THE PREVALENCE, DETERMINANTS, NATURAL HISTORY AND IMPACT OF ATRIAL FIBRILLATION AND ATRIAL FLUTTER IN PATIENTS WITH TUBERCULOUS PERICARDITIS – INSIGHTS FROM THE IMPI TRIAL

BY

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DECLARATION

I, Chishala Chishala, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, or is to be submitted for another degree in this or any other University. This work has not been reported or published prior to registration for the abovementioned degree.

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ACRONYMS AND ABBREVIATIONS

ACC	American College of Cardiology
ADA	Adenosine Deaminase
AF	Atrial fibrillation
AFL	Atrial flutter
AF/AFL	Atrial fibrillation and/or Atrial flutter
AHA	American Heart Association
CAD	Coronary Artery Disease
CHA_2DS_2VASc	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 Interval
CRFs	Case Report Forms
DM	Diabetes Mellitus
ECGs	Electrocardiograms
EF	Ejection Fraction
ESC	European Society of Cardiology
HF	Heart Failure
HIV	Human immunodeficiency virus
HREC	Human Research and Ethics Committee
HTN	Hypertension
IMPI	Investigation of Pericarditis in Africa Trial
IQR	Inter-quartile range
mm	Millimetres
mmHg	Millimetres of mercury
NT-pro BNP	N-terminal pro-B-type-natriuretic peptide
NYHA	New York Heart Association

OR	Odds ratio
RHD	Rheumatic heart disease
S2	Second heart sound
S3	Third heart sound
S4	Fourth heart sound
SD	Standard Deviation
SR	Sinus rhythm
TB	Tuberculosis
TBP	Tuberculous pericarditis
TIA	Transient ischaemic attack
VHD	Valvular heart disease

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PART A: PROTOCOL

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Abstract

Background

Tuberculosis is the most common cause of pericarditis in Africa. The dual human immunodeficiency virus (HIV)-tuberculosis epidemics are major contributors to the burden of extra-pulmonary tuberculosis, including tuberculous pericarditis. Mortality rates remain unacceptably high.

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. It is associated with increased cardiovascular mortality and morbidity, as well as complications related to thromboembolic disease and haemodynamic instability.

Similarly, atrial flutter (AFL) is a common macro-reentry arrhythmia, often associated with AF and its complications. While there is a recognized association between atrial fibrillation and / or atrial flutter (AF/AFL) and tuberculous pericarditis, there are limited data regarding the prevalence, determinants, natural history, and outcomes of AF/AFL in tuberculous pericarditis.

Hypothesis:

In patients with tuberculous pericarditis, AF/AFL is common, and when compared to tuberculous pericarditis patients that are in sinus rhythm, is associated with increased morbidity and mortality.

Aims

In participants with tuberculous pericarditis enrolled into the Investigation of the Management of Pericarditis (IMPI) trial, we intend to:

1. Estimate the prevalence of AF/AFL
2. Describe the natural history of AF/AFL
3. Identify clinical, biochemical and, echocardiographic predictors of AF/AFL
4. Determine the clinical impact of AF/AFL

Study design

The study will be a retrospective study of serial electrocardiograms (ECGs) of the 1400 patients who were enrolled in the IMPI trial. The study will compare patients with AF/AFL to those in sinus rhythm. The primary aim is to determine whether patients with tuberculous pericarditis and AF/AFL have worse clinical outcomes than those with tuberculous pericarditis and sinus rhythm.

The natural history of AF/AFL will be determined by reviewing ECGs over the course of the patients' follow-up (ranging from 6 months to 48 months). The primary outcome will be a composite of death (all-cause mortality), stroke (fatal and non-fatal) or thromboembolic event. Only clinically appreciable thromboembolic events as determined in the IMPI trial will be assessed. The secondary outcomes of interest are death, constrictive pericarditis, cardiac tamponade requiring pericardiocentesis and, cardiovascular-related hospitalizations.

Data collection and analyses

Data captured using pre-existing standardized case report forms (CRFs) in the IMPI trial have been stored in a central online repository called iDataFax. A specific CRF for ECGs will be designed to record the ECG findings of patients in the study. Thus, the prevalence of AF/AFL will be determined once all ECGs have been read. Outcomes of interest will be assessed and comparisons between patients in AF/AFL and those in sinus rhythm will be made. Survival analyses curves will be plotted. Furthermore, possible clinical, biochemical and echocardiographic risk factors will be determined by means of logistic regression.

Background

Tuberculosis, caused by *Mycobacterium tuberculosis*, is the most common cause of pericarditis in Africa[1]. The resurgence of tuberculosis, due to the human immunodeficiency virus (HIV) epidemic, has led to an increase in the incidence of tuberculous pericarditis[2]. In sub-Saharan Africa, the overall mortality due to tuberculous pericarditis is 18%[3].

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. It can cause haemodynamic impairment and thromboembolic events that result in significant morbidity and mortality[4]. The risk factors for AF include coronary artery disease, rheumatic mitral valve disease, hypertension, cardiomyopathy, lung and pericardial disease. The pathophysiology of AF is complex, involving electrical and structural remodeling of the left atrium[5]. Additionally, there is mounting evidence to support the influence of inflammation in the pathogenesis of AF[6].

After AF, atrial flutter (AFL) is the most important and most common atrial tachyarrhythmia. It is due to a macro-reentrant atrial rhythm. Acute AFL may be complicated by haemodynamic instability and myocardial ischaemia. Permanent AFL with a rapid ventricular rate may lead to a tachycardia-mediated cardiomyopathy. There is also a risk of thromboembolisation [7]. Risk factors for AFL are similar to those for AF[8].

There is a paucity of data regarding tuberculous pericarditis-associated atrial fibrillation and/or atrial flutter (AF/AFL), specifically the true prevalence of AF/AFL, the natural history and, prognostic significance of these arrhythmias in tuberculous pericarditis. The limited data describing the association between AF/AFL and tuberculous pericarditis are in the form of case reports and small observational studies. The estimated prevalence of AF in tuberculous pericarditis ranges widely from 1.2 to 69% [9-13]. Studies of constrictive pericarditis have shown that the presence of pericardial calcification and an increase in disease duration are determinants of AF[11, 13]. The prevalence of AFL in tuberculous pericarditis is not known. The determinants of AF/AFL in the other forms of tuberculous pericarditis are largely unknown[14].

Regarding the clinical impact of AF/AFL in tuberculous pericarditis, a non-significant trend towards increased deaths in patients with tuberculous pericarditis complicated by AF, was noted in a small observational study[9]. A recent review of pericarditis-associated AF/AFL made several cardinal observations. Firstly, pericarditis causes atrial fibrillation in the absence of structural heart disease and, it does recur in some patients with concomitant pericardial effusion. Secondly, pericarditis-associated AF is a transient arrhythmia in acute and subacute pericarditis while persistent AF occurs in chronic constrictive pericarditis. Lastly, the elevated $CHA_2\ DS_2$ –VASc scores in patients with pericarditis-associated AF suggest the need for oral anti-coagulant therapy. However, this is not supported by the low rates of thromboembolic complications that have been seen thus far in pericarditis-associated AF[14].

Thus, there is a need for a large study addressing the prevalence, determinants, natural history and clinical impact of AF/AFL in a large group of patients with tuberculous pericarditis such as that comprising the Investigation and Management of Pericarditis (IMPI) trial.

The IMPI trial was a prospective multicenter, international, double-blind; placebo controlled randomized trial, evaluating the effects of immunotherapy on clinically significant outcomes and safety in tuberculous pericarditis. The trial had 1400 participants with suspected tuberculous pericarditis who were followed up over a period of minimum 6 months to maximum of 48 months[15]. We plan to use the data collected in this trial to assess the prevalence, determinants, natural history and impact of AF/AFL in patients with tuberculous pericarditis.

Hypothesis:

In patients with tuberculous pericarditis, AF/AFL is common, and compared to tuberculous pericarditis patients that are in sinus rhythm, is associated with significant morbidity and mortality.

Aims

In participants with tuberculous pericarditis enrolled into the IMPI trial, we intend to:

1. Estimate the prevalence of AF/AFL
2. Describe the natural history of AF/AFL
3. Identify clinical, biochemical and, echocardiographic predictors of AF/AFL
4. Determine the clinical impact of AF/AFL

Methods

1. Study population

The study population will be the participants of the Investigation and Management of Tuberculous Pericarditis in Africa (IMPI) trial. The IMPI trial was a prospective multicenter, international, double blind; placebo controlled randomized trial, evaluating the effects of immunotherapy on safety and clinically-important outcomes in tuberculous pericarditis. The trial recruited1400 participants with tuberculous pericarditis and these participants were followed up over a period of minimum 6 months to maximum of 48 months[15]. Data captured using pre-existing standardized case report forms (CRFs) in the IMPI trial have been stored in a central online repository called iDataFax. A specific CRF for ECGs will be designed to record the ECG findings of patients in the study **(appendix 1).** We plan to use the data collected in this trial to assess the prevalence, determinants, natural history and impact of AF/AFL in patients with tuberculous pericarditis.

2. Definition and measurement of AF

2.1 Diagnosis of AF

Participants in the IMPI trial had ECGs done at enrolment (baseline ECG) into the study and (if available) at 2 weeks, 4 weeks, 6 weeks, 3 months, 6 months, 12 months, 18 months, 24 months, 36 months and, 48 months. These ECGs were copied and stored in iDataFax. The ECGS will be printed for analysis. AF will be diagnosed if an ECG shows fine oscillations of the baseline (fibrillation or f waves) with no clear P waves and, an irregular QRS rhythm, irrespective of when it was done[16]. AF will be further sub-classified in accordance with the American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) guidelines as follows[4]:

a. First detected AF: only one diagnosed episode of AF (based on our follow-up schedule this translates to AF being present on only one ECG among patients with baseline ECGs).
b. Paroxysmal AF: recurrent episodes of AF that resolve spontaneously within 7 days (based on our follow-up schedule this translates to AF being present on two or more non-consecutive ECGs among patients with baseline ECGs).
c. Persistent AF: recurrent episodes of AF that last more than 7 days (based on our follow-up schedule this translates to AF being present on two or more consecutive ECGs among patients with baseline ECGs).
d. Permanent AF: an ongoing long-term episode of AF (based on our follow-up schedule this translates to AF being present on all available ECGs among those with baseline ECGs).

Analysis of serial ECGs done over the follow up period of 48 months, with sub-classification of AF as defined above will allow both the prevalence and the natural history of AF in tuberculous pericarditis to be described. Additionally, patients who are in sinus rhythm at baseline, but who on subsequent ECGs demonstrate AF/AFL will be considered to have new onset AF/AFL.

The standard operating procedure for ECG interpretation is included in the appendix **(appendix 2).**

3. Definition and measurement of AFL

3.1 Diagnosis of AFL

AFL will be diagnosed if the ECG shows regular saw-tooth like atrial flutter (F waves) between QRS complexes[16]. By analyzing serial ECGs that were done over the 48-month follow up period, the prevalence and natural history of AFL in tuberculous pericarditis will be described.

4. Determination of the clinical impact of AF/AFL in tuberculous pericarditis

4.1 Primary outcome

The primary outcome will be a composite of death (all-cause mortality), stroke (fatal and non-fatal) or thromboembolic events. These endpoints will be counted based on events recorded in

the IMPI trial in accordance with the IMPI definitions and coding for hospitalization and death[3]. Only clinically appreciable thromboembolic events as determined in the IMPI trial will be assessed.

4.2 Secondary outcomes

The secondary outcomes will be death, constrictive pericarditis, cardiac tamponade requiring pericardiocentesis and cardiovascular-related hospitalizations. These endpoints will be counted based on events recorded in the IMPI trial in accordance with the IMPI definitions and coding for these events[3].

5. Identification of the predictors of AF/AFL

Logistic regression analysis will be used to determine factors associated with AF/AFL at presentation and at follow-up. The factors that will be considered for analysis are:

a. Age in years
b. Sex:
    - Male
    - Female
b. Functional class
    - NYHA (New York Heart association) I
    - NYHA II
    - NYHA III
    - NYHA IV
c. Heart rate/minute
    - <100
    - >100
d. Systolic blood pressure in millimeters of mercury (mmHg)
e. Diastolic blood pressure in mmHg

f. HIV status:
    - Positive
    - Negative
g. CD4 count if HIV positive
h. Creatinine
i. White cell count
j. Haemoglobin
k. Left ventricular systolic dysfunction: ejection fraction
    - < 35%,
    - 35 to 45%
    - 45 to 55%
l. Constrictive pericarditis (the definition used in IMPI is provided in the appendix)
m. Size of pericardial effusion
    - Small (<1cm)
    - Moderate (1-2cm)
    - Large (>2cm)
n. Cardiac Tamponade (the definition used in IMPI is provided in the appendix)
    - Yes
    - No
o. Tuberculous pericarditis diagnosis (the definition used in IMPI is provided in the appendix)
    - Definite
    - Probable

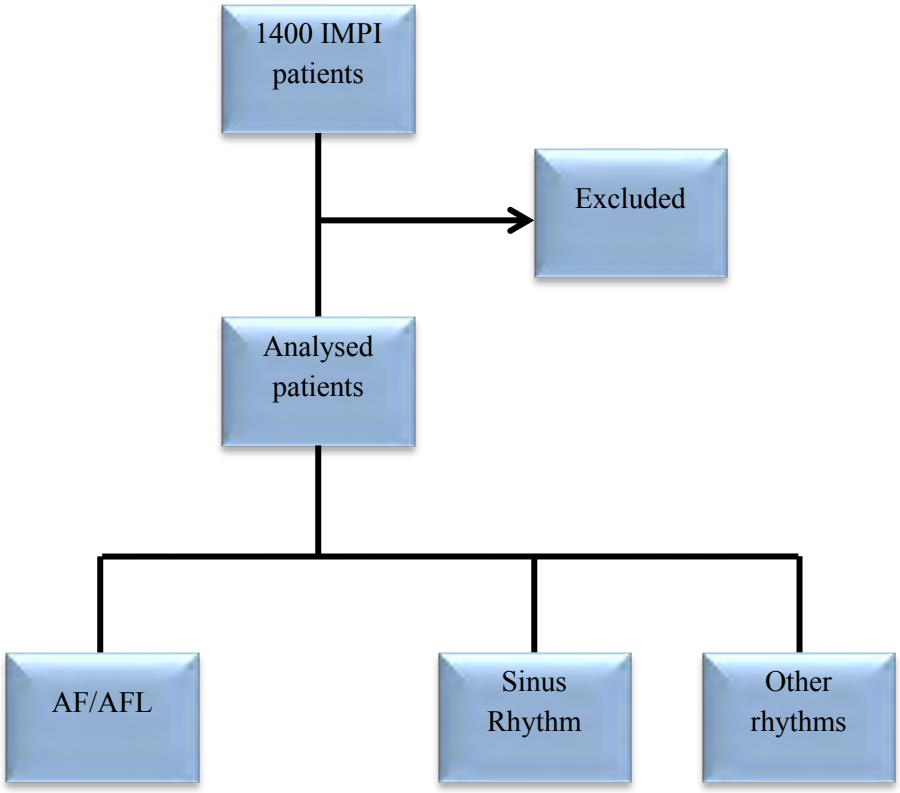
6. Eligibility criteria

All patients in IMPI that had ECGs recorded will be screened for eligibility. Those that did not have ECGs done will be excluded. For patients who had ECGs recorded, poor technical quality of ECGs that render them uninterpretable will be an additional exclusion criterion. The rhythm of baseline and

follow up ECGs of these patients will be analysed for the following rhythms: sinus, AF, AFL, ectopic atrial rhythms, junctional rhythms, ventricular and, other supraventricular arrhythmias. Patients with sinus rhythm, AF and AFL will be compared for the outcomes of interest.

