Is Secondary Atrial Fibrillation Different? Or Is Atrial Fibrillation Just Atrial Fibrillation?

Michael J. Quon MD and Louise Pilote MD MPH PhD

DOI: 10.22374/cjgim.v13iSP1.305

About the Authors

Michael J. Quon is with the Division of General Internal Medicine, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada.

Louise Pilote is with the Divisions of General Internal Medicine and of Clinical Epidemiology, Department of Medicine, The Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada.

Address for correspondence: louise.pilote@mcgill.ca

ABSTRACT

Secondary atrial fibrillation (AF) is self-limited AF associated with an acute reversible precipitant. About 1/3 of all Framingham Heart Study patients with first-detected AF had a potentially reversible, precipitant. There are limited reports assessing outcomes of secondary AF and risks to established primary AF remain unclear. Evidence-based recommendations to guide management of these patients are limited and prior studies suggests practice patterns are different in secondary AF. In this review, we summarize the current evidence on risks of AF recurrence, ischemic stroke and outcomes of anticoagulation in secondary AF, compared to primary AF. We provide an overview and recommend management approach in monitoring for AF recurrence and thromboembolic prophylaxis in these patients.

Self-limited or transient atrial fibrillation (AF) occurring during an acute reversible precipitant has been referred to as secondary AF,¹ temporary cause of AF,² and AF occurring transiently during stress.³ Alternatively, it has been classified as either 'reversible' or 'provoked' AF, varying in terms of the underlying cardiac substrate and risk for AF recurrence.⁴ Given it was described in prior American Heart Association / American College of Cardiology / Heart Rhythm Society guidelines,¹ we continue using the defining term 'secondary AF'. In this article, we review prior studies and provide an overview of long-term management approaches to secondary AF. We will use the term 'primary AF' to describe established AF, without an associated secondary precipitant.

Potentially reversible precipitants of secondary AF include surgery (both cardiothoracic and non-cardiothoracic), acute cardiac pathology (including acute coronary syndrome (ACS), myocarditis, acute pericardial disease), acute pulmonary pathology (including influenza, pneumonia, bronchitis, COPD exacerbation, pulmonary embolism, pneumothorax and bronchoscopy-related), acute infection (including sepsis and non-pulmonary infections), acute alcohol consumption, electrocution, thyrotoxicosis, and other metabolic disorders.^{2,5,6} Secondary AF is not an uncommon clinical scenario faced by clinicians. In fact, the Framingham Heart Study showed 31% of patients with first-detected AF had a secondary, potentially reversible, precipitant. The most common precipitants observed in this study were cardiothoracic surgery (30%), acute infection (23%), non-cardiothoracic surgery (20%) and ACS (18%).⁵

Despite its prevalence, studies examining outcomes in secondary AF are limited. Previous retrospective studies also have used different definitions of secondary AF. Some have included only *transient* AF, and excluded persistent AF,^{2,7-9} while others have included all types of AF associated with a secondary precipitant.^{10,11} Moreover, it is unclear if the risks associated with each secondary precipitant is the same. As a result, there are limited evidence-based recommendations to guide management of these patients. In our review, we focus on long term management of secondary AF. We review AF recurrence and ischemic stroke; we do not describe the approach to acute management of AF nor rate and rhythm control strategies in secondary AF. We highlight the existing research, compare risks to primary AF, and propose treatment recommendations for secondary AF. We provide an overview of approaches to monitoring for AF recurrence and thromboembolic prophylaxis in this patient population.

