Supplemental Material for: Resuming anticoagulation following upper gastrointestinal bleeding — a microsimulation analysis

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1. Literature search to identify timing of rebleeding

We searched the Medline database for articles that matched the following phrase, and limited the results to systematic reviews:

”Time Factors"[MeSH Terms] AND "Recurrence"[MeSH Terms] AND ("Peptic Ulcer"[MAJR] OR "Duodenal Ulcer"[MAJR] OR "Gastrointestinal hemorrhage”[MAJR])

As of October 11, 2017, Medline included 775 articles that matched these search terms, 8 of which were categorized as systematic reviews. We reviewed those 8 articles for data with which one could estimate the probability of rebleeding as a function of day; only the cited article by El Ouali and colleagues included such estimates.

El Ouali and colleagues provide the following interval estimates of rebleeding:

Interval:	Rebleeding rate:
0-3 days	39.5%
3-7 days	36.6%
7-14 days	19.7%
14-29 days	6.2%

From these interval estimates, we estimated the following point estimates (interval rate/days in interval):

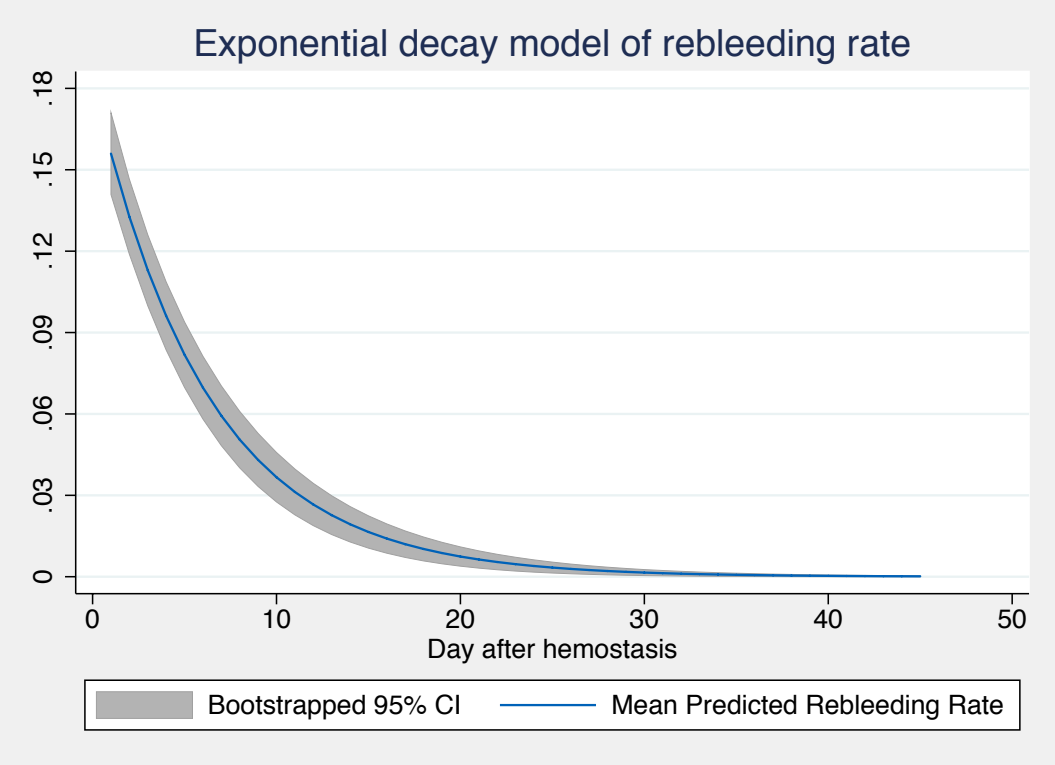
Point:	Rebleeding rate:
Day 2	13.2%
Day 5	9.2%
Day 11	2.8%
Day 21	0.4%

To these point estimates, we fitted the following exponential:

