at highest risk of stroke recurrence. The risk score classification was revised, and now low risk = a score of 0, moderate risk = a score of 1 and high risk a score of 2 or greater. This score has since been validated in numerous other studies.^{56,61,64}

It was noted however, that even those with moderate scores, i.e. CHADS₂ scores of 1, had a significantly higher stroke rate compared to those with a CHADS₂ score of 0; it thus

classified many patients as having intermediate risk for stroke, even though some of them might be at truly low risk, with the risk of oral anticoagulation therefore outweighing the benefit and resulting in more people being anticoagulated as was necessary. Conversely, among 25 286 Asian patients with a CHADS₂ score of 0, annual stroke rate of 1.15% to 4.47%.⁶⁵ Their CHA₂DS₂VASc score ranged from 0 to 3. The need arose to risk stratify these patients further and to identify those who were truly at low risk (and thus not requiring anticoagulation).

The CHA₂DS₂VASC score uses the following variables: – Congestive heart failure or LV dysfunction, Hypertension, Age 75 or older (2), Diabetes mellitus, Stroke/TIA(2), Vascular disease, Age 65-74, Female gender (Addendum 6, Table 2 in the Appendix- Section D) A score of 0=low risk, 1=intermediate risk and 2 or more=high risk of stroke.

This score was developed in 2010 and was better at predicting those patients who were truly at low risk for developing thromboembolism. It added 3 more factors – the 65-74 year old age group, female gender and vascular disease (in the form of a prior MI, peripheral arterial disease or aortic plaque). In the initial validation study, it only classified 9% as low risk (with no thromboembolic events occurring in this group). The same cohort classified according to the CHADS₂ score had an event rate of 1.4%.⁶¹ The added benefit of the CHA₂DS₂VASC score was also seen in a Danish cohort of 19 444 patients who had CHADS₂ scores of 0. Their stroke rates ranged from 0.8% to 3.2% per year. The 28 132 patients who had a CHADS₂ score of 1 had stroke rates of up to 8.18% at 1 year.⁶² The CHA₂DS₂VASC score was particularly helpful in further delineating those patients with a CHADS₂ score of 0 and 1 - if the CHA₂DS₂VASC score was 0 in males or 1 in females (with female sex being the only risk factor), no oral anticoagulation was required. All other patients would therefore require oral anticoagulation.⁶¹ This is now the recommended risk scheme of choice suggested by most guidelines and cardiology societies.^{19,20}

Neither of the 2 risk scores are fool-proof with c-statistics in the order of 0.69.⁶⁵ It also does not include more complex parameters such as renal impairment or AF burden that have been shown to be associated with an increased risk of stroke.^{66,67}

Risk factor prediction tools in valvular AF

Both of these stroke-risk prediction scores have been widely used in studies to compare the newer oral anticoagulation drugs (NOACS) to the established treatment option (Vitamin K antagonists) in patients with non-valvular AF. These drugs trials have previously excluded patients with valvular AF.

Conclusion

Oral anticoagulation is advised in all patients with valvular AF. This group of patients has however not been studied in the contemporary era and little is known about the outcomes of stroke and mortality. Furthermore, the utilization of the CHADS₂ and CHA₂DS₂VASC scores for the prediction of stroke in these patients has not been assessed and these scores may well be of incremental benefit in prognostication. This awareness of a more defined stroke risk in valvular AF patients will hopefully result in the more diligent prescription and monitoring of adequate anticoagulation.

REFERENCES

1. Wolf PA, Abbott RD, Kannel WB. Atrial Fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; **22**(8) 983-988.
2. Fleming HA, Bailey S. Mitral valve disease, systemic embolism and anticoagulants. *Postgraduate Medical Journal* 1971; 47: 599-604
3. Diker E, Aydogdy S, Ozdemir M, Kural T et al. Prevalence and Predictors of Atrial Fibrillation in Rheumatic Valvular Heart Disease. *Am J Cardio* 1996; **77**:96-98.
4. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomised controlled trials. *Arch Intern Med* 1994; **154**: 1449-1457.
5. Hart RG, Benavente O, McBride R et al. Antithrombotic therapy to prevent stroke in patients with Atrial Fibrillation: a meta-analysis. *Ann Intern Med* 1999; **131**:492-501.
6. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with non-rheumatic atrial fibrillation. *N Engl J Med* 1990; **323**: 1505-1511
7. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stroke. *Lancet* 1993; **342**: 1255-1262.
8. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994; **343**: 687-691.
9. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted dose warfarin versus low-intensity, fixed dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet* 1996; **348**: 633-688.
10. Petersen P, Boysen G, Godtfredsen J et al. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* 1989; **1**: 175-179.
11. Pengo V, Zasso A, Barbero F et al. Effectiveness of fixed minidose warfarin in the prevention of thromboembolism and vascular death in non-rheumatic atrial fibrillation. *Am J Cardiol* 1998; **82**: 433-437.

12. Gullov AL, Koefoed BG, Petersen P et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation Study. *Arch Intern Med* 1998; **158**: 1513-1521.
13. Ezekowitz MD, Bridgers SL, James KE et al. Warfarin in the prevention of stroke associated with non-rheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med* 1992; **327**: 1406-1412.
14. Connolly SJ, Laupacis A, Gent M et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. *J Am Coll Cardiol* 1991; **18**: 349-355.
15. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991; **84**: 527-539.
16. Hellemons BS, Langenberg M, Lodder J et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin. *BMJ* 1999; **319**: 958-964.
17. Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicentre, prospective randomized trial. Japanese Nonvalvular Atrial Fibrillation-Embolic Secondary Prevention Cooperative Study Group. *Stroke* 2000; **31**: 817-821.
18. National Institute for Health and Care Excellence. Atrial Fibrillation: the management of atrial fibrillation. <http://guidance.nice.org.uk/CG180>. Published June 2014. Accessed June 18,2014.
19. Kirchhof P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal* 2016 ; **37**:2893-2962
20. January CT, Wann LS, Alpert JS, et al. American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology* 2014; **64**(21):e1-e76.
21. Go AS, Hylek EM, Phillips KA et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the

AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; **285**: 2370-2375.

22. Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995; **155**: 469-473.
23. Chugh SS, Harmceller R, Narayan K, Singh D, Rienstra M, Benjamin EJ et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;**129**: 837-847
24. Schnabel R, Yin X, Gona P, Larson M, Beiser A, McManus D, et al. 50 Year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in Framingham Heart Study: a cohort study. *Lancet* 2015; **386**: 154-62.)
25. Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation [published erratum appears in *Lancet* 1987; **1**: 878]. *Lancet* 1987; **1**: 526-529.
26. Furberg CD, Psaty BM, Manolio TA, et al. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994; **74**: 236-241.
27. Stevenson WG, Stevenson LW, Middlekauff HR, et al. Improving survival for patients with atrial fibrillation and advanced heart failure [published erratum appears in *J Am Coll Cardiol* 1997; **30**: 1902] *J Am Coll Cardiol* 1996; **28**: 1458-1463.
28. Wipf JE, Lipsky BA. Atrial Fibrillation. Thromboembolic risk and indications for anticoagulation. *Arch Intern Med* 1990; **150**: 1598-1603
29. Bentivoglio LG, Uricchio JF, Waldo A et al. An electrocardiographic analysis of sixty five cases of mitral regurgitation. *Circulation* 1958; **18**: 572.
30. Probst P, Goldschlager N, Selzer A. Left atrial size and the risk of stroke and death. The Framingham Heart Study. *Circulation* 1995; **92**: 835.
31. Sliwa K, et al. Spectrum of Heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. *Lancet* 2008; **371**: 915-922
32. Kannel WB, Abbott RD, Savage DD et al. Coronary heart disease and atrial fibrillation: the Framingham Study. *Am Heart J* 1983; **106**: 389-396.
33. Krahn AD, Manfreda J, Tate RB et al. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-up Study. *Am J Med* 1995; **98**: 476-84.
34. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in AF: Virchow's triad revisited. *Lancet* 2009; 373 (9658): 155-166.

35. Steele PP, Weily HS, Davies H, Genton E. Platelet survival in patients with rheumatic heart disease. *New England Journal of Medicine* 1974; 290: 537-539.
36. Toy JL, Lederer DA, Tulpule AT, Tandon AP, Taylor SH, McNicol GP. Coagulation studies in rheumatic heart disease. *British Heart Journal* 1980;43: 301-305.
37. Olesen JB, Lip GY, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: a nationwide cohort study. *Br Med J* 2011;**342**:d124
38. Wood PH. An Appreciation of mitral stenosis Part I: Clinical features. *British Medical Journal* 1954;1: 1051.
39. Szekely P. Systemic Embolism and Anticoagulant Prophylaxis in Rheumatic Heart Disease. *BMJ* 1964; **1**: 1209-1212.
40. Coulshed N, Epstein EJ, McKendrick CS, Galloway RW, Walker E. Systemic embolism in mitral valve disease. *British Heart Journal* 1970;32:26-34.
41. Wolf PA, Dawber TR, Thomas HE Jr et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978; **28**: 973-977.
42. Rowe JC, Bland EF, Sprague HB, White PD. The course of mitral stenosis without surgery: ten-and twenty year perspectives. *Ann Intern Med* 1960;**52**:741-749.
43. Caplan LR, D'Cruz I, Hier DB, Reddy H, Shah S. Atrial size, atrial fibrillation, and stroke. *Ann Neurol* 1986;**19**:158-161.
44. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. *Br H J* 1962; **24**: 349-357
45. Laupacis A, Albers G, Dunn M, Feinberg W. Antithrombotic therapy in Atrial Fibrillation. *Chest* 1992;**102**: 4265-4335.
46. De Caterina R, Camm AJ. What is 'valvular' atrial fibrillation? A reappraisal. *European Heart Journal* 2014;**35**: 3328-3335.
47. Wada Y, Mizushige K, Ohmori K, Iwado Y, Kohno M, Matsuo H. Prevention of cerebral thromboembolism by low-dose anticoagulant therapy in atrial fibrillation with mitral regurgitation. *J Cardiovasc Pharmacol* 2001;**37**:422-426
48. Freed LA, Levy D, Levine RA, Larson MG, Evans JC, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical outcome of mitral valve prolapse. *N Eng J Med* 1999;**341**: 1-7.
49. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications

- in patients with mechanical heart valve prostheses. *Circulation* 1994;**89**: 635-641.
50. Abernathy WS, Willis PW 3rd. Thromboembolic complications of rheumatic heart disease. *Cardiovasc Clin* 1973;**5**: 131-175.
51. Owren PA. The results of anticoagulation therapy in Norway. *Archives of Internal Medicine* 1963;110:240.
52. Casella L, Abelmann WH, Ellis LB. Patients with mitral stenosis and systemic emboli: Hemodynamic and clinical observations. *Archives of Internal Medicine* 1964;114: 773
53. Roy D, Marchand E, Gagne P, Chabot M, Carter R. Usefulness of anticoagulation therapy in the prevention of embolic complications of AF. *American Heart Journal* 1986;112(5) 1039-1043.
54. Hinton RC, Kistler JP, Fallon JT, Friedlich AL, Fisher CM. Influence of aetiology of AF on incidence of systemic embolism. *American Journal of Cardiology* 1977;40(4) 509-513.
55. Hart RG, Pearce LA, McBride R, et al. the Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. *Stroke* 1999;30: 1223-1229.
56. Olesen JB, Fauchier L, Lane DA, Taillandier S, Lip GY. Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest* 2012; 141(1):147-153.
57. Pisters R, Lane DA, Marin F, et al. Stroke and thromboembolism in atrial fibrillation. *Circ J.* 2012; 76:2289-2304.
58. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *European Heart Journal* 2012; 33: 1500-1510.
59. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic treatment to prevent stroke in patients who have non-valvular AF. *Ann Intern Med* 2007;**146**: 857-867.
60. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in non-valvular atrial fibrillation: an individual patient meta-analysis. *J Am Med Assoc* 2002;**288**: 2441-2448.
61. Lip GY, Nieuwlaat R, Pisters R et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based

