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Comparison of Warfarin and Aspirin in Preventing Symptoms Caused by Atherosclerotic Intracranial Arterial Stenosis by Using Principal Stratification

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By
Yaping Wang
M.Sc, Peking Union Medical College, 2006

Advisor: Dr. Vicki Stover Hertzberg

An abstract of the thesis submitted to the
Department of Biostatistics and Bioinformatics
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Abstract

Comparison of Warfarin and Aspirin in Preventing Symptoms Caused by Atherosclerotic Intracranial Arterial Stenosis by Using Principal Stratification

Yaping Wang

When estimating causal effects, most currently available methods focus on adjusting pre-treatment variables, while ignoring the post-treatment variables. However, the post-treatment variables are also important in sample classification and need to be considered in causal effect estimation. Recently, the principal stratification strategy provides a way to take account of post-treatment variables in causal inference. The object of this study is to compare the efficiency and safety of aspirin and warfarin in preventing the risk of stroke by using principal stratification strategy.

The dataset used in our study came from Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study, where 569 patients were enrolled. The dose of warfarin was controlled by making the target International Normalized Ratio (INR) in the range from 2 to 3, and the dose of aspirin was 1300 mg/day. The INR score was treated as a post-treatment variable, which was potentially influenced by the use of warfarin.

Based on the principal stratification models, the estimated Odds Ratio of primary end point for warfarin versus aspirin treatment is 0.78 [95% CI (0.38, 1.60)], which is attributable to the INR ranges. From the results obtained by applying principal stratification, we conclude that warfarin and aspirin are not significantly different in preventing the outbreak ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke. Moreover, warfarin is found to be associated with significantly higher rates of death and major hemorrhage[1]. Hence, the common practice of administering warfarin rather than aspirin for symptomatic intracranial arterial stenosis is not supported.

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Table of Contents

Chapter 1 – Introduction

1.1 Stroke

A transient ischemic attack (TIA) is caused by the changes in the blood supply to a particular area of the brain; resulting in brief neurologic dysfunction that persists, by definition, for less than 24 hours; if symptoms persist then it is categorized as a stroke. There were about as much as 900,000 strokes or transient ischemic attacks in the United States every year [2]. Atherosclerotic stenosis of the major intracranial arteries was believed to be one of the most important causes of transient ischemic attack (TIA) or stroke, and it could cause about 8 – 10% of the strokes or transient ischemic attacks every year in the United States [3, 4]. Moreover, the risk of recurrent stroke of these patients, which had the history of atherosclerotic stenosis of the major intracranial arteries, can be as high as 15% per year [5-9].

To lower the risk of stroke, several anti-clotting agents were used. Among these, aspirin's efficacy as an anti-clotting agent was proved by some studies from the 1960s to the 1980s. Hence, it was widespread used as a preventive treatment for heart attacks and strokes from the last decades of the twentieth century. In addition to aspirin, another anticoagulant, warfarin, which was initially marketed as a pesticide against rats and mice, was also frequently used for the treatment of intracranial stenosis based on the results of several retrospective studies, some of which suggested that warfarin may be more effective than aspirin [6, 7, 10, 11]. Both aspirin and warfarin were usually used

for the treatment of intracranial stenosis, but it was still not clear which strategy is better. A recent survey illustrated uncertainty about optimal antithrombotic therapy for intracranial arterial stenosis. It showed that the number of neurologists who prefer warfarin therapy for this disease was similar with that of those who prefer aspirin therapy in the United States [12]. Given the importance of intracranial stenosis and lack of studies to compare treatments [13], a clinical trial was conducted to compare the effects between aspirin and warfarin in patients with this disease [14].

1.2 WASID Study Design

As a randomized, double-blind, multi-center clinical study, the main object of Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study was to compare the effects and safety of aspirin with those of warfarin in preventing stroke and vascular death in patients with symptomatic stenosis of a major intracranial artery. The dose of warfarin was controlled by making the target International Normalized Ratio (INR) in the range from 2 to 3, and the dose of aspirin was 1300 mg/day.

