Anticoagulant therapy and survival among COVID-19 admitted patients

- Problem statement
    - Is Anticoagulant use effective for reducing mortality among covid19 positive patients who were on anticoagulants prior to in-patient admission compared to patients on no oral anticoagulants?
- Sample
    - 3740 Covid19+ patients who had at least one ED or In-patient visit
- Inclusion + Exclusion
    - Patients under 60 were excluded in order to focus on a higher risk population (1945 excluded. n = 1795)
    - Patients with a positive Covid19 test order date after April 22d were excluded (479 excluded, n = 1316
    - Patients that had only had an ED visit were excluded due to concerns over information loss regarding mortality (183 excluded. n=1133)
    - One patient was excluded for unknown date of death (n = 1132)
    - Patients not ever placed on oral anticoagulants were put in the Control Group (n=894)
    - Patients with a history of oral anticoagulants had chart review performed (n=238)
    - Of those with a history of oral anticoagulants, 105 were excluded because the oral anticoagulant was started during their COVID admission. (n=133)
    - One patient who was initially in the warfarin group was excluded due to chart review finding that they had not been placed on Coumadin (n=1)
- Treatment Groups
    - Two treatment groups were identified.
        - 28 patients who were only on Warfarin prior to admission
        - 104 patients who were only on DOAC prior to admission
    - 894 patients were identified in the control group

Sample Characteristics (n = 1026)

Group	Mean Age	Median (IQR)	p val (vs control)
Warfarin Only	81.6	85 (69.5 – 100.5)	0.01
DOAC Only	78.3	79 (71.5-86.5)	0.02
Control	76.1	75 (67-85)	NA

P values calculated via t-test

Group	Male n (%)	Female n (%)	p val (vs control)
Warfarin Only	13 (46.4%)	15 (53.6%)	1
DOAC Only	67 (64.4%)	37 (35.6%)	0.0003
Control	407 (45.5%)	487 (54.5%)	NA

P values calculated via chi-square test

Race / Ethnicity	Control group n (%)	Warfarin Only n (%; p-value)	DOAC Only Percent n (%; p-value)
White	500 (55.9%)	18 (64.3%; 0.44)	72 (69.2%; 0.01)
Hispanic	145 (16.2%)	4 (14.3%; 1)	6 (5.8%; 0.003)
Black	196 (21.9%)	6 (21.4%; 1)	21 (20.2%; 0.80)
Other/Unknown	32(3.6%)	0 (0.0%; 1)	4 (3.9%; 1)
Asian	17(1.9%)	0 (0.0%; 1.)	1 (1.0%; 1)
Native American	1 (0.1%)	0 (0.0%; 1)	0 (0.0%; 1)

Group	Mean Body Mass Index	Median Body Mass Index	P val (vs control)
Warfarin Only	28.7	27.1	0.64
DOAC only	29.3	28.6	0.03
Control	28.0	27.0	NA

P values calculated via t test

Comorbid Diagnosis	Control Group n (%)	Warfarin Only n (%; p-value)	DOAC Only n (%;p-value)
Coronary Artery Disease	172 (19.2%)	12 (42.9%; 0.007)	47 (45.2%; <0.001)
Congestive Heart Failure	178 (19.9%)	14 (50%; <0.001)	56 (53.9%; <0.001)
Atrial Fibrillation	116 (13.0%)	24 (85.7%; <0.001)	76 (73.1%; <0.001)
Hypertension	649 (72.6%)	25 (89.3%; 0.08)	88 (84.6%; 0.009)
Diabetes	335 (37.5%)	15 (53.6%; 0.12)	47 (45.2%; 0.14)
Chronic Kidney Disease	194 (21.7%)	6 (21.4%; 1)	35 (33.7%; 0.009)
Cancer	195 (21.8%)	7 (25%; 0.81)	30 (28.9%; 0.108)
Gastric Bleed	99 (11.1%)	4 (14.3%; 0.55)	19 (18.3%; 0.04)
Liver Disease	79 (8.8%)	5 (17.9%; 0.17)	8 (7.7%; 0.85)

Diagnoses

- All diagnoses found through ICD10 search in patient encounter and problem list diagnoses. No date or active status exclusions were placed on thee diagnoses. Diagnoses may be present from old encounters.
    - CAD: ICD10 codes: I25*, I05*, I06*, I07*, I08*, I09*
    - CHF: ICD10 codes: I50*, Z86.79*, I11.0*, I13.0*, I13.2*
    - AFib: ICD10 codes: I48*
    - Hypertension: ICD10 codes: I10*, I11*, I12*, I13*, I15*
    - Diabetes: ICD10 codes: E08*, E09*, E10*, E11*, E13*
    - CKD: ICD10 codes: N18*
    - Cancer: ICD10 Codes: C*, D0*, Z85*
    - Gastric Bleed: ICD10 Codes: K92.2*, Z87.19*
    - Liver Disease: ICD10 codes: K7*, Z87.19*

