Chapter 9
Anticoagulation for Atrial Fibrillation in the Emergency Department or Observation Unit

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Introduction

Patients with atrial fibrillation (AF) are at an increased risk of thromboembolic stroke, and anticoagulation to reduce the risk of stroke and other thromboembolic events has become a standard part of the management of this arrhythmia. The benefit of anticoagulation must be weighed against the increased risk of bleeding, and this is an important part of the initial management of most patients with newly diagnosed AF. Historically, heparin followed by the vitamin K antagonists such as warfarin was the treatment of choice, but recently a number of novel oral anticoagulants, or non-vitamin K antagonist oral anticoagulants (NOACs), have been developed which offer simplified dosing and perhaps some benefit over warfarin. The decision to start anticoagulation in the emergency department (ED) or observation unit (OU) requires thoughtful consideration of all of these factors [1].

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Pathophysiology of Thromboembolism in Atrial Fibrillation

The precise mechanisms of thrombus formation in AF are not known, but it is hypothesized that stasis of blood flow, hypercoagulability, and damaged endothelium may all contribute. Atrial fibrillation is characterized by the disorganized and erratic contraction and relaxation of the myocytes of both atria. As a result the atria do not contract in an organized and hemodynamically efficient manner leading to stasis of blood and thrombus formation, most often in the left atrial appendage. A left atrial thrombus may then dislodge and embolize to the cerebral circulation causing an ischemic stroke, or, less commonly, to the systemic circulation causing infarction of the limbs or other organs.

Anticoagulation to Prevent Thromboembolism

The 2014 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for the management of nonvalvular atrial fibrillation (NVAF) recommend long-term anticoagulation with warfarin (class 1A recommendation) or a NOAC (class 1B recommendation) in patients with history of prior stroke/transient ischemic attack (TIA) or a CHA_2DS_2-VASc score ≥ 2 [2]. They also recommend that antithrombotic therapy be based on "shared decision making, discussion of the risks of stroke and bleeding, and patient preferences." Starting anticoagulation for stroke reduction in AF is not an emergency, as the day-to-day risk of stroke is very small, and the decision to start anticoagulation should be shared between the patient, ED/OU physician, and outpatient physicians. An exception to this is the patient who will undergo electrical or pharmacologic cardioversion; in this case anticoagulation should be started prior to the cardioversion to reduce the risk of stroke when sinus rhythm is restored [3].

This chapter primarily concerns patients with nonvalvular atrial fibrillation. Valvular AF refers to patients with prosthetic heart valves, mitral stenosis, or any severe valvular disease likely to require imminent repair. These patients were excluded from most major trials of AF, and distinct guidelines have been published for the management of prosthetic heart valves and mitral stenosis [4, 5]. Many patients with valvular AF do require anticoagulation, and, for the time being, heparin or warfarin should be used exclusively. The NOACs should be avoided in these patients, as only dabigatran has been evaluated for this purpose, and it did not adequately protect against stroke when compared with warfarin [6].

The decision to start an anticoagulant for a patient with new NVAF in the OU can be safe and effective if the following four factors are considered:

1. Risk of thromboembolism/stroke
2. Risk of bleeding
3. Choice of anticoagulant
4. Practical considerations

Risk of Thromboembolism/Stroke

Certain patients with NVAF are at higher risk of stroke than others, and stratification of patient risk has proven useful in guiding the decision to start anticoagulation. The preferred method is the CHA_2DS_2-VASc score, a recently developed model that has superseded the better-known $CHADS_2$ score, as it is more predictive and better able to stratify risk among patients with lower scores (Tables 9.1 and 9.2) [7, 8].

Comparing the two scoring systems, it can be seen that the CHA_2DS_2-VASc better distinguishes the risk among patients with scores ≤2 (0 correlates with 0 % risk, 1 with 1.3 %, 2 with 2.2 %), whereas a $CHADS_2$ score of 0 connotes a 1.9 % risk. Other notable features of the CHA_2DS_2-VASc score include a score of 2 or greater for all patients who have a history of stroke or TIA and for all patients aged ≥75 years; in both of these groups, anticoagulation is strongly recommended, but it must be kept in mind that both of these groups are also at increased risk of bleeding.

