Current Cardiology Reports (2021) 23: 179
https://doi.org/10.1007/s11886-021-01611-2

INVASIVE ELECTROPHYSIOLOGY AND PACING (E. KEVIN HEIST, SECTION EDITOR)

Management of Atrial Fibrillation in the Emergency Department

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Accepted: 5 August 2021 / Published online: 16 October 2021

Abstract

Purpose of Review Atrial fibrillation (AF) is the most common arrhythmia in adults and is responsible for 600,000 emergency department (ED) visits each year in the USA. Over 60% of these patients are admitted to inpatient units. The prevalence of AF is increasing, resulting in higher numbers of AF-related ED visits and inpatient admissions. These trends underscore the need for improvements in the efficiency of AF management in the ED.

Recent Findings Several treatment protocols have been developed to address challenges associated with AF management in the ED, including: initiation of oral anticoagulant (OAC) therapy, cardioversion, and arranging for outpatient follow-up. Studies of these protocols have demonstrated that they can be utilized safely and effectively.

Summary Published treatment protocols for AF in the ED have been shown to reduce unnecessary hospital admissions and improve adherence to guideline-directed OAC therapy. Widespread adoption of AF treatment protocols could improve patient outcomes and reduce the costs associated with inpatient AF treatment.

Keywords Atrial fibrillation · Emergency department · Cardioversion · Oral anticoagulation therapy · Quality improvement

Introduction

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in the adult population. According to recent estimates, 1–2% of people in the USA are affected by AF [1, 2]. The incidence and prevalence of AF are increasing, due to the aging of the population and the increase in the incidence of risk factors such as hypertension and obesity [1, 3, 4].

AF is frequently encountered in the emergency department (ED). In 2014, AF accounted for 0.5% of all ED visits [1, 5, 6]. The number of ED visits for AF increased by 31% from 2007 to 2014 [5, 7]. More than 60% of AF-related ED visits in the USA result in admission to an inpatient unit [5, 8]. These admissions are responsible for almost 75% of AF-related treatment costs (over $6 billion annually) [9–11]. Observed increases in the number of AF-related ED visits and hospital admissions emphasize the need for more efficient strategies to treat AF in the ED.

Guidelines for AF management in the ED are not as well-validated as the guidelines for outpatient AF management [12–14]. This has been cited as a leading reason for the variability in AF management in the ED and for potentially avoidable hospital admissions [15–19]. In recent years, considerable efforts have been devoted to establishing comprehensive AF treatment protocols in the ED.

Challenges Associated with Management of AF in the ED

Management of AF in the ED can be divided into discrete phases, each of which presents distinct challenges (Fig. 1). When a patient with AF first arrives in the ED, the managing clinicians should first determine if AF is the primary problem. Contributions of other comorbidities (e.g., coronary artery disease or heart failure) to the patient's presenting symptoms should be addressed as early as possible. If AF is confirmed to be the primary problem leading to the ED visit, the managing clinicians then need to decide if a rate or a rhythm control strategy is most appropriate. Several factors contribute to this decision, including (1) hemodynamic

This article is part of the Topical Collection on *Invasive Electrophysiology and Pacing*

