A Statistical Methodology for Adjustment of Stroke Event Rates for $CHADS_2$ Score for Indirect Comparison across Trials - a Case Study

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Abstract

Stroke event rates in patients with atrial fibrillation vary according to patients' baseline characteristics reflected by a $CHADS_2$ score based on prior heart failure, hypertension, diabetes mellitus, prior stroke, and age 75 year or older. Adjustment for $CHADS_2$ score would help in indirect comparison of drugs across studies.

We have illustrated a methodology to adjust stroke event rates for $CHADS_2$ score, using published results of 3 new anticoagulants trials (dabigatran, apixaban, rivaroxaban) where warfarin was the common comparator. Mean $CHADS_2$ score was ~2.1 in both dabigatran and apixaban trials, and 3.5 in rivaroxaban trial.

Adjustment factors were derived using regression of natural log of event rates on $CHADS_2$ scores from warfarin treatment group only. Estimates were transformed back to the original scale.

Event rates adjusted to a $CHADS_2$ score of 3.0 for dabigatran, apixaban and rivaroxaban all compared with warfarin were 1.35 vs 1.93, 1.46 vs 1.87, and 1.36 vs 1.82, respectively. Whereas, the originally reported event rates were 1.11 vs 1.69, 1.27 vs 1.60, and 1.70 vs 2.20, respectively. Adjustment to a $CHADS_2$ score of 3.0 gave the minimum mean square error. The increase or decrease in adjusted event rates was relative to the baseline $CHADS_2$ score. Adjusted event rates were meaningful and realistic.

Key Words: Stroke, Atrial Fibrillation, $CHADS_2$ score, Indirect Comparison, Hazard Ratio.

1. Introduction

The $CHADS_2$ score is a measure of the risk of stroke in which prior heart failure, hypertension, diabetes mellitus, and an age of 75 years or older are each assigned 1 point and previous stroke or transient ischemic attack are assigned 2 points, and the score is calculated by summing all the points for each patient. The $CHADS_2$ score can range from 0 to 6. Stroke event rates are higher with increasing $CHADS_2$ score [1-11] showing a linear tend. The $CHADS_2$ score is also associated with all-cause mortality after stroke [12], and risk of bleeding [13]. The $CHADS_2$ score has been often categorized as 0-1, 2, and $\geq$3, indicating low, moderate and high severity, respectively.

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It is unreasonable to compare the outcomes across studies unless patients' characteristics are similar. We also feel that the only risk ratio should not be regarded as the sole criterion for comparing efficacy across studies. Risk ratio can be numerically lower in a study having high event rates than in another study with lower event rates. Risk ratio is specific to a study. A low event rate should be considered an important indicator of clinical efficacy. In this study, we have attempted to adjust stroke event rates for differences in $CHADS_2$ score, thus enabling indirect comparison across studies.

2. Objectives

The aim of this study was to develop a statistical methodology to adjust stroke event rates to a common $CHADS_2$ score to enable indirect comparisons across studies, using published results from 3 major randomized clinical trials for prevention of stroke in non-valvular atrial fibrillation populations. We are asking a question; what would be the outcome rates if the patients' baseline characteristics were similar or if there were head to head comparison of dabigatran, apixaban, and rivaroxaban.

3. Materials

Stroke event rates from published results of 3 major randomized clinical trials RE-LY for dabigatran [4], ARISTOLTLE for apixaban [6], and ROCKET-AF for rivaroxaban [9], having warfarin as the common comparator, were used to derive adjustment factors to adjust event rates of stroke or systemic embolism to a common $CHADS_2$ score. Actual data of these clinical trials was not used. Percentage of patients with different $CHADS_2$ scores in dabigatran and apixaban trials were quite similar, whereas the majority of patients in rivaroxaban trial were more severe with a $CHADS_2$ score of 3 to 6 (Figure 1). From RE-LY trial, we used information of dabigatran 150 mg and warfarin groups only. We derived adjustment factors using results of warfarin only. It was assumed that the response (i.e. event rate) under warfarin should be similar between studies for patients having the same $CHADS_2$ score. This assumption was apparently reasonable as indicated by published event rates of 1.38%, 1.40%, and 1.52% for a $CHADS_2$ score of 2 in RE-LY, ARISTOTLE, and ROCKET-AF trials, respectively. The information on event rates for each $CHADS_2$ score was not available for RE-LY and ARISTOTLE studies. However, the trend in event rates and $CHADS_2$ score in ROCKET-AF trial was quite linear for the both rivaroxaban and warfarin groups (Figure 2).