Guideline Recommendations

Current AF guidelines do not directly address the recommended management of patients with secondary AF. The most recent

American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines acknowledge the limited long-term data in patients with AF occurring with potentially 'reversible' conditions. They state that the AF may recur so these patients "should receive careful follow-up."⁶

They do provide recommendations on AF associated with ACS, hyperthyroidism, acute non-cardiac illness, pulmonary disease and post-op cardiac and thoracic surgery. For patients with new onset, transient AF as a complication of ACS, "the need for OAC and duration of OAC should be based on the patient's CHA₂DS₂VASC risk score." For acute non-cardiac illnesses (reversible precipitants such as hypertension, post-operative state, pulmonary embolism, viral infection), treatment of the underlying condition and correction of any contributing factors is advised. "For many of these patients, AF will spontaneously terminate with correction of the underlying condition." In these non-cardiac illnesses, "the role of OAC is less clear, likely disease-specific and needs to be addressed on the basis of the patient risk profile and duration of AF". In hyperthyroidism and AF, OAC "should be guided by CHA₂DS₂VASC risk score" in thyrotoxicosis. Meanwhile, restoring a euthyroid state often results in reversion to sinus rhythm, after which, treatment recommendations with OAC are not provided. In post-operative cardiothoracic surgery patients, "it is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as advised for nonsurgical patients."⁶

European and Canadian guidelines make fewer recommendations regarding secondary AF. Canadian guidelines make recommendations on concomitant AF in association with NSTEMI and STEMI, but do not specifically address patients with self-limited AF in these diagnoses.^{12,13} European guidelines recommend that long term OAC be considered in patients with AF after cardiac surgery at risk for stroke considering individual stroke and bleeding risk.¹⁴ Among these most recent guidelines, there are no recommendations for management of other precipitants of secondary AF nor any recommendations on monitoring for AF recurrence in secondary AF.^{6,13,14}

AF Recurrence

Existing research does not support the concept that patients with secondary AF are cured of AF after effective treatment of the potentially 'reversible' associated condition. In the Framingham Heart Study, 5-, 10-, and 15-year incidences of recurrent AF were determined after retrospective review of subsequent outpatient and hospital visits. AF recurrence rates were greater among individuals without a secondary AF precipitant (59–71%) compared with those with a precipitant (42–62%).⁵ In secondary AF associated with sepsis, 1- to 5-year rates of recurrent AF were 44–55%, compared to 57–64% in individuals with prior AF.¹⁰

In new-onset, perioperative AF, 1-year rates of post-discharge encounters with a recorded diagnosis of AF was 37%.¹¹ These studies show that secondary AF often recurs after treatment of the precipitant, however they suggest that the relative risk of recurrence may be lower than primary AF.

At present, there is limited data to predict which patients will develop recurrent AF. Evaluation of a patient with secondary AF for risk of recurrence is advised following conversion to sinus rhythm. Establishing a pre-test probability of underlying AF should include review for patient demographics and established chronic risk factors for clinical AF including age, male sex, white race, hypertension, diabetes mellitus, valve disease, left ventricular dysfunction, obesity, sleep apnea, chronic kidney disease and alcohol consumption.^{15,16} While not well studied, factors in secondary AF that have been associated with recurrent AF include higher age, body weight, and valvular heart disease.⁵ Similar to primary AF, most patients with first-detected secondary AF should undergo echocardiography to evaluate cardiac structure and function.

Following conversion to sinus rhythm, the recommended rhythm monitoring approach for recurrent AF remains unclear in secondary AF patients. To our knowledge, there have been no previous studies that have systematically monitored secondary AF patients for AF recurrence. Retrospective studies on AF recurrence often have reviewed administrative claims or clinic visits and hospitalizations for any detected AF on 12-lead ECG or Holter monitor. In addition to 24- or 48-hour Holter monitoring, further monitoring for recurrence can be considered with extended continuous external ECG monitoring. Rates of recurrence or cost-effectiveness in these more sensitive, long-term monitoring strategies has not been evaluated in the secondary AF population.

