A New Approach for Evaluating Benefit-Risk in Anticoagulation Studies – a Case Study

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Abstract

The benefit-risk has been quantified in some studies as the net clinical benefit (NCB) or net clinical outcome of a composite endpoint consisting of efficacy and safety endpoints. The efficacy and safety endpoints included in a composite endpoint are implicitly assumed to be clinically equally important. However, there is a need to consider weight for each endpoint, according to relative clinical importance when estimating NCB.

The aim of this study was to evaluate benefit-risk as NCB, weighing efficacy and safety endpoints. We estimated NCB as the aggregate odds ratio by combining the risk ratios for efficacy and safety endpoints, alternatively using weight of 1.00 to each endpoint, using the inverse of variance of risk ratio as weight, and using weight based on clinical importance. Published data from dabigatran (RE-LY) and apixaban (ARISTOTLE) trials were used to illustrate our method.

Estimates of NCB from various combinations of endpoints were robust, leading to an inference that the NCB was higher from apixaban than dabigatran. The analyses using the inverse of variance of risk ratio as the weight were considered more efficient, because of narrow confidence intervals.

The aggregate odds ratio is a simple and robust means of combining different outcomes. This method can be equally applied to any set of multiple outcomes in any therapeutic areas. Since the trials are mainly powered for the primary efficacy endpoint, we suggest weighing the risk ratios of different endpoints by the inverse of variance of the risk ratio for estimating NCB.

Key Words: benefit-risk; net clinical benefit; net clinical outcome; composite endpoint; stroke; atrial fibrillation.

1. Introduction

Overall clinical benefit is becoming increasingly important to regulatory agencies, medical practitioners, and drugs developers for understanding of clinical benefit-risk. It has been conventionally predicted as the net clinical benefit (NCB) or the net clinical outcome of composite endpoints of efficacy and safety endpoints [1, 2]. The outcome of a composite endpoint means the occurrence of an event of any of the endpoints included in a composite endpoint. For example, if a composite endpoint consists of stroke, myocardial infarction (MI) and all-cause death, then the occurrence of any of these endpoints is regarded as an outcome of the composite endpoint. It is implicitly assumed that all endpoints included in a composite endpoint are considered clinically equally important. This assumption is unrealistic because the outcomes such as MI and death cannot be regarded clinically equal. Some kind of weight assigned to each endpoint according to clinical relevance may be useful in estimating NCB. Since the clinical trials are not generally powered to test treatment differences for all endpoints, the outcomes of efficacy and safety variables included in a composite endpoint are subjected to sampling.

The NCB in the RE-LY [1] trial was estimated from the outcome of a composite endpoint of stroke or systemic embolism, MI, pulmonary embolism (PE), major bleeding, or all-cause death, and in the ARISTOTLE [2] trial as the outcome of i) composite of stroke or systemic embolism, or MI, and ii) composite of stroke or systemic embolism, MI, or all-cause death. We believe that an endpoint with frequent occurrence such as major bleeding may drive the outcome of a composite endpoint. In anticoagulation studies for prevention of stroke, about 75% of patients who experience major bleeding do not have outcomes of stroke or systemic embolism, MI or all cause death (unpublished data). When major bleeding is included in a composite endpoint, we could argue whether such composite endpoint would predict net clinical benefit or net safety benefit.

2. Objectives

We have attempted in this study to quantify the benefit-risk as the estimate of NCB in the form of aggregate odds ratio, combining odds ratios for efficacy and safety endpoints, and applying weights to endpoints. We have used published results of dabigatran from the RE-LY [1] and of apixaban from the ARISTOTLE [2] trials to illustrate our method as a case study. Our method does not require patient level data. We have also attempted to contrast our estimates with published results of NCB based on composite endpoints.

These two clinical trials had similar design and the same primary efficacy endpoint (i.e. stroke or systemic embolism). Both trials had warfarin as the comparator, and the baseline characteristics of patients were also similar. The dabigatran is an oral anticoagulant tested in RE-LY trial and approved by the FDA in 2010 as PRADAXA® for prevention of stroke in patients with non-valvular atrial fibrillation. Apixaban is another anticoagulant recently tested in ARISTOTLE trial for prevention of stroke in patients with non-valvular atrial fibrillation. Apixaban is presently approved in Europe under the brand name of ELIQUIS® for preventing venous thrombosis after elective hip or knee replacement.