Patients with history of transient ischemic attack TIA or stroke, which were caused by ≥50% stenosis of a major intracranial artery, were assigned to warfarin or aspirin groups randomly. The common termination date was at 4.4 years after enrollment for all the participants on average. An outbreak of ischemic stroke, hemorrhagic stroke, or vascular death was defined as primary end point. The study was designed using a two-sided Type I error (α) of 0.05 and 80% power.

There were two kinds of packs of medication in each medication kit, which was assigned to each patient based on the group they belonged. Of the two packs in each medication kit, one was labeled as warfarin/placebo (containing 100 × 2 mg warfarin or placebo warfarin tablets), and the other was labeled as aspirin/placebo (containing 100 × 325 mg aspirin or placebo aspirin tablets). One of these packs contained active drug, the other contained placebo agent. Hence, patients in the trial received either active warfarin and placebo aspirin or active aspirin and placebo warfarin, but not both.

1.3 WASID Study Results

Based on the analysis by Chimowitz M. et al.[1], two study groups (aspirin vs. warfarin) were created, and the 569 patients were randomly assigned to the two groups. The follow-up time was 1.8 years for each patient on average. 13 participants (2.3%) withdrew from the trial after six months. By the end of the study, 128 patients (22.5%) were permanently discontinued totally, and the discontinuation rate is significantly higher in the warfarin group (28.4%) than in the aspirin group (16.4%) ($P<0.001$).

In the wafarin group, the maintenance time is defined as the follow-up period after the first INR ≥2.0 was achieved. In the warfarin group, the percentages of the maintenance time that patients spent at the pre-specified INR ranges were shown in table 1. In the aspirin group, the percentage of follow-up time at a dose of 1300 mg per day was 93.7%.

No baseline characteristic was found to be significantly different between the two treatment groups (Table 2). 22.1% of the patients in the aspirin group were terminated with primary end point, and the primary end rate in the warfarin group was 21.5% [hazard ratio, 1.04; 95% CI is (0.73, 1.48); P=0.83] (Table 3).

1.4 Question

Chimowitz M. et al[1] did not find any significant difference between aspirin and warfarin in preventing the outbreak of primary end point, but they reported that INRs of less than 2.0 were associated with a significantly higher risk of ischemic stroke (P<0.001) and major cardiac events (P<0.001), whereas INRs greater than 3.0 were associated with a significantly higher risk of major hemorrhages.

Considering the INRs were affected by the warfarin usage, and a post hoc on-treatment analysis of the patients assigned to warfarin showed that ischemic stroke, major cardiac events, and major hemorrhages were less likely to occur when the INR was at least 2.0 but not more than 3.0, we thought a causal analysis using principal stratification might be proper to estimate the causal effect of the treatments.

Chapter 2 – Method

2.1 Causal Analysis

Causal Analysis seeks to identify and understand the reasons why things are as they are, and hence enable focus on change activity. The basic object of causal analysis is to find causes that you can treat. Hence, appropriate evaluation of competing causes is important in making decisions in medicine, public health, and social policy. It is broadly viewed the causal inference is the extraction of information about such comparisons. There are several methods for the estimation of causal effects. A statistical method for causal inference based on "potential outcomes", often termed as Rubin's causal model [15], was developed recently. In this method, each unit is considered at a particular place and time; each treatment is applied to each unit from each group; and potential outcomes are all the outcomes that would be observed from each of the units. Then, a causal comparison between two treatments is a comparison of the potential outcomes from two groups of units under the two treatments respectively.

2.2 Principal Stratification

Most methods just focused on adjusting pre-treatment variables, when estimate causal effects. However, the post-treatment variables, which are also important in sample classification, were always neglected. To adjust for post-treatment variables, a method, which estimates principal effects based on principal stratification, was developed. In this

method, named Principal Stratification, all the subjects were cross-classified with respect to the joint potential values of a post-treatment variable. Principal effects are defined as causal effects within a principal stratum. The advantage of principal strata is that it is not affected by treatment; that means samples in the same principal strata are identical. As a result, the principal effects are always actual casual effects.

