Comparing the Effectiveness of Aspirin and Subcutaneous Heparin in Preventing Recurrent Stroke and Death

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1 Introduction

1.1 Background

In the United States, 1 in every 6 deaths from cardiovascular disease is due to stroke, and every 4 minutes, someone dies of stroke. Around 87% of all strokes are ischemic strokes, in which blood flow to the brain is blocked. Hemorrhagic strokes occur when a blood vessel ruptures inside the brain. Stroke leads to long-term physical and psychological disability. [1][2]

Patients are at high risk of experiencing another stroke in the first few days after having the initial one. Blood-thinning medications are used to prevent blood from clotting, therefore they may help reduce the risk of a recurrent stroke and death. There are two main types of blood-thinners, anticoagulants and antiplatelet medications. Aspirin is a common antiplatelet drug which prevents platelets from coming together to form a clot. Heparin is an anticoagulant which slows the process of making clots in the body. Both these medications might reduce the likelihood of experiencing another stroke, but they follow different mechanisms of action, and previous research suggests that their comparative effectiveness is not clear. [3][4]

1.2 Research Goals

In this research, we intend to explore the comparative effectiveness of early administration of aspirin and subcutaneous heparin by focusing on two objectives: a) the difference in time from diagnosis of the acute stroke until death, and b) the difference in time from diagnosis of the acute stroke until a recurrent stroke. The null hypotheses for these objectives would be that the treatments do not differ after controlling for potential confounders.

1.3 Data

The data used in this project was modified from the original International Stroke Trial publication by Sandercock et al, who anonymized, formatted, and made the dataset publicly available. [5] IST was a randomized, open label trial that was conducted from 1991 to 1996. Patients were administered aspirin, subcutenous heparin, both, or neither, and then followed throughout the clinical course of their stroke. The treatment was given immediately upon randomization. Both the physicians and the patients were aware of the treatment assigned. All patients included in the study were clinically diagnosed with acute stroke in the previous 48 hours, and showed no clear indication for neither aspirin or heparin. There was no upper age limit, and the CT scan confirmed the diagnosis of the stroke before randomization. The primary outcomes of the trial were recurrent stroke within 14 days, and death within 6 months of diagnosis. [6]

1.4 Variables

The response variables for the objectives are: (a) time-to-death and (b) time-to-recurrent stroke. The main predictor variable of interest is the treatment group, and the other variables are included to control for their effect on the treatment outcome. Across both objectives, the predictor variables include age, sex, atrial fibrillation, physical deficit, state of consciousness and stroke subtype. These variables were chosen because they provide insight on the state of health of the patients at the time of randomization, and because existing literature has indicated a relationship between these variables and stroke fatalities.

Sex, age, and atrial fibrillation are considered critical factors in stroke pathology in previous studies. [7][8] Moreover, the association between different stroke subtypes and mortality is an active area of research, with several studies suggesting a possible relationship between the two, therefore we deemed it appropriate to include it in our study. Lastly, we believe that the presence of multiple stroke-related physical deficits and the state of consciousness of the patient might be indicators of the severity of the stroke and the area of brain affected by it, which then might have an effect on recurrent strokes and/or death.

1.5 Data Cleaning

The death variable was created to indicate if the patients were alive within 6 months after the stroke. The recurrent stroke variable was created to indicate if the patients experienced a second stroke (regardless of type) within 14 days after the initial stroke. Events happening after 14 days or 6 months were censored. This decision was made in support with our objectives for the study.

The treatment variable was created to describe the type of treatment that each patient received. This variable is categorical and has two levels: aspirin and heparin. Since we are focusing on the comparative effectiveness of the two drugs, patients who were treated with both or neither drug were not included in the analysis. Moreover, given that most patients presented with a mixture of physical symptoms (face deficit, leg/foot deficit, hand/arm deficit, dysphasia, hemianopia, visuospatial disorder, brainstem/cerebellar signs), it was deemed appropriate to create the physical deficit variable to indicate the total number of symptoms that the patient experienced. Each symptom was considered present only if a physician had successfully diagnosed it. The physical deficit variable, age, and atrial fibrillation are treated as numerical. Following the classification from Oxfordshire Community Stroke Project [9], the stroke subtype variable is treated as categorical, with five levels: total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), posterior circulation syndrome (POCS), lacunar syndrome (LACS) and other (in the case where the physician could not identify the subtype). Finally, the state of consciousness is treated as a categorical variable with three levels: fully conscious, drowsy and unconscious. It should be noted that a small number of patients with missing or incomplete trial data in any of the fields mentioned above were excluded from the study. The final dataset used in this analysis contains information on 9146 patients.

