AFIB Stroke Risk
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This is the first of two documents on AFIB risk -- the second concerns bleeding 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!

Abbreviations: AFIB = atrial fibrillation (and flutter)
             OAC = oral anticoagulant
             NOAC = "new" oral anticoagulants like apixaban
             AHA = American Heart Association
             CI = confidence interval

Overview

There are many web-accessible articles describing atrial fibrillation and atrial flutter which we group together under the moniker AFIB. In the two documents *AFIB Stroke Risk* and *AFIB Bleed Risk* we explore the risks associated with having AFIB and the benefits of taking oral anticoagulants ("blood thinners", such as warfarin or newer drugs) to reduce stroke risk. The role of catheter ablation is mentioned in passing.

The main risk associated with AFIB is *stroke,* as reviewed below. The main risk associated with *reducing* the risk of stroke with oral anticoagulants is internal hemorrhage, either in the brain or elsewhere. In both documents we make use of a large AFIB drug study to assess these risks for the "average" AFIB patient. We then examine various stratification schemes which attempt to show how a specific AFIB patient's risk differs from that of the average AFIB patient due to factors like age, sex and medical history.

It happens that our drug study of interest was funded by the makers of apixaban (Eliquis), and so we use apixaban as a representative "novel" oral anticoagulant. There is no intention to promote this drug relative to its currently approved competitors dabigatran (Pradaxa) and rivaroxaban (Xarelto).

Summary

Section 1 describes the term "stroke" in some detail.

Section 2 then computes the annual stroke risk for *non*-AFIB people who are in the same age range as most AFIB patients. Our conclusion is that these non-AFIB people have an annual stroke risk of about 1% per year.

Section 3 then develops a table (3.12) which compares this background stroke risk to the stroke risk encountered by AFIB patients taking various kinds of oral anticoagulants, or taking no anticoagulant. The average AFIB patient who takes no anticoagulant is faced with a 4-fold increased risk of stroke compared to the background population -- on the order of 4-5% per year. That is to say, the chance of having a stroke is on the order of 40%-50% for each decade of having AFIB. This fact should certainly encourage even the most recalcitrant AFIB patient to do something about the problem.

Sections 4, 5 and 6 summarize various stratification schemes which allow an AFIB patient to assess his or her personal stroke risk, which may be more or less than that of the average AFIB patient.

Section 7 notes that the statistics of AFIB studies are always weak, and conclusions which are smartly presented with 2 or 3 significant figures of precision in fact have less than 1 digit of accuracy. Strata scheme bin results are roughly ±30% accurate. Problems with definitions of terms are mentioned.

Section 8 addresses the risk status of an AFIB patient who has had a "successful" catheter ablation.

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

1. What is a stroke?

A **stroke** refers to the interruption of blood flow somewhere in the brain. This can happen in two ways.

An **embolus** is some object traveling through a blood vessel that is not supposed to be there. It could be a chunk of clotted blood or fat or cholesterol or even an air bubble. If this embolus gets wedged and blocks blood flow, one has an **embolism**. Blockage could also be caused by a locally formed blood clot (**thrombus**). In either case, when this blockage occurs in the brain one has an **ischemic stroke**.

ischemic: [< L < Gk *iskhaimos* 'stopping blood', from *iskhein* 'keep back' + *haima* 'blood'.]

For AFIB, the main issue is an embolus which is a blood clot -- a thrombus that forms in the AFIBing heart and then flows downstream and becomes an embolism (thus, a **thromboembolism**).

A **mini-stroke** or **TIA** (Transient Ischemic Attack) is an ischemic stroke of short duration which might do only limited damage but acts as a warning to the patient. For most stroke studies, including the Apixaban Study discussed below, a TIA is counted as a stroke only if it lasts more than 24 hours.

A **hemorrhagic stroke** is due to a blood vessel that bursts in the brain, allowing blood to leak out and not arrive at its proper destination. This happens either due to vessel malformation, or due to a balloon-like vessel bulge (**aneurysm**) which ruptures.

hemorrhagic: [< L < Gk *haimorrhagia*: 'bleeding violently,' from *haima* 'blood' + *rhage* 'a breaking']

Possible causes include high blood pressure, weak vessels, and possibly undetected emboli which "transform", see below. A small such event might quickly clot and be OK, but anticoagulants prolong the bleeding and thus permit more blood deprivation.

Both kinds of strokes can result in an **infarct** (localized dead tissue) leading to a "deficit" in the patient and possible death.

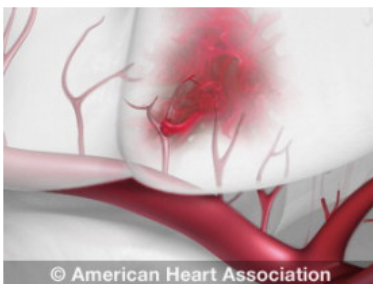About 87% of strokes are ischemic and 13% are hemorrhagic.   (1.1)

Here are some AHA stroke pictures:

Ischemic (Clots)
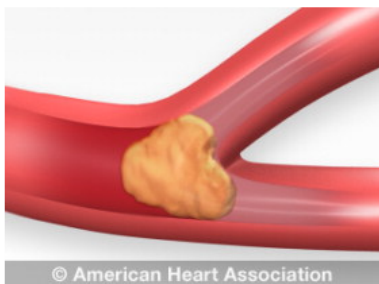
Ischemic stroke occurs as a result of an obstruction within a blood vessel supplying blood to the brain. It accounts for 87 percent of all stroke cases.

Hemorrhagic (Bleeds)

Hemorrhagic stroke occurs when a weakened blood vessel ruptures. Two types of weakened blood vessels usually cause hemorrhagic stroke: aneurysms and arteriovenous malformations (AVMs). But the most common cause of hemorrhagic stroke is uncontrolled hypertension (high blood pressure).

TIA (Transient Ischemic Attack)

TIA (transient ischemic attack) is caused by a temporary clot. Often called a "mini stroke", these warning strokes should be taken very seriously.

(1.2)

http://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/Types-of Stroke_UCM_308531_SubHomePage.jsp

A **systemic embolism** as used below is a embolism occurring somewhere in the body other than the brain. An example is a pulmonary embolism in the lungs.

Sometimes an ischemic stroke transforms (converts) into a hemorrhagic stroke in the sense that that there is bleeding secondary to the causative embolism. It is possible that the original embolism might dissolve before being detected, causing the ischemic stroke to appear as a hemorrhagic stroke. Such **hemorrhagic transformations** (HT) are poorly documented in IDC-9 ($\geq$ 1978) and IDC-10 ($\geq$ 1994) hospital codes. An HT event might be coded as an ischemic stroke, as a bleeding event, or both. This fact creates some ambiguity in retrospective studies based on hospital codings. In the Apixaban Study discussed below, for warfarin patients 20 of 155 ischemic strokes transformed (12.9%) while for the apixaban patients 12 of 149 transformed (8.1%). HT therefore provides a pathway for AFIB embolisms, detected or not, to increase AFIB patient bleeding risk, in addition to the direct bleeding risk due to oral anticoagulants.

Two varieties of hemorrhagic strokes are indicated in this graphic. Note that both occur on the brain side of the web-like arachnoid membrane. Later we shall discuss bleeds which occur outside this membrane.

Bursts and Breaks: Causes of Hemorrhagic Stroke
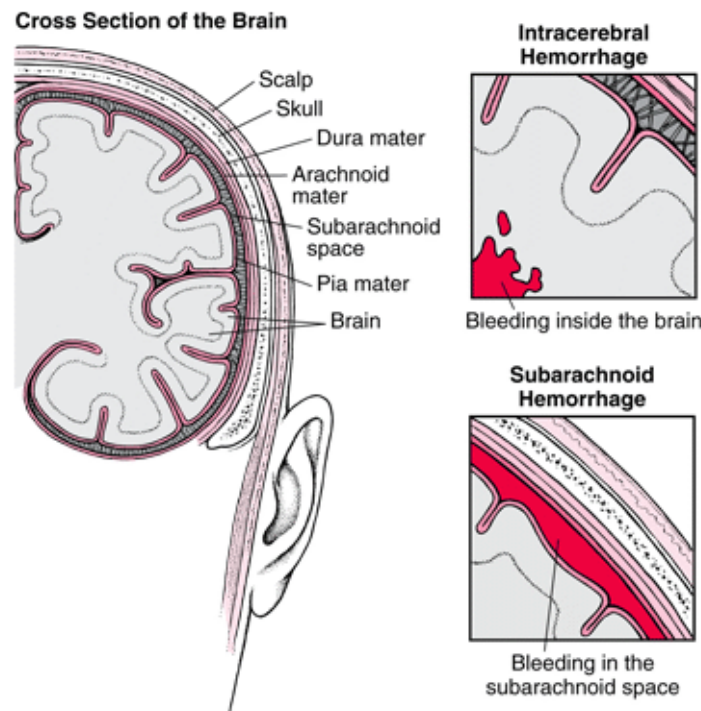
When blood vessels of the brain are weak, abnormal, or under unusual pressure, a hemorrhagic stroke can occur. In hemorrhagic strokes, bleeding may occur within the brain, as an intracerebral hemorrhage. Or bleeding may occur between the inner and middle layer of tissue covering the brain (in the subarachnoid space), as a subarachnoid hemorrhage.

(1.3)

http://www.merckmanuals.com/home/brain_spinal_cord_and_nerve_disorders/stroke_cva/overview_of_hemorrhagic_stroke.html#v739658

A possible cause of such a stroke is "banging the head", usually in an unexpected fall. Such traumatic events are usually excluded from stroke and bleed study databases, but are counted in strata schemes (see below) which add scoring points for a previous stroke or bleed. Similarly, some TIA's are often excluded from stroke databases, but are counted as a previous stroke in these strata schemes.

2. Computation of stroke rate for non-AFIB patients in the AFIB-age population

As a baseline, we shall attempt to calculate the average stroke rate for *non-AFIB* people in a special population that is age-matched to the age distribution of AFIB patients. Then later when we compute AFIB stroke rates, we can compare these rates to the aged-matched population who have no AFIB, and this then tells us the added stroke danger that is caused by (associated with) AFIB.

