Supplemental Material for

Practice patterns and outcomes associated with anticoagulation use following sepsis hospitalization with new-onset atrial fibrillation

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Table S1.		
	ICD-9	**ICD-10**
Major bleeding	423, 430, 431, 432, 432.1, 432.9, 455.2, 455.5, 455.8, 456, 456.2, 459, 530.7, 530.82, 531.0-531.6, 532.0-532.6, 533.0-533.6, 534.0-534.6, 535.01-535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578, 578.1, 578.9, 599.7, 719.11, 784.7, 784.8, 786, 852.0x, 852.2x, 852.4x, 853	I312, I609, I619, I62.X, I621, I629, I8501, I8511, K226, K228, K250-K256, K260-K266, K270-K276, K280-K286, K2901, K2921, K2941-K2951, K2961, K2971, K2991, K31811, K5521, K5711, K5713, K5731, K5733, K625, K644, K648, K648, K661, K920, K921, K922, M25019, R040-R041, R042, R0481, R0489, R049, R310-R312, R319, R58, S06.310A - S06.389S, S064x, S065x, S066x
Transient Ischemic Attack	435, 435.1, 435.2, 435.3, 435.8, 435.9	G45, G45.0, G45.1, G45.2, G45.8, G45.9, G46.0, G46.1, G46.2, I67.84, I67.841, I67.848, M47.0, M47.02, M47.021, M47.022
Ischemic Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 436	G43.6, G43.601, G43.609, G43.611, G43.619, G46.3, G46.4, G95.11, I63, I63.0, I63.00, I63.01, I63.011, I63.012, I63.013, I63.019, I63.02, I63.03, I63.031, I63.032, I63.033, I63.039, I63.09, I63.1, I63.10, I63.11, I63.111, I63.112, I63.113, I63.119, I63.12, I63.13, I63.131, I63.132, I63.133, I63.139, I63.19, I63.2, I63.20, I63.21, I63.211, I63.212, I63.213, I63.219, I63.22, I63.23, I63.231, I63.232, I63.233, I63.239, I63.29, I63.3, I63.30, I63.31, I63.311, I63.312, I63.313, I63.319, I63.32, I63.321, I63.322, I63.323, I63.329, I63.33, I63.331, I63.332, I63.333, I63.339, I63.34, I63.341, I63.342, I63.343, I63.349, I63.39, I63.4, I63.40, I63.41, I63.411, I63.412, I63.413, I63.419, I63.42, I63.421, I63.422, I63.423, I63.429, I63.43, I63.431, I63.432, I63.433, I63.439, I63.44, I63.441, I63.442, I63.443, I63.449, I63.49, I63.5, I63.50, I63.51, I63.511, I63.512, I63.513, I63.519, I63.52, I63.521, I63.522, I63.523, I63.529, I63.53, I63.531, I63.532, I63.533, I63.539, I63.54, I63.541, I63.542, I63.543, I63.549, I63.59, I63.6, I63.8, I63.9, I97.810, I97.811, I97.82, I97.820, I97.821
Any bleeding as a coviariate	285.1, 423, 430, 431, 432, 432.1, 432.9, 455.2, 455.5, 455.8, 456, 456.2, 459, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x,	D62, I312, I312, I60, I609, I61, I610, I611, I614, I615, I618, I619, I62, I6200, I6201, I6202, I6203, I629, I85.01, J94.2, K2211, K2211, K226, K25.0, K25.2, K25.4, K25.6, K254, K26.0, K26.2, K26.4, K26.6, K264, K27.0, K27.2, K27.4, K27.6, K274, K28.0, K28.2,

534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 568.81, 569.3, 569.85, 578, 578.1, 578.9, 593.81, 599.7, 623.8, 626.2, 626.6, 719.1x, 784.7, 784.8, 786.3, 790.01, 852.0x, 852.2x, 852.4x, 853, 997.02, 998.1x	K28.4, K28.6, K29.0, K2901, K2971, K2971, K2981, K2981, K31811, K31811, K3182, K3182, K5521, K5521, K5731, K5731, K62.5, K625, K6381, K6381, K66.1, K661, K92.0, K92.1, K92.2, K920, K921, K922, M25.0, N02, N92.0, N92.1, N92.4, N93.8, N93.9, N938, N939, N95.0, N950, R04.0, R04.1, R04.2, R04.8, R04.9, R040, R042, R0489, R233, R31, R310, R319, R58, R58, S06.310A -S06.389S, S064x, S065x, S065X0A, S065X9A, S066x, S066X0A, S066X9A

Table S2. Prescriptions of oral anticoagulants (OAC) within 30 days after new-onset atrial fibrillation during sepsis, per year

Year	Number with OAC prescription within 30 days of sepsis	Number with sepsis	% with OAC prescription within 30 days of sepsis
2011	97	541	18%
2012	98	622	16%
2013	119	631	19%
2014	120	619	19%
2015	110	555	20%
2016	158	580	27%
2017	105	444	24%

Table S3. Multivariable adjusted logistic regression model exploring factors associated with receipt of anticoagulants within 30 days of sepsis hospitalization discharge.

Characteristics	Odds ratio	p-value
Pre-sepsis hospitalization		
Age, per year	0.966	<0.001
Race and Ethnicity		
Asian	reference	
Black	1.072	0.806
Hispanic	0.805	0.383
Other	0.645	0.425
White	1.068	0.717
Sex, male	0.955	0.764
Body mass index	0.992	0.334
Smoking history	1.030	0.801
Atherosclerotic cardiovascular disease score	1.142	0.729
Medications prior to sepsis hospitalization		
Anti-platelet	0.465	0.017
Statin	1.383	0.027
Anti-hypertensive	1.317	0.117
Charlson comorbidity Index	0.708	0.004
Chronic pulmonary disease	1.527	0.015
Hemiplegia or paraplegia	1.024	0.970
Acquired Immunodeficiency Syndrome	23.616	0.017
Chronic kidney disease	1.526	0.004
Dementia	0.831	0.716
Diabetes	2.030	0.001
Diabetes with chronic complications	1.236	0.374
Malignancy, including leukemia and lymphoma	1.821	0.039
Mild liver disease	1.375	0.515
Metastatic solid tumor	2.627	0.126
Peptic ulcer disease	1.430	0.280
Peripheral vascular disorder	1.836	0.001
Renal Disease	1.968	0.018
Rheumatologic disease	1.200	0.541
Moderate or severe liver disease	3.795	0.070
Myocardial Infarction	1.069	0.754
CHADS2-VASc Score for Atrial Fibrillation Stroke Risk	1.104	0.275
During sepsis hospitalization		

