CHEST

Atrial Fibrillation in the ICU

Nicholas A. Bosch, MD; Jonathan Cimini, BS; and Allan J. Walkey, MD

Atrial fibrillation (AF) is the most common arrhythmia encountered in the ICU. Preexisting AF is highly prevalent among older patients with chronic conditions who are at risk for critical illness, whereas new-onset AF can be triggered by accelerated atrial remodeling and arrhythmogenic triggers encountered during critical illness. The acute loss of atrial systole and onset of rapid ventricular rates that characterize new-onset AF often lead to decreased cardiac output and hemodynamic compromise. Thus, new-onset AF is both a marker of disease severity as well as a likely contributor to poor outcomes, similar to other manifestations of organ dysfunction during critical illness. Evaluating immediate hemodynamic effects of new-onset AF during critical illness is an important component of rapid clinical assessment aimed at identifying patients in need of urgent direct current cardioversion, treatment of reversible inciting factors, and identification of patients who may benefit from pharmacologic rate or rhythm control. In addition to acute hemodynamic effects, new-onset AF during critical illness is associated with both short- and long-term increases in the risk of stroke, heart failure, and death, with AF recurrence rates of approximately 50% within 1 year following hospital discharge. In the absence of a strong evidence base, there is substantial practice variation in the choice of strategies for management of new-onset AF during critical illness. We describe acute and long-term evaluation and management strategies based on current evidence and propose future avenues of investigation to fill large knowledge gaps in the management of patients with AF during critical illness.

CHEST 2018; 154(6):1424-1434

KEY WORDS: atrial fibrillation; critical illness; sepsis

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a lifetime risk in the community of 25%[1] and associated complications of heart failure, stroke, and death.[2-4] As a comorbidity of aging, preexisting AF is common among patients presenting to the ICU. As a frequent complication of critical illness,[5] new-onset AF is also a problem familiar to ICU physicians. Thus, clinicians encounter either prevalent (preexisting) or incident (new-onset) AF among nearly one in three critically ill patients.[6]

The present review discusses the clinical impact of, and evidence-based approaches to, AF in critically ill patients, with specific consideration of risk factors,

ABBREVIATIONS: AF = atrial fibrillation; AV = atrioventricular; BB = beta-blocker; CCB = calcium channel blocker; CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥ 75 years, diabetes, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; DCCV = direct current cardioversion; RVR = rapid ventricular response; SR = sinus rhythm

AFFILIATIONS: From the Department of Medicine (Drs Bosch and Walkey), The Pulmonary Center, Boston University School of Medicine, Boston, MA; Massachusetts College of Pharmacy and Health Sciences (Mr Cimini), Worcester Campus, Boston, MA; and the Center for Implementation and Improvement Sciences (Dr Walkey), Boston University School of Medicine, Boston, MA.

FUNDING/SUPPORT: Dr Walkey is supported by the National Heart, Lung, and Blood Institute [Grants 5K01HL116768-03 and 1R01HL136660-01].

CORRESPONDENCE TO: Allan J. Walkey, MD, The Pulmonary Center, 72 E Concord St, R-304, Boston, MA 02118; e-mail: alwalkey@bu.edu

DOI: https://doi.org/10.1016/j.chest.2018.03.040

pathophysiology, treatments, and outcomes of new-onset AF during critical illness.

New-onset AF During Critical Illness: Risk Factors and Mechanisms

Mechanisms of new-onset AF during critical illness are only partially elucidated. To better grasp the mechanisms and risk factors of AF during critical illness, we first review the current understanding of the mechanisms of AF in the community setting.

Sustained AF is believed to occur through a two-step process that includes the following: 1) the formation of an arrhythmogenic atrial substrate as fertile ground for the development of AF, and 2) the "seed" that initiates AF through an arrhythmogenic trigger. Remodeling of atria into a proarrhythmic substrate is most often due to the development of atrial fibrosis. Chronic heart failure, hypertension, valve disease, and myocardial infarction result in multiple, common pathways of inflammation, renin-angiotensin system activation, and generation of reactive oxygen species that produce atrial fibrosis.[7] In addition to atrial fibrosis, persistent tachycardia can produce electrical remodeling that leads to an atrial substrate susceptible to AF through changes in intracellular calcium ion handling and ion channel expression.[8] AF may be initially triggered through multiple factors that perturb normal electrical conduction such as hypokalemia, hypomagnesemia, hypovolemia, and alterations in parasympathetic and sympathetic activity, leading atrial foci to develop abnormal automaticity, self-sustaining action potentials, or re-entrant circuits.[7,9-12] When arrhythmogenic triggers occur in the absence of an arrhythmogenic substrate, AF is generally fleeting and self-terminating. However, when arrhythmogenic triggers combine with atrial fibrosis or electrical remodeling, AF can be sustained and becomes increasingly difficult to terminate through further electrical remodeling.[13]

Although critical illness-induced AF also likely follows the development of a susceptible atrial substrate combined with a triggering event, the specific factors that contribute to the arrhythmogenic substrate and the specific triggers may differ from community-acquired AF. For example, traditional risk factors associated with AF in the community setting (ie, structural and valvular heart disease) have not been consistently linked to new-onset AF during critical illness.[14] Rather, emerging evidence suggests that acute events during critical illness accelerate cardiac remodeling and fibrosis to rapidly produce a susceptible atrial substrate, providing fertile ground for the development of sustained AF in response to the myriad arrhythmogenic triggers of critical illness.