- approach: the Euro Heart Survey on Atrial Fibrillation. *Chest* 2010; 137:263-272.
62. Olesen JB, Torp-Pedersen C, Hansen ML, et al. The value of the CHA₂DS₂VASC score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS₂ score 0-1: a nationwide cohort study. *Thromb Haemost* 2012;107:1172-1179.
 63. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864-2870
 64. Lip G. Can we predict stroke in Atrial Fibrillation? *Clinical Cardiology* 2012; 35 (S1): 21-27
 65. Chao TF, Liu CJ, Tuan TC et al. Comparisons of CHADS₂ and CHA₂DS₂-Vasc scores for stroke risk stratification. *Heart Rhythm* 2016;13: 46-53
 66. Olesen JB, Lip GY, Kamper AL, Hammel K, Kober L, Lane DA, Lindhardtsen J, Gislason GH, Torp-Pedersen C. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Eng J Med* 2012; 367:625-635.
 67. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilkler CM, Clanton QD, Ziegler PD. The relationship between daily tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TREDIDS Study. *Circ Arrhythm Electrophysiol* 2009;2: 474-480.
 68. Karthikeyan G, Zuhlke L, et al. Rationale and design of a Global Rheumatic Heart Disease Registry: the REMEDY Study. *American Heart Journal* 2012; 163 (4) 535-540
 69. Zuhlke L, Engel M, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *European Heart Journal* 2015; 36 (18):1115-1122.
 70. Hart RG. Atrial Fibrillation and Stroke Prevention. *N Engl J Med* 2003; 349(11): 1015-1016.
 71. Wessler S, Gitel S. Seminars in Medicine of the Beth Israel Hospital, Boston: Warfarin: From bedside to bench. *New Engl J Med* 1984; 311(10): 645-652.
 72. Fuster V, Ryden L, Cannom D et al. ACC/AHA/ESC Guidelines for the management of patients with atrial fibrillation: executive summary Report
 73. Whitlock RP, Sun JC, Fries SE, et al. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic therapy and Prevention of thrombosis, 9th ed:

American College of Chest Physicians Evidence-based Clinical Practice Guidelines.
Chest 2012; **141(2)**: e576S-e600S.

72. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines. *Chest* 2012; **141(2)**: e531S- e575S.



*Prevalence, characteristics and additional stroke risk stratification: An analysis of the
Atrial Fibrillation cohort in the REMEDY study*

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PART C: MANUSCRIPT

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and may be complicated by embolic stroke or peripheral emboli. In addition, it is associated with a significant risk of mortality and heart failure.

Rheumatic heart disease (RHD) remains a major problem in the developing world. Systemic embolism (of which 60% are due to strokes)¹ is a well recognized complication of mitral valve disease. In this population, the AF prevalence was previously described to be around 20% . It occurs in a much younger age group, even when compared to RHD patients in the developed world² In the Framingham study there was a 17 fold increase in the stroke rate compared to age matched controls.³

There has been much debate in the definition of valvular AF. It is widely recognized and accepted that mitral stenosis (MS) is associated with an increased risk of thromboembolism⁴, but it is unclear if the pathogenesis is identical to that of non-valvular AF. In those patients with MS, and a previous ischemic cerebral event, the rate of recurrence is high. The studies showing increased stroke rates in mitral regurgitation are conflicting⁵, and no studies have shown an increased stroke risk in other native valve lesions. Mechanical valves are associated with a definite increased risk of thromboembolic events.⁶ There are no randomized trials examining the effectiveness of anticoagulation specifically in mitral stenosis. Observational studies utilizing warfarin as an anticoagulant show a reduced embolic event rate.⁷

Over time, many additional risk factors for stroke have been identified. Those that have consistently emerged as independent risk factors were: a history of previous stroke or TIA, age, hypertension and diabetes.⁸ A few other studies also implicated female gender and congestive heart failure.⁹ With the decline of RHD in the developed world and the increasing conglomerate of risk factors in the setting of non-valvular AF, stroke risk stratification tools such as the CHADS₂¹⁰ (Congestive heart failure, hypertension, age of 75 or older, diabetes mellitus or stroke/TIA) or CHA₂DS₂VASc¹¹ (with the addition of a second age category, female gender, and peripheral artery disease) scores have been developed. These are increasingly being utilized to determine the need for anticoagulation, and are now recommended by major cardiac society guidelines.^{12,13} Their main value lies in identifying those patients who are at sufficient risk for stroke, where the benefit of using anticoagulation

would outweigh the risk of bleeding. Stroke prevention with the use of anticoagulation (mainly Vitamin K antagonists, and now, in recent times also NOACS) for those who score 2 or more on the above risk scores, have been evaluated in randomized controlled trials. Patients with valvular AF have traditionally been excluded from these studies since they were already deemed to be an extremely high risk group.

Valvular AF has not been extensively studied in the contemporary era. Older data suggested that oral anticoagulation is advised in all patients with valvular AF – mainly based on the observational studies showing up to a 17 fold risk.¹ This group of patients has however not been studied in the contemporary era and very little is known about the outcomes of stroke and mortality in this cohort. The utilization of the CHADS₂ and CHA₂DS₂VASc scores for the prediction of stroke has not been assessed and these scores may well provide incremental benefit in prognostication and resultantly, more diligent prescription and monitoring of anticoagulation, and consequently improved outcomes.

The objectives of this study were as follows -

1. To determine the prevalence of AF in the REMEDY study and in the GSH cohort.
2. To assess the demographic, social and clinical characteristics of patients with AF in the REMEDY study and in the GSH cohort.
3. To assess the frequency of CHADS₂ and CHA₂DS₂VASc risk factors in the GSH cohort and to calculate a CHADS₂ and CHA₂DS₂VASc score on each of the patients with AF.
4. To determine whether CHADS₂ and CHA₂DS₂VASc scores further increase the risk of stroke and death in this cohort of patients with valvular AF.

Methods

Participants

The participants were patients already enrolled in the REMEDY study.¹⁴ This is a multicentre, international registry collecting contemporary demographic and clinical data in patients with rheumatic heart disease. In total, 3343 patients were enrolled in 25 sites in Africa, India and Yemen.¹⁵ In this sub-study, we assessed those with AF from the entire cohort for prevalence and outcome data. Patients with Atrial flutter/other arrhythmias were excluded. The patients with ECG or Holter proven AF from the Groote Schuur Hospital site were analysed and further risk stratified using the CHADS₂ and CHA₂DS₂VASc scores. Groote Schuur Hospital is a tertiary care centre in Cape Town, South Africa and one of two cardiology referral units in the Western Cape. It provides general cardiology care to the Western and Southern Cape Province. All subjects had given written informed consent to participate in the study. Ethics approval for this substudy was granted by the University of Cape Town Human Research Ethics Committee.

Study data collection

A standardized data collection form was used to capture relevant demographic, clinical, ECG and echocardiography data from both patient interviews and medical charts/records. For the entire REMEDY cohort, the diagnosis of AF was clinical and/or on ECG and Holter. The ECG's and Holter traces for each of the GSH patients was reviewed by a cardiologist, the diagnosis of AF verified and only those with ECG and Holter proven AF included. An additional form was utilized to capture other AF risk factors to determine a CHADS₂ and CHA₂DS₂VASc score for each patient. Additional information was obtained from hospital charts and occasionally telephonic interviews.

Congestive heart failure is defined as symptoms or clinical signs of heart failure. Hypertension was defined patient self-reporting, antihypertensive medications on prescription charts, documented blood pressures of >140/90.

Two age categories were defined as age 75 or older: In the CHADS₂ score this scored one point; in the CHA₂DS₂VASc score, this scored 2 points. The age 64-75 category did not

apply to the CHADS₂ score but scored 1 point in the CHA₂DS₂VASc score. Diabetes mellitus was defined as self-reported, antiglycaemic medication (oral anti-glycaemics and insulin), random glucose of 11mmol/l or fasting glucose of 6.7mmol/l. Stroke/TIA was defined on the basis of self-reported symptoms or signs of a stroke or TIA or objective clinical or CT scan evidence of a stroke. Vascular disease included those with a history of previous myocardial infarction or significant coronary disease on coronary angiography, peripheral vascular disease by symptoms, clinical signs or Doppler as well as proven aortic plaque on imaging (CT or MRI).

The CHADS₂ and CHA₂DS₂VASc scores for each patient with AF in the GSH cohort was calculated and for each score, 3 categories will be considered: Low risk - score of 0, intermediate risk – score of 1 and high risk, score of 2 or more.

Patients were followed up annually for a 2-year period. Information pertaining to the outcomes of death and most importantly stroke was captured from medical records and patient interviews in accordance with the REMEDY protocol. These outcomes were correlated with the CHADS₂ and CHA₂DS₂VASc scores.

Statistics

The prevalence of AF in the entire cohort of REMEDY patients and well as in the local GSH cohort was calculated using the total REMEDY enrollments (n=3343) and the total Groote Schuur enrolments (n=489) as denominators. These are presented as percentages. The clinical characteristics of the AF cohort were compared to those patients in sinus rhythm. Continuous variables are expressed as means with standard deviations, or medians with interquartile ranges as appropriate. Categorical variables are expressed as frequencies and percentages. Linear regression models assessed the relationship between the variables. Cox regression models are used to assess the risk of stroke/thromboembolism using CHA₂DS₂VASc score. Kaplan-Meier estimates of event –free survival at 2 years were obtained, relating it to the CHA₂DS₂VASc score categories of 0, 1 and 2 or more.

Results

Prevalence

A total of 3343 patients were enrolled in REMEDY but only 2624 patients reported detailed ECG findings. Of the 2624 patients with full ECG information, 586 (22.3%) had AF. (Fig 1) Within the GSH cohort, the prevalence of AF was 38.2%. (Fig 2) A total of 187 out of 489 patients in the GSH cohort had AF but complete data sets regarding the CHA₂DS₂VASc risk factors were only available in 130 patients.

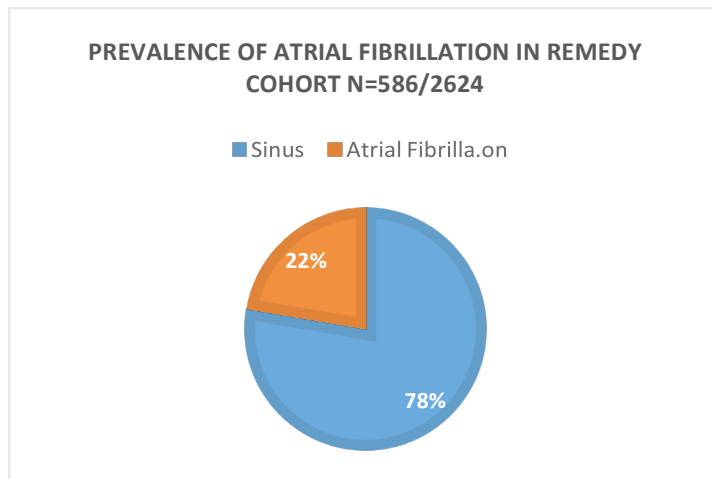


Figure 1. Prevalence of AF in total cohort

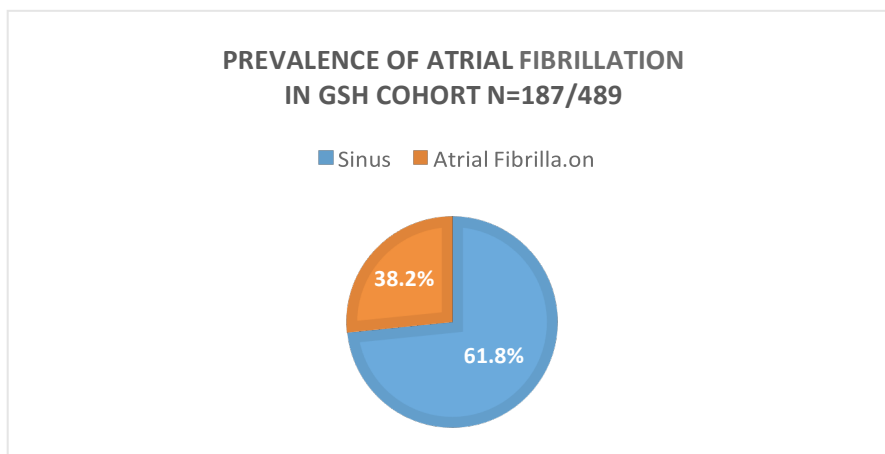


Fig 2. Prevalence of AF in the GSH cohort

Baseline Characteristics

Table 1 summarises the baseline clinical characteristics of the entire cohort at the time of enrolment. The patients with AF were older than those in sinus rhythm (SR) (median age: 35 years in AF and 25 years in SR, $p < 0.0001$). Patients were also more likely to be female and have a history of congestive heart failure than those in SR (female gender: 73.1% in AF, 65.7% in SR: $p=0.001$ and for a prior history of congestive heart failure: 41% in AF and 33.3% in SR: $p=0.001$). The AF group had significantly more strokes or TIA's compared to those in sinus rhythm and were more likely to have a NYHA III-IV effort tolerance. AF patients were more likely to have had previous interventions (both surgical and percutaneous), which may reflect more severe disease. No other significant differences were found between the two groups at baseline.

