

AFIB Bleed Risk
Phil Lucht
Rimrock Digital Technology, Salt Lake City, Utah 84103
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rimrock@xmission.com

This is the second of two documents on AFIB risk -- the first concerns stroke risk.
Both documents are located here: <http://user.xmission.com/~rimrock/>.

The author is not a medical doctor and the unreviewed data and conclusions presented below are just for readers curious about the origins of AFIB risk numbers. If you have AFIB, go see your doctor!

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Please read Section 1 of the *AFIB Stroke Risk* document for a brief discussion of strokes.

Figure numbers referenced to *AFIB Stroke Risk* are preceded by an S, such as S(2.5).

Abbreviations: IC = intracranial AFIB = atrial fibrillation (and flutter)
GI = gastrointestinal OAC = oral anticoagulant
CI = confidence interval NOAC = "new" oral anticoagulants like apixaban

Summary

The structure of *AFIB Bleed Risk* parallels that of *AFIB Stroke Risk* and that is why the two documents were kept separate.

In what follows, we often refer to "AFIB-age" people or patients. Strictly speaking, we are referring to the age profile shown in S(2.2) which has an average age of 73.5. The average age in the Apixaban Study referenced below is 70. The incidence of bleeding events in this age group is of course much higher than in the general population. The US for example has an average age of 37. In fact bleed rates are a dramatic and rather sobering exponential function of age as shown in (1.7) below.

Section 1 attempts to calculate the risks of various kinds of internal bleeding for the average AFIB-age (but non-AFIB) person who takes no anticoagulant. For example, (1.10) shows that the risk of such a non-AFIB person having an intracranial bleed is about 0.2 %/yr, while the risk of having a gastrointestinal bleed is about 0.5 %/yr. A later calculation (2.7) concludes that the total risk for having a "major bleed" is about 1.4 %/yr among this AFIB-age but non-AFIB group.

Section 2 investigates the bleeding risk for the average AFIB patient who takes oral anticoagulants to reduce stroke risk. As shown in (2.4), (2.5) and (2.8), warfarin increases the rates of IC, GI and major bleeds (over no-OAC rates) by factors 3.8, 1.7 and 2.3. For apixaban those factors are 1.6, 1.5 and 1.6, showing an improvement over warfarin particularly for IC bleeds.

Sections 3, 4, and 5 summarize various stratification schemes which allow an AFIB patient to assess his or her personal bleeding risk, which may be more or less than that of the average AFIB patient. These strata schemes always include age as one of the factors.

Section 6 then combines the average-patient stroke and bleeding risks reviewed in our two documents into a single table (6.1) with main conclusions stated in (6.2). A second table (6.3) provides a sample assessment for a particular AFIB patient with certain stratification scores.

Section 7 describes the need for warfarin-taking AFIB patient to control INR very carefully.

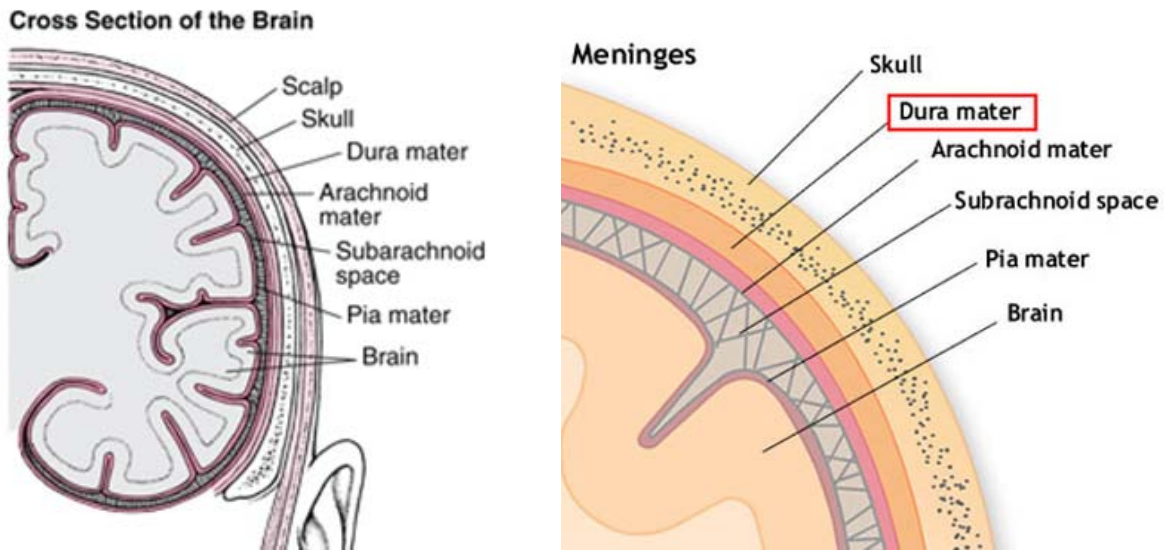
Appendix A does a conversion of average bleeding rates from a very broad population profile to the profile that characterizes AFIB patients.

References are provided in the final section, most of which are freely downloadable on the web.

1. What is the bleeding risk for non-AFIB patients in the AFIB-age population?

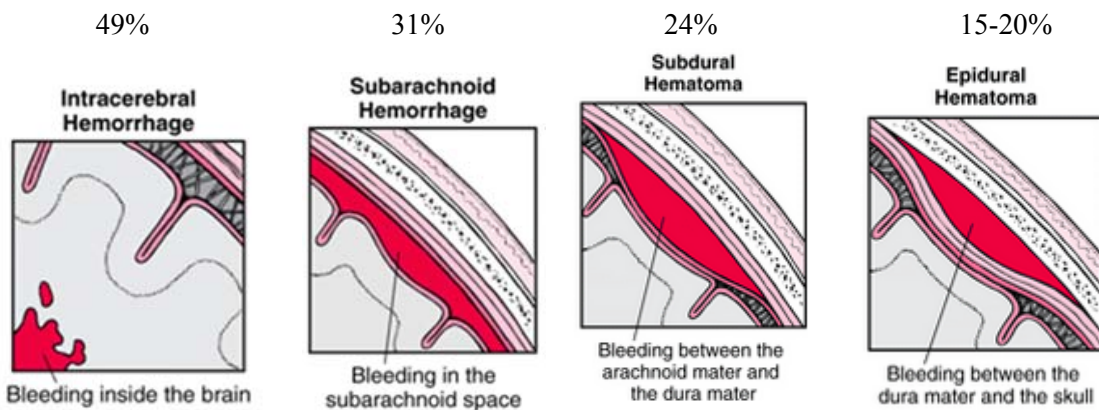
We shall treat two kinds of bleeds in this section. First are intracranial bleeds which are extremely serious, and second are gastrointestinal bleeds which are serious but less so.

There are four major kinds of intracranial (inside the skull) bleeds. The two kinds that occur inside the arachnoid (web-like) membrane are classified as hemorrhagic strokes. The other two kinds occur outside the arachnoid membrane, and are known as subdural and epidural hematomas depending on whether blood is pooled inside or outside the dura mater layer (the tough mother, a complicated etymology). Here are some useful pictures. The first two denote the various layers encasing the brain,



(1.1)

and here then are illustrations of the four kinds of intracranial bleeds:



These two are hemorrhagic strokes

These occur outside the arachnoid layer

(1.2)

http://www.merckmanuals.com/home/brain_spinal_cord_and_nerve_disorders/stroke_cva/overview_of_hemorrhagic_stroke.html#v739658
http://www.merckmanuals.com/home/injuries_and_poisoning/head_injuries/intracranial_hematomas.html#v740117

Intracranial bleeds are by far the most serious AFIB complications. The percentages shown above the pictures give the 30-day **mortality rates** for each kind of bleed. The first three numbers are quoted from the 2012 RE-LY trial (p 1512-13, see Refs), while the last is from the wiki page on epidural hematoma. For comparison, the 30-day mortality for an *ischemic* stroke is around 13% (various web sources). To restate the obvious, if you get an intracerebral bleed, your chances of living >30 days are about 50%.

In the Apixaban Study data presented below in (2.2), $0.47/0.80 = 59\%$ of the warfarin patient intracranial bleeds are of the two kinds shown on the left above -- the hemorrhagic strokes. Among the apixaban patients the percentage is 73%. The RE-LY paper concerning the NOAC dabigatran quotes the warfarin fraction as "about two thirds", supporting the Apixaban Study result. We shall assume that about 67% of intracranial bleeds are hemorrhagic strokes, accepting the two thirds RE-LY suggestion.

In order to learn by how much oral anticoagulants (OAC) increase the intracranial (IC) bleed rate of AFIB patients, we wish first to know the IC bleed rate for non-AFIB people in the AFIB-age population.

A crude calculation can be done as follows, making some assumptions. For the overall population, about 13% of all strokes are hemorrhagic strokes and 87% are ischemic. We assume this is true as well for the AFIB-age population. Since the non-AFIB but AFIB-age stroke rate is about 1.15 %/yr, as claimed in S(2.5), we conclude that the hemorrhagic stroke rate is $1.15 \cdot 13 = 0.15$ %/yr. Assuming also that hemorrhagic strokes account for 67% of all IC bleeds (as noted just above), we would conclude that the IC bleed rate was $.15 / .67 = 0.22$ %/yr .

To get a "second opinion" on this number, and also to obtain data for GI bleeds, we consult the following reference which is associated with the Qbleed algorithm and website (see Sec 5 below).

Hippisley-Cox (epidemiology) and Coupland (medical statistics) ("Cox Study", 2014) have studied **upper GI and intracranial bleed risk** using an English database of 14 million patients at 753 general practices. They used standard ICD-10 (International Classification of Diseases, 10th revision) codes to glean information. They used a "derivation cohort" to develop their model, and then a "validation cohort" to test the model. The derivation cohort had 4.4 million patients having 16.4 million patient-years of analysis (follow-up). The derivation cohort had 52,485 warfarin patients, but only 1,641 NOAC patients (drugs are new). Patient age ranged from 21 to 99.

Here then are the main results (for an average patient in the Cox Study) :

Table 2| Incident haemorrhagic events in derivation cohort recorded on mortality or hospital records

Haemorrhagic events	Cases on mortality or hospital data	Person years	Age standardised incidence rate per 1000 person years* (95% CI)
Upper gastrointestinal bleed:			
No anticoagulants	21 143	16 332 684	1.34 (1.32 to 1.36)
Warfarin	492	71 597	5.83 (4.33 to 7.33)
New anticoagulants	6	664	2.69 (0.36 to 5.03)
Intracranial bleed:			
No anticoagulants	8 670	16 332 684	0.55 (0.54 to 0.56)
Warfarin	365	71 597	1.89 (1.46 to 2.32)
New anticoagulants	5	664	1.49 (1.27 to 2.86)

*Age standardised to derivation cohort population.

