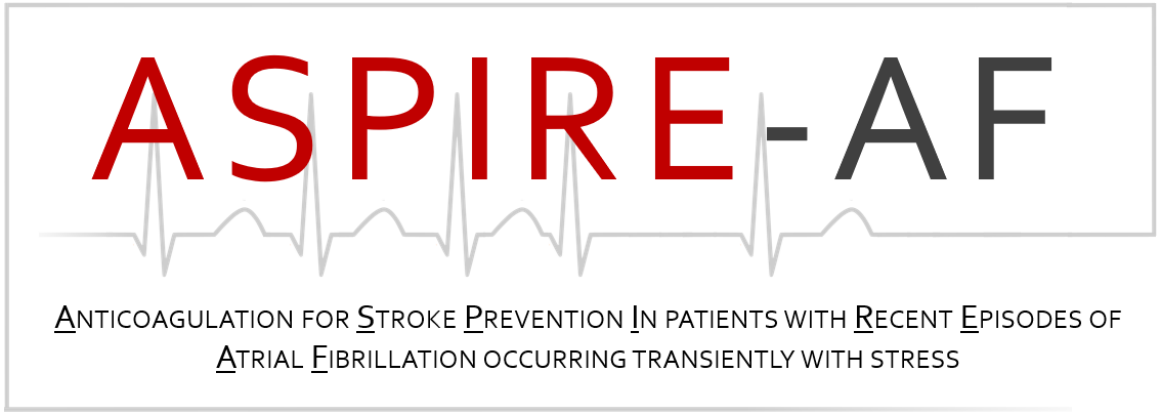


Study Overview

Study Design and Sample Size

- Prospective, randomized, open-label clinical trial with blinded outcome assessment (PROBE design)
- 2,270 patients with AFOTS and additional stroke risk factors after noncardiac surgery in sinus rhythm at the time of randomization
- Randomized 1:1 to non-vitamin K oral anticoagulant (NOAC) or no anticoagulation (strategy trial not involving investigational drugs)
- Follow-ups will occur every 3 months (in-clinic, telephone) until a common end date

Co-Primary Outcomes

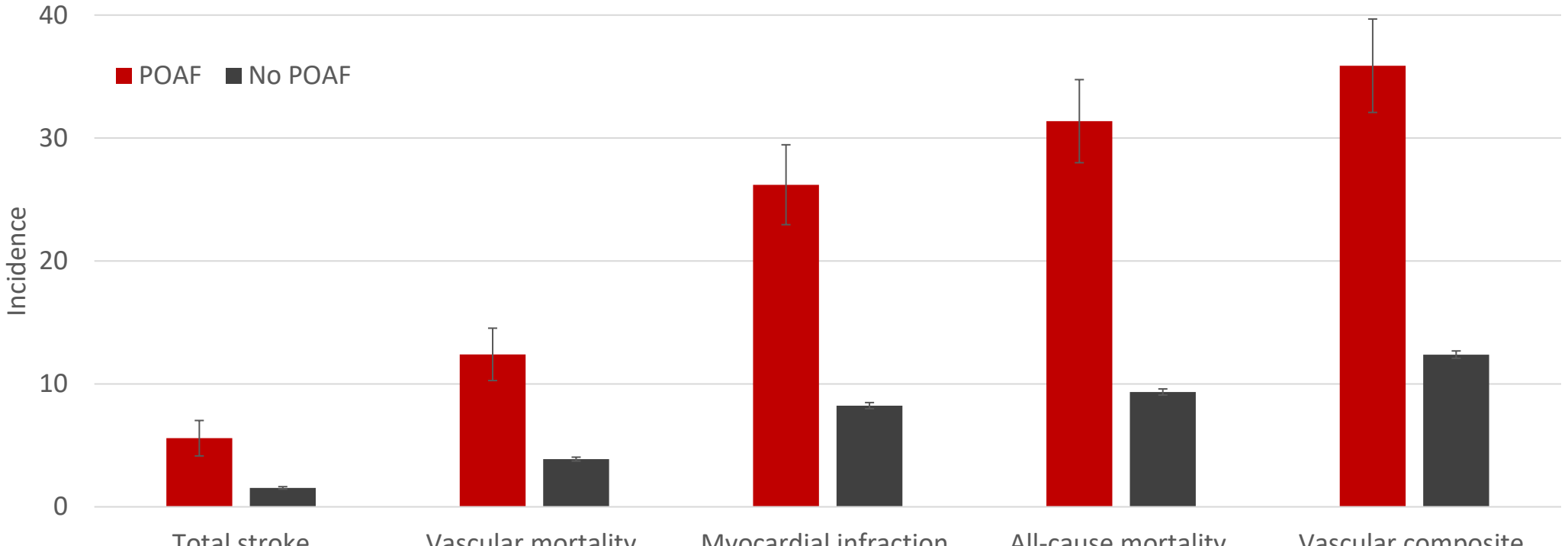
The ***primary objective*** is to determine whether NOACs versus no anticoagulation reduce the risk of the co-primary outcomes:

1. Composite of non-hemorrhagic stroke and systemic embolism; and
2. Composite of vascular mortality, and non-fatal non-hemorrhagic stroke, myocardial infarction, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism.