Percentage of cardiac flowsheet with atrial fibrillation	1.006	0.001
Atrial fibrillation diagnosis code (all patients had atrial fibrillation on cardiac flowsheet)	3.315	<0.001
Atrial fibrillation on cardiac flowsheet on day of discharge	2.137	<0.001
Maximum Sequential Organ Failure Assessment score	1.006	0.873
Laboratory acute physiology score, version 2	0.994	<0.001
Medications		
Anticoagulants	19.4	<0.001
Aspirin	0.949	0.692
Other Antiplatelet	0.557	0.030
Statin	1.071	0.631
Inotrope (Dobutamine or Milrinone)	1.224	0.502
Vasopressor	1.102	0.644
Other inpatient procedures		
First EF measure (%), median [Interquartile Range] (IQR)	0.986	0.040
Intensive care unit admission	1.061	0.681
Days of invasive mechanical ventilation, median [IQR]	0.934	0.293
Days of non-invasive mechanical ventilation, median [IQR]	0.978	0.622
Hemodialysis	0.629	0.278
Head computerized tomography scan	0.669	0.057
Coronary artery bypass graft procedure	1.387	0.608
Percutaneous intervention procedure	0.836	0.707
Red blood cell transfusion	0.712	0.168
Cryoprecipitate transfusion	0.584	0.339
Platelet transfusion	1.397	0.559
Total blood product volume	1.000	0.951
Other diagnoses during hospitalization		
Peripheral arterial disease	1.734	0.433
Bleeding	0.619	0.014

Fall	0.410	<0.001
Malignancy	0.653	0.143
Dementia	0.287	0.001
Heart failure	1.458	0.006
Myocardial infarction	0.495	0.002
Hospital baseline vital signs and laboratory values (median [IQR])		
Systolic blood pressure mmHg	1.005	0.156
Heart rate, beats per minute	1.001	0.793
Hemoglobin	1.119	0.003
Hemoglobin A1c %	0.879	0.123
Blood urea nitrogen	0.991	0.058
Platelets, x 10^3	1.002	0.033
Creatinine	1.023	0.823
Hospital most extreme selected laboratory values (median [IQR])		
Troponin I	1.017	0.048
Brain Natriuretic Peptide	1.000	0.733
Creatinine	0.989	0.853
Lactic Acid	0.941	0.130
Prothrombin time	1.064	<0.001
Lowest platelet count x 10^3	1.000	0.685
Hospital length of stay, days	0.957	0.095

Table S4. Distribution of unstabilized inverse probability weights from SuperLearner for each observation of follow up time among patients prescribed anticoagulants

Inverse probability weights	Number of observations	Proportion of observations	Cumulative proportion
(-infinity, 0)	0	0.0	0.0
[0,0.5)	0	0.0	0.0
[0.5,1)	375	0.0015	0.0015
[1,10)	236909	0.9677	0.9692
[10,20)	6296	0.0257	0.9949
[20,30)	749	0.0031	0.9980
[30,40)	277	0.0011	0.9991
[40,50)	99	0.0004	0.9995
[50,60)	31	0.0001	0.9997
[60,70)	22	0.0001	0.9998
[70,80)	14	0.0001	0.9998
[80,90)	11	0.00001	0.9999
[90,100)	20	0.00008	0.9999
[100,150)	5	0.00002	0.9999
[150, Inf)	11	0.00005	1.0

Table S5. Distribution of unstabilized inverse probability weights from SuperLearner for each observation of follow up time among patients not prescribed anticoagulants

Inverse probability weights	Number of observations	Proportion of observations	Cumulative proportion
[-Inf,0)	0	0.0	0.0
[0,0.5)	0	0.0	0.0
[0.5,1)	3590	0.0043	0.0043
[1,10)	837712	0.9914	0.9956
[10,20)	3349	0.0040	0.9996
[20,30)	262	0.0003	0.9999
[30,40)	38	0.00005	0.9999
[40,50)	25	0.00003	0.9999
[50,60)	8	0.00001	1.0
[60,70)	0	0.0	1.0
[70,80)	0	0.0	1.0
[80,90)	0	0.0	1.0
[90,100)	0	0.0	1.0
[100,150)	0	0.0	1.0
[150, Inf)	0	0.0	1.0

Table S6. Combined distribution of stabilized inverse probability weights from Super Learner for each observation of follow up time

Inverse probability weights	Number of observations	Proportion of observations	Cumulative proportion
(-infinity, 0)	0	0	0
[0,0.5)	120956	0.110989	0.110989
[0.5,1)	516666	0.474091	0.58508
[1,10)	451788	0.414559	0.999639
[10,20)	348	0.000319	0.999959
[20,30)	34	3.12E-05	0.99999
[30,40)	0	0	0.99999
[40,50)	0	0	0.99999
[50,60)	0	0	0.99999
[60,70)	0	0	0.99999
[70,80)	0	0	0.99999
[80,90)	0	0	0.99999
[90,100)	0	0	0.99999
[100,150)	0	0	0.99999
[150, Inf)	11	1.01E-05	1

Table S7. Combined distribution of stabilized inverse probability weights from logistic regression for each observation of follow up time

Inverse probability weights	Number of observations	Proportion of observations	Cumulative proportion
(-infinity, 0)	0	0	0
[0,0.5)	41621	0.0412779	0.0412779
[0.5,1)	517031	0.5127689	0.5540468
[1,10)	448427	0.4447304	0.9987772
[10,20)	955	0.0009471	0.9997243
[20,30)	131	0.0001299	0.9998542
[30,40)	46	0.0000456	0.9998998
[40,50)	44	0.0000436	0.9999435
[50,60)	19	0.0000188	0.9999623
[60,70)	16	0.0000159	0.9999782
[70,80)	7	0.0000069	0.9999851
[80,90)	4	0.000004	0.9999891
[90,100)	0	0	0.9999891
[100,150)	0	0	0.9999891
[150, Inf)	11	0.0000109	1

Table S8. Results of marginal structural models using *untruncated* inverse probability of treatment weights evaluating causal associations between anticoagulation and risks of stroke/transient ischemic attack (TIA) and bleeding within 1-year after hospitalization with sepsis and new-onset atrial fibrillation.

