Objectives: To describe the prevalence of preinjury warfarin use in a large national sample of trauma patients and to define the relationship between preinjury warfarin use and mortality.

Design: Retrospective cohort study.

Setting: The National Trauma Databank.

Patients: All patients admitted to eligible trauma centers during the study period; 1,230,422 patients (36,270 warfarin users) from 402 centers were eligible for analysis.

Main Outcome Measures: Prevalence of warfarin use and all-cause in-hospital mortality. Multivariate logistic regression was used to estimate the odds ratio (OR) for mortality associated with preinjury warfarin use.

Results: Warfarin use increased among all patients from 2.3% in 2002 to 4.0% in 2006 (P < .001), and in patients older than 65 years, use increased from 7.3% in 2002 to 12.8% in 2006 (P < .001). Among all patients, 9.3% of warfarin users died compared with only 4.8% of nonusers (OR, 2.02; 95% confidence interval [CI], 1.95-2.10; P < .001). After adjusting for important covariates, warfarin use was associated with increased mortality among all patients (OR, 1.72; 95% CI, 1.63-1.81; P < .001) and patients 65 years and older (OR, 1.38; 95% CI, 1.30-1.47; P < .001).

Conclusions: Warfarin use is common among injured patients and its prevalence has increased each year since 2002. Its use is a powerful marker of mortality risk, and even after adjusting for confounding comorbidities, it is associated with a significant increase in death.

who had fallen. To account for confounders, Grandhi et al. used propensity scores to establish pseudorandomization and detected a higher mortality rate in preinjury warfarin users (39% vs 23%; P = .04).

Even if one assumes a relationship between warfarin use and increased mortality, it remains uncertain as to whether the increased mortality is due to preinjury anticoagulation or if warfarin use serves as a marker for comorbidities that contribute to worse outcomes. Our objective was to describe the national prevalence of preinjury warfarin use among patients presenting to a sample of US trauma centers and to describe the use-specific risk of mortality associated with warfarin. We hypothesized that the preinjury warfarin use would be independently associated with worse outcomes after trauma. To our knowledge, this is the first study that details preinjury warfarin use and its use-specific mortality after trauma across of large number of US trauma centers.

METHODS

STUDY DESIGN AND DATA SOURCE

We conducted a retrospective cohort study of trauma centers submitting data to the National Trauma Databank (NTDB) from 2002 to 2007. The NTDB is a large aggregated database with nearly 2 million individual deidentified records about trauma incidents from more than 770 voluntarily participating trauma centers across the United States and Puerto Rico. The registry is administered by the American College of Surgeons and aims to inform the medical community and policy makers about a wide variety of issues that characterize the current state of care for injured persons (https://www.ntdbdatacenter.com). The data set consists of 14 separate files. It contains patient-level data for each patient’s demographics, mechanism of injury, procedures, hospital course, complications, and outcomes, as well as facility-level data for each hospital’s type, size, and region.

PATIENT SELECTION AND DEFINITIONS

Eligible patients included all patients admitted to eligible trauma centers during the study period. Eligible trauma centers included all trauma centers contributing to the NTDB who submitted data for at least 1 comorbidity code during the 2002 to 2007 study period. Each data element of the NTDB is voluntary, and many centers choose not to submit information on comorbidities. Since this field is required for classification of warfarin use, centers not submitting at least 1 comorbidity code were excluded. Individual patients were excluded if they were younger than 16 years since children typically lack indications for long-term anticoagulation and their inclusion would falsely lower the prevalence of warfarin users presenting to adult trauma centers. Patients were classified into the warfarin users group if they had “Coumadin use” listed in the comorbidity field. Patient age, sex, and comorbidities as well as injury-specific information were also obtained from the NTDB.

The primary outcome of interest was the prevalence of warfarin use among eligible trauma patients represented in the NTDB and all-cause in-hospital mortality. The proportion of patients classified as warfarin users was reported for all patients and for those older than 65 years. These proportions were also stratified by year of discharge. Mortality odds were reported for all patients and those older than 65 years and adjusted for clinically important covariates. Secondary outcomes of interest included injury mechanism, severity and patterns, hospital length of stay, intensive care unit length of stay, and injury-specific mortality.