Table 9.1 The $CHADS_2$ and CHA_2DS_2-VASc scores

$CHADS_2$	Risk factor	CHA_2DS_2-VASc
1	Congestive HF	1
1	Hypertension	1
1	Age ⩾75	2
1	Diabetes mellitus	1
2	History of stroke/ TIA	2
	Vascular disease[a]	1
	Age 65–74	1
	Sex (female)	1
6	*Maximum score*	*9*

HF heart failure, *TIA* transient ischemic attack
[a]Myocardial infarction, peripheral arterial disease, or aortic plaque

Table 9.2 Adjusted risk of stroke/thromboembolism stratified by $CHADS_2$ and CHA_2DS_2-VASc scores

$CHADS_2$ score	Annual risk of stroke (%) [9]	CHA_2DS_2-VASc score	Annual risk of thromboembolism (%) [10]
0	1.9	0	0.0
1	2.8	1	1.3
2	4.0	2	2.2
3	5.9	3	3.2
4	8.5	4	4.0
5	12.5	5	6.7
6	18.2	6	9.8
		7	9.6
		8	6.7
		9	15.2

Anticoagulation is strongly recommended in patients with CHA_2DS_2-VASc $\geqslant 2$, as in these patients, the benefit of anticoagulation outweighs the risk of bleeding and intracranial hemorrhage; this holds true for both warfarin and the NOACs [11–13]. Further support for this recommendation comes from meta-analyses of the major trials comparing warfarin with placebo which have demonstrated that warfarin significantly reduces the risk of all stroke, disabling stroke, and all-cause mortality [14]. In general, oral anticoagulation reduces the risk of ischemic stroke by about two thirds; thus the absolute risk reduction depends on the patient's baseline risk [15].

Whether anticoagulation benefits patients with a CHA_2DS_2-VASc score of 1 is less clear, and there is variability in practice. The AHA/ACC does not recommend for or against anticoagulation in this group, and thus these patients require careful individualized decision-making. The true risk of stroke in these patients is uncertain; a number of recent retrospective cohorts have cited estimates of annual risk varying from as low as <1 % to as high as 3.5 % [16, 17]. This discrepancy seems to be in part due to the definition of "stroke" used and to variability in the actual risk imparted by the various risk factors that can give a patient a CHA_2DS_2-VASc score of 1, and prospective studies are needed in order to better define these patients' true risk. In patients with a CHA_2DS_2-VASc score of 1, consideration of the patient's risk of bleeding is imperative, and it may be advisable to defer the initiation of anticoagulation to the outpatient setting, where a patient's long-term physicians can more thoroughly discuss the matter with the patient.

The risk of stroke with a CHA_2DS_2-VASc score of 0 is minimal, and there is a general consensus that anticoagulation does not offer a meaningful benefit. These patients should be followed closely for the development of any conditions that would increase their CHA_2DS_2-VASc score and thus prompt consideration of anticoagulation.

Risk of Bleeding

The inevitable consequence of anticoagulation with warfarin and the NOACs is an increased risk of bleeding. A patient's individual risk of hemorrhage should always be considered prior to starting an anticoagulant.

The average rate of major hemorrhage in patients taking warfarin has been estimated as 1–3 % per year in the major clinical trials; community-based cohorts have shown a slightly higher rate of 3–4 % with a significantly increased risk during the first 30 days of therapy (as high as 11.8 % per person-year) [18]. Intracranial hemorrhage (ICH) is the most feared complication of anticoagulation therapy. Warfarin increases the risk of ICH by two to five times, and higher degrees of anticoagulation are associated with increased rates of hemorrhage and death [19, 20]. Estimates of the incidence of ICH vary, but one large community-based cohort found the incidence of ICH to be 0.23 per 100 person-years among those patients not taking

warfarin and 0.46 per 100 person-years among those taking warfarin [21]. The major NOAC trials have all demonstrated a reduced rate of ICH with NOACs as compared with warfarin, with rates ranging from 0.3 to 0.8 % per year. Thus, while ICH is a serious and often deadly or disabling consequence of anticoagulation, it occurs at a significantly lower rate than ischemic stroke in patients with CHA_2DS_2-VASc $\geqslant 2$ and does not negate the benefit of anticoagulation in these patients.