What is the age distribution of AFIB patients? We assume the AFIB age distribution does not change radically over time, so we can start with this 1995 chart of US AFIB prevalence taken from the 2006 AHA Guidelines (p 11), to which we have added some approximate counts in red :
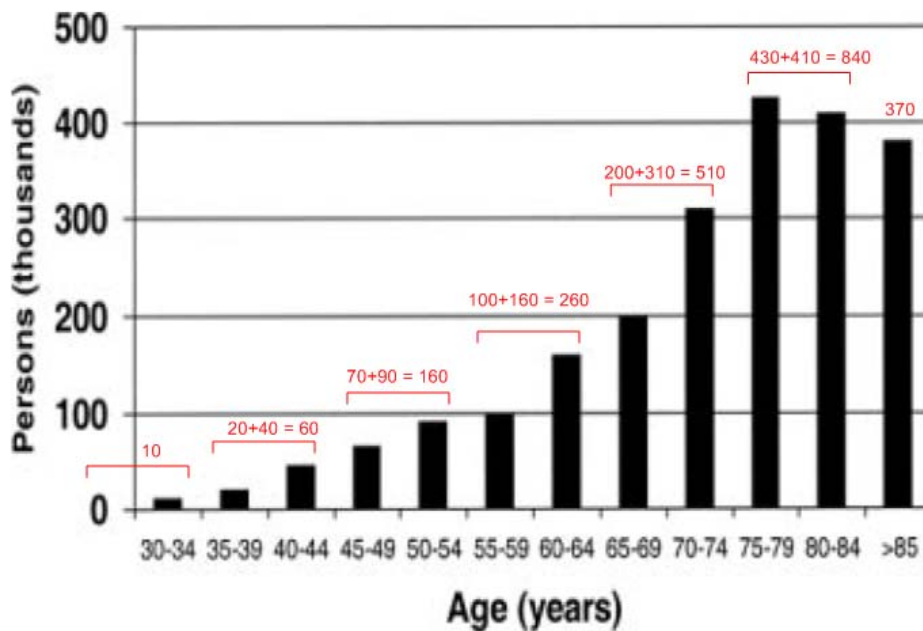
(2.1)

Our first task is to re-bin the data into bins that are 10 years wide. This gives,

age range	(1000's) number	fraction
25-34	10	0.5%
35-44	60	2.7%
45-54	160	7.2%
55-64	260	11.8%
65-74	510	23.1%
75-84	840	38.0%
>85	370	16.7%
	2210	100.0%
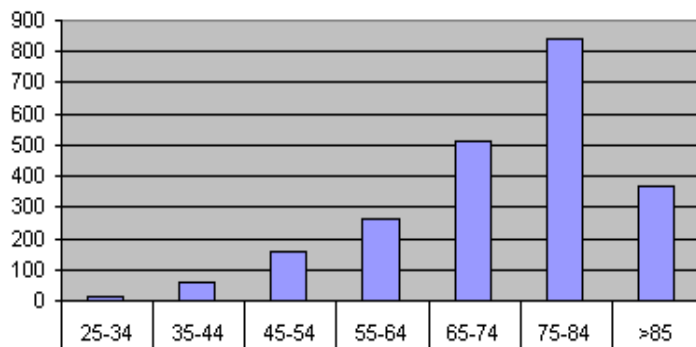
(2.2)

The "fraction" column shows the percentage in each age bin, and the total number of AFIB patients was 2.2 million in 2006 ("America"; 4.5 million in the EU). It seems clear that AFIB is primarily a disease

of "older people", but not entirely so. Due to the strong peaks in the older age bins, study results are moderately influenced by the average age of the participants in the study. This is because older people tend to have more *other* medical problems ("comorbidity") besides AFIB. One wonders how this distribution will change in the coming decades. We can estimate the average age of the above distribution in this manner: $(30*10 + 40*60 + 50*160 + 60*260 + 70*510 + 80*840 + 90*370)/2210 = 73.53$.
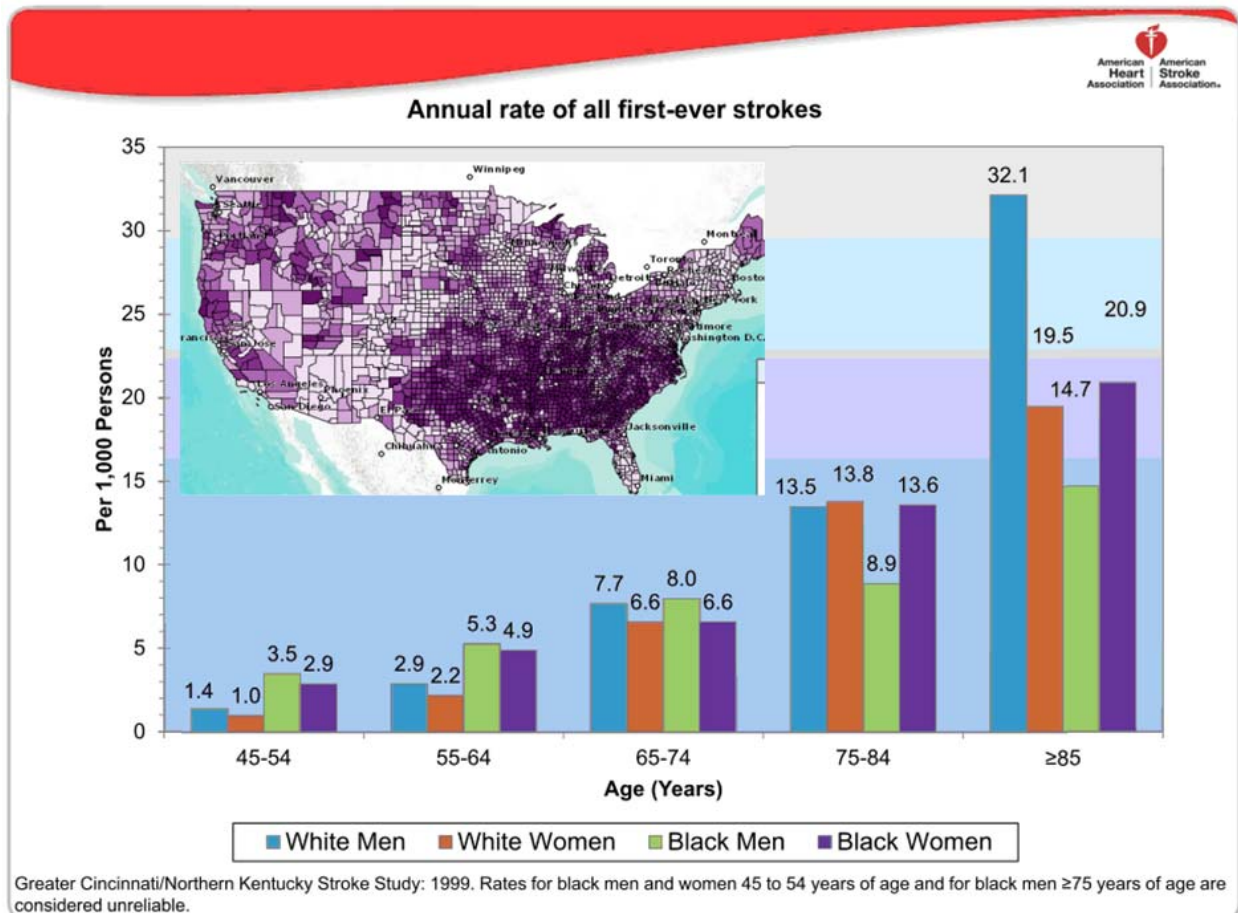
The Apixaban Study has a median age of 70, close to our average number.

To obtain stroke rates, we use a certain 2011 AHA update to a 1998 Cincinnati/Kentucky Stroke Study (see Refs). Perhaps the numbers are not exact for the entire US population, but they are good enough for our rough calculation.

Annual rate of all first-ever strokes

Greater Cincinnati/Northern Kentucky Stroke Study: 1999. Rates for black men and women 45 to 54 years of age and for black men ≥75 years of age are considered unreliable.

(2.3)

It is a sad fact that stroke rates are much higher for blacks than whites, and this causes the *population-adjusted* US stroke rate distribution to be geographically larger in the southeast, as shown by the inset. To simplify our quick analysis, and since blacks are perhaps only 13% of the population, and since the chart states that much of the black data is unreliable, we shall just use the white component of the data. Notice that the age bins match those of our AFIB distribution in (2.2). Using the numbers in the above graphic, we now compute the expected annual rate of a first stroke for the average person in the AFIB-age population (but not having AFIB). It is true that a tiny fraction have AFIB, but we ignore that fact.

| age range	(1000's) number	fraction	stroke rate WM	stroke rate WW	stroke rate W	frac*W
25-34	10	0.5%	0.0	0.0	0.0	0.00
35-44	60	2.7%	0.0	0.0	0.0	0.00
45-54	160	7.2%	1.4	1.0	1.2	0.09
55-64	260	11.8%	2.9	2.2	2.6	0.30
65-74	510	23.1%	7.7	6.6	7.2	1.65
75-84	840	38.0%	13.5	13.8	13.7	5.19
>85	370	16.7%	32.1	19.5	25.8	4.32
	2210	100.0%				
						11.54

(2.4)

We enter the white men and white women rates from the chart, average them in the W column, then weight that result by the AFIB population fraction. The conclusion is that about 11.54 per 1000 of the AFIB-age population have a first-ever stroke each year. Therefore (AFIB prevalence is ~ 2/300 < 1% so can be neglected here),

Average stroke rate for non-AFIB patients in the AFIB-age population   =   1.15 %/year   (2.5)