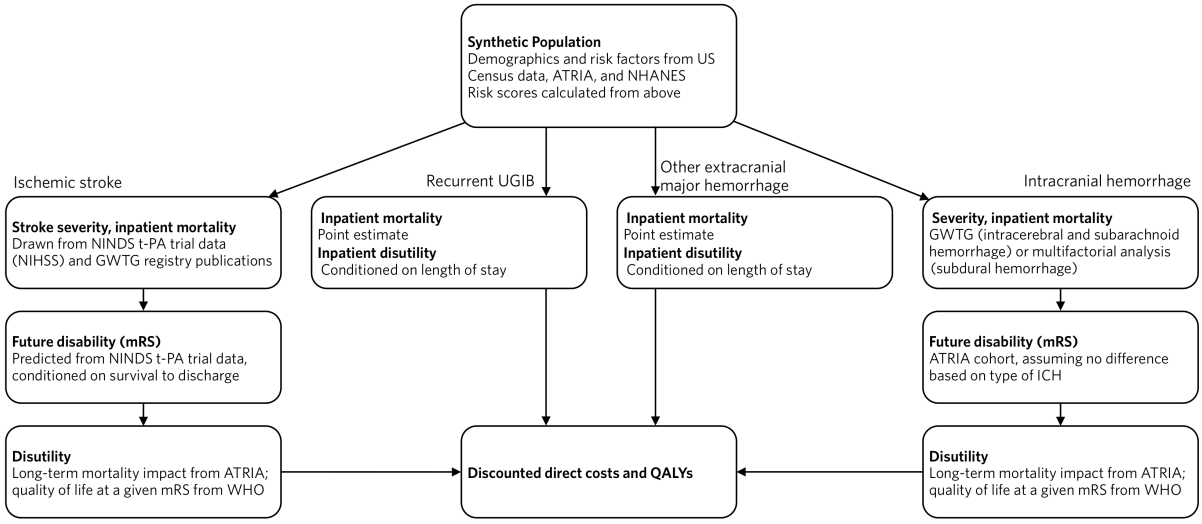
$$\text{Conditional probability of rebleeding by day} = b_0 * \exp(b_1 * \text{day})$$

where $b_0 = 0.1843$ (standard error: 0.0136) and $b_1 = -0.1563$ (standard error: 0.0188)

This decay function is graphed below, with bootstrapped 95% confidence intervals.



2. Schematic diagram of microsimulation model



3. In-hospital mortality

Estimating in-hospital mortality required some assumptions. Worth noting are (all of the following point estimates are from GWTG-Stroke):

- We assumed that ischemic stroke patients who took an ambulance from the scene were an independent and randomly distributed 53.4% of that population.
- We assumed that ischemic stroke patients who did not present via the ED were an independent and randomly distributed 5.7% of that population.
- We assumed that ischemic stroke patients who arrived during regular business hours were an independent and randomly distributed 46.8% of that population.
- We assumed that intracerebral hemorrhage patients who took an ambulance from the scene were an independent and randomly distributed 65.9% of that population.
- We assumed that intracerebral hemorrhage patients who did not present via the ED were an independent and randomly distributed 7.6% of that population.
- We assumed that intracerebral hemorrhage patients who arrived during regular business hours were an independent and randomly distributed 40.8% of that population.
- We assumed that subarachnoid hemorrhage patients who took an ambulance from the scene were an independent and randomly distributed 53.7% of that population.
- We assumed that subarachnoid hemorrhage patients who did not present via the ED were an independent and randomly distributed 17.1% of that population.
- We assumed that subarachnoid hemorrhage patients who arrived during regular business hours were an independent and randomly distributed 33.1% of that population.
- We assumed that all patients taking anticoagulants at the time of their stroke had a coagulopathy as defined in the GWTG-Stroke risk estimation function.