Model	Cumulative one-year incidence of outcome in Anticoagulation-exposed	Cumulative one-year incidence of outcome in Anticoagulation-Unexposed	Risk difference (95% Confidence Interval) Exposed-Unexposed
		Outcome: Stroke/TIA	
Primary adjusted model: Anticoagulation within 30-days of discharge, per-protocol, Super Learner propensity score	6.2%	2.3%	3.9% (0, 7.7%)
Sensitivity Analyses			
Anticoagulation within 30-days of discharge, per-protocol, logistic regression propensity score	2.8%	2.2%	0.6% (-2.6, 3.8%)
Anticoagulation within 30-days of discharge, intention to treat, Super Learner	3.6%	2.3%	1.3% (-0.2, 2.9%)
Anticoagulation within 24 hours of hospital discharge, per protocol, Super Learner	8.4%	2.3%	6% (-0.2, 12%)
Anticoagulation within 24 hours of hospital discharge, intention to treat, Super Learner	4.9%	2.4%	2.5% (-0.1, 5%)
		Outcome: Major Bleeding	
Primary adjusted model: Anticoagulation within 30-days of discharge, per-protocol, Super Learner propensity score	6.4%	7.3%	-0.9% (-1.7, 3.4%)
Sensitivity Analyses			
Anticoagulation within 30-days of discharge, per-protocol, logistic regression propensity score	6.1%	10%	-4.0% (-8.7, 0.94%)
Anticoagulation within 30-days of discharge, intention to treat, Super Learner	7.7%	7.3%	0.4% (-2.7%, 1.9%)

Anticoagulation within 24 hours of hospital discharge, per protocol, Super Learner	7.5%	7.4%	0.3% (-2.1, 2.7%)
Anticoagulation within 24 hours of hospital discharge, intention to treat, Super Learner	7.6%	7.1%	0.5% (-3.8, 2.8%)

Figure S1. Cumulative incidence of stroke and transient ischemic attack following hospitalization with sepsis and new-onset atrial fibrillation.
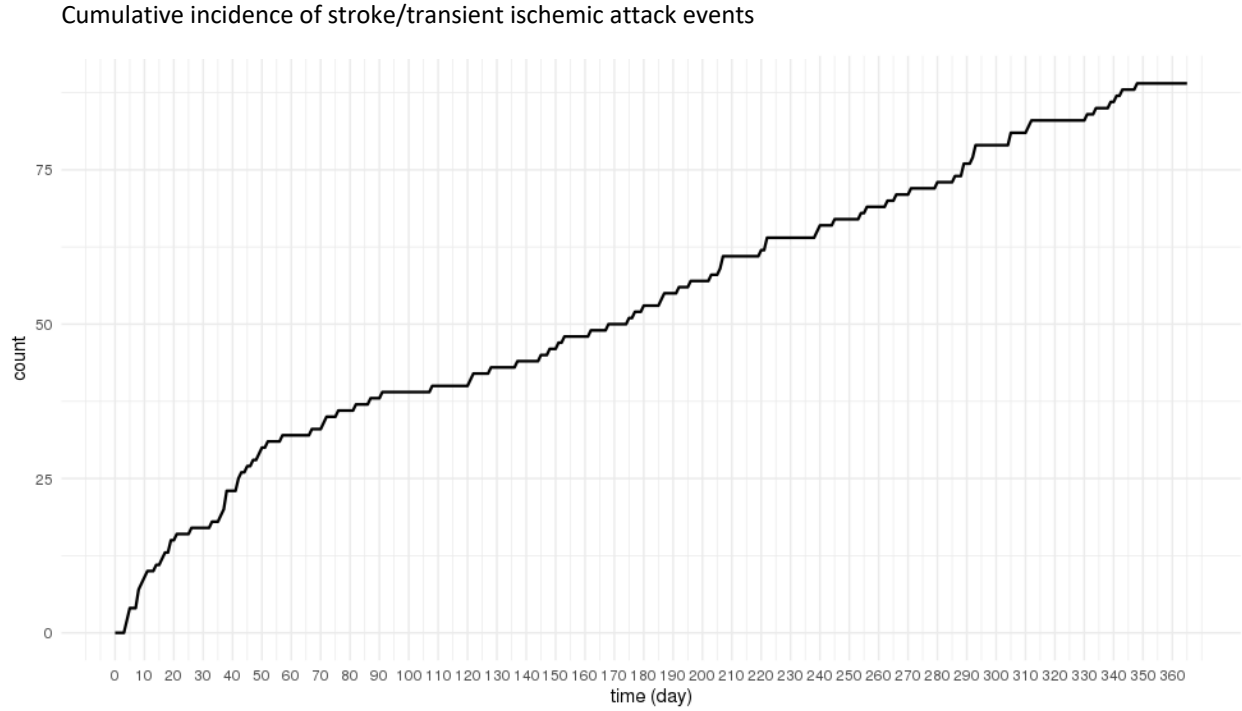

