ATRIAL FIBRILLATION OCCURRING TRANSIENTLY WITH STRESS

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By WILLIAM FINLAY MCINTYRE, BSc MD FRCPC

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AUTHOR: William F McIntyre, BSc (Mount Allison University), MD (Queen's University)

SUPERVISOR: Richard P. Whitlock

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ABSTRACT

Atrial fibrillation (AF) is frequently detected in the setting of an acute physiologic stressor, such as medical illness or surgery. It is uncertain if AF detected in these settings (AFOTS: AF occurring transiently with stress) is secondary to a reversible trigger or is simply paroxysmal AF. This distinction is critical for clinicians and patients, as they must decide if AFOTS can be dismissed as a reversible phenomenon, or if it justifies the need for chronic therapy; in particular, anticoagulation to reduce the risk of disabling stroke. The uncertainty in the management of AFOTS is exacerbated by a poor understanding of its epidemiology. How frequently does AFOTS occur? Are there higher risk groups? What is the natural history of this condition? Across 8 chapters, this thesis systematically assesses previously published literature on this topic, focusing on patients who have an acute medical illness or have undergone noncardiac surgery, and addresses knowledge gaps therein.

Chapter 1 is an introduction that outlines the justification of each of the studies in the thesis.

Chapter 2 is a narrative review that defines AFOTS conceptually and outlines research priorities.

Chapter 3 is a systematic review that explores the incidence and recurrence of AFOTS associated with acute medical illness.

Chapter 4 is a systematic review and meta-analysis that explores the incidence and recurrence of AFOTS associated with acute noncardiac surgery.

Chapter 5 examines the profiles of pacemaker-detected "subclinical" AF occurring

before and after a hospitalization for medical illness or noncardiac surgery

Chapter 6 reports the design, rationale and final results of a prospective study that

aimed to provide a precise and accurate estimate of the incidence of AFOTS in critically

ill patients.

Chapter 7 reports the design and rationale of a matched prospective cohort study

designed to estimate the rate of recurrence of AF following hospitalization with AFOTS

and to compare it to similar patients who did not have AFOTS.

Finally, **Chapter 8** outlines the conclusions, discusses the limitations, and presents the

implications of the research in this PhD thesis.

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I dedicate this thesis to the memory of my grandfather, Armin Rach. He always wanted a "doctor" in the family. I hope I have made you proud, Opa.

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CONTRIBUTIONS BY OTHERS

A full account of authors' contributions appears at the end of each chapter.

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List of Abbreviations

ACEi
Angiotensin Converting Enzyme Inhibitor

AF
Atrial Fibrillation

AFOTS
Atrial Fibrillation Occurring Transiently with Stress

APACHE II
Acute Physiologic Assessment and Chronic Health Evaluation II

ARB
Angiotensin Receptor Blocker

ASPIRE-AF
Anticoagulation for Stroke Prevention In Patients With Recent Episodes of Perioperative Atrial Fibrillation After Noncardiac Surgery

ASSERT
Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial

AV
Atrioventricular

BMI
Body Mass Index

BPM
Beats Per Minute

CANet
Cardiac Arrhythmia Network of Canada

CCS
Canadian Cardiovascular Society

$CHADS_2$-
Congestive heart failure, Hypertension, Age $\geq$ 75, Diabetes, and Stroke/TIA (2 points)

CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age >= 75, Diabetes, Stroke/TIA (2 points), Vascular Disease, Female Sex Category

CI
Confidence Interval

CIHR
Canadian Institutes of Health Research

C-SPIN
Canadian Stroke Prevention Intervention Network
ECG
Electrocardiogram

HR
Hazard Ratio

ICU
Intensive Care Unit

IQR
Interquartile Range

LV
Left Ventricular

OR
Odds Ratio

PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SA
Sinoatrial

SD
Standard Deviation

SE
Standard Error

Chapter 1

Introduction

1.1 Background

Atrial fibrillation (AF), the most common serious heart rhythm disorder, is associated with a 4–5-fold increase in the risk of a disabling ischemic stroke, a doubling in the risk of death, an increase in the risk of heart failure and an impaired quality of life.[1,2] Fortunately, there are several evidence-based therapies that have been shown to improve both quality and quantity of life for patients with AF.[3-5] The most notable of these therapies is oral anticoagulation (OAC), which reduces the risk of stroke by about two-thirds and the risk of death by about a quarter.[5] However, for many patients, AF is often detected for the first time in the setting of a transient physiologic stressor such as surgery or acute medical illness (AFOTS; AF Occurring Transiently with Stress). In this setting, the significance of AF is unclear. One possibility is that AF could be considered to have been "caused" by the acute stressor and pending its resolution, any risk associated with AF would disappear. On the other hand, AFOTS could be the first presentation of paroxysmal AF – meaning that patients with AFOTS are at long-term risk of adverse outcomes but also have a high likelihood of benefitting from established therapies. Realistically, among the many patients who experience AFOTS, there are likely to be patients of each kind. Despite long-standing and wide-spread use of terms like "secondary AF", "AF with a presumed temporary cause", "peri-operative AF" and "provoked AF", little progress has been made in

identifying therapeutic options for this population.[6-8] The lack of guidance in managing this population may stem from a poor understanding of the epidemiology and natural history of this condition.[9,10]

1.2 Pathophysiologic and clinical questions in AFOTS

Challenges in managing AFOTS may stem from its complex pathophysiology. Acute factors (*e.g.* inflammation, adrenergy, sympathetic drive, ischemia, metabolic disturbances, volume shifts) and chronic factors (*e.g.* valvular disease, atrial myopathy, hypertension) are both thought to contribute to arrhythmogenesis.[11-23] However, the relative importance of these two types of factors is unclear and may vary between patients, making it difficult to predict the likelihood that AF will recur, and by extension the effect of AFOTS on the long-term prognosis for stroke, heart failure and death.

There are two possible phenotypes of AFOTS patients: i) those in whom AFOTS is directly due to the acute factors and ii) those in whom AFOTS is a first presentation of chronic AF (*i.e.* paroxysmal, persistent or permanent). Accordingly, some studies that have assessed the relationship between AFOTS and long-term outcomes have found increased risk in patients with AFOTS, whereas others have not.[24-30] Distinguishing the phenotype of any given patient with AFOTS is imperative. Patients who have a chronic form of AF (*i.e.* paroxysmal, persistent, permanent) would be expected to benefit from evidence

based-therapies including rate and rhythm control, management of co-morbidities and thromboprophylaxis.[4] In contrast, patients in whom AFOTS has been proven to be reversible may not require any specific follow-up or therapy.

Chapter 2 defines AFOTS and reviews the state of knowledge at the time of beginning the research work in this thesis.

1.3 Incidence and recurrence of AFOTS associated with acute medical illness

In the short-term, AFOTS has been associated with increased hospital length-of-stay, morbidity and death.[26,31,32] However, there is more uncertainty regarding the long-term prognosis of such patients. Where AFOTS is by definition transient, its incidence may be affected by different approaches used for electrocardiographic (ECG) monitoring. Before embarking on prospective studies, we sought to summarize and appraise existing literature.

In **Chapter 3**, we present the results of a systematic review and meta-analysis that aimed to answer two important questions with respect to AFOTS occurring in patients with acute medical illness: i) *How frequently does AFOTS occur?* and ii) *How likely is AF to recur over the long-term in patients who had AFOTS during an earlier hospitalization?* Additionally, we systematically assessed the potential contribution of different approaches to ECG monitoring on the variability of estimates to existing studies.

1.4 Incidence and recurrence of AFOTS associated with noncardiac surgery

AFOTS occurs not only in the setting of acute medical illness, but also around the time of noncardiac surgery. This population is likely to be different from the medical illness population, owing to differences in baseline risk of populations and the acute physiologic stressors associated with different noncardiac surgical procedures. Although published systematic reviews have assessed AFOTS in noncardiac surgery, they have important limitations in that they have focused on specific types of surgeries and have not systematically assess study methodology.[33,34]

For **Chapter 4**, we performed a systematic review and meta-analysis that aimed to answer the same questions as the acute medical review in Chapter 3, but this time focused on any and all noncardiac surgeries.

1.5 Profiling AFOTS using continuous ECG monitoring from pacemakers

Existing studies have assessed both the incidence of AFOTS and the long-term recurrence of AF after AFOTS using variable methods. These include 12-lead ECGs, diagnostic codes in administrative databases, in-patient telemetry and outpatient ambulatory ECG monitoring. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) provides a unique opportunity to assess the temporal patterns of AF associated with physiologic stress in an unbiased fashion.[35] This trial followed more than 2500 patients without a history of AF and with an implanted pacemaker, allowing for full-disclosure of heart rhythm over a

mean follow-up of approximately 2.5 years. [36-39] ASSERT captured data on the timing and nature of hospitalizations in study subjects.

In **Chapter 5**, we compared the incidence of pacemaker-detected AF around the time of hospitalization for acute medical illness or non-cardiac surgery to the remainder of the follow-up period and assessed the association of pacemaker detected AF around the time of hospitalization with the occurrence of prior episodes of pacemaker-detected AF.

1.6 Estimating the incidence of AFOTS in the ICU

Our systematic reviews identified wide ranges of estimates of the incidence of AFOTS in the intensive care unit (ICU) setting, ranging from 1% to 44% in patients hospitalized for medical illness, and from 1% to 35% for non-cardiac surgery.[40] We identified study design as a potentially impactful contributor to this observed variability; studies that employed continuous monitoring reported the highest incidences of AFOTS.[41]

In two separate manuscripts, **Chapter 6** describes the rationale and methodology of a prospective study that aimed to generate a reliable estimate of the true incidence of AFOTS in ICU patients and the primary results of this study.

1.7 Recurrence of AF after AFOTS

Ultimately, patients and clinicians want to know whether patients with AFOTS should be treated using evidence-based therapies that have been shown

to be effective for other patients with AF. Some prior studies that have assessed the relationship between AFOTS and long-term outcomes (stroke, heart failure, death) have found increased risk in patients with AFOTS, whereas others have not.[24-30] For patients who have had AFOTS, documentation of an episode of AF after the resolution of the initial physiologic stress makes it more likely that the initial presentation of AFOTS was actually paroxysmal AF. Our systematic reviews found a small number of studies that had assessed recurrence rates of AF following AFOTS: recurrence rates were often upwards of 50% within a few years of the index event. [40] However, continuous ECG monitoring was rarely used to produce these estimates.

Chapter 7 outlines the design and rationale of an ongoing cohort study that is using continuous ECG monitoring to compare rates of AF detected after hospitalization between patients with AFOTS and matched controls who have never had AF.[42]

1.8 Conclusions and future directions

In **Chapter 8**, we examine the limitations of the work in this thesis, enumerate conclusions generated from the work in this thesis, and outline future research plans and priorities in this field.

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Chapter 2

Atrial Fibrillation Occurring Transiently with Stress

William F. McIntyre, Stuart J. Connolly, Jeff S. Healey

Population Health Research Institute and McMaster University,
Hamilton, Ontario, Canada

STRUCTURED ABSTRACT

Purpose of review

Atrial fibrillation (AF) may be detected in the setting of an acute stressor, such as medical illness or surgery. It is uncertain if AF detected in these settings (AFOTS: AF Occurring Transiently with Stress) is secondary to a reversible trigger or is simply paroxysmal AF. This distinction is critical for clinicians, who must decide if AFOTS can be dismissed as a reversible phenomenon, or if it signals the need for chronic therapy; in particular, anticoagulation.

Recent findings

Published studies report incidences of AFOTS ranging from 1-44 % in patients with acute medical illness and 1-35% following non-cardiac surgery. The highest estimates have been reported in critically ill patients and in those undergoing continuous monitoring. A small number of studies have reported the recurrence of AF after AFOTS to be 55%-68% within five years of medical illness and 37% within one year after non-cardiac surgery. These studies are limited by retrospective design and low-sensitivity ascertainment.

Summary

AFOTS commonly occurs in patients with acute medical illness or in the post-operative state, and AF recurs in over 50% of individuals. Prospective post-discharge studies using sensitive AF detection strategies are needed to define

the relationship between AFOTS and clinical AF.

Key Points (4)

- AFOTS is detected in 1-44% of patients during acute medical illness and 1-35% of patients following non-cardiac surgery. Higher incidences of AFOTS are reported in studies that use prospective, continuous monitoring.

- There is uncertainty in the optimal post-discharge management of patients with AFOTS.

- Retrospective studies with low-sensitivity detection methods have shown that more than 50% of patients with AFOTS have recurrent AF detected within 5 years.

- Prospective studies that employ systematic long-term monitoring may yield higher recurrence rates of AF after AFOTS.

Introduction

Atrial fibrillation (AF) is the most common serious heart rhythm disorder and is associated with a 4-5-fold increase in the risk of ischemic stroke.[1,2,43,44] In higher-risk patients with AF, oral anticoagulation (OAC) therapy reduces the risk of stroke by approximately two-thirds and the risk of all-cause mortality by approximately one-quarter.[5] However, OAC therapy is associated with an increased risk of bleeding and this risk must be weighed against the benefits of thromboprophylaxis.[5,45]

AF is often first detected while the patient is being treated for an acute medical illness or after surgery. In these settings, AF is oftentimes transient and frequently asymptomatic and detection often occurs during prolonged periods of continuous ECG monitoring in an intensive care unit (ICU) or on a telemetry ward. When AF is detected in this manner, patients frequently do not receive OAC; rates of OAC prescription were only 24 and 36% in two recent series.[24,46] This rate of OAC use is substantially lower than the rate among stable outpatients with AF, where OAC usage ranges from 44 to 80%.[47-52] Post-operative bleeding and abnormal liver or kidney function may in part explain the lower rate of OAC use for AFOTS. Alternatively, clinicians may perceive AFOTS as temporary and not likely to recur - since provoked by an acute and reversible stressor - and question its long-term significance.[7,13,24,46,49,52-55]

Atrial Fibrillation Occurring Transiently with Stress (AFOTS) describes the manifestation of AF in the acute care setting as the only evidence of AF, for which there is uncertainty regarding its appropriate management (**Figure 1**).[9]

It is possible that AFOTS is directly and uniquely due to a reversible precipitant and is thus unlikely to recur after this precipitant is removed, thereby having minimal impact on the patient's long-term prognosis. Alternatively, AFOTS might be the first detection of a chronic condition that is already present but undiagnosed - facilitated by inpatient continuous ECG monitoring. In this case, it would be expected that AF would recur and that the AFOTS would be associated with an increased risk of stroke.[56] The management of patients with AFOTS is not directly addressed in current AF guidelines.[6-8] However, the most recent guidelines from the United States (American College of Cardiology/American Heart Association/Heart Rhythm Society) call for more data to guide the long-term management of patients who experience AFOTS.[7]

In this article, we review the current state of knowledge on the incidence of AFOTS and the risk of recurrence of AF. We focus our discussion on patients who experience AFOTS in the context of acute non-cardiovascular illness and after non-cardiac surgery. We do not discuss primary cardiovascular conditions (*e.g.* myocardial infarction, heart failure) or cardiac surgery. These are believed to be separate entities with differing prognoses, based on published observational data, and based on their different mechanism of AF genesis, due to direct atrial infarction and/or inflammation of the myocardium and pericardium.[7,29,57,58]

AFOTS During Acute Medical Illness

AFOTS may be detected during acute medical illness **(Table 1)**. The reported incidence of AFOTS in these patients appears to depend on the clinical setting and the methods of AF detection that were used. In a systematic review, we reported that incidence estimates ranged from 1 to 44%.[22,26,32,59-82] Sepsis is one of the most-studied conditions associated with AFOTS. This inflammatory syndrome invokes many of the stress factors believed to potentiate AF (*e.g.* inflammation, catecholamine excess, metabolic changes).[26,83,84] In patients with sepsis, the incidence of AFOTS has been reported to range from 5-44%, with higher estimates in patients with septic shock.[26,32,65-72] AFOTS is also frequently associated with acute pulmonary syndromes (*i.e.* pneumonia, exacerbation of chronic obstructive pulmonary disease and pulmonary embolism), where reported incidences range from 4-18%.[73-78] Patients who are critically ill and being cared for in an ICU tend to have a higher incidence of AFOTS, with 6 different series reporting an incidence of at least 20%.[31,32,65,70,85,86] A higher incidence of AFOTS could be explained by the notion that patients with more severe illness have more potential triggers (*e.g.* sympathetic drive, organ dysfunction, inflammation).[83,84] However, higher incidences in critically ill patients could also be explained by the fact that patients who are critically ill are more likely to be subject to continuous electrocardiographic monitoring (see Impact of Detection Strategies on Estimates of the Incidence of AFOTS).[82] Studies done in

an ICU setting using prospective, continuous monitoring have reported a weighted mean incidence of 24%.[31,65,72,85,86] In contrast, studies done in an ICU setting but without prospective, continuous monitoring have a reported a weighted mean incidence of only 12%.[32,62,70,87,88]

AFOTS After Non-Cardiac Surgery

AFOTS is also detected during recovery from non-cardiac surgery (**Table 1**). Incidence estimates have ranged from 1-35%, with higher rates in emergency, major and thoracic surgeries.[17,29,89-103] Gialdini and colleagues reported a retrospective, multi-centre analysis of over 1 million patients using administrative claims data. They reported that among all patients undergoing non-cardiac surgery, 1% had AFOTS detected during the peri-operative period.[29] Another large study using administrative claims data found that the rate of AFOTS among adults who underwent major non-cardiac surgery at 375 US hospitals was 1%.[97] As in medical illness, study design appears to influence incidence estimates. Studies that were done prospectively and focus on specific surgical populations have reported higher rates of AFOTS than these two studies based on administrative claims. In thoracic surgery, the reported incidence of AFOTS ranges from 10-35%.[89-93] Single-centre studies of colorectal surgery patients have reported the incidence of AFOTS to be 9 and 14%[99,100].   A large longitudinal prospective study of 4181 patients undergoing major, nonemergency surgery (defined by an expected length of stay $\geq$2 days) estimated the incidence

of AFOTS at 5%.[101] In this study, supraventricular arrhythmias, of which AFOTS

constituted 55%, occurred in 24% of thoracic surgeries, 16% of abdominal aortic

aneurysm repairs, 9% of abdominal/gastrointestinal surgeries, 8% of vascular

surgeries, 3% of orthopaedic surgeries and 3% of 'other' surgeries. Similar to

medical illness, patients who are critically ill following surgery might have even

higher incidences of AFOTS.

Potential Mechanisms of AFOTS

Where the pathophysiology of AF is complex, it could be theorized that the

mechanism of AFOTS likely involves an interaction between fixed and transient

arrhythmogenic factors (**Figure 2**).[12-23] However, the relative importance of these

two types of factors is unclear and may vary between patients, making it difficult

to predict the likelihood that AF will recur, and by extension the effect of AFOTS

on the long-term prognosis for stroke, heart failure and death.

Conceptually, arrhythmogenesis in AF involves the interplay between

structural abnormalities, electrophysiological changes, triggering factors and the

autonomic nervous system.[12-15,23] Chronic risk factors for AF include age, male

sex, Caucasian race, hypertension, diabetes mellitus, valve disease, left

ventricular dysfunction, obesity, sleep apnea, chronic kidney disease and alcohol

consumption.[14,16,104] These risk factors are present in many patients and

contribute to *atrial myopathy*, a term that has been used to describe the

arrhythmogenic and thrombogenic histologic changes that occur in the

atria.[23,105,106] Age and Caucasian race are both recognized major risk factors for clinical AF. [14,104,107,108] These two factors were also frequently associated with AFOTS in a recent systematic review.[82] Shared risk factors may suggest some overlap in these clinical entities.

In the setting of acute medical illness or surgery, multiple transient and potentially provoking factors come into play. Sympathetic activity leads to an increase in heart rate and catecholamine release. This can be further exacerbated by hypo- or hypervolemia, hypo- or hypertension, anemia, pain, electrolyte imbalances, metabolic alterations (*e.g.* acidosis or hyperglycemia), hypo- or hyperthermia, hypoxia and inflammation.[17-22,109] In AFOTS, resolution of the stressor tends to coincide with disappearance of AF.[9] What is not known is whether patients who manifest AFOTS have a propensity to go into AF again in the future. This uncertainty affects the view of whether or not a patient with AFOTS can be considered to have true, "clinical" AF and therefore the accompanying risks of stroke, mortality and heart failure and likewise the propensity to respond to established treatments for AF.

Impact of Detection Strategies on Estimates of the Incidence of AFOTS

Estimates of the incidence of AFOTS appear to be influenced by study designs.[82] Studies in which patients were continuously monitored tend to report higher incidences than those that do not. The incidence of AFOTS was >20% in 5

out of 8 studies employing prospective and continuous monitoring.[31,61,65,72,81,85-87] In contrast, the incidence of AFOTS was <10% in 14 of 18 studies that did not employ prospective and continuous monitoring.[26,32,60,62,66,67,70,74-78,88,110-114] Because AFOTS is, by definition, a transient and/or intermittent phenomenon, continuous, rather than intermittent monitoring, would be expected to be a more sensitive detection strategy. The highest incidence of AFOTS that has been reported in the literature comes from a prospective study in which 7-day Holter monitors were applied to patients admitted to the ICU.[65] The Holter monitors found that 44% of patients had at least one episode of AFOTS lasting at least 30 seconds. However, the patients' physicians recognized only two-thirds of cases. This study, in particular, illustrates how the incidence of AFOTS could differ based on the detection strategy that is employed.

Recurrence of Atrial Fibrillation After Discharge from Hospital

Data on the recurrence of AF after AFOTS are sparse and limited by retrospective methodology and insensitive, non-systematic screening methods **(Table 2)**.

Walkey and colleagues used administrative data to track long term outcomes in patients who developed AFOTS while hospitalized for sepsis.[115] The authors reported that 44% of patients with AFOTS experienced an episode of AF in the first year following hospitalization. This was significantly higher than the rate of AF among patients who did not have AFOTS during sepsis (7.7%,

p<0.001). The proportion of patients in whom a recurrence of AF was detected within 5 years of an episode of AFOTS during sepsis was 55%. Patients with AFOTS during sepsis had greater 5-year risks of ischemic stroke (5.3% vs. 4.7%, multivariable- adjusted hazard ratio (HR) 1.22, 95%CI 1.10-1.36, and mortality (74.8% vs. 72.1%, HR 1.04; 95%CI 1.01-1.07), as compared to patients who did not.

Investigators from The Framingham Heart Study studied long-term outcomes in patients who had AF diagnosed in the setting of a "secondary precipitant" (*i.e*. AFOTS). AFOTS precipitants included surgery (both cardiac and non-cardiac), acute myocardial infarction, acute infection, acute alcohol consumption, thyrotoxicosis, acute pericardial disease and acute pulmonary syndromes.[46] The authors reported that 42% of patients with AFOTS experienced an episode of AF in the five years following the initial episode. This was modestly lower than the rate of AF re-detection in patients whose first presentation of AF was not in the setting of AFOTS ((*i.e.* incident paroxysmal AF), *i.e.* 59%; multivariable-adjusted HR, 0.65 [95% CI 0.54–0.78]). However, in patients whose AFOTS "precipitant" was classified as infection, 'other' (acute alcohol consumption, thyrotoxicosis, acute pericardial disease, acute non-infectious pulmonary pathology) or non-cardiac surgery, the rates of AF recurrence at a median of 5.4 years of follow-up were 61% and 68% 64%, respectively. There was no evidence of differences between patients with AFOTS and patients with incident paroxysmal AF with respect to the risks of stroke (HR 1.13, 95%CI; 0.82-

1.57; P=0.45) or mortality (HR 1.00, 95%CI 0.87-1.1.5; P=0.95). There was a

modest decrease in the risk of heart failure among AFOTS patients (HR 0.74

[95% CI, 0.56–0.97]).

Gialdini and colleagues used administrative data to track long term

outcomes in patients who developed AFOTS while recovering from non-cardiac

surgery.[29] The authors reported that 37% of patients with AFOTS had AF

detected in the first year following surgery. This was significantly higher than the

proportion of patients who did not have AFOTS detected following surgery (1.5%,

P < 0.0001). Patients with AFOTS after surgery had greater 1-year risks of stroke

(1.47% vs. 0.36%, (multivariable adjusted HR for all stroke = 2.0, 95%CI 1.7-2.3;

HR for embolic stroke = 4.9, 95%CI 3.5-6.7) as compared to patients who did not.

In each of these three studies, a substantial proportion of patients had

recurrence of AF following AFOTS. Moreover, the rate of AF recurrence in

AFOTS patients was higher than in those who did not experience AFOTS and not

substantially different than in those who were identified as having incident

"clinical" AF. However, each of these studies has important limitations that impair

their sensitivity for ascertaining recurrent AF. Consequently, it is reasonable to

postulate that these studies have underestimated the rate of AF recurrence after

AFOTS. One important limitation is that these studies are retrospective in design

and consequently may be limited by recall or misclassification bias. Another

limitation is detection bias; patients with AFOTS and clinical AF were likely to

have been treated differently in terms of frequencies of follow-up appointments,

further testing and treatments. Additionally, these studies do not offer information on how AF was detected. The duration of any ambulatory monitoring used on patients would likely be low (*e.g.* 24 or 48 hour Holter monitors). These tools offer poor sensitivity compared to currently available methods (*i.e.* 14-day patch ECG monitors, implantable loop recorder), and would have produced lower estimates of recurrence than contemporary technology.[116,117] A final limitation is that none of the studies systematically followed patients for AF recurrence. Most of the diagnoses of recurrent AF would have been driven by symptoms, or "opportunistic" diagnoses made during health care encounters for other reasons. Consequently, these studies would be expected to have underestimated the recurrences of asymptomatic or minimally symptomatic AF. This is particularly relevant given that rates of AF detection are high in asymptomatic individuals and the presence of symptoms does not appear to have any bearing on AF detection with long-term monitoring[36,118,119]. Taken together, these limitations imply that where the specificity for the diagnosis of recurrent AF is likely high, the ability to rule out AF is much more limited. It is also important to consider that that because these studies did not employ a prospective and systematic strategy for monitoring for recurrent AF, we cannot draw conclusions from them about how to approach post-discharge rhythm monitoring in patients who manifest AFOTS.

Future Directions

Prospective studies with systematic and sensitive screening are required to better define the recurrence rate of AF after AFOTS. We speculate that if the recurrence of AF after AFOTS were investigated with a sensitive strategy, employing contemporary technology in a prospective and systematic fashion, the resultant rates of AF detection would be much higher than previously published, as has been seen in patients with cryptogenic stroke and in older adults with risk factors.[36,117,119,120] An ongoing AFOTS cohort study (NCT03221777) is using 14-day continuous ECG patch to monitor patients for AF recurrence. If this strategy documents a very high recurrence rate of AF following hospital discharge in patients who had experienced AFOTS, it might suggest that AFOTS is a first presentation of paroxysmal AF and that patients with AFOTS can be managed as if they had clinical AF. Otherwise, the results could inform a clinical trial of OAC or ongoing rhythm-monitoring strategies for patients with AFOTS.

Conclusions

In patients without a history of AF, AFOTS is frequently detected in the setting of acute medical illness or during recovery from non-cardiac surgery. The incidence of AFOTS varies widely and is higher when patients are critically ill and/or are undergoing prospective, continuous monitoring. The existing literature suggests that a recurrence of AF will be detected within 5 years in more than half of these patients, although the true rate of recurrence may in fact be much higher. In order to inform clinical management and further research, there is a

need for studies that clarify both the rate of AF recurrence following AFOTS and the risk of stroke associated with this entity.

Figures/Tables

Figure 1. Atrial Fibrillation Occurring Transiently with Stress (AFOTS)

> **Definition**
> *Atrial fibrillation that is detected in a patient who has no prior history of the arrhythmia and is hospitalized for treatment of an acute non-cardiovascular medical condition or for recovery from non-cardiac surgery. The definition also requires that the patient be discharged from hospital in sinus rhythm, either because of spontaneous reversion or because of active cardioversion by pharmacological or electrical means.*
>
> **Also known as**
> - *"Secondary" AF*   *- "Provoked" AF*
> - *AF "due to a 'reversible' cause"*   *- "New-onset peri-operative" AF*
>
> **Significance**
> *AFOTS may be a benign phenomenon that resolves when a precipitating condition is reversed. On the contrary, AFOTS could represent a first presentation of paroxysmal atrial fibrillation and consequent risk of stroke and other adverse events.*

Figure 2. *Conceptual model of Atrial Fibrillation Occurring Transiently with Stress (AFOTS)*
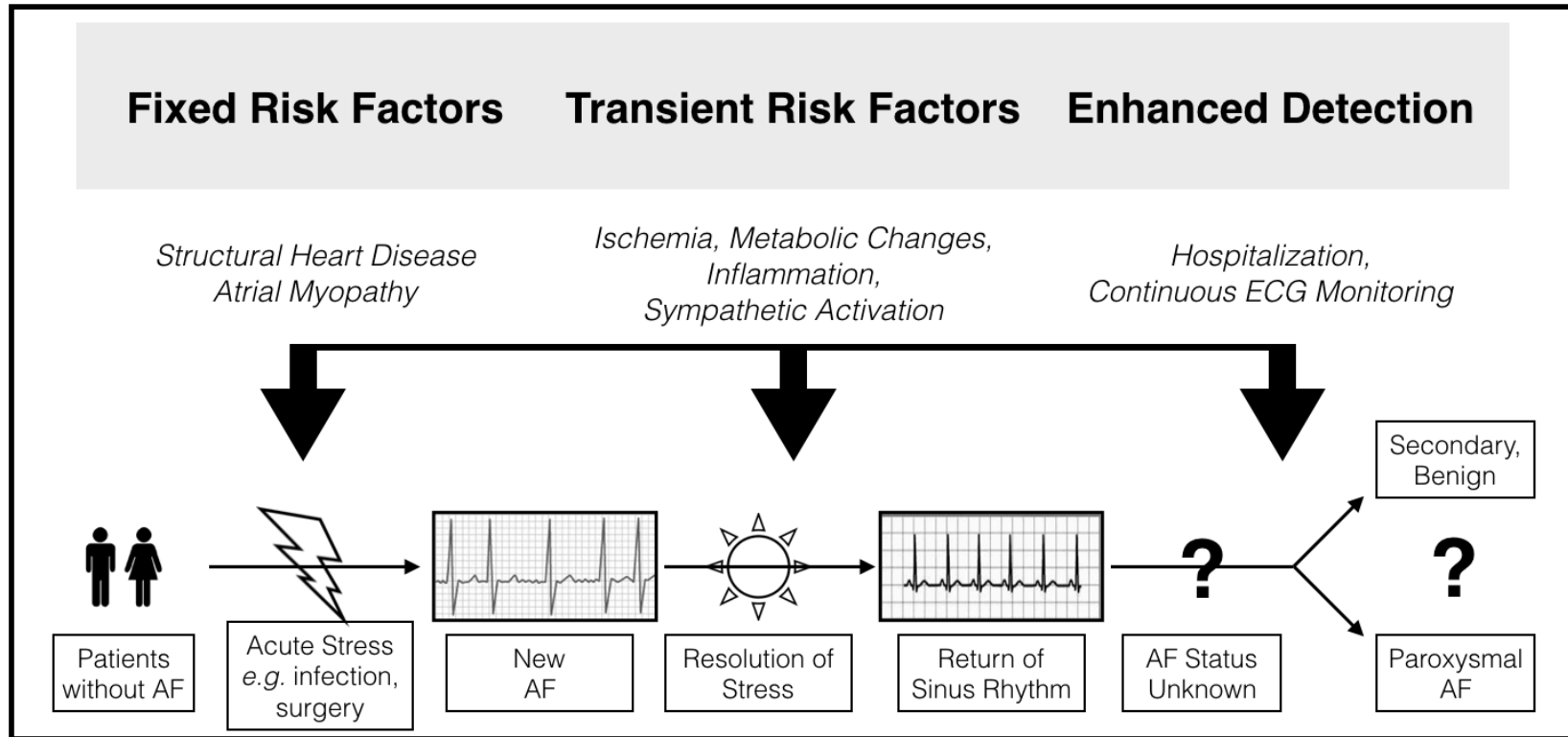
Table 1
Reported Incidence of Atrial Fibrillation Occurring Transiently with Stress (AFOTS)

Medical Illness		Non-cardiac Surgery	
Overall	1-44%[82]	*Overall*	1%[29,97]
Sepsis	5-44%[26,32,65-72]	*Major Nonemergency*	5%[101]
Acute Pulmonary Disease	4-18%[73-78]	*Thoracic*	10-35%[89-93]
Hyperthyroidism	10-25%[79,80]	*Gastrointestinal*	8.8-14%[99,100]
		Vascular	4-8%[97]

Table 2
Detection of Atrial Fibrillation Recurrence after Atrial Fibrillation Occurring Transiently with Stress (AFOTS)

Author and Year	Study Design	Population	Recurrence Rate
Walkey 2014[115]	Administrative Claims Data	Sepsis	44% at 1 year 55% at 5 years
Lubitz 2015[46]	Retrospective Analysis of a Longitudinal, Population-based Cohort	Infection	61%, median 5.4 years follow-up
		"Other"*	64%, median 5.4 years follow-up
		Non-cardiac surgery	68%, median 5.4 years follow-up
Gialdini 2014[29]	Administrative Claims Data	Non-cardiac surgery	37% at 1 year

*Other, as defined by study authors: acute alcohol consumption, thyrotoxicosis, acute pericardial disease, and acute non-infectious pulmonary pathology

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AUTHORS' CONTRIBUTIONS

William McIntyre contributed significantly to the paper's concept. He drafted the first and final versions of the submitted manuscript.