Other assumptions worth pointing out include:

- All patients have a baseline modified Rankin Score of 0.
- A uniformly distributed random 10% of ischemic stroke patients receive thrombolytics, unless they have already resumed anticoagulation.
- All intracranial hemorrhages lead to similar future disability, if a patient survives to discharge.

4. Future disability following ischemic stroke

We performed an ordinal logistic regression on the NINDS-tPA trial data to predict mRS months following discharge, among atrial fibrillation patients who survived to discharge, using NIHSS, age, baseline mRS, and use of t-PA as predictors. Because we expected that the GWTG-Stroke inpatient mortality prediction would be a better-calibrated predictor of death before discharge, we conditioned this regression on survival to discharge. Those interested in reproducing this from the same dataset, using Stata:

```
. ologit rank3m c.baseline i.nrankin c.age i.treatcd if patrial==100 & hdchg!=5

[…]

Ordered logistic regression                     Number of obs   =         93
                                                LR chi2(7)      =      52.26
                                                Prob > chi2     =     0.0000
Log likelihood = -146.93877                     Pseudo R2       =     0.1510
```

rank3m	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
baseline	.2143078	.0357894	5.99	0.000	.1441619	.2844537
nrankin						
1	1.921345	.9009003	2.13	0.033	.1556126	3.687077
2	.2743499	1.082268	0.25	0.800	−1.846857	2.395556
3	−.2003374	1.550749	−0.13	0.897	−3.239749	2.839074
4	1.504423	1.517393	0.99	0.321	−1.469613	4.478459
age	.0318417	.0221059	1.44	0.150	−.011485	.0751684
2.treatcd	.6418311	.4022874	1.60	0.111	−.1466377	1.4303
/cut1	2.996363	1.69073			−.3174077	6.310133
/cut2	4.728834	1.726345			1.34526	8.112408
/cut3	5.1216	1.732927			1.725125	8.518075
/cut4	6.331271	1.76648			2.869033	9.793509
/cut5	7.859279	1.825368			4.281623	11.43693
/cut6	8.86914	1.864487			5.214812	12.52347

We assessed the goodness of fit of this model, compared with the original dataset, using both a weighted kappa of the model's weighted average mRS prediction (0.44) and the model's most likely mRS prediction (weighted kappa 0.52).

5. Covariance of risk scores

The covariance among input scores (Rockall, CHADS2, and HAS-BLED) in our simulated population is demonstrated in the following tables. Some combinations of scores are impossible, due to the variables included in each. Note the population changes slightly for patients restarting apixaban, due to exclusion of patients with an eGFR of less than 25 from our apixaban simulation.

	$CHADS_2$						
Rockall Score	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
1	89,592	15,980	0	0	0	0	105,572
2	504,856	198,352	43,164	1,692	193	0	748,257
3	852,332	666,235	214,481	39,798	14,548	3,727	1,791,121
4	629,482	920,541	379,431	145,999	63,955	17,954	2,157,362
5	586,914	732,352	352,792	193,319	88,876	23,965	1,978,218
6	216,314	581,721	277,590	147,037	62,414	17,148	1,302,224
7	88,139	229,778	155,953	119,101	55,170	15,342	663,483
8	13,890	86,675	60,348	53,608	20,893	5,566	240,980
Total	2,981,519	3,431,634	1,483,759	700,554	306,049	83,702	8,987,217

	HAS-BLED						
Rockall Score	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
1	7,942	63,083	33,396	1,150	1	0	105,572
2	25,389	283,198	324,534	108,790	6,194	152	748,257
3	28,567	423,288	872,628	390,826	56,879	18,933	1,791,121
4	24,723	366,357	1,011,973	511,121	166,884	76,304	2,157,362
5	17,474	297,165	889,241	477,019	199,054	98,265	1,978,218
6	7,258	133,665	600,590	340,925	148,210	71,576	1,302,224
7	2,154	53,670	266,094	168,953	113,882	58,730	663,483
8	198	13,296	92,686	64,594	47,139	23,067	240,980
Total	113,705	1,633,722	4,091,142	2,063,378	738,243	347,027	8,987,217