3. Benefits of Anticoagulation for AFIB patients; Benefits of Ablation

Warfarin properly managed reduces the risk of a stroke for people having either intermittent (paroxysmal) or continuous (persistent) AFIB. Most AFIB-related strokes are thought to arise from blood clots forming in the left atrial appendage during AFIB which then flow through the left ventricle to the brain. Below is data from the 2014 AHA AFIB Guidelines (p 31) on the stroke reduction benefit of taking warfarin versus taking nothing at all (control group, placebo). Since some in the control group were taking aspirin, the results are more dramatically in favor of warfarin than the data below indicate:
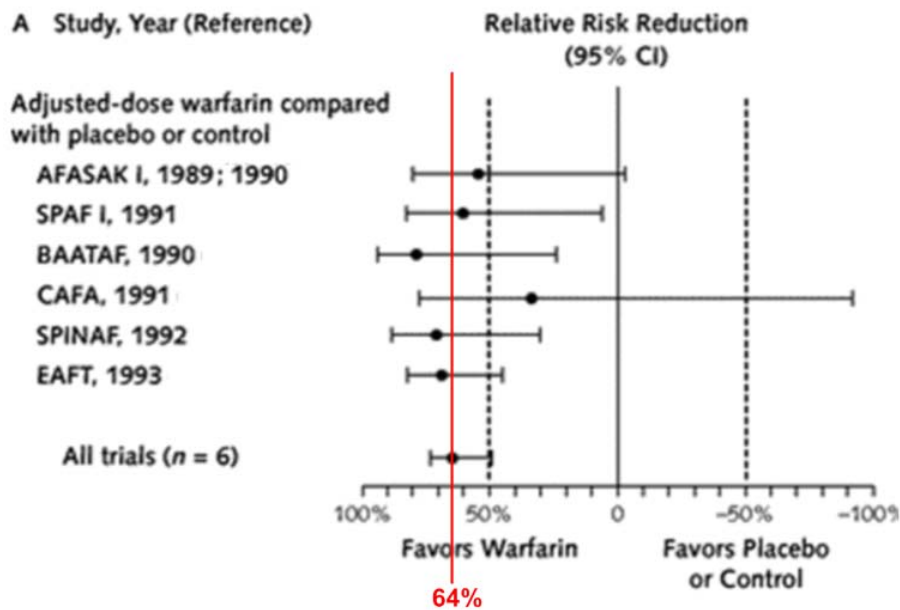
(3.1)

If we give less weight to the CAFA result which has a huge error bar, an eyeball average of the results suggests that warfarin provides a 64% reduction in the rate of strokes compared to taking nothing, so one writes Risk Reduction = RR = 0.64. If a rate r_1 is reduced by some RR to give r_2 then $r_2 = r_1 (1-RR)$. The Risk Reduction *Factor* would then be RRF = r_1/r_2 = $1/(1-RR)$. For example, if RR = 80%, then RRF = 5, and one would say the rate was reduced by a factor of 5. For the above, RR = 0.64 so RRF = $1/.36 \approx 2.78$ and so warfarin cuts the stroke rate by a factor of about 3! This figure is so dramatic that no new similar studies will ever be done on ethical grounds (last was 1993). For example, the BAATAF Boston study was terminated early when the large ~ 300% benefit of warfarin was detected.

Support for a 64% stroke rate reduction for warfarin (and 22% for aspirin) comes from Hart *et al.* (2007) from which the above graphic was taken (without our red line). Hart did a meta-analysis of 29 trials involving a total of 28,140 AFIB patients. These Hart reduction rates 64% and 22% are often quoted in the literature. Recently the 22% rate reduction for aspirin has been challenged, especially for older patients, as coming from weaker studies which overestimate its stroke reduction benefit, but we shall assume it applies below. So,

stroke reduction rate for warfarin	64%	
stroke reduction rate for aspirin	22%	(3.2)

The Apixaban Study

The large Apixaban Study (2011, N=18,201) had two cohorts of about ~9000 patients each, one cohort taking apixaban (a new oral anticoagulant, brand name Eliquis) and the other taking the traditional warfarin (Coumadin). This study, known informally as ARISTOTLE, was funded by the apixaban makers Pfizer and Bristol-Myers Squibb. Here are the stroke rates found in this study for the two cohorts,

Table 2. Efficacy Outcomes.*

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	%/yr	no.	%/yr		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70

(3.3)

We interpret this data to read:

	Apixaban			Warfarin		
ischemic stroke	0.97 %/yr	80%	75%	1.05 %/yr	69%	65%
hemorrhagic stroke	0.24 %/yr	20%	18%	0.47 %/yr	31%	29%
	1.21 %/yr	100%		1.52 %/yr	100%	
systemic embolism	0.09 %/yr		7%	0.10 %/yr		6%
total stroke rate	1.30 %/yr		100%	1.62 %/yr		100%

(3.4)

Presumably these numbers are for strokes which began as indicated. Some of the ischemic strokes "transformed" into hemorrhagic ones due to bleeding secondary to the embolism blockage.

Notice that the percentage of strokes that are hemorrhagic for these anticoagulated patients (20% and 31%) are much higher than for the baseline population taking no anticoagulation (13%).

The systemic embolism rate contributes a small amount to the sums as shown. If we include such embolisms in a broad definition of "stroke", we find that, for the average AFIB patient,

			ratio	
stroke risk while taking apixaban	1.30 %/year		0.29	
stroke risk while taking warfarin	1.62 %/year		0.36	
stroke risk while taking aspirin	3.51 %/year	// = 4.50*.78	0.78	
stroke risk while taking nothing	4.50 %/year	// = 1.62/.36	1.00	(3.5)

The first two numbers come from the bottom line in (3.4). The fourth number 4.50 is then obtained from the warfarin number 1.62 using the 64% reduction of stroke rate attributed to warfarin in (3.2),

$$r_1 = r_2 /(1\text{-}RR) = 1.62/(1\text{-}0.64) = 1.62/0.36 = 4.5 \ .$$

Once this number is known, (3.2) says the aspirin stroke rate is $r = (1\text{-}.22)4.5 = .78*4.5 = 3.51$.

The fourth line of (3.5) should be eye-popping to any AFIB patient. It says that if no OAC is taken, the probability of having a stroke is 4.5% per year or 45% per decade and 90% over 20 years. This is very bad news.

Footnote on Apixaban Study Numbers: Here is a version of (3.4) showing event counts. The first two rows' numbers come from page 7 of the Study, while the last two rows' numbers are taken from (3.3) :

	Apixaban		Warfarin	
ischemic stroke	149		155	
uncertain stroke type	14	149+14 = 163	21	155+21 = 176
hemorrhagic strokes	40		78	
systemic embolisms	15		17	
	218		271	(3.6)

For some unspecified reason, the sums here differ slightly from the sums 212 and 265 shown in (3.3). Probably for the same reason, our total rates 1.30 and 1.62 shown in (3.4) differ from 1.27 and 1.60 shown in the first line of (3.3). This could be related to patients who left the study prematurely. We shall base our work on the 1.30 and 1.62 numbers for total stroke rate shown in (3.4).

Now, using the result (2.5) that the non-AFIB stroke rate as 1.15 %/yr and the (3.5) rate of 4.50 %/yr, we reach this conclusion:

$$\frac{\text{stroke rate for the average AFIB patient (no-OAC)}}{\text{stroke rate for the average non-AFIB but age-matched person}} = \frac{4.50}{1.15} = 3.91 \qquad (3.7)$$

It would be nice to have some external support for this AFIB/noAFIB stroke ratio of 3.91. Our derivation of the ratio is specific to the AFIB age distribution (2.1) and the stroke distribution (2.3).

The Framingham Study: just what is the AFIB/noAFIB Stroke Ratio?

Since ethical modern trials only include coagulated AFIB patients (due to the 4.5 %/yr number above), we have to look back at older work, and a key piece of older work is known as the Framingham Study (Framingham is a town west of Boston). In this impressive study 5,209 AFIB patients were followed up every two years from 1948-1982 (34 years!). The goal was to study the rates of incidence and prevalence of AFIB (versus age, for example) and to learn more about the association of atrial fibrillation with other medical conditions, and with stroke.

Various papers have been written analyzing this study, and we show three of them in our References. In a 1987 paper, Wolf, Abbott and Kannel say "In recent years, chronic atrial fibrillation in the absence of rheumatic valvular heart disease has been found to be associated with more than a fivefold increased incidence of stroke, even when age and hypertensive status are taken into account." Thus enters the notion of "5-fold" for the AFIB/noAFIB stroke ratio, and this ratio appears in the 2014 AHA Guidelines (p 27 4.1.1). The 1987 paper indicates that anticoagulants like warfarin were "seldom used". In their Table 3, the authors present the following values of our ratio of interest for four different age bins:

Stroke Risk Factor	Age Group, y			
	50-59	60-69	70-79	80-89
Atrial fibrillation	4.1† (1.5, 10.8)	2.6† (1.4, 4.9)	4.0† (2.6, 6.2)	4.8‡ (2.5, 9.2)

(3.8)

Notice the fairly large error bars on these numbers (see Section 7 for general comments on error bars). The paper says that the ratio is 4 for "lone AFIB" patients -- those having no heart disease other than AFIB.

In a later 1991 paper, the same authors present a similar chart showing the age-binned ratios, but the four numbers are lowered slightly to 4.0, 2.6, 3.3 and 4.5 which appear in the bottom row below,

TABLE 2. Estimated Relative Risk of Stroke for Persons With Given Cardiovascular Condition Compared to Those Without Condition by Age

Cardiovascular condition	Age group			
	50–59 yr	60–69 yr	70–79 yr	80–89 yr
Hypertension*	3.5†	3.2†	2.5†	1.7
Coronary heart disease‡	2.9†	2.0†	1.7§	0.7
Cardiac failure‡	3.9§	2.4†	2.2†	1.7
Atrial fibrillation	4.0†	2.6†	3.3†	4.5†

Each relative risk is adjusted for the other stroke risk factors.
*‡$p<0.05$ and 0.001, respectively, significant decline in estimated relative risk of stroke with advancing age.
†§$p<0.001$ and 0.01, respectively, significant excess of stroke in those with cardiovascular condition.

(3.9)

If we average the four numbers, the result is (4.0+2.6+3.3+4.5)/4 = 3.6. If we weight the numbers by the AFIB prevalence counts in Table 1 of the 1991 paper, the mean ratio is 3.36 as shown on the left below. But in this same 1991 paper, the summary describes the ratio as "near fivefold", and the paper's Figure 1 suggests the ratio is 4.8. Alternatively, we can weight the ratios of the 1991 paper by our 1995 population distribution (2.1) and this gives 3.62 as shown on the right below :

	1991			
Age	Num	f	ratio	f * ratio
50-59	109	10%	4.1	0.42
60-69	351	33%	2.6	0.85
70-79	429	40%	3.3	1.32
80-89	184	17%	4.5	0.77
	1073	100%		3.36

	1995			
Age	Num	f	ratio	f * ratio
50-59	190	10%	4.1	0.42
60-69	360	20%	2.6	0.51
70-79	720	39%	3.3	1.29
80-89	575	31%	4.5	1.40
	1845	100%		3.62

(3.10)

Here we assume that half the patients age > 85 are in the range 85-89, but the result is not very sensitive to this assumption.