Cumulative incidence of stroke/transient ischemic attack events

Figure S2. Counts of patients following the treatment protocols of the control and exposed arms during follow-up in the primary analyses (per-protocol, exposure arm defined by a stochastic treatment regimen providing a 30-day grace period to initiate anticoagulant therapy, control arm defined by a static treatment regimen).
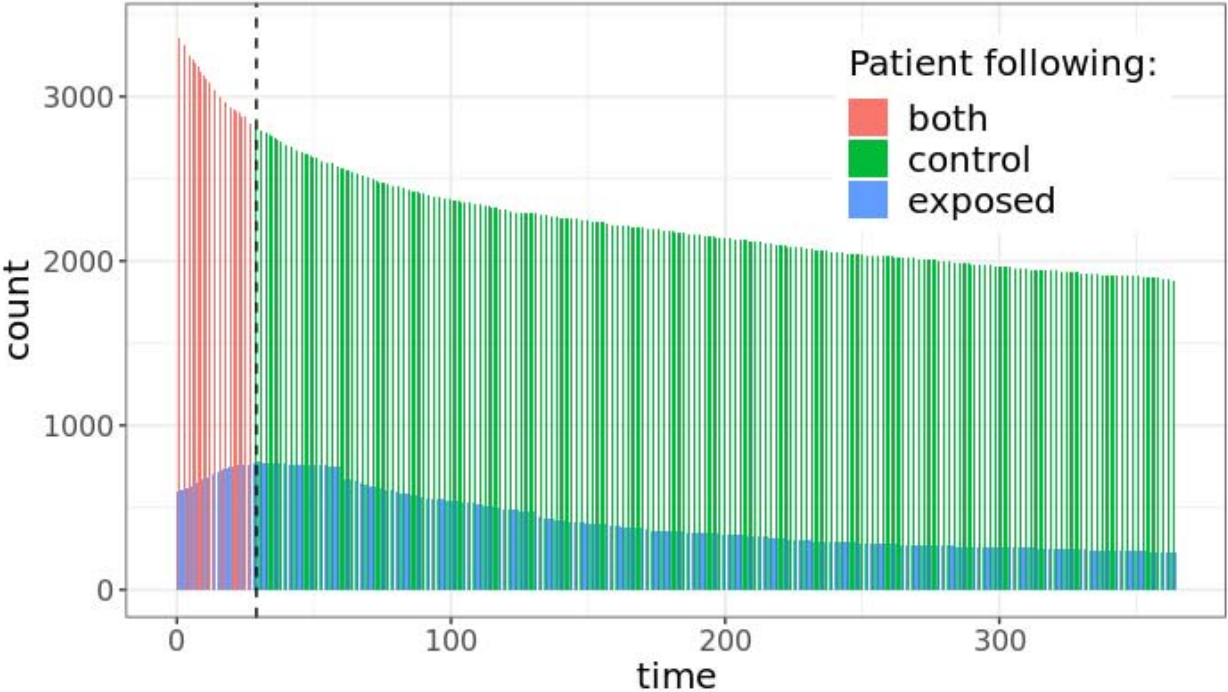
Figure S3. Sensitivity analysis, stroke/transient ischemic attack outcome: Per-protocol analysis, exposure arm defined by a stochastic treatment regimen providing a 30-day grace period to initiate anticoagulan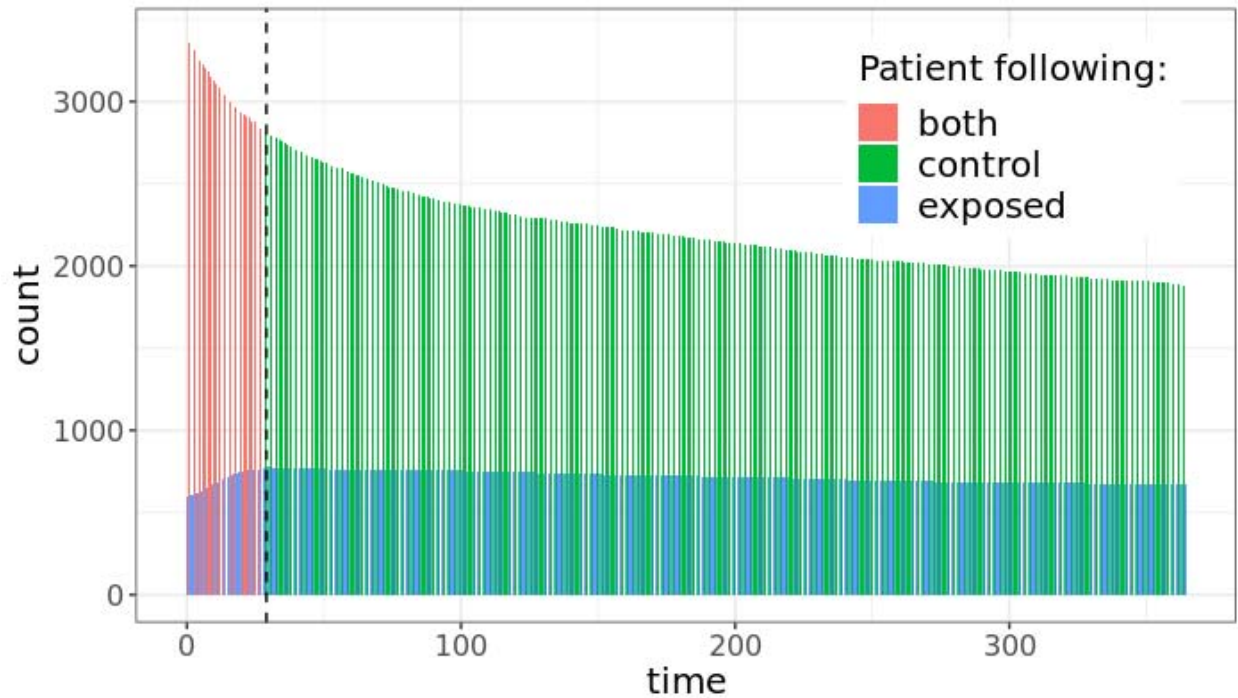t therapy, control arm defined by a static treatment regimen, inverse probability of treatment weights calculated from logistic regression model. Blue line: anticoagulant group; red line: No anticoagulant group.

Outcome: Stroke/Transient Ischemic Attack – Per-protocol – Stochastic Intervention (Non-machine Learning) Inverse Probability of Treatment Weighting 99th Percentile Truncated
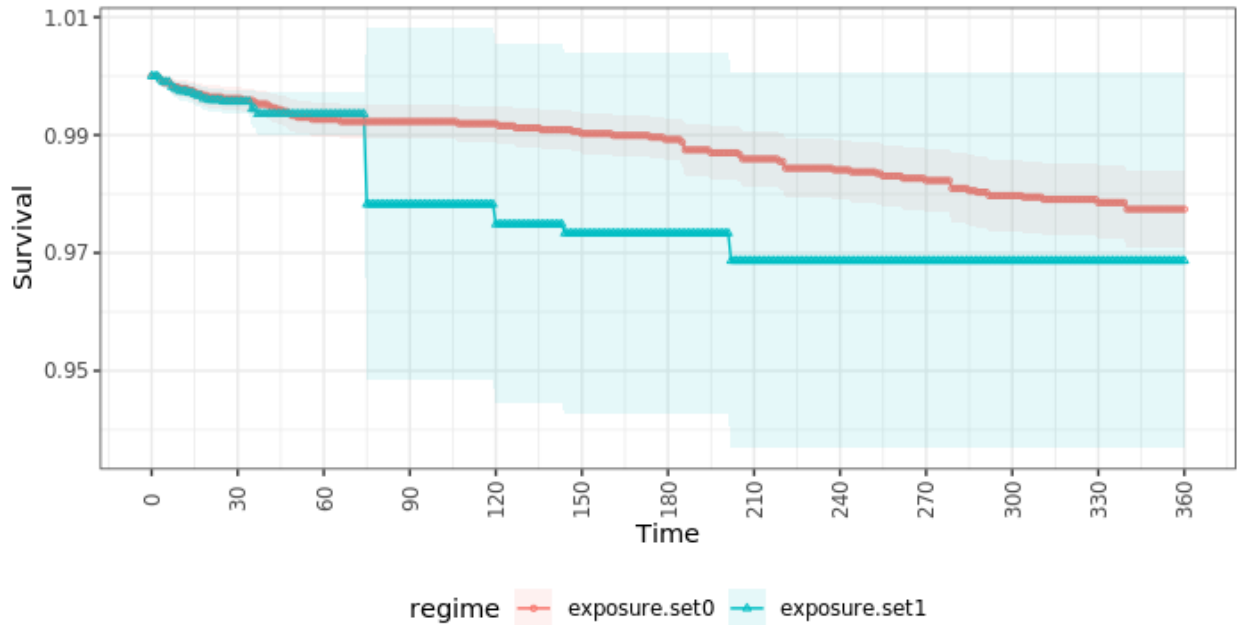
Figure S4. Patient counts across the study timeline and outcomes in the sensitivity analysis using an intention-to-treat approach and a 30-day grace period to initiate anticoagulant therapy. Blue line: anticoagulant group; red line: No anticoagulant group.

Figure S4A. Counts of patients following the treatment protocols of the control and exposed arms during follow-up in secondary, intention-to-treat analysis (exposure arm defined by a stochastic treatment regimen providing a 30-day grace period to initiate anticoagulant therapy, control arm defined by a static treatment regimen).