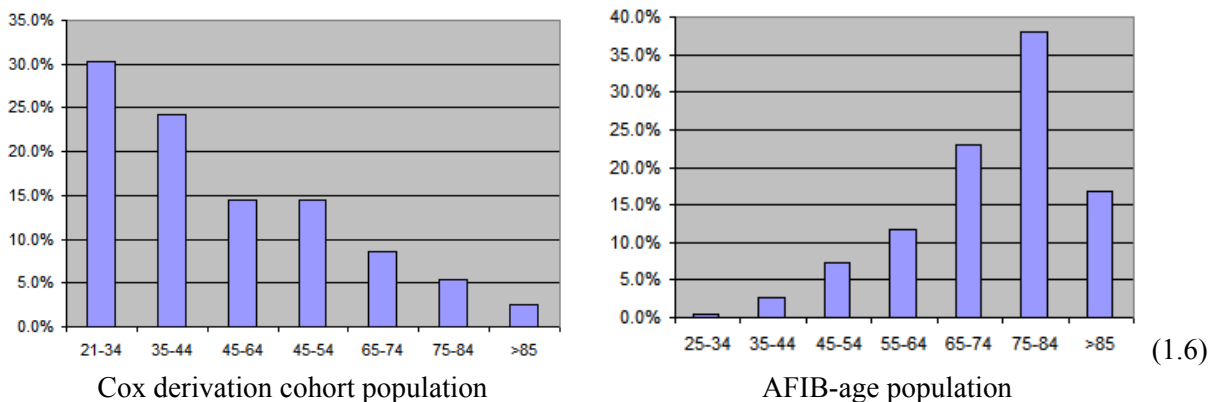
(1.3)

The first numeric column is number of bleeds, the second the number of person-years those bleeds arose from, and the last column is the adjusted rate per 1000 person-years. We can convert the results for the "No anticoagulants" rows to our annual rate notation:

$$\text{Annual Upper GI Bleed rate for Cox Study population} = .134 \text{ \%/yr} \quad (1.4)$$

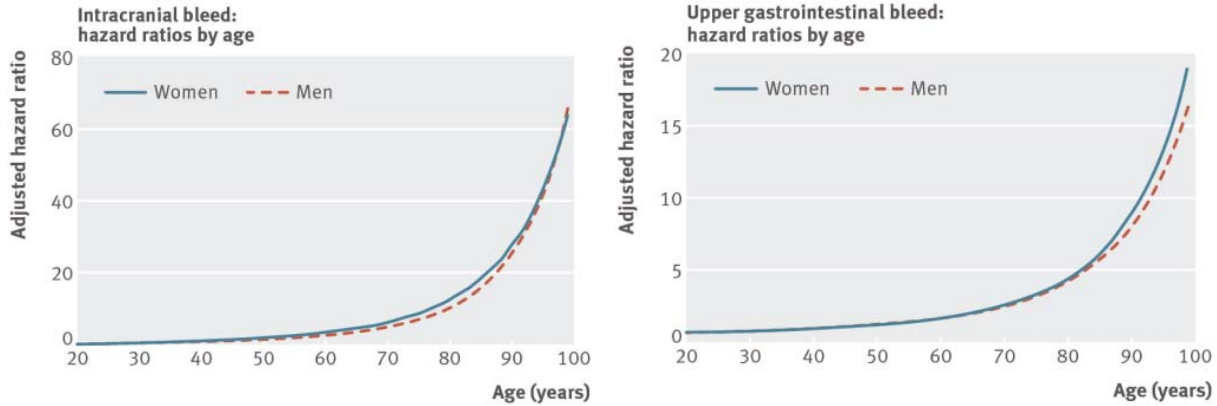
$$\text{Annual Intracranial (IC) Bleed rate for Cox Study population} = .055 \text{ \%/yr} \quad (1.5)$$

At first we are disappointed to find that the IC bleed rate is .055 %/yr, whereas our first opinion above was 0.22% /yr. However, the .055%/yr figure is for the Cox Study population which has the age profile (A.4) shown on the left below, whereas our AFIB-age population has the S(2.2) age profile shown on the right :



(1.6)

The Cox paper also presents the following (relative) risk rate curves for IC bleeds and GI bleeds:



(1.7)

It is possible to compute the average IC and upper GI bleed rates for the two age profiles shown in (1.6) using the data in (1.7). Since the Cox paper supplies *absolute* averages for its derivation cohort profile, we can then deduce the absolute average for our AFIB-age profile using the ratio of the relative averages. This task is carried out in our Appendix A and here are the results:

For non-AFIB patients in the AFIB-age range taking no OAC:

intracranial bleed rate:	Ratio = 3.89	rate = .055 * 3.85 = 0.212 % / yr	
upper GI bleed rate:	Ratio = 2.74	rate = .134 * 2.70 = 0.362 % / yr	(1.8)

So our "second opinion" calculation for IC bleeds 0.21 is fairly close to our first calculation of 0.22. The surprising closeness of these calculations is coincidental due to our ballpark number 67% used above, but in general the two numbers will be close. We shall use the 0.21 %/yr figure shown in (1.8).

Upper GI runs from the mouth to the duodenum, lower GI is from the small intestine on down, but small intestine bleeds are rare, and lower GI is usually interpreted as meaning colon and below. Here is some data on the percentages of bleeds in the various areas:

III. Causes: Sources of acute Gastrointestinal Bleeding

- A. Upper Gastrointestinal Bleeding (70%)
 - 1. Annual Incidence (U.S.): 100-200 per 100,000
- B. Small Intestinal Bleeding (5%)
- C. Lower Gastrointestinal Bleeding (24%)
 - 1. Annual Incidence (U.S.): 20-27 per 100,000

<http://www.fpnotebook.com/GI/Sx/GstrntstnlBldng.htm> (1.9)

These percentages have large error bars, but we shall assume that the ratio of upper GI bleeds to total GI bleeds is 70%. Then based on (1.8), the *total* GI bleed rate from above would be $.36/.70 = 0.51$ %/yr.

We may compute the hemorrhagic stroke rate two different ways. By the first method noted a few paragraphs above, using the 1.15 %/yr stroke rate from S(2.5) and the 13%/87% ratio of hemorrhagic to ischemic strokes from S(1.1), we obtain $1.15 * .13 = 0.15$ %/yr as our non-AFIB but AFIB-age

hemorrhagic stroke rate. By the second method, we use the warfarin result noted above that 67% of intracranial bleeds are hemorrhagic strokes, and this then gives $.67 * 0.21 = .14$ %/yr, where the 0.21 is from (1.8) above. Both methods give about the same result, and we shall use the former value 0.15.

Here then are the main results of this section:

For non-AFIB patients in the AFIB-age range taking no OAC:

intracranial bleed rate:	0.21 %/yr	// from (1.8)	
hemorrhagic stroke rate:	0.15 %/yr	// paragraph just above	
total GI bleed rate:	0.51 %/yr.	// from (1.8) / 0.7 as noted above	
upper GI bleed rate:	0.36 %/yr.	// from (1.8)	(1.10)

At this point we have no numbers for *AFIB* patients taking no OAC. They will appear later.

Comment: As shown in (1.3), the Cox Study has some results for patients who took warfarin or NOAC's (New Oral Anticoagulants) which included dabigatran, rivaroxaban, apixaban and phenindione. Because people take such blood thinners for reasons other than AFIB (valvular heart disease, deep vein thrombosis, etc.), and because we don't really know the age distribution of these OAC patients within the broad Cox-Study age range of 21-99, this data is not particularly useful for our efforts. Even if it were true that all bleeding arises from the OAC regardless of the reason the OAC is taken, the lack of an OAC population profile makes the data not useful. We shall deal with OAC effects on bleeding in the next Section.

2. What is the bleeding risk for AFIB patients taking warfarin or apixaban?

We first seek to learn the warfarin (or other OAC) bleeding risk for the *average* AFIB patient, then in later Sections we ponder the stratification of bleeding risk with respect to factors like age, having had a previous bleed, etc. We again use the 2011 Apixaban Study (ARISTOTLE) with its 18,201 AFIB patients in two nearly equal size cohorts: apixaban and warfarin. Here are the conclusions of that report regarding bleeding, which is the "safety outcome" of that study: (average age 70 in both cohorts)

Table 3. Bleeding Outcomes and Net Clinical Outcomes.*

Outcome	Apixaban Group (N=9088)		Warfarin Group (N=9052)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	%/yr	no.	%/yr		
Primary safety outcome: ISTH major bleeding†	327	2.13	462	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	52	0.33	122	0.80	0.42 (0.30–0.58)	<0.001
Other location	275	1.79	340	2.27	0.79 (0.68–0.93)	0.004
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70–1.15)	0.37
Major or clinically relevant nonmajor bleeding	613	4.07	877	6.01	0.68 (0.61–0.75)	<0.001
GUSTO severe bleeding	80	0.52	172	1.13	0.46 (0.35–0.60)	<0.001
GUSTO moderate or severe bleeding	199	1.29	328	2.18	0.60 (0.50–0.71)	<0.001
TIMI major bleeding	148	0.96	256	1.69	0.57 (0.46–0.70)	<0.001
TIMI major or minor bleeding	239	1.55	370	2.46	0.63 (0.54–0.75)	<0.001
Any bleeding	2356	18.1	3060	25.8	0.71 (0.68–0.75)	<0.001
Net clinical outcomes						
Stroke, systemic embolism, or major bleeding	521	3.17	666	4.11	0.77 (0.69–0.86)	<0.001
Stroke, systemic embolism, major bleeding, or death from any cause	1009	6.13	1168	7.20	0.85 (0.78–0.92)	<0.001

ISTH International Society on Thrombosis and Haemostasis TIMI Thrombolysis in Myocardial Infarction.
 GUSTO Global Use of Strategies to Open Occluded Coronary Arteries (2.1)

One's initial impression might be that the ISTH major bleeding rate (see later) is partitioned into the three categories as presented on the following three rows. Adding up event counts, one sees that this is a wrong impression. The phrase "Other location" here means "location other than intracranial", and the Gastrointestinal events are included in the Other location events. We find it helpful to reorganize this data as follows :

	<u>Apixaban</u>		<u>Warfarin</u>	
GI bleeds	0.76 %/yr •	36%	0.86 %/yr •	28%
non-IC and non-GI bleeds	1.03 %/yr	48%	1.41 %/yr	46%
total "Other Location" bleeds	1.79 %/yr •		2.27 %/yr •	
hemorrhagic stroke	0.24 %/yr *	73% of IC	0.47 %/yr *	59% of IC
other intracranial bleed	0.09 %/yr		0.33 %/yr	
total intracranial bleed (IC)	0.33 %/yr •	15%	0.80 %/yr •	26%
total major bleed (ISTH)	2.13 %/yr •	100%	3.09 %/yr •	100%
Any bleeding	18.1 %/yr •		25.8 %/yr •	(2.2)

Items followed by • are taken directly from the Safety Outcome (2.1) above, while items followed by * come from the Efficacy Outcome S(3.4). Unmarked numbers are then deduced from these numbers. The data may be regrouped again as follows:

Apixaban Arm					Warfarin Arm				
intracranial bleeds	0.33	%/yr	•	15%	intracranial bleeds	0.80	%/yr	•	26%
total gastro bleeds	0.76	%/yr	•	36%	total gastro bleeds	0.86	%/yr	•	28%
other major bleeds	1.04	%/yr		49%	other major bleeds	1.43	%/yr		46%
Total major bleeds	2.13	%/yr	•	100%	Total major bleeds	3.09	%/yr	•	100%

(2.3)

Our term "other major bleeds" means major bleeds that are neither intracranial nor GI. The items marked by • are taken from (2.2) and then the "other major bleeds" rate is obtained by subtraction. These last numbers 1.04 and 1.43 differ slightly from those in (2.2) due to rounding error.

We now review the various kinds of bleeding.

Any Bleeding. Each year a whopping 26% of warfarin patients have *some* kind of bleed (apixaban 18%), though most of these bleeds are presumably minor such as white of the eye, bloody nose, bitten tongue, etc.

Intracranial Bleeding. Here are the numbers from the Apixaban Study (2.2) for this kind of bleed (for the average AFIB patient), and we add a third line from (1.10) for an average AFIB-aged but non-AFIB person not taking anticoagulants :

				Ratios	
risk of intracranial bleed on warfarin	0.80	%/year	1.00	2.42	3.81
risk of intracranial bleed on apixaban	0.33	%/year	0.41	1.00	1.57
(non-AFIB, no OAC) risk of intracranial bleed	0.21	%/year	0.26	0.64	1.00

(2.4)

The conclusion (last column) is that an average warfarin AFIB patient has a 3.8 times higher intracranial bleed risk than a corresponding non-AFIB no-OAC person, and this factor is lowered to 1.6 for apixaban.

