Findings on Repeat Posttraumatic Brain Computed Tomography Scans in Older Patients With Minimal Head Trauma and the Impact of Existing Antithrombotic Use

Stephen Flaherty, MD; Saptarshi Biswas, MD; Dorraine D. Watts, PhD; Nina Y. Wilson, MSN; Yan Shen, PhD; Jeneva M. Garland, PharmD; Ransom J. Wyse, MPH; Mark J. Lieser, MD; Therèse M. Duane, MD; Patrick J. Offner, MD; Joseph D. Love, DO; William C. Shillinglaw, DO; Darrell L. Hunt, MD; Randy W. Gauny, MBA; Samir M. Fakhry, MD*; the Delayed TBI Hemorrhage Research Group†

*Corresponding Author. E-mail: samir.fakhry@hcahealthcare.com.

Study objective: Evaluate the utility of routine rescanning of older, mild head trauma patients with an initial negative brain computed tomography (CT), who is on a preinjury antithrombotic (AT) agent by assessing the rate of delayed intracranial hemorrhage (dICH), need for surgery, and attributable mortality.

Methods: Participating centers were trained and provided data collection instruments per institutional review board-approved protocols. Data were obtained from manual chart review and electronic medical record download. Adults ≥55 years seen at Level I/II Trauma Centers, between 2017 and 2019 with suspected head trauma, Glasgow Coma Scale 14 to 15, negative initial brain CT, and no other Abbreviated Injury Scale injuries >2 were identified, grouped by preinjury AT therapy (AT- or AT+) and compared on dICH rate, need for operative neurosurgical intervention, and attributable mortality using univariate analysis (α=.05).

Results: A total of 2,950 patients from 24 centers were enrolled; 280 (9.5%) had a repeat brain CT. In those rescanned, the dICH rate was 15/126 (11.9%) for AT- and 6/154 (3.9%) in AT+. Assuming nonrescanned patients did not suffer clinically meaningful dICH, the dICH rate would be 15/2001 (0.7%) for AT- and 6/949 (0.6%) for AT+. No surgical operations were done for dICH. All-cause mortality was 9/2950 (0.3%) and attributable mortality was 1/2950 (0.03%). The attributable death was an AT+, dICH patient whose family declined intervention.

Conclusion: In older patients with an initial Glasgow Coma Scale of 14 to 15 and a negative initial brain CT scan, the dICH rate is low (<1%) and of minimal clinical consequence, regardless of AT use. In addition, no patient had operative neurosurgical intervention. Therefore, routine rescanning is not supported based on the results of this study. [Ann Emerg Med. 2022;■:1-11.]

Please see page XX for the Editor's Capsule Summary of this article.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2022.08.006

INTRODUCTION

Background

As the population ages, increasing numbers of patients taking pharmacologic agents to prevent the occurrence of thromboembolic events are being seen in trauma centers.[1] Unfortunately, the protection of these antithrombotic (AT) agents, defined as anticoagulant and antiplatelet medications, confer under normal conditions may become a liability during trauma when uncontrolled bleeding may lead to increased morbidity and even death. Consequently, clinicians face daily challenges that require a balance of medical science and clinical judgment to provide patients with optimal care in a cost-conscious health care system.

Importance

The evaluation of older patients who sustain a mild head injury and are taking AT agents is not yet firmly established by consensus or evidence-based guidelines, while the use of these medications is simultaneously increasing in frequency in this population.[1,2] The initial evaluation of older patients with a mild head injury is guided by protocols that include head computed tomography (CT), such as the Canadian CT Head Rule and the New Orleans Criteria that have been externally validated for sensitivity and specificity.[3-7] However, for those patients with a mild head injury who are taking an AT and have a normal initial brain CT, there is no clear consensus regarding subsequent management. Resource-intensive practices vary and include discharge to

Editor's Capsule Summary

What is already known on this topic

Clinical practice varies regarding observation and repeat imaging for older adults with mild traumatic brain injury.

What question this study addressed

Among emergency department patients aged 55 years and older with mild traumatic brain injury and negative initial computed tomography scan (n=2950), what is the rate of delayed intracranial hemorrhage?

What this study adds to our knowledge

Assuming nonrescanned patients did not experience delayed hemorrhage, rates of delayed hemorrhage were low and similar in patients taking and not taking antithrombotic medications (0.6% and 0.7%, respectively).

How this is relevant to clinical practice

These limited results suggest a low value of routine head rescanning of older adults with mild traumatic brain injury, including in those taking antithrombotic medications.

home, interval imaging to assess for delayed intracranial hemorrhage (dICH), admission for serial examinations to guide further care, and obtaining a repeat CT scan or keeping patients for observation for several hours.[8-15] A meta-analysis and other retrospective studies have suggested an increased risk of death for patients taking AT agents who suffer a mild head injury.[16,17]

This variation in practice, along with conflicting literature, necessitates further investigation.

Goals of This Investigation

The goal of this study is to ascertain if the use of a preinjury AT agent affects the rate of dICH, need for surgery, and mortality in head injury patients ≥55 years with an initial Glasgow Coma Scale (GCS) of 14 to 15, and a negative initial head CT scan to determine the utility of repeat scanning and inform best clinical practice.

MATERIALS AND METHODS

Study Design and Participants

This was a retrospective study with a manual chart review of patients aged ≥55 years from the Level I and II trauma centers who were seen by the trauma service as a trauma activation or consultation between 2017 and 2019. Patients were included if they met all of the following clinical criteria: (1) suffered blunt injury, (2) were evaluated for suspected brain trauma, (3) presented with an initial GCS of 14 to 15, (4) had a negative initial brain CT, and (5) had no injuries with an Abbreviated Injury Scale score >2 in any region other than the head. Patients were excluded if they met any of the following conditions: (1) transferred into or out of the facility, (2) had a *Do Not Resuscitate* order, (3) had a hereditary bleeding disorder or coagulopathy (defined as the presence of any International Classification of Diseases Tenth Revision [ICD-10] D65-D69 diagnosis), or(4) had a positive initial head CT for traumatic injury or preexisting intracranial pathology. Before data collection commenced, this study was ruled exempt by the hospital network's enterprise centralized process for institutional review board exemption and the local institutional review boards of the participating trauma center if required.

