

Decision aid for early identification of acute underlying illness in emergency department patients with atrial fibrillation or flutter

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CLINICIANS CAPSULE

What is known about the topic?

Patients with atrial fibrillation and flutter (AFF) and an underlying condition are at risk of iatrogenic events.

What did this study ask?

Can a decision tool identify ED AFF patients with underlying illness early in the evaluation?

What did this study find?

Of patients with potential underlying illness, 93% arrive by ambulance; present with chest pain, dyspnea, or weakness; or have CHA₂DS₂-VASc > 2.

Why does this study matter to clinicians?

Physicians have a decision tool to evaluate undifferentiated AFF patients for underlying illness.

Results: Of 1,083 consecutive undifferentiated ED AFF patients, 400 (36.9%) had an acute underlying illness; they were older with more comorbidities. Modeling demonstrated that three predictors (ambulance arrival; chief complaint of chest pain, dyspnea, or weakness; CHA₂DS₂-VASc score greater than 2) identified 93% of patients with acute underlying illness (95% confidence interval [CI], 91–96%) with 54% (95% CI, 50–58%) specificity. The decision aid missed 28 patients; (7.0%) simple blood tests and chest radiography identified all within an hour of presentation.

Conclusions: In ED patients with undifferentiated AFF, this simple predictive model rapidly differentiates patients at risk of acute underlying illness, who will likely merit investigations before AFF-specific therapy.

RÉSUMÉ

Contexte: Les patients atteints de fibrillation auriculaire ou de flutter auriculaire (FA/FA) confondus, et examinés au service des urgences (SU), chez qui se cache une affection aiguë comme une sepsie ou de l'insuffisance cardiaque et dont le traitement repose sur la maîtrise de la fréquence ou la maîtrise du rythme connaissent un pronostic sombre. Toutefois, ces affections peuvent être difficiles à reconnaître au début du processus d'évaluation au SU, au moment où se prennent des décisions cruciales relatives au traitement. L'étude avait donc pour but l'élaboration d'une aide facile à la décision permettant le repérage rapide des patients atteints de FA/FA confondus, qui connaissent un risque élevé d'affection aiguë sous-jacente.

Méthode: L'équipe a recueilli des données sur des patients consécutifs, examinés au SU et souffrant de FA/FA confirmés à l'ECG sur une période de 1 an, et procédé à un examen des dossiers afin de s'assurer des données démographiques, des maladies concomitantes et des résultats des examens.

ABSTRACT

Background: Emergency department (ED) patients with atrial fibrillation or flutter (AFF) with underlying occult condition such as sepsis or heart failure, and who are managed with rate or rhythm control, have poor prognoses. Such conditions may not be easy to identify early in the ED evaluation when critical treatment decisions are made. We sought to develop a simple decision aid to quickly identify undifferentiated ED AFF patients who are at high risk of acute underlying illness.

Methods: We collected consecutive ED patients with electrocardiogram-proven AFF over a 1-year period and performed a chart review to ascertain demographics, comorbidities, and investigations. The primary outcome was having an acute underlying illness according to prespecified criteria. We used logistic regression to identify factors associated with the primary outcome, and developed criteria to identify those with an underlying illness at presentation.

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Le principal critère de recherche consistait en la présence d'une affection aiguë sous-jacente selon des critères prédéterminés. La recherche de facteurs associés au principal critère de recherche a été réalisée par régression logistique, puis l'équipe a établi des critères pour faciliter le repérage des patients souffrant d'une affection sous-jacente au moment de la consultation au SU.

Résultats: Sur 1083 patients consécutifs, examinés au SU et souffrant de FA/FA confondus, 400 (36,9%) étaient atteints d'une affection aiguë sous-jacente; ces derniers étaient plus âgés que les autres et présentaient davantage de maladies concomitantes. La modélisation a démontré que la présence de trois facteurs prévisionnels (arrivée en ambulance; principal motif de consultation : douleur thoracique, dyspnée ou faiblesse; score CHA₂DS₂-VASc supérieur à 2) permettait le

repérage de 93% des patients atteints d'une affection aiguë sous-jacente (IC à 95% : 91–96%), et ce, avec une spécificité de 54% (IC à 95% : 50 to 58%). L'aide à la décision a connu un taux d'échec de 7% (28 patients), mais de simples analyses de sang et une radiographie des poumons ont permis le repérage de ces derniers patients en l'espace d'une heure, depuis leur arrivée au SU.