1.5 Exploratory Data Analysis

For both objectives, we chose an intention-to-treat analysis, which means that the study included all the patients regardless if they followed the protocol for their treatment. Because the reasons for nonadherence to the directions might be related to the patients' prognosis, the ITT analysis is considered more appropriate. Previous research has has showed strong indication to using ITT analysis in such cases. [10]

1.5.1 Objective 1

We compared duration from the patients' stroke admission date to the patients' death date between the aspirin and heparin treatment groups. The Kaplan-Meier curve below shows that patients who received aspirin seem to have a higher survival probability than those who received heparin. However, it should be noted that the confidence intervals of these curves overlap throughout the whole clinical course, especially in the earlier days, therefore it is not clear whether this observation is statistically significant.

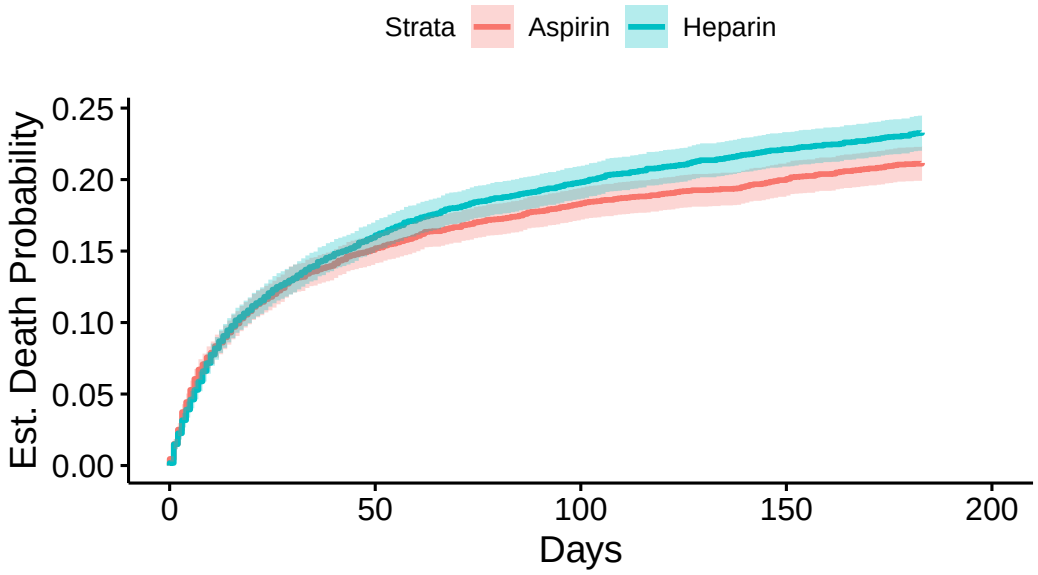

Figure 1. Kaplan-Meier estimate of the survival curve in intention-to-treat analysis, estimated death probability over time

1.5.2 Objective 2

We compared duration from the patients' stroke admission date to the patients' recurrent stroke date between the aspirin and heparin treatment groups. The Kaplan-Meier curve below shows that patients who received heparin seem to have a similar probability to experience recurrent strokes to those who received aspirin. There is significant overlap in the confidence intervals of the Kaplain-Meier curves.