We performed an a priori power analysis using the pwr package in R testing for equality of proportions to determine the sample size needed for each study group, with an alpha of 0.05 and power of 0.8.[18] The sample calculation was done assuming a rate of dICH of 0.74% in patients taking ATs and 0.0% in those not taking ATs and using these to calculate Cohen's h through an Arcsine transformation to obtain the effect size. Arcsine transformation was used, as it is able to calculate an effect size when 1 arm has 0 events without giving specious values. In our case, the effect size calculated was 0.17, a "small" effect size. This effect size was then used to calculate the required sample, with the results showing the required sample size to be 530 for each arm. Assuming a 15% proportion of missing data, the target sample size was 1,200, with 600 in each arm.

DATA COLLECTION

The research coordinating center identified potential study candidates who met the initial inclusion criteria from the hospital network's centralized trauma registry for each trauma center. Centers were required to attend an online training session provided by the research coordinating center, with detailed instructions on ensuring data consistency and validity across centers. Individual participating centers then screened their respective list of potential study candidates for the exclusion criteria through individual chart review and hand collected the required data. Variables collected through a Study Data Collection form included (1) exclusion criteria screening results, (2) agent, dose, and timing of preinjury AT therapies, (3)

reasons for AT use, (4) agent, dose, and timing of reversal agent(s) if given, (5) if chemical venous thromboembolism prophylaxis was administered before repeat CT including agent, route, timing, and dose, (6) if a repeat CT scan was performed (yes/no) with results, and (7) any cranial surgical intervention performed, including specific procedures and timing. Required data for eligible patients were submitted to the research coordinating center either through a secure file transfer protocol or an encrypted e-mail using only an anonymous study identification number assigned to each patient to preserve confidentiality.

Additional trauma-specific patient data that are routinely collected in the trauma registry were extracted electronically from the enterprise-wide trauma registry at the end of the study review period, including patient demographics, injury details, injury scores, outcomes, and discharge information. In addition, results of laboratory tests were extracted from the enterprise-wide electronic medical records using the first available blood draw test results for blood specimens that were collected up to 3 hours after the recorded patient arrival time. To obtain information on attributable death, an experienced trauma nurse and trauma surgeon from the research team conducted chart reviews to determine the cause of death for patients who died. No protected health information was collected. The chart abstracted data and electronically collected data were merged to create the study dataset, after which the dataset was anonymized. Data quality was assured by chart review and data validation of a 10% sample of patient charts as they were submitted. Errors, including missing data points, outliers, and duplication, were eliminated from the final research dataset (Figure 1). All deaths and all readmissions were manually reviewed by an experienced trauma surgeon and trauma nurse. In addition, after data collection was completed, an extensive *a posteriori* electronic and manual chart review was conducted.

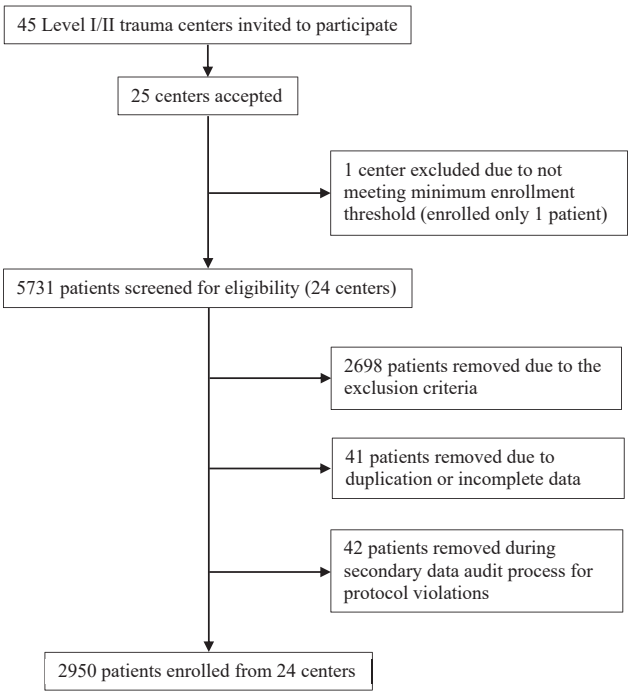

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram exhibiting the selection of patients included in the study.

Exposure and Outcome Variables

The exposure of interest in this study was preinjury AT therapy status (yes/no, ie, +/-), which was determined from chart reviews of AT agent usage and dose. Patients were classified as having preinjury usage (AT+) if they had documentation of any AT use with the name and dose of the AT agent. Otherwise, patients were considered not to have AT usage (AT-). For example, patients who took only aspirin 81 mg were considered not receiving AT therapy (AT-). For those on preinjury AT therapy, patients were further categorized into single AT agents or combinations of multiple AT agents based on documented generic or brand name of the AT agent, namely aspirin, warfarin, clopidogrel, apixaban, rivaroxaban, other single agents, aspirin + clopidogrel, other combination of 2 ATs, and combination of 3+ ATs. Patients documented as receiving AT therapy without providing the specific agent name were grouped into "other single agent." If the percentage of a single agent or combination of more than 1 agent was below 2%, patients were classified into the group of "other single agent" or "other combination of 2 ATs."

The primary outcome of the study was dICH, defined as the presence of intracranial pathology including cerebral edema, intraventricular hemorrhage, subdural hemorrhage, cerebral contusion (focal or diffuse), subarachnoid hemorrhage, or epidural hemorrhage on a repeat head CT scan within 48 hours following an initial negative head CT scan. Secondary outcomes included the need for dICH-related surgical intervention, inhospital mortality, hospital length of stay, and intensive care unit (ICU) length of stay. Inhospital mortality was determined based on hospital discharge disposition. Hospital length of stay and ICU length of stay was calculated for patients who had a hospital stay or had a stay in ICU.

To assess the follow-up status of patients who did not have a repeat brain CT scan performed during the initial clinical encounter within the first 48 hours, our electronic medical record was searched to determine the disposition

status of patients discharged from the emergency department (ED) and, in the case of those admitted to the hospital, the hospital discharge disposition.