In a still later 1998 paper of Kannel, Wolf, Benjamin and Levy the ratio is stated as "4-5-fold" in the summary, but later in the text they say "Epidemiologic and clinical studies have generally indicated that AF constitutes a major independent risk factor for stroke, with a 3–5-fold increased risk after adjusting for other risk factors (Table V)", and Table V restates the data of (3.9) above. In fact, if we weight the four ratios using the population distribution stated in Fig 1 of the 1998 paper, we find an average ratio of 3.90:
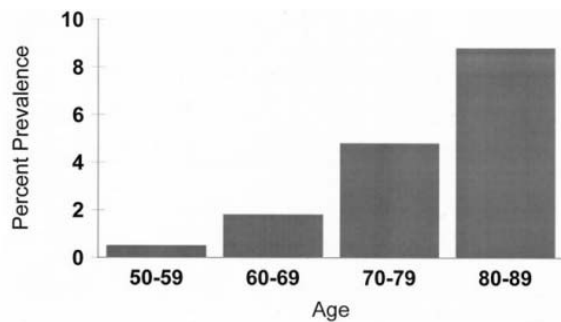

FIGURE 1. Prevalence of atrial fibrillation by decade of age. Framingham Study, subjects aged 50–89 years. (Adapted with permission from *Stroke*.[20])

	1998			
Age	Num	f	ratio	f * ratio
50-59	0.5	3%	4.1	0.13
60-69	1.9	12%	2.6	0.30
70-79	5.0	31%	3.3	1.01
80-89	8.9	55%	4.5	2.46
	16.3	100%		3.90

(3.11)

Based on this tour of the various Framingham analyses, we feel that for the population distribution (2.1), the average ratio of 3.91 shown in (3.7) is "reasonable". Based on the comments of Section 7 below, a true statement would probably be that the ratio is 4 ± 1, but we shall continue with our 3.91 number.

Conclusion on average stroke rates for various OAC

Having validated the 3.91 ratio as being "reasonable", we go ahead and extend our table (3.5) by adding a first row for non-AFIB but age-matched people, using the 1.15 %/yr non-AFIB rate from (2.5),

	rates			rate ratios			
non-AFIB but age-matched stroke rate	1.15	%/yr	1.00	0.88	0.71	0.33	0.26
AFIB stroke risk while taking apixaban	1.30	%/yr	1.13	1.00	0.80	0.37	0.29
AFIB stroke risk while taking warfarin	1.62	%/yr	1.41	1.25	1.00	0.46	0.36
AFIB stroke risk while taking aspirin	3.51	%/yr	3.05	2.70	2.17	1.00	0.78
AFIB stroke risk while taking no OAC	4.50	%/yr	3.91	3.46	2.78	1.28	1.00

(3.12)

The rightmost 5 columns show rate *ratios* normalized five different ways to make it easy to read off conclusions from the table. The ratio 3.91 of (3.7) is then visible at the bottom of the first ratio column. Here are a few conclusions from this table:

• **Warfarin** provides a factor of 2.78 reduction in total stroke risk (isch+hem+emb) compared to no anticoagulation, and reduces the AFIB patient's stroke risk to a point only 41% higher than that of an aged-matched non-AFIB person.   (3.13)

• **Apixaban** provides a factor of 3.46 reduction in total stroke risk (isch+hem+emb) compared to no anticoagulation, and reduces the AFIB patient's stroke risk to a point only 13% higher than that of an aged-matched non-AFIB person.   (3.14)

The ratios indicate that apixaban decreases stroke risk by 20% compared to warfarin, while taking nothing *increases* stroke risk 278% compared to warfarin. This then explains why it is that AFIB people historically have taken warfarin and why they might be interested in the "novel" anticoagulation drugs (NOACs) such as apixaban (Eliquis).   (3.15)

The rates shown are for an average patient. If patients are stratified according to some risk factor(s), such as in $CHADS_2$ scoring (see below), perhaps the ratios above stay constant. Then for example if one's stroke risk due to having some set of risk factors (hypertension, previous stroke, etc.) is twice the average, the stroke rates in (3.12) would all be multiplied by 2.

The good news then is that anticoagulation brings the stroke risk of the AFIB patient down to a level not too much larger than that of the same-age non-AFIB population. The *anticoagulated* AFIB patient stroke risk is not 4-5 times that of the non-AFIB patient risk.

How does this all relate to catheter ablation?

Assuming that ablation completely restores a patient to the non-AFIB baseline (which is questioned, see Section 8 below), the post-ablation patient no longer taking anticoagulants has a stroke risk 29% (12%) lower than he or she had while taking warfarin (apixaban) before ablation (this from (3.12) ratios). This is not a particularly dramatic rate decrease, but the post-ablation patient no longer taking anticoagulation has a dramatically reduced *bleeding* risk, as discussed in our second document. Unfortunately, recent Guidelines recommend that anticoagulation be continued indefinitely after catheter ablation for people with CHA_2DS_2-VASc score ≥ 2 (discussed below), so for those people the bleeding rate is not reduced, and the stroke rate is only moderately reduced by ablation. But even for *those* patients, assuming they have active AFIB, there are still significant benefits for ablation:

• removal of the discomfort of AFIB and of reduced heart output making patients weak and tired
• lowered risks of dementia and heart problems (and mortality) resulting from the heart's reduced output and general malfunctioning during AFIB.

If a patient is unable or unwilling to take anticoagulation drugs, we can add this third ablation benefit :

• lowered stroke rate by a very significant factor of about 4   (3.16)

4. What is the CHADS$_2$ scoring system?

This stratification scheme allows one to compute the risk multiplier like the factor of 2 mentioned above. The original CHADS$_2$ system was concocted in 2001 by Gage *et al*. Each *letter* of the mnemonic CHADS$_2$ stands for a factor which increases an AFIB patient's risk : (read the capital letters down)

CHADS$_2$ acronym	
Congestive HF	1
Hypertension	1
Age ≥75 y	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum Score	6

// 2014 AHA Guidelines   (4.1)

The subscript 2 on S$_2$ means that a previous Stroke gets 2 points in the scoring, while other factors get 1 point. For example, if you have hypertension, are over age 75 and had a TIA, your CHADS$_2$ score is 4 out of 6.

This study dealt with ischemic strokes in a patient set called NRAF (National Registry of Atrial Fibrillation) that was relatively old and sick and could thus give good statistics for the various risk factors. There were 1,733 AFIB patients, none of whom took warfarin, and 31% of whom took aspirin. Average age was 81. For those 1,204 in the set taking no OAC the average CHADS$_2$ score was 2.1, while for the 529 who took aspirin, average score was 2.3. The Gage paper calculations of annual stroke risk (%) versus CHADS$_2$ score are shown in the rightmost column below:

Table 2. Risk of Stroke in National Registry of Atrial Fibrillation (NRAF) Participants, Stratified by CHADS$_2$ Score*

CHADS$_2$ Score	No. of Patients (n = 1733)	No. of Strokes (n = 94)	NRAF Crude Stroke Rate per 100 Patient-Years	NRAF Adjusted Stroke Rate, (95% CI)†
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.6-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

*CHADS$_2$ score is calculated by adding 1 point for each of the following conditions: recent congestive heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischemic attack. CI indicates confidence interval.
†The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken.
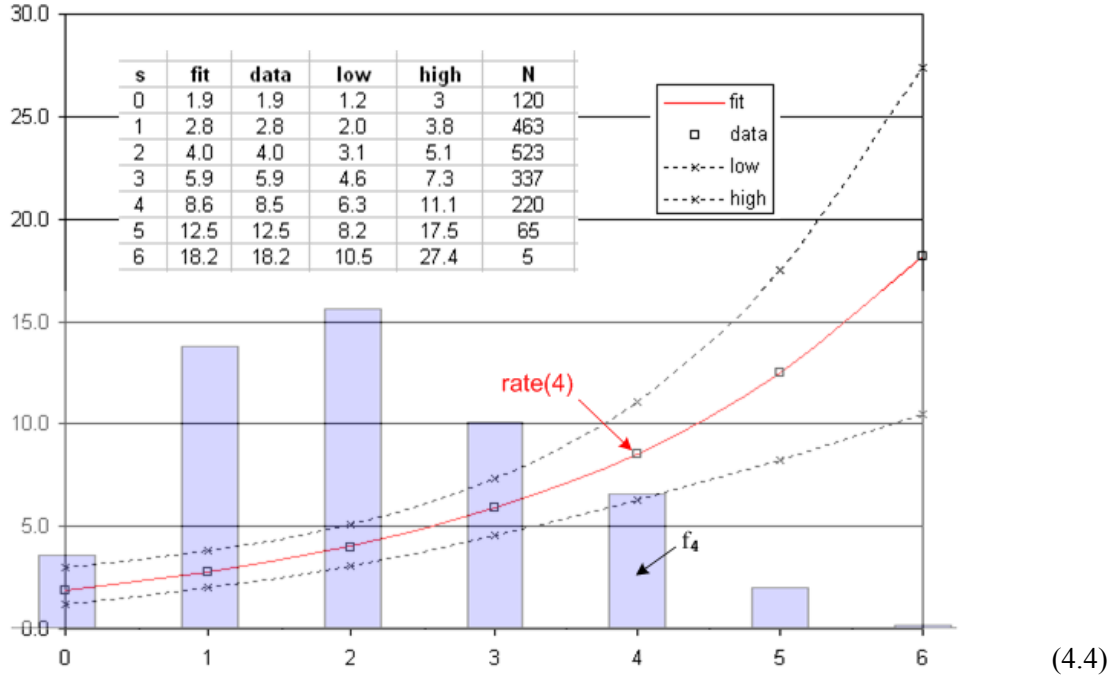
(4.2)

The authors' footnote **†** presumably implies the rates were adjusted to remove the aspirin effect, so it is as if all 1733 patients were taking nothing.