Figure S4B. Sensitivity analysis, stroke/transient ischemic attack: Intention-to-treat approach, exposure arm defined by a stochastic treatment regimen providing a 30-day grace period to initiate anticoagulant therapy, control arm defined by a static treatment regimen, inverse probability of treatment weights calculated from Super Learner suite.
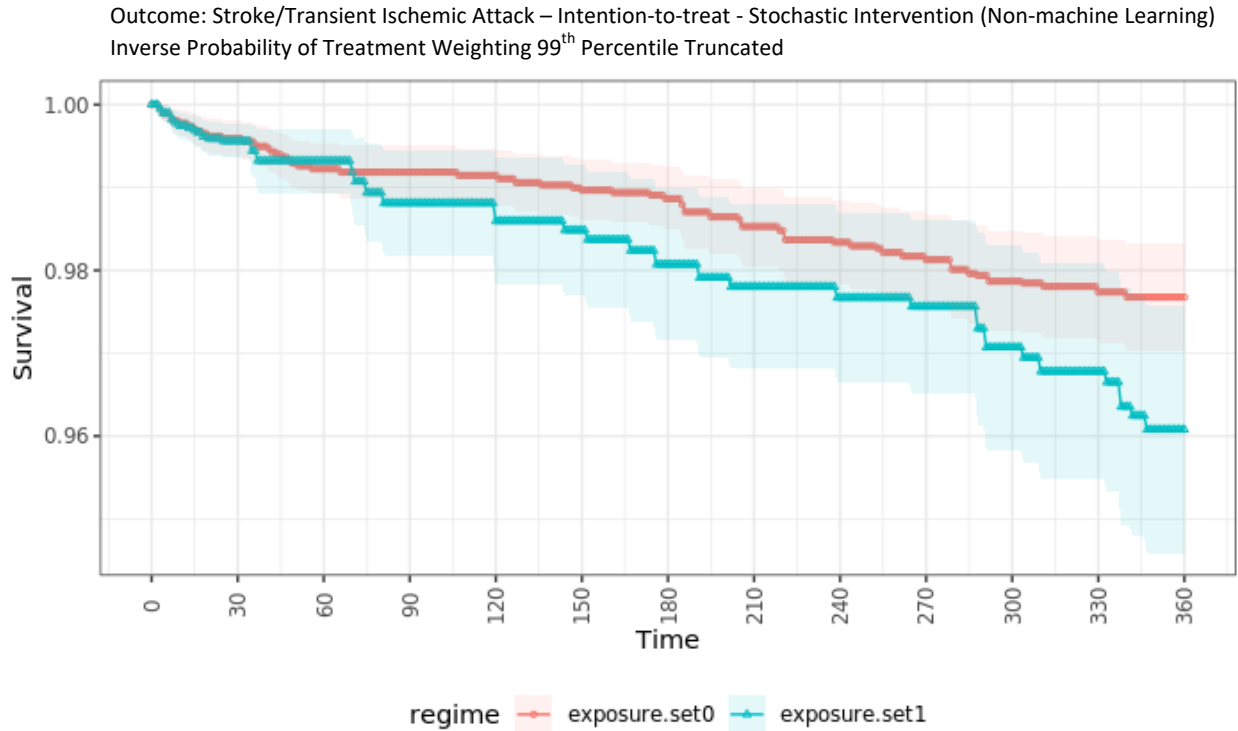

Outcome: Stroke/Transient Ischemic Attack – Intention-to-treat - Stochastic Intervention (Non-machine Learning) Inverse Probability of Treatment Weighting 99th Percentile Truncated

Figure S5. Patient counts across the study timeline and outcomes in the sensitivity analysis using a per-protocol approach and initiation of anticoagulant therapy within 24 hours of hospital discharge. Blue line: anticoagulant group; red line: No anticoagulant group.

Figure S5A. Counts of patients following the treatment protocols of the control and exposed arms during follow-up in the secondary per protocol analysis with anticoagulation exposure arm defined within 24 hours of hospital discharge.
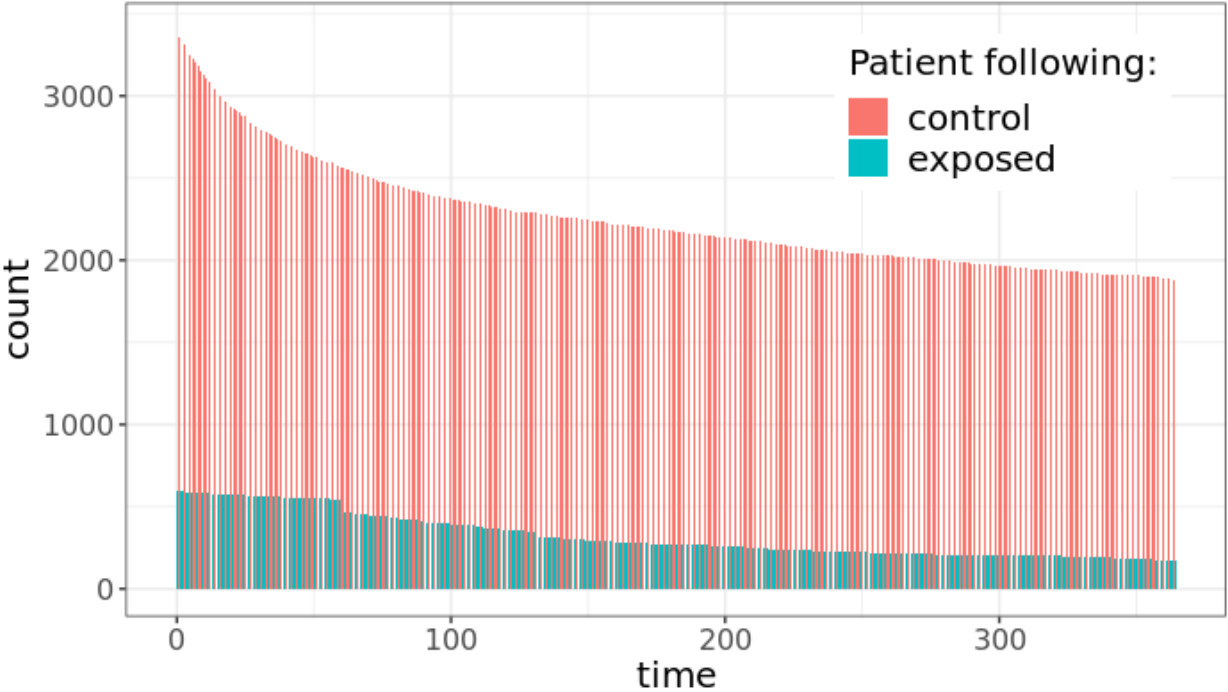
Figure S5B. Sensitivity analysis, stroke/transient ischemic attack: Per-protocol approach, exposure arm defined by anticoagulant therapy dispensed at hospital discharge, control arm defined by a static treatment regimen, inverse probability of treatment weights calculated from Super Learner suite.
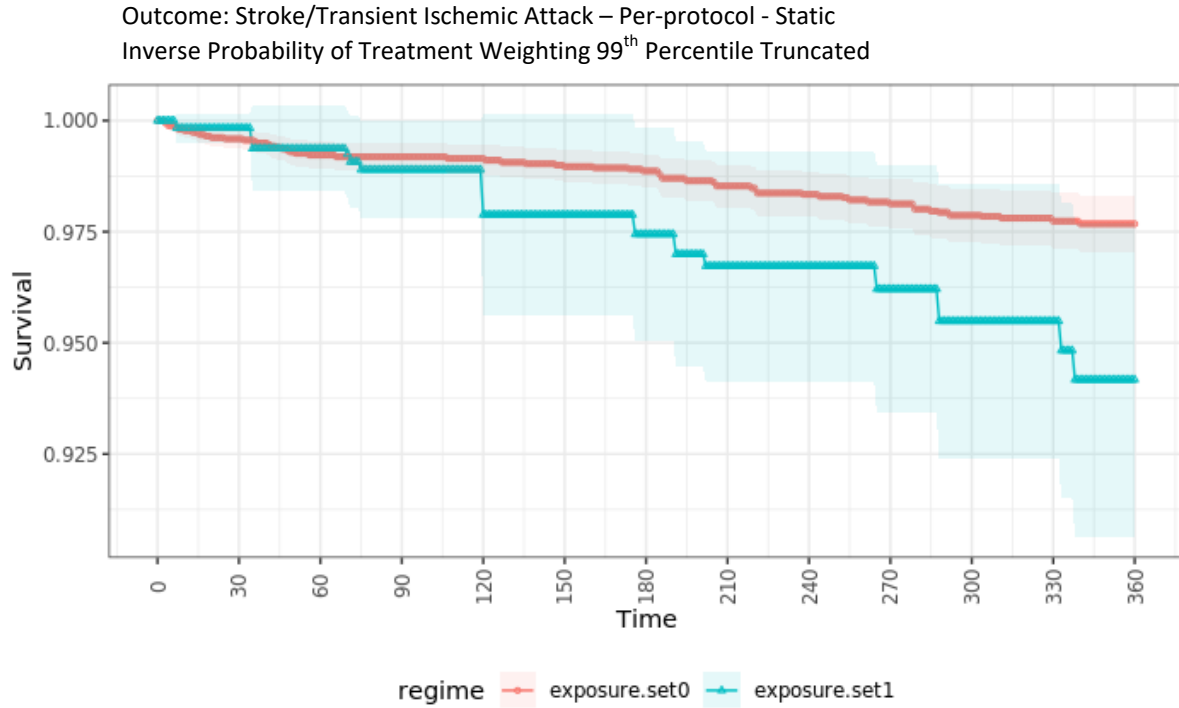