- For patients admitted to the hospital, the electronic medical record records of all hospitalized patients were searched for any hospital discharge diagnosis of head injury (ICD-10_Clinical Modification [CM] S-06), and these were manually reviewed to identify those with intracranial bleeding (S06.31 to S06.38, S06.4 to S06.6).
- For patients discharged home from the ED without a repeat CT scan, the electronic medical record records were searched for any diagnosis of head injury (ICD-10_CM S-06 series), and these were manually reviewed to identify those with intracranial bleeding (S06.31 to S06.38, S06.4 to S06.6). These electronic medical record records were also searched to determine if any of these patients required readmission to one of the hospitals in the researcher's hospital system within 5 days of their index visit or admission.
- For readmissions, the electronic medical record records from the return hospitalization were then also searched for any discharge diagnosis of head injury (ICD-10-CM S-06 series) to determine whether they were readmitted for sequelae of their head injury, and these were manually reviewed to identify those with intracranial bleeding (S06.31 to S06.38, S06.4 to S06.6).

Manual chart reviews of any patient records from the above review with an ICD-10-CM diagnosis of intracranial bleeding (S06.31 to S06.38, S06.4 to S06.6) were performed to determine whether follow-up imaging demonstrated that a dICH had occurred.

Statistical Analyses

Patient characteristics and injury patterns were compared by preinjury AT status (AT+ versus AT-) using univariate summary statistics. For continuous variables, median and interquartile range (IQR) were reported. In addition, the number and percentage of patients who received a repeat CT scan were reported (1) by the preinjury AT status (+/-) and (2) by specific AT agents (Tables E1 and E2, available online at http://www.annemergmed.com). Patients who received and did not receive a repeat CT scan were analyzed separately for their outcomes. For categorical outcomes, unadjusted comparisons by preinjury AT status were performed using Pearson χ^2 tests, and absolute differences between groups and 95% confidence interval (CI) were reported. Fisher's exact tests were performed to determine statistical significance when the sample size was too small, in which cases, 95% CIs were unable to be obtained. For continuous outcomes, bootstrapping (ie, resampling with replacement) was used to calculate the 95% CI for the difference in medians between groups.

For patients with a repeat CT scan unadjusted preinjury AT status comparisons were conducted for the primary and secondary outcomes. In addition, unadjusted and multivariable logistic regressions were performed to assess the association between preinjury AT status and dICH, with or without adjusting for potential confounders including age, sex, race, and activation type, mechanism of injury, injury severity score (ISS), and GCS.

For patients without a repeat CT scan, only secondary outcomes were compared by preinjury AT status. To assess the robustness of the results, sensitivity analyses were performed to (1) analyze patients taking aspirin 81 mg as their own group or (2) combine them with patients receiving preinjury AT (AT+). R software version 4.0.5 was used for all statistical analyses.[18] The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were utilized in the reporting of this research (Tables E3, available online at http://www.annemergmed.com).[19]

RESULTS

Characteristics of Study Subjects

All 45 Level I and II trauma centers from a national hospital network were invited to participate in the study. A total of 5,731 patients from 24 Level I or Level II trauma centers were screened for eligibility, and 2,950 met eligibility, had complete, nonduplicated records suitable for analysis, and constituted the sample for analysis (Figure 1). The study sample included 49.7% women, 84.8% White, with a median age of 74 years (IQR: 63 to 83), a median ISS of 4 (IQR: 2 to 5), and 86.2% with a GCS of 15. Of these, 949 (32.2%) patients received AT therapy prior to the injury. Details on patient characteristics and injury patterns are described in Table 1. Compared to patients with no AT use, those on preinjury AT therapy were older (absolute difference in medians: 9 years, 95% CI 8.2, 11.1 years), with a higher proportion of white (absolute difference: 6.6%, 95% CI 3.9%, 9.2%), female patients (absolute difference: 5.1%, 95% CI 1.2%, 9.1%), having had a same level fall (absolute difference: 24.1%, 95% CI 20.3%, 28.0%), and lower ISS (absolute difference in medians: -1.0, 95% CI -1.1, -0.9).

Among the 949 patients (32.2%) taking AT therapy prior to the injury, 10.0% received aspirin, 17.5% warfarin, 26.2% clopidogrel, 16.9% apixaban, 10.5%

Table 1. Demographics and injury patterns.

Variables	All Patients n=2,950	Preinjury AT-n=2,001	Preinjury AT+ n=949
Age, y; median [IQR]	74 [63-83]	70 [61-81]	79 [72-86]
Female, n (%)	1,467 (49.7)	962 (48.1)	505 (53.2)
Race, n (%)			
White	2,481 (84.8)	1,638 (82.7)	843 (89.3)
Black	249 (8.5)	191 (9.6)	58 (6.1)
Asian	57 (1.9)	45 (2.3)	12 (1.3)
Other	137 (4.7)	106 (5.4)	31 (3.3)
Activation type, n (%)			
Full	468 (15.9)	340 (17.0)	128 (13.5)
Partial	1,620 (54.9)	1,036 (51.8)	584 (61.5)
Consult	862 (29.2)	625 (31.2)	237 (25.0)
MOI, n (%)			
Same level fall	1,326 (44.9)	744 (37.2)	582 (61.3)
Other fall	578 (19.6)	396 (19.8)	182 (19.2)
MVC	853 (28.9)	699 (34.9)	154 (16.2)
Assault	33 (1.1)	29 (1.4)	4 (0.4)
Motor vehicle nontraffic	43 (1.5)	36 (1.8)	7 (0.7)
Other	117 (4.0)	97 (4.8)	20 (2.1)
GCS of 15, n (%)	2,544 (86.2)	1,710 (85.5)	834 (87.9)
ISS, median [IQR]	4 [2-5]	5 [2-6]	4 [1-5]

AT, Antithrombotic therapy; *GCS,* Glasgow Coma Scale; *IQR,* interquartile range [Q1-Q3]; *ISS,* injury severity score; *MOI,* mechanism of injury; *MVC,* motor vehicle crash.

rivaroxaban, and 10.7% one other single agent. The stated reasons for receiving AT therapy included atrial fibrillation (27.0%), history of venous thromboembolism (7.5%), a single other reason (27.6%), and 2 or more reasons (8.2%), and no reason listed (29.7%).

