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Warfarin Versus Warfarin and Aspirin in Atrial Fibrillation

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Abstract

Background
Anticoagulation with warfarin is an important therapy for preventing strokes in patients with atrial fibrillation (AF). Physicians often combine warfarin with aspirin despite evidence for increased bleeding. We investigated the hemorrhagic outcomes related to the differential management of AF with warfarin alone versus combination therapy.

Methods and Results
This retrospective cohort study of 695 patients enrolled at a university hospital-based anticoagulation clinic includes patients who received anticoagulation with warfarin or warfarin and aspirin between June 1, 2007 and September 30, 2008. All patients were ≥45 years old, had AF as the indication for anticoagulation, and did not have mechanical heart valves. Hemorrhages were classified as major if they caused death, involved critical sites, or required hospitalization with transfusion of ≥2 units of blood. All other bleeds were classified as minor. Of the 695 patients 307(44.2%) received combination therapy. Hemorrhage rates in the warfarin and the combination cohorts were 5.2% and 7.0% per 100-people years (p=0.29), respectively. There were 17 (3.4%) patients with major hemorrhages in the warfarin only group and 9 (2.8%) in the combination group (p=0.62). On average, patients on combination therapy had lower international normalized ratio (INR) values circa presentation (4.27 vs 3.13 p=0.049). In either group, any history of hemorrhage was associated with a 3.8 (95% CI, 1.79-8.13) times higher risk of hemorrhaging compared to patients without such a history.

Conclusions
This study highlights the high incidence of combination therapy and suggests that patients on combination therapy may bleed at lower INR levels. However, hemorrhagic outcomes did not differ significantly.

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Introduction

Oral anticoagulation with vitamin K antagonists, such as warfarin, reduces the risk of stroke in patients with atrial fibrillation by up to 60% thereby preventing serious morbidity and mortality.[1-3] Warfarin is also effective in preventing coronary artery thrombosis, though it is not often used for this indication.[4-6] The significant bleeding risks associated with warfarin mandate close monitoring and have limited its broader application.[7-9] Antiplatelet agents, specifically aspirin, tend to reduce the risk of stroke in patients with atrial fibrillation, although less effectively than warfarin does.[10] Aspirin and clopidogrel, often in combination, are used to prevent coronary artery thrombosis in patients with coronary artery disease, especially following coronary artery stent deployment.[11] In patients with coronary artery disease and atrial fibrillation, previous studies have reported a high incidence of combination warfarin and aspirin therapy.[12] Combination therapy has been associated with an increased risk of hemorrhage, but has ill-defined antithrombotic benefit over warfarin alone.[13,14]

The primary goal of this study was to better characterize the demographics of patients who are placed on combination therapy and how the different treatment regimens affect hemorrhagic risk. Furthermore, we aimed to identify independent risk factors predictive of hemorrhagic events. We hypothesized that atrial fibrillation patients would be more likely to be on combination therapy if they have coronary artery disease risk factors. We also predicted that receiving combination therapy would increase the risk of clinically significant bleeding, especially major bleeding events.

Methods

We performed a retrospective cohort study of patients with atrial fibrillation who were treated with warfarin alone or combination warfarin and aspirin at a university-based anticoagulation clinic. This study was approved by the institutional review board of the University of Massachusetts Medical School, Worcester, MA. The inclusion criteria included 1) receiving oral anticoagulation with warfarin or warfarin and aspirin between June 1, 2007 and September 30, 2008 under the direction of the anticoagulation clinic, 2) atrial fibrillation as the indication for anticoagulation, 3) hospital and anticoagulation clinic electronic medical records updated during the study period, and 4) age ≥45 years on June 1, 2007. Patients with mechanical heart valves and those taking clopidogrel were excluded. Patients with non-mechanical bio-prosthetic valves were not excluded.

