Trauma patients on new oral anticoagulation agents have lower mortality than those on warfarin

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BACKGROUND: Although anticoagulation with warfarin has been associated with increased risk of adverse outcomes after trauma, the effects of the new oral agents (NOA) such as dabigatran, apixaban, rivaroxaban are not yet well characterized.

METHODS: A retrospective review of a level 1 trauma center database identified all patients aged ≥ 50 admitted after trauma during a 24 month period starting September 2013. Demographics, including preadmission anticoagulation agents, injuries, hospital course and outcomes were abstracted from the electronic medical record.

RESULT: Over the 24-month period, 3,392 patients were admitted; 112 (3.3%) were anticoagulated with NOA and 373 (11.0%) with warfarin with a trend toward increasing utilization of the new agents compared with warfarin over that period. Although comparable in age, injury severity scores, and mechanism of injury, patients anticoagulated with warfarin had both a higher overall mortality (10.9%) compared with the NOA (6.25%) and the non-anticoagulated control (5.5%) groups ($p < 0.001$) as well as a higher trauma-related mortality (9.0%) versus NOA (2.8%) and control (3.7%) groups ($p < 0.001$). Patients on warfarin or NOA were admitted to intensive care unit or step down unit more frequently than control patients. (45.0% and 41.9% vs. 35.7% respectively; $p < 0.001$). The incidence of traumatic brain injury was similar among the three groups. Although it did not reach statistical significance, trauma-specific mortality in the traumatic brain injury subset was higher in the warfarin group (19.3%) than the NOA (16.7%) or control (10.9%) groups ($p = 0.08$). In a multivariable logistic regression, warfarin (odds ratio, 2.215; 95% confidence interval, 1.365–3.596; $p = 0.001$), but not the NOA (odds ratio, 0.871; 95% confidence interval, 0.258–2.939; $p = 0.823$), was an independent predictor for mortality.

CONCLUSIONS: Although the experience with the new oral anticoagulation agents is still limited, patients on these agents appear to have lower mortality after traumatic injury than patients on warfarin. (*J Trauma Acute Care Surg.* 2016;81: 652–657. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Epidemiologic study, level III.

KEY WORDS: Warfarin; trauma; dabigatran; apixaban; rivaroxaban; outcomes; mortality.

Oral anticoagulation has become standard therapy for a number of conditions including prevention of stroke in patients with atrial fibrillation, structural heart disease, and mechanical valves as well as for treatment of venous thromboembolism and peripheral vascular disease. Although the exact number is unknown, it is estimated that at least 2 million people are currently anticoagulated in North America alone, and the prevalence is expected to increase as the population ages.[1] Since its approval in 1954, warfarin has been the traditional oral anticoagulant of choice. It acts by inhibiting the recycling of vitamin K thus deterring the vitamin K–dependent synthesis of coagulation factors II, VII, IX, and X as well as proteins C and S. The duration of action of single dose of warfarin is about 2 to 5 days but can be reversed by vitamin K, fresh-frozen plasma, concentrated factor VII, or prothrombin complex concentrate (PCC) administration. Warfarin, however, requires routine therapeutic drug monitoring because its efficacy is dependent on a number of factors including dietary vitamin K intake and interactions with other medications.

Since 2010, new oral anticoagulants have been approved by the Food and Drug Administration (FDA) including dabigatran (Pradaxa; Boehringer Ingelheim, Ingelheim, Germany), rivaroxaban (Xarelto; Bayer, Leverkusen, Germany) and apixaban (Eliquis; Pfizer and Bristol-Myers Squibb, New York City, NY). Other agents are also currently in development. These agents have been initially approved for stroke reduction in patients with atrial fibrillation but are now also used for other indications. Dabigatran is a direct thrombin inhibitor that prevents the conversion of fibrinogen to fibrin. It is renally cleared with a rapid onset of action (1–2 hours) and a half-life of 12 to 14 hours in patients with normal creatine clearance.[2] Rivaroxaban and apixaban are both direct factor Xa inhibitors. Rivaroxaban is excreted via both renal and hepatic routes with a half-life of 5 to 9 hours in healthy volunteers and 9 to 13 hours in the elderly. It achieves peak plasma concentration within 2 hours.[2] Apixaban has an onset of 3 hours and a half-life of 8 to 15 hours with predominantly hepatic clearance.

