Antithrombotic Therapy Practices in US Hospitals in an Era of Practice Guidelines

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Background: Antithrombotic therapy is efficacious for the prevention of thromboembolic disease, but it necessitates careful risk-benefit assessment.

Methods: Antithrombotic therapy data were retrospectively collected from inpatient medical records at 38 US hospitals. Patients treated for atrial fibrillation, acute myocardial infarction, deep vein thrombosis, or pulmonary embolism and patients given prophylaxis for total knee replacement, total hip replacement, or hip fracture surgery between July 1, 2000, and June 30, 2003, were randomly selected.

Results: The medical records of 3778 patients (53.3% men) were included. The mean patient age was 66.1 years. Of patients with atrial fibrillation at high risk for stroke, only 54.7% received warfarin sodium, and 20.6% received neither aspirin nor warfarin. Of patients with acute myocardial infarction, only 75.5% received aspirin on hospital arrival. After orthopedic surgery procedures, only 85.6% of patients received prophylaxis with a parenteral anticoagulant agent or warfarin. In 49.4% of patients with deep vein thrombosis or pulmonary embolism were rarely discharged from the hospital with bridge therapy (an injectable anticoagulant agent plus warfarin), although the length of hospitalization was significantly shorter than if discharged taking warfarin alone (4.0 vs 8.1 days; \( P < .001 \)).

Conclusions: A significant percentage of hospitalized patients do not receive adequate antithrombotic therapy for the primary and secondary prevention of thromboembolic disease.

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THROMBOSIS IS THE MOST common singular cause of death and a significant public health concern in the United States. Arterial disease accounts for an estimated 1.5 million patients with acute myocardial infarction (AMI)\(^1,2\) and 780 000 strokes annually.\(^3,4\) Venous disease affects another 2 million patients, with approximately 600 000 of those developing pulmonary embolism (PE).\(^5\) Acute and chronic illness increases the predisposition to thrombosis. In an era of broadly accepted guidelines for thromboembolic disease, our nation’s hospitals can favorably affect disease burden in individuals with inherent risks of initial and subsequent thrombotic events by identifying at-risk individuals and initiating preventive treatment.

See also pages 1455 and 1469

Methods

The National Anticoagulation Benchmark and Outcomes Report (EPI-Q Inc) is a national multicenter benchmark database. It was created in December 2002 with input from an advisory board of practicing clinicians in the area of anticoagulation. Hospitals were invited to participate to achieve an approximate balance of 1:1 between academic and community-based providers, with even regional distribution throughout the United States. We included 4 Veterans Affairs medical centers. Seventy-five invitations were issued, and the first 40 hospitals that responded were selected. Two hospitals withdrew from the study because they could not secure trained data collection personnel.

Author Affiliations are listed at the end of this article.

Group Information: A list of the members of the NABOR Steering Committee appears on page 1464.

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Patient medical records were eligible for inclusion based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes after hospital discharge. Included were patients discharged with a diagnosis of AMI (ICD-9-CM codes 410.01-410.91), AF (ICD-9-CM code 427.31), PE (ICD-9-CM codes 415.11 and 415.19), DVT (ICD-9-CM code 433.8), pregnancy-related DVT (ICD-9-CM codes 671.00-671.94), pregnancy-related PE (ICD-9-CM codes 673.0-673.8), THR (Current Procedural Terminology [CPT] code 81.51), TKR (CPT code 81.54), hip fracture repair (ICD-9-CM codes 820-820.19 or 820.8-820.9 plus CPT code 81.32 for partial hip replacement or 78.35, 79.10, 79.15, 79.30, or 79.35 for internal fixation). Patients were excluded if they were younger than 18 years, were admitted from another acute care hospital where therapy was already instituted, or were discharged to another acute care hospital to continue treatment or if medical records were miscoded.

Lists of patients were generated by each medical center for the study period (January 1, 2002, through June 30, 2003). From these lists, 25 medical records for each of the 4 anticoagulation indications were selected randomly. One medical center included patients treated beginning July 1, 2000, to obtain the requested number of medical records for that site.