Ischemic Stroke

Limited studies have examined the risk of ischemic stroke in patients with secondary AF. Understanding relative stroke risk compared to primary AF patients is important to determine optimal treatment of these patients. With inclusion of all secondary AF precipitants, the Framingham Heart Study observed the risk of stroke in patients with secondary AF was similar to those with primary AF.⁵ Meanwhile, another retrospective study found a secondary AF cohort had lower stroke risk when compared to a similar primary AF cohort (1.1 - 1.6 compared to 1.6 - 2.5 per person-years).¹⁷

In ACS, secondary AF has been associated with an increased risk of in-hospital stroke¹⁸ and post-hospitalization stroke.⁵ Annual risks of stroke following hospitalization with AF in ACS have been variable, reported from 0.4–10%.^{7–9,19} A meta-analysis of 14 studies of new-onset AF complicating ACS, AF was associated with an increased risk of stroke, after adjustment of ischemic

stroke risk factors. This association persisted in patients with transient, secondary AF.²⁰

In sepsis, secondary AF has also been associated with higher rates of both in-hospital stroke²¹ and stroke following discharge,¹⁰ when compared to patients without AF. Within 5 years of hospitalization, stroke risk in sepsis patients with new onset AF (5.3%) was increased compared to patients without AF (4.7%) but lower compared to patients with prior AF (5.9%).¹⁰ Understanding the relative risk of ischemic stroke in secondary AF requires further study.

Anticoagulation

Given the poor quality of evidence and limited treatment recommendations, practice patterns are variable on thromboembolic stroke prevention in secondary AF. On one side of the spectrum, secondary AF could be considered like primary AF with OAC initiated based on current guideline recommendations.^{6,13,14} On the other side, secondary AF could be considered a reversible event unlikely to recur after the precipitant is removed without OAC initiation. Overall, it seems clinicians are initiating OAC less frequently in secondary AF compared to primary AF. In a retrospective study, one third of patients who developed secondary AF were discharged on OAC,¹⁷ compared to rates of 46–60% in similar studies examining primary AF.^{22–24} In another retrospective study the OAC prescription rates observed (36%) were similar in secondary AF patients.²

To our knowledge, there are no studies examining benefits of OAC in secondary AF compared to primary AF. In secondary AF associated with ACS, OAC has been associated with a decreased incidence of stroke in some reports.^{8,19} While it may have been underpowered to detect a significant benefit, no trends towards benefit of OAC in stroke reduction were observed in secondary AF associated with ACS, acute pulmonary disease, and sepsis.¹⁷ It has been further hypothesized that benefits of OAC may vary depending on the associated precipitant.⁴

In addition, there is minimal data on bleeding risks in secondary AF patients that are prescribed OAC. Secondary AF is frequently observed in patients with high bleeding risks, including older patients with multiple comorbidities, taking other anti-thrombotic medications.^{5,17} OAC was associated with higher bleeding risks in secondary AF patients (3.6–6.2 per 100 person-years)¹⁷ compared to primary AF patients in similar cohort studies (1.5–4.3 per 100 person-years).^{22–24}

The benefits and risks of OAC in secondary AF require further research. At present, it is unclear if the benefits of stroke reduction and risks of bleeding apply equally in secondary AF patients compared to primary AF. It remains unknown if current OAC recommendations for thromboembolic prophylaxis in primary AF should apply directly to patients with secondary

AF. Careful individual assessment is warranted while we await randomized trials assessing OAC in secondary AF.

Approach to Management

Due to limited evidence-based recommendations, there are various approaches to management of secondary AF. After resolution of a transient episode of new-onset AF with an associated precipitant, clinicians are often faced with assessment of stroke risk, similar to treatment of primary AF. Unlike established primary AF, secondary AF decisions may additionally depend on the patient's risk of AF recurrence, in addition to balancing the risks of ischemic stroke, bleeding and the patient's goals of care.

Risk factors for secondary AF being a presentation of underlying, unmasked sub-clinical AF should be identified. Patient characteristics and risk factors to develop AF including age, hypertension and structural heart disease should be considered. Echocardiogram could identify further structural risk factors of primary AF, such as severe LA dilation,²⁵ mitral stenosis or mod-severe mitral regurgitation.

