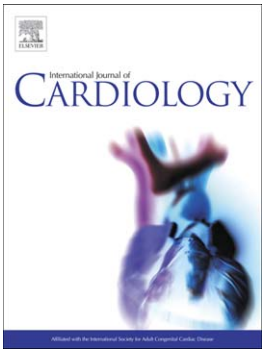
Accepted Manuscript



Predictors of significant coronary artery disease in atrial fibrillation: Are cardiac troponins a useful measure

Alaa Alghamry, Joseph Hanna, Anita Pelecanos, Stephen Kyranis, Vinod Khelgi, Peter O'Rourke, Oran Carroll, Cassie Oxenford, Swetha Rangaswamaiah, Christopher Tan

PII: S0167-5273(16)31974-X
DOI: doi: 10.1016/j.ijcard.2016.08.267
Reference: IJCA 23538

To appear in: *International Journal of Cardiology*

Received date: 22 March 2016
Accepted date: 16 August 2016

Please cite this article as: Alghamry Alaa, Hanna Joseph, Pelecanos Anita, Kyranis Stephen, Khelgi Vinod, O'Rourke Peter, Carroll Oran, Oxenford Cassie, Rangaswamaiah Swetha, Tan Christopher, Predictors of significant coronary artery disease in atrial fibrillation: Are cardiac troponins a useful measure, *International Journal of Cardiology* (2016), doi: 10.1016/j.ijcard.2016.08.267

Title page

Article Title: Predictors of significant coronary artery disease in atrial fibrillation: are cardiac troponins a useful measure.

Article Type: Original article.

Corresponding author: Dr. Alaa Alghamry.

Address: Department of Medicine, Redcliffe Hospital, Anzac Ave, Redcliffe QLD 4020, Australia.

E-mail address: alaa.alghamry@health.qld.gov.au.

Telephone: +61731394000

Keywords: Atrial fibrillation, Troponin, Acute Coronary Syndrome, Coronary Artery Disease.

Word count: 4324 words.

Authors order: Alaa Alghamry [1,3], Joseph Hanna [1,2], Anita Pelecanos [4], Stephen Kyranis [2], Vinod Khelgi [3], Peter O'Rourke [4], Oran Carroll [3], Cassie Oxenford [3], Swetha Rangaswamaiah [3], Christopher Tan [3].

[1]University of Queensland, Australia.

[2]Department of Cardiology, The Prince Charles Hospital, Brisbane, Australia.

[3]Department of Medicine, Redcliffe Hospital, Redcliffe, Australia.

[4]QIMR Berghofer Medical Research Institute, Brisbane, Australia.

Abstract

Background: Cardiac Troponin I (cTnI) is frequently measured in patients presenting with symptomatic Atrial Fibrillation (AF). The significance of elevated cTnI levels in this patient cohort is unclear. We investigated the value of cTnI elevation in this setting and whether it is predictive for significant Coronary Artery Disease (sCAD).

Methods: We conducted a retrospective, single-center, case-control study of 231 patients who presented with symptomatic AF to The Prince Charles Hospital emergency department, Brisbane, Australia between 2006 and 2014. Patients who underwent serial cTnI testing and assessment for CAD were included. Clinical variables that are known to predict CAD and could potentially predict cTnI elevation were collected. Binary logistic regression was performed to identify predictors of sCAD and cTnI elevation.

Results: Cardiac Troponin I elevation above standard cut off was not predictive for sCAD after adjustment for other predictors (OR 1.62, 95% CI 0.79 – 3.32. p= 0.19). However, the highest cTnI concentration value (cTnI peak) was predictive for sCAD (OR 2.02, 95% CI 1.02 -3.97, p=0.04).

Dyspnea on presentation (OR 4.52, 95% CI 1.87 – 10.91, p=0.001), known coronary artery disease (OR 3.44, 95% CI 1.42 – 8.32, p=0.006), and ST depression on the initial electrocardiogram (OR 2.57, 95% CI 1.11 – 5.97,

p=0.028) predicted sCAD in our cohort, while heart rate on initial presentation was inversely correlated with sCAD (OR 0.99, 95% CI 0.971 – 1.00, p=0.034).

Conclusion: Troponin elevation is common in patients presenting to hospital with acute symptomatic AF and it is not a reliable indicator for underlying sCAD in this patient cohort. However, cTnI peak was a predictor of significant coronary artery disease.

1-Introduction

AF is the most common cardiac arrhythmia requiring hospital care with a prevalence that rises with age. It has an estimated prevalence of approximately 4% among patients 60 years or older and approximately 9% among patients 80 years or older [1]. AF is frequently associated with cardiovascular diseases such as hypertension (HTN), valvular and congenital heart disease, cardiomyopathies and coronary artery disease [1-3].

Patients with AF can present with symptoms suggestive of myocardial ischemia such as chest pain and dyspnea. Their electrocardiogram (ECG) often demonstrates ST depression in association with rapid ventricular rate, which has been termed a stress test equivalent [4, 5]. Hence, it is not surprising that looking for CAD or ruling out an Acute Coronary Syndrome (ACS) is a significant part of the clinical burden of managing this patient cohort [5, 6].