ASPIRE-AF
ANTICOAGULATION FOR STROKE PREVENTION IN PATIENTS WITH RECENT
EPISODES OF PERIOPERATIVE ATRIAL FIBRILLATION AFTER NONCARDIAC SURGERY

Background

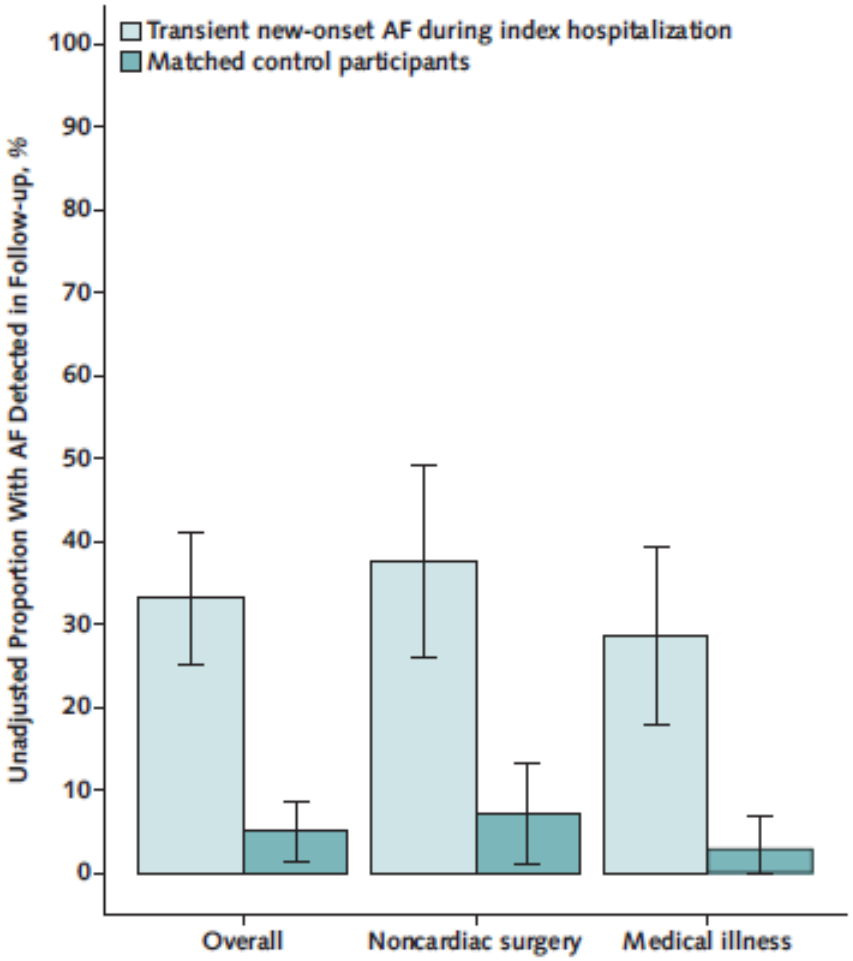
Perioperative AF and Adverse Events

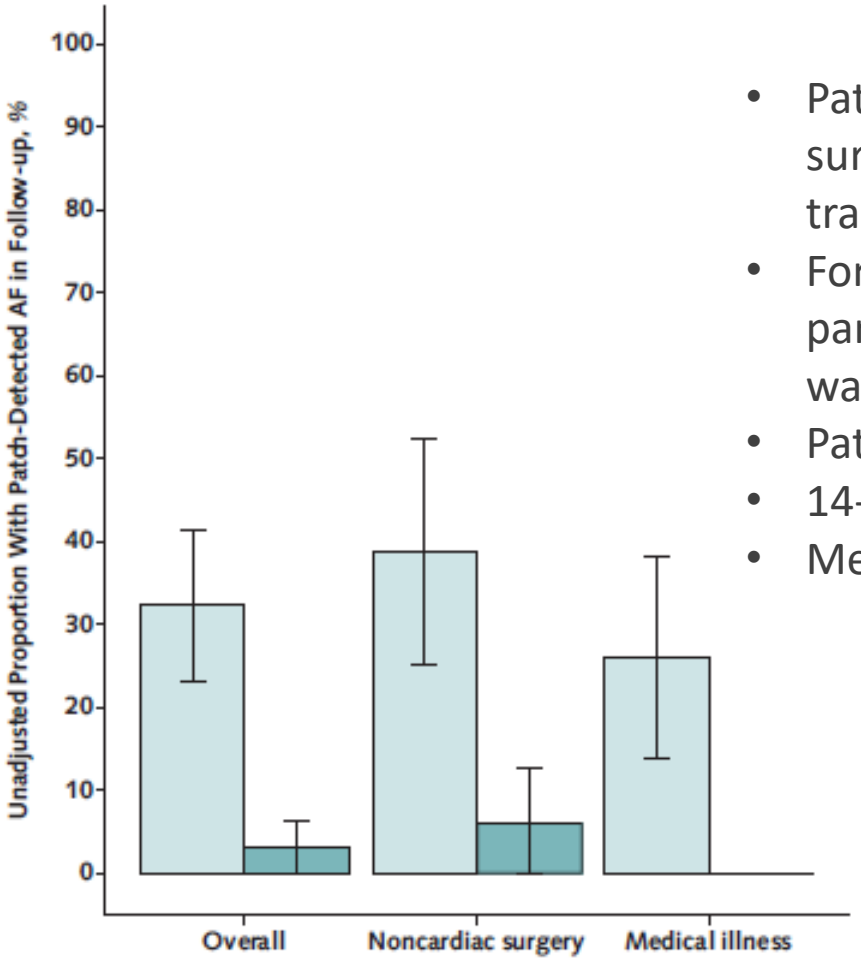


	Total stroke	Vascular mortality	Myocardial infraction	All-cause mortality	Vascular composite
Adjusted HR (95% CI)	3.43 (2.00-5.90)	2.74 (1.92-3.90)	5.10 (3.91-6.64)	2.51 (2.01-3.14)	3.93 (3.14-4.91)