Critical Illness and Atrial Remodeling

Accelerated cardiac structural and electrical remodeling can occur due to infection and inflammation that are common during critical illness. Murine and primate models of pneumonia show that bacteria deposit within the myocardium and result in development of atrial fibrosis and an arrhythmogenic substrate, despite treatment with antibiotics.[15-17] Bacteria can also alter calcium ion channel gene expression through toxin release, resulting in a shortened atrial-effective refractory period which produces electrical remodeling that further predisposes to AF during sepsis.[18]

Inflammation, regardless of the presence of infection, may also play a role in the development of AF. Elevated inflammatory markers in patients with sepsis and postoperative patients are associated with an increased risk of developing AF.[19] Inflammation may predispose to arrhythmia development as a result of direct inflammatory cell infiltration and oxidative damage to atrial myocytes.[20,21] Inflammation and oxidative damage may also help explain associations between obesity and new-onset AF, both in the community and during critical illness.[19,22] In turn, early reports suggest that anti-inflammatory agents such as glucocorticoids and statins may decrease the incidence of AF; these agents warrant further study.[23]

AF Triggers During Critical Illness

In the ICU, AF is more frequent among patients receiving vasopressor agents, in patients with electrolyte derangements, and in patients with greater disease severity.[24-26] For example, hypokalemia and changes in the balance of autonomic activity as a result of vasopressors may alter ion channel activity and cell automaticity that predispose to AF.[9,27] Dopamine and epinephrine in particular have chronotropic effects that can lead to increased atrial ectopic discharges triggering new AF.[27] Greater illness severity is also associated with the risk of new AF development, which may be a consequence of increased release of catecholamines and progressive autonomic dysfunction.[19,25,28] Lastly, atrial size on echocardiography is associated with new-onset AF in the ICU, suggesting that iatrogenic atrial pressure/volume overload may also be important in the development of AF in the critically ill.[29] Figure 1 summarizes proposed mechanisms for AF development in patients who are critically ill.

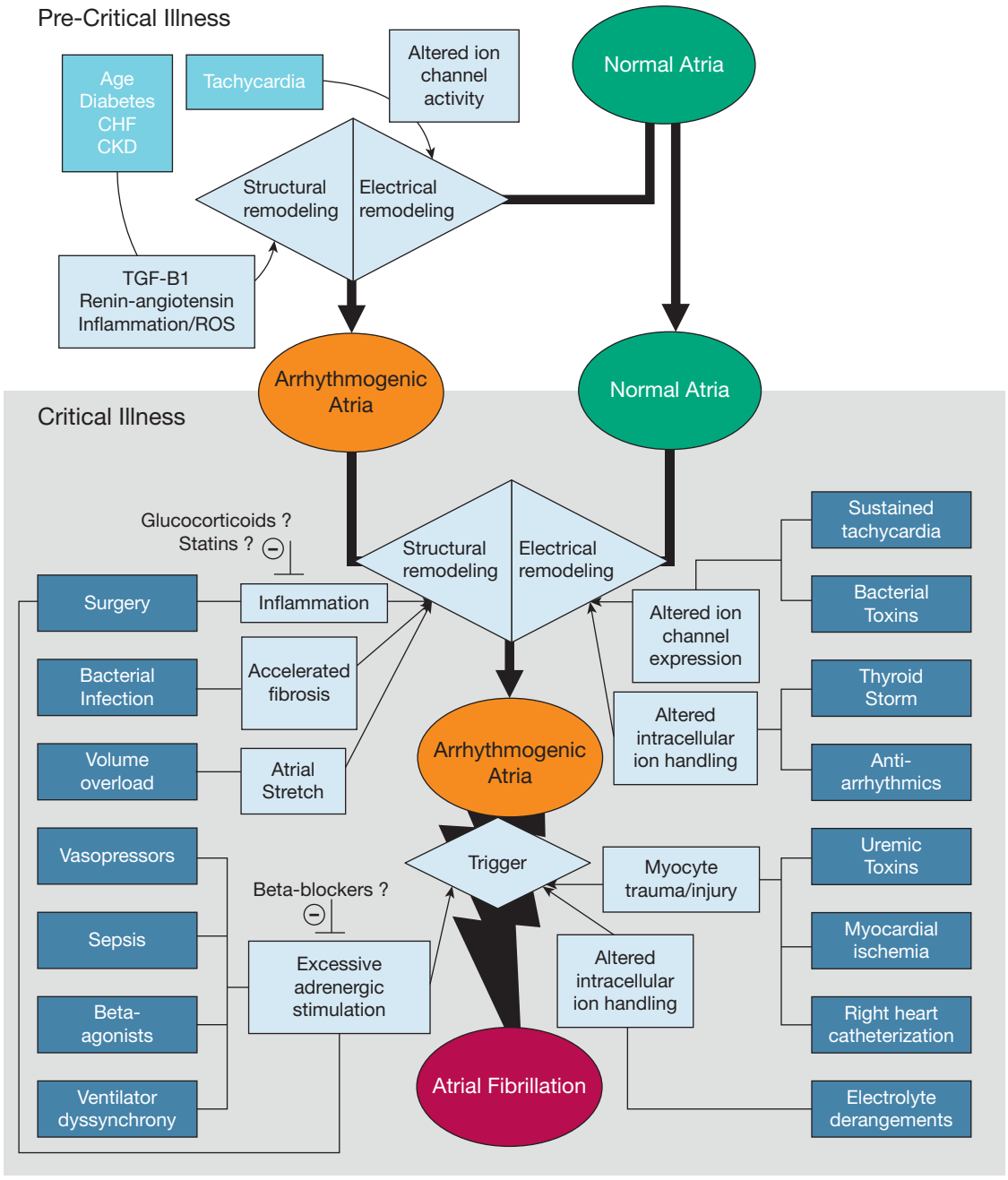

Figure 1 – *Proposed mechanisms and risk factors for new-onset AF during critical illness. AF develops through a two-step process: creation of an arrhythmogenic substrate followed by a triggering event. During critical illness, both acute (dark blue boxes) and chronic risk factors (light blue boxes) have roles in the development of AF. Prior to critical illness, chronic risk factors for AF may alter the normal atrial myocardium into an arrhythmogenic substrate predisposing to AF during critical illness. During critical illness, patients with both normal and arrhythmogenic atria can develop new-onset AF in the setting of acute risk factors. Risk factors potentially lead to accelerated structural and electrical remodeling and may then trigger AF through multiple mechanisms, including adrenergic stimulation. Proposed pathways by which these risk factors lead to AF may be optimal targets for future preventative strategies. AF = atrial fibrillation; CHF = congestive heart failure; CKD = chronic kidney disease; ROS = reactive oxygen species; TGF = transforming growth factor.*

Prediction of New-onset AF During Critical Illness

Tools that identify patients at high risk for new-onset AF during critical illness may inform mechanisms of AF, identify potential targets for intervention, and enrich future trials studying AF preventative strategies. Klein

Klouwenberg et al[19] recently developed a prediction tool for new-onset AF based on clinical factors, including time since admission, age, obesity, immunocompromise, elevation of inflammatory markers, shock, renal failure, potassium level, and F_{IO_2}. This tool can identify the risk

for AF in patients with sepsis with a C statistic of 0.81 (https://safescore.shinyapps.io/safe).

