

Approach to and Management of the Acute Stroke Patient with Atrial Fibrillation: A Literature Review

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Stroke remains an increasing worldwide cause of disability and mortality, and it is the second leading cause of death in industrialized countries.¹ Patients with atrial fibrillation form a unique group with increased risk of cardioembolic stroke. Despite the widespread application of the National Institutes of Health stroke scale and guidelines,^{2,3} patients with atrial fibrillation represent a clinically challenging group that deserves a special approach during the acute stroke phase.

The mechanism of stroke in these patients is either cardioembolic [especially with an international normalized ratio (INR) < 2.0] or hemorrhagic (especially with INR > 5.0)^{4,5} (Figure 1). Atrial fibrillation with valvular heart disease significantly increases the risk for ischemic stroke. Specifically, patients with mitral stenosis who develop atrial fibrillation increase their risk of cardioembolism by 3 to 7 times.⁶ Many patients with atrial fibrillation still develop ischemic or hemorrhagic stroke despite appropriate use of anticoagulation. Prior stroke, transient ischemic attacks, congestive heart failure, hypertension, age > 75, and diabetes mellitus are all well-established risk factors for the development of stroke in patients with atrial fibrillation.^{7,8} The CHADS-2 score is the most widely studied and clinically used method for stratifying patients with nonrheumatic atrial fibrillation.⁸ In our review, we present the most recent clinical guidelines and trends for the approach to and management of this patient group. *Journal of Hospital Medicine* 2008;3:326–332. © 2008 Society of Hospital Medicine.

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INITIAL EVALUATION

The approach to patients with acute stroke symptoms should always start with the stabilization of the airway, breathing, and circulation. A fast clinical investigation for possible “mimickers” of an acute stroke (head trauma, migraines, epilepsy, infection, hypoglycemia, other metabolic derangements, and intoxications) is the next step. The history and physical examination should be guided by the National Institutes of Health stroke scale, which has been widely accepted by the American Stroke Association (ASA), the American Academy of Neurology, and the National Institute of Neurological Disorders and Stroke.^{2,9} Strict control of electrolytes, glucose, and fever, management of blood pressure depending on the type of stroke, and prophylaxis for deep vein thrombosis/pulmonary embolism, aspiration, dehydration, hypoxemia, malnutrition, and pressure sores should be initiated.^{9,10} All patients with suspected acute stroke must be promptly assessed for thrombolytic therapy on the basis of the time since onset of symptoms and the National

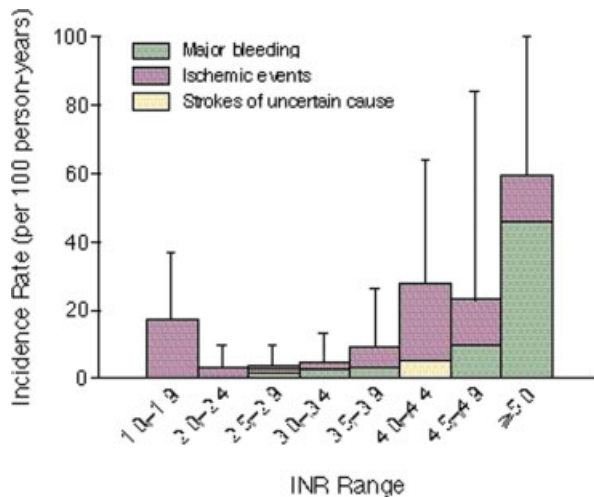


FIGURE 1. INR-specific incidence rates for the occurrence of a first ischemic or hemorrhagic complication in the study patients. T bars indicate 95% confidence intervals. **Abbreviation:** INR, international normalized ratio. Reprinted with permission from *New England Journal of Medicine*.⁴ Copyright 1995, Massachusetts Medical Society.

