Delayed Intracranial Hemorrhage after Blunt Head Trauma while on Direct Oral Anticoagulant: Systematic Review and Meta-Analysis

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The use of anticoagulants continues to rise in conjunction with the increasing age of our population.[1] Direct oral anticoagulants (DOACs) are rapidly becoming usual care for the treatment of venous thromboembolism and atrial fibrillation. They have similar efficacy and reduced bleeding complications compared with traditional warfarin therapy, but their degree of anticoagulation is not as easily measured.[2]

Anticoagulation places patients at high risk of immediate intracranial hemorrhage (ICH) and in general, these patients have poor outcomes.[3] In the elderly population, anticoagulant medications can also present a significant challenge, as falls are the leading cause of traumatic brain injury.[4] Patients who suffer a trauma while on anticoagulation may also be at risk for a delayed ICH after an initial negative CT scan.[1] At some trauma centers, patients suffering blunt head trauma on DOACs are kept in observation for 24 hours, or a follow-up CT scan is arranged to rule out delayed ICH despite an initial negative head CT. There is a paucity of literature to support this practice, and the rate of delayed ICH after ground level fall while on anticoagulation remains unclear.

We performed a systematic review of the literature and meta-analysis to evaluate the risk of delayed ICH after a normal CT scan in patients on DOACs who suffered blunt head trauma. We hypothesized that patients on DOACs would have a low risk of delayed ICH after blunt head trauma, so consequently, a period of observation or systematic repeat CT scans may not be warranted.

METHODS

Data sources and search

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were followed.[5] In June 2020, an electronic literature search of MEDLINE (Ovid), Embase (Elsevier), and Cochrane Library was performed by a medical librarian (TH) using a combination of keywords and subject headings. Databases were searched from inception through June 2020. Search terms included the names and descriptions of oral anticoagulant medications (eg anticoagulants, dabigatran, DOACs, novel anticoagulants [NOACs] and warfarin), variations of terms related to brain trauma (eg craniocerebral trauma, ICHs), and language related to imaging (eg tomography, CT scan) (eDocument 1).

Study selection and quality assessment

All titles and abstracts were reviewed independently by 2 reviewers (TP, HK); articles selected for full review were analyzed by 3 reviewers (TP, HK, JH); and consensus was used for final inclusion. We included studies meeting the following criteria: patients suffering blunt head trauma and on anticoagulation, age $\geq$18 years, English language, and reported outcomes in patients on DOACs. Studies with fewer than 3 patients (case reports), conference abstracts, and studies without patients who were taking DOACs were excluded (Fig. 1). Study quality was determined using the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses.[6] "Good quality" studies met 3 or 4 criteria in the selection domain, 1 or 2 criteria in the comparability domain, and 2 or 3 criteria in the outcome/exposure domain. "Fair quality" studies met 2 criteria in the selection domain, or 1 or 2 criteria in the comparability domain, or 2 or 3 criteria in the outcome/exposure domain. "Poor quality" met 0 or 1 criteria in the selection domain or 0 criteria in the comparability domain, or 0 or 1 criteria in the outcome/exposure

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Abbreviations and Acronyms

DOAC = direct oral anticoagulants
ICH = intracranial hemorrhage
INR = international normalized ratio
NNT = number needed to treat

domain. Study quality assessment was completed independently by 2 reviewers (TP and HK), and a third (PM) provided consensus for any disagreements.

Data extraction and statistical analysis

The primary outcome was development of delayed ICH. Secondary outcomes evaluated included neurosurgical bedside procedures to measure intracranial pressure, operative intervention, and mortality. A detailed review of each study was performed and data were extracted in duplicate. Patient demographics, including age and mechanism of injury, were analyzed. Study characteristics, including protocol for repeat head CT, and type of anticoagulant/antiplatelet were determined. Finally, rate of delayed ICH, resultant complications, and mortality were evaluated. A planned meta-analysis was performed. A random effects model was used to calculate pooled event rates for single outcomes and to calculate proportions, and 95% confidence intervals. The number needed to treat (NNT) was calculated for the number of patients who would need to be observed in order to detect 1 additional delayed ICH and for the number of patients who would need to be observed to prevent 1 excess mortality from a delayed ICH.[7] The NNTs were derived by the taking the inverse of the absolute risk reduction between groups, as estimated in this meta-analysis.

Heterogeneity was assessed based on clinical diversity, methodologic diversity, and statistical heterogeneity. Clinical diversity was assessed by comparing study protocols for duration of patient observation, use of a routine follow-up head CT, and selection of the study populations. Statistical heterogeneity was assessed using the I^2 statistic representing the percentage of variability across studies attributable to differences between studies due to underlying differences rather than sampling error. The interpretation of I^2 depends on the magnitude and direction of the effects and the strength of evidence for heterogeneity (p value from the chi-square test); a p value of 0.1 was considered significant.[8] We used accepted values for ascribing heterogeneity as follows: considerable (75%–100%); substantial (50%–90%); moderate (30%–60%), and low/not important (0%–40%).[8] Publication bias was visually assessed using inverted funnel plots (eFigs. 4–6). All analyses were performed using MedCalc Statistical Software version 16.4.3 (MedCalc Software; https://www.medcalc.org; 2016).

RESULTS

The search returned 5,719 articles, and after removal of duplications and screening of title and abstract, 72 underwent full review, and 12 met final inclusion/exclusion criteria (Fig. 1). Four studies were prospective; 8 were retrospective in nature (Table 1).

Overall, 5,289 patients were included, 1,263 (23.9%) were on a DOAC, and 1,788 (33.8%) patients were on warfarin. One hundred four patients were on concomitant anticoagulant and antiplatelet medications. All studies involved a period of hospital observation. Four studies reported performing routine repeat CT scans during this period of observation on all patients, while the remaining studies repeated CT scans only if symptoms were observed. We included studies with patients over 18 years, but all studies evaluated elderly patients with reported mean ages 75 to 83 years. Ninety-two percent suffered a ground level fall.