Conclusion: Ce simple modèle prévisionnel permet différencier rapidement les patients, atteints de FA/FA confondus, et examinés au SU, qui connaissent un risque d'affection aiguë sous-jacente et chez qui il y aurait lieu d'effectuer des examens avant de décider du choix du traitement antiarythmique.

Keywords: Atrial fibrillation, cardiac disease, arrhythmia

INTRODUCTION

Atrial fibrillation accounts for 0.5% of Canadian emergency department (ED) visits.¹ A proportion of these patients will have an acute underlying illness,^{2,3} and the use of dysrhythmia-specific therapies such as rate or rhythm control is associated with a higher risk of adverse outcomes along with a low rate of success. In 416 ED atrial fibrillation and flutter (AFF) patients with an acute underlying condition (32% sepsis, 28% heart failure, 11% acute coronary syndrome), physicians administered rate or rhythm control in nearly one-third, and the median time of administration was 90 minutes after registration,³ illustrating that, in many cases, rate or rhythm control was likely administered before completion of diagnostic investigations.

Identification of such high-risk patients early in the ED assessment remains a challenge, and unfortunately there is little evidence to assist clinicians. The Canadian Association of Emergency Physicians 2018 guidelines⁴ recommend that these patients be identified and treatment directed at the underlying cause. Both patients and physicians would benefit from a tool to rapidly identify such patients: if a patient was deemed high-risk, physicians should investigate for the presence of an underlying illness, rather than administering early AFF-specific therapies.

We sought to develop a decision aid that could quickly identify undifferentiated ED AFF patients who might have an acute underlying illness, who would then merit further investigations to confirm or refute this illness. We also sought to describe patients the decision had

missed and ascertain how they could have been identified.

METHODS

Study design and setting

This was a health record review at two Canadian university-affiliated teaching EDs whose setting and patients have been previously described.^{3,5–7} St Paul's Hospital is an inner-city referral center with 70,000 annual ED visits and comprehensive cardiology services, while Mount St Joseph's Hospital is a community ED with 25,000 yearly visits and a general medicine ward. The University of British Columbia ethics review approved this study. During the study period, emergency physicians managed AFF patients at their discretion.

Patient selection

This dataset has been previously described.³ We identified all ED patients who with AFF identified on an electrocardiogram (ECG) from January 1, 2009, to December 31, 2009. ECGs are generally performed in any patient with chest pain, palpitations, a history of arrhythmia, syncope or dizziness, weakness, or dyspnea, and in any patient over 50 with abdominal complaints. Every ECG was stored in the MUSE (GE Healthcare Clinical Systems, Waukesha, WI, USA) database, and cardiologists confirmed results within 24 hours. We

retained the patients' unique identifier, date, and time of acquisition, and conducted a structured chart review of the ED encounter. We excluded patients with cardiac arrest, ST-elevation myocardial infarction, or stroke symptoms, because these require non-AFF related management; those with cardiac procedures in the prior 7 days because cardiac specialists typically direct care; those referred for direct admission; those from out-of-region because no follow-up was available; and those evaluated solely for adjustments to anticoagulation.

Data collection

The sites share an electronic database that records patient demographics, arrival mode, triage level,⁸ chief complaint,⁹ and initial vitals, and the results of all ED and hospital investigations, consultations, and discharge summaries.

Health record review

We adhered to accepted methodological criteria for health record reviews.¹⁰ Two emergency physicians and two final-year medical students, blinded to study hypotheses and outcomes, independently abstracted records onto electronic spreadsheets, documenting vital signs, comorbidities, and all ED-based laboratory testing and imaging. We trained reviewers on the first 10 health records and they submitted data at regular intervals, which were examined for obvious errors. We clarified missing or discrepant data by looking for clinic visits, ED visits, hospitalizations, discharge summaries, laboratory testing, and procedures back to 1999. We recorded conflicting information and reconciled this at regular meetings. An independent reviewer blinded to the first abstraction assessed a random 10% of records, and we calculated inter-rater reliability for the variable "prior AFF."

