Original Article

Analysis of Antithrombotic Therapy After Cardioembolic Stroke Due to Atrial Fibrillation or Flutter

Evan J. Peterson, PharmD^{*}; Anne B. Reaves, PharmD[†]; Jennifer L. Smith, PharmD[‡];
and Carrie S. Oliphant, PharmD[§]

Abstract

Background: Guidelines recommend that all patients with atrial fibrillation and a history of ischemic stroke should receive an anticoagulant. Prior analyses show that warfarin is underutilized in most populations.

Objective: To examine the use of antithrombotic and anticoagulant therapy in patients with atrial fibrillation or flutter during the index hospitalization for acute, ischemic stroke.

Methods: Retrospective electronic medical record review of 200 patients treated at a tertiary care hospital with a primary ICD-9 code for ischemic stroke and a secondary ICD-9 code for atrial fibrillation or flutter. Exclusion criteria were active bleeding, pregnancy, age less than 18, pre-existing warfarin allergy, or dabigatran use.

Results: Fifty-two percent of patients received at least one dose of warfarin during the index hospitalization. There was no relationship between CHADS₂ score and likelihood of receiving warfarin ($P > .05$). There was no significant difference in adverse event rate in patients receiving warfarin compared to those receiving aspirin (3.8% vs 9.1%; $P = .14$), but the rate of hemorrhagic transformation was lower in patients receiving warfarin (1% vs 7%; $P = .03$). The composite of hemorrhagic stroke or hemorrhagic transformation was significantly lower in patients receiving bridging therapy (0% vs 11%; $P = .03$). Sixteen patients were readmitted for stroke within 3 months of discharge. Ten were readmitted for ischemic stroke, 3 for hemorrhagic stroke or hemorrhagic transformation, and 3 for systemic bleeding. Ten patients (62.5%) were receiving warfarin at re-admission, but only one of these patients had a therapeutic INR.

Conclusions: Warfarin was underutilized as secondary stroke prophylaxis in these high-risk patients. Bridging therapy appeared to be safe and was not associated with an increase in adverse events.

Key Words—anticoagulant, atrial fibrillation, atrial flutter, stroke, warfarin

Hosp Pharm—2013;48(2):127–133

Atrial fibrillation (AF) is the most common arrhythmia and has an increasing prevalence with increasing age. The incidence is approximately 0.9% in the general population but 5.9% in those over the age of 65.¹ Nonvalvular AF is an independent risk factor for stroke, increasing the risk 5-fold.² Atrial flutter (AFL) also increases the risk of stroke, but possibly to a lesser extent than AF.³ Stroke prophylaxis with antithrombotic therapy is recom-

mended for patients with AF or AFL; possible therapies include anticoagulants such as warfarin sodium, dabigatran etexilate mesylate, and rivaroxaban and antiplatelet therapy such as aspirin (ASA) or the combination of ASA and clopidogrel sulfate.

The choice of antithrombotic therapy is determined by the patient's risk of stroke. The most commonly used scale for determining the risk of cardioembolic stroke in a patient with nonvalvular AF or AFL is the CHADS₂

^{*}Clinical Pharmacy Specialist – Cardiology, Seton Healthcare Family, Austin, Texas; [†]Clinical Specialist – Ambulatory Care, [‡]Clinical Specialist – Emergency Medicine, [§]Clinical Specialist – Cardiology/Anticoagulation, Methodist University Hospital, Memphis, Tennessee; [At the time of writing, Dr. Peterson was PGY-1 Pharmacy Resident, Methodist University Hospital, Memphis, Tennessee.] Corresponding author: Carrie Oliphant, PharmD, BCPS (AQ Cardiology), Methodist University Hospital, Department of Pharmacy, 1265 Union Avenue, Memphis, TN 38104; e-mail: Carrie.Oliphant@mlh.org