The rates of bleeding correlate with a number of risk factors, including increasing age, history of gastrointestinal bleeding, concurrent use of antiplatelet agents, uncontrolled hypertension, chronic kidney disease, chronic liver disease, history of uncontrolled international normalized ratio (INR), and increasing $CHADS_2$ score, among others [22]. A number of risk assessments such as the HAS-BLED and RIETE scores have been developed with the intent of predicting an individual patient's risk of hemorrhage with anticoagulation, but they unfortunately have poor predictive value and have not been prospectively validated [23]. Therefore, none of them are ideal for routine clinical use. When estimating a patient's risk of bleeding with anticoagulation, clinical judgment and consideration of the risk factors above are the standard.

Choosing an Anticoagulant

For decades warfarin, with or without a heparin "bridge," has been the preferred oral anticoagulant for thromboprophylaxis in patients with atrial fibrillation, but since 2010 several direct-acting oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) have been developed and approved by the US Food and Drug Administration (FDA). Patients and providers now face a choice and must weigh the risks and benefits of the available drugs when choosing an anticoagulant (Table 9.3).

Warfarin

Warfarin is a vitamin K antagonist that leads to production of hemostatically inactive forms of the clotting factors II, VII, IX, and X. It has been in regular use since the 1950s and its efficacy is well established [14]. Warfarin has a narrow therapeutic window and must be closely monitored to ensure that the patient is neither over- nor under-anticoagulated. This requires regular laboratory INR checks, every few days upon initiating warfarin and at least every few weeks thereafter. The goal INR is typically 2–3. Most health centers have "Coumadin clinics" with staff dedicated to monitoring and titrating patients' warfarin, but, despite this, the average time spent in the therapeutic range for most patients is only 50–66 % [24, 25]. This puts patients at increased risk of both treatment failure and bleeding, and warfarin is among the top ten medications associated with serious adverse events as monitored by the FDA. Bleeding complications

Table 9.3 Summary of anticoagulants for nonvalvular atrial fibrillation

Drug	Mechanism of action	Dosing	Renal dosing	Monitoring/ safety	Comments
Warfarin (Coumadin)	Vitamin K antagonist; inhibits production of factors II, VII, IX, and X	2.5–5 mg daily, use lower dose if liver disease, CHF, elderly, poor nutrition, high risk of bleeding Adjust dose to meet INR goal	No adjustment necessary; increased risk of bleeding in patients with advanced CKD Preferred anticoagulant in patients with severe CKD or ESRD on dialysis	Check INR every 3–4 days initially; may reduce checks to once monthly once stable regimen is achieved	Patient must be able to adhere to frequent INR checks Patient should consume a steady amount of vitamin K in the diet
Dabigatran (Pradaxa)	Direct thrombin inhibitor	150 mg twice daily	CrCl 30–50 ml/ min: reduce to 75 mg twice daily only if concurrently taking ketoconazole or dronedarone CrCl <30 ml/ min: avoid use	No routine monitoring of anticoagulation necessary Monitor renal function annually	May increase the risk of major GI bleeding compared with warfarin Avoid in patients >80 years of age Avoid in patients taking Pgp inducers or inhibitors
Rivaroxaban (Xarelto)	Direct factor Xa inhibitor	20 mg once daily with evening meal	CrCl 30–50 ml/ min: Reduce dose to 15 mg daily CrCl <30 ml/ min: avoid use	No routine monitoring of anticoagulation necessary Monitor renal function annually	May reduce ICH and fatal bleeding compared with warfarin Avoid in patients concurrently taking medications that are Pgp and strong CYP3A4 inhibitors

(continued)

Table 9.3 (continued)