Outcomes

The a priori outcome was the presence of an acute underlying medical illness. Separate from the above analysis, two emergency physicians also blinded to study hypothesis and outcomes independently reviewed charts to identify patients with an acute underlying medical illness. We defined the following acute underlying conditions a priori^{3,5-7} (Appendix 1): sepsis (including pneumonia), acute coronary syndrome,

acute decompensated heart failure, pulmonary embolism, exacerbation of chronic obstructive pulmonary disease, thyrotoxicosis, hypertensive emergency, acute valvular disease, hypothermia, acute renal failure, or acute bleeding. Characteristics that defined the presence of an acute underlying condition had to be present during the ED encounter, so a medical event or diagnostic abnormality occurring days later would not constitute an acute underlying illness. In case the two emergency physician reviewers did not agree whether there was an underlying illness, the health record was referred to two additional physicians, a cardiologist and a hematologist, who were unaware of study hypothesis or outcomes, for adjudication of underlying illness and the diagnosis. If the two adjudicators could not agree, the primary investigator provided the final determination.

Model development

We collected potential predictor variables including demographics (age, sex, ambulance arrival) presenting complaints and timing, initial vital signs, and comorbidities, including prior AFF, hypertension, diabetes, acute coronary syndrome, stroke, and vascular disease. Given that our decision aid should be useful early in the ED evaluation, and that patients did not undergo standardized investigations, we omitted all diagnostic testing from the model.

We calculated the unadjusted odds ratio for underlying illness versus no underlying illness. We used a data-splitting approach¹¹ and randomly used 75% of the dataset to fit the model (derivation set) and 25% for the validation set. From the derivation set, we developed multivariable logistic regression models to predict the presence or absence of acute underlying illness using the following potential predictor variables: ambulance arrival, time in AF (either greater or less than 48 hours), presenting complaint (palpitations, chest pain, dyspnea, weakness, other), arrival heart rate, systolic and diastolic blood pressure, CHA₂DS₂-VASc score¹² (this incorporates age and sex), and pre-existing comorbidities (prior AFF, hypertension, diabetes, prior acute coronary syndrome, stroke, or vascular disease). We compared models by stepwise forward selection and retained only those with an adjusted odds ratio (aOR) of >2.0. We calculated sensitivity and specificity, predictive values, and likelihood ratios, all with 95% confidence intervals (CIs). We also assessed the receiver-operating characteristic curve and used the

Hosmer-Lemeshow goodness of fit test to calculate model performance.

Model evaluation

After model development, we assessed performance of the decision aid using area under the receiver-operating characteristic curve (AUC) as the measure of interest. We used bootstrapping with 1,000 resamples to obtain a fitting and validation distribution of all AUC values.

We also analyzed the data using different cutoffs of the CHA₂DS₂-VASc score. Finally, we conducted the same analysis in the subgroup of patients with an initial heart rate >100 beats per minute, because these patients are more likely to undergo rate or rhythm control and, therefore, potentially be more at risk for treatment-related adverse events.

Data analysis

We used Microsoft Excel 2008 (Microsoft Corp, Redmond, WA, USA) for data entry, and R (R Foundation for Statistical Computing, Vienna, Austria) for analysis. We reported discrete variables as percentages and presented continuous variables as means with standard deviations if normally distributed, or medians with interquartile ranges (IQR).

RESULTS

We collected 1,083 ED AFF patients with 400 (36.9%) having an acute underlying medical illness (Figure 1). For the chart review, inter-rater agreement was 0.74 (95% CI, 0.70–0.79) for the variable of “prior atrial fibrillation.” Overall, 23/1,083 patients (2.1%) required adjudication to ascertain “underlying illness”; the primary investigator was required for final determinations in five patients.

Patients with an acute underlying medical illness were older; more likely to arrive by means of ambulance; more likely to have a chief complaint of chest pain, dyspnea, or weakness; to have altered vital signs; and to have cardiovascular comorbidities. New AFF diagnoses were made in 42.2% and 35.6% of patients with and without underlying illness, respectively (Table 1).