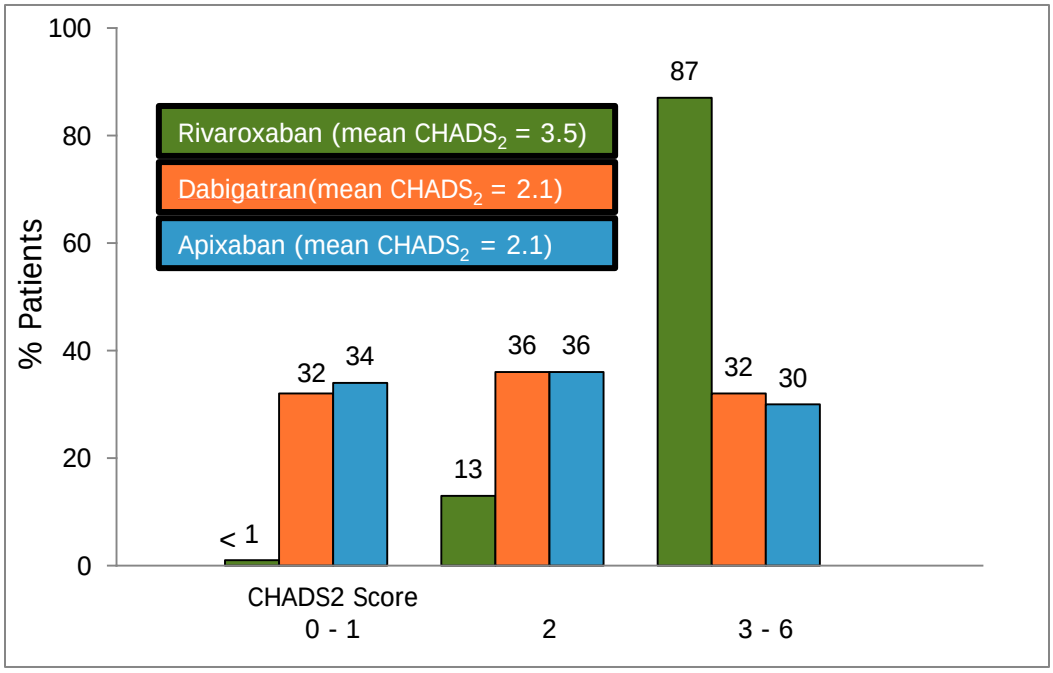

Figure 1. Distribution of patients by $CHADS_2$ score in rivaroxaban, dabigatran and apixaban trials.