Main Results

A total of 280 (9.5%) patients had a repeat brain CT scan. The frequency of repeat brain CT scans at individual centers varied between 0% and 62.9% among the 24 trauma centers, with a median of 8.50%, an IQR of 5.02%

Table 2. Outcomes by preinjury antithrombotic therapy status for patients with a repeat computed tomography (n=280).

Variables	Total	Preinjury AT-[†]	Preinjury AT+	Absolute Change, AT- to AT+ [95% CI]
All Patients, n	2,950	2,001	949	-
Patients with Rescan	280	126	154	-
Rescan (%)	9.5	6.3	16.2	9.9 [7.3, 12.6][‡]
dICH, n (%)	21/280 (7.5)	15/126 (11.9)	6/154 (3.9)	-8.0 [-15.2, -0.9][‡]
Surgical Intervention, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0
Mortality, n (%)	3 (1.1)	0 (0.0)	3 (1.9)	1.9[§]
Hospital LOS,* Median [IQR]	3.0 [1.0-7.0]	4.0 [2.0-7.0]	3.0 [1.0-6.0]	-1.0 [-2.3, 0.3]
ICU LOS,* Median [IQR]	3.0 [2.0-7.0]	3.0 [2.0-7.0]	4.0 [2.0-6.0]	1.0 [-0.8, 3.1]

AT, Antithrombotic therapy; *CI,* confidence interval; *dICH,* delayed intracranial hemorrhage; *ICU,* intensive care unit; *IQR,* interquartile range [Q1-Q3]; *LOS,* length of stay.
*Hospital and ICU LOS was calculated for patients who had a hospital or ICU stay, respectively.
[†]Aspirin 81 mg was considered as preinjury AT-.
[‡]Statistically significant compared to the preinjury AT- group.
[§]Fisher's exact test was performed to determine the statistical significance due to the small sample size; however, it was unable to obtain 95% CI.

Table 3. Outcomes by preinjury antithrombotic therapy status for patients without a repeat computed tomography (n=2,670).

Variables	Total	Preinjury AT-[†]	Preinjury AT+	Absolute Change, AT- to AT+ [95% CI]
Patients without Rescan	2,670	1,875	795	-
Surgical Intervention, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0
Mortality, n (%)	6 (0.2)	1 (0.1)	5 (0.6)	0.6[§,‡]
Hospital LOS,* Median [IQR]	2.0 [1.0-5.0]	2.0 [1.0-5.0]	3.0 [1.0-5.0]	1.0 [0.4, 2.0][‡]
ICU LOS,* Median [IQR]	3.0 [2.0-4.0]	3.0 [2.0-5.0]	3.0 [2.0-4.0]	0.0 [-0.2, 0.2]

AT, Antithrombotic therapy; *CI,* confidence interval; *ICU,* intensive care unit; *IQR,* interquartile range [Q1-Q3]; *LOS,* length of stay.
*Hospital and ICU LOS was calculated for patients who had a hospital or ICU stay, respectively.
[†]Aspirin 81 mg was considered as preinjury AT-.
[‡]Statistically significant compared to the preinjury AT- group.
[§]Fisher's exact test was performed to determine the statistical significance due to the small sample size; however, it was unable to obtain 95% CI.

to 12.20%, and 2 centers having a rescan rate above 50%. The proportion of patients having a repeat CT scan was higher in patients on preinjury AT therapy compared to those not on AT (absolute difference: 9.9%, 95% CI 7.3%, 12.6%; Table 2). Compared to patients not on AT, a higher proportion of patients taking preinjury warfarin (absolute difference: 13.0%, 95% CI 6.6%, 19.4%), clopidogrel (absolute difference: 8.6%, 95% CI 3.8%, 13.1%), apixaban (absolute difference: 18.7%, 95% CI 11.6%, 25.8%) and rivaroxaban (absolute difference: 10.7%, 95% CI 2.7%, 18.7%) received a repeat CT scan, whereas a lower proportion of patients taking full-dose aspirin (≥325 mg) received a repeat brain CT (3.2% versus 6.3%, based on Fisher's exact test).

Among 280 patients who had a repeat brain CT scan, 21 (7.5%) had a new intracranial hemorrhage on the repeat CT scan. A statistically significant difference in the raw proportion of dICH between patients on preinjury AT therapy versus those not on AT was observed (absolute difference: -8.0%, 95% CI -15.2%, -0.9%, Table 2; unadjusted odds ratio [OR]=0.30, 95% CI 0.11 to 0.80). Adjusted logistic regression controlling for age, gender, race, activation type, mechanism of injury, ISS, and GCS showed no significant association between preinjury AT status and dICH (adjusted OR=1.03, 95% CI 27 to 3.88). When an omnibus statistical test, ie, Fisher's exact test, was performed to compare specific preinjury AT agents to the patients, not on AT, no difference was found between AT agent types and dICH rates (Tables E1 and E2, available online at http://www.annemergmed.com). There were no cases of surgical intervention for dICH. In addition, unadjusted comparisons showed no statistically significant difference in mortality (1.9% versus 0%, based on Fisher's exact test), hospital length of stay (absolute difference in medians: -1.0 day, 95% CI -2.3, 0.3), or ICU length of stay (absolute difference in median: 1.0 day, 95% CI -0.8, 3.1; Table 2) for those on preinjury AT versus not on AT. In the adjusted analysis, there was no significant association between preinjury AT status and hospital length of stay or between preinjury AT status and ICU length of stay.

Among 2,670 patients without a repeat CT scan, no surgical interventions were performed. Compared to those not on AT, patients on AT had statistically significantly higher mortality using Fisher's exact test (0.6% versus 0.1%, Table 3) and had a slightly longer hospital length of stay (absolute difference in medians: 1.0 day, 95% CI 0.4, 2.0); however, no difference was found for ICU length of stay (absolute difference in median: 0.0 day, 95% CI -0.2, 0.2). The proportion of admissions from ED was 76.0% overall, 87.5% for patients with repeat CT scans, and 74.8% for those without repeat CTs. Regardless of the repeat CT status, patients on preinjury AT had a lower proportion of admissions from ED (for patients with repeat CT: absolute difference: -9.9%, 95% CI -17.8%, -1.9%; for patients without repeat CT: absolute difference: -4.6%, 95% CI -8.4%, -0.8%).