Univariate analysis showed the strongest potential predictor variables were ambulance arrival (aOR, 3.5; 95% CI, 2.6–4.7); chief complaint of weakness, chest pain, or dyspnea (aOR, 4.7; 95% CI, 3.2–7.0); no prior

history of AFF (aOR, 1.2; 95% CI, 0.9–1.5); prior history of hypertension (aOR, 4.0; 95% CI, 2.9–5.8), heart failure (aOR, 6.4; 95% CI, 4.1–10.0), diabetes (aOR, 2.7; 95% CI, 1.8–4.4), vascular disease (aOR, 2.9; 95% CI, 1.9–4.5), or stroke (aOR, 2.8; 95% CI, 1.8–5.0).

The most accurate derived multivariable predictive model combined ambulance arrival (aOR, 3.5; 95% CI, 2.6–4.7) and presenting complaint of chest pain, weakness, or dyspnea (aOR, 4.7; 95% CI, 3.2–7.0) and CHA₂DS₂-VASc score greater than 2 (aOR, 4.6; 95% CI, 2.9–7.0) (Table 2). This model was 93% sensitive (372/400; 95% CI, 91–96%) and 54% specific (366/683; 95% CI, 50–58%) for identifying patients with acute underlying illness. The positive predictive value was 0.54 (95% CI, 0.50–0.58), negative predictive value was 0.93 (95% CI, 0.90–0.95), positive likelihood ratio was 2.0 (95% CI, 1.8–2.2), and negative likelihood ratio was 0.13 (95% CI, 0.09–0.18) (Table 3). The Hosmer-Lemeshow goodness of fit was 0.16, and the AUC was 0.79.

For assessment of model performance over 1000 iterations, the AUC fitting had a median of 0.79 (IQR, 0.77–0.81) and AUC validation had a median of 0.79 (IQR, 0.72–0.85). Changing CHA₂DS₂-VASc cutoffs provided the following results. A score > 1 had a sensitivity of 95% (95% CI, 92–97%) with specificity of 48% (95% CI, 43–53%). A score > 3 had a sensitivity of 89% (95% CI, 86–92%) with specificity of 60% (95% CI, 56–64%). In both cases, the AUC was 0.77 (IQR, 0.75–0.79).

Among 541 patients with initial heart rate ≥ 100 beats per minute, 185 (34.2%) had an underlying illness. The above model had an aOR of 3.7 (95% CI, 2.4–5.7) for ambulance arrival; an aOR of 7.9 (95% CI, 4.4–14.5) for presenting complaint of weakness, chest pain, or dyspnea; and an aOR of 4.0 (95% CI, 2.3–6.9) for CHADS-VASC > 2. This model was 87% sensitive (161/185; 95% CI, 83–92%) and 66% specific (235/356; 95% CI, 61–72%) for identifying patients with acute underlying illness. The positive predictive value was 0.57 (95% CI, 0.51–0.63), negative predictive value was 0.91 (95% CI, 0.88–0.95), positive likelihood ratio was 2.6 (95% CI, 2.2–3.0), and negative likelihood ratio was 0.19 (95% CI, 0.13–0.28). The Hosmer-Lemeshow goodness of fit was 0.49, and the AUC was 0.84.

Overall, of the 28 (7.0%; 95% CI, 4.7–10.0%) patients in whom the model was falsely negative, 8 had sepsis, 7 had a gastrointestinal bleed, 5 had acute heart failure, 2 each had thyrotoxicosis, an acute coronary syndrome, and an acute kidney injury, and 1 had a pulmonary embolus. All 28 patients were identified with a