By searching the anticoagulation clinic medical records for patients with atrial fibrillation, 832 patients were identified and screened for eligibility. Of these patients 137 were excluded. Reasons for exclusion included incomplete medical records (66), clopidogrel use (38), mechanical heart valve (30), and age less than forty-five (3). We identified 695 (83.5%) patients with atrial fibrillation who were 45 years or older, did not have a mechanical heart valve, and had electronic hospital and anticoagulation clinic records updated during the study period. We collected demographic, comorbidity, medication, laboratory, and hemorrhagic outcome data over the period of 16 months by searching and reviewing the anticoagulation clinic and affiliated hospital electronic records. A small cohort of an additional 36 patients on warfarin, aspirin, and clopidogrel was also identified. This subgroup will be referred to as the triple therapy group. The triple thera-

py group was considered separately from the main study group. Two patients were on warfarin and clopidogrel without aspirin. These two patients were excluded from the subgroup analysis due to the small cohort size.

Exposure time to warfarin and aspirin therapy was calculated as follows. We counted June 1, 2007 as the start date for patients entering the study already on warfarin alone or combination. For those who initiated warfarin therapy during the study time, exposure length was calculated, and averaged into the final data proportionally. Warfarin therapy start and stop dates were derived from the anticoagulation clinic records. Exposure time ceased on September 30, 2008 or earlier if warfarin was permanently discontinued or death occurred. If warfarin was discontinued or if death occurred, then calculation of exposure to other medications and the following of outcomes stopped. If patients on combination therapy stopped taking aspirin during the study, then the time off aspirin accrued towards the warfarin alone group. Likewise, if patients on warfarin only therapy started aspirin during the study, then that time accrued towards the combination group. Refer to Table 1 for warfarin exposure durations. Exposure to warfarin before June 1, 2008 was indexed as "None", <90 days, 90 days to 1 year, and $\geq$ 1 year.

CHADS$_2$ scores were calculated for all patients. Patients received a score of 0 to 6 depending upon their risk factors which were identified by reviewing the anticoagulation clinic and hospital electronic records. Patients were given one point for each of the following risk factors: congestive heart failure, hypertension, age >75 years on June 1, 2007, and diabetes mellitus. Patients received two points for a history of stroke or transient ischemic attack.[15]

The primary outcome was any clinically significant hemorrhagic events which were classified as major or minor. Major hemorrhages, as previously defined by Hylek et al 2007,[9] included any which were fatal, required hospitalization and transfusion of $\geq$2 units of packed red blood cells, or involved a critical site (i.e. retroperitoneal, intraocular, intracranial, etc). All hemorrhages not meeting these criteria were classified as minor. In most cases, INR values were measured upon presentation for hemorrhage. In four cases, INR values were not available upon admission. Two of the four patients had INR measured within one day of evaluation for hemorrhage, one within three days, and one within five days. Not all patients were admitted when they presented with hemorrhages and some were admitted to outside facilities from which we could not obtain admission INR values.

Statistical Analysis

Data were analyzed using SAS software release 9.1.3 (SAS Institute, Cary, NC). Continuous variables were tested for statistical significance using the t-test. Categorical variables were tested with chi-square analysis. Statistical significance was defined by $p < 0.05$ for all tests.

Multivariate analysis using logistic regression was performed in order to examine likelihood of bleeding while adjusting for variables of interest. These variables included patient demographics, coronary artery disease, CHADS$_2$ score, history of warfarin exposure, prior bleeding history and dual therapy. All variables that were significant at the level of $p < 0.25$ at the univariate level were also included in the logistic regression. A Hosmer-Lemeshow goodness-of-fit test was performed to confirm the final model. All results in the regression model were represented by an odds ratio and 95% confidence