Until recently, there were no specific approved antidotes for these agents. Idarucizumab was approved by the FDA in October 2015 to reverse dabigatran and studies are in progress regarding a recombinant protein (andexanet alpha) to counteract the direct factor Xa inhibitors.[3,4] The PCC and activated PCCs administration have been suggested in cases of major bleeding for apixaban and rivaroxaban, and hemodialysis may have some utility in removing dabigatran.

Despite their beneficial effects on stroke prevention, all anticoagulants are associated with increased risk of bleeding complications. Warfarin use has been associated with increased adverse outcomes after traumatic injury, especially in patients with traumatic brain injury (TBI), in some,[5–7] but not all, studies.[8,9] The effects of the new oral agents (NOA) on outcomes after injury are, however, not yet well characterized. Given the previous lack of specific reversal agents, there is concern in the trauma community that these agents may lead to increased morbidity and mortality.[10] We therefore conducted a retrospective single-center study to compare the outcomes after traumatic injury in patients on warfarin, the NOAs, and control non-anticoagulated patients.

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METHODS

The study protocol was approved by the Human Investigation Committee of the Yale School of Medicine. Yale-New Haven Hospital is an urban, American College of Surgeons-verified and state-designated level I regional resource trauma center and quaternary referral center. Query of the Yale-New Haven Hospital's trauma registry (TraumaBase; Clinical Data Management; Denver, CO) identified all patients aged 50 years or older admitted to the hospital during a 24-month period starting September 2013. The trauma registry and electronic medical record (EPIC, Verona, WI) was then reviewed to abstract demographics, including preadmission anticoagulation status and antiplatelet agents and common comorbidities, mechanism of injury, injuries sustained, and the hospital course and outcomes. To optimize the number of medical records reviewed, we limited our search to this age group because anticoagulant use would be more likely in this age bracket compared with younger patients. Missing data, mainly International Normalized Ratio (INR), were present in approximately 5% of the cases.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 21 (IBM Corporation, Somers, NY) using analysis of variance and χ^2 as appropriate; statistical significance was assumed for $p < 0.05$. A multivariable logistic regression was performed to determine whether the anticoagulation agent was an independent predictor of mortality after initially selecting potential independent variables using univariate analysis with the criteria $p < 0.2$. The model performance was evaluated using Hosmer and Lemeshow goodness-of-fit test and receiver operating characteristics curve. Multicollinearity was evaluated using variance inflation factor and tolerance.

RESULTS

During the study period, our center admitted 3,392 trauma patients who were aged 50 years or older. The most common mode of injury was ground-level fall (67.7%) followed by fall from 3 to 5 feet (9.6%) and motor vehicle crash (7.9%). There were slight differences in the mode of injury across the 3 anticoagulation groups. Ground-level falls were more common (81.5%) in the warfarin group compared with 76.8% and 65.7% in the NOA and control groups, whereas falls from 3 to 5 feet were more common in the NOA group (12.5% vs. 8.0% in the warfarin group and 9.7 % control, respectively) ($p < 0.004$) (Table 1).

TABLE 1. Comparison of Modes of Injury

	Warfarin (n = 373)	New anticoagulants (n = 112)	Not anticoagulated (n = 2907)	Total
Fall < 3 feet (%)	81.5	76.8	65.7	67.8
Fall 3–5 feet (%)	8.0	12.5	9.7	9.6
Fall > 5 feet (%)	1.6	0.9	3.8	3.4
Motor vehicle crash (%)	5.6	4.5	8.4	7.9
Pedestrian struck (%)	0.3	1.8	2.1	1.9
Gunshot wound (%)	0.3	0	0.3	0.3

TABLE 2. Demographics

	Warfarin (n = 373)	New anticoagulants (n = 112)	Not anticoagulated (n = 2907)	*p*
Age (years)*	80.9 ± 9.4	79.5 ± 10.4	72.9 ± 13.8	0.0001
Male sex (%)	52.0	43.8	45.8	0.063
Aspirin (%)	21.9	20.5	36.9	0.001
Clopidogrel (%)	2.1	2.7	6.7	0.001
Cardiac disease (%)	58.7	55.4	22.2	0.001
End-stage renal disease (%)	2.1	0.9	1.8	0.67
Stroke (%)	16.9	10.7	8.1	0.001
COPD (%)	13.4	16.1	11.8	0.286
Diabetes mellitus (%)	28.2	22.3	18.9	0.001
Atrial fibrillation (%)	67.8	70.5	6.0	0.001
Cirrhosis (%)	1.3	4.5	2.4	0.145

*Mean ± SD.