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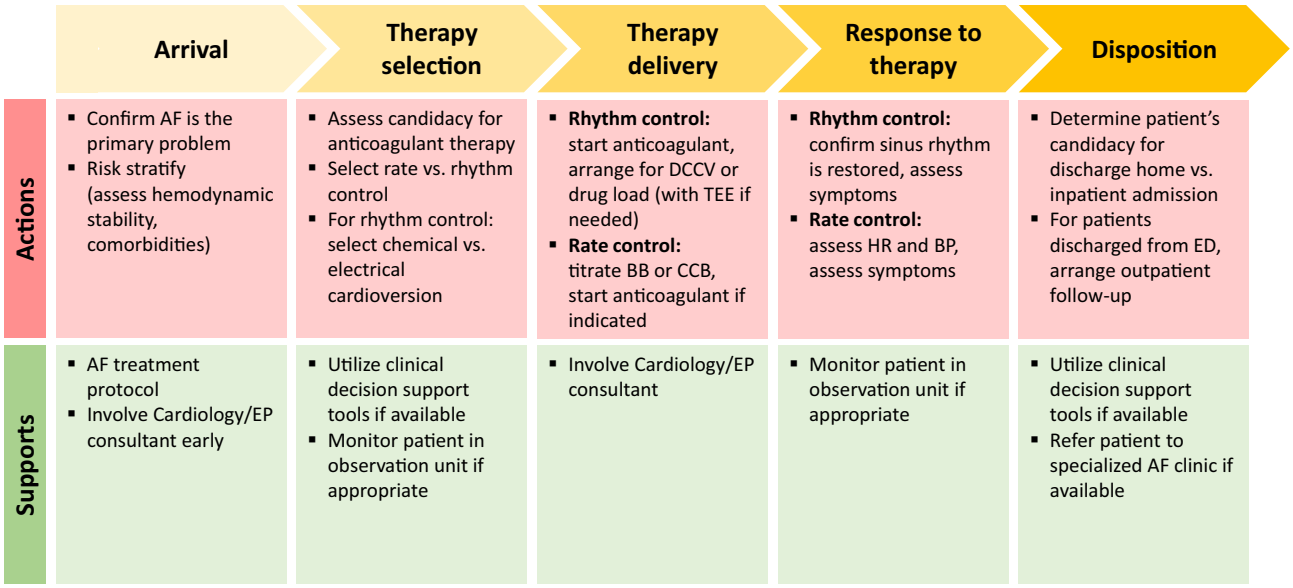

Fig. 1 Phases of AF management in the ED. For each phase of AF management in the ED, recommended actions and relevant supports that can improve the efficiency of care are listed. AF, atrial fibrillation; BB, beta-blocker; CCB, calcium channel blocker; DCCV, direct current cardioversion; EP, electrophysiology; ED, emergency department; OAC, oral anticoagulation

stability of the patient, (2) presence of other serious medical problems that may also need to be addressed, (3) adequacy of rate control, (4) presence of symptoms even if adequate rate control can be achieved, and (5) patient's candidacy for oral anticoagulant (OAC) therapy.

Efficient management of AF in the ED frequently requires the input of clinicians from multiple disciplines (e.g., emergency medicine, noninvasive cardiology, cardiac electrophysiology). Communication among these specialties early in the patient's ED visit can prevent delays in treatment. Once a treatment plan is implemented, the patient's response to treatment needs to be assessed. Response to treatment will determine the appropriateness of discharge versus inpatient admission. If the decision is made to discharge the patient from the ED, arrangements for outpatient follow-up should be made prior to discharge.

Utilization of a Rhythm Control Strategy to Treat AF in the ED Can Reduce the Rate of Inpatient Admissions

Multiple studies have demonstrated that chemical and electrical cardioversion of AF can be performed effectively in the ED [20•, 21–23]. One of the first treatment protocols for AF management in the ED involved the use of electrical cardioversion. This protocol was evaluated with a multicenter, retrospective cohort study that included patients who presented to the ED with recent-onset AF (duration less than 48 h) [24]. In this study, sinus rhythm was restored in 86% of the patients (Table 1). Less than 10% of cardioverted patients experienced an adverse event. Inpatient admission was reported for 14% of patients, and a return to the ED within 7 days was reported for 10% of patients.

A subsequent retrospective cohort study reported the outcomes associated with intravenous procainamide use for chemical cardioversion of patients with acute-onset AF or atrial flutter (AFL) [22]. In this study, procainamide restored sinus rhythm in 52% of patients who presented with AF and 28% of patients who presented with AFL (a lower success rate than was reported for electrical cardioversion). A 10% adverse event rate was reported. Inpatient admission was required for 5.6% of patients. Of the patients who underwent cardioversion, 2.9% returned to the ED due to a recurrence of AF/AFL within 7 days.