Figure 1 below summarizes the study design.

Figure 1



7. Data extraction

Data captured using pre-existing standardized CRFs in the IMPI trial have been stored in a central repository called iDataFax. The ECGs from iDataFax will be printed out for interpretation, following which the findings will be recorded on the ECG CRF and then entered into iDataFax. For ECGs that are not interpretable, the contributing sites will be asked to re-scan and re-enter the ECGs (using the same allocation number as previously to avoid duplication of ECGs) into iDataFax. If the ECGs are still uninterpretable, the sites will be asked to fax the ECGs to us in the conventional way.

8. Sample size

This is a retrospective study and there is inadequate data from literature regarding power and effect size. Thus all available data from all 1400 patients will be included in the analysis.

9. Analytic plan

Baseline characteristics will be compared for participants in AF/AFL versus sinus rhythm, as well as comparison within the AF/AFL group stratified by rhythm status. The data will be reported as mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for non-normally distributed continuous variables, and, percentages for categorical variables. The distributions of categorical variables will be compared using a chi square test or Fisher exact test. Multiple group comparisons of medians will be done using the Kruskal-Wallis equality-of-proportions rank test. The analysis of variance test will be used for multiple group comparisons of means. Logistic regression analysis will be used to determine factors associated with AF/AFL at presentation and at follow up. The variables to be considered for analysis include **(Table 1)**: age, sex, New York Heart Association functional class (NYHA), heart rate, systolic blood pressure, diastolic blood pressure, human immune deficiency virus (HIV) status and CD4 count if positive, creatinine, haemoglobin, white cell count, definite tuberculous pericarditis diagnosis or probable tuberculous pericarditis diagnosis, left ventricular systolic dysfunction on echocardiography, presence of constriction or cardiac tamponade and, the size of pericardial effusion when present, on echocardiography. Covariates that are at least marginally associated with the endpoint of interest in univariate analyses ($p<0.10$) and *a priori* clinical factors of interest will be included in these multivariate models. Our findings will be reported as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value <0.05 will be considered significant. Time-to-event analyses will be done using Kaplan-Meier curves.

Table 1: Baseline characteristics of participants

Characteristics	AF/AFL		Sinus Rhythm	P value
	Atrial fibrillation	Atrial flutter		
Participants				
Age in years				
Sex				
Male				
Female				
Functional class				
- NYHA I				
- NYHA II				
- NYHA III				
- NYHA IV				
Heart rate beats/minute				
- <100				
- >100				
Systolic blood pressure/mmHg				
Diastolic blood pressure/mmHg				
HIV status				
- Positive				
- Negative				
CD4 count cells/µL				
Creatinine/µmolL^{-1}				
White cell count cells x 10^9/L				
Haemoglobin g/dL				
Tuberculous pericarditis diagnosis				
- Definite				
- Probable				
Left ventricular ejection fraction				
- <35%				
- 35-45%				
- 45-50%				
Constrictive pericarditis				
- Yes				
- No				
Pericardial effusion				
- Small effusion				
- Moderate effusion				
- Large effusion				
Cardiac tamponade				
- Yes				
- No				

10. Bias

10.1 Selection bias

The selected participants will be those that had ECGs at baseline and at follow-up. Not all patients had ECGs at baseline and not all patients had follow-up ECGs. As the reasons for non-performance of ECGs may not be random (e.g. broken ECG machine, very ill patient requiring urgent intervention) this is a potential source of bias.

10.2 Performance bias

Performance bias has been defined by Cochrane Methods as, "systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest."[17] There are no interventions being offered in this study. Furthermore there is no risk of differential treatment of participants in either study arm. Therefore, there will be negligible performance bias.

10.3 Attrition bias

The IMPI trial had a low loss to follow-up rate. At the time this document was initially written only 26 of the 1400 participants (0.02%) had been lost to follow up. Unfortunately not all participants had the full complement of 11 ECGs. This has the theoretical potential to bias the determination of the natural history of AF/AFL, as under detection of these arrhythmias may occur. This potential bias arising from non-performance of some ECGs has been outlined above and is an anticipated limitation.

10.4 Detection bias

Detection bias is unlikely for several reasons. Firstly, strict definitions of AF and AFL will be used. Secondly, the ECG reader is blinded from the ECG diagnosis because the follow up ECGs will be read at a different time from the baseline ECGs and thus the reader will be unaware of whether the baseline ECG showed AF/AFL or sinus rhythm. Additionally, the ECG reader will also be blinded from the clinical data. A second ECG reader will be asked to review difficult or complex ECGs. However, detection bias is not completely avoidable given that subclinical episodes of AF/AFL cannot be detected in a study of this nature as there is no extended continuous rhythm monitoring. Subclinical AF has been shown to be associated with an increased risk of ischaemic stroke or systemic embolism in patients whose atrial rhythms have been monitored by pacemakers[18].

11. Confounding variables

The major confounding variables include age, sex, human immunodeficiency virus (HIV) status and treatment thereof and multi-organ TB. These variables will be measured and will be dealt with in the analysis by stratification and regression models.

Strengths of the study

This is the largest study of AF/AFL in patients with pericarditis[14]. This study addresses a problem of major public health importance. The research question addresses unknown areas of tuberculosis and will thus determine the prevalence of AF/AFL in tuberculous pericarditis, its natural history as well as the clinical impact of these arrhythmias in a large study population.

Limitations

The anticipated limitations include missing or uninterpretable ECGs, difficult ECGs and the presence of confounding variables that have an independent risk of causing AF/AFL such as valvular heart disease, hypertension and cardiomyopathy. The process of dealing with illegible and missing ECGs has been described above. For difficult ECGs e.g. AFL with bundle branch block that appears like ventricular tachycardia, the second ECG reader, a cardiologist will assist with making the ECG diagnosis.

Ethical considerations

This is a sub-study of a trial that has been granted ethical approval and there will be no patient contact or additional interventions performed. Ethics approval for this study has been granted by the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (HREC/REF: 598/2014). A copy of the ethics approval letter has been included in the appendix.

References

1. Mayosi BM, Volmink JA, Commerford PJ. Pericardial disease: An evidence-based approach to diagnosis and treatment. In: Yusuf S, Cairns JA, Camm AJ, Fallen BJ, eds. *Evidence-Based Cardiology*. 2nd ed. London: BMJ Books; 2003:735–748.

2. Mayosi BM, Burgess LJ, Doubell AF. Tuberculous Pericarditis. *Circulation*. 2005; 112; 3608-3616.
3. Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F, Pogue J, Thabane L, Smieja M, Francis V, Joldersma L, Thomas KM, Thomas B, Awotedu AA, Magula NP, Naidoo DP, Damasceno A, Banda AC, Brown B, Manga P, Kirenga B, Mondo C, Mntla P, Tsitsi JM, Peters F, Essop MR, Russell JBW, Hakim J, Matenga J, Barasa AF, Sani MU, Olunuga T, Ogah O, Ansa V, A. Aje, Danbauchi S, Ojji D, Yusuf S. Prednisolone and Mycobacterium indicus pranii in Tuberculous Pericarditis. *N Engl J Med*. 2014; 371: 1121-1130.
4. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Catherine Despres C, Dickstein K, John Lekakis, McGregor K, Metra M, Joao Morais, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines 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 European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006; 114: e257–354.
5. Colledge NR, Walker BR, Ralston SH. *Davidson's Principles and Practice of Medicine*. 21st ed. Edinburgh: Churchill Livingstone; 2010: 562.
6. Boos CJ, Anderson RA, Lip GYH. Is atrial fibrillation an inflammatory disorder*? Eur Heart J*. 2006; 27: 136-149.
7. Dhar S, Lidhoo P, Koul D, Dhar S, Bakhshi M, Deger FT. Current concepts and management strategies in atrial flutter. *South Med J*. 2009; 102: 917-922.
8. Wellens HIJ. Contemporary Management of Atrial Flutter. *Circulation*. 2002; 106: 649-652

9. Syed FF, Ntsekhe M, Wiysonge CS, Badri M, Oh JK, Mayosi BM. Atrial fibrillation as a consequence of tuberculous pericardial effusion. *Int J Cardiol.* 2012; 158: 152-154.
10. Bozbuga N, Erentug V, Eren E, Erdogan HB, Kirali K, Antal A, Akinci E,Yakut C. Pericardiectomy for chronic constrictive tuberculous pericarditis. *Tex Heart Inst J*. 2003; 30: 180-185.
11. Rezaian GR, Poor-Moghaddas M, Kojuri J, Rezaian S, Liaghat L, Zare N. Atrial fibrillation in constrictive pericarditis: The significance of pericardial calcification. *Ann Noninvasive Electrocardiol*. 2009; 14:258-261.
12. Desai HN. Tuberculous pericarditis: A review of 100 cases. *S Afr Med J*. 1979; 55: 877-878
13. Mutyaba AK, Balkaran S, Cloete R, du Plessis N, Badri M, Brink J, Mayosi BM. Constrictive pericarditis requiring pericardiectomy at Groote Schuur Hospital, Cape Town, South Africa: causes and perioperative outcomes in the HIV era (1990–2012). *J Thorac Cardiovasc Surg*. 2014; 148:3058–65.e1.
14. Mayosi BM. Pericarditis-associated atrial fibrillation. *Heart*. 2015; 101:1439-1440.
15. Mayosi BM, Ntsekhe M, Bosch J, Pogue J, Gumedze F, Badri M, Jung H, Pandie S, Smieja M, Thabane L, Francis V, Thomas KM, Thomas, Awotedu AA, Magula NP, Naidoo DP, Damasceno A, Banda AC, Mutyaba A, Brown B, Ntuli P, Mntla P, Ntyintyane L, Ramjee R, Manga P, Kirenga B, Mondo C, Russell JBW, Tsitsi JM, Peters F, Essop MR, Barasa AF, Mijinyawa MS, Sani MU, Olunuga T, Ogah O, Adebiyi A, Aje A, Ansa V, Ojji D, Danbauchi S. Rationale and design of the investigation of the Management of Pericarditis (IMPI) trial: A 2 x 2 factorial randomized double-blind multicenter trial of adjunctive prednisolone and Mycobacterium w immunotherapy in tuberculous pericarditis. *Am Heart J*. 2012; 165: 109-117.
16. Kumar P, Clark M. *Kumar and Clark's Clinical Medicine*.7th ed. Edinburgh: 2009; Elsevier Saunders; 2009: 724-725.
17. Cochrane methods. *Assessing the risk of bias in included studies*. Available: http://bmg.cochrane.org/assessing-risk-bias-included-studies [2016, January, 2]

18. Healey JS, Conolly S, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012; 366: 120-129.

Appendices

Appendix 1. ECG CRF

IMPI Trial **ECG Shuttle Form**

DataFax #128 Plate #084 **Report No #**

PARTICIPANT ID# Center number Medication Kit number Participant Initials F M L

Date of ECG year month day

Please indicate when the attached ECG was done:

☐ Baseline ☐ 2 weeks ☐ 4 weeks ☐ 6 weeks ☐ 3 months ☐ 6 months ☐ 12 months ☐ 18 months ☐ 24 months ☐ 36 months ☐ 48 months

Person Completing Report _____ *initials*

Please attach the ECG report here and fax to the Project Office.

1. Date of ECG: year month day **2. ECG quality:** *(select one)* ☐ uninterpretable ☐ 12 Lead ECG ☐ rhythm strip ☐ other

3. Rate bpm

4. Rhythm Ectopic Atrial Rhythm ☐ Junctional Rhythm ☐ Sinus ☐ Atrial Flutter ☐ Ventricle ☐ Atrial Fibrillation ☐ Other SVT ☐

5. PR Segment

		I	II	III	AVR	AVF	AVL	V_1	V_2	V_3	V_4	V_5	V_6
PR interval ms													
PR elevation	N ☐ Y ☐ →	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
PR depression	N ☐ Y ☐ →	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

6. QRS

duration ms RBBB ☐ LBBB ☐

		I	II	III	AVR	AVF	AVL	V_1	V_2	V_3	V_4	V_5	V_6
microvoltage	N ☐ Y ☐ →	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
electrical alteration	N ☐ Y ☐ →	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

7. ST-T wave segments

		I	II	III	AVR	AVF	AVL	V_1	V_2	V_3	V_4	V_5	V_6
peaked T waves	N ☐ Y ☐ →	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
inverted T waves	N ☐ Y ☐ →	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
ST segment elevated	N ☐ Y ☐ →	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
ST segment depression	N ☐ Y ☐ →	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
T wave alterations	N ☐ Y ☐ →	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

8. QTc

ms normal ☐ prolonged ☐ shortened ☐

Person completing the form _____ Name **Date Completed** *year* *month* *day*

Investigation of the Management of Tuberculous Pericarditis Version 6.1 dated 2015 JUL 17

Appendix 2

ECG Interpretation - Standard Operating Procedure

1. ECG initially read and interpreted at site of ECG recording.
2. Independent review of the above ECG by a physician blinded from the initial ECG diagnosis.
3. Comparison of ECG diagnoses in steps 1 and 2.
4. If the ECG diagnoses are congruent, the diagnosis is accepted for capture into the database and for analysis.
5. If there is a discrepancy between the site ECG diagnosis and the physician ECG diagnosis, the ECG in question is to be marked as “difficult” and referred to a cardiologist for final arbitration.
6. Additionally, if in step two, the physician is uncertain of the ECG diagnosis, the ECG will also be labelled as “difficult” and referred to a cardiologist for interpretation.