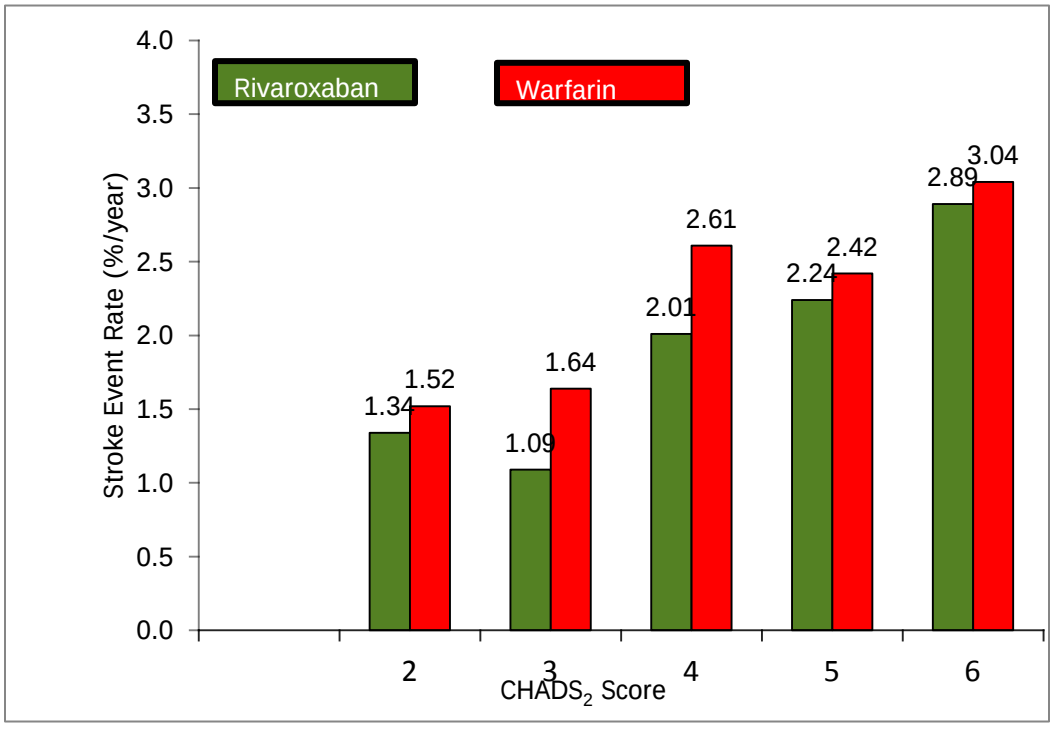

Figure 2. Event rate (%/year) of stroke or systemic embolism for rivaroxaban versus warfarin in ROCKET-AF trial. Event rates were scaled by 1.7 years duration of study to approximate event rates on a percent-year basis.

Published results of stroke event rates from these 3 studies are summarized in Table 1. Adjustments were derived using a regression technique applied to log transformed values of event rates, and then transformed back to original scale. Event rates displayed in Table 1 are on a percent-year basis. For ROCKET-AF study, we divided the reported event rates by the study duration of 1.7 years [9] to approximate event rates on a percent-year basis because the published event rates for different $CHADS_2$ scores were over the entire duration of study.

Table 1. Published data used for deriving adjustment factors to adjust stroke event rates for $CHADS_2$ score.

Study	$CHADS_2$ score	Active drug		Comparator drug	
		No. of patients	Event Rate (%/year)	N	Event Rate (%/year)
RE-LY		Dabigatran		Warfarin	
	~ 2.1	6076	1.11	6,022	1.69
	0-1	1958	0.65	1859	1.05
	2	2137	0.84	2230	1.38
	3-6	1981	1.88	1933	2.68
ARISTOTLE		Apixaban		Warfarin	
	~ 2.1	9120	1.27	9081	1.60
	0-1	3100	0.70	3083	0.90
	2	3262	1.20	3254	1.40
	3-6	2758	1.90	2744	2.80
ROCKET-AF*		Rivaroxaban		Warfarin	
	3.5	7061	1.70	7081	2.20
	2	922	1.34	931	1.52
	3	3025	1.09	3131	1.64
	4	2073	2.01	1988	2.61
	5	918	2.24	875	2.42
	6	122	2.89	155	3.04
*Event rates were divided by the reported mean follow-up period of 1.7 years to approximate event rates on a %/year basis.					

4. Methods

We calculated regression coefficients of natural log of event rate on $CHADS_2$ score, using the below model. A log transformation was applied for normality.

$$\log(y) = \alpha + \beta_1 x + \beta_2 x^2 + \varepsilon$$

where,

y = event rate (percent per year)

α = Intercept

x = $CHADS_2$ score

ε = random error associated with y

β_1 and β_2 are the linear and quadratic regression coefficients of natural log event rates on values of $CHADS_2$ score, respectively.

The mean square error (MSE) criterion was used to determine the efficiency of adjustment factors. Stroke event rates for RE-LY and ARISTOTLE studies were available for $CHADS_2$ scores categories of 0-1, 2 and 3-6 only. We assigned mid-point values of 0.5 and 4.5 for categories 0-1 and 3-6, respectively, for regression analysis. Stroke event rates from the primary efficacy analysis populations were used. We adjusted the observed event rates to $CHADS_2$ score values of 2, 3, and 4. The adjustment was performed in the 2 steps outlined below, and an example of the calculations is given in Table 2.