Gastrointestinal Bleeding. Again, the numbers from the Apixaban Study are shown on the first two lines, then the third line states our estimate from (1.10),

				Ratios	
risk of gastro bleed on warfarin	0.86	%/year	1.00	1.13	1.69
risk of gastro bleed on apixaban	0.76	%/year	0.88	1.00	1.49
(non-AFIB, no OAC) risk of gastro bleed	0.51	%/year	0.59	0.67	1.00

(2.5)

The conclusion is that an average warfarin AFIB patient has a 1.7 times higher GI bleed risk than a corresponding non-AFIB person, and this factor is lowered to 1.5 for apixaban.

Major Bleeding

The ISTH definition of "major bleed" used in the Apixaban Study is given by Schulman *et al.* (2004),

Definition of major bleeding

As general principles, a definition of major bleeding needs to be based on objective criteria, and major bleeds are those that result in death, are life-threatening, cause chronic sequelae or consume major health-care resources. With this in mind, the Control of Anticoagulation Subcommittee recommends the following criteria for major bleeding in non-surgical patients:

- 1 Fatal bleeding, and/or
- 2 Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
- 3 Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.

(2.6)

Item 2 in this list is quite a grab-bag. For the layman, the terms intra-cranial, intra-spinal, intra-ocular (*inside* the eyes) seem self explanatory. Pericardial refers to bleeding into the pericardium sac that surrounds the heart, possibly causing increased pressure which can reduce heart output (acute cardiac tamponade). Intra-muscular with compartment syndrome refers to bleeding in a muscle structure which increases local pressure enough to impede blood flow to muscles and nerves inside the structure.

The term retroperitoneal is more complicated. Strictly it refers to organs that lie outside (and behind) the abdominal peritoneum membrane like the esophagus, kidneys, adrenal glands, ureters, bladder and parts of the duodenum and colon. The liver, stomach, appendix and small intestines are not retroperitoneal since they lie inside the peritoneum, but certainly a major bleed of the liver would be counted as a "major bleed". Certainly the liver would qualify as a critical area or organ, so this is accounted for in Item 2 by the words "such as". Item 3 would be triggered in a major bleed regardless of location.

Notice that the ISTH definition does not mention hospitalization for the bleed as an and/or item, but one could assume that pretty much any bleed in items 1,2,3 would put a patient in a hospital. In the HEMORR₂HAGES and HAS-BLED strata schemes discussed below, hospitalization is included as the entire criterion or as an and/or criterion.

For the average AFIB-age person who does not have AFIB, we can use two of the numbers from (1.10) to begin construction of a table as shown on the left below,

AFIB-age but no AFIB		
intracranial bleeds	0.21	%/yr
total gastro bleeds	0.51	%/yr
other major bleeds	x	%/yr
Total major bleeds	y	%/yr

AFIB-age but no AFIB		
intracranial bleeds	0.21	%/yr
total gastro bleeds	0.51	%/yr
other major bleeds	.47y	%/yr
Total major bleeds	y	%/yr

where x and y are unknown. On the two sides of (2.3) we see that "x" is 49% or 46% of the total. Picking a number 47% which is a little weighted to the warfarin arm, we might then assume that for our AFIB-age but non-AFIB people the rate of "other major bleeds" is 47% of the total. This then gives the situation shown on the right above. But this says $.21 + .51 + .47y = y$ or $.72 = .53y$ so $y = 72/53 = 1.36$. It follows then that $x = .47y = .47 * 1.36 = 0.64$, and we arrive at this filled-in table,

AFIB-age but no AFIB		
intracranial bleeds	0.21	%/yr
total gastro bleeds	0.51	%/yr
other major bleeds	0.64	%/yr
Total major bleeds	1.36	%/yr

(2.7)

In this slightly indirect manner, we arrive at a major bleed rate of 1.36 %/yr for our non-AFIB group, and we can then construct a table similar to (2.4) and (2.5) above for "major bleeding". The first two rates come from (2.3) and the third from (2.7),

			Ratios		
risk of major bleed on warfarin	3.09	%/year	1.00	1.45	2.27
risk of major bleed on apixaban	2.13	%/year	0.69	1.00	1.57
(non-AFIB, no OAC) risk of major bleed	1.36	%/year	0.44	0.64	1.00

(2.8)

The conclusion is that an average warfarin AFIB patient has a 2.3 times higher major bleed risk than a corresponding non-AFIB person, and this factor is lowered to 1.6 for apixaban.

3. Stratification of bleeding risk: HEMORR₂HAGES

A 2006 bleeding strata scheme (Gage *et al.*) is called HEMORR₂HAGES with this scoring system :

H	Hepatic	1	liver problems	
E	Ethanol	1	in hospital drunk, delirium, hallucinations	
M	Malignancy	1	cancer	
O	Older	1	≥ 75	
R	Reduced platelet count	1		
R ₂	Rebleeding	2	hospitalized due to a previous bleed	
H	Hypertension	1	hypertension when uncontrolled (no #)	
A	Anemia	1		
G	Genetic factors	1	CPY 2CY polymorphism	
E	Excessive fall risk	1		
S	Stroke	1	had a prior stroke	(3.1)

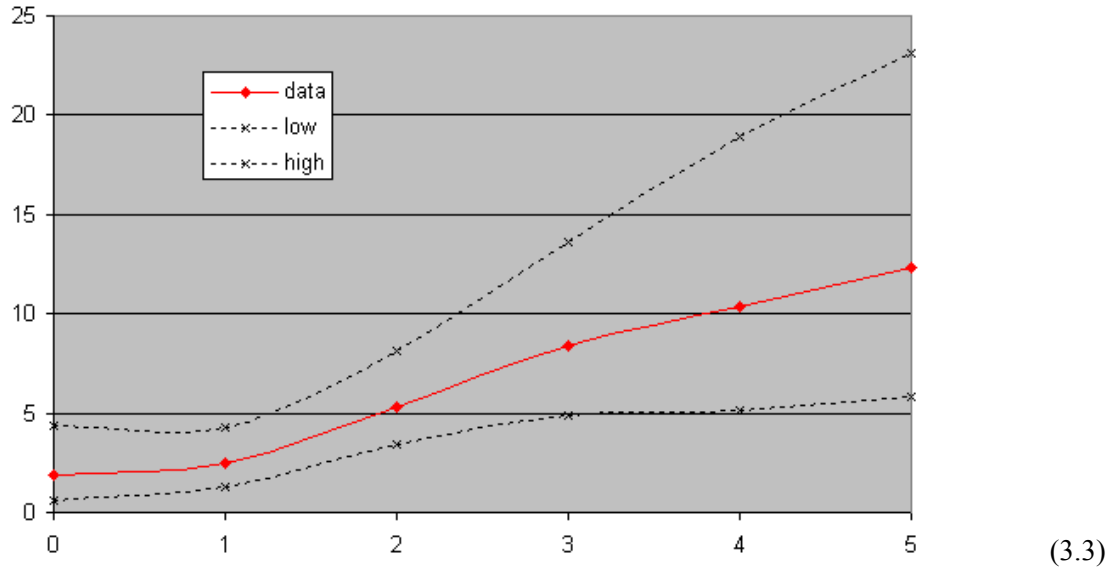
Gage was also the lead author of the CHADS₂ effort described in our stroke document, and as with that study the patient set was taken from the NRAF group (National Registry of Atrial Fibrillation). The CHADS₂ NRAF set consisted of 1733 patients (mean age 81) not taking warfarin, whereas the HEMORR₂HAGES NRAF set consists of 1604 patients (mean age 79) *all* taking warfarin (113 also took aspirin, a fact we ignore). The study outcome was a hospitalized major bleed (67% GI, 15% intracranial, 18% other) with an ICD-9-CM code indicating hemorrhage. The bleed risk rates stratified by score are shown in the "Bleeds per 100" column of this table (presumably a "point-year" is a patient-year for patients within a scoring point bin),

Table II. Risk of major bleeding in NRAF participants prescribed warfarin, stratified by HEMORR₂HAGES score

HEMORR ₂ HAGES score*	n	No. of bleeds	Bleeds per 100 point-years warfarin (95% CI)
0	209	4	1.9 (0.6-4.4)
1	508	11	2.5 (1.3-4.3)
2	454	20	5.3 (3.4-8.1)
3	240	15	8.4 (4.9-13.6)
4	106	9	10.4 (5.1-18.9)
≥5	87	8	12.3 (5.8-23.1)
Any score	1604	67	4.9 (3.9-6.3)

(3.2)

The maximum possible score is 12, but in the study the number of people with scores larger than 5 was small, so the scores 5 through 12 are put into a single bin ≥ 5. The following graph shows the rates in the last column of (3.2) along with the 95% CI error band,



We now follow the general method presented in the CHADS₂ discussion of our stroke risk document. Using the same method which led to S(4.7), we compute the average score and major bleed rate as follows:

HEMORR2HAGES Average Score and Average Rate					
s	r	n	f	s*f	r*f
0	1.9	209	13.0%	0.00	0.25
1	2.5	508	31.7%	0.32	0.79
2	5.3	454	28.3%	0.57	1.50
3	8.4	240	15.0%	0.45	1.26
4	10.4	106	6.6%	0.26	0.69
6	12.3	87	5.4%	0.33	0.67
		1604	100.0%	1.92	5.15
				<score>	<rate>

(3.4)

Notice that we have replaced score bin ≥ 5 by a bin with score 6. The number in this box does not affect the average rate 5.15, but does affect that average score, and using 6 probably gives a better estimate of the average score than 5 (since some of the 87 patients with score ≥ 5 likely had scores > 5). Using the average rate 5.15 from (3.4), we obtain this table in analogy with table S(4.9).

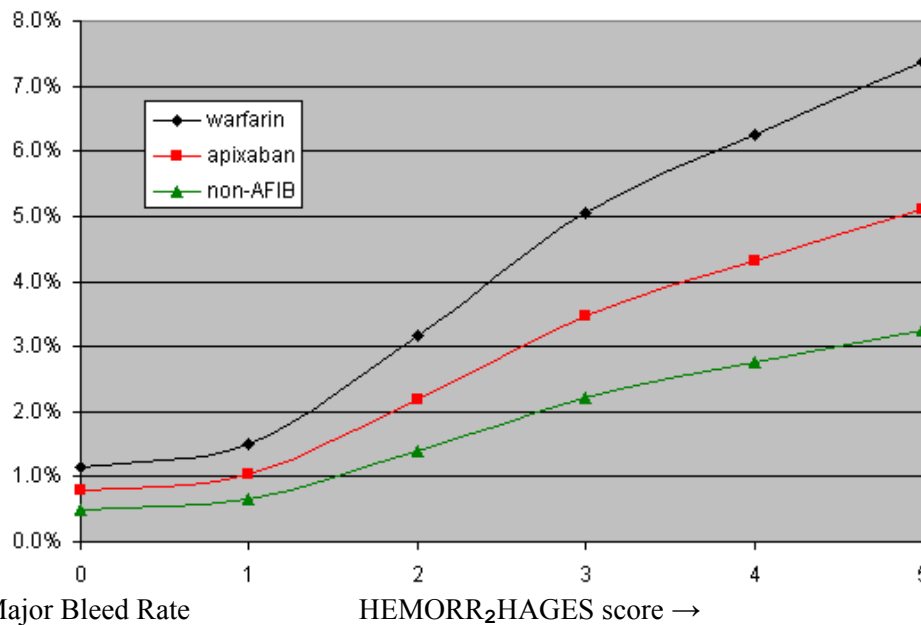
Major Bleed Risk (annual rate)						
			(average score = 1.92)			
sf	r	sf*r	HEMORR2HAGES	warfarin	apixaban	non-AFIB
0.6	1.9	1.14	0	1.14%	0.79%	0.50%
0.6	2.5	1.50	1	1.50%	1.04%	0.66%
0.6	5.3	3.18	2	3.18%	2.19%	1.40%
0.6	8.4	5.04	3	5.04%	3.48%	2.22%
0.6	10.4	6.24	4	6.24%	4.31%	2.75%
0.6	12.3	7.38	5	7.38%	5.09%	3.25%
0.6	5.15	3.09	average rates:	3.09%	2.13%	1.36%

(3.5)

The ratios 1.00, 0.69 and 0.44 across the top come from the first ratio column of (2.8). The scale factor is set to 0.6 in order to calibrate the table so the average rates match those shown in (2.8). A plausible explanation for this scale factor is that the NRAF trial patients had an average age of 80, whereas the Apixaban Study average age was 70 (see rate curves versus age in (1.7)).