	CHADS$_2$						
HAS-BLED	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
1	111,290	2,415	0	0	0	0	113,705
2	1,217,689	380,291	35,742	0	0	0	1,633,722
3	1,269,482	1,957,655	757,962	106,043	0	0	4,091,142
4	369,525	1,027,743	518,689	141,072	6,349	0	2,063,378
5	13,406	62,354	135,957	294,749	177,129	54,648	738,243
6	127	1,176	35,409	158,690	122,571	29,054	347,027
Total	2,981,519	3,431,634	1,483,759	700,554	306,049	83,702	8,987,217

6. Meta-model: assessing sensitivity to input parameters

To assess the sensitivity of our model, we created a meta-model (a regression model comparing our model output to various input parameters). In larger simulations (>10 million subjects), essentially all parameters were statistically significant. We tested for interactions, finding that most were statistically significant, but many reduced, rather than improved, R^2. The following is our final meta-model command and results for apixaban. The model for warfarin was identical but for the dependent variable.

```
. regress discounted_QALYs_apix c.day_resuming_anticoag##c.day_resuming_anticoag c.rockall_score##c.day_resuming_anticoag
c.chads2vasc_score##c.day_resuming_anticoag c.chads2vasc_score##c.rockall_score i.hasbled_score##c.chads2vasc_score
i.hasbled_score##c.rockall_score c.age##c.age c.age##c.discount_rate c.discount_rate##c.discount_rate i.male
note: day_resuming_anticoag omitted because of collinearity
note: day_resuming_anticoag omitted because of collinearity
note: chads2vasc_score omitted because of collinearity
note: rockall_score omitted because of collinearity
note: chads2vasc_score omitted because of collinearity
note: rockall_score omitted because of collinearity
note: age omitted because of collinearity
note: discount_rate omitted because of collinearity

      Source |       SS           df       MS      Number of obs   =  10628766
-------------+----------------------------------   F(28, 10628737) >  99999.00
       Model |   326600008        28    11664286   Prob > F        =    0.0000
    Residual |    30663440  10628737  2.88495614   R-squared       =    0.9142
-------------+----------------------------------   Adj R-squared   =    0.9142
       Total |   357263448  10628765  33.6128842   Root MSE        =    1.6985

------------------------------------------------------------------------------------------------------------------
                         discounted_QALYs_apix |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-----------------------------------------------+------------------------------------------------------------------
                         day_resuming_anticoag |   .0084452   .0001508    56.01   0.000     .0081497    .0087407
                                               |
```