Data were abstracted from each medical record using a standard data collection form and data dictionary. Medical record review was performed on site by health system personnel after a training session. Data were entered into the National Anticoagulation Benchmark and Outcomes Report data entry software and were validated by the software program for completeness and consistency of entry, with patient-identifying information removed. On receipt of data at EPI-Q, data were queried again for inconsistencies, and all queries were resolved before data analysis.

STATISTICAL ANALYSIS

Descriptive and univariate methods were used to describe the distribution of patients among anticoagulation categories and to examine indicator performance between the site and the benchmark. Descriptive statistics were used to describe the baseline prevalence of risk factors for bleeding and embolic events, to evaluate treatment selection and use among the antithrombotic indications, and to describe deviation of treatment from nationally accepted evidence-based guidelines. Differences in treatment selection for AF based on classification were examined using a chi² test for categorical data. Differences in treatment selection by type of procedure were also examined using a chi² test. Differences in length of stay (LOS) were examined using a Mann-Whitney U test for nonnormally distributed data.

A total of 3778 patient medical records were included from 21 teaching, 13 community, and 4 Veterans Affairs hospitals located in 28 different states. There were 945, 966, 939, and 928 patients with the diagnoses of AF, AMI, DVT or PE, and orthopedic surgery, respectively. The mean patient age was 66.1 years, ranging from a low of 59.4 years in patients with DVT or PE to a high of 71.5 years in those with AF. Of the total population, 2013 (53.3%) were men. The most frequently reported comorbidities included hypertension, coronary artery disease, a history of AF, and diabetes mellitus (Table 1).

Of the 945 patients with AF, 486 (51.4%) were classified as paroxysmal vs 453 (47.9%) as persistent or permanent. Six patients (0.6%) had insufficient documentation to determine classification. Of this entire group, 321 (34.0%) represented new AF and 622 (65.8%) had documented recurrence. Two patients (0.2%) had insufficient documentation to determine the type of event. Most patients hospitalized with AF (n=814; 86.1%) were classified as having a high stroke risk using the American College of Chest Physicians risk stratification schemata (Table 2). However, there was a large gap between practice and treatment according to guidelines. Of the 814 high-risk patients, only 445 (54.7%) received warfarin sodium. The remainder of the high-risk patients received aspirin alone (n=201) or no treatment at all (n=168) (Figure 1). Of these patients, 207 did not receive warfarin. Patients with persistent or permanent AF were more likely to receive warfarin (Table 3).

Of the 369 high-risk patients not receiving warfarin, 159 (43.1%) had no documented contraindications. Conversely, 133 (41.3%) were subjectively determined to be at risk for falls, 62 (16.8%) had neuropsychiatric impairment, 54 (14.6%) had previous bleeding, 47 (12.7%) had ulcer disease, and 19 (5.1%) had a history of aneurysm. Of 168 high-risk patients receiving no treatment, 32 (19.0%) were receiving nonsteroidal anti-inflammatory agents and 6 (3.6%) were receiving clopidogrel bisulfate.

Of the 928 patients included who had undergone orthopedic surgery, 358 (38.6%) had THR, 284 (30.6%) had THR, and 291 (31.4%) had hip fracture repair. Inadequate prophylaxis was administered in 134 patients (14.4%); 77 (8.3%) received only aspirin and 57 (6.1%) received no prophylaxis (Table 4). Patients who underwent hip fracture repair were more likely than those who underwent THR and THR to receive no prophylaxis (13.4% vs 2.8% and 3.2%, respectively; P < .001).

Patients who underwent THR and THR received a mean±SD of 3.2±2.4 and 3.4±3.0 days of postprocedure anticoagulation therapy, respectively. Only 261 patients who underwent THR (72.9%) and 206 patients who underwent THR (72.5%) received a prescription for postdischarge anticoagulant agents. Patients who underwent hip fracture repair received a mean±SD of 4.7±3.1 days of postprocedure therapy, and fewer (n=153; 52.6%) received a prescription for postdischarge therapy (Figure 2).