Cardiac troponins, including cTnI, are the most sensitive and specific biomarkers of myocardial injury, whereby troponin elevation is part of the universal definition of myocardial infarction [7, 8]. Cardiac troponins can be elevated in a wide variety of clinical settings including AF, even in the absence of sCAD [9-14]. This has been attributed to myocardial oxygen supply and demand mismatch (Type two myocardial infarction) [15]. However, troponin elevation in these settings translates into poorer prognosis and increased mortality [16-19].

Although major society guidelines do not include troponin measurement as a part of the diagnostic workup for AF, approximately 86% of patients presenting with AF will have their cardiac biomarkers tested with approximately 4% of patients with elevated troponin diagnosed with ACS [20-22]. The challenge for physicians treating patients presenting with symptomatic AF and an elevated troponin concentration is to astutely judge which patient should be aggressively investigated and treated for ACS caused by significant CAD.

The aim of this study is to determine the reliability of cardiac troponin elevation in diagnosing significant coronary artery stenosis in patients presenting with symptomatic atrial fibrillation. We also aim to investigate other possible predictors of sCAD and cardiac troponin elevation in these patients.

2- Methods

2.1. Patients Selection

We conducted a retrospective case-control study of patients who presented to the emergency department of The Prince Charles Hospital, Brisbane, Australia between January 2006 and January 2014 with a primary diagnosis of AF. This hospital is a 630-bed quaternary, university-affiliated teaching center.

Patients were included if they were ≥ 18 years of age, presented with cardiac symptoms (chest pain, dyspnea or palpitations), had serial cardiac troponin measurements taken, with an admission twelve-lead ECG result showing AF. Patients required an invasive or non-invasive coronary artery assessment during or within six months of the index hospital admission to be included.

We excluded patients with ST-Elevation Myocardial Infarction (STEMI), AF due to concomitant predisposing illness or asymptomatic AF. Patients with prior cardiac surgery including coronary bypass surgery, underlying complex congenital heart disease, or valvular AF were also excluded.

The sample was identified using the coding system utilized for hospital reimbursement. During the study period, 3548 patients presented with AF. Of these, 2627 did not satisfy the inclusion criteria on review of the patient's imaging results, laboratory data and discharge summaries. After medical charts review, a further 690 patients were excluded due to the absence of cardiac symptoms, and/or no coronary artery testing on or within six months from the index hospital admission. Subsequently, 231 were included in the

final study set. Of these 231 patients, 107 had cTnI elevation, and 124 had negative cTnI on serial measurements (Fig. 1).

2.2. Data collection:

Data was collected through a careful review of patient records using a standardized data collection template. We recorded patient demographics, their presenting symptoms, risk factors for CAD and the CHADS2 stroke risk model scores. Heart rate and degree of ST segment depression were measured from a 12 lead ECG. Left ventricular ejection fraction (EF) and presence of valvular AF were determined from echocardiography results. Laboratory data including two serial troponin measurements on admission and within six to nine hours from the initial measurement were collected. We examined the results of coronary angiography or non-invasive cardiac imaging to determine the presence of sCAD.

2.3. Definitions:

Significant CAD was defined as one or more of the following coronary artery stenosis:

1- ≥ 70% diameter
2- 50% to 70% diameter stenosis with Fractional Flow Reserve (FFR) confirmed hemodynamic significance
3- 50% to 70% Left Main Coronary Artery (LMCA) disease confirmed by Intravascular Ultrasound (IVUS) to be significant.

This definition is in keeping with The American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions for percutaneous coronary intervention (ACCF/AHA/SCAI) 2011 guidelines [23]. Non-invasive coronary artery disease test results were interpreted by a cardiologist or a radiologist specialised in cardiac imaging. Any reported positive test with a high probability of CAD was followed by gold standard invasive coronary angiography .

AF was classified into the categories of first diagnosed AF, paroxysmal AF, persistent AF, long-standing persistent AF and permanent AF. These categories are in accordance with the 2014 American College of Cardiology /American Heart Association/ Heart Rhythm Society (AHA/ACC/HRS) task force on practice guidelines, and the 2010 European Society of Cardiology (ESC) Guidelines [24, 25].

Known CAD was defined as prior angiography showing non-significant disease or previous percutaneous coronary intervention. ST-segment depression was defined as ≥1.0-mm horizontal or downsloping depression 0.08 second after the J-point on a 12-lead electrocardiogram[10]

2.4. Troponin assay:

cTnI testing was performed on Beckman Coulter AccuTnI analyzers (Beckman Coulter, Brea, CA, USA) with 99th percentile cut-off value of 0.040 µg/L.

2.5. Statistical analysis:

Descriptive statistics were reported as mean (standard deviation (SD)), median (interquartile range (IQR)) or frequency (percent). Univariable analyses were performed to assess the relationship between potential predictors against sCAD and cTnI elevation. Chi-square tests were used for categorical predictors (Fisher's exact test was used when the assumptions of the chi-square test were not met) and one-way ANOVAs for parametric continuous variables (Mann-Whitney U test was used in place of ANOVA for non-parametric data). Those with a p-value less than 0.15 were considered for modeling via binary logistic regression. Backwards elimination was used to obtain the final model.