Clinical Consequences of AF during Critical Illness

AF may lead to clinical decompensation through interrelated mechanisms. During AF, the coordinated depolarization and contraction of the heart is disrupted by innumerable, disorganized atrial electrical impulses leading to erratic contraction and loss of the "atrial kick" that assists with ventricular filling during diastole. Patients with diastolic dysfunction may be prone to hemodynamic decompensation during episodes of AF because of the increased reliance on the "atrial kick" during left ventricular filling. Loss of atrial systole may be particularly important in critical illnesses such as sepsis, during which approximately one half of patients have impaired ventricular relaxation.[30] In critical illness, excess sympathetic tone can also alter the depolarizing properties of conducting fibers in the atrioventricular (AV) node, allowing increased conduction of atrial impulses to the ventricles and rapid ventricular responses (RVRs) that further impair cardiac output.[31] In one study evaluating hemodynamic consequences of new-onset AF during critical illness, 37% of critically ill patients with new-onset AF developed immediate hemodynamic instability, 25% had heart rates $>$ 150 beats/min, and 11% exhibited new signs of cardiac ischemia and heart failure.[32] Thus, although AF during critical illness often presents during times of high disease severity, it also seems to increase the severity of the disease itself.

Outcomes of AF During and After Critical Illness

Because development of AF during critical illness is associated with more severe illness prior to onset, as well as clinical worsening following onset, ascertaining the causal role of AF in patient outcomes is difficult. In one study of 1,782 patients admitted to the ICU with sepsis, 418 (23%) developed new-onset AF; the new-onset AF was associated with increased hospital mortality after accounting for competing risks and multiple, time-varying cofounding variables (subdistribution hazard ratio, 2.10 [95% CI, 1.61-2.73]).[19] Multiple other studies have identified associations between new-onset AF and increased risk of death during sepsis and critical illness.[5,25,29,33] Thus, new-onset AF is a dysfunctional cardiac response to infection with strong prognostic implications beyond traditional organ dysfunction measures (eg, Sequential Organ Failure Assessment) and may represent an underrecognized sepsis-defining organ dysfunction.[34]

Among survivors of critical illness, new-onset AF frequently resolves prior to discharge,[35] and thus "secondary AF" has long been thought of as a self-limited event[36] in patients in whom the AF trigger is transient. However, emerging evidence suggests that AF following critical illness often reoccurs after resolution of the critical illness and that long-term outcomes following critical illness may be associated with arrhythmia persistence or reoccurrence. For example, in a large observational study, 55% of patients with new-onset AF who survived a sepsis hospitalization had AF occurrence within 5 years compared with 16% of patients who did not have AF during a sepsis hospitalization.[37] Interestingly, patients with new-onset AF during sepsis had higher 5-year risks of ischemic stroke, heart failure, and death compared with patients with no AF but a reduced risk compared with patients with preexisting AF. These data suggest a potential pathway in which new-onset AF during critical illness increases the risk of recurrent AF following critical illness, which then increases the risk of long-term poor outcomes. Thus, AF during sepsis may contribute to the development of the "post-ICU syndrome" and may represent an opportunity for intervention to improve long-term outcomes following critical illness.

Acute Management

Breaking the self-propagating cycles of AF and disease progression represents a potential target to improve outcomes during and following critical illness. The treatment priorities of AF in the ICU depend on multiple factors, including the goals of care of the patient, inciting events/reversible triggers, comorbid disease, hemodynamic effects, and the risks of potential therapeutic agents. Within this context, we recommend a multifaceted approach to the management of acute AF in critical illness based on current physiological understanding and observational evidence. Therefore, a general approach to AF in the ICU setting includes the following: (1) assessment for potential hemodynamic effects and mechanisms of hemodynamic change likely attributable to AF, (2) removal of offending agents that increase the risk for AF (ie, beta-agonists) and/or correction of reversible arrhythmogenic triggers (electrolyte imbalances, airway obstruction, and atrial stretch), and (3) choice of an initial treatment strategy that maximizes potential benefit and minimizes risk

when AF seems to be causing harm. Considerations for initial pharmacologic strategies include rate control when adverse effects of AF seem due to an elevated heart rate, or rhythm control when adverse effects of AF may be due to loss of atrial systole, or where a rate control strategy is ineffective or has unacceptable side effects. In the event of precipitous hemodynamic compromise due to AF, urgent direct current cardioversion (DCCV) should be used. Finally, patients should be assessed for candidacy for arterial thromboembolism prophylaxis. Figure 2 summarizes treatment priorities of new-onset AF during critical illness (outlined in the following sections).

Direct Current Cardioversion

In hemodynamically unstable patients with AF with RVR or when AF with RVR contributes to ongoing myocardial ischemia, the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society 2014 guidelines make a strong recommendation, based on limited evidence, for DCCV.[38] Despite this recommendation, the success