Table 1: Baseline Clinical Characteristics for total cohort at time of enrollment (n= 2,624)

<u>CLINICAL PARAMETERS</u>	<u>SINUS</u> N=2038 (77.7)	<u>ATRIAL</u> <u>FIBRILLATION</u> N=586 (22.3)	<u>P</u>
Age (med, IQR)	25 (16-35)	35 (28-50)	<0.0001
Female n (%)	1332 (65.7)	434 (73.1)	0.001
Unemployed	1679 (82.6)	484 (83.0)	0.844
History of Congestive Heart Failure n (%)	676 (33.3)	237 (41.0)	0.001
History of Stroke/TIA n (%)	100 (5.0)	81 (13.8)	<0.0001
History of Peripheral embolism n (%)	15 (0.7)	6 (1.0)	0.44
History of Major Bleeding n (%)	45 (2.2)	18 (3.1)	0.249
History of previous percutaneous intervention	60 (2.96)	46 (7.9)	<0.0001
History of previous surgery	342 (16.8)	171 (29.4)	<0.0001
NYHA Class			

I	685 (34.5)	172 (29.3)	0.002
II	808 (40.5)	233 (39.7)	
III	408 (20.5)	134 (22.7)	
IV	93 (4.7)	48 (8.1)	
NYHA III&IV	501 (25.2)	182 (30.8)	0.002

Continuous data are mean \pm SD unless otherwise indicated

Table 2 describes the frequency of each valve lesion within the AF cohort, as present on clinical examination. The majority of patients with AF had been diagnosed with mitral stenosis and regurgitation; less so were found to have aortic valve disease. As expected, only a small number of patients had clinical features of pulmonary valve disease. In total, 88 (15.3%) were in overt heart failure at enrolment.

Table 2: Frequency of Clinical Valve lesions in the total AF cohort of patients (n=586)

	Mild	Moderate	Severe	n
Mitral Regurgitation	145 (35.3)	117 (28.5)	149 (36.3)	411
Mitral Stenosis	78 (20.2)	110 (28.5)	198 (51.3)	386
Aortic Regurgitation	173 (57.8)	92 (30.8)	34 (11.4)	299
Aortic Stenosis	41 (47.1)	25 (28.8)	21 (24.1)	87
Tricuspid Regurgitation		152 (57.4)	113 (42.6)	265
Tricuspid Stenosis	15 (51.7)	5 (17.2)	9 (31.0)	29
Pulmonary Regurgitation		13 (72.2)	5 (27.8)	18
Pulmonary Stenosis	3 (33.3)	5 (55.6)	1 (11.1)	9

Table 3: Echo features at baseline in total AF cohort

	<u>SINUS</u>	<u>ATRIAL</u> <u>FIBRILLATION</u>	P
LVID (Diastolic) (med, IQR) N=2528	49.8 (43.0-58.0)	43.8 (50.0-59.0)	0.1088
LVID (systolic) (med, IQR)	33.0 (27.6- 40.0)	35.0 (28.7-43.0)	<0.0001
LVEF (med, IQR) N=2516	61.0 (55.0-68.0)	57 (49-65.0)	<0.0001
Decreased EF n (% yes) N=2510	457 (23.5)	216 (38.4)	<0.0001
Dilate LV n (% yes)	760 (38.7)	206 (37.1)	0.5060
LA Size (med, IQR)	44.8 (36.8-53.0)	55.0 (48.0-64.0)	<0.0001
LA Thrombus n (% yes)	18 (0.9)	20 (3.7)	<0.0001
Spontaneous echo contrast	58 (3.0)	42 (7.9)	<0.0001

Prosthetic valves had been implanted in 145 (34.7%) of those with AF. Of these, 94.5% were mechanical prosthetic valves. Compared to the SR group, those with AF were more likely to have dilated left atria [55 vs 44.8mm in AF compared to SR: p <0.0001] and a lower LV ejection fraction [EF 57 vs 61%: p < 0.0001]. Spontaneous echo contrast and LA thrombus was more frequently seen in the AF group. (Table 3)

Just over 2/3 of patients (68%) with AF had been given a prescription for warfarin (Fig 3). A further 9.2% were given aspirin. More than a fifth of patients with significant valvular heart disease and AF therefore did not receive any anticoagulation.

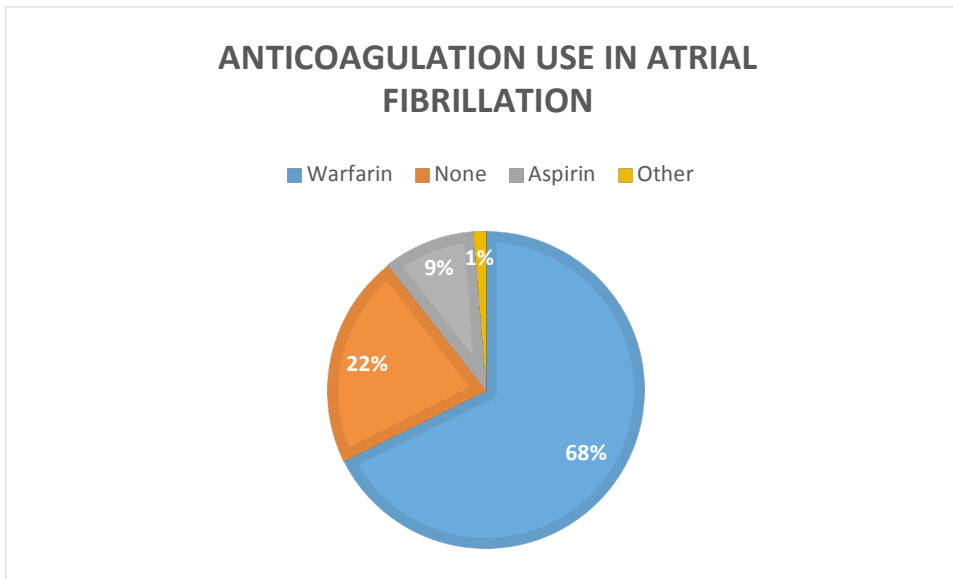


Figure 3. Anticoagulation in Atrial Fibrillation

GSH Cohort: Assessing CHADS₂ and CHA₂DS₂VASc risk factors and scores

Table 4: CHADS₂ score distribution of GSH AF cohort (complete data points n=130)

<u>CHADS₂ score</u>	<u>Freq</u>	<u>%</u>
0	30	23.1
1	36	27.7
2	37	28.5
3	23	17.7
4	4	3.1
5	0	0
6	0	0
Total	130	100%

The cohort of AF patients at the Groote Schuur Hospital, Cape Town was scored according to the CHADS₂ and CHA₂DS₂VASc scores. Table 4 shows that half of patients have a CHADS₂ score of 0 or 1 signifying a low level of comorbidity.

Table 5: CHA₂DS₂VASc score distribution of GSH AF cohort

<i>CHA₂DS₂VASc score</i>	<i>Freq</i>	<i>%</i>
0	7	5.4
1	27	20.8
2	26	20
3	38	29.2
4	16	12.3
5	14	10.8
6	2	1.5
7	0	0
8	0	0
9	0	0
Total	130	100%

When the same cohort of patients was scored using the CHA₂DS₂Vasc score (Table 5), the score of 0 dropped from 23,1% to 5.4%, with considerably more patients scoring 2 or above. On assessment of the individual risk factors making up the CHA₂DS₂VASc score this difference appears to be driven mainly by the addition of a category for female gender. In contrast to non-valvular AF, most patients in our cohort were younger 65 years of age (median age 28 years)

GSH cohort: Outcomes

Table 6 shows the outcomes of death and stroke being significantly greater in the AF group compared to the SR group at 2-year follow-up – for deaths 13.1% vs 5.5% (p=0.016) and for stroke 4.6% vs 1.5% (p=0.09).

Table 6: At 2 year Follow-up:

	<u>N(%) AF</u>	<u>N(%) Sinus</u>	<u>Total</u>	<u>P</u>
Deaths	17 (13.1)	11 (5.5)	28	0.016
Stroke	6 (4.6)	3 (1.5)	9	0.09

Figures 4 and 5 represent the Kaplan-Meier survival curves. It is evident in both the total REMEDY and GSH cohorts that the presence of AF at enrollment significantly reduces survival. From initial enrollment, the lines continue to diverge. In the total REMEDY cohort (Fig 4), there is a greater than 20% mortality at 2 years in the AF group. Even at a tertiary level center, (Fig 5) the mortality rate at 2 years is greater than 15%. The survival at 2 years is 84.6% with AF and 94.5 % with sinus rhythm.

