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Design and rationale of the atrial fibrillation occurring transiently with stress (AFOTS) incidence study

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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 to 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 ≥ 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 h after admission. The primary endpoint is the incidence of AF lasting ≥30 s. The study is powered to detect an AF incidence of 17% ± 5%.

Results: We conducted a vanguard feasibility study, and 55 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.

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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 [1–4]. 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 [5]. As a result, there is uncertainty as to whether patients with AFOTS should receive long-term oral anticoagulation (OAC) for the prevention of stroke [6–10]. 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 [5]. 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 [5].

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 [11]. 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 [12].

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.

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Methods

Objectives

The primary objective of the AFOTS Incidence study (NCT03552588) is to determine the incidence of AF, lasting 30 s 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; [5] to explore clinical factors that predict clinical detection of AF, and [6] to explore the association between AF and clinical outcomes.

Population

This prospective, descriptive epidemiological study will enroll 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)) [13].

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 h. 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 [5]. We will also exclude patients who are not screened within 12 h 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 s, 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 min or more, 1 h or more, 6 h or more and 24 h or more; (3) the burden of patch-detected AF, defined as time spent in AF per 24 h 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 [14]), 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 ICU (Fig. 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 <90 min after admission, a high sensitivity 14-day ECG patch monitor will be applied (ZIO XT Patch, iRhythm, Chicago USA) [15–18]. Informed consent will be obtained—either from the patient or an appropriate substitute decision-maker—with a target time of <72 h. 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 ICU setting [19].

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 [11]. 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 (Table 1, Fig. 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-