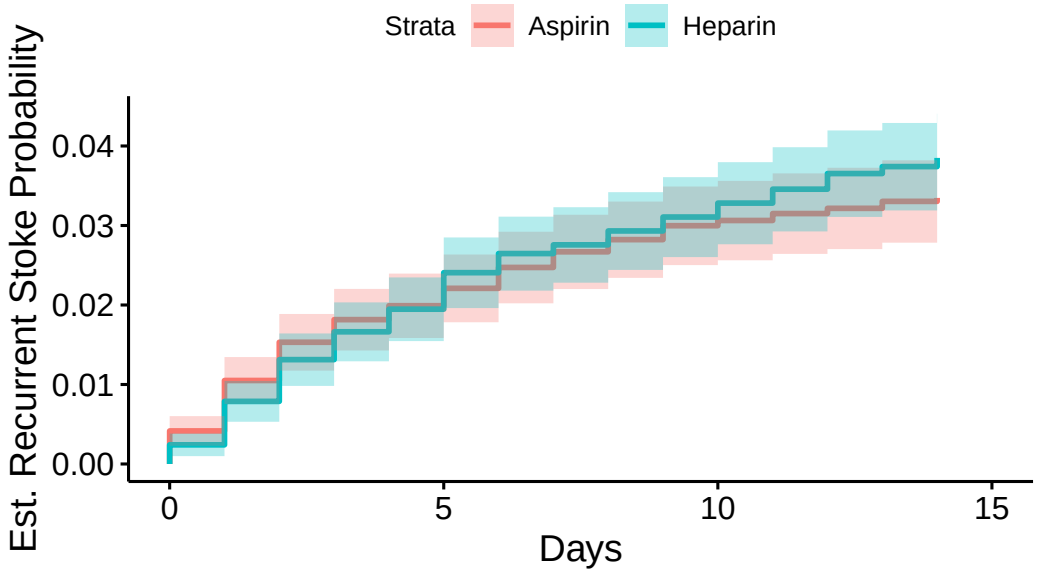

Figure 2. Kaplan-Meier estimate of the survival curve in intention-to-treat analysis, estimated recurrent stroke probability over time

2 Methodology

2.1 Model Choice

The statistical methods used in the original IST publication consisted of simple analyses of the total number of patients affected. [11] The relative frequency of baseline characteristics among patients with different drug use were compared with odds ratios and their 95% confidence intervals. The means of continuous variables were compared and tested for differences using a t-test. [12] Later publications in stroke research, such as the third International Stroke Trial (IST-3), use a survival analysis framework. [13]

We also decided to fit a survival model, as it is a common approach in analyzing clinical trial data, and it allows us to control for potential confounders. We initially considered a parametric Accelerated Failure Time model. AFT models are fully parametric, and they include an error term which is assumed to follow a specific probability distribution. We do not have enough knowledge to appropriately specify such distribution, therefore we decided to use a more flexible model. Semiparametric AFT models were briefly considered, however their use is relatively scarce in applied research. [14] We ultimately chose the Cox Proportional Hazard model, because it is a semiparametric model, and we do not have to make assumptions about the distribution of the baseline hazard function. Moreover, the Cox proportional hazard model is widely used in the medical community, which makes this analysis interpretable to other researchers in this field. [15]

2.1.1 Objective 1

The Kaplan-Meier survival curves in subsection 1.5.1 showed significant overlap, thus the log-rank test is not very powerful in determining if there is a difference in risk of death within 6 months of acute stroke. We decided to fit a Cox Proportional Hazard model in order to explore the difference in risk of death within 6 months of acute stroke between the two treatment groups, after adjusting for potential confounders. We calculated the Schoenfeld residuals in order to evaluate the proportional hazards assumption, and the deviance residuals in order to asses model assumptions. More details can be found in the Appendix section.

The equation of our model is specified below:

$$\lambda_i(t) = \lambda_0(t) * exp(\beta_1 * I(treatment_i = Heparin) +$$
$$\beta_2 * I(atrial\ fibrillation_i = Yes) + \beta_3 * I(sex_i = M) +$$
$$\beta_4 * I(age) + \beta_5 * I(concious_i = Drowsy) + \beta_6 * I(concious_i = Unconcious) +$$
$$\beta_7 * I(physical\ deficit_i) + \beta_8 * I(stroke\ subtype_i = LACS) +$$
$$\beta_9 * I(stroke\ subtype_i = POCS) + \beta_{10} * I(stroke\ subtype_i = TACS) +$$
$$\beta_{11} * I(stroke\ subtype_i = Other))$$

where i describes the i-th patient.

2.1.2 Objective 2

The Kaplan-Meier survival curves in subsection 1.5.2 had significant overlap, thus using the same logic as above, we decided to fit a Cox Proportional Hazard Model with the same specification. More details regarding proportional hazard assumptions and model assumptions for this objective can be found in the Appendix section.