Three hundred seventy-three patients were anticoagulated with warfarin and 112 with the NOA (25 with dabigtraban, 59 with rivaroxaban, and 28 with apixaban). Aspirin use was similar in the warfarin (22%) and NOA (21%) groups but overall lower compared with control group (37%) ($p < 0.001$). Clopidogrel was coadministered in a small subset of patients in each group (Table 2). Although the percent of anticoagulated patients varied each month (8–20%), there was an overall trend toward increased utilization of the NOA compared with warfarin over the study period (Fig. 1). The mean INR in the warfarin group was 2.66 ±1.57, and INR was therapeutic (≥2) in 257 (67%) patients.

Patients anticoagulated on warfarin were comparable in age to those on NOA, but both groups were slightly older than the non-anticoagulated patients (Table 2). Not surprisingly, review of the medical comorbidities demonstrated an increased prevalence of cardiac disease, stroke, and atrial fibrillation in the warfarin and NOA groups ($p = 0.001$). Other common preexisting comorbidities were evenly distributed. Injury severity scores and incidence of TBI, rib, spine, long bone, and pelvic fractures were also comparable across the 3 groups (Table 3A).

Although the 3 groups had statistically significant differences ($p = 0.032$) in the severity of TBI as measured by the Head

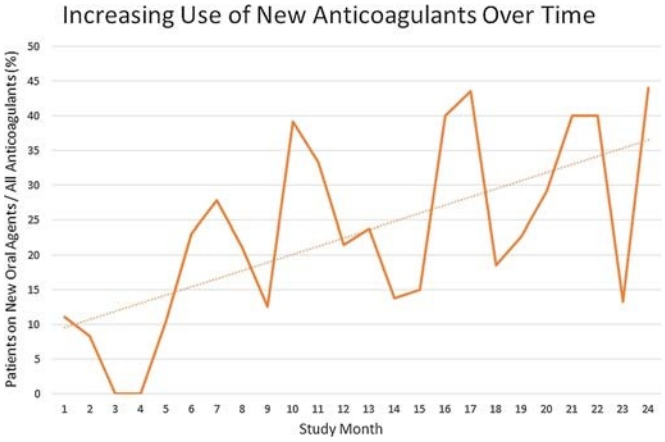

Figure 1. Increasing use of new anticoagulants over time.

TABLE 3A. Injuries

	Warfarin (n = 373)	New Anticoagulants (n = 112)	Not Anticoagulated (n = 2907)	*p*
Injury severity score*	9 (5–10)	9 (5–10)	9 (4–10)	0.648
Traumatic brain injury (%)	22.5	16.9	20.7	0.431
Rib fracture (%)	17.7	16.9	18.9	0.953
Spine fractures (%)	11.8	17.9	16.6	0.053
Pelvic fracture (%)	8.31	10.7	8.3	0.661
Long bone fractures (%)	39.1	45.5	43.2	0.276
Spleen injury (%)	0.3	0.9	1.3	0.208
Liver injury (%)	0.5	0.9	0.6	0.891

*Median (interquartile range, 25th–75th).

Abbreviated Injury Scale (AIS) (Table 3B), there was no clear-cut pattern. Patients on warfarin had a higher rate of AIS 5 (27.4 %) than NOA (10.5%) and control (15.3%) patients but lower rate of AIS 4 (14.3%) compared with NOA (42.1%) and control (18.1%) patients, respectively. Furthermore, the NOA patients had a higher combined rate (52.6%) of severe TBI (AIS ≥ 4) compared with the warfarin group (41.7%) and the control group (33.3%).