Table 1: Patient characteristics*

Characteristic	Overall n=695 (100%)	Warfarin n=388 (55.8%)	Combination n=307 (44.2%)	p Value
Age				
Mean (±Std Dev)	72.9 (±10.3)	73.5 (±10.7)	72.0 (±9.7)	0.06
Median	74	75	73	
Female	286 (41.2)	193 (49.7)	93 (30.3)	<0.001
Paroxysmal	149 (21.4)	76 (19.6)	73 (23.8)	0.18
Warfarin Exposure Time[a]				0.36
None	197 (28.4)	102 (26.3)	96 (30.9)	
<90 days	36 (5.2)	20 (5.2)	16 (5.2)	
≥90 days but <1 year	92 (13.2)	48 (12.4)	44 (14.3)	
≥1 year	370 (53.2)	218 (56.2)	152 (49.5)	
CHADS$_2$ Score				0.49
0	38 (5.5)	25 (6.4)	13 (4.2)	
1	162 (23.3)	92 (23.7)	70 (22.8)	
2	244 (35.1)	127 (32.7)	117 (38.1)	
3	133 (19.1)	78 (20.1)	55 (17.9)	
≥4	118 (17.0)	66 (17.0)	52 (16.9)	
Cardiovascular History				
Hypertension	594 (85.5)	327 (84.3)	267 (87.0)	0.32
Dyslipidemia	475 (68.4)	237 (61.1)	238 (77.5)	<0.001
Myocardial infarction	132 (19.0)	34 (8.8)	98 (31.9)	<0.001
Coronary artery disease	290 (41.7)	105 (27.1)	185 (60.3)	<0.001
Coronary artery stent	76 (10.9)	20 (5.2)	56 (18.2)	<0.001
CABG[b]	106 (15.3)	33 (8.5)	73 (23.8)	<0.001
Heart Failure	199 (28.6)	108 (27.8)	91 (29.6)	0.60
Stroke or TIA[c]	137 (19.7)	76 (19.6)	61 (19.9)	0.93
Pacemaker/Defibrillator	157 (22.6)	76 (19.6)	81 (26.4)	0.03
Other Characteristics				
Diabetes Mellitus	184 (26.5)	87 (22.4)	97 (31.6)	0.007
Renal Failure[d]	95 (13.7)	53 (13.7)	42 (13.68)	0.99
Liver Disease[e]	20 (2.9)	12 (3.1)	8 (2.6)	0.70
Hypothyroidism	113 (16.3)	65 (16.8)	48 (15.6)	0.92
Malignancy[f]	98 (14.1)	59 (15.2)	39 (12.7)	0.35
Obstructive Sleep Apnea	89 (12.8)	42 (10.8)	47 (15.3)	0.08
History of falls	69 (9.9)	40 (10.3)	29 (9.5)	0.71
Bleeding history				
GI hemorrhages[g]	48 (6.9)	33 (8.5)	15 (4.9)	0.06
Non-GI hemorrhages	52 (7.5)	27 (7.0)	25 (8.1)	0.56

[a] Warfarin exposure as of June 1, 2007. Patients denoted as "None" started warfarin on or after June 1, 2007.
[b] CABG = Coronary artery bypass grafting surgery
[c] TIA = Transient ischemic attack
[d] Documented history of chronic renal failure and/or persistently elevated creatinine ≥1.5mg/dL
[e] Liver disease was defined as any document history of hepatitis B or C, cirrhosis, hepatic steatosis, or persistently abnormal liver function
[f] Any history of malignancy excluding basal cell carcinoma
[g] GI = Gastrointestinal

Results

Demographic characteristics of patients with atrial fibrillation are shown in Table 1. The main study population consisted of 695 patients on warfarin alone or combination therapy who met the inclusion criteria. We separated patients into the warfarin only or the warfarin plus aspirin groups. These groups had similar characteristics including age, rates of paroxysmal atrial fibrillation, CHADS$_2$ scores, and other comorbidities as specified in Table 1. The groups also had similar exposure times to warfarin at the start of the study which did not differ significantly (p=0.36). Approximately half of the patients in each group were on warfarin for over a year before the study start date, 218 (56.2%) in the warfarin only group and 152 (49.5%) in the combination group. A sizable portion of each group initiated warfarin therapy during the study period including 102 (26.3%) in the warfarin alone group and 96 (30.9%) in the combination group.

Overall, 44.2% of patients took aspirin and warfarin in combination for some length of

interval (CI). All regression models were performed separately with and without missing fields; the data were unchanged in both models.

Table 2: Patient medication profile

Medication	Overall	Warfarin	Combination	p Value
Aspirin, n (%)				
81 mg	-	-	246 (80.1)	-
162 mg	-	-	10 (3.3)	-
325 mg	-	-	51 (16.6)	-
Beta blocker	477 (68.6)	250 (64.4)	227 (72.9)	0.007
Dihydropyridine CCB[a]	122 (17.6)	68 (17.5)	54 (17.6)	0.98
Non-dihydropyridine CCB	92 (13.2)	60 (15.5)	32 (10.4)	0.05
Anti-arrhythmic[b]	168 (24.2)	77 (19.9)	91 (29.6)	0.003
Diuretic	395 (56.8)	219 (56.4)	176 (57.3)	0.82
Statin	457 (65.8)	214 (55.2)	243 (79.2)	<0.001
ACEI/ARB[c]	426 (61.3)	214 (55.2)	212 (69.1)	<0.001
Digoxin	127 (18.3)	73 (18.8)	54 (17.59)	0.68