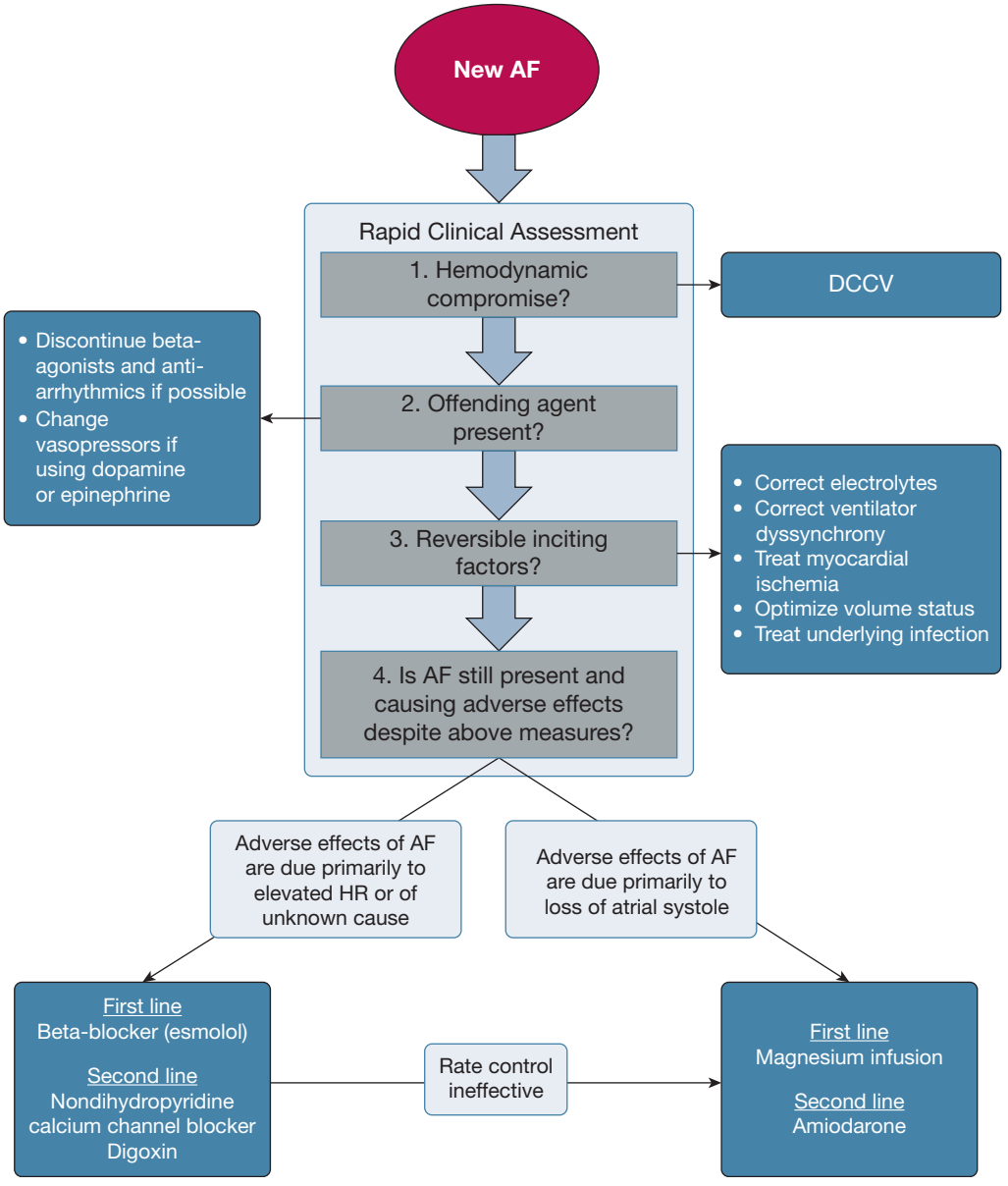

Figure 2 – *Acute management priorities in new-onset AF during critical illness. Identification of new-onset AF during critical illness should prompt a four-step rapid clinical assessment: (1) assessment for hemodynamic compromise requiring urgent DCCV, (2) removal of potential offending agents, (3) reversal of inciting acute factors, and (4) treatment to reduce rate or convert to sinus if AF persists and is associated with adverse effects. DCCV = direct current cardioversion; HR = heart rate. See Figure 1 legend for expansion of other abbreviation.*

rates of attempted cardioversion of AF during critical illness are low: in postoperative patients who developed AF, attempted cardioversion resulted in immediate conversion to sinus rhythm (SR) in 71% of patients, but after 1 h, only 43% patients remained in SR, and after 24 h, only 23% patients remained in SR.[39] Thus, in critically ill patients in whom cardioversion is attempted, concurrent administration of rate or rhythm control therapy should be considered given the high likelihood of AF recurrence soon after a successful cardioversion attempt. When DCCV is used during critical illness, there is often inadequate time or patient stability to assess for left atrial thrombus. In addition, comorbid disease (ie, coagulation defects, recent stroke) is often present, which increases the risk of instituting anticoagulation. It is unknown if administering anticoagulation in critically ill patients prior to DCCV decreases the risk of thromboembolic events or if there is an optimal timing of anticoagulation prior to DCCV. Thus, we recommend that the decision to administer periprocedural anticoagulation be informed by the urgency of DCCV and relative or absolute contraindication to such therapy.

Medication Options for Rate and Rhythm Control

In critically ill patients without severe hemodynamic decompensation resulting from AF, clinicians have a range of medical therapies to consider for rate or rhythm control. Frequently chosen rate control medications are nondihydropyridine calcium channel blockers (CCBs), beta-blockers (BBs), and cardiac glycosides such as digoxin. Medications selected for rhythm control most often include magnesium and amiodarone, both of which have rhythm- and rate-controlling properties. CCBs, such as verapamil and diltiazem, inhibit voltage-gated calcium channels, decreasing depolarization of the AV node and slowing heart rate; however, these agents also have vasodilatory and negative inotropic effects and are contraindicated in patients with acute heart failure. BBs have rate-controlling, negative inotropic and vasodilatory effects similar to CCBs, but they function as sympatholytic agents through antagonism of the $beta_1$-receptor, leading to decreased conduction through the AV node and reduced effects of catecholamines on the myocardium. A distinct pharmacokinetic advantage of BBs is the ultra-short-acting preparation esmolol, which allows rapid titration and discontinuation with fast recovery from potential drug-related hypotension.[40] Digoxin slows heart rate by increasing vagal tone; it is associated with low rates of hypotension but has a narrow therapeutic index. Observational studies show associations between digoxin use and increased mortality, especially in patients with underlying heart failure with serum digoxin levels $>$ 1.2 ng/ml. In addition, the vagomimetic effects of digoxin may be less effective during critical illnesses characterized by high catecholamine states.[41-43] Magnesium affects ion channel activity to decrease cardiac automaticity and prolong AV node refractoriness, which may improve rate control and lead to SR conversion without substantial negative inotropic activity.[44] Amiodarone inhibits adrenergic stimulation and blocks the delayed rectifier current, which can lead to conversion to SR as well as prolonged AV node refractoriness slowing AV conduction. A main advantage of amiodarone, unlike several other antiarrhythmic agents, is that it is not contraindicated in patients with structural or coronary heart disease.[45] Potential disadvantages to amiodarone are hypotension during IV infusion and pro-arrhythmic and organ toxicity effects, including an increased risk of chronic interstitial pneumonitis and organizing pneumonia. Acutely, amiodarone lung toxicity can mimic ARDS.[46-48]