The procainamide-based treatment protocol was then modified to include an option for electrical cardioversion in those patients where chemical cardioversion was not successful. This modified protocol was evaluated in a retrospective cohort study [25]. The combined chemical/electrical cardioversion protocol led to the restoration of sinus rhythm in 92% of patients (more effective than procainamide alone). The rate of adverse events was 7.6% (no reported strokes or death), which was comparable to prior studies. A recent randomized trial confirmed that both chemical-first and electrical-first strategies can be safely used in the ED but that the electrical-first strategy is associated with a significantly shorter ED length of stay [26].

There is evidence that the benefits of restoring sinus rhythm in the ED may extend beyond reduction in inpatient

Table 1 Patient outcomes observed in selected studies of cardioversion in the ED

Study	AF duration	Intervention	Study type	Hospital type	No. of patients	Sinus rhythm restoration rate (%)	Inpatient admission rate (%)	Major adverse event rate (%)	ED return rate (%)
Burton et al. [24]	< 48 h	DCCV or CC	Retrospective cohort study	Tertiary care	388	86	14	8	10 (7 days)
Stiell et al. [22]	Acute onset	Procainamide IV	Retrospective cohort study	Tertiary care	341	52 (AF) 28 (AFL)	5.6	10	2.9 (7 days)
Stiell et al. [25]	Recent onset	Procainamide IV, followed by DCCV if needed	Retrospective cohort study	Tertiary care	660 (procainamide attempted), 243 (DCCV attempted)	58 (procainamide IV), 92 (DCCV)	3.2	7.6	8.6 (7 days)
DeMeester et al. [20•]	New or recurrent	DCCV only if rate control failed	Retrospective cohort study	Community	1108	n/a	67	n/a	1.0 (3 days) and 3.6 (30 days)
Vinson et al. [64]	Recent onset	Ibutilide IV, followed by DCCV if needed	Retrospective cohort study	Community	361	57 (ibutilide), 91 (ibutilide × 2 doses and DCCV)	25	0.6	0 (1 day)
Scheuermeyer et al. [26]	< 48 h	Randomization to 1) CC with procainamide followed by DCCV if needed or 2) DCCV, followed by procainamide IV as needed	Multicenter randomized study	Tertiary care	41 (CC first), 43 (DCCV first)	100 (CC first), 98 (DCCV first)	0	25	Within 3 days: 12.2 (CC first), 2.4 (DCCV first); within 30 days: 22 (CC first), 7.1 (DCCV first)
Martin et al. [27]	Recent onset	CC or DCCV	Multicenter, observational, cross-sectional	Tertiary care, community	421	70	14	n/a	n/a
Ptaszek et al. [31•]	New or recurrent	CC or DCCV	Prospective, 2-stage study at 2 hospitals	Tertiary care	208	76	15	n/a	11 (4 months)

AF atrial fibrillation, *ED* emergency department, *DCCV* direct current cardioversion, *CC* chemical cardioversion, *IV* intravenous, *AFL* atrial flutter, *VT* ventricular tachycardia

admission rate. A multicenter, observational, cross-sectional study of patients with recent-onset AF addressed the impact of a rhythm control strategy on both admission rate and patient-reported symptoms. In this study, a rhythm control strategy was associated with a low rate of inpatient admissions (14%) [27]. In addition, a multivariate analysis revealed a statistically significant association between the use of a rhythm control strategy and patient-reported symptom alleviation.

Selection of a Rate Versus Rhythm Control Strategy for Treatment of AF in the ED

Multiple protocols for AF treatment in the ED utilize a rhythm control strategy. A smaller number of protocols include the use of an initial rate control strategy. In one observational study, a rate control strategy was utilized for patients who were hemodynamically stable and whose symptoms could be well-controlled. These patients were discharged with early follow-up in an AF specialty clinic. At 30 days after discharge, 83% of patients had spontaneously returned to sinus rhythm [28]. A recently reported noninferiority trial compared rhythm control (with electrical cardioversion) to rate control for the management of patients with recent-onset AF in the ED [29]. The primary endpoint of this study was the restoration of sinus rhythm 4 weeks after initial presentation. The proportions of patients in the rate control and cardioversion groups who achieved the study endpoint were not significantly different.