[a] CCB = Calcium channel blockers
[b] Includes class Ia, Ib, Ic, and class III anti-arrhythmic medications.
[c] ACE/ARB = Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker

Table 3: Hemorrhagic outcomes

Variable	Warfarin	Combination	p Value
Any Hemorrhage[a]	27 (5.2)	24 (7.0)	0.29
Major	17 (3.4)	9 (2.8)	0.62
INR (SD)[b]	4.27 (±3.1)	3.13 (±1.5)	0.049[c]
Bleed Types			
Intracranial	5 (18.5)	2 (8.3)	0.41
Gastrointestinal	8 (29.6)	8 (33.3)	0.64

[a] Includes both major and minor hemorrhages.
[b] INR=International normalized ratio. INR measured on admission for hemorrhage or within 2 days prior to the admission. Most patients had INRs on admission recorded, 4 patients did not. SD = standard deviation
[c] One-tailed

Table 4: Characteristics of patients who hemorrhaged

Characteristic	Warfarin (n=27)	Combination (n=24)	p Value
Age	77.9	73.3	0.10
Female	13 (48.1)	7 (29.2)	0.17
Warfarin Exposure Time[a]			0.03
None	3 (11.1)	11 (45.8)	
<90 days	3 (11.1)	3 (12.5)	
≥90 days but <1 year	2 (3.9)	2 (3.9)	
≥1 year	19 (70.4)	8 (33.3)	
Target INR[b]			
1.7-2.0	1 (3.7)	0 (0)	
1.8-2.2	1 (3.7)	0 (0)	
2.0-2.5	0 (0)	2 (8.3)	
2.5-3.0	0 (0)	1 (4.2)	
2.0-3.0	25 (92.6)	21 (87.5)	
Bleeding history	12 (44.4)	5 (20.8)	0.07
GI hemorrhages	5 (18.5)	3 (12.5)	0.56
Non-GI hemorrhages	7 (25.9)	4 (16.7)	0.42

[a] Warfarin exposure as of June 1, 2007. Patients denoted as "None" started warfarin on or after June 1, 2007.
[b] Target INR specified in patient anticoagulation clinic record.

time during the study period. Cardiovascular risk factors were strong predictors for combination therapy use. Patients in the combination group had higher rates of documented dyslipidemia (77.5% vs 61.1%, p<0.001), prior myocardial infarction (31.9% vs 8.8%, p<0.001), coronary artery stent placement (18.2% vs 5.2%, p<0.001), coronary artery bypass grafting surgery (23.8% vs 8.5%, p<0.001), and diabetes mellitus (31.6% vs 22.4%, p<0.001). Males were more likely to be on combination therapy than females (69.7% vs 50.3%, p<0.001). Patients with an implanted pacemaker and/or cardiac defibrillator were more likely to be on combination therapy also (26.4% vs 19.6%, p=0.03). History of bleeding was similar in both groups. Other characteristics such as hypertension and a history of prior stroke or transient ischemic attack did not have a statistically significant difference between groups.

Concurrent medications are listed in Table 2. Of patients on combination therapy, 246 (80.1%) took 81 mg, 10 (3.3%) took 162mg, and 51 (16.6%) took 325mg daily. Patients on combination therapy were more likely to have concomitant use of statins, beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, as well as class Ia, Ib, Ic, and III anti-arrhythmic medications.

Tables 3 and 4 list the characteristics of the patients with hemorrhages and their bleeding events. Of 695 patients, 51 (7.3% of all patients or 6.3% per 100-people years) experienced hemorrhages of which 27 (5.2% per 100-people years) were on warfarin only and 24 (7.0% per 100-people years) were on combination therapy (p=0.29). Major hemorrhages comprised 26 (51.0%) of the 51 hemorrhages. Of the major hemorrhages, the warfarin only group experienced 17 (3.4% per 100-people years) and the combination group experienced 9 (2.8% per 100-people

years) (p=0.62). Intracranial hemorrhages accounted for 7 (0.87% per 100-people years) events overall with no significant difference between the groups (p=0.40). Gastrointestinal bleeding was the most common hemorrhage type and it accounted for 16 (2.0% per 100-people years) events. Each group experienced 8 gastrointestinal hemorrhages which accounted for 29.6% of bleeds in the warfarin only groups and 33.3% of bleeds in the combination group (p=0.64). No patients died of anticoagulation related hemorrhages.