Stuart Connolly contributed to the paper's concept. He provided critical revisions and gave final approval of the submitted manuscript.

Jeff Healey contributed to the paper's concept. He provided critical revisions and gave final approval of the submitted manuscript.

Chapter 3

Atrial Fibrillation Detected Initially during Acute Medical Illness: a Systematic Review

William F. McIntyre[1,2], Kevin J. Um[1], Christopher C. Cheung[3],
Emilie P. Belley-Côté[1], Orvie Dingwall[4], PJ Devereaux[1],
Jorge A. Wong[1], David Conen[1], Richard P. Whitlock[1],
Stuart J. Connolly[1], Colette M. Seifer[2], Jeff S. Healey[1]

1. Population Health Research Institute, McMaster University,
Hamilton, Ontario, Canada
2. Section of Cardiology, Department of Internal Medicine,
University of Manitoba, Winnipeg, Manitoba, Canada
3. Division of Cardiology, University of British Columbia,
Vancouver,
British Columbia, Canada
4. Health Sciences Libraries, University of Manitoba,
Winnipeg, Manitoba, Canada

Key Points

- Among patients who are hospitalized for acute, medical illness, AF is detected during the hospitalization in 1 to 44%.

- The in-hospital incidence of AF is higher in studies that prospectively use continuous electrocardiographic monitoring.

- Following hospital discharge, recurrent AF is detected in over 50% of individuals. The rate of recurrence could even been higher if long-term electrocardiographic monitoring were systematically used

- Further studies are required in this population to more precisely estimate the rate of long-term AF recurrence, to characterize the relationship between AF, stroke and other cardiovascular outcomes and to evaluate the impact of oral anti-coagulation.

ABSTRACT

Objective

There is uncertainty about the incidence of and prognosis associated with atrial fibrillation (AF) that is documented for the first time in the setting of an acute stressor, such as surgery or medical illness. Our objective was to perform a systematic review of the incidence and long-term recurrence rates for AF occurring transiently with stress (AFOTS) in the setting of acute medical illness.

Data Sources

Medline, Embase and Cochrane Central to September 2017.

Study Selection

We included retrospective and prospective observational studies, and randomized controlled trials. The population of interest included patients hospitalized for medical (*i.e.* non-surgical) illness who developed newly-diagnosed AF. Studies were included if they included data on either the incidence of AF or the rate of AF recurrence in AFOTS patients following hospital discharge.

Data Extraction

Two reviewers collected data independently and in duplicate. We characterized each study's methodology for ascertainment of prior AF history, AF during hospitalization and AF recurrence after hospital discharge.

Data Synthesis

Thirty-six studies reported the incidence of AF. Ten used a prospective design and included a period of continuous electrocardiographic (ECG) monitoring. AF incidence ranged from 1% to 44%; which was too heterogeneous to justify meta-analysis (I^2=99%). In post-hoc meta-regression models, the use of continuous ECG monitoring explained 13% of the variance in AF incidence, while care in an intensive care unit explained none. Two studies reported the long-term rate of AF recurrence following AFOTS. Neither of these studies used prospective, systematic monitoring. Recurrence rates at five years ranged from 42% to 68%.

Conclusions

The incidence of AF with medical illness may be as high as 44%, with higher estimates in reports using continuous ECG monitoring. Within 5 years following hospital discharge, AF recurrence is documented in approximately half of patients; however, the true rate may be higher.

Protocol Registration

PROSPERO CRD42016043240

INTRODUCTION

Atrial fibrillation (AF) is the most common heart rhythm disorder, with a lifetime incidence of 1 in 4, and is a major cause of death and disability. [121] AF is associated with a 4 to 5 fold increase in the risk of ischemic stroke.[1,122] The appropriate use of oral anticoagulation (OAC) can reduce this risk by two-thirds and the risk of death by approximately one-quarter.[5,45] However, when physicians judge that new-onset AF has occurred due to an acute, potentially reversible stressor, they frequently do not prescribe OAC therapy.[7,9,10,13,24,54,55,123] AF is often observed for the first time following surgery or during a major acute medical illness.[10,124] In this setting, AF is often intermittent and detection may be more likely to occur during prolonged periods of ECG monitoring in an intensive care unit (ICU) or on a telemetry ward.

In the short-term, new-onset AF has been associated with increases in length-of-stay, morbidity and death.[26,31,32] However; in the long-term, it is not known whether AF Occurring Transiently with Stress (AFOTS) is secondary to reversible factors and can be considered cured once it resolves, or if it is simply the first documentation of paroxysmal AF and is therefore associated with an increased risk of stroke – a risk that is modifiable with chronic OAC.[10] Clinical practice guidelines have suggested that "secondary" AF due to potentially reversible factors may have a different prognosis than true, "primary" AF.[7,54,55,123] These guidelines do not, however, make specific recommendations for the use of OAC in patients with AF in the setting of surgery or medical illness and acknowledge

that data to guide management are lacking.[6-8,123] As uncertainty exists regarding the incidence of AFOTS, and long-term recurrence of AF after AFOTS,[10] our objective was to perform a systematic review to inform these issues, focusing on patients with acute medical (*i.e.* non-surgical) illness (PROSPERO CRD42016043240).

METHODS

Eligibility criteria

This systematic review included retrospective and prospective observational studies, and prospective randomized controlled trials; we treated the latter as prospective observational studies. The population of interest included patients admitted for medical (*i.e.* non-surgical) illness who developed newly-diagnosed AF during hospitalization. We excluded data from patients with a primary cardiovascular reason for diagnosis (*e.g.* myocardial infarction, heart failure, arrhythmia, pericardial disease, ischemic stroke), patients who underwent surgery, and patients with any history of AF. Studies were included if they included data on either: *i*) an estimate of the incidence of AFOTS or *ii*) an estimate of the rate of AF recurrence in AFOTS patients following hospital discharge. Attempts were made to contact study authors to clarify study populations wherever necessary.

Search strategy

A librarian created the search strategies with input from the other authors (Appendix 1). We searched the databases of Ovid MEDLINE (1946 – September 2017), Ovid Embase (1974 – September 2017) and The Cochrane Central Register of Controlled Trials Library (Wiley) (September 2017). We did not apply language restrictions. The search strategy combined concepts of AF and medical illnesses postulated as acute stressors. All records identified by the searches were imported into citation management software (Endnote X8, The Thomson Corp, USA) and were screened for duplicates. Two investigators independently screened the studies by title and abstract for potential eligibility using a pre-defined template. If either reviewer thought the citation was potentially eligible, it was selected for full review, and these papers were retrieved. The same two authors independently screened full texts to determine study eligibility. Disagreements were resolved by having the two reviewers discuss the reason for their decision and this always resulted in one reviewer recognizing an error in their decision. Reference lists of all included studies were checked manually to identify other potentially relevant studies.

Data extraction and outcomes

Two investigators abstracted data independently onto a pre-defined data extraction form. Disagreements were resolved through the consensus process as described above. We recorded data on study and participant characteristics, including the medical illness acting as stressor, setting (*i.e.* ward or ICU) and risk

factors from univariate and multivariable analyses. We extracted the data

required to calculate the incidence of AF in patients without a history of AF,

contacting study authors where necessary. Finally, we recorded the methods

used to rule out a prior history of AF, detect AF and detect recurrence of AF

(recurrence studies only).

Methodological quality of data

Two investigators assessed methodological quality of data in two key domains for

incidence and in one additional domain for recurrence. Disagreements were

resolved by consensus. We based our assessment on the Newcastle-Ottawa

Scale [125]. The following domains were assessed in each study: *i*) Ascertainment

of AF free status at baseline, *ii*) Ascertainment of AF incidence in hospital, and *iii*)

Ascertainment of AF recurrence after hospital discharge (recurrence studies

only). Criteria are summarized in Table 1.

Meta-analysis and Meta-regression

We used RevMan 5.3 (The Cochrane Collaboration, Denmark) to conduct the

analyses. Incidence and recurrence rates were entered as binomial proportions

with standard error. Heterogeneity was assessed qualitatively and quantitatively

using an I^2 test, with a plan to combine data using a random effects model if

heterogeneity was judged not to be substantial (i.e. $I^2 < 50\%$)[126]. After we

determined that data were too heterogeneous to combine, we conducted two

post hoc meta-regression analyses (CMA Software, Biostat Inc, Englewood, NJ). First, we hypothesized that studies with high quality for ascertainment of AF *(i.e.* continuous monitoring and prospective design) would have higher rates of AF capture than those that did not. In a separate model, we hypothesized that AF detection would correlate positively with illness severity, as represented by study setting (*i.e.* ICU versus ward).

RESULTS

Screening Process

Based on initial search results, 20,120 articles were screened, of which 181 were selected for full text screening (Appendix 2). In all, 38 studies met eligibility criteria, including 36 reporting on AF incidence and 2 on AF recurrence after hospitalization (Figure 1).

Study Characteristics

Thirty-six studies reported on the incidence of AF (Table 2).[26,32,60-62,65-67,69,70,72,74,76,77,81,85-88,110-114,127-138] One study was published in Hebrew, while all others were in English. Twenty-three studies evaluated patients in an ICU, and 13 studies evaluated patients in a hospital ward setting. Twenty-one studies used a prospective cohort design; fifteen were retrospective (six of which used administrative data). Seventeen studies included patients with sepsis, five included patients with pneumonia, two included patients with chronic obstructive

pulmonary disease, nine included a general medical ICU population, and individual studies examined patients with alcohol withdrawal, pulmonary embolism and acute respiratory distress syndrome. The mean age of study participants ranged from 32 to 80 years.

Two studies reported on the recurrence of AF (Table 3). One study was derived from a population-based cohort.[46] The other study was an administrative sample of United States Medicare patients who were hospitalized with sepsis.[115]

Methodological quality of data

Overall, methodological quality of studies varied widely (Table 2 for Incidence, Table 3 for Recurrence). Twenty-five (69%) incidence studies used high quality methods to rule out a prior history of AF. Ten (28%) incidence studies used high quality methods to ascertain AF. Eight incidence studies used methods that were judged to be high quality in both domains. Neither of the two studies on recurrence used a high quality method to ascertain AF recurrence.

AF Incidence, Meta-Analysis and Meta-Regression

The reported incidence of AF during medical illness ranged from 1.0 to 44% (Table 2 and Figure 2). The incidence ranged from 3-44% in the ICU setting, from 1-22% in the non-ICU setting and from 5-44% in studies using prospective continuous monitoring. There was substantial (I^2=99%) heterogeneity between studies; therefore, the results were not pooled to form a summary estimate. We

performed binary logistic meta-regression using a random effects model to determine the relationship between continuous monitoring and AF detection (Quality Score 1 versus Quality Scores 2,3,4 for AF ascertainment, Table 1). AF detection rate was significantly higher in studies with continuous monitoring compared to studies without (Test of model P = 0.0037). However; the Goodness-of-fit test (p < 0.00001) indicated remaining unexplained variance (Appendix 3). The R^2 analog was 0.13, indicating that 13% of the variance could be explained by differences in monitoring. We performed a separate binary logistic meta-regression analysis using a random effects model to determine the relationship between severity of illness, as approximated by care in an ICU versus non-ICU setting, and AF detection. The AF detection rate was significantly higher in patients who were in an ICU (Test of model P = 0.0009). Again, the Goodness-of-fit test (p <0.00001) indicated residual unexplained variance (Appendix 4). The R^2 analog was 0.00, suggesting that none of the variance could be explained by differences in illness severity.

Risk Factors

Risk factors for detection of AF, as collected from individual studies, are listed in Appendix 5. The following risk factors had positive, independent, multivariable associations reported in multiple studies: increasing age, male gender, Caucasian race, heart failure, diabetes mellitus, dyslipidemia, ischemic heart disease, malignancy, obesity, sepsis, respiratory infection, abdominal infection,

acute renal failure, acute respiratory failure, vasopressor use, mechanical ventilation, elevated APACHE II score and right heart catheterization.

Long-term Recurrence of AF and Other Clinical Outcomes

Lubitz *et al.* used data from the Framingham cohort, [46] and identified patients with first-detected AF occurring in the setting of a "secondary precipitant" (*i.e.* AFOTS) and reported two groups of interest: 1) infection and 2) "other" (thyrotoxicosis, alcohol intoxication, pulmonary embolism or other acute pulmonary disease, pericarditis, tamponade) (Table 3). AF at each time point was ascertained by examining ECGs from study visits and those obtained from patient care outside the study. Twenty-four percent of patients with AF "due to a secondary precipitant" were taking an anti-thrombotic at baseline. Five-, ten- and fifteen-year recurrence rates were 42%, 56%, and 62%, respectively for the entire population (which included patients who had surgery and patients who experienced myocardial infarction). After a median follow-up of 5.4 years (Interquartile range 2.3, 10.1), AF had recurred in 33 of 54 participants (61%) in the infection group and 19 of 28 participants (68%) in the "other" group. Compared to patients without a secondary AF precipitant, the AFOTS group had a similar long-term risk of stroke (HR 1.13, 95%CI, 0.82–1.57) and of mortality (HR 1.00, 95% CI, 0.87–1.15).

Walkey *et al.* used United States Medicare claims to investigate long-term outcomes in patients with severe sepsis with and without AFOTS (Table 3).[115]

The authors did not report information on anti-thrombotic use. Using ICD-9 codes in a cohort of 9540 patients, the rates of post-discharge detection of AF (accounting for the competing risk of mortality) were 44%, 49% and 55% at 1, 2 and 5 years, respectively, all of which were significantly higher than in patients without AFOTS (8%, 11% and 16% at 1, 2 and 5 years respectively, p < 0.001). Patients with AFOTS had greater 5-year risks of ischemic stroke (5.3% versus 4.7%; HR, 1.22; 95%CI 1.10-1.36), hospitalization for heart failure (11.2% versus 8.2%; HR, 1.25, 95%CI 1.16-1.34), and death (74.8% versus 72.1%; HR, 1.04, 95%CI 1.01-1.07) compared to patients without AFOTS.

DISCUSSION

This systematic review found a wide range in the incidence of AF during medical illness. Marked heterogeneity in data precluded the generation of a pooled incidence estimate. While the methods used to detect AF were found to have an influence on the variance between studies, the severity of illness did not appear to have an influence. The risk of AF recurrence following AF was only reported in two studies. Despite using low-sensitivity methods for ascertaining AF recurrence (*i.e.* standard ECGs during hospital visits or administrative codes), both studies reported that AF recurred in approximately half of patients by 5 years. As these recurrence rates are likely underestimations of the true recurrence rate, prospective, systematic screening for AF recurrence after AFOTS in the setting of acute illness may identify large numbers of patients who could be risk-stratified

for OAC for stroke prevention.

A 2014 systematic review by Kuipers *et al.* focused on "new-onset" AF in patients with sepsis[84]. From 1212 articles screened, the authors included 11 studies and reported an AF incidence ranging from 0 to 46%. They noted increasing AF incidence as patients progressed from sepsis to severe sepsis to septic shock. A 2015 review by Yoshida *et al.* performed a PubMed search focused on "new-onset" AF in the critically ill [83]. From 1132 articles screened, the authors included 15 studies and reported an incidence of new-onset AF ranging from 5% to 46%. Our systematic review offers important incremental advantages over the prior two reviews. First, the scope of our at-risk population was wider (*i.e.* all medical illness), as reflected by the number of articles we screened and included. The range of incidences found by our review (1-44%) is similar to that found in the two reviews limited to critically ill patients. Second, our review made a targeted effort to exclude patients with known paroxysmal AF from the at-risk population. This is important because there is certainty around the long-term prognosis of an episode of "new onset" AF in a patient known to have paroxysmal AF. Third, our review rigorously appraised the methodology for ascertainment of AF and the impact of AF ascertainment and illness severity on estimates of incidence. We found that the severity of illness did not appear to have an impact on variance but that the ascertainment method did. This finding suggests that the incidence of AF is influenced by the intensity of monitoring, as has been seen in patients with cryptogenic stroke and in the general population.[36,117,120,139,140] An appropriately

designed and powered prospective study would generate a precise estimate of the incidence of AFOTS and could investigate the effects of illness severity and monitoring intensity on this estimate.

Our review improves the understanding of factors that contribute to the detection of AF in acutely ill patients. We found substantial differences in the study methods used to ascertain AF and that these methods play a role in the rates of AF detection. Given that most hospitalized patients are not continuously monitored and AF is not always specifically ruled in or out in those that are, we might be underestimating the incidence of AF in the existing literature and in clinical practice. The study by Guenancia *et al.* is illustrative of the proportion of AF that could go unrecognized with less sensitive detection strategies.[65] The authors used 7-day continuous Holter monitors on patients admitted to the ICU and reported an AF incidence of 44%. In the study, treating physicians did not recognize one-third of cases of AF (lasting at least 30 seconds) that were detected by the Holter. Our review also looked at patients across a wide spectrum of illness type and severity. Although the patients located in the ICU had higher incidences of AF, meta-regression suggested that being in the ICU explained none of the variance between study results. This suggests that continuous monitoring may be a stronger driver of AF detection than illness severity. This finding is contrary to single studies in the literature that have found a linear relationship between illness severity and the incidence of AF.[31,141] However, high incidences of AF in critically ill patients could be confounded by

the fact that they are usually continuously monitored. For example, one study that found an increase in the incidence of AF with more severe forms of sepsis included "requiring treatment (for AF)" as part of their definition for AF.[31] This raises the possibility of confounding, as sicker patients may be watched more closely, and their physicians will likely have a lower threshold for clinical intervention. Ultimately, this result should be considered hypothesis generating and carefully-designed prospective studies are required to define the relationships between illness severity, monitoring intensity and the incidence of AF.

Our review found that high long-term rates of AF recurrence have been reported in this population despite studies having used low-sensitivity detection strategies. In the two studies that evaluated the long-term AF recurrence rates, approximately half of patients developed AF by 5 years.[46,115] However, both studies used non-systematic surveillance to ascertain AF recurrence, and participants were likely assessed with relatively short-duration ambulatory monitoring technology (*e.g.* 48 hour Holter), if any. It is plausible that if monitoring for AF recurrence were done employing a more sensitive strategy, in a prospective and systematic fashion, the resultant estimate would be much higher. Such a strategy is being used, specifically a 14-day ECG patch monitor, in the ongoing AFOTS cohort studies (NCT03221777). If a very high recurrence rate of AF is detected in patients who have experienced AFOTS, it would suggest that

AFOTS is a first presentation of paroxysmal AF and that these patients should be managed as if they had "primary" or "clinical" AF.

Limitations of review

This review has several limitations. Given there is no subject term for acute medical illness, our search strategy included a broad string of potential etiologies as identified by our authors and could be subject to bias. Among included studies, there are also likely important differences in study design, population and treatment that contributed to the heterogeneity in AF incidence. Where studies would report the onset of AF, they generally did not report on offset, and we assumed new-onset AF to be transient (*i.e.* AFOTS) in these studies. Similarly, only a few studies reported on the minimum duration of AF they required for detection. Because our study focused on AF incidence and recurrence, we did not systematically assess stroke or other outcomes that are known to be associated with AF. We were also unable to evaluate the impact of OAC on stroke in this population. Recent observational studies have reached contradictory conclusions about this, and this is a subject area that requires further research.[24,27]

CONCLUSIONS

The incidence of AF during acute medical illness varies widely. The incidence may be influenced more by the ECG monitoring strategy than by severity of

illness; this requires confirmation in prospective studies. AF recurrence rates are high, but may be underestimated. Prospective studies using systematic, and sensitive AF detection strategies are needed to determine the true incidence of AF in this population and whether it is simply the first presentation of paroxysmal AF.

Figure 1. Incidence of Atrial Fibrillation during hospitalization for acute medical illness

and subsequent recurrence

Figure 2. Incidence of AF in Included Studies

Study	Incidence	SE	Weight	IV, Random, 95% CI
Ambrus 2015	0.0764	0.016	3.0%	0.08 [0.05, 0.11]
Arora 2007	0.3871	0.0875	0.4%	0.39 [0.22, 0.56]
Asfar 2014	0.0477	0.0076	3.8%	0.05 [0.03, 0.06]
Baumfeld 2014	0.0576	0.0169	2.9%	0.06 [0.02, 0.09]
Calvo-Romero 2005	0.0649	0.0199	2.7%	0.06 [0.03, 0.10]
Chen 2015	0.0715	0.0095	3.6%	0.07 [0.05, 0.09]
Cheng JSCD 2017	0.011	0.0012	4.1%	0.01 [0.01, 0.01]
Cheng QJM 2017	0.019	0.0005	4.1%	0.02 [0.02, 0.02]
Cuculi 2006	0.0204	0.0202	2.6%	0.02 [-0.02, 0.06]
Duarte 2017	0.122	0.0234	2.3%	0.12 [0.08, 0.17]
Dunser 2003	0.3448	0.0883	0.4%	0.34 [0.17, 0.52]
Guenancia 2015	0.4394	0.0611	0.7%	0.44 [0.32, 0.56]
Hayase 2016	0.053	0.0182	2.8%	0.05 [0.02, 0.09]
Jaffer 2016	0.218	0.0239	2.3%	0.22 [0.17, 0.26]
Klein-Klouwenberg 2014	0.2431	0.0119	3.4%	0.24 [0.22, 0.27]
Koyfman 2015	0.2372	0.0341	1.6%	0.24 [0.17, 0.30]
Launey 2017	0.218	0.0256	2.2%	0.22 [0.17, 0.27]
Lewis 2016	0.198	0.0348	1.5%	0.20 [0.13, 0.27]
Liu 2016	0.44	0.0212	2.5%	0.44 [0.40, 0.48]
Makyrgiannis 2014	0.2113	0.0484	1.0%	0.21 [0.12, 0.31]
Mandal 2011	0.093	0.0044	4.0%	0.09 [0.08, 0.10]
Morelli 2009	0.093	0.0507	0.9%	0.09 [-0.01, 0.19]
Moss 2017	0.137	0.0067	3.8%	0.14 [0.12, 0.15]
Musher 2007	0.0144	0.0101	3.6%	0.01 [-0.01, 0.03]
Nakanishi 2015	0.028	0.0077	3.8%	0.03 [0.01, 0.04]
Seedat 1993	0.0098	0.0098	3.6%	0.01 [-0.01, 0.03]
Seguin 2004	0.0636	0.0233	2.4%	0.06 [0.02, 0.11]
Shaver 2015	0.0692	0.0075	3.8%	0.07 [0.05, 0.08]
Short 2012	0.1154	0.0087	3.7%	0.12 [0.10, 0.13]
Soto-Gomez 2013	0.0803	0.0015	4.1%	0.08 [0.08, 0.08]
Terzano 2014	0.2176	0.0297	1.9%	0.22 [0.16, 0.28]
Vadiei 2017	0.195	0.0234	2.3%	0.20 [0.15, 0.24]
Violi 2017	0.055	0.0078	3.8%	0.06 [0.04, 0.07]
Walkey 2011	0.0351	0.0004	4.1%	0.04 [0.03, 0.04]
Walkey 2013	0.0879	0.0013	4.1%	0.09 [0.09, 0.09]
Wells 2011	0.2839	0.0209	2.6%	0.28 [0.24, 0.32]

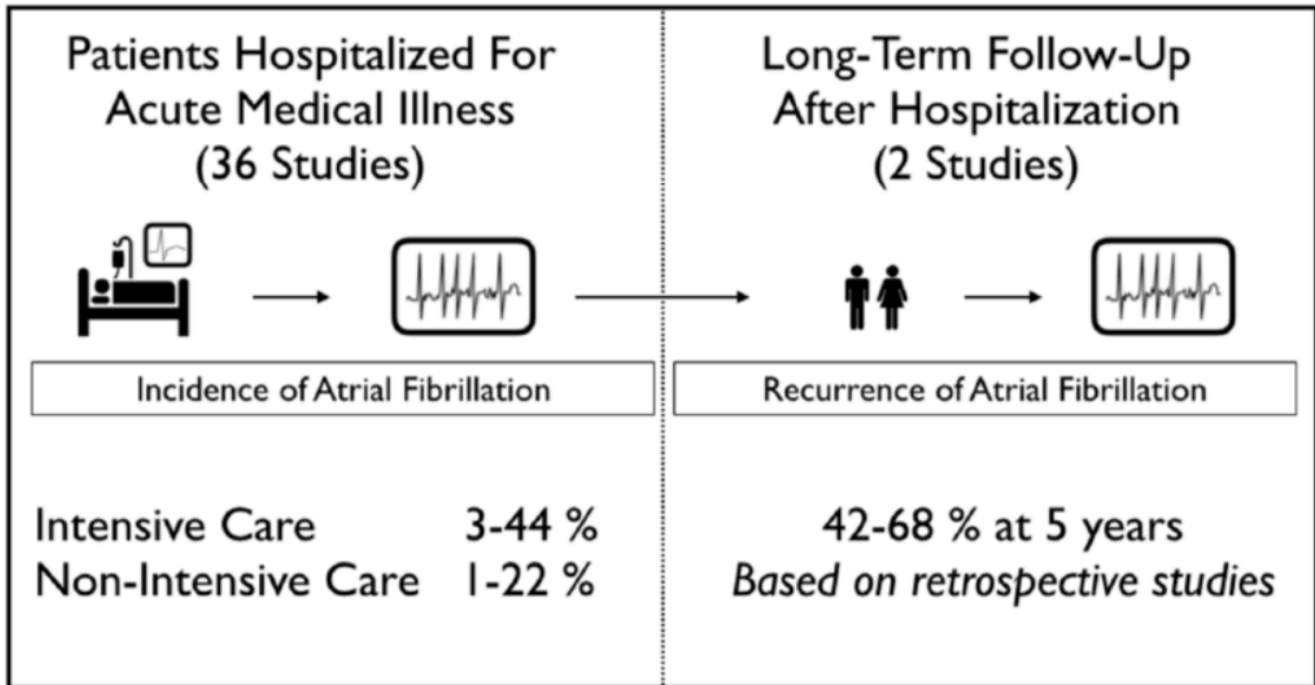Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5696.58$, df = 35 (P < 0.00001); $I^2 = 99\%$

0% 25% 50%
Incidence of AFOTS

Table 1. Methodological quality assessment framework

Domain		Ascertainment of History of AF	Ascertainment of New AF	Ascertainment of AF recurrence
Applicable studies		*Incidence and recurrence studies*	*Incidence and recurrence studies*	*Recurrence studies only*
Selection	**1**	✪ Demonstration of searching a prior source (e.g. medical records)	✪ Continuous monitoring and systematic ECG review	✪ Prospective, systematic monitoring protocol
	2	✪ Reported as no history of AF	Routine ECGs or prospective, continuous monitoring without meeting selection 1	Retrospective, systematic search for collected ECGs
	3	Terms like "new-onset" are used without meeting selections 1 or 2	Retrospective review of diagnoses or of ECGs collected non-systematically	Retrospective, systematic review of diagnoses or non-systematic search for collected ECGs
	4	No description	No description	No description

✪ Denotes "high quality" in this domain.

AF = Atrial Fibrillation

Table 2. Characteristics of Included Studies on AF Incidence

Study	Condition	Design	Setting	Age	History of AF Ascertainment Method and Quality Score		AFOTS Ascertainment Method and Quality Score		Total n	AFOTS n	AFOTS Incidence
Ambrus 2015	ARDS	POC	ICU	52±16	Reports patients with hx AF	3	No description	4	275	21	[†]7.6%
Arora 2007	ICU	POC	ICU	71	Recorded hx cvdisease, excluded if AF at admit	2	Continuous monitoring, 12-lead ECG/rhythm strip for dx	1	31	12	[†]38.7%
Asfar 2014	Septic Shock	POC	ICU	65±14*	"Newly-diagnosed"	3	No description	4	776	37	4.8%
Baumfeld 2014	ICU	POC	ICU	67±11	Hx PAF mentioned, excluded if AF at admit	2	Continuous monitor, 12-lead ECG for irregular rhythms	1	191	11	[†]5.8%
Calvo 2005	PE	POC	WARD	69±13	"Presumed new onset"	3	Twelve-lead ECG	3	154	10	6.5%
Chen 2015	ICU	POC	ICU	67±14	Documented hx AF in the medical record	1	ICD-9 Codes	3	741	53	7.2%
Cheng QJM 2017	Sepsis	ADMIN	HOSP	NA	Administrative Data Search	1	Administrative Data Search	3	67278	1286	[†]1.9%
Cheng JSCD 2017	Sepsis	ADMIN	HOSP	55±24*	Prior AF Excluded	1	Administrative Data Search	3	7419	82	[†]1.1
Cuculi 2006	Alcohol	ROC	WARD	48	"ECG Changes"	3	ECG on admission	3	49	1	2.0%
Duarte 2017	ICU	POC	ICU	63±17	Chronic AF Excluded	2	Multiparametric monitor or ECG	2	196	24	12.2%
Dunser 2003	Septic Shock	POC	ICU	68±11*	"New-onset"	3	Continuous monitoring, tachyarrhythmias monitored	1	29	10	[†]34.5%
Hayase 2016	Septic Shock	POC	ICU	NA	Review of medical records	1	hourly on nursing sheets.	1	151	8	[†]5.3%
Guenancia 2015	Septic Shock	POC	MICU	71±14	Excluded known AF (paroxysmal or sustained)	1	Continuous Holter, ≥30 s	1	66	29	44%
Jaffer 2016	Septic Shock	ADMIN	ICU	NA	"New-onset"	3	No description	4	298	65	21.8%
Klein 2014	Sepsis	POC	ICU	70 (72-76)	Excluded chronic/paroxysmal AF	1	Hourly recording, dx if >1 h duration or cardioversion	1	1304	317	[†]24.3%
Koyfman 2015	Sepsis	ROC	ICU	74±14	Patients had no past hx AF	2	Developed an episode of paroxysmal AF	3	156	37	[†]23.7%
Launey 2017	Septic Shock	POC	ICU	64±14*	Excluded AF history, pacemaker	1	Detected in real time, daily review of events	1	261	57	21.8%
Lewis 2016	Severe Sepsis	ROC	ICU	69±12*	Excluded history of AF	1	Not described	4	131	26	19.8%
Liu 2016	Sepsis	ROC	ICU	77±11	Excluded AF history	1	Continuous monitoring with 12 lead	3	546	240	44%
Makyrgiannis 2014	ICU	POC	ICU	53±19*	Excluded chronic/intermittent AF, AF at admit	1	Continuously monitor, 12-lead if high rate, arrhythmia	1	71	15	[†]21.1%
Mandal 2011	Pneumonia	ROC	WARD	73 (52-82)*	Without a prior history of AF	2	Physician diagnosis based on ECG	3	4408	410	9.3%
Morelli 2009	Septic Shock	POC	ICU	66 (59-74)	"New-onset"	3	Continuous recording of ECG	2	45	6	13.3%
Moss 2017	ICU	POC	ICU	NA	Excluded AF history	1	ECGs reviewed using computer algorithm	1	2672	367	*13.7%
Musher 2007	Pneumonia	ROC	WARD	71	Review of prior records	1	Reviewed electronic medical records	3	139	2	[†]1.4%
Nakanishi 2015	ICU	POC	ICU	71 (48-80)	Excluded Pre-existing AF	1	Patients were monitored	2	462	13	2.8%
Seedat 1993	Pneumonia	POC	WARD	32 (15-50)*	"Without underlying cardiorespiratory illness"	2	Daily EKG	2	102	1	1.0%
Seguin 2004	MICU	POC	ICU	64±13	Excluded AF at admission, pacemaker	3	Continuously monitored, events reviewed daily	1	110	7	[†]6.4%
Shaver 2015	Mixed ICU	POC	ICU	68 (61-77)	Medical history from medical records	1	AF in MD or nurse note, ECG by cardiologist	3	1156	80	[†]6.9%
Short 2012	COPD	POC	WARD	N/A	"New-onset"	3	No description	4	1343	155	11.5%

Soto 2013	Pneumonia	ADMIN	WARD	75±7	Administrative data search	1	ICD Code	3	32689	2625	8.0%
Terzano 2014	COPD	POC	WARD	78±5	Excluded patients with hx AF	2	ECG	3	193	42	21.8%
Vadiei 2017	Septic Shock	ROC	ICU	62±15*	"developed"	3	Nurse documentation of rhythm.	3	287	56	19.5%
Violi 2017	Pneumonia	ROC	HOSP	73±14*	Medical records searched	1	No description	4	843	46	†5.5%
Walkey 2013	Sepsis	ADMIN	HOSP	80±8*	ICD-9 Codes	1	ICD-9 Codes	3	49164	4320	8.8%
Walkey 2011	Sepsis	ADMIN	HOSP	74±12	ICD-9 Codes	1	ICD-9 Codes	3	229357	8040	3.5%
Wells 2011	Sepsis	ROC	ICU	72±13	"Incidence of AF"	3	Identified by telemetry, confirmed by ECG.	3	465	132	28.4%

ADMIN = Administrative Data, AF = Atrial Fibrillation, ARDS = Acute Respiratory Distress Syndrome, CAP = Community Acquired Pneumonia, COPD = Chronic Obstructive Pulmonary Disease, Dx = Diagnosis, HOSP = Ward and ICU sub-populations, Hx = History of, ICD = International Classification of Diseases, ICU = Intensive Care Unit, MICU = Medical Intensive Care Unit, MD = Medical Doctor, PAF = Paroxysmal AF, PE = Pulmonary Embolism, POC = Prospective Observational Cohort, RCT = Randomized Controlled Trial, ROC = Retrospective Observational Cohort,

* = Age is for entire cohort, others are AF only. Age measurements are Mean $\pm$ Standard Deviation or Median (Interquartile Range), as reported by study authors

† = Incidence calculation required removal of surgical patients and/or patients with a history of AF.