ROC curve analyses were performed, and Youden Indices calculated to determine a suitable cut-off point of cTnI peak to predict sCAD. Youden Index was defined as the sensitivity + specificity – 1. This ROC analysis was repeated stratified by model covariates. Data analyses were performed using IBM SPSS Statistics for Windows (2013, IBM Corp., Armonk, NY., USA).

3-Results

The mean age was 66.1 (SD 12.7) years with 49.4% being females (114). The mean BMI of the participants was 30.6 (SD 6.6) kg/m^2. 100 patients underwent Invasive coronary angiography (43%) of patients, including 46 with

negative cTnI and 54 with elevated cTnI. CT Coronary Angiography (CTCA), myocardial perfusion scan, exercise stress test, stress echocardiography were used in 15%, 39%, 7% and 4% of patients respectively.

One hundred and twenty-four patients (54%) had negative cTnI, and 107 (46%) had elevated cTnI. A total of 42 patients had sCAD requiring revascularization (18.2%), of which 24 patients had elevated cTnI (57%) and 18 had negative cTnI (43%). In patients with elevated cTnI, the mean cTnI peak was 1.14 (range 0.041 – 47), compared to 0.02 (range 0.01 - 0.04) in the cTnI negative group. Troponin I elevation above the 99th percentile cut-off value used to diagnose ACS had a sensitivity of 57% and specificity of 56% for detection of sCAD.

3.1. Modeling troponin elevation

The relationships between troponin elevation and possible predictors are detailed in Table 1.

An initial model was run incorporating age, BMI, heart rate, gender, DM, CHADS2, dyslipidemia and ST depression to predict cTnI elevation. We had concerns given CHADS2 score is a composite measure, which includes diabetes mellitus and age along with other stroke risk measures. Therefore, the collinearity between these variables was investigated, but showed no concerns. We also carefully considered that these factors were one of five measures used in the CHADS2 composite score and were still important to

specify their individual effects in modeling cTnI elevation given that their effects may be diluted by the other CHADS2 measures. After removal of predictors that did not contribute to the model, the following final model resulted (Table 2).

Heart rate and ST depression were significant predictors of cTnI elevation. The model shows that for every unit increase in heart rate, the odds of positive cTnI (>0.04) were 1.02 (95% CI: 1.01 – 1.03). Those with ST depression had 2.24 increased odds of having a positive cTnI measurement compared to those who did not.

3.2. Modeling sCAD

Similarly, patient characteristics and clinical variables against the outcome of sCAD were explored (Table 3).

Two initial models were set up; one with cTnI elevation as the main predictor of interest (model 1) and another with cTnI peak as the main predictor of interest (model 2). Each of these models were initially set up with heart rate, EF, creatinine, TSH, gender, CCF, known CAD, ST depression, dyspnea, palpitation and type of AF as predictors of sCAD outcome. The final adjusted model resulted after removal of non-significant covariates. Table 4 outlines the associations between troponin measures before and after final adjustment for other significant predictors.

Troponin elevation above the 99th percentile cut-off did not predict significant coronary artery disease in patients presenting with atrial fibrillation (OR 1.62, 95% CI 0.79 – 3.32. p= 0.19). However, the highest cTnI concentration measured (cTnI peak) was a strong predictor of sCAD, after adjustment for heart rate, known CAD, ST depression, and dyspnea (adjusted OR 2.02, 95% CI 1.02 -3.97, p=0.04).

Other clinical predictors of sCAD apart from cTnI peak (model 2) included dyspnea (OR 4.52, 95% CI 1.87 – 10.91, p=0.001); ST depression on the electrocardiogram (OR 2.57, 95% CI 1.11 – 5.97, p=0.028) and known history of coronary artery disease (OR 3.44, 95% CI 1.42 – 8.32, p=0.006). Rapid heart rate was inversely correlated with subsequent finding of sCAD (OR 0.99, 95% CI 0.97 – 1.00, p=0.034).

3.3. Youden Index for cut-off point for cTnI peak as a predictor of CAD

To determine if a suitable threshold level of cTnI peak could be used to classify sCAD, ROC curve analysis for classification of sCAD from cTnI peak was performed (Fig. 2).

Although statistically significant (p=0.001), the area under the curve value of 0.67 (95% CI 0.58 – 0.76) indicates that cTnI peak as a diagnostic test is inadequate in discriminating between those with sCAD and those without sCAD and no sensible cut-off point for cTnI peak was able to be determined. The Youden index was 0.25 with a corresponding cTnI peak cut-off of 0.1.

This analysis was also performed stratified by the covariates of known CAD, ST depression and dyspnea but did not yield a large improvement in area under the curve.