Institutes of Health stroke scale. Noncontrast computed tomography of the brain is the first step for differentiating between ischemic and hemorrhagic events.^{3,9} There is an increased interest in the use of magnetic resonance imaging to detect acute intracranial hemorrhage (ICH) and its ability to detect stroke earlier than computed tomography.⁹⁻¹¹ Multimodal computed tomography and magnetic resonance imaging provide additional information that will improve the diagnosis of ischemic stroke, and they have been added as a class I recommendation to the most recent stroke guidelines.^{9,12} Computed tomographic angiography and perfusion computed tomography may precisely describe details regarding the site of occlusion, infarct core, salvageable brain tissue, and collateral flow that can improve patient selection for intravenous or intra-arterial thrombolysis and exclude stroke mimics.^{9,13}

ISCHEMIC STROKE

Thrombolysis

In the setting of acute ischemic stroke, the patient should be promptly evaluated for thrombolytic therapy according to the American College of Chest Physicians guidelines.¹⁴ Intravenous r-TPA (recombinant tissue plasminogen activator) is given only to 1% to 2% of stroke patients in the

United States. This low percentage is mainly due to delayed presentation to an emergency department beyond the 3-hour treatment window.¹⁵ Clear benefit has been proven for eligible patients if thrombolytic therapy is administered within 3 hours from the initiation of symptoms, although no subgroup analysis has been done in patients with atrial fibrillation.⁹ The efficacy of intravenous thrombolysis within the 3-hour time window is similar between different stroke subtypes; therefore, its administration should not be delayed in order to investigate its etiology.¹⁶ Intravenous thrombolysis remains the standard of care, but recent studies have demonstrated that intra-arterial administration, despite its risks, may be more effective in selected patients.^{9,17-19} Patients most likely to benefit from intra-arterial thrombolysis are those with middle cerebral artery occlusion of less than 6 hours (Prolyse in Acute Cerebral Thromboembolism Trials I and II) and patients with severe basilar artery stroke.^{17,19} A recent study in Germany has demonstrated that intra-arterial thrombolysis may be superior to intravenous thrombolysis in the 3- to 6-hour treatment window.¹⁹ The updated 2007 guidelines from the American Heart Association (AHA)/ASA have included intra-arterial thrombolysis for specific patients who are not eligible for intravenous thrombolysis when this can be performed at experienced stroke centers.⁹ Thrombolysis reduces overall disability and improves the quality of life in appropriately selected patients. The risk of hemorrhage is approximately 5.2%.²⁰ After intravenous thrombolysis, approximately one-third of patients ultimately develop re-occlusion of the artery, especially patients with only partial recanalization. This may lead to neurologic deterioration and higher in-hospital mortality.²¹ According to more recent studies, ultrasound-enhanced thrombolysis may augment tissue plasminogen activator induced arterial recanalization by continuous transcranial Doppler.²² Symptomatic hemorrhagic transformation of the infarction remains the primary concern with the administration of intravenous rtTPA.^{23,24} Despite the apparent risks of ICH, atrial fibrillation patients not on warfarin should always be promptly referred for thrombolysis whenever they are eligible.

Heparin

For many years, clinicians have believed in the role of heparin in patients with atrial fibrillation,

especially after intracranial hemorrhage is excluded by negative initial noncontrast head computed tomography.²⁵ The most obvious pathophysiologic mechanism in patients with atrial fibrillation is cardioembolism. Therefore, it was believed that heparin could contribute to the resolution of the responsible clot. Two large international trials (the Heparin in Acute Embolic Stroke Trial and the International Stroke Trial), confirmed by multiple smaller ones, have investigated the use of heparin (unfractionated or low-molecular-weight heparin) at therapeutic doses in the setting of an acute ischemic event.^{26–28} Surprisingly, none of them showed a statistically significant benefit, but instead they showed a clear increase in hemorrhagic events. Therefore, routine use of unfractionated heparin or low-molecular-weight heparin at therapeutic doses should be avoided in the acute setting of a stroke.^{28,29}