scale, which assigns patients 1 point for having congestive heart failure (C), hypertension (H), age greater than or equal to 75 (A), and diabetes mellitus (D) and 2 points for previous transient ischemic attack (TIA) or stroke (S₂).⁴ Until the approval of dabigatran in 2010, patients with a score of at least 2, which includes all patients with a prior ischemic stroke or TIA, were recommended to receive warfarin with a target international normalized ratio (INR) of 2 to 3.^{3,5-7} Dabigatran is now also appropriate for stroke prophylaxis in these patients⁸ and is the preferred oral anticoagulant in the most recent guidelines from the American College of Chest Physicians.^{9,10} Rivaroxaban, another potential option, was approved by the FDA for stroke prophylaxis in November 2011. The American Heart Association in conjunction with the American Stroke Association has recently issued a science advisory on oral antithrombotic therapy for the prevention of stroke in nonvalvular atrial fibrillation.¹¹ Both dabigatran and rivaroxaban are recommended as alternative agents to warfarin although the level of recommendation differs with dabigatran receiving a Class I recommendation and rivaroxaban receiving a Class IIa recommendation.¹¹ Clopidogrel and ASA may^{9,12} or may not¹³ be used in patients who are unable to take warfarin. In clinical trials, dual antiplatelet therapy was inferior to warfarin but was associated with a decreased rate of stroke and an increased risk of bleeding relative to aspirin monotherapy.^{14,15}

Studies conducted prior to the current AF guidelines found that warfarin was underutilized. One study of ambulatory care patients with AF found that only 55% of all patients who had no contraindications received warfarin.¹⁶ Another evaluation found that only 40% of patients with AF, at least 1 other risk factor, and no contraindications were receiving warfarin prior to admission.¹⁷ More recent studies suggest that warfarin may still be underutilized relative to guideline recommendations, with reported inpatient warfarin utilization rates of 56.2% to 74%.¹⁸⁻²¹

The use of full-dose, injectable anticoagulation after an acute stroke as bridging therapy to therapeutic warfarin is currently not recommended due to a lack of data showing net benefit.^{5,10,22} In addition, any potential decrease in stroke recurrence may also be associated with an increased risk of bleeding at the site of the initial ischemic stroke, a phenomenon referred to as *hemorrhagic transformation*.^{5,13,22} One small, retrospective analysis of treatment after an acute, cardioembolic stroke in patients who did not receive tissue plasminogen activator (tPA) found an increased

incidence of favorable outcomes with the use of bridging therapy, but also showed an increase in delayed, symptomatic intracranial hemorrhage associated with low molecular weight heparin use.²³

METHODS

This retrospective electronic medical record review was conducted at Methodist University Hospital, a 690-bed facility that is a Joint Commission certified primary stroke center. Methodist University Hospital is a primary adult teaching hospital for the University of Tennessee and is served by a mixture of academic and private physicians. Patients admitted between January 1, 2008 and December 31, 2010 were eligible for inclusion. A total of 200 patients were enrolled in reverse chronological order, with the most recently admitted patients enrolled first. The index hospitalization was defined as the initial admission during the study timeframe during which ischemic stroke was diagnosed. Patient medical records for all admissions within 3 months from discharge were reviewed for possible readmission due to stroke of any type or a bleeding event. This study was approved by the University of Tennessee Institutional Review Board, which is the official institutional review board for Methodist University Hospital.

Patients were included if they were at least 18 years old with diagnoses of acute, ischemic stroke and either concurrent or documented history of AF or AFL. Exclusion criteria were active bleeding at the time of stroke diagnosis, pregnancy, pre-existing warfarin allergy, and use of dabigatran. Patients were identified by a health informatics report with a primary ICD-9 code of ischemic stroke (434.91, 434.11, 434.01, 433.11, or 433.01) and a secondary ICD-9 code of AF (427.31) or AFL (427.32).

Antithrombotic therapies were defined as warfarin, ASA, clopidogrel or extended-release dipyridamole and ASA. Bridging therapy was defined as initiation of warfarin and concomitant treatment with unfractionated heparin intravenous infusion, enoxaparin sodium (doses greater than 60 mg per day), fondaparinux sodium (doses greater than 2.5 mg per day), lepirudin intravenous infusion, or argatroban intravenous infusion. Bleeding was defined as the need for blood transfusion or antidote use (phytonadione, fresh frozen plasma, platelets, protamine sulfate, prothrombin complex concentrate, or activated Factor VII) due to gastrointestinal bleed, intra-abdominal bleed, or external bleed; this did not include antidote use to reverse anticoagulation prior to a procedure. An adverse event was defined as bleeding, allergic reaction, or

other medication effect requiring discontinuation of antithrombotic or anticoagulant therapy. Hemorrhagic stroke was defined as development of an intracranial hemorrhage in a different location than the ischemic stroke identified during the index hospitalization, in contrast to hemorrhagic transformation that was development of an intracranial hemorrhage in the same location as the previous ischemic stroke from the index hospitalization. Recurrent stroke was defined as readmission to the hospital due to stroke symptoms with a physician diagnosis of stroke or identification of a new stroke in a new location during index hospitalization.