Appendix 3. IMPI definition of pericardial constriction[1]

1. a) Echo evidence of an absent or small pericardial effusion, and a structurally and functionally normal heart (Ejection Fraction>50%)

PLUS any 4 NEW clinical features:

b) Palpable pulsus paradoxus

c) Jugular venous pressure > 4 cm

d) Pericardial knock or early third heart sound

e) Sudden instantaneous split of the second heart sound on inspiration

f) Peripheral oedema

g) Hepatomegaly

h) Ascites

OR

2. a) Echo evidence of an absent or small pericardial effusion, and a structurally and functionally normal heart (EF>50%)

PLUS any 2 NEW clinical features:

b) Palpable pulsus paradoxus

c) Pericardial knock or S3

d) Sudden instantaneous split of S2 in inspiration

e) Peripheral oedema

f) Hepatomegaly

g) Ascites

PLUS 2 of the following:

h) New pericardial thickening >3mm

i) Early diastolic septal bounce

j) Exaggerated septal shift toward left ventricle with inspiration

k) Doppler evidence of reduced early mitral flow with onset of inspiration or reciprocal effect on tricuspid flow

l) Dilated inferior vena cava (with reduced inspiratory collapse)

Appendix 4. IMPI definition of cardiac tamponade[1]

1. a) New or persistent moderate to large pericardial effusion

PLUS 2 of the following NEW clinical findings:

b) Heart rate > 90

c) Systolic blood pressure < 100 mmHg

d) Pulsus paradoxus > 10 mmHg

e) Jugular venous pressure > 4 cm

OR

2. a) Clinical deterioration with new or persistent echo confirmed moderate to large

pericardial effusion

PLUS 1 of the following:

b) Swinging heart

c) Right or left ventricular diastolic collapse

d) Greater than 25% variation in mitral flow velocities with respiration

e) Dilated Inferior Vena Cava > 21 mm with less than 40% collapse

Appendix 5. IMPI diagnostic categories of tuberculous pericarditis[1]

Category	Description
Definite tuberculous pericarditis	Tuberculosis diagnosis confirmed on a pericardial sample based on finding acid and alcohol fast bacilli on microscopy, positive microbiological culture for Mycobacterium tuberculosis, presence of caseating granulomata on histology, or positive nucleic acid test (tissue or fluid)
Probable tuberculous pericarditis – tuberculosis proven elsewhere	Pericardiocentesis performed but no evidence of definite tuberculous pericarditis: presence of a lymphocytic pericardial exudate with elevated adenine deaminase (ADA) activity ≥ 40IU/L or Pericardiocentesis not performed: A Tygerberg TB Pericarditis Diagnostic Index Score ≥ 6 and other causes of pericarditis have been excluded and Proven tuberculosis on a non-pericardial sample (e.g.,sputum, pleural fluid, lymph node, urine, and gastric lavage.)
Alternate (nontuberculous) cause of pericarditis	Evidence of probable tuberculous pericarditis with or without pericardiocentesis, but an alternate non-tuberculosis diagnosis was confirmed after randomization

Reference

1. Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F, Pogue J, Thabane L, Smieja M, Francis V, Joldersma L, Thomas KM, Thomas B, Awotedu AA, Magula NP, Naidoo DP, Damasceno A, Banda AC, Brown B, Manga P, Kirenga B, Mondo C, Mntla P, Tsitsi JM, Peters F, Essop MR, Russell JBW, Hakim J, Matenga J, Barasa AF, Sani MU, Olunuga T, O. Ogah O, Ansa V, A. Aje, Danbauchi S, Ojji D, Yusuf S. Prednisolone and Mycobacterium indicus pranii in Tuberculous Pericarditis. *N Engl J Med*. 2014; 371: 1121-1130. Supplementary appendix.

Appendix 6

Ethics Approval Letter

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

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14 August 2014

HREC/REF: 598/2014

Dr S Pandie
Cardiology
E-17
NGSH

Dear Dr Pandie

Project Title: EVALUATION OF THE PREVALENCE, DETERMINANTS, NATURAL HISTORY AND IMPACT OF ATRIAL FIBRILLATION AND ATRIAL FLUTTER IN PATIENTS WITH TUBERCULOUS PERICARDITIS: INSIGHTS FROM THE IMPI TRIAL (MMeD candidate- Dr C Chishala)

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 the 30 August 2015.

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.

We acknowledge that the following students:-Dr C Chishala is also involved in this project.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

Hrec/ref:598/2014

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

07 JAN 2015

HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)
This serves as notification of annual approval, including any documentation described below.

☑ Approved	Annual progress report	Approved until next renewal date	30. 8. 2015
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	6/1/2015

THE PREVALENCE, DETERMINANTS, NATURAL HISTORY AND IMPACT OF ATRIAL FIBRILLATION AND ATRIAL FLUTTER IN PATIENTS WITH TUBERCULOUS PERICARDITIS – INSIGHTS FROM THE IMPI TRIAL

BY

CHISHALA CHISHALA

CHSCHI003

PART B: LITERATURE REVIEW

CONTENTS PAGE

Introduction

In regions such as sub-Saharan Africa where *Mycobacterium tuberculosis* (*M. tuberculosis)* is endemic, tuberculosis is the most common cause of pericarditis affecting 80,000 – 160,000 people per year[1, 2]A large South African prospective study of pericardial effusions reported that 69.5% of patients had tuberculosis and over 50% of the participants were infected with the human immunodeficiency virus (HIV) [3]. In contrast to the pre-HIV era where the pericardium was only involved in 1% of people with tuberculosis, tuberculosis is the cause of pericardial effusion in over 85% of HIV-infected persons that have a pericardial effusion[1, 4]. The dual HIV-tuberculosis epidemics have led to an increase in incident cases of tuberculous pericarditis in sub-Saharan Africa. One reason for this is that the immune deficiency caused by HIV raises the lifetime risk of tuberculosis from 10%, to an annual risk of between 10 and 30%[1].

Tuberculous pericarditis is associated with significant morbidity and mortality. In sub-Saharan Africa, the overall mortality due to tuberculous pericarditis is 18%. In spite of appropriate anti-tuberculous therapy and adjunctive steroids, 4 to 6% of patients with tuberculous pericarditis develop constrictive pericarditis, one of the most feared complications of the disease[5].

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. It can cause haemodynamic impairment and thromboembolic events that result in significant morbidity and mortality[6]. There is emerging data to support the association between inflammatory disorders and AF[7]. In a recent review of pericarditis-associated AF several pertinent observations were made[8]. Firstly, pericarditis causes atrial fibrillation in the absence of structural heart disease and, it does recur in some patients with concomitant pericardial effusion. Secondly, in acute and subacute pericarditis, AF is transient, with persistent AF occurring more frequently in chronic constrictive pericarditis. Thirdly, the temporal relationship between recurrences of pericarditis with associated AF as well as emerging evidence to support the role of inflammation in the development of AF puts the spotlight on inflammatory pathways as a mechanism for the development of AF. Thus therapies directed towards specific anti-inflammatory targets may have a role in the prevention and treatment of AF. Lastly, the

elevated CHA_2DS_2 –VASc scores in patients with pericarditis-associated AF suggest the need for oral anti-coagulant therapy. However, this is not supported by the low rates of thromboembolic complications that have been seen thus far in pericarditis-associated AF[8]. The occurrence of AF as a consequence of tuberculous pericarditis has seldom been studied and, there are no large prospective studies of the prevalence, natural course and impact on prognosis of AF in tuberculous pericarditis.

After AF, atrial flutter (AFL) is the most common atrial tachyarrhythmia. AFL can cause harm by impairing cardiac output and by encouraging atrial thrombus formation that can lead to systemic embolization[9]. The occurrence of AFL as a consequence of tuberculous pericarditis has not been studied and, there are no large prospective studies of the prevalence, natural course and impact on prognosis of AFL in tuberculous pericarditis.

The combination of AF and/or AFL and tuberculous pericarditis in one patient is, in theory, a malignant combination that would be detrimental to the survival and quality of life of the patient. This chapter will review AF/AFL and tuberculous pericarditis, with specific focus on the prevalence, determinants, natural history and, impact of these two arrhythmias in tuberculous pericarditis.

Search strategy

A comprehensive literature search was performed by using electronic bibliographic databases (i.e. MEDLINE, Scopus, Web of Science, Google Scholar, Clinical Key, Clinical Evidence and Cochrane Library) using the following keywords: arrhythmia, atrial fibrillation, atrial flutter, electrocardiogram, pericarditis, constrictive pericarditis, tuberculosis, tuberculous pericardial effusion, tuberculous pericardial constriction, tuberculous pericarditis and, cardiovascular tuberculosis. Studies with AF/AFL and pericarditis were retrieved without restriction to language. This search strategy yielded 20 references: 13 observational studies, 6 case reports and, 1 editorial from May 1, 1967 to May 29, 2015. There were a total of 2,046 patients, of which 829 had tuberculous pericarditis.

Prevalence of tuberculous pericarditis-associated AF/AFL

The first and, to date, the only prospective study of the prevalence, correlates and natural history of AF in tuberculous pericarditis was done by Syed et al. This group studied the rhythm on 12-lead electrocardiography (ECG) of 80 patients with tuberculous pericarditis, at diagnosis of tuberculous pericarditis, as well as on serial ECGs done during a 6 month follow up period. 25% of their patients had AF. There was a rapid reduction in the prevalence of AF during the follow up period, with 84% of cases resolving within the first 2 weeks and complete remission in all cases by 6 months[10]. They did not report on the occurrence of AFL.

The largest study that was found in the literature is by Chowdhury et al. They performed a clinical, echocardiographic and haemodynamic evaluation of two surgical techniques in 395 patients that had undergone pericardiectomy for constrictive pericarditis. Tuberculous pericarditis was reported to be the cause of constriction in 351/395 (89%) of their patients. They found AF in 18% of their cohort[11].They did not report on what percentage of those with AF had tuberculous pericarditis. They did not report on the occurrence of AFL.

Overall, the prevalence of AF in tuberculous pericarditis varies widely from 1.2 to 69%[10-19]. The prevalence of AFL in tuberculous pericarditis is unknown. The major limitation of these earlier studies is their small sample sizes and this explains the wide range in prevalence. The occurrence of AFL as a consequence of tuberculous pericarditis has been reported in case studies[20 - 22] but, there are no large prospective studies of the prevalence of AFL in tuberculous pericarditis.

Risk factors for tuberculous pericarditis-associated AF/AFL

The risk factors for AF in the general population include older age, hypertension, diabetes, heart failure and valvular heart disease **(Figure 1)** [23]. Furthermore, there is mounting evidence linking inflammation to the development of AF[7, 8, 23]. In acute pericarditis, AF/AFL has occurred on a background of older age, hypertension and left atrial enlargement[24].

A number of risk factors for tuberculous pericarditis-associated AF have been identified. Syed et al found that echocardiographic left ventricular systolic dysfunction and elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) were independently associated with AF[10]. Rezaian et al found that in patients with constrictive pericarditis, the presence of pericardial calcification and increasing disease duration are associated with a higher chance of developing AF (odds ratio [OR], 7.87; 95% CI, 1.73-35.78, p=0.008). It was observed that with each year of increase in disease duration, the risk of developing AF increased by 27%[12]. The limitations of this study are that they had a small sample size of 44 patients of whom only 13 (29%) had tuberculosis.

The determinants of AFL in tuberculous pericarditis are unknown.

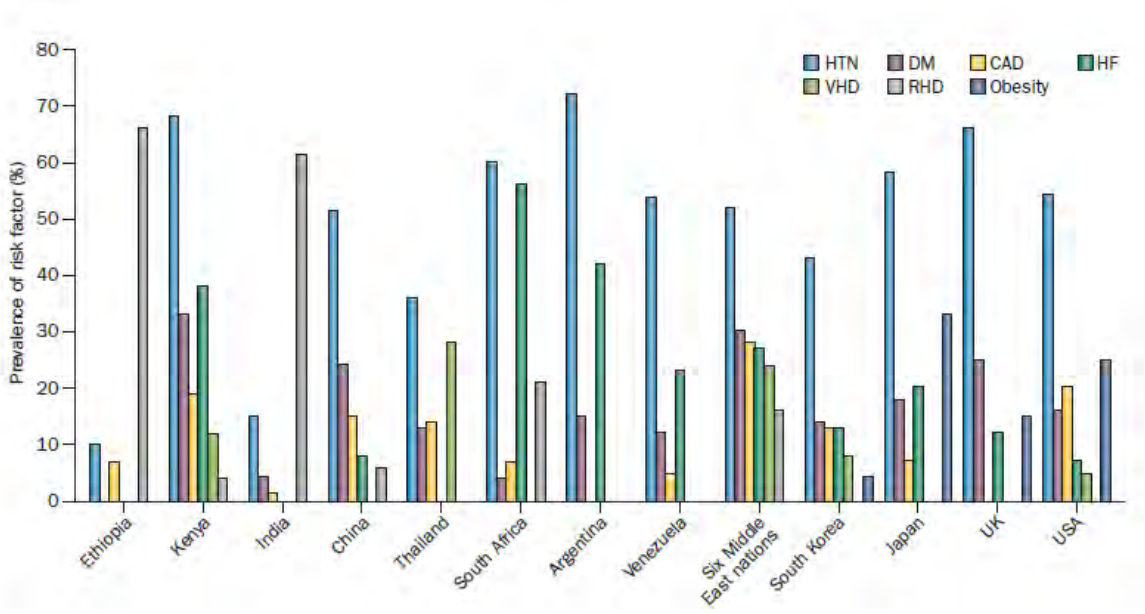

Figure 1: Risk factors for atrial fibrillation by country. Abbreviations: HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; HF, heart failure; VHD, valvular heart disease; RHD, rheumatic heart disease[23].

Natural history of tuberculous pericarditis-associated AF/AFL

The natural history of AF in tuberculous pericarditis is complete resolution of the arrhythmia in six months, with treatment of tuberculous pericarditis with anti-tuberculous chemotherapy **(Figure 2)**. This pattern of resolution of AF has been attributed to specific treatment of the underlying inflammatory condition [10].