Although both rate and rhythm control strategies have merits, a growing body of evidence supports the use of a treatment plan that can be adjusted to match each patient's individual needs. A recently reported AF treatment pathway (so called because it did not mandate the use of specific treatments, as had previously reported protocols) allowed the managing clinician to choose either a rate or a rhythm control strategy [30]. This treatment pathway also allowed for the placement of patients in an ED observation unit, a strategy that had previously been shown to be effective [23]. In addition, this treatment pathway included patients with both recent-onset and longstanding AF, as distinct from many other treatment protocols that excluded patients in whom AF had been present for more than 48 h. In a prospective, two-stage study, utilization of this multidisciplinary pathway was found to significantly reduce the rate of inpatient admissions as compared with routine care (from 55 to 15%, $P < 0.001$) [31•]. Even though this treatment pathway did not mandate a rhythm control strategy, sinus rhythm was restored in a significantly higher proportion of patients who were treated according to the pathway (76%) than in patients who received routine care (61%, $P = 0.02$).

Risk Stratification of AF Patients in the ED

Utilization of a rhythm control strategy for AF may not be appropriate for all patients in the ED who have significant medical comorbidities. A retrospective cohort study performed in two urban, Canadian university-affiliated hospitals investigated the impact of impaired renal function on AF outcomes. This study found that utilization of a rhythm control strategy in AF patients with low GFR (less than 60 ml/min) was associated with a 10% higher adverse event rate than rhythm control in patients with normal GFR [32].

Elevated serum levels of cardiac biomarkers are also markers of increased risk. Two retrospective studies involving multivariate analyses found that patients with AF and an elevated hs-TnT had a higher mortality rate than patients with AF and normal hs-TnT levels [33, 34]. A non-interventional cohort study revealed that elevations in both hs-TnT and NT-proBNP are associated with higher mortality rates for patients with AF who present to the ED [35]. Multivariate analysis in this study did not find an interaction between hs-TnT and NT-proBNP.

The observation that medical comorbidities and elevated cardiac biomarkers are associated with worse patient outcomes led to the creation of a risk scoring system for patients who present to the ED with AF [36, 37•]. This risk score identifies patients who are at high risk of readmission and 30-day mortality. It may be that patients who are categorized as high risk according to this score are better served by inpatient admission than discharge from the ED.

Since each patient with AF enters the ED with unique circumstances and comorbidities, it stands to reason that the treatment strategy should be adjusted to fit the patient. One study described the utilization of a best practices checklist that facilitates the systematic description of comorbidities that may contribute to the choice of treatment strategy [38]. In one cohort study, utilization of an ED triage system that is based on AF patient risk stratification significantly reduced inpatient admissions with respect to routine care (57% vs 81%, $P < 0.001$) [39].

Utilization of AF Treatment Protocols in the ED Can Improve Adherence to OAC Guidelines

The use of oral anticoagulation (OAC) to reduce the risk of AF-related stroke is supported by multiple clinical guidelines [12, 40]. Many patients are first diagnosed with AF in the ED. Therefore, an ED visit can provide an excellent opportunity to ensure that qualifying patients are prescribed appropriate OAC therapy. It has been demonstrated

that patients with AF for whom warfarin was started in the ED were more likely to remain on warfarin long term than those patients for whom the anticoagulation decision was deferred to another provider [41, 42]. Initiation of OAC for patients with AF in the ED setting has also been shown to contribute to lower mortality [43].

Despite the abundance of data supporting the use of OAC in patients with AF, underutilization of OACs in the ED remains an issue [44–47]. Initiation of OAC in the ED is limited by several challenges. The fast pace of the ED is not necessarily well-suited to the shared decision making recommended by guidelines [40]. In addition, emergency medicine clinicians have multiple competing demands on their time, and it may not always be possible to establish outpatient follow-up for patients who qualify for OAC therapy without delaying the care of an acutely ill patient [48, 49]. Consequently, the decision to initiate OAC therapy is frequently deferred to the clinicians who are involved in the longitudinal care of the patient.