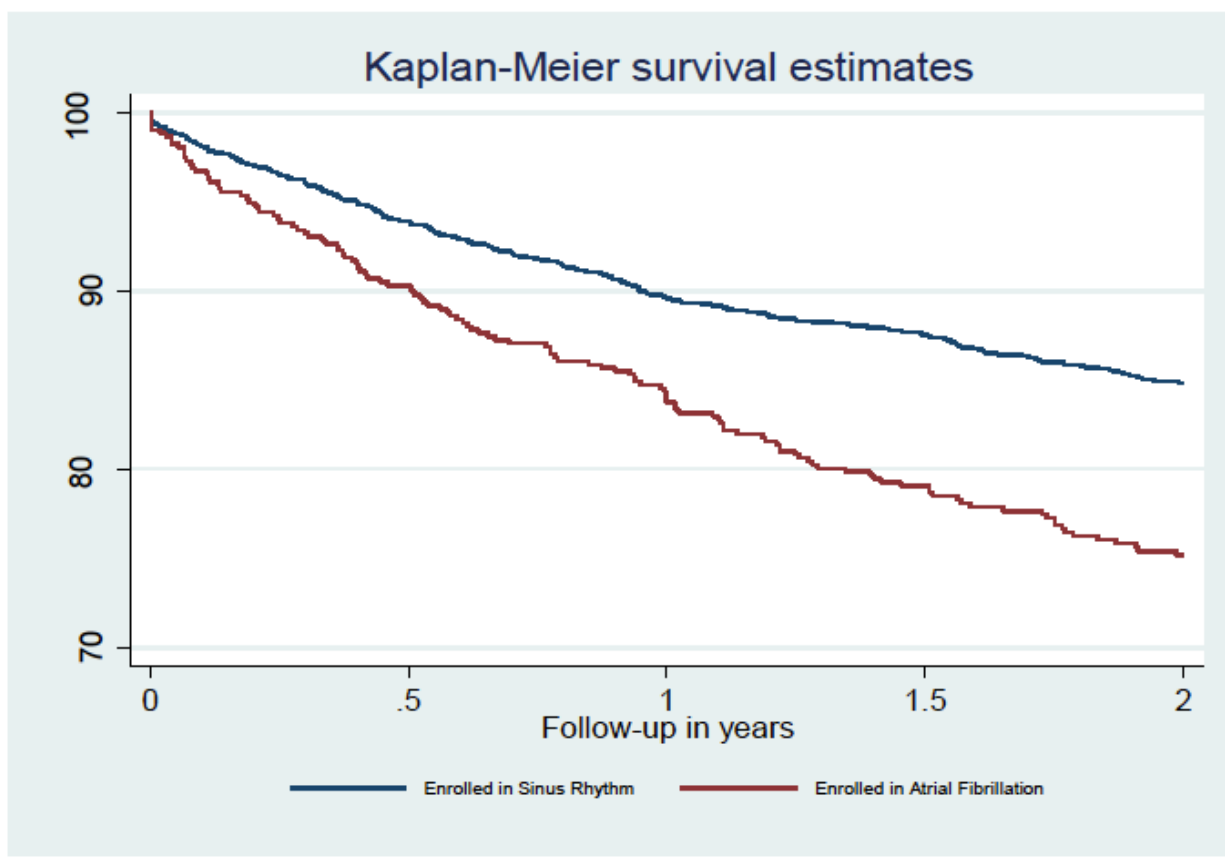


Fig 4. Survival curves for the entire REMEDY cohort

Log-rank test for survival <0.000 for entire cohort

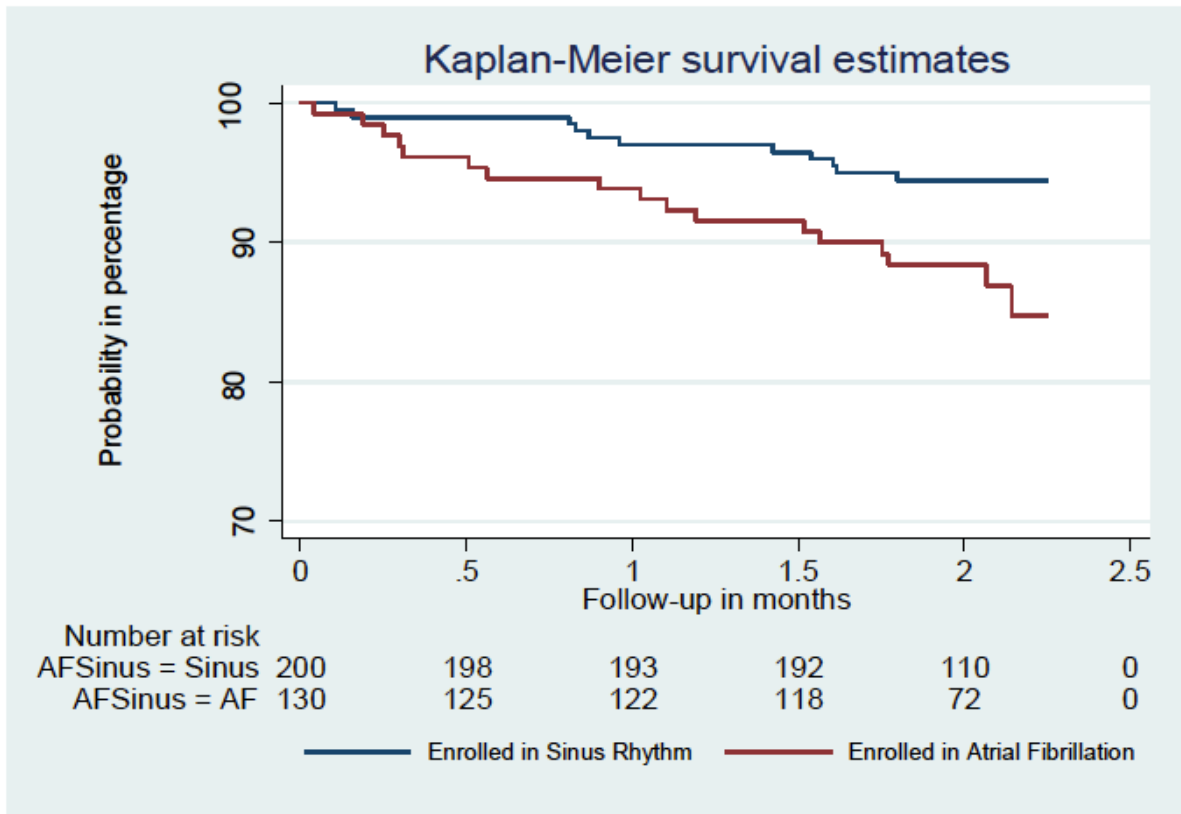


Fig 5. Survival curves for the GSH cohort

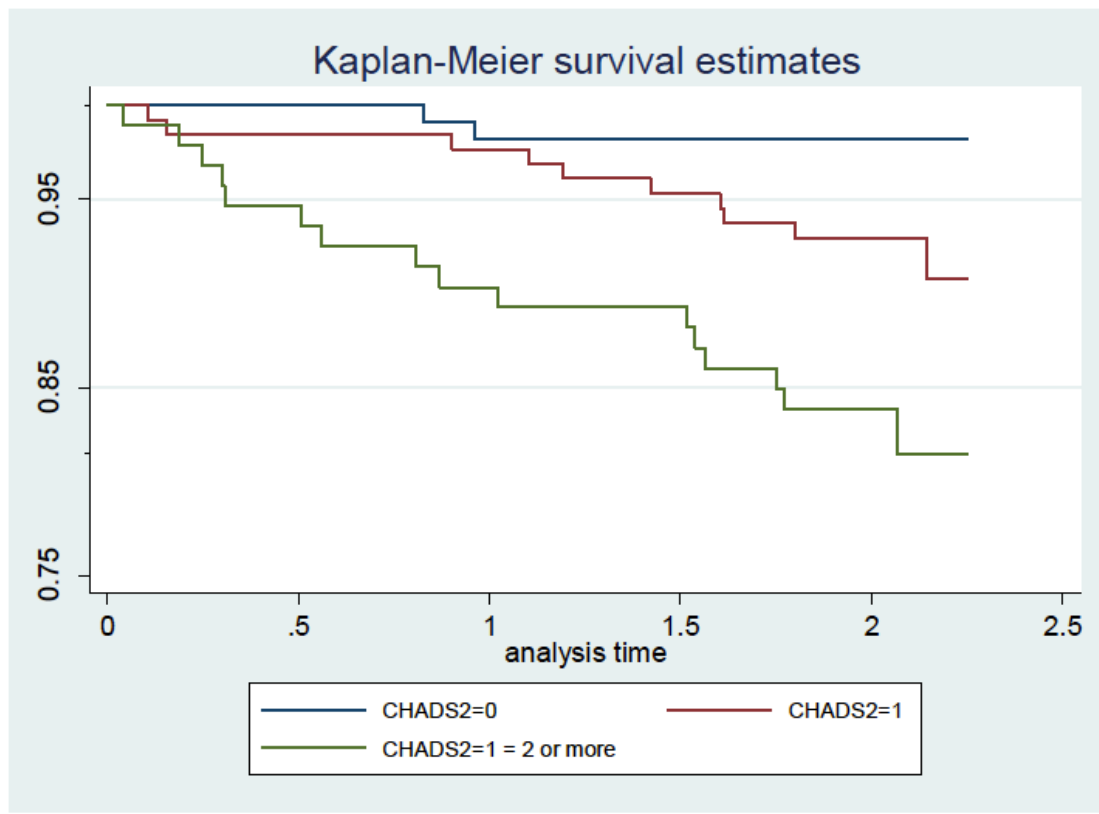


Fig 6. Survival estimates of the GSH cohort by CHADS₂ categories

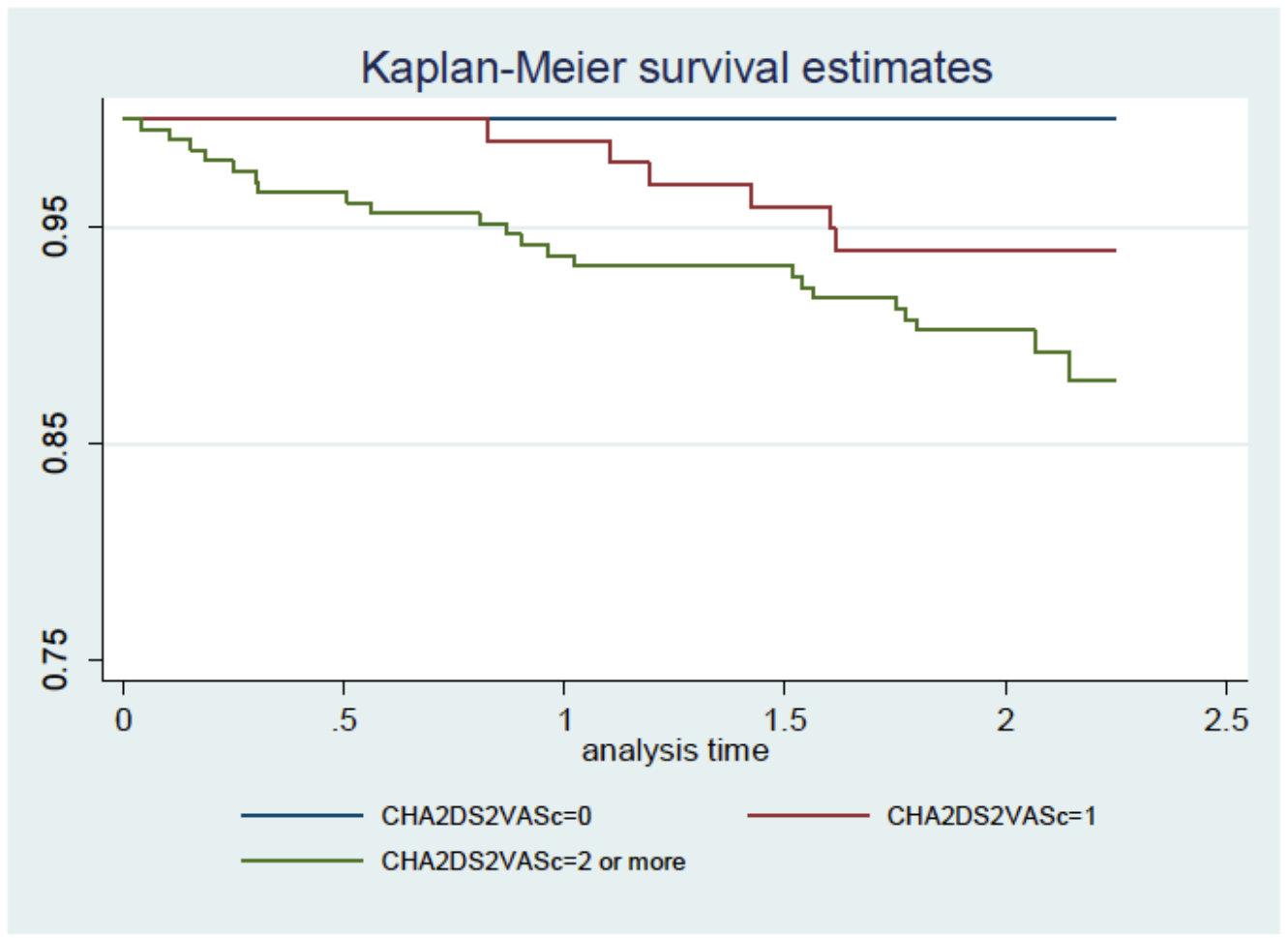


Fig 7. Survival estimates of the GSH cohorts by CHA₂DS₂VASc categories

Kaplan-Meier curves (figures 6 and 7) in the AF cohort demonstrated that the presence of any additional co-morbidities significantly reduces survival in both the short and long term. This was true for risk stratification by both the CHADS₂ and CHA₂DS₂VASc scores. A CHADS₂ score of 0 was still associated with a small number of events (Fig 6) but when the same group was re-stratified with the CHA₂DS₂VASc score, the ‘true low risk group’ with a score of 0 had no events (Fig 7). Greater CHA₂DS₂VASc score categories (CHA₂DS₂VASc 1 and CHA₂DS₂VASc 2 or more) conferred a higher risk of death.