Drug	Mechanism of action	Dosing	Renal dosing	Monitoring/ safety	Comments
Apixaban (Eliquis)	Direct factor Xa inhibitor	5 mg twice daily, unless patient has any two of the following: age ≥80 years, weight ≤60 kg, creatinine ≥1.5 mg/dl, then decrease to 2.5 mg twice daily	SCr 1.5–2.5 mg/dl: reduce dose to 2.5 mg twice daily if age ≥80 years or weight ≤60 kg SCr >2.5 mg/dl or CrCl ≤25 ml/min: avoid use	No routine monitoring of anticoagulation necessary Monitor renal function annually	May reduce stroke/SEE, major bleeding, and death compared with warfarin In patients taking strong inhibitors of CYP3A4 and Pgp concomitantly, reduce the 5 mg twice-daily dose by 50%, and if already on 2.5 mg twice-daily dose, then avoid coadministration with the strong dual inhibitors
Edoxaban (Savaysa)	Direct factor Xa inhibitor	60 mg once daily in patients with CrCl 51–95 ml/min. Do not use in patients with normal renal function	CrCl >95 ml/min: Avoid use CrCl 51-95 ml/min: no adjustment necessary CrCl 15-50 ml/min: reduce dose to 30 mg daily CrCl <15 ml/min: avoid use	No routine monitoring of anticoagulation necessary Monitor renal function annually	May reduce major bleeding and ICH compared with warfarin.

CHF congestive heart failure, *INR* international normalized ratio, *CKD* chronic kidney disease, *CrCl* creatinine clearance, *GI* gastrointestinal, *Pgp* P-glycoprotein, *ICH* intracranial hemorrhage, *SCr* serum creatinine, *SEE* systemic embolic event

associated with warfarin account for about 29,000 emergency department visits each year [26].

Warfarin is subject to many drug-drug interactions, most importantly antibiotics and a number of drugs that affect warfarin metabolism. All concurrent medications and any new medications should be carefully reviewed for interactions in patients taking warfarin. Finally, the vitamin K content of the diet significantly impacts the effect of warfarin, and all patients should be counseled about maintaining a steady intake of vitamin K.

Despite these limitations, many patients do well with warfarin and maintain stable INRs with monthly laboratory visits. INR correlates well with the anticoagulant effect of warfarin, allowing clinicians both to monitor adherence and to assess a patient's risk of thrombosis or bleeding. This is especially useful in cases of treatment failure or significant bleeding events. Reversal of warfarin's anticoagulant effect is sometimes desired in cases of bleeding or prior to invasive procedures, and protocols for reversal with vitamin K, plasma transfusion, and prothrombin complex concentrates are well established.

Heparin and Low-Molecular-Weight Heparins

The anticoagulant effect of warfarin is not immediate, and three to seven days' administration is often required for the INR to reach the therapeutic range. For those patients at high risk of thromboembolism and low risk of bleeding, it may be reasonable to provide a heparin or low-molecular-weight heparin (LMWH) "bridge" concurrently with warfarin until the INR is therapeutic. In patients without a prior history of thromboembolism, the daily risk of stroke is very low, and thus a heparin or LMWH bridge is often not prescribed. Patients at higher risk of stroke, such as those with a prior history of thromboembolism, a mechanical valve, or mitral stenosis, are generally bridged with heparin or LMWH as long as their risk of hemorrhage is not too great. This strategy has not been prospectively studied to any great extent, and thus, when deciding whether to bridge with a parenteral anticoagulant, each individual's likelihood of benefit should be weighed against his or her risk of hemorrhage [2]. Low-molecular-weight heparin is administered subcutaneously and is often preferred to intravenous unfractionated heparin, as it does not generally require laboratory monitoring and may be administered by the patient at home. However, in patients with significant renal dysfunction or extreme obesity, LMWH dosing can be more challenging than unfractionated heparin. Unfractionated heparin and LMWH have demonstrated equivalence in achieving short-term anticoagulation in patients with atrial fibrillation [27]. These considerations apply not only when initiating warfarin but also when an oral anticoagulant is being held in preparation for an invasive procedure, though recent data have called routine use of bridging into question. Bridging is not required when starting NOACs, as their onset of action is a matter of a few hours.

Dabigatran

Dabigatran is a direct thrombin inhibitor and was the first non-vitamin K oral anticoagulant approved for the prevention of thromboembolism in NVAF. The RE-LY trial compared dabigatran to warfarin and showed that the 150 mg twice-daily dose of dabigatran reduced the primary outcome of stroke or systemic embolism by one third; the rates of intracranial hemorrhage and fatal bleeding were also reduced, but there was an increased rate of gastrointestinal bleeding with dabigatran (1.6 % per year versus 1.0 % per year with warfarin) [28]. There was no significant difference in mortality between the two groups. This trial and a subsequent meta-analysis have demonstrated that there may be a slightly higher risk of myocardial infarction (MI) with dabigatran as compared with warfarin, and this should be taken into consideration when considering its use [29]. Certain subgroups are at an increased risk of bleeding complications, most notably African-Americans and those with chronic kidney disease [30].