Aspirin

Among the antiplatelet agents, aspirin is the only well-studied agent for the treatment of acute ischemic stroke. It has been proven that during the first 24 hours after stroke, there is substantial platelet activation that can be inhibited by aspirin.^{30,31} Two major trials, the Chinese Acute Stroke Trial and the International Stroke Trial, have demonstrated the benefit of early aspirin use in patients with stroke and atrial fibrillation.³⁰ Both proved a decrease in recurrent stroke without a significant increase in hemorrhaging. The recommended dose of aspirin is 325 mg/day.⁹ Currently, clopidogrel alone or in combination with aspirin and the intravenous administration of antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor are class III recommendations. They should not be used outside the setting of clinical trials.⁹

Warfarin

It is well known that atrial fibrillation increases the risk of ischemic stroke by a factor of 5.³² Studies have shown that maintaining the INR above 2.0 decreases not only the frequency but also the severity and mortality of ischemic events.^{4,8,32} The National Anticoagulation Benchmark Outcomes Report has shown that in the highest risk atrial fibrillation patients, only 55% receive warfarin and 21% do not receive aspirin or warfa-

rin.³³ This discrepancy results from the fact that warfarin is the second most common drug, after insulin, responsible for adverse drug events in emergency room visits. In atrial fibrillation patients on warfarin who present to the emergency with an acute stroke, there are no clear guidelines regarding the continued use of warfarin at therapeutic doses (target INR = 2.0–3.0). Warfarin is usually not initiated in the acute setting until the patient is medically stable. The exact time at which warfarin can be started or resumed after an acute ischemic stroke remains to be determined.³⁴ Usually, it is preferable to start it within 1 week after the event, given the risk of early recurrent acute stroke during the next 2 to 4 weeks after the initial stroke.³⁵

HEMORRHAGIC STROKE/ICH

Introduction

The risk of spontaneous ICH is 0.15%/year in patients over 70 years old and increases to 0.3% to 0.8% when patients are on therapeutic doses of warfarin with INR between 2 and 3.^{36,37} Given the multiple interactions of warfarin with other medications, this is a significant concern because ICH is associated with substantial neurological deterioration.³⁸ Although most warfarin-induced ICH occurs in patients with therapeutic INR, it becomes the most prevalent mechanism when the INR exceeds 5.0, and it should be highly suspected.^{1,4} Therefore, prompt determination of INR is critical in the initial evaluation of acute stroke in patients with atrial fibrillation. Age is the most important predisposing factor for ICH in patients with atrial fibrillation. There is almost a 50% increase in warfarin-induced bleeding for every decade of age above 40.³⁹ Cerebral amyloid angiopathy plays an important role in warfarin-associated lobar ICH in the elderly, and it may contribute to the patient candidacy for warfarin treatment in the near future.⁴⁰ On the other hand, a hemorrhagic stroke can be an iatrogenic complication of initiation of warfarin, heparin, or early thrombolysis because symptomatic hemorrhagic transformation of the infarction is the main and most lethal side effect of intravenous rtTPA in the treatment of acute ischemic stroke.²⁴ ICH is associated with a 30% to 50% mortality rate, and it represents the most lethal and least treatable form of stroke.³² It has been suggested that macroalbuminuria is an independent predictor of hemor-

rhagic transformation and particularly of severe hemorrhage in patients with acute ischemic stroke, but specific guidelines for screening or special management of those patients do not currently exist.³³ ICH is a medical emergency with high mortality and should be recognized and treated promptly. Recently, the AHA and ASA have published updated guidelines for the management of spontaneous ICH in adults.¹²

Vitamin K

All experts agree that anticoagulation should be urgently reversed in the setting of ICH. Although high doses of intravenous vitamin K (10–20 mg) are usually enough to reverse the anticoagulant effect of warfarin, it may take up to 12 to 24 hours to act, and it depends on intact liver function. Given the high mortality of this condition, vitamin K as monotherapy is considered inadequate, and a more aggressive approach is recommended.⁴¹