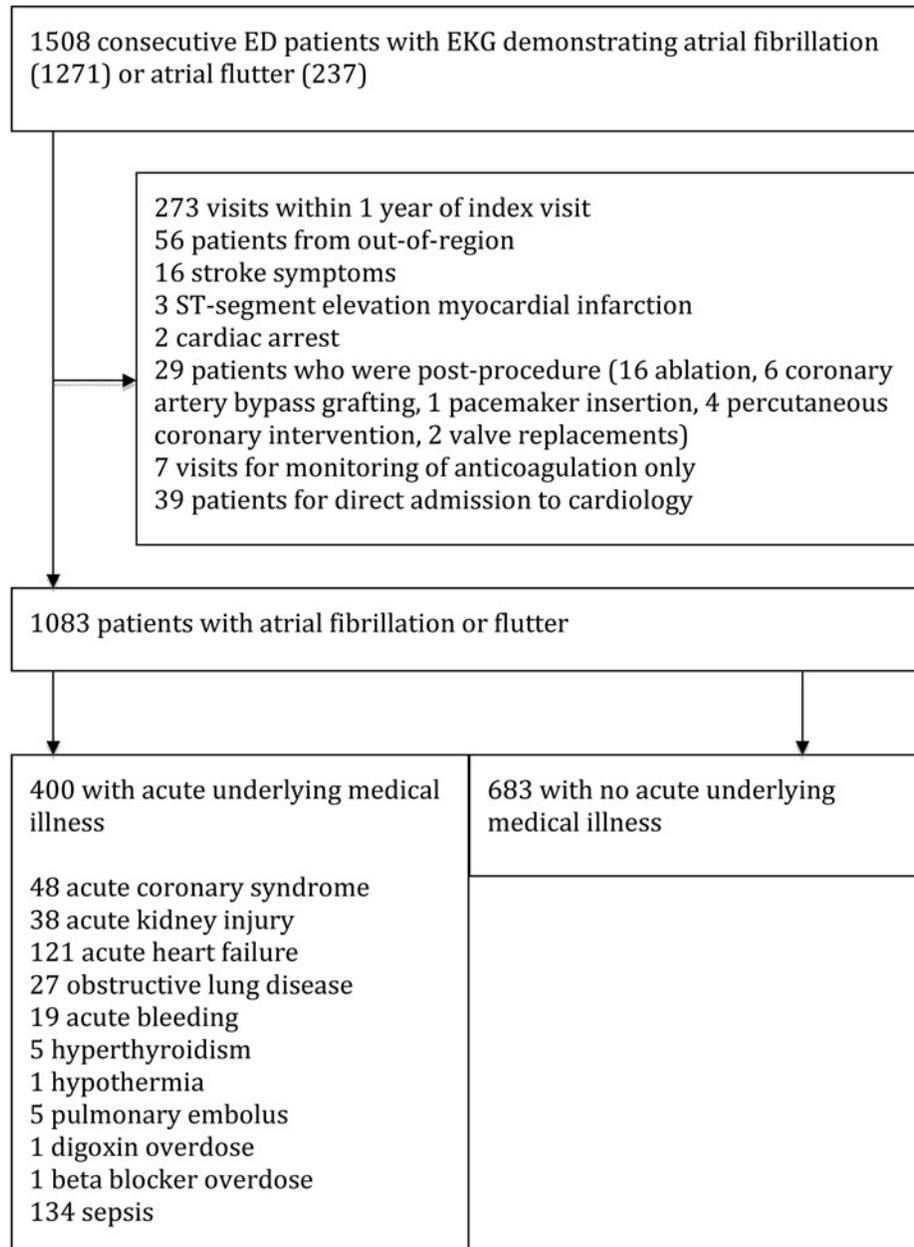


Figure 1. Study flow diagram.

combination of basic physical examination, simple blood testing, and chest radiography (Appendix 2).

DISCUSSION

In 1,083 consecutive ED patients with AFF, with nearly 40% having an acute underlying illness, we demonstrate that a parsimonious decision aid based upon presentation

characteristics and comorbidities can identify most patients at high risk of an underlying illness within minutes of assessment. Our decision aid missed few patients, and straightforward testing identified these within an hour of assessment. The subgroup of tachycardic patients showed similar results. This assists emergency physicians by providing a reliable aid to quickly select patients who may be at high risk of an acute medical illness from a cohort of undifferentiated ED AFF patients.

Table 1. Patient characteristics stratified by presence of acute underlying illness (n = 1083)