3. Materials and Methods

We have used the published results on event rates of different endpoints from RE-LY and ARISTOTLE trials summarized in Table 1 [1, 2]. Hazard ratios (HR) and confidence intervals (CI) are also included in this table. The stroke or systemic embolism was the primary efficacy endpoint both trials. The event rates of stroke or systemic embolism for dabigatran versus warfarin were 1.11% and 1.69% per year (HR 0.66; 95% CI 0.53-0.82), and for apixaban versus warfarin 1.27% and 1.60% per year (HR 0.79; 95% CI 0.66-0.95).

3.1 Statistical Analysis

We calculated odds ratio (OR) and 95% confidence interval (CI) individually for stroke or systemic embolism, ischemic stroke, myocardial infarction (MI), intracranial hemorrhage (ICH), pulmonary embolism (PE), major bleeding, and all-cause death. We combined ORs into an aggregate OR and 95% CI, using the following weights: i) equal to 1.00 for each endpoint, ii) equal to the inverse of the variance of the odds ratio, and iii) according to annual fatality rate as clinical relevance of each endpoint. Based on general information available on the web, 1 out of 4 patients suffering from stroke or systemic embolism, and 1 out of 5 patients suffering from MI die each year. Annual mortality rate is extremely high in patients with intracranial hemorrhage or pulmonary embolism. Therefore, we used a weight of 0.25 for stroke or systemic embolism, or ischemic stroke, 0.20 for MI, and 0.90 and 1.00 for intracranial hemorrhage or pulmonary embolism.

Table 1. Published results for dabigatran and apixaban - Event rates (%/yr) and HR (95% CI)

	dabigatran (RE-LY)			apixaban (ARISTOTLE)		
Endpoint	warfarin	dabigatran	HR (95% CI)	warfarin	apixaban	HR (95% CI)
Number of subjects	6022	6076		9081	9120	
Stroke or systemic embolism (primary efficacy endpoint)	1.69	1.11	0.66 (0.53,0.82)	1.60	1.27	0.79 (0.66,0.95)
Ischemic stroke or uncertain type of stroke	1.20	0.92	0.76 (0.60,0.98)	1.05	0.97	0.92 (0.74,1.13)
Myocardial Infarction (MI)	0.53	0.74	1.38 (1.00,1.91)	0.61	0.53	0.88 (0.66,1.17)
Pulmonary embolism or deep vein thrombosis (PE)	0.09	0.15	1.61 (0.76,3.42)	0.05	0.04	0.78 (0.29,2.10)
Major bleeding	3.36	3.11	0.93 (0.81,1.07)	3.09	2.13	0.69 (0.60,0.80)
Intracranial hemorrhage (ICH)	0.74	0.30	0.40 (0.27,0.60)	0.80	0.33	0.42 (0.30,0.58)
All-cause death	4.13	3.64	0.88 (0.77,1.00)	3.94	3.52	0.89 (0.80,0.99)
Composite of stroke or systemic embolism, PE, MI, major bleeding, and all-cause death (net clinical benefit outcome)	7.64	6.91	0.91 (0.82,1.00)	Not reported	Not reported	Not reported
Composite of stroke or systemic embolism, and major bleeding (net clinical outcome)	Not reported	Not reported	Not reported	4.11	3.17	0.77 (0.69,0.86)
Composite of stroke or systemic embolism, major bleeding, and all-cause death (net clinical outcome)	Not reported	Not reported	Not reported	7.20	6.13	0.85 (0.78,0.92)
Composite of stroke or systemic embolism, and all-cause death (as other secondary efficacy outcome)	Not reported	Not reported	Not reported	5.04	4.49	0.89 (0.81,0.98)
Composted of stroke or systemic embolism, MI, and all-cause death (as other secondary efficacy outcome)	Not reported	Not reported	Not reported	5.49	4.85	0.88 (0.80,0.97)

Our approach of estimating net clinical benefit is different from that of analysis of a composite endpoint reported from several studies (e.g., RE-LY, ARISTOTLE). We estimated NCB as the aggregate odds ratio based on meta-analysis procedures [3]. The outcome of composite endpoint in these studies was mainly driven by the bleeding endpoint, when included in a composite endpoint. Therefore, we calculated aggregate ORs for endpoints included in composite endpoints reported from RE-LY and ARISTOTLE trials.