The mechanism of principal stratification can be summarily described as follows. Suppose we are considering a trial, which compares two treatments ($z = 1, 2$) in a group of units $i = 1, \dots, n$, where each unit can be potentially assigned either a standard treatment ($z = 1$) or a new treatment ($z = 2$). As the response to the treatment, an outcome $Y_i(z)$ is measured at a specific time for each unit, where $Y_i(z)$ is the value of Y of unit i that is assigned treatment z. Then, a comparison between two sets of potential outcomes,

$$\{Y_i(1) : i \in set_1\} \; and \; \{Y_i(2) : i \in set_2\} \tag{2.1}$$

is defined as a causal effect, if set_1 and set_2 are identical[16, 17].

However, the causal effects are not detectable usually, since the potential outcomes are not always measurable. As an alternative, subgroup causal effects of the assignment can be detected by comparing potential outcomes in the subgroup of unites, when other pre-treatment variables are measured.

In the principal stratification, a post-treatment variable is taken into account to classify subgroups. To apply this method, a post-treatment variable S_i^{obs} is measured with a

potential outcome Y, after a treatment Z_i is assigned to each unit i. To make it simple, we assume the variable S_i^{obs} is a binary variable.

In principal stratification, features of the units and assignments are usually implied by the variable S_i^{obs}. For example, in the WASID study, the post-treatment variable implied the influence of the warfarin use to the change of the INR score. By using principal stratification, we pay our attention on comparing the treatments effects on Y after adjusting for the post-treatment variables.

Since post-treatment variables are always affected by assignment strategy, they are usually adjusted by comparing the two distributions as below:

$$\Pr\{Y_i^{obs} | S_i^{obs} = s, Z_i = 1\} \; and \; \Pr\{Y_i^{obs} | S_i^{obs} = s, Z_i = 2\}, \tag{2.2}$$

where $Y_i^{obs} = Y_i(Z_i)$ is the observed outcome for unit i when it was treated by Z_i. By applying this strategy, the outcomes from both groups were compared in a same stratum ($S_i^{obs} = s$). The comparison in the same stratus is named as "net treatment" of assignment Z , adjusting for the post-treatment variable S^{obs} [18].

For simplicity, the treatment assignment Z_i is assumed to be completely random. Then the net treatment comparison (2.2) can be rewritten as the comparison between

$$\Pr\{Y_i^{obs}(1) | S_i^{obs}(1) = s\} \; and \; \Pr\{Y_i^{obs}(2) | S_i^{obs}(2) = s\}, \tag{2.3}$$

Since subject in groups $\{S_i^{obs}(1) = s\}$ and $\{S_i^{obs}(2) = s\}$ may not be in the same stratum, it is necessary to make sure the treatment has no effect on the post-treatment variable[18], if we want to use (2.3) to estimate the causal effect.

Summarily, the reason that causal effects can be estimated by adjusting for the post-treatment variable is because the potential outcomes are compared in a set of people with identical characters. Considering all the importance of the post-treatment variable in the estimation of causal effects, the following definition for principal stratification and principal effect were conducted to classify subjects by post-treatment variables.

DEFINITION (a) *Two units i, j are defined to be in the same stratum, if $S_i(1) = S_j(1)$ and $S_i(2) = S_j(2)$. The basic principal stratification P_0 with respect to post-treatment variable S is the partition of units $i = 1, \dots, n$ to these stratums. (b) A principal stratification with respect to post-treatment variable is a partition of the units whose sets are unions of sets in the basic principal stratification P_0.*

Generally, a principal stratification generates the following estimands.