As seen in Table 3A, median length of stay was slightly longer in the warfarin group (5 days; interquartile range [IQR], 3–7) compared with the NOA (4 days; IQR, 3–5) and control groups (4 days; IQR, 2–6) ($p = 0.017$). Patients on warfarin or NOA were more frequently admitted to intensive care unit or stepdown unit than control patients (45.0% and 41.9% vs. 35.7%, respectively; $p < 0.001$). Patients anticoagulated with warfarin had a higher overall mortality (10.9%) compared with the NOA (6.25%) and the non-anticoagulated control group (5.5%) ($p < 0.001$). On subset analysis of patients with specifically identified traumatic cause of death, the mortality in the warfarin group remained higher (9.0% [33/365]) compared with 2.8% (3/108) in the NOA group and 3.7% (105/2852) in the control group ($p < 0.001$). Withdrawal of care before death occurred in 70% of all patients who died, but there were no differences between the 3 study groups.

After selecting potential independent variables using univariable analysis (selection criteria, $p < 0.2$), a multivariable logistic regression was performed and demonstrated that the use of warfarin (odds ratio, 2.215; 95% confidence interval [CI], 1.365–3.596; $p = 0.001$) but not NOA (odds ratio, 0.871; 95% CI, 0.258–2.939; $p = 0.823$) was an independent risk factor for mortality (Table 3B). Other significant risk factors included age, history of cardiac disease, cancer and renal insufficiency, the mode of injury, injury severity score, TBI, and hemothorax.

TABLE 3B. Severity of Traumatic Brain Injury

	Warfarin (n = 84)	New anticoagulants (n = 19)	Not anticoagulated (n = 602)	*p*
AIS Head 3 (%)	26.2	21.1	34.6	0.032
AIS Head 4 (%)	14.3	42.1	18.1	
AIS Head 5 (%)	27.4	10.5	15.3	

Prior studies have demonstrated an increased mortality in warfarin anticoagulated patients who suffer a TBI. In the present study, a nonsignificant trend in increased trauma-related mortality in the TBI subset was identified in the warfarin group (19.3%) and the NOA group (16.7%) compared with the control group (10.9%) ($p = 0.08$). Traumatic brain injury was also the most common cause of traumatic death in all 3 groups: 45% (15/33) in the warfarin, 100% (3/3) in the NOA, and 49% (52/105) in the control group (Tables 4 and 5).

DISCUSSION

Results of this study indicate that patients who are anticoagulated with warfarin have an increased mortality after traumatic injury compared to patients who are non-anticoagulated or to patients who are on the NOAs. Previous studies comparing warfarin with control patients have demonstrated similar results. Howard et al.[7] demonstrated that geriatric patients on warfarin had increased mortality after fall from standing (8.6 vs. 5.7%; $p = 0.015$). In an analysis of 1,493 adult blunt head trauma patients, Franko et al.[11] showed a mortality of 23.9% in patients on warfarin compared with 4.9% in the control group. The current trauma literature on outcomes in patients on NOA is very limited. One identified study, which examined the outcomes of patients on dabigatran, demonstrated a 22% mortality in patients with TBI and 10% mortality in trauma patients without TBI but did not contain a control group of patients who were not on anticoagulation.[12]

The medical literature however contains a number of large randomized controlled trials that not only primarily demonstrated the efficacy of these agents for stroke prevention but also reported the risks of bleeding. In the RE-LY trial, the risk of bleeding with dabigatran versus warfarin was dependent on the dose and patient age.[13] Dabigatran 150 mg twice daily

TABLE 4. Comparison of Outcomes

	Warfarin (n = 373)	New anticoagulants (n = 112)	Not anticoagulated (n = 2907)	*p*
Length of stay (days)*	5 (3–7)	4 (3–5)	4 (2–6)	0.017
ICU/SDU (%)	45.0	41.9	35.7	<0.001
Overall mortality (%)	10.9	6.25	5.5	<0.001
Trauma mortality (%)	9.0 (n = 365)	2.8 (n = 105)	3.7 (n = 2852)	<0.001
Urinary tract infection (%)	12.3	11.6	7.5	0.015
Myocardial infarct (%)	1.9	2.7	1.1	0.438
Respiratory failure (%)	9.9	12.5	8.9	0.383
Acute kidney injury (%)	8.9	8.0	4.1	0.001
Arrhythmias (%)	11.8	10.7	4.8	0.001

*Median (interquartile range, 25th–75th).
ICU, intensive care unit; SDU, stepdown unit.

