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Data 623 P1roject

623 Project

Background

A stroke is a serious and potentially life-threatening medical condition that occurs when blood flow to the brain is disrupted. This can be caused by a blockage in a blood vessel (ischemic stroke) or by bleeding in the brain (hemorrhagic stroke). Aspirin and high-dose heparin treatments are used for the stroke. Both treatments can help prevent blood clots from forming. Recent studies have shown that aspirin can reduce the risk of recurrent ischemic stroke by around 60% within six weeks, especially in patients who have experienced TIAs (Transient ischemic attack) or minor strokes (Rothwell, Peter M, 2016). Large, prospective and randomized controlled trial data from the International Stroke Trial is used for this study. For this study, we would like to mainly investigate the difference in survival rates in the aspirin group and the high-dose heparin group after six months.

Research Question

The primary purpose of the study is to investigate when the patients who have not received any aspirin within 3 days prior to randomization or heparin within 24 hours prior to randomization and who have not have any symptoms noted on waking (wake-up stroke), the hazard ratio for death difference in the aspirin group and high-dose heparin group in a stroke trial.

The secondary purpose of the study is to investigate differences in efficacy (survival rate) among treatments for various stroke subtypes (ischaemic stroke, haemorrhagic stroke and indeterminate stroke) after six months.

Methodology

The IST dataset includes data on 19 435 patients with acute stroke, with 99% complete follow-up. Over 26.4% of patients were aged over 80 years at study entry. Background stroke care was limited and none of the patients received thrombolytic therapy. Patients are randomized and assigned to the aspirin group and high-dose heparin group based

on the doctor's opinion on the final diagnosis of the initial event. Condition criteria are applied to filter out raw data as follows:

1. Patients with wake-up-stroke are excluded since it is a type of ischemic stroke that occurs during sleep, and the individual only becomes aware of it upon waking up. Its onset time is unknown so the effectiveness of time-sensitive treatment may be limited or uncertain for this. Excluding wake-up stroke, patients from research datasets may help ensure that the results of the study are more representative of the population of interest and can help prevent bias in the results.

2. Patients with heparin within 24 hours prior to randomization are excluded because patients might have a lower risk of blood clots forming and may not show as much improvement with aspirin or heparin treatment compared to patients who have not received heparin.

3. Patients without aspirin within 3 days prior to randomization are excluded based on the study that finds Aspirin reduced the 6-week risk of recurrent ischaemic stroke by about 60% (Rothwell, Peter M, 2016) to minimize the potential impact on the results.

4. Patients' final diagnosis of initial events needs to be filled in categories of Ischaemic Stroke, Haemorrhagic Stroke or Indeterminate Stroke to satisfy the study purpose of survival rate investigation in stroke and subgroup analysis.

5. Patients who only received aspirin or high-dose heparin to ensure patients belong to either group.

6. Patients have known alive or dead status to ensure unknown status will not have any impact on the final results.

Analysis of survival was performed by means of a two-sided stratified log-rank test and Cox Regression. An event considered death occurs within 6 months and censoring is considered as death occurs over 6 months or loss to follow-up/withdrawal. The hazard ratio is estimated with a 95% confidence interval.

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Result

The result in baseline characteristics of 6969 patients indicates the demographic information for aspirin and high-dose heparin group is similar with a mean age of 71.6 and 71.9 years, and 47.4% and 45.1% females in each group. Overall 70.4% of patients do not have a wake-up stroke since this type of stroke is not considered the majority of strokes and its symptoms are not recognized immediately. The percentage of people who take aspirin within 3 days is greater than the percentage of people who take heparin within 24 hours before randomization. It might be because aspirin is a widely available and commonly prescribed medication that can be used for a variety of conditions; however, the use of heparin is typically limited to specific patient populations or situations. The prevalence of death in the aspirin group is 20.6% and it is 23.5% in the high-dose heparin group. For further overall survival analysis, 3502 patients are excluded based on the condition criteria we have for the study which is mentioned in the methodology.

After applying a Kaplan-Meier curve for treatment groups, the result shows the survival probability drops slowly in both groups within 6 months. The null hypothesis failed to reject with a hazard ratio for death of 1.07 (95%CI: 0.92 to 1.25; p-value = 0.4 by the log-rank test). It indicates that there is no significant survival rate difference between the aspirin group and the high-dose heparin group, and no statistical evidence showing the effectiveness of the two treatments in reducing death in patients with acute stroke is different. By looking at the risk table, the result shows after 150 days, there are two significant drops from 150 days to 200 days, and from 200 days to 250 days. From the KM curve, it shows a large drop from 300 days to 350 days. The majority reason for these significant drops might be that the international stroke trial is designed to follow patients for a period of six months after stroke onset, so after 6 months of follow-ups, a large population of patients might lose follow-ups or drop out of the trial. Another reseason might be that the IST data have a total age of over 26.4% of patients who were over 80 years old at study entry, patients might die due to natural death rather than stroke.

Data is separated into three subsets based on the type of stroke (ischemic stroke, haemorrhagic stroke, and indeterminate stroke). For each subset, KM curves are applied to investigate the difference in efficacy between the aspirin group and the high-dose heparin group. Based on results from the log-rank test of three subtypes, there is a significant survival rate difference between the two groups in patients who have a hemorrhagic stroke with a p-value of 0.04 by log-rank test, the hazard ratio for death is 2.88 with a 95% CI from 1.00 to 8.33 which indicates

the high-dose heparin group has a higher risk of death compared to the aspirin group. However, due to the population of patients in this subtype of stroke, the result might not be representative of the whole population. There is no statistical evidence that shows the survival rates in the other two subtypes of stroke are significantly different. As the study is mainly focused on the majority type of stroke which is ischemic stroke, in general, based on results we can conclude there is a non-significant survival rate difference between the aspirin group and the high-dose heparin group in patients who have an ischemic stroke within a six months follow-ups.

In further exploration of having both groups and subtypes of stroke in a Cox regression model which represents the relative risk of the event occurring in patients with the predictor variable compared to patients without the predictor variable. As a result, the indeterminate stroke is significant to the model which might have an impact on the survival time. For future studies, it might be important to investigate how each subtype of stroke impact patients' survival time and specifically researchers might want to discover any other treatments for patients who have haemorrhagic stroke rather than high-dose heparin.

Limitations

Data are unblinded which might be subject to some degree of bias.
Short-term follow-up trials with patients may not have any insight into the long-term effectiveness of aspirin and high-dose heparin.

Reference

Rothwell, Peter M., et al. “Effects of Aspirin on Risk and Severity of Early Recurrent Stroke after Transient Ischaemic Attack and Ischaemic Stroke: Time-Course Analysis of Randomised Trials.” Lancet (London, England), vol. 388, no. 10042, July 2016, pp. 365–75. PubMed Central, https://doi.org/10.1016/S0140-6736(16)30468-8.

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