

Stat 4893W: Group Project Report

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1 Introduction

Aspirin as a therapeutic agent for cardiovascular disease has been the focus of many clinical studies. Taken preventatively in doses of 81 mg and 325 mg, aspirin has been shown to reduce the risk of myocardial infarction (MI), stroke, and angina. Aspirin inhibits platelet function and prolongs bleeding time; this specific action of aspirin lowers blood pressure and reduces the risk of MI and stroke [1, 2]. In this study, we examine the anti-hypertensive effect of aspirin therapy. Specifically, we test whether daily intake of aspirin has the potential to lower blood pressure among heart patients.

Using the data collected by the biostatistics students, we test for evidence that daily aspirin therapy results in changes in patient blood pressure, or positive heart outcomes. We find that, despite prior power calculations designed to find a meaningful clinical difference, no such difference is observed. In fact, the aspirin therapy does not appear to have had any meaningful clinical effect.

2 Study Design and Data

To test the hypothesis that aspirin can positively effect a heart patient's blood pressure, a clinical trial was designed. The population of study were male and female Islanders of adult age (18 and older) diagnosed with cardiovascular disease. Islanders with cardiovascular disease were excluded if they had diabetes or other chronic illnesses that would have been adversely affected by receiving a daily dose of aspirin. A list of eligible patients diagnosed with cardiovascular disease was compiled by the investigators from the three Island hospitals and a sample population of 100 patients was randomly selected from this list. Each Islander was randomly assigned to a treatment group. One treatment group was given a daily dose of 500 mg of aspirin and the other group was given a placebo, thus representing the control group. A total of 102 individuals from the various island hospitals were included; 40 were given the placebo and 62 the 500 mg of aspirin daily.

Before the investigators began administering the treatments, they measured each Islander's blood pressure. This first measurement was used as a baseline for comparison. The treatment was then administered for five days (65 days

	Control	Treatment
Mean Arterial Pressure, mean(sd)	103.17 (9.51)	101.17 (9.57)
Age, mean(sd)	61.74 (18.02)	55.28 (17.78)
Female, n(percent)	12 (38.7%)	19 (38%)
Male, n(percent)	19 (61.3%)	31 (62%)

Table 1: Descriptive Statistics Before Treatment

Island time) at different times of the day. After the full course of treatment, the investigators measured each Islander's blood pressure and the difference between the before and after treatment for the two groups were compared to determine if aspirin was effective at reducing blood pressure in patients with cardiovascular disease. For analysis purposes, the systolic and diastolic blood pressure rates were converted to mean-arterial blood pressure, which is approximated as two-thirds the diastolic pressure, plus one-third of the systolic pressure. Based on the recommendation of the investigators, island of residence, age, and gender were collected as potentially influential factors. Figure 1 shows the descriptive statistics for the two groups before treatment.

We also test the assumption of normality for the mean arterial blood pressures of the patients before treatment by drawing a quantile-quantile plot (Figure 1). The theoretical quantiles approximately match the observed ones; we conclude that our data are normal, or nearly so.

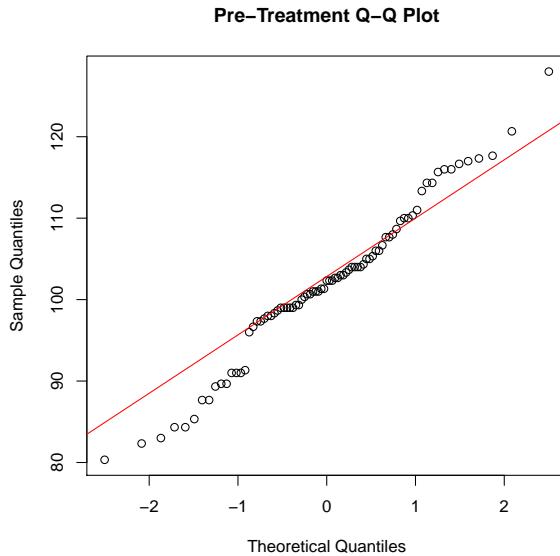


Figure 1: Quantile-quantile plot for the pre-treatment distribution of mean arterial pressure.