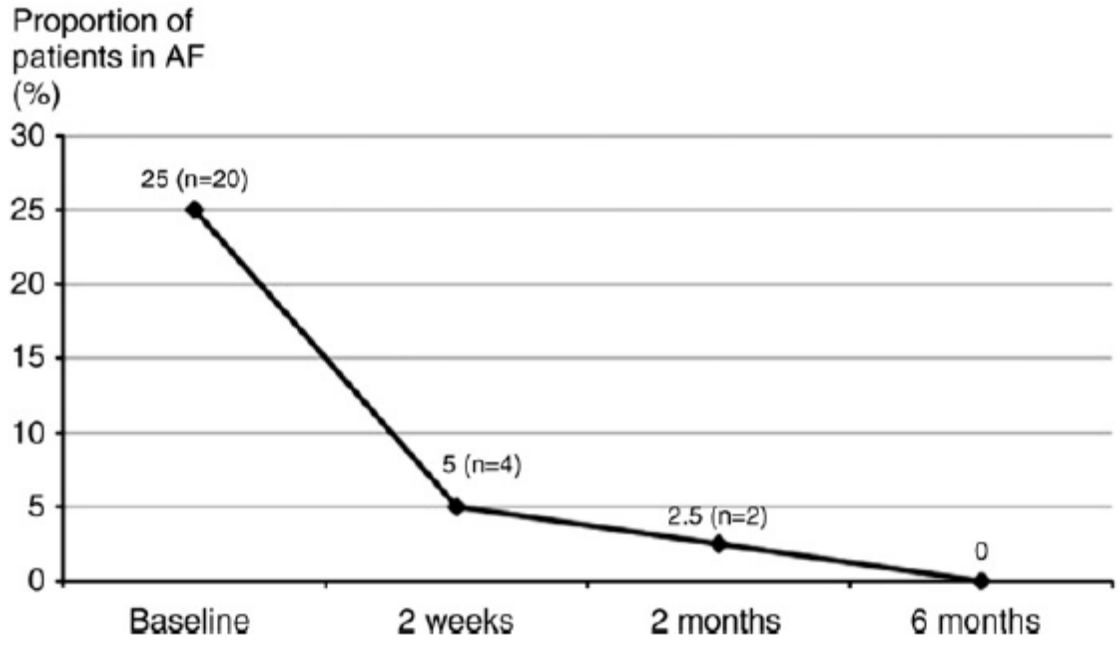

Figure 2. Natural history of atrial fibrillation in patients with tuberculous pericardial effusion[10].

In contrast, in a recent study of acute pericarditis-associated AF, which had a total of 822 cases, of which 23 were tuberculous pericarditis, 74.3% of the arrhythmias resolved, but the recurrence rate was high (35%)[24]. Interestingly, AF recurred in association with pericardial effusion[24], and this association is thought to support a causal link between inflammation and AF[8].

Prognosis of tuberculous pericarditis-associated AF/AFL

AF in the general population is associated with embolic stroke, heart failure, myocardial infarction, dementia, chronic kidney disease as well as increased morbidity and mortality[23, 25, 26]. In a large cohort

of patients with acute pericarditis-associated AF/ AFL, no cases of stroke or transient ischaemic attack (TIA), peripheral embolism or deaths were recorded during the 30-month follow up period[24].

Information on the impact of AF on the prognosis of patients with tuberculous pericarditis has come from surgical studies of constrictive pericarditis. Bozbuga et al studied 36 patients who had undergone pericardiectomy for constrictive tuberculous pericarditis. This group found that pre-operative AF was a significant negative predictor of survival[13]. Similarly, Chowdhury et al, in the study described above, also found that pre-operative AF was a significant risk factor for death in patients undergoing pericardiectomy for constrictive pericarditis[11]. Srivastava et al studied subtotal pericardiectomy via sternotomy for constrictive pericarditis. They also identified pre-operative AF as being a significant predictor of poor outcome[14]. Unfortunately, their study did not define what was meant by 'poor outcome'. In a recent South African retrospective study Mutyaba et al studied total and subtotal pericardiectomy for constrictive pericarditis but they did not find AF to be a predictor of post-operative mortality[19]. Syed et al found that in patients with tuberculous pericardial effusion, there was a non-significant trend towards an increased death rate in the AF group[10]. The small nature of this study has been highlighted. Further research focusing on a large group of patients with tuberculous pericarditis needs to be to done to assess the impact of AF/AFL on death and thromboembolic events in this setting.

Conclusion

Tuberculous pericarditis is a common condition that is associated with significant morbidity and mortality. AF and AFL are common arrhythmias that have a significant clinical impact. The combination of these arrhythmias with tuberculous pericarditis appears to have a marked negative effect on survival in patients undergoing pericardiectomy for constrictive pericarditis due to tuberculosis. While the prevalence of AF in tuberculous pericarditis appears to be high, the prevalence of AFL in the same setting is unknown. Pericardial calcification and increased disease duration are predictors of AF in constrictive pericarditis. The predictors of AFL in constrictive pericarditis are unknown. Left ventricular systolic dysfunction and elevated levels of NT-proBNP are determinants of

AF in tuberculous pericardial effusion. The determinants of AFL in tuberculous pericardial effusion are not known. Although resolution of AF in tuberculous pericarditis with treatment of the underlying tuberculous has been suggested as the natural course of this arrhythmia, this finding has yet to be validated in a large study. The natural course of AFL in tuberculous pericarditis is not known. In constrictive pericarditis, the presence of AF is a negative predictor of survival. The influence of AF in other forms of tuberculous pericarditis needs to be elucidated. The impact of AFL in tuberculous pericarditis has not been studied.

There is therefore a paucity of data regarding the clinical epidemiology of AF/AFL associated with tuberculous pericarditis. This highlights the need for large studies in which the relationships between these conditions are evaluated, in populations where these three conditions are common.

References

1. Ntsekhe M, Mayosi B. Tuberculous pericarditis with and without HIV. *Heart Fail Rev*.2013; 18: 367-373.
2. Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. *Circulation*. 2005; 112:3608-3616.
3. Reuter H, Burgess LJ, Doubell AF. Epidemiology of pericardial effusions at a large academic hospital in South Africa. *Epidemiol Infect*. 2005; 133: 393-399.
4. Pandie S, Peter JG, Kerbelker ZS, Meldau R, Theron G, Govender U, Ntsekhe M, Dheda K, Mayosi BM. Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous pericarditis compared to adenosine deaminase and unstimulated interferon-gamma in a high burden setting: a prospective study. *BMC Med*. 2014; 12:101.
5. Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F, Pogue J, Thabane L, Smieja M, Francis V, Joldersma L, Thomas KM, Thomas B, Awotedu AA, Magula NP, Naidoo DP, Damasceno A, Banda AC, Brown B, Manga P, Kirenga B, Mondo C, Mntla P, Tsitsi JM, Peters F, Essop MR, Russell JBW, Hakim J, Matenga J, Barasa AF, Sani MU, Olunuga T,

Ogah O, Ansa V, A. Aje, Danbauchi S, Ojji D, Yusuf S. Prednisolone and Mycobacterium indicus pranii in Tuberculous Pericarditis. *N Engl J Med*. 2014; 371: 1121-1130.

6. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Catherine Despres C, Dickstein K, John Lekakis, McGregor K, Metra M, Joao Morais, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines 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 European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006; 114: e257–354.
7. Boos CJ, Anderson RA, Lip GYH. Is atrial fibrillation an inflammatory disorder? *Eur Heart J*. 2006; 27: 136-149.
8. Mayosi BM. Pericarditis-associated atrial fibrillation. *Heart*. 2015; 101:1439-1440.
9. Dhar S, Lidhoo P, Koul D, Dhar S, Bakhshi M, Deger FT. Current concepts and management strategies in atrial flutter. *South Med J*. 2009; 102: 917-922.
10. Syed FF, Ntsekhe M, Wiysonge CS, Badri M, Oh JK, Mayosi BM. Atrial fibrillation as a consequence of tuberculous pericardial effusion. *Int J Cardiol.* 2012; 158: 152-154.
11. Chowdhury UK, Subramaniam GK, Sampath Kumar AS, Airan B, Singh R, Talwar S, Seth S, Mishra PK, Pradeep KK, Sathia S, MS, Venugopal P. Pericardiectomy for constrictive pericarditis: A clinical, echocardiographic and hemodynamic evaluation of two surgical techniques. *Ann Thorac Surg*. 2006; 81:522-530.
12. Rezaian GR, Poor-Moghaddas M, Kojuri J, Rezaian S, Liaghat L, Zare N. Atrial fibrillation in constrictive pericarditis: The significance of pericardial calcification. *Ann Noninvasive Electrocardiol*. 2009; 14:258-261.

13. Bozbuga N, Erentug V, Eren E, Erdogan HB, Kirali K, Antal A, Akinci E,Yakut C. Pericardiectomy for chronic constrictive tuberculous pericarditis. *Tex Heart Inst J*. 2003; 30: 180-185.
14. Srivastava AK, Ganjoo AK, Misra B, Chaterjee T, Kapoor A, Pandey CM. Subtotal pericardiectomy via sternotomy for constrictive pericarditis. *Asian Cardiovas Thorac Ann*. 2000; 8: 134-136.
15. Desai HN. Tuberculous pericarditis: A review of 100 cases. *S Afr Med J*. 1979; 55: 877-878
16. Habashy AG, Mittal A, Ravichandran N, Cherian G. The Electrocardiogram in Large Pericardial Effusion: The Forgotten "P" Wave and the Influence of Tamponade, Size, Etiology, and Pericardial Thickness on QRS Voltage. *Angiology*. 2004; 55: 303-307.
17. Levine HD. Myocardial fibrosis in constrictive pericarditis: Electrocardiographic and pathologic observations. *Circulation*. 1973; 48: 1268-1281.
18. Yang CC, Lee MH, Liu JW, Leu HS. Diagnosis of tuberculous pericarditis and treatment without corticosteroids at a tertiary teaching hospital in Taiwan: a 14-year experience. J *Microbiol Immunol Infect*. 2005; 38: 47-52.
19. Mutyaba AK, Balkaran S, Cloete R, du Plessis N, Badri M, Brink J, Mayosi BM. Constrictive pericarditis requiring pericardiectomy at Groote Schuur Hospital, Cape Town, South Africa: causes and perioperative outcomes in the HIV era (1990–2012). *J Thorac Cardiovasc Surg*. 2014; 148:3058–65.e1.
20. Chen IC, Chiu TF, Chen JC. Atrial flutter with cardiac tamponade as initial presentation of tuberculosis pericarditis. *Am J Emerg Med* 2007; 25(1): 108-110.
21. Ogimoto A, Hamada M, Shigematsu Y, Hara Y, Saeki H, Katayama H, Hamada H, Higaki J. Cardiac tamponade with paroxysmal atrial flutter controlled by antituberculous therapy. . *Nihon Ronen Igakkai Zasshi*. 2004; 41:112-6.
22. Darwish Y, Mushannen B, Hussain KM, Nititham K, Dadkhah S, Atkinson J, Zar F, Kogan A. Pancardiac tuberculosis - a case report. *Angiology*. 1998; 49:151-6.
23. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol*. 2014; 11: 639-654.

24. Imazio M, Lazaros G, Picardi E, Vasileiou P, Orlando F, Carraro M, Tsiachris D, Vlachopoulos C, Georgiopoulos G, Tousoulis D, Belli , Gaita F. Incidence and prognostic significance of new onset atrial fibrillation/flutter in acute pericarditis. *Heart*. 2015; 101: 1463-1467.
25. Stambler BS, Ngunga LM. Atrial fibrillation in Sub-Saharan Africa: epidemiology, unmet needs, and treatment options. *Int J Gen Med*. 2015; 8: 231-242.
26. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim Y, McAnulty JH, Zheng Z, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJL. Worldwide Epidemiology of Atrial Fibrillation: A Global Burden of Disease 2010 Study. *Circulation.* 2014; 129: 837-847.

THE PREVALENCE, DETERMINANTS, NATURAL HISTORY AND IMPACT OF ATRIAL FIBRILLATION AND ATRIAL FLUTTER IN PATIENTS WITH TUBERCULOUS PERICARDITIS – INSIGHTS FROM THE IMPI TRIAL

BY

CHISHALA CHISHALA

CHSCHI003

PART C: MANUSCRIPT

The Prevalence, Determinants, Natural History and Impact of Atrial Fibrillation and Atrial Flutter in 1160 patients with Tuberculous Pericarditis: Observations from the IMPI Trial

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Word count: 6615

Journal Subject Terms: Arrhythmia, Atrial Fibrillation, Pericardial Disease

Abstract

Background— The prevalence, determinants, natural history and clinical impact of atrial fibrillation and atrial flutter (AF/AFL) in patients with tuberculous pericarditis are largely unknown. Using data from the Investigation of the Management of Pericarditis (IMPI) trial we sought to evaluate these parameters.

Methods and Results— Serial electrocardiograms of 1160 patients enrolled in the IMPI trial were analysed. Patients diagnosed with AF/AFL were compared to those in sinus rhythm (SR). The primary outcomes were a composite of all-cause mortality, stroke and thromboembolic events. The prevalence of AF/AFL was 5.8% [atrial fibrillation (AF) - 5.2%; atrial flutter (AFL) - 0.6%] of which 1.2% was persistent/permanent AF. Independent predictors of AF at baseline were older age (odds ratio [OR], 1.030; 95% CI, 1.017-1.053, p=0.001) and New York Heart Association functional class (NYHA) III and IV (OR, 1.759; 95% CI, 1.06 - 2.917, p=0.028). AF/AFL was less likely to occur in females (OR, 0.543; 95% CI, 0.311- 0.947, p=0.013). AF/AFL resolved in 98.8% of patients by 12 months. There was no difference in the composite of all-cause mortality, stroke or thromboembolic events at 12 months (AF/AFL event rate - 22.7% versus SR event rate - 20.3%, p=0.356). AF/AFL patients had significantly higher cardiovascular-related hospitalisations - [proportions: AF/AFL, 5/71 (7%) versus sinus rhythm 15/1148 (1.3%), p<0.0001] and, cardiovascular-related deaths - [proportions: AF/AFL, 3/67 (4.5%) versus sinus rhythm, 6/1039 (0.6%), p=0.012].

Conclusions— AF/AFL occurs in 5.8% of patients with tuberculous pericarditis; is associated with older age, greater dyspnoea and male gender and, has no impact on the composite of death, stroke and thromboembolism. It is associated with greater cardiovascular-related hospitalisations and deaths. It tends to resolve and women are protected against its development.

Key words: arrhythmia; death; electrocardiography; fibrillation; pericardium

In regions such as sub-Saharan Africa where *Mycobacterium tuberculosis* (*M. tuberculosis)* is endemic, tuberculous pericarditis is the most common cause of pericarditis affecting 80,000 – 160,000 people per year[1, 2]. A large South African prospective study of pericardial effusions reported that 69.5% of patients had tuberculosis and over 50% of the participants were infected with the human immunodeficiency virus (HIV)[3].Tuberculous pericarditis is associated with significant morbidity and mortality. In sub-Saharan Africa, the overall mortality due to tuberculous pericarditis is 18%[4].

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. Haemodynamic impairment and thromboembolic events related to AF result in significant morbidity, mortality, and cost[5]. There is emerging data to support the association between inflammatory disorders and AF[6]. Furthermore, anti-inflammatory therapy has been shown to ameliorate the condition[7].