There is significant practice variability regarding initial medication choice for AF during critical illness. In the United States, CCBs are administered as initial treatment most frequently (36%) for patients with AF and sepsis, followed by BBs (28%), digoxin (20%). and amiodarone (16%). Practices also vary according to country: a survey of intensivists in the United Kingdom found that $>$ 80% would choose amiodarone as first-line treatment, whereas 12% chose BBs.[49] Despite being a less commonly used initial treatment, preliminary BB use for AF was associated with a lower risk of in-hospital mortality compared with CCBs, digoxin, or amiodarone in an observational analysis among patients with sepsis.[50] In addition, a study using granular ICU data showed that initial use of metoprolol for AF with RVR was associated with lower need for administration of a second agent compared with amiodarone and better rate control at 4 h compared with diltiazem.[51] Other studies suggest that use of esmolol during sepsis enhances arterial elastance and ventricular-arterial coupling,[52] which may improve cardiovascular efficiency and reduce mortality.[53] Thus, use of BBs to treat arrhythmias during critical illness is a promising area of investigation.

Two small randomized trials comparing rate vs rhythm control medications in AF with RVR in the acute (but non-ICU) setting supplement observational studies during critical illness. In a single-center study of 150 patients with uncomplicated acute symptomatic AF with

RVR requiring hospital admission, randomization to diltiazem was associated with a higher percentage of sustained ventricular rate control (90%) compared with digoxin (74%) and amiodarone (74%) (BBs were not evaluated).[54] In a single-center study of 60 ICU patients with supraventricular tachycardia (AF: n = 57; atrial flutter: n = 2; atrial tachycardia: n = 1), randomization to diltiazem compared with two dosing strategies of amiodarone did not seem to result in different rates of adequate heart rate control within 4 h (70% for diltiazem vs 55% for amiodarone load vs 75% for amiodarone load and maintenance); however, diltiazem was associated with an increased rate of drug discontinuation due to hypotension (30% vs 0% vs 5%, respectively).[46] Given the observational findings of decreased mortality, improved heart rate control, better ventriculo-arterial coupling, and pharmacokinetic advantages, it is reasonable to use esmolol as a first-line treatment for hemodynamically significant AF during critical illness if no contraindications exist. If additional control is needed, second-line agents may include magnesium, diltiazem, and amiodarone, with digoxin reserved for situations in which other agents are ineffective or contraindicated. The strong safety profile of magnesium and similar rate of conversion to SR compared with amiodarone make magnesium a reasonable choice prior to amiodarone if rhythm control strategy is chosen.[55] Table 1 summarizes AF treatment strategies.[56-68]

Subacute Management

After rate and rhythm management of AF during critical illness, the next clinical dilemma is often the decision to start arterial thromboembolism prophylaxis with anticoagulation. Patients with critical illness and AF have a twofold increased risk of in-hospital ischemic stroke compared with those without AF,[25] but they also have higher bleeding risk and often require invasive procedures that may necessitate interruption of anticoagulation; decisions regarding anticoagulation of critically ill patients are complex. In a nationwide study of patients with AF and sepsis in the United States, 35.3% received parenteral anticoagulant agents. In propensity score-matched patients, there was no difference in rate of in-hospital ischemic stroke between patients who received or did not receive parental anticoagulant agents; however, there was an increase in clinically significant bleeding (8.6% vs 7.2%) in the patients who received parenteral anticoagulation.[69] It is unknown if similar associations exist for nonsepsis causes of critical illness.

There are currently no anticoagulation guidelines for AF during sepsis; further studies are direly needed to clarify potential benefits/harms prior to standardized treatment being recommended. Given the lack of clear benefit and the potential for harm, in critically ill patients with new-onset AF during sepsis who do not have planned cardioversion, we do not currently recommend routinely initiating parenteral anticoagulation for arterial thromboembolism prophylaxis during the acute phases of critical illness.

Approaches to Long-term Management

Following critical illness, decisions to initiate anticoagulation to reduce thromboembolic risk depend on the persistence of arrhythmia, thromboembolic and bleeding risks, and goals of care. AF during critical illness frequently resolves prior to discharge (86% resolution in a single-center study of patients with septic shock), but long-term thromboembolic risk of patients with new AF during critical illness seems to remain relatively high.[35] Among survivors who developed new-onset AF during sepsis and who experience an ischemic stroke following the sepsis hospitalization, one half did not have another AF diagnosis recorded prior to the stroke.[37] Thus, among patients with new-onset AF during the critical illness that seems to be "resolved," there may be opportunity to reduce post-critical illness stroke events through increased AF surveillance following hospital discharge.

In patients without contraindications to anticoagulation whose AF persists following hospital discharge, thromboembolism prophylaxis should be initiated in those not at low risk (as determined by using CHA_2DS_2VASc [congestive heart failure, hypertension, age $\geq$ 75 years, diabetes, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category] score).[70] Once the decision is made to initiate anticoagulation, we agree with the 2014 guideline recommendations of the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society regarding choice of anticoagulant medication.[38] The timing of prophylaxis initiation should be informed according to the patient's goals of care, renal function, bleeding risk, and medication interactions.[71] For patients who have no evidence of AF persistence following critical illness, measures should be instituted to facilitate detection of subclinical AF. Specifically, outpatient cardiac monitoring should be considered in patients without AF persistence but with elevated CHA_2DS_2VASc scores to identify patients who