We also estimated NCB using an equation provided by Singer *et al.* [4] who treated some outcomes (e.g. stroke, MI, and death) as clinical benefit, and some (e.g. intracranial hemorrhage) as clinical harm. The harm was subtracted from the benefit, and the difference was regressed by an arbitrary weight of 1.5. We used their equation for calculating NCB based on event rates (ER) of stroke or systemic embolism and ICH as follows:

Net Clinical Benefit = $(ER_{warfarin} - ER_{Test\ drug} - \text{weight x } (ICH_{Test\ drug}\text{-}ICH_{warfarin})$,

Where,

ICH = intracranial hemorrhage,

ER=Event rate of stroke or systemic embolism.

This method of linear combination of outcomes of efficacy and safety endpoints seems to be inappropriate because these outcomes follow a non-linear distribution.

3.2 Aggregate Odds Ratio

We estimated aggregate odds ratio for various combinations of the following endpoints:

a) Stroke or systemic embolism
b) Ischemic stroke
c) Major bleeding
d) Intracranial hemorrhage
e) MI
f) PE
g) All- cause death

Let,

O_i = log odds ratio for an endpoint

S_i = standard error of log odds ratio

b_i = weight assigned to an endpoint

Index = aggregate log odds ratio

SE = standard error of aggregate log odds ratio

The SE was calculated by transformation of confidence interval (CI) of log odds.

Then,

Index = $\sum b_i O_i / \sum b_i$

SE (Index) = $\sqrt{(\sum(b_i S_i)^2/\sum b_i^2)}$

Aggregate OR = e^{Index}

CI of Aggregate OR = $[e^{Index-1.96*SE}, e^{Index+1.96*SE}]$

4. Results

The aggregate ORs and 95% CI for various combinations of efficacy and safety endpoints, using weights equal to 1.00, and as the inverse of variance of OR are presented in Table 2. Aggregate ORs and 95% CI for NCB estimated using weights according to annual fatality rate as clinical relevance are in Table 3. Net Clinical benefit estimated as aggregate ORs for endpoints included in composite endpoints in RE-LY and ARISTOTLE studies, along with published values of hazard ratios are summarized in Table 3. Smaller the aggregate odds ratio, the higher the net clinical benefit.

4.1 Net clinical benefit based on aggregate odds ratio using weight equal to 1.00

Table 2 contains aggregate ORs for 9 different sets of combinations of efficacy and safety endpoints, using weight equal to 1.00 for each endpoint. The aggregate ORs for all combinations of efficacy and safety endpoints were smaller for apixaban than for dabigatran, suggesting a higher net clinical benefit from apixaban.

The absolute difference between the risk ratios is regarded as absolute risk reduction (ARR). The ARRs based on aggregate ORs for apixaban were higher by 20 to 38% for combinations of endpoints that included pulmonary embolism (sets 5, 6, 9 in Table 2), which is attributable to the observation that the efficacy of apixaban for pulmonary embolism was higher than of dabigatran. The aggregate ORs for the combination of stroke or systemic embolism, MI and pulmonary embolism (set 6), and also for the combination of ischemic stroke, MI and pulmonary embolism (set 9) were smaller for apixaban, indicating a higher NCB with apixaban than dabigatran.

Since the event rate of pulmonary embolism was very low in both trials, we estimated aggregate ORs from the combination of efficacy and safety endpoints that excluded pulmonary embolism. The aggregate ORs for combination of stroke or systemic embolism and MI showed a 12% ARR (set 1) in favor of apixaban (apixaban: OR 0.83, 95% CI 0.59-1.17; dabigatran: OR 0.95, 95% CI 0.63-1.43). The ARR for the combination of ischemic stroke, MI and major bleeding (set 7) was also higher by 18% for apixaban (dabigatran: OR 1.00, 95% CI 0.69-1.44; apixaban: OR 0.82, 95% CI 0.61-1.10). The ARRs for other combinations of efficacy and safety endpoints were also consistently in favor of apixaban.