3 Results

3.1 Objective 1

The results of the Cox Proportional Hazard model are presented in the table below. The coefficient estimate for the treatment variable is statistically significant at the 0.05 level, and the 95% confidence interval does not include zero. Several other variables are also statistically significant, similar to what prior studies have suggested.

term	estimate	standard error	95% confidence interval	p-value
Treatment = Heparin	0.093	0.045	0.006 to 0.181	0.037 *
Atrial fibrillation	0.350	0.050	0.252 to 0.449	<0.001 **
Sex = Male	0.117	0.046	0.027 to 0.207	0.011 *
Age	0.044	0.003	0.039 to 0.049	<0.001 **
Conscious = Drowsy	0.960	0.051	0.860 to 1.061	<0.001 **
Conscious = Unconscious	2.285	0.106	2.077 to 2.492	<0.001 **
Infarct	0.097	0.047	0.005 to 0.188	0.038 *
Physical deficit	0.144	0.022	0.101 to 0.187	<0.001 **
Stroke subtype = LACS	-0.361	0.086	-0.529 to -0.193	<0.001 **
Stroke subtype = POCS	-0.014	0.083	-0.176 to 0.149	0.871
Stroke subtype = TACS	0.277	0.061	0.158 to 0.396	<0.001 **
Stroke subtype = Other	0.598	0.504	-0.390 to 1.586	0.235

Output of Cox Proportional Hazard Model for Mortality (* p<0.05, ** p<0.001)

3.2 Objective 2

The results of the Cox Proportional Hazard model are presented in the table below. In contrast to the first objective, the coefficient estimate for treatment is statistically insignificant. Besides drowsy state of consciousness, no additional variables have statistically significant estimates.

term	estimate	standard error	95% confidence interval	p-value
Treatment = Heparin	0.139	0.111	-0.078 to 0.355	0.210
Atrial fibrillation	0.128	0.142	-0.15 to 0.406	0.367
Sex = Male	-0.003	0.113	-0.226 to 0.219	0.976
Age	0.004	0.005	-0.006 to 0.014	0.462
Conscious = Drowsy	0.292	0.135	0.027 to 0.556	0.031 *
Conscious = Unconscious	-0.480	0.584	-1.625 to 0.665	0.411
Infarct	0.044	0.118	-0.186 to 0.275	0.706
Physical deficit	0.029	0.052	-0.073 to 0.132	0.576
Stroke subtype = LACS	-0.205	0.164	-0.526 to 0.116	0.211
Stroke subtype = POCS	0.120	0.181	-0.236 to 0.475	0.509
Stroke subtype = TACS	-0.004	0.160	-0.318 to 0.310	0.981
Stroke subtype = Other	0.974	0.721	-0.439 to 2.387	0.177

Output of Cox Proportional Hazard Model for Recurrent Stroke (* p<0.05, ** p<0.001)

4 Discussion

4.1 Interpretation of Results

We find evidence at the 0.05 level to reject the null hypothesis that treatment does not play a role in mortality at 6 months. Our analysis suggests that holding all else equal, there is an 0.093 multiplicative increase in hazard when patients are treated with heparin instead of aspirin, as indicated by the coefficients of the first Cox model. The 95% confidence interval for this effect ranges from 0.006 to 0.181 as a multiplicative increase. Despite assumption concerns which we address in the subsection below, our finding is consistent with that of the original IST publication, which showed that heparin treatment did not offer a clinical advantage at 6 months, while aspirin showed small but worthwhile improvement. [16] The Chinese Acute Stoke Trial has also produced similar results, in which aspirin reduced the risk of death during the first few weeks. In contrast, for our second objective we did not find sufficient evidence to reject the null hypothesis that treatment does not play a role in recurrent strokes at 14 days.