Conen et al. Eur Heart J 2019

AF occurring transiently with stress (AFOTS)

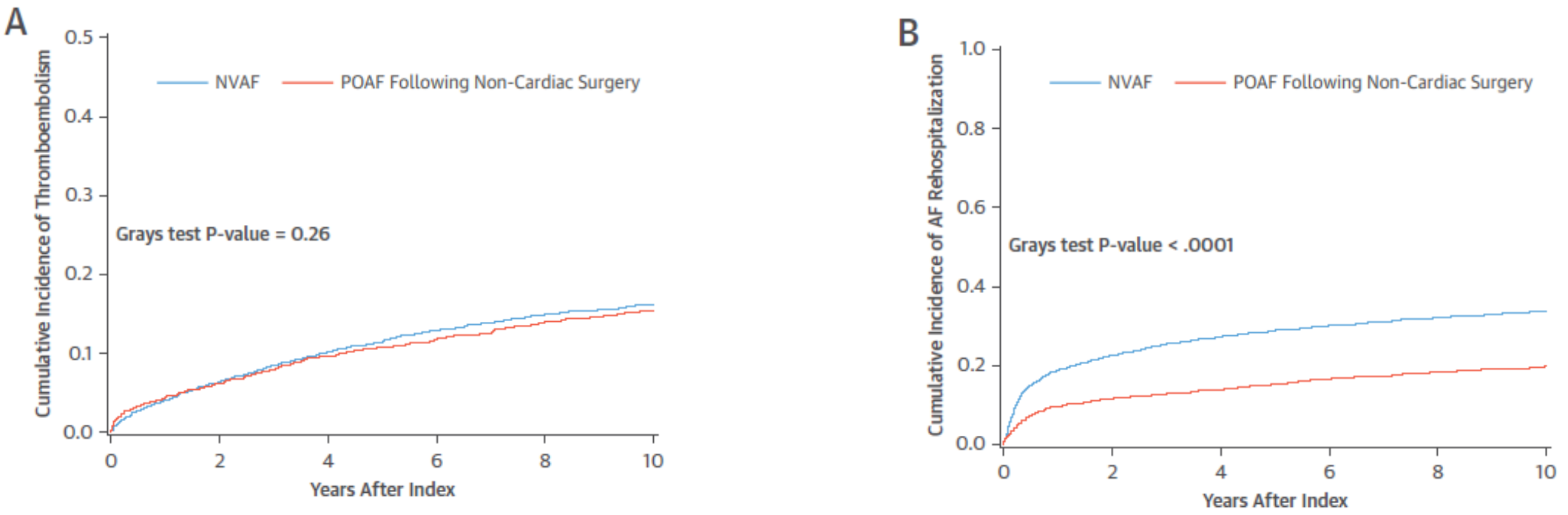




- Patients hospitalized for noncardiac surgery or medical illness with transient new-onset AF.
- For each patient, a matched control participant with no history of AF was recruited from the same ward.
- Patients left hospital in SR
- 14-day Holter at 1 and 6 months
- Mean CHA_2DS_2-VASc was 3.0