Because of the retrospective nature of this research, a follow-up brain CT scan was unavailable for all patients. However, other follow-up data were available on many of the 2,670 patients without a follow-up brain CT scan through various data linkages to our enterprise data warehouse system. For example, as shown in Figure 2, we were able to obtain follow-up information on nearly all the 2,670 patients as follows:

1. Thousand nine hundred ninety-seven patients were admitted to the hospital. Their discharge diagnoses were electronically reviewed for any discharge ICD-10-CM diagnosis code in the S06 series (brain injury). The patients with concussions and other

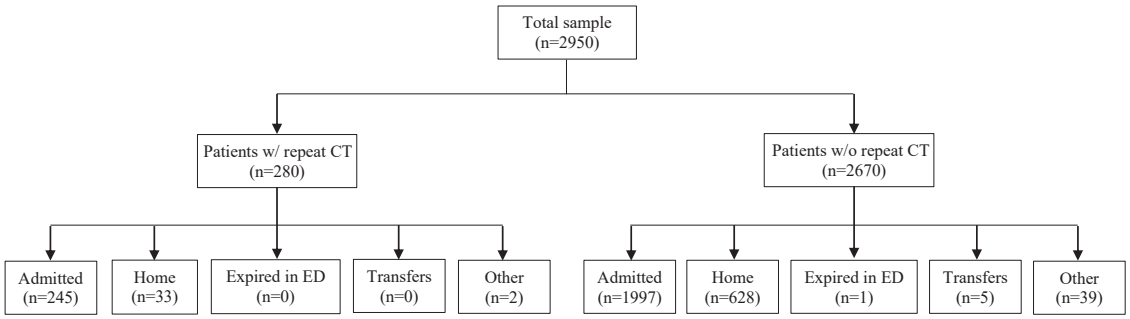

Figure 2. Emergency department disposition by repeat computed tomography status. CT, computed tomography; ED, emergency department.

nonintracranial hemorrhages (ICHs) discharge diagnoses were separated from those with S06 diagnoses consistent with ICH (S06.31 to S06.38, S06.4 to S06.6). The electronic medical records of patients admitted to the hospital without a second brain CT scan at the initial encounter and who were discharged from the hospital with an ICD-10-CM diagnosis code consistent with dICH were identified. A manual chart review was then conducted to confirm that they had imaging showing dICH. Two potential cases of dICH were identified, both detected on magnetic resonance imaging (MRI). These patients had initial CT scans that were negative for ICH, and because MRI is more sensitive than CT scan, we are unable to determine if the bleeding detected on MRI represents an instance of dICH or if the ICH was present from the outset but was not detectable on brain CT scan.

2. Six hundred twenty-eight patients without a second CT scan at the index encounter were discharged home from the ED, and our enterprise data warehouse was searched for subsequent admission of these patients to one of our system hospitals in the 5 days following the index encounter. A total of 87 patients of the entire sample (20 of whom were discharged home from ED) were admitted to one of the system hospitals within 5 days of the index encounter. A manual chart review of their electronic records was performed, and none of the admissions were found to be for intracranial bleeding.

Given the above available follow-up data, assuming that patients without a repeat CT scan did not suffer clinically significant dICH and survived without surgical intervention, the proportion of dICH would be 0.6% (6/[154 with repeat CT+795 without repeat CT]) for those on preinjury AT therapy and 0.7% (15/[126 with repeat CT+1,875 without repeat CT]) for those not on AT therapy. All-cause mortality was 0.3% (9/2,950) and attributable mortality was 0.03% (1/2,950). The single attributable death was a patient who was on preinjury warfarin, arrived with a supratherapeutic international normalized ratio (INR), and suffered a massive dICH, but the family declined interventions. This patient's time from ED to initial CT scan was 20 minutes, and time from ED to second CT scan was 7.5 hours.

Laboratory test results for INR were available for 68.4% of patients. Among these patients, there was a statistically significant difference in INR between patients on preinjury AT and those not on AT (absolute difference in median: 0.1, 95% CI 0.0, 0.1); however, the small difference is likely not clinically meaningful. Among the 42 patients with an INR >3, 7 had a repeat CT scan and none had a dICH. A total of 26 patients received reversal agents before a repeat CT scan. A higher proportion of patients on preinjury warfarin received reversal agents (7.2% [12/166]); of these patients, 50.0% received vitamin K, 25.0% prothrombin complex concentrate (human), and 16.7% plasma.

To determine the effect, if any, of including patients taking aspirin 81 mg in the group of patients, not on ATs, sensitivity analyses were performed (1) to analyze patients on aspirin 81 mg as their own group or (2) to combine them with patients receiving preinjury ATs. The results of neither method differed materially from the original results for primary and secondary outcomes (Tables E4 and E5, available online at http://www.annemergmed.com).

LIMITATIONS

Our study has several limitations. Beyond the inherent limitations of a retrospective study design, such as sample size considerations and the underrepresentation of minority groups, patients may have developed dICH following their evaluation at one of the included participating centers and been managed elsewhere; thus, their ultimate outcome would not be known. The analysis included the assumption

that patients who did not have a repeat brain CT scan did not have a dICH, and although this is likely based on the available follow-up described above and on rates of dICH in other available literature, it represents a significant limitation absent comprehensive follow-up of the patients in this sample with a brain CT scan. This study is slightly underpowered (power=72.4%) given the low detected frequency of dICH and the low rates of early rescanning patients in this sample. The patients in this study incurred predominantly low-energy mechanism of injuries, such as ground-level falls, which could limit generalizability, but this may be mitigated by the inclusion of only patients with a GCS of 14 to 15. Another potential limitation to generalizability may be the inclusion of only Level I and II trauma centers and only trauma activations and consultations. Furthermore, as a multicenter study, the care practices of participating institutions and provider decisionmaking may have introduced variances regarding AT agent reversal and other diagnostic and therapeutic interventions. As such, inherent selection bias may indicate the need for repeat imaging in these patients that were not elucidated in this study and would justify observation and/or repeat imaging. For example, the care practices of participating institutions and provider decisionmaking may have introduced variances regarding AT agent reversal and other diagnostic and therapeutic interventions. Therefore, there may be indications for repeat imaging in these patients that were not elucidated in this study and would justify observation and/or repeat imaging, emphasizing the need for a prospective study. As double abstraction was not conducted, we were also unable to assess an inter-rater reliability or kappa statistic, but data quality was assured by chart review and validation of a 10% sample of patient charts as they were submitted.