The non-AFIB column is the model's risk rate for non-AFIB people in the AFIB-age population (who are not taking anticoagulants). This should not be confused with data for AFIB patients who are taking nothing as an anticoagulant. Presumably the major bleeding risk for this AFIB group would be slightly larger than that of the non-AFIB group due to hemorrhagic transformations as discussed in Section 1 of our stroke document.

Here is a plot of the columns of (3.5), where the values at score 5 really mean for score ≥ 5 :



(3.6)

The plots show how anticoagulants increase the major bleed risk over the age-matched non-AFIB background.

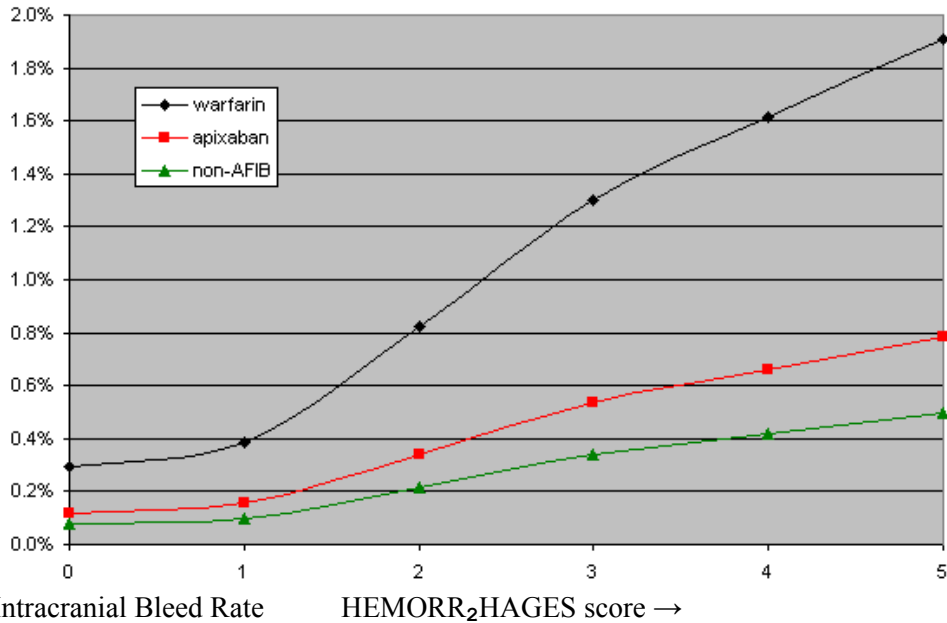
In an attempt to model the *intracranial* bleed rates, we replace the .6 scale factor in (3.5) by .155 and across the top we use the ratios from the first ratio column of (2.4) to relate the different anticoagulants :

			Intracranial Bleed Risk (annual rate)			
			(average score = 1.92)	1.00	0.41	0.26
sf	r	sf*r	HEMORR2HAGES	warfarin	apixaban	non-AFIB
0.155	1.9	0.29	0	0.29%	0.12%	0.08%
0.155	2.5	0.39	1	0.39%	0.16%	0.10%
0.155	5.3	0.82	2	0.82%	0.34%	0.21%
0.155	8.4	1.30	3	1.30%	0.53%	0.34%
0.155	10.4	1.61	4	1.61%	0.66%	0.42%
0.155	12.3	1.91	≥ 5	1.91%	0.78%	0.50%
0.155	5.15	0.80	average rates:	0.80%	0.33%	0.21%

(3.7)

The scale factor causes the average rates in the last row to match those shown in (2.4).

Here is a plot of the columns of (3.7) showing IC bleed rate for various OAC choices, and again the rates for score 5 are really for score ≥ 5 :



(3.8)

The plots show how anticoagulants increase the intracranial bleed risk over the age-matched non-AFIB background. The negative aspect of warfarin is more dramatic here than in (3.6) for major bleeds.

Example: An AFIB patient on warfarin has a HEMORR₂HAGES score of 1 .
 Major bleed rate is 1.5 %/yr, from table (3.5) or graph (3.6).
 Intracranial bleed rate is 0.4 %/yr, from table (3.7) or graph (3.8) .

(3.9)

4. Stratification of bleeding risk: HAS-BLED

The strata method of the previous section had "too many letters" (and nobody can spell hemorrhage anyway) so Pisters *et al.* (2010) came up with a simpler scheme called HAS-BLED. Here is its scoring system -- each item is one point (max score = 9 since there are two 2-point items) :

H	Hypertension	> 160 systolic if uncontrolled
A	Abnormal renal or liver (1 pt each)	dialysis etc; cirrhosis etc.
S	Stroke	ischemic stroke or TIA
B	Bleeding	previous major bleed (needing > 2U transfusion, etc)
L	Labile INR	in the 2-3 INR range less than 60% of the time
E	Elderly	≥ 75
D	Drugs or alcohol (1 pt each)	alc > 8 U/wk (> 4.4 US standard drinks per week)

(4.1)

The score is used to determine the annual risk rate for a major bleed. Pisters defined a major bleed in a somewhat complicated way as a bleed which (required hospitalization) and/or (caused a hemoglobin decrease of .2 g/L) and/or (required a blood transfusion in the case the event was not a hemorrhagic stroke). The hospital clause alone would seem to capture all IC bleeds and other serious bleeds.

In a 2011 paper Lip *et al.* apply this strata scheme to an AFIB database of 7,329 patients (mean age 71) from certain SPORTIF III and V trials. Of interest to us is the separate HAS-BLED application to the subset of the above database who were taking warfarin, a total of 3,665 patients. The results for this subset are shown in the last two columns below,

Table 4 Major Bleeding Rates by HAS-BLED Score in the Overall SPORTIF Cohort (n = 7,329) and Those Taking Warfarin Only (n = 3,665)				
HAS-BLED Score	Patients With Particular Score in the Whole Cohort*	Major Bleeding Events†	Patients With Particular Score Among Those Taking Warfarin Only*	Major Bleeding Events†
0	1,757 (24.0)	21 (1.2)	746 (20.4)	7 (0.9)
1	2,717 (37.1)	75 (2.8)	1,283 (35.0)	44 (3.4)
2	1,752 (23.9)	63 (3.6)	950 (25.9)	39 (4.1)
3	834 (11.4)	50 (6.0)	483 (13.2)	28 (5.8)
4	241 (3.3)	23 (9.5)	180 (4.9)	16 (8.9)
5	27 (0.4)	2 (7.4)	22 (0.6)	2 (9.1)
6	1 (0.0)	0	1 (0.0)	0
c-statistic = 0.654; p value for trend <0.0001		c-statistic = 0.659; p value for trend <0.0001		

Values are n (%). *Percentage of column total. †Percentage of row total.

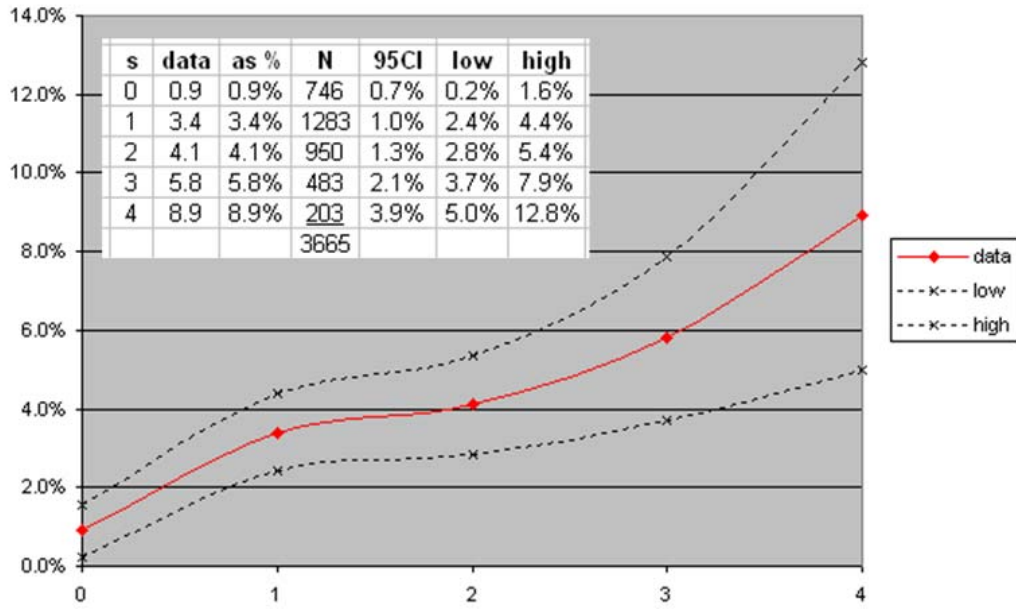
HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; SPORTIF = Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation.

(4.2)

The rates shown in parentheses in the right column are obtained simply as ratios such as $44/1283 = 3.4\%$. Since it is not claimed that the trials were exactly 1 year long, we regard these only as relative rates.

Due to the low patient counts in the last two bins, we shall move these 23 patients and their 2 bleeds into the score 4 bin, giving a bleed rate of $18/203 = 8.9\%$ for the adjusted score 4 bin.

The following graph shows the rates in the last column of (4.2) along with a 95% CI error band,



(4.3)

Since confidence intervals are not stated in (4.2), we have generated our own error band. Modeling the bleed/no-bleed study as a Bernoulli trial (like a weighted coin toss head/tail), the standard error of the mean is given by the expression $\sigma_{\text{mean}} = \sigma/\sqrt{N}$, where $\sigma = \sqrt{p(1-p)}$ is the standard deviation for a single patient. Here p is the probability of having a bleed which we identify with the rates given in the right column of (4.2). The 95% confidence interval is then $\text{rate} \pm 1.96\sigma_{\text{mean}}$. These error bars are approximate, just to give the reader a feel for the accuracy of the rate data represented by the red curve above.

The "hump" in the red curve at score 1 seems unusual since the curve cups down at that point, which is different from our other three curves S(4.4), S(5.3) and (3.3), but we presume the data is correct.

Using the same method which led to S(4.7), we compute the average score and average major bleed rate as follows:

HAS-BLED Average Score and Average Rate					
s	r	n	f	s*f	r*f
0	0.9	746	20.4%	0.00	0.18
1	3.4	1283	35.0%	0.35	1.19
2	4.1	950	25.9%	0.52	1.06
3	5.8	483	13.2%	0.40	0.76
4	8.9	203	5.5%	0.22	0.49
		3665	100.0%	1.49	3.69
				<score>	<rate>

(4.4)

As a second adjustment, we scale down the Lip study relative rates by factor .837 to cause the average rates to be calibrated with rates from the Apixaban Study. Using the average rate 3.69 from (4.4), we then obtain this risk table in analogy with table S(4.9).