DEFINITION (b) *Let P be a principal stratification with respect to the post-treatment variable S, and let S_i^P indicate the stratum of P to which unit i belongs. Then, a principal effect with respect to that principal stratification is defined as a comparison of potential outcomes under standard versus new treatment within a principal stratum ς in P , that is, a comparison between the ordered sets*

$$\{Y_i(1): S_i^P = \varsigma\} and \{Y_i(2): S_i^P = \varsigma\} \quad (2.4)$$

The expectation of principal effects relies on stratification of principal strata. Based on the definition of principal stratification; the value of pair $(S_i(1), S_i(2))$ should be same as $(S_j(1), S_j(2))$, if units i, j are in the same stratum; the order is not affected by treatment. Hence, we have properties shown as below:

PROPERTY 1 *The stratum S_i^P , to which unit i belongs, is not affected by treatment for any principal stratification P .*

And, by definition (2.1), we also have:

PROPERTY 2 Any *principal effect, as defined in (2.1), is a causal effect.*

Based on the definitions and properties above, stratifying the subjects by S_i^P means adjusting for the subjects characteristics reflected in the post-treatment variable without introducing treatment selection bias caused by the principal stratification .

2.3 Brief Review of Principal Effect in Needle Exchange Program

In the study by Frangakis et al. [19], they evaluated the effect of a partially controlled longitudinal treatment using principal stratification in the Needle Exchange Program[20, 21].

The study was partly based on the following assumptions: (1) Subjects' follow-up time cannot be directly controlled by the study; (2) subjects' exposure to the treatment of interest cannot be directly controlled by the study, and it may vary over time; (3)

another factor, which can affect subjects' exposure to the treatment of and subjects' follow-up time, is controlled by the study. It is not proper to estimate the treatment effects by standard methods, when the first two conditions are present. Hence, the strategy of principal stratification was applied to estimate the causal effects in this situation.

1,170 injection drug users were enrolled and followed, in the needle exchange program (NEP). The subjects were offered blood tests for human immunodeficiency virus (HIV), at each regular 6-month visit. With the hope to reduce HIV transmission, the NEP also operated some sites where drug users can exchange used needles for clean ones. The NEP staff controlled the places of the NEP sites. Hence, they treated the distance as a controlled factor to provide an indirect evaluation of the NEP's effect on HIV transmission.

In NEP study, distance were binarized to two levels, D=1 when the drug users lived within 3 miles from any NEP site, and D=2 when farther than 3 miles. After applying the Principal Stratification Model, the Odds Ratio of HIV seroconversion for close versus far from NEP sites is 0.11 (95% CI: 0.0003, 2.23), which is attributable to the needle exchange indirectly.

Chapter 3 – Construct Principal Stratification

We return to the WASID study. Our goal is to evaluate the Warfarin's versus Aspirin's impacts on the primary end point with the Principal Stratification Model. First, we discuss the background of our dataset.

3.1 WASID dataset

In the WASID dataset, none of the baseline characteristics differed significantly between the two treatment groups (Table 2). 22.1 percent of the patients in the aspirin group and 21.8 percent of those in the warfarin group ended with primary end point occurred (Table 3).

The format of our data is a frame where each row contains information for a subject at one time point. The variables includes: subject id, fixed (not varying with time) covariates, time, controlled factor (Warfarin or Aspirin), exposure (INR levels), outcome (time-varying), and censoring indicator (time varying). The time varying variables were measured at each visit. Five baseline variables were used as fixed covariates; they were Sex, IS (History of ischemic stroke), Hyper (History of hypertension), Diab (History of diabetes), and Cad (History of coronary artery disease). The exposure variable (E) is binary indicating the INR levels of subject at each time point. The outcome variable (Y) is binary indicating whether the subject got primary outcome or not. If a patient drops-out at a particular time point, then the outcome is designated as "-999" at that point.

In the WASID study, there were 569 patients. Each subject has a unique ID. Time ranges are different between different patients.

3.2 Models used in Principal Stratification

Our goal is to evaluate the effect of warfarin versus aspirin on the primary outcome, which is attributable to INR ranges, using principal stratification. The three models that were applied to estimate the principal effect are shown as below:

Logistic model for the ordinal principal strata $S_{i,t} \geq d$:

$$logit[pr(S_{i,t} \geq d | H_{i,t} = h, X_{i,t} = 1, \beta^{(S)})] = \beta_d^{(S)} + link^{(S)}(h,t)\beta_h^S, \quad (3.1)$$

where $link^{(S)}(h,t)$ is a link function.