There is a paucity of data regarding tuberculous pericarditis-associated atrial fibrillation and/or atrial flutter (AF/AFL), specifically the true prevalence of AF/AFL, the natural history and, prognostic significance of these arrhythmias in tuberculous pericarditis.

In a recent large study of the natural history of atrial fibrillation and atrial flutter in acute pericarditis, in a population with a low prevalence of tuberculosis, AF/AFL was found in 4.3% of patients[8]. In an observational study of AF in tuberculous pericardial effusion (sample size = 80), 25% of patients had AF[9]. A study of clinical, echocardiographic and haemodynamic associations of two surgical techniques in 395 patients that had undergone pericardiectomy for constrictive pericarditis found tuberculous pericarditis to be the cause of constriction in 351/395 (89%) patients. AF was seen in 18% of patients[10]. The authors did not report on what percentage of those with AF had tuberculous pericarditis nor did they state whether AF developed during the acute inflammatory phase of illness or following established constriction. Overall, the prevalence of AF in tuberculous pericarditis varies widely from 1.2 to 69%[9-18]. A major limitation of these studies is that they either had small numbers of patients with tuberculous pericarditis or AF was not the main focus of investigation.

After AF, atrial flutter (AFL) is the most common atrial tachyarrhythmia. AFL can cause harm by impairing cardiac output and by encouraging atrial thrombus formation that can lead to systemic embolization[19]. The occurrence of AFL as a consequence of tuberculous pericarditis has been reported in case studies[20, 21] but, there are no large prospective studies of the prevalence, natural course and impact on prognosis of AFL in tuberculous pericarditis.

In a recent review of pericarditis-associated AF several pertinent observations were made[22]. Firstly, pericarditis causes atrial fibrillation in the absence of structural heart disease and, it does recur in some patients with concomitant pericardial effusion. Secondly, in acute and subacute pericarditis, AF is transient, with persistent AF occurring more frequently in chronic constrictive pericarditis. Thirdly, the temporal relationship between recurrences of pericarditis with associated AF as well as emerging evidence to support the role of inflammation in the development of AF puts the spotlight on inflammatory pathways as a mechanism for the development of AF. Thus therapies directed towards specific anti-inflammatory targets may have a role in the prevention and treatment of AF[22].

The aim of this study was to prospectively evaluate the prevalence, determinants, natural history and, impact of AF/AFL in patients with tuberculous pericarditis that were enrolled in the Investigation of the Management of Pericarditis (IMPI) trial. Our hypothesis was that in patients with tuberculous pericarditis, AF/AFL is common, and compared to tuberculous pericarditis patients that are in sinus rhythm, is associated with increased morbidity and/or mortality.

Methods

Study Population and Study Design

The participants of the IMPI trial comprised the study population. The IMPI trial was a prospective multicentre, international, double blind; placebo controlled randomized trial that evaluated the effects of immunotherapy on clinical outcomes and safety in tuberculous pericarditis. The IMPI trial had 1400 participants with tuberculous pericarditis who were followed up over a period of minimum 6 months to a maximum of 48 months[23]. Being an IMPI trial sub-study, this was an exploratory post hoc analysis. Ethics approval was obtained from the Human Research Ethics Committee in the Faculty of

Health Sciences, at the University of Cape Town (HREC/REF: 598/2014). Patients that had ECGs recorded were screened for eligibility while those without ECGs or those with uninterpretable ECGs were excluded. Baseline and follow up ECGs of these patients were analysed for the following rhythms: sinus, AF, AFL, ectopic atrial rhythms, junctional rhythms, ventricular and, other supraventricular arrhythmias. Comparisons were made between those patients with AF/AFL and those with sinus rhythm. The primary outcomes considered during follow up were a composite of all-cause mortality, stroke and, thromboembolic events. Only clinically appreciable thromboembolic events as determined in the IMPI trial were assessed. The secondary outcomes were death, constrictive pericarditis, cardiac tamponade requiring pericardiocentesis and, cardiovascular-related hospitalization - detailed definitions of the outcomes were provided in the IMPI trial[4].

Logistic regression analysis was used to determine factors associated with AF/AFL at presentation and at follow up. The baseline features that were included in this analysis are: age, sex, New York Heart Association functional class (NYHA), heart rate, systolic blood pressure, diastolic blood pressure, human immune deficiency virus (HIV) status and CD4 count if positive, creatinine, haemoglobin, white cell count, definite tuberculous pericarditis diagnosis or probable tuberculous pericarditis diagnosis (as defined in the IMPI trial[4]), left ventricular systolic dysfunction on echocardiography, presence of constriction or cardiac tamponade (as defined in the IMPI trial[4]), and, the size of pericardial effusion when present on echocardiography.

ECG Analyses

Participants had ECGs done at enrolment (baseline ECG) into the study and (if available) at 2 weeks, 4 weeks, 6 weeks, 3 months, 6 months, 12 months, 18 months, 24 months, 36 months and, 48 months. These ECGs were copied and stored in an online central repository called iDataFax. The ECGs were printed from iDataFax for analysis. AF was diagnosed if an ECG showed fine oscillations of the baseline (fibrillation or f waves) with no clear P waves and, an irregular QRS rhythm, irrespective of when it was done[24]. AF was further sub-classified in accordance with the American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC)

guidelines as follows[5]: First detected AF (only one diagnosed episode of AF: based on our follow-up schedule this was defined as AF present on only one ECG among patients with baseline ECGs) ;paroxysmal AF (recurrent episodes of AF that resolve spontaneously within 7 days: based on our follow-up schedule this was defined as AF present on two or more non-consecutive ECGs among patients with baseline ECGs); persistent AF (recurrent episodes of AF that last more than 7 days: based on our follow-up schedule this was defined as AF present on two or more consecutive ECGs among patients with baseline ECGs); and permanent AF (an ongoing long-term episode of AF: based on our follow-up schedule this was defined as AF present on all available ECGs among those with baseline ECGs).

AFL was diagnosed if the ECG showed regular saw-tooth like atrial flutter (F waves) between QRS complexes[24]. By analysing serial ECGs that were done over the 48-month follow up period, the prevalence and natural history of AF/AFL in tuberculous pericarditis was described.

Statistical Analysis

STATA version 13.1 was used for data analysis. Baseline characteristics were compared for participants in AF/AFL versus sinus rhythm, as well as comparison within the AF/AFL group stratified by rhythm status. The data were reported as mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for non-normally distributed continuous variables, and, percentages for categorical variables. The distributions of categorical variables were compared using a chi square test or Fisher exact test. The distributions of continuous variables by systolic blood pressure, diastolic blood pressure and creatinine were compared using the Kruskal-Wallis equality-of-proportions rank test. The analysis of variance test was used to compare distributions of age, white cell count and haemoglobin. Logistic regression analysis was used to determine factors associated with AF/AFL at presentation and at follow up. The variables that were considered for analysis included: age, sex, New York Heart Association functional class (NYHA), heart rate, systolic blood pressure, diastolic blood pressure, human immune deficiency virus (HIV) status and CD4 count if positive, creatinine, haemoglobin, white cell count, definite tuberculous

diagnosis or probable tuberculous diagnosis, left ventricular systolic dysfunction on echocardiography, presence of constriction or cardiac tamponade and, the size of pericardial effusion when present, on echocardiography. Covariates that were at least marginally associated with the endpoint of interest in univariate analyses ($p<0.10$) and *a priori* clinical factors of interest were included in these multivariate models. Our findings are reported as odds ratios (ORs) with95% confidence intervals (CIs). A p-value <0.05 was considered significant. Time-to-event analyses were done using Kaplan-Meier curves.

Results

Baseline characteristics

A total of 1160 patients were analysed **(Figure 1).** AF/AFL was found in 67/1160 (5.8%) patients [AF 60/1160 patients (5.2%); AFL 7/1160 patients (0.6%)]. Baseline characteristics of the study population are reported in **Table 1**. Patients with AF and AFL were older than those in sinus rhythm [mean values (SD): AF, 43.9 (16.5); AFL, 51.8 (13.7) versus SR, 38.5 (13.2), p=0.0005]. AF and AFL groups had more males than the sinus rhythm group, [percentages: AF, 70%; AFL, 71.4% versus SR, 56% p=0.007]. Creatinine values for AF and AFL patients were significantly higher than for those in sinus rhythm [median values (IQR): AF, 85 (67 – 97), AFL, 105 (78 – 132) versus SR, 74 (60 – 90), p=0.001]. No significant differences were found in other baseline features or when comparing AF and AFL patients **(supplementary table S1).** Comparison was also made between the included and excluded patients. This showed that included patients had more diagnoses of constrictive pericarditis (percentages: included patients, 48.5% versus excluded patients, 23.3%, p <0.0001), larger pericardial effusions (percentages: included patients, 70% versus excluded patients, 57.1%, p <0.0001) and more episodes of cardiac tamponade (percentages: included patients, 58.9% versus excluded patients, 47.5%, p=0.006) than those that were excluded **(supplementary table S2).**

Natural history of AF/AFL

AF/AFL declined dramatically in patients that had AF/AFL at baseline, over the follow-up period **(Figure 2).** First detected AF was seen in 60/1160 (5.2%) patients; paroxysmal AF was observed in

60/1160 (5.2%) patients; persistent AF was seen in 5/1160 (0.4%) and, permanent AF was noted in 9/1160 (0.8%). At the end of the study 113 of the initial 1160 patients who had had baseline ECGs had ECGs done at 48 months. Of these 1/113 (0.9%) had AF/AFL.

Impact of AF/AFL

There was no significant difference in incidence rate of the composite of death, stroke and thromboembolic events in the AF/AFL group compared to the sinus rhythm group **(Figure 3)** – (12 month event rates: AF/AFL, 22.7% versus sinus rhythm, 20.3% , p=0.356).There were no significant differences in the individual outcomes of death **(Figure 4)** – (12 month event rates: AF/AFL, 16.6% versus sinus rhythm,13.5% , p=0.217); constriction **(Figure 5)** – (12 month event rates: AF/AFL, 3.5% versus sinus rhythm, 6.8% , p=0.274) and, cardiac tamponade **(Figure 6)** – (12 month event rates: AF/AFL, 3.4% versus sinus rhythm, 3.5% , p=0.218). Patients in AF/AFL had a significantly higher proportion of cardiovascular-related deaths than those in sinus rhythm **(Table 2)** – [proportions: AF/AFL, 3/67 (4.5%) versus sinus rhythm, 6/1039 (0.6%), p=0.012]. AF/AFL patients compared to those in sinus rhythm had a significantly higher proportion of cardiovascular-related hospitalisations – [proportions: AF/AFL, 5/71 (7%) versus sinus rhythm 15/1148 (1.3%), p<0.0001].

Factors associated with AF/AFL

Multivariate logistic regression analysis revealed older age (odds ratio [OR], 1.030; 95% CI, 1.017-1.053, p=0.001) and NYHA III and IV (OR, 1.759; 95% CI, 1.061-2.917, p=0.028) to be independently associated with AF at presentation. Female sex (OR, 0.543; 95% CI, 0.311- 0.947, p=0.013) was protective against AF at presentation **(Table 3)**. In multivariate logistic regression analysis at all time points, older age (OR, 1.064; 95% CI, 1.034-1.095, p<0.0001) and NYHA III and IV (OR, 2.297; 95% CI, 1.065-4.951, p=0.034) were independent predictors of AF. Increased time spent in the study (OR, 0.867; 95% CI, 0.820-0.920, p<0.0001) was found to be protective against the development of AF **(Table 4)**.

Discussion

In this study, we evaluated the largest cohort of tuberculous pericarditis-associated AF/AFL. The prevalence of AF was 5.2% while that of AFL was 0.6%. Patients with AF/AFL were older than those in sinus rhythm and were predominantly male. Older age and poorer NYHA functional class were both independently associated with AF at presentation, and predictive of development of AF in patients with tuberculous pericarditis. Female sex was protective against AF at presentation and, on follow-up, increased duration of being in the study in addition to female sex was protective against the development of AF. The burden of AF/AFL decreased during follow-up but did not completely resolve. In terms of outcomes, the rates of the composite of mortality, stroke and thromboembolic events, as well as the endpoints of constrictive pericarditis and cardiac tamponade did not differ significantly between the two groups. However, AF/AFL patients had significantly higher proportions of cardiovascular-related hospitalisations and deaths.

Prevalence of tuberculous pericarditis-associated AF/AFL

Previous studies have reported the prevalence of AF in tuberculous pericarditis to range widely from 1.2 to 69%[9-18]. However, the major limitation of these earlier studies is their small sample sizes and this explains the wide range in prevalence. Therefore the prevalence of 5.8% determined by our study is more representative as it was a large study that had an excellent follow-up rate with the primary-outcome status known for 97.9% of patients[4]. Contemporary data on the epidemiology of AF in sub-Saharan Africa show the prevalence of AF in this region to be in the range of 0.7 – 5.5%[25].The reported prevalence of AF in Australia, Europe and the USA in adults is 1 – 4 % and in individuals over the age of 80, it rises to more than 13%[26]. In our study population, given its demographics of age, sex, functional class, HIV status etc. we did not find the prevalence of tuberculous pericarditis associated -AF to be as high as 70% but closer to the figures reported for both sub-Saharan Africa and the European acute pericarditis- associated AF group[8, 25].

We believe our finding of the prevalence of 0.6% for AFL in tuberculous pericarditis to be the first report of the prevalence of AFL in a large group of patients with tuberculous pericarditis.

Risk factors for tuberculous pericarditis-associated AF/AFL

The risk factors for AF in the general population include older age, hypertension, diabetes, heart failure and valvular heart disease[26]. In acute pericarditis, AF has occurred on a background of older age, hypertension and left atrial enlargement[8, 22]. Previously reported determinants of AF in tuberculous pericarditis include: left ventricular systolic dysfunction, elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), pericardial calcification and, increasing disease duration[9, 11, 18]. In the larger cohort that we had, we found that older age is a predictor of AF just as it is in the general population, despite a relatively lower mean age of less than 50 years. Poor NYHA functional class is the clinical surrogate for NT-proBNP, but we did not find left ventricular systolic dysfunction and pericardial calcification to be associated with AF. It is likely that in our larger cohort, more patients had preserved left ventricular function. We did not measure NT-proBNP. In cardiac tamponade, diastolic ventricular filling and ultimately, cardiac output become dependent on atrial systole[27]. Thus the association between poor NYHA functional class and AF in tuberculous pericarditis is significant as it suggests the loss of atrial systole due to AF, in these patients. Interestingly, female sex was protective to the development of AF (at baseline and on follow-up). One explanation for the impact of gender on AF is that women have a higher age of onset of AF[28] and thus the fact that the mean (SD) age of AF patients in our study was 43.9 (16.5) is consistent with our patients being relatively young. This combination of young patient age and female sex leading to less AF is a unique finding.