Roughly, stroke risk increases by a factor of 1.5 for each unit increase in the score. In fact, a nearly perfect fit to the 7 rates shown in the right column in (4.2) is obtained from

annual no-OAC stroke risk rate = $1.9 * (1.457)^{score}$ or $rate(s) = 1.9 * (1.457)^s$.   (4.3)

In the graphic below, the fit (4.3) is shown as a red curve, while the black squares show the rate values from the right column of (4.2), and one can see that the red curve fits the data very closely. The dashed curves show the error bands also from (4.2).

s	fit	data	low	high	N
0	1.9	1.9	1.2	3	120
1	2.8	2.8	2.0	3.8	463
2	4.0	4.0	3.1	5.1	523
3	5.9	5.9	4.6	7.3	337
4	8.6	8.5	6.3	11.1	220
5	12.5	12.5	8.2	17.5	65
6	18.2	18.2	10.5	27.4	5

(4.4)

Superposed on this plot is a blue histogram showing the relative number of patients in the study for each score bin, taken from the second column of (4.2). If the red rate curve displays the function rate(s) where s is the score, and if the histogram bar heights are fractions f_i such that $\Sigma_i f_i = 1$, then we claim that [here "average" means for the average person in the study],

average rate ≡ <rate> = $\Sigma_s\ f_s\ rate(s)$

average score ≡ <s> = $\Sigma_s\ f_s\ s$.   (4.5)

Since the red rate curve is *non-linear*, the value of the rate function evaluated at the average score does not equal the average rate! That is to say, rate(<s>) ≠ <rate>. If the rate happens to be a *linear* function rate(s) = ms + b, *then* these two quantities are in fact equal, since

rate(<s>)   = m <s> + b = m $\Sigma_s\ f_s\ s$ + b

<rate>   = $\Sigma_s\ f_s$ rate(s) = $\Sigma_s f_s$ [ms+b] = m $\Sigma_s\ f_s\ s$ + $(\Sigma_s f_s)$b = m $\Sigma_s\ f_s\ s$ + b .   (4.6)

In our stroke and bleed documents we shall be seeing several of these stratification schemes, and the rate curves are never linear, so it is important to understand the fact that in general rate($<$s$>$) $\neq$ $<$rate$>$. Thus, if one wants to know $<$s$>$ and $<$rate$>$, one has to compute each separately. We now do exactly this using the data shown in (4.2) and the expressions shown in (4.5),

CHADS2 Average Score and Average Rate					
s	r	n	f	s*f	r*f
0	1.9	120	6.9%	0.00	0.13
1	2.8	463	26.7%	0.27	0.75
2	4.0	523	30.2%	0.60	1.21
3	5.9	337	19.4%	0.58	1.15
4	8.5	220	12.7%	0.51	1.08
5	12.5	65	3.8%	0.19	0.47
6	18.2	5	0.3%	0.02	0.05
		1733	100.0%	**2.17**	**4.83**
				$<$score$>$	$<$rate$>$

(4.7)

The columns are s = score, r = rate, n = number of study patients with score s, f = fraction f_s of patients at that score (obtained from the n column and its sum 1733), and the last two columns are f_s*s and f_s* rate(s) which appear in (4.5). Adding these columns then does Σ_s and we find the average score and the average rate to be 2.17 and 4.83. As a check on our non-equality of the two quantities, we find that

$$\text{rate}(<s>) = \text{rate}(2.17) = 1.9 * (1.457)^{2.17} = 4.29 \quad \neq \quad <\text{rate}> = 4.83 \tag{4.8}$$

With this long-winded introduction (which we shall not repeat for later strata schemes), we now display the following stroke risk table based on the NRAF study, but where the rates are scaled by an overall scale factor sf = 0.93:

			TOTAL STROKE RISK (annual rate)					no-OAC
			(average score = 2.17)	1.00	0.78	0.36	0.29	0.26
sf	r	sf*r	CHADS2	no-OAC	aspirin	warfarin	apixaban	non-AFIB
0.93	1.9	1.77	0	1.77%	1.38%	0.64%	0.51%	0.46%
0.93	2.8	2.60	1	2.60%	2.03%	0.94%	0.76%	0.68%
0.93	4.0	3.72	2	3.72%	2.90%	1.34%	1.08%	0.97%
0.93	5.9	5.49	3	5.49%	4.28%	1.98%	1.59%	1.43%
0.93	8.5	7.91	4	7.91%	6.17%	2.85%	2.29%	2.06%
0.93	12.5	11.63	5	11.63%	9.07%	4.19%	3.37%	3.02%
0.93	18.2	16.93	6	16.93%	13.20%	6.09%	4.91%	4.40%
0.93	4.83	4.49	average rates:	4.49%	3.50%	1.62%	1.30%	1.17%

(4.9)

We now explain this table in some detail. The scale factor 0.93 (next paragraph) is in the leftmost column, followed by the rates "r" taken from the right column of (4.2). The bottom entry of this column is the average rate 4.83 taken from (4.7). The r column rates are then scaled down by the scale factor to give rates in column sf*r. These scaled-down rates are then copied over to the no-OAC column under the number 1.00. The CHADS$_2$ score is shown in the CHADS2 column. The remaining 4 columns are then obtained from the numbers in the 1.00 column by scaling with the fractions shown across the top (.78, .36 and so on). These fractions come from the last column of (3.12), so we are assuming the relative stroke rates among the different OAC's are the same at each CHADS$_2$ score.

Now why this 0.93 overall scale factor? This causes table (4.9) to be calibrated to the Apixaban Study population. Recall from that Study as shown in (3.4) that the average stroke rates for apixaban and warfarin patients were 1.30 %/yr and 1.62 %/yr. The factor 0.93 causes the bottom numbers in the apixaban and warfarin columns in (4.9) to match these values. Once these match, all the average rates match those in (3.12). [Although the absolute CHADS$_2$ rates are for ischemic stroke, we calibrate (4.9) to match the total stroke numbers of (3.4)]

The left no-OAC column in (4.9) shows stroke rates for AFIB patients at each CHADS$_2$ score level who are not taking any anticoagulant. The rightmost no-OAC column shows rates for the age-matched non-AFIB population. Here then is a plot of the data in table (4.9) :

Annual Total Stroke Rate   CHADS$_2$ score $\rightarrow$ (4.10)
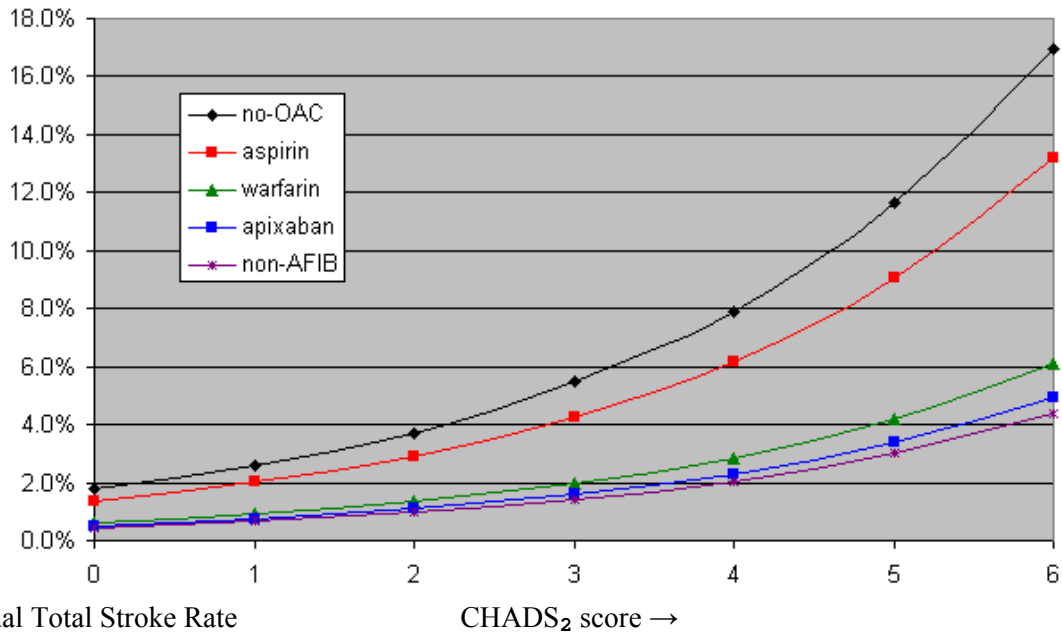
The benefits of taking oral anticoagulants (OAC) for AFIB especially at higher CHADS$_2$ scores could not be more dramatic. It is helpful to multiply the risk by a factor of 10 to get risk per decade of having AFIB. For example, a person with score 4 taking no OAC has an 79% chance of having a stroke over 10 years.

Example: A relatively healthy AFIB patient has a CHADS$_2$ score of 1:
- taking no OAC, this patient has a 26 %/decade risk of stroke
- taking warfarin, the risk drops to 9 %/decade
- taking apixaban, the risk drops to 8 %/decade
- a corresponding no-AFIB patient has a risk of 7 %/decade   (4.11)

Comment: The scale factor 0.93 required to calibrate the NRAF data to the Apixaban Study data might be attributed to the fact that the average age of the NRAF group was 81, while the Apixaban Study had an median age of 70, so we are not surprised to see that the NRAF results have to be scaled down a bit.

5. What is the CHA$_2$DS$_2$-VASc scoring system?

Lip *et al.* (Lip is from Birmingham, UK) came up with a more refined version of the CHADS$_2$ strata scheme which better accounts for the effect of Age and the Sex of the patient (older and/or female increase stroke rate) and adds a Vascular risk factor. This new schema is usually pronounced "chads-two-vask" and here is the scoring plan (from Lip *et al.* 2010 "Refining Clinical Risk...") :

Table 2—The 2009 Birmingham Schema Expressed as a Point-Based Scoring System, With the Acronym CHA$_2$DS$_2$-VASc

Risk Factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65-74 y	1
Sex **c**ategory (ie female gender)	1

LV = left ventricular; TE = thromboembolism. See Table 1 for expansion of other abbreviations.

(5.1)

In this refinement, previous stroke S still gives 2 scoring points, but now age ≥ 75 also gives 2 scoring points, hence the two "2" subscripts A$_2$ and S$_2$. Presumably the "c" suffix on the last letter was installed to distinguish that S from the S for stroke. There are now two age measures instead of one, called A and A$_2$, so age can add 0, 1 or 2 points to a score. Whereas the CHADS$_2$ score ranged 0 to 6, the CHA$_2$DS$_2$-VASc score ranges 0 to 9, and women cannot have a 0 score even if under age 65.