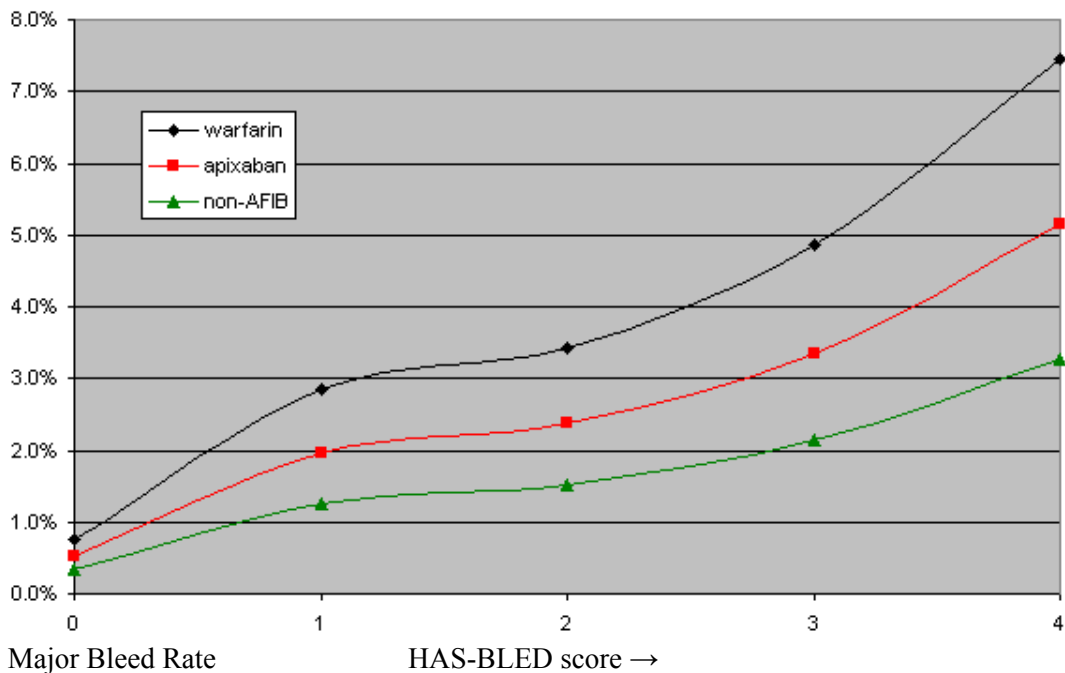
			Major Bleed Risk (annual rate)			
			(ave score = 1.49)	1.00	0.69	0.44
sf	r	sf*r	HAS-BLED	warfarin	apixaban	non-AFIB
0.837	0.9	0.75	0	0.75%	0.52%	0.33%
0.837	3.4	2.85	1	2.85%	1.96%	1.25%
0.837	4.1	3.43	2	3.43%	2.37%	1.51%
0.837	5.8	4.85	3	4.85%	3.35%	2.14%
0.837	8.9	7.45	4	7.45%	5.14%	3.28%
0.837	3.69	3.09	average rates:	3.09%	2.13%	1.36%

(4.5)

Calibration checks:

- For the average rates row, the three rates match those shown in the first column of (2.8) which are derived from the Apixaban Study (due to our scale factor)
- For lowest score = 0, the three HAS-BLED rates (0.75, 0.52, 0.33) are close to but somewhat smaller than the HEMORR₂HAGES values (1.14, 0.79, 0.50) for its lowest score = 0 as shown in (3.5). The bleed count for this bin is quite small in both strata applications (4 and 7), so statistics are poor, error bars large.

Here is a plot of the columns of the above table:



(4.6)

In an attempt to model the *intracranial* bleed rates, we replace the above .837 scale factor by 0.217 and use the first ratio column of (2.4) to relate the different anticoagulants :

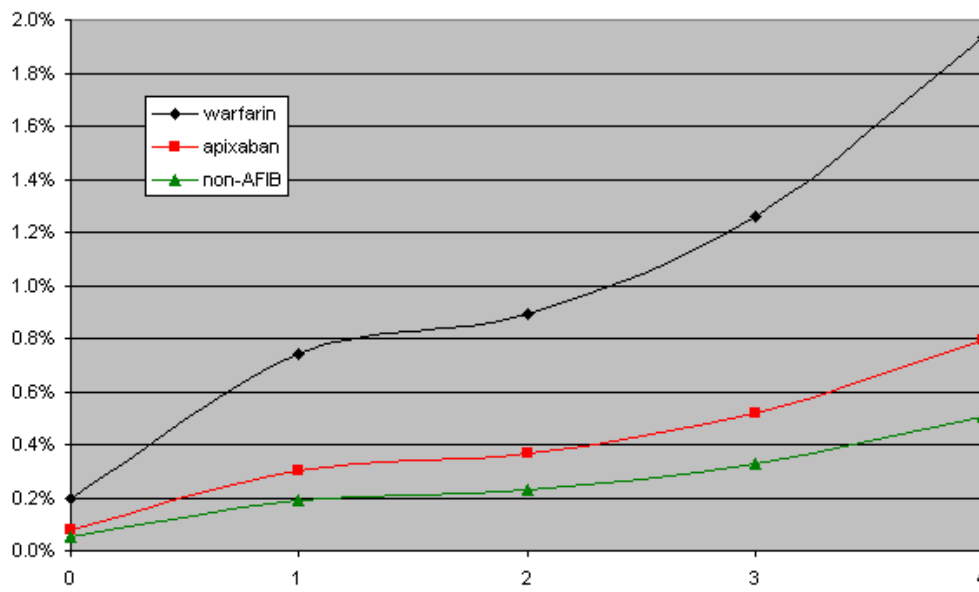
			Intracranial Bleed Risk (annual rate)			
			(ave score = 1.49)	1.00	0.41	0.26
sf	r	sf*r	HAS-BLED	warfarin	apixaban	non-AFIB
0.217	0.9	0.20	0	0.20%	0.08%	0.05%
0.217	3.4	0.74	1	0.74%	0.30%	0.19%
0.217	4.1	0.89	2	0.89%	0.36%	0.23%
0.217	5.8	1.26	3	1.26%	0.52%	0.33%
0.217	8.9	1.93	4	1.93%	0.79%	0.50%
0.217	3.69	0.80	average rates:	0.80%	0.33%	0.21%

(4.7)

Calibration checks:

- For the average rates row, the three rates match those shown in (2.4) which are derived from the Apixaban Study (due to our scale factor).
- For lowest score = 0, the three HAS-BLED rates (0.20, 0.08, 0.05) are close to but somewhat smaller than the HEMORR₂HAGES values (0.29, 0.12, 0.08) for its lowest score = 0 as shown in (3.7). As noted above, this could be a result of low statistics.

Here is a plot of the columns of the above table for HAS-BLED score 0 through 4 :



Annual Intracranial Bleed Rate

HAS-BLED score →

(4.8)

Example: An AFIB patient on warfarin has a HAS-BLED score of 1.

Major bleed rate is 2.8 %/yr from table (4.5) or graph (4.6).

Intracranial bleed rate is 0.74 %/yr from table (4.7) or graph (4.8).

(4.9)

5. Stratification of bleeding risk: QBleed

QBleed is an algorithm for computing a particular individual's intracranial and GI bleed rates. The algorithm is developed in the paper of Hippisley-Cox and Coupland (2014) mentioned above in Section 1. Rather than produce a mnemonic with lots of capital letters, they provide an open source algorithm for computing bleed rates based on 21 "predictors". The algorithm is intended for all people, not just AFIB patients, and AFIB is just one of the predictors. Results are given with and without anticoagulation, so anticoagulation does not appear in the list of predictors. Some predictors are discrete (sex) while others have a continuum of values (body mass index).

What factors are needed to calculate a QBleed[®] score?

QBleed uses the following factors in addition to anticoagulants:

- Age
- Sex
- Ethnicity
- Deprivation
- Smoking
- Alcohol
- Atrial fibrillation
- Heart failure
- Treated hypertension
- Venous thromboembolism
- Current or prior cancer
- Chronic liver disease/pancreatitis
- Previous bleed (GI, intracranial, haematuria, haemoptysis)
- Body mass index
- Current antiplatelet use
- Current regular steroid use
- Current NSAID use
- Current anticonvulsant (phenytoin or carbamazepine)
- Current antidepressant use
- Oesophageal varices
- Abnormal platelet count

(5.1)

The patient interested in personal risk rates enters data into a simple form at <http://qbleed.org> and is given a simple result. Here is an Example: (one US "standard drink" equals 1.8 UK "units" of alcohol)

About you

Age (21-99):

Sex: Male Female

Ethnicity:

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status:

Alcohol status:

Do you have...

atrial fibrillation?

heart failure?

high blood pressure needing medication?

a current or previous diagnosis of cancer?

chronic liver disease or chronic pancreatitis?

oesophageal varices?

a platelet count less than 150 or greater than 480?
(both units $\times 10^9$ /litre)

Have you had

previous bleed (gastrointestinal, intracranial, haematuria, haemoptysis)?

venous thromboembolism?

Are you currently taking

antiplatelet drugs (e.g. aspirin, clopidogrel or dipyridole)?

non-steroidal anti-inflammatory pain killers (NSAIDs)?

regular steroid tablets?

antidepressants?

anticonvulsants (phenytoin or carbamazepine)?

Leave blank if unknown

Body mass index

Height (cm):

Weight (kg):

Calculate risk over years.

(5.2)

For this particular patient, here are the resulting annual bleed risk rates from Qbleed:

	Before anticoagulant	On anticoagulant
Upper gastrointestinal bleed	0.2%	0.5%
Haemorrhagic stroke	0.1%	0.4%

Example (5.3)

And here are the corresponding *average* AFIB-age patient annual rates from our earlier models,

	(non-AFIB, no OAC)	warfarin
upper GI bleed	.36% (1.10)	.60% // = 0.7*.86 from (1.9) and (2.2)
hemorrhagic stroke	.15% (1.10)	.47% (2.2)

(5.4)

As expected, our healthier-than-average Qbleed patient of (5.3) has lower rates on all four numbers compared to the average patient of (5.4).

Effects of alcohol and AFIB on bleeding risk

The Hippisley-Cox and Coupland paper discusses the influence of various factors on the two kinds of bleeding risk it considers. Here is an interesting item concerning alcohol's influence on bleeding risk (applied to the overall cohort of whom only a small fraction were taking anticoagulation):

Table 3| Adjusted hazard ratios (95% confidence intervals) in derivation cohort for upper gastrointestinal haemorrhagic events recorded on mortality or hospital records

Characteristics	Adjusted hazard ratio*(95% CI)	
	Women	Men
Alcohol intake (units/day):		
None	1	1
Trivial (<1)	0.87 (0.83 to 0.92)	0.82 (0.78 to 0.86)
Light (1-2)	0.79 (0.74 to 0.85)	0.82 (0.77 to 0.87)
Moderate (3-6)	0.99 (0.92 to 1.07)	0.89 (0.85 to 0.95)
Heavy (7-9)	1.85 (1.47 to 2.32)	1.35 (1.21 to 1.50)
Very heavy (>9)	2.85 (2.27 to 3.59)	1.79 (1.57 to 2.04)
Atrial fibrillation	1.24 (1.11 to 1.39)	1.21 (1.07 to 1.36)
Venous thromboembolism	1.16 (1.04 to 1.30)	1.12 (0.98 to 1.28)

(5.5)

Table 4| Adjusted hazard ratios (95% confidence interval) in the derivation cohort for intracranial haemorrhagic events recorded on mortality or hospital records

Characteristics	Adjusted hazard ratio*(95% CI)	
	Women	Men
Alcohol intake (units/day):		
None	1	1
Trivial (<1)	0.96 (0.89 to 1.03)	0.84 (0.77 to 0.92)
Light (1-2)	1.03 (0.92 to 1.16)	0.85 (0.77 to 0.93)
Moderate (3-6)	1.05 (0.93 to 1.18)	0.97 (0.88 to 1.06)
Heavy (7-9)	2.13 (1.49 to 3.03)	1.58 (1.34 to 1.86)
Very heavy (>9)	2.62 (1.73 to 3.97)	1.48 (1.14 to 1.92)
Atrial fibrillation	1.17 (1.01 to 1.35)	1.36 (1.18 to 1.57)
Treated hypertension	1.06 (1.00 to 1.14)	1.18 (1.09 to 1.26)

(5.6)

For men, bleed risks *drop* slightly for daily alcohol consumption below 6 U/day (3.3 std drinks/day), but then go up steeply for heavier use as shown. Women have a similar pattern, but being less massive the penalty for the same alcohol abuse amount is higher.