Table 2. Aggregate odds ratio from different sets of efficacy and safety endpoints, using weight of 1.00 for each endpoint									
Endpoint	The different sets of combinations of efficacy and safety endpoint used in NCB equation								
	Set 1	Set 2	Set 3	Set 4	Set 5	Set 6	Set 7	Set 8	Set 9
Stroke or sys. embolism	✓	✓	✓	✓	✓	✓			
Ischemic stroke							✓	✓	✓
Major bleeding							✓	✓	
Intracranial hemorrhage			✓	✓	✓				
MI	✓	✓	✓	✓	✓	✓	✓	✓	✓
PE or DVT					✓	✓			✓
All cause death		✓		✓				✓	
Estimates of aggregate odds ratio using a weight of 1.00 for each endpoint									
dabigatran	0.95 (0.63, 1.43)	0.92 (0.66, 1.29)	0.71 (0.44, 1.14)	0.75 (0.49, 1.13)	0.89 (0.42,1.90)	1.17 (0.52,2.62)	1.00 (0.69, 1.44)	0.97 (0.70, 1.33)	1.24 (0.55,2.80)
apixaban	0.83 (0.59,1.17)	0.85 (0.64,1.12)	0.66 (0.50,0.87)	0.71 (0.56,0.90)	0.69 (0.54,0.88)	0.82 (0.62,1.08)	0.82 (0.61,1.10)	0.84 (0.65,1.08)	0.86 (0.64,1.15)
Estimates of aggregate odds ratio using weights equal to the inverse of the variance of odds ratios for each endpoint									
dabigatran	0.82 (0.57,1.17)	0.86 (0.76,0.97)	0.72 (0.50,1.05)	0.82 (0.71,0.93)	0.75 (0.51,1.10)	0.85 (0.59,1.22)	0.94 (0.74, 1.19)	0.91 (0.78, 1.06)	0.99 (0.66,1.49)
apixaban	0.81 (0.62,1.08)	0.86 (0.78,0.96)	0.72 (0.55,0.94)	0.82 (0.74,0.91)	0.72 (0.55,0.94)	0.81 (0.62,1.08)	0.76 (0.66, 0.87)	0.82 (0.76,0.89)	0.90 (0.65,1.25)

Note: Endpoints with check mark were included in aggregate odds ratio.

Table 3. Aggregate odds ratio from different sets of efficacy and safety endpoints using weights according to clinical relevance for annual fatality rate.								
Endpoint	The different sets of weights used in calculating aggregate odds ratio for net clinical benefit							
	Set 1	Set 2	Set 3	Set 4	Set 5	Set 6	Set 7	Set 8
Stroke or systemic embolism	0.25	0.25				0.25		
Ischemic stroke			0.25	0.25	0.25		0.25	0.25
Intracranial hemorrhage	0.90	0.90	0.90	0.90			0.90	0.90
MI	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
PE or DVT					1.00	1.00	0.90	0.90
All cause death	1.00		1.00					1.00
dabigatran	0.65 (0.44, 0.96)	0.52 (0.30,0.92)	0.92 (0.78,1.08)	0.95 (0.75,1.21	1.49 (0.44,5.03)	1.45 (0.43,4.88)	1.22 (0.50,2.97)	1.10 (0.54,2.23)
apixaban	0.65 (0.61, 0.70)	0.52 (0.47, 0.58)	0.81 (0.74,0.87)	0.75 (0.67,0.84)	0.83 (0.74,0.92)	0.81 (0.73,0.89)	0.77 (0.70,0.84)	0.80 (0.75,0.86)
Note: Endpoints with non-missing weights for each set were included in aggregate odds ratio.								