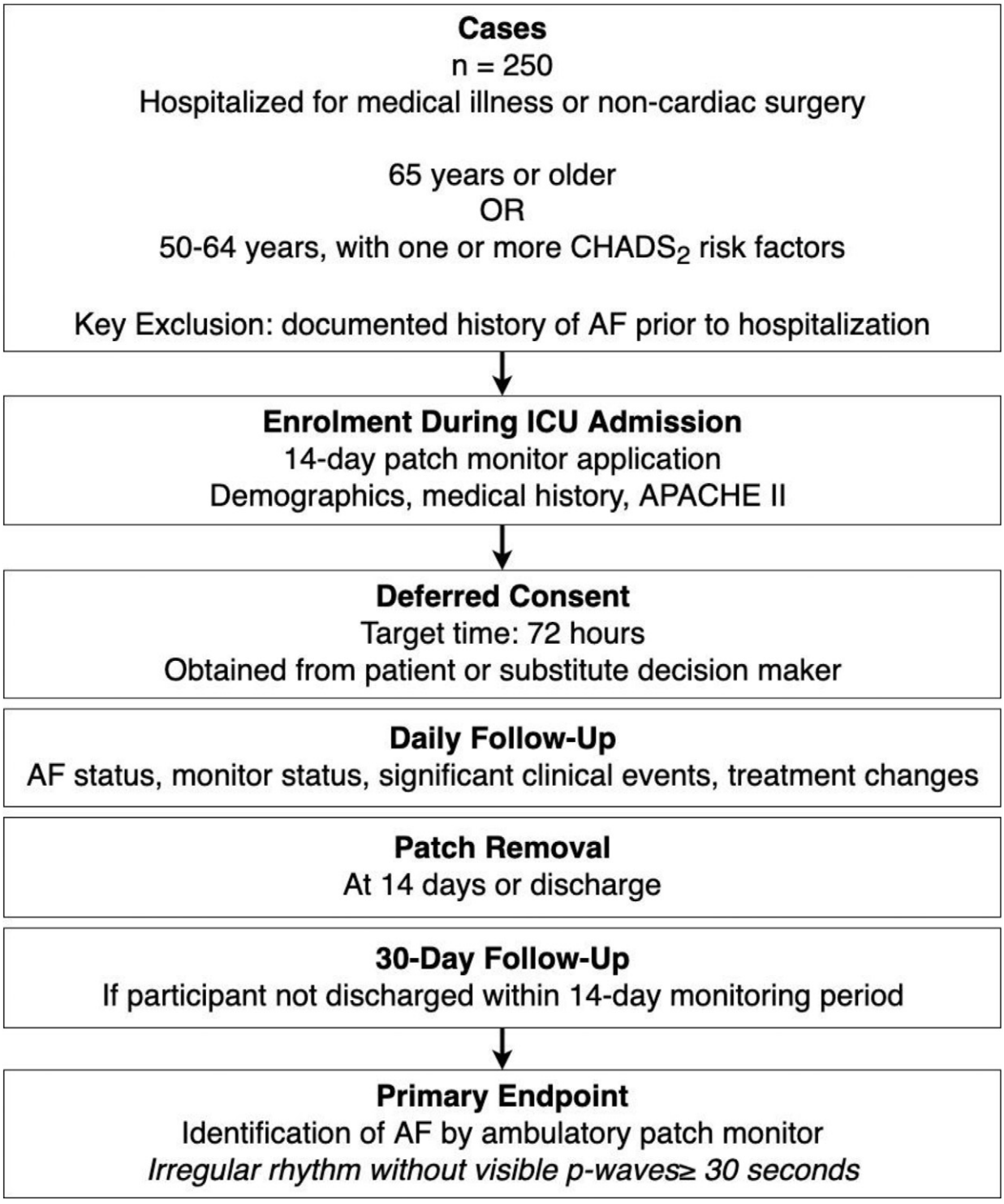

Fig. 1. Work flow of the AFOTS Incidence study. AF: Atrial Fibrillation; $CHADS_2$-: Congestive heart failure, Hypertension, Age ≥ 75, Diabetes, and Stroke/TIA (2 points); APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II Scoring System.

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 [11]. This

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_2DS_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)

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)

discrepancy is similar in estimates of incidence in patients following non-cardiac surgery, ranging from 1% to 35% [11]. 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 [11]. 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 [11].

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 [11]. Meanwhile, 17 of 26 studies that did not use prospective and continuous monitoring reported incidences of <10% [11]. In keeping with this, the highest incidence was reported in a small ($n = 66$) prospective study employing seven-day continuous Holter monitoring [11,20]. 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 s occurred in 44% of participants [20]. 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 [20]. 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 [5]. This study will allow us to systematically assess the

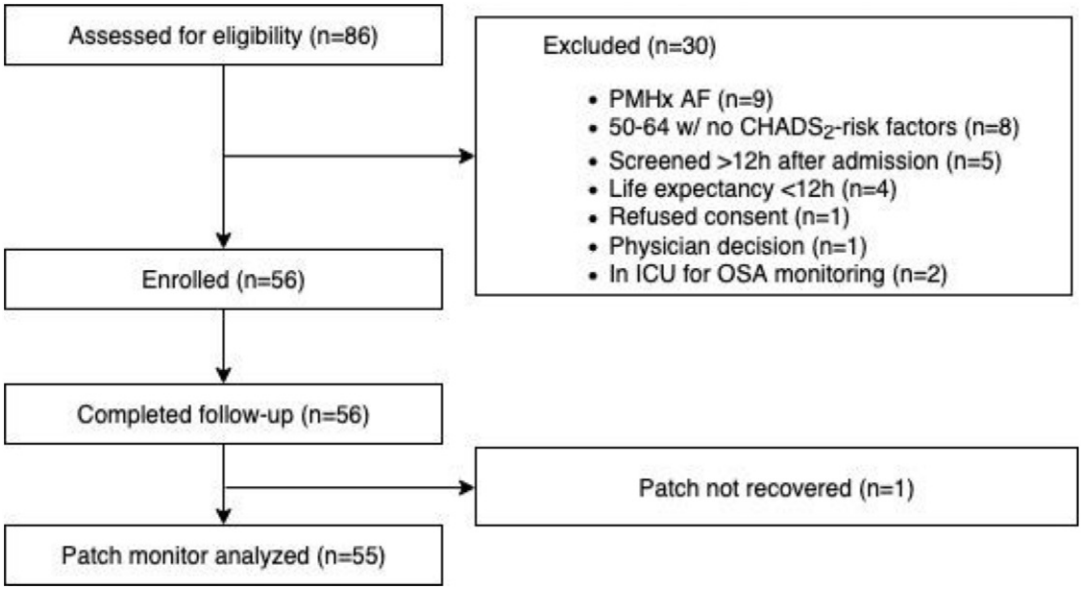

Fig. 2. Patient flow in the AFOTS Incidence vanguard study. $CHADS_2$-: Congestive heart failure, Hypertension, Age ≥ 75, Diabetes, and Stroke/TIA (2 points); ICU: Intensive Care Unit, OSA = Obstructive Sleep Apnea; PMHx AF = Past Medical History of Atrial Fibrillation.

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) [21], 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.

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 <48 h 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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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.

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