DISCUSSION

This is the largest assessment to date of outcomes in older patients who sustained a mild traumatic brain injury and had an initial negative brain CT scan. One-third of the patients were taking ATs prior to the injury. Of the 9.5% enrolled patients who had a repeat brain CT scan, 7.5% had dICH detected for an overall rate of less than 1% dICH for the entire sample. No patients underwent neurosurgical intervention, and attributable mortality was 0.03%. Additional review of enterprise data warehouse data supported the assumption that there were few, if any, additional cases of dICH among patients who did not have a second CT scan as part of their initial encounter. Our analysis shows that in this patient group, for those with initial brain CT imaging showing no acute injury, discharge without further imaging or observation may be acceptable management.

Establishing an evidence-based care process for this patient group is important because traumatic brain injury is a major health concern in older patients, and as the population ages, the problem has become more profound. According to health statistics data from the Centers for Disease Control and Prevention, elderly trauma patients, ie, those aged ≥75 years, experienced the highest rates of traumatic brain injury-related hospitalizations (32%) and associated mortality (28%).[20] It is well documented that traumatic brain injury in older patients is associated with higher morbidity, mortality, and functional impairment.[21-23] Although much research seems to be concentrated on severe traumatic brain injury, more than 75% of traumatic brain injury patients in the US experience a mild traumatic brain injury.[24]

Current protocols using routine repeat CT scans after negative initial CT imaging are resource intensive.[15] According to a report published in 2015, 6,359 of 100,000 adults aged 65 or older experienced an unintentional nonfatal fall, resulting in a cost burden of $31billion to the US health care system.[25,26] Li reported that the average cost to detect a single dICH was $1,016,960 when using a universal screening protocol.[25] Borst et al[27] evaluated 1,676 patients on AT therapy with blunt trauma. Only 0.9% developed dICH identified on the second brain CT following a negative initial CT scan. None of the patients with dICH developed a change in neurologic status, required an intracranial pressure monitor, or underwent neurosurgical intervention. The total direct cost of the negative brain CT scans was estimated to be $926,247. The authors concluded that routine repeat brain CT imaging in patients with a negative scan on admission is not cost-effective.

The relatively common use of AT agents in the geriatric age group presents a challenge in managing traumatic brain injury. Historically, the primary medications influencing clot formation were warfarin and aspirin, but there are now numerous agents that affect platelet function, such as P2Y12 inhibitors, or those that affect clotting factors, such as the direct oral anticoagulants (DOACs). In a recent series of 33,710 patients from 90 US hospitals, Fakhry et al[28] found that the intake of ATs had inconsistent effects on the risk of traumatic brain injury after ground-level falls in geriatric patients, suggesting there was a minimal increased risk of significant bleeding in those taking ATs compared to those not taking these medications.

Others have investigated the occurrence of dICH in patients on AT therapy. In their descriptive study, Barmparas et al[29] evaluated the incidence of dICH in

trauma patients on preinjury DOACs, which was found to be 1.2%. The authors concluded routine head CT scan was unnecessary, as no patients with dICH required neurosurgical intervention or died. Studies comparing DOACs to warfarin have reported inconsistent results. In a multicenter study by Cohan et al,[30] no statistically significant difference was reported in the incidence of dICH among patients taking DOACs compared to those on warfarin. Higher rates of dICH in patients on warfarin compared to those on DOACs were reported in many smaller observational studies.[31-33] Conversely, among traumatic brain injury patients on preinjury anticoagulants who had a repeat brain scan following an initial negative scan, Cocca et al[34] found a 14% incidence of dICH for those on DOACs compared to 0% on warfarin. Similarly, Battle et al[35] and Mann et al[15] reported an increased incidence of dICH in patients on DOAC therapy compared to warfarin. The systematic review by Puzio et al[36] of 3,051 patients found the pooled weighted rate of dICH to be similarly low in DOACs (2.31%) compared to warfarin (2.43%).

In this study, dICH was uncommon in patients taking ATs, as well as those not on ATs. In addition, the dICH rates were low regardless of the AT agent the patient was taking, with no patient undergoing neurosurgical intervention. Clinicians appeared to be more concerned about patients on preinjury AT agents, as there was significantly more repeat CT scans obtained in patients on these drugs (16.2% versus 6.3%; Table 2). Similarly, clinicians appeared more concerned about some AT agents than others, with varying repeat brain CT scan rates for patients on warfarin (19.3%), clopidogrel (14.9%), apixaban (25.0%), and rivaroxaban (17.0%), all significantly higher compared to the rate for patients not taking AT agents (6.3%). Whether or not aspirin 81 mg per day was considered an AT agent had no association with the outcome per our sensitivity analysis; thus, the initial classification of aspirin 81 mg intake as AT- did not affect the results. Adjusted logistic regression controlling for age, sex, race, activation type, mechanism of injury, ISS, and GCS showed no significant association between preinjury AT status and dICH (adjusted OR,1.03; 95% CI, 0.27 to 3.88). Based on these findings, neither preinjury AT status nor the intake of any particular AT agent appears to be a major driver of the decision to obtain repeat imaging in these patients, absent other indications.

Because of the retrospective nature of this research, a follow-up CT scan was unavailable for all patients in our sample. To remedy this limitation, we performed additional data linkages to our enterprise data warehouse in an effort to secure follow-up information on the patients who did not have a repeat brain CT scan as part of their initial encounter. The review of the hospital discharge diagnoses of 1,997 patients who did not have a second brain CT initially, but were hospitalized, revealed there were 2 potential cases of dICH detected on MRI. The search of our system enterprise data warehouse for readmissions for the 628 patients who were discharged home from the ED revealed that 87 patients (20 of whom were discharged home from ED) were readmitted to one of our system hospitals, and a manual chart review confirmed that none were readmitted for dICH. It is important to note that patients do not always return to the same hospital: Hsia et al[37] determined that 18.9% of California adults with a traumatic brain injury diagnosis sought care at a different hospital following their initial visit. Brito et al[38] found that 16.4% of traumatic brain injury patients sought further care at a different facility than the one they initially presented. This additional follow-up review, coupled with the absence of neurosurgical intervention and additional attributable mortality, reinforces our assumption that the vast majority of patients did not sustain dICH and supported the estimate of a $<1\%$ dICH in these patients.