STATISTICAL ANALYSIS

Normally distributed continuous variables are summarized by the mean and standard deviation and compared using the t test. Nonnormally distributed continuous variables are summarized by the median and interquartile range and compared using the Wilcoxon rank sum test. Proportions are compared using the χ² test. Univariate and multivariate logistic regression was used to estimate the odds of mortality associated with warfarin use. Multivariate models were constructed by including clinically relevant variables that were found to be differentially distributed in the univariate analysis (P < .05). The NTDB contains completely deidentified data and the Vanderbilt University institutional review board granted exemption status for this project.

RESULTS

During the study period, 770 trauma centers submitted data on 1,926,245 patients to the NTDB. At least 1 comorbidity code was reported by 402 centers (52%). These centers accounted for 1,416,708 patients (73%). The excluded trauma centers were primarily state-designated level IV centers or had missing information regarding center designation. Of the 1,416,708 patients from eligible centers, 186,286 patients (13%) and 35 warfarin users (<0.01%) were excluded because of a reported age younger than 16 years. In total, the eligible cohort included 52% of centers, 64% of patients, and more than 99% of warfarin users.

THE PREVALENCE OF WARFARIN USE IN US TRAUMA CENTERS

Of the 1,230,422 eligible patients, 36,270 patients (3%) and 26,841 patients older than 65 years (9%) were classified as warfarin users. The proportion of patients classified as warfarin users increased from 2.3% (2002) to 4.0% (2006) in all patients and from 7.3% (2002) to 12.8% (2006) in patients older than 65 years (Figure 1).
Table 1. Demographics and Clinical Characteristics of Patients by Preinjury Warfarin Use

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=1 194 152)</th>
<th>Warfarin Users (n=36 270)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>43.2 (20.3)</td>
<td>71.8 (12.7)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Female</td>
<td>35</td>
<td>47</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian or Pacific Island</td>
<td>1.2</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>16.3</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>7.9</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>7.9</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>White, not Hispanic</td>
<td>66.9</td>
<td>87.4</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7.0</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.04</td>
<td>0.24</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>COPD</td>
<td>2.0</td>
<td>0.7</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.2</td>
<td>1.3</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Dialysis dependence</td>
<td>0.7</td>
<td>11.9</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>0.1</td>
<td>0.7</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Prior cardiac surgery</td>
<td>0.02</td>
<td>0.02</td>
<td>.89b</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.5</td>
<td>10.2</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Insulin-dependent diabetes</td>
<td>0.07</td>
<td>0.37</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Non–insulin-dependent diabetes</td>
<td>2.3</td>
<td>12.4</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Obesity</td>
<td>7.0</td>
<td>20.0</td>
<td>&lt;.001b</td>
</tr>
</tbody>
</table>

Abbreviation: COPD, chronic obstructive pulmonary disease.

a Compared using t test.

b Compared using chi² test.

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PREINJURY WARFARIN USERS

The demographic and clinical characteristics of all patients by warfarin use are summarized in Table 1. Preinjury warfarin use is a function of age, with the prevalence increasing dramatically between the ages of 45 and 70 years (Figure 2). Warfarin users were also more likely to be female and non-Hispanic white and to have a number of comorbidities, including coronary artery disease, congestive heart failure, dialysis dependence, nonemphysematous pulmonary disease, hypertension, diabetes mellitus, and obesity. These patterns persisted when stratifying for age older than 65 years (Table 2).

Among all patients, warfarin users were more likely to have blunt mechanism injuries (87% vs 96%; P < .001) and were more likely to sustain these injuries in the home or in residential institutions. They were less likely to sustain injuries on streets or highways (Table 3). As a group, warfarin users had more severe injuries as compared with non–warfarin users (median Trauma-Related Injury Severity Score, 0.99 for nonusers and 0.97 for warfarin users; P < .001 and mean Injury Severity Score of 10 for nonusers and 11 for warfarin users; P < .001). Warfarin users were more likely to present with an intracranial hemorrhage (2.8% vs 5.0%; P < .001 for all patients and 4.0% vs 5.3%; P < .001 for patients >65 years). Among all patients, warfarin users were less likely to be classified as having a severe head injury (Glasgow Coma Scale score of <8 on presentation) if an intracranial hemorrhage was present (27% vs 16%; P < .001 for all patients), but there was no difference in severity for patients with intracranial hemorrhage who were 65 years or older (16% vs 15%; P = .27).