Identifying confounders

- We first wanted to identify potential confounding variables. Specifically variables that were potentially associated with both Anticoagulant use and mortality
- To do this we fit a logistic regression on anticoagulant use including Age, Race/Ethnicity, BMI, Gender, and all Diagnosis variables
    - Coefficients: (Note: White/Caucasian was taken as the reference category for Race/Ethnicity)

variable	Estimate	Std. Error	z value	p value
(Intercept)	-4.80	1.27	-3.79	< 0.001
Age	0.00	0.01	0.24	0.808
Patient.GenderMale	0.44	0.24	1.86	0.063
BMI	0.03	0.02	1.97	0.049
Race_and_EthHispanic or Latino	-0.51	0.41	-1.24	0.214
Race_and_EthBlack or African American	0.20	0.31	0.63	0.526
Race_and_EthOther/Unknown	-0.04	0.67	-0.06	0.955
Race_and_EthAsian	-0.99	1.18	-0.84	0.399
Race_and_EthAmerican Indian or Alaska Native	-10.18	535.41	-0.02	0.985
DX_CADY	0.41	0.27	1.54	0.123
DX_CHFY	0.51	0.26	1.95	0.051
DX_AfibY	2.90	0.26	11.07	< 0.001
DX_HypertensionY	0.08	0.34	0.23	0.822
DX_DiabetesY	0.32	0.25	1.27	0.204
DX_CKDY	-0.59	0.28	-2.10	0.036

DX_CancerY	0.05	0.27	0.20	0.844
DX_Gastro_BleedY	0.07	0.33	0.22	0.829
DX_LiverY	-0.37	0.41	-0.92	0.358

After considering these adjusted associations as well as unadjusted associations, we decided to include the following variables in the analysis

- Age, Gender, Race/Ethnicity, CAD, CHF, Afib, and CKD

Evaluating anticoagulant use and mortality

- We used a multivariable logistic regression to evaluate anticoagulant use and mortality, including all identified potential confounders

Propensity Score development:

Propensity scores were developed using a multivariable gradient boosting machine (GBM) model on variables identified as having association with both treatment and outcome likelihood. Specifically Patient Age, BMI, Gender, Race, Ethnicity, and history of Coronary Artery Disease, Congestive Heart Failure, Atrial Fibrillation, Hypertension, and Chronic Kidney Disease. Probabilities from this model were mean-stabilized and inverted to be used as inverse probabilities weights in the primary multivariable logistic regression models[citation: https://pubmed.ncbi.nlm.nih.gov/20822250/] . This process was repeated for both the DOAC and Warfarin groups separately. Propensity score models were evaluated for standardized effect size balance and overall fit. The DOAC propensity score model had a C-statistic of 0.92 and all but one variable was found to have a standardized bias above 0.25 (Race category other. standardized bias: 0.26). The warfarin propensity score model also had a C-statistic of 0.92, though the covariates were found to be less well balanced with six variables having residual bias over 0.25. These were Age (0.44), Race: Other (0.48), Ethnicity:Hispanic (0.58), Ethnicity: Non-hispanic(0.51), History of Atrial Fibrillation:No (0.29) and History of Atrial Fibrillation:Yes (0.29). These variables were included in the final multivariable logistic regression models in order to control for these residual differences between comparison groups.

Patient Mortality (crude):

	Non-Survival	Survival
DOAC	15 (14.4%)	89 (85.6%)
Warfarin	9 (32.1%)	19 (67.9%)
Control	213 (23.8%)	681 (76.2%)

DOAC Only:

Crude OR estimate-- OR: 0.54 (95%CI: 0.29 – 0.92), p val = 0.03

Table 2 – Outcomes of multivariable logistic regression comparing DOAC versus control group for all-cause 21 day mortality after inverse propensity weighting.

	OR	OR 2.5%	OR 97.5%	p value
DOAC vs Control	0.44	0.20	0.90	0.033
Age (per 10 years)	1.88	1.68	2.09	<0.001
log(BMI)	2.77	1.31	5.93	0.008
Gender: Male	1.87	1.33	2.64	<0.001
Race: Black	0.78	0.50	1.21	0.280
Race: Unknown/Other	0.67	0.32	1.35	0.267
Ethnicity: Hispanic/Latinx	0.92	0.43	1.92	0.821
Ethnicity: Unknown/Other	0.82	0.16	2.98	0.780
Coronary Artery Disease	0.97	0.63	1.47	0.875
Congestive Heart Failure	1.49	0.98	2.27	0.062
Atrial Fibrillation	1.49	0.99	2.24	0.057
Hypertension	0.98	0.64	1.50	0.910
Chronic Kidney Disease	1.21	0.82	1.80	0.336

Warfarin Only:

Crude OR estimate -- OR: 1.51 (0.64-3.31). p val = 0.31

Table 3 – Outcomes of multivariable logistic regression comparing Warfarin versus control group for all-cause 21 day mortality after inverse propensity weighting.

	OR	OR 2.5%	OR 97.5%	p value
Warfarin vs Control	0.29	0.02	1.62	0.237
Age (per 10 years)	1.87	1.67	2.09	<0.001
log(BMI)	2.55	1.20	5.48	0.016
Gender: Male	1.96	1.38	2.81	0.000
Race: Black	0.84	0.53	1.31	0.448
Race: Unknown/Other	0.65	0.31	1.32	0.245
Ethnicity: Hispanic/Latinx	1.01	0.47	2.14	0.980
Ethnicity: Unknown/Other	0.88	0.18	3.17	0.863
Coronary Artery Disease	0.97	0.62	1.51	0.905
Congestive Heart Failure	1.65	1.06	2.55	0.026
Atrial Fibrillation	1.54	0.98	2.39	0.056
Hypertension	0.94	0.62	1.45	0.779
Chronic Kidney Disease	0.96	0.63	1.46	0.852

Bleeding Events:

Bleeding events for all groups were captured by ICD-10 encounter diagnosis search. Between group statistical comparisons were carried out using fisher's exact test.

	Any Bleeding Event	No Bleeding Event	P val (vs Control)
Warfarin	2 (7.1%)	26	0.65
DOAC	6 (5.8%)	98	0.67
Control	46 (5.1%)	848	NA