Study Objectives

The primary objective of this study was to determine the percentage of patients with AF or AFL and a diagnosis of acute, ischemic stroke who received warfarin during the index hospitalization.

Secondary objectives were to determine the incidence of adverse events that required changes in antithrombotic therapy, the percentage of patients treated with bridging therapy, the incidence of adverse events associated with the use of injectable anticoagulants, and the incidence of readmission for bleeding or recurrent stroke of any type within 3 months of discharge. Patients who received tPA were excluded from the analysis of bridging therapy.

Statistical Analysis

Descriptive statistics were used to analyze the population. Categorical variables were analyzed using Fisher exact tests. A 2-sided *P* value less than .05 was considered statistically significant.

RESULTS

There were 210 patients who were evaluated; 10 patients were excluded. Eight patients were excluded because of active bleeding at the time of stroke diagnosis, 1 for dabigatran use, and 1 for known warfarin allergy. Baseline characteristics and comorbidities are shown in Table 1. There was a high prevalence of stroke risk factors; the mean CHADS₂ score was 4.06. More than one-third of patients had documentation of a previous stroke or TIA prior to the index hospitalization. The median length of stay was 7 days.

The use of warfarin in this study population is summarized in Table 2. During the index hospitalization, 103 patients (51.5%) received at least 1 dose of warfarin. A significantly higher proportion of patients who survived received warfarin compared to those who died or were discharged to hospice (60% vs 16%; *P* < .01). There was no significant association

Table 1. Baseline patient characteristics of patients with acute, cardioembolic stroke and atrial fibrillation or flutter (n = 200)

Characteristics	n (%)
Mean age, years (±SD)	73.4 (±12.4)
Female	113 (57)
African American	129 (65)
AF	180 (90)
AFL	18 (9)
AF and AFL	2 (1)
Hypertension	174 (87)
Age ≥ 75	103 (52)
Diabetes mellitus	73 (32)
Heart failure	73 (32)
Previous history of stroke or TIA	68 (34)
Mean CHADS ₂ score	4.06

Note: Values given as n (%) unless otherwise indicated. AF = atrial fibrillation; AFL = atrial flutter; TIA = transient ischemic attack; CHADS₂ = Congestive Heart Failure (C), Hypertension (H), Age ≥ 75 (A), Diabetes Mellitus (D), and Stroke or TIA (S₂)

between prior history of stroke or TIA and warfarin use; 36 patients (52.9%) with a prior history of stroke or TIA received warfarin compared to 67 (50.8%) of those with no prior history of stroke or TIA (*P* = .88). There was no relationship between warfarin use and CHADS₂ score (*P* > .05), but patients with a CHADS₂ score of 3 were more likely than those with a CHADS₂ score of 4 to receive warfarin (63.8% vs 42.5%; *P* = .03). There were no other significant differences among groups. Of those discharged on warfarin, 35 (36.1%) had an INR within the therapeutic range of 2 to 3 at the time of discharge. The median INR at discharge was 1.7.

Documented reasons for not prescribing warfarin are listed in Table 3. The most common reasons were

Table 2. Warfarin use in study patients by CHADS₂ score

CHADS ₂ score	Received warfarin, n (%)	Did not receive warfarin, n (%)
2	4 (66.7)	2 (33.3)
3	30 (63.8)	17 (36.2)
4	34 (42.5)	46 (57.5)
5	29 (52.7)	26 (47.3)
6	6 (50.0)	6 (50.0)
2-6	103 (51.5)	97 (48.5)

Note: CHADS₂ = Congestive Heart Failure (C), Hypertension (H), Age ≥ 75 (A), Diabetes Mellitus (D), and Stroke or TIA (S₂).