Logistic model for the target probability of the primary outcome $Y = 1$:

$$logit[pr(Y_{i,t}(d) = 1 | H_{i,t} = h, X_{i,t} = 1, S_{i,t} = d', \beta^{(Y)})] = link^{(Y)}(d,d',h,t)\beta^{(Y)}, \quad (3.2)$$

where $link^{(Y)}(d,d',h,t)$ is a link function.

Logistic model for the analogous probability of censoring $C = 1$ of the event:

$$logit[pr(C_{i,t}(d) = 1 | H_{i,t} = h, X_{i,t} = 1, S_{i,t} = d', \beta^{(C)})] = link^{(C)}(d,d',h,t)\beta^{(C)}, \quad (3.3)$$

where $link^{(C)}(d,d',h,t)$ is a link function.

Then, we can obtain the likelihood of observing the data of person i at time t, as

$l(d', d, y, c, h, t; \beta)$

$:= pr(S_{i,t} = d' | H_{i,t} = h, X_{i,t} = 1, \beta^{(S)})$

$$\times \left\{pr\left(Y_{i,t}(d) = y \middle| H_{i,t} = h, X_{i,t} = 1, S_{i,t} = d', \beta^{(Y)}\right)\right\}^{(1-c)}$$

$$\times pr(C_{i,t}(d) = c | H_{i,t} = h, X_{i,t} = 1, S_{i,t} = d', \beta^{(C)}),$$

Then, using the previous likelihood function, we can obtain a partial likelihood function:

$$L(\beta) = \prod_t \prod_{i:X_{i,t}=1} \sum_{s \in S(D_{i,t}, E_{i,t})} l(s, D_{i,t}, R_{i,t}, X_{i,t}, t; \beta).$$

Frangakis C. et al. developed a program for maximizing $L(\beta)$ for general levels of principal strata S and time t, using an EM algorithm[19, 22].

Chapter 4 – Result

To estimate the causal effect, and to have the models for outcome and censoring satisfy the compound exclusion restriction[19], we fitted the link function introduced in (3.1)-(3.3) as

$$link^{(S)}\left(H_{i,t},t\right)\beta_{(b)}^{(S)} := \beta_{(b)}^{(S)}B_i + \beta_{(e-)}^{(S)}E_{i,t-1} + \beta_{(d-)}^{(S)}D_{i,t-1} + \beta_{(t)}^{(S)}t\ , \tag{4.1}$$

$$link^{(Y)}\left(D_{i,t},S_{i,t},H_{i,t},t\right)\beta^{Y} := \beta_{(0)}^{(Y)} + \beta_{(b)}^{(Y)}B_i + \beta_{(e-)}^{(Y)}E_{i,t-1} + \beta_{(d-)}^{(Y)}D_{i,t-1} + \beta_{(t)}^{(Y)}t + \beta_{(s)}^{(Y)}S_{i,t} + \beta_{(s,d)}^{(Y)}E_{(S,D)}(S_{i,t},D_{i,t}), \tag{4.2}$$

$$link^{(C)}\left(D_{i,t},S_{i,t},H_{i,t},t\right)\beta^{Y} := \beta_{(0)}^{(C)} + \beta_{(b)}^{(C)}B_i + \beta_{(e-)}^{(C)}E_{i,t-1} + \beta_{(d-)}^{(C)}D_{i,t-1} + \beta_{(t)}^{(C)}t + \beta_{(s)}^{(C)}S_{i,t} + \beta_{(s,d)}^{(C)}E_{(S,D)}(S_{i,t},D_{i,t}), \tag{4.3}$$

Our software was based on the PSpack, a software package for evaluating the causal effect of a longitudinal treatment on a binary outcome using the method of principal stratification. [19].