4- Discussion

When a patient presents to the hospital with symptomatic AF, ST depression on the ECG or a troponin elevation, the treating clinician needs to decide on how aggressively to investigate for underlying CAD. Recognizing patients with significant underlying CAD can improve outcomes with appropriate medical therapy or revascularisation [26, 27]. Accurately excluding those without significant CAD would also mitigate the increased bleeding risk associated with the unnecessary use of antiplatelet therapy added to the standard anticoagulation therapy for stroke prevention in AF. Additionally, a subset of patients who would benefit from class 1C antiarrhythmic therapy would need exclusion of sCAD prior to commencing such therapy for AF [28, 29].

The reported prevalence of sCAD in patients with AF varies widely from 22% to 49% due to heterogeneous patient cohorts and variable diagnostic criteria for defining sCAD [4, 30-36]. It was slightly lower in our patient cohort (18.2%) perhaps due to strict selection of patients presenting primarily with symptomatic AF and applying the ACCF/AHA/SCAI guideline definitions for significant coronary disease. Although CAD and AF share common risk factors including age, hypertension, obesity, and Diabetes Mellitus [37], our

analysis showed that these risk factors did not predict sCAD in patients presenting with symptomatic AF.

There is now increasing awareness that troponin elevation in patients presenting with symptomatic AF may not need to be managed as an acute coronary syndrome. Our data showed that cTnI elevation above the 99th percentile cut value used to diagnose ACS did not predict sCAD with a sensitivity of 57% and specificity of 56%. Nonetheless, the peak troponin value was a strong predictor of sCAD. Higher troponin concentrations are more specific to myocardial infarction due to significant CAD with higher troponin values representing larger infarct size [15]. In this study, all patients with a cTnI value exceeding 2.1 µg/L had CAD requiring revascularization. However, the study was not able to define a reliable cut-off to accurately diagnose sCAD. The addition of a relative or absolute change in cTnI concentration between serial readings might improve the diagnostic accuracy in this setting [38].

ST segment depression has been thought of as a “positive stress test equivalent” in patients presenting with AF and rapid ventricular response. As a result, the value of ST segment depression in diagnosing sCAD has been explored in multiple studies, but the results are conflicting [4, 33, 36]. In our patient cohort, ST depression was a significant covariate in the prediction of sCAD, which supports the theory that ST depression in those patients reflects sub-endocardial ischemia. Interestingly, the presenting complaint of dyspnea was found to have a strong relationship with the presence of CAD in

symptomatic AF patients. The mechanism of dyspnea in AF is poorly understood and it has been attributed to low cardiac output as a consequence of impaired diastolic left ventricular filling and increased left-sided intra-cardiac pressure due to diastolic dysfunction[39, 40]. However, hemodynamic studies in AF have previously shown normal or even low intra-cardiac pressures[41]. The exact mechanism of dyspnea in these patients requires future dedicated hemodynamic study.

In contrast to a previous study, where heart rate, left ventricular function, the presence of angina pectoris, serum creatinine and hemoglobin were associated with troponin rise in atrial fibrillation patients [14], heart rate on presentation, CHADS2 score, and presence of ST depression on admission ECG were the significant predictors in our study. In the setting of AF with fast ventricular response, cTnI elevation and ST depression may be due to oxygen demand-supply mismatch caused by the increased metabolic requirements of the fast beating ventricles coupled with impaired subendocardial blood flow due to the shortening of diastole[12].

Our study has several strengths. Namely, this is one of very few studies that looked at predictors of severe coronary disease in AF patients using cardiac biomarkers. We excluded patients with prior cardiac surgery, complex congenital heart disease and AF due to acute reversible causes. Unlike other studies of similar nature, we did not exclude patients with a diagnosis of ACS and a serial troponin measurement was an essential inclusion criterion [14, 26, 27].

This was a retrospective case-control study that carries all the inherent limitation of retrospective research. We depended on a hospital record coding system to identify our patient cohort, and we only included patients who had been investigated for coronary artery disease either by invasive coronary angiography or non-invasive cardiac testing. This design may have led to selection and information biases. However, we endeavored to obtain good quality data through the use of well-defined end points (e.g. cTnI measurement, ST depression and cardiac catheterization results) that are less subject to bias. Our sample size (n=231) is similar to previously reported studies on this subject[14]. Still, our sample size was still inadequate to identify a precise cTnI peak cut-off value that could accurately predict significant underlying CAD.

Invasive coronary angiography was performed in only 43% of patients whilst non-invasive modalities including functional tests and CTCA were used in most of our patients. All forms of non-invasive cardiac testing for significant CAD in patients with AF are plagued by a lower specificity [4, 42]. However the impact of potential false positive non-invasive test results was minimal in our study, as only 2 patients with positive non-invasive testing did not proceed to coronary angiography. Due to the retrospective nature of this study, we were also unable to control for the types of cardiac testing used in the groups with and without cTnI elevation.