Table 3. Documented reasons for not prescribing warfarin in study patients after acute, cardioembolic stroke (n = 97)

Reason	n (%)
Death or hospice	31 (32.0)
Reason not documented	17 (17.5)
Bleeding risk	12 (12.4)
Age/dementia	9 (9.3)
Fall risk	8 (8.2)
Hemorrhagic transformation risk	8 (8.2)
Other ^a	6 (6.2)
Noncompliance/substance abuse	3 (3.1)
Planned to assess as outpatient	2 (2.1)
Patient/family refused	1 (1.0)

^aHypotension believed to cause stroke (1); lesion believed to be infectious not from ischemic stroke and atrial fibrillation believed to be incidental to stress (1); “rhythm stable” (1); patient refused transesophageal echocardiogram and was do not resuscitate/do not intubate (1); “rhythm controlled on metoprolol, on Aggrenox” (1); “recent CVA” (1).

death or admission to hospice and bleeding risk. For 17 patients (17.5%), no documentation for the lack of warfarin could be found. This included patients who were deemed “not a candidate for anticoagulation” without a specific contraindication. Eight patients did not receive warfarin while inpatients because of the risk of hemorrhagic transformation, but they were to be assessed for possible warfarin initiation after discharge. Only 1 patient did not receive warfarin because of the family’s refusal.

There were 21 adverse events that occurred during the index hospitalization: 3 hemorrhagic strokes (14.3%), 14 hemorrhagic transformations (66.7%), and 4 gastrointestinal bleeding events (19.0%). The median time to hemorrhagic transformation from the index ischemic stroke was 2 days, and all transformations occurred within 4 days. All 3 hemorrhagic strokes (100%) and 10 of the hemorrhagic transformations (71.4%) occurred in patients only receiving ASA. One hemorrhagic transformation (7.1%) occurred in a patient receiving both ASA and clopidogrel and 2 (14.2%) occurred in patients receiving only clopidogrel. The adverse event rate was lower in patients who received warfarin than those who received ASA, but it did not reach statistical significance (3.9% vs 9.3%; $P = .14$). Three (75%) of the gastrointestinal bleeding events (INRs 1.0, 1.5, 1.6) and 1 (7.1%) hemorrhagic transformation (INR 1.8) occurred in patients receiving warfarin. The rate of hemorrhagic transformation was lower in patients who received any doses of warfarin

compared to those who received any doses of ASA (1.0% vs 6.8%; $P = .03$).

There were 182 patients who did not receive tPA and were included in the assessment of bridging therapy. Forty (22.0%) of these patients received bridging therapy during the index hospitalization. The median time for starting an injectable anticoagulant for bridging therapy was 2 days, and the median duration of in-hospital bridging therapy was 5 days. There were no incidences of hemorrhagic stroke or transformation in patients who received bridging therapy. Three patients had a gastrointestinal bleed while receiving bridging therapy, 2 with unfractionated heparin and 1 with enoxaparin. The INRs were 1.0, 1.5, and 1.6 on the day that bleeding was identified. No other adverse events requiring changes or discontinuation of therapy occurred. None of the bleeding events required anti-dote administration.

There was no difference in the rate of intracranial and extracranial bleeding in patients who received bridging therapy compared to those who received antithrombotic treatment alone (7.5% vs 11.9%; $P = .58$). There was a significantly lower rate of the composite of hemorrhagic stroke or transformation in patients receiving bridging therapy compared to those who only received antithrombotic therapy (0% vs 11.3%; $P = .03$).

Sixteen patients, or 10% of those who survived the index hospitalization and were not discharged to hospice, were readmitted for an ischemic stroke or bleeding event within 3 months of discharge. Reasons for readmission and antithrombotic therapy at readmission are shown in Table 4. Three patients were receiving warfarin monotherapy, 7 were receiving warfarin plus an antiplatelet drug, 4 were receiving ASA monotherapy, and 2 were receiving ASA plus clopidogrel. Of the 10 patients readmitted with an ischemic stroke on warfarin therapy, 5 (50%) had an INR less than 2. Bleeding events and rate of hemorrhagic transformation did not correspond to an elevated INR level. The INR was above the goal range for the 1 patient who developed a hemorrhagic stroke.