Death, stroke, thromboembolic events, constriction and cardiac tamponade

AF is associated with embolic stroke, heart failure, myocardial infarction, dementia, chronic kidney disease as well as increased morbidity and mortality[25, 26, 29]. In a large cohort of patients with acute pericarditis-associated AF/ AFL, no cases of stroke or transient ischaemic attack (TIA), peripheral embolism or deaths were recorded during the 30-month follow up period[8]. In the first prospective study of the prevalence, correlates, and natural history of AF in patients with tuberculous pericarditis, rates of deaths were not significantly increased in the AF group nor were any cases of stroke

recorded[9]. While we did not find a difference in the composite of deaths, stroke and thromboembolic events in patients with AF/AFL compared to those in sinus rhythm, we found that the rates of cardiovascular-related hospitalisations and deaths were higher in the AF/AFL group. This is hypothesis generating, however, the absolute numbers of these events were small and the exact aetiology of the cardiovascular deaths was not determined.

Natural history of tuberculous pericarditis-associated AF/AFL

In tuberculous pericarditis, the major burden of AF/AFL occurs at presentation and rapidly reduces over time. By 48 months less than 2% of tuberculous pericarditis patients are affected. This is unlike acute pericarditis-associated AF, where recurrence rates exceed 30% [8]. Increased duration spent in the study was protective against the development of AF. Patients in the IMPI trial exhibited good compliance to anti-tuberculous therapy[4] and the decrease of AF with time suggests a response to treatment and a decrease in the inflammatory burden. As noted by others[9], this finding corroborates mounting data that support the association between inflammatory disorders and AF[6, 7]. The anti-inflammatory impact of the corticosteroids that patients in the prednisolone arm of the trial received, on the natural history of AF is difficult to determine in a post hoc review of this nature. The question would be best answered by a study powered to determine the effect of steroids.

Study Limitations

Our study has some limitations. Firstly, being a post hoc review, the study is hypothesis generating, particularly with regard to the influence of inflammation given that no specific markers of inflammation such as C-reactive protein were measured. The study was able to answer the crucial question of the true prevalence of AF/AFL in tuberculous pericarditis and shed light on associated risk factors, the natural history and clinical impact of these arrhythmias. Secondly, patients with confounding variables that have an independent risk of AF such as valvular heart disease, hypertension and cardiomyopathy were not excluded. However, given the small number of participants with AF/AFL overall, it is likely that the contribution of such variables was limited if present. Thirdly, 240/1400 patients either did not have an ECG recorded or did not have a technically

acceptable one and therefore some cases of AF/AFL might have been missed. We compared the included and excluded patients and found that the included patients had more outcomes than those excluded for evaluation, thus the contribution of missed AF/AFL is likely to be minimal. It is possible that based on the frequency of ECG recording in the study some episodes of paroxysmal AF could have been missed but it is reassuring that the AF group did not have increased rates of stroke or thromboembolic events to support this theory. An additional limitation is that detection bias is not completely avoidable given that subclinical episodes of AF/AFL cannot be detected in a study of this nature as there is no extended continuous rhythm monitoring. Subclinical AF has been shown to be associated with an increased risk of ischaemic stroke or systemic embolism in patients whose atrial rhythms have been monitored by pacemakers[29]. Despite this limitation very few thromboembolic events were recorded. Another limitation is that assumptions were made about the true nature of AF i.e. first detected, paroxysmal, persistent and permanent AF, in order to meet the ACC/AHA/ESC guidelines. Lastly, comprehensive echocardiographic evaluation (which was not done in the IMPI trial), including parameters such as left atrial volumes indexed for body surface area and left atrial filling pressures would have been ideal to make additional associations.

Conclusions

This is to-date, the largest study of prevalence, determinants, natural history and impact of AF/AFL in patients with tuberculous pericarditis. Tuberculous pericarditis-associated AF/AFL has a frequency not dissimilar to that seen in epidemiological studies of AF in sub-Saharan Africa and in acute pericarditis in Europe. It tends to resolve with only a minority having persistent or permanent AF. AF/AFL was associated with more cardiovascular-related hospitalizations and deaths but did not influence rates of thromboembolic disease. The predictors of AF were not different to traditional risk factors including older age and poor NYHA class. Males are more likely to develop tuberculous-pericarditis associated AF/AFL.

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Conflict of Interest Disclosures: None.

References

1. Ntsekhe M, Mayosi B. Tuberculous pericarditis with and without HIV. *Heart Fail Rev*.2013; 18: 367-373.
2. Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. *Circulation*. 2005; 112:3608-3616.
3. Reuter H, Burgess LJ, Doubell AF. Epidemiology of pericardial effusions at a large academic hospital in South Africa. *Epidemiol Infect*. 2005; 133: 393-399.
4. Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F, Pogue J, Thabane L, Smieja M, Francis V, Joldersma L, Thomas KM, Thomas B, Awotedu AA, Magula NP, Naidoo DP, Damasceno A, Banda AC, Brown B, Manga P, Kirenga B, Mondo C, Mntla P, Tsitsi JM, Peters F, Essop MR, Russell JBW, Hakim J, Matenga J, Barasa AF, Sani MU, Olunuga T, Ogah O, Ansa V, A. Aje, Danbauchi S, Ojji D, Yusuf S. Prednisolone and Mycobacterium indicus pranii in Tuberculous Pericarditis. *N Engl J Med*. 2014; 371: 1121-1130.
5. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Catherine Despres C, Dickstein K, John Lekakis, McGregor K, Metra M, Joao Morais, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines 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 European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006; 114: e257–354.

6. Boos CJ, Anderson RA, Lip GYH. Is atrial fibrillation an inflammatory disorder? *Eur Heart J*. 2006; 27: 136-149.
7. Pena JM, Macfayden J, Glynn RJ, Ridker PM. High-sensitivity C-reactive protein, statin therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial. *Eur Heart J*. 2012; 33: 531-537.
8. Imazio M, Lazaros G, Picardi E, Vasileiou P, Orlando F, Carraro M, Tsiachris D, Vlachopoulos C, Georgiopoulos G, Tousoulis D, Belli , Gaita F. Incidence and prognostic significance of new onset atrial fibrillation/flutter in acute pericarditis. *Hear.t* 2015; 101: 1463-1467.
9. Syed FF, Ntsekhe M, Wiysonge CS, Badri M, Oh JK, Mayosi BM. Atrial fibrillation as a consequence of tuberculous pericardial effusion. *Int J Cardiol.* 2012; 158: 152-154.
10. Chowdhury UK, Subramaniam GK, Sampath Kumar AS, Airan B, Singh R, Talwar S, Seth S, Mishra PK, Pradeep KK, Sathia S, MS, Venugopal P. Pericardiectomy for constrictive pericarditis: A clinical, echocardiographic and hemodynamic evaluation of two surgical techniques. *Ann Thorac Surg*. 2006; 81:522-530.
11. Rezaian GR, Poor-Moghaddas M, Kojuri J, Rezaian S, Liaghat L, Zare N. Atrial fibrillation in constrictive pericarditis: The significance of pericardial calcification. *Ann Noninvasive Electrocardiol*. 2009; 14:258-261.
12. Bozbuga N, Erentug V, Eren E, Erdogan HB, Kirali K, Antal A, Akinci E,Yakut C. Pericardiectomy for chronic constrictive tuberculous pericarditis. *Tex Heart Inst J*. 2003; 30: 180-185.

13. Srivastava AK, Ganjoo AK, Misra B, Chaterjee T, Kapoor A, Pandey CM. Subtotal pericardiectomy via sternotomy for constrictive pericarditis. *Asian Cardiovas Thorac Ann*. 2000; 8: 134-136.
14. Desai HN. Tuberculous pericarditis: A review of 100 cases. *S Afr Med J*. 1979; 55: 877-878
15. Habashy AG, Mittal A, Ravichandran N, Cherian G. The Electrocardiogram in Large Pericardial Effusion: The Forgotten "P" Wave and the Influence of Tamponade, Size, Etiology, and Pericardial Thickness on QRS Voltage. *Angiology*. 2004; 55: 303-307.
16. Levine HD. Myocardial fibrosis in constrictive pericarditis: Electrocardiographic and pathologic observations. *Circulation*. 1973; 48: 1268-1281.
17. Yang CC, Lee MH, Liu JW, Leu HS. Diagnosis of tuberculous pericarditis and treatment without corticosteroids at a tertiary teaching hospital in Taiwan: a 14-year experience. J *Microbiol Immunol Infect*. 2005; 38: 47-52.
18. Mutyaba AK, Balkaran S, Cloete R, du Plessis N, Badri M, Brink J, Mayosi BM. Constrictive pericarditis requiring pericardiectomy at Groote Schuur Hospital, Cape Town, South Africa: causes and perioperative outcomes in the HIV era (1990–2012). *J Thorac Cardiovasc Surg*. 2014; 148:3058–65.e1.
19. Dhar S, Lidhoo P, Koul D, Dhar S, Bakhshi M, Deger FT. Current concepts and management strategies in atrial flutter. *South Med J*. 2009; 102: 917-922.
20. Chen IC, Chiu TF, Chen JC. Atrial flutter with cardiac tamponade as initial presentation of tuberculosis pericarditis. *Am J Emerg Med*. 2007; 25: 108-110.
21. Purvis JA, Roberts M, Harbinson MT. Constriction infection. *Int J Cardiovasc Imaging*. 2010; 26:1-3.
22. Mayosi BM. Pericarditis-associated atrial fibrillation. *Heart*. 2015; 101:1439-1440.
23. Mayosi BM, Ntsekhe M, Bosch J, Pogue J, Gumedze F, Badri M, Jung H, Pandie S, Smieja M, Thabane L, Francis V, Thomas KM, Thomas, Awotedu AA, Magula NP, Naidoo DP, Damasceno A, Banda AC, Mutyaba A, Brown B, Ntuli P, Mntla P, Ntyintyane L, Ramjee R, Manga P, Kirenga B, Mondo C, Russell JBW, Tsitsi JM, Peters F, Essop MR, Barasa AF, Mijinyawa MS, Sani MU, Olunuga T, Ogah O, Adebiyi A, Aje A, Ansa V, Ojji D, Danbauchi

S. Rationale and design of the investigation of the Management of Pericarditis (IMPI) trial: A 2 x 2 factorial randomized double-blind multicenter trial of adjunctive prednisolone and Mycobacterium w immunotherapy in tuberculous pericarditis. *American Heart Journal*. 2012; 165: 109-117.

24. Kumar P, Clark M. *Kumar and Clark's Clinical Medicine*.7th ed. Edinburgh: 2009; Elsevier Saunders; 2009: 724-725.
25. Stambler BS, Ngunga LM. Atrial fibrillation in Sub-Saharan Africa: epidemiology, unmet needs, and treatment options. *Int J Gen Med*. 2015; 8: 231-242.
26. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol*. 2014; 11: 639-654.
27. Irwin RS, Rippe J. *Irwin and Rippe's Intensive Care Medicine*. 6th ed. Philadelphia: 2008; Lippincott Williams & Wilkins, 2008: 371.
28. Ozaa NM, Swati Bavejab S, Tedrowc U. Bridging the gender gap in atrial fibrillation. *Expert Rev Cardiovasc Ther*. 2015; 13: 317-323.
29. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim Y, McAnulty JH, Zheng Z, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJL. Worldwide Epidemiology of Atrial Fibrillation: A Global Burden of Disease 2010 Study. *Circulation.* 2014; 129: 837-847.
30. Healey JS, Conolly S, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012; 366: 120-129.

Figure Legends:

Figure 1. Flow chart for analysis of patients.

*other supraventricular arrhythmias [44/1160 (3.8%)] and ventricular rhythms [1/1160 (0.1%)]

Figure 2. Proportion with AF/AFL by month of visit

	baseline	2 weeks	4 weeks	6 weeks	6 months	12 months	18 months	24 months	36 months	48 months
Total	1160	971	957	1012	898	682	565	443	250	113
No. with AF/AFL	68	17	16	11	5	6	4	3	2	1
Proportion with AF/AFL	0.059	0.018	0.017	0.011	0.004	0.009	0.007	0.007	0.008	0.009

Figure 3. Kaplan-Meier analysis of the composite by rhythm status.

6 month event rate: AF/AFL – 22.7% versus Sinus Rhythm (SR) – 17.8%

1 year event rate: AF/AFL – 22.7% versus SR – 20.3%

Figure 4. Kaplan-Meier analysis of death by rhythm status.

6 month event rate: AF/AFL – 16.6% versus SR – 10.5%

1 year event rate: AF/AFL – 16.6% versus SR – 13.5%

Figure 5. Kaplan-Meier analysis of constrictive pericarditis by rhythm status

6 month event rate: AF/AFL – 3.5% versus SR – 3.6%

1 year event rate: AF/AFL – 3.5% versus SR – 6.8%

Figure 6. Kaplan-Meier analysis of cardiac tamponade by rhythm status

6 month event rate: AF/AFL – 6.7% versus SR – 6.7%

1 year event rate: AF/AFL – 3.4% versus SR – 3.5%

Table 1. Baseline characteristics by AF/AFL and Sinus rhythm status

Characteristics	**AF/AFL**				**Sinus Rhythm**		**P value**
	Atrial fibrillation		**Atrial flutter**				
Participants - no. (%)	60/1160	5.2	7/1160	0.6	1048/1160	90.3	-
Age in years – no., mean (SD)	60/1115	43.9 (16.5)	7/1115	51.8 (13.7)	1048/1115	38.5(13.2)	0.0005*
Sex – no. (%)							0.007†
Male	42/60	70.0	5/7	71.4	587/1048	56.0	
Female	18/60	30.0	2/7	28.6	481/1048	44.0	
Functional class – no. (%)							0.053†
NYHA I - II	35/60	58.3	3/7	42.9	733/1048	69.9	
NYHA III - IV	25/60	41.7	4/7	57.1	315/1048	30.1	

Heart rate /minute – no. (%)							0.521†
<100	29/60	48.3	2/7	28.6	448/1046	42.8	
>100	31/60	51.7	5/7	71.4	598/1046	57.2	
Systolic blood pressure /mmHg – no., median (IQR)	60/60	112.5 (100-125)	7/7	113 (105-123)	1047/1048	111 (102-125)	0.919‡
Diastolic blood pressure /mmHg – no., median (IQR)	60/60	70 (63.5-80)	7/7	80 (76-83)	1047/1048	72 (66-80)	0.294‡
HIV status – no. (%)							0.330†
Positive	19/56	33.9	4/7	57.1	326/1033	31.6	
Negative	37/56	66.1	3/7	42.9	707/1033	68.4	
CD4 count cells/µL – no. (%)							0.914†
>350	4/31	12.9	0/3	0	77/549	14.0	
200-350	8/31	25.8	0/3	0	126/549	23.0	

50-200	14/31	45.2	2/3	66.7	258/549	47.0	
0-50	5/31	16.1	1/3	33.3	88/549	16.0	
Creatinine/µmolL^{-1} – no., median (IQR)	57/60	85 (67-97)	7/7	105 (78-132)	960/1048	74 (60-90)	0.001[†]
White cell count cells x 10^9/L – no., mean (SD)	60/60	6.7 (3.1)	7/7	6.6(1.1)	1046/1048	6.3 (2.6)	0.524*
Haemoglobin g/dL – no., mean (SD)	60/60	10.3 (2.3)	7/7	11.5 (2.9)	1044/1048	10.0 (2.3)	0.084*
Diagnosis of tuberculous pericarditis – no. (%)							0.768[§]
Definite	11/60	18.3	2/7	28.6	190/1037	18.3	
Probable	49/60	81.7	5/7	71.4	847/1037	81.7	
Left ventricular ejection fraction – no. (%)							0.247[§]
<35%	1/37	2.7	0/4	0.0	12/638	1.9	
35-45%	2/37	5.4	0/4	0.0	29/638	4.6	
45-50%	34/37	91.9	4/4	100.0	597/638	93.6	

Constrictive pericarditis – no. (%)							0.794[§]
Yes	23/47	48.9	1/4	25.0	363/744	48.8	
No	24/47	51.1	3/4	75.0	381/744	51.2	
Pericardial effusion – no. (%)							0.375[§]
Small effusion (<1cm)	2/57	3.5	0/7	0.0	82/1020	8.0	
Moderate effusion (1-2cm)	11/57	19.3	0/7	0.0	235/1020	23.0	
Large effusion (>2cm)	44/57	77.2	7/7	100.0	703/1020	68.9	

Cardiac Tamponade – no. (%)							0.344[§]
Yes	18/38	47.4	2/5	60.0	432/729	59.3	
No	20/38	52.6	3/5	40.0	297/729	40.7	

*Analysis of variance test.