McIntyre et al Ann Intern Med 2023

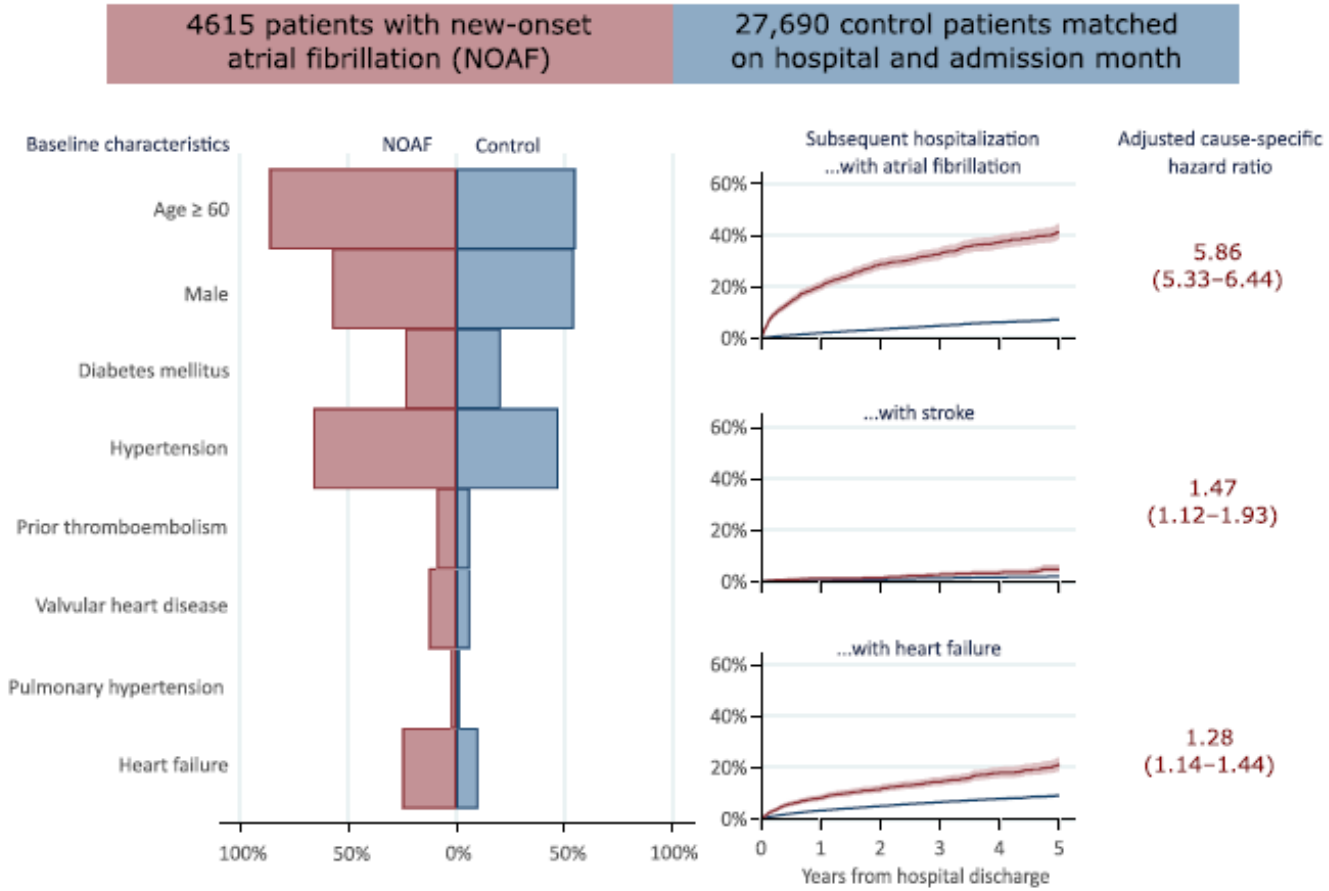
Risk of thromboembolism associated with new-onset inhospital AF (AFOTS)



POAF versus new onset "NVAF" in hospital (most of them likely acute medical illness related), matched for age, sex, CHF, HTN, DM, previous thromboembolism, IHD, year of discharge