Table 2. Example of the calculations of event rate adjusted to a $CHADS_2$ score of 3.0 for the dabigatran group of RE-LY.

$CHADS_2$ score	$CHADS_2$ score mid-point	No. of patients (n_i)	Published event rate (%/yr): y	Adjustment factor for a $CHADS_2$ score (j=3): $e^{(\hat{y}_j)} - e^{(\hat{y}_i)}$	Adjusted event rate: $A_{i=} y + e^{(\hat{y}_j)} - e^{(\hat{y}_i)}$	Weighted mean of adjusted event rate: $w = \sum(n_i A_i)/\sum n_i$
0-1	0.5	1958	0.65	+0.95	1.60	1.35
2	2	2137	0.84	+0.42	1.26	
3-6	4.5	1981	1.88	-0.67	1.21	

4.1 Calculation of predicted event rates and adjustment to a common $CHADS_2$ score.

Let,

$$\hat{y} = \hat{\alpha} + \hat{\beta}_1 x + \hat{\beta}_2 x^2$$

where,

$\hat{y}$ = predicted event rate on a log scale,

$\hat{\alpha}$ = estimated intercept on a log scale,

$\hat{\beta}_1$ and $\hat{\beta}_2$ are estimated linear and quadratic regression coefficients on a log scale

Then, event rate on original scale for the i^{th} $CHADS_2$ score adjusted to the j^{th} $CHADS_2$ score (A) = $y + e^{(\hat{y}_j)} - e^{(\hat{y}_i)}$

MSE was calculated as $(\sum(y-A)^2)/(n-1)$; where n is the number of patients with event rates and specific $CHADS_2$ score.

4.2 Weighted mean of event rate (w) combining event rates for all $CHADS_2$ scores was calculated as follows. Let there be i $CHADS_2$ scores;

then,

$w = \sum(n_i A_i)/ \sum n_i$

where,

n_i = number of patients in the i^{th} $CHADS_2$ score

A_i = adjusted event rate for the i^{th} $CHADS_2$ score

A simulation was also performed to evaluate the validity of estimated regression parameters, and adjustment factors. For each value of stroke event rate in the warfarin for each $CHADS_2$ score summarized in Table 1, a sample of 10,000 values was generated using an exponential distribution, and each generated value was based on mean of 100 simulated values. Simulation size was determined to ensure that the mean simulated value was equal to the value used as a parameter in the simulation.

5. Results

Predicted event rates for different values of $CHADS_2$ score are displayed in Figure 3. The relationship between predicted values of stroke event rate and $CHADS_2$ score was quite linear. Adjustment factors to adjust published event rate to a common $CHADS_2$ score are presented in Table 3. The MSE values in Table 3 indicated that the adjustment to a $CHADS_2$ score of 3.0 was most efficient. We have presented adjustment factors for $CHADS_2$ score values of 2, 3 and 4 only, as the adjustment to other values may not be of clinical interest for comparisons.