THE RELATIONSHIP BETWEEN PREINJURY WARFARIN USE AND MORTALITY

Among all patients, 9.3% of warfarin users died compared with only 4.8% of nonusers (odds ratio [OR], 2.02; 95% confidence interval [CI], 1.95-2.10; P < .001). Because of the significant relationship between age and war-
Warfarin use, we stratified these unadjusted ratios by age. For patients younger than 65 years, the OR for death of warfarin users was 1.51 (95% CI, 1.38-1.65; P < .001). For patients older than 65 years, the OR was 1.41 (95% CI, 1.36-1.47; P < .001). These unadjusted mortality odds suggest that whether or not warfarin user has a mechanistic link to increased trauma mortality, its use indicates a constellation of demographic and clinical characteristics that collectively increases the odds of death in all patients taking warfarin. Among all patients with intracranial hemorrhage (n = 34,920), warfarin users had a significantly increased mortality as compared with nonusers (22% vs 18%; OR, 1.30; 95% CI, 1.15-1.45; P < .001). However, among patients 65 years and older with intracranial hemorrhage (n = 12,180), there was no difference in mortality by warfarin use (23% for nonusers and 24% for users; P = .67). The most significant difference between warfarin groups in patients with intracranial hemorrhage was among younger patients with an intracranial hemorrhage classified as severe. Among these patients, 51% of warfarin users died while only 37% of nonusers died (P < .001).

As evidenced by the univariate analysis, warfarin use is associated with a number of demographic and clinical characteristics that are known to be related to trauma mortality. To adjust for potential confounding, we created a multivariate logistic model using demographic and clinical characteristics (comorbidities) determined to be related to warfarin use in the univariate analysis. The most parsimonious model adjusted sex, age, Trauma-Related Injury Severity Score, race, chronic obstructive pulmonary disease, nonemphysematous pulmonary disease, coronary artery disease, dialysis dependence, and treatment facility (Table 4). In this model, warfarin use was associated with a significantly higher odds of death both among all patients (OR, 1.72; 95% CI, 1.63-1.81; P < .001; R² = 0.27; area under the receiver operating characteristic curve = 0.792; Hosmer-Lemeshow goodness-of-fit P < .01). For patients with intracranial hemorrhage, chronic obstructive pulmonary disease and coronary artery disease did not contribute significantly to the model and were therefore dropped. Among all patients with intracranial hemorrhage, the OR for death was 1.26 for warfarin users (OR, 1.07-1.48; P = .005; R² = 0.21; area under the receiver operating characteristic curve = 0.833), but the OR for death increased significantly to the model and were therefore dropped. Among all patients with intracranial hemorrhage, the OR for death was 1.26 for warfarin users (OR, 1.07-1.48; P = .005; R² = 0.21; area under the receiver operating characteristic curve = 0.833), but the OR for death increased to 1.46 (OR, 1.00-2.12; P = .05; R² = 0.24; area under the receiver operating characteristic curve = 0.847) for patients younger than 65 years.

### Comment

Warfarin is a commonly used anticoagulant and its use among trauma patients has become increasingly significant. These data provide an important estimate of the prevalence of preinjury warfarin use among patients treated at centers submitting data to the NTDB. Not only is preinjury warfarin use common among these patients—particularly those 65 years and older—it is also increasing. Warfarin use is primarily a function of age, but it is also associated with a number of comorbidities in younger patients as well. Understanding the relationship between preinjury warfarin use and trauma outcomes and how to mitigate its adverse effects in the injured patient becomes of critical importance. These data support other reports that suggest that patients who undergo preinjury anticoagulation with warfarin are at increased risk of death after trauma.4-11 Among all patients and injury patterns, warfarin use is associ-
ated with a 2-fold increase in mortality. While stratification for age and injury pattern reduced the magnitude of this association, warfarin use remains a significant independent risk factor for death from injury. The most profound impact is among younger patients with head injuries. While older patients with severe head injuries have high mortality rates whether or not they are warfarin users, preinjury warfarin use increases the mortality from severe head injury by 50% in patients younger than 65 years.

