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Association of Mortality among Trauma Patients Taking Pre-Injury Direct Oral Anticoagulants vs. Vitamin K Antagonists

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Disclosure Statement of Financial Interest

Zachary Laduke, Jason Hecht, and Wendy Wahl have nothing to disclose

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Background

- Pre-injury warfarin has been shown to increase morbidity and mortality despite effective reversal agents[1-3]
- Direct oral anticoagulants (DOACs) have been shown to have significantly less spontaneous major bleeding events compared to warfarin[4-8]
- Prior studies of outcomes following traumatic injury in patients on pre-injury DOACs are limited mostly to single center studies or isolated traumatic injuries[9-11]

1. Batchelor JS, et al. *Br J Neurosurg.* 2012;26(4):525-30.
2. Grandhi R, et al.. *J Trauma.* 2015;78(3):614-21.
3. Ivascu FA, et al. *J Trauma.* 2005;59:1131-1139.
4. Inohara T, et al. *JAMA.* 2018;319(5):463-473.
6. Granger CB, et al. *N Engl J Med.* 2011;365(11):981-92
7. Giugliano RP, et al. *N Engl J Med.* 2013;369(22):2093-104.
8. Patel MR, et al. *N Engl J Med.* 2011;365(10):883-91.
11. Maung AA, et al. *J Trauma.* 2016;81(4):652-7.

Hypothesis

Traumatically injured patients on pre-injury DOACs will have lower mortality and complications than those patients injured while taking VKAs

Study Design

- Multicenter retrospective cohort study of 29 trauma centers in the Michigan Trauma Quality Improvement Program (MTQIP) registry
- Cohorts were stratified by pre-injury anticoagulation and antiplatelet agents
- Study dates: January 2012 – December 2017

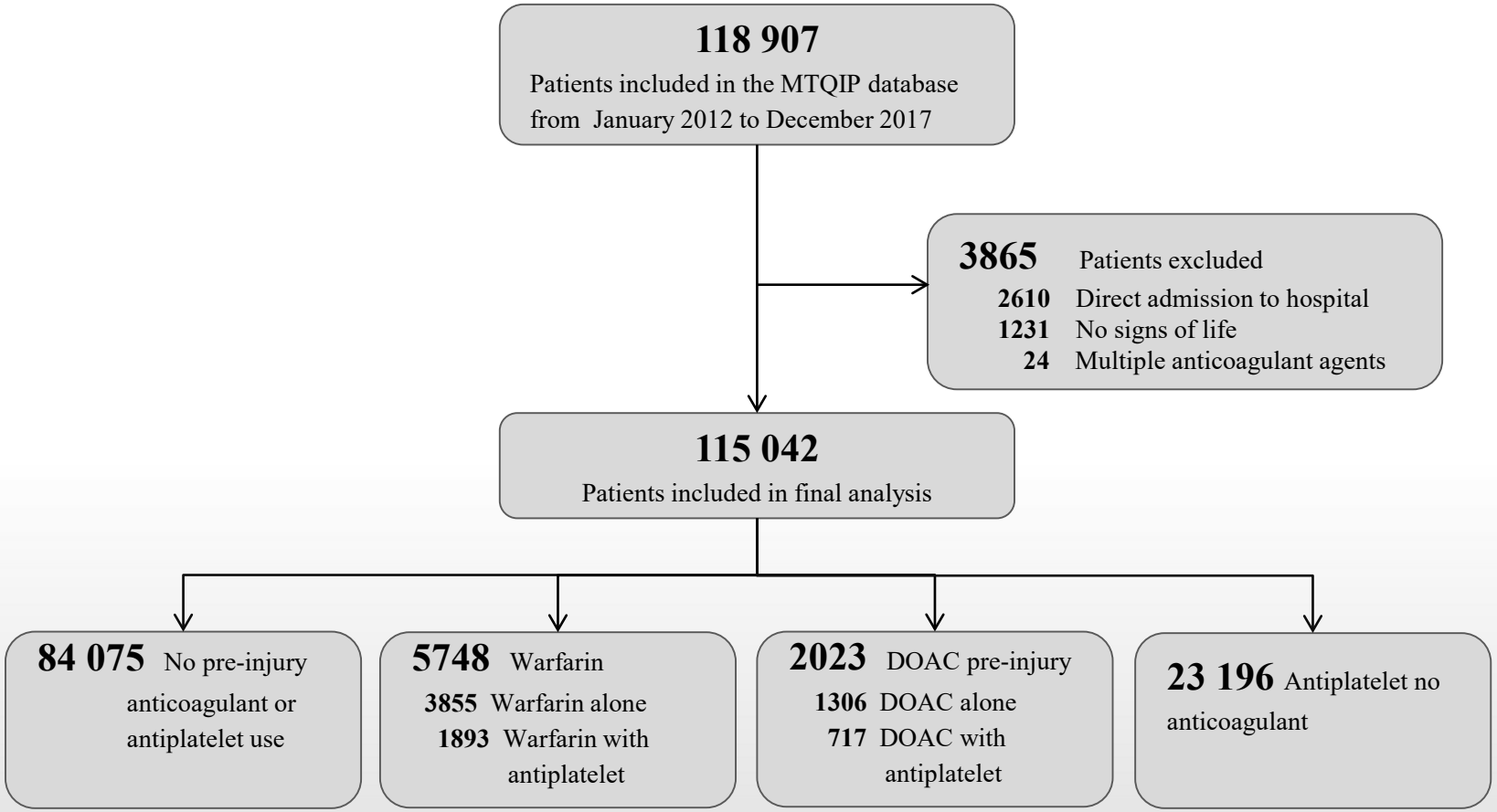
Inclusion Criteria	Exclusion Criteria
• Age ≥ 16 years old • Trauma code on admission • Injury Severity Score (ISS) ≥ 5	• No signs of life on initial evaluation • Direct hospital – hospital transfer • Multiple anticoagulant agents