Butt et al J Am Coll Cardiol 2023

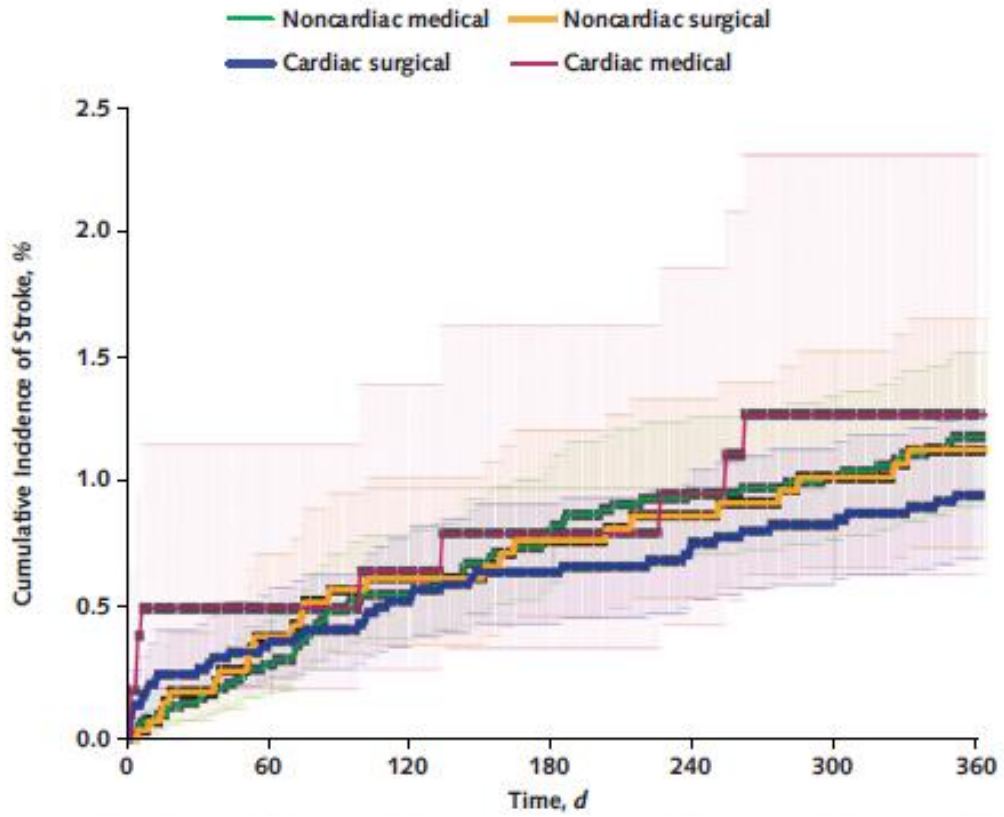
New onset atrial fibrillation in ICU

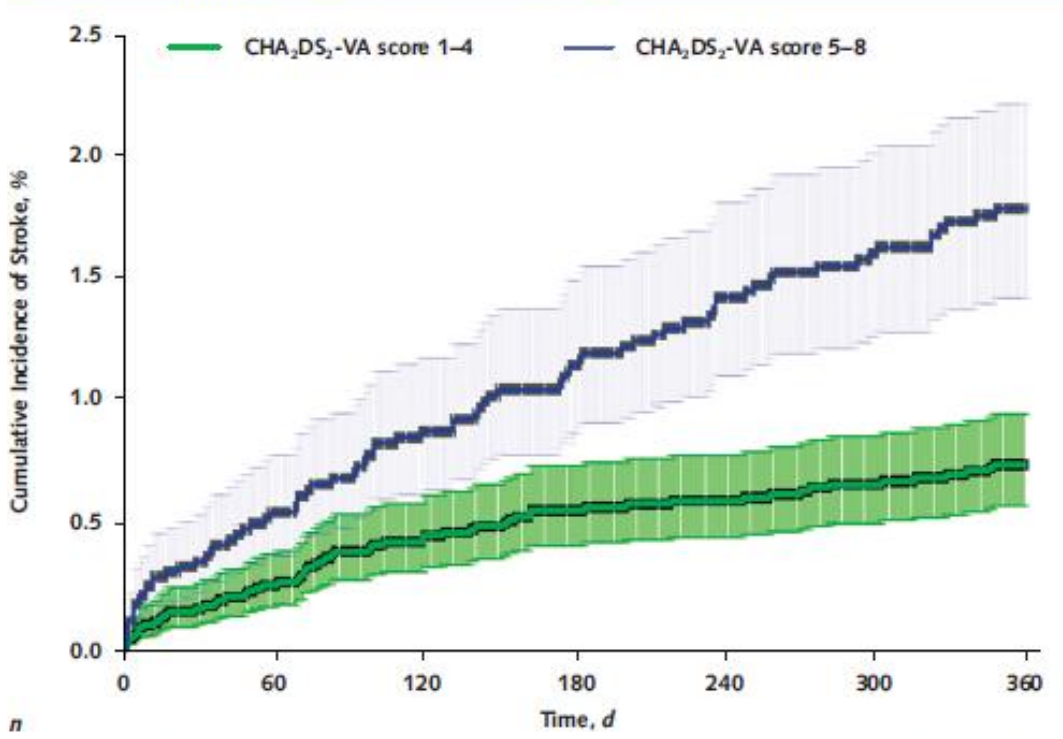


Baseline characteristics and outcomes of patients in intensive care with new-onset atrial fibrillation compared with patients without atrial fibrillation in a large UK nationwide cohort study.

Bedford et al Eur Heart J ACC 2022

Risk of stroke after new-onset AF during hospitalization for other primary diagnoses





Patients 66+ discharged alive from hospital with newly diagnosed AF, followed for incident stroke, not on OAC

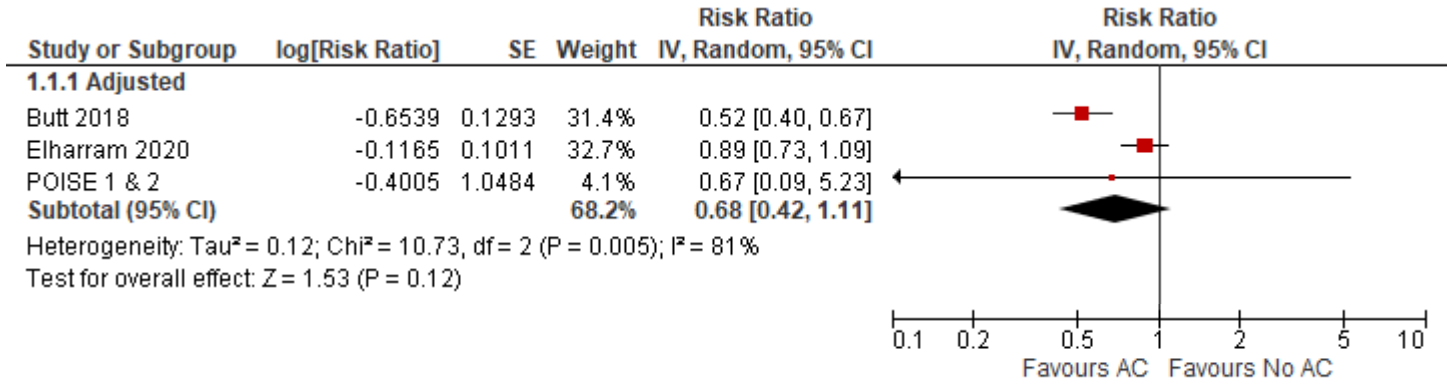
Abdel-Qadir et al Ann Intern Med 2025

Oral anticoagulation in AFOTS

- There is no clinical trial to show that oral anticoagulation is effective and safe among patients with AFOTS (both surgical and medical patients)