4.2 Net clinical benefit based on aggregate odds ratio using the inverse of the variance of odds ratio as weight

The aggregate ORs, using the inverse of variance of odds ratio as weight, were quite similar for both drugs for combinations of stroke or systemic embolism and MI (set 1), stroke or systemic embolism, MI, and all-cause mortality (set 2), stroke or systemic embolism, MI and intracranial hemorrhage (set 3), stroke or systemic embolism, MI, intracranial hemorrhage, and all-cause mortality (set 4), stroke or systemic embolism, MI, PE, and intracranial hemorrhage (set 5), and stroke or systemic embolism, MI and PE (set 6). The combinations of endpoints that included ischemic stroke (sets 7, 8 and 9) gave a 9 to 18% higher ARR for apixaban in comparison to dabigatran, suggesting a higher NCB from apixaban in preventing ischemic stroke. Estimates of aggregate odds ratio using weight equal to 1.00 or equal to the inverse of variance of odds ratio showed that NCB with apixaban was generally equal or higher than with dabigatran. The differences in the values of estimates of NCB using different weights suggest that the variance of risk ratio should be considered when estimating NCB.

4.3 Net clinical benefit based on aggregate odds ratio using weight according to annual fatality rate

All estimates of aggregate ORs, using weight corresponding to annual fatality rate, for combinations of endpoints that included ischemic stroke or pulmonary embolism (sets 3 to 8) were in favor of apixaban, showing a higher ARR of 11 to 66% (Table 3).

The aggregate ORs for combinations of stroke or systemic embolism, MI and intracranial hemorrhage (set 1), and stroke or systemic embolism, MI, intracranial hemorrhage, and all cause mortality (set 2) were however quite similar. This similarity is attributable to the offsetting of the higher risk of MI by the lower risk of stroke or systemic embolism for dabigatran, and offsetting of the higher risk of stroke or systemic embolism by the lower risk of MI for apixaban. The published values of hazard ratios for intracranial hemorrhage and all-cause mortality were similar in both studies (Table 1).

4.4 Net clinical benefit from composite endpoint versus aggregate odds ratio

None of the composite endpoints analyzed for reporting net clinical benefit in RE-LY and ARISTOTLE were common to the two studies. Therefore, the published estimates of NCB from these trials could not be compared. Table 4 contains estimates of aggregate odds ratio based on outcomes of endpoints that were included in composite endpoints for estimating NCB in these studies.

The comparison of the values of hazard ratio of 0.91 (95% CI 0.82, 1.00) for dabigatran for a composite endpoint of stroke or systemic embolism, MI, PE, major bleeding or all-cause death with a hazard ratio of and 0.85 (95% CI 0.78, 0.92) for apixaban for a composite endpoint of stroke or systemic embolism, MI, major bleeding or all-cause death, indicated that the hazard ratio would have been further smaller for apixaban if PE was included in the composite endpoint in the apixaban study, because the hazard ratio for PE was much lower with apixaban. This argument is supported by a value of aggregate odds ratio of 0.80 (95% CI 0.65, 1.00) in Table 4 for apixaban from combination of stroke or systemic embolism, MI, PE, major bleeding and all-cause death.

Estimates of aggregate ORs presented in Table 4 for various combinations of efficacy and safety endpoints consistently indicated that the NCB was higher for apixaban than dabigatran. These combinations were taken from the published articles on these two studies [1, 2].

Table 4. Net Clinical Benefit or Net Clinical Outcome – Published Hazard Ratio (95% CI) and Estimates of Aggregate Odds Ratio

Composite Endpoints as analyzed in RE-LY and ARISTOTLE trials	Published Hazard Ratio (95% CI)		Estimated aggregate odds ratio (95% CI)	
	dabigatran (RE-LY)	apixaban (ARISTOTLE)	dabigatran (RE-LY)	apixaban (ARISTOTLE)
Net clinical benefit using definitions of net clinical benefit outcomes from RE-LY				
Composite of stroke or Systemic embolism, MI, PE, major bleeding, and all cause death	0.91 (0.82,1.00)	Not reported	1.05 (0.56,1.98)	0.80 (0.65,1.00)
Net clinical benefit using definitions of net clinical outcomes from ARISTOTLE				
Composite of stroke or systemic embolism, and major bleeding (net clinical outcome)	Not reported	0.77 (0.69,0.86)	0.77 (0.59,1.01)	0.74 (0.62,0.88)
Composite of stroke or systemic embolism, major bleeding, and all cause death (net clinical outcome)	Not reported	0.85 (0.78,0.92)	0.81 (0.65,1.01)	0.78 (0.68,0.91)
Composite of stroke or systemic embolism, and MI (other secondary efficacy outcome)	Not reported	0.89 (0.81,0.98)	0.95 (0.63,1.43)	0.83 (0.59,1.17)
Composite of stroke or systemic embolism, MI, and all cause death (other secondary efficacy outcome)	Not reported	0.88 (0.80,0.97)	0.92 (0.66,1.29)	0.85 (0.64,1.12)