The study population initially consisted of 100 subjects, but due to patient discharge or withdrawal from the study, it ended with only 81 participating subjects. This resulted in unequal treatment group sizes; the control group ended with 31 subjects and the treatment group ended with 50 subjects. The unequal treatment group sizes may affect the analysis.

3 Treatment Effect

Here, in following our study proposal, we compare the distributions of the change in mean arterial blood pressure for the placebo group to the aspirin group. Comparing the patient's pre-trial and post-trial blood pressures, we calculate the change over the course of therapy, excluding the discharged patients, for which no post-trial measurements are available. Figure 1 plots the distribution of the change in mean arterial blood pressure by treatment group.

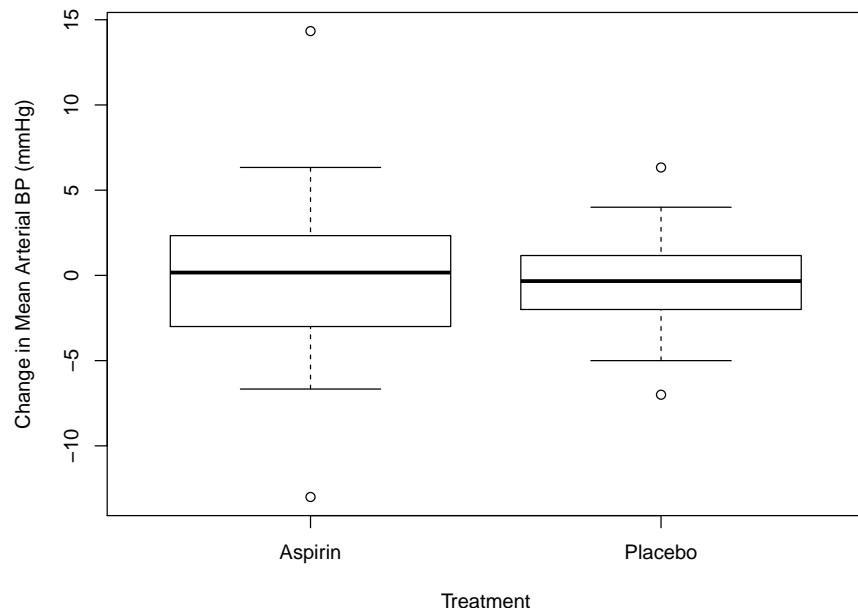


Figure 2: Change in mean arterial blood pressure by treatment group.

Both distributions appear to be centered at zero, with a standard deviation of about 5 mmHg. This standard deviation is consistent with our pilot study's estimate of variance in the population. However, it was hypothesized that the aspirin therapy could induce as much as 10 mmHg drop in blood pressure. This does not appear to be the case.

We can confirm this observation with a formal statistical procedure. Using the standard two-sample t-test, testing the hypothesis H_0 : true treatment means are equal versus H_1 : true treatment means are unequal, results in a p-value of 0.5632, which is highly insignificant. It is also important to note that the mean in the placebo group was a decrease of 0.56 mmHg, while the mean in the aspirin group was a decrease of only 0.07 mmHg. We find essentially no evidence that aspirin reduces blood pressure.

4 Adjusting for Additional Covariates

Having recorded patient island of residence, age, and gender, we can adjust for these covariates to attempt to explain the observed differences in blood pressure between individuals. We include two linear models in Table 1, each predicting a patient's change in mean arterial blood pressure given all four recorded covariates (some of which are factors with multiple degrees of freedom).