Table 7: Hazard Ratios for deaths according to the various CHADS₂ and CHA₂DS₂VASc scores

Predictor	Hazard Ratio	95% Confidence Interval	P Value
CHADS₂			
CHADS ₂ of 1	4.35	0.95 – 19.83	0.058
CHADS ₂ of 2	9.63	2.11 – 43.96	0.003
CHADS ₂ of 3	6.49	1.08 – 38.87	0.040
CHADS ₂ of 4	44.09	7.34 – 264.56	0.000
CHA₂DS₂VASc			
CHA ₂ DS ₂ VASc of 1	4.02	4.83 – 3.34	0.000
CHA ₂ DS ₂ VASc of 2	3.66	4.41 – 3.04	0.000
CHA ₂ DS ₂ VASc of 3	1.14	1.46 – 8.92	0.000
CHA ₂ DS ₂ VASc of 4	3.56		0.000
CHA ₂ DS ₂ VASc of 5	1.37	1.42 – 1.32	0.000
CHA ₂ DS ₂ VASc of 6	6.79	6.14 – 7.50	0.000

Table 7 describes the hazard ratios by CHADS₂ and CHA₂DS₂VASc scores. All CHA₂DS₂VASc scores of one or greater is associated with a significant risk of death, though an incremental difference with each consecutive increasing score is not observed. This is likely due to the small sample size for each individual CHA₂DS₂VASc score category.

The stroke and death rate per CHA₂DS₂VASc category is depicted in Figure 8. A CHA₂DS₂VASc score of 1 or more confers significant risk of death and this is particularly marked if the score is 2 or more (p <0.0001). This observation holds true for strokes as well (p < 0.032).

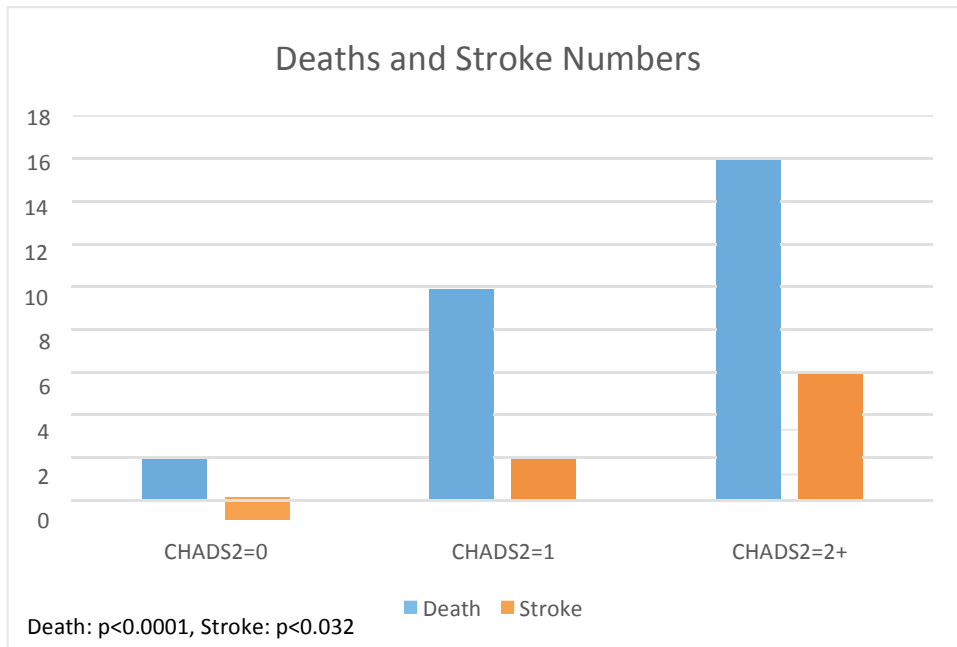


Fig 8. Stroke and death rate as per CHA₂DS₂VASc Categories

Discussion

In this study, we assessed AF in a contemporary cohort of patients with rheumatic heart disease enrolled in the REMEDY study.¹⁴ Our key findings are as follows:

1. Prevalence

The prevalence of AF in this cohort was 22.3%. This is considerably higher than that of non-valvular AF where the prevalence reached around 8%¹⁶ in the ninth decade. For the GSH cohort – a tertiary referral center cohort – the prevalence was 38.2%. This higher prevalence compared to the overall REMEDY cohort most likely reflects a greater disease severity as evidenced by more interventional and surgical procedures in the tertiary center compared to those patients in the general community. Furthermore, the ECG's of this entire cohort was re-assessed and verified as AF by a cardiologist. A number of patients with rhythms classified as 'other' were re-classified from paced rhythm or atrial flutter to AF when the underlying atrial rhythms were carefully scrutinized. In historic cohorts of RHD, the prevalence of AF ranged from 20 to 70% depending on disease severity or method and timing of sampling.^{1,2,17}

2. Baseline characteristics

The median age of the GSH cohort was 28 (35 in the total cohort) and more than 70% were female, once again in keeping with previous RHD cohorts.¹ AF patients had a greater history of heart failure, accompanied by a worse NYHA class, as well as a history of intervention, both percutaneous and surgical, once again reflecting increased disease severity in AF cohort.

Most patients had mitral valve disease (regurgitation and stenosis) and at least two thirds had some degree of aortic regurgitation as well. Aortic stenosis was uncommon and pulmonary valve involvement rare. The LV diastolic dimensions on echo were not significantly different between the two groups, however the systolic dimensions were greater in the AF group, reflecting a reduced LV ejection fraction. The LA size was dramatically greater in the AF group with thrombus visualized in 3.7%. Though this number seems low, it is statistically more than in sinus rhythm cohort, but it is noted that transthoracic echo is not the most ideal modality to assess for LA thrombus since the left atrial appendage is poorly visualized on

transthoracic echo in adults and this would be where most thrombi form. Spontaneous echo contrast was seen in 7.9% of the AF cohort.

Observational studies in valvular AF suggested long term oral anticoagulation as a method to prevent systemic emboli. In a review of 254 patients, Roy et al. found an embolic event rate of 5.46 per 100 patient years in patients with no anticoagulant therapy compared to 0.7 per 100 patient years in those receiving oral anticoagulation.¹⁸ In our cohort, only 68% received a prescription for warfarin. A further 9% had aspirin. This however does not constitute appropriate anticoagulation in the setting of AF.^{19,20} Twenty-three percent of patients with valvular AF received no form of anticoagulation or antiplatelet therapy at all. We do not have data pertaining to the adequacy of anticoagulation or the reasons for non-prescription in these patients. The lack of adequate anticoagulation may well be an additional factor contributing to the high rates of stroke and death we observed at two years. In the GSH cohort, the survival seemed slightly better compared to the general cohort. This may reflect intensification of care and follow-up.

3. CHADS₂ and CHA₂DS₂VASC risk factors

The CHADS₂ and CHA₂DS₂VASc scores for 130 of the AF patients in the GSH cohort were calculated. For the CHADS₂ score, 23.1% had no additional risk factors for AF and 27.7% had a score of 1. When the CHA₂DS₂VASc score was applied to the same cohort, the score of 0 dropped to only 5.4%. This difference was mainly driven by the addition of female gender as a risk factor. Forty percent of patients had a prior history of congestive heart failure and 15% had a prior history of stroke or TIA. The frequencies of the other individual risk factors and comorbidities were low. This is likely due to this being a younger cohort when compared to non-valvular AF studies.

4. Outcomes

We assessed the outcomes of stroke and death at two year follow-up. All forms of AF are known to increase morbidity and mortality significantly.^{21,22} Despite the low level of comorbidity in terms of the individual risk factor profile and the younger age of the cohort in general, 4.6% strokes and 13.1% mortality were observed in the AF group at two years. This

was significantly greater than the group with sinus rhythm (1.5% strokes and 5.5% mortality at 2 years). In this setting, AF in its own right, without additional risk factors, dramatically increases morbidity and mortality. Thirty-five percent of patient with AF has prosthetic valves, the majority being mechanical valves. This was not corrected for in the outcomes assessments.

The CHADS₂ and CHA₂DS₂VASc scores were originally derived to assess the need for oral anticoagulation for stroke prevention in patients with non-valvular AF and validated in numerous studies.^{10,11} Scores of 2 or above were associated with worse outcomes in terms of stroke and in some studies, even mortality.²³ Traditionally, the studies assessing the efficacy of the scoring systems excluded valvular AF, especially rheumatic patients, since they already represent a high-risk group. It is well established that RHD carries up to a 17-fold increased risk for stroke and warrants anticoagulation in its own right.³

In our study, the rates for both stroke and death increase incrementally and significantly with increasing score category (CHA₂DS₂VASc category 0, 1 or 2 or more). The sample size was too small to show any significant differences for each consecutive individual score category of 0-9. Though we cannot conclusively denote the role of these scoring systems in RHD in the decision to anticoagulate or not, we can conclude that the scoring systems have an important role in prognostication for stroke and mortality. This would hopefully drive stricter control of existing anticoagulation regimens and the development of potential new anticoagulation strategies in RHD.

Study limitations

This is a post-hoc review of the AF cohort of the REMEDY study. REMEDY is a hospital-based registry. Most of our participating centers are referral units, so it is likely that only the more severe cases of RHD are included in this study. This would therefore hamper the widespread generalization of these results to the entire AF community. The diagnosis of AF in the general cohort is on clinical and/or ECG grounds; at GSH, All ECG's and Holter tracings were reviewed and true diagnosis of AF verified resulting in a larger total number of AF patients. If the same holds true for the larger cohort, the prevalence of 22% may well be an underestimate.

The data pertaining to the CHADS₂ and CHA₂DS₂VASc scores were collected retrospectively – full data sets were only obtained in 130 patients. In light of this, the sample size is small when considering each CHA₂DS₂VASc category individually. Pertaining to the death and stroke rates, the confounders (e.g., the presence of prosthetic valves) were not accounted for.

Furthermore, given the differences in chronicity between RHD in the developed world (i.e., disease of older people) and RHD in developing countries (i.e., disease of the young), these results cannot be extrapolated to those living in the first world.

Conclusions

In this study, we evaluated AF in a contemporary cohort of patient with RHD. We found a prevalence of 22% in the general cohort, and of 39% in a tertiary cohort. AF patients displayed clinical and echocardiographic features of more severe disease. The outcomes of stroke and mortality in the AF group were found to be 4.6% and 13.1 % respectively, despite these patients being young and having relatively few comorbidities. This was significantly greater than the stroke and death rates in the sinus rhythm group (1.5% and 5.5% respectively). Greater CHADS₂ and CHA₂DS₂VASc scores were associated with significantly worse outcomes for stroke and death. Larger studies are required to determine the role of these scoring systems in the decisions around anticoagulation.