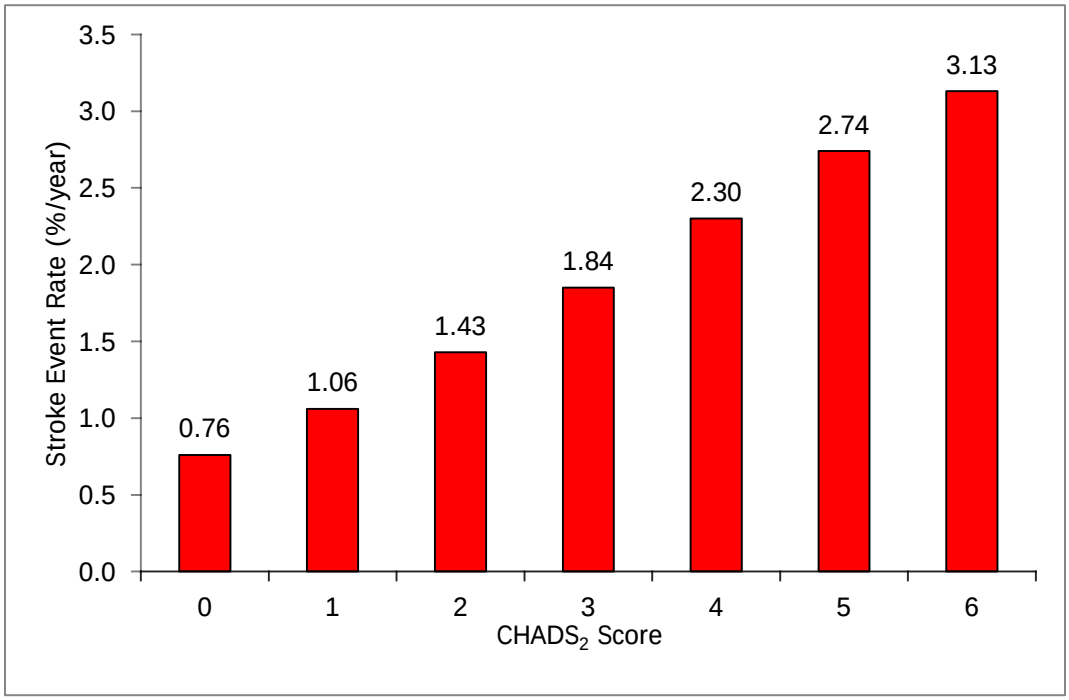

Figure 3. Predicted event rate (%/year) of stroke or systemic embolism in warfarin group based on 3 studies.

Table 3. Adjustment factors to adjust stroke event rates for different values of $CHADS_2$ score, based on regression parameters estimated from warfarin group**s.**

$CHADS_2$ score	Adjustment factors to adjust stroke event rates to different $CHADS_2$ score values		
	2	3	4
0.5	+0.53	+0.95	+1.39
1	+0.37	+0.79	+1.23
2	0.00	+0.42	+0.87
3	-0.42	0.00	+0.45
4	-0.87	-0.45	0.00
4.5	-1.09	-0.67	-0.22
5	-1.31	-0.89	-0.44
6	-1.70	-1.28	-0.84
MSE	0.75	0.53	0.69

Table 4 contains adjusted values of stroke event rates for above 3 studies, using the regression parameters estimated from event rates in these studies, and also from regression parameters estimated from simulation. The overall effect of adjustment on the increase or decrease in published event rates was relative to the mean $CHADS_2$ score originally reported. Adjusted event rates for a $CHADS_2$ score of 3.0 for dabigatran vs. warfarin were 1.35 vs. 1.93; apixaban vs. warfarin 1.46 vs. 1.87, and rivaroxaban vs. warfarin 1.36 vs. 1.82. In contrast, published event rates for dabigatran vs. warfarin were 1.11 vs. 1.69; apixaban vs. warfarin 1.27 vs. 1.60, and rivaroxaban vs. warfarin 1.70 vs. 2.20. Published event rates were not comparable because of differences in mean $CHADS_2$ scores. Adjusted event rates for a $CHADS_2$ score of 3.0 are also displayed in Figure 4. The odds ratios (OR) from comparison with warfarin in each study and based on event rates adjusted to a $CHADS_2$ score of 3.0 were 0.70, 0.78, and 0.74 for dabigatran, apixaban, and rivaroxaban, respectively. Whereas, the reported hazard ratios were 0.66, 0.79, and 0.79, respectively.

Table 4. Adjusted event rates for stroke for different values of $CHADS_2$ score**.**

Clinical Trial	Drug	Adjusted event rates for different $CHADS_2$ scores (based on regression parameters estimated from warfarin data of three studies)			Adjusted event rates for different $CHADS_2$ score (based on regression parameters estimated from simulation)		
		2	3	4	2	3	4
RE-LY	Dabigatran	0.93	1.35	1.80	0.94	1.34	1.77
	Warfarin	1.51	1.93	2.37	1.51	1.92	2.35
ARISTOTLE	Apixaban	1.04	1.46	1.90	1.04	1.45	1.88
	Warfarin	1.45	1.87	2.31	1.46	1.86	2.29
ROCKET-AF	Rivaroxaban	0.94	1.36	1.81	0.96	1.37	1.80
	Warfarin	1.40	1.82	2.26	1.42	1.82	2.25