Overall, 10 studies were of good quality and 2 were determined to be of poor quality (Table 2). Studies had low clinical and methodologic heterogeneity. Most studies had similar patient populations, composed largely of elderly patients suffering ground level falls. Management protocols were similar, with either 24 hours of observation or repeat CT head scans. Statistical heterogeneity was low to moderate depending on the analysis. The I^2 for the percentage of delayed ICH for DOACs was 46.4% (95% CI 0.0–72.6,

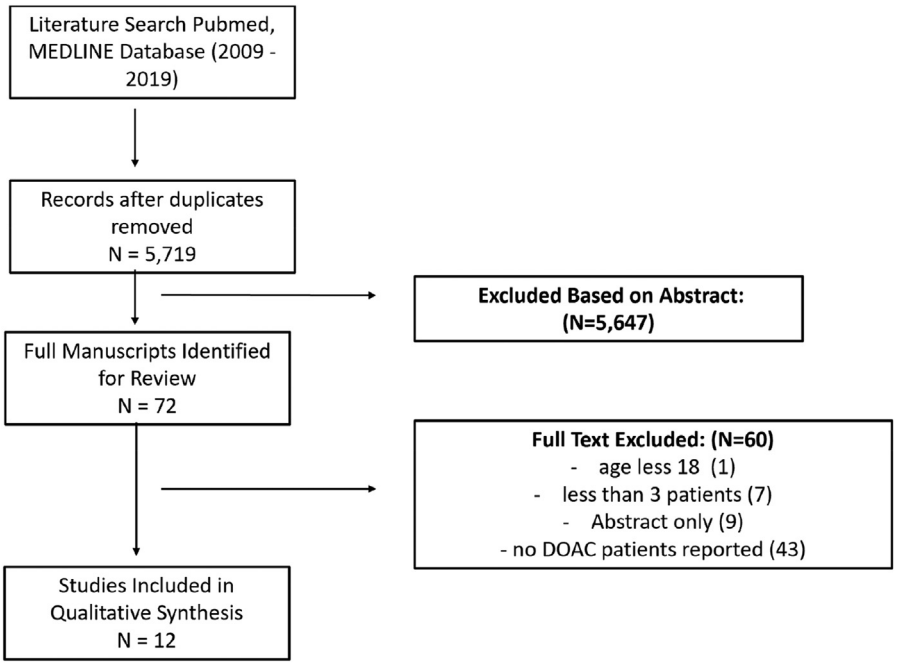

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Diagram. DOAC, direct oral anticoagulant.

$p = 0.04$). The I^2 for the percentage of delayed ICH for warfarin was 60.4% (95% CI 23.4−79.5, $p = 0.01$). The I^2 for the odds of delayed ICH for DOACs compared to warfarin was 24.4% (95% CI 0.0−62.4, $p = 0.21$). There was no evidence of publication bias based on visual analysis of funnel plots (eFigs. 4−6).

Overall, 25 patients on a DOAC and 44 patients on warfarin suffered a delayed ICH. Based on a random effects model, the percentages of patients who suffered delayed ICH for DOAC were 2.43% (95% CI 1.31%−3.88%) and 2.31% (95% CI 1.26%−3.66%) on warfarin. (Tables 3, 4 and eFigs. 1, 2) The odds of developing delayed ICH were not statistically different between patients on DOAC vs patients on warfarin, odds ratio 0.89 (95% CI, 0.44−1.81, $p = 0.76$) (Table 5 and eFig. 3). No patient on both an anticoagulant and antiplatelet medication developed delayed ICH. There were 516 patients not on any anticoagulation included in 1 study, and 2 suffered delayed ICH (0.39%). Using the weighted random effects estimates from our meta-analysis and the data from Chenoweth and colleagues,[9] the rate of delayed ICH in patients on DOACs is 2.43% and the rate in patients not on anticoagulation is 0.4%. The absolute reduction is 2.4−0.4 = 2.0%, and the NNT is 1/0.02 = 50.

Overall, 4 patients required neurosurgical intervention with 1 intraventricular drain, 1 burr hole procedure, and 2 craniectomies. Overall, 10 patients died from complications related to bleeding. Fifty-nine of sixty-nine patients (86%) who suffered delayed ICH, had no change in their clinical course, while 2 patients on DOAC and 8 patients on warfarin died from complications after delayed ICH. The mortality rate was low, which prohibited calculation of a pooled rate, but the overall crude risk of death from delayed ICH among the DOAC and warfarin patients combined was 0.33% (10 of 3,051), and was lower in patients on DOAC (0.16%) than that in patients on warfarin (0.45%).

DISCUSSION

Based on available literature, the percentage of patients on DOAC or warfarin who experience a delayed ICH or mortality after an initially negative head CT is low. In addition, there was no evidence of a significant difference in the rates of delayed ICH in patients taking DOACs compared with warfarin. Lastly, the majority of patients experiencing a delayed ICH did not require subsequent neurosurgical intervention, and mortality was rare.

One of the earliest studies illustrating a risk of delayed ICH while on anticoagulants was by Menditto and colleagues.[10] The authors prospectively analyzed 97 patients on warfarin who suffered blunt trauma and had a mild traumatic brain injury. In their study, all patients were observed for 24 hours and a mandatory repeat CT scan was performed to evaluate patients for delayed ICH. Five patients (5%) developed delayed ICH, 3 with an