Methodological Quality Scores are defined in Table 1

Table 3 Characteristics of Included Studies on AF Recurrence after AFOTS

Study ID	Condition	Design	Setting	Age	History of AF Ascertainment and Quality Score		AFOTS Ascertainment and Quality Score		AF Recurrence Ascertainment and Quality Score		AFOTS N	Recurrent AF N	Recurrence Rate	Follow up time
Lubitz 2015	Various*	Cohort	Population	74.3± 11.3	Med history, study/external ECGs	1	External ECGs	3	Med history, study/external ECGs	2	116	49	42%	5 years
	Infection										54	33	61%	Median 5.4 y
	"Other" (i.e. acute alcohol consumption, thyrotoxicosis, acute pericardial disease, acute pulmonary pathology)										28	19	68%	(IQR 2.3,10.1)
	* Included Cardiothoracic Surgery; Noncardiothoracic surgery, acute myocardial infarction, infection, and others													
Walkey 2014	Sepsis	Admin Data	US Medicare	80.7± 7.6	Admin Codes	1	Admin Codes	3	Admin Codes	2	9540	4193	44%	1 year
											9540	4651	49%	2 years
											9540	5074	53%	5 years

AF = Atrial Fibrillation, IQR = Interquartile Range

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Appendix

SUPPLEMENTARY MATERIAL

Table of Contents

<u>Appendix 1 – Search Strategies</u>

<u>Ovid MEDLINE – September 2017</u>

1. atrial fibrillation.sh.
2. (atri* adj5 fibrillat*).ti,ab,kw,kf.
3. (auricular* adj5 fibrillat*).ti,ab,kw,kf.
4. afib.ti,ab,kw,kf.
5. a fib.ti,ab,kw,kf.
6. atrial flutter.sh.
7. (atrial adj5 flutter*).ti,ab,kw,kf.
8. (auricular* adj5 flutter*).ti,ab,kw,kf.
9. or/1-8
10. (acute adj3 stress*).ti,ab,kw,kf.
11. infection.sh.
12. infection*.ti,ab,kw,kf.
13. arthritis, infectious.sh.
14. (arthrit* adj3 (viral or bacterial or suppurative* or septic)).ti,ab,kw,kf.
15. exp osteomyelitis/
16. osteomyelitis.ti,ab,kw,kf.
17. exp endocarditis, bacterial/
18. (endocarditi* adj3 bacterial).ti,ab,kw,kf.
19. catheter-related infections.sh.
20. diverticulitis.sh.
21. diverticulitis.ti,ab,kw,kf.
22. exp peritonitis/
23. peritonitis.ti,ab,kw,kf.
24. prosthesis-related infections.sh.
25. respiratory tract infections.sh.
26. exp sepsis/
27. sepsis.ti,ab,kw,kf.
28. septic*.ti,ab,kw,kf.
29. py?emia*.ti,ab,kw,kf.
30. pyohemia*.ti,ab,kw,kf.
31. (blood adj3 poison*).ti,ab,kw,kf.
32. bacteremia*.ti,ab,kw,kf.
33. endotoxemia*.ti,ab,kw,kf.
34. toxemia*.ti,ab,kw,kf.
35. fungemia*.ti,ab,kw,kf.
36. candidemia*.ti,ab,kw,kf.
37. parasitemia*.ti,ab,kw,kf.
38. viremia*.ti,ab,kw,kf.

39. soft tissue infections.sh.
40. abscess.sh.
41. lung abscess.sh.
42. abscess*.ti,ab,kw,kf.
43. cellulitis.sh.
44. cellulitis.ti,ab,kw,kf.
45. phlegmon.ti,ab,kw,kf.
46. urinary tract infections.sh.
47. bacteriuria.sh.
48. bacteriuria*.ti,ab,kw,kf.
49. pyuria.sh.
50. pyuria*.ti,ab,kw,kf.
51. exp pneumonia/
52. pneumoni*.ti,ab,kw,kf.
53. bronchopneumonia*.ti,ab,kw,kf.
54. pleuropneumonia*.ti,ab,kw,kf.
55. lung diseases, interstitial.sh.
56. exp lung diseases, obstructive/
57. lung disease*.ti,ab,kw,kf.
58. asthma*.ti,ab,kw,kf.
59. bronchiti*.ti,ab,kw,kf.
60. bronchiolitis.ti,ab,kw,kf.
61. pulmonary disease*.ti,ab,kw,kf.
62. COPD.ti,ab,kw,kf.
63. (pulmonary adj3 embolism*).ti,ab,kw,kf.
64. venous thrombosis.sh.
65. venous thromboembolism.sh.
66. thromboembolism.sh.
67. phlebothrombos?s.ti,ab,kw,kf.
68. (venous adj3 thrombos?s).ti,ab,kw,kf.
69. deep vein thrombos?s.ti,ab,kw,kf.
70. deep venous thrombos?s.ti,ab,kw,kf.
71. thromboembolism.ti,ab,kw,kf.
72. respiratory distress syndrome, adult.sh.
73. shock lung.ti,ab,kw,kf.
74. severe acute respiratory syndrome.sh.
75. (respiratory adj3 syndrome*).ti,ab,kw,kf.
76. SARS.ti,ab,kw,kf.
77. exp empyema/
78. empyema*.ti,ab,kw,kf.
79. pleural effusion.sh.
80. (pleura* adj3 effusion*).ti,ab,kw,kf.

81. pneumothorax.sh.
82. pneumothorax*.ti,ab,kw,kf.
83. exp alcohol induced disorders/
84. exp alcohol related disorders/
85. (alcohol* adj5 disorder*).ti,ab,kw,kf.
86. drug overdose.sh.
87. (drug* adj3 overdos*).ti,ab,kw,kf.
88. exp shock/
89. shock.ti,ab,kw,kf.
90. (circulat* adj3 (fail* or collaps*)).ti,ab,kw,kf.
91. hemorrhage.sh.
92. exp gastrointestinal hemorrhage/
93. exp intracranial hemorrhage, traumatic/
94. hemorrhag*.ti,ab,kw,kf.
95. hematoma*.ti,ab,kw,kf.
96. multiple trauma.sh.
97. (multiple adj3 (trauma* or wound*)).ti,ab,kw,kf.
98. polytrauma*.ti,ab,kw,kf.
99. (multiple adj3 injur*).ti,ab,kw,kf.
100. soft tissue injuries.sh.
101. (soft tissue adj3 injur*).ti,ab,kw,kf.
102. spinal cord injuries/
103. (spinal cord adj3 (trauma* or injur* or transection* or lacerat* or contusion*)).ti,ab,kw,kf.
104. (myelopath* adj5 trauma*).ti,ab,kw,kf.
105. exp trauma, nervous system/
106. ((nervous system* or cranio* or cerebrovascular or vascular or brain or head or temporal or skull or occipital or parietal or frontal or forehead) adj3 (trauma* or injur*)).ti,ab,kw,kf.
107. accidental falls.sh.
108. fall*.ti,kw,kf.
109. or/10-108
110. epidemiologic studies.sh.
111. exp case control studies/
112. case control.ti,ab,kw,kf.
113. retrospective.ti,ab,kw,kf.
114. exp cohort studies/
115. (cohort adj3 (study or studies)).ti,ab,kw,kf.
116. cohort analy*.ti,ab,kw,kf.
117. (follow up adj (study or studies)).ti,ab,kw,kf.
118. longitudinal.ti,ab,kw,kf.
119. Prospective.ti,ab,kw,kf.
120. Retrospective.ti,ab,kw,kf.
121. cross-sectional studies.sh.

122. cross sectional.ti,ab,kw,kf.
123. (observational adj (study or studies)).ti,ab,kw,kf.
124. comparative study.sh.
125. recurrence.sh.
126. recurrent*.ti,ab,kw,kf.
127. recurrenc*.ti,ab,kw,kf.
128. risk factors.sh.
129. risk factor*.ti,ab,kw,kf.
130. incidence.sh.
131. incidence*.ti,ab,kw,kf.
132. prevalence.sh.
133. prevalence*.ti,ab,kw,kf.
134. secondary prevention.sh.
135. proportional hazards models.sh.
136. or/110-135
137. 9 and 109 and 136
138. exp animals/ not humans.sh.
139. 137 not 138
140. remove duplicates from 139

Ovid Embase Search Strategy – September 2017

1. *heart atrium fibrillation/
2. (atri* adj5 fibrillat*).ti,ab,kw.
3. (auricular* adj5 fibrillat*).ti,ab,kw.
4. afib.ti,ab,kw.
5. a fib.ti,ab,kw.
6. *heart atrium flutter/
7. (atri* adj5 flutter*).ti,ab,kw.
8. (auricular* adj5 flutter*).ti,ab,kw.
9. or/1-8
10. (acute adj3 stress*).ti,ab,kw.
11. infection.sh.
12. infection*.ti,ab,kw.
13. *infectious arthritis/
14. (arthrit* adj3 (viral or bacterial or suppurative* or septic)).ti,ab,kw.
15. exp *osteomyelitis/
16. osteomyelitis.ti,ab,kw.
17. bacterial endocarditis.sh.
18. (endocarditi* adj3 bacterial).ti,ab,kw.
19. *catheter infection/

20. *diverticulitis/
21. diverticulitis.ti,ab,kw.
22. exp *peritonitis/
23. peritonitis.ti,ab,kw.
24. respiratory tract infection.sh.
25. exp *sepsis/
26. sepsis.ti,ab,kw.
27. septic*.ti,ab,kw.
28. py?emia*.ti,ab,kw.
29. pyohemia*.ti,ab,kw.
30. (blood adj3 poison*).ti,ab,kw.
31. bacteremia*.ti,ab,kw.
32. endotoxemia*.ti,ab,kw.
33. toxemia*.ti,ab,kw.
34. fungemia*.ti,ab,kw.
35. candidemia*.ti,ab,kw.
36. parasitemia*.ti,ab,kw.
37. viremia*.ti,ab,kw.
38. *soft tissue infection/
39. *abscess/
40. *lung abscess/
41. abscess*.ti,ab,kw.
42. *cellulitis/
43. cellulitis.ti,ab,kw.
44. phlegmon.ti,ab,kw.
45. *urinary tract infection/
46. *bacteriuria/
47. bacteriuria*.ti,ab,kw.
48. *pyuria/
49. pyuria*.ti,ab,kw.
50. exp *pneumonia/
51. pneumoni*.ti,ab,kw.
52. bronchopneumonia*.ti,ab,kw.
53. pleuropneumonia*.ti,ab,kw.
54. *interstitial lung disease/
55. exp *obstructive airway disease/
56. lung disease*.ti,ab,kw.
57. asthma*.ti,ab,kw.
58. bronchiti*.ti,ab,kw.
59. bronchiolitis.ti,ab,kw.
60. pulmonary disease*.ti,ab,kw.
61. COPD.ti,ab,kw.

62. (pulmonary adj3 embolism*).ti,ab,kw.
63. vein thrombosis.sh.
64. venous thromboembolism.sh.
65. thromboembolism.sh.
66. phlebothrombos?s.ti,ab,kw.
67. (venous adj3 thrombos?s).ti,ab,kw.
68. deep vein thrombosis.sh.
69. deep vein thrombos?s.ti,ab,kw.
70. deep venous thrombos?s.ti,ab,kw.
71. thromboembolism*.ti,ab,kw.
72. *adult respiratory distress syndrome/
73. shock lung.ti,ab,kw.
74. *severe acute respiratory syndrome/
75. (respiratory adj3 syndrome*).ti,ab,kw.
76. SARS.ti,ab,kw.
77. exp *empyema/
78. empyema*.ti,ab,kw.
79. *pleura effusion/
80. (pleura* adj3 effusion*).ti,ab,kw.
81. (pleural adj3 effusion*).ti,ab,kw.
82. *pneumothorax/
83. pneumothorax*.ti,ab,kw.
84. *alcoholism/
85. (alcohol* adj5 disorder*).ti,ab,kw.
86. *drug overdose/
87. (drug* adj3 overdos*).ti,ab,kw.
88. exp *shock/
89. shock.ti,ab,kw.
90. (circulat* adj3 (fail* or collaps*)).ti,ab,kw.
91. *hemorrhage/
92. exp *gastrointestinal hemorrhage/
93. exp *brain hemorrhage/
94. hemorrhag*.ti,ab,kw.
95. hematoma*.ti,ab,kw.
96. *multiple trauma/
97. (multiple adj3 (trauma* or wound*)).ti,ab,kw.
98. polytrauma*.ti,ab,kw.
99. (multiple adj3 injur*).ti,ab,kw.
100. *soft tissue injury/
101. (soft tissue adj3 injur*).ti,ab,kw.
102. *spinal cord injury/
103. (spinal cord adj3 (trauma* or injur* or transection* or lacerat* or contusion*)).ti,ab,kw.

104. (myelopath* adj5 trauma*).ti,ab,kw.
105. exp *nervous system injury/
106. ((nervous system* or cranio* or cerebrovascular or vascular or brain or head or temporal or skull or occipital or parietal or frontal or forehead) adj3 (trauma* or injur*)).ti,ab,kw.
107. *falling/
108. fall*.ti,kw.
109. or/10-108
110. clinical study.sh.
111. case control study.sh.
112. family study.sh.
113. longitudinal study.sh.
114. retrospective study.sh.
115. prospective study.sh.
116. "randomized controlled trial (topic)"/
117. 115 not 116
118. cohort analysis.sh.
119. (Cohort adj (study or studies)).mp.
120. (Case control adj (study or studies)).ti,ab.
121. (follow up adj (study or studies)).ti,ab.
122. (observational adj (study or studies)).ti,ab.
123. (epidemiologic$ adj (study or studies)).ti,ab.
124. (cross sectional adj (study or studies)).ti,ab.
125. recurrence.sh.
126. recurrent*.ti,ab,kw.
127. recurrenc*.ti,ab,kw.
128. or/110-114,117-127 [SIGN Observational Studies Filter]
129. 9 and 109 and 128
130. exp animal/ not human.sh.
131. 129 not 130
132. remove duplicates from 131

Cochrane Central Register of Controlled Trials Search Strategy – September 2017

#1   MeSH descriptor: [Atrial Fibrillation] explode all trees
#2   atri* fibrillat*:ti,ab,kw
#3   auricular* fibrillat*:ti,ab,kw
#4   afib:ti,ab,kw
#5   a fib:ti,ab,kw
#6   MeSH descriptor: [Atrial Flutter] explode all trees
#7   atrial flutter*:ti,ab,kw
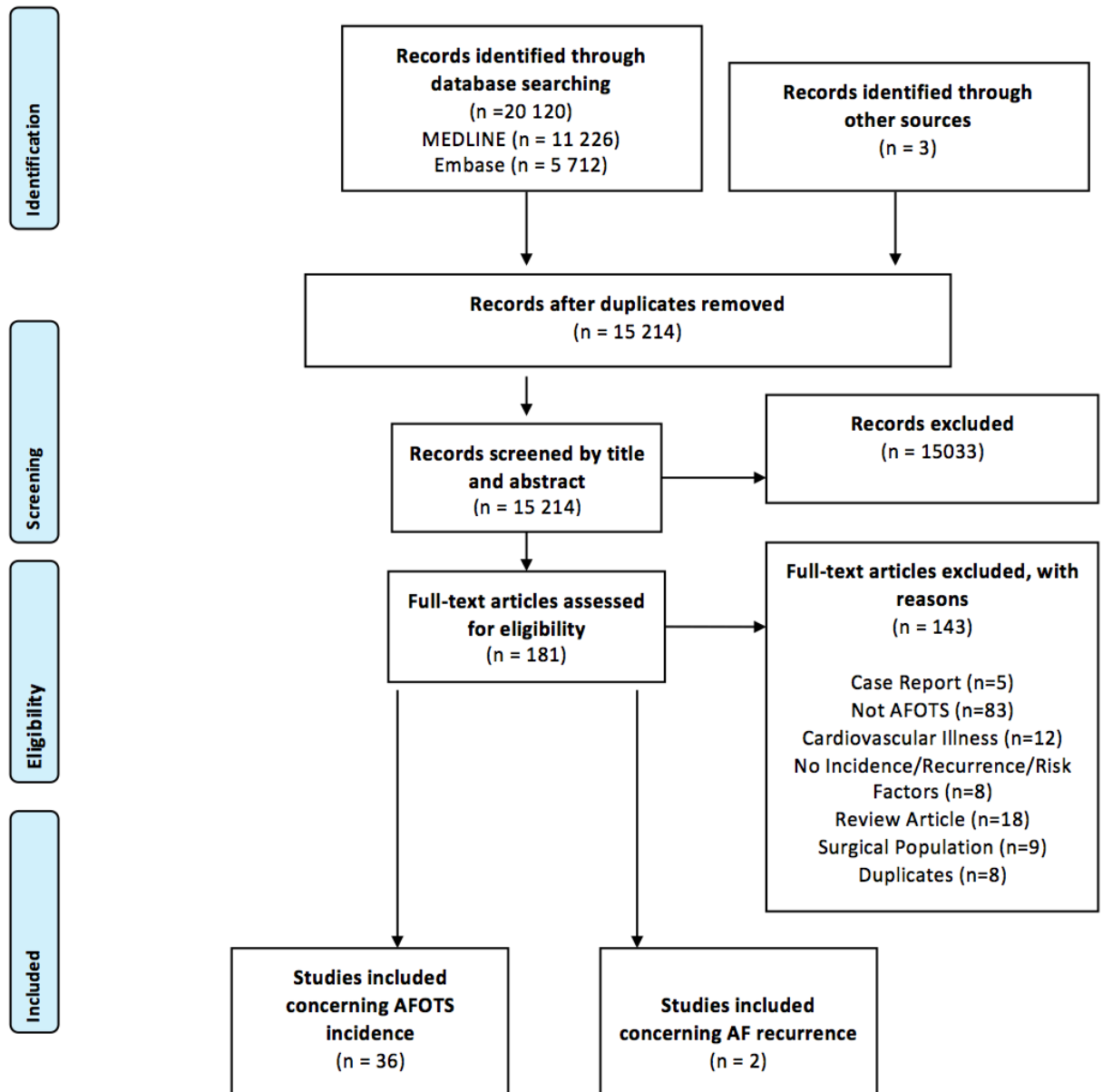
#8	auricular* flutter*:ti,ab,kw
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	acute stress*:ti,ab,kw
#11	infection*:ti,ab,kw
#12	MeSH descriptor: [Arthritis, Infectious] this term only
#13	MeSH descriptor: [Infection] this term only
#14	MeSH descriptor: [Osteomyelitis] explode all trees
#15	osteomyelitis:ti,ab,kw
#16	MeSH descriptor: [Endocarditis, Bacterial] explode all trees
#17	endocarditi* bacterial:ti,ab,kw
#18	MeSH descriptor: [Catheter-Related Infections] this term only
#19	MeSH descriptor: [Diverticulitis] this term only
#20	diverticulitis:ti,ab,kw
#21	MeSH descriptor: [Peritonitis] explode all trees
#22	peritonitis:ti,ab,kw
#23	MeSH descriptor: [Prosthesis-Related Infections] this term only
#24	MeSH descriptor: [Respiratory Tract Infections] this term only
#25	MeSH descriptor: [Sepsis] explode all trees
#26	sepsis:ti,ab,kw
#27	septic*:ti,ab,kw
#28	pyemia*:ti,ab,kw
#29	pyohemia*:ti,ab,kw
#30	blood poison*:ti,ab,kw
#31	bacteremia*:ti,ab,kw
#32	endotoxemia*:ti,ab,kw
#33	toxemia*:ti,ab,kw
#34	fungemia*:ti,ab,kw
#35	candidemia*:ti,ab,kw
#36	parasitemia*:ti,ab,kw
#37	viremia*:ti,ab,kw
#38	MeSH descriptor: [Soft Tissue Infections] this term only
#39	MeSH descriptor: [Abscess] this term only
#40	abscess*:ti,ab,kw
#41	MeSH descriptor: [Lung Abscess] this term only
#42	MeSH descriptor: [Cellulitis] this term only
#43	cellulitis:ti,ab,kw
#44	phlegmon:ti,ab,kw
#45	MeSH descriptor: [Urinary Tract Infections] this term only
#46	MeSH descriptor: [Bacteriuria] this term only
#47	MeSH descriptor: [Pyuria] this term only
#48	bacteriuria*:ti,ab,kw
#49	pyuria*:ti,ab,kw

#50   MeSH descriptor: [Pneumonia] explode all trees
#51   pneumoni*:ti,ab,kw
#52   bronchopneumonia*:ti,ab,kw
#53   pleuropneumonia*:ti,ab,kw
#54   MeSH descriptor: [Lung Diseases, Interstitial] this term only
#55   MeSH descriptor: [Lung Diseases, Obstructive] explode all trees
#56   lung disease*:ti,ab,kw
#57   asthma*:ti,ab,kw
#58   bronchiti*:ti,ab,kw
#59   bronchiolitis:ti,ab,kw
#60   pulmonary disease*:ti,ab,kw
#61   COPD:ti,ab,kw
#62   pulmonary embolism*:ti,ab,kw
#63   thromboembolism*:ti,ab,kw
#64   MeSH descriptor: [Respiratory Distress Syndrome, Adult] this term only
#65   shock lung:ti,ab,kw
#66   MeSH descriptor: [Severe Acute Respiratory Syndrome] this term only
#67   respiratory syndrome*:ti,ab,kw
#68   SARS:ti,ab,kw
#69   MeSH descriptor: [Empyema] explode all trees
#70   empyema*:ti,ab,kw
#71   MeSH descriptor: [Pleural Effusion] this term only
#72   pleura* effusion*:ti,ab,kw
#73   MeSH descriptor: [Pneumothorax] this term only
#74   pneumothorax*:ti,ab,kw
#75   MeSH descriptor: [Alcohol-Induced Disorders] explode all trees
#76   MeSH descriptor: [Alcohol-Related Disorders] explode all trees
#77   alcohol* disorder*:ti,ab,kw
#78   MeSH descriptor: [Drug Overdose] this term only
#79   drug* overdos*:ti,ab,kw
#80   MeSH descriptor: [Shock] explode all trees
#81   shock:ti,ab,kw
#82   circulat* fail*:ti,ab,kw
#83   circulat* collaps*:ti,ab,kw
#84   MeSH descriptor: [Hemorrhage] this term only
#85   MeSH descriptor: [Gastrointestinal Hemorrhage] explode all trees
#86   MeSH descriptor: [Intracranial Hemorrhage, Traumatic] explode all trees
#87   hemorrhag*:ti,ab,kw
#88   hematoma*:ti,ab,kw
#89   MeSH descriptor: [Multiple Trauma] this term only
#90   multiple trauma*:ti,ab,kw
#91   multiple wound*:ti,ab,kw

#92   polytrauma*:ti,ab,kw
#93   multiple injur*:ti,ab,kw
#94   MeSH descriptor: [Soft Tissue Injuries] this term only
#95   soft tissue injur*:ti,ab,kw
#96   MeSH descriptor: [Spinal Cord Injuries] this term only
#97   spinal cord trauma*:ti,ab,kw
#98   spinal cord injur*:ti,ab,kw
#99   spinal cord transection*:ti,ab,kw
#100   spinal cord lacerat*:ti,ab,kw
#101   spinal cord contusion*:ti,ab,kw
#102   myelopath* trauma*:ti,ab,kw
#103   MeSH descriptor: [Trauma, Nervous System] explode all trees
#104   nervous system* trauma*:ti,ab,kw
#105   nervous system* injur*:ti,ab,kw
#106   cranio* trauma*:ti,ab,kw
#107   cranio* injur*:ti,ab,kw
#108   cerebrovascular trauma*:ti,ab,kw
#109   cerebrovascular injur*:ti,ab,kw
#110   vascular trauma*:ti,ab,kw
#111   vascular injur*:ti,ab,kw
#112   brain trauma*:ti,ab,kw
#113   brain injur*:ti,ab,kw
#114   head trauma*:ti,ab,kw
#115   head injur*:ti,ab,kw
#116   temporal trauma*:ti,ab,kw
#117   temporal injur*:ti,ab,kw
#118   skull trauma*:ti,ab,kw
#119   skull injur*:ti,ab,kw
#120   occipital trauma*:ti,ab,kw
#121   occipital injur*:ti,ab,kw
#122   parietal trauma*:ti,ab,kw
#123   parietal injur*:ti,ab,kw
#124   frontal trauma*:ti,ab,kw
#125   frontal injur*:ti,ab,kw
#126   forehead trauma*:ti,ab,kw
#127   forehead injur*:ti,ab,kw
#128   MeSH descriptor: [Accidental Falls] this term only
#129   fall*:ti,kw
#130   MeSH descriptor: [Venous Thrombosis] this term only
#131   MeSH descriptor: [Venous Thromboembolism] this term only
#132   MeSH descriptor: [Thromboembolism] this term only
#133   phlebothrombosis:ti,ab,kw

#134   phlebothromboses:ti,ab,kw

#135   venous thrombosis:ti,ab,kw

#136   venous thromboses:ti,ab,kw

#137   deep vein thrombosis:ti,ab,kw

#138   deep vein thromboses:ti,ab,kw

#139   deep venous thrombosis:ti,ab,kw

#140   deep venous thromboses:ti,ab,kw

#141   thromboembolism:ti,ab,kw

#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119 or #120 or #121 or #122 or #123 or #124 or #125 or #126 or #127 or #128 or #129 or #130 or

#142   #131 or #132 or #133 or #134 or #135 or #136 or #137 or #138 or #139 or #140 or #141

#143   #9 and #142

Appendix 2 – PRISMA Study Selection From Diagram

Identification

Records identified through database searching
(n =20 120)
MEDLINE (n = 11 226)
Embase (n = 5 712)

Records identified through other sources
(n = 3)

Records after duplicates removed
(n = 15 214)

Screening

Records screened by title and abstract
(n = 15 214)

Records excluded
(n = 15033)

Eligibility

Full-text articles assessed for eligibility
(n = 181)

Full-text articles excluded, with reasons
(n = 143)

Case Report (n=5)
Not AFOTS (n=83)
Cardiovascular Illness (n=12)
No Incidence/Recurrence/Risk Factors (n=8)
Review Article (n=18)
Surgical Population (n=9)
Duplicates (n=8)

Included

Studies included concerning AFOTS incidence
(n = 36)

Studies included concerning AF recurrence
(n = 2)

Appendix 3 – Meta Regression on Continuous Monitoring

Main results for Model 1, Random effects (MM), Z-Distribution, Logit event rate

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-2.3811	0.1568	-2.6884	-2.0737	-15.19	0.0000
Continuous Monitoring: 1	0.8679	0.2987	0.2826	1.4532	2.91	0.0037

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
$Q = 8.45$, df = 1, p = 0.0037
Goodness of fit: Test that unexplained variance is zero
$Tau^2 = 0.5665$, Tau = 0.7527, $I^2 = 99.50\%$, Q = 6868.44, df = 34, p = 0.0000

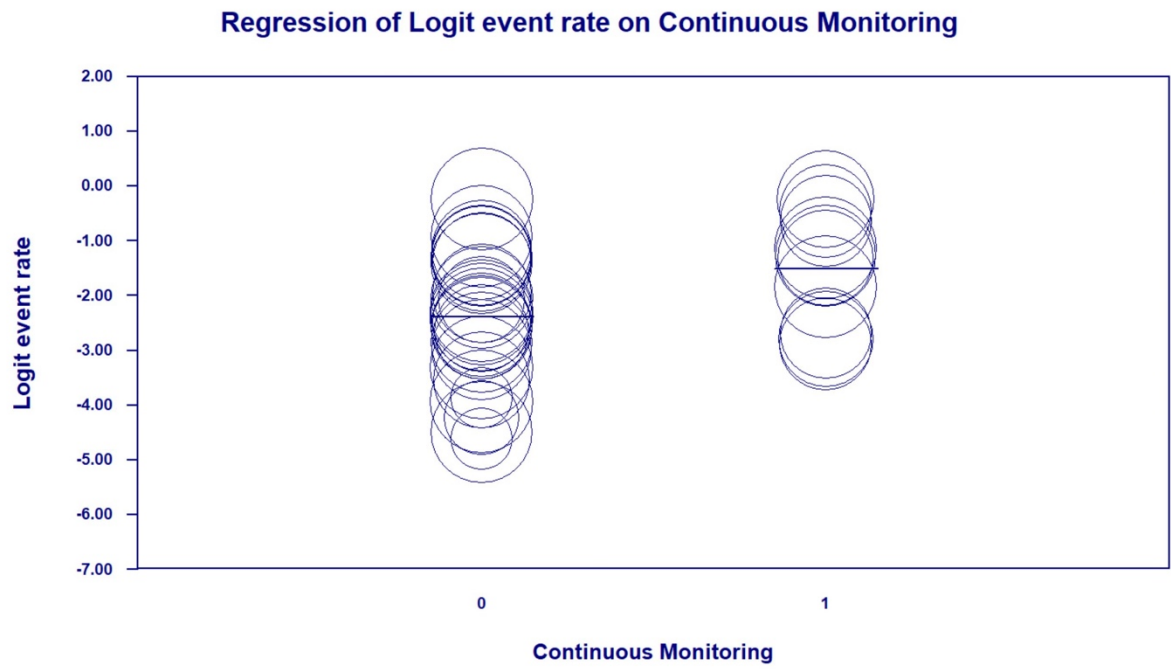**Comparison of Model 1 with the null model**

Total between-study variance (intercept only)
$Tau^2 = 0.6477$, Tau = 0.8048, $I^2 = 99.57\%$, Q = 8123.43, df = 35, p = 0.0000
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.13

Number of studies in the analysis   36

Appendix 4 – Meta Regression on ICU

Main results for Model 1, Random effects (MM), Z-Distribution, Logit event rate

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-2.9954	0.2989	-3.5813	-2.4096	-10.02	0.0000
Intensive Care: 1	1.1737	0.3533	0.4812	1.8662	3.32	0.0009

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 11.04, df = 1, p = 0.0009
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.8325, Tau = 0.9124, I^2 = 99.58%, Q = 8118.29, df = 34, p = 0.0000

Comparison of Model 1 with the null model

Total between-study variance (intercept only)
Tau^2 = 0.6477, Tau = 0.8048, I^2 = 99.57%, Q = 8123.43, df = 35, p = 0.0000
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.00 (computed value is -0.29)