Several protocols for the treatment of AF in the ED have been found to increase the rate of appropriate OAC use (Table 2). One reported protocol included clinical decision support (CDS) tools, including a reminder statement regarding OAC therapy that was added to ECGs with a preliminary finding of AF/AFL. In a prospective observational study performed in Canadian EDs, utilization of this protocol resulted in an 8.5% increase ($P = 0.04$) in OAC prescriptions within 90 days of the index ED visit [50]. Another study of an AF treatment protocol that included a CDS was also evaluated in Canadian EDs. A chart review study showed that this intervention increased the rate of appropriate OAC prescriptions from 49 to 70% ($P < 0.01$) at the time of ED discharge [51]. A prospective, multicenter, observational study performed in Spanish EDs found that initiation of OAC in the ED for patients at high risk for stroke resulted in lower mortality (hazard ratio, 0.40; 95% confidence interval, 0.231–0.686) without an increase in the risk of bleeding (hazard ratio, 0.98; 95% confidence interval, 0.29–3.24) [43].

A multidisciplinary AF treatment pathway utilized in a tertiary ED in the USA did not lead to a statistically significant increase in OAC prescriptions as compared with patients who received routine care. Comparisons between the treatment pathway and routine care cohorts were performed at ED discharge and 4 months after discharge [31•]. It is possible that the absence of a difference between cohorts was the result of the high rate of OAC prescriptions written routinely by ED providers in the hospitals in which this study was conducted.

Protocols that facilitate the establishment of outpatient follow-up before the patient leaves the ED have been shown to improve patient outcomes. A protocol that involved placement of a referral to a nurse-led AF clinic prior to ED discharge resulted in improved OAC guideline adherence compared with a historical control group of patients who were followed by a cardiologist or primary care physician. This protocol also involved the distribution of education materials to patients prior to ED discharge. Utilization of this protocol was associated with a decrease in AF-related complications (32% vs 48%, $P = 0.005$) at 1 year after presentation [52].

Table 2 Anticoagulation rates associated with utilization of different treatment pathways for AF in the ED

Study	AF type	Intervention type	Study type	No. of patients	Patients who qualify for OAC who received appropriate prescription (%)	*P* value
Vinson et al. [47]	Any (high risk for stroke) Not currently on OAC	No intervention	Prospective, multicenter observational	312	41	n/a
Barbic et al. [51]	Uncomplicated AF	AF/AFL treatment pathway (including clinical decision support)	Pre–post evaluation	Pre: 129 Post: 172	At discharge: 49 (pre), 70 (post)	< 0.01
Rezazadeh et al. [50]	Any, not currently on OAC, CHADS65 ≥ 1	Clinical decision support	Pre–post evaluation	Pre: 414 Post: 212	Pre: 39 Post: 48	0.04
Ptaszek et al. [31•]	AF as primary problem	AF/AFL treatment pathway	Two-stage	Routine care: 104 AF pathway: 104	At discharge: 88 (routine care), 91 (AF pathway)	0.5
					Four months post-discharge: 78 (routine care), 88 (AF pathway)	0.07
Abadie et al. [56•]	AF as primary problem (hemodynamically stable, low-to-moderate symptom severity)	Referral to AF "transitions" clinic after hospital discharge	Retrospective	Routine outpatient care: 78 AF clinic: 160	88 (Routine outpatient care) 97 (AF clinic)	0.03

AF atrial fibrillation, *ED* emergency department, *OAC* oral anticoagulation

Transitional AF Care Clinics Have Been Shown to Improve Patient Outcomes

Careful outpatient management is a key part of optimizing outcomes for patients with AF. Arranging for prompt outpatient follow-up for patients seen in the ED for AF is a recognized problem [53]. Several recent studies have demonstrated that establishing outpatient follow-up in an AF clinic at the time of ED discharge can improve patient outcomes.