The impact on stroke risk from the secondary AF and characteristics of each precipitant has been minimally studied. While not previously validated in a secondary AF population, the CHADS2 score could be used to further stratify stroke risk. The CHADS2 score would be similarly used in patients who have underlying sub-clinical AF.¹³ In addition to structural heart disease, echocardiogram could identify further stroke risk factors such as left atrial spontaneous echo contrast, thrombus or complex aortic plaque.²⁶ While not studied in all precipitants, longer duration of AF was shown to increase stroke risk in secondary AF associated with ACS.⁸

After conversion of secondary AF to sinus rhythm, we recommend rhythm monitoring for sub-clinical paroxysmal AF. At minimum, routine diagnostic screening techniques, such as inpatient cardiac telemetry and outpatient 24- or 48-hour Holter monitoring, should be performed. While widely available, these strategies are limited by their modest sensitivity in detecting paroxysmal AF. Should decisions on antithrombotic therapy warrant further investigation for management decisions, further longer-term monitoring, such as external event monitor (e.g., ECG patch) can be considered.

Secondary AF patients should be evaluated for risk for underlying AF and recurrence of AF in addition to risks of stroke and bleeding. Given the frequently observed recurrence of secondary AF and its association with ischemic stroke, we recommend careful consideration of an antithrombotic strategy in these patients. Unless low stroke risk (e.g. CHADS2 = 0 with age < 65 years), high bleeding risk, or not in congruence with

the patient's goals of care, it seems reasonable to initiate an antithrombotic therapy, until results from echocardiogram and rhythm monitoring for paroxysmal AF are available.

Recommendations on ischemic stroke prevention can include the following:

- Initiation of long term OAC indefinitely
- Initiation of OAC while awaiting results from echocardiogram and monitoring strategy for sub-clinical AF
- Initiation of ASA while awaiting results from echocardiogram and monitoring strategy for sub-clinical AF

After rhythm monitoring and echocardiogram results are obtained, all patients should have clinical follow-up with re-assessment of stroke and bleeding risks. While 24-hour Holter monitoring is not sufficiently sensitive in detecting AF, observation of paroxysmal AF could provide a clear diagnosis of primary AF. Similarly, echocardiogram showing left atrial spontaneous contrast, thrombus or rheumatic mitral disease would offer clear evidence-based treatment recommendations with OAC.

Conclusions

While not extensively studied, secondary AF is not infrequently observed in patients with first-detected AF. Studies show that secondary AF frequently recurs, yet there is limited data to predict which patients will develop recurrent AF. Stroke rates are elevated following episodes of secondary AF. When compared to primary AF, both risks of AF recurrence and ischemic stroke require further study in secondary AF patients. Randomized trials of OAC in secondary AF are needed to understand the optimal approach to antithrombotic therapy in these patients. Until then, patients should be assessed for risks of pre-existing AF and AF recurrence in addition to stroke and bleeding risks. After conversion to sinus rhythm and treatment of the associated precipitant, further monitoring for AF recurrence and careful individual assessment of antithrombotic therapy are warranted.

Funding

There is no relationship with industry. Research was funded by a grant from the Canadian Institutes of Health Research. Dr. Pilote holds a James McGill chair at McGill University.

References

1. Valentin Fuster V, Rydén LE, Cannom DS et al. 2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology Foundation/American Heart Association Task Force of Practice Guidelines. *Circulation* 2011;123:269–367.