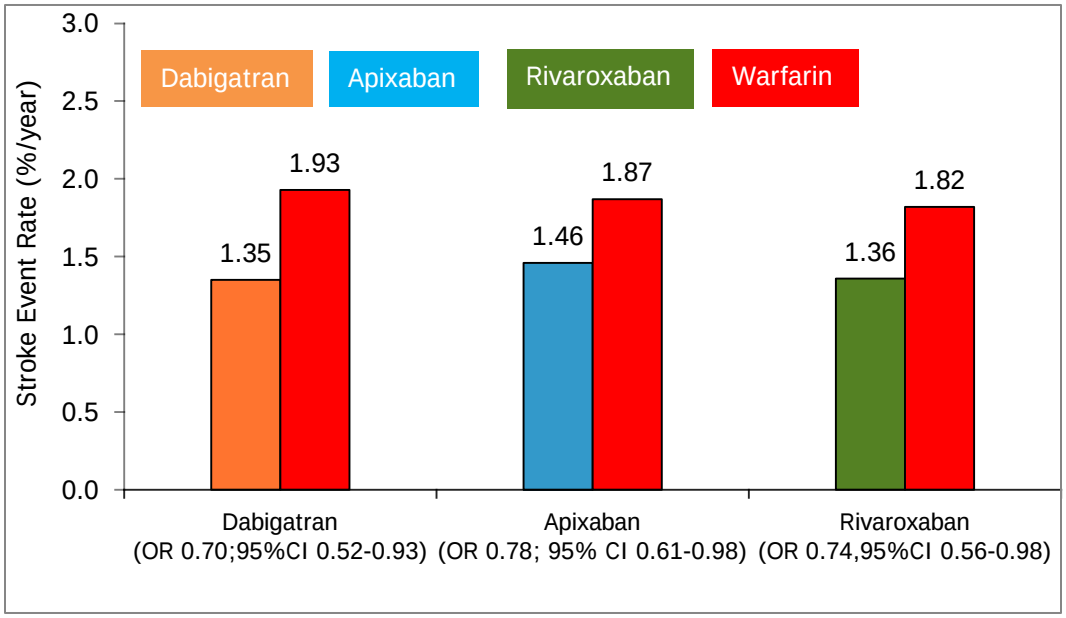

Figure 4. Adjusted event rates (%/year) of stroke or systemic embolism adjusted for baseline $CHADS_2$ score of 3.0.

6. Discussion

We have developed and applied a method for adjusting and then comparing event rates across studies which differ in their patients' characteristics. Our study showed that adjusted results were meaningful as the adjusted values were apparently realistic for a population with similar patients' characteristics.

Regression parameters would have been more precise if the event rates for each $CHADS_2$ score were available from the RE-LY and ARISTOTLE studies, and if actual percent-year event rates from ROCKET-AF study were available. Such adjustments may be of particular interest to drug developers and medical practitioners.

For deriving adjustment factors, we used the data on warfarin only, as it was reasonable to assume the same relationship between event rate and $CHADS_2$ score across studies. We did not use the stroke events data from active groups from these studies as it could be argued that relationship between event rate and $CHADS_2$ score may be different in active groups. However, the treatment by $CHADS_2$ score interaction was non-significant in the above 3 studies [4, 6, 9].

We suggest that such adjustments may be further investigated based on results from a good number of large studies or using individual patients' data. To ensure wider application in the industry, adjustment factors should preferably be derived from an independent source such as meta-analysis results from a good number of studies. In addition to adjustment for $CHADS_2$ score, it may be also useful to adjust stroke event rates for other potential risk factors for indirect comparisons.

Pre-adjustment of data for defined environmental effects is commonly used in other academic communities. For example, adjustment for factors such as age is widely used

by the dairy industry to adjust the production data to a mature equivalent level [14, 15] for comparison of genotypes.

If the stroke event rates for each treatment group from the RE-LY and ARISTOTLE trials are available for each $CHADS_2$ score, the estimates of the adjustment factors could be developed more precisely. It would be further useful if more studies with warfarin as a comparator are included for deriving adjustment factors.

7. Conclusions

The increase or decrease in observed event rates as a result of adjustment to a common $CHADS_2$ score was relative to the original $CHADS_2$ score. Derived adjustment factors were meaningful and realistic.

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