Table 1. Study Characteristics

Characteristic	Antoni et al 2019[22]	Barmparas et al 2018[17]	Battle et al 2011[13]	Bauman et al 2017[1]	Chenoweth et al 2018[9]	Cipriano et al 2018[19]	Cocca et al 2019[18]	Cohan et al 2020[21]	Mann et al 2018[20]	Marques et al 2019[23]	Riccardi et al 2017[14]	Turcato et al 2019[24]
Type of study	Single institution retros pective review	Multicenter retrospective review	Single institution retrospective	Multicenter prospective obser vational	Multicenter prospective obser vational	Single institution prospective obser vational	Single institution retrospective	Multicenter retrospective review	Single institution retrospective	Single institution retrospective	Single institution prospective obser vational	Single institution retros pective
Study dates	2012 −2014	2014−2017	2015−2016	2013−2014	2015−2016	2016−2017	2017−2018	2016−2018	2014−2015	2017−2018	2015−2016	2017−2018
No. of patients	793	249	110	1180	859	206	61	777	218	201	225	410
Age, y (mean)	18+ (81)	18+ (81)	65+ (N/A)	18+ (80)	55+ (75)	18+ (82)	64+ (80)	18+ (76)	65+ (82)	18+ (82)	18+ (82)	18+ (83)
Population												
Blunt trauma on AC or AP, n (% ground −level fall)	753 (95)	–	–	–	–	–	–	–	–	–	–	–
Blunt trauma on DOAC, n (% ground −level fall)	–	199 (80)	–	–	–	–	–	–	–	–	–	–
Fall on AC or AP, n (%)	–	–	110 (100)	1180 (100)	–	–	–	–	218 (100)	–	–	–
Blunt trauma on AC, n (% fall)	–	–	–	–	678 (79 ground −level)	188 (91)	–	662 (85.3)	–	198 (99)	–	419 (93)
Fall on AC, n (%)	–	–	–	–	–	–	61 (100)	–	–	–	225 (100)	–
Study characteristic												
Repeat CT	50% in 24 h	82% in 24 h	100% in 6 h	100% in 12 h	–	72 (40.5%)	31 (51%)	54%	100% in 6 h	90%	60%	100% in 24 h
Medication, n or n (%)*												
ASA	46.4	–	–	69	156 (45.5)	–	36.4	–	–	–	–	–
Warfarin	32.3	–	39	19	75 (21.9)	121 (58.7)	42.8	55	33	57.5	52.4	59.4
DOAC	4	–	19	–	37 (10.8)	–	57.1	45	13.7	38	47.6	40.6
AC + AP	0	0*	0	0	34 (3.4)	10 (4.9)	30 (49.2)	0	13.8	–	0	0
Rivaroxaban	–	47	–	3	–	29 (34.1)	–	–	–	–	–	–
Apixaban	–	41.4	–	–	–	21 (24.7)	–	–	–	–	–	–
Dabigatran	–	11.6	–	–	–	34 (40.0)	–	–	–	–	–	–
Plavix	–	–	26.3	17	–	–	–	–	16.5	–	–	–
Edoxaban	–	–	–	–	–	1 (1.2)	–	–	–	–	–	–
INR, mean	–	–	–	–	–	–†	–	2.7	–	2.64‡	–	–

(Continued)

Table 1. Continued

Characteristic	Antoni et al 2019[22]	Barmparas et al 2018[17]	Battle et al 2011[13]	Bauman et al 2017[1]	Chenoweth et al 2018[9]	Cipriano et al 2018[19]	Cocca et al 2019[18]	Cohan et al 2020[21]	Mann et al 2018[20]	Marques et al 2019[23]	Riccardi et al 2017[14]	Turcato et al 2019[24]
Outcomes/ conclusions												
Delayed ICH, n (%)	7 (0.9)	3 (1.2) [§]	2 (1.8)	7 (0.51)	3 (0.3) [‖]	3 (1.7) [¶]	6 (9.6)	14 (1.8)	1 (0.46)	3 (1.7)	15 (6.7)	13/451 (2.9)
Neurologic decline and death, n	1 (Warfarin)	–	–	–	–	1 (DOAC)	1	–[#]	–	–	2 (warfarin)	1 (warfarin)
Clinical consequences	–	None required operative intervention	None	None	1 on no AC required operative intervention with burr holes; 1 died from complication (warfarin)	–	–	–	None	None	–	–
INR	–	–	–	2.5 and 3 in delayed ICH	2.3 in delayed ICH	–	–	>3 in 3/10 on Coumadin	–	None >3 on warfarin	–	–
Delayed ICH, n/N												
DOAC	1/38	2/249	1/21	1/45	0/37	2/85	6/44	4/346	1/30	0/78	3/107	4/183
Warfarin	6/255	N/A	0/43	2/285	1/75	1/93	0/33	10/431	0/72	3/115	12/118	9/268

12 articles were identified encompassing 5,289 patients, 1,263 (23.9%) on a DOAC, and 1,788 (33.8%) on warfarin.
*Barmparas et al 2018,[17] 4.8% also on antiplatelet; Bauman et al 2017,[1] 11% combination; Chenoweth et al 2018,[9] 516 (60%) on no AC or AP; Riccardi et al 2017,[14] AC + ASA excluded.
[†]35 (28.9) had INR > 3.
[‡]20% on warfarin with INR > 3.
[§]1 patient with ICH received tissue plasminogen activator then developed subarachnoid hemorrhage.
[‖]2 patients on no antiplatelet or anticoagulant developed delayed ICH (0.4%).
[¶]2 delayed ICH were 7+ days.
[#]2 patients underwent neurosurgical intervention, then died (warfarin); 3 total died from neurosurgical complication (warfarin).
AC, anticoagulant; AP, antiplatelet; ASA, aspirin; DOAC, direct oral anticoagulant; ICH, intracranial hemorrhage; INR, international normalized ratio.