4.2 Strengths and Weaknessess

A strength of this analysis is attributed to the quality of the data used. The dataset is large, with complete baseline data and over 99% follow-up data. There is a large number of patients over 80, despite the historical underrepresentation of elderly patients in stroke trials. [17] Moreover, our findings are consistent with those of previous publications in the field as discussed above, despite the use of a different approach. Given the international and inclusive nature of this trial, the results appear to be relevant to a wide, diverse population. There are however several weaknesses in this study. The main concern is the violation for the proportional hazard assumption for both models for the age variable. A possible reason for violation of this assumption for age is intuitive; the ratio of the hazards for patients of different age increases with time (instead of staying constant, as the model assumes), since the brain and body lose their ability to recover at older age. We recommend in the future that a modified Cox model, such as the Stratified Cox Proportional Hazards model is used instead. In this approach, covariates with nonproportional effects such as age, are included in the model as stratification factors rather than predictors. [18] There is also concern for model assumptions violation for the time-to-recurrent stroke model, as Deviance residuals are not distributed around mean 0 with a variance of 1.

Furthermore, some degree of bias might have been introduced to the study, because even though treatment assignment was randomized, the doctors were aware of the treatment each patient received. This might have influenced how they cared for the patient during the clinical course of the stroke after randomization, by possibly prescribing additional medications, or suggesting different physical or psychotherapies. Moreover, the results from this analysis may not be generalizable to entire population of stroke patients nowadays, because acute stroke care has improved in the recent years. [19] At the time of this trial, thrombolytic therapy, such as tissue plasminogen activator therapy [20], was not widely available, and none of the patients in this dataset received it. [21] Thus, the background stroke care for the included patients might be more reflective of current stroke care in resource poor environments. [22]

4.3 Future Work

The framework of this analysis provides a promising opportunity for future developments in stroke research. First, different methods should be used in order to try to satisfy model assumptions, such as the stratification technique described above. Other methods besides survival analysis may also be useful, but we believe that this is the most appropriate method, given the nature of the time-to-event data and interpretability within the medical field. The developing world is facing an increase in the average age of the population, and an increase in acute stroke, and analysis on IST data is a good start to gain a deeper understanding of stroke, especially in elderly patients.