DISCUSSION

At the end of the era in which warfarin was the only oral anticoagulant available for stroke prophylaxis in AF or AFL patients, the utilization rate in this single-center, observational study was similar to that reported in previous trials from more than 10 years prior.^{20,21} This study should reflect the most contemporary practice because of the reverse chronological manner of patient enrollment. This utilization rate is

Table 4. Reasons for readmission in study patients after acute, cardioembolic stroke, and antithrombotic therapies at readmission

Readmission reason	Total	Warfarin only	Warfarin + antiplatelet ^a	Antiplatelet ^a only
Ischemic stroke	10	3	3 ^b	4 ^c
Hemorrhagic stroke	1	0	1	0
Hemorrhagic transformation	2	0	1	1
Bleeding	3	0	2	1
Total	16	3	7	6

^aAntiplatelet denotes aspirin except where otherwise stated.

^bOne patient receiving clopidogrel.

^cTwo patients receiving aspirin + clopidogrel.

also lower than that seen in previous data from *Get With the Guidelines – Stroke* quality improvement program, which found that 63.9% of patients with AF received warfarin after an ischemic stroke.¹⁹

This low rate of warfarin use conflicts with consensus guidelines; warfarin was indicated in all of these patients because of a history of ischemic stroke and a CHADS₂ score greater than or equal to 2. The patients in this study would potentially derive a larger benefit from warfarin because of the high mean CHADS₂ score, indicating a high risk of subsequent ischemic strokes. It is well established that patients with the highest risk of stroke have the highest absolute risk reduction with the use of warfarin.²⁴ In this study, warfarin use was suboptimal and was not associated with stroke risk, as measured by CHADS₂ score. This suboptimal use of warfarin could not be explained by adverse events, because warfarin was associated with fewer adverse events than ASA during the index hospitalization. This lower rate of warfarin-associated adverse events may be due to differences in patient characteristics between those who received each treatment or because ASA was initiated sooner.

It is possible that warfarin utilization rates would be higher if they were examined at a later time after this immediate poststroke period when concern for hemorrhagic transformation is high. However, this was not possible in the current study in which only inpatient records were available. It is also possible that examining outpatient use may not have been associated with a large increase in warfarin utilization rate, because there were only 8 patients in whom the documented reason for avoiding inpatient warfarin use was the risk of hemorrhagic transformation. The initial stroke severity may have precluded the use of warfarin as nearly 20% of patients died or were discharged to hospice. The documented reasons for not initiating warfarin therapy also appear to be inappropriate in

some cases, such as patients not being in AF at discharge or being “rhythm controlled on metoprolol.”

In the patients who did receive warfarin, dosing may have also been suboptimal. More than half of these patients were discharged with a subtherapeutic INR and only 1 of the 10 patients receiving warfarin at readmission had an INR within therapeutic range. The reasons for this low rate of therapeutic INR attainment are unknown but may demonstrate the difficulty of managing warfarin therapy, especially in high-risk patients. Even among the patients who received warfarin during the index hospitalization, the benefits would not be realized if the medication could not be managed appropriately in the outpatient setting.

The use of poststroke bridging therapy was associated with relatively few adverse events. Unlike the previously mentioned study by Hallevi et al that examined bridging therapy after cardioembolic stroke,²³ there was no increase in hemorrhagic transformation or hemorrhagic stroke in our study. In fact, there were no identified incidences of hemorrhagic stroke or transformation in patients who received bridging therapy. This discrepancy may be related to patient selection. It is possible that only the patients deemed to be at a low risk for hemorrhagic transformation received bridging therapy. The efficacy of bridging therapy cannot be assessed as there was only one recurrent stroke during the index hospitalization, which occurred in a patient not receiving bridging therapy. Large, randomized trials are necessary to determine the efficacy and safety of bridging therapy after cardioembolic stroke, but this analysis suggests it may be safe in selected patients, even in the immediate poststroke period.