A prospective study where all patients presenting with symptomatic AF subsequently undergo coronary angiography would give a clearer answer as

to whether patient risk factors, symptoms, troponin measurement or ST depression on ECG are accurate predictors for significant CAD in this cohort. This type of study may be difficult to perform ethically because many patients would undergo invasive angiography unnecessarily. Perhaps research needs to move beyond the assessment of sensitivity, specificity and accuracy of a given test to predict significant CAD in this patient group. Studies are needed to investigate whether looking for CAD in patients with AF affects hard cardiovascular outcomes.

5- Conclusion:

Troponin elevation *per se* is common in patients presenting to hospital with symptomatic AF and it is not a reliable indicator for underlying significant CAD. However, higher cTnI concentration on serial measurements is strongly associated with underlying significant coronary artery disease. Dyspnea, previous history of coronary disease, lower heart rate, and ST segment depression were additional predictors of significant CAD. These findings may help guide the decision on how aggressively to investigate for CAD in this group of patients.

Acknowledgments

We thank Dr Joel Dulhunty for his assistance on the statistical analysis before and after data collection.

References

1. Furberg, C.D., et al., *Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study).* Am J Cardiol, 1994. **74**(3): p. 236-41.
2. Kannel, W.B., et al., *Coronary heart disease and atrial fibrillation: the Framingham Study.* Am Heart J, 1983. **106**(2): p. 389-96.
3. Liberthson, R.R., et al., *Atrial tachyarrhythmias in acute myocardial infarction.* Am J Med, 1976. **60**(7): p. 956-60.
4. Androulakis, A., et al., *Transient ST-segment depression during paroxysms of atrial fibrillation in otherwise normal individuals: relation with underlying coronary artery disease.* J Am Coll Cardiol, 2007. **50**(19): p. 1909-11.
5. Zimetbaum, P.J., et al., *Incidence and predictors of myocardial infarction among patients with atrial fibrillation.* J Am Coll Cardiol, 2000. **36**(4): p. 1223-7.
6. Friedman, H.Z., et al., *Cardiac care unit admission criteria for suspected acute myocardial infarction in new-onset atrial fibrillation.* Am J Cardiol, 1987. **59**(8): p. 866-9.
7. Adams, J.E., 3rd, et al., *Cardiac troponin I. A marker with high specificity for cardiac injury.* Circulation, 1993. **88**(1): p. 101-6.
8. Thygesen, K., et al., *Third universal definition of myocardial infarction.* Circulation, 2012. **126**(16): p. 2020-35.
9. Bakshi, T.K., et al., *Causes of elevated troponin I with a normal coronary angiogram.* Intern Med J, 2002. **32**(11): p. 520-5.
10. Nunes, J.P., J.C. Silva, and M.J. Maciel, *Troponin I in atrial fibrillation with no coronary atherosclerosis.* Acta Cardiol, 2004. **59**(3): p. 345-6.
11. Kanjwal, K., et al., *Troponin elevation in patients with various tachycardias and normal epicardial coronaries.* Indian Pacing Electrophysiol J, 2008. **8**(3): p. 172-4.
12. Bukkapatnam, R.N., et al., *Relationship of myocardial ischemia and injury to coronary artery disease in patients with supraventricular tachycardia.* Am J Cardiol, 2010. **106**(3): p. 374-7.
13. Korff, S., H.A. Katus, and E. Giannitsis, *Differential diagnosis of elevated troponins.* Heart, 2006. **92**(7): p. 987-93.
14. Parwani, A.S., et al., *Atrial fibrillation-induced cardiac troponin I release.* Int J Cardiol, 2013. **168**(3): p. 2734-7.
15. Agewall, S., et al., *Troponin elevation in coronary vs. non-coronary disease.* Eur Heart J, 2011. **32**(4): p. 404-11.
16. Hijazi, Z., et al., *Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy.* Circulation, 2012. **125**(13): p. 1605-16.
17. van den Bos, E.J., et al., *Minor elevations in troponin I are associated with mortality and adverse cardiac events in patients with atrial fibrillation.* Eur Heart J, 2011. **32**(5): p. 611-7.
18. Conti, A., et al., *Abnormal troponin level as short-term predictor of poor outcome in acute atrial fibrillation.* Am J Emerg Med, 2013. **31**(4): p. 699-704.