Number of studies in the analysis   36
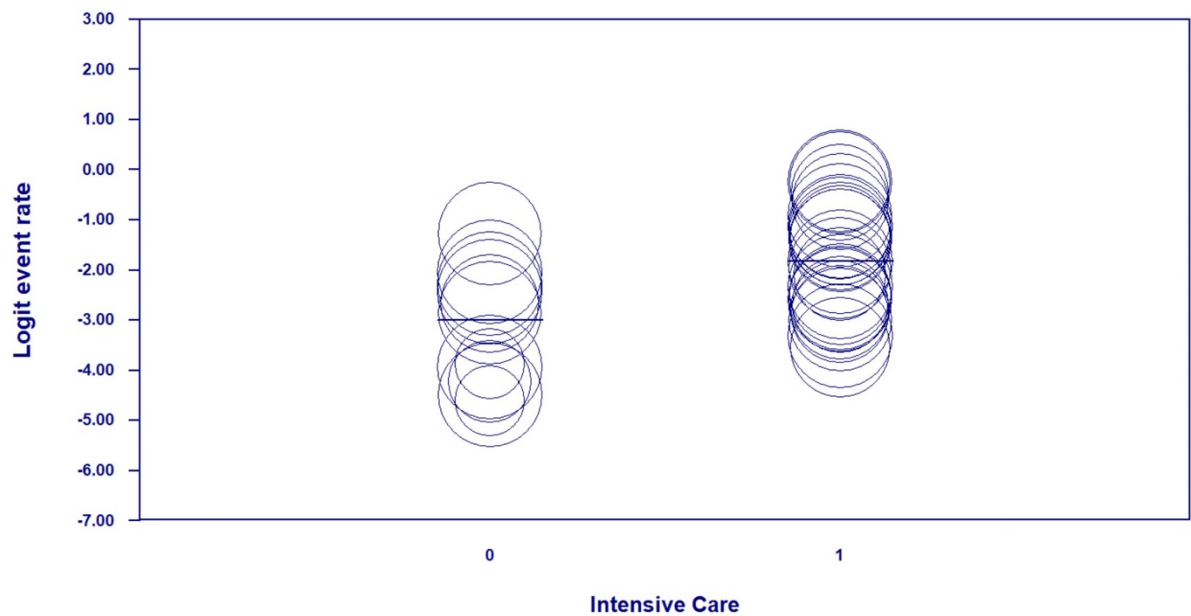
Appendix 5 – Risk Factors

RISK FACTORS	OR 95% CI	OR 95% CI	OR 95% CI	OR 95% CI
DEMOGRAPHICS				
Age per 10 years	1.79[65] 1.10-2.84	1.79[31] 1.48-1.97	1.22[113] 1.22-1.34	18.67[142] 3.11-117
	1.63[61] 1.10-2.37	1.34*,[77] 1.10-1.97	1.52[26] 1.47-1.56	
Age 65+	5.70[76] 4.21-7.71	7.00[86] 2.00-24.6		
Age 75+	1.26[a,66] 1.18-1.36	4.79[61] 1.16-19.8		
Age 85+	1.44[a,66] 1.33-1.55			
Male Gender	1.20[26] 1.11-1.32	1.06[66] 1.00-1.12	1.28[31] 1.01-1.62	
Non-White Race	0.67[b,26] 0.58-0.78	0.63[b,66] 0.57-0.70	0.68[c,26] 0.50-0.63	
	0.78[26] 0.69-0.87	0.69[66] 0.59-0.79	0.76[113] 0.63-0.93	
	0.73*,[31] 0.50-1.08	0.58*,[142] 0.36-0.93		
CO-MORBIDITIES				

Heart Failure	1.61[26] 1.41-1.83	0.94[66] 0.88-1.00	1.34[113] 1.22-1.46	1.47*,d,[31] 1.13-1.90
	2.81[127] 2.47-3.19	3.84[132] 1.45-10.15		
Chronic Kidney Disease	0.77[66] 0.72-0.84	2.46*,[31] 1.96-3.09		
Diabetes Mellitus	0.82[26] 0.75-0.90	1.37[76] 1.01-1.87	0.82[66] 0.78-0.87	1.49*,[31] 1.12-1.97
	0.73[127] 0.64-0.84			
Dyslipidemia	3.67[61] 1.17-11.5	10.04[132] 3.1-32.51		
Hypertension	0.88[26] 0.81-0.95	0.88[66] 0.83-0.95	0.87[127] 0.77-0.98	
Immunocompromised	1.38[31] 1.06-1.79			
Ischemic Heart Disease/ Myocardial Infarction	1.53[76] 1.28-1.84	0.94[66] 0.86-1.03	4.80*,[77] 2.95-7.80	1.47*,d,[31] 1.13-1.90
Malignancy	1.41*,[31] 1.01-1.97	1.23[26] 1.09-1.39		
Obesity	1.20[26] 1.03-1.40	1.37[31] 1.02-1.84	0.94[132] 0.88-0.99	
Prior Stroke	1.64[26] 1.35-2.01			
Charlson Index	0.77[127] 0.73-0.81			
ACUTE CONDITIONS				
Abdominal/GI Infection	1.77[26] 1.59-1.97	1.18[66] 1.08-1.30	0.74[127] 0.58-0.93	
Endocarditis	1.54[66] 1.23-1.92			
Fungal Infection	1.59[26] 1.27-2.00			
Infection, Gram +	1.29[26] 1.18-1.55			
Infection, Respiratory	1.27[26] 1.14-1.40	1.24[66] 1.17-1.32	0.85[127] 0.75-0.97	
Infection, Skin/Tissue	0.80[66] 0.70-0.93	1.33[26] 1.14-1.55	0.58[127] 0.4-0.82	
Infection, Urinary Tract	0.89[26] 0.81-0.99	0.71[66] 0.67-0.75	0.6[127] 0.53-0.68	
Sepsis	6.50[86] 2.00-21.0	4.87[81] 1.24-18.7		
Bacteremia	1.17[26] 1.02-1.36			
Inflammation	1.50[31]			

	1.24-1.82		
INTERVENTIONS			
Beta-blocker withdrawal	2.05[31],* 1.58-2.67		
Intensive Care Stay	2.47[66] 2.32-2.62		
Mechanical Ventilation	1.76[66] 1.65-1.87	2.15[113] 1.88-2.46	1.01*,[31] 0.73-1.40
Right Heart Catheterization	1.01*,[31] 0.43-2.37	2.25[26] 1.87-2.70	2.00[66] 1.66-2.41
Vasopressor Use	1.57[113] 1.33-1.84	4.20[64] 1.40-13.0	
ORGAN FAILURE			
Organ failure, cardiovascular	1.83[31] 1.40-2.41		
Organ failure, renal	1.53[31] 1.19-1.97	1.40[26] 1.26-1.56	1.57[i,66] 1.28-1.93
Organ failure, Respiratory	1.30*,[31] 1.09-1.55	2.81[26] 2.48-3.19	1.75[127] 1.47-2.1
Any organ failure	1.77[66] 1.66-1.88	0.69[127] 0.62-0.76	
Number of organs failing	1.12[26] 1.05-1.19		
DIAGNOSTIC TESTS			
Acidosis	0.87[26] 0.77-0.97		
Albumin	0.26[132] 0.11-0.63		
APACHE II Score	0.96[61] 0.90-1.03	3.90[81] 1.00-16.7	3.20[64] 1.1-9.3
LBBB on EKG	11.7*,[142] 2.1-66.0		
LAE on EKG	0.21*,[142] 0.05-0.87		
LVH on EKG	0.31*,[142] 0.12-0.83		
LVEF <45% on Echo	13.00[65] 1.36-124.2		
Serum Sodium	0.95*,[142] 0.91-0.99	1.08[60] 1.01-1.16	
MRC Dyspnea Score	1.74*,[77] 1.31-2.29		
LENGTH OF STAY			
Length of Stay in days	1.03[61] 1.01-1.06	0.69[31] 0.63-0.76	
Length of Stay > 7 days	1.83[66] 1.73-1.94		

* Univariate OR
a = versus ages 67-74

b= black race
c = Hispanic race
d= reported as "cardiovascular co-morbidity"
e = BMI

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AUTHORS' CONTRIBUTIONS

William McIntyre contributed significantly to the study's concept and design, data collection and analysis, and interpretation of the results. He wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

Kevin Um contributed to the data collection and analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Christopher Cheung contributed to the data collection and analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Emilie P Belley-Côté contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Orvie Dingwall contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

PJ Devereaux contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Jorge Wong contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

David Conen contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Richard Whitlock contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Stuart Connolly contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Collette Seifer contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Jeff Healey contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Chapter 4

Incidence and recurrence of new-onset atrial fibrillation detected during hospitalization for non-cardiac surgery:
A systematic review and meta-analysis

William F. McIntyre[1,2,3], Maria E. Vadakken[1], Anand S. Rai[1], Terry Thach[4],
Wajahat Syed[4], Kevin J. Um[2], Omar Ibrahim[2], Shreyash Dalmia[2],
Akash Bhatnagar[1], Pablo A. Mendoza[3], Alexander P. Benz[1,3],
Shrikant I. Bangdiwala[1,3], Jessica Spence[1,2,3], Graham R. McClure[5],
Jessica T. Huynh[2], Tianyi Zhang[1], Toru Inami[6], David Conen[1,2,3],
P.J. Devereaux[1,2,3], Richard P. Whitlock[1,2,5], Jeff S. Healey[1,2,3],
Emilie P. Belley-Côté[1,2]

1. Population Health Research Institute, McMaster University,
   Hamilton, Ontario, Canada
2. Department of Medicine, McMaster University, Hamilton, Ontario, Canada
3. Department of Health Research Methods, Evidence, and Impact,
   McMaster University, Hamilton, Ontario, Canada
4. Faculty of Health Sciences, McMaster University, Hamilton, Ontario,
   Canada
5. Department of Surgery, McMaster University, Hamilton, Ontario, Canada
6. Department of Cardiovascular Medicine, Nippon Medical School,
   Tokyo, Japan

Implication Statement

We performed a systematic review to assess the incidence of new-onset

postoperative atrial fibrillation and its long-term recurrence following non-cardiac

surgery. In 346 studies, the incidence ranged from 0.004% to 50.3%. In 13

studies, the recurrence ranged from 0-37.3%. Intensity of electrocardiographic

monitoring and surgery type may account for this wide variation.

STRUCTURED ABSTRACT

Purpose: This systematic review aimed to summarize reports of the incidence and long-term recurrence of new-onset Atrial fibrillation (AF) associated with non-cardiac surgery.

Sources: We searched CENTRAL, MEDLINE and EMBASE to November 2019. We included studies that reported on the incidence of new-onset perioperative AF during hospitalization for non-cardiac surgery and/or AF recurrence in such patients following discharge. Reviewers screened articles and abstracted data independently and in duplicate. We assessed study quality by appraising methodology for the ascertainment of past medical history of AF, incident AF during hospitalization, and AF recurrence after discharge.

Principal findings: From 39,233 citations screened, 346 studies that enrolled a total of 5,829,758 patients met eligibility criteria. Only 27 studies used prospective, continuous inpatient electrocardiographic monitoring to detect incident AF. Overall, the incidence of postoperative AF during hospitalization ranged from 0.004% to 50.3%, with a median of 8.7% (interquartile range 3.8-15.0%). AF incidence varied with type of surgery. Prospective studies using continuous ECG monitoring reported significantly higher incidences of AF than those that did not (13.9% versus 1.9%, p <0.0001). A total of 13 studies (25,726 patients) with follow-up as long as 5.4 years reported on AF recurrence following hospital discharge; only one study used a prospective systematic monitoring protocol. Recurrence rates ranged from 0-37.3%.

Conclusions: Rates of incidence of and long-term recurrence of AF first detected following non-cardiac surgery vary markedly. Differences in the intensity of electrocardiographic monitoring and type of surgery may account for this variation.

Registration: PROSPERO CRD42017068055 [01 September 2017]

INTRODUCTION

Atrial fibrillation (AF) is the most common serious heart rhythm disorder, and is frequently detected for the first time after surgery.[10,121,124] Published articles report a wide range in the incidence of new-onset perioperative AF.[10,40] The incidence of new-onset perioperative AF may vary according to the type of surgery, the baseline risk in the population under study, the approach to electrocardiography (ECG) monitoring, and the definition used for perioperative AF (e.g., ≥30 seconds AF duration, or AF detected on a monitor, or AF that results in symptoms or requires treatment).[10,40] New-onset perioperative AF has been associated with higher rates of adverse outcomes and mortality as well as longer length of hospital stay after non-cardiac surgery.[97,102,143] In the perioperative setting, AF often resolves before hospital discharge, and the long-term prognosis of patients with AF Occurring Transiently with Stress (AFOTS) is not well-defined.[10,42,144,145] The occurrence of AFOTS could be secondary to physiologic stressors associated with surgery with no long-term consequences; but it may also be newly detected paroxysmal AF.[10] Understanding whether AFOTS is a short-term problem or the first presentation of a chronic disease (i.e., paroxysmal AF) is critical, because the risk of ischemic stroke associated with paroxysmal AF can be reduced with oral anticoagulation (OAC).[10] Clinical practice guidelines and position statements have reinforced this position.[6-8,54,55,123] Variation in the incidence estimates and the risk of recurrence of

perioperative AF may contribute to the uncertainty in how to manage these patients.

The objective of this study was to systematically review the published literature in order to estimate: 1) the proportion of patients in whom new-onset AF is detected during hospitalization for non-cardiac surgery, and 2) the proportion of such patients in whom a recurrence of AF is detected over long-term follow-up. We also hypothesized that prospective studies with continuous ECG monitoring would have higher rates of AF detection than those that did not.

METHODS

Protocol

The original review protocol was pre-registered (PROSPERO CRD42017068055) [01 September 2017]. The differences between the original and final protocol are summarized below. Types of study to be included: We initially planned to include observational and interventional studies including more than ten participants. However, in order to make the number of eligible studies manageable, we changed this threshold to more than one hundred participants. Secondary outcomes: We initially planned to collect data on risk factors for development of atrial fibrillation during hospitalization for non-cardiac surgery. However, in order to make the review manageable and because these data are not readily combinable, we elected to forego collection of these data.

Eligibility criteria

This systematic review included prospective and retrospective observational studies of patients hospitalized for non-cardiac surgery. Included studies reported the incidence of new-onset AF during hospital admission for non-cardiac surgery, and/or the rate of AF recurrence following discharge from hospital in patients who had new-onset perioperative AF. We only included studies of >100 participants. We excluded data from patients with a history of AF before hospital admission and from patients underwent cardiac surgery.

Search strategy

We created the search strategy (e**Appendix 1**) with input from a librarian. We searched Ovid EMBASE (1974 – November 2019), Ovid MEDLINE (1946 – November 2019), and The Cochrane CENTRAL Library (Wiley) (November 2019). We did not impose language restrictions. The references of eligible papers were screened and experts were consulted to identify additional studies. We did not systematically hand-search conference abstracts or search or grey literature, but we did include conference abstracts that were captured by our database searches. Search results were imported into Covidence Systematic review software (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). Pairs of reviewers independently screened studies' titles and abstracts for eligibility using a pre-piloted template. If either reviewer thought the citation could be eligible, the full text article underwent evaluation for eligibility. Full texts of the potentially eligible studies were retrieved and screened by pairs of reviewers. Reviewers recorded the principal reason for exclusion. Disagreements were resolved through discussion. Reviewers recorded the principal reason for exclusion.

Data extraction and outcomes

Independently, pairs of reviewers extracted data pertaining to study and participant characteristics, AF incidence, and AF recurrence into a pre-piloted database. Disagreements were resolved through discussion. Reviewers recorded

type of surgery, methods for AF diagnosis, approach used to rule out a prior history of AF, and whether studies used continuous ECG monitoring. Standard Error (SE) for each study was calculated using the following formula: *SE= √ ((New-onset AF/Total Population) * (1- (New-onset AF/ Total Population))/Total Population).* We grouped studies according to the major organ system under operation. We included studies that combined multiple types of surgeries under the heading "Non-cardiac". Reviewers extracted the number of patients with AF and at risk, excluding those with a prior history of AF when this was reported. Reviewers contacted study authors to clarify ambiguities.

Methodological quality of included studies

Pairs of reviewers appraised the methodological quality of included studies using a pre-piloted tool based on the Newcastle-Ottawa Scale (**Table 1**).[40,125] The three domains evaluated in each study were: exclusion of patients with a history of AF, detection of AF in hospital, and detection of AF recurrence following the initial hospitalization. A score was allotted for each domain in each study. We considered studies to be of high-quality if they searched medical records to exclude patients with a history of AF, used prospective, continuous, and systematic ECG review to detect AF in hospital; and employed a systematic monitoring protocol to detect AF recurrence.

Meta-analysis and Subgroup Tests

We used CMA Software (Biostat Inc, Englewood, NJ) to perform analyses. For each study, we input the incidence of perioperative AF as binomial proportions and calculated the accompanying standard errors.[146] For the overall group of studies and for each type of surgery, we performed meta-analysis using a DerSimonian and Laird random effects model. [126] We assessed between-study heterogeneity quantitatively with the I^2 test and we planned to present a pooled estimate o only if $I^2 < 50\%$.[126] We hypothesized that prospective studies with continuous ECG monitoring (i.e. Quality Score 1 as defined in Table 1) would have higher rates of AF detection than those that did not, both in the overall population and in each different type of surgery. We tested this by creating a DerSimonian and Laird random effects model that pool studies based on quality score, and compared subgroup effects with an interaction test. In order to estimate of the proportion of variance explained by continuous monitoring, we created a binary logistic meta-regression model and calculated a goodness-of-fit statistic and accompanying R^2 analog.[147]

RESULTS

Screening Process

The electronic search generated 39,233 unique citations **(Figure 1)**. After reference and full-text screening, 346 studies met eligibility criteria, including 345 that reported AF incidence and 1 exclusively reported AF recurrence after

hospital discharge. Twelve reported data on both incidence and recurrence.

Incidence Studies

Study Characteristics

Three hundred and forty-five studies published between 1973 and 2019 reported the incidence of new-onset AF associated with non-cardiac surgery (**Table 2** and e**Appendix 2**). Five studies were published in Mandarin, 4 studies in Spanish, 2 studies in French, 2 studies in Japanese and 1 study was published in each of Hungarian, Russian, Icelandic, Romanian and Italian (e**Appendix 3**). The remaining studies were published in English. The Intensive Care Unit (ICU) was the primary setting in 55 studies. Seventy studies were prospective cohort studies and 275 were retrospective. One hundred and fifty-three studies included patients who underwent pulmonary surgery, 32 studies included patients who underwent esophagectomy, 20 studies included patients who underwent thoracic surgery not otherwise specified, 60 studies included patients who underwent abdominal or digestive surgery, 10 studies included patients who underwent vascular surgery, 26 studies included patients who underwent orthopedic surgery and 44 studies reported aggregate data from patients who had undergone different types of non-cardiac surgery. The mean age of patients in the included studies ranged from 32 to 80 years.

The methodologic quality of included studies varied greatly (e**Appendix 2)**. One hundred and sixty-two studies (47.0%) reported AF incidence after ruling out a prior history of AF based on high-quality methods – 74 (21.4%) described explicit searching of medical records to rule out a prior history of AF (Quality Score 1) and 88 (25.5%) reported that patients in the study did not have a history of AF but did not mention searching medical records (Quality Score 2). Only 27 (7.8%) studies monitored for AF using high quality methods (prospective design with continuous ECG monitoring, Quality Score 1); five (1.4%) of these studies used high-quality methods in both domains.

The incidence of new-onset AF during hospitalization for non-cardiac surgery reported in 345 studies (n = 5,829,758) ranged from <0.01% to 50.3%. **Table 2** reports the ranges of AF incidences according to type of surgery performed and whether continuous monitoring was used. **Figure 2** summarizes the estimates of the incidence of new-onset AF in studies that used continuous, prospective monitoring. Heterogeneity was substantial (I^2>90%) both overall, and by surgical subgroup (e**Appendices 4 and 5**); we therefore did not pool results to generate a summary estimate. We tested the hypothesis that prospective studies with continuous ECG monitoring would find higher incidences of AF. To do this, we created a random effects binary logistic meta-regression model that compared the incidence of AF in studies with AF ascertainment Quality Scores of 1 to those with AF ascertainment Quality Scores of 2,3 or 4 as defined in **Table 1**. Reported AF incidences were significantly higher in studies with continuous

monitoring as compared to those without (test of model $P < 0.001$). The

goodness-of-fit test (P <0.001) and R^2 analog 0.02 (e**Appendix 5**). However, it

suggested that only a small amount of variance (2%) was explained by

differences in monitoring intensity. We found no evidence of a subgroup effect

when comparing studies using continuous monitoring to those that did not across

surgical subtypes (e**Appendix 4**).

Studies of Long-term Recurrence of AF

Thirteen studies (n = 25,726) reported the long-term recurrence of AF

following the index hospitalization (**Table 3**). Follow up ranged from 1 month to

5.4 years after discharge. Four studies were prospective cohort studies and 9

were retrospective. Follow-up duration and the methods used for AF detection

varied markedly (**Table 3**). Only one study was assessed as having high quality

methods for AF detection – Higuchi et al used a systematic 12-month protocol for

the surveillance of AF recurrence in cancer surgery patients with postoperative

AF. Seventy-seven patients with confirmed postoperative AF wore either a 2-

week event-triggered recorder or a 24-hour Holter monitor at 1 month and 12

months postoperatively. AF recurrence of at least 30 seconds, as confirmed by a

cardiologist, was documented in 24 (31.1%) patients. Four other studies reported

AF recurrence rates of greater than 15%. Jesel et al followed patients with

postoperative AF following lung transplant for an average of 2.9±2.4 years.[148]

Patients were assessed weekly for 3 months, then monthly until 1 year and every

3 months thereafter. AF was documented by 12-lead ECG or ambulatory ECG

monitoring, as reviewed by 2 cardiologists. The rate of AF recurrence was 16.5%. Rachwan et al followed patients who developed postoperative AF following liver transplant.[149] All were discharged from hospital in sinus rhythm. Of the 42 that had a 12-lead ECG in follow-up, 10 (24%) were in AF. Gialdini et al used administrative claims data to identify Californian patients with new-onset peri-operative AF.[29] Among 12,874 patients with no prior history of AF who developed new-onset perioperative AF, 4799 (37.3%) had another healthcare encounter for AF in the ensuing 12 months. Kim and colleagues used a similar approach with 11,347 patients in South Korea, finding that over a median of 47 months of follow-up, 2289 (20.2%) had another encounter for AF.[150]

DISCUSSION

In this systematic review, we found that among 345 published articles, the reported incidence of new-onset AF during hospitalization for non-cardiac surgery ranged anywhere from very rare (<0.01%) to extremely common (~50%). This variability prohibited pooling data, even when reports of the same type of surgery were considered. Consistent with our hypothesis, prospective studies that used continuous ECG monitoring found higher incidences of AF than those that did not. Although some of the variability in study results was explained by detection methods and different surgical populations, much remains unexplained. There was similar variability in the thirteen articles reporting on the long-term rate of AF recurrence in this population. Several studies, however, reported recurrence

rates upwards of 20%. Rigorously designed studies with continuous and prospective monitoring are required to more accurately and precisely estimate the incidence and long-term recurrence of new-onset postoperative AF in patients who have undergone non-cardiac surgery.

To the best of our knowledge, this is the first systematic review to broadly assess the incidence and recurrence of new-onset perioperative AF following non-cardiac surgery. Most reviews to date have focused on cardiac surgery.[151,152] Reviews in non-cardiac surgery have assessed surgical sub-populations and did not systematically assess study methodology for detection.[33,34] This review has two important strengths. First, when possible, we excluded data from patients with a prior history of AF to isolate the population for whom the long-term prognosis is in question. Second, our methodological appraisal focused on methods used for AF detection and specifically tested the hypothesis that prospective studies with continuous ECG monitoring reported higher incidences of AF. As AF is often an intermittent arrhythmia, the probability of detecting AF increases with the intensity of ECG monitoring.[9,120,153] As in our previous review of medical patients, studies with continuous monitoring found a significantly higher incidence of AF, although meta-regression modeling suggested significant unexplained variance.[82] These findings have informed the design of the AFOTS incidence study (NCT03552588) which is enrolling consecutive at-risk patients admitted to an ICU and continuously monitoring them with a continuous ECG monitor for up to 14 days.[154]

Accurate estimates of the incidence of new-onset peri-operative AF are critical to guide future research in this patient population. There is interest in preventing new-onset perioperative AF and in optimizing outcomes for patients who develop it.[6-8,54,55,123] New-onset perioperative AF has been associated with adverse outcomes during the index hospital stay in at least two large, multi-centre studies.[97,143] However, the incidences of new-onset AF in these two studies (2.5 and 3.0%) are at the lower end of what we found in this review.[97,143] Confounding may explain these findings; AF may be noticed more frequently in patients who are more acutely ill with closer monitoring and in patients with longer lengths of stay with longer monitoring. In addition, worse outcomes for patients with AF could be explained by a higher burden of co-morbidities.[14,18,155] This review underscores the need for standardized detection of AF to minimize detection bias using prospective designs with continuous ECG monitoring. Continuous monitoring will also help estimate the minimum burden of AF that is associated with adverse outcomes.

Evidence is lacking to guide the long-term management of patients with new-onset perioperative AF. The majority of patients are discharged from hospital in sinus rhythm, whether it is due to spontaneous, pharmacological, or electrical cardioversion.[144,145] However, clinicians are faced with the decision as to whether these patients should be treated for AF, with the most pressing question being whether to start them on long-term OAC. New-onset perioperative AF has been associated with an increased long-term risk of stroke in large observational

studies.[28-30] However, the incidences of AF in these studies is again at the lower end of what was seen in our review (0.4%, 0.8%, 2.2%), raising the question of selection bias.

We assessed long-term rates of AF recurrence in this population. This interest was driven by the hypothesis that patients who have a recurrence of AF following an initial presentation of AF perioperatively could be more likely to have paroxysmal AF and might therefore benefit from OAC.[10,42,156] However, we found very wide ranges in the long-term recurrence of AF. Only one 77-patient study systematically re-assessed patients using long-term ECG monitoring and found a cumulative recurrence rate of 31.1% over one year.[156,157] Long-term ambulatory ECG monitoring may identify patients with recurrent AF who might benefit from OAC as we await the results of randomized clinical trials. Ongoing studies are attempting to better define the long-term prognosis and management of this population. The AFOTS follow-up study attempts to overcome some of the limitations of prior studies.[42] This study identifies patients with new-onset AF during hospitalization for medical illness or non-cardiac surgery who have returned to sinus rhythm at the time of hospital discharge. Cases and matched controls wear two 14-day Holter monitors over the ensuing 12 months. At least one randomized trial is being conducted in this population –Anticoagulation for Stroke Prevention In Patients With Recent Episodes of Perioperative Atrial Fibrillation After Noncardiac Surgery (ASPIRE-AF) is a pilot trial (NCT03968393) assessing the feasibility of a full study of OAC versus no OAC in this population.
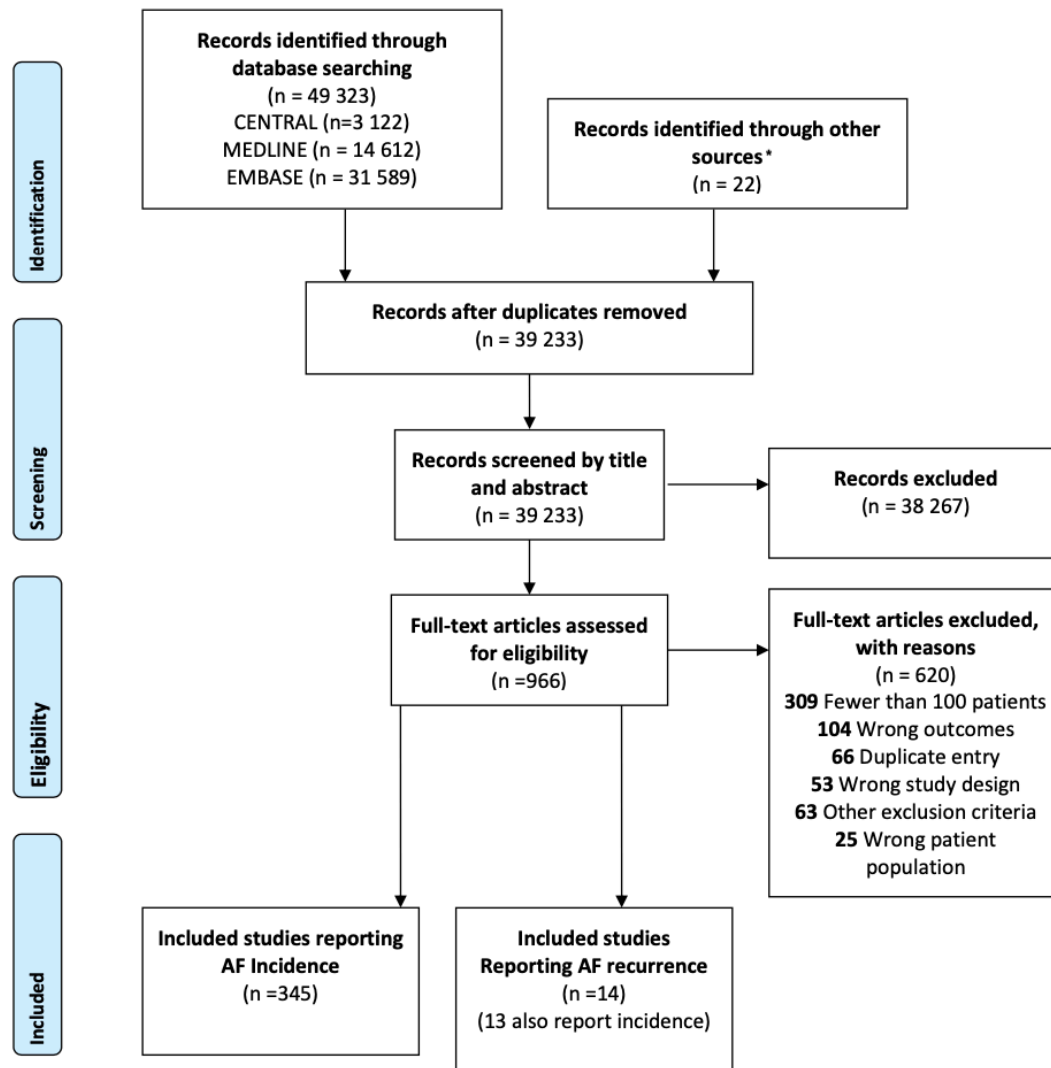
Limitations of review

This review is principally limited by the design and methodologic descriptions of the included studies. Most studies were either single centre or combined heterogeneous types of surgery. A small number of studies defined the minimum length of AF episodes they considered to be relevant. We did not collect data on the long-term risk of stroke associated with new-onset AF following non-cardiac surgery in this review. We are, however, assessing this in a separate, dedicated review (PROSPERO 2017:CRD42017054309).

CONCLUSIONS

Rates of incidence of and long-term recurrence of AF first detected following non-cardiac surgery vary markedly. Differences in the intensity of ECG monitoring and type of surgery may account for this variation. Atrial fibrillation recurs after hospital discharge in up to 37% of patients.

Figure 1. Study Selection Diagram (PRISMA Format)

* Identified by experts or by screening the references of eligible studies

Figure 2. Incidence of New-onset Atrial Fibrillation After Non-cardiac Surgeries in Prospective Studies that Used Continuous ECG

Study name	Statistics for each study			Event rate
	Event rate	Lower limit	Upper limit	
Pulmonary Surgery Amar D. 2000	0.182	0.144	0.227	
Pulmonary Surgery Amar D. 2015	0.139	0.090	0.207	
Pulmonary Surgery Barbetakis 2004	0.191	0.142	0.252	
Pulmonary Surgery Cagirici U. 2005	0.073	0.038	0.134	
Pulmonary Surgery Ciszewski P. 2013	0.162	0.106	0.241	
Pulmonary Surgery Curtis J. 1998	0.211	0.145	0.295	
Pulmonary Surgery Gomez-Caro A. 2006	0.114	0.072	0.176	
Pulmonary Surgery Jesel L. 2017	0.337	0.282	0.398	
Pulmonary Surgery Khalil M. 2013	0.140	0.116	0.169	
Pulmonary Surgery Mita N. 2017	0.207	0.143	0.290	
Pulmonary Surgery Nojiri 2010	0.230	0.165	0.312	
Pulmonary Surgery Pu 2019	0.222	0.171	0.284	
Pulmonary Surgery Riber 2014	0.202	0.157	0.258	
Pulmonary Surgery Salvatici 2010	0.180	0.145	0.221	
Pulmonary Surgery Tisdale 2009	0.238	0.173	0.319	
Esophagectomy Hou JL. 2008	0.077	0.043	0.134	
Esophagectomy Ojima 2017	0.200	0.133	0.290	
Thoracic Surgery Cardinale D. 1999	0.122	0.084	0.173	
Thoracic Surgery Cardinale D. 2007	0.180	0.145	0.221	
Thoracic Surgery Cardinale D. 2016	0.087	0.071	0.105	
Thoracic Surgery Salvatici 2014	0.252	0.213	0.295	
Thoracic Surgery Xie 2018	0.125	0.080	0.190	
Vascular Surgery Brathwaite 1998	0.077	0.054	0.107	
Vascular Surgery Winkel 2010	0.037	0.024	0.057	
Noncardiac Surgery Higuchi 2019	0.102	0.083	0.126	
Noncardiac Surgery Seguin 2004	0.053	0.036	0.078	
Noncardiac Surgery Xia 2014	0.120	0.094	0.152	
Overall Incidence	0.145	0.120	0.175	

0.00   0.10   0.