	Estimate	Std. Error	t value	Pr(> t)
(Intercept)	-0.0733	0.5177	-0.14	0.8877
Placebo	-0.4858	0.8368	-0.58	0.5632

	Estimate	Std. Error	t value	Pr(> t)
(Intercept)	0.5552	1.0374	0.54	0.5941
Placebo	-0.7819	0.8642	-0.90	0.3685
Male	0.1411	0.9161	0.15	0.8780
Kiyobico Resident	-1.9580	1.1264	-1.74	0.0862
Maeva Resident	-0.9990	1.0059	-0.99	0.3238
Age \geq 50	0.6685	0.8810	0.76	0.4503

Table 2: Two linear models predicting change in mean arterial blood pressure.

The hypothesis test for the coefficient of the “Placebo” indicator in the regression with treatment group as the sole indicator is mathematically equivalent to our two sample t-test, with p-value 0.5632. Fitting the regression with all predictors gives similarly negative results. No recorded predictors appear to significantly explain changes in patient blood pressure. This was confirmed with additional Analysis of Variance testing, including exploratory data analysis of factor interaction, none of which produced significant results.

As a further check that no significant trends are present, we perform step-wise, backwards elimination on the larger model in Table 1, using the Akaike Information Criterion (AIC) for model selection. AIC with backwards elimination selects a model with no (non-unitary) predictors.

5 Explaining Discharge Probabilities

Having found no significant trend in the observed change in mean arterial blood pressure among the patients who remained in the trial to its conclusion, we naturally turn to the question of whether the aspirin therapy resulted in patient discharge (presumably due to improvement in health outcomes). We test this hypothesis by constructing a binomial logistic regression model, predicting the probability of patient discharge from the predictors we have available (treatment group, gender, island of residence, and age). The results are included in Table 2.

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.5339	0.3324	-4.61	0.0000
Treatment Placebo	0.2972	0.5039	0.59	0.5553
	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.3450	0.8389	-2.80	0.0052
Placebo	0.4495	0.5404	0.83	0.4055
Male	-0.7270	0.5507	-1.32	0.1868
Kiyobico Resident	1.6796	0.8561	1.96	0.0498
Maeva Resident	1.0479	0.8438	1.24	0.2142
Age \geq 50	0.0399	0.5680	0.07	0.9440

Table 3: Two binomial logistic regression models predicting patient discharge.

Naturally, the intercepts for both the small model (only treatment group as a predictor) and the large model (all covariates as predictors) are significant. This means that the probability of discharge is significantly different from 50%, but has no other relevant clinical interpretation. Examining the coefficients in the small model, treatment group is not a significant predictor of discharge probability. In the large model, none of the other predictors have strong evidence of significance.

Again, we perform stepwise model selection using AIC, starting from the large model, with all covariates included. Backwards elimination again chooses a model with no (non-unitary) predictors.

6 Conclusion

Despite our original hypothesis that aspirin therapy could produce a difference of up to 10 mmHg in measured blood pressures of heart patients, we find no statistically significant change in blood pressure for either treatment group. Furthermore, despite patient discharge limiting our data measurement for some patients, treatment group is not a significant predictor of discharge. In this trial, the data are very clear: we find no evidence that aspirin has any positive effect on heart health.

In future trials, it may be valuable to record other data, like diet, stress status, smoking status, height, weight, or exercise history, which could effect blood pressure. It was difficult for us to get this information from the Islanders, but it may have additional explanatory power in terms of the changes in blood pressure. Other explanations for why our data were insignificant include a lack of uniformity in the administration of aspirin, a small, overall sample size, or the genuine possibility that aspirin has no effect on blood pressure. Our results necessitate a serious re-evaluation of our research team's hypotheses.

References

- [1] Leonelo E. Bautista and Lina M. Vera. Antihypertensive effects of aspirin: What is the evidence? *Current Hypertension Reports*, 12(4):282–289, 2010.
- [2] Michael D. Miedema, Joseph Huguet, and Salim S. Virani. Aspirin for the primary prevention of cardiovascular disease: In need of clarity. *Current Atherosclerosis Reports*, 18(1):1–6, 2016.