2. Fauchier L, Lecoq C, Clementy N et al. Oral anticoagulation and the risk of stroke or death in patients with atrial fibrillation and one additional stroke risk factor: The Loire Valley Atrial Fibrillation Project. *Chest* 2016;149:960–8.
3. McIntyre WF, Connolly SJ, Healey JS Atrial fibrillation occurring transiently with stress. *Curr Opin Cardiol* 2018;33:58–65.
4. Cheung CC, Andrade JG. Reversible or provoked atrial fibrillation? The Devil in th Details. *J Am Coll Cardiol EP* 2017
5. Lubitz SA, Yin X, Rienstra M et al. Long-term outcomes of secondary atrial fibrillation in the community: The Framingham Heart Study. *Circulation* 2015;131:1648–55.
6. January CT, Wann LS, Alpert JS et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;130:199–267.
7. Siu CW, Jim MH, Ho HH et al. Transient atrial fibrillation complicating acute inferior myocardial infarction: implications for future risk of ischemic stroke. *Chest* 2007;132:44–9.
8. Asanin MR, Vasiljevic ZM, Matic MD et al. The long-term risk of stroke in patients with acute myocardial infarction complicated with new-onset atrial fibrillation. *Clin Cardiol* 2009;32:467–70.
9. Bishara E, Telman G, Bahouth F et al. Transient atrial fibrillation and risk of stroke after acute myocardial infarction, *Thromb. Haemost* 2011;106:877–84
10. Walkey AJ, Hammill BG, Curtis LH et al. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest* 2014;146:1187–95.
11. Gialdini, G, Nearing K, Bhav P et al. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA*. 2014;312(6):616–22.
12. Cairns JA, Connolly S, McMurtry S et al. CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. *Can J Cardiol* 2011;27:74–90.
13. Macle L, Cairns J, Leblanc K et al. 2016 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. *Can J Cardiol* 2016;32:1170–85.
14. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration With EACTS. *Eur J Cardiothorac Surg* 2016 Nov;50(5):e1–e88. Epub 2016 Sep 23.
15. Krahn AD, Manfreda J, Tate RB, et al. The natural history of atrial fibrillation: Incidence, risk factors, and prognosis in the manitoba follow-up study. *Am J Med* 1995;98:476–84.
16. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res* 2014;114:1453–68.
17. Quon MJ, Behloul H, Pilote L. Anticoagulant Use and risk of ischemic stroke and bleeding in patients with secondary atrial fibrillation associated with acute coronary syndromes, acute pulmonary disease, or sepsis. *J Am Coll Cardiol EP* 2017
18. Crenshaw BS, Ward SR, Granger CB et al. Atrial fibrillation in the setting of acute myocardial infarction: The GUSTO-I Experience. *J Am Coll Cardiol* 1997;30:406–13.
19. Zusman OI, Amit G, Gilutz H et al. The significance of new onset atrial fibrillation complicating acute myocardial infarction. *Clin Res Cardiol* 2012;101:17–22.
20. Luo J, Li H, Qin X et al. Increased risk of ischemic stroke associated with new-onset atrial fibrillation complicating acute coronary syndrome: A systematic review and meta-analysis. *J Cardiol Int J Cardiol*. 2018 Aug 15;265:125–31. doi: 10.1016/j.ijcard.2018.04.096. Epub 2018 Apr 23.
21. Walkey AJ, Wiener RS, Ghobrial JM et al. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA* 2011;306:2248–54.
22. Tsadok MA, Jackevicius CA, Essebag V et al. Rhythm versus rate control therapy and subsequent stroke or transient ischemic attack in patients with atrial fibrillation. *Circulation* 2012;126:2680–7.
23. Avgil Tsadok MA, Jackevicius CA, Rahme E et al. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. *JAMA* 2012; 307:1952–8.
24. Shah M, Tsadok MA, Jackevicius CA et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. *Circulation* 2014;129:1196–1203.
25. Baturova MA, Sheldon SH, Carlson J. Electrocardiographic and Echocardiographic predictors of paroxysmal atrial fibrillation detected after ischemic stroke. *BMC Cardiovasc Disord* 2016;16:209
26. Zabalgoitia M1, Halperin JL, Pearce LA et al. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. *Stroke Prevention in Atrial Fibrillation III Investigators. J Am Coll Cardiol* 1998;Jun;31(7):1622–6.