   Lip *et al.* (2010, "Identifying patients...") then present this table of stroke rate versus CHA$_2$DS$_2$-VASc score for patients *on warfarin* in an amalgamated study group of 7,329 AFIB patients: [PY = patient-years. TE = thromboembolic]

Table 4. Stroke or Other Thromboembolism Events per Patient Year Based on the CHA$_2$DS$_2$VASc Scoring System

| CHA$_2$DS$_2$ VASc Score	N	No. of TE Events/PY	taking warfarin TE Rate During 1 Year (95% CI)	TE Rate During taking nothing 1 Year, Adjusted for Warfarin use*
0	1	0/2	0.00	0.0
1	422	3/653	0.46 (0.10, 1.34)	1.3
2	1230	15/1913	0.78 (0.44, 1.29)	2.2
3	1730	31/2673	1.16 (0.79, 1.64)	3.2
4	1718	38/2665	1.43 (1.01, 1.95)	4.0
5	1159	42/1732	2.42 (1.75, 3.26)	6.7
6	679	36/1016	3.54 (2.49, 4.87)	9.8
7	294	15/436	3.44 (1.94, 5.62)	9.6
8	82	3/125	2.41 (0.53, 6.88)	6.7
9	14	1/18	5.47 (0.91, 27.0)	15.2
Total	7329	184/11233	*P* value for trend	*P*<0.0001

TE = thromboembolic

*Theoretical TE rates without therapy: assuming that warfarin provides a 64% reduction in TE risk, based on Hart et al.[34] CI indicates confidence interval.

(5.2)

• Unlike the CHADS$_2$ table (4.2) (which was for patients taking no anticoagulation), the 2nd last column stroke rates of (5.2) are for patients taking warfarin. Using the warfarin RR = 64% reduction idea noted earlier above (3.2), with corresponding RRF = 1/(1-RR) = 1/.36 = 2.78, Lip gives rates in the last column as 2.78 times the rates in the second last column.

• Unlike the CHADS$_2$ score, a patient with score 0 (a male AFIB patient under age 65 with no risk factors) gets a stroke risk of 0% and can forego anticoagulation.

• Unlike the CHADS$_2$ score, the stroke risk percentages are not monotonically increasing with score, which seems a bit strange -- a fluke of low statistics we presume. Consider these two plots,


(5.3)

18
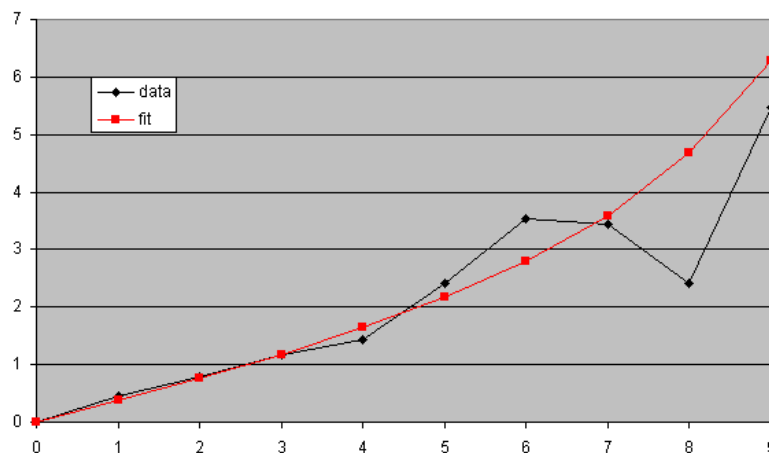
The black points are the actual Lip rates from the 2nd last (warfarin) column of (5.2).
The red curve is the following simple fit to the data :

$$\text{rate} = 3 \tan(\text{score}/8) \qquad \text{// red curve, tan argument is radians not degrees} \qquad (5.4)$$

The fit is "reasonable" except for score = 8 which seems to be an outlier since rate goes down there as the score goes up. Certainly the red curve is "legal" in terms of the upper and lower 95% confidence interval boundaries which are included is this plot as dashed lines (we lowered the top right x from 27 by 10 to make things more visible)

(5.5)
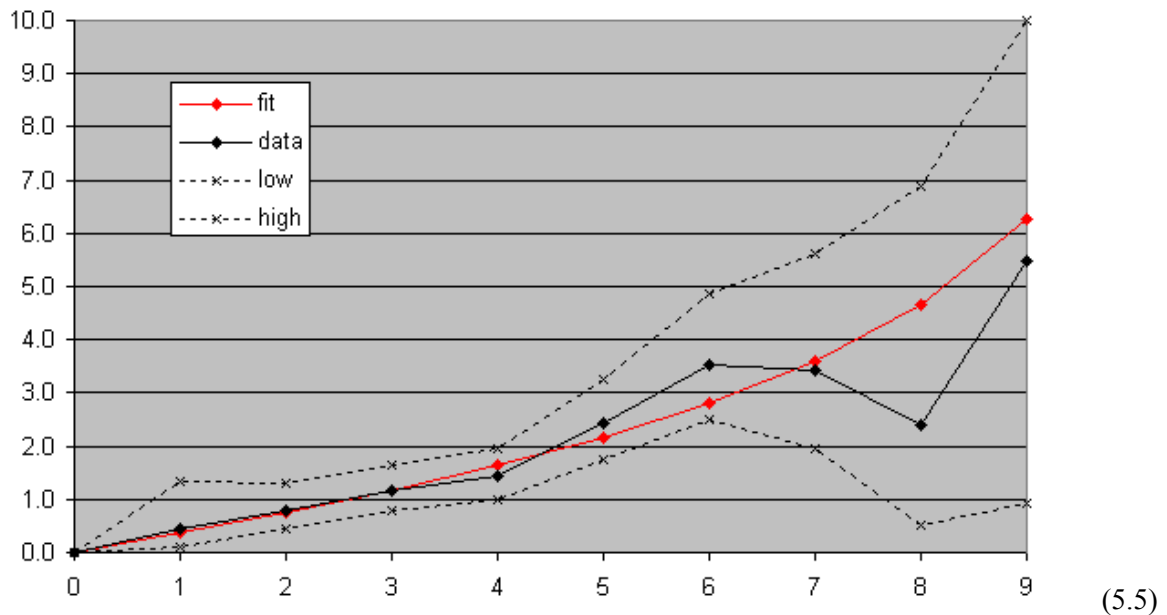
The above graphs come from the following spreadsheet :

CHA2DS2-VASc	warfarin						no-OAC	
	data	fit	low	high	(d-f)/d		data	fit
0	0	0.00	0	0			0.0	0.0
1	0.46	0.38	0.10	1.34	18%		1.3	1.0
2	0.78	0.77	0.44	1.29	2%		2.2	2.1
3	1.16	1.18	0.79	1.64	-2%		3.2	3.3
4	1.43	1.64	1.01	1.95	-15%		4.0	4.6
5	2.42	2.16	1.75	3.26	11%		6.7	6.0
6	3.54	2.79	2.49	4.87	21%		9.8	7.8
7	3.44	3.59	1.94	5.62	-4%		9.6	10.0
8	2.41	4.67	0.53	6.88	-94%		6.7	13.0
9	5.47	6.28	0.91	10	-15%		15.2	17.5

(5.6)

The (d-f)/d column shows that the percent alteration of the fit from the original data is within 20% except for the outliner point with score 8. The data in the last two columns are 2.78 times the data in the warfarin columns, as noted above. We shall use the more "logical" monotonic tangent fit data in our work below.

Footnote. The Lip *et al.* cohort of 7,329 patients was obtained from two studies called SPORTIF III and V. The people in these trials were taking either warfarin or ximelagatran (Exanta, Exarta), a trial anticoagulant. When the two SPORTIF studies were combined, warfarin and ximelagatran had about the same risk for preventing stroke, so we can just pretend that all 7,329 patients were taking warfarin. Thus, the 2nd last column stroke rate percentages shown above in (5.2) are (in effect) for patients taking warfarin. It happens that ximelagatran was withdrawn from trials in 2006 due to liver enzyme issues in 5% of patients. This reminds one that a modest delay in starting even an approved new replacement drug might be something to consider.

Using the same method leading to (4.7), we now compute the average CHA_2DS_2-VASc score and rate:

CHA2DS2-VASc Average Score and Average Rate					
s	r	n	f	s*f	r*f
0	0.00	1	0.0%	0.00	0.00
1	0.38	422	5.8%	0.06	0.02
2	0.77	1230	16.8%	0.34	0.13
3	1.18	1730	23.6%	0.71	0.28
4	1.64	1718	23.4%	0.94	0.38
5	2.16	1159	15.8%	0.79	0.34
6	2.79	679	9.3%	0.56	0.26
7	3.59	294	4.0%	0.28	0.14
8	4.67	82	1.1%	0.09	0.05
9	6.28	14	0.2%	0.02	0.01
		7329	100.0%	**3.77**	**1.62**
				\<score\>	\<rate\>

(5.7)

Then using the average rate 1.62 we construct a stroke risk table in exact analogy with the $CHADS_2$ table (4.9),

|			TOTAL STROKE RISK (annual rate)					no-OAC
			(average score = 3.77)	2.78	2.17	1.00	0.80	0.71
sf	r	sf*r	CHA2DS2-VASc	no-OAC	aspirin	warfarin	apixaban	non-AFIB
1.00	0.00	0.00	0	0.00%	0.00%	0.00%	0.00%	0.00%
1.00	0.38	0.38	1	1.05%	0.82%	0.38%	0.30%	0.27%
1.00	0.77	0.77	2	2.13%	1.66%	0.77%	0.61%	0.54%
1.00	1.18	1.18	3	3.28%	2.56%	1.18%	0.94%	0.84%
1.00	1.64	1.64	4	4.55%	3.55%	1.64%	1.31%	1.16%
1.00	2.16	2.16	5	6.01%	4.69%	2.16%	1.73%	1.54%
1.00	2.79	2.79	6	7.76%	6.06%	2.79%	2.24%	1.98%
1.00	3.59	3.59	7	9.98%	7.78%	3.59%	2.87%	2.55%
1.00	4.67	4.67	8	12.98%	10.12%	4.67%	3.74%	3.32%
1.00	6.28	6.28	9	17.44%	13.60%	6.28%	5.02%	4.46%
1.00	1.62	1.62	average rates:	4.50%	3.51%	1.62%	1.30%	1.15%

(5.8)

The rates in the r column are the adjusted fit rates shown in (5.6). As we shall see, this time no scale factor is required, so we set sf = 1.00 and then the rates from the r column just copy to the sf*r column. They are copied once again to the warfarin column (since the data in this study are for warfarin patients, whereas the $CHADS_2$ study was for no-OAC patients). The remaining columns are then filled out using the multipliers shown at the top (2.78, 2.17, etc) which come from the middle ratio column of (3.12).