Table 2. Study Quality

			Selection					Outcomes		
Study	Total stars	Study quality	Representativeness	Selection non-exposed cohort	Ascertainment of exposure	Demonstration outcome not present at start	Comparability of cohort	Assessment of outcome	Was follow-up long enough?	Adequacy of follow-up
Antoni[22] 2019	6	Good	Somewhat representative	No description	Structured interview	Yes	Study controls for other factors	Record linkage	Yes, 24 h	No statement
Barmparas[17] 2018	6	Good	Somewhat representative	No description	Structured interview	Yes	Study controls for other factors	Record linkage	Yes, 24 h	No statement
Battle[13] 2017	5	Poor	Somewhat representative	No description	Structured interview	Yes	Study controls for other factors	Record linkage	No, 6-h repeat scan	No statement
Bauman[1] 2017	6	Good	Somewhat representative	No description	Structured interview	Yes	Study controls for other factors	Record linkage	Yes, 24 h	No statement
Chenoweth[9] 2018	6	Good	Somewhat representative	No description	Structured interview	Yes	Study controls for other factors	Record linkage	Yes, 14 d	No statement
Cipriano[19] 2018	6	Good	Somewhat representative	No description	Structured interview	Yes	Study controls for other factors	Self-report (repeat CT not routine)	Yes, 30 d	Yes, subjects lost unlikely to introduce bias
Cocca[18] 2019	4	Poor	Somewhat representative	No description	Structured interview	Yes	Study controls for other factors	Self-report (repeat CT not routine)	No (CT was not consistently repeated)	No statement
Cohan[21] 2020	6	Good	Somewhat representative	No description	Structured interview	Yes	Study controls for other factors	Self-report (repeat CT not routine)	Yes, 30 d	Yes
Mann[20] 2018	6	Good	Somewhat representative	No description	Structured interview	Yes	Study controls for other factors	Record linkage	Yes	No statement
Marques[23] 2019	7	Good	Somewhat representative	No description	Structured interview	Yes	Study controls for other factors	Record linkage	Yes, 30 d	Yes
Riccardi[14] 2017	6	Good	Somewhat representative	No description	Structured interview	Yes	Study controls for other factors	Self-report (repeat CT not routine)	Yes, 30 d	Yes
Turcato[24] 2019	7	Good	Somewhat representative	No description	Structured interview	Yes	Study controls for other factors	Record linkage	Yes, 30 d	Yes

See eDocument 2 for scale and scoring manual.

Table 3. Studies Evaluating Direct Oral Anticoagulant

Study (year)	Sample size	% delayed ICH, not weighted, (n/N)	95% CI	Weight, %	
				Fixed	Random
Antoni22 (2019)	38	2.63 (1/38)	0.07 − 13.81	3.06	5.28
Barmparas17 (2018)	249	0.80 (2/249)	0.10 − 2.87	19.61	14.19
Battle13 (2017)	21	4.76 (1/21)	0.12 − 23.82	1.73	3.35
Bauman1 (2017)	45	2.22 (1/45)	0.06 − 11.77	3.61	5.96
Chenoweth9 (2018)	37	0.00	0.00 − 9.49	2.98	5.18
Cipriano19 (2018)	85	2.35 (2/85)	0.29 − 8.24	6.75	8.90
Cocca18 (2019)	44	13.64 (6/44)	5.17 − 27.35	3.53	5.86
Cohan21 (2020)	346	1.16 (4/346)	0.32 − 2.93	27.22	15.54
Mann20 (2018)	30	3.33 (1/30)	0.08 − 17.22	2.43	4.43
Marques23 (2019)	78	0.00	0.00 − 4.62	6.20	8.47
Riccardi14 (2017)	107	2.80 (3/107)	0.58 − 7.98	8.47	10.06
Turcato24 (2019)	183	2.19 (4/183)	0.60 − 5.50	14.43	12.76
Total (random effects)	1,263	2.43	1.31 − 3.88	100.00	100.00

"Total random effects" based on pooled weighted estimates.
Test for heterogeneity: Q = 20.5; DF = 11; significance level: p = 0.04; I^2 (inconsistency) 46.4% (I^2 test for heterogeneity defined as follows: considerable [75%-100%]; substantial [50%-90%]; moderate [30%-60%]; and low/not important [0%-40%]); 95% CI for I^2: 0−72.6.
DOAC, direct oral anticoagulant; ICH, intracranial hemorrhage.

international normalized ratio (INR) greater than 3 on presentation, and 1 patient required neurosurgical intervention.[10] Subsequent retrospective and prospective observational studies have reported similar risks of delayed ICH while on warfarin.[3,11]

Due to the infrequency of delayed ICH on warfarin, risk factors have been difficult to identify and only elevated INR has been associated with development of delayed ICH.[10,11] A systematic review of 7 studies evaluating delayed ICH in trauma patients on warfarin showed the overall rate to be low (0.6%), and it largely occurred in patients who had supratherapeutic INR.[12] Our systematic review excluded studies without patients taking DOACs and therefore, was not comprehensive of all studies evaluating warfarin. Despite this, 11 of 12 studies we reviewed included 1,788 patients taking warfarin, but INR values were inconsistently measured or recorded. Therefore, the true rate of patients with supratherapeutic INR was not able to be determined. The higher rate of delayed ICH in patients on warfarin may have been due to a larger percentage of patients with elevated INR. Unlike warfarin, DOAC medications have no easily discernable measure of anticoagulation degree, so risk factors for developing delayed ICH in these patients are even more elusive.

The first studies to analyze the risk of delayed ICH associated with DOAC medications were published on patient

Table 4. Studies Evaluating Warfarin

Study (year)	Sample size	% delayed ICH, not weighted (n/N)	95% CI	Weight, %	
				Fixed	Random
Antoni22 (2019)	255	2.35 (6/255)	0.87 − 5.05	14.23	12.04
Battle13 (2017)	43	0.00	0.00 − 8.22	2.45	5.09
Bauman1 (2017)	285	0.70 (2/285)	0.09 − 2.51	15.90	12.41
Chenoweth9 (2018)	75	1.33 (1/75)	0.03 − 7.21	4.22	7.21
Cipriano19 (2018)	93	1.08 (1/93)	0.03 − 5.85	5.23	8.09
Cocca18 (2019)	33	0.00	0.00 − 10.58	1.89	4.23
Cohan21 (2020)	431	2.32 (10/431)	1.12 − 4.23	24.01	13.61
Mann20 (2018)	72	0.00	0.00 − 4.99	4.06	7.04
Marques23 (2019)	115	2.61 (3/115)	0.54 − 7.44	6.45	8.98
Riccardi14 (2017)	118	10.17 (12/118)	5.37 − 17.09	6.61	9.08
Turcato24 (2019)	268	3.36 (9/268)	1.55 − 6.28	14.95	12.21
Total (random effects)	1,788	2.31	1.26 − 3.66	100.00	100.00

"Total Random Effects" based on pooled weighted estimates.
Test for heterogeneity: Q = 25.3; DF = 10; significance level: p = 0.005; I^2 (inconsistency) 60.4% (I^2 test for heterogeneity defined as follows: considerable [75%−100%]; substantial [50%−90%]; moderate [30%−60%] and low/not important [0−40%]); 95% CI for I^2: 23.4−79.6.
DOAC, direct oral anticoagulant; ICH, intracranial hemorrhage.