Several weaknesses exist with this study. It was a nonrandomized, retrospective study. Complete data were available for most but not all patients. The quality of the data relied on the quality of the

documentation, which was not optimal, as demonstrated by the 17.5% of patients who did not have a specific contraindication to warfarin documented. However, records were extensively examined to obtain what data were available. Patients were also only classified on the basis of their CHADS₂ score and not their CHA₂DS₂-VASc score, a system that incorporates moderate risk factors of vascular disease, age 65 to 74 years, and female sex.²⁵ However, the CHADS₂ score was the primary risk score used in clinical practice when these patients were treated, and all of these patients were already deemed high risk. This review was also limited by its single-center nature; other institutions may have higher or lower rates of warfarin utilization. The study site is located within the "Stroke Belt."²⁶ A mix of private and academic neurologists, cardiologists, internists, and other physicians were involved in the care of these patients, so it may better represent real-world practices. Long-term efficacy could also not be established due to the short duration of follow-up and the possibility of death out of the hospital or admission to a different hospital.

CONCLUSION

AF is a risk factor for stroke, and the agent for prophylaxis is recommended based on risk. Guidelines recommend warfarin treatment for secondary stroke prophylaxis in this population, because of the high risk for subsequent stroke. In our study, warfarin was underutilized during the index hospitalization for acute, ischemic stroke. Warfarin use was associated with few adverse events. Bridging therapy with injectable anticoagulants also seemed to be safe in this population, but this must be assessed in larger trials.

ACKNOWLEDGMENTS

We would like to thank Joyce Broyles, PharmD, BCNSP, Donna Hunt, and Andrew Faust, PharmD, BSPS, for their assistance with data analysis.

REFERENCES

1. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. *Arch Intern Med*. 1995;155:469-473.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983-988.
3. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report from the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol*. 2011;57:e101-198.
4. Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BSP, Petersen P. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation*. 2004;110:2287-2292.
5. The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for the management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457-507.
6. Singer DE, Albers GW, Dalieri JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133:546S-592S.
7. Kalra L, Lip GYH; on behalf of the Guideline Development Group for the NICE Clinical Guideline for the Management of Atrial Fibrillation. Antithrombotic treatment in atrial fibrillation. *Heart*. 2007;93:39-44.
8. Wann LS, Curtis LB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol*. 2011;57:1330-1337.
9. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:531S-575S.
10. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:601S-636S.
11. Furie KL, Goldstein LB, Albers GW, et al; on behalf of the American Heart Association Stroke Council, Council on Quality of Care and Outcomes Research, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the AHA/American Stroke Association. *Stroke*. 2012;43:3442-3453.
12. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;123:104-123.
13. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack. A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2010;42:227-276.

14. The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anti-coagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903-1912.
15. The ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360:2066-2078.
16. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *Ann Intern Med*. 1999;131:927-934.
17. Brass LM, Krumholz HM, Scinto JM, Radford M., Warfarin use among patients with atrial fibrillation. *Stroke*. 1997;28:2382-2389.
18. Agarwal S, Bennett D, Smith DJ. Predictors of warfarin use in atrial fibrillation patients in the inpatient setting. *Am J Cardiovasc Drugs*. 2010;10:37-48.
19. Lewis WR, Fonarow GC, LaBresh KA, et al. Differential use of warfarin for secondary stroke prevention in patients with various types of atrial fibrillation. *Am J Cardiol*. 2009;103:227-231.
20. Desai H, Aronow WS, Gandhi K, et al. Association of warfarin use with CHADS₂ score in 441 patients with non-valvular atrial fibrillation and no contraindications to warfarin. *Prev Cardiol*. 2010;13:172-174.
21. Kowey PR, Reiffel JA, Myerburg R, et al. Warfarin and aspirin use in atrial fibrillation among practicing cardiologist (from the AFFECTS registry). *Am J Cardiol*. 2010;105:1130-1134.
22. Adams Jr. HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with acute ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38:1655-1711.
23. Hallevi H, Albright KC, Martin-Schild S, et al. Anti-coagulation after cardioembolic stroke: To bridge or not to bridge?. *Arch Neurol*. 2008;65:1169-1173.
24. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med*. 1999;131:492-501.
25. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;137:263-272.
26. Feinlib M, Ingster L, Rosenberg H, Maurer J, Singh G, Kochanek K. Time trends, cohort effects, and geographic patterns in stroke mortality – United States. *Ann Epidemiol*. 1993;3:458-465. ■