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Direct oral anticoagulants compared with warfarin in patients with severe blunt trauma

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ABSTRACT

Methods: We queried our Trauma Quality Improvement Program registry for patients who presented between 6/1/2011 and 9/1/2015 with severe (injury severity score (ISS) > 15) blunt traumatic injury during anticoagulant use. Patients were then grouped into those prescribed warfarin and patients prescribed any of the available novel Direct Oral Anticoagulants (DOAC) medications. We excluded severe (AIS $\geq$ 4) head injuries.

Results: There were no differences between DOAC and warfarin groups in terms of age, gender mean ISS, median hospital or intensive care unit lengths of stay, complication proportions, numbers of complications per patient, or the proportion of patients requiring transfusion. Finally, excluding patients who died, the observed proportion of discharge to skilled nursing facility was similar.

In our sample of trauma patients, DOAC use was associated with significantly lower mortality (DOAC group 8.3% vs. warfarin group 29.5%, $p < 0.015$). The ratio of units transfused per patient was also lower in the DOAC group (2.8 ± 1.8 units/patient in the DOAC group vs. 6.7 ± 6.4 units per patient in the warfarin group; $p = 0.001$).

Conclusion: In conclusion, we report an association with decrease in mortality and a decrease in transfused blood products in severely injured trauma patients with likely minimal or no head injury taking novel DOACs over those anticoagulated with warfarin for outpatient anticoagulation.

Introduction

With the clinical advent of Direct Oral Anticoagulants (DOACs), trauma surgeons and neurosurgeons everywhere held their collective breath awaiting the onslaught of patients with DOAC associated traumatic bleeding and no reversal options. Early industry data suggested that the risk of severe hemorrhage was lower with the DOACs compared with warfarin [1,2], but the question of what would happen if and when a patient actually had bleeding from severe trauma (usually defined as an Injury Severity Score (ISS) of >15) was, and still is, unanswered. Patients for whom anticoagulation is recommended face stroke risks that are unacceptable to them, but the mitigation of those risks confers a wholly unquantified risk of severe bleeding from (obviously unexpected) trauma [3,4]. Because of that dearth of information surrounding cessation of traumatic bleeding, or injury progression, patients are effectively unable to weigh risks and benefits between stroke risk and the possibility of traumatic bleeding; they are therefore unable to make informed choices between treatment options [3].

That inability is because there is scarce outcomes data on severe blunt trauma in the presence of pre-injury DOACs [3–5]. Much of that data concerns incidence, prevalence or management of severe bleeding [2], with some comparisons of DOAC use with no antithrombotic use [3]. However, foregoing anticoagulation altogether is typically not a therapeutic option offered to patients requiring anticoagulation for outpatient mitigation of substantial stroke or embolic risks. Comparison of patient outcomes with warfarin, then, the logical therapeutic alternative to DOACs, is

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Table 1
Demographics, injury characteristics.

	DOAC	Warfarin	p
Mean Age (y ± SD)	78.1 (±8.1)	79.0 (±14.1)	0.72
Gender (% Male, 95% CI)	66.7% (49.5%–80.3%)	62.8% (51.7%–72.7%)	0.83
Mean ISS (±SD)	22.1 (±4.9)	23.2 (±5.7)	0.32
Mean AIS Head (±SD)	2.1 (±1.0)	2.3 (±0.9)	0.31
Mean AIS Face (±SD)	1.6 (±0.6)	1.6 (±0.5)	1.0
Mean AIS Chest (±SD)	2.6 (±1.1)	2.7 (±1.0)	0.64
Mean AIS Abdomen (±SD)	2.4 (±0.9)	2.6 (±0.7)	0.24
Mean AIS Extremities (±SD)	1.9 (±0.9)	2.1 (±0.6)	0.23
MOI: Falls (%) (95% CI)	72.2% (55.9%–84.3%)	76.9% (66.4%–84.0%)	0.64
MOI: MVC (%) (95% CI)	27.7% (15.7%–44.1%)	20.5% (12.9%–30.9%)	0.47
MOI: Assault (%) (95% CI)	–	2.6% (0.2%–9.4%)	1.0

(DOAC = Direct Oral Anticoagulants; ISS = Injury Severity Score, HLOS = Hospital Length of Stay, ICU LOS = Intensive Care Unit Length of Stay; AIS = Abbreviated Injury Scale; MOI = Mechanism of Injury; MVC = Motor Vehicle Collision; SD = Standard Deviation, 95%CI = 95% Confidence Interval).

appropriate to assist in those conversations about risks and benefits.