Funding

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References

1. Fleming HA, Bailey S. Mitral valve disease, systemic embolism and anticoagulants. *Postgraduate Medical Journal* 1971; 47: 599-604
2. Diker E, Aydogdy S, Ozdemir M, Kural T et al. Prevalence and Predictors of Atrial Fibrillation in Rheumatic Valvular Heart Disease. *Am J Cardio* 1996; 77:96-98.
3. Wolf PA, Abbott RD, Kannel WB. Atrial Fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; 22(8)983-988.
4. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. *Br H J* 1962; 24: 349-357
5. Freed LA, Levy D, Levine RA, Larson MG, Evans JC, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical outcome of mitral valve prolapse. *N Eng J Med* 1999;341: 1-7.
6. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation* 1994;89: 635-641.
7. Abernathy WS, Willis PW 3rd. Thromboembolic complications of rheumatic heart disease. *Cardiovasc Clin* 1973;5: 131-175.
8. Hart RG, Pearce LA, McBride R, et al. the Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. *Stroke* 1999;30: 1223-1229.
9. Pisters R, Lane DA, Marin F, et al. Stroke and thromboembolism in atrial fibrillation. *Circ J.* 2012; 76:2289-2304.
10. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864-2870
11. Lip GY, Nieuwlaat R, Pisters R et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest* 2010; 137:263-272.
12. Kirchhof P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal* 2016 ; 37:2893-2962

13. January CT, Wann LS, Alpert JS, et al. American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology* 2014; 64(21):e1-e76.
14. Karthikeyan G, Zuhlke L, et al. Rationale and design of a Global Rheumatic Heart Disease Registry: the REMEDY Study. *American Heart Journal* 2012; 163 (4) 535-540
15. Zuhlke L, Engel M, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *European Heart Journal* 2015; 36 (18):1115-1122.
16. Furberg CD, Psaty BM, Manolio TA, et al. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994; **74**: 236-241.
17. Wipf JE, Lipsky BA. Atrial Fibrillation. Thromboembolic risk and indications for anticoagulation. *Arch Intern Med* 1990; **150**: 1598-1603
18. Roy D, Marchand E, Gagne P, Chabot M, Carter R. Usefulness of anticoagulation therapy in the prevention of embolic complications of AF. *American Heart Journal* 1986;112(5) 1039-1043.
19. Lip GY. The role of aspirin for stroke prevention in atrial fibrillation. *Nat Rev Cardiol* 2011;8:602–606.
20. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin vs. aspirin for stroke prevention in an elderly community population with atrial fibrillation (The Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomized controlled trial. *Lancet* 2007;370:493–503.
21. Krahn AD, Manfreda J, Tate RB et al. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-up Study. *Am J Med* 1995; **98**: 476-84.
22. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomised controlled trials. *Arch Intern Med* 1994; **154**: 1449-1457.
23. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification

schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864-2870



Prevalence, characteristics and additional stroke risk stratification: An analysis of the Atrial Fibrillation cohort within the REMEDY registry

Blanche J Cupido

University of Cape Town student number: CPDBLA001

PART D: SUPPORTING DOCUMENTS

PART D: SUPPORTING DOCUMENTS

Addendum 1: Informed Consent Form

Addendum 2: Baseline CRF

Addendum 3: CHADS₂ and CHADS₂VASc form

Addendum 4: Follow-up CRF

Addendum 5: Event Forms

Addendum 6: Table 1 – CHADS₂ Score

Table 2 – CHA₂DS₂VASc Score

Addendum 7: Ethics Approval

ADDENDUM 1: INFORMED CONSENT FORM

Consent Form

1. STATEMENT BY THE PERSON AGREEING TO PARTICIPATE IN THIS STUDY

I have read this Participant Information Sheet and informed consent document describing the benefits, risks and procedures for the research study titled “Global Registry of Rheumatic Heart Disease in Cape Town, South Africa” or it was read to me. I freely and voluntarily choose to participate in the study.

Name of participant: _____

Date:

Signature or thumbprint of participant

2. STATEMENT BY PARENT/GUARDIAN AGREEING FOR HIS/HER CHILD TO PARTICIPATE IN THIS STUDY

I have read this Participant Information Sheet and informed consent document describing the benefits, risks and procedures for the research study titled “All Africa Registry of Rheumatic Heart Disease in Cape Town, South Africa” or it was read to me. I freely and voluntarily choose to allow my son/ daughter to participate in the study.

Name of child participant _____

Date

Signature or thumbprint of parent/guardian

3. IF THE PARENT/GUARDIAN CANNOT READ THE FORM THEMSELVES, A WITNESS MUST SIGN HERE:

I was present while the informed consent document with benefits, risks and procedures were read to the parent/guardian and the participant. The parent/guardian has freely and voluntarily agreed to allow her/his daughter/son to take part in the research.

Date

Signature of witness

Principal Investigator: Bongani M. Mayosi, D.Phil. Groote Schuur Hospital Tel: 27-21-406-6200 [bongani.mayosi@uct.ac.za]	Concerns or Complaints: Human Research Ethics Committee (021) 406-6338.
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Assent Form for Children 8 years and older

We are doctors and nurses from Red Cross Childrens', Groote Schuur Hospitals and Tygerberg Hospitals and we are doing a study of hearts of children.

We would like to ask you a few questions about your health. This will not hurt at all and is very quick.

If you agree to take part in this study, you will be helping doctors to know how better to treat other children in the future.

You are allowed to say that you don't want to be in the study. Nobody will be angry with you if you say no.

Before you decide, you can ask us questions. If you want to be in the study, you must write your name on this sheet of paper. This means that you are happy to be involved in the study.

Child Participant:

Printed name	Signature	Date
--------------	-----------	------

Study doctor or research nurse:

Printed name	Signature	Date
--------------	-----------	------

Witness:

Printed name	Signature	Date
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Principal Investigator: Bongani M. Mayosi, D.Phil. Groote Schuur Hospital Tel: 27-21-406-6200 [bongani.mayosi@uct.ac.za]	Concerns or Complaints: Human Research Ethics Committee (021) 406-6338.
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**Global Registry of
Rheumatic Heart Disease**

Baseline Questionnaire

INSTRUCTIONS

Please complete Subject's Initials on every page



F= first letter of first name M= first letter of middle name

L= first letter of last name

Please answer EACH question by marking
an X in ONE BOX on each line:
(unless otherwise instructed)



OR

By writing number(s) in the spaces provided:



OR

By specifying the answer on the line(s) provided

Version 2.0b - 2011 Mar 02



Subject ID

Centre#

Subject #

Subject Initials
F M L

Today's date: / /
year month day

Enrolment visit

1. Date of birth: / / OR Age (years) accurate estimate
year month day

2. Sex: Male Female → Is this participant pregnant? No Yes

3. Ethnicity: (Please refer to facing page for codes)

4. Marital status: (check one only)
 Never married Currently married Common law/Living with partner
 Widowed Separated

5. What level of formal education have you **completed**? (check highest level only):
(If younger than 7 years of age, check the level of formal education completed by the mother)
 None Secondary/High school/Higher secondary College/University
 Primary Trade school/Vocational school Unknown

6. Are you currently employed?
 No
 Yes → If yes, what is your average income per month in local currency?
What is the local currency? _____ → US\$ (for coordinating office only)

7. (a) During your working life, what was your main occupation? _____

(b) Please indicate which group best describes your main occupation. Current or past daily activity
 Group 1 Group 2 Group 3 Group 4 Group 5 Group 6
 Group 7 Group 8 Group 9 Group 10 Group 11 Group 12
 Never worked Other: _____

8. Measurements:

a) Blood Pressure / mmHg (Systolic / Diastolic) b) Pulse rate beats/min
c) Weight . kg d) Irregular rhythm No Yes
e) Height . cm



Subject ID

Centre# Subject #

Subject Initials
 F M L

9. Presenting features: Status at the enrollment visit

a) Symptoms: (please mark (X) as appropriate)

- | | | |
|---------------------------------------|-------------------------------------|--|
| <input type="checkbox"/> Asymptomatic | <input type="checkbox"/> Chest pain | <input type="checkbox"/> Routine clinic visit |
| <input type="checkbox"/> Dyspnea | <input type="checkbox"/> Fever | <input type="checkbox"/> Palpitations |
| <input type="checkbox"/> Syncope | <input type="checkbox"/> Fatigue | <input type="checkbox"/> Other, Specify: _____ |

b) NYHA class → (please refer to facing page for codes)

- I II III IV

10. Past medical history: (As taken from doctor's notes and patient's recollection)

		Date	Source documents available	Additional Relevant Details:
a) Congestive heart failure/ Pulmonary edema	<input type="checkbox"/> No <input type="checkbox"/> Yes →	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> year month	<input type="checkbox"/>	_____
b) Rheumatic fever in the past	<input type="checkbox"/> No <input type="checkbox"/> Yes →	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> year month	<input type="checkbox"/>	_____
c) Stroke/TIA	<input type="checkbox"/> No <input type="checkbox"/> Yes →	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> year month	<input type="checkbox"/>	_____
d) Peripheral embolism	<input type="checkbox"/> No <input type="checkbox"/> Yes →	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> year month	<input type="checkbox"/>	_____
e) Major bleeding	<input type="checkbox"/> No <input type="checkbox"/> Yes →	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> year month	<input type="checkbox"/>	_____
f) Infective endocarditis	<input type="checkbox"/> No <input type="checkbox"/> Yes →	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> year month	<input type="checkbox"/>	_____
g) Percutaneous valvuloplasty	<input type="checkbox"/> No <input type="checkbox"/> Yes →	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> year month	<input type="checkbox"/>	_____
h) Previous heart valve surgery	<input type="checkbox"/> No <input type="checkbox"/> Yes →	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> year month	<input type="checkbox"/>	_____
i) Sickle cell anaemia	<input type="checkbox"/> No <input type="checkbox"/> Yes →	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> year month	<input type="checkbox"/>	_____
j) Co-existing morbidities	<input type="checkbox"/> No <input type="checkbox"/> Yes →	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> year month	<input type="checkbox"/>	_____



Subject ID

Centre# Subject #

Subject Initials
 F M L

13. Most recent ECG:

a) Was an ECG performed at this visit?

- No → Will you be obtaining an ECG for this participant? No → go to section 14.
 Yes → Complete sections 13.b-e when ECG obtained
 Yes → Complete section 13.b-e

b) Date:
 year month day

c) Source documentation available: No Yes

d) Rhythm: Sinus Atrial fibrillation Atrial flutter Other Dysrhythmia

e) Other comments (specify): _____

14. Most Recent CXR:

a) Was a chest x-ray (CXR) performed within last 12 months?

- No → Will you be obtaining a CXR for this participant? No → go to section 15.
 Yes → Complete sections 14.b-g when CXR obtained
 Yes → Complete section 14.b-g

b) Date:
 year month day

c) CXR report available: No Yes

d) Cardiomegaly No Yes

e) Pleural effusion No Yes

f) Pulmonary edema No Yes

g) Other comments (Specify): _____

Please proceed to complete Page 5 →



Subject ID

Control# [][][] Subject # [][][][]

Subject Initials [][] [][] [][]
F M L

15. Echocardiogram

a) Was an Echocardiogram (ECHO) performed at this visit?

No → Has an ECHO been scheduled for this visit?
 Yes → Complete section 15.b-m

No → Please Schedule an ECHO now...
 Yes → Complete sections 15.b-m when ECHO obtained

Date of most recent Echo report: [][][] [][] [][]
year month day

Report available: No Yes

Valve Lesions

b) Does the patient have prosthetic valves?

No Yes → If yes, please mark (X) as appropriate:

	Mechanical	Bioprosthesis	Details: (eg type or size)
Mitral	<input type="checkbox"/>	<input type="checkbox"/>	_____
Aortic	<input type="checkbox"/>	<input type="checkbox"/>	_____
Pulmonary	<input type="checkbox"/>	<input type="checkbox"/>	_____
Tricuspid	<input type="checkbox"/>	<input type="checkbox"/>	_____

c) Has the patient had an annuloplasty?

No
 Yes → If Yes, please specify: Mitral
 Tricuspid

d) Mitral Valve

Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stenosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please provide gradient information in section i, ii and iii below, if the Mitral valve is prosthetic or stenotic:

→ i) MVA: [][] - [][] cm²
 ii) End-diastolic gradient: [][][] - [][] mmHg
 iii) Mean gradient: [][][] - [][] mmHg

Calcification No Yes
Vegetations No Yes

DataFax #164 Plate #015 Visit #002

Subject ID

Centre# Subject #

Subject Initials
F M L

f) Aortic Valve Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation

Stenosis

Please provide gradient information in section i, ii, iii and iv below, if the Aortic valve is prosthetic or stenotic:

i) Jet velocity: . m/s ii) Mean gradient: . mmHg
 iii) Valve area : . cm² iv) Peak gradient: . mmHg

Calcification No Yes
 Vegetations No Yes

g) Tricuspid Valve Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation

Stenosis

Please provide doppler gradient information below, if the Tricuspid valve is prosthetic or stenotic:

Doppler gradients (in mmHg): mean . End-diastolic .

Calcification No Yes
 Vegetations No Yes

Tricuspid valve annulus . mm

h) Pulmonary Valve Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation

Stenosis

Please provide doppler gradient information below, if the Pulmonary valve is prosthetic or stenotic:

Doppler gradients (in mmHg): peak . mean .