*All studies in this plot have a Quality Score of 1 for Methods for Detection of AF in Hospital, as defined in Table 1 of the Main Paper.

^The solid square symbols for each study are proportional in area to that study's weight in the analysis.

Table 1. Quality assessment framework

Domain	Methods for Exclusion of a History of AF	Methods for Detection of AF in Hospital	Methods for Detection of AF Following Hospital Discharge
Applicable studies	*Incidence and recurrence studies*	*Incidence and recurrence studies*	*Recurrence studies only*
Score 1	✪ Demonstration of searching a prior source (e.g., medical records)	✪ Continuous monitoring and systematic ECG review	✪ Systematic ECG monitoring protocol
2	✪ Reported as no history of AF	Routine ECGs or prospective, continuous monitoring without systematic review	Systematic search for collected ECGs
3	Terms like "new-onset" are used without meeting selections 1 or 2	Retrospective review of ECGs collected non-systematically	Systematic review of diagnoses or non-systematic search for collected ECGs
4	No description	No description	No description

✪ Denotes item identified as "high quality" in this domain.

Table 2. Median Incidence of New-Onset Atrial Fibrillation According to Type of Surgery

Surgery Type	Continuous Monitoring n=27 Studies			No Continuous Monitoring n=318 studies		
	N Studies	Total Number of Patients	Median and Ranges of AF Incidence by Study	N Studies	Total Number of Patients	Median and Ranges of AF Incidence by Study
Pulmonary Resection/Transplant	15	3300	19.1%; 7.3-33.7%	138	432,661	11.9%; 0.1-50.3%
Esophagectomy	2	242	13.9%; 7.8-20.0%	30	13,421	13.4%; 1.1-27.7%
Thoracic Surgery NOS*	5	2280	12.5%; 8.7-25.2%	15	19,706	16.0%; 1.1-29.0%
Abdominal Surgery	-	-	-	60	194,498	3.3%; 0.004-16.9%
Vascular Surgery	2	917	5.7%; 3.7-7.7%	8	29,135	5.4%; 3.7-22.6%
Orthopedic Surgery	-	-	-	26	585,613	3.0%; 0.1-9.3%
Other	3	1705	10.2%; 5.3-12.0%	41	4,546,280	3.6%; 0.3-17.2%
Total	27	8444	16.2%; 3.7%-33.7%	318	5,821,314	8.1%; 0.004%-50.3%

*NOS: not otherwise specified

Table 3 Characteristics of Included Studies on AF Recurrence for Atrial Fibrillation after non-cardiac surgery

Study ID	Condition	Design	Setting	Age	History of AF Ascertainment and Quality Score*		New-Onset AF Ascertainment and Quality Score*		AF Recurrence Ascertainment and Quality Score*		New-Onset AF (N)	Recurrent AF (N)	Recurrence Rate	Follow up time
Cardinale 1999[158]	Pulmonary Thoracotomy	Prospective Cohort Study	ICU	59±11 y	Patients with history of AF were excluded	2	Continuous ECG Monitoring Daily; 12-Lead ECG	1	Monthly follow-up questionnaire for symptoms related to AF	3	26	1	3.8%	18±8 mo.
Ciriaco 2000[159]	Pneumonectomy	Retrospective Cohort Study	Hospital	64± 10 y	Patients with history of AF were excluded after medical records review	1	Continuous ECG Until Postop Day 3	2	Patients seen in clinic and assessed for symptoms of AF	4	22	0	0%	7-21 mo.
Curtis 1998[90]	Pneumonectomy	Prospective Cohort Study	ICU	60 y	Mentions AF as postoperative complication	3	Holter Monitor with Continuous ECG Monitoring	1	Patients were assessed for AF after discharge in clinic, not all patients received ECG	3	24	0	0%	1-1.5 mo.
Garner 2017[160]	Pneumonectomy	Retrospective Review	Hospital	67 y	Patients were excluded if they had an arrhythmia history, or if were on any antiarrhythmics	2	Routine ECG With ECG Prior To Discharge	2	ECG at follow-up visit	2	43	3	7%	At 1 mo.
Gialdini 2014[29]	Non-cardiac Surgery	Retrospective Review	Hospital	72±12 y	Review of medical records	1	ICD Diagnosis	3	According to ICD-9 Codes. Follow-up visit with ECG monitoring	3	12, 874	4799	37.3%	Up to 12 mo.
Henri 2012[161]	Pulmonary Transplantation	Retrospective Cohort Study	Hospital	47 y	Patients with history of AF excluded through medical record review	1	12-lead ECG, telemetry monitoring performed during the postoperative period	2	Postoperative clinic follow-up and chart review at 1 Year postop.	3	221	8	3.6%	Up to 12 mo.
Higuchi 2019[157]	Oncological Non-cardiac Surgery	Prospective Cohort Study	Hospital	68 ± 11 y	Review of medical records	1	Patients medical records, ICD codes	3	Continuous recorder used for AF surveillance for approximately 2 weeks at postoperative months 1 and 12.	1	77	24	31.3%	Up to 12 mo.
Hyun 2018[162]	Pneumonectomy	Retrospective Review	Hospital	67 y	Review of medical records	1	No description	4	No Description	4	449	60	13.4%	Up to 24 mo.
Jesel 2018[163]	Pulmonary Transplantation	Prospective Cohort Study	ICU	49 ± 14 y	Mentions patients with h/o AF as separate subgroups	1	Continuous ECG Monitoring Daily; 12-Lead ECG	1	AF documented via 12-lead, ambulatory ECG monitoring	2	79	13	16.5%	2.9±2.4 y

Kim 2019[164]	Non-cardiac Surgery	Retrospective Cohort Study	National Health Insurance Service	66 [57-73] y	No Description	4	No Description	4	According to ICD-10 code I48. ECG's reviewed on hospitalization or outpatient visits	3	11, 347	2,289	20.2%	3.9 y (2.0–6.2)
Lee 2010[165]	Thoracic Surgery	Retrospective Cohort Study	ICU	52±16 y	Patients with history of AF excluded through medical record review	1	Retrospective routine 12-lead ECG, continuous ECG monitoring in ICU	2	Follow-up phone call with patients to determine new symptoms, medications or diagnoses for AF. Charts were reviewed.	3	508	40	7.9%	5.4±2.9 y
Rachwan 2020[149]	Liver Transplantation	Retrospective Cohort Study	Hospital	57 ± 11 y	Patients with history of AF were excluded	2	ECG done	2	12 lead ECGs done on select patients	2	42	10	24%	Up to 90 d
Turaga 2009[166]	Abdominal Surgery	Retrospective review	University Hospital	67 ± 9 y	Mentions AF as postoperative complication	2	AF confirmed by 12 Lead ECG	3	Patients were followed up in clinic. No other description	4	14	0	0%	Not specified

*High Quality = 1 and Low Quality = Quality Scores 2,3 or 4 for Methods for Detection of AF in Hospital, as defined in Table 1 of the Main Paper
AF = Atrial Fibrillation, ECG = Electrocardiogram, ICD = International Classification of Diseases, ICU = Intensive Care Unit

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Chapter 5

Device-Detected Atrial Fibrillation Before and After Hospitalization for Non-cardiac Surgery or Medical Illness: Insights from ASSERT

William F. McIntyre[1], Jia Wang[1], Alexander P. Benz[1], Emilie P. Belley-Côté[1], David Conen[1], P.J. Devereaux[1], Jorge A. Wong[1], Stefan H. Hohnloser[2], Alessandro Capucci[3], Chu-Pak Lau[4], Michael R. Gold[5], Carsten W. Israel[6], Richard P. Whitlock[1], Stuart J. Connolly[1], Jeff S. Healey[1]

1. Population Health Research Institute, McMaster University, Hamilton, Canada
2. Department of Electrophysiology, J.W. Goetshe University, Frankfurt, Germany
3. Department of Cardiovascular Sciences, Università Politecnica delle Marche, Ancona, Italy
4. Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong, China
5. Department of Medicine, Medical University of South Carolina, Charleston, South Carolina
6. Evangelical Hospital Bielefeld, Department of Medicine, Division of Cardiology, Bielefeld, Germany

ABSTRACT

Background

Atrial fibrillation (AF) is often detected during hospitalization for surgery or medical illness and is often assumed to be due to the acute condition.

Methods

ASSERT enrolled patients $\geq$65 years old without AF. Pacemakers or implantable cardioverter defibrillators recorded device-detected AF. We identified participants who were hospitalized and compared the prevalence of AF before and after hospitalization.

Results

Among 2580 participants, 436 (16.9%) had a surgical or medical hospitalization. In the 30 days following a first hospitalization, 43 participants (9.9%, 95% confidence interval [CI] 7.2%-13.1%) had >6 minutes of device-detected AF; 20 (4.6%, 95% CI 2.8%-7.0%) had >6 hours. More participants had AF >6 minutes in the 30 days following hospitalization, as compared to the period 30-60 days before hospitalization (9.9% versus 4.4%, $P < 0.001$). Similar results were observed for episodes >6 hours (4.6% versus 2.3%, $P = 0.03$).

Roughly half of participants with device-detected AF in the 30 days following hospitalization had $\geq$1 episodes of the same duration in the 6 months prior (50% [95% CI 31.3%-68.7%] for >6 minutes; 68.8% [95% CI 41.3%-89.0%] for >6 hours). Those with AF in the 30 days following hospitalization were more likely to have had AF in the past (adjusted OR 7.2 95%CI 3.2-15.8 for episodes >6 minutes; adjusted OR 32.6, 95%CI 10.3-103.4 for >6 hours).

Conclusions

The prevalence of device-detected AF increases around the time of hospitalization for non-cardiac surgery or medical illness. About half of patients with AF around the time of hospitalization previously had similar episodes.

What's new?

The prevalence of pacemaker-detected atrial fibrillation (AF) increases around the time of hospitalization for non-cardiac surgery or medical illness. About half of patients with AF in this setting have a prior history of pacemaker-detected AF. Further research is needed to assess the management of patients with new-onset AF detected during hospitalization for non-cardiac surgery or medical illness. The roles of follow-up ECG monitoring and oral anticoagulation must be defined.

INTRODUCTION

Atrial fibrillation (AF) is often detected for the first time when patients are hospitalized due to an acute physiologic stressor such as surgery or medical illness (*e.g.* infection, pulmonary embolism).[10,40] It is unclear whether AF detected in these settings (AF Occurring Transiently with Stress; or AFOTS) is secondary to reversible triggers (*e.g.* inflammation, ischemia, metabolic disturbances, adrenergic surge, *etc.)* or is a manifestation of a recurring arrhythmia (*e.g.* paroxysmal AF) that has been detected by inpatient ECG monitoring.[10] This distinction is important, since patients in whom AF was due to a reversible cause would not be expected to benefit from chronic oral anticoagulation (OAC) therapy to reduce their risk of ischemic stroke. Previous studies have assessed the long-term prognosis of patients with AFOTS by detecting the recurrence of AF after hospital discharge or identifying the occurrence of adverse events.[26,29,40,42,46] Knowledge of the patient's rhythm history *before* the stressor would be useful to establish temporality and assess a potential causal relationship between physiologic stress and AFOTS in patients without previously documented AF.

Contemporary implantable cardiac rhythm devices (*i.e.* pacemakers, implantable cardioverter defibrillators and loop recorders) capture and store continuous rhythm data; this permits a complete and unbiased review of past arrhythmic episodes. These devices frequently capture episodes of AF without recognizable symptoms.[36,37] This phenomenon has been termed *subclinical AF*.[38,39] Review of the temporal profile of device-detected AF before and after a physiologic stressor may provide insight into the pathophysiology of AF

associated with stress. If a high proportion of patients with device-detected AF around the time of stress also have device-detected AF *prior* to stress, it is less likely that episodes of AFOTS are directly due to the physiologic stressor and more likely that AFOTS is a manifestation of paroxysmal AF.

The objective of this study was to use continuous heart rhythm profiles from patients enrolled in the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) to compare the prevalence of episodes of device-detected AF before and after physiologic stress events. We hypothesized that the prevalence of device-detected AF would increase around the time of hospitalization for medical illness or non-cardiac surgery. Additionally, we hypothesized that device-detected AF around the time of hospitalization would be associated with prior episodes of device-detected AF.

MATERIAL AND METHODS

The design, rationale and primary results of ASSERT have been published previously.[35,37] The trial enrolled 2580 patients, aged ≥65 years and with a history of hypertension who recently underwent implantation of a St. Jude Medical (St Paul, Minnesota) dual-chamber pacemaker or implantable cardioverter-defibrillator. Patients were excluded if they had a history of AF or atrial flutter or if they required OAC therapy for any reason. An institutional review committee at each participating center approved the primary study and participants provided written informed consent. Device electrograms showing AF (atrial rate >190 bpm

for >6 minutes) were adjudicated centrally. These parameters for rate and duration were chosen for consistency with the original ASSERT analysis, where episode durations of >6 minutes had a false positive rate of 17%.[167] Over a mean follow-up of 2.5 years, device-detected AF of >6 minutes in duration occurred in >40% of participants.[35,37] For this *post hoc* analysis, we examined stored device data including the date, time of onset, and duration of device-detected AF episodes over the follow-up period.[38]

Hospitalization Events

During ASSERT, site investigators recorded the occurrence and date of clinical events including hospitalizations. Hospitalizations were defined as an overnight stay in hospital. Hospitalizations were reviewed and classified as surgical and medical. Hospitalizations for cardiac surgery and primary cardiac diagnoses (e.g. myocardial infarction, heart failure, etc.) were excluded from this analysis, as they are thought to have a different physiology and prognosis than hospitalizations for non-cardiac reasons.[10] Study participants with a first hospitalization were the subject of this analysis. The date of a medical or surgical hospitalization was designated as time "zero". Thus, episodes of device-detected AF happening before and after the initial date of hospitalization were considered as occurring in negative and positive time, respectively.

Statistical Analyses

We conducted statistical analyses with SAS 9.4 software (SAS Institute, Inc., Cary, NC, USA). All analyses were limited to patients with complete rhythm

data in the time window of the analysis. P values were two-sided with significance level at p<0.05. Normalities of continuous variables were examined by visual inspection of histogram with fitted normal curve and Q-Q plot and assessment of skewness and kurtosis. Comparisons of continuous baseline variables between patients with and without device-detected AF in the 30 days following the hospitalization were performed with the *t* test or Wilcoxon rank-sum test, as appropriate. Categorical variables between groups were compared with Chi-square test or Fisher's exact test, depending on the expected cell count.

Our primary analysis was designed to assess the association of physiologic stress on the occurrence of device-detected AF. We assessed this graphically by plotting the prevalence of AF with accompanying 95% confidence intervals (CI) in 3-month intervals before and after the date of hospitalization. To assess this statistically, we compared the proportion of patients with at least one episode of AF in the 30, 90 and 180 days following hospitalization to a period of equal duration prior to the hospitalization. For this comparison, we blanked the 30 days immediately prior to hospitalization, because of uncertainty in defining the precise onset of illness. Therefore, we compared to the periods from days -60 to -30, days -120 to -30 and days -210 to -30, respectively. We performed this comparison for episodes of >6 minutes, >6 hours and >24 hours and separately for a first medicsl and surgical hospitalization using McNemar's test for paired data. For this analysis, we only included study participants with full heart rhythm data over the corresponding time window.

Our secondary analysis was designed to assess whether patients with device-detected AF during physiologic stress had a prior history of device-detected AF. In a nested case-control analysis, we compared the incidence of device-detected AF in the period that preceded a hospitalization between patients with and without device-detected AF in the 30 days following the hospitalization. As in our primary analysis, we blanked the 30 days immediately prior to hospitalization. Specifically, we compared the 6-month period occurring between 30 and 210 days prior to hospitalization. The association between prior device-detected AF and device-detected AF during physiologic stress was analyzed with a logistic regression model adjusting for CHA_2DS_2-VASc score. We reported adjusted odds ratios (OR) and corresponding 95% CI. We performed this analysis using device-detected AF durations of > 6 min, > 6 hours and >24 hours on the overall population as well as the medical and surgical subgroups. For this analysis, we only included study participants with full heart rhythm data over the corresponding time window.

RESULTS

Among 2580 patients enrolled in ASSERT, 436 (16.9%) had at least 1 documented hospitalization and complete heart rhythm data for the primary analysis; 257 had only 1 hospitalization; 112 had 2 hospitalizations; 47 had 3 hospitalizations; 15 had 4 hospitalizations and 5 had 5 hospitalizations. Among 436 patients with a hospitalization, 13 (3.0%) patients had their first-ever episode of device-detected AF >6 in the 30 days following their first hospitalization.

Among those patients, 8 (61.5%) had at least one more episode of AF >6 minutes during the remainder of study follow-up. Only 3 (0.69%) out of the 436 participants had AF reported on surface ECG within 30 days following the first hospitalization. **Table S1** compares baseline characteristics of patients who were and were not hospitalized during the follow up period. Median time from enrolment to first hospitalization was 432 days and median time from the first hospitalization to end of follow-up was 563 days.

Table 1 shows the characteristics of patients with and without device-detected AF > 6 minutes within 30 days of hospitalization. The median CHA_2DS_2-VASc score did not differ between the two groups (4.0; IQR 3.0-5.0, p = 0.90), nor did any other baseline characteristic.

Figure 1 shows the 30-day prevalence of device-detected AF >6 mins, >6 hours and > 24 hours according to time from hospitalization, respectively. Among 436 patients with a first medical or surgical hospitalization, the incidence of device-detected AF >6 minutes in the 30 days following the date of hospitalization was 9.9% (95% CI 7.2%-13.1%), while the incidence of device-detected AF >6 hours was 4.6% (95% CI 2.8%-7.0%) and the incidence of device-detected AF >24 hours was 3% (95% CI 1.6%-5.0%). Among 336 participants with a first medical hospitalization, the incidence of device-detected AF >6 minutes in the 30 days following the date of hospitalization was 10.1% (95% CI 7.1%-13.9%) and among 212 participants with a first hospitalization for non-cardiac surgery, the incidence of device-detected AF >6 minutes was 7.5% (95% CI 4.4%-12.0%).

Table S2 shows the prevalence of device-detected AF > 6 mins within 30 days after each recurrent hospitalization, up to the 4th hospitalization.

Table 2 shows the proportion of patients with device-detected AF in the 30 days before and after the date of a first medical or non-cardiac surgical hospitalization. In 30-day sampling windows, a significantly higher proportion of patients had device-detected AF following hospitalization as compared to prior to hospitalization. However, this difference was not significant when comparing 90- and 180-day before-and-after sampling windows.

Table 3 shows the association between the incidence of device-detected AF within 30 days after hospitalization and a prior history of device-detected AF. The majority of patients with device-detected AF in the 30 days following hospitalization had at least one episode of device-detected AF of the same duration in the 6 months prior to hospitalization. Patients with device-detected AF in the 30 days following hospitalization were also significantly more likely to have had a prior history of device-detected AF than those who did not have device-detected AF in the 30 days following hospitalization. The magnitude of the association increased with longer episode durations and was consistent when only a first medical or surgical hospitalization was considered.

As compared to patients who did not have device-detected AF within 30 days of hospitalization, patients who had device-detected AF within 30 days after hospitalization were more likely to have AF detected by surface ECG during subsequent follow-up (8.1%/year versus 1.2%/ year, hazard ratio [HR] 6.6, 95% confidence interval [CI] 1.9-22.4; p =0.003). However, there were no significant

differences in thromboembolic events (0.0%/year versus 1.4%/year), in

hospitalization for heart failure (7.2%/year versus 4.0%/year, HR 1.9, 95% CI 0.6-

5.4, p = 0.3), or in all-cause mortality (17.8%/year versus 9.7%/year, HR 1.8, 95%

CI 1.0-3.5 p = 0.063).

DISCUSSION

We observed device-detected AF in approximately 10% of patients in the

30 days following a hospitalization for a medical or non-cardiac surgical reason.

This is within the range observed in earlier studies of clinical AF,[10,28,40,154] but is a

more accurate estimate, as implanted pacemakers facilitated complete and

unbiased ascertainment of AF for all participants. Although device-detected AF

was more frequent following hospitalization, a majority of patients who developed

device-detected AF had at least one similar episode of AF in the period prior to

hospitalization. This pattern suggests that physiologic stress may be an acute

trigger for AF. However, it also suggests these episodes of AF are often a

manifestation of a condition that is likely to recur.

We found that the prevalence of device-detected AF > 6 minutes in the 30

days following the date of hospitalization was 9.9% with 95% CI 7.2%-13.1%.

This remained consistent up to the 4th hospitalization, with point estimates

ranging from 7.8-10.4%. These estimates are within the expected range shown in

our systematic review, where the incidence of new-onset AF detected by surface

ECG ranged from 1-44% overall and 1-22% in patients who were not being cared

for in an intensive care unit.[40] However, only 0.69% of the 436 study participants

had AF detected on surface ECG within 30 days following the first hospitalization. This highlights the value of a continuous implantable monitor to permit precise, accurate and unbiased measurements of AF pattern and burden. Statistical testing showed that the prevalence of device-detected AF was higher in the 30 days after hospitalization than during a similar period prior to hospitalization. However, when wider intervals (90 and 180 days) were compared, device-detected AF occurred with similar frequency before and after hospitalization. Taken together, these findings show a consistent increase in the prevalence of device-detected AF in the period immediately following hospitalization.

In this analysis, roughly half of patients with device-detected AF following hospitalization, particularly those with longer episodes, had device-detected AF in the period preceding hospitalization. This burden was higher than those without device-detected AF following hospitalization. This relationship was more pronounced in patients with longer episodes of device-detected AF, raising the question of whether these stress-associated episodes may indicate underlying paroxysmal AF. The proportion of patients with a prior history of AF was upwards of 50%. These estimates are congruent with previous reports for AF detected by surface ECG following stress: recurrence rates have ranged from 42% to 68% up to 5 years after medical illness and from 37% to 68% up to 5 years following non-cardiac surgery.[29,40,46,115] We observed a similar pattern with 180-day rates of post-hospitalization AF recurrence in patients without any AF prior to the index hospitalization.

What remains unknown is whether an episode of device-detected AF occurring during hospitalization for medical illness or non-cardiac surgery confers the same long-term prognosis as paroxysmal AF detected clinically and would be expected to respond to evidence-based therapies for paroxysmal AF, particularly OAC. A recent systematic review by our group found that perioperative AF is associated with an increased long-term risk of stroke, but that the absolute risk was somewhat lower than might be expected for typical AF patients.[30,157,168] Individual studies have reported similar findings in patients with medical illness.[24,46,115,150,168] We propose three plausible explanations for the intermediate risk of stress-associated AF (*i.e.* higher risk than no AF, but lower risk than typical AF). First, different phenotypes of patients with stress-associated AF may exist – one where stress precipitates AF and it is likely to recur and another where AF is uniquely and directly caused by the stressor and unlikely to recur.[10] Second, stress-associated AF may represent a low burden form of AF, associated with a lower absolute risk of stroke.[9,169-171] Third, AF occurring at the time of physiologic stress may not be causally related to adverse events such as stroke and the association is explained by shared risk factors and co-morbidities. Two ongoing large clinical trials are aimed at identifying optimal antithrombotic strategies in patients with device-detected AF,[172,173] and one pilot trial is assessing OAC for patients with peri-operative AF (NCT03968393). While we await these data a long-term ambulatory ECG performed following resolution of the acute illness may be a useful strategy to identify patients with recurrent AF who might benefit from OAC.[42]

Strengths

The principal strength of this analysis is the continuous, unbiased recording of cardiac rhythm over a prolonged follow-up period. This is, to the best of our knowledge, the first report examining the association between device-detected AF and physiologic stress. A committee of blinded experts adjudicated all episodes of device-detected AF.

Limitations

The key weakness of this *post hoc* study is its observational design. The total number of patients remains small, and precludes subgroup analyses based on sub-types of medical and non-cardiac surgical hospitalizations. Analyses conducted over 90 and 180 day time windows may not be statistically significant due to a lack of statistical power as compared to the analyses conducted over 30 day time windows. Because this study is based on patients aged 65 years and older with hypertension and a pacemaker or ICD, the participants in the study have a higher likelihood of underlying heart disease than the general population. Thus, our findings may not be generalizable to younger patients without a pacemaker or ICD who have AF detected by surface ECG.

Conclusions

In patients without a prior history of AF who have a pacemaker or implantable cardioverter defibrillator, device-detected AF is common around the time of hospitalization for medical illness or non-cardiac surgery. We observed a

spike in the occurrence of device-detected AF around the time of hospitalization, but roughly half of patients with AF around the time of hospitalization had at least one similar episode in the past. These findings suggest that a large number of patients with AF detected around the time of a hospitalization will have a chronic or recurring pattern of AF.

Figure 1:
Prevalence of episodes of device-detected AF before and after hospitalization for non-cardiac surgery or acute medical illness
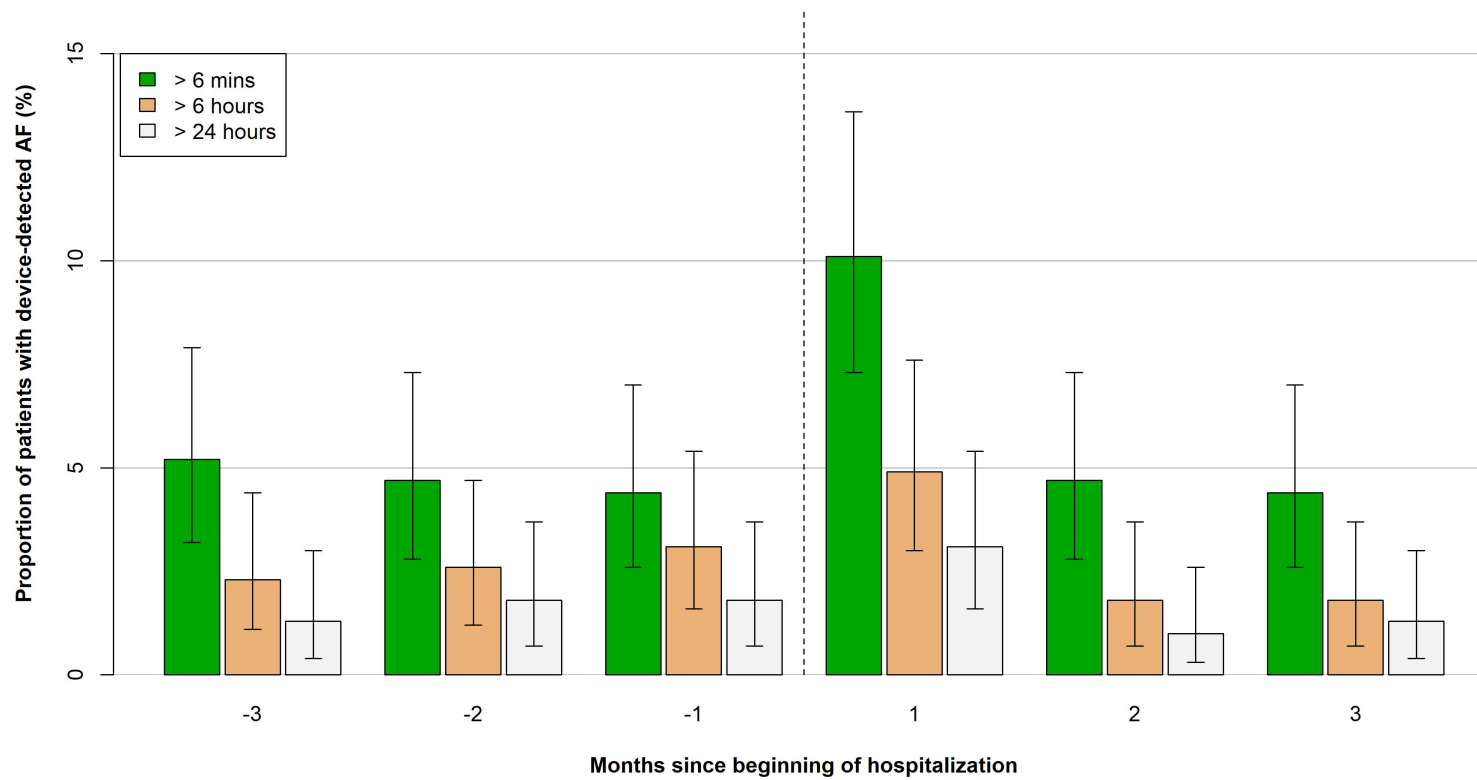
* Only considered 386 participants who have complete heart rhythm data from -90 to +90 days. Error bars represent 95% confidence intervals of the proportions.