Dabigatran is hepatically metabolized and renally cleared, and patients with severe liver disease or creatinine clearance (CrCl) <30 ml/min were excluded from the RE-LY trial. A reduced dose, 75 mg twice daily, has been approved for use in patients with CrCl 15–30 ml/min, but this dose has not been prospectively tested, and warfarin is probably a safer anticoagulant in this population [31]. Dabigatran should be avoided in all patients with CrCl <15 ml/min, in those on dialysis, and in those with advanced liver disease. Its use should also be avoided in the presence of P-glycoprotein (Pgp) inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) and inhibitors (e.g., verapamil, ketoconazole, amiodarone, dronedarone, quinidine, clarithromycin).

A distinct advantage of dabigatran and all the NOACs is that no routine laboratory monitoring is required; the unfortunate corollary is that there is no widely available laboratory test that measures the anticoagulant effect of dabigatran. Most reliable is the dilute thrombin time, but this assay is not commonly available and varies between laboratories [32]. A normal activated partial thromboplastin time (aPTT) rules out a clinically significant effect of dabigatran, but the aPTT does not linearly correlate with dabigatran levels.

Rivaroxaban

Rivaroxaban was the first factor Xa (FXa) inhibitor approved to prevent stroke and embolism in atrial fibrillation. The ROCKET-AF trial showed that rivaroxaban 20 mg once daily was noninferior to warfarin in the prevention of stroke and systemic embolism [33]. There was a reduction in the rate of intracranial hemorrhage and fatal bleeding and no change in the rates of clinically relevant bleeding, MI, or death.

Rivaroxaban is metabolized by the liver and principally excreted by the kidneys. It should be avoided in patients with severe liver or end-stage kidney disease. A

reduced dose of 15 mg once daily has been approved for patients with CrCl 15–50 ml/min, but caution should be used in patients with CrCl <30 ml/min, as rivaroxaban has not been prospectively evaluated in this group. Rivaroxaban is a substrate of both CYP3A4 and Pgp and should be avoided when a patient's medical regimen includes medications that inhibit both of these concurrently. There is no laboratory test approved to monitor the anticoagulant effect of rivaroxaban, although a normal INR can rule out clinically significant levels of the drug [32]. Assays for anti-Xa activity can correlate with rivaroxaban activity when the assay is calibrated to the drug itself.

Apixaban

Apixaban is an FXa inhibitor that demonstrated superior efficacy and safety when compared with warfarin in the ARISTOTLE trial [34]. Apixaban achieved a reduction in stroke or systemic embolism, major bleeding, intracranial hemorrhage, and death. The standard dose of 5 mg twice daily should be reduced to 2.5 mg twice daily in patients with two or more of the following factors: age ≥80 years, weight ≤60 kg, or a serum creatinine ≥1.5 mg/dl. Apixaban should be avoided in patients with creatinine >2.5 mg/dl or with CrCl <25 ml/min, as these patients were excluded from the major trials of the drug. The FDA has recently approved apixaban for use in patients with end-stage renal disease on stable hemodialysis, but the 2014 ACC/AHA guidelines do not support this recommendation due to a lack of experience with the drug in these patients. In patients taking concomitant strong inhibitors of the CYP3A4 and Pgp systems, the 5 mg twice-daily dose should be decreased by 50 %, and the 2.5 mg twice-daily dose should be avoided in favor of warfarin. Apixaban activity can be determined by an anti-Xa activity assay calibrated to apixaban, but INR and PTT do not reliably reflect apixaban activity.

Edoxaban

Edoxaban is the most recently approved FXa inhibitor for thromboprophylaxis in atrial fibrillation. It was compared with warfarin in the ENGAGE AF-TIMI 48 trial and demonstrated similar efficacy to warfarin with fewer major bleeding events, intracranial hemorrhages, and cardiovascular deaths [35]. It should be used at a 60 mg once-daily dose in patients with CrCl 51–95 ml/min and at 30 mg once daily for CrCl 15–50 ml/min. Note that, per the FDA, it should be avoided in patients with normal renal function (CrCL >95 ml/min), as these patients experienced an increased rate of stroke and thromboembolism in the trial. As with all NOACs, it should not be used in patients with severe liver dysfunction. Edoxaban is best measured by anti-Xa activity calibrated to either heparin or edoxaban [36] (Table 9.3).