Whether warfarin plays a mechanistic role in adverse outcomes or serves as a marker for a comorbidity constellation that leads to worse outcomes cannot completely be settled via retrospective studies. In these data, the relationship between increased mortality and death persisted after controlling for covariates available in the NTDB. Whether there are other unmeasured confounders that account for these findings rather than warfarin use is unknown. Pieracci et al reported that the degree of anticoagulation as measured by the international normalized ratio rather than warfarin use itself predicted adverse outcomes. This would suggest that warfarin does indeed play a mechanistic role. Possible mechanisms of the association between preinjury warfarin use and death include exsanguination or worsening injury patterns due to coagulopathy, complications due to increased rates of blood product transfusions, and other thromboembolic complications associated with the reversal of anticoagulation.

The best method of warfarin reversal is controversial, and there are few published studies to guide best practice. Options include vitamin K administration, fresh frozen plasma, cryoprecipitate, prothrombin complex concentrate, factor IX complex, and factor VIIa. Published studies of various reversal methods are limited by small sample sizes and lack of control groups. At least 1 study suggests that an established protocol reduces the time to international normalized ratio correction, but the implications on outcomes are uncertain.

The strengths of this study include the large number of patients and centers available for analysis in the latest version of the NTDB. These data provide a broad view of US trauma centers contributing to the NTDB and allow for generalization of these results. Despite these strengths, there are a several limitations. First, only patients presenting to trauma centers participating in the NTDB were eligible for inclusion in this study; this introduces the potential for selection bias, though these eligibility criteria should be nondifferential with respect to warfarin use. Also, a known source for potential bias is the varying rates of reporting procedures and diagnostic and comorbidity codes by individual centers. We have attempted to minimize this bias by including only centers that report at least 1 procedure code and at least 1 diagnosis or comorbidity code. While the proportion of patients classified as warfarin users appears to have external validity, other common comorbidities appear to be undercoded. Another important limitation of this study is the inability to classify users of other antiplatelet and anticoagulant agents since these data are not available in the NTDB. Since the presumed mechanistic impact of warfarin on trauma outcome is coagu-

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topathy, patients not classified as warfarin users may use antiplatelet agents that introduce this same mechanism, thereby underestimating the effect of warfarin. Conversely, warfarin users may also use antiplatelet agents and differential outcomes could be a result of these drugs rather than warfarin. Other large national databases containing information regarding the use of antiplatelet agents lack the injury-specific data present in the NTDB and therefore are unlikely to substantially aid in answering this question. Another limitation of this study is the inability to assess the degree of anticoagulation or compliance with outpatient warfarin therapy. Patients classified as warfarin users may have been former users of warfarin or subtherapeutic at the time of presentation. Despite possible limitations, these data have several important implications for the use of warfarin in patients at risk for trauma and injured patients presenting as warfarin users. Warfarin prescribers should consider these data in the overall risk-benefit analysis when opting to prescribe warfarin, and these data provide further rationale for discontinuing warfarin when the clinical evidence no longer supports its use. For trauma centers treating patients who present as warfarin users, these data should highlight the importance of seeking an accurate history of warfarin use and its indication, as well as the immediate initiation of its reversal. Centers should also develop and implement protocols for reversing warfarin after injury in a way that minimizes morbidity, mortality, and costs.

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Correspondence: Lesly A. Dossett, MD, MPH, 1306 SW Webster St, Seattle, WA 98106 (ladossett@gmail.com).
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Additional Information: The NTDB remains the full and exclusive copyrighted property of the American College of Surgeons.

REFERENCES