Table 5. Direct Oral Anticoagulant vs Warfarin Meta-Analysis

Study (year)	Delayed ICH DOAC, not weighted, n/N (%)	Delayed ICH warfarin, not weighted, n/N (%)	Odds ratio	95% CI	Weight, % Fixed	Weight, % Random
Antoni22 (2019)	1/38 (2.63)	6/255 (2.35)	1.122	0.13 − 9.58	6.99	8.50
Battle13 (2017)	1/21 (4.76)	0/43 (0)	6.366	0.25 − 163.11	3.06	4.22
Bauman1 (2017)	1/45 (2.22)	2/285 (0.70)	3.216	0.29 − 36.21	5.49	6.99
Chenoweth9 (2018)	0/37 (0)	1/75 (1.33)	0.662	0.03 − 16.65	3.09	4.26
Cipriano19 (2018)	2/85 (2.35)	1/93 (1.08)	2.217	0.20 − 24.90	5.50	7.00
Cocca18 (2019)	6/44 (13.64)	0/33 (0)	11.312	0.61 − 208.38	3.79	5.10
Cohan21 (2020)	4/346 (1.16)	10/431 (2.32)	0.492	0.15 − 1.58	23.56	19.07
Mann20 (2018)	1/30 (3.33)	0/72 (0)	7.373	0.29 − 186.23	3.08	4.25
Marques23 (2019)	0/78 (0)	3/115 (2.61)	0.205	0.01 − 4.02	3.63	4.91
Riccardi14 (2017)	3/107 (2.80)	12/118 (10.17)	0.255	0.07 − 0.93	19.22	17.05
Turcato24 (2019)	4/183 (2.19)	9/268 (3.36)	0.643	0.20 − 2.12	22.59	18.65
Total (random effects)*	(2.43)	(2.31)	0.894	0.44 − 1.81	100.00	100.00

11 of 12 studies were included in this analysis because 1 of 12 articles only included patients on DOAC (Barmparas et al17).
"Total random effects" based on pooled weighted estimates.
Test for heterogeneity: Q = 13.2; DF = 10; significance level: p = 0.2; I^2 (inconsistency) 24.4% (I^2 test for heterogeneity defined as follows: considerable [75%−100%]; substantial [50%−90%]; moderate [30%−60%]; and low/not important [0%−40%]); 95% CI for I^2: 0 − 62.4.
*z = -0.312; p = 0.755
DOAC, direct oral anticoagulant; ICH, intracranial hemorrhage.

data from 2013 to 2015.[1,13-15] This reflects the introduction of dabigatran, the first DOAC in the USA market, in 2010.[16] The first paper addressed delayed ICH in patients solely on DOACs, as opposed to all anticoagulants, and found a 1.2% risk among 249 patients.[17] Studies comparing the risk of delayed ICH in patients taking DOAC vs warfarin have reported inconsistent results. A recent study by Cocca and colleagues,[18] which included 44 patients on DOACs, found that 14% developed a delayed ICH, while none of 33 patients anticoagulated with warfarin suffered delayed ICH. A higher rate of delayed ICH in DOAC patients was also seen in several smaller studies.[13,19,20] This is in direct contrast with results from the largest study of DOAC patients (n = 346) by Cohan and associates,[21] which found the risk of delayed ICH to be lower than the risk in 431 patients on warfarin (1.2% vs 2.3%). A higher rate of delayed ICH in patients anticoagulated with warfarin compared with DOACs was also seen in several smaller retrospective and prospective observational studies.[1,14,21-24] Our systematic review of 3,051 patients on DOAC or warfarin found the pooled, weighted rate of delayed ICH to be similarly low in patients on DOACs compared with those on warfarin (2.43% vs 2.31%). There was low clinical and statistical heterogeneity between studies.

The perceived risk of delayed ICH has prompted some trauma centers to obtain repeat head CT scans on all anticoagulated patients after blunt trauma with an initial negative CT. Other centers simply observe patients and repeat imaging only for patients with symptoms. There are no prospective trials comparing repeat head CT to observation or discharge to home immediately from the emergency department. Therefore, the best available evidence to guide management of patients on systemic anticoagulation is from observational studies. Previously, authors of studies with low rates of delayed ICH (<1%−2%) have recommended against routine repeat head CT.[1,13]

There are limited data regarding the risk of delayed ICH after an initially negative head CT in patients not on any anticoagulation or on antiplatelet therapy alone. Chenoweth and coworkers[9] reported a rate of 0.4% (2 of 516) delayed ICH, all of which survived, in patients not on any anticoagulation, and Scantling and colleagues[15] found a rate of 0.8% (1 of 131) delayed ICH in patients on aspirin alone. Using the data from our meta-analysis and the data from Chenoweth and coworkers,[9] the rate of delayed ICH in patients on DOACs is 2.4% and the rate in patients not on anticoagulation is 0.4%. Therefore, the number needed to treat would be 50; in other words, an additional 50 patients would need to be observed in order to detect 1 additional delayed ICH. Assuming no deaths due to delayed ICH in patients on anticoagulation, the number needed to treat to prevent mortality would be 303 patients (assuming an absolute risk reduction of 0.33%). These estimates can be used as a starting point for discussions with patients without another indication for admission regarding observation in the hospital. Additionally, these numbers can guide trauma centers in determining their policies for patients with blunt head trauma on systemic anticoagulation.