To estimate the causal effects by using principal stratification in our study. The variables D (Drug) and E (Exposure) were assigned as below:

$$\begin{Bmatrix} D = 1, when\ Warfarin\ was\ used;\ D = 2, when\ Aspirin\ was\ used \\ E = 1, when\ INR \in [2,3];\ E = 0\ when\ INR \in (0,2) \cup (3,+\infty) \end{Bmatrix}$$

Then, the causal effect for Warfarin versus Aspirin is $\exp\left[\beta_{(s,d)}^{(Y)}(1-0)\right] = \exp\left(\beta_{(s,d)}^{(Y)}\right)$.

Hence, the causal effect can be estimated by applying principal stratification models

jointly (4.1)-(4.3). The estimated Odds Ratio of primary end point for warfarin versus aspirin treatment is 0.78 [CI of (0.38, 1.60)], which is attributable to the INR ranges.

Based upon analysis above, we cannot conclude that warfarin and aspirin are different in preventing the outbreak of primary end points (ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke).

Chapter 5 – Discussion

5.1 Result compared to WASID study

Compared to the WASID study by Chimowitz et al, the results we obtained by applying principal stratification are consistent with theirs. Moreover, warfarin was found to be associated with significantly higher rates of death and major hemorrhage. Furthermore, no evidence was found to support warfarin provided advantage over aspirin in the prevention of ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke. The rate of death from any cause was significantly higher in the warfarin group than in the aspirin group (P=0.02)[1]. Based on both studies, the common practice of administering warfarin rather than aspirin for symptomatic intracranial arterial stenosis is not supported.

5.2 Implication for Practice

The results of this study have important implications for clinical practice. We verified the previous results by applying principal stratification, and we support the conclusion that, aspirin, rather than warfarin, should be used to treat intracranial arterial stenosis. Although there was no significant difference between Aspirin and Warfarin in preventing primary end points, Warfarin may cause more permanent interruptions caused by other diseases.

Using aspirin rather than warfarin in these patients will substantially lower the risk of other risks that caused permanent interruption in this study, and eliminate the inconvenience of using warfarin. In addition, considerable savings can be achieved by avoiding the costs of warfarin, INR testing, and treatment of warfarin associated hemorrhages.[23]

5.3 Limitation of findings

Based on Chimowitz M. et al., INRs greater than 3.0 were associated with a significantly higher risk of major hemorrhages ($P<0.001$) than INRs of 3.0 or less[1], we could construct an optimization problem. However, since we did not have any variables for advent effects in our dataset which included the major hemorrhages, it was impossible to get the highest INR score, which attributes to the low total outbreak rate of primary end point and adverse event.

5.4 Recommendations

Information from more other end point variables is needed. This information may be helpful to construct an optimization model to calculate the highest INR score, which provides advantage to lowing primary end point rate, and doesn't cause too many adverse events.

Acknowledgement

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Tables

Table 1. Percentages of maintenance time at the prespecified INR ranges in WASID

INR	Percentage (%)
INR<2.0	22.7
2.0≤INR≤3.0	63.1
3.1≤INR≤4.4	12.9
4.5≤INR	1.2

Table 2. Baseline Characteristics of the Patients[1]