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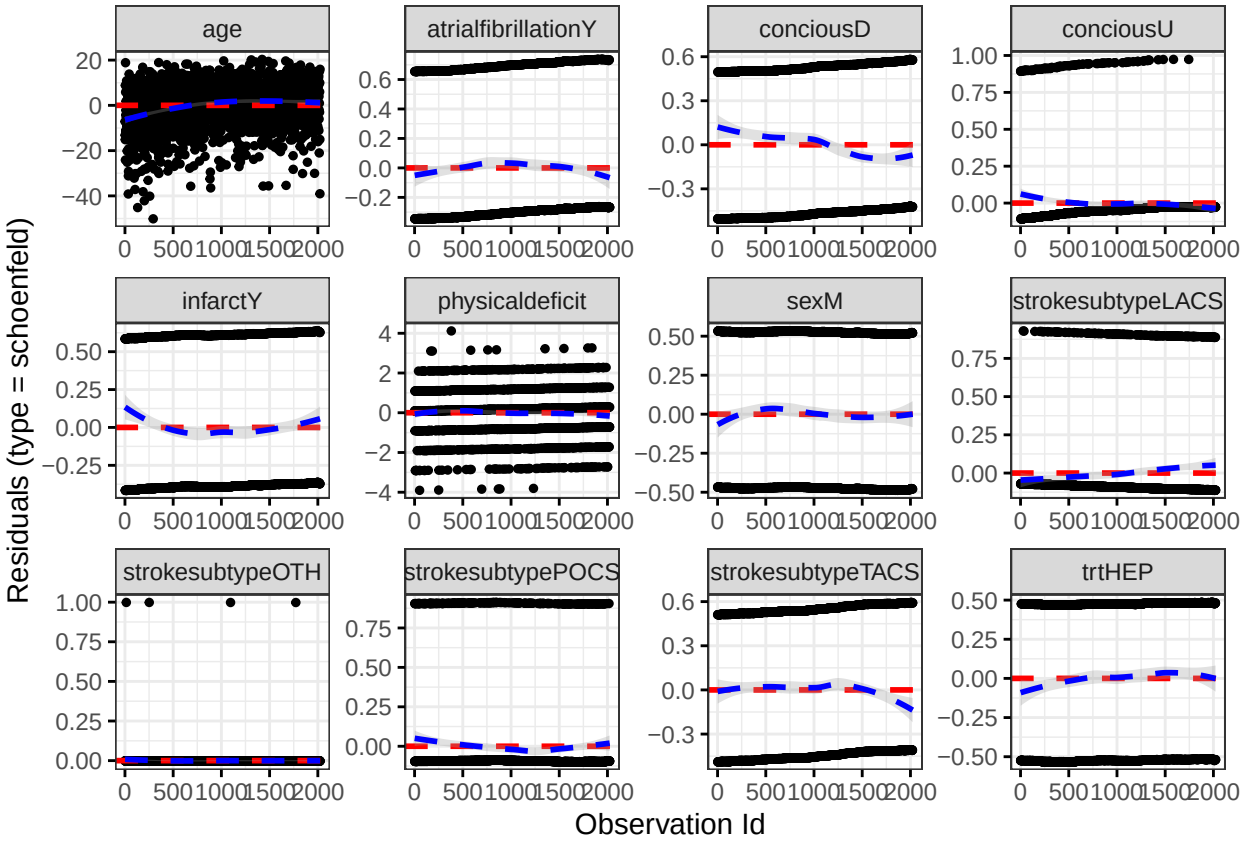
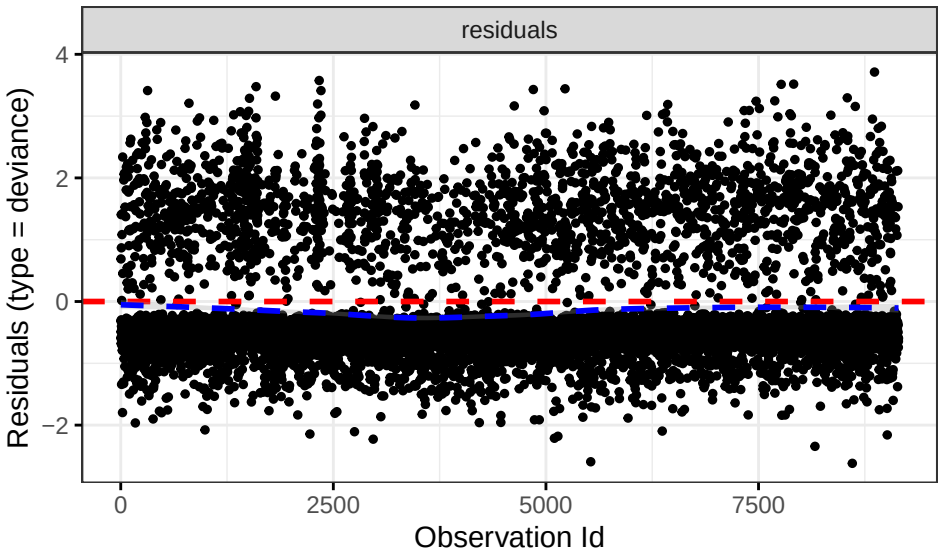
5 Appendix