TABLE 1] AF Rate and Rhythm Control Treatment Strategies During Critical Illness

Intervention and Dose	Class and Mechanism	Expected Efficacy[a]	Onset of Effect	Contraindications	Potential Adverse Effects
Esmolol: Load 500 μg/kg IV (may repeat); followed by 50-300 μg/kg/min[56]	Beta-blocker: blocks binding of catecholamines to beta$_1$-receptors, decreases AV node conduction, reduces arrhythmia induction and inotropy	Noncritical illness SVT with RVR: mean decrease in heart rate of 39 beats/min[57]	5 min[56]	Bradycardia; decompensated heart failure; 2nd or 3rd degree heart block; sick sinus syndrome; AF with an accessory pathway[56,58]	Bradyarrhythmia hypotension; heart block; hyperkalemia; hypoglycemia; bronchospasm (rare with beta$_1$-antagonist)[56,58]
Metoprolol tartrate: 2.5-5 mg IV every 2 to 5 min[58]	Same as above	Noncritical illness SVT: mean decrease in heart rate of 28 beats/min[59]	20 min[58]	Same as above	Same as above
Diltiazem: Load 0.25 mg/kg IV, followed by 5-15 mg/h[60]	Nondihydropyridine calcium channel blocker: inhibits L-type voltage-gated calcium channels, decreases AV node conduction, reduces inotropy	Critical illness SVT with RVR: mean decrease in heart rate of 44 beats/min after 4 h[46]	3 min[60]	Bradycardia; decompensated heart failure; 2nd or 3rd degree heart block; sick sinus syndrome; AF with an accessory pathway[60,61]	Bradyarrhythmia peripheral edema; hypotension; constipation[60,61]
Verapamil: Load 0.075-0.15 mg/kg IV, followed by 0.005 mg/kg/min[61]	Same as above	Noncritical illness AF or atrial flutter with RVR: mean decrease in heart rate of 45 beats/min[57]	10 min[61]	Same as above	Same as above
Digoxin: Load 0.25 mg IV, followed by repeat dosing (maximum 1.5 mg/24 h).[62] Dose lower in renal failure	Cardiac glycoside: inhibits Na-K ATPase increasing intracellular sodium and calcium, vagomimetic	Noncritical illness AF with RVR: mean decrease in heart rate of approximately 30 beats/min within 6 h of administration[54]	5-30 min[62]	Ventricular fibrillation[62]	Digoxin toxicity (monitor levels); dysrhythmias; increased myocardial oxygen demand[62]
Amiodarone: Load 150 mg IV over 10 min, followed by 1 mg/min for 6 h, followed by 0.5 mg/min for 18 h[63]	Class 3 antiarrhythmic: blocks adrenergic signaling and ion flow, extends refractory period, decreases AV node conduction, reduces membrane excitability	Critical illness AF or atrial flutter with RVR: mean decrease in heart rate of 37 beats/min[64] Noncritical illness AF: restoration of SR in 83% 20 h after administration[65]	8 h (mean time to SR)[65]	Bradycardia; Cardiogenic shock, 2nd or 3rd degree heart block; severe sinus node disorders[63]	Bradyarrhythmia ventricular arrhythmias; hypotension (IV formulation); organ toxicity (liver, thyroid, skin, and lung)[63]

(Continued)

TABLE 1 (*Continued*)

Intervention and Dose	Class and Mechanism	Expected Efficacy[a]	Onset of Effect	Contraindications	Potential Adverse Effects
Magnesium sulfate: 1-3 g over 10 min; repeat if no response in 15 min[66]	Electrolyte: blocks calcium channels and activates Na-K ATPase promoting resting polarization[67]	Combined critical and noncritical illness AF with RVR: 21.4% have resolution of RVR[66]	Within 30 min[66]	2nd or 3rd degree heart block[67]	Heart block; hypotension; CNS depression; hyporeflexia; respiratory depression[67]
Direct current cardioversion: QRS synchronized 120-200 J biphasic or 200 J monophasic	Electrical shock: electrical energy depolarizes all excitable membranes	Postoperative AF: 71% initial conversion to SR, 23% in SR after 24 h[39]	Instant	Digitalis toxicity	Embolic stroke, pain, skin burns, arrhythmias[68]

AF = atrial fibrillation; AV = atrioventricular; HR = heart rate; RVR = rapid ventricular rate; SR = sinus rhythm; SVT = supraventricular tachycardia.
[a]Studies of treatment efficacy of AF during critical illness are limited. Thus, inclusion of arrhythmia type (AF, atrial flutter, and SVT) and context (critical illness, noncritical illness, or postoperative) are included.

may benefit from anticoagulation, a strategy that has shown promise in patients following cryptogenic stroke.[72]

Prevention of AF

Prevention of new-onset AF in the ICU is an appealing strategy to potentially improve outcomes and mitigate the often-difficult short- and long-term management of critically ill patients who have AF with RVR. To date, few studies have analyzed prevention of AF in the general ICU setting. In a recent, prospective nonrandomized study, the administration of hydrocortisone in patients with septic shock was associated with lower rates of new-onset AF following propensity score matching.[73] Randomized trials have shown lower rates of new-onset AF following cardiac surgery in patients administered magnesium infusions, glucocorticoids, and BBs[23,55,74]; it is unknown whether these strategies are of benefit in a general ICU population. Specific therapies to reduce AF during critical illness cannot be recommended at this time.

Future Considerations

Future studies of AF in the ICU will help guide our ability to predict, prevent, and manage this frequent and potentially devastating arrhythmia. Improvements in technology to identify the timing and duration of AF in the ICU using automated detection algorithms and mining of large ICU electronic medical records will help us to understand the temporal association between risk factors and AF and potentially inform mechanisms (projectreporter.nih.gov [1R01HL136660-01]). Long-term AF detection techniques may also help to identify patients following ICU hospitalizations who are most likely to benefit from thromboembolism prophylaxis. Randomized trials to address gaps in our knowledge of acute rate and rhythm control therapies in the critically ill are ongoing, assessing the effect of magnesium infusions on AF with RVR in the ICU[75] and specific dosing strategies of amiodarone for AF during sepsis.[76] Further randomized trials are needed to identify the optimal rate or rhythm strategy for patients in the ICU and to clarify the differences, if present, between specific medications within these strategies.