Characteristic	Aspirin (N=280)	Warfarin (N=289)
Age — yr	62.8±11.3	64.3±11.5
Male sex — no. (%)	168/280 (60.0)	182/289 (63.0)
Race — no. (%)		
Black	83/280 (29.6)	91/289 (31.5)
White	162/280 (57.9)	169/289 (58.5)
Other	35/280 (12.5)	29/289 (10.0)
History of hypertension — no. (%)	230/280 (82.1)	247/287 (86.1)
History of diabetes — no. (%)	101/279 (36.2)	115/289 (39.8)
History of a lipid disorder — no. (%)	188/274 (68.6)	203/278 (73.0)
Blood pressure — mm Hg		
Systolic	139.0±16.7	140.6±17.4
Diastolic	76.6±10.3	77.1±10.4
Glycosylated hemoglobin — %	7.8±2.5	7.9±2.3
Cholesterol — mg/dl		
High-density lipoprotein	43.6±13.1	43.4±12.1
Low-density lipoprotein	124.6±38.0	126.2±37.3
Smoking status — no. (%)		
Never	96/280 (34.3)	106/289 (36.7)
Previously	115/280 (41.1)	131/289 (45.3)
Currently	69/280 (24.6)	52/289 (18.0)
History of coronary artery disease — no. (%)	68/273 (24.9)	83/284 (29.2)
History of ischemic stroke — no. (%)	58/271 (21.4)	80/286 (28.0)
Qualifying event		
Stroke	164/280 (58.6)	183/289 (63.3)
Transient ischemic attack	116/280 (41.4)	106/289 (36.7)
Use of antithrombotic therapy at time of qualifying event — no. (%)	143/280 (51.1)	156/288 (54.2)
Time from qualifying event to randomization — days	18.0±14.0	16.0±12.0
Concomitant medications at randomization — no. (%)		
Statin	163/280 (58.2)	184/289 (63.7)
Diuretic	64/280 (22.9)	68/289 (23.5)
ACE inhibitor or angiotensin II receptor blocker	113/280 (40.4)	121/289 (41.9)
Stenotic artery		
Internal carotid	55/271 (20.3)	64/280 (22.9)
Middle cerebral	92/271 (33.9)	87/280 (31.1)
Vertebral	53/271 (19.6)	54/280 (19.3)
Basilar	55/271 (20.3)	57/280 (20.4)
Multiple arteries	16/271 (5.9)	18/280 (6.4)
Percent stenosis of affected artery	64.1±16.5	63.3±16.0
<50 — no. (%)	34/276 (12.3)	36/285 (12.6)
50–69 — no. (%)	138/276 (50.0)	142/285 (49.8)
70–99 — no. (%)	103/276 (37.3)	105/285 (36.8)
100 — no. (%)	1/276 (0.4)	2/285 (0.7)

* No significant differences were found between the two groups at the P=0.05 level. ACE is the short for angiotensin-converting enzyme.

Table 3. Primary End Points and Permanent Interrupiton in WASID

Event	**Aspirin (N=280)** Patients with an Event *no. (%)*	**Warfarin (N=289)** Patients with an Event *no. (%)*	**P Value**
Primary end point Ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke	62 (22.1)	63 (21.8)	0.83
Permanent Interruption	46 (8.1)	82 (14.4)	<.01

Appendix: SAS and R code

SAS Code:

```
libname wasid 'D:\Thesis\Data';
options FMTSEARCH=(wasid.formats);

*list the format library;
proc format library=wasid.formats FMTLIB;
run;


* all baseline info;
data baseline;
    set wasid.base_char;
run;


data baseline_sub;
    set baseline;
    keep ID SEX;
run;


data status;
    set wasid.vickistatus;
run;


proc sort data=status;
     by ID;
run;


data inr_temp;
    set wasid.vickiinr;
run;


proc sort data=inr_temp;
    by ID CDATE;
run;


data wasid01;
    merge inr_temp (in=x) status (in=y);
    by ID;
```

```
    if x=1 and y=1;
run;


data wasid02;
    merge baseline_sub (in=x) wasid01 (in=y);
    by ID;
    if x=1 and y=1;
     if PRIEND=0 then PRIEND_GRP=0;
    else PRIEND_GRP=1;
     keep ID SEX INRSEQ INR TREATMNT PRIEND_GRP PERMANENT;
run;


data wasid03;
    set wasid02;
    if INR=. then delete;
    time=INRSEQ;
     if TREATMNT="W" then D=1;
    else D=2;
     if (INR<2 OR INR>3) then E=0;
    else E=1;
     Y=PRIEND_GRP;
     if PRIEND^=0 then C=1;
    else C=0;
    drop INRSEQ INR TREATMNT PERMANENT PRIEND_GRP PRIEND;
run;


proc sort data=wasid03;
     by ID time;
run;


data wasid04;
     set wasid03;
     by ID time;
     if C=1 and last.ID=1 then y=-999;
     else C=0;
run;
```