Calcification No Yes
 Vegetations No Yes

DataFax #164

Plate #016

Visit #002

Subject ID

Centre#

Subject #

Subject Initials
F M L

i) Pulmonary hypertension TR gradient: . mmHg

TR velocity: . m/s

j) Left ventricular dimensions LVIDd . mm

LVIDs . mm

k) Left ventricular ejection fraction: . %

l) Left ventricular shortening fraction: . %

m) Left atrium AO: . mm

LA: . mm

LA:AO ratio: .

n) Additional echo findings:

Spontaneous echo contrast No Yes

Pericardial effusion No Yes

Left atrial thrombus No Yes Details: _____

Size: x mm

Thrombi other than LA No Yes Details: _____

Size: x mm

o) Further comments: _____



Subject ID

Control# Subject #

Subject Initials
F M L

Medication:

18. Secondary prophylaxis

a) Approximate date of commencing secondary prophylaxis: → IMI P.O.

year month day

b) Currently on secondary prophylaxis: No (*Please proceed to question 19*)
 Yes → Specify: Benzathine penicillin
 Oral agents

i) Benzathine penicillin dose → 4wkly 3wkly 2wkly

No. of injections received in the past year:
 (According to records/ Physician's estimate)

% adherence %
 (See facing page for calculation)

ii) Oral agents: (mark (x) as appropriate)

Oral penicillin
 (specify compound and dosage): _____

Others
 (specify compound and dosage): _____

No. of oral prescriptions filled in past year:
 (According to Physician's estimate)

% adherence %
 (According to Physician's estimate)

Please proceed to complete Page 10 →



Subject ID

Centra# [][] [][] Subject # [][][][]

Subject Initials [][] [][] [][] F M L

21. Does the participant have Poor oro-dental hygiene: [] No [] Yes (including dental caries, gum disease)

Completing question 22 is optional:

22. HIV Status: [] Negative [] Positive [] Unknown [] non-disclosure

Please provide details below if information available:

a) Opportunistic infections: [] No [] Yes -> Details: _____

b) If HIV positive, WHO Clinical stage I-IV: [][] Date of WHO staging: [][][][] [][] [][] year month day

c) CD4 count or % at diagnosis: [][][][] Date of diagnosis: [][][][] [][] [][] year month day OR [][] %

d) Most recent CD4 Count or %: [][][][] Date of CD4 count or %: [][][][] [][] [][] year month day OR [][] %

e) ARVs: [] No [] Yes -> If yes, please provide Date of commencement: [][][][] [][] [][] year month day

f) Other comments including regime: _____

Person Completing Report: _____ Print Last Name

Initial Date: 2 0 [][] [][] [][]

ADDENDUM 3:

CHADS₂ AND CHADS₂VASc RISK FACTOR DATA SHEET

CHADS₂ score frequency of variables for GSH cohort		
Risk Factor	Present	Absent
CHF (recent)		
Hypertension (history of)		
Age 75 or older		
Diabetic Mellitus		
Stroke/TIA		
Maximum score		

CHA₂DS₂VASc score frequency of variables for GSH cohort		
Risk factor	Present	Absent
CHF/LV dysfunction		
Hypertension		
Age 75 or greater		
Diabetes Mellitus		
Stroke/TIA/TE		
Vascular disease (prior MI,PAD, or aortic plaque)		
Age 65-74		
Sex - female		
Maximum score		

ADDENDUM 4: FOLLOW-UP QUESTIONNAIRES

**Global Registry of
Rheumatic Heart Disease**

12 Month Visit Questionnaire

INSTRUCTIONS

Please complete Subject's Initials on every page

F	M	L
---	---	---

F= first letter of first name M= first letter of middle name
L= first letter of last name

Please answer EACH question by marking
an X in ONE BOX on each line:
(unless otherwise instructed)

X

OR

By writing number(s) in the spaces provided:

1	8
---	---

OR

By specifying the answer on the line(s) provided

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Subject ID

Centre# Subject #

Subject Initials
 F M L

4. Status at the current visit:

a) Symptoms: (please mark (X) as appropriate)

- | | | |
|---------------------------------------|-------------------------------------|--|
| <input type="checkbox"/> Asymptomatic | <input type="checkbox"/> Chest pain | <input type="checkbox"/> Routine clinic visit |
| <input type="checkbox"/> Dyspnea | <input type="checkbox"/> Fever | <input type="checkbox"/> Palpitations |
| <input type="checkbox"/> Syncope | <input type="checkbox"/> Fatigue | <input type="checkbox"/> Other, Specify: _____ |

b) NYHA class → (please refer to facing page for codes)

- I II III IV

5. Events: (As taken from doctor's notes and patient's recollection)

	No	Yes	Number of Episodes	Report#	Report#
a) Congestive Heart Failure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 2 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 2 <input type="text"/>
b) Stroke/TIA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 3 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 3 <input type="text"/>
c) Hospitalization	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 4 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 4 <input type="text"/>
d) Major Bleeding	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 5 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 5 <input type="text"/>
e) Infective endocarditis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 6 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 6 <input type="text"/>
f) Prosthetic Valve Thrombosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 7 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 7 <input type="text"/>
g) Acute Rheumatic Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 8 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 8 <input type="text"/>
h) Valvuloplasty	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 2 <input type="text"/> 0 <input type="text"/>	<input type="text"/> 2 <input type="text"/> 0 <input type="text"/>
i) Valve surgery	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 2 <input type="text"/> 1 <input type="text"/>	<input type="text"/> 2 <input type="text"/> 1 <input type="text"/>
j) Systemic embolism	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 2 <input type="text"/> 3 <input type="text"/>	<input type="text"/> 2 <input type="text"/> 3 <input type="text"/>
k) Atrial Fibrillation / Flutter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 2 <input type="text"/> 2 <input type="text"/>	<input type="text"/> 2 <input type="text"/> 2 <input type="text"/>

6. Pregnancy: (For Women Only)

Has this participant become pregnant since her last visit? No
 Yes → Please complete "Pregnancy Report" 1 9



Subject ID

Centre#

Subject #

Subject Initials
F M L

f) Aortic Valve Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation

Stenosis

Please provide gradient information in section I, II, III and IV below, if the Aortic valve is prosthetic or stenotic:

I) Jet velocity: m/s III) Mean gradient: . mmHg

II) Valve area : cm² IV) Peak gradient: . mmHg

Calcification No Yes

Vegetations No Yes

g) Tricuspid Valve Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation

Stenosis

Please provide doppler gradient information below, if the Tricuspid valve is prosthetic or stenotic:

Doppler gradients (In mmHg): mean . End-diastolic: .

Calcification No Yes

Vegetations No Yes

h) Pulmonary Valve Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation

Stenosis

Please provide doppler gradient information below, if the Pulmonary valve is prosthetic or stenotic:

Doppler gradients (In mmHg): peak . mean .

Calcification No Yes

Vegetations No Yes



Subject ID

Centre#
 Subject #

Subject Initials
 F M L

i) Pulmonary hypertension TR gradient: . mmHg

TR velocity: . m/s

j) Left ventricular dimensions LVIDd . mm

LVIDs . mm

k) Left ventricular ejection fraction: . %

l) Left ventricular shortening fraction: . %

m) Left atrium AO: . mm

LA: . mm

LA:AO ratio: .

n) Additional echo findings:

Spontaneous echo contrast No Yes

Pericardial effusion No Yes

Left atrial thrombus No Yes

Details: _____

Size: x mm

Thrombi other than LA No Yes

Details: _____

Size: x mm

o) Further comments: _____



Subject ID

Centre# Subject #

Subject Initials
 F M L

13. Does the participant have Poor oro-dental hygiene: No Yes
 (Including dental caries, gum disease)

Completing question 14 is optional:

14. HIV Status: Negative Positive Unknown non-disclosure

Please provide details below if information available:

a) Opportunistic Infections: No Yes → Details: _____

b) If HIV positive, WHO Clinical stage I-IV: Date of WHO staging:
year month day

c) CD4 count or % at diagnosis: Date of diagnosis:
year month day
 OR %

d) Most recent CD4 Count or %: Date of CD4 count or %:
year month day
 OR %

e) ARVs: No Yes → If yes, please provide Date of commencement:
year month day

f) Other comments including regime: _____

Person Completing Report: _____ Date: 2 0
Print Last Name Initial

Global Registry of Rheumatic Heart Disease

24 Month Visit Questionnaire

INSTRUCTIONS

Please complete Subject's Initials on every page



F= first letter of first name M= first letter of middle name

L= first letter of last name

Please answer EACH question by marking
an X in ONE BOX on each line:
(unless otherwise instructed)



OR

By writing number(s) in the spaces provided:



OR

By specifying the answer on the line(s) provided

Version 1.0 - 2011 Aug 01



Subject ID

Centre# Subject #

Subject Initials
 F M L

4. Status at the current visit:

a) Symptoms: (please mark (X) as appropriate)

- | | | |
|---------------------------------------|-------------------------------------|--|
| <input type="checkbox"/> Asymptomatic | <input type="checkbox"/> Chest pain | <input type="checkbox"/> Routine clinic visit |
| <input type="checkbox"/> Dyspnea | <input type="checkbox"/> Fever | <input type="checkbox"/> Palpitations |
| <input type="checkbox"/> Syncope | <input type="checkbox"/> Fatigue | <input type="checkbox"/> Other, Specify: _____ |

b) NYHA class → (please refer to facing page for codes)

- I II III IV

5. Events: (As taken from doctor's notes and patient's recollection)

	No	Yes	Number of Episodes	Report#	Report#
a) Congestive Heart Failure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 2 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 2 <input type="text"/>
b) Stroke/TIA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 3 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 3 <input type="text"/>
c) Hospitalization	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 4 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 4 <input type="text"/>
d) Major Bleeding	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 5 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 5 <input type="text"/>
e) Infective endocarditis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 6 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 6 <input type="text"/>
f) Prosthetic Valve Thrombosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 7 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 7 <input type="text"/>
g) Acute Rheumatic Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 8 <input type="text"/>	<input type="text"/> 1 <input type="text"/> 8 <input type="text"/>
h) Valvuloplasty	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 2 <input type="text"/> 0 <input type="text"/>	<input type="text"/> 2 <input type="text"/> 0 <input type="text"/>
i) Valve surgery	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 2 <input type="text"/> 1 <input type="text"/>	<input type="text"/> 2 <input type="text"/> 1 <input type="text"/>
j) Systemic embolism	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 2 <input type="text"/> 3 <input type="text"/>	<input type="text"/> 2 <input type="text"/> 3 <input type="text"/>
k) Atrial Fibrillation / Flutter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 2 <input type="text"/> 2 <input type="text"/>	<input type="text"/> 2 <input type="text"/> 2 <input type="text"/>

6. Pregnancy: (For Women Only)

Has this participant become pregnant since her last visit? No
 Yes → Please complete "Pregnancy Report" 1 9

Remedy #104 Plate #D14 Visit #004

Subject ID

Centre# [][] Subject# [][][]

Subject Initials [][] [][] [][]
F M L

8. Echocardiogram

a) Was an Echocardiogram (ECHO) performed at this visit?