5.2 Cox Model Assumptions

5.2.1 Objective 1

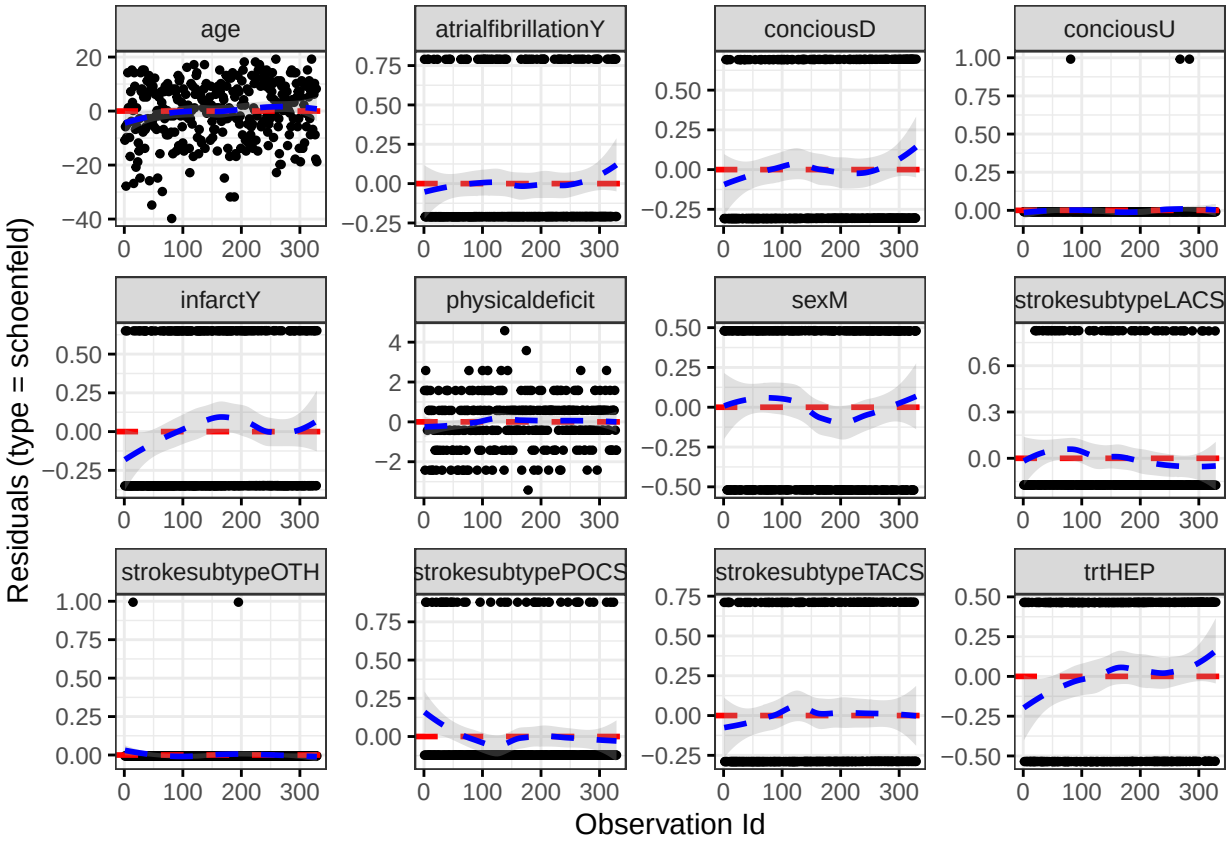


Schoenfeld residuals are distributed around 0 for all variables excluding age and physical deficit. There are some patterns, but the residuals are largely random. There is concern for violation of proportional hazard assumption for the age and physical deficit variable.

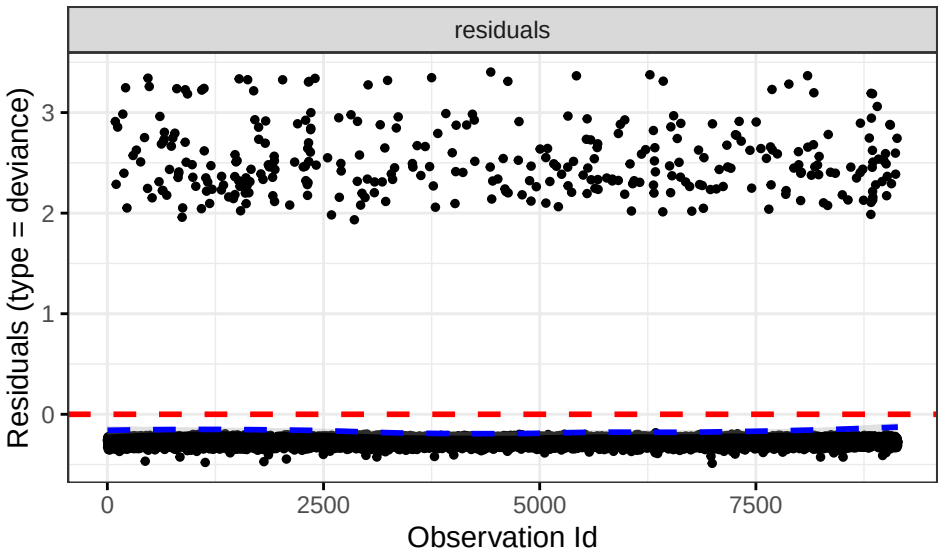


Deviance residuals are randomly distributed around 0. There is no concern for model assumption violation. The independence assumption is satisfied as the survival times are independent across distinct patients.

5.2.2 Objective 2



Schoenfeld residuals are randomly distributed around 0 for variables excluding age and physical deficit.



Deviance residuals are distributed around 0, however the variance is not 1. There is concern for violation of both model and proportional hazard assumptions.