In (5.7) the average rate came out 1.62 which happens to exactly match the 1.62 average rate of the Apixaban Study as shown in (3.4). For this reason, the bottom row of (5.8) exactly matches the rates shown in (3.12), and that is why no extra scale factor is required. So the Lip data is already "calibrated" to the Apixaban Study. This is largely due to the fact that the Lip amalgamated data set and the Apixaban data sets have the same mean age.

Comment: It is of course just a coincidence that the average rate came out 1.62 exactly matching the Apixaban Study number to 3 significant figures, especially in light of our crude tangent fit adjustment and the usual wide error bands shown in (5.5). Had this exact match not occurred, we would have added a scale factor in the left column of (5.8) to effect the calibration to the Apixaban Study as we did for $CHADS_2$ in (4.9).

Here is a plot of the data in table (5.8) :
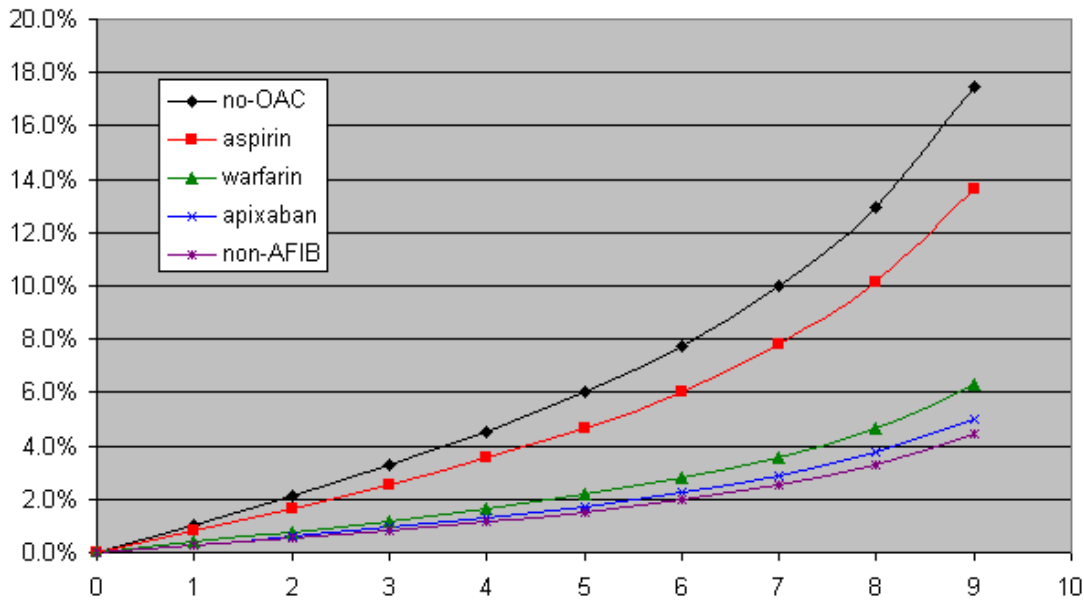
Annual Total Stroke Rate CHA_2DS_2-VASc score $\rightarrow$ (5.9)

The highest (worst) curve is for the AFIB patient taking no anticoagulation.
The lowest (best) curve is for age-matched people who don't have AFIB.

Unlike the $CHADS_2$ plot (4.10), all five curves meet at the origin since (5.2) indicates zero stroke rate for score 0.

Again, the benefit of taking oral anticoagulants (OAC) for AFIB especially at higher CHA_2DS_2-VASc scores is dramatic. For example, a person with score 6 taking no OAC has a 78% chance of having a stroke over 10 years.

Example: A relatively healthy AFIB patient has a CHADS$_2$-VASc score of 2:

- taking no OAC, this patient has a 21 %/decade risk of stroke
- taking warfarin, the risk drops to 8 %/decade
- taking apixaban, the risk drops to 6 %/decade
- a corresponding no-AFIB patient has a risk of 5 %/decade   (5.10)

 The "taking nothing" column of (5.2) and the last column of (4.2) for CHADS$_2$ appear on page 27 of the 2014 AHA Guidelines, but the Guidelines fail to note that this data is for no anticoagulation :

CHA$_2$DS$_2$-VASc acronym†

Score	%	tangent fit
0	0%	0.0
1	1.3%	1.0
2	2.2%	2.1
3	3.2%	3.3
4	4.0%	4.6
5	6.7%	6.0
6	9.8%	7.8
7	9.6%	10.0
8	6.7%	13.0
9	15.20%	17.5

CHADS$_2$ acronym*

Score	%
0	1.9%
1	2.8%
2	4.0%
3	5.9%
4	8.5%
5	12.5%
6	18.2%

              // no anticoagulation   // no anticoagulation   (5.11)

Our tangent fit CHA$_2$DS$_2$-VASc no-OAC rates are shown to the right of the Guidelines numbers, taken from the right column of (5.6).

<u>Taking a Warfarin Break and Pill-in-a-Pocket ?</u>   (5.12)

For our Example (5.10) -- AFIB patient with a CHA$_2$DS$_2$-VASc score of 2 -- the *annual* stroke risk is about 0.8 % if on warfarin, and 2.1% off warfarin. Since these are per-year risk rates, going off warfarin for a few *days* for dental work or whatever represents only a tiny stroke risk. For example, if one's INR drops to 1.0 for 2 days, the absolute stroke risk for those days would be (2/365)*2.1% = .01% = 1/10,000.

     For people who rarely go into AFIB (as far as they know), this does suggest the "pill in a pocket" idea for warfarin use. One only takes warfarin on those rare occasions when AFIB occurs. There are doubtless counterarguments to this plan based on the idea that clots could in theory form in a few minutes or hours while it might take 2 to 4 days for the warfarin INR 2-3 therapeutic range to be restored. Moreover, the "AFIB begets AFIB" philosophy argues for a quick electrocardioversion soon after AFIB occurs, but the 2014 AHA Guidelines (p 52) recommend warfarin be taken "for at least 3 weeks" prior to such a cardioversion. This delay might increase the chances of electrocardioversion not working or increase the patient's paroxysmal recurrence frequency.

6. The QStroke Calculator

Algorithms like QStroke are likely to become more prevalent since they are trivial to use online or perhaps with a smartphone app. You quickly enter your particular data and it computes risk based on your data. Such methods can allow for arbitrarily complicated models based on "machine learning" (Big Data approach) where one does a logistic regression fit to many factors ("predictors"). QStroke is available as free software under a Gnu public license.

Here is a data entry Example (http://www.qstroke.org/) : [notice the AFIB check box]

(6.1)

And here is the result of pushing the button:

(6.2)

In the two examples (4.11) and (5.10) given earlier (all examples apply to the same patient), being on warfarin with a $CHADS_2$ score of 1 predicted a stroke rate of 0.9 %/yr, while being on warfarin with a CHA_2DS_2-VASc score of 2 predicted an annual stroke risk of 0.8 %/yr. Both these numbers are quite close to the QStroke prediction of 0.8 %/yr. It is always encouraging when different methods lead to the same result.

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7. Accuracy and Ambiguity

Accuracy of AFIB Study Results

Here we momentarily pull back the curtain and take a brief look at the seamy underside of AFIB trials and studies, which is their accuracy, then we quickly restore the curtain and look the other way.

Most of the studies/trials regarding AFIB stroke (and bleeding) have insufficient statistics to be truly conclusive in terms of the quoted percentage risk rates, as shown for example in Fig (5.5) where the dashed curves show the error band. Uncertainty is presented in term of a 95% confidence interval (CI), or perhaps the standard deviation (SD) is given, or error bars are simply displayed as in our Fig (3.1) above,


```
SPAF I, 1991
BAATAF, 1990
CAFA, 1991
```
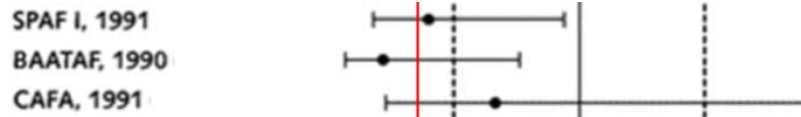
The relative largeness of the error bars is due to the fact that:

    (1) a study is hard pressed (by cost and time) to get more than a few thousand AFIB patients

    (2) if these patients are classified into strata scheme bins, the number per bin is smaller still

    (3) the annual risk rates for stroke or bleeding are relatively small, on the order of 1-5%

To show how these three items conspire to cause trouble, we consider a simple model for the statistics of a trial known as the Bernoulli Trial model. A study of N patients with outcome stroke or no-stroke can be treated like flipping a weighted coin N times where p is the probability of getting a head (a stroke) on one toss (watch patient for a year). After doing the N flips (carrying out one AFIB study), by counting the number of heads H one will find that the fraction H/N is close to p, the mean. The probability distribution for the fraction of heads is the binomial distribution which has mean p and SD = $\sigma_{mean} = \sqrt{p(1-p)/N}$. Since the binomial distribution is close to the normal (gaussian) distribution for large N, the 95% confidence interval is $1.96\sigma_{mean}$ in either direction. Thus one would describe the study outcome (p = percentage of patients having strokes in one year) as lying with 95% confidence in this interval,
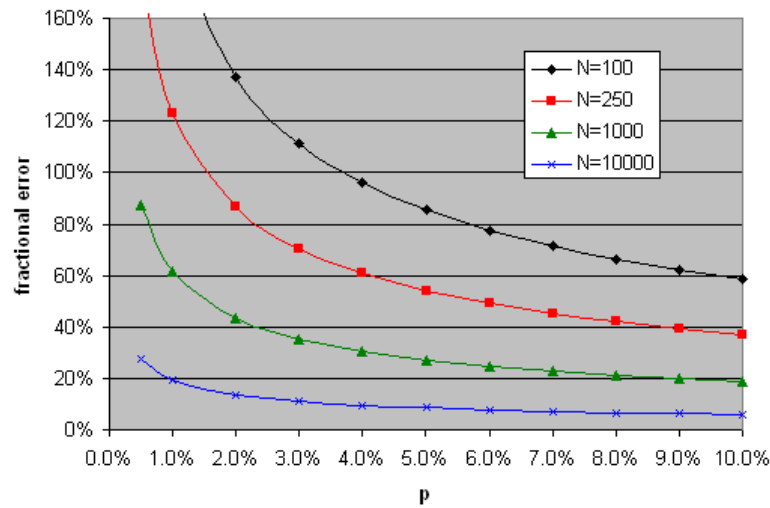
$$p \pm 1.96\, \sigma_{mean} \;=\; p \pm 1.96\sqrt{\frac{p(1-p)}{N}} \;\;=\; p\left(1 \pm 1.96\sqrt{\frac{(1-p)}{Np}}\right) \;=\; p\,(1 \pm \text{fractional error})$$

$$\text{fractional error} = 1.96\sqrt{\frac{(1-p)}{Np}} \;\approx\; 1.96\,\sqrt{\frac{1}{Np}} \text{ (if p is small)} \tag{7.1}$$

Here we see the penalty inflicted on the fractional error by small N and/or small p.