4.5 Net clinical benefit estimates based on method of Singer *et al.* [4]

The estimates of NCB calculated using the method of Singer *et al*. [4] for the benefit in stroke or systemic embolism minus the harm caused by intracranial hemorrhage (ICH) were 1.02 (95% CI 0.99-1.03), 1.24 (95% CI 1.21-1.26), and 1.46 (95% CI 1.41-1.47) for dabigatran, and 0.80 (95% CI 0.78-0.81), 1.04 (95% CI 1.02-1.06), and 1.27 (95% CI 1.23-1.28) for apixaban, respectively, using weights of 1.00, 1.50 and 2.00. In addition to a value of 1.5 as a weight used by these authors for the harm, we also investigated values of 1.0 and 2.0 as weights to evaluate the robustness. We are not in agreement with this method since it ignores the distributional property of outcome of endpoints. This method was a linear combination of benefit and harm, whereas the event rates for the above endpoints follow a non-linear distribution. Results from their method mainly depended on the outcome rate of the endpoint of benefit in the comparator drug. Estimates from their method are biased due to the fact that the event rate of stroke or systemic embolism in the warfarin group in RE-LY was relatively higher than the warfarin group in ARISTOTLE. This resulted in higher NCB for dabigatran than apixaban.

5. Discussion

The published results of dabigatran and apixaban summarized in Table 1 clearly indicated a lower risk for stroke or systemic embolism for dabigatran (HR 0.66; 95% CI 0.53-0.82) compared to apixaban (HR 0.79; 95% CI 0.66-0.95). But the results for MI, PE and major bleeding indicated that the patients treated with dabigatran were at higher risk of MI, PE, and major bleeding

compared to apixaban. It was difficult to explain the overall clinical benefit without a point estimate of overall clinical benefit from combination of outcomes of these 4 endpoints. There were no published results available from these trials on analysis of a composite endpoint from combination of stroke or systemic embolism, MI, PE and major bleeding. Therefore, the results from aggregate odds ratio method were considered useful.

As expected, the CIs of all estimates of aggregate ORs using weight equal to the inverse of variance of OR were narrower than the CIs of estimates from weight equal to 1.00. Therefore, we suggest that the variance of the risk ratio should be accounted for, when estimating net clinical benefit. The hazard ratios for endpoints with rare event rate, such as pulmonary embolism in RE-LY and ARISTOTLE trials, had wider confidence intervals (Table 1). The CIs of aggregate odds ratios from combinations of efficacy and safety endpoints that included PE and used weight of 1.0 were also wider. Our attempt to use weights according to the rate of annual fatality due to each endpoint also provided reasonable estimates of NCB. However, some medical practitioners may outweigh the reduction in risk of comorbidities by the reduction in risk of mortality.

The estimates of NCB from various combinations of efficacy and safety endpoints and with different methods of weighing the risk ratios were consistently in favor of apixaban. This serves as an illustration of our proposed method, which could be equally applied to any set of treatments for which multiple outcomes are of importance. We have presented and illustrated a simple and robust method to combine efficacy and safety endpoints for estimating net clinical benefit.

There seems to no unique method to estimate NCB. Therefore, we suggest that extensive sensitivity analysis should be performed to evaluate the robustness of results. A general trend in estimates of NCB from various combinations of endpoints should be useful information for medical practitioners in understanding the relative overall clinical benefit from anticoagulants.

6. Conclusions

The aggregate odds ratio is a simple and robust means of combining outcomes. This method can be equally applied to any set of multiple outcomes in therapeutics areas also. The weights equal to the inverse of variance of odds ratios, or according to clinical relevance provided meaningful and realistic estimates of net clinical benefit.

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