Limitations

The major limitation of this review is the strength of the studies available for qualitative analysis. There are no

randomized studies on this topic and our review was limited to retrospective case series and nonrandomized prospective observational studies. The risk of reporting and publication bias was inherent in all included studies. Some studies did not perform repeat head CTs on all patients and in elderly patients who may have some degree of cognitive impairment at baseline, neurological exams may not be sensitive for early detection of expanding intracranial bleeds. Therefore, the true rate of delayed ICH is unknown. Additionally, we were unable to determine the rate of ICH based on different imaging strategies. The influence of concomitant antiplatelet medications on the risk of delayed ICH is not accurately reflected by our systematic review and the use of reversal agents was rarely reported. Additionally, compliance with anticoagulation was not reported in any studies and given the inability to measure the degree of anticoagulation with DOACs, it is possible that many patients were subtherapeutic. Lastly, INR values were inconsistently recorded so we were unable to determine the influence of supratherapeutic INR on delayed ICH.

CONCLUSIONS

Based on our systematic review of 1,263 patients on a DOAC, the risk of delayed ICH after low energy blunt head trauma for patients on DOAC is low, and the risk of a clinically significant bleed is even lower. The practice of routinely observing or systematically repeating head CT in patients on DOACs after low energy blunt head trauma with initially negative head CT may not be warranted. Furthermore, the estimated risks from this review can be used as a starting point for shared decision-making regarding optimal management.

Author Contributions

Study conception and design: Puzio, Ellis, Kao, Harvin
Acquisition of data: Puzio, Kregel, Holder, Harvin
Analysis and interpretation of data: Puzio, Murphy, Kregel, Wade, Kao, Harvin
Drafting of manuscript: Puzio, Murphy, Holder, Kao
Critical revision: Puzio, Murphy, Kregel, Ellis, Holder, Wandling, Wade, Kao, McNutt, Harvin

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Invited Commentary

Direct Oral Anticoagulant and Head Trauma: Much Ado About Nothing

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In this paper by Puzio and colleagues,[1] the authors have performed a systematic review and meta-analysis of published data to compare the relative risk of delayed intracranial hemorrhage after blunt head trauma in patients on direct oral anticoagulants (DOACs) compared with warfarin. We know that patients with head trauma who are on anticoagulants are more likely to have cerebral hemorrhage and worse outcomes. With an aging population and rapidly increasing use of DOACs, every trauma center is seeing an increasing number of elderly patients on these agents, who present after blunt head injury, most frequently due to low intensity ground level falls. As opposed to warfarin, for which the degree of anticoagulation can be quickly determined and reversed if needed, therapeutic levels of DOACs are difficult to determine precisely. This creates a heightened level of concern about the possibility of delayed intracranial hemorrhage (ICH) in these patients, which frequently leads to hospital admission for observation and repeat imaging studies that would not have been done otherwise.

The authors found 5,719 papers in the literature, and after screening, 72 underwent full review; of these, 12 met final inclusion/exclusion criteria. Four studies were prospective while 8 were retrospective in nature, and a total of 5,289 patients were included: 1,263 (23.9%) were on a DOAC, and 1,788 (33.8%) were on warfarin, whereas 104 patients were on concomitant anticoagulant and antiplatelet medications. The vast majority (92%) of these patients had suffered a ground-level fall. Overall, the percentages of patients who developed delayed ICH were only 2.43% and 2.31%, for the DOAC- and warfarin-treated patients, respectively. Most of these delayed ICH were clinically inconsequential. The overall crude risk of death from delayed ICH among the DOAC and warfarin patients combined was 0.33% (10/3,051), and was lower in the patients on DOAC (0.16%) compared with patients on warfarin (0.45%). The authors concluded that, "The practice of routinely observing or systematically repeating head CT in patients on DOACs after low energy blunt head trauma with initially negative head CT may not be warranted."

I think the methodology is solid, their conclusions are reasonable, and this paper should alleviate the exaggerated concerns that most physicians have related to the risk of developing a delayed intracranial hemorrhage in this patient population. However, there are many caveats that must be kept in mind. These patients had low energy trauma and the findings cannot be generalized to all patients with traumatic brain injury (TBI). It is unknown whether these patients simply had head trauma, or real TBI/ICH on the initial CT scan. Clearly, a head trauma patient with a negative initial CT scan is not the same as someone with signs of cerebral injury on the study. The severity of TBI and the anatomic location of the injury are equally important variables. Many of the elderly patients have baseline neurologic issues (eg dementia, Alzheimer's disease) that make clinical examination unreliable, and these patients may have to be admitted for a period of observation and undergo repeat imaging studies anyway. Similarly, because routine follow-up CT scans were not done in all the patients, the true incidence of delayed ICH remains unknown (subclinical ICH cannot be detected without an imaging study). Investigators have a clear bias in favor of publishing good outcomes, and unless a rigorous randomized clinical trial is done, the incidence of ICH is likely to be under-reported. Finally, it is well known that in patients on DOACs, about a quarter are prescribed inappropriate doses, with nearly 80% of them being underdosed.[2] This is further compounded by the fact that even in patients who are prescribed appropriate doses of DOACs, many are not fully compliant. Regardless of these limitations, I think this meta-analysis provides valuable data that should reassure the providers that DOACs are no worse than warfarin when it comes to low energy head trauma in elderly patients. This realization can lead to a much more balanced discussion of the risks with the patients and family members, and more judicious use of healthcare resources.