The above clips also show the effect of having AFIB and having "treated hypertension". The penalty for AFIB is a factor 1.36 for men and 1.17 for women, but these could be meaningless since it is likely that AFIB people in the study were taking warfarin which then is the cause of the elevated risk, not the AFIB *per se*. The ultimate answer is provided by the Qbleed algorithm which has a checkbox for AFIB.

6. Integration of Stroke Risk and Bleed Risk Data

We now present combined data gleaned from both our documents concerning AFIB stroke and bleeding risks. For our **average** AFIB patient, the risk rates are as follows: (notes follow)

Risks for Average AFIB Patient taking no OAC :

total stroke S(5.8)	4.50 %/yr		45% over 10 years
ischemic stroke	3.92 %/yr	87% S(1.1)	
hemorrhagic stroke	0.59 %/yr	13% S(1.1)	
intracranial bleed [0.59/.67]	0.88 %/yr		9% over 10 years
major bleed [1.36+(0.88-0.21)]	2.03 %/yr		

Risks for Average AFIB Patient taking warfarin :

total stroke S(5.8)	1.62 %/yr		16% over 10 years
ischemic stroke	1.12 %/yr	69% S(3.4)	
hemorrhagic stroke	0.50 %/yr	31% S(3.4)	
intracranial bleed (4.7)	0.80 %/yr		8% over 10 years
major bleed (4.5)	3.09 %/yr		

Risks for Average AFIB Patient taking apixaban :

total stroke S(5.8)	1.30 %/yr		13% over 10 years
ischemic stroke	1.04 %/yr	80% S(3.4)	
hemorrhagic stroke	0.26 %/yr	20% S(3.4)	
intracranial bleed (4.7)	0.33 %/yr		3% over 10 years
major bleed (4.5)	2.13 %/yr		

Risks for the Average age-matched non-AFIB person (no OAC) :

total stroke S(5.8)	1.15 %/yr		11% over 10 years
ischemic stroke	1.00 %/yr	87% S(1.1)	
hemorrhagic stroke	0.15 %/yr	13% S(1.1)	
intracranial bleed (4.7)	0.21 %/yr		2% over 10 years
major bleed (4.5)	1.36 %/yr		(6.1)

Notes:

1. Although risk rates are displayed with 2 or 3 significant digits, their accuracy is in fact less than 1 digit. The fractional error in the above rates for our average AFIB patient is roughly $\pm 10\%$ with a 95% CI. The rates given below in (6.3) for the stratified patient "Joe" have a fractional error on the order of $\pm 30\%$ with 95% CI and perhaps $\pm 15\%$ with 68% CI. This subject is discussed in Section 7 of our stroke document.
2. The "total stroke" risk includes ischemic strokes, hemorrhagic strokes and systemic embolisms. The last item is only about 6% of the total and we think of it as part of the ischemic stroke rate.
3. Hemorrhagic stroke is included in both the total stroke and major bleed numbers, so it is not correct to add the total stroke and major bleed rates together.
4. The separate ischemic and hemorrhagic stroke rates are determined from the percentages shown of the total stroke rate number.
5. For AFIB patients taking no OAC, we estimate the intracranial bleed rate as the hemorrhagic stroke rate divided by 67% as suggested below (1.2). The major bleed rate is then estimated as the major bleed rate for the non-AFIB person plus the increase in intracranial bleed rate due to the AFIB.

A surprising result is that warfarin slightly *lowers* (or does not much alter) the intracranial bleed rate and the hemorrhagic stroke rate, whereas intuition is that warfarin should raise these rates. A possible explanation is that this results from the OAC's dramatic lowering of *total* stroke rate, mostly caused by AFIB emboli. This means a corresponding reduction in the transformed ischemic stroke rate including transformations which are detected and those which are not (see Sec 1 of our stroke document). The effect is even more dramatic for an AFIB patient going from no-OAC to apixaban.

Main Conclusions for the Average AFIB patient (but see Note 1 above)

If an average AFIB patient taking no OAC starts taking **warfarin** :

- Total stroke rate drops from 4.5 to 1.6 %/yr, a 64% reduction.
- The major bleed rate increases from 2.0 to 3.1 %/yr, a 52% increase.
- The intracranial bleed rate drops from 0.9% to 0.8%, a 9% reduction.

If an average AFIB patient taking no OAC starts taking **apixaban** :

- Total stroke risk drops from 4.5 to 1.3 %/yr, which is a 71% reduction.
- The major bleed risk increases from 2.0 to 2.1 %/yr, an 5% increase.
- The intracranial bleed rate drops from 0.9% to 0.3%, a 63% reduction.

(6.2)

Here are the corresponding rates for our Example AFIB patient "Joe". From Note 1 above, the fractional error in these rates is on the order of $\pm 30\%$ with 95% CI and $\pm 15\%$ with 68% CI so the triple-digit notation grossly overstates the real precision.

Joe : stroke score bleeding score
 CHA₂DS₂-VASc = 2 HAS-BLED = 1

Risks for Joe taking no OAC :

total stroke S(5.8)	2.13 %/yr		21% over 10 years
ischemic stroke	1.85 %/yr	87% S(1.1)	
hemorrhagic stroke	0.28 %/yr	13% S(1.1)	
intracranial bleed [0.28/.67]	0.42 %/yr		4% over 10 years
major bleed [1.25+ (0.42-0.19)]	1.48 %/yr		

Risks for Joe taking warfarin :

total stroke S(5.8)	0.77 %/yr		8% over 10 years
ischemic stroke	0.53 %/yr	69% S(3.4)	
hemorrhagic stroke	0.24 %/yr	31% S(3.4)	
intracranial bleed (4.7)	0.74 %/yr		7% over 10 years
major bleed (4.5)	2.85 %/yr		

Risks for Joe taking apixaban :

total stroke S(5.8)	0.61 %/yr		6% over 10 years
ischemic stroke	0.49 %/yr	80% S(3.4)	
hemorrhagic stroke	0.12 %/yr	20% S(3.4)	
intracranial bleed (4.7)	0.30 %/yr		3% over 10 years
major bleed (4.5)	1.96 %/yr		

Risks for an age and health matched non-AFIB version of Joe (no OAC) :

total stroke S(5.8)	0.54 %/yr		5% over 10 years
ischemic stroke	0.47 %/yr	87% S(1.1)	
hemorrhagic stroke	0.07 %/yr	13% S(1.1)	
intracranial bleed (4.7)	0.19 %/yr		2% over 10 years
major bleed (4.5)	1.25 %/yr		(6.3)

Main Conclusions for Joe (but see note above)

If Joe taking no OAC starts taking **warfarin** :

- Total stroke rate drops from 2.1 to 0.8 %/yr, a 64% reduction.
- The major bleed rate increases from 1.5 to 2.9 %/yr, a 95% increase.
- The intracranial bleed rate *increases* from 0.4% to 0.7%, a 76% increase.

If Joe taking no OAC starts taking **apixaban** :

- Total stroke risk drops from 2.1 to .61 %/yr, which is a 71% reduction.
 - The major bleed risk increases from 1.5 to 2.0 %/yr, a 34% increase.
 - The intracranial bleed rate *drops* from 0.4% to 0.3%, a 29% decrease.
- (6.4)

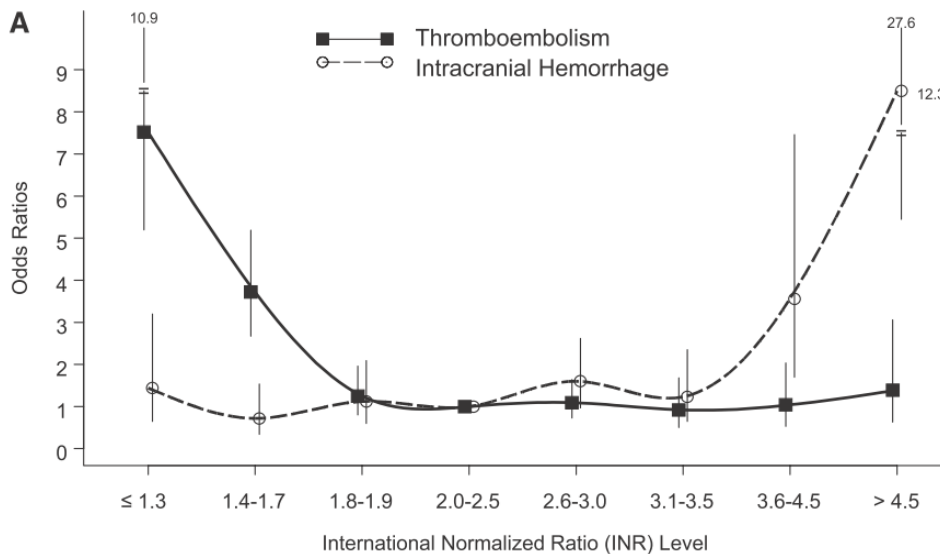
7. Warfarin and INR: Scylla and Charybdis

As noted earlier, the purpose of an anti-coagulant like warfarin is to prevent a blood clot from forming in the AFIBing heart which can break free and become an embolism in the brain, causing a stroke.

Warfarin-taking AFIB patients must keep their blood "thinness" within a certain band as described below. A lab test is done periodically (perhaps monthly) which measures the ratio of the blood coagulation time of the warfarin patient (PT = prothrombin time) to that of a standard non-warfarin person (PT₀). This ratio is called the PTR (prothrombin ratio) = PT/PT₀. In order to adjust for the fact that different reagents were used in this lab test in different countries, this measure was replaced in the 1980's by the INR (international normalized ratio) = (PTR)^α where exponent α adjusts for those reagents and generally lies in the range 1 to 2. Monitored warfarin patients are usually told their INR (perhaps 2.4) and their PT ("pro time", perhaps 26.2 seconds).

Warfarin is a "vitamin K antagonist" and increases coagulation time by reducing the natural coagulating effect of vitamin K in the blood. Many green vegetables such as spinach, kale and broccoli have large amounts of vitamin K and tend to lower INR. Alcohol often has the opposite effect, raising INR. The warfarin patient must either decline all such affecting foods in the diet, or must maintain a near-constant daily intake. This issue led to the development of the NOAC drugs which do not require periodic INR monitoring since they work at a different point in the body's coagulation pathway.