Utilization of Transitional AF Clinics is Associated with Improvement in Adherence to OAC Guidelines

Several studies have demonstrated that arrangement for outpatient AF follow-up during an ED visit is feasible. In one cohort study, patients with new-onset AF presenting to emergency departments in Canada were referred to a nurse-run, physician-supervised AF clinic [54]. The primary outcome of this study (composite of death, cardiovascular hospitalization, and AF-related emergency department visits) was observed less frequently in patients who were referred to the AF clinic than in patients who received routine care (17% vs 26%, $P = 0.05$). Patient enrollment in this AF clinic was also associated with a significant increase in the rate of appropriate OAC prescriptions in patients with CHADS2 score ≥ 2 (88% vs 59%; $P < 0.01$). This strategy was also found to be cost-effective, with an average cost reduction of CAD $210.83 and an average improvement in quality-adjusted life years (QALY) of 0.0007 per patient [55].

In another retrospective study, patients who presented with AF to the emergency department of a large academic hospital in the USA and were discharged from the ED were either referred to an AF clinic (run by an advanced practice provider, supervised by a cardiologist) or received routine outpatient follow-up care [56•]. Patients who were followed in this AF clinic were more likely to undergo stroke risk assessment with documentation of CHA2DS2-VASc score (99% vs 26%; $P < 0.01$), to have higher rates of appropriate anticoagulation prescription (97% vs 88%; $P = 0.03$), and to be less likely to be prescribed inappropriate combinations of anticoagulant and antiplatelet therapy (1% vs 9%; $P < 0.01$).

The common feature of these protocols is the use of a clinical decision support tool that helps clinicians in the ED schedule follow-up visits in an outpatient AF clinic. This intervention can decompress busy EM clinicians and facilitate outpatient follow-up for patients with AF. Follow-up in the AF clinics described in these studies was associated with improved adherence to clinical performance metrics, including appropriate OAC prescription, as compared with routine outpatient care [57].

Utilization of Transitional AF Clinics is Associated with a Decrease in Rehospitalization and Mortality

The impact of a post-ED AF clinic on mortality was described in a randomized controlled trial conducted in the Netherlands. In the intervention cohort, patients were managed in a nurse-driven, cardiologist-supported AF clinic. Patient outcomes associated with this software-supported, nurse-driven clinic were compared with standard of care. With a focus on patient education and guideline adherence, this approach resulted in a >30% reduction in cardiovascular death and hospitalization (hazard ratio: 0.65; 95% confidence interval (CI) 0.45–0.93; $P = 0.02$) [58]. A subsequent analysis of the intervention described in this trial was found to be cost-effective [59].

This post-ED AF clinic shares some features in common with an AF clinic that was designed to follow inpatient admission. This inpatient-based AF clinic involved discharge instructions given by a cardiac nurse followed by a home visit and Holter monitoring 7 to 14 days after discharge. Subsequent follow-up and multidisciplinary support were provided as needed. This protocol was evaluated with a multicenter, randomized controlled trial that included patients admitted to Australian hospitals with chronic non-valvular atrial fibrillation [60]. Utilization of this protocol resulted in a significant increase in the number of days alive and out of hospital (effect size 0.22, 95% CI 0.21–0.23; $P = 0.04$). These studies indicate that outpatient AF clinics utilized after ED or inpatient discharge produce improved patient outcomes, OAC guideline adherence, and cost-effectiveness. The impact of specialized AF clinics on long-term outcomes has not been determined.

AF Management in the ED is Variable

Guidelines for AF management in the ED are not as well-validated as the guidelines for outpatient AF management [14]. This has been cited as one reason for the variability in AF management in the ED [8, 16, 18]. Published guidelines support the use of either a rate or a rhythm-control strategy in the ED [14]. Consequently, clinicians may exhibit preferences for one strategy over the other. Even among patients in whom a rhythm control strategy is selected, there is considerable variability in a choice of a chemical-first versus an electrical-first strategy [19].

Several other factors have been shown to influence AF management in the ED. These include geographic region and hospital type (tertiary versus community). There is also a growing appreciation of the impact of patient demographics on AF management in the ED.

Regional Variability of AF Management in the ED

The proportion of ED visits for AF that lead to hospital admission varies between countries. In the USA, over 60% of the patients who present to the ED with AF are admitted [7, 19, 61]. In Canada, where treatment protocols for AF in the ED were more widely adopted, the admission rate is less than 40% over the same time period [61, 62].