19. Gupta, K., et al., *Clinical utility and prognostic significance of measuring troponin I levels in patients presenting to the emergency room with atrial fibrillation.* Clin Cardiol, 2014. **37**(6): p. 343-9.
20. Meshkat, N., et al., *Troponin utilization in patients presenting with atrial fibrillation/flutter to the emergency department: retrospective chart review.* Int J Emerg Med, 2011. **4**(1): p. 25.
21. Camm, A.J., et al., *Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).* Eur Heart J, 2010. **31**(19): p. 2369-429.
22. Fuster, V., et al., *2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society.* J Am Coll Cardiol, 2011. **57**(11): p. e101-98.
23. Levine, G.N., et al., *2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions.* Circulation, 2011. **124**(23): p. e574-651.
24. January, C.T., et al., *2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society.* J Am Coll Cardiol, 2014. **64**(21): p. e1-76.
25. European Heart Rhythm, A., et al., *Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).* Eur Heart J, 2010. **31**(19): p. 2369-429.
26. Conti, A., et al., *Hypertension and atrial fibrillation: prognostic aspects of troponin elevations in clinical practice.* Crit Pathw Cardiol, 2014. **13**(4): p. 141-6.
27. Conti, A., et al., *Coronary atherosclerosis and adverse outcomes in patients with recent-onset atrial fibrillation and troponin rise.* Am J Emerg Med, 2015. **33**(10): p. 1407-13.
28. Van Gelder, I.C., et al., *Efficacy and safety of flecainide acetate in the maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation or atrial flutter.* Am J Cardiol, 1989. **64**(19): p. 1317-21.
29. Lafuente-Lafuente, C., et al., *Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation.* Cochrane Database Syst Rev, 2007(4): p. Cd005049.
30. *Baseline characteristics of patients with atrial fibrillation: the AFFIRM Study.* Am Heart J, 2002. **143**(6): p. 991-1001.
31. Hohnloser, S.H., et al., *Effect of dronedarone on cardiovascular events in atrial fibrillation.* N Engl J Med, 2009. **360**(7): p. 668-78.
32. Kralev, S., et al., *Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography.* PLoS One, 2011. **6**(9): p. e24964.

33. Pradhan, R., A. Chaudhary, and A.A. Donato, *Predictive accuracy of ST depression during rapid atrial fibrillation on the presence of obstructive coronary artery disease.* Am J Emerg Med, 2012. **30**(7): p. 1042-7.
34. Weijs, B., et al., *Patients originally diagnosed with idiopathic atrial fibrillation more often suffer from insidious coronary artery disease compared to healthy sinus rhythm controls.* Heart Rhythm, 2012. **9**(12): p. 1923-9.
35. Nucifora, G., et al., *Prevalence of coronary artery disease assessed by multislice computed tomography coronary angiography in patients with paroxysmal or persistent atrial fibrillation.* Circ Cardiovasc Imaging, 2009. **2**(2): p. 100-6.
36. Tsigkas, G., et al., *Diagnostic accuracy of electrocardiographic ST-segment depression in patients with rapid atrial fibrillation for the prediction of coronary artery disease.* Can J Cardiol, 2014. **30**(8): p. 920-4.
37. Benjamin, E.J., et al., *Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study.* Jama, 1994. **271**(11): p. 840-4.
38. Liebetrau, C., et al., *Identification of acute myocardial infarction in patients with atrial fibrillation and chest pain with a contemporary sensitive troponin I assay.* BMC Med, 2015. **13**: p. 169.
39. Skinner, N.S., Jr., et al., *HEMODYNAMIC CONSEQUENCES OF ATRIAL FIBRILLATION AT CONSTANT VENTRICULAR RATES.* Am J Med, 1964. **36**: p. 342-50.
40. Lau, C.P., et al., *Haemodynamics of induced atrial fibrillation: a comparative assessment with sinus rhythm, atrial and ventricular pacing.* Eur Heart J, 1990. **11**(3): p. 219-24.
41. Alboni, P., et al., *Hemodynamics of idiopathic paroxysmal atrial fibrillation.* Pacing Clin Electrophysiol, 1995. **18**(5 Pt 1): p. 980-5.
42. Smit, M.D., et al., *Myocardial perfusion imaging does not adequately assess the risk of coronary artery disease in patients with atrial fibrillation.* Europace, 2010. **12**(5): p. 643-8.

Figures

Figure 1: Flow chart for final cohort
Figure 2. ROC curve for cTnI peak for prediction of sCAD