- No reliable data on Chadsvasc score (or any other risk scoring system) in AFOTS patients (calibration)

Meta-analysis: OAC for Perioperative AF

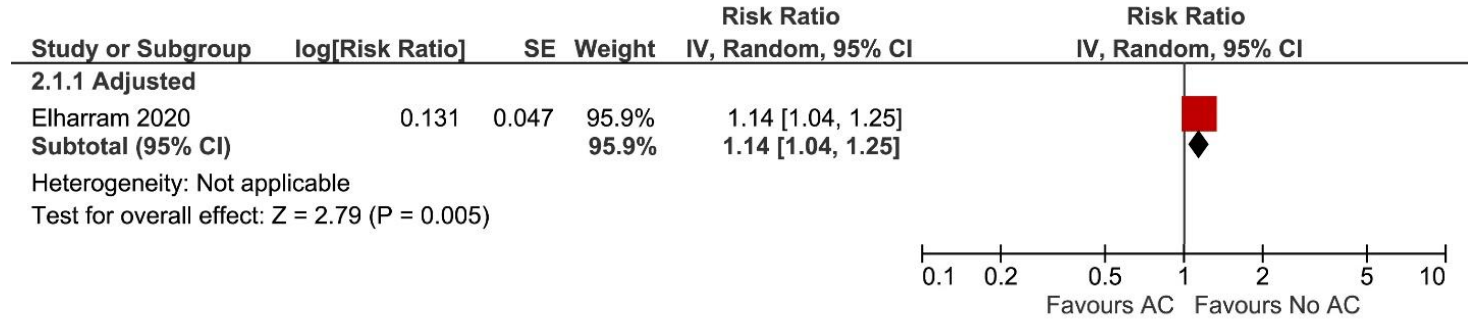


Stroke Risk

No RCTs,

3 observational studies

with adjusted relative risks



Bleeding Risk

1 observational study

with adjusted relative risk

Wang et al. Swiss Med Wkly 2023

Anticoagulation for AFOTS

- Only 20 to 40% of patients with AFOTS are anticoagulated at hospital discharge
- Anticoagulation therefore cannot be considered the standard of care in this patient population
- **2020 ESC Guidelines for atrial fibrillation:**
  - It is unclear whether and how long patients with postoperative AF should be anticoagulated and call for research to inform this issue

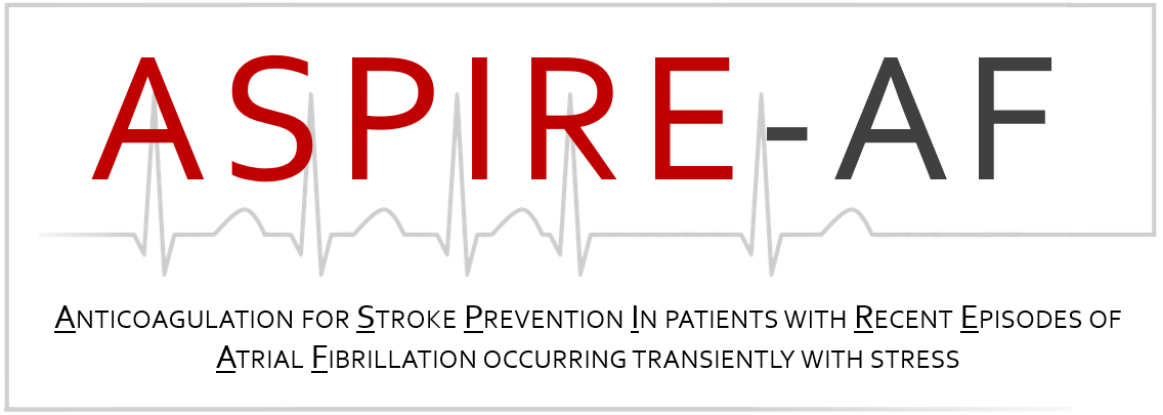
Hindricks et al. Eur Heart J 2020

Anticoagulation for AFOTS

- Must weigh potential benefits and risks of anticoagulation
  - Absolute stroke risk may be lower in patients with perioperative AF
  - The minimum amount/burden of perioperative AF needed to increase stroke risk is unknown (ARTESIA suggests benefit despite low burden)
  - Bleeding risk associated with NOACs increases with age
- Relative risk reduction associated with anticoagulation may not be the same as in nonoperative AF, as stroke etiologies may differ