[†]Pearson chi square test.

[‡]Kruskal-Wallis equality-of- proportions rank test.

[§] Fisher's exact test.

Table 2. Deaths

Characterististics	**AF/AFL**		**Sinus**		**P value**
Total deaths – no. (%)	14/67	20.9	180/1093	16.5	0.346*
Stroke – no. (%)	0/67	0.0	2/1093	100.0	1.000†
Thromboembolic events – no. (%)	0/67	0.0	8/1093	100.0	1.000†
Cardiovascular related death – no. (%)	3/67	4.5	6/1093	0.6	0.012†

*Pearson chi square test

†Fisher's exact test

Table 3. Logistic regression analysis for factors associated with atrial fibrillation at baseline

Characteristic	**Univariate analysis**		**Multivariate analysis**	
	Odds ratio (95%CI)	P-value	Odds ratio (95% CI)	P-value
Age	1.030 (1.014-1.047)	<0.0001	1.030 (1.017-1.053)	0.001
Sex (female)	0.545 (0.319-.0.933)	0.027	0.543 (0.311-0.947)	0.013
Functional class NYHA III - IV	1.734 (1.052-2.859)	0.031	1.759 (1.061-2.917)	0.028
Heart rate (>100 beats/minute)	0.847 (0.516-1.389)	0.796		
Systolic blood pressure/mmHg	1.004 (0.990-1.018)	0.580		
Diastolic blood pressure/ mmHg	0.999 (0.979-1.018)	0.901		
HIV positive	0.784 (0.462-1.330)	0.367		
CD4 Count cells/μL				
CD4 200-350	1.188 (0.347-4.073)	0.784		

CD4 50-200	1.162 (0.378-3.574)	0.794		
CD4 0-50	1.288 (0.351-4.728)	0.703		
Creatinine/ µmol L^{-1}	1.002 (0.999-1.005)	0.193		
Haemoglobin g/dL	1.111 (0.999-1.234)	0.052	1.027 (0.911-1.157)	0.667
White cell count cells x 10^{-9}/L	1.046 (0.961-1.138)	0.299		
Left ventricular ejection fraction				
35-45%	0.903 (0.076-10.808)	0.936		
45-50%	0.859 (0.110-6.710)	0.885		
Pericardial effusion				
Medium (1-2cm)	1.917 (0.416-8.826)	0.404		
Large (>2cm)	2.899 (0.693-12.12)	0.145		
Cardiac tamponade				

Yes	0.652 (0.352-1.206)	0.173		
Constrictive pericarditis Yes	0.939 (0.532-1.656)	0.827		
TBP diagnosis Probable	0.948 (0.507-1.770)	0.866		

Table 4. Logistic regression analysis for factors associated with atrial fibrillation (all time points)

Characteristic	**Univariate analysis**		**Multivariate analysis**	
	Odds ratio (95%CI)	P-value	Odds ratio (95% CI)	P-value
Time*	0.858 (0.808-0.911)	<0.0001	0.867 (0.820-0.920)	<0.0001
Age	1.067 (1.040-1.094)	<0.0001	1.064 (1.034-1.095)	<0.0001
Sex (female)	0.490 (0.224-1.068)	0.073	0.549 (0.246-1.223)	<0.0001
Functional class NYHA III-IV	2.597 (1.184-5.695)	0.017	2.297 (1.065-4.951)	0.034
Heart rate (>100 beats/minute)	0.897 (0.420-1.914)	0.778		
Systolic blood pressure/mmHg	1.008 (0.987-1.030)	0.458		
Diastolic blood pressure/mmHg	0.997 (0.967-1.028)	0.838		
Creatinine μmol L^{-1}	1.006 (1.000-1.0128)	0.045	1.003 (0.997-1.010)	0.343
Haemoglobin g/dL	1.234 (1.043-1.460)	0.014	1.047 (0.873-1.255)	0.624
White cell count cells x 10^{-9}/L	1.023 (0.892-1.174)	0.742		

HIV positive	0.529 (0.233-1.204)	0.129	
CD4 count cells/μL			
CD4 200-350	1.848 (0.391-8.723)	0.438	
CD4 50-200	1.688 (0.408-6.987)	0.470	
CD4 0-50	1.688 (0.315-9.036)	0.541	
Left ventricular ejection fraction			
35-45%	0.778 (0.009-66.680)	0.912	
45-50%	0.789 (0.017-35.701)	0.903	
Pericardial effusion			
Medium (1-2cm)	1.690 (0.281-10.150)	0.566	
Large (>2cm)	2.731 (0.523-14.253)	0.233	

Cardiac tamponade Yes	0.463 (0.175-1.226)	0.121	
Constrictive pericarditis Yes	0.950 (0.387-2.333)	0.911	
TBP diagnosis Probable	0.74 (0.286-1.914)	0.535	

*Time refers to every 1 month period spent by a participant in the study

Supplementary table S1. Baseline characteristics by AF and AFL rhythm status

Characteristics	**AF/AFL**				**P value**
	Atrial fibrillation		**Atrial flutter**		
Participants- no. (%)	60/67	89.6	7/67	10.5	-
Age in years – no. mean (SD)	60/60	43.9 (16.5)	7/7	51.8(13.7)	0.114*
Sex – no. (%)					0.938†
Male	42/60	70.0	5/7	71.4	
Female	18/60	30.0	2/7	28.6	
Functional class – no. (%)					0.434†
NYHA I & II	35/60	58.3	3/7	42.9	
NYHA III & IV	25/60	41.7	4/7	57.1	
Heart rate /minute – no. (%)					0.321†
<100	29/60	48.4	2/7	28.6	
>100	31/60	51.6	5/7	71.4	
Systolic blood pressure /mmHg – no., median (IQR)	60/60	112.5 (100-125)	7/7	113(105-123)	0.758*
Diastolic blood pressure /mmHg – no., median (IQR)	60/60	70 (63.5-80)	7/7	80 (76-83)	0.134*

HIV status – no. (%)					0.229[†]
Positive	37/56	66.1	3/7	42.9	
Negative	19/56	33.9	4/7	57.1	
CD4 count cells/μL – no. (%)					0.711[‡]
>350	4/31	12.9	0/3	0.0	
200-350	8/31	25.8	0/3	0.0	
50-200	14/31	45.2	2/3	66.7	
0-50	5/31	16.1	1/3	33.3	
Creatinine/μmolL^{-1} – no., median (IQR)	57/60	85 (67-97)	7/7	105 (78-132)	0.282[*]
White cell count cells x 10^9/L – no., mean (SD)	60/60	6.7(3.1)	7/7	6.6(1.1)	0.545[*]
Haemoglobin g/dL – no., mean (SD)	60/60	10.4(2.3)	7/7	11.5(2.9)	0.110[*]
Diagnosis of tuberculous pericarditis – no. (%)					0.517[†]
Definite	11/60	18.3	2/7	28.6	
Probable	49/60	81.7	5/7	71.4	
Left ventricular ejection fraction – no. (%)					1.000[‡]
<35%	1/37	2.7	0/4	0.0	
35-45%	2/37	5.4	0/4	0.0	
45-50%	34/37	91.9	4/4	100.0	

Constrictive pericarditis – no. (%)					0.357†
Yes	23/47	48.9	1/4	25.0	
No	24/47	51.1	3/4	75.0	
Pericardial effusion – no. (%)					0.473‡
Small effusion (<1cm)	2/57	3.5	0/7	0.0	
Moderate effusion (1-2cm)	11/57	19.3	0/7	0.0	
Large effusion (>2cm)	44/57	77.2	7	100.0	
Cardiac Tamponade – no. (%)					0.595†
Yes	18/38	47.4	3/5	60.0	
No	20/38	52.6	2/5	40.0	

*Two-sample t test.

†Pearson chi square test.

‡Fisher's exact test.

Supplementary table S2. Baseline characteristics by analysed and excluded status

Characteristics	**Participants**				**P value**
	Analyzed participants		**Excluded participants**		
Age in years – no., mean (SD)	1160	38.8 (13.4)	240	38.0 (13.4)	0.792*
Sex – no. (%)					0.103†
Male	661/1160	57.0	123/240	51.3	
Female	499/1160	43.0	117/240	48.7	
Functional class – no. (%)					0.212†
NYHA I & II	797/1160	68.7	153/240	64.6	
NYHA III & IV	363/1160	31.3	84/240	35.4	
Heart rate /minute – no. (%)					0.071†
<100	491/1160	42.4	117/240	48.8	
>100	667/1160	57.6	123/240	51.2	
Systolic blood pressure /mmHg – no., median (IQR)	1159/1160	110 (102-120)	240/240	110 (102-120)	0.037‡

Diastolic blood pressure /mmHg – no., median (IQR)	1159/1160	72 (66-80)	240/240	70 (62-80)	0.004[‡]
HIV status – no. (%)					0.875[†]
Positive	781/1138	68.6	158/232	68.1	
Negative	357/1138	31.4	74/232	31.9	
CD4 count– no. (%)					0.998[§]
>350 cells/μL	83/610	13.6	14/105	13.3	
200-350 cells/μL	141/610	23.1	24/105	22.9	
50-200 cells/μL	288/610	47.2	51/105	48.6	
0-50 cells/μL	98/610	16.1	16/105	15.2	
Creatinine/μmolL^{-1} – no., median (IQR)	1068/1160	75 (60-92)	206/240	72 (59-87)	0.133[‡]
White cell count cells x 10^9/L – no., mean (SD)	1158	6.4 (2.7)	238	6.5 (2.8)	0.287[*]
Haemoglobin g/dL – no., mean (SD)	1156	10.0 (2.3)	237	9.8 (2.4)	0.852[*]
Diagnosis of TBP – no. (%)					0.002[†]
Definite TBP	214	18.6	24	10.1	

Probable TBP	935	81.4	213	89.9	
Left ventricular EF – no. (%)					0.850[§]
<35%	15	2.1	2	1.3	
35-45%	33	4.7	8	5.0	
45-50%	657	93.2	149	93.7	
Constrictive pericarditis					<0.0001[†]
Yes – no. (%)	400	48.5	41	23.3	
No – no. (%)	424	51.5	135	76.7	
Pericardial effusion – no. (%)					<0.0001[§]
Small effusion (<1cm)	86	7.6	20	8.7	
Moderate effusion (1-2cm)	252	22.3	79	34.2	
Large effusion (>2cm)	790	70.0	132	57.1	

Cardiac Tamponade					0.006[†]
Yes – no. (%)	472	58.9	84	47.5	
No – no. (%)	330	41.2	93	52.5	

[*]Two-sample t test.

[†]Pearson's chi-squared test.

[‡]Two-sample Wilcoxon rank sum test.

[§]Fisher's exact test.