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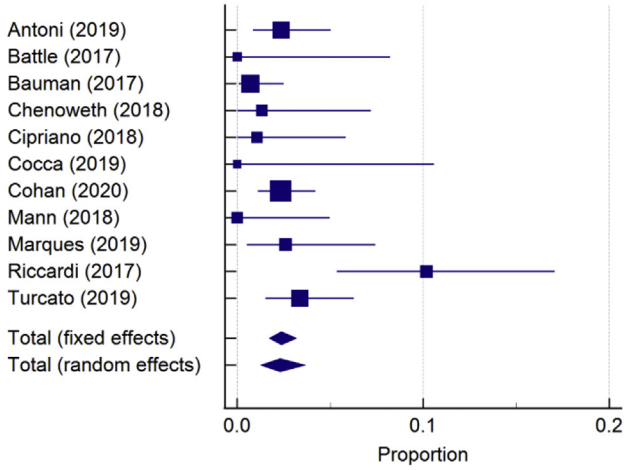
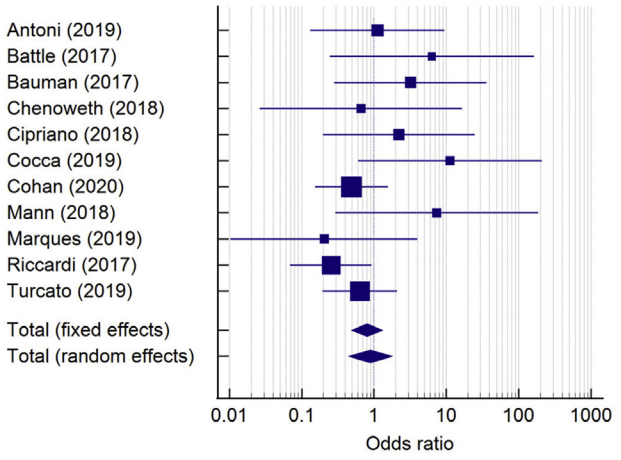
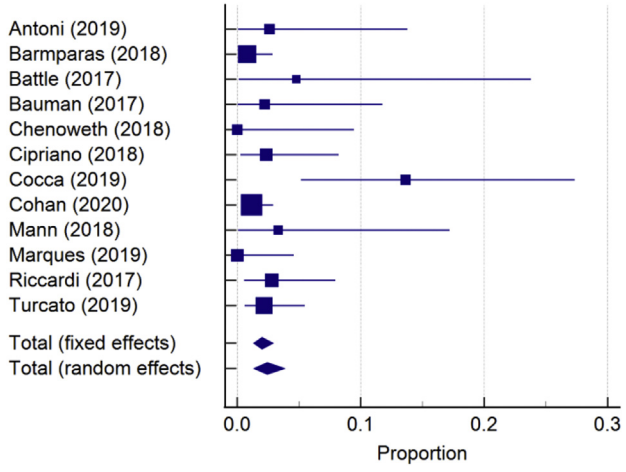
Disclosure Information: Nothing to disclose.



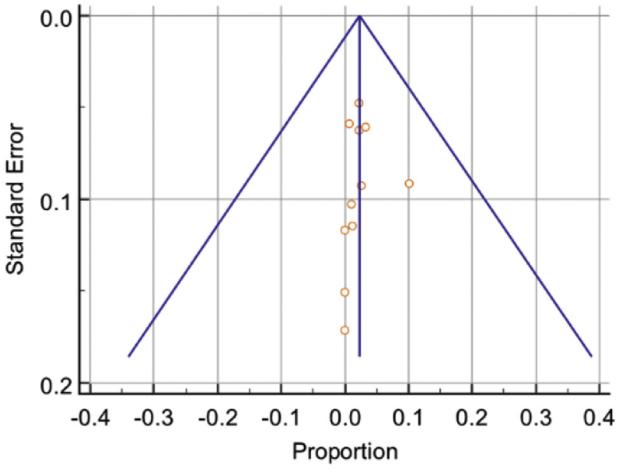
eFigure 1. Forest plot of warfarin.



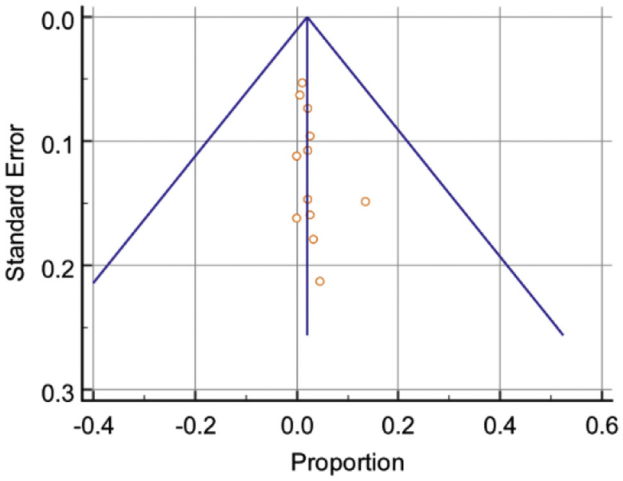
eFigure 3. Warfarin vs direct oral anticoagulant forest plot.



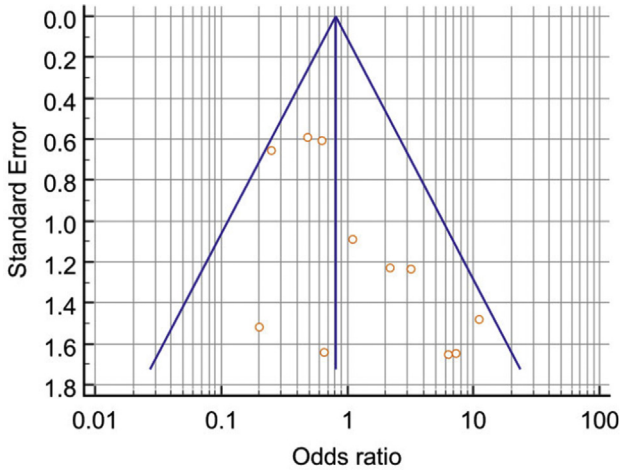
eFigure 2. Forest plot of direct oral anticoagulant.



eFigure 4. Funnel plot of warfarin depicting no evidence of publication bias.



eFigure 5. Funnel plot of direct oral anticoagulant depicting no evidence of publication bias.



eFigure 6. Funnel plot of warfarin vs direct oral anticoagulant depicting no evidence of publication bias.