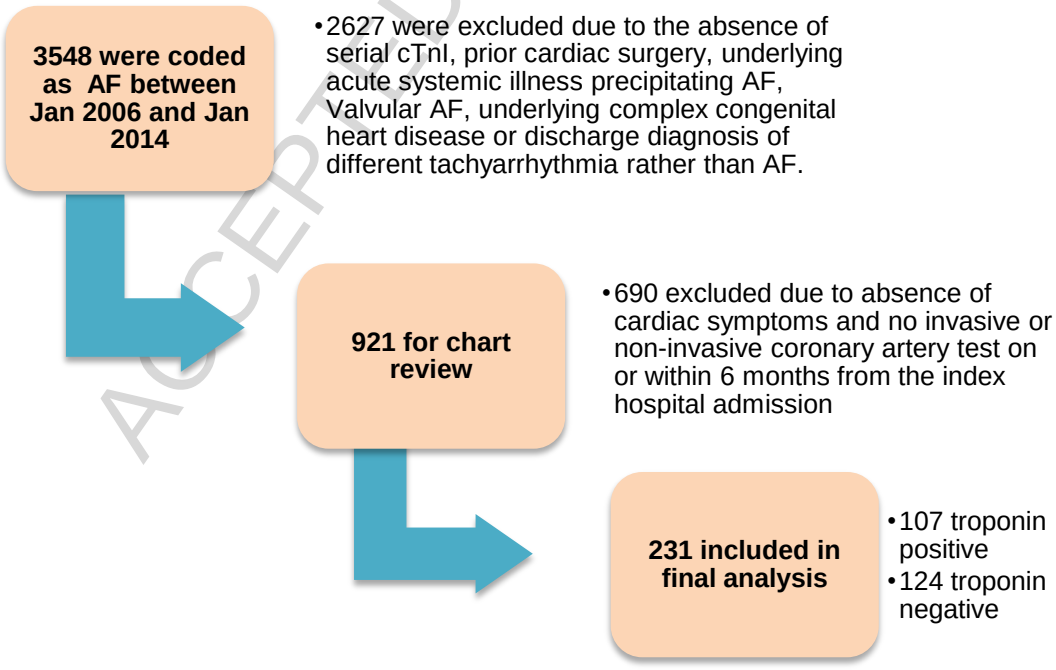


Figure 1: Flow chart for final cohort

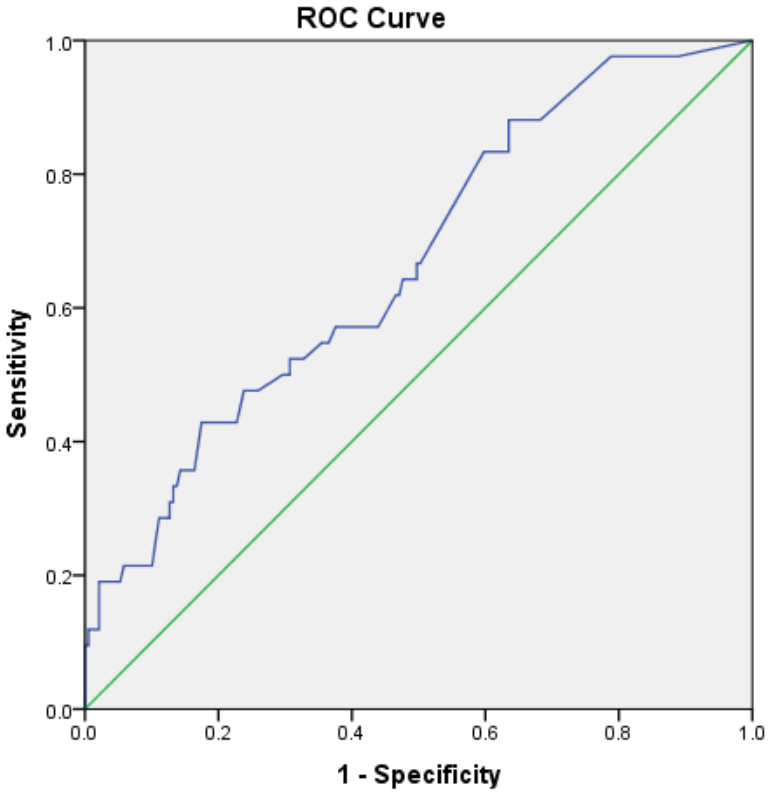


Figure 2. ROC curve for cTnI peak for prediction of sCAD

Tables

Table 1. Relationship of patient characteristics and clinical variables against cTnI elevation

Variable	**Categories**	**cTnI negative (n=124)**	**cTnI positive (n=107)**	**p-value**
Gender	Female	55 (48.2%)	59 (51.8%)	0.10
	Male	69 (59.0%)	48 (41.0%)	
Congestive Cardiac Failure (CCF)	No	107 (55.4%)	86 (44.6%)	0.23
	Yes	17 (44.7%)	21 (55.3%)	
Hypertension (HTN)	No	48 (59.3%)	33 (40.7%)	0.21
	Yes	76 (50.7%)	74 (49.3%)	
Diabetes mellitus (DM)	No	95 (50.3%)	94 (49.7%)	0.027
	Yes	29 (69.0%)	13 (31.0%)	
Cerebrovascular accident/ transient ischaemic attack (CVA/TIA)	No	118 (54.9%)	97 (45.1%)	0.18
	Yes	6 (37.5%)	10 (62.5%)	
CHADS2 (stroke risk score)	0 - 1	80 (58.8%)	56 (41.2%)	0.11
	2	28 (43.1%)	37 (56.9%)	
	3+	16 (53.3%)	14 (46.7%)	
Dyslipidaemia	No	71 (60.2%)	47 (39.8%)	0.043