Fresh Frozen Plasma (FFP)

In the United States, for many years FFP has been considered the standard of care for the acute reversal of warfarin-associated anticoagulation.⁴² In general, 10 to 15 cc/kg FFP is used.⁴³ Timing rather than dosage seems to be more important for a better clinical outcome.⁴⁴ The use of FFP is complicated by the delayed time for thawing and compatibility check, volume overload, and sometimes inadequate and unpredictable correction. The median time for door-to-INR normalization is 30 hours, which is a significant delay for such a potentially fatal condition. Another possible complication of FFP is the report of increasing hematomas.⁴⁵

Prothrombin Complex Concentrates (PCCs)

PCCs contain vitamin K dependent coagulation factors II, VII, IX, and X, the factors deficient in warfarin therapy.^{44,46} Therefore, a PCC dose of 25 to 59 U/kg has been used in life-threatening bleeding, resulting in a decrease in the median INR from 3.8 to 1.3 immediately after administration.⁴² PCCs should always be given with vitamin K. Thrombotic events have been described with the infusion of PCCs, but no clear guidelines have been published.⁴² A recent study from the Mayo Clinic showed that many experts suggest its use in the urgent condition of warfarin-associated ICH.⁴¹ PCCs are widely used in the European community

and have previously been cited as the agent of choice for urgent warfarin reversal.^{42,47,48} A recent study comparing PCCs with FFP and vitamin K has demonstrated that PCCs may be superior to FFP and vitamin K by reducing the risk of hematoma growth.⁴⁹

Recombinant Factor VIIa

Recombinant factor VIIa is a preparation of activated coagulation factor VII (factor VIIa) that is produced by recombinant DNA technology.⁵⁰ It was initially used for the treatment of inhibitors in patients with hemophilia. It has also been used in the past to correct anticoagulation in patients with acute ICH,³⁶ but most studies have been done in patients with hemophilia or factor VII deficiency.⁵⁰ Major limitations include cost, prothrombotic potential, and lack of correction of other coagulation factors dependent on vitamin K. Studies have shown that factor VII may be a safe, rapid, and effective way of reversing anticoagulation and may offer an improved quality of life to patients with ICH.^{51,52} Factor Seven for Acute Hemorrhagic Stroke Treatment, a large phase III trial, is in progress, but preliminary results are controversial regarding the reduction in the size of hemorrhage, mortality, and improvement of functional outcome.³² In a recent article from the Mayo Clinic,⁴¹ several experts on clinical stroke, neurologic intensive care, and hematology suggest its use, alone or with FFP, for the urgent reversal of INR in the clinical setting of warfarin-associated ICH. Currently, according to the 2007 AHA/ASA updated guidelines, recombinant factor VIIa can be administered within the first 3 to 4 hours after onset of ICH to slow progression of bleeding, although its efficacy and safety remain to be confirmed (class IIb recommendation).¹²

Surgical Evacuation

Despite the clear guidelines for the indications of surgery in spontaneous intracranial bleeding,¹² the role of surgical evacuation in patients with supratherapeutic INR is not well defined. Many neurosurgeons are reluctant to operate in the setting of impaired hemostasis. The International Surgical Trial in Intracerebral Hemorrhage showed no clear benefit of early neurosurgical intervention compared to conservative treatment.⁵³ Different surgical trials have shown different outcomes.⁵⁴

TABLE 1
Questions That Need To Be Answered

1. When can warfarin be safely started after an acute cardioembolic stroke?
2. Could heparin in lower doses be beneficial without the risk of bleeding?
3. Should we repeat thrombolysis in cases of re-occlusion?
4. What is the role of other antithrombotic and antiplatelet agents in these patients?