Summary

- Characteristics of AF associated with acute medical illness appear similar to those with postoperative AF after noncardiac surgery
- To improve recruitment rates and further increase the impact of ASPIRE-AF we made the decision to amend the protocol to allow for recruitment of patients with AF associated with acute medical illness
- At their last session, the DMC has strongly endorsed these changes
- **ASPIRE-AF: Anticoagulation for Stroke Prevention In patients with Recent Episodes of Atrial Fibrillation occurring transiently with stress (AFOTS)**



Eligibility Criteria

Inclusion Criteria

(all of the following)

- **have ≥1 episode of clinically important AFOTS during any of the following conditions:**
  - noncardiac surgery in the past 35 days, with ≥1 overnight hospital admission after surgery;
  - noncardiac day surgery resulting in a large enough physiological insult to be able to cause AFOTS, as judged by the local investigator; or
  - acute medical illness requiring hospital admission in the past 35 days and resulting in a large enough physiological insult to be able to cause AFOTS, as judged by the local investigator;
- **sinus rhythm at the time of randomization;**
- **have any of the following high-risk criteria:**
  - age 55-64 years, and having either established CVD, recent major vascular surgery, a CHA_2DS_2VASc score ≥3, or an elevated postoperative troponin level;
  - age 65-74 years, and having either established CVD, recent major vascular surgery a CHA_2DS_2VASc score ≥2, or an elevated postoperative troponin level; or
  - age ≥75 years; and
- **provide written informed consent to participate.**

Main Exclusion Criteria

(please refer to protocol for entire list)

- any cardiac diagnosis as the primary reason for hospital admission (e.g., acute coronary syndrome, congestive heart failure, peri-myocarditis)
- history of documented chronic (i.e., non-transient) AF;
- need for long-term systemic anticoagulation treatment;
- ongoing need for long-term dual antiplatelet treatment;
- contraindication to oral anticoagulation (e.g., severe renal insufficiency with CrCl <20 ml/min, severe liver cirrhosis Child-Pugh Class C);
- history of nontraumatic intracranial, intraocular, or spinal bleeding;
- hemorrhagic disorder or bleeding diathesis;
- expected to be non-compliant with follow-up and/or study medications;
- known life expectancy <1 year due to concomitant disease;

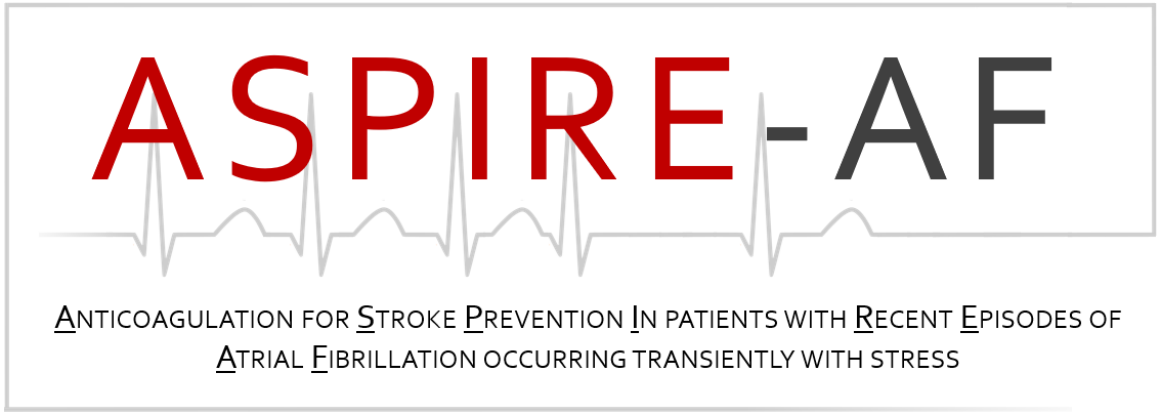
Clinically Important AF Definition

- Clinically important AFOTS is defined as any of the following:
  - AF documented on a 12-lead ECG
  - Confirmed AF (e.g., rhythm strip) resulting in angina, heart failure, or symptomatic hypotension
  - Confirmed AF requiring treatment with a rate control drug, antiarrhythmic drug, or electrical cardioversion
  - Confirmed continuous AF with a minimum duration of 1 hour

Non-Vitamin K Oral Anticoagulants

In the NOAC arm, the following treatments can be prescribed
(dosed according to product label, availability is dependent on the country):

- **Edoxaban** 60 mg once daily
  - Dose reduction to 30 mg daily if any of the following are present: creatinine clearance 30 to 50 mL/min, weight ≤60 kg, concomitant treatment with a potent P-Gp inhibitor (e.g., cyclosporine, dronedarone, erythromycin, ketoconazole, quinidine)
- **Apixaban** 5 mg twice daily
  - Dose reduction to 2.5 mg twice daily if two or more of the following criteria are present: creatinine ≥133 µmol/L, weight ≤60 kg, age ≥80 years
- **Dabigatran** 110 mg twice daily
  - Only the 110mg dose to be used based on its known efficacy for stroke prevention in non-operative AF[1] and its efficacy and safety after noncardiac surgery in patients with MINS[2].
- **Rivaroxaban** 20 mg once daily
  - Dose reduction to 15 mg once daily if creatinine clearance less than 50 mL/min