TABLE 5. Multivariable Logistic Regression of Predictors of Mortality

		95% CI for odds ratio		
	Odds ratio	Lower	Upper	*p*
Warfarin	2.215	1.365	3.596	0.001
New oral anticoagulants	0.871	0.258	2.939	0.823
Age	1.025	1.006	1.044	0.008
Male sex	1.207	0.796	1.831	0.375
Cardiac disease	1.988	1.290	3.063	0.002
Cancer	1.861	1.127	3.074	0.015
Diabetes mellitus	0.628	0.365	1.080	0.093
Renal insufficiency	1.740	0.912	3.318	0.093
Fall, 3–5 feet	0.890	0.449	1.766	0.7339
Fall, > 5 feet	1.710	0.631	4.635	0.292
Pedestrian struck	4.644	1.650	13.066	0.004
Motorcycle	3.102	1.040	9.253	0.042
Motor vehicle crash	1.167	0.525	2.595	0.705
Gunshot wound	34.188	7.785	150.138	0.001
Injury severity score	1.110	1.084	1.137	0.001
Traumatic brain injury	1.888	1.161	3.069	0.01
Hemothorax	2.909	1.155	7.324	0.023
Rib fractures	0.771	.457	1.299	0.329
Splenic injury	1.345	0.377	4.792	0.648
Liver injury	4.1	0.775	21.697	0.097

Hosmer and Lemeshow test: $\chi^2(8) = 10.817$, $p = 0.212$.
Area under curve, 0.882 (95% CI, 0.856–0.908; $p < 0.001$).

(FDA-approved dose) was associated with lower risk of major bleeding in those younger than 75 years (2.12% vs. 3.04%; $p < 0.001$) and a trend toward increased bleeding in those 75 years or older (5.1% vs. 4.37%; $p = 0.07$). However, the risk of intracranial bleeding was reduced with dabigatran compared with warfarin, irrespective of age (0.32% vs. 0.76%; $p < 0.001$). Similarly, in a retrospective cohort study using a random sample of Medicare beneficiaries, dabigatran was associated with higher risk of overall bleeding relative to warfarin (hazard ratio, 1.30; 95% CI, 1.20–1.41) but decreased risk of intracranial hemorrhage (hazard ratio, 0.32; 95% CI, 0.20–0.50).[14] Rivaroxaban was associated with a similar rate of clinically relevant bleeding (14.9% vs. 14.5% per year; $p = 0.44$) compared with warfarin but with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%; $p = 0.02$) and fatal bleeding (0.2% vs. 0.5%; $p = 0.003$).[15] In the ARISTOTLE trial of 1,8201 patients comparing apixaban to warfarin in patients with atrial fibrillation, the rate of major bleeding in the apixaban group was 2.13% per year compared with 3.09% per year in the warfarin group ($p < 0.001$).[16] Although none of these trials specifically evaluated the risk of bleeding after traumatic injury, their data support the observed improved outcomes with NOA compared with warfarin in the current study.

The observed differences in outcomes as well as the need for reversal agents may be related to the differences in pharmacokinetics among the agents. Warfarin has a significantly longer half-life (2–5 days) than the NOA and therefore the degree of coagulopathy and extent of bleeding with the NOA may be more dependent on the period between the last dose and the time of injury compared with warfarin. The time of the last dose may also impact the quantity of required reversal agents for NOA versus warfarin because the effects of NOA may be already fading at the time of hospital presentation.

This study has several limitations including its retrospective single center nature. Even though there was an increasing prevalence of NOA use over the study period, we identified a limited number of patients on these agents and combined the 3 agents into 1 analysis group. Subset analysis, however, demonstrated a nonsignificant trend toward decreased mortality with each of the individual NOA agents compared with warfarin. Our center also did not use other measures of coagulation besides Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and INR during the study period. Since these parameters are not typically altered by NOA, the study does not contain quantitative data about the degree of anticoagulation in the NOA group. Finally, the 3 groups had discrepancies in TBI severity. Although the difference in mortality could be attributed to this variation, an alternative explanation is that the observed difference in severity of TBI itself was secondary to anticoagulation. Despite these limitations, our study suggests that, in the setting of trauma, the new oral anticoagulants may be safer than warfarin. Larger multicenter trials will be required to confirm these findings.

AUTHORSHIP

A.A.M. participated in the study design, data collection, data analysis, data interpretation and writing. B.B. participated in data collection, data interpretation and writing. K.M.S. participated in data interpretation and writing. K.A.D. participated in data interpretation and writing.

DISCLOSURE

The authors declare no conflicts of interest.

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