Variable, n (%) unless otherwise indicated	Underlying illness (n = 400)	No underlying illness (n = 683)	Crude odds ratio (95% CI)
Median age (IQR)	80 (72, 86)	69 (62, 77)	n/a
Female	181 (45.2)	286 (41.9)	1.1 (0.84, 1.3)
EMS arrival	230 (57.5)	147 (21.5)	4.5 (3.5, 5.9)
Median initial vitals (IQR)			n/a
Heart rate	100 (92, 109)	107 (98, 117)	
Systolic blood pressure	128 (122, 135)	133 (126, 139)	
Diastolic blood pressure	76 (71, 80)	78 (72, 84)	
Respiratory rate	22 (20, 22)	20 (18, 22)	
Oxygen level	96 (96, 97)	97 (96, 98)	
Temperature (C)	36.7 (36.6)	36.7 (36.6)	
Presenting complaint			
Palpitations	28 (7.0)	290 (42.4)	0.10 (0.07, 0.15)
Chest pain	46 (11.5)	74 (10.8)	1.0 (0.7, 1.5)
Weakness	149 (37.3)	153 (22.4)	2.1 (1.6, 2.8)
Dyspnea	159 (39.8)	130 (19.0)	2.8 (2.1, 3.7)
Other	18 (0.5)	36 (5.3)	1.1 (0.68, 1.9)
Atrial fibrillation			
Prior atrial fibrillation	231 (57.8)	440 (64.4)	0.69 (0.54, 0.88)
Prior atrial flutter	17 (0.4)	19 (0.3)	1.5 (0.77, 2.9)
Prior ablation	4 (1.0)	64 (9.4)	0.09 (0.03, 0.26)
Prior electrical conversion	12 (3.0)	68 (10.0)	0.04 (0.01, 0.18)
Comorbidities			
Heart failure	120 (30.0)	25 (3.7)	7.9 (5.2, 11.9)
Hypertension	357 (89.3)	381 (55.8)	4.8 (3.5, 6.6)
Diabetes	103 (25.8)	61 (9.8)	3.3 (2.4, 4.7)
Stroke	85 (21.3)	45 (6.6)	3.6 (2.5, 5.4)
Vascular disease	119 (29.8)	71 (10.4)	3.4 (2.4, 4.7)
CHA ₂ DS ₂ -VASc score			
0	9 (2.3)	144 (21.1)	0.08 (0.04, 0.17)
1	22 (5.5)	125 (18.3)	0.25 (0.16, 0.40)
2	26 (7.0)	103 (15.1)	0.39 (0.25, 0.62)
3	82 (20.5)	136 (20.0)	1.0 (0.76, 1.4)
4	106 (26.5)	94 (13.8)	2.1 (1.6, 2.9)
5	105 (28.3)	53 (7.8)	4.2 (3.0, 6.0)
6 or greater	66 (18.0)	28 (4.1)	4.6 (2.9, 7.3)
Clinical investigations			
Electrocardiogram	400 (100.0)	683 (100.0)	n/a
Signs of ischemia	13 (3.3)	8 (1.2)	2.8 (1.2, 6.7)
White blood cell count	400 (100.0)	592 (86.6)	n/a
WCC < 4 or > 11	112 (28.0)	35 (5.9)	6.2 (4.1, 9.1)
Hemoglobin	400 (100.0)	592 (86.6)	n/a
Hb < 100	54 (13.5)	29 (4.9)	3.0 (1.9, 4.8)
eGFR	400 (100.0)	577 (84.4)	
eGFR < 60	176 (44.0)	68 (11.9)	5.8 (4.3, 8.1)
Troponin	215 (53.8)	347 (50.8)	1.1 (0.88, 1.4)
Troponin > 0.05	29 (13.4)	13 (3.7)	4.0 (2.0, 7.9)
TSH	68 (17.0)	121 (17.7)	0.96 (0.68, 1.3)
TSH < 0.10 or > 6.20	3 (4.4)	2 (1.7)	2.7 (0.45, 17)
Chest radiography	289 (72.3)	157 (23.0)	8.7 (6.6, 11.6)

(Continued)

Table 1. Continued.

Variable, n (%) unless otherwise indicated	Underlying illness (n = 400)	No underlying illness (n = 683)	Crude odds ratio (95% CI)
Normal	171 (59.1)	157 (100.0)	n/a
Infiltrate	63 (21.8)	0 (0.0)	n/a
Pulmonary edema	55 (19.0)	0 (0.0)	n/a

CHA₂DS₂-VASc = stroke risk stratification score (Congestive heart failure, Hypertension, Age, Diabetes, Stroke, Vascular disease, Sex, where age is 0, 1, or 2 points, stroke is 2 points, and female is 1 point); EMS = ambulance; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; TSH = thyroid stimulating hormone.
 For the clinical investigations, the first line is the number of patients in each group who had the investigation, and the second is the number of abnormal investigations. Crude ORs are calculated for both having the test performed (and cannot be obtained if zero or all patients had a test, or if zero or all test results were normal) and for an abnormal result. "Signs of ischemia" is new onset ST-segment elevation, or ST-segment depression, or new T-wave inversions, or dynamic ST-segment changes during sequential ECG.