The following graph taken from Singer *et al.* (2009, Fig 1A) demonstrates the reason that INR must be carefully controlled. These authors did a retrospective study based on hospital IDC-9 codes with a group of 9,217 warfarin AFIB patients from a larger cohort known as ATRIA taken from the Northern California Kaiser Permanente system. There were 364 ischemic strokes and 164 intracranial bleeds in this group. The average age for patients with events was about 77 years. For each event, the INR value of the patient was observed at hospital entry, the data was binned, and the result is the plot below (we simplify this carefully done case-control study) :



(7.1)

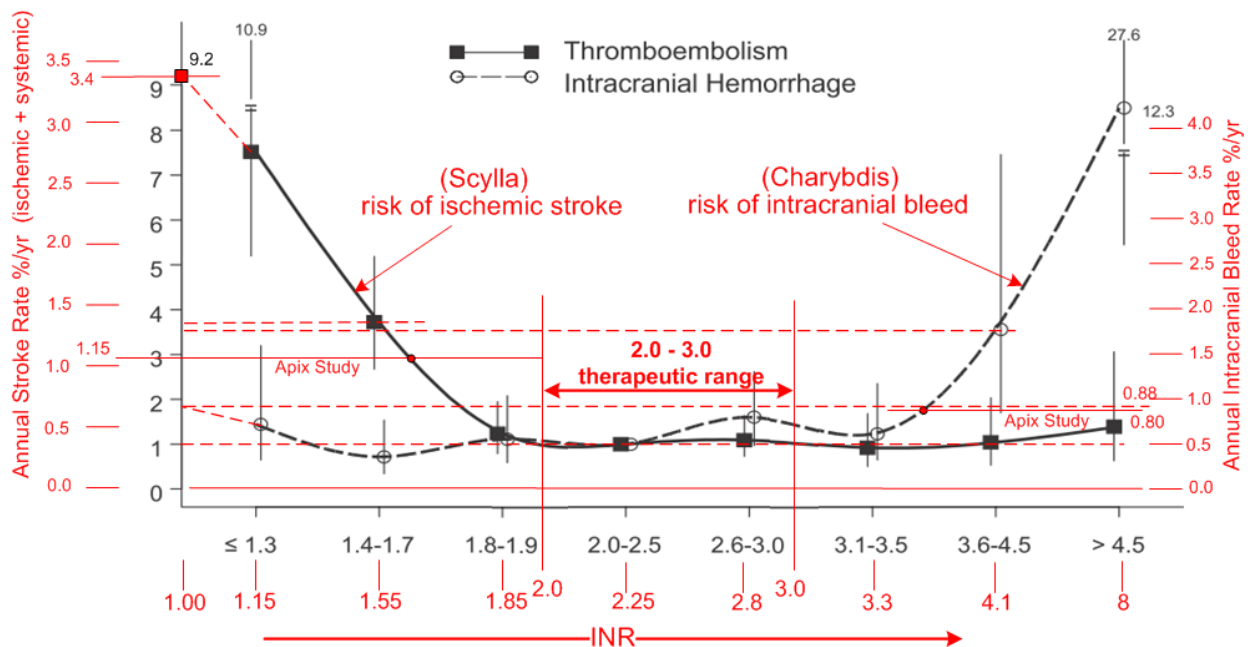
The graphic contains two separate curves, and each one is normalized to its value at the INR marking 2.0-2.5. The graphs thus show the *relative* stroke and IC bleed rates presented as an odds ratio compared to the normalization point which has odds ratio 1.

The main point is this: If INR goes too low, ischemic stroke risk increases rapidly (solid curve on the left side). If INR goes too high, intracranial bleed risk increases rapidly (dashed curve on the right). For example, if INR drops to the 1.4-1.7 range, ischemic stroke rate increases by a factor of 4 relative to its value at the normalization point. And if INR rises to the 3.6-4.5 range, the IC bleed rate rises by a factor of 4 relative to its value at the normalization point. The warfarin AFIB patient is thus found navigating between a rock and a hard place, Scylla and Charybdis.

We are going to add some annotations to the above graphic, but first one should be aware of a few facts about the above curves :

- Thromboembolism (TE) includes both ischemic stroke and systemic embolism.
- The bins along the INR axis have different widths. The interior bins range from 0.2 INR units wide to 0.9 INR units wide. Although a non-AFIB person taking no OAC has an INR in the range 0.8 to 1.2, we shall take that value to be 1.0, so the left bin has a width of 0.3 INR units. We don't know the highest INR which occurred in the study, but if it was 8, then the rightmost bin is 3.5 INR units wide. Therefore, the curves shown above are distorted from how they would appear with a linear INR axis.
- The thin vertical line segments show 95% confidence interval error bars. The left and right extremal bars are particularly large and couldn't even fit into the graphic.

Having computed absolute stroke and bleed rates calibrated to the warfarin arm of the Apixaban Study, we can convert the left and right odds-ratio axes in (7.1) to absolute annual rates for the average warfarin patient in the Apixaban Study :



(7.2)

How the red annotations were developed.

1. First, the red numbers along the INR axis provide a guideline for where particular INR values are located. The axis is still very non-linear since we have not altered the picture. In particular, we have roughly located the 2.0 and 3.0 INR values which are the boundaries of the official "therapeutic range". One purpose of the Singer *et al.* paper was to verify that this range is the right target range to choose.

2. To arrive at the 9.2 stroke odds ratio estimate for INR = 1, we did a linear fit to the two black-square points (1.55, 3.8) and (1.15, 7.6) and extended it to INR = 1. If the equation of this line is $y = mx + b$, the slope m is then given by $m = (y_1 - y_2) / (x_1 - x_2) = (3.8 - 7.6) / (1.55 - 1.15) = -9.75$ and then $b = y_1 - mx_1 = 18.9$. Then for $x = 1$ we find that $y = mx + b = (-9.75)1 + 18.9 = 9.15 \approx 9.2$.

3. The INR = 1 point refers to AFIB patients who take no OAC. We found from the warfarin arm of the Apixaban Study in S(3.4) that the percentages of IS, HS and SE are 69%, 29% and 6%. The total stroke rate including all three for AFIB patients taking no OAC was shown in S(3.12) to be 4.5%. If we exclude the hemorrhagic strokes (HS), we get a total absolute TE rate of $(.69 + .06) 4.5 = 3.38 \approx 3.4 \%$ /yr.

3. We then create an absolute linear rate scale on the left side of (7.2) which aligns at 0 and for which the value 3.4 % aligns with the odds ratio 9.2, as computed in items 3 and 2 above.

4. For the average warfarin patient in the Apixaban Study we find from S(3.4) that $TE = IS + SE = 1.05 + 0.10 = 1.15 \%$ /yr. This point is marked on the newly created left scale and a red line is extended right through the black curve. Had the Study warfarin patients stayed exactly in the 2-3 INR range, the resulting TE rate would have been about 0.4 %/yr (as read from (7.2)) instead of 1.15 %/yr. This suggests that the Study's average warfarin patient had INR < 2 some significant fraction of the time. The Study claims that patients were in the 2-3 range 62% of the time. Sometimes people "prepare for the test", so actual INR compliance might be less than measured.

5. We next create on the right side of (7.2) an absolute scale for IC bleed rate calibrated to the Apixaban Study warfarin arm. In (6.1) it is estimated that an AFIB patient taking no-OAC has an IC bleed rate of 0.88 %/yr (as explained in Note 5 following that figure). In (7.2) this patient has INR = 1. We crudely extend the dashed line leftward to INR = 1 and note the intercept y value. This is then carried over to the right chart edge by a dashed red line and that vertical location is assigned the value 0.88. Using that value and the 0 location, the right side scale for IC bleed rate can be constructed as shown.

The bump in the dashed IC curve within the 2-3 INR region is probably not real and the dashed curve is probably monotonic increasing moving to the right from the normalization point. If we ignore this bump, then a patient staying strictly in the 2-3 INR range would have an IC bleed rate of about 0.5 %/yr. The average patient in the Apixaban warfarin arm had an IC bleed rate of 0.80 %/yr from (2.2), so again this increase is due to the fact that INR is > 3.0 some fraction of the time for the Apixaban Study warfarin patients.

Our left and right side absolute rate risk scales should be regarded as "ballpark accurate" since their construction depends on so many assumptions, not to mention that everything in sight has large error bars. Nevertheless, we feel that these rates are "reasonable" for application to the warfarin arm of the Apixaban Study. These figures make it abundantly clear why a warfarin patient should try to stay in the therapeutic range, and if that is a problem, why they might switch to a NOAC and/or get ablated.

Appendix A: Adjusting the Cox Bleed Risk Data to the AFIB-Age Population

A population is partitioned into age bins. For bin i , the fraction of the population in that bin is f_i and the average annual rate for some process (for example, the rate of intracranial bleeds for age bin i) is r_i . Then the average rate r_{av} over the population is given by $r_{av} = \sum_i f_i r_i$.

1. Intracranial Bleeds

It is our task to compute r_{av} (Cox age profile) and r_{av} (AFIB-age profile) as just outlined. Once this is done, we may write (since the ratio of relative rates must equal the ratio of absolute rates),

$$\begin{aligned}
 r_{av}^{ABS}(\text{AFIB-age profile}) &= r_{av}^{ABS}(\text{Cox age profile}) * \frac{r_{av}(\text{AFIB-age profile})}{r_{av}(\text{Cox age profile})} \\
 &= r_{av}^{ABS}(\text{Cox age profile}) * \text{Ratio} \qquad \text{Ratio} = \frac{r_{av}(\text{AFIB-age profile})}{r_{av}(\text{Cox age profile})} \qquad (A.1)
 \end{aligned}$$

where ABS indicates an absolute rate. We do this because r_{av}^{ABS} (Cox age profile) is a result appearing in the Cox paper in the rightmost column of their Table 2 (we use the No anticoagulants numbers only) :

Table 2| Incident haemorrhagic events in derivation cohort recorded on mortality or hospital records

Haemorrhagic events	Cases on mortality or hospital data	Person years	Age standardised incidence rate per 1000 person years* (95% CI)
Upper gastrointestinal bleed:			
No anticoagulants	21 143	16 332 684	1.34 (1.32 to 1.36)
Warfarin	492	71 597	5.83 (4.33 to 7.33)
New anticoagulants	6	664	2.69 (0.36 to 5.03)
Intracranial bleed:			
No anticoagulants	8 670	16 332 684	0.55 (0.54 to 0.56)
Warfarin	365	71 597	1.89 (1.46 to 2.32)
New anticoagulants	5	664	1.49 (1.27 to 2.86)

*Age standardised to derivation cohort population.