- No → Has an ECHO been scheduled for this visit? No → Please Schedule an ECHO now...
 Yes → Complete section 8.b-m Yes → Complete sections 8.b-m when ECHO obtained

Date of most recent Echo report: [][][] [][] [][] Report available: No Yes
year month day

Valve Lesions

b) Does the patient have prosthetic valves? No Yes → If yes, please mark (X) as appropriate:

	Mechanical	Bioprosthesis	Details: (eg type or size)
Mitral	<input type="checkbox"/>	<input type="checkbox"/>	_____
Aortic	<input type="checkbox"/>	<input type="checkbox"/>	_____
Pulmonary	<input type="checkbox"/>	<input type="checkbox"/>	_____
Tricuspid	<input type="checkbox"/>	<input type="checkbox"/>	_____

c) Has the patient had an annuloplasty? No Yes → If Yes, please specify: Mitral Tricuspid

d Mitral Valve	Absent	Present →	Mild	Moderate	Severe (please refer to facing page)
Regurgitation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stenosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please provide gradient information in section I, II and III below, if the Mitral valve is prosthetic or stenotic:

I) MVA: [][] - [][] cm²
 II) End-diastolic gradient: [][][] - [][] mmHg
 III) Mean gradient: [][][] - [][] mmHg

Calcification No Yes
 Vegetations No Yes

Remedy #164 Plate #015 Visit #004

Subject ID

Centre# Subject #

Subject Initials
F M L

f) Aortic Valve Absent Present → Mild Moderate Severe (please refer to facing page)
 Regurgitation
 Stenosis

Please provide gradient information in section I, II, III and IV below, if the Aortic valve is prosthetic or stenotic:

I) Jet velocity: m/s III) Mean gradient: mmHg
 II) Valve area: cm² IV) Peak gradient: mmHg

Calcification No Yes
 Vegetations No Yes

g) Tricuspid Valve Absent Present → Mild Moderate Severe (please refer to facing page)
 Regurgitation
 Stenosis

Please provide doppler gradient information below, if the Tricuspid valve is prosthetic or stenotic:

Doppler gradients (In mmHg): mean End-diastolic

Calcification No Yes
 Vegetations No Yes

h) Pulmonary Valve Absent Present → Mild Moderate Severe (please refer to facing page)
 Regurgitation
 Stenosis

Please provide doppler gradient information below, if the Pulmonary valve is prosthetic or stenotic:

Doppler gradients (In mmHg): peak mean

Calcification No Yes
 Vegetations No Yes



Subject ID

Centre#
 Subject #

Subject Initials
 F M L

i) Pulmonary hypertension TR gradient: . mmHg

TR velocity: . m/s

j) Left ventricular dimensions LVIDd . mm

LVIDs . mm

k) Left ventricular ejection fraction: . %

l) Left ventricular shortening fraction: . %

m) Left atrium AO: . mm

LA: . mm

LA:AO ratio: .

n) Additional echo findings:

Spontaneous echo contrast No Yes

Pericardial effusion No Yes

Left atrial thrombus No Yes

Details: _____

Size: x mm

Thrombi other than LA No Yes

Details: _____

Size: x mm

o) Further comments: _____



Subject ID

Centre#
 Subject#

Subject Initials
 F M L

11. Oral anticoagulation

a) Is patient in sinus rhythm? No Yes (Please proceed to question 13.) ECG available No Yes

If no, has oral anticoagulation been prescribed? No Yes (If yes, please provide details below)

Warfarin → i) How many measurements of INR have been performed in the last 6 months?
 None 1-3 4-6 >6

ii) Is patient aware of what his/her INR should be?
 No Yes → If yes, what is the target INR? - to -
 (According to patient)

iii) Last three INR values:

1- <input type="text"/> - <input type="text"/>	→	Dated: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
		<small>year month day</small>
2- <input type="text"/> - <input type="text"/>	→	Dated: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
		<small>year month day</small>
3- <input type="text"/> - <input type="text"/>	→	Dated: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
		<small>year month day</small>

- Acenocoumalone
- Aspirin
- Others specify: _____

12. Other medication: (Please mark (X) as appropriate)

	No	Yes
a) Beta-adrenergic blockers	<input type="checkbox"/>	<input type="checkbox"/>
b) Calcium channel blockers	<input type="checkbox"/>	<input type="checkbox"/>
c) Diuretics	<input type="checkbox"/>	<input type="checkbox"/>
d) ACE inhibitors	<input type="checkbox"/>	<input type="checkbox"/>
e) Antiarrhythmics	<input type="checkbox"/>	<input type="checkbox"/>
f) Digoxin	<input type="checkbox"/>	<input type="checkbox"/>
g) Contraceptives	<input type="checkbox"/>	<input type="checkbox"/> Specify: _____
h) Others	<input type="checkbox"/>	<input type="checkbox"/> Specify: _____

ADDENDUM 5: EVENT FORMS:

ATRIAL FIBRILLATION

**Global Registry of
Rheumatic Heart Disease**

Atrial Flutter/ Fibrillation

INSTRUCTIONS

Please complete Subject's Initials on every page

F	M	L
---	---	---

F= first letter of first name M= first letter of middle name

L= first letter of last name

Please answer EACH question by marking
an X in ONE BOX on each line:
(unless otherwise instructed)

X

OR

By writing number(s) in the spaces provided:

1	8
---	---

OR

By specifying the answer on the line(s) provided

Version 1.1 - 01 Aug, 2011



Report # 2 2

Subject ID

Centre# [][][] Subject # [][][][]

Subject Initials F M L [][][]

6. Complications accompanying the episode of Atrial Fibrillation (Please mark (X) on all that apply)

- Death -> Complete a death report.
Congestive Heart Failure -> Complete a CHF report and enter the # here: [][][][]
Stroke -> Complete a stroke report and enter the # here: [][][][]
Other Embolic Event -> Complete a systemic embolism report and enter the # here: [][][][]
Other please specify: _____

7. Was the patient cardioverted?

No [] Yes []
Electrical -> Successful [] Unsuccessful []
Chemical -> Successful [] Unsuccessful []

8. Treatment given:

- Calcium Channel Blocker [] Oral anticoagulants []
Beta Blocker [] Heparin []
Amlodarone [] Digitalis []
Ticlopidine [] Aspirin []
Clopidogrel [] Other antiarrhythmics []
Sotalol []
Other Please Specify: _____

Person Completing Report: _____ Date: 2 0 [][][] [][][]

EVENT FORMS:

STROKE

**Global Registry of
Rheumatic Heart Disease**

Stroke/ TIA

INSTRUCTIONS

Please complete Subject's Initials on every page



F= first letter of first name M= first letter of middle name

L= first letter of last name

Please answer EACH question by marking
an X in ONE BOX on each line:
(unless otherwise instructed)



OR

By writing number(s) in the spaces provided:



OR

By specifying the answer on the line(s) provided

Version 1.0 - 01 Aug 2011



Report # 1 3

Subject ID

Centre# [][] Subject # [][][][]

Subject Initials F M L [][] [][] [][]

Diagnosis (see facing pages for definition and, choose only one): Stroke TIA

Date of Stroke/TIA onset: [][][][] year [][] month [][] day Time: [][] : [][] 24-hour clock

1. Was patient hospitalized from this Stroke/TIA? No Yes -> Complete hospitalization report [][][][]

2. Status at 7 days or discharge, whichever is earliest, after stroke/TIA: (Select best description at 7 days or discharge, whichever is earliest, after stroke/TIA)

- Full recovery from all symptoms
 Persistent symptoms which do not limit the patient's functional status
 Some functional impairment but patient can manage all activities independently
 Patient needs help from another person to perform everyday activities
 Patient incapacitated, unable to perform everyday activities even with help
 Death -> Complete death report

3. Was a CT scan, MRI or autopsy done to confirm diagnosis? No Yes -> Specify and retain relevant source docs CT MRI Autopsy Report

4. Final diagnosis: (at time of completing the form)

- Cerebral Infarction (confirmed by CT, MRI or autopsy)
 Lacunar Infarct Large artery Infarct Cardioembolic Infarct Unclassified Infarct
 Full recovery from all symptoms
 Persistent symptoms which do not limit the patient's functional status
 Some functional impairment but patient can manage all activities independently
 Patient needs help from another person to perform everyday activities
 Patient incapacitated, unable to perform everyday activities even with help

Person Completing Report: _____ Date: 2 0 [][][] [][][]

EVENT FORMS:

SYSTEMIC EMBOLISM

**Global Registry of
Rheumatic Heart Disease**

Systemic Embolism/Thrombosis

INSTRUCTIONS

Please complete **Subject's Initials** on every page

F	M	L
---	---	---

F= first letter of first name M= first letter of middle name

L= first letter of last name

Please answer **EACH** question by marking
an **X** in **ONE BOX** on each line:
(unless otherwise instructed)

X

OR

By writing number(s) in the spaces provided:

1	8
---	---

OR

By specifying the answer on the line(s) provided

Version 1.1 - 01 Aug 2011



Report # 2 3

Subject ID

Centre# [][] Subject # [][][][]

Subject Initials [][] F M L

9. Confirmation of diagnosis:

- CT scan
Angiography
Other, Specify:

10. Treatment given:

- Fibrinolysis: Streptokinase, Urokinase, Other, Specify
Surgery: Thrombectomy, Other, Specify

11. Status at discharge:

- Complete recovery
Complication during treatment -> Death, Stroke, Other, Specify
No recovery

Person Completing Report: _____ Print last name, first initial

Date: 2 0 [][] [][] [][]

EVENT FORMS:

DEATH

**Global Registry of
Rheumatic Heart Disease**

Death Report

INSTRUCTIONS

Please complete Subject's Initials on every page

F M L

F= first letter of first name M= first letter of middle name

L= first letter of last name

Please answer EACH question by marking
an X in ONE BOX on each line:
(unless otherwise instructed)

X

OR

By writing number(s) in the spaces provided:

1 8

OR

By specifying the answer on the line(s) provided

Version 1.0- 01 Aug 2011



Subject ID

Centre# [][][] Subject# [][][]

Subject Initials F M L [][] [][] [][]

1. Date of death: 2 0 [][] [][] [][]
year month day

2. Death witnessed: No Yes

3. Primary Cause of Death (check (X) one box only)

- Congestive heart failure
- Stroke/TIA
- Acute rheumatic fever
- Systemic embolism
- Infective endocarditis
- Valve surgery
- Pregnancy related
- Major bleeding

Complete corresponding event report and enter report # [][][]

- Pulmonary embolism
- Sickle-cell disease
- Tuberculosis
- Trauma
- Cancer-specify: _____
- Other - specify: _____

4. Did patient die in hospital:

- No —> Please provide the clinical details of cause of death*
- Yes —> Was the participant hospitalized for 24 hours or more?
 - No —> Please provide the clinical details of cause of death*
 - Yes —> Complete hospitalization report and enter the report # [][][]

*Clinical details of cause of death: _____

Please check appropriate box(es) to indicate supporting documentation retained:

- Death Certificate
- Autopsy
- Emergency department report
- Other - specify: _____

Person Completing Report: _____ Date: 2 0 [][] [][] [][]
Print last name/first initial Signature

ADDENDUM 6: CHADS₂ and CHA₂DS₂VASc Scores:

Table 1: Stroke Risk Stratification with the CHADS₂ Score			
Risk Factor	Score	CHADS₂ Score	Stroke rate, %
CHF (recent)	1	0	1.9
Hypertension (history of)	1	1	2.8
Age 75 or older	1	2	4.0
Diabetic Mellitus	1	3	5.9
Stroke/TIA	2	4	8.5
		5	12.5
		6	18.2
Maximum score	6		

Table 2: Stroke Risk stratification with the CHA₂DS₂-VASc score			
Risk factor	Score	CHA₂DS₂-VASc score	Thromboembolic event rate
CHF/LV dysfunction	1	0	0
Hypertension	1	1	1.3
Age 75 or greater	2	2	2.2
Diabetes Mellitus	1	3	3.2
Stroke/TIA/TE	2	4	4.0
Vascular disease (prior MI,PAD, or aortic plaque)	1	5	6.7

Age 65-74	1	6	9.8
Sex - female	1	7	9.6
		8	6.7
		9	15.2
Maximum score	9		

ADDENDUM 7: ETHICS APPROVAL



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
Email: posi.bsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

09 March 2016

HREC REF: 127/2016

Prof B Mayosi
Medicine Department
Old Main Building

Dear Prof Mayosi

PROJECT TITLE: PREVALENCE, CHARACTERISTICS AND ADDITIONAL STROKE RISK STRATIFICATION: AN ANALYSIS OF THE ATRIAL FIBRILLATION COHORT WITHIN THE REMEDY REGISTRY- SUBSTUDY OF 028/2006 (MPhil candidate- Dr B Cupido)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until 30 March 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student, Dr B Cupido will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

HREC 127/2016