In conclusion, this multicenter, retrospective, observational study of 2,950 enrolled patients, 949 of whom were on AT medications, demonstrates that in older patients with an initial GCS of 14 to 15 and a negative initial brain CT scan, the rate of dICH is small and is associated with a minimal clinical consequence, regardless of AT use. Furthermore, no patient had an operative neurosurgical intervention, and the attributable mortality was very low. Therefore, the practice of routinely keeping patients for observation or repeating a brain CT scan following an initial negative scan does not appear to be supported based on the findings of this study. However, selected patients may be rescanned or observed based on unique clinical findings of concern to the physician. These results should be confirmed in a large, prospective validation study.

Supervising editor: Timothy F. Platts-Mills, MD, MSc. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

Author affiliations: From the Department of Surgery, Del Sol Medical Center, El Paso, TX (Flaherty); Trauma Surgery, Grand Strand Medical Center, Myrtle Beach, SC (Biswas); Center for Trauma and Acute Care Surgery Research, Clinical Services Group, HCA Healthcare, Nashville, TN (Watts, Wilson, Shen, Garland, Wyse, Fakhry); Department of Trauma Surgery, Research Medical Center, Kansas City, MO (Lieser); Department of Surgery, Medical City Plano, Plano, TX (Duane); Trauma Services, Sky Ridge Medical Center, Lone Tree, CO (Offner); Department of Surgery,

Regional Medical Center Bayonet Point, Hudson, FL (Love); Department of Surgery, Mission Hospital, Asheville, NC (Shillinglaw); Department of Surgery, TriStar Skyline Medical Center, Nashville, TN (Hunt); Trauma Services, HCA Houston Healthcare Conroe, Conroe, TX (Gauny).

Author contributions: SF, SMF, DDW, RJW, and JMG conceived the study and designed the trial. SB, PJO, JDL, WCS, DLH, and RWG contributed significantly to the revision of the final design of the trial. DDW, RJW, and NYW supervised the trial's conduct and data collection. YS and NYW managed the data, including quality control. SF, SMF, MJL, and TMD undertook the recruitment of participating centers. SF, SB, PJO, JDL, WCS, DLH, RWG, and Delayed Hemorrhage TBI Research Group abstracted charts, including quality control, and provided substantial data for the study. YS provided statistical consultation and analyzed the data. SB, SMF, RJW, DDW, JMG, and YS drafted the manuscript, and all masthead authors contributed substantially to its revision. All authors certified that they contributed to the design, data acquisition, data analysis/interpretation, and drafting/revising of the manuscript. The authors have approved the version to be published. SF and SMF take responsibility for the paper as a whole.

Authorship: All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

Publication dates: Received for publication March 3, 2022. Revisions received June 10, 2022; June 24, 2022, and July 20, 2022. Accepted for publication August 2, 2022.

Presented as an oral podium presentation at the 35th Annual Meeting of the Eastern Association for the Surgery of Trauma (EAST) on January 14, 2022, in Austin, Texas.

This research was supported (in whole or part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. However, the views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

REFERENCES

1. Barnes GD, Lucas E, Alexander GC, et al. National trends in ambulatory oral anticoagulant use. *Am J Med*. 2015;128:1300-1305.e2.
2. Dossett LA, Riesel JN, Griffin MR, et al. Prevalence and implications of preinjury warfarin use: an analysis of the National Trauma Databank. *Arch Surg*. 2011;146:565-570.
3. Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT Head Rule for patients with minor head injury. *Lancet*. 2001;357:1391-1396.
4. Haydel MJ, Preston CA, Mills TJ, et al. Indications for computed tomography in patients with minor head injury. *N Engl J Med*. 2000;343:100-105.
5. Edmonds M. The Canadian CT Head Rule reduced the need for CT scans more than the New Orleans Criteria in minor head injury. *Evid Based Med*. 2006;11:61-62.
6. Smits M, Dippel DW, de Haan GG, et al. External validation of the Canadian CT Head Rule and the New Orleans Criteria for CT scanning in patients with minor head injury. *JAMA*. 2005;294:1519-1525.
7. Stiell IG, Clement CM, Rowe BH, et al. Comparison of the Canadian CT Head Rule and the New Orleans Criteria in patients with minor head injury. *JAMA*. 2005;294:1511-1518.
8. Cohn B, Keim SM, Sanders AB. Can anticoagulated patients be discharged home safely from the emergency department after minor head injury? *J Emerg Med*. 2014;46:410-417.
9. Miller J, Lieberman L, Nahab B, et al. Delayed intracranial hemorrhage in the anticoagulated patient: a systematic review. *J Trauma Acute Care Surg*. 2015;79:310-313.
10. American College of Surgeons. ACS TQIP best practices in the management of traumatic brain injury. Published January 2015. Accessed October 15, 2021. https://www.facs.org/-/media/files/quality-programs/trauma/tqip/tbi_guidelines.ashx
11. Kaen A, Jimenez-Roldan L, Arrese I, et al. The value of sequential computed tomography scanning in anticoagulated patients suffering from minor head injury. *J Trauma*. 2010;68:895-898.
12. Menditto VG, Lucci M, Polonara S, et al. Management of minor head injury in patients receiving oral anticoagulant therapy: a prospective study of a 24-hour observation protocol. *Ann Emerg Med*. 2012;59:451-455.
13. Peck KA, Sise CB, Shackford SR, et al. Delayed intracranial hemorrhage after blunt trauma: are patients on preinjury anticoagulants and prescription antiplatelet agents at risk? *J Trauma*. 2011;71:1600-1604.
14. Schoonman GG, Bakker DP, Jellema K. Low risk of late intracranial complications in mild traumatic brain injury patients using oral anticoagulation after an initial normal brain computed tomography scan: education instead of hospitalization. *Eur J Neurol*. 2014;21:1021-1025.
15. Mann N, Welch K, Martin A, et al. Delayed intracranial hemorrhage in elderly anticoagulated patients sustaining a minor fall. *BMC Emerg Med*. 2018;18:27-28.
16. Batchelor JS, Grayson A. A meta-analysis to determine the effect of anticoagulation on mortality in patients with blunt head trauma. *Br J Neurosurg*. 2012;26:525-530.
17. Franko J, Kish KJ, O'Connell BG, et al. Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma. *J Trauma*. 2006;61:107-110.
18. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing Program. 2021. Vienna, Austria: R Core Team. Accessed August 27, 2021. https://www.R-project.org/
19. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology*. 2007;18:800-804.
20. National Center for Health Statistics Mortality Data on CDC WONDER. Atlanta, GA: Centers for Disease Control and Prevention. Accessed November 29, 2021. https://wonder.cdc.gov/mcd.html
21. Frankel JE, Marwitz JH, Cifu DX, et al. A follow-up study of older adults with traumatic brain injury: taking into account decreasing length of stay. *Arch Phys Med Rehabil*. 2006;87:57-62.
22. Mosenthal AC, Lavery RF, Addis M, et al. Isolated traumatic brain injury: age is an independent predictor of mortality and early outcome. *J Trauma*. 2002;52:907-911.
23. Rapoport MJ, Feinstein A. Outcome following traumatic brain injury in the elderly: a critical review. *Brain Inj*. 2000;14:749-761.