Our institution participates in the American College of Surgeons Trauma Quality Improvement Program (TQIP), and in that capacity maintains a trauma registry of all patients seen with traumatic injury. We conducted a retrospective review of our TQIP database comparing trauma patients taking DOACs with those taking warfarin in order to define differences in outcomes associated with these different therapeutic alternatives.

Methods

This study was exempted by the Institutional Review Board at Saint Francis Hospital and Medical Center, an ACS verified level II trauma center in Hartford, CT. We queried our TQIP registry for patients who presented between 6/1/2011 and 9/1/2015 with severe (ISS > 15) blunt traumatic injury during anticoagulant use. We excluded patients who were taking antiplatelet agents, and those with an Abbreviated Injury Scale score (AIS) for head ≧ 4. Patients were then grouped into those prescribed warfarin and patients prescribed any of the available novel DOAC medications.

The two groups were then compared with respect to demographics, primary endpoints, and secondary endpoints. Demographics included age, gender, ISS, individual AIS scores, and mechanisms of injury (MOI). The primary endpoint was in-hospital mortality, and the secondary endpoints included hospital length of stay (HLOS), intensive care unit length of stay (ICU LOS), proportion of patients transfused packed red blood cells (PRBC) (and their transfusion requirements in numbers of PRBC units per patient), and discharge to skilled nursing facility (SNF).

Fisher's exact test was used to compare mortality, gender, comorbidities, number of comorbidities, causes of death, and SNF discharge. Student's-t test was used to compare mean age and mean ISS. Mann Whitney *U* test was used to compare median HLOS, and median ICU LOS. Categorical data was reported with 95% Confidence Intervals (95%CI); continuous data was reported with standard deviations (±SD).

Results

We identified 114 patients who met inclusion and exclusion criteria from the hospital TQIP registry. Thirty-six patients were taking DOACs and 78 were taking warfarin. Twenty-one patients (21/36; 58.3%) were taking dabigatran (Xarelto), fourteen (14/36; 38.9%) were taking rivaroxaban (Pradaxa), and one (1/36; 2.8%) was taking apixaban (Eliquis). There were no differences between DOAC and warfarin groups in terms of age, gender, or mean ISS. Mean International Normalized Ratio (INR) for the warfarin group was 2.8 (±1.6) (range 1.1–8.4). The proportion of patients taking warfarin with subtherapeutic or normal INR (INR 1.1–1.8) was 19/78 (24.3% 95% CI 16.1%–35.0%) and the proportion of patients with therapeutic INR (2–2.5) was 22/78 (28.2%, 95% CI 19.4–39.1%). The remainder of patients had INR 2.6–8.4 (37/78, 47.4%, 95% CI 36.7%–58.4%) (data not shown in tabular form). Mechanisms of injury are listed in Table 1; there were no differences between the groups in terms of mechanisms of injury.

Median HLOS was not significantly different, and the median ICU LOS associated with DOAC use was also similar to the ICU LOS for warfarin (Table 1). The proportion of patients requiring transfusion was also not significantly different. Finally, excluding patients who died, the observed proportion of patients discharged to SNF was similar between the DOAC group and the warfarin group (Table 2).

In our sample of trauma patients, DOAC use was associated with significantly lower mortality (DOAC group 3/36, 8.3% (95% CI 0.7%–17.3%) vs. warfarin group 23/78, 29.5% (95% CI 19.4%–39.6%) $p < 0.015$). The ratio of PRBC units transfused per patient was also lower in the DOAC group (Table 2).

Additionally, we also noted a significant increase in the proportion of patients with hypertension (HTN) as a comorbidity in the DOAC group. However, there was no difference in the proportion of patients with other comorbidities (Table 3). Also, we were unable to find a difference between the proportions of patients taking DOACs or those taking warfarin with only one identified comorbidity, with two comorbidities, three comorbidities, four comorbidities, or five or more listed comorbidities. Causes of death are also presented in Table 3; there were no differences in proportions of patients with specific causes of death between the group prescribed warfarin and the group prescribed DOACs (Table 3).

Discussion

Direct Oral anticoagulants were initially approved by the US Food and Drug Administration in November, 2011. The promises of a safer therapeutic window and an improved mitigation of stroke risk with less monitoring and fewer drug interactions made the drugs instantly appealing. However, the risks of intractable bleeding were hard to ignore, and physicians tempered their enthusiasm for the positive aspects of the drugs with caution for the bleeding risks [6–8]. Comparatively, the risks seemed similar to warfarin, however, most of the data in early and Phase III clinical trials dealt with incidence and prevalence of hemorrhage, not with outcomes [3].

Warfarin, the erstwhile gold standard for outpatient anticoagulation, has a narrow therapeutic index, and its efficacy is influenced by several other medications, or even by changes in dietary habits [4,5]. Once taken, warfarin is quickly absorbed