Antiplatelet Agents

Aspirin and clopidogrel have been studied as alternatives to anticoagulants for the prevention of stroke in atrial fibrillation, but they have poor efficacy with a similar or greater risk of bleeding [15]. Antiplatelet agents should not be considered adequate prophylaxis against stroke and systemic embolism in patients with atrial fibrillation. The addition of an anticoagulant to antiplatelet therapy in patients with coronary artery disease and atrial fibrillation is known to increase the risk of bleeding, and a benefit to warfarin plus aspirin over warfarin alone has not been demonstrated [37]. Patients with atrial fibrillation who have undergone recent percutaneous coronary intervention are at an even higher risk of bleeding if warfarin is added to aspirin and a $P2Y_{12}$ inhibitor such as clopidogrel ("triple therapy"); in these cases it may be preferable to omit aspirin from the regimen to reduce the risk of bleeding [38]. Overall, there is little evidence to guide decision-making when patients require both an anticoagulant and antiplatelet medications, and these cases should be considered on a patient-by-patient basis in consultation with the patient's longitudinal physicians [39, 40].

Practical Considerations

Because anticoagulation for the prevention of thromboembolism in AF is generally not urgent, it is prudent to carefully consider the practical and long-term implications of starting a patient on anticoagulation in the ED or OU.

Decision to Anticoagulate

For some patients the decision to start anticoagulation will not be straightforward, and in these cases consulting with the outpatient physicians prior to starting an anticoagulant can be helpful. Such patients include those at marginal risk of thromboembolism (CHA_2DS_2-VASc of 1), those at high risk of bleeding, and those on interacting medications, especially dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ inhibitor) which significantly increases the risk of bleeding with an oral anticoagulant [41]. Some patients may prefer to discuss starting an anticoagulant with their primary care physician or cardiologist, and this is a reasonable option as long as there is no evidence of an intracardiac thrombus on echocardiography and no plan for cardioversion.

Choice of Anticoagulant

The recent development of the NOACs as alternatives to warfarin therapy demands that the physician and patient be informed and thoughtful when choosing an oral anticoagulant. Many physicians are comfortable with warfarin given its many

years on the market, the ability to monitor levels by INR, and the widespread availability of reversal agents. Drawbacks include problematic drug-drug and drug-food interactions and the need for frequent laboratory visits to monitor the INR. The NOACs offer fewer drug interactions, no dietary restrictions, and no need for routine laboratory monitoring. Furthermore, in some cases they appear to have superior safety profiles when compared with warfarin. These drugs are, however, more expensive than warfarin, and some clinicians are hesitant to use them due to the limited amount of long-term safety data and the lack of reversal agents in case of emergencies. Patients prescribed NOACs should also be aware that missing even a single dose results in loss of anticoagulant effect and puts them at increased risk of stroke. Finally, it is generally not necessary to "bridge" a patient with a parenteral anticoagulant such as heparin or LMWH when initiating a NOAC for NVAF. Bridging may be considered when starting warfarin in a patient at high risk of stroke, with evidence of active thrombosis, or with valvular AF, but is generally not necessary in nonvalvular AF with NOACs which take effect within a couple of hours.

Patient Follow-Up

If a patient is started on oral anticoagulation for new AF in the ED/OU, appropriate outpatient follow-up must be arranged. For patients on warfarin, this includes an INR check 3–4 days after initiation and a visit with the provider who will monitor the INR. Any patient prescribed a NOAC should have an outpatient appointment to monitor for signs of bleeding, but no routine laboratory monitoring is necessary.

Conclusion

Atrial fibrillation is an increasingly prevalent and costly disease. Hospitalizations for AF in the United States increased by 23 % between 2000 and 2010, and three quarters of the $6.7 billion spent on AF care annually is attributed to these hospitalizations [42]. The thoughtful and timely initiation of anticoagulation in the ED or OU could have a substantial impact on these figures by avoiding unnecessary admissions and increasing adherence to the anticoagulation guidelines for patients with atrial fibrillation.

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