Table 1. Baseline characteristics of patients according to the presence of device-detected AF > 6 mins within 30 days after hospitalization*

	All (N=436)	Device-detected AF following hospitalization (N=43)	No Device-detected AF following hospitalization (N=393)	P value
Age (years), mean ± SD	76.4±6.7	76.8±7.8	76.3±6.5	0.699
Female, n (%)	184 (42.2)	17 (39.5)	167 (42.5)	0.709
Heart failure, n (%)	89 (20.4)	10 (23.3)	79 (20.1)	0.626
Hypertension, n (%)	436 (100.0)	43 (100.0)	393 (100.0)	-
Coronary arterial disease, n (%)	152 (34.9)	15 (34.9)	137 (34.9)	0.998
Peripheral arterial disease, n (%)	31 (7.1)	6 (14.0)	25 (6.4)	0.107
Diabetes mellitus, n (%)	145 (33.3)	11 (25.6)	134 (34.1)	0.260
Prior stroke, n (%)	34 (7.8)	4 (9.3)	30 (7.6)	0.762
Prior transient ischemic attack, n (%)	31 (7.1)	6 (14.0)	25 (6.4)	0.107
CHA_2DS_2-VASc score, mean ± SD	4.2±1.3	4.3±1.6	4.2±1.3	0.757
CHA_2DS_2-VASc score, median (IQR)	4.0 (3.0-5.0)	4.0 (3.0-5.0)	4.0 (3.0-5.0)	0.936
BMI (kg/m^2), mean ± SD	27.6±5.2	26.9±4.2	27.7±5.2	0.291
LVEF (%), mean±SD	55.7±13.5	56.5±9.9	55.6±13.8	0.735
Device indication				

	All (N=436)	Device-detected AF following hospitalization (N=43)	No Device-detected AF following hospitalization (N=393)	P value
SA node disease with/without AV node disease, n(%)	195 (44.7)	21 (48.8)	174 (44.3)	0.568
AV node disease without SA node disease, n(%)	203 (46.6)	21 (48.8)	182 (46.3)	0.752
ACEi/ARB, n(%)	328 (75.2)	32 (74.4)	296 (75.3)	0.897
Beta blocker, n(%)	203 (46.6)	18 (41.9)	185 (47.1)	0.515

* Only considered patients who have complete heart rhythm data between -60 days to +30 days

ACEi = Angiotensin Converting Enzyme Inhibitor, AF = Atrial Fibrillation, ARB = Angiotensin Receptor Blocker, AV = Atrioventricular, LV = Left Ventricular, SA = Sinoatrial SD = Standard Deviation, IQR = Interquartile Range

Table 2. Proportion of patients with device-detected AF before and after the first medical or non-cardiac surgical hospitalization

Time Window	N	Proportion of Participants with Device-Detected AF			P value†
Episode duration		After but not before hospitalization n (%)	Both before and after hospitalization n (%)	Before but not after hospitalization n (%)	
30 days before and after hospitalization$					
> 6 mins	436	33 (7.6)	10 (2.3)	9 (2.1)	<0.001
> 6 hours		14 (3.2)	6 (1.4)	4 (0.9)	0.031
> 24 hours		9 (2.1)	4 (0.9)	3 (0.7)	0.146
90 days before and after hospitalization #					
> 6 mins	358	32 (8.9)	17 (4.8)	21 (5.9)	0.131
> 6 hours		13 (3.6)	8 (2.2)	12 (3.4)	0.841
> 24 hours		9 (2.5)	3 (0.8)	10 (2.8)	>0.999

180 days before and after hospitalization@					
> 6 mins	269	26 (9.7)	21 (7.8)	24 (8.9)	0.777
> 6 hours		10 (3.7)	13 (4.8)	15 (5.6)	0.317
> 24 hours		9 (3.4)	7 (2.6)	10 (3.7)	>0.999

$ Post-hospitalization interval starts Day 0 (*i.e.* Days 0-30; Pre-hospitalization interval ends Day -30 (*i.e.* Days -60 to -30)

Post-hospitalization interval starts Day 0 (*i.e.* Days 0-90); Pre-hospitalization interval ends Day -30 (*i.e.* Days -120 to -30)

@ Post-hospitalization interval starts Day 0 (*i.e.* Days 0-180); Pre-hospitalization interval ends Day -30 (*i.e.* Days -210 to -30)

* Only considered patients who have full heart rhythm data over the corresponding time window

† P value is from McNemar's test for paired data

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> 6 hours		14 (3.2)	6 (1.4)	4 (0.9)	0.031
> 24 hours		9 (2.1)	4 (0.9)	3 (0.7)	0.146

$ Post-hospitalization interval starts Day 0 (*i.e.* Days 0-30; Pre-hospitalization interval ends Day -30 (*i.e.* Days -60 to -30)

† P value is from McNemar's test for paired data

Table 3. Association of device-detected AF in the 30 days following a first hospitalization with device-detected AF in the 6 months prior to hospitalization^

	Device-detected AF following hospitalization n/N (%)	No Device-detected AF following hospitalization n/N (%)	Adjusted OR* (95% CI)	P value
Any hospitalization				
Prior Device-detected AF > 6 min	15/30 (50.0)	37/302 (12.3)	7.16 (3.24-15.84)	<0.001
Prior Device-detected AF > 6 h	11/16 (68.8)	20/316 (6.3)	32.64 (10.30-103.4)	<0.001
Prior Device-detected AF > 24 h	6/10 (60.0)	13/322 (4.0)	36.31 (9.03-146.0)	<0.001
Medical hospitalization				
Prior Device-detected AF > 6 min	12/24 (50.0)	30/232 (12.9)	6.72 (2.76-16.33)	<0.001
Prior Device-detected AF > 6 h	9/13 (69.2)	19/243 (7.8)	26.72 (7.51-95.15)	<0.001
Prior Device-detected AF > 24 h	5/8 (62.5)	13/248 (5.2)	29.93 (6.40-139.9)	<0.001
Surgical hospitalization				
Prior Device-detected AF > 6 min	6/12 (50.0)	20/164 (12.2)	7.30 (2.12-25.11)	0.002
Prior Device-detected AF > 6 h	3/6 (50.0)	12/170 (7.1)	13.94 (2.44-79.57)	0.003
Prior Device-detected AF > 24 h	2/5 (40.0)	7/171 (4.1)	16.15 (2.25-115.8)	0.006

*Adjusted for CHA_2DS_2-VASc score
^ 6 months prior defined as 210 to 30 days before hospitalization

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AUTHORS' CONTRIBUTIONS

William McIntyre contributed significantly to the study's concept and design, data collection and analysis, and interpretation of the results. He wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

Jia Wang contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Alexander Benz contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Emilie Belley-Côté contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

David Conen contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

PJ Devereaux contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Jorge Wong contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

PJ Devereaux contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Stefan Hohnloser contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Alessandro Capucci contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Chu-Pak Lau contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Carsten Israel contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Richard Whitlock contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Stuart Connolly contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Jeff Healey contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Chapter 6

Design and Rationale of the Atrial Fibrillation Occurring Transiently with Stress (AFOTS) Incidence Study

William F. McIntyre, Alexandra P. Lengyel, Jeff S. Healey, Maria E. Vadakken,

Anand S. Rai, Bram Rochwerg, Akash Bhatnagar, Bishoy Deif, Jessica Spence,

Shrikant I. Bangdiwala, Emilie P. Belley-Côté, Richard P. Whitlock

Population Health Research Institute, McMaster University,
Hamilton, Canada

ABSTRACT

Background: Atrial fibrillation (AF) is often detected for the first time in patients hospitalized for medical illness or non-cardiovascular surgery. AF occurring transiently with stress (AFOTS) describes this manifestation of AF, which may either be the result of a non-cardiac stressor, or existing paroxysmal AF that was not previously detected. Current estimates of AFOTS incidence are imprecise: ranging from 1-44%, owing to the marked heterogeneity in patient populations, identification and methods used to detect AFOTS.

Methods: The prospective, two-centre epidemiological AFOTS incidence study will enroll 250 consecutive participants without a history of AF but with at increased risk of AF (Age $\geq$ 65 or > 50 with one risk factor for AF) admitted to intensive care units (ICUs) for medical illness or non-cardiac surgery. Upon admission, participants will wear an ECG patch monitor that will remain in place for 14 days, or until discharge from hospital. Patients' consent to participation is deferred for up to 72 hours after admission. The primary endpoint is the incidence of AF lasting $\geq$ 30 seconds. The study is powered to detect an AF incidence of 17% $\pm$ 5%.

Results: We conducted a vanguard feasibility study, and 56 participants have completed participation. The median duration of monitoring was seven days. AF was detected by the clinical team in 8 participants (14%; 95% Confidence Interval 7-26%).

Conclusions: The AFOTS Incidence study will employ a systematic and highly sensitive protocol for detecting AFOTS in medical illness and non-cardiac surgery

ICU patients. This study is feasible and will provide a reliable estimate of the true incidence of AFOTS in this population.

BACKGROUND AND RATIONALE

Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia and is associated with a nearly five-fold increase in the risk of ischemic stroke.[174-177] AF is often detected for the first time in an acute care setting, particularly when a patient is hospitalized for a medical illness or surgery. Atrial fibrillation occurring transiently with stress (AFOTS) refers to this subset of AF that has not previously been diagnosed, is often asymptomatic, and reverts to sinus rhythm before the patient leaves the hospital.[10] As a result, there is uncertainty as to whether patients with AFOTS should receive long-term oral anticoagulation (OAC) for the prevention of stroke.[9,178-181] It is possible that AFOTS is the result of a medical or surgical stressor and is alleviated after removal of the stressor, therefore posing little risk to long-term prognosis.[10] In contrast, it is also possible that cases of AFOTS are a first detection—aided by continuous monitoring—of previously undiagnosed AF that may be treatable with OAC.[10]

The published literature reports a wide range of estimates of the incidence of AFOTS in the intensive care unit (ICU) setting, ranging from 1% to 44% in patients hospitalized for medical illness, and from 1% to 35% for non-cardiac surgery.[40] In other words, AFOTS could either be a rare occurrence, or impact 3 to 4 out of every 10 patients in these settings. This discrepancy makes

management challenging for clinicians and clouds long-term implications for patients with AFOTS.

Study design likely plays a large part in influencing the disparity between these estimates. As AFOTS is transient and often sporadic, events would be expected to be detected more reliably with continuous, rather than intermittent, monitoring. This is supported by the literature, with studies that employed continuous monitoring reporting the highest incidences of AFOTS.[182]

We aim to generate a reliable estimate of the true incidence of AFOTS in both medical and non-cardiac surgical ICU patients by systematically using high-sensitivity continuous 14-day monitoring.

METHODS

Objectives

The primary objective of the AFOTS Incidence study (NCT03552588) is to determine the incidence of AF, lasting 30 seconds or more, among patients admitted to the ICU who are over the age of 65 and do not have a prior history of AF, or between the ages of 50 and 64 with no history of AF and with one or more CHADS$_2$ risk factors.

The secondary objectives of this study are: (1) to compare the incidence of AF as captured by our study device to the incidence of AF captured clinically; (2) to determine the incidence of AF episodes of different durations; (3) to determine the burden of AF; (4) to document heart rates during AF; and (5) to explore

clinical factors that predict clinical detection of AF, (6) explore the association between AF and clinical outcomes.

Population

This prospective, descriptive epidemiological study will enrol 250 total participants from two centres in Hamilton, Ontario: the Hamilton General Hospital and the Juravinski Hospital.

Participants will include consecutive patients without a confirmed history of AF admitted to the non-cardiac intensive care units. We will include participants who are either 65 and older, or between the ages of 50 and 64 but with at least one risk factor for AF (*i.e.* those eligible for oral anticoagulation (OAC) therapy as per current Canadian Cardiovascular Society guidelines (with a documented history of at least one of: congestive heart failure, hypertension, stroke, transient ischemic attack, thromboembolism or diabetes mellitus)).[183]

We will exclude patients if they have a documented history of AF, if they have a known allergy to ECG electrode adhesive, if the 14-day monitor is expected to interfere with necessary care, or if the patient is not expected to survive for at least 12 hours. We will also exclude patients with a primary cardiovascular admission diagnosis (*e.g.* heart failure, pericarditis, arrhythmia), as transient AF in such patients is believed to occur as a direct result of cardiac injury as opposed to systemic stress.[10] We will also exclude patients who are not screened within 12 hours and those who are admitted to the ICU solely for post-operative oximetry monitoring due to sleep apnea.

Outcomes

The primary outcome will be the proportion of patients with at least one episode of AF lasting > 30 seconds, as detected by the 14-day monitor, and confirmed by a blinded arrhythmia specialist. Secondary AF outcomes will include: (1) the proportion of patients who have AF documented by the clinical team, either by 12-Lead ECG or telemetry strip posted to the patient's hospital chart; (2) the proportion of patients with patch-detected AF lasting 5 minutes or more, 1 hour or more, 6 hours or more and 24 hours or more; (3) the burden of patch-detected AF, defined as time spent in AF per 24 hours of analyzable rhythm; (4) the proportion of AF episodes that occur with an average heart rate of ≤40 bpm, 41-60 bpm, 61-80 bpm, 81-100 bpm, 101-120 bpm, and 121-140 bpm and > 140 bpm; and (5) factors that predict clinical identification of AF, including patient characteristics, hospital unit characteristics and AF characteristics (burden, duration and heart rate) . Secondary clinical outcomes will include in-hospital occurrence of major bleeding (ISTH definition[184]), stroke (defined as the rapid onset of a new neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent nonvascular cause and imaging evidence), cardiac arrest requiring cardiopulmonary resuscitation and death.

Study procedure

We will screen consecutive admissions to the non-cardiac intensive care unit (Figure 1). Study personnel, with the aid of nursing staff, will assess every

new admission for any prior physician-confirmed history of AF and risk factors for

AF. Upon confirmation of participant eligibility, with a target time of less than 90

minutes after admission, a high sensitivity 14-day ECG patch monitor will be

applied (ZIO XT Patch, iRhythm, Chicago USA).[185-188] Informed consent will be

obtained—either from the patient or an appropriate substitute decision-maker—

with a target time of less than 72 hours. The ECG monitor will remain in place

until the participant is discharged from hospital or until 14 in-patient days have

elapsed. We will follow participants until hospital discharge or until 30 in-patient

days have elapsed.

We will collect baseline data, including patient demographics and

admission information, medical history, CHA_2DS_2-VASc score, home

medications, and APACHE II score. Follow-up data will be collected daily,

tracking changes in treatment, significant clinical events, and AF status.

Ethics and safety considerations

Because any risk related to study participation is minimal and the validity

of this study could be jeopardized without timely application of the monitors, the

Hamilton Integrated Research Ethics Board has approved use of a deferred

consent model to facilitate informed consent of critically ill patients. Our group

has previously employed this model successfully in the intensive care setting.[189]

Sample size and statistical analyses

In our systematic review, the weighted mean incidence of AF was 17% in

the population that was continuously and prospectively monitored.[40] If we assume

17% to be the true incidence of AF, using a margin of error of 5% (*i.e.* incidence 12-22%), we will require a sample of 217 patients. We expect some patients to have unreadable monitoring data due to improper device placement, necessary device removal for medical care, very short hospital stays, or refusal of consent. To accommodate for this, we will increase the sample size to 250 so that we can accommodate a 13% reduction in actual sample size and still have the desired precision as described above.

We will present proportions and percentages descriptively, including for the primary outcome. We will calculate 95% confidence intervals around point estimates. For our prediction models, we will create logistic regression models with AF as the dependent variable. Co-variates will include patient, hospital unit and AF characteristics (burden, duration and heart rate). As we expect the number of events to be small, we will only report individual, unadjusted, univariable odds ratios.

Study organization

This study is co-ordinated by the Population Health Research Institute, a joint institute of McMaster University and Hamilton Health Sciences. The study consists of a steering committee and an adjudication committee for ECGs and clinical events. ECG reports and clinical events will first be reviewed by a clinical specialist. If their assessment is discordant with the ECG/site report, they will involve a second reviewer and reach consensus.

Results

We conducted a vanguard feasibility study. A total of 56 eligible participants were enrolled (Figure 2). We successfully obtained consent from 51 participants: 18 directly, and 33 through a substitute decision-maker. Four participants passed away before we were able to request consent; their data were included. One patient's substitute decision-maker declined consent; their data were excluded. One patch was lost during the study period. The final number of participants with complete data was 55. Median duration of monitoring was seven days, and AF was detected by the clinical team in eight patients (Table 2).

DISCUSSION

We have demonstrated the feasibility of enrolling and monitoring consecutive, at-risk patients, without a history of AF who are admitted to the ICU. The deferred consent process was efficient and acceptable to patients and their substitute decision-makers. The completed AFOTS Incidence study will provide a reliable estimate of the incidence of AFOTS in patients in the ICU setting. These data will improve our understanding of factors that affect its detection and assist in evaluating this entity's long-term prognosis and optimal management.

Current estimates of the incidence of AFOTS range from 1% to 44% in medical illness patients, indicating that AFOTS is either very rare, or occurs in almost half of non-cardiovascular, acute care patients.[40] This discrepancy is similar in estimates of incidence in patients following non-cardiac surgery, ranging from 1% to 35%.[40] This disparity is seen even when different diagnoses

are considered. For example, studies reporting the incidence of AFOTS in patients hospitalized for sepsis generated estimates ranging from 5% to 44%, with cases of septic shock tending to produce higher estimates.[40] Patients who were critically ill or hospitalized for thoracic, emergency, or major surgeries also tended to have higher incidences of AFOTS. This difference may be due to the increased magnitude of the stressor in such patients. However, this may also be confounded by the fact that sicker patients are more likely to undergo continuous ECG monitoring.[40]

Detection strategy and study design are likely to underlie much of the disparity among existing estimates. As AFOTS is, by definition, transient and possibly also intermittent, continuous monitoring would be expected to capture more events than discontinuous or short-term monitoring. Prospective designs would also be expected to miss fewer events than other designs. This is reflected in previous studies, particularly among patients with a medical illness. Incidences of over 20% were seen in six of 10 studies employing prospective and continuous monitoring.[40] Meanwhile, 17 of 26 studies that did not use prospective and continuous monitoring reported incidences of less than 10%.[40] In keeping with this, the highest incidence was reported in a small (n=66) prospective study employing seven-day continuous Holter monitoring.[40,190] The investigators analyzed the incidence of newly-onset AF in septic shock patients, finding that at least one episode of AFOTS lasting a minimum of 30 seconds occurred in 44% of participants.[190] Additionally, they found that the AF events would have been

missed in one third of participants were it not for continuous monitoring, emphasizing how study design can influence the disparity seen in current estimates.[190] The present study will employ a highly sensitive, continuous 14-day ECG monitor that will maximize capture of AF episodes. There is ongoing controversy, both in hospitalized patients and in the general population about the minimum duration of AF that should be considered clinically significant. Unfortunately, few published studies have described the duration of episodes of AFOTS. The AFOTS Incidence study will collect data on episodes of different durations. Where the study will not be powered to comment on the risk associated with specific durations, this detailed information will facilitate comparison with other studies.

Impact

AFOTS could be a very common and potentially modifiable risk factor for stroke.[10] This study will allow us to systematically assess the incidence of AFOTS, addressing the wide range of estimates that currently exist in the literature. In conjunction with other AFOTS studies, particularly our AFOTS Follow-Up Cohort study (NCT03221777),[42] we aim to construct an understanding of the incidence of AFOTS and the recurrence of AF following its occurrence. This series of studies will guide future monitoring and treatment when AFOTS is encountered in the clinical setting and will inform definitive randomized studies in this area.

Strengths

This study offers several improvements over existing studies in this area (Table 3). The results of this prospective, descriptive epidemiological study will provide a systematic and reliable estimate of AF incidence in ICU patients, addressing the variability in current literature. A thorough search for documented history of AF by both study and ICU personnel will be conducted to rule out pre-existing AF. The employment of a high sensitivity continuous 14-day monitor will allow us to capture more arrhythmic events than the use of traditional 48-hour Holter monitors, or in-patient telemetry. The deferred consent model will minimize missing data; it will also allow us to enroll a representative sample and to capture data shortly after ICU admission, a time when physiological stressors are often at their peak and thus more likely to trigger AFOTS events.

Limitations

As with other adhesive devices, the monitor may fall off or be removed. As a drawback of the deferred consent model, participants or substitute decision-makers may decline consent after the monitor has been applied. However, our vanguard feasibility study proved this is an infrequent occurrence, suggesting that our low risk intervention is acceptable to critically ill patients and their substitute decision-makers. We also concede the risk that clinicians may pay closer attention to arrhythmic events during the study period, leading to detection bias. This would obscure the difference between clinical detection and patch monitor detection but would not affect our primary outcome. Finally, the clinical

importance of shorter episodes of AF is still debated. As a result, our secondary outcomes are exploratory.
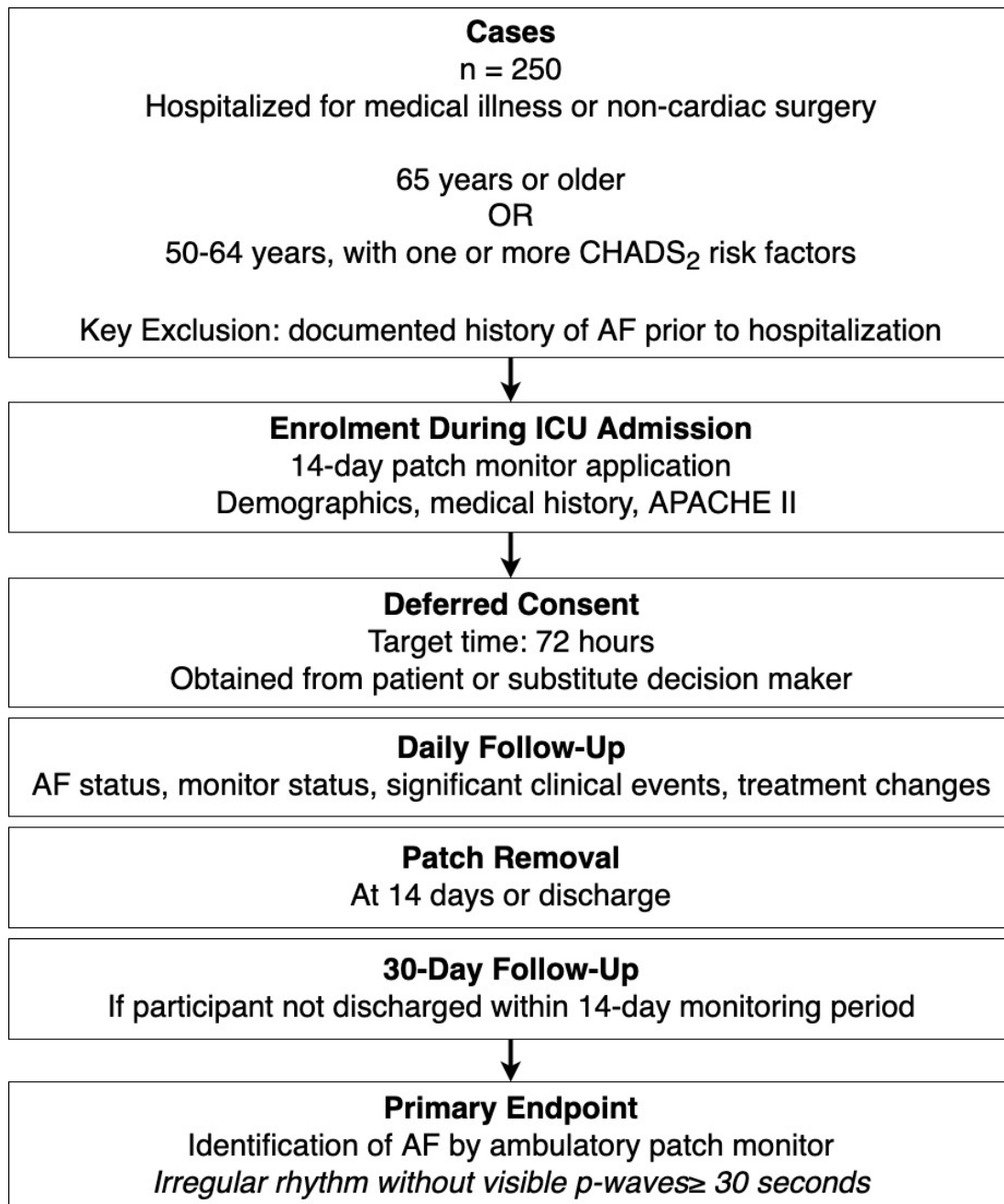
CONCLUSION

The AFOTS Incidence study will employ a 14-day ECG monitor in a systematic and highly sensitive protocol for detecting AFOTS in patients admitted to the ICU due to medical illness or non-cardiac surgery. This study is feasible and will provide a reliable estimate of the true incidence of AFOTS in this population.

Figure 1: Work flow of the AFOTS Incidence study

Cases
n = 250
Hospitalized for medical illness or non-cardiac surgery

65 years or older
OR
50-64 years, with one or more CHADS$_2$ risk factors

Key Exclusion: documented history of AF prior to hospitalization

↓

Enrolment During ICU Admission
14-day patch monitor application
Demographics, medical history, APACHE II

↓

Deferred Consent
Target time: 72 hours
Obtained from patient or substitute decision maker

Daily Follow-Up
AF status, monitor status, significant clinical events, treatment changes

Patch Removal
At 14 days or discharge

30-Day Follow-Up
If participant not discharged within 14-day monitoring period

↓

Primary Endpoint
Identification of AF by ambulatory patch monitor
Irregular rhythm without visible p-waves≥ 30 seconds

AF: Atrial Fibrillation; CHADS$_2$-: Congestive heart failure, Hypertension, Age ≥ 75, Diabetes, and Stroke/TIA (2 points); APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II Scoring System

Figure 2: Patient Flow in the AFOTS Incidence Vanguard Study
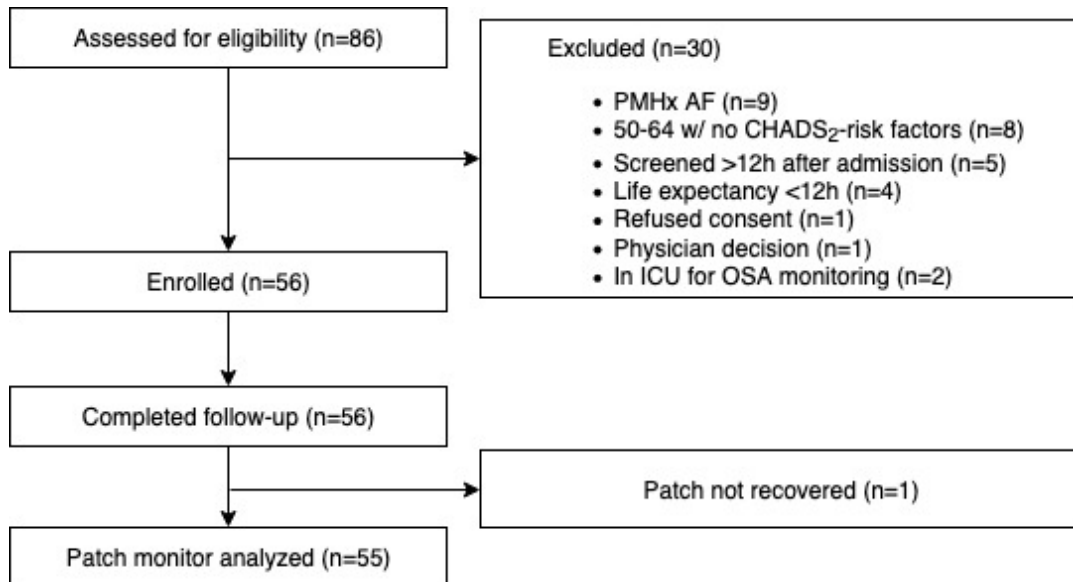
CHADS$_2$-: Congestive heart failure, Hypertension, Age ≥ 75, Diabetes, and Stroke/TIA (2 points); ICU: Intensive Care Unit, OSA = Obstructive Sleep Apnea; PMHx AF = Past Medical History of Atrial Fibrillation

Table 1: Baseline demographics in the Vanguard feasibility phase

	N = 55
Age in years (mean [SD])	71.1 (10.0)
Female sex (*n* [%])	19 (33.9)
CHA$_2$DS$_2$-VaSC score (median [IQR])	3.00 (2.0-4.0)
APACHE II score (median [IQR])	18 (14-27)
BMI (median [IQR])	26.0 (24.2-31.4)
Primary admission diagnosis	
Medical illness (*n* [%])	34 (60.7)
Infection (*n* [%])	11 (19.6)
Respiratory (*n* [%])	11 (19.6)
Cardiac (*n* [%])	2 (3.6)
Gastrointestinal (*n* [%])	2 (3.6)
Metabolic (*n* [%])	2 (3.6)
Neurologic (*n* [%])	3 (5.4)
Vascular (*n* [%])	2 (3.6)
Nephrologic (*n* [%])	1 (1.8)
Undifferentiated shock (*n* [%])	1 (1.8)
Surgery (*n* [%])	17 (30.4)
Neurosurgery (*n* [%])	4 (7.2)
Orthopedic surgery (*n* [%])	3 (5.4)
Vascular surgery (*n* [%])	3 (5.4)
General/abdominal/hepatobiliary surgery (*n* [%])	4 (7.2)
Urological surgery (*n* [%])	2 (3.6)
Other surgery (*n* [%])	1 (1.8)
Trauma (*n* [%])	5 (8.9)
Surgical (*n* [%])	3 (5.4)
Non-surgical (*n* [%])	2 (3.6)

BMI = Body Mass Index; CHADS$_2$-VASc: Congestive heart failure, Hypertension, Age ≥ 75 , Diabetes, Stroke/TIA (2 points), Vascular Disease, Female Sex Category. IQR = Interquartile Range, SD = Standard Deviation

Table 2: Clinical Events during Vanguard phase

	N = 55
Duration of monitoring in days (median [IQR])	7 (5-13.3)
Clinical AF detected (*n* [%])	8 (14.5)
Major clinical events (*n* [%])	8 (14.5)
Major bleed (*n* [%])	5 (9.1)
Stroke (*n* [%])	0 (0)
Arrest requiring CPR (*n* [%])	1 (1.8)
Death in hospital (*n* [%])	14 (25.4)

Table 3: Methodical strengths of the AFOTS Incidence study

	Previous studies	AFOTS Incidence study
Pre-hospital AF history	• Administrative data or patient interview	• Review of medical records by study and ICU personnel
In-hospital incidence of AFOTS	• Intermittent or <48h ECG monitoring • AF treated as a binary variable	• 14-day high-sensitivity ECG monitoring • Will capture incidence of different durations of AF
Consent	• A priori consent in prospective studies	• Deferred consent
Setting	• Single-centre	• 2 hospitals in Hamilton, Ontario, Canada
Collection of heart rhythm upon admission	• Infrequent	• Yes
Follow-up	• Follow-up during monitoring period	• Up to 14 days of daily data collection and 30-day follow-up

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AUTHORS' CONTRIBUTIONS

William McIntyre contributed significantly to the study's concept and design, data collection and analysis, and interpretation of the results. He wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

Alexandra Lengyel contributed to the data collection and analysis, and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

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Jessica Spence contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Shrikant Bangdiwala contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Emilie Belley-Côté contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Richard Whitlock contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

High-sensitivity Estimate of the Incidence of New-onset Atrial Fibrillation in Critically Ill Patients

William F. McIntyre[1,2,3], Emilie P. Belley-Côté[1,2], Maria E. Vadakken[1],
Anand S. Rai[1], Alexandra P. Lengyel[1,4],
Bram Rochwerg[1,2,3], Akash K Bhatnagar[1],
Bishoy Deif[1], Kevin J. Um[1,3], Jessica Spence[1,3],
Stuart J. Connolly[1,2,3], Shrikant I. Bangdiwala[1,3],
Purnima Rao-Melacini[1], Jeff S. Healey[1,2,3],
Richard P Whitlock[1,2,5]

1. Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada
2. Department of Medicine, McMaster University, Hamilton, Ontario, Canada
3. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
4. Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada
5. Department of Surgery, McMaster University, Hamilton, Ontario, Canada

ABSTRACT

Objective

To estimate the incidence of new-onset atrial fibrillation (AF) in critically ill patients.

Design

Prospective Cohort.

Subjects

Consecutive patients without a history of AF but with AF risk factors.

Setting

Medical-surgical Intensive Care Unit (ICU)

Interventions

ECG patch monitor until discharge from hospital or up to 14 days.

Measurements and Main Results

A total of 249 participants (median age of 71 (interquartile range (IQR) 64 – 78) years, 35% female) completed the study protocol of which 158 (64%) were admitted to ICU for medical illness, 78 (31%) following non-cardiac surgery and 13 (5%) with trauma. Median APACHE II score was 16 (IQR 12-22). Median duration of patch ECG monitoring, ICU and hospital lengths of stay were 6 (IQR 3-12), 4 (IQR 2-8) and 11 days (IQR 5-23), respectively.

AF ≥30 seconds was detected by the patch in 44 participants (17.7%), and 3 (1.2%) participants had AF detected clinically after patch removal, resulting in an overall AF incidence of 18.9% (95% confidence interval 14.2 - 24.3%).

Total duration of AF ranged from 53 seconds to the entire monitoring time. The proportion of participants with ≥ 1 episode(s) of ≥6 min, ≥1 h, ≥12 h and ≥24 h duration was 14.8%, 13.2%, 7.0%, 5.3%, respectively. The clinical team recognized only 70% of AF cases that were detected by the ECG patch.

Conclusions

Among patients admitted to an ICU, the incidence of new-onset AF is

approximately 1 in 5, although approximately one third of cases are not recognized by the clinical team.

INTRODUCTION

Atrial fibrillation (AF), the most common cardiac arrythmia, is often newly diagnosed in patients hospitalized for another reason.[10,43,191] However, uncertainty surrounds the epidemiology and management of AF detected in this setting. Challenges in managing new-onset AF during acute illness are driven in part by its complex pathophysiology. Acute factors (*e.g.* inflammation, catecholamine response, ischemia, metabolic disturbances, volume shifts) and chronic factors (*e.g.* valvular disease, atrial myopathy, hypertension) may contribute to arrhythmogenesis.[11,192] Both the arrhythmia and the underlying conditions may result in adverse outcomes over the short and long-term. Although new-onset AF during acute illness has been associated with worse outcomes, including increased length of stay, stroke and death, no clear management guidelines exist.[88,97,102,138,143,191,193-195] AF occurring transiently with stress (AFOTS) refers to the subset of AF that reverts to sinus rhythm before leaving the hospital, and for whom the optimal post-discharge management (*i.e.* anticoagulation and rhythm control) is uncertain.[10,196] The lack of reliable descriptive data further complicates this issue; the published incidence of new onset AF varies markedly, ranging from 1% to 44%, depending on the population, setting and detection methods.[40,191]

The primary aim of the present study was to use systematic, high-sensitivity continuous ECG monitoring to obtain accurate estimates of the incidence of new-onset AF in critically ill patients with risk factors for AF. The

secondary aims were to describe patterns of AF, risk factors for AF onset and AF detection and the association between AF and clinical outcomes.

METHODS

We have previously reported the full design of the AFOTS Incidence study (NCT03552588).[154] Briefly, we enrolled consecutive eligible patients admitted to 2 tertiary Canadian medico-surgical ICUs.[154] We included patients without a history of AF who were at least 65 years old, or between the ages of 50 and 64 and had one or more CHADS$_2$ risk factors.[197] We included patients without a prior documented history of AF who were in AF on admission to the ICU. We excluded patients with known ECG electrode adhesive allergy, those in whom the 14-day monitor was expected to interfere with necessary care, those not expected to survive for at least 12 hours, those with a primary cardiovascular admission diagnosis, those not screened within 12 hours from admission and those with sleep apnea admitted to the ICU exclusively for post-operative monitoring. Consecutive eligible participants had a 14-day ECG patch monitor (ZIO XT Patch, iRhythm, Chicago USA) applied at the time of enrolment.[198] This single-lead monitor collects heart rate information continuously and detects AF using a proprietary algorithm, calculating heart rates on a beat-to-beat basis. The local ethics board approved a deferred consent model (Hamilton Integrated Research Ethics Board Project Number 4740); the study was performed in accordance with

the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The ECG patch remained in place for 14 days, until it fell off or had to be removed, or until the participant was discharged from hospital, whichever occurred first. We collected baseline characteristics at admission and outcome information daily. We followed participants to hospital discharge or until 30 days following enrolment.