Given that the presence of an acute underlying illness is likely a relative contraindication to AFF-specific therapies, such as rate and rhythm control,⁵ our decision aid should allow clinicians to consider diagnostic investigations in potentially high-risk patients before empirical AFF therapies.

These high-risk patients were acknowledged in the 2018 CAEP guidelines⁴ as a critical early decision node. The consensus expert opinion identified risk factors for an acute underlying illness, including permanent AF; prescription for oral anticoagulants; absence of prior cardioversion; a heart rate less than 150 beats per minute; or presenting symptoms of fever, dyspnea, or pain. Our study confirms the importance of some of these and provides clinicians with a tool to help identify these potentially high-risk AFF patients within minutes of arrival.

The few patients our decision aid incorrectly labeled as having no underlying illness were all identified early in the ED evaluation through physical findings, including fevers or rectal examination, basic laboratory investigations, or plain chest radiography. All tests should be routinely available and quickly available in any ED, ensuring that most patients can undergo timely investigations before administration of AFF-specific therapies.

This review at two urban Canadian sites may not be applicable elsewhere and the proportion of AFF patients with an acute underlying illness may vary. While

presenting complaints are standardized,¹² inter-rater reliability is unknown. Because emergency physician-directed testing was instrumental in defining an acute underlying diagnosis, both ascertainment or incorporation bias must be considered, although the direction of bias is unclear and the overall number of affected patients may be small. We did not include diagnostic testing because our goal was to construct a decision rule applicable early during the ED evaluation.

Seven percent of the patients were misclassified by the rule, but rather by basic laboratory and imaging tests within the first hour of ED evaluation. The retrospective nature of the study, as well as the data analysis, ensures that an external validation will likely underperform this model. We were unable to test our decision aid directly against physician judgment.¹³ However, given that the same dataset reported that physicians used rate or rhythm control in 135/416 patients with underlying illness, often shortly after arrival,³ we propose that our decision aid may assist physicians in more careful selection of patients with potential underlying illness before administration of AFF-specific therapies.

Table 2. Performance of decision aid

	Underlying illness	No underlying illness	Total
Decision aid +	372	317	689
Decision aid -	28	366	394
Total	400	683	1083

Table 3. aORs in the final model

Variables	aOR (95% CI)
Male sex	1.6 (1.0, 2.6)
Ambulance arrival	3.5 (2.6, 4.7)
Initial heart rate	0.99 (0.98, 1.0) per beat
Initial systolic blood pressure	0.98 (0.97, 0.99) per mm Hg
Initial diastolic blood pressure	1.03 (1.01, 1.05) per mm Hg
Chest pain, dyspnea, or weakness	4.7 (3.2, 7.0)
CHA ₂ DS ₂ -VASc > 2	4.6 (2.9, 7.0)

CHA₂DS₂-VASc =: A composite measure of stroke risk; the constituent variables are age, sex, hypertension, diabetes, heart failure, stroke, and vascular disease. Note that age, hypertension, diabetes, heart failure, stroke, and vascular disease were significant in the univariate analysis and incorporated into this single risk score.

CONCLUSION

We have developed a decision tool with sensitive criteria for identifying AFF patients who may have acute underlying condition and who should undergo further evaluation before empiric administration of rate or rhythm control.

We suggest the following clinical approach: First, there is a very small group of unstable AFF patients who require immediate conversion.⁴ However, the vast majority of ED AFF patients could be stratified upon initial assessment. Patients with none of the high-risk criteria we have identified (EMS arrival, chest pain, dyspnea or weakness presentation, CHA₂DS²-VASc > 2) are unlikely to have an underlying condition and may be appropriate for rate or rhythm control. Patients meeting any high-risk criteria should be investigated to rule out underlying causes. The brief delay required to obtain these investigations is unlikely to adversely impact outcomes.

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