Table 3 also shows the duration of exposure to warfarin before June 1, 2007 in relation to hemorrhagic events. In comparing the duration of warfarin exposure between the groups with hemorrhages, the combination group was more likely to have started warfarin during the study period than the warfarin only group. Of the patients in the combination group who bled, 11 (45.8%) started warfarin during the study period compared to 3 (11.1%) in the warfarin only group (p=0.03). Patients in the warfarin only group who had hemorrhages were likely to have been on warfarin for longer than one year (70.4% vs 33.3%).

The INR measured on presentation for any hemorrhage (or within 2 days of presentation in 4 cases) is shown in Table 3. The INR values for the warfarin alone group averaged 4.27 ±3.1 compared to the combination group which averaged 3.13 ±1.5 (one-tailed p=0.049). The target INR ranges for these patients are shown in Table 4. The groups had similar target INR ranges with the majority of patients targeted at an INR between 2.0 -3.0.

A multivariate analysis revealed that patients with a history of a prior gastrointestinal hemorrhage were 2.6 times more likely to have a bleed of any type compared with those who

did not have such a history (95% CI, 1.08-6.06). Likewise, patients with a history of non-gastrointestinal hemorrhages were 3.8 times more likely to have a bleed of any type compared with those who did not have a prior bleed (95% CI, 1.79-8.13). Patients in the combination group tended to be less likely to have a history of GI bleeding compared with the warfarin alone group (p=0.06).

In addition to the main study group of 695 patients, a small subgroup of 36 patients on triple therapy with warfarin, aspirin, and clopidogrel was identified. These patients were not included in the main study group, but we did observe and take note of a high rate of hemorrhages in this group. Six of the thirty-six patients (16.7%) experienced hemorrhagic events during the study period. These events included two major GI bleeds, three minor GI bleeds, and one minor spontaneous diffuse subcutaneous hemorrhage.

Discussion

Combination therapy with warfarin and aspirin is highly prevalent in patients with atrial fibrillation. Patients on combination therapy were more likely to be male with a history of coronary artery disease, have had interventions for coronary artery disease, and have diabetes mellitus. When used in combination, the most common dose of aspirin was 81 mg daily. Patients in this study who were on combination therapy were not statistically more likely to have hemorrhages when compared to the warfarin alone group. Both groups had hemorrhage rates similar to those reported by other studies.[9,13,16] However, patients on combination therapy had on average lower INR measurements when they presented with bleeding. This finding suggests that combination therapy may alter the risk of bleeding independent of the INR level. Triple therapy deserves further research as it appears to be associated with a much higher risk of bleeding, particularly gastrointestinal bleeding. Though the sample size was small in this study, other studies have found that triple therapy dramatically increases the risk of major bleeding compared to other antithrombotic regimens including warfarin alone.[17,18]

This study does not show a statistically significant difference in hemorrhagic outcomes between warfarin alone and combination warfarin and aspirin. In considering our results in the context of the current literature on this topic, we recommend caution in using combination therapy. No strong data substantiates a benefit to the aspirin and warfarin combination, and several prior studies have demonstrated an increased rate of major hemorrhage with combination therapy.[13,14,19,20] Combination therapy appears to be as safe as monotherapy in our study population which was closely managed by a dedicated physician and nurse practitioner staffed anticoagulation clinic. Patients in this study received frequent and well documented counseling about the hemorrhagic risks of warfarin. Early identification of bleeding events and elevated INR measurements by the anticoagulation clinic led to interventions such as modifying warfarin dosing, altering doses of other medications, counseling on behavioral factors, and direction to go to the emergency department. We believe these interventions may have reduced major bleeds and likely prevented bleeding in general. Bleeding risk may vary depending on the practice settings. Clinical pharmacy anticoagulation services, such as the anticoagulation clinic in this study, have been shown to provide closer monitoring and improved outcomes compared with care provided by personal physicians alone.[21,22]