SECONDARY PREVENTION

Of 966 patients with AMI, 592 (61.3%) were classified as having unstable angina/non–ST-segment elevation myocardial infarction (UA/NSTEMI) and 365 (37.8%) as having ST-segment elevation myocardial infarction (STEMI). The remaining 9 patients had insufficient documentation to classify. Most patients were men (n=592; 61.3%). Of the total, 501 patients (51.9%) were revascularized, occurring more frequently in patients with STEMI (n=251;
Of 939 patients diagnosed as having DVT, PE, or both, 32 (3.4%) died during hospitalization. Of these 939 patients, 495 (52.7%) had DVT without diagnosed PE, 267 (28.4%) had PE without diagnosed DVT, and 177 (18.8%) had DVT and PE. Most patients (n=562; 59.8%) received parenteral unfractionated heparin. Low-molecular-weight heparin was also widely used (n=527; 56.1%). There was a small subset of patients (n=78; 8.3%) who received adjusted-dose subcutaneous unfractionated heparin (Table 5). There was inconsistent practice regarding discontinuation of the use of unfractionated heparin or low-molecular-weight heparin. Of the 486 patients who received overlapping (bridge) therapy (a parenteral agent plus warfarin), only 246 (50.6%) had an international normalized ratio (INR) of at least 2.0 for 2 consecutive days before discontinuation of the parenteral agent. In those without 2 consecutive days of a therapeutic INR, only 30.8% had 4 or more days of concurrent treatment. Of 362 patients who were discharged without 2 consecutive days of an INR of 2.0 or greater, 39.5% (n=143) did not receive unfractionated heparin or low-molecular-weight heparin after discharge. Most patients were not discharged from the hospital until the parenteral drug was discontinued (n=460; 50.7%), with only 241 patients (26.6%) being discharged taking a bridge regimen. In patients discharged taking a bridge regimen vs warfarin alone (long-term therapy), mean±SD LOS was 8.7 (7.5%) received clopidogrel or ticlopidine hydrochloride at hospital discharge.

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ing which treatment was discontinued before hospital discharge. These patients were categorized as “other” and had a mean±SD LOS of 12.7±17.8 days.

ANTICOAGULATION MANAGEMENT

Of the 1749 patients who received warfarin at any time during hospitalization, 157 (9.0%) had at least 1 INR value greater than 4.0, 14 (0.8%) experienced major hemorrhage, 120 (6.9%) experienced minor hemorrhage (hematoma, microscopic hematuria, epistaxis, or ecchymosis), and 65 (3.7%) were administered phytonadione. Of the total patient population, 1640 (43.4%) were discharged from the hospital taking warfarin, and 300 of these patients (18.3%) were referred to an anticoagulation management service at discharge. Overall, the mean±SD INR at hospital discharge was at the lowest end of the therapeutic range at 2.0±0.9.

COMMENT

Despite substantial evidence that risk-modifying therapy and appropriate treatment can reduce morbidity and mortality from thrombosis, these findings indicate that there is an important opportunity for improving the primary and secondary prevention of thromboembolic disease. Our results demonstrate that an unacceptable number of patients with high-risk AF, orthopedic surgery, AMI, or DVT or PE did not receive adequate prophylaxis or treatment. Although our sample of hospitals was geographically balanced, more than half were academic institutions, which is overrepresentative of the population of US hospitals as a whole. However, studies suggest that adherence to accepted standards of care is greater at academically affiliated hospitals, and it is possible that our findings actually exceed typical practice in the United States.