Statistical Analysis

- Multivariate logistic regression modeling used to account for differences in characteristics
- Goodness-of-fit was assessed and validated using c-statistics
- Primary Outcome:
  - Mortality or discharge to hospice
- Secondary Outcomes:
  - Serious in-hospital complications[1]
  - Resource utilization (ORs, transfusion in first 4 hours)

1. Hemmila MR, et al. *J Trauma*. 2017;82:867-876.

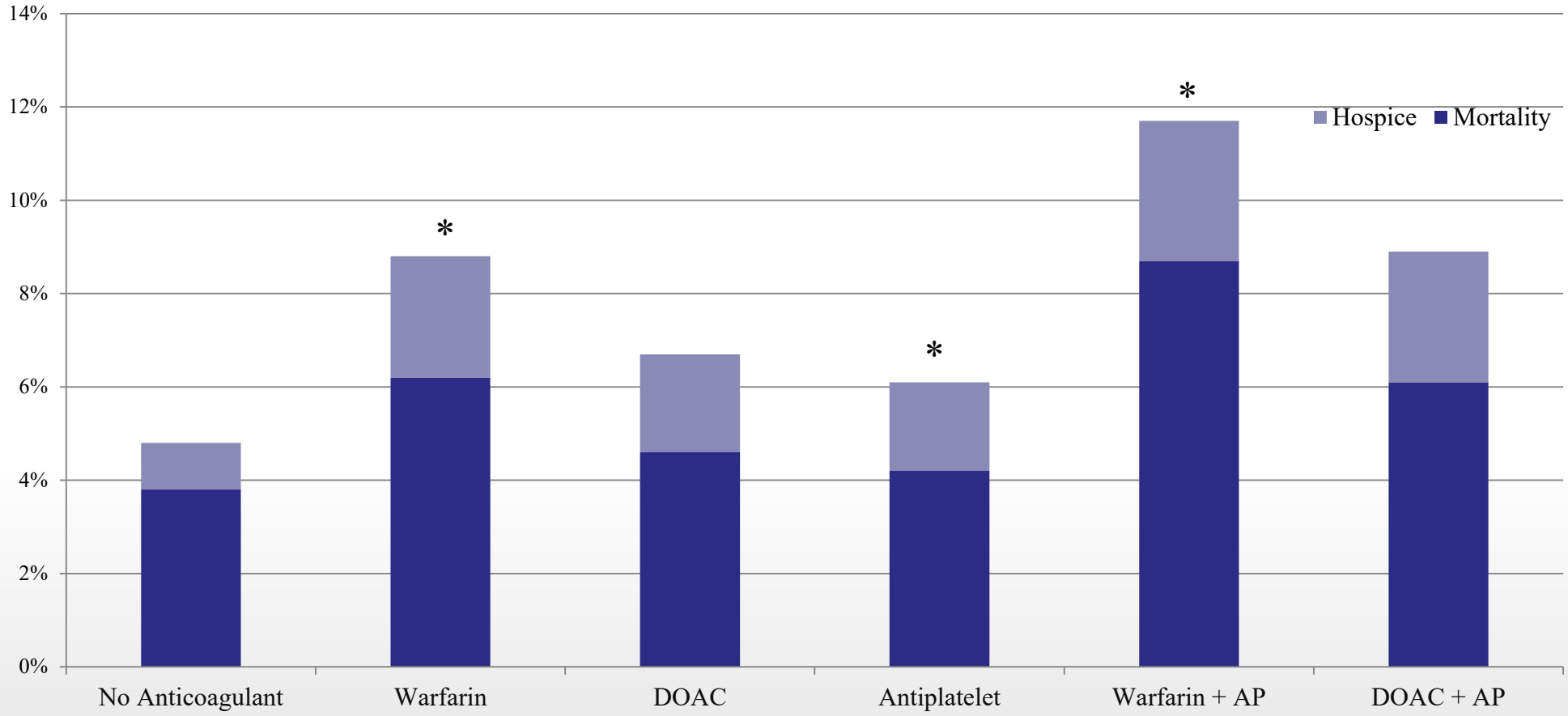
Study Population



Demographics

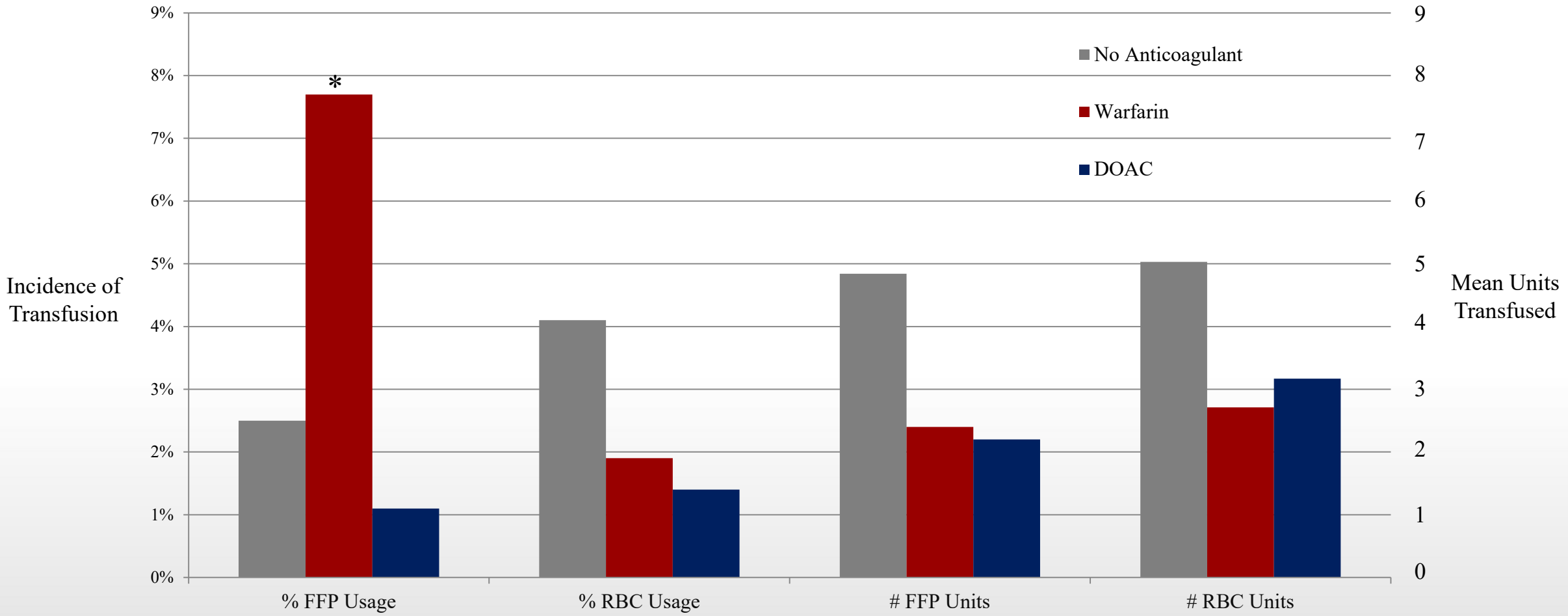
	None (N=84075)	Warfarin (N=3855)	DOAC (N=1306)	p value
Age, years ± SD	52.7 ± 22.8	77.7 ± 13.2	77.1 ± 13.1	<0.001
Female, No. (%)	34129 (40.6)	2104 (54.6)	761 (58.3)	<0.001
White, No. (%)	62109 (73.9)	3535 (91.7)	1222 (93.6)	<0.001
Uninsured, No. (%)	9421 (11.2)	65 (1.7)	15 (1.1)	<0.001
Penetrating trauma, No. (%)	7046 (8.4)	24 (0.6)	4 (0.3)	<0.001