The selection of patients who would benefit from surgery depends on the location and size of the hemorrhage, coagulation status, and Glasgow Coma Scale.⁵⁵ Patients with rapidly expanding hematomas in a surgically accessible intracranial territory are more likely to benefit from a neurosurgical intervention. Newer surgical techniques with a computed-tomography-guided stereotactic approach or endoscopy-guided evacuation in emerging ICH may offer better outcomes.⁵⁶

RECENT ADVANCES

Mechanical Embolectomy

Mechanical embolectomy is a growing field of neurology with a promising interventional approach to the treatment of embolic strokes.^{57,58} Patients with atrial fibrillation will probably be one of the patient groups who will receive maximum benefit when the efficacy and safety of the procedure are established. Endovascular reperfusion via mechanical embolectomy is offered to patients who are ineligible for thrombolytics, and it extends the time window up to 8 hours.⁵⁸ For the first time, in 2007 the AHA/ASA guidelines have included the Mechanical Embolus Removal in Cerebral Ischemia device as a reasonable intervention for extraction of intra-arterial thrombi in carefully selected patients.⁹

Left Atrial Appendage (LAA) Occlusion

The LAA is the source of 91% of embolic thrombi in patients with atrial fibrillation.⁵⁹ Therefore, surgical or percutaneous removal or occlusion of the LAA would be an important treatment option, especially in high-risk patients intolerant of warfarin or with recurrent strokes, despite anticoagulation. Several surgical techniques and percutaneous LAA occlusion devices have been studied with different success rates and safety characteristics.^{60–63} Currently, there are no official guidelines for the use of those interventions.

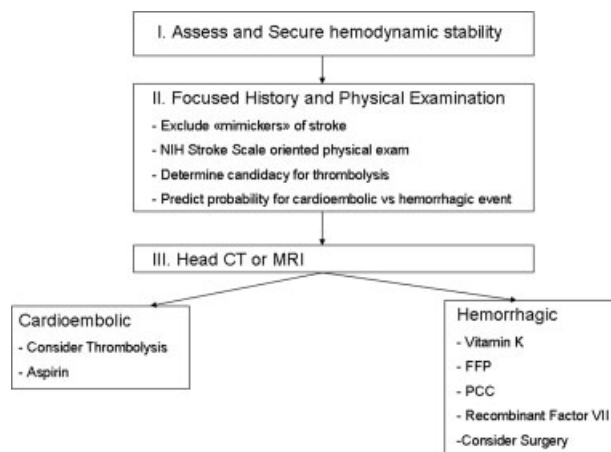


FIGURE 2. Suggested approach to the acute stroke patient with atrial fibrillation. **Abbreviations:** CT, computed tomography; FFP, fresh frozen plasma; MRI, magnetic resonance imaging; NIH, National Institutes of Health; PCC, prothrombin complex concentrates.

Genetic Testing for Warfarin Sensitivity

Warfarin is the second most common drug, after insulin, to require emergency room visits for adverse drug events. In September 2007, the Food and Drug Administration approved the “Nanosphere Verigene Warfarin Metabolism Nucleic Acid Test,” which detects variants of 2 genes (CYP2C9 and VKORC1) implicated in the unexpected response to warfarin.^{64–66} Guidelines for the applied use of these tests are currently under development.⁶⁶

CONCLUSION

On average, there is a new stroke every 45 seconds, and every 3 to 4 minutes, someone dies from a stroke in the United States. Atrial fibrillation accounts for one-fourth of all strokes in the elderly population. Acute stroke in anticoagulated patients with atrial fibrillation is a common, challenging scenario in emergency departments because many questions remain unanswered (Table 1). A special and prompt approach from the clinician is needed to achieve effective management and avoid potentially fatal complications (Figure 2). Many hospitals in the United States have formed “stroke teams” to ensure prompt clinical and radiographic assessment of stroke patients. Only early recognition of cardioembolic or hemorrhagic strokes in atrial fibrillation patients can lead to aggressive management of this potentially fatal and disabling condition.

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