Acknowledgments

Financial/nonfinancial disclosures: None declared.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References

1. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110(9):1042-1046.
2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98(10):946-952.
3. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology*. 1978;28(10):973-977.
4. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation*. 2016;133(5):484-492.
5. Moss TJ, Calland JF, Enfield KB, et al. New-onset atrial fibrillation in the critically ill. *Crit Care Med*. 2017;45(5):790-797.
6. Artucio H, Pereira M. Cardiac arrhythmias in critically ill patients: epidemiologic study. *Crit Care Med*. 1990;18(12):1383-1388.
7. Aldhoon B, Melenovsky V, Peichl P, Kautzner J. New insights into mechanisms of atrial fibrillation. *Physiol Res*. 2010;59(1):1-12.
8. Yue L, Feng J, Gaspo R, Li GR, Wang Z, Nattel S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. *Circ Res*. 1997;81(4):512-525.
9. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiol Rev*. 2011;91(1):265-325.
10. Krijthe BP, Heeringa J, Kors JA, et al. Serum potassium levels and the risk of atrial fibrillation: the Rotterdam Study. *Int J Cardiol*. 2013;168(6):5411-5415.
11. Lu YY, Cheng CC, Chen YC, Lin YK, Chen SA, Chen YJ. Electrolyte disturbances differentially regulate sinoatrial node and pulmonary vein electrical activity: a contribution to hypokalemia- or hyponatremia-induced atrial fibrillation. *Heart Rhythm*. 2016;13(3):781-788.
12. Khan AM, Lubitz SA, Sullivan LM, et al. Low serum magnesium and the development of atrial fibrillation in the community: the Framingham Heart Study. *Circulation*. 2013;127(1):33-38.
13. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation*. 1995;92(7):1954-1968.
14. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. *N Engl J Med*. 1982;306(17):1018-1022.
15. Brown AO, Orihuela CJ. Visualization of Streptococcus pneumoniae within cardiac microlesions and subsequent cardiac remodeling. *J Vis Exp*. 2015;(98).
16. Brown AO, Mann B, Gao G, et al. Streptococcus pneumoniae translocates into the myocardium and forms unique microlesions that disrupt cardiac function. *PLoS Pathog*. 2014;10(9):e1004383.
17. Reyes LF, Restrepo MI, Hinojosa CA, et al. Severe pneumococcal pneumonia causes acute cardiac toxicity and subsequent cardiac remodeling. *Am J Respir Crit Care Med*. 2017;196(5):609-620.
18. Watanabe H, Ma M, Washizuka T, et al. Thyroid hormone regulates mRNA expression and currents of ion channels in rat atrium. *Biochem Biophys Res Commun*. 2003;308(3):439-444.
19. Klein Klouwenberg PM, Frencken JF, Kuipers S, et al. Incidence, predictors, and outcomes of new-onset atrial fibrillation in critically ill patients with sepsis a cohort study. *Am J Respir Crit Care Med*. 2017;195(2):205-211.
20. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation*. 1997;96(4):1180-1184.
21. Mihm MJ, Yu F, Carnes CA, et al. Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation. *Circulation*. 2001;104(2):174-180.
22. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004;292(20):2471-2477.
23. Jacob KA, Nathoe HM, Dieleman JM, van Osch D, Kluin J, van Dijk D. Inflammation in new-onset atrial fibrillation after cardiac surgery: a systematic review. *Eur J Clin Invest*. 2014;44(4):402-428.
24. Seguin P, Laviolle B, Maurice A, Leclercq C, Mallédant Y. Atrial fibrillation in trauma patients requiring intensive care. *Intensive Care Med*. 2006;32(3):398-404.
25. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA*. 2011;306(20):2248-2254.
26. Walkey AJ, Greiner MA, Heckbert SR, et al. Atrial fibrillation among Medicare beneficiaries hospitalized with sepsis: incidence and risk factors. *Am Heart J*. 2013;165(6):949-955.e943.
27. Vieillard-Baron A, Boyd J. Non-antiarrhythmic interventions in new onset and paroxysmal sepsis-related atrial fibrillation. *Intensive Care Med*. 2017.
28. Seemann A, Boissier F, Razazi K, et al. New-onset supraventricular arrhythmia during septic shock: prevalence, risk factors and prognosis. *Annals of Intensive Care*. 2015;5.
29. Shaver CM, Chen W, Janz DR, et al. Atrial Fibrillation Is an Independent Predictor of Mortality in Critically Ill Patients. *Crit Care Med*. 2015;43(10):2104-2111.
30. Landesberg G, Gilon D, Meroz Y, et al. Diastolic dysfunction and mortality in severe sepsis and septic shock. *Eur Heart J*. 2012;33(7):895-903.
31. Clark DM, Plumb VJ, Epstein AE, Kay GN. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol*. 1997;30(4):1039-1045.
32. Kanji S, Williamson DR, Yaghchi BM, Albert M, McIntyre L. Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. *J Crit Care*. 2012;27(3):326.e321-326.e328.
33. Chen AY, Sokol SS, Kress JP, Lat I. New-onset atrial fibrillation is an independent predictor of mortality in medical intensive care unit patients. *Ann Pharmacother*. 2015;49(5):523-527.
34. Walkey AJ, McManus D. When rhythm changes cause the blues: new-onset atrial fibrillation during sepsis. *Am J Respir Crit Care Med*. 2017;195(2):152-154.
35. Meierhenrich R, Steinhilber E, Eggermann C, et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. *Crit Care*. 2010;14(3):R108.
36. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology. *Circulation*. 2001;104(17):2118-2150.
37. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest*. 2014;146(5):1187-1195.
38. 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;64(21):e1-e76.
39. Arrigo M, Jaeger N, Seifert B, Spahn DR, Bettex D, Rudiger A. Disappointing Success of Electrical Cardioversion for New-Onset Atrial Fibrillation in Cardiosurgical ICU Patients. *Crit Care Med*. 2015;43(11):2354-2359.
40. Abrams J, Allen J, Allin D, et al. Efficacy and safety of esmolol vs propranolol in the treatment of supraventricular tachyarrhythmias: a multicenter double-blind clinical trial. *Am Heart J*. 1985;110(5):913-922.
41. Ang EL, Chan WL, Cleland JG, et al. Placebo controlled trial of xamoterol versus digoxin in chronic atrial fibrillation. *Br Heart J*. 1990;64(4):256-260.

42. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *Jama*. 2003;289(7):871-878.

43. Eisen A, Ruff CT, Braunwald E, et al. Digoxin Use and Subsequent Clinical Outcomes in Patients With Atrial Fibrillation With or Without Heart Failure in the ENGAGE AF-TIMI 48 Trial. *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease*. 2017;6(7):e006035.

44. Davey MJ, Teubner D. A randomized controlled trial of magnesium sulfate, in addition to usual care, for rate control in atrial fibrillation. *Ann Emerg Med*. 2005;45(4):347-353.

45. Zimetbaum P. Antiarrhythmic drug therapy for atrial fibrillation. *Circulation*. 2012;125(2):381-389.

46. Delle Karth G, Geppert A, Neunteufl T, et al. Amiodarone versus diltiazem for rate control in critically ill patients with atrial tachyarrhythmias. *Crit Care Med*. 2001;29(6):1149-1153.