Injury Severity Score, No. (%)				
5-15	66742 (79.4)	3179 (82.5)	1134 (86.8)	
16-24	10650 (12.7)	379 (9.8)	106 (8.1)	<0.001
25-35	5204 (6.2)	283 (7.3)	59 (4.5)	
>35	1479 (1.8)	14 (0.4)	7 (0.5)	
AIS >2, No. (%)				
Head/neck	16681 (19.8)	929 (24.1)	248 (19.0)	<0.001
Chest	14922 (17.7)	448 (11.6)	173 (13.2)	
GCS – Motor, No. (%)				
6	71289 (84.8)	3267 (84.7)	1111 (85.1)	<0.001
5-2	4101 (4.9)	122 (3.2)	28 (2.1)	
1	3382 (4.0)	75 (1.9)	13 (1.0)	
Ventilator Support, No (%)	34825 (41.4)	1467 (38.1)	522 (40.0)	<0.001
Comorbid diseases, No. (%)				
Cerebrovascular accident	1004 (1.2)	220 (5.7)	110 (8.4)	
COPD	6463 (7.7)	611 (15.8)	211 (16.2)	
Chronic renal failure	711 (0.8)	131 (3.4)	20 (1.5)	
Congestive heart failure	1521 (1.8)	477 (12.4)	131 (10.0)	<0.001
Diabetes	8094 (9.6)	845 (21.9)	271 (20.8)	
Functionally dependent	5916 (7.0)	833 (21.6)	439 (33.6)	
Hypertension	24055 (28.6)	2658 (68.9)	930 (71.2)	