Outcome: Stroke/Transient Ischemic Attack – Per-protocol - Static
Inverse Probability of Treatment Weighting 99th Percentile Truncated

Figure S6. Patient counts across the study timeline and outcomes in the sensitivity analysis using an intention-to-treat approach and initiation of anticoagulant therapy within 24 hours of hospital discharge. Blue line: anticoagulant group; red line: No anticoagulant group.

Figure S6A. Counts of patients following the treatment protocols of the control and exposed arms during follow-up in the secondary intention-to-treat analysis with anticoagulation exposure arm defined within 24 hours of hospital discharge.
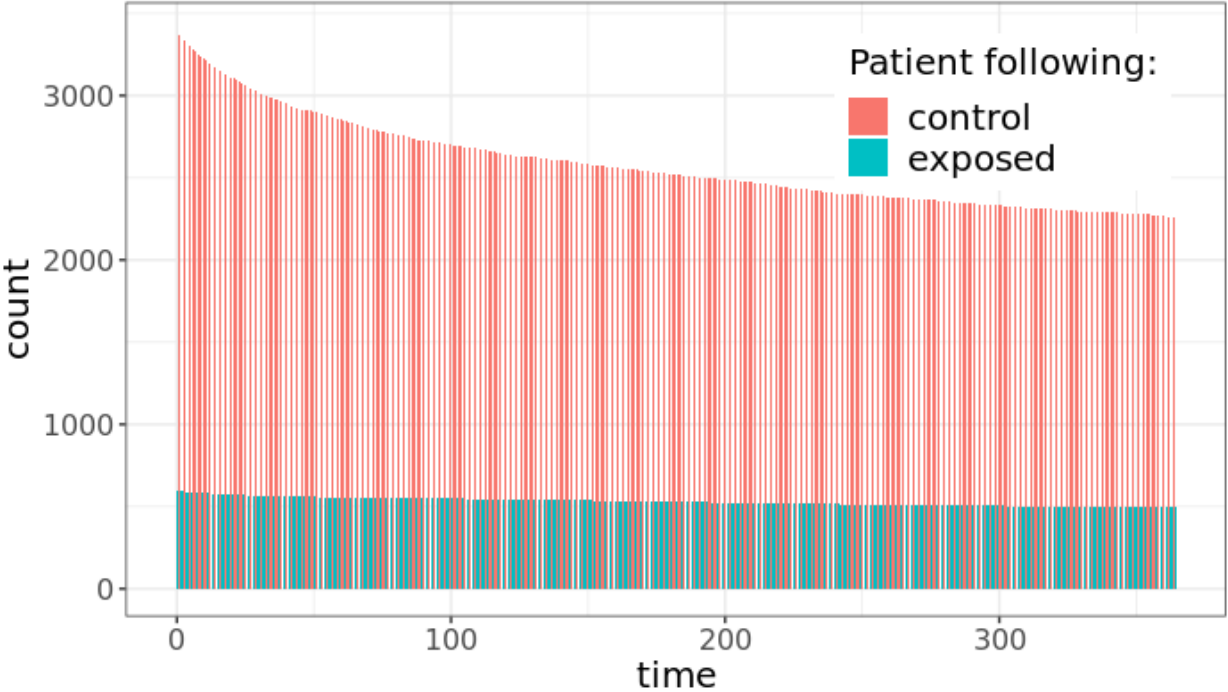
Figure S6B. Sensitivity analysis, stroke/transient ischemic attack: Intention-to-treat approach, exposure arm defined by anticoagulant therapy dispensed at hospital discharge, control arm defined by a static treatment regimen, inverse probability of treatment weights calculated from Super Learner suite.
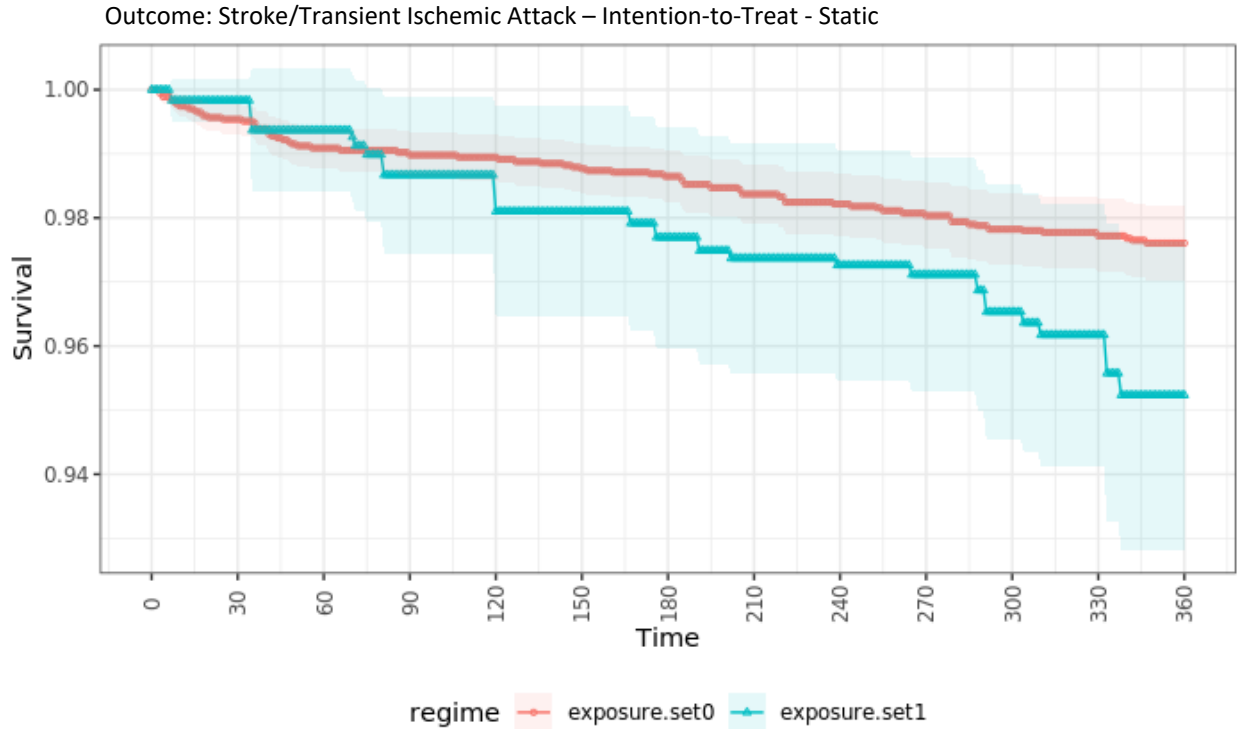