R code:

```
# load all the required functions and libraries

source("routines.r")
```

```
dyn.load("routines.dll")
require(MASS)
rngseed(12345) # Initial seed for the random numbers generation



# Step 1. get big object, databig, with columns: (id,fixed
X's,time-dependent Z's,time,D,E,Y,C)
#
# Input: datawide with columns: (id,fixed
X's,Z1.1,Z1.2,...,Z1.K,Z2.1,...,Zp.K,D.1,...,D.K,
#    E.1,...,E.K,Y.1,...,Y.K)                  so

nvary <- 0
nfix <- 1
databig.temp <- read.csv(file="Full05.short.csv", head=T, sep=",")
databig <- model.matrix(~id + Sex + time + D + E + Y + C,
databig.temp)
databig<- databig[,-1]
databig <- data.frame(databig)



# Step 2. Create auxiliary variables, such as lagged distance and
exposure (lag=1),
#  needed for defining models. Add these variables to databig.
# Inputs: databig, idcol, dcol, ecol; in the colume E, 1:
Warfarin, 0: Aspirin

idcol <- 1  # column no. of the subject ID variable in databig
dcol <- as.integer(1+nfix+nvary+2)  # column no. of Distance
variable in databig
ecol <- as.integer(dcol+1)   # column no. of Exchange variable in
databig

lagvar <- makelagvars(data=databig,id=idcol,dcol=dcol,ecol=ecol)
databig$Dm1 <- lagvar$Dlag
databig$Em1 <- lagvar$Elag



# Step 3. make the "full" object, datafull.
# Inputs: databig, dcol, ecol
# In additional to dataful, other outputs are:
# sbig: a random draw from the allowable principal strata for
each subject-time unit
# nsbig: number of allowable principal strata for each subject-
time unit

fullobj <- makefull(data=databig,dcol=dcol,ecol=ecol)
datafull <- fullobj$datafull
sbig <- fullobj$sbig
```

```
nsbig <- fullobj$nsbig



# Step 4. define formulas and design matrices in full dimensions.
# INPUT: formulas

y.fmla <- as.formula("Y ~ SexMale + Dm1 + Em1 + time + S + E")
c.fmla <- as.formula("C ~ SexMale + Dm1 + Em1 + time + S + E")
s.fmla <- as.formula("as.factor(S) ~ SexMale + Dm1 + Em1 + time")



# Step 5. Obtain good initial starting values for the EM
algorithm
# Input: formulas, sbig, databig

theta.0 <-
EMstart(smodel=s.fmla,ymodel=y.fmla,cmodel=c.fmla,sbig,data=datab
ig)



# Step 6. Run the EM algorithm until convergence
# Input: formulas, sbig, theta.0, nsbig, datafull,
rel.tol(convergence criterion), and
#     maxiter(maximum number of iterations).
# Ouputs:  Converged parameter values and hessian matrix

ans <-
EM.ps(smodel=s.fmla,ymodel=y.fmla,cmodel=c.fmla,theta.0,nsbig,dat
a=datafull, rel.tol=1.e-04, maxiter=100)
theta <- ans$par
theta[length(theta)]  # causal effect parameter
se <- sqrt(diag(ans$vcov))

CI.low <- exp(theta[length(theta)]-se[length(se)])
CI.up <- exp(theta[length(theta)]+se[length(se)])
CI.OR <- c(CI.low, CI.up)
CI.OR
#####################################################################
```

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Support from Pharmaceutical Companies

Bristol-Myers-Squibb (after incorporating DuPont Pharma) are supplying the warfarin (Coumadin) and placebo warfarin tablets, and Bayer are supplying the aspirin and placebo aspirin tablets for the trial. Neither of these companies is supplying direct funding for the trial. The FDA has assigned an IND number of 57,138 for Coumadin (warfarin sodium) for this trial.

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