Mortality or Hospice



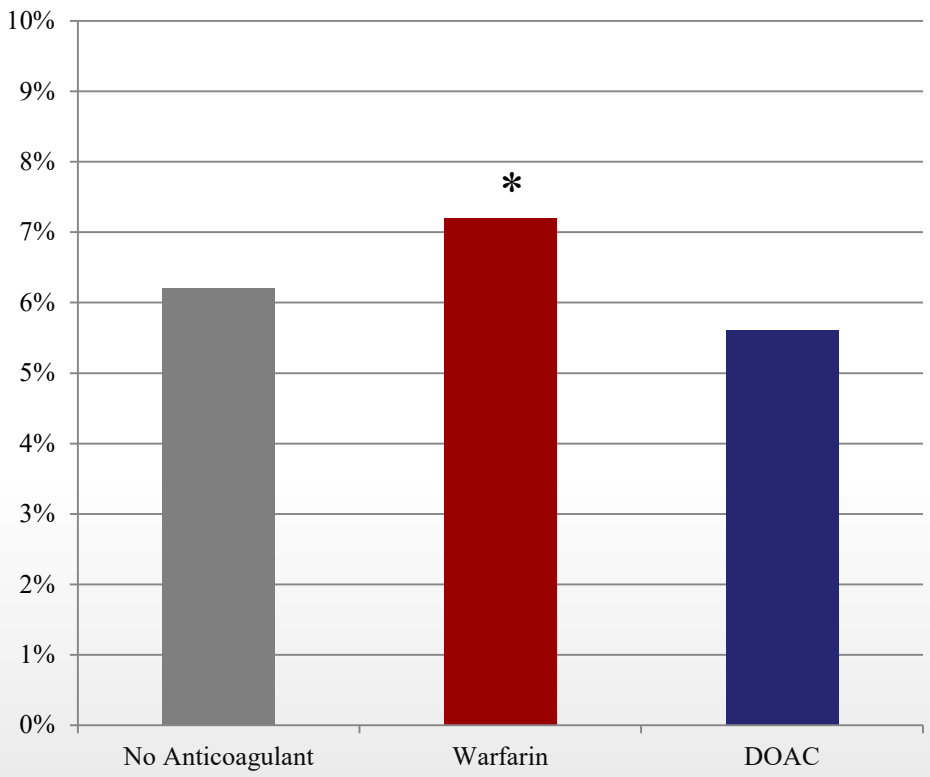
	No Anticoagulant	Warfarin	DOAC	Antiplatelet	Warfarin + AP	DOAC + AP
AOR (95% CI)	Reference	1.23 (1.04 – 1.44)	1.05 (0.81 – 1.71)	1.12 (1.01 – 1.24)	1.44 (1.10 – 1.88)	1.21 (0.90 – 1.63)

Resource Utilization



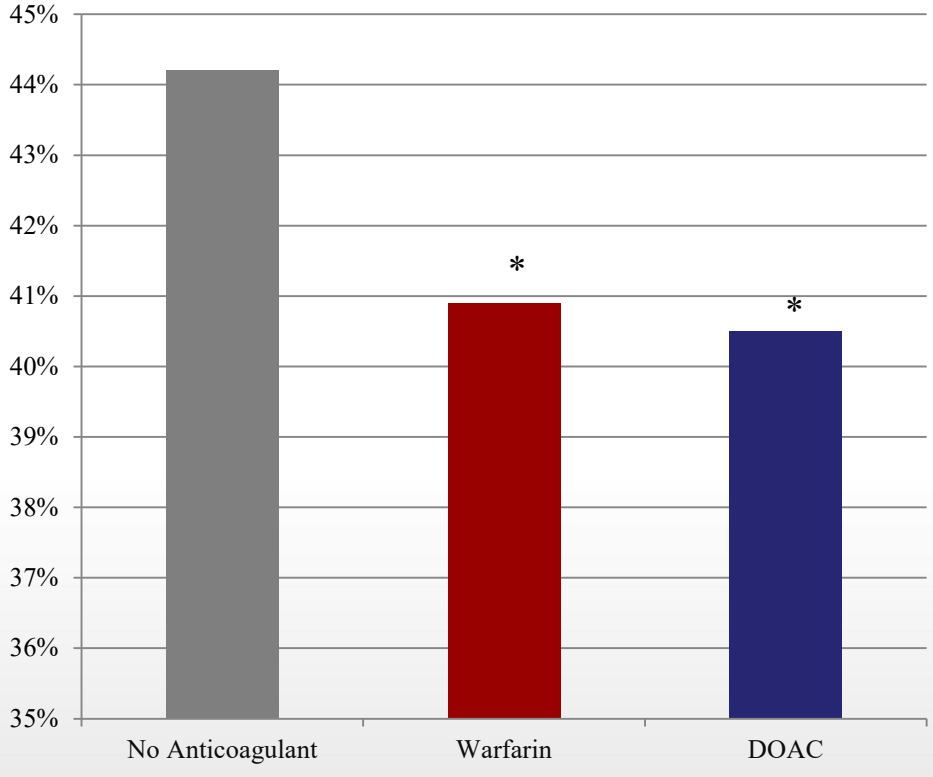
Resource Utilization

Serious Complications



Reference	1.19 (1.00 – 1.42)	1.03 (0.74 – 1.44)