The primary outcome was the proportion of patients with at least one episode of AF lasting > 30 seconds, as detected by the 14-day monitor, and confirmed by a blinded arrhythmia specialist. We also captured the following secondary outcomes: (1) the proportion of patients with AF documented by the clinical team; (2) the proportion of patients with $\geq$ 6 minutes, $\geq$ 1 hour and $\geq$ 24 hours of patch-detected AF; (3) the burden of patch-detected AF(defined as % of the time in AF); (4) the frequency of AF episodes occurring within pre-specified heart rate ranges (>50 bpm; 50-110 bpm, >110 bpm); (5) and factors associated with clinical identification of AF. We also captured clinical outcomes including major bleeding (International Society on Thrombosis and Hemostasis definition[184]), stroke, cardiac arrest necessitating cardiopulmonary resuscitation, and death.

As part of their routine clinical care in the ICU, all patients underwent continuous cardiac monitoring using systems which employ the ST/AR algorithm (Philips Healthcare, Latham, New York). This algorithm performs analysis using

R-R interval irregularity, PR interval variability, and P-wave variability for detection of AF. Events are stored in the alarm section of the telemetry interface. After ICU discharge, treating clinicians decided whether patients required ongoing cardiac monitoring (i.e. telemetry versus not). We reviewed nursing and physician sections of participants' charts on a daily basis for documentation of AF.

This study was designed to enroll 250 participants based on an anticipated AF incidence of 17% and desired precision of confidence intervals (CIs) of ±5% half-widths; this was based on the mean weighted incidence in our group's prior systematic review.[40] We present descriptive statistics including means and proportions with 95% CIs around point estimates, and medians with interquartile ranges. Continuous variables were compared between groups with a t-test or Wilcoxon rank sum test. Categorial variables were compared using the Chi-square test or Fisher's exact test. We created univariate Poisson regression models with robust error variances including AF as the dependent variable and patient, hospital unit and AF characteristics as independent variables. [199]

Results

Study Population

We approached 457 patients, of which 317 were eligible, and after exclusions, we enrolled a total of 260 eligible participants (only 3 refused consent), among whom 249 had analyzable patch data (**Figure 1**). **Table 1**

displays baseline characteristics of enrolled analyzable patients. Primary admission diagnosis was medical illness in 158 (64%), noncardiac surgery in 78 (31%) and trauma in 13 (5%). **Table 2** displays characteristics of ICU care and ECG monitoring. Median duration of patch ECG monitoring, ICU and hospital stay were 6 (IQR 3-12), 4 (IQR 2-8) and 11 days (IQR 5-23), respectively. Of 249 participants, 40 (16.1%) wore the patch for 14 days. The patch fell off prematurely in 50 (20.0%), was removed for medically necessary reasons (e.g. magnetic resonance imaging, prone ventilation, wound care, planned procedure in area) in 13 (5.2%), removed because the patient was being discharged from hospital in 85 (34.1%) and removed from 61 (24.5%) participants who expired.

Atrial Fibrillation Incidence and Characteristics

AF ≥30 seconds was detected by the ECG patch in 44 participants (17.7%), and 3 (1.2%) additional participants had AF detected clinically by 12-lead ECG after patch removal, resulting in an overall AF incidence of 18.9% (95%CI 14.2 - 24.3%). Of those participants who developed AF, AF first occurred in the ICU in 44 (93.6%, including those who were in AF on arrival to ICU from another unit), on a step-down unit in 1 (2.1%) and on the ward in 2 (2.1%). The clinical care team recognized and documented 70% of cases of patch-detected AF. Among the 30 participants who had AF documented by the clinical team, 8 (26.7%) received rate control alone, chemical cardioversion was attempted in 5 (16.7%), 9 (30.0%) received rate control and attempted chemical cardioversion, 1 (3.3%)

received rate control and attempted chemical and electrical cardioversion, 1 (3.3%) received rate control and attempted electrical cardioversion and 6 (20.0%) received neither. **Table A1** compares characteristics between patients with AF that was and was not recognized by the clinical team. Of the 14 participants in whom the clinical team did not recognize patch-detected AF, 2 (14.3%) were not on telemetry at the time that AF occurred. **Table 3** shows the incidence of AF according to episode length, divided by whether or not AF was detected clinically. **Table 4** describes the burden of AF. Total duration of AF ranged from 53 seconds to the entire duration of monitoring time. The proportion of participants with episodes lasting ≥6 min, ≥1 h, ≥12 h and ≥24 h was 14.8%, 13.2%, 7.0%, 5.3%, respectively. Seven patients were in AF the entire duration of monitoring, with total monitoring durations ranging from 9 hours to 13 days, 16 hours and 38 min; four were discharged from hospital in sinus rhythm and the remaining three died. Longer durations of AF were more likely to be recognized by the clinical team. **Table 5** provides descriptive data for heart rates in AF. The median overall heart rate in AF was 114 bpm (IQR 94 – 134). Three-quarters of patients with AF reached a heart rate in AF of at least 164 bpm. When in AF, heart rates were roughly evenly split between rapid (>110 bpm) and controlled rates (50-110 bpm). Among the pre-specified variables tested, all had significant univariable associations with AF: Age (per year, relative risk (RR) 1.07, 95%CI 1.04-1.10, P value from the modified Poisson approach with robust error variances < 0.001); APACHE II score (per 1 point, RR 1.03, 95%CI 1.00-1.07, p = 0.034; CHA_2DS_2-

VASc Score (per 1 point, RR 1.26, 95%CI 1.07-1.47, p = 0.004; use of vasopressors or inotropes at any point during the study (RR 2.28, 95%CI 1.36-3.84, p = 0.002 and log(Peak high sensitivity Troponin(ng/mL), RR 1.10, 95%CI 1.01-1.20, p = 0.024.

Clinical Outcomes

Patients with AF were more likely to die in hospital (38.3% vs 21.3%, p = 0.015). There was no difference between major bleeding (14.9% versus 9.4%, p = 0.27) or non-fatal cardiac arrest requiring cardiopulmonary resuscitation in those with versus those without AF (2.1% versus 1.0%, p = 0.520). None of the study patients experienced an ischemic stroke or systemic embolism following hospital admission.

DISCUSSION

This study provides a practical estimate of the incidence of new-onset AF in critically ill patients, at a rate of nearly 1 in 5 (18.9%; 95% CI 14.2 - 24.3%). Additionally, new-onset AF was missed by the clinical team in approximately a third of cases. Finally, AF can be predicted by several common baseline variables, and is associated with higher mortality.

Two systematic reviews have identified more than a dozen previous studies that estimated the incidence of new-onset AF, and these found a wide range of estimates.[40,191] We believe the estimate generated by this study is more accurate

for several reasons. First, we enrolled a consecutive sample of patients and confirmed the absence of a history of AF, minimizing selection bias. Second, we used a continuous, full-disclosure external monitor with an AF detection algorithm, ensuring capture of all episodes, regardless of length and perceived clinical importance. Third, the study was large enough to estimate the incidence of AF within a practical precision of $\pm$5%.

In addition to estimating the incidence of new-onset AF in the ICU, we have described patterns of AF and risk factors for onset and detection. As expected, longer episodes of AF were more likely to be recognized by the clinical team. Interestingly, patients were tachycardic (HR > 110 bpm) only about half of the time while in AF; higher heart rates were not associated with a higher likelihood of detection. Participants who had higher baseline risk for AF (*i.e.* those with older age and higher CHA$_2$DS$_2$-VASc Scores) had higher rates of AF in the ICU.[14,200] Patients who were sicker at baseline (*i.e.* higher APACHE-II score) and with evidence of myocardial injury, were at higher risk for AF. The use of vasopressors or inotropes was also associated with higher rates of AF.[124]

These results have important implications for conducting and interpreting research addressing AF in the ICU. First, we have the most credible published estimate of the incidence of AF. Our findings can be used by future studies as guide for power calculations. Second, clinicians should raise concerns about important confounding and selection bias in studies that report low incidences of AF (*i.e.* <10%), and examine risk factors for AF and/or the association of AF with

adverse outcomes. Third, we have demonstrated the importance of continuous monitoring to ensure capture and documentation of all AF episodes. These results are consistent with a smaller study of 66 patients who wore an ECG monitor, in whom 1/3 of AF cases were not noted by the clinical team.[65]

Limitations

This study used an AF duration cut-off of 30 seconds although the minimum clinically relevant duration of AF remains unknown.[9] This study was designed to evaluate all-comers to the ICU, and is not powered to make inferences about any specific subgroups of ICU populations. This study was not designed to assess the association of patient characteristics with the development of AF – all RRs are unadjusted, univariable measures and underlying confounding is likely. Similarly, this study was not designed to assess the association of AF with in-hospital outcomes. Finally, The study was also not designed to assess long-term outcomes, although some participants were co-enrolled into our ongoing AFOTS Follow-Up Study.[42]

CONCLUSION

Among patients admitted to an ICU, the incidence of new-onset AF is approximately 1 in 5; one third of cases are not recognized by the clinical team.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no relevant conflict of interest.

Figure 3: Patient Flow in the AFOTS Incidence Study
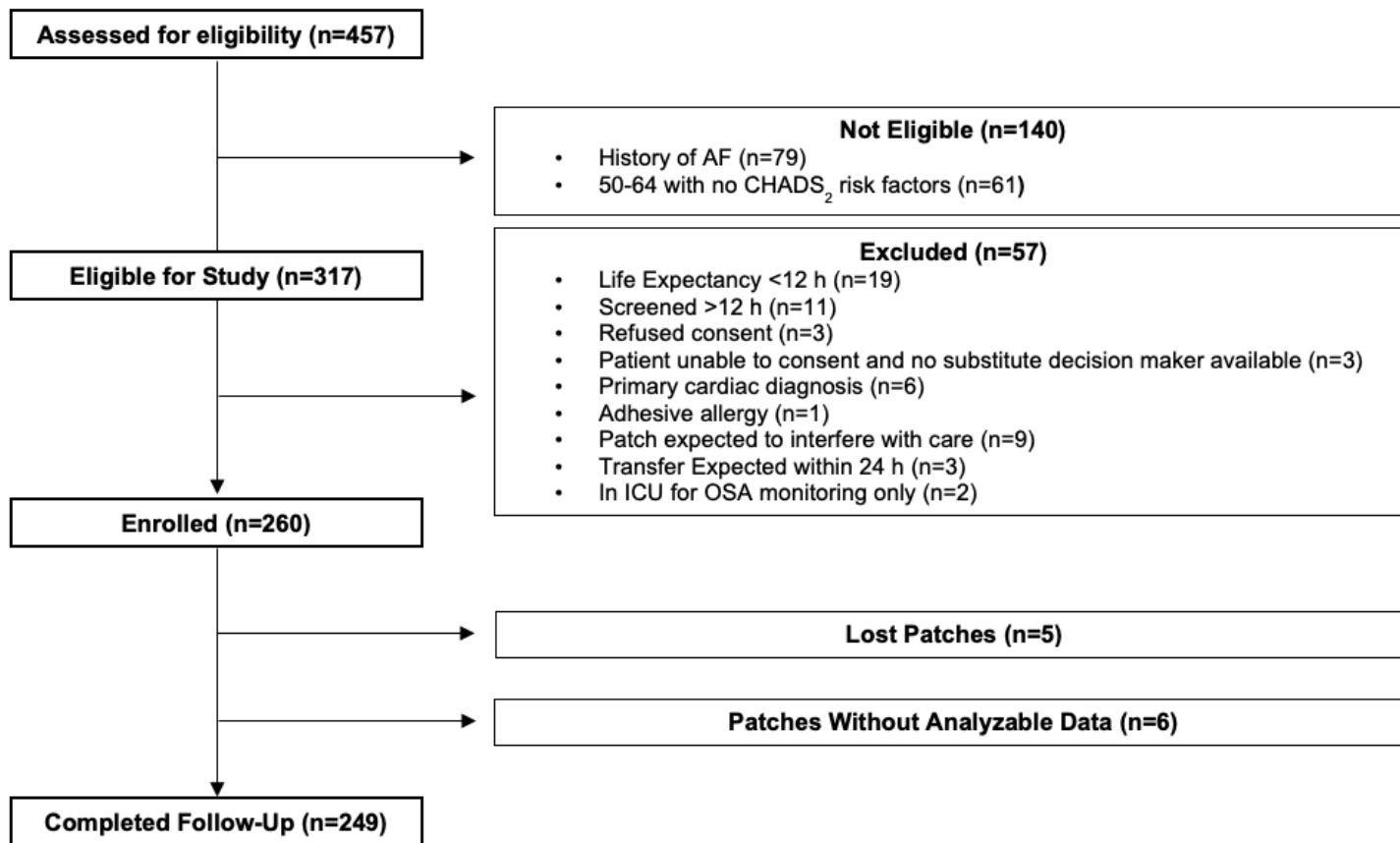
CHADS$_2$-: Congestive heart failure, Hypertension, Age ≥ 75, Diabetes, and Stroke/TIA (2 points);
ICU: Intensive Care Unit, OSA = Obstructive Sleep Apnea

Table 1: Baseline Characteristics

	Overall N = 249	Atrial Fibrillation N = 47	No Atrial Fibrillation N = 202	P-value*
Age in years (median [IQR])	71.0 [64.0 - 78.0]	77.0 [72.0 - 83.0]	69.0 [63.0 - 76.0]	<0.001
Female sex (n [%])	88 [35.3%]	16 [34.0%]	72 [35.6%]	0.8
CHA$_2$DS$_2$-VaSC score (median [IQR])	3.0 [2.0 - 4.0]	4.0 [3.0 - 5.0]	3.0 [2.0 - 4.0]	0.002
APACHE II score (median [IQR])	16.0 [12.0 - 22.0]	18.0 [13.0 - 24.0]	16.0 [11.0 - 21.0]	0.06
BMI (median [IQR])	27.2 [23.9 - 31.8]	26.8 [23.0 - 30.8]	27.5 [24.0 - 32.0]	0.3
Primary Admission Diagnosis				
Medical Illness (n [%])	158 [63.5%]	34 [72.3%]	124 [61.4%]	0.2
Infection (n [%])	36 [14.5%]	6 [12.8%]	30 [14.9%]	
Respiratory (n [%])	36 [14.5%]	9 [19.1%]	27 [13.4%]	
Gastrointestinal (n [%])	16 [6.4%]	4 [8.5%]	12 [5.9%]	
Metabolic (n [%])	5 [2.0%]	1 [2.1%]	4 [2.0%]	
Ischemic Stroke (n [%])	8 [3.2%]	3 [6.3%]	5 [2.5%]	
Other Neurologic (n [%])	31 [12.4%]	4 [8.5%]	27 [13.4%]	
Vascular (n [%])	4 [1.6%]	1 [2.1%]	3 [1.5%]	
Renal (n [%])	6 [2.4%]	2 [4.3%]	4 [2.0%]	
Hematologic (n [%])	1 [0.4%]	0 [0.0%]	1 [0.5%]	
Oncologic (n [%])	3 [1.2%]	0 [0.0%]	3 [1.5%]	
Undifferentiated shock (n [%])	12 [4.8%]	4 [8.5%]	8 [4.0%]	
Non-Cardiac Surgery (n [%])	78 [31.3%]	12 [25.5%]	66 [32.7%]	0.3
Neurosurgery (n [%])	18 [7.2%]	3 [6.4%]	15 [7.4%]	
Orthopedic surgery (n [%])	15 [6.0%]	2 [4.3%]	13 [6.4%]	
Vascular surgery (n [%])	11 [4.4%]	2 [4.3%]	9 [4.5%]	
General surgery (n [%])	25 [10.0%]	4 [8.5%]	21 [10.4%]	
Urological surgery (n [%])	7 [2.8%]	0 [0.0%]	7 [3.5%]	
Other surgery (n [%])	2 [0.8%]	1 [2.1%]	1 [0.5%]	
Trauma (n [%])	13 [5.2%]	1 [2.1%]	12 [5.9%]	0.5
Surgical (n [%])	7 [2.8%]	0 [0.0%]	7 [3.5%]	
Non-surgical (n [%])	6 [2.4%]	1 [2.1%]	5 [2.5%]	

BMI = Body Mass Index; CHADS2-VASc: Congestive heart failure, Hypertension, Age >= 75, Diabetes, Stroke/TIA (2 points), Vascular Disease, Female Sex Category. IQR = Interquartile Range, SD = Standard Deviations
* P-value is either from a Pearson's Chi-square test/Fisher's exact test, 2 sample t-test or Wilcoxon Rank Sum test.

Table 2: Characteristics of Intensive Care Unit Care and ECG Monitoring

	Overall N = 249	AF N = 47	No AF N = 202	P-Value*
	Median (IQR)	Median (IQR)	Median (IQR)	
Days of Invasive ventilation	1 (0 - 3)	3 (0 - 9)	0 (0- 3)	0.001
Days in intensive care unit	4 (2 - 8)	7 (4 - 14)	3. (2 - 7)	<0.001
Days in hospital	11 (5 - 23)	14 (7 - 30)	9.5 (5 - 21)	0.023
Days on patch monitoring	6 (3 - 12)	10 (5 - 13)	6 (3 - 11)	0.001
Days of telemetry monitoring	4 (2 - 9)	7 (4 - 13)	3 (1 - 9)	0.001
Peak high sensitivity Troponin (ng/mL)	32 (11- 252)	69 (21 - 338)	28(9 - 224)	0.015
	N (%)	N (%)	N (%)	
Invasive ventilation^	131 (52.6%)	32 (68.1%)	99 (49.0%)	0.018
Dialysis at any point **	15 (6.0%)	7 (14.9%)	8 (4.0%)	0.005
Vasopressors/inotropes^	87 (34.9%)	26 (55.3%)	61 (30.2%)	0.001
Clinical AF detected N (%)	33 (13.3%)	33 (70.2%)	0 (0.0%)	<0.001

% is out of Total Analyzed
^ At any point during the study
*P-value for categorical variables from Chi-square or Fisher's exact test is used; P-value for continuous variables from Wilcoxon Rank sum test

Table 3: Incidence of Atrial Fibrillation According to Episode Length

Episode Duration	Overall	AF Incidence^	Patch detected AF and Clinically-detected AF N = 28	Patch detected AF but No Clinically-detected AF N = 13	P-value**
≥ 30 s*	47	18.9%	-	-	-
>=6 m^	36	14.8%	28	8	0.0006
>=1 h^	32	13.2%	26	6	0.0003
>=12 h^	17	7.0%	15	2	0.001
>=24 h^	13	5.3%	12	1	0.002

*Denominator 249 – all patients who completed the study protocol
^Denominator 243 (Excludes 3 participants with patch-detected AF for whom AF duration data were not available and 3 patients with clinically detected AF that was captured after patch discontinuation)
** binomial test exact p-values

Table 4: Burden of Atrial Fibrillation

	Overall N = 41* Median (IQR)	Patch detected AF and Clinically-detected AF N = 28 Median (IQR)	Patch detected AF and No Clinically- detected AF N = 13 Median (IQR)	P-value[&]
Burden of Atrial Fibrillation (%) *	11.0 (3.0 - 53.0)	25.0 (7.0 - 58.0)	1.0 (0.1 - 7.0)	0.005
#AF episodes	3.0 (1.0 - 46.0)	4.0 (1.5 - 61.0)	2.0 (1.0 - 14.0)	0.155
Total AF duration(min)	1091 (468.0 - 5738)	2612 (903.5 - 8199)	42.0 (9.0 - 540.0)	<0.001
Total AF duration(hrs)	18.2 (7.8 - 95.6)	43.5 (15.1 - 136.6)	0.7 (0.2 - 9.0)	<0.001
Duration of longest episode (min)	633.0 (103.0 - 2640)	1135 (440.5 - 5493)	17.5 (1.1 - 467.0)	0.001
Duration of longest episode (hrs)	10.6 (1.7 - 44.0)	18.9 (7.3 - 91.5)	0.3 (0.0 - 7.8)	0.001
Time to 1st AF (hrs)	24.0 (0.0 - 69.0)	14.5 (0.0 - 53.0)	45.0 (20.0 - 106.0)	0.074

*% is out of Total Analyzed

[&] P-value: from Wilcoxon Rank sum test

*Denominator includes all patients with patch-detected AF and available duration data. 3 participants with patch-detected AF did not have duration data.

Table 5: Heart Rates in Atrial Fibrillation

	Overall		Patch detected AF and Clinically-detected AF		Patch detected AF and No Clinically-detected AF		P-value *
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	
Total Analyzed among Patch detected AF -N	44		30		14		
Minimum Heart Rate (bpm) in AF**		62 (47 - 85)		60.5 (47 - 82)		70 (46 - 101)	0.387
Median Heart Rate (bpm) in AF**	41	114 (94 - 134)	28	108.5 (88.5 - 131)	13	126 (116 – 135)	0.201
Maximum Heart Rate (bpm) in AF**		174 (164 - 194)		175.5 (166 - 190		170 (152 - 195	0.839
% of Time in AF>110 bpm^		51.5 (12 - 94)		48 (11 - 87)		83 (49 - 99)	0.125
% of Time in AF 51-110 bpm^	35	48.5 (8.5 - 88)	25	52 (13 - 88)	10	16.5 (1 - 51)	0.104
% of Time in AF<=50 bpm^		0 (0 - 0)		0 (0 - 0)		0 (0 - 0)	0.821

bpm = beats per minute
% is out of Total Analyzed
** P-value: from t-test
^ P-value: from Wilcoxon Rank sum test

Table A1: Characteristics of ICU Care according to whether or not AF was detected clinically

	Overall	
	N(%), Mean(SD)	Median (IQR)
Total Analyzed among Patch detected AF	44	
Days of Invasive ventilation	44/ 4.8 (5.0)	4 (0 - 9)
Days in ICU	44/ 8.0 (4.6)	7 (4 - 14)
Days in Hospital	44/ 17.5 (10.7)	14.5 (7 - 30)
Days on vasopressors/inotropes	44/ 1.7 (2.2)	1 (0 - 2)
Days on patch monitoring	44/ 9.4 (4.3)	11 (5.5 - 1)
Days of telemetry monitoring	44/ 8.0 (4.7)	7.5 (4.0 - 13)
Invasive ventilation^	30 (68.2%)	
Dialysis at any point**	6 (13.6%)	
Vasopressors/inotropes^	25 (56.8%)	
Peak high sensitivity Troponin (ng/mL)	43/ 1791 (6166)	69 (21 - 255)
Clinical AF detected	30 (68.2%)	

	Patch detected AF and Clinical AF		Patch detected AF and No Clinical AF		P-value*
	N (%), Mean (SD)	Median (IQR)	N (%), Mean (SD)	Median (IQR)	
Total Analyzed among Patch detected AF	30		14		
Days of Invasive ventilation	30/ 5.6 (5.4)	4.5 (0 - 10)	14/ 3.1 (3.5)	2 (0 - 6)	0.166
Days in ICU	30/ 8.9 (4.5)	8.5 (5 - 14)	14/ 6.0 (4.3)	5 (2 - 9)	0.052
Days in Hospital	30/ 19.1 (10.4)	17 (11 - 30)	14/ 14.2 (10.9)	10.5 (5 - 26)	0.110
Days on vasopressors/inotropes	30/ 1.8 (2.4)	1 (0 - 2)	14/ 1.4 (1.9)	1 (0 - 2)	0.854
Days on patch monitoring	30/ 9.8 (4.0)	11.5 (6 - 13)	14/ 8.5 (5.0)	9 (4 - 13)	0.525
Days of telemetry monitoring	30/ 9.0 (4.6)	10 (5 - 13)	14/ 5.8 (4.4)	4 (2 - 9)	0.027
Invasive ventilation^	22 (73.3%)		8 (57.1%)		0.283
Dialysis at any point**	6 (20.0%)		0 (0.0%)		0.072
Vasopressors/inotropes^	18 (60.0%)		7 (50.0%)		0.533
Peak high sensitivity Troponin (ng/mL)	30/ 1926 (7083)	47.5 (20 - 190)	13/ 1477 (3416)	84 (30 - 365)	0.284
Clinical AF detected	30 (100.0%)		0 (0.0%)		<0.001

^ At any point during the study
% is out of Total Analyzed
* P-value: for the categorical variables, Chi-square test or Fisher's exact test is used; for the continuous variables, Wilcoxon Rank sum test is used.

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AUTHORS' CONTRIBUTIONS

William McIntyre contributed significantly to the study's concept and design, data collection and analysis, and interpretation of the results. He wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

Emilie Belley-Côté contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Maria Vadakken contributed to the data collection and analysis, and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Anand Rai contributed to the data collection and analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Alexandra Lengyel contributed to the data collection and analysis, and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Bram Rochwerg contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Akash Bhatnagar contributed to the data collection and analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Bishoy Deif contributed to the data collection and analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Kevin Um contributed to the data collection and analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Jessica Spence contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Stuart Connolly contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Shrikant Bangdiwala contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Purnima Rao-Melacini contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Jeff Healey contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Richard Whitlock contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Chapter 7

Design and Rationale of the Atrial Fibrillation Occurring Transiently with Stress (AFOTS) Follow-Up Cohort Study

William F. McIntyre[1,2,3], Pablo A. Mendoza[2,3],
Emilie P. Belley-Côté[1,2,3,4], Richard P. Whitlock[2,3,4,6],
Kevin J. Um[3,5], Natalie Maystrenko[3], PJ Devereaux[1,2,3],
David Conen[1,2,3], Jorge A. Wong[1,2,3],
Stuart J. Connolly[1,2,3], Jeff S. Healey[1,2,3]

1. Division of Cardiology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
2. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
3. Population Health Research Institute, Hamilton, Ontario, Canada
4. Division of Critical Care, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
5. Michael G. DeGroote School of Medicine, McMaster University,
6. Hamilton, Ontario, Canada
7. Division of Cardiac Surgery, Department of Surgery, McMaster University, Hamilton, Ontario, Canada

Abstract

Background

Atrial fibrillation occurring transiently with stress (AFOTS) describes the first detection of AF in a patient who is hospitalized for a non-cardiac medical illness or following non-cardiac surgery. Uncertainty exists whether episodes of AFOTS are due to reversible precipitants and will not recur after recovery, or if they are paroxysmal AF that is detected during inpatient cardiac monitoring. Previous studies have used retrospective, non-systematic and ultimately low-sensitivity protocols to investigate the recurrence of AF in patients with AFOTS.

Methods

The prospective, multi-centre, investigator-initiated AFOTS Follow-Up Cohort Study will enrol 138 case patients with AFOTS in the setting of non-cardiac surgery or medical illness, matched 1:1 with control patients for age, sex, stressor, and hospital unit. Participants will wear a 14-day ECG heart monitor at 1 and 6 months after hospital discharge. Over 12 months of follow-up, we will collect data regarding participant's medications, and clinical events. The primary endpoint is detection of 30 or more seconds of AF after hospital discharge.

Results

To date, 50% of the target sample has been enrolled. The study is expected to complete enrolment in mid- 2019 and conclude one year later.

Conclusion

The AFOTS Follow-up Study will employ a systematic protocol to detect AF and will provide a precise and valid estimate of AF recurrence following AFOTS. This study will establish whether patients with AFOTS have an increased propensity to AF after hospitalization as compared to matched controls and may inform the management of this population.

Background and rationale

Atrial fibrillation (AF) is the most common cardiac arrhythmia and increases a patient's risk of ischemic stroke by a factor of up to five.[1] Accordingly, physicians can prescribe oral anticoagulation (OAC) to patients with clinical AF (*i.e.* paroxysmal, persistent or permanent) to reduce their long-term risk of stroke. However, they must balance the benefits in stroke reduction against an increased risk of bleeding.[201] Clinical practice guidelines, including those published by the Canadian Cardiovascular Society (CCS), American Heart Association (AHA), and the European Society of Cardiology (ESC), recommend that health care providers risk-stratify patients with clinical AF to predict their risk-benefit ratio for taking OAC.[7,202,203] However, in many cases where AF is detected transiently while patients are hospitalized for an acute stressor (*e.g.* medical illness or following surgery), OAC is not prescribed.[24,27,46] AF in this setting may be due to a combination of underlying myocardial substrate and triggering pathophysiologic factors, but its detection may also be explained in some part by continuous inpatient heart rhythm monitoring.[204]

Overall, clinicians remain uncertain whether atrial fibrillation occurring transiently with stress (AFOTS) is due to a reversible precipitant and will not recur, or if AF in this setting is actually the first documentation of paroxysmal AF, and hence, is associated with a modifiable risk of stroke.[9,10]

Atrial fibrillation occurring transiently with stress (AFOTS)

AFOTS is detected with variable frequency.[10,24,26,29,46,124] In our previous work, we reviewed the incidence of AFOTS and the recurrence of AF following an acute medical stressor. [82] We found that AFOTS was detected following medical illness (*e.g.* sepsis, pneumonia) with an incidence of 1 to 44%.[82] Similarly, incidence estimates of AFOTS following non-cardiac surgery range from 1 to 35%.[10] However, clinicians lack evidence to guide the management of patients with AFOTS.[7] It is imperative to document outcomes in AFOTS patients following hospital discharge.

Recurrence of AF Following AFOTS

For a patient who had experienced AFOTS, the documentation of an episode of AF after the resolution of the stressing condition would make it likely that the initial presentation of AFOTS was actually paroxysmal AF. This is analogous to the approach to treating and evaluating gestational hypertension.[205] In this population, the clinician works to differentiate the chronic form of the disease from that caused by pregnancy. To differentiate, the patient is retested after delivery or when the stressor has been removed. If the disease persists postpartum (*i.e.* high blood pressure), then a diagnosis of chronic hypertension can be made. This concept can be extrapolated to the population level; as the proportion of patients who experience a recurrence of AF after AFOTS approaches 100%, it becomes increasingly likely that AFOTS is just clinical AF and was not "caused" by the initial stressor.

Three recent retrospective studies found that between 37 to 44% of patients had a documented recurrence of AF within 1 year following AFOTS.[26,29,46] However, these studies had limitations in the sensitivity of their ascertainment for recurrence of AF. These limitations include the use of administrative data, a lack of a systematic approach to following patients and employment of rhythm-monitoring technology for shorter durations and with less sophisticated detection algorithms than what is currently available.

Methods

Specific Objectives

Primary objective

To determine the rate of recurrent AF using a highly sensitive, 14-day continuous ZIO XT Patch ECG monitoring device among patients who experienced AFOTS following non-cardiac surgery or during medical illness, as compared to groups of controls matched for age, sex and stressor. We hypothesize that patients who experience AFOTS will have a higher incidence of AF lasting at least 30 seconds in the year following hospital discharge, as compared to a group of matched controls that did not experience AFOTS.

Secondary objectives

The secondary objectives of the AFOTS study are to: i) explore predictors of AF recurrence, ii) describe the pattern and burden of AF in patients with AFOTS who experience AF recurrence, iii) describe long-term adverse event

rates after an episode of AFOTS, and iv) document contemporary use of thromboprophylaxis for patients with AFOTS.

Study Design

This investigator-initiated study (NCT03221777) comprises two prospective, multi-center, observational cohorts. Each cohort will include a group of 69 AFOTS patients and 69 matched controls, for a total of 276 participants (Table 1).

At baseline, we will collect demographics and medical history from all participants. Following discharge from hospital, all participants will wear a 14-day adhesive ECG monitor at 1 and 6 months after discharge and will return for a final study visit at 12-months post enrollment. The Hamilton Integrated Research Ethics Board and Health Canada have approved this protocol. Written informed consent will be obtained from participants prior to any study procedures being performed.

Population

We will enroll participants from three academic hospitals in Hamilton, Canada: Hamilton General Hospital, Juravinski Hospital and Cancer Centre and St. Joseph's Healthcare Hamilton – Charlton Campus. All hospitals are publically funded with universal health care coverage for the surrounding population and between them cover the full range of medical and surgical inpatient services.