24. National Center for Injury Prevention and Control. Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem. Atlanta, GA: Centers for Disease Control and Prevention. Published September 2003. Accessed November 29, 2021. https://www.cdc.gov/traumaticbraininjury/pdf/mtbireport-a.pdf
25. Li J. Admit all anticoagulated head-injured patients? A million dollars versus your dime. You make the call. *Ann Emerg Med*. 2012;59:457-459.
26. National Center for Injury Prevention and Control. WISQARS™ (Web-Based Injury Statistics Query and Reporting System). Atlanta, GA: Centers for Disease Control and Prevention; updated July 1, 2020. Accessed November 29, 2021. www.cdc.gov/injury/wisqars/index.html
27. Borst J, Godat LN, Berndtson AE, et al. Repeat head computed tomography for anticoagulated patients with an initial negative scan is not cost-effective. *Surgery*. 2021;170:623-627.
28. Fakhry SM, Morse JL, Garland JM, et al. Antiplatelet and anticoagulant agents have minimal impact on traumatic brain injury incidence, surgery, and mortality in geriatric ground level falls: A multi-institutional analysis of 33,710 patients. *J Trauma Acute Care Surg*. 2021;90:215-223.
29. Barmparas G, Kobayashi L, Dhillon NK, et al. The risk of delayed intracranial hemorrhage with direct acting oral anticoagulants after trauma: a two-center study. *Am J Surg*. 2019;217:1051-1054.
30. Cohan CM, Beattie G, Bowman JA, et al. Repeat computed tomography head scan is not indicated in trauma patients taking novel anticoagulation: A multicenter study. *J Trauma Acute Care Surg*. 2020;89:301-310.
31. Riccardi A, Spinola B, Minuto P, et al. Intracranial complications after minor head injury (MHI) in patients taking vitamin K antagonists (VKA) or direct oral anticoagulants (DOACs). *Am J Emerg Med*. 2017;35:1317-1319.
32. Antoni A, Schwendenwein E, Binder H, et al. Delayed intracranial hemorrhage in patients with head trauma and antithrombotic therapy. *J Clin Med*. 2019;8:1780-1781.
33. Marques RSF, Antunes C, Machado MJ, et al. Reappraising the need for a control CT in mild head injury patients on anticoagulation. *Eur J Trauma Emerg Surg*. 2021;47:1461-1466.
34. Cocca AT, Privette A, Leon SM, et al. Delayed intracranial hemorrhage in anticoagulated geriatric patients after ground level falls. *J Emerg Med*. 2019;57:812-816.
35. Battle B, Sexton KW, Fitzgerald RT. Understanding the value of repeat head CT in elderly trauma patients on anticoagulant or antiplatelet therapy. *J Am Coll Radiol*. 2018;15:319-321.
36. Puzio TJ, Murphy PB, Kregel HR, et al. Delayed intracranial hemorrhage after blunt head trauma while on direct oral anticoagulant: systematic review and meta-analysis. *J Am Coll Surg*. 2021;232:1007-1016.e5.
37. Hsia RY, Markowitz AJ, Lin F, et al. Ten-year trends in traumatic brain injury: a retrospective cohort study of California emergency department and hospital revisits and readmissions. *BMJ Open*. 2018;8:e022297-e022298.
38. Brito A, Costantini TW, Berndtson AE, et al. Readmissions after acute hospitalization for traumatic brain injury. *J Surg Res*. 2019;244:332-337. d.

APPENDIX

†The Delayed TBI Hemorrhage Research Group includes Kenneth S. Helmer, MD; Gary J. Curcio, MD; Doreen Gilligan, RN, Dallas A. Taylor, MSN, RN; Frances Hughes, RN; Ralph J. Barker, MD, PhD; Carol M. Bissinger, BSN, RN; Charles J. Miller, MD; Lori F. Harbour, BS; Therèse M. Duane, MD, MBA; Matthew M. Carrick, MD; Mark J. Lieser, MD; Stephen Flaherty, MD; Valeria Blair, BSN, RN; Julia Perez, MSN, RN; Carli Cervantes, MPH, BSN; Christopher Hogan, MD; Chris R. Ruiz, BSN, RN; Meredith Tinti, MD; Cecilia A. Romero; Karla J. Jones, MSN, RN; Tara Neeley, BSN, RN; Kimberly Wright, MSN, RN; James Dunne, MD; Tatiana Eversley-Kelso, MPH; Melissa A. Harte, DNP, RN; Richard A. Kline, MD; Joseph D. Love, DO; Erika van Doorn, MD; Christie M. Brock, DO; David L. Acuna, DO; Jamie L. Shaddix, MSN, RN; Heather Rhodes, PhD, DHS; Saptarshi Biswas, MD; William C. Shillinglaw, DO; Andrea Slivinski, DNP, RN; Patrick J. Offner, MD, MPH; Jeffrey H. Levine, MD; Kaysie L. Banton, MD, MHA; Burt Katubig, MD.