Data from longitudinal studies indicate recent increases in the use of warfarin in AF from a low of 12% in 1990 to a high approaching 58% in 2001. The Centers for Medicare & Medicaid Services reported similar findings, with a national median of 57% of patients hospitalized with AF receiving warfarin. Our findings are comparable, with 57% adherence to treatment guidelines for all risk strata and 54.7% utilization of warfarin in those at high risk for stroke. Most alarming was the observation that 20.6% of high-risk patients received no anticoagulation therapy, with many having no apparent contraindication to warfarin. There is no guideline recommendation that aspirin is indicated for stroke prevention in those older than 75 years or others in the high-risk group, although aspirin was the only prophylaxis provided to 24.7% of the patients in this group.

![Figure 1. Atrial fibrillation treatment by American College of Chest Physicians risk category: low-risk patients (n=70) (A), moderate-risk patients (n=61) (B), high-risk patients (n=814) (C), and all patients (N=945) (D).](image-url)

Table 3. Treatment of Atrial Fibrillation by Classification and Type of Event

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Classification, No. (%)</th>
<th>Type of Event, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paroxysmal (n=486)</td>
<td>Persistent/Permanent (n=453)</td>
</tr>
<tr>
<td></td>
<td>First (n=321)</td>
<td>Recurrent (n=622)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>128 (26.3)</td>
<td>189 (41.7)</td>
</tr>
<tr>
<td>Warfarin plus aspirin</td>
<td>102 (21.0)</td>
<td>85 (18.8)</td>
</tr>
<tr>
<td>Aspirin alone</td>
<td>145 (29.8)</td>
<td>87 (19.2)</td>
</tr>
<tr>
<td>No treatment</td>
<td>111 (22.8)</td>
<td>92 (20.3)</td>
</tr>
</tbody>
</table>

P Value: *By χ² test for categorical variables.
Taking nonsteroidal anti-inflammatory drugs.22 Our study gastrointes- 
tinal tract bleeding or in those concurrently vorced therapy in in-
dividuals with a high risk of upper the low-risk population that warfarin may not be the fa-
ture therapy in individuals with a high risk of upper gastrointestinal tract bleeding or in those concurrently taking nonsteroidal anti-inflammatory drugs.22 Our study shows that among patients hospitalized with AF, those older than 80 years are less likely to receive warfarin, yet AF is responsible for as many as 25% of strokes in individuals aged 75 to 84 years.23,24 A potentially poor un-
derstanding of the risk-benefit ratio of warfarin sug-

WEIGHING THE RISKS AND BENEFITS OF ORAL ANTICOAGULATION THERAPY WITH WARFARIN

The decision to use warfarin requires consideration of risk and benefit.1415 In AF, randomized trials20-21 show virtually no increase in the frequency of major hemorrhage comparing warfarin (1.3%), aspirin (1.0%), and placebo (1.0%) groups, and these trials show an observed rate of intracranial hemorrhage in patients older than 75 years of only 0.8% per year. Yet, it has been shown in the low-risk population that warfarin may not be the fa-
vored therapy in individuals with a high risk of upper gastrointestinal tract bleeding or in those concurrently taking nonsteroidal anti-inflammatory drugs.22 Our study shows that among patients hospitalized with AF, those older than 80 years are less likely to receive warfarin, yet AF is responsible for as many as 25% of strokes in individuals aged 75 to 84 years.23,24 A potentially poor under-
standing of the risk-benefit ratio of warfarin sug-

gests the need for practitioner education that promotes primary prevention. Almost 15% of patients who under-
went orthopedic surgery received aspirin only or no pro-
phylaxis. No prophylaxis use was most frequently ob-
served, except in patients who took a routine dose of as-
pirin within 24 hours of the event. Centers for Medicare 
and Medicaid Services data13 from 2000-2001 demon-
strate a higher occurrence of early aspirin administra-
tion. Our findings indicate that the duration of therapy is inadequate for many patients.