Outcome: Stroke/Transient Ischemic Attack – Intention-to-Treat - Static

Figure S7. Survival curves for sensitivity analysis models evaluating association between anticoagulation and bleeding outcomes across different specifications of inverse probability of treatment weight models, timing of anticoagulant initiation, and analysis frameworks (per protocol vs. intention-to-treat). Blue line: anticoagulant group; red line: No anticoagulant group.

Figure S7A. Sensitivity analysis, major bleeding outcome. Per-protocol analysis, exposure arm defined by a stochastic treatment regimen providing a 30-day grace period to initiate anticoagulant therapy, control arm defined by a static treatment regimen, inverse probability of treatment weights calculated from logistic regression model.

Outcome: Bleeding – Per-protocol – Stochastic Intervention (Non-machine Learning)
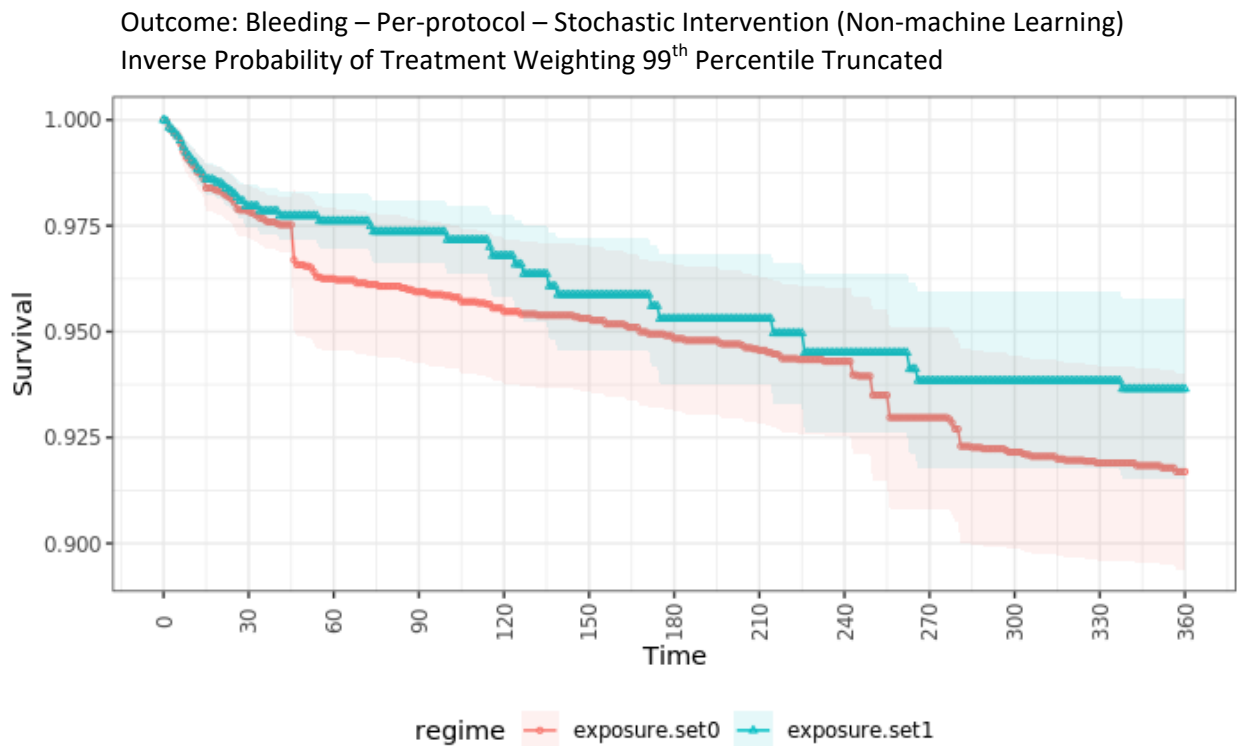Inverse Probability of Treatment Weighting 99th Percentile Truncated

Figure S7B. Sensitivity analysis, major bleeding outcome. Intention-to-treat approach, exposure arm defined by a stochastic treatment regimen providing a 30-day grace period to initiate anticoagulant therapy, control arm defined by a static treatment regimen, inverse probability of treatment weights calculated from Super Learner suite.