	Yes	53 (46.9%)	60 (53.1%)	
Known CAD	No	107 (55.2%)	87 (44.8%)	0.30
	Yes	17 (45.9%)	20 (54.1%)	
Smoking	No	63 (51.6%)	59 (48.4%)	0.51
	Yes	61 (56.0%)	48 (44.0%)	
ST Depression	No	103 (60.6%)	67 (39.4%)	<0.001
	Yes	21 (34.4%)	40 (65.6%)	
Dyspnea	Negative	104 (54.7%)	86 (45.3%)	0.49
	Positive	20 (48.8%)	21 (51.2%)	
Palpitation	Negative	78 (55.3%)	63 (44.7%)	0.53
	Positive	46 (51.1%)	44 (48.9%)	
Chest pain	Negative	66 (50.4%)	65 (49.6%)	0.25
	Positive	58 (58.0%)	42 (42.0%)	
Atrial fibrillation (AF)	New AF	57 (52.3%)	52 (47.7%)	0.52
	PAF	48 (52.2%)	44 (47.8%)	
	Persistent, long standing persistent, permanent AF	19 (63.3%)	11 (36.7%)	
Age		63.8 (12.4)	68.7 (12.6)	0.004
Body Mass Index (BMI)		31.3 (6.7)	29.7 (6.4)	0.078
Heart Rate		119.4 (30.4)	133.4 (25.4)	<0.001
Ejection Fraction % (EF)		59.2 (11.9)	57.7 (14.4)	0.39
Haemoglobin (Hb)		142.9 (16.2)	141.5 (16.1)	0.52

Creatinine		83.8 (21.3)	87.7 (27.5)	0.23
Thyroid stimulating hormone (TSH)		1.9 (1.5)	2.5 (5.4)	0.29

* EF, Creatinine and TSH checked using Mann-Whitney U test which yielded similar results with p=0.77, p=0.43, and p=0.66 respectively.

Table 2. Binary logistic regression model for cTnI elevation

	OR (95% CI)	**p-value**
Heart rate	1.02 (1.01 – 1.03)	0.002
Diabetes Mellitus	0.32 (0.14 – 0.73)	0.007
CHADS2 **2** **3+**	 2.20 (1.10 – 4.38) 2.44 (0.97 – 6.13)	0.038
ST depression	2.24 (1.17 – 4.29)	0.015

Table 3. Relationship of patient characteristics and clinical variables against sCAD

Variable	Categories	No significant CAD (n=189)	Significant CAD (n=42)	p-value
Gender	Female	99 (86.8%)	15 (13.2%)	0.051
	Male	90 (76.9%)	27 (23.1%)	
CCF	No	162 (83.9%)	31 (16.1%)	0.06
	Yes	27 (71.1%)	11 (28.9%)	
HTN	No	68 (84.0%)	13 (16.0%)	0.54
	Yes	121 (80.7%)	29 (19.3%)	
DM	No	156 (82.5%)	33 (17.5%)	0.55
	Yes	33 (78.6%)	9 (21.4%)	
CVA/TIA	No	175 (81.4%)	40 (18.6%)	0.74
	Yes	14 (87.5%)	2 (12.5%)	
CHADS2 score	0 - 1	113 (83.1%)	23 (16.9%)	0.19
	2	55 (84.6%)	10 (15.4%)	
	3+	21 (70.0%)	9 (30.0%)	
Dyslipidaemia	No	95 (80.5%)	23 (19.5%)	0.60

	Yes	94 (83.2%)	19 (16.8%)	
Known CAD	No	166 (85.6%)	28 (14.4%)	0.001
	Yes	23 (62.2%)	14 (37.8%)	
Smoking	No	101 (82.8%)	21 (17.2%)	0.69
	Yes	88 (80.7%)	21 (19.3%)	
ST Depression	No	143 (84.1%)	27 (15.9%)	0.13
	Yes	46 (75.4%)	15 (24.6%)	
Dyspnea	No	161 (84.7%)	29 (15.3%)	0.013
	Yes	28 (68.3%)	13 (31.7%)	
Palpitation	No	107 (75.9%)	34 (24.1%)	0.003
	Yes	82 (91.1%)	8 (8.9%)	
Chest pain	No	110 (84.0%)	21 (16.0%)	0.33
	Yes	79 (79.0%)	21 (21.0%)	
AF	New AF	83 (76.1%)	26 (23.9%)	0.057
	PAF	82 (89.1%)	10 (10.9%)	
	Persistent, long standing persistent, permanent AF	24 (80.0%)	6 (20.0%)	

Age		65.7 (13.1)	67.5 (10.5)	0.43
BMI		30.8 (6.8)	29.6 (5.8)	0.33
Heart Rate		127.3 (29.3)	119.6 (27.1)	0.12
Ejection Function % (EF)		59.8 (12.2)	52.7 (15.5)	0.001
Haemoglobin (Hb)		142.0 (15.9)	143.6 (17.3)	0.57
Creatinine		83.4 (22.6)	95.4 (29.4)	0.004
TSH		1.9 (1.4)	3.5 (8.4)	0.013

*EF, creatinine and TSH checked using Mann-Whitney U test which yielded similar results with p=0.006, p=0.006, and p=0.061 respectively.

Table 4. Models of sCAD from troponin

*Model 1 adjusted for EF, known CAD and palpitations. Model 2 adjusted for heart rate, known CAD, ST depression, and dyspnea.

	Unadjusted		**Adjusted***	
	OR (95% CI)	p-value	OR (95% CI)	p-value
(Model 1) **cTnI > 0.04**	1.70 (0.87 – 3.35)	0.12	1.62 (0.79 – 3.23)	0.19
(Model 2) **cTnI peak**	2.01 (1.10 – 3.69)	0.024	2.02 (1.02 – 3.97)	0.042