USE OF ASPIRIN AFTER AMI

Aspirin is generally the preferred agent for the second-
ary prevention of vascular events and death after AMI be-
cause of its ease of use, low cost, and proven efficacy. Sup-
porting data31-33 indicate that early administration of aspirin improves survival and reperfusion rates over later administration. Therefore, we measured the frequency of aspirin administration within 8 hours of arrival at the hospital or within 8 hours of an event when hospital-
ized, except in patients who took a routine dose of as-
pirin within 24 hours of the event. Centers for Medicare & Medicaid Services data13 from 2000-2001 demon-
strate a higher occurrence of early aspirin administra-
tion (85%) than our results (75.5%). The difference is possibly because Centers for Medicare & Medicaid Ser-

cifics indicators define aspirin administration within 24 hours and our results reflect administration within 8 hours. Our findings indicate that improvement is still needed to realize the clinical and public health impact of aspirin therapy.
GUIDELINES recommend that unfractionated heparin or low-molecular-weight heparin administration be continued for a minimum of 4 to 5 days and until the INR has been at least 2.0 for a minimum of 2 consecutive days. Our data suggest that only half of all patients who initiated warfarin therapy reached an INR of 2.0 or greater for 2 consecutive days before the parenteral agent was discontinued. Only a few patients without a therapeutic INR for 2 consecutive days had 4 days of concurrent unfractionated heparin or low-molecular-weight heparin and warfarin therapy. Concurrent therapy must be long enough to ensure adequate anticoagulation.

We observed that a large proportion of patients with DVT or PE had their hospital discharge delayed until parenteral therapy was discontinued. Only one-fourth were discharged with bridge therapy. The success of outpatient treatment programs demonstrates that DVT may often be safely managed outside the hospital. The mean reduction in LOS was 4.1 days for those discharged with bridge therapy. The low rate of referral to anticoagulation management clinics may have affected the hospital discharge decision. Our results point to a potential economic benefit in the treatment of DVT in the outpatient setting.

IMPLICATIONS

Inconsistent adherence to guidelines and use of antithrombotic therapy may reflect differences in physician knowledge, attitudes, and beliefs and system inefficiencies, skewed incentives, organizational culture, or deference to patient preference. Some researchers have suggested that more importance is attached to the perceived risks of therapy than to the benefits, foretelling an unwillingness to accept the risk associated with current therapies. The complex management required to administer an anticoagulant, maintain a therapeutic range, or simply screen for drug interactions and educate patients about diet may also be issues. It is crucial to overcome these potential barriers so that we can better protect patients from initial and recurrent thrombotic events. Failure has too great a price from a greater public health perspective and for individuals unnecessarily afflicted.

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Table 5. Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) Treatment Selection*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>DVT (n = 495)</th>
<th>PE (n = 267)</th>
<th>DVT and PE (n = 177)</th>
<th>Total (N = 939)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-molecular-weight heparin</td>
<td>286 (57.8)</td>
<td>147 (55.1)</td>
<td>94 (53.1)</td>
<td>527 (56.1)</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>256 (51.7)</td>
<td>185 (69.3)</td>
<td>121 (68.4)</td>
<td>562 (59.8)</td>
</tr>
<tr>
<td>Adjusted-dose subcutaneous heparin</td>
<td>45 (9.1)</td>
<td>23 (8.6)</td>
<td>10 (5.6)</td>
<td>78 (8.3)</td>
</tr>
<tr>
<td>Direct thrombin inhibitor</td>
<td>3 (0.6)</td>
<td>2 (0.7)</td>
<td>1 (0.6)</td>
<td>6 (0.6)</td>
</tr>
</tbody>
</table>

*Includes deaths. Percentages sum to greater than 100% because some patients received multimodality therapy.

**Figure 3.** Treatment at hospital discharge (A) and mean±SD length of stay (LOS) (B) for patients with deep vein thrombosis, pulmonary embolism, or both. The following were statistically significant by the Mann-Whitney U test: acute vs bridge (P<.01), acute vs long-term (P<.01), and long-term vs bridge (P<.001). Acute therapy consists of injectable anticoagulation only; bridge therapy, a parenteral agent plus warfarin sodium; long-term therapy, warfarin alone; and other, either discontinuous treatment or an extended LOS during which treatment was discontinued before hospital discharge.

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REFERENCES