Screening & Recruitment

Systematic screening for ASPIRE-AF

- No established treatment path for patients with AFOTS, you must actively go out and find them

- **Screening most efficient tool for successful ASPIRE-AF recruitment**
- EMR to screen for perioperative AF /AFOTS on medical wards
- Electronic ECG database
- Promote ECG recordings in elderly patients after surgery (POD 1-3)
- Monitor medication use (BB, amiodarone) on surgical floors

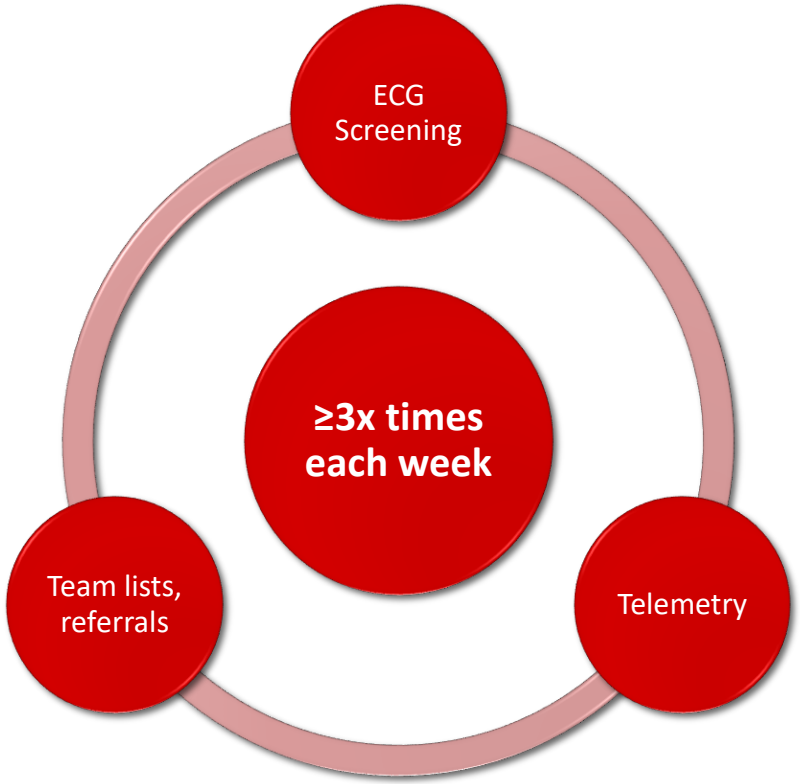
Use **multiple** screening approaches

#1 ECG screening
- EMR search for postop AF and/or ECGs
- Screen paper ECGs on surgical wards

#2 Team lists & referrals
- Medicine, cardiology, surgery
- Regular contact (text, call, email)

#3 Telemetry screening
- ICU, CCU, ward telemetry

#4 Study promotion
- Divisional rounds and lectures
- Posters in hospital workspaces



Recruitment tips and tricks

- **Present ASPIRE-AF as a strategy trial of two well-established ways to treat patients with AFOTS (i.e., no experimental drugs or placebo)**
- Approach patients as early as you can, preferably with a study MD
- **Don't prematurely exclude patients due to older age, acute illness, or complex comorbidities (e.g., cancer)**
- You can still recruit patients started on NOAC for AFOTS by their care team
- **Review CT/MRI imaging for atherosclerosis (high-risk criterion)**
- If patient has not converted to sinus rhythm at discharge, book outpatient follow-up within 35 days of surgery OR admission
- **Patients get routine follow-up with specialist which is better than standard of care**

Please review our "Enrollment Guide" for helpful tips on different scenarios

Where do you find the most postop patients?

Type of procedure (N=604)	
General	212 (35.1%)
Thoracic	154 (25.5%)
Orthopedic	98 (16.2%)
Major urological	44 (7.3%)
Vascular	37 (6.1%)
Major spinal	19 (3.1%)
Low risk	11 (1.8%)
Gynecological	9 (1.5%)
Major plastic	4 (0.7%)
Other plastic	2 (0.3%)

Urgency rating	
Elective	353 (58.4%)
Urgent	185 (30.6%)
Emergent	52 (8.6%)

Recent or Index surgery was for cancer	
Yes	184 (30.5%)

Acute medical illness patients have positively impacted recruitment numbers

# pts on protocol v7.0	76
No. of Acute Medical Illness(es)	20 (26.3%)
Infection	**9 (45%)**
Sepsis	**5 (25%)**
Acute respiratory exacerbation	**1 (5%)**
Metabolic/electrolyte derangement	**1 (5%)**
Venous thromboembolism	-
Uncontrolled thyrotoxicosis	-
Acute kidney injury	**4 (20%)**
Acute anemia/hemorrhage	-
Acute neurologic event	-
Dehydration/hypovolemia	**1 (5%)**
Alcohol intoxication/withdrawal	**1 (5%)**
Other substance intoxication/withdrawal	**1 (5%)**
Medication side effect/toxicity	-
Trauma	-
Other	**7 (35%)**

Contact Information

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