Case identification will occur by screening consecutive admissions in the intensive care units, surgical and medical wards for patients who have a primary,

non-cardiac diagnosis other than AF and have had AFOTS recognized by their clinical team. On a daily basis, study personnel will screen applicable hospital units for patients who have had AF. This will occur by conversing with physicians and nursing staff, by reviewing telemetry strips posted to patients' charts and by reviewing 12 lead ECGs from patients admitted within the last 72 hours. A cardiologist from the study team will confirm AF on a qualifying ECG or telemetry strip. When AF is identified, the patient's medical history and reason for admission will be reviewed for eligibility. We aim to enroll consecutive patients and will keep a log of those who are eligible but not included.

Inclusion Criteria

Complete inclusion and exclusion criteria are detailed in Table 2. Cases will be patients without a history of AF in whom AF has been detected for the first time in the setting of acute non-cardiovascular medical illness or non-cardiac surgery. AF can be present upon presentation or occur some time thereafter. Participants must also be in sinus rhythm upon hospital discharge, either because of spontaneous or physician-assisted cardioversion.

Controls will be patients without a history of AF who are hospitalized for an acute non-cardiovascular medical illness or non-cardiac surgery. Each control will be matched to a case by screening for a patient on the same hospital unit who is of the same sex and is within $\pm$5 years of age.

Participants in the case and control groups will be candidates for OAC as per current CCS guidelines. The CCS algorithm, also known as CHADS65, states

that individuals are eligible for OAC if they are either $\geq$ 65 years of age or have one or more of the following risk factors: congestive heart failure/left ventricular ejection fraction $\leq$ 40%, hypertension, diabetes mellitus or a history of stroke/transient ischemic attack.[203]

Exclusion Criteria

Patients will be excluded if they have an implanted pacemaker or defibrillator, if they have an allergy to ECG electrode adhesive, or if they live in a chronic care facility. We will exclude patients who have stage V chronic kidney disease. We will exclude patients with cardiac primary admitting diagnoses (*e.g.* heart failure, myocardial infarction, pericarditis, *etc.*). We chose to exclude patients with a primary cardiac diagnosis because AFOTS in these patients is thought to occur through direct cardiac insult rather than a manifestation of systemic stress.[10] Patients with ischemic stroke and systemic embolism will also be excluded, as AF would generally be expected to have been causative for patients with these diagnoses.

Outcomes

The primary outcome will be the detection of 30 seconds or more of AF by study device or through regular clinical care within the 12-months following discharge from hospital. AF detection rates will be reported separately for each method. Definitions for all outcomes are provided in the Appendix.

Exploratory secondary outcome measures for the AFOTS cohort study include; predictors of AF recurrence after AFOTS; time to AF recurrence, daily and total AF burden; total duration of AF all episodes; longest AF episode; AF with duration > 5 minutes, >5 hours, and >24 hours; detection of the primary outcome at 1 and 6 months; clinical events (*i.e.* death, stroke, bleeding, embolism and hospitalization for heart failure or myocardial infarction) occurring within 12-months post enrollment. We will also document the proportion of patients with AFOTS who are prescribed OAC.

In separate analyses, we will explore cost-effectiveness and cost-utility for AF monitoring, patient adherence and satisfaction with the ECG monitor, the sensitivity and specificity of ECG capture of AF outside the study protocol and the detection of clinically important arrhythmias other than AF.

Study Procedure

We will offer study participation to eligible patients and obtain written informed consent (Figure 1). Following consent, eligible participants will undergo a baseline assessment including their demographics, medical history, stroke, AF risk factors, and CHA_2DS_2-VASc Score. We will also collect data on when, where and how AF was detected, how much time the patient spent in AF and whether they returned to sinus rhythm spontaneously or with the assistance of electrical or pharmacological cardioversion.

Participants will wear the ZIO XT Patch, an ultra-portable, adhesive ECG patch monitor. The Food and Drug Administration (FDA) has approved this device for arrhythmia detection; it is in clinical use in the United States.[198] This small lightweight, water resistant ambulatory ECG patch is capable of detecting of AF and quantifying AF burden.[198,206-208] In head-to-head comparison, this device has captured significantly more arrhythmic events than shorter-duration Holter monitoring and has done so without missing episodes of AF.[116,198,207] The device includes a recording button that the wearer can press to indicate that they have had symptoms. Electrograms from the ZIO XT Patch will be processed centrally at the iRhythm National Clinical Center, Chicago. An arrhythmia physician who is blinded to the patient's prior history will adjudicate all rhythm events.

Follow-up Schedule

The three scheduled study follow-ups consist of a telephone or in-person assessment at 1 month, 6 and 12 months (Figure 1). At the 1 and 6-month follow-ups, patients will apply the 14-day ECG Patch. At all follow up visits, using a telephone questionnaire and medical records, we will collect data regarding patients' medications, and any new occurrence of AF (outside of the study protocol), death, stroke, bleeding, embolism and hospitalization for heart failure or myocardial infarction) occurring within 12-months after enrollment. Clinical events will be defined as reported by the study participants' personal physician.

When AF is detected as part of the study protocol, the study participant's personal physician will receive a copy of the heart rhythm monitor report. Study physicians will not recommend or prescribe OAC, but will facilitate referral to an independent arrhythmia physician where required or requested by the participant's personal physician.

Sample Size and Statistical Analyses

Based on our previous review of the literature, we expect that the one-year rate of AF recurrence will be at least 37-44% in the AFOTS group, but that it will likely be much higher because these estimates represent AF ascertained through administrative data. [10,26,29,46] Conservatively, the incidence of AF in the control group can be expected to be similar to the one found when screening the general population with similar intensity, *i.e.*11 to 21%.[209,210] For a sample size calculation, we estimated that 20% of participants in the control group will have AF and that 45% of participants in the AFOTS group will have AF. Based on these estimates, we require 69 patients in each of the four groups (Case and control; medical illness and non-cardiac surgery), or a total of 276 patients to detect an effect with 80% power at the 5% significance level using a two-tailed chi-squared test. The primary analysis population will consist of participants who wore at least one ECG patch; where a participant is unable or unwilling to wear an ECG patch, they will continue to be followed and a replacement will be enrolled. We will first test our primary hypothesis on the overall population (*i.e.*

medical illness and cardiac surgery) and then on the two illness cohorts separately. We will report a secondary analysis that is adjusted for duration of analyzable ECG time, as this value may differ between patients due to electrical artifact, variable compliance or premature device discontinuation.

Study Organization

The study is co-ordinated by the Population Health Research Institute, a joint institute of McMaster University and Hamilton Health Sciences. The study consists of a steering committee and a separate ECG adjudication committee. Committee membership and site principal investigators are listed in the Appendix.

Results

To date, 50% of the target sample size has been enrolled. The study is on track to enrol its final patient in mid-2019 and report final results one year later. Baseline characteristics of the case participants enrolled to date are shown in Table 3.

Discussion

There is uncertainty as to whether AFOTS represents a manifestation of underlying physiological stress or if it is undiagnosed AF whose detection has been facilitated by continuous ECG monitoring. The AFOTS Follow-Up Cohort Study was designed to investigate the AF recurrence rate among patients who

have AF detected while hospitalized for a non-cardiac primary diagnosis. We hypothesize that AFOTS is the first documentation of paroxysmal AF. If this true, AFOTS patients will have a higher incidence of AF detected after hospitalization, when compared to a group of matched controls.

Three studies investigated the recurrence of AF and stroke following AFOTS, and found a high rate of recurrence of AF in these patients. Walkey and colleagues published a retrospective study that used administrative data from a United States Medicare 5% sample to detect the long-term prognosis of AFOTS in patients who had sepsis. This study used healthcare claims based on International Classification of Diseases (ICD-9) codes and recognized a 44% recurrence of AF within 1 year after discharge.[115] Gialdini and colleagues used a similar retrospective approach to screen health care claims using ICD-9 codes and found a 37% AF recurrence rate after AFOTS in over a million surgical patients.[29] The Framingham Heart Study investigated a broader range of patients with AFOTS precipitants (*i.e.* surgery and acute medical illness) and found a 44% recurrence after 5 years of follow-up.[46] Although these studies suggest that AFOTS is associated with a high recurrence of AF, the manner in which they collected their data limits the validity of the reported rates of AF recurrence following AFOTS. First, two of the three studies used medical administrative data to identify history of AF, AFOTS incidence and AF recurrence. Administrative data have reported sensitivity for ascertaining prevalent AF of 88-95%, and some cases would be missed.[26,211] Second, these studies relied on opportunistic

methods of AF diagnosis, as compared to a prospective, systematic approach to monitor for AF recurrence. Thus, they may have missed a large portion of asymptomatic AF. Finally, because they most likely would have used no longer than 48-hours of continuous ambulatory ECG monitoring, they would be liable to miss up to 38% of episodes of AF that would be captured by a longer, 14-day patch ECG monitor.[198,206-208] Based on these limitations, prior studies have likely underestimated the true rate of recurrent AF in the AFOTS population. We designed the AFOTS cohort study to overcome these limitations. Figure 2 highlights all three phases of the study that enhance the internal and external validity of the study: i) defining patient population, ii) approach for screening and enrollment, and iii) follow-up protocol.

Experts accept that the risk of stroke increases with higher burdens of AF.[171,212,213] However, controversy exists around the minimum duration of AF after which this risk becomes clinically meaningful.[203,214] In studies that used continuous monitoring in patients with AF risk factors but without a history of stroke, AF duration cutoffs of 5 or 6 minutes were used because they corresponded to a high positive predictive value that the automatic algorithm has actually captured AF, instead of artifact or another arrhythmia.[35,36,139,140] In contrast, a minimum AF duration of 30 seconds was used as the primary endpoint in two clinical trials testing long-term monitoring in patients with cryptogenic stroke.[117,120] Thirty seconds of AF was chosen as the primary endpoint in the present study because it is commonly used in practice, can be

detected by the patch monitor with a high positive predictive value and was recommended during discussions with experts.[215,216] Although the present study will employ a more intensive and higher-sensitivity detection strategy than other studies, it still uses intermittent (as opposed to continuous) monitoring. Thus, any AF detected in this study may correspond to a higher overall burden, but the relationship between short episodes of AF and clinical outcomes remains uncertain. [217] We are collecting other durations of AF as secondary endpoints in order to facilitate comparison with other studies.

The AFOTS Follow-Up Study will match patients with AFOTS to a group of controls who were hospitalized but did not have AF. This matching will occur on the basis of age, gender and the hospital unit where AF is detected. We will use hospital unit in lieu of primary diagnosis, as matching on this basis would not be practical and patients who are cared for in the same are of the hospital should have similar chances of having AF detected. By including a comparator group, we will be able to test whether the recurrence rates of AF detected in our protocol are specific to the AFOTS population. Other studies of intensive monitoring in high-risk patients have ultimately tested a detection strategy and not whether the population of interest is high risk. [117,120] For example, in the intervention group in the CRYSTAL AF study, patients with cryptogenic stroke received an implantable, continuous cardiac monitor and the incidence of AF by 18 months was approximately 17%.[117] However, when descriptive studies used the same technology to screen for subclinical AF in patients with risk factors but without a

history of stroke, the rates of AF at 18 months ranged from 25-34%.[36,139,140] In the AFOTS Follow-Up cohort study, the inclusion of a control group will permit us to draw inferences about the risk of AF recurrence that is specific to this population.

Impact

The results of this prospective observational cohort study will guide physicians managing patients with AFOTS. If the recurrence rate of AF after AFOTS is sufficiently high (*e.g.* >80%), a case could be made to abandon further heart rhythm monitoring for patients with AFOTS. Instead, clinicians would diagnose clinical AF in patients who manifest AFOTS and prescribe long-term OAC according to criteria in clinical practice guidelines.[202,203] If the recurrence rate of AF is below 80% in this cohort study, the results will inform a screening strategy to investigate for AF after an episode of AFOTS. The results of this study will also be useful to inform the design of a randomized controlled trial to test the impact of anti-coagulation for stroke prevention in patients with AFOTS.

Strengths

The prospective AFOTS Follow-Up cohort study is designed to overcome the limitations of previous publications that assessed AF recurrence after AFOTS (Figure 2, Table 2). It will provide clinicians with a valid portrayal of the tendency to AF recurrence after AFOTS and may inform the management of patients with AFOTS.

The screening protocol is designed to minimize against misclassification bias. Research staff will coordinate on a daily basis with clinical staff to systematically screen the surgical and medical wards for patients who have AFOTS. AF history will be verified by communicating with the patient, their providing healthcare team, and through electronic medical records. Concurrently, we will record when these patients return to sinus rhythm - a unique aspect of the AFOTS cohort study that was not captured in prior studies. By enrolling a matched control population, we will not only test the hypothesis that AF recurrence is frequent among AFOTS patients, but also that it is significantly higher than in patients without AFOTS. The 14-day cardiac monitors used in this study represent some of the most sensitive available technology in intermittent ambulatory heart rhythm monitoring and a significant improvement when compared with previous monitoring strategies.

Limitations

Along with cost and time, other limitations must be considered. Even with the proposed systematic and collaborative approach to AFOTS detection, some AF might still go undetected. However, this would bias our results towards the null. Enrolled participants may withdraw during follow-up due to unforeseen circumstances related to their co-morbidities or functional status. Although 28 days of monitoring will give a reasonable estimate of the burden of AF, it will under-detect the true burden as compared to what would be detected by an
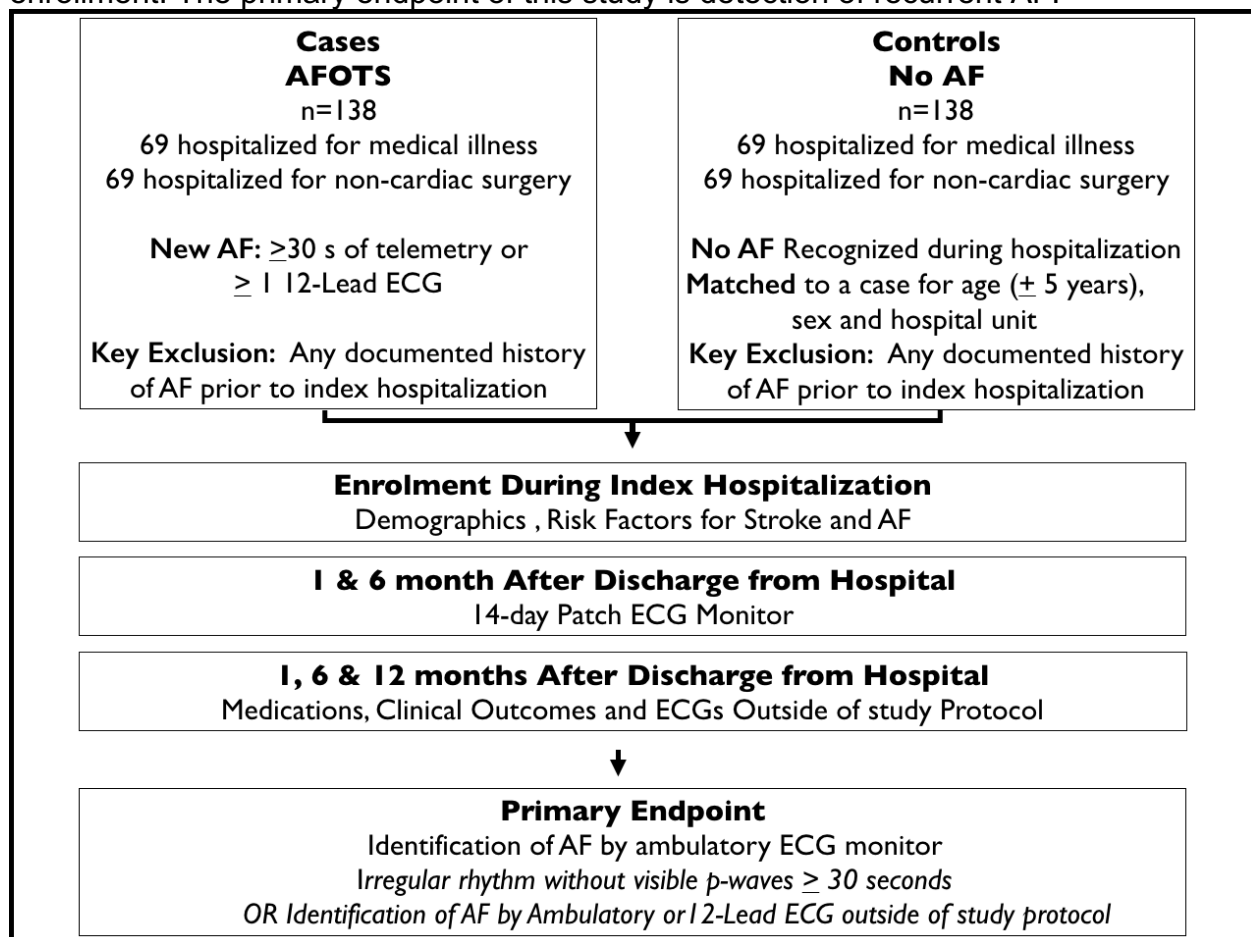
implantable loop recorder. Given the current uncertainty that surrounds the relationship between shorter episodes of AF and clinical outcomes, it may remain unclear whether shorter episodes of AF detected in this study may predict a risk of adverse outcomes, including stroke. Finally, although our research team is interested in defining the stroke risk in patients who had AFOTS, this cohort will be too small to generate precise estimates and our secondary clinical outcomes are thus exploratory.

Conclusion

The AFOTS cohort study will provide crucial data around the rate and risk of recurrent AF among patients who experience AFOTS. The sensitive and systematic design of the AFOTS cohort study will expand the understanding of arrhythmia recurrence and may inform management in this population.

Figure 1: Study design

The study comprises of two prospective, observational cohort studies. Each cohort includes a group of 69 AFOTS patients and 69 matched controls. During enrolment, all participants will have their demographics and medical history collected. All participants will wear a 14-day adhesive ECG monitor at 1 and 6 months after discharge and will return for a final study visit at 12-months post enrollment. The primary endpoint of this study is detection of recurrent AF.

AF : atrial fibrillation

Figure 2: Conceptual model of the Atrial Fibrillation Occurring Transiently with Stress (AFOTS) study strengths

CHF: Congestive Heart Failure; ECG: Electrocardiogram; OAC: oral anticoagulation

Table 1: Inclusion and exclusion criteria for cases and controls

Inclusion Criteria: Cases
- Primary admission diagnosis of non-cardiac surgery (within 7 days following operation) or non-cardiac medical illness.
- AFOTS: Defined as AF for the duration of a 12-lead ECG, or 30 seconds of telemetry. AF can be present on presentation to hospital or occur at any time during the hospital stay.
- Candidates for OAC by CCS Algorithm (Age $\geq$ 65 or one or more of the following risk factors: congestive heart failure/left ventricular ejection fraction $\leq$ 40%, hypertension, diabetes mellitus, a history of stroke/transient ischemic attack.)
- In the surgical cohort, the proportion of patients who have undergone any one type of surgery will not exceed 25% of the total study population (*i.e.* 17 cases and 17 controls)
- In the surgical cohort, the proportion of patients who have undergone emergency surgery will not exceed 60% of the total study population (*i.e.* 41 cases and 41 controls)
- In the medical study, the proportion of patients who have been diagnosed with sepsis will not exceed 60% of the total study population (*i.e.* 41 cases and 41 controls)

Inclusion Criteria: Controls
- Primary admission diagnosis of non-cardiac surgery (within 7 days following operation) or non-cardiac medical illness.
- No AFOTS detected in hospital
- Matched to a case for:
  - Sex
  - Age within $\pm$5 years
  - Surgery or medical illness (based on respective cohort)
  - Hospital unit and medical center
- Would-be Candidates for OAC by CCS Algorithm (Age $\geq$ 65 or one or more of the following risk factors: congestive heart failure/left ventricular ejection

fraction $\leq$ 40%, hypertension, diabetes mellitus, a history of stroke/transient ischemic attack.)

Exclusion Criteria
- Documented prior history of AF
- Patients whose rhythm is AF at the time of discharge from hospital
- Patients unsuitable for study follow-up because the patient:
    ○ is unreliable concerning the follow-up schedule
    ○ cannot be contacted by telephone
    ○ has a life expectancy less than one year
- Unwilling or unable to participate in the study
- Presence of an implanted pacemaker or defibrillator
- Documented significant allergy to ECG electrode adhesive
- Residence in a chronic care facility
- Diagnosed with ischemic stroke or systemic embolism on admission
- Primary cardiac admitting diagnosis (*i.e.* myocardial infarction, heart failure, pericarditis, arrhythmia)
- Patients with Stage V chronic kidney disease

CCS: Canadian Cardiovascular Society

Table 2: Methodological Strengths of AFOTS Follow-Up Cohort Study

	Previous Studies	**AFOTS Follow-Up Cohort Study**
Pre-hospital AF history	*Administrative Data or Patient Interview*	*Patient Interview and Review of Medical Records*
In-hospital incidence of AFOTS	*Administrative Data or Discharge Records*	*Daily screening of hospital in-patients*
Evaluation of Heart Rhythm at the Time of Hospital Discharge	*No*	*Yes*
Recurrence of AF	*Administrative Data or Review of Medical Records*	*Two 14 day ECG monitors, Review of Medical Records*
Use of Oral Anticoagulation	*Administrative Data or Review of Medical Records*	*Patient Interview*
Occurrence of Stroke or Other Hospitalization	*Administrative Data or Review of Medical Records*	*Patient interview and Review of Medical Records*

Table 3: Baseline characteristics of AFOTS cases enrolled in the AFOTS Follow-up cohort to date.

	N = 90
Age in years [Median (IQR)]	76.50 (66.0-83.5)
Female Sex [n (%)]	47 (53.4)
CHA2DS2-VASC Score [Median (IQR)]	3.00 (2.0- 4.0)
Duration of AF in hours [Median (IQR)]	15.00 (3.0-51.0)
Method of Cardioversion	
Spontaneous [n (%)]	39 (50.6)
Electrical [n (%)]	3 (3.9)
Pharmacological [n (%)]	35 (45.5)
Discharged on OAC [n (%)]	36 (40.9)
Primary Diagnosis	
Non-Cardiac Surgery [n (%)]	46 (51.1)
Neurosurgery [n (%)]	3 (6.5)
Thoracic Surgery [n (%)]	6 (13.0)
Vascular Surgery [n (%)]	8 (17.4)
Urological surgery [n (%)]	1 (2.2)
Digestive Surgery [n (%)]	8 (17.4)
Female reproductive Surgery [n (%)]	4 (8.7)
Orthopedic Surgery/Trauma [n (%)]	11 (23.9)
Other Surgeries [n (%)]	3 (6.5)
Medical Illness [n (%)]	44 (48.9)
COPD Exacerbation [n (%)]	2 (4.5)
Pulmonary Embolism [n (%)]	2 (4.5)
Infection [n (%)]	23 (52.3)
Bleed [n (%)]	4 (9.1)

	N = 90
Acute Kidney Injury/Rhabdomyolysis [n (%)]	3 (6.8)
Hypertensive Emergency [n (%)]	2 (4.5)
Other* [n (%)]	9 (20.5)

*Other = One each of: Diabetic Ketoacidosis, Drug toxicity, Altered Mental Status Not Yet Diagnosed, Pleural Effusion, Seizure, Stem Cell Transplant for B Cell Lymphoma, Non-operative Trauma, Thyrotoxicosis

IQ: Inter Quartile Range

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Appendix

1. Definition of Outcomes

2. Study Organization

1. Definition of Outcomes

Primary Outcome

Detection of Recurrent Atrial Fibrillation within 12 months:

- AF by ambulatory monitor: 30 seconds of irregular rhythm without

  visible p-waves

  OR

- AF by ECG: occurring for the duration of a 12-Lead ECG or 30 seconds

  of ambulatory monitoring done outside of the study protocol

All ECGs showing atrial fibrillation will be adjudicated by an arrhythmia physician

who is blinded to the participant's prior history.

Secondary Outcomes

1. Predictors of capturing recurrent AF after AFOTS.

2. Among AFOTS patients with the primary endpoint detected by the ECG patch monitor: time to first detection of AF >30 s; daily and total AF burden; average duration per AF episode.

3. Among AFOTS group patients, detection of any AF episode ≥30 seconds, ≥30 seconds to 5 minutes, > 5 minutes, >5 hours, and >24 hours (to facilitate comparison with other studies in the literature).

4. Detection of the primary outcome at 1 and 6 months post enrolment.

5. Clinical outcome events within 12 months post-enrolment (death, stroke, bleeding, embolism and hospitalization for heart failure or myocardial infarction), physician visits, hospitalizations and medication prescriptions.

6. Oral anticoagulant therapy use at 1, 6 and 12 months post-enrolment.

7. Cost-effectiveness (cost per life year saved) and cost-utility (cost per quality adjusted life year (QALY) gained) of AF monitoring.

8. Patient adherence with the monitoring devices (defined as the average number of monitoring days completed and reasons for non-adherence), patient satisfaction with the monitoring devices (as measured by user satisfaction surveys), and tolerability of the ECG monitor

(defined as the incidence of adverse skin reactions related to the adhesive patch).

9. Estimated sensitivity, specificity of non-patch ECG monitoring (*i.e.* monitoring done outside of the study protocol), with ECG patch monitor as the gold standard.

10. Detection of other potentially clinically important non-AF arrhythmias: atrial tachycardia, pause >3 seconds, high-grade atrioventricular block (Mobitz type II or third-degree AV block), ventricular tachycardia, polymorphic ventricular tachycardia/ventricular fibrillation.

2. Study Organization

Co-ordinating Centre:

Population Health Research Institute, a joint institute of McMaster University and Hamilton Health Sciences in Hamilton, Ontario, Canada

Executive Committee:

Dr. JS Healey MD MSc (Senior Principal Investigator), Dr. WF McIntyre MD (Junior Principal Investigator), Dr. SJ Connolly MD MSc, Dr. EP Belley-Côté MD MSc, Dr. RP Whitlock, MD PhD

Study Sites and Site Investigators:

Hamilton General Hospital: Dr. RP Whitlock, MD PhD

Juravinski Hospital and Cancer Centre: Dr. PJ Devereaux MD PhD

St Joseph's Healthcare Hamilton, Charlton Campus: Dr. D Conen MD MSc

ECG Adjudication Committee:

Dr. JA Wong MD MPH (Chair), Dr. JG Acosta MD

AUTHORS' CONTRIBUTIONS

William McIntyre contributed significantly to the study's concept and design, data collection and analysis, and interpretation of the results. He wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

Pablo Mendoza contributed to the data collection and analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Emilie Belley-Côté contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Richard Whitlock contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Kevin Um contributed to the data collection and analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Natalie Maystrenko contributed to the data collection and analysis, and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

PJ Devereaux contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

David Conen contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Jorge Wong contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Stuart Connolly contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Jeff Healey contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Chapter 8

Conclusions and Future Directions

8.1 Background

This doctoral thesis studied the epidemiology of Atrial Fibrillation Occurring Transiently with Stress (AFOTS). The included studies summarize the existing literature on the subject, examine the incidence and recurrence of AFOTS using continuous monitoring from pacemakers, estimate the incidence of AFOTS using patch electrocardiogram (ECG) monitors in the Intensive Care Unit (ICU) and systematically follow patients with AFOTS after the index hospitalization.

8.2 Pathophysiologic and Clinical Questions in AFOTS

In **Chapter 2**, we provided a narrative review and contextualized the clinical problems posed by AFOTS.

For some patients, AFOTS could be uniquely and directly due to a precipitating primary medical or surgical condition and ultimately of no consequence to the patient's long-term health. For other patients, AFOTS may be the first detection of paroxysmal AF. This would mean that they stand to benefit from evidence-based therapies for this condition, including oral anticoagulation for stroke prevention. We discuss the potential impact of different intensities of ECG monitoring on the incidence and recurrence of AF.

The studies in this thesis are guided by this dichotomy and are designed to use the most sensitive of ECG methods.

8.3 Incidence and recurrence of AFOTS associated with acute medical illness

In **Chapter 3**, we systematically reviewed existing literature on the incidence and recurrence of AFOTS associated with acute medical illness. We found that among patients who are hospitalized for acute medical illness, new-onset AF is detected during the hospitalization in anywhere from 1 to 44% of patients. Substantial heterogeneity in estimates precluded pooling data to form a summary estimate. The in-hospital incidence of AF was higher in studies that prospectively used continuous electrocardiographic monitoring, and in studies of patients being cared for in an ICU. Following hospital discharge, recurrent AF was detected in about half of individuals over follow up periods ranging from 1 to 5 years. These studies did not prospectively use continuous ECG monitoring, raising the question of whether the rate of recurrence would be even higher if such methods were used.

The results of this systematic review, along with the review in non-cardiac surgery presented in **Chapter 4**, were used to guide the design of the incidence study in **Chapter 6** and the long-term follow-up study in **Chapter 7**.

8.4 Incidence and recurrence of AFOTS associated with noncardiac surgery

In **Chapter 4**, we systematically reviewed the literature pertaining to the incidence and recurrence of AFOTS associated with noncardiac surgery. Although we odentified 346 studies that met inclusion criteria, only 27 studies used prospective, continuous inpatient ECG monitoring to detect incident AF. There was very wide range in the incidence of new-onset post-operative AF, ranging from 0.004% to 50.3%, with a median of 8.7% (interquartile range 3.8-15.0%). The rate of AF incidence in prospective studies that used continuous ECG monitoring was significantly higher as compared to those that did not (13.9% versus 1.9%, p<0.0001). We identified 13 studies with follow-up up to 5.4 years that reported on AF recurrence following hospital discharge. A single study used a prospective systematic monitoring protocol, documenting a recurrence rate of 31% at 12 months. Otherwise, recurrence rates ranged from 0-37%.

The results of this systematic review, along with the review in medical illness presented in **Chapter 3**, were used to guide the design of the incidence study in **Chapter 6** and the long-term follow-up study in **Chapter 7**.

8.4 Profiling AFOTS using continuous ECG monitoring from pacemakers

In **Chapter 5**, we used the continuous electrograms from pacemakers to compare the temporal profile of device-detected AF before and after a hospitalization for acute medical illness or noncardiac surgery. This approach minimized detection bias.

We found that the prevalence of pacemaker-detected atrial fibrillation (AF) increases around the time of hospitalization for non-cardiac surgery or medical illness. Interestingly, about half of patients with AF in this setting have a prior history of pacemaker-detected AF. This pattern suggests that physiologic stress may be an acute trigger for AF. However, it also suggests these episodes of AF are often a manifestation of a condition that is likely to recur. New-onset AF around the time of acute illness or surgery cannot be dismissed nor can it be assumed to be a manifestation of chronic AF.

8.6 Estimating the incidence of AFOTS in the ICU

In **Chapter 6**, we estimated the incidence of new-onset AF in consecutive patients admitted to the ICU using a continuous patch ECG monitor. We found that Among patients admitted to an ICU, the incidence of new-onset AF is approximately 1 in 5. However, approximately one third of cases were not recognized by the clinical team. In this study, we have provided a useful estimate of the incidence of new-onset AF for use in future studies. Furthermore, we have highlighted that studies that investigate AF as an outcome or prognostic factor must consider method of detection.

8.7 Recurrence of AF after AFOTS

Chapter 7 describes the rationale and methodology of a prospective cohort study that is using continuous ECG monitoring to compare rates of AF

detected after hospitalization between patients with AFOTS and matched controls who have never had AF. The design of this study was informed by the work conducted in the preceding chapters of this thesis

This study will establish whether patients with AFOTS have an increased propensity to AF after hospitalization as compared to matched controls and may inform the management of this population. Presently, this study has enrolled more than 95% of its target sample and aims to report its final results in late 2021.

8.8 Conclusions and future directions

Through the research contained in this thesis, I have learned and applied the methodology needed to address research questions using multiple study designs. These skills will serve me in my career as a clinician scientist.

The work in this thesis could impact research and patient care in multiple way. First, I hope that clinicians and researchers will see that AFOTS is neither a benign entity nor equivalent to the common form of AF. Clinicians will need to follow and re-assess these patients carefully to help understand whether each individual patient has AF. The approach being tested in the AFOTS Follow-Up Study in **Chapter 7** may be useful for clinicians. Second, we need to employ the best available tools to stratify patients – long-term continuous ECG is becoming widely available and must be used to its full potential. We should also study and make use of other emerging tools to help stratify patients, including genomics

and biomarkers. Third, these approaches can be applied to another important population that was not studied in this thesis: patients who have AFOTS in the setting of a cardiac illness. Cardiac surgery and acute coronary syndromes are thought to be associated with even higher rates of AFOTS than medical illness and noncardiac surgery, but are believed to be less likely to have recurrences of AF due to direct cardiac injury. These assumptions remain largely unproven and answering these questions for this population is imperative due to the large absolute numbers of patients affected.