Outcome: Bleeding – Intention-to-treat – Stochastic Intervention
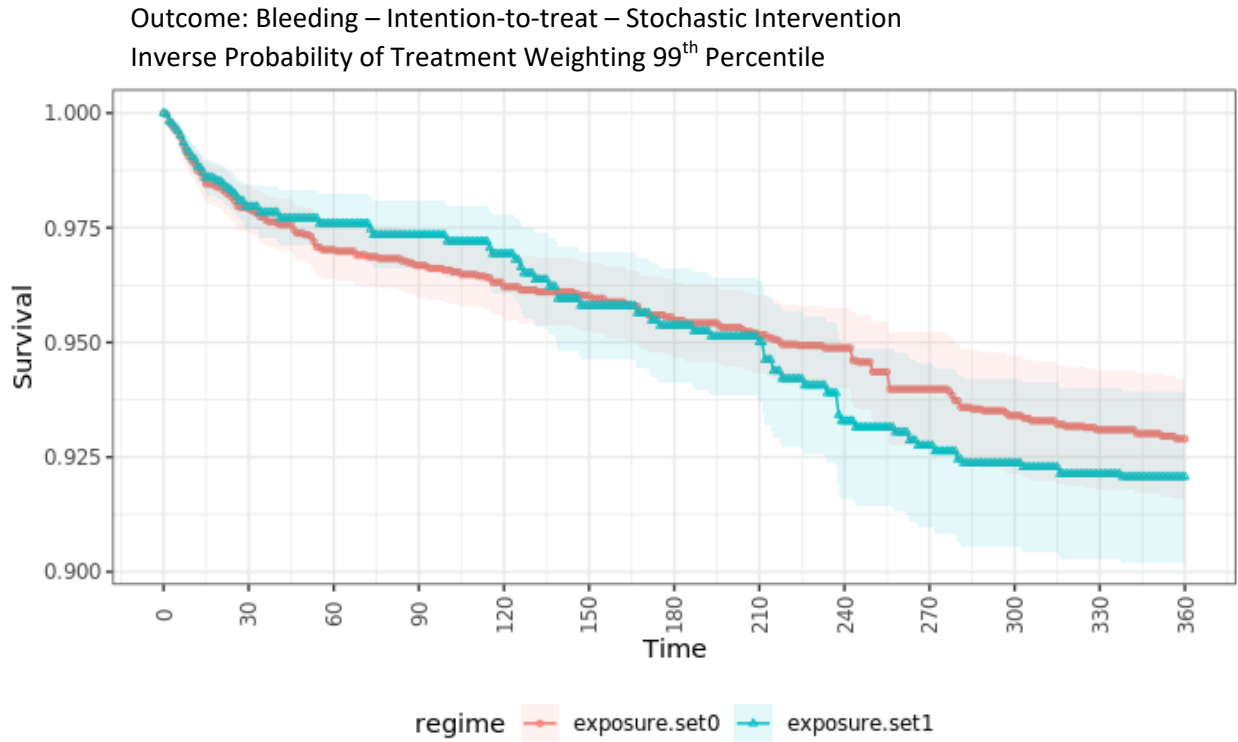Inverse Probability of Treatment Weighting 99th Percentile

Figure S7C. Sensitivity analysis, major bleeding outcome. Per protocol approach, exposure arm defined by anticoagulant therapy dispensed at hospital discharge, control arm defined by a static treatment regimen, inverse probability of treatment weights calculated from Super Learner suite.

Outcome: Bleeding – Per-protocol – Static
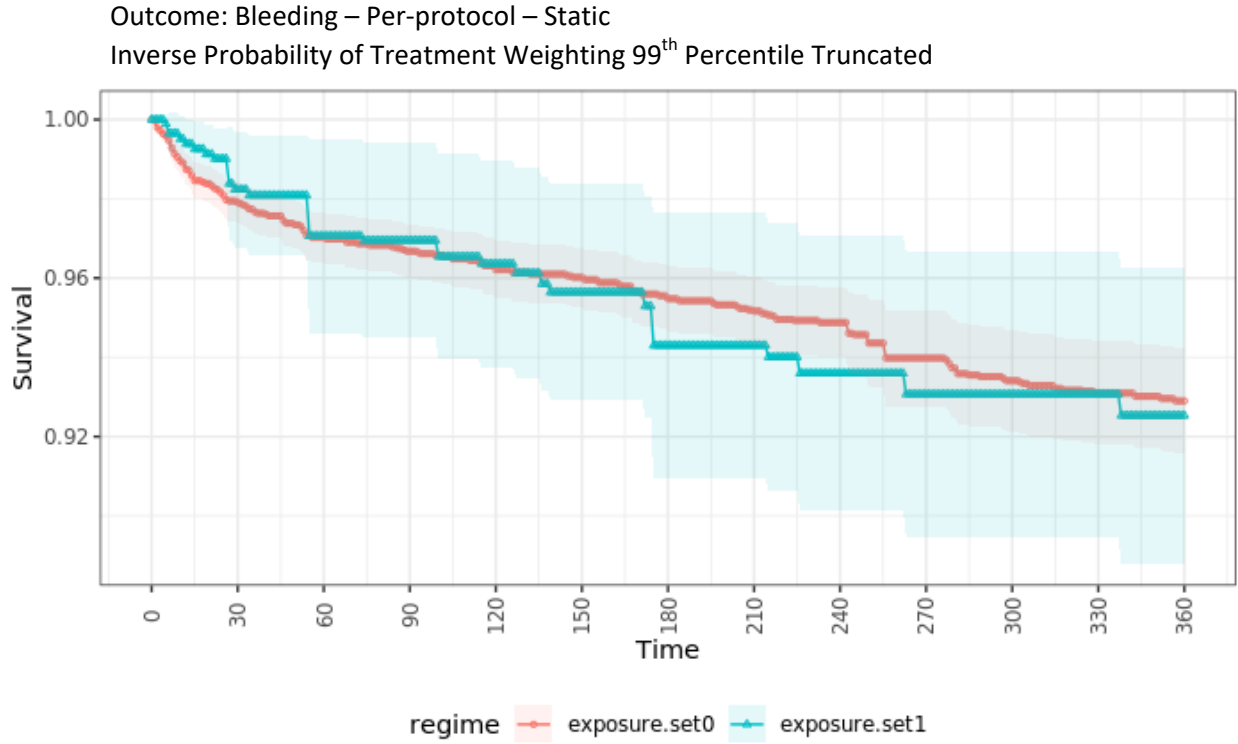Inverse Probability of Treatment Weighting 99th Percentile Truncated

Figure S7D. Sensitivity analysis, major bleeding outcome. Intention-to-treat approach, exposure arm defined by anticoagulant therapy dispensed at hospital discharge, control arm defined by a static treatment regimen, inverse probability of treatment weights calculated from Super Learner suite.

Outcome: Bleeding – Intention-to-treat - Static
Inverse Probability of Treatment Weighting 99th Percentile Truncated