The following spreadsheet computes fractional error as a function of N and p for this model :

	100	250	1000	10000
p	N=100	N=250	N=1000	N=10000
0.5%	276%	175%	87%	28%
1%	195%	123%	62%	20%
2%	137%	87%	43%	14%
3%	111%	70%	35%	11%
4%	96%	61%	30%	10%
5%	85%	54%	27%	9%
6%	78%	49%	25%	8%
7%	71%	45%	23%	7%
8%	66%	42%	21%	7%
9%	62%	39%	20%	6%
10%	59%	37%	19%	6%

(7.2)

For example, if the mean value of a stroke rate is 4.0% and the patient count associated with that rate is N=1000, then with a 95% CI one would express that rate as$(1 \pm .30)*4.0\%$ and one would say the mean value was *fractionally* accurate to $\pm 30\%$. The actual CI range would be [0.7, 1.3] 4% = [2.8%, 5.2%].

In actual studies, the Bernoulli model is replaced by a model which gives somewhat smaller error bars. For example, in the censured exponential survival model used in the $CHADS_2$ study (footnote in (4.2)), one observes the actual times at which strokes occur during the study. This information, ignored in the Bernoulli model, allows for smaller and asymmetric error bars. However, the error bars are in the same general range as the Bernoulli model bars and do not do much to reduce uncertainty.

The bins in the $CHADS_2$ and CHA_2DS_2-VASc studies have from N ≈ 100 to N ≈ 1700 patients. In our bleed document we deal with similar strata schemes called $HEMORR_2HAGES$ and HAS-BLED which have similar binned patient counts. For each strata scheme, we consider one particular study (normally carried out by the inventor of the scheme), and here we show the fractional error on the low and high side of the data (felo and fehi) for each of our four strata cases:

CHADS2

s	felo	fehi
0	37%	58%
1	29%	36%
2	23%	28%
3	22%	24%
4	26%	31%
5	34%	40%
6	42%	51%

CHA2DS2-VASc

s	felo	fehi
0		
1	78%	191%
2	44%	65%
3	32%	41%
4	29%	36%
5	28%	35%
6	30%	38%
7	44%	63%
8	78%	185%
9	83%	83%

HEMORR2HAGES

s	felo	fehi
0	68%	132%
1	48%	72%
2	36%	53%
3	42%	62%
4	51%	82%
5	53%	88%

HAS-BLED

s	felo	fehi
0	75%	75%
1	29%	29%
2	31%	31%
3	36%	36%
4	44%	44%

(7.3)

For HAS-BLED the fractional errors are symmetric because we generate them ourselves using the Bernoulli model above, but in the other cases the fractional errors are computed from the absolute error bands provided by the study.

The large sizes of these fractional errors are discouraging, and are due to the low bin N counts as noted above. If we ignore the $HEMORR_2HAGES$ study errors, we might generously claim that, for the non-extremal scores, the other three strata schemes produce rates with a ballpark ±30% fractional error at 95% CI. Dropping down from two to one standard deviation, these rates are roughly ±15% accurate at a 68% confidence interval.

Thus, the rate numbers appearing for example in table (5.8) presented gloriously with 2 or 3 significant figures really have less than 1 significant digit of accuracy. For example:

$$0.78 \quad \rightarrow \quad 0.78 \pm .30*0.78 \; = \; 0.78 \pm 0.23 \quad \approx \; 0.8 \pm 0.2 \qquad 95\% \text{ CI}$$

$$3.16 \quad \rightarrow \quad 3.16 \pm .30*3.16 \; = \; 3.16 \pm 0.95 \quad \approx \; 3 \pm 1 \qquad 95\% \text{ CI}$$

$$6.88 \quad \rightarrow \quad 6.88 \pm .30*6.88 \; = \; 6.88 \pm 2.06 \quad \approx \; 7 \pm 2 \qquad 95\% \text{ CI}$$

In the last case, if the result can be 5,6,7,8 or 9, one cannot claim there is even one digit of precision in the result. That would require the result being 7 ± 0.5 or better. For 68% CI one has 7 ± 1, and still there is not one digit of precision. So we give up on making any fancy claims (such as a "half digit" of precision) and just stick with the ±30% for 95% CI and ±15% for 68% CI as our ballpark strata scheme error ranges. If one wants something more accurate for errors, one can look at (7.3).

Nevertheless, we maintain the 3 digit notation to make it easier for the reader to follow the numbers as they get moved around between our various spreadsheets, and also to reduce any further error arising from computation.

Numbers derived for an average patient in an arm of the Apixaban Study with $N \approx 9000$ might be accurate to ±10% with 95% CI, just looking at the graph in (7.2).

Our rate tables are all based on OAC *ratios* such as those appearing across the top of (5.8) and of course these ratios also have error bars. For example, comparing apixaban to warfarin the Apixaban Study gives stroke rates of 1.27 and 1.60 in the top row of (3.3), and the ratio of these rates is .79 but the error range is (.66, .95) giving a low and high side fractional error of (16%, 20%) with 95% CI. At least this is better than the ±30 % range for the strata scheme studies. So we might generally claim that any statement regarding ratios of rates for different OAC values might be accurate to about ±20 % fractional error with 95% CI.

Ambiguity in AFIB Study Results

Everything should have a clean definition but often clean definitions are not provided, are not available, or differ from study to study. For example, what exactly is a "stroke"? Usually it means a blood flow blockage (ischemic) stroke, but it might include a bleeding stroke (hemorrhagic stroke). Normally it is in the brain (cerebral), but it could be elsewhere such as in the lungs (pulmonary embolism). Does a TIA

count as a stroke? Do the stroke effects have to last more than 24 hours for the stroke to be counted? Are strokes induced by trauma counted? How does one deal with ischemic strokes which transform into hemorrhagic ones? Often retrospective studies use historical hospital IDC code data and things are not always clear. If a stroke patient is discharged on warfarin, should one assume he or she was on warfarin during the time period leading up to the stroke?

Some other examples: in a CHADS type scoring, does "Hypertension" mean the patient *would* have high BP without drug control, or does it mean he/she has high BP as a diagnosis for a controlling drug, or does it mean the person actually *has* high BP? If hypertension means systolic > 160, does that refer to the patient's average value BP over a day, or the awake day, or does it refer to a peak value during a day? In a similar vein, exactly what is alcohol abuse in the HEMORR$_2$HAGES and HAS-BLED scorings which appear in our bleed document?

In our AFIB bleed document there are similar ambiguities for the definition of a "major bleed". The Apixaban Study felt compelled to present results by three different major bleed standards, and each of the two strata schemes (HEMORR$_2$HAGES and HAS-BLED) has its own slightly different definition. Probably events counted by all these definitions are very similar.

8. Long term anticoagulation after successful catheter ablation?

This seems to be a delicate subject right now. The 2014 AHA Guidelines are silent on the topic. However, here is what the 2012 ESC Guidelines have to say regarding peri- and post-ablation anticoagulation (p 2741):

ESC Guidelines

Such a regimen may help to reduce peri-procedural strokes, possibly including silent cerebral infarcts. As already recommended in the 2010 Guidelines,[1] continuation of long-term OAC therapy post-ablation is recommended in all patients with a CHA_2DS_2-VASc score of ≥ 2, irrespective of apparent procedural success.

(8.1)

The problem is a lack of data (so far) on AFIB recurrences after "successful" ablation, and on post-ablation stroke rates for those on and off long term OAC (oral anticoagulation). Doctors have seen post-ablation people go off OAC and die, for example. It is possible that "silent AFIB" will start up undetected by the patient, or regular symptomatic AFIB might start up. Things are not well understood, and some doctors don't want to take the risk of patients going off OAC for CHA_2DS_2-VASc scores ≥ 2. One approach would be to wait a year, then do a 30 day Holter test, then maybe go off if it is clean. Here is another comment on the subject (Levitt, 2009) in which an elevated $CHADS_2$ risk means a score ≥ 2 :

Prev Cardiol. 2009 Winter;12(1):39-42.

Is there a need to continue anticoagulation following "successful" atrial fibrillation ablation?

Levitt HL[1], Toor SZ, Coplan NL.

⊕ Author information

Abstract

Atrial fibrillation (AF) is the most common clinically significant arrhythmia worldwide, and its incidence is increasing. There has been increasing interest in ablation therapy to treat atrial fibrillation. One reason some patients undergo AF ablation might be to obviate the need for warfarin therapy, although current guidelines do not support this rationale. The current review shows that it is difficult to define a true "cure" postablation, as many of these patients will go on to experience future paroxysms of AF (either symptomatic or silent). The mechanism underlying embolism in patients with AF is not completely understood, and no long-term evidence exists that "successfully ablated" patients return to a baseline risk of stroke comparable to an AF-naive population. The authors recommend continued long-term anticoagulation post-AF ablation in patients satisfying CHADS criteria for elevated stroke risk.

PMID: 19301690 [PubMed - indexed for MEDLINE]

(8.2)

The ESC Guideline is more stringent, requiring long-term post-ablation OAC for a CHA_2DS_2-VASc score ≥ 2 . Hopefully more data will be collected on this subject.

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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However, our Fig (2.3) appears as a black and white Chart 4-4 in the following 2011 update,

Véronique LR *et al.* Heart Disease and Stroke Statistics—2011 Update : A Report From the American Heart Association, *Circulation* February 1, 2011 vol. 123 no. 4 e18-e209.
[doi: 10.1161/CIR.0b013e318200970]

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The actual color figure we used came from here:

https://www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_449858.pdf.

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

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www.excellence.acforum.org/sites/default/files/Gage.CHADS2_.pdf

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See also page 2741 of the previous reference ESC 2012.