Surgical Intervention



Reference	0.69 (0.56 – 0.85)	0.59 (0.47 – 0.73)

Study Limitations

- Unable to randomize patients prior to their traumatic injuries
- Reversal agents outside of blood products were not recorded in the registry until 2018
- Data was from level 1 and 2 trauma centers in Michigan so may not be applicable to other regions or classification of trauma systems
- Unable to account for patient frailty and potential biased prescribing towards warfarin
- Did not look at specific DOAC agents

Conclusions

- Compared to no anticoagulation, patients taking warfarin prior to traumatic injury have a higher incidence of mortality or hospice and serious complications
- Pre-injury DOAC was not associated with any difference in hospital outcomes as compared to no anticoagulation
- Pre-injury antiplatelet therapy alone and in combination with warfarin worsened outcomes
- This study contributes to the growing body of evidence showing the superior safety profiles of DOACs as compared to warfarin

Reviewer's comments

What about severely injured patients with high AIS?

How did the different DOAC agents do? Do factor IIa inhibitors (thrombin inhibitors) perform differently than Xa inhibitors?

Mortality/Discharge to Hospice for AIS of 3-5

Group	Odds Ratio [95% CI]	P value
Antiplatelet agent only	1.15 [1.03-1.28]	0.011
Warfarin+antiplt agent	1.39 [1.07-1.80]	0.012
Warfarin only	1.34 [1.137-1.60]	0.001
DOAC+antiplt agent	1.32 [0.996-1.75]	0.053
DOAC only	1.20 [0.86-1.68]	0.275

Serious Complications for AIS 3-5

Group	Odds Ratio [95% CI]	P value
Antiplatelet agent only	1.16 [1.05-1.26]	0.001
Warfarin+antiplt agent	1.29 [1.03-1.60]	0.021
Warfarin only	1.19 [0.998-1.41]	0.052
DOAC+antiplt agent	1.02 [0.68-1.51]	0.916
DOAC only	1.08 [0.81-1.43]	0.583

DOAC Comparison

group_split	Freq.	Percent	Cum.
Antiplatelet Only	23,196	20.16	20.16
Coumadin + Antiplatelet	1,893	1.65	21.81
Coumadin Only	3,855	3.35	25.16
Direct thrombin + Antiplatelet	137	0.12	25.28
Direct thrombin only (IIa inh)	197	0.17	25.45
Factor Xa + Antiplatelet	580	0.50	25.95
Factor Xa only	1109	0.96	26.92
None	84,075	73.08	100.00
Total	115,042	100.00	

Mortality/Discharge to Hospice for DOACs, Warfarin, Antiplatelet Agents Compared to None

Group	Odds Ratio [95% CI]	P value
Antiplatelet agent only	1.11 [1.01-1.24]	0.033
Warfarin+antiplt agent	1.43 [1.10-1.87]	0.008
Warfarin only	1.22 [1.04-1.43]	0.013
Thrombin inhib (aIIa+antiplt)	2.26 [1.25-4.10]	0.007
Thrombin inhib (anti-IIa)	1.09 [0.55-2.16]	0.785
Factor Xa inhibitor+antiplt	0.98 [0.70-1.3]	0.920
Factor Xa inhibitor only	1.04 [0.78-1.39]	0.758

Summary

- Patients on DOACs appear to have better outcomes than those on VKAs
- There appear to be differences among the types of DOACs, with Xa inhibitors associated with better outcomes
  - Small numbers
  - Platelet effect?

Summary

- The timing of reversal agents and which agents were used was not known for most of the study time period
  - More study will help us elucidate how to manage our injured patients on anticoagulants and antiplatelet agents

Thanks to all the MTQIP members!