The interpretation of this study must be tempered with a consideration of its limitations. The reporting of hemorrhagic events was

heterogeneous. Most patients presented to the university hospital or its affiliated institutions which reported bleeding events to the anticoagulation clinic. Some patients presented to outside hospitals and later reported their bleeding to the anticoagulation clinic or to their primary care physician whose records we reviewed. Therefore, hemorrhage rates may be understated as they depended on patient self-reporting. The patients in this study had a high level of coronary artery disease and other cardiac conditions, which may account for the high incidence of combination therapy. Patient populations with less cardiac disease may find a lower incidence of combination therapy. In addition, our patients were exclusively managed by the anticoagulation clinic. The findings of this study may not be generally applicable to all patient settings. Finally, this study did not systematically evaluate outcomes other than hemorrhages. Therefore, this study was not equipped to examine efficacy of treatment with warfarin versus warfarin plus aspirin.

In conclusion, in this study of patients with atrial fibrillation, combination therapy with warfarin and aspirin did not statistically increase the risk of hemorrhage. A prior history of any type of bleeding was associated with an increased risk of future bleeding when using warfarin. Physicians should exercise caution in prescribing warfarin either alone or in combination when there has been a history of bleeding. Patients on combination therapy frequently hemorrhaged with INR levels at or near therapeutic levels, suggesting that they may need closer monitoring to ensure that the target INR is not exceeded. Further study of the relationship between combination therapy and INR accuracy in predicting hemorrhage is needed. The issue of triple therapy, which was only tangentially examined in this study, requires closer examination as it appears to be associated with a high rate of hemorrhages.

References

1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-867.
2. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA 2003;290:2685-2692.
3. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with nonvalvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. Cochrane Database of Syst Rev 2005;3:CD001927.
4. Harrington RA, Becker RC, Ezekowitz M, et al. Antithrombotic therapy for coronary artery disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:513S-548S.
5. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. JAMA 1999;282:2058-2067.
6. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969-974.
7. Gattellari M, Worthington J, Zwar N, Middleton S. Barriers to the use of anticoagulation for nonvalvular atrial fibrillation: a representative survey of Australian family physicians. Stroke 2008;39:227-30.
8. Darkow T, Vanderplas AM, Lew KH, Kim J, Hauch O. Treatment patterns and real-world effectiveness of warfarin in nonvalvular atrial fibrillation within a managed care system. Curr Med Res Opin 2005;21:1583-1594.
9. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial

fibrillation. Circulation 2007;115:2689-2696.

10. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database of Syst Rev 2007;3:CD006186.

11. Clappers N, Brouwer MA, Verheugt FW. Antiplatelet treatment for coronary heart disease. Heart 2007;93:258-265.

12. Johnson SG, Witt DM, Eddy TR, Delate T. Warfarin and antiplatelet combination use among commercially insured patients enrolled in an anticoagulation management service. Chest 2007;131:1500-1507.

13. Johnson SG, Rogers K, Delate T, Witt DM. Outcomes associated with combined antiplatelet and anticoagulation therapy. Chest 2008;133:948-954.

14. Flaker GC, Gruber M, Connolly SJ, et al. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: an exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials. Am Heart J 2006;152:967-973.

15. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-2870.

16. Copland M, Walker ID, Tait RC. Oral anticoagulation and hemorrhagic complications in an elderly population with atrial fibrillation. Arch Intern Med 2001;161:2125-2128.

17. Hermosillo AJ, Spinler SA. Aspirin, clopidogrel, and warfarin: is the combination appropriate and effective or inappropriate and too dangerous? Ann Pharmacother 2008;42:790-805.

18. Manzano-Fernández S, Pastor FJ, Marín F, et al. Increased major bleeding complications related to triple antithrombotic therapy usage in patients with atrial fibrillation undergoing percutaneous coronary artery stenting. Chest 2008;134:559-567.

19. Shireman TI, Howard PA, Kresowik TF, Ellerbeck EF. Combined anticoagulant-antiplatelet use and major bleeding events in elderly atrial fibrillation patients. Stroke 2004;35:2362-2367.

20. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. Stroke 2005;36:1588-1593.

21. Witt DM, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ. Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. Chest 2005;127:1515-1522.

22. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. Arch Intern Med 1998;158:1641-1647.