c.day_resuming_anticoag#c.day_resuming_anticoag	-.0000836	1.91e-06	-43.79	0.000	-.0000874	-.0000799
rockall_score	-.0684665	.0018205	-37.61	0.000	-.0720347	-.0648983
day_resuming_anticoag	0	(omitted)				
c.rockall_score#c.day_resuming_anticoag	.0001989	.0000206	9.64	0.000	.0001585	.0002394
chads2vasc_score	.1088877	.005442	20.01	0.000	.0982215	.1195539
day_resuming_anticoag	0	(omitted)				
c.chads2vasc_score#c.day_resuming_anticoag	-.0004957	.0000206	-24.02	0.000	-.0005362	-.0004553
chads2vasc_score	0	(omitted)				
rockall_score	0	(omitted)				
c.chads2vasc_score#c.rockall_score	-.0023595	.0003027	-7.79	0.000	-.0029528	-.0017661
hasbled_score						
2	-.0350067	.0077275	-4.53	0.000	-.0501524	-.019861
3	-.0919714	.0082092	-11.20	0.000	-.1080612	-.0758816
4	-.1517398	.0096843	-15.67	0.000	-.1707206	-.132759
5	-.1838737	.0147352	-12.48	0.000	-.2127541	-.1549933
6	-.2241881	.0225967	-9.92	0.000	-.2684769	-.1798994
chads2vasc_score	0	(omitted)				
hasbled_score#c.chads2vasc_score						
2	-.1222265	.0054044	-22.62	0.000	-.1328189	-.1116341
3	-.1401813	.0053116	-26.39	0.000	-.1505919	-.1297707
4	-.1308291	.0053874	-24.28	0.000	-.1413882	-.12027
5	-.1237515	.0054722	-22.61	0.000	-.1344767	-.1130262
6	-.1185103	.0059091	-20.06	0.000	-.1300918	-.1069287
rockall_score	0	(omitted)				
hasbled_score#c.rockall_score						
2	.0152868	.0018109	8.44	0.000	.0117376	.018836
3	.025515	.0018409	13.86	0.000	.0219068	.0291231
4	.029067	.0020001	14.53	0.000	.0251469	.0329872
5	.0383718	.0025893	14.82	0.000	.0332968	.0434468
6	.036077	.0031626	11.41	0.000	.0298783	.0422756
age	-.577752	.0003148	-1835.29	0.000	-.578369	-.577135
c.age#c.age	-.000181	2.19e-06	-82.83	0.000	-.0001853	-.0001768
age	0	(omitted)				
discount_rate	-581.7298	.2150055	-2705.65	0.000	-582.1512	-581.3084

```
                    c.age#c.discount_rate |   6.515738   .0024032  2711.30   0.000     6.511028    6.520448
                                          |
                            discount_rate |          0  (omitted)
                                          |
          c.discount_rate#c.discount_rate |    482.511   1.942083   248.45   0.000     478.7046    486.3174
                                          |
                                   1.male |  -1.078407   .0011756  -917.34   0.000    -1.080711   -1.076103
                                    _cons |   56.40798   .0127486  4424.65   0.000     56.38299    56.43296
------------------------------------------------------------------------------------------------------------
```

7. Optimal day of apixaban resumption following UGIB, by CHA2DS2-Vasc and Rockall scores

The range of predicted days on which resumption would confer at least 99.99% of optimal utility are included in parentheses. Blank cells denote impossible combinations of scores.

	Rockall Score								
$CHADS_2$-Vasc Score	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	48 (44 – 51)	49 (46 – 52)	50 (47 – 53)	51 (48 – 54)	52 (49 – 55)	53 (51 – 56)	55 (52 – 58)	56 (53 – 59)	57 (54 – 60)
2		46 (43 – 49)	47 (44 – 50)	48 (45 – 51)	49 (46 – 52)	51 (48 – 53)	52 (49 – 55)	53 (50 – 56)	54 (51 – 57)
3		43 (40 – 46)	44 (41 – 47)	45 (42 – 48)	46 (43 – 49)	48 (45 – 50)	49 (46 – 52)	50 (47 – 53)	51 (48 – 54)
4			41 (38 – 44)	42 (39 – 45)	43 (41 – 46)	45 (42 – 47)	46 (43 – 49)	47 (44 – 50)	48 (45 – 51)
5			38 (35 – 41)	39 (36 – 42)	40 (38 – 43)	42 (39 – 44)	43 (40 – 46)	44 (41 – 47)	45 (42 – 48)
6			35 (32 – 38)	36 (33 – 39)	37 (35 – 40)	39 (36 – 41)	40 (37 – 43)	41 (38 – 44)	42 (39 – 45)
7				33 (30 – 36)	35 (32 – 37)	36 (33 – 39)	37 (34 – 40)	38 (35 – 41)	39 (36 – 42)
8				30 (28 – 33)	32 (29 – 34)	33 (30 – 36)	34 (31 – 37)	35 (32 – 38)	36 (34 – 39)
9				27 (25 – 30)	29 (26 – 31)	30 (27 – 33)	31 (28 – 34)	32 (29 – 35)	33 (31 – 36)