eDocument 1. Search Strategy

Ovid - MEDLINE

1. exp Anticoagulants/ or anticoagula*.mp. or "anti-coagula*".mp. or antithromb*.mp. or "anti-thromb*".mp. or DOAC?.mp. or NOAC?.mp. or TSOA?.mp. or (thrombin adj2 inhibit*).mp.
2. exp Coumarins/ or Dabigatran/ or Pyrazoles/ or Pyridones/ or Rivaroxaban/ or Vitamin K/ or Warfarin/ or (acenocoumarol or acenocumarol or apixaban or befarin or betrixaban or bevyxxa or circuvit or coumad?n or coumadin* or coumafene or coumaphene or coumarin* or dabigatran or dexxience or edoxaban or eliqu?s or jantoven or lixiana or phenprocoumon or phenprocumon or pradaxa or rivaroxaban or roteas or savaysa or wafarin or warfarin* or xarelto or "4-hydroxicoumarin?").mp.
3. exp Administration, Oral/ or ((oral* or "per os" or "p.o.") adj2 (administ* or intake)).mp.
4. exp Craniocerebral Trauma/ or exp Intracranial hemorrhages/ or intracerebral hemorrhage*.mp. or intracranial hemorrhage*.mp. or brain hemmorrhage.mp.
5. exp Craniocerebral Trauma/ or exp Intracranial hemorrhages/ or ((brain or cerebrocranial or head or intracerebral or intra-cerebral or intracranial or intracranial) adj1 (haemorrhag* or haemmorhag* or hemorrhag* or hemmorrhag* or hemorhag* or hemorrag* or heamorrhag* or injur* or lesion? or trauma? or wound?)).mp.
6. exp Tomography, X-Ray Computed/ or (compute? adj2 tomograph*).mp. or ((CAT or CT) adj1 scan*).mp. or "head CT".mp.

3 and 6 and 7

Elsevier – EMBASE

#1. 'anticoagulant agent'/exp OR anticoagula* OR 'anticoagula*' OR antithromb* OR 'anti-thromb*' OR doac? OR noac? OR tsoa? OR (thrombin NEXT/2 inhibit*)

#2. 'acenocoumarol'/de OR 'apixaban'/de OR 'betrixaban'/de OR 'coumarin derivative'/exp OR 'dabigatran'/de OR 'edoxaban'/de OR 'phenprocoumon'/de OR 'pyrazole derivative'/exp OR 'pyridone derivative'/exp OR 'rivaroxaban'/de OR 'vitamin k group'/exp OR 'warfarin'/exp OR acenocoumarol? OR acenocumarol? OR apixaban OR betrixaban OR bevyxxa OR coumadin* OR coumarin* OR dabigatran OR dexxience OR edoxaban OR eliqu?s OR jantoven OR lixiana OR phenprocoumon OR phenprocumon OR pradaxa OR rivaroxaban OR roteas OR savaysa OR warfarin* OR xarelto OR '4-hydroxicoumarin?'

#3. 'oral drug administration'/de OR ((oral* OR 'per os' OR 'p.o.') NEXT/2 (administ* OR intake))

#4. 'head injury'/de OR ((brain OR cerebrocranial OR head OR intracerebral OR 'intra cerebral' OR intracranial OR 'intra cranial') NEXT/1 (haemorrhag* OR haemmorhag* OR hemorrhag* OR hemmorrhag* OR hemorhag* OR hemorrag* OR heamorrhag* OR injur* OR lesion? OR trauma? OR wound?))

#5. 'x-ray computed tomography'/exp OR (compute? NEXT/2 tomograph*) OR ((cat OR ct) NEXT/1 scan*) OR 'head ct'

#6. #1 OR #2

#7. #4 AND #5 AND #6

eDocument 2. Scale and Scoring Manual

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE FOR COHORT STUDIES

Note: A study can be awarded a maximum of 1 star for each numbered item within the Selection and Outcome categories. A maximum of 2 stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) Truly representative of the average _____ (describe) in the community ☆
   b) Somewhat representative of the average _____ in the community ☆
   c) Selected group of users, eg, nurses, volunteers
   d) No description of the derivation of the cohort
2) Selection of the non-exposed cohort
   a) Drawn from the same community as the exposed cohort ☆
   b) Drawn from a different source
   c) No description of the derivation of the non-exposed cohort
3) Ascertainment of exposure
   a) Secure record (eg surgical records) ☆
   b) Structured interview ☆
   c) Written self-report
   d) No description
4) Demonstration that outcome of interest was not present at start of study
   a) Yes ☆
   b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) Study controls for _____ (select the most important factor) ☆
   b) Study controls for any additional factor * (This criterion could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) Independent blind assessment ☆
   b) Record linkage ☆
   c) Self report
   d) No description
2) Was follow-up long enough for outcomes to occur?
   a) Yes (select adequate follow-up for outcome of interest) ☆
   b) No
3) Adequacy of follow-up of cohorts
   a) Complete follow-up - all subjects accounted for ☆
   b) Subjects lost to follow-up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow-up, or description provided of those lost) ☆
   c) Follow-up rate < ____% (select an adequate %) and no description of those lost
   d) No statement

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CODING MANUAL FOR COHORT STUDIES

1) **Representativeness of the Exposed Cohort**

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of women from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health-oriented women are likely to be representative of postmenopausal estrogen users while they are not representative of all women (eg members of a health maintenance organization [HMO] will be a representative sample of estrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users of estrogen).

SELECTION

Allocation of stars as per rating sheet

2) **Selection of the Non-Exposed Cohort**

Allocation of stars as per rating sheet

3) **Ascertainment of Exposure**

Allocation of stars as per rating sheet

4) **Demonstration That Outcome of Interest Was Not Present at Start of Study**

In the case of mortality studies, the outcome of interest is still the presence of a disease/ incident, rather than death. That is to say, a statement of no history of disease or incident earns a star.

COMPARABILITY

1) **Comparability of Cohorts on the Basis of the Design or Analysis**

A maximum of 2 stars can be allotted in this category.

Both exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable for each variable used in the adjustment.

There may be multiple ratings for this item for different categories of exposure (eg ever vs never, current vs previous or never)

Age =☆, Other controlled factors =☆

OUTCOME

1) **Assessment of Outcome**

For some outcomes (eg fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes, where reference to x-rays would be required.

a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.).
b) Record linkage (eg identified through ICD codes on database records).
c) Self-report (ie no reference to original medical records or x-rays to confirm the outcome).
d) No description.

2) **Was Follow-Up Long Enough for Outcomes to Occur**

An acceptable length of time should be decided before quality assessment begins (eg 5 years, for exposure to breast implants).

3) **Adequacy of Follow-up of Cohorts**

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

Allocation of stars as per rating sheet.