Variation in hospital admission rates has been observed among different geographic regions within individual countries (e.g., Western versus Northeast regions of the USA) [8]. Hospital volume also has an impact on AF-related admissions. Patients with AF who visit an ED in a high-volume medical center are less likely to be admitted than patients with AF who visit an ED in a lower-volume medical center [63].

Most of the treatment protocols described in the literature were evaluated in academic or tertiary hospitals. These protocols frequently require resources that may not be available at non-tertiary centers. The absence of key resources (e.g., a continuously available cardiology consultant) likely contributed to the observed differences in outcomes observed in high- and low-volume centers. Although it may not be practical to expect that all the treatment protocols validated in academic/tertiary centers can be routinely utilized in the community setting, it is noteworthy that several AF treatment protocols have been designed to work efficiently in a community ED. For example, the safety and efficacy of intravenous ibutilide infusion to treat AF in a community ED was evaluated with a retrospective cohort study involving 21 hospitals [64]. The safety and efficacy of ibutilide use in this study were comparable to those observed in clinical trials performed in larger hospitals.

An AF treatment protocol that included both rate and rhythm control strategies was evaluated in an academic community hospital [20•]. In this study, utilization of the protocol was associated with a statistically significant reduction in the rate of inpatient admissions compared with the routine care cohort (80% with routine care, 67% with use of the algorithm). These findings are promising and raise the possibility that treatment protocols originally designed for use in a tertiary/academic hospital can be successfully adapted for use in a community hospital setting.

Gender and Race Disparities in AF Management in the ED

Race and gender at birth have been shown to impact care administered to Medicare beneficiaries for AF [65]. There are few studies that explore gender differences in care delivered to patients with AF in the ED. One such study demonstrated that the time between ED presentation due to AF and a first outpatient follow-up visit was shorter for women. Time to a follow-up visit with a specialist was longer for women. In addition, women were more likely than men to die within 30 to 90 days after an ED visit due to AF [66]. Another study found that women who presented to the ED with AF had more comorbidities and were more likely to be admitted. Despite the difference in baseline comorbidities and admission rate, this study did not find a significant difference in treatment outcomes between men and women [67]. There are currently no published studies that specifically address the impact of race on AF care in the ED.

Conclusions

The inpatient admission rate for patients presenting to the ED with AF is much higher in the USA (over 60%) than in Canada (less than 40%) [7, 19, 61]. The lower admission rates in Canada have been attributed to the widespread adoption of comprehensive treatment protocols for AF in the ED [68]. These protocols are designed to address potential delays in AF management that can increase the likelihood of admission.

The earliest versions of treatment protocols for AF in the ED specified the treatments to be administered to patients (e.g., use of procainamide in the context of a rhythm control strategy). There is a growing body of evidence emphasizing the importance of AF patient risk stratification and the creation of an individualized care plan for each patient. A multidisciplinary treatment pathway for AF in the ED that does not mandate any specific care decisions was found to be successful in reducing hospital admissions without prolonging ED stay or increasing the rate of hospital return [31•]. This treatment pathway, which was evaluated in EDs in the USA, produced admission rates comparable to those observed in Canadian EDs.

Prompt outpatient follow-up after an ED visit for AF has been shown to improve OAC adherence and improve patient outcomes. Treatment protocols that assist ED clinicians in arranging for outpatient care prior to ED discharge can improve patient outcomes. Recent studies highlight the potential of "transitional" AF clinics to optimize adherence to OAC therapy guidelines and to improve patient outcomes.

The success of an ED-based AF treatment protocol is dependent on the availability of key resources. The absence of these resources in smaller hospitals may contribute to regional variability in care. Despite these disparities, several studies have demonstrated that it is possible to successfully implement AF treatment protocols in a community hospital [20•, 64]. A large body of evidence has demonstrated that gender at birth, race, and socioeconomic status can impact cardiac care. More study is needed to determine how these factors impact AF care delivery in the ED.

Compliance with Ethical Standards

Conflict of Interest W Bode: no relationships to disclose. L.M. Ptaszek: consultant for Abbott, Broadview Ventures, Bristol Myers Squibb, Moderna, Pfizer, and World Care Clinical.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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