47. Hou ZY, Chang MS, Chen CY, et al. Acute treatment of recent-onset atrial fibrillation and flutter with a tailored dosing regimen of intravenous amiodarone. A randomized, digoxin-controlled study. *Eur Heart J*. 1995;16(4):521-528.

48. Ott MC, Khoor A, Leventhal JP, Paterick TE, Burger CD. Pulmonary toxicity in patients receiving low-dose amiodarone. *Chest*. 2003;123(2):646-651.

49. Chean CS, McAuley D, Gordon A, Welters ID. Current practice in the management of new-onset atrial fibrillation in critically ill patients: A UK-wide survey. *PeerJ*. 2017;2017(9).

50. Walkey AJ, Evans SR, Winter MR, Benjamin EJ. Practice patterns and outcomes of treatments for atrial fibrillation during sepsis a propensity-matched cohort study. *Chest*. 2016;149(1):74-83.

51. Moskowitz A, Chen KP, Cooper AZ, Chahin A, Ghassemi MM, Celi LA. Management of Atrial Fibrillation with Rapid Ventricular Response in the Intensive Care Unit: A Secondary Analysis of Electronic Health Record Data. *Shock*. 2017;48(4):436-440.

52. Morelli A, Singer M, Ranieri VM, et al. Heart rate reduction with esmolol is associated with improved arterial elastance in patients with septic shock: a prospective observational study. *Intensive Care Med*. 2016;42(10):1528-1534.

53. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. *Jama*. 2013;310(16):1683-1691.

54. Siu CW, Lau CP, Lee WL, Lam KF, Tse HF. Intravenous diltiazem is superior to intravenous amiodarone or digoxin for achieving ventricular rate control in patients with acute uncomplicated atrial fibrillation. *Crit Care Med*. 2009;37(7):2174-2179; quiz 2180.

55. Onalan O, Crystal E, Daoulah A, Lau C, Crystal A, Lashevsky I. Meta-analysis of magnesium therapy for the acute management of rapid atrial fibrillation. *Am J Cardiol*. 2007;99(12):1726-1732.

56. Esmolol Hydrochloride. *Micromedex Solutions Truven Health Analytics, Inc*. http://www.micromedexsolutions.com. Accessed March 5, 2018.

57. Platia EV, Michelson EL, Porterfield JK, Das G. Esmolol versus verapamil in the acute treatment of atrial fibrillation or atrial flutter. *Am J Cardiol*. 1989;63(13):925-929.

58. Metoprolol tartrate. *Micromedex Solutions Truven Health Analytics, Inc*. http://www.micromedexsolutions.com. Accessed March 5, 2018.

59. Amsterdam EA, Kulcyski J, Ridgeway MG. Efficacy of cardioselective beta-adrenergic blockade with intravenously administered metoprolol in the treatment of supraventricular tachyarrhythmias. *J Clin Pharmacol*. 1991;31(8):714-718.

60. Diltiazem hydrochloride. *Micromedex Solutions Truven Health Analytics, Inc*. http://www.micromedexsolutions.com. Accessed March 5, 2018.

61. Verapamil hydrochloride. http://www.micromedexsolutions.com. Accessed March 5, 2018.

62. Digoxin. http://www.micromedexsolutions.com. Accessed March 6, 2018.

63. Amiodarone hydrochloride. http://www.micromedexsolutions.com. Accessed March 5, 2018.

64. Clemo HF, Wood MA, Gilligan DM, Ellenbogen KA. Intravenous amiodarone for acute heart rate control in the critically ill patient with atrial tachyarrhythmias. *Am J Cardiol*. 1998;81(5):594-598.

65. Cybulski J, Kulakowski P, Budaj A, et al. Intravenous amiodarone for cardioversion of recent-onset atrial fibrillation. *Clin Cardiol*. 2003;26(7):329-335.

66. Ho KM, Sheridan DJ, Paterson T. Use of intravenous magnesium to treat acute onset atrial fibrillation: a meta-analysis. *Heart*. 2007;93(11):1433-1440.

67. Magnesium sulfate. http://www.micromedexsolutions.com. Accessed March 6, 2018.

68. Resnekov L, McDonald L. Complications in 220 patients with cardiac dysrhythmias treated by phased direct current shock, and indications for electroconversion. *Br Heart J*. 1967;29(6):926-936.

69. Walkey AJ, Quinn EK, Winter MR, McManus DD, Benjamin EJ. Practice patterns and outcomes associated with use of anticoagulation among patients with atrial fibrillation during sepsis. *JAMA Cardiol*. 2016;1(6):682-690.

70. Lip GY, Lane DA. Modern management of atrial fibrillation requires initial identification of "low-risk" patients using the CHA2DS2-VASc score, and not focusing on "high-risk" prediction. *Circ J*. Vol. 78. Japan2014:1843-1845.

71. Walkey AJ, Hogarth K, Lip GYH. Optimizing atrial fibrillation management from ICU and beyond. *Chest*. 2015;148(4):859-864.

72. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014;370(26):2478-2486.

73. Launey Y, Lasocki S, Asehnoune K, et al. Impact of low-dose hydrocortisone on the incidence of atrial fibrillation in patients with septic shock. *J Intensive Care Med*. 2017. 885066617696847.

74. Frendl G, Sodickson AC, Chung MK, et al. 2014 AATS guidelines for the prevention and management of peri-operative atrial fibrillation and flutter (POAF) for thoracic surgical procedures. *J Thoracic Cardiovasc Surg*. 2014;148(3):e153-e193.

75. National Institutes of Health Clinical Center. Magnesium sulphate for treatment of new onset atrial fibrillation in medical intensive care unit patient (EMSAF). NCT01049464. ClinicalTrials.gov. Bethesda, MD: National Institutes of Health; 2018. http://clinicaltrials.gov/ct2/show/NCT01049464. Updated March 29, 2016.

76. National Institutes of Health Clinical Center. Use of amiodarone in atrial fibrillation associated with severe sepsis or septic shock. NCT02668432. ClinicalTrials.gov. Bethesda, MD: National Institutes of Health; 2018. http://clinicaltrials.gov/ct2/show/NCT02668432. Updated May 30, 2017.