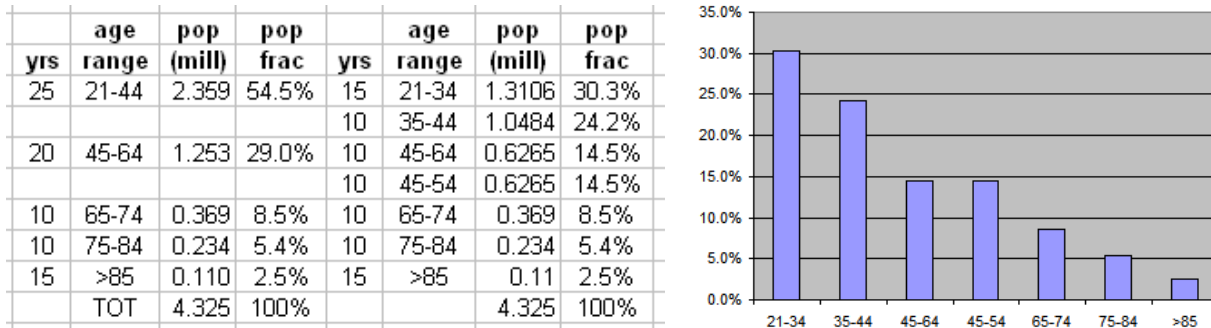
(A.2)

As stated in this table, the presented results are "age standardized to the derivation cohort population" which has the age profile shown in our table (A.4) below. This means that the numbers shown in the right column in (A.2) apply to the average person in the derivation cohort. They do not apply to the average person in our AFIB-age distribution, which is why we have this Appendix A. Here then is the Cox Study age distribution :

Characteristics	Derivation cohort (n=4 378 851)		
	No anticoagulant	Warfarin	Other anticoagulant
Female	22 10 508 (51.1)	23 740 (45.2)	841 (51.2)
Male	2 114 217 (48.9)	28 745 (54.8)	800 (48.8)
Age group (years):			
21-24	2 359 220 (54.6)	3438 (6.6)	57 (3.5)
45-64	1 252 978 (29.0)	11 810 (22.5)	301 (18.3)
65-74	369 120 (8.5)	13 914 (26.5)	473 (28.8)
75-84	233 567 (5.4)	16 932 (32.3)	544 (33.2)
≥85	109 840 (2.5)	6391 (12.2)	266 (16.2)

(A.3)

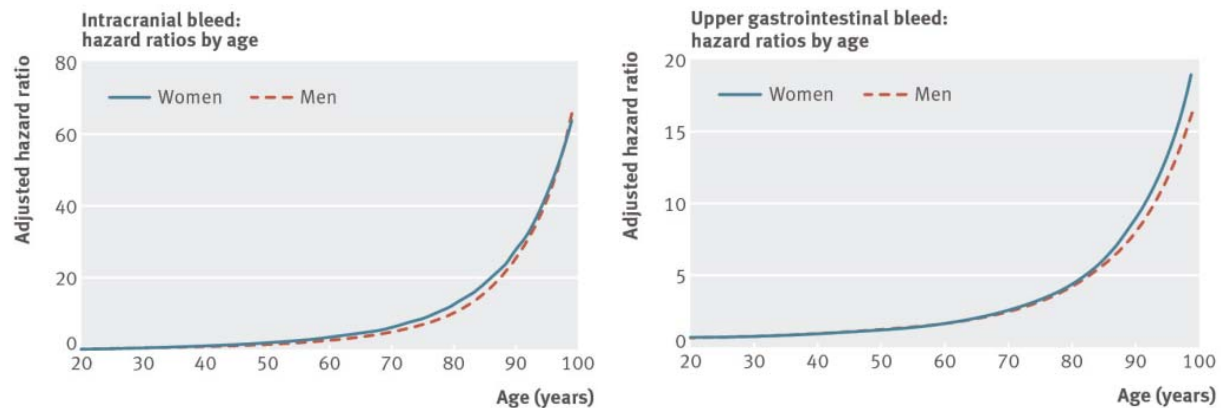
There are two small typos in this Table. The female no anticoagulant count is 2 210 508 (spacing) and the first age bin should say 21-44 instead of 21-24. Notice that the ratio of males to females is close to 1. Here then is the Cox derivation cohort age distribution for participants mostly not taking anticoagulants:



(A.4)

The first four spreadsheet columns analyze the age distribution shown in (A.3). The last four columns adjust the distribution by breaking each of the two initial wide bins into two bins in proportion to the bin widths. The resulting Cox age distribution is shown in the rightmost column and in the graph.

These adjustments have only a small effect on the results because the rates r_i for the low bins are very small, as shown in our next figures, taken from the Cox Study: (rates are relative, not absolute)



(a) Cox IC Bleed Rate, Fig 2 (p 19)

(b) Cox GI Bleed Rate, Fig 1 (p 18)

(A.5)

The vertical axes in these two charts say "hazard ratio" because each displays its rate as compared to the rate for a person of age 40. In other words, both graphs are normalized to have rate = 1 at age 40.

Here then are the spreadsheets that compute r_{av} (AFIB-age profile) [left side] and r_{av} (Cox age profile) [right side] :

INTRACRANIAL BLEED							
age	f	r	f * r		f	r	f * r
range	AFIB age fraction	IC bleed rate		age range	Cox age fraction	IC bleed rate	
25-34	0.45%	0.5	0.00	21-34	30.3%	0.5	0.15
35-44	2.71%	1.2	0.03	35-44	24.2%	1.2	0.29
45-54	7.24%	2.0	0.14	45-54	14.5%	2.0	0.29
55-64	11.76%	3.0	0.35	55-64	14.5%	3.0	0.43
65-74	23.08%	5.5	1.27	65-74	8.5%	5.5	0.47
75-84	38.01%	12.0	4.56	75-84	5.4%	12.0	0.65
>85	16.74%	35.1	5.88	>85	2.5%	35.1	0.89
TOT	100.00%			TOT	100.0%		
			12.24				3.18
0.055	0.212			RATIO	3.85		

(A.6)

The bold numbers 12.24 and 3.15 are $r_{av} = \sum_i f_i r_i$ as noted at the start of this section, and then 3.89 is the ratio of these two averages. The AFIB age fractions appear in our Fig S(2.2); recall that this AFIB age profile comes from processing the 2006 AHA Guidelines plot Fig S(2.1). The Cox age fractions come from the last column of the spreadsheet in (A.4). The IC bleed rates are taken from the plot (A.5a) as detailed in the blowup shown below in (A.9). We have then found that

$$\text{Ratio} = \frac{r_{av}(\text{AFIB-age profile})}{r_{av}(\text{Cox age profile})} = \frac{12.24}{3.18} = 3.85 . \quad (\text{A.7})$$

Then the absolute intracranial bleed rate for non-AFIB no-OAC people of AFIB age is given by

$$r_{av}^{ABS}(\text{AFIB-age profile}) = r_{av}^{ABS}(\text{Cox age profile}) * \text{Ratio} = .055 * 3.85 = 0.212 \% / \text{yr} \quad (\text{A.8})$$

where the .055 comes from (A.2) above.

In the following figure, Fig (A.5a) is pasted into Visio, made transparent and then aligned with the Visio grid to allow a rough manual extraction of the rates for each bin which are used in the spreadsheets above. For the rightmost bin, the bin height was selected to make the areas of the red and green triangles the same, using Visio's area tool. We have attempted to average the curves for women and men. This is of course an approximate graphical analysis.



(A.9)

2. Upper Gastrointestinal Bleeds

The process used here is identical to that outlined above for intracranial bleeds -- only the bleed rates are different. Here is the pair of spreadsheets for this upper GI case:

UPPER GASTRO BLEED							
	f	r	f * r		f	r	f * r
age	AFIB age	u gastro		age	Cox age	u gastro	
range	fraction	rate		range	fraction	rate	
25-34	0.45%	0.75	0.00	21-34	30.3%	0.75	0.23
35-44	2.71%	0.9	0.02	35-44	24.2%	0.9	0.22
45-54	7.24%	1.2	0.09	45-54	14.5%	1.2	0.17
55-64	11.76%	1.6	0.19	55-64	14.5%	1.6	0.23
65-74	23.08%	2.6	0.60	65-74	8.5%	2.6	0.22
75-84	38.01%	4.2	1.60	75-84	5.4%	4.2	0.23
>85	16.74%	10.25	1.72	>85	2.5%	10.25	0.26
TOT	100.00%			TOT	100.0%		
			4.22				1.56
0.134	0.362			RATIO	2.70		

(A.10)

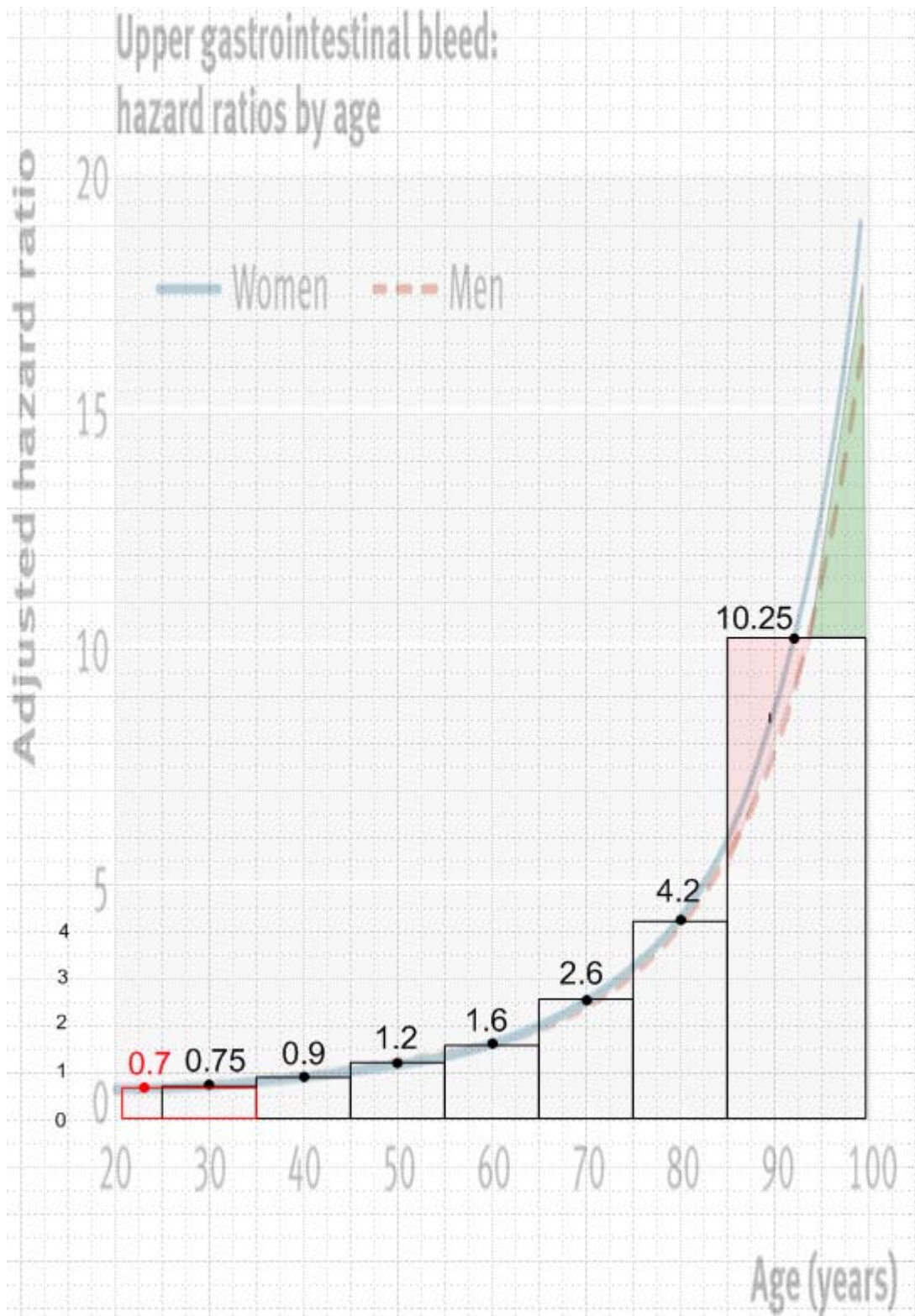
$$\text{Ratio} = \frac{r_{\text{av}}(\text{AFIB-age profile})}{r_{\text{av}}(\text{Cox age profile})} = \frac{4.22}{1.56} = 2.70. \quad (\text{A.11})$$

Then the upper gastrointestinal bleed rate for non-AFIB no-OAC people of AFIB age is given by

$$r_{\text{av}}^{\text{ABS}}(\text{AFIB-age profile}) = r_{\text{av}}^{\text{ABS}}(\text{Cox age profile}) * \text{Ratio} = .134 * 2.70 = 0.362 \% / \text{yr} \quad (\text{A.12})$$

where the .134 comes from (A.2) above.

Finally, here is the Visio image used to obtain the upper GI rates from Fig (A.5b),



(A.13)

References

Current public-free-access web links are given for most papers. Where possible, Digital Object Identifier links of the form doi = prefix/suffix are also given for use as <http://doi.org/prefix/suffix>. References are listed in the order first encountered in the our document. [all links verified 13 Feb 2015]

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[A Supplement containing contributor names and event *definitions* appears also at the above link.]

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