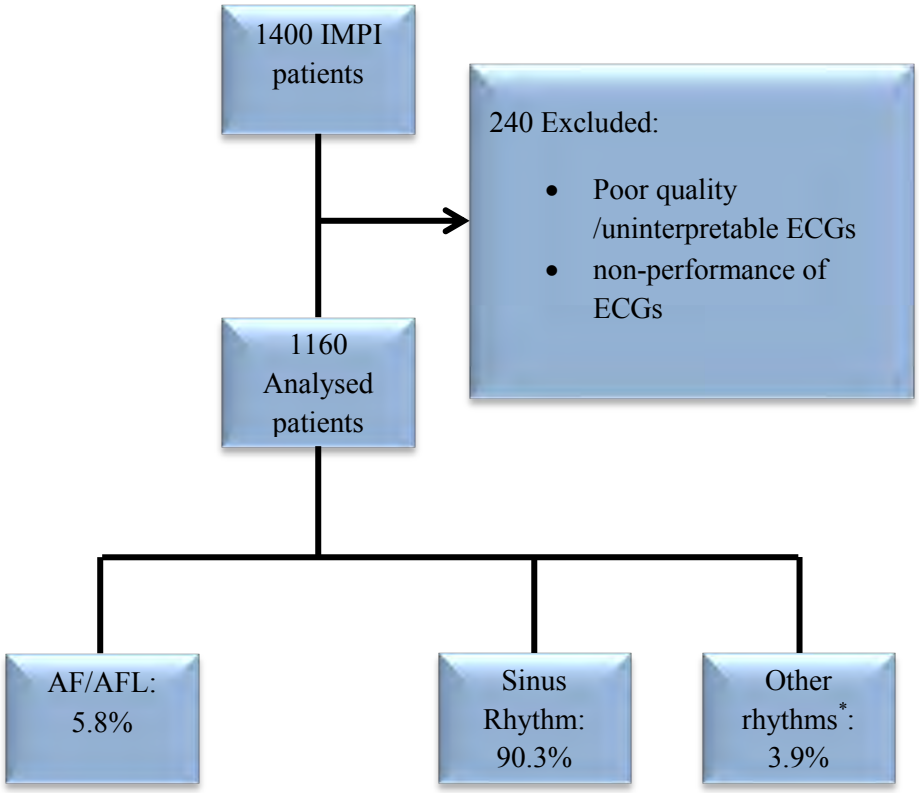
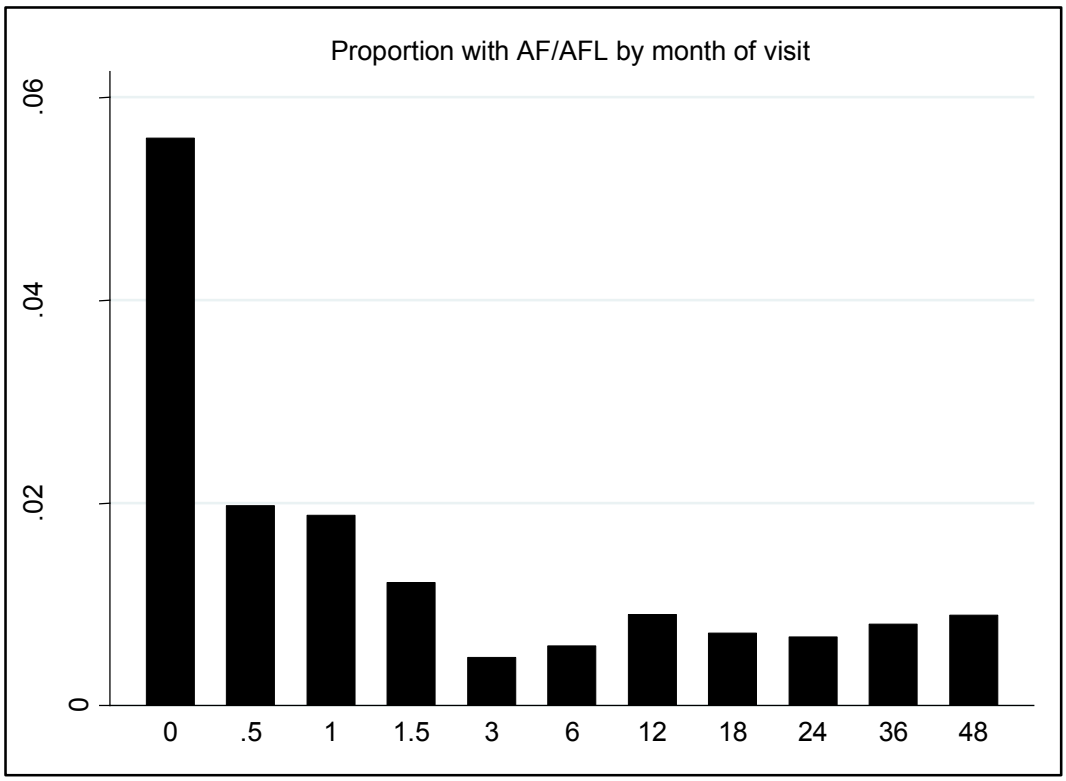

1400 IMPI patients
240 Excluded:
Poor quality /uninterpretable ECGs
non-performance of ECGs
1160 Analysed patients
AF/AFL: 5.8%
Sinus Rhythm: 90.3%
Other rhythms*: 3.9%

Figure 1


Proportion with AF/AFL by month of visit
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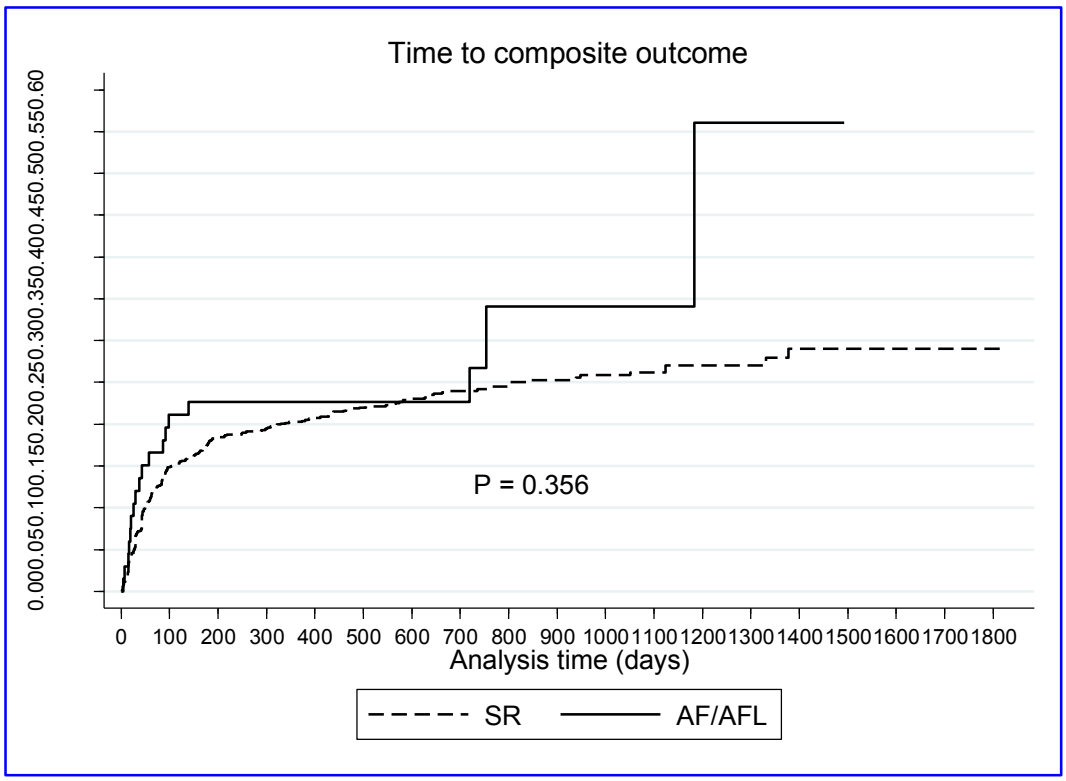
.04
.02
0
0
.5
1
1.5
3
6
12
18
24
36
48

Figure 2


Time to composite outcome
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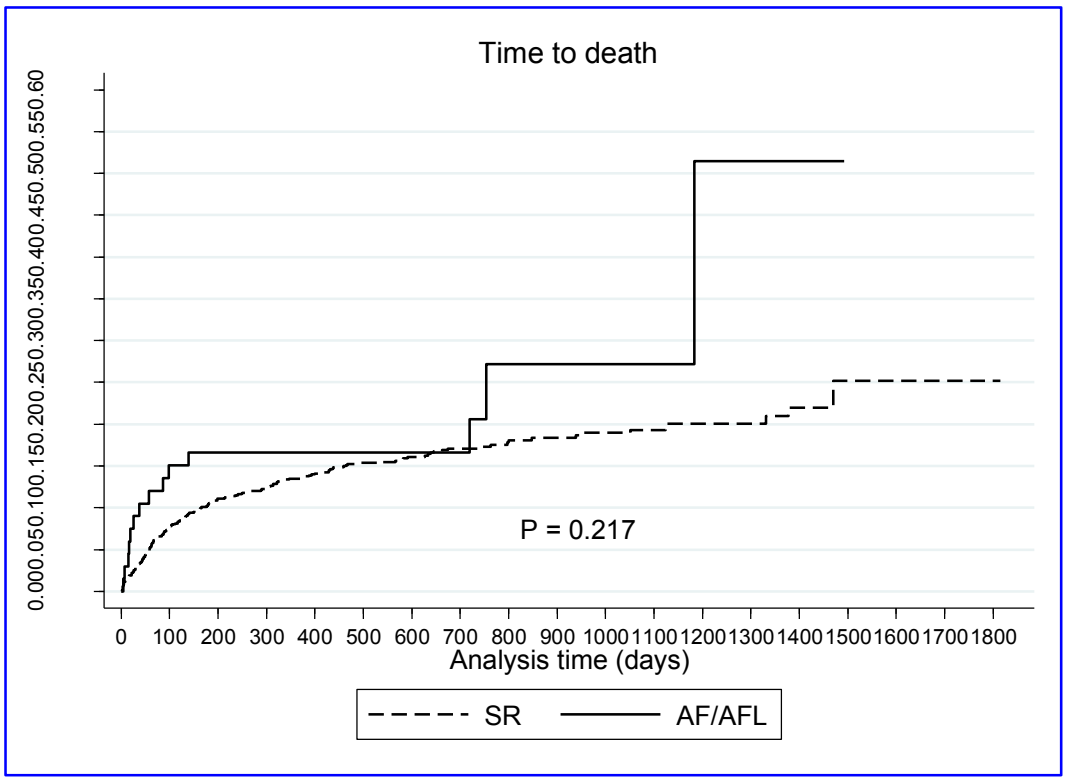
Analysis time (days)
SR
AF/AFL

Figure 3


Time to death
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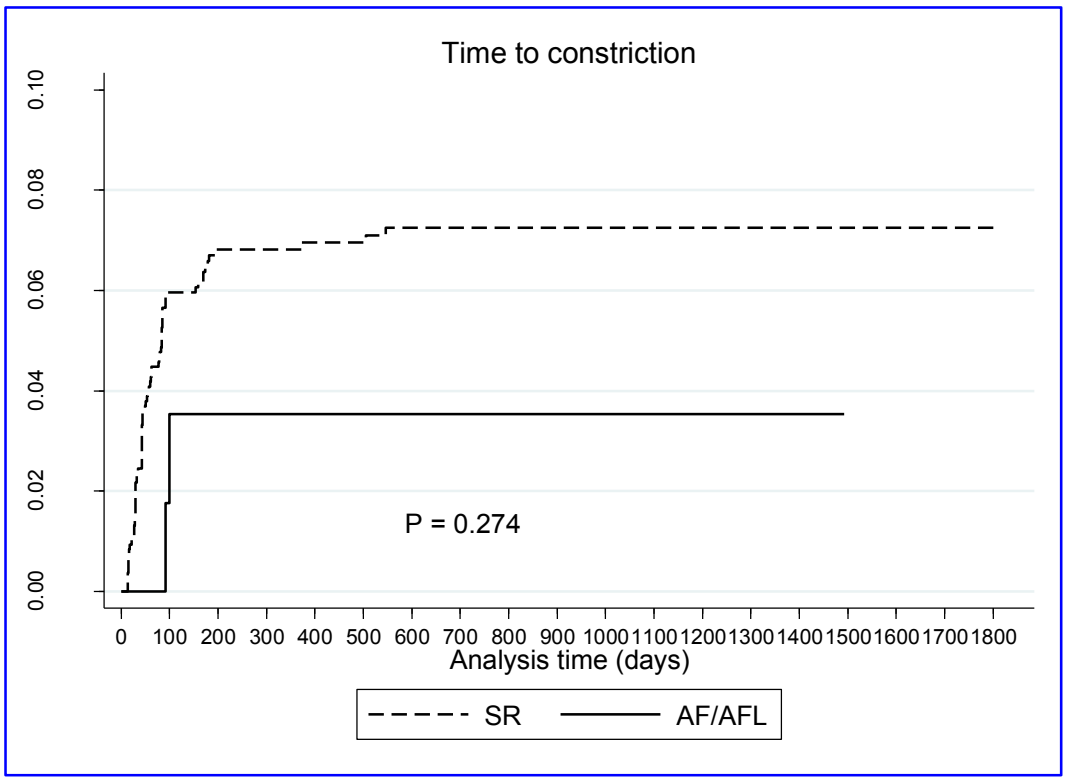
Analysis time (days)
SR
AF/AFL

Figure 4


Time to constriction
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0.02
0.04
0.06
0.08
0.10
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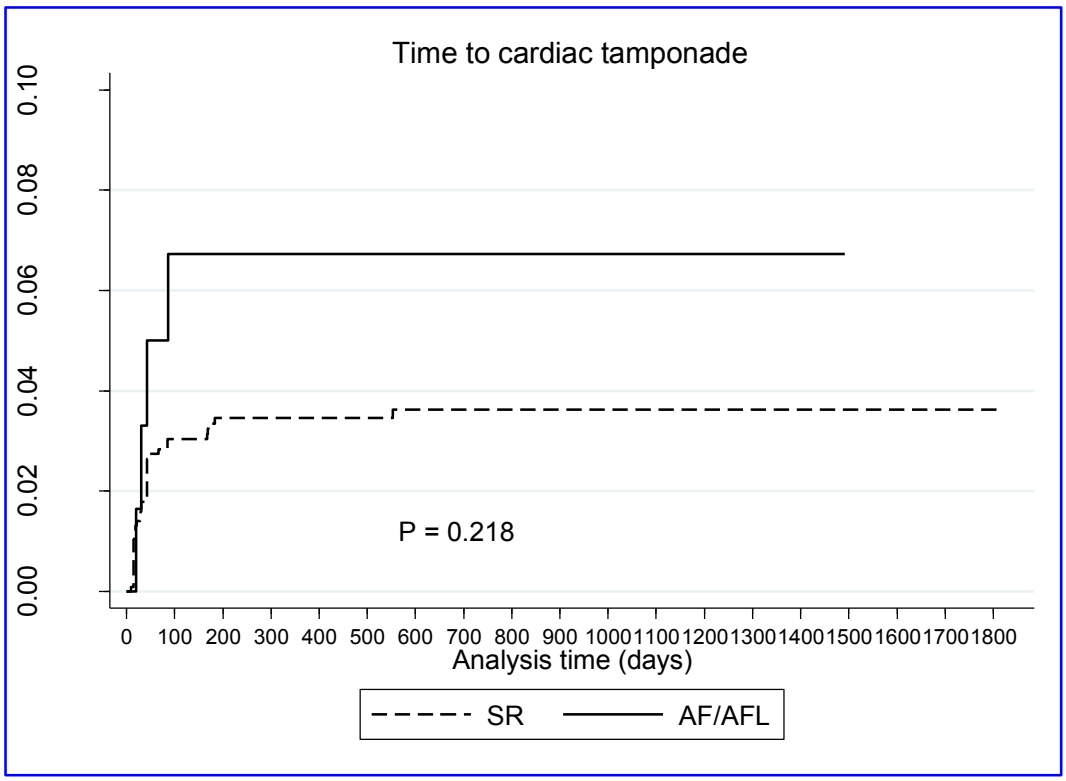
Analysis time (days)
SR
AF/AFL

Figure 5


Time to cardiac tamponade
0.00
0.02
0.04
0.06
0.08
0.10
P = 0.218
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Analysis time (days)
SR
AF/AFL

Figure 6