Final Report

Introduction: The observational study aimed at detecting effects of different heart valves differing on the type of the tissue implanted in the aortic position, homograft or stentless porcine tissue. A 10-year period study involving 256 patients was conducted to evaluate the short and long term profiles and determine the factors that influence the effect and rate of ventricular mass regression with time after aortic valve replacement.

Methods: We used the (log-) left ventricular mass index (lvmi) as the outcome for this project. To observe the relationship between log lvmi over time for the two treatment groups, we draw scatter plots with smooth lines. To examine whether there appears to be differences comparing patients by gender or by baseline age or by preoperative left ventricular hypertrophy (lvh); and investigate if individuals who died in the study have different characteristics from those who were alive by the end of the follow-up, stratified scatter plots with lowess lines were drawn to show the differences. To answer the question that whether implanting a homograft valve is superior to stentless in terms of changes in log lvmi over time, we used a non-adjusted generalized estimating equation (GEE) model with a linear spline knot at 2 years. In addition, we used the same model to answer the question that whether the rate of lvmi regression depends on the type of aortic valve replacement and lvh, including the above two covariates as effect modifiers, adjusting for gender and baseline age. Then, we performed additional joint testing of interactions. We used the working independence correlation structure and robust standard errors to account for within-subject correlation.

Results

Part 1. Exploratory analyses

Figure 1a shows log lvmi over time stratified by two treatment groups with lowess curves. We observed that the log lvmi is higher for patients in the stentless valve group than those in the homograft group. 2-year is a turning point in this figure. Before 2-year, we observed a decreasing linear trend of log lvmi as age increases and the trend is similar in the two groups. After 2-year, it becomes an increasing linear trend and the homograft group has a faster rate per year. Figure 1b/c/d show log lvmi over time stratified by two treatment groups and gender/lvh/ living status with lowess curves, respectively. The rate of short-term or long-term log lvmi change against

time behaves differently comparing males and females, patients with lvh or not, and patients alive or dead, respectively. Figure 1e shows log lvmi against baseline age stratified by two treatment groups. Patients tend to use stentless valves from an older age and they tend to have higher log lvmi than patients who use homograft.

Part 2. Inferential analyses

log.lvmi=5.045+0.07*StentlessValve-0.074*Time+0.094*AgeSpline2 ----(a)

log.lvmi=5.038+0.083*StentlessValve-0.072*Time+0.094*AgeSpline2-0.004*StentlessValve*Time ----(b)

We fitted a linear spline model with GEE of log lvmi on valve replacement type and time since surgery(a). The regression coefficients were shown in Table 3. On average, individuals who had stentless valve replacement had 0.07 higher log lvmi than those with homograft, although it remains non-significant at the level of 0.05. Before 2 years, the log lvmi decreased by 0.074 per year on average; while after 2 years, the log lvmi increased by 0.02 per year on average. In our sensitivity analysis (b) with an interaction term, the rate of change in log lvmi over time did not vary significantly by valve type (p=0.73).

log.lvmi=5.25-0.0001*Age0-0.162*Sex-0.148*Lvh+0.125*StentlessValve-0.064*Time+0.093*AgeSpline2-0.007*Lvh*Time-0.009*StentlessValve*Time ----(c)

We fitted another GEE model with two interaction terms between lvh, valve replacement type and time, after adjusting baseline age and gender (c). As shown in Table 4, among patients of the same baseline age and gender, the difference in rate of log lvmi change was 0.009 lower in those with stentless valve than with homograft (95%CI: -0.033, 0.014; p=0.44). The difference in rate of log lvmi change was 0.007 lower in those with lvh than without lvh (95%CI: -0.050, 0.036; p=0.754). The joint tests of interactions suggested that the interactions were not significant (p=0.7) (Table 5). Therefore, we reject the null hypothesis that the rate of lvmi regression depends on the type of aortic valve replacement and preoperative left ventricular hypertrophy, controlling for gender and baseline age.

Tables and Figures

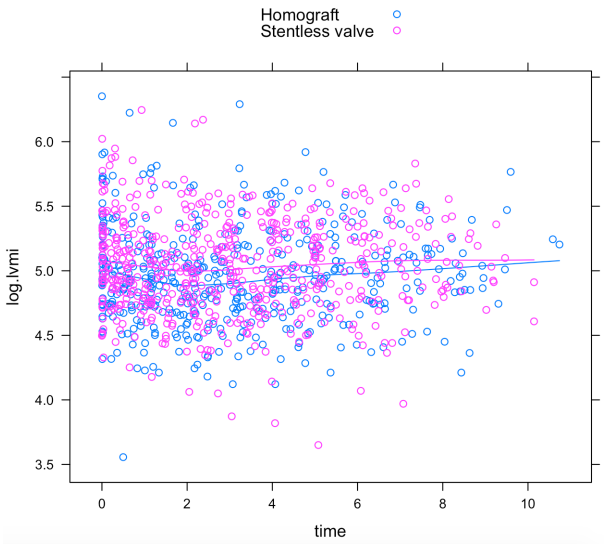
Table 1: Mean (Standard deviation) for continuous or % for binary variables (Patient characteristics)

	Homograft (N=457)	Stentless valve (N=531)
Age (years)	59.2 (12.60)	69.0 (9.30)
Male	70.90%	71.40%
Died	7.22%	24.10%

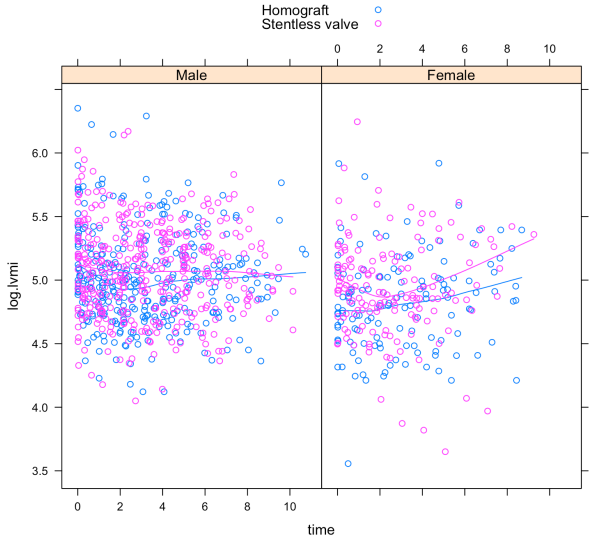
Table 2: Mean (Standard deviation) for continuous or % for binary variables (Outcomes)

	Homograft (N=457)	Stentless valve (N=531)
Lvmi	155 (67.60)	164 (63.10)
Log.lvmi	4.96 (0.38)	5.03 (0.37)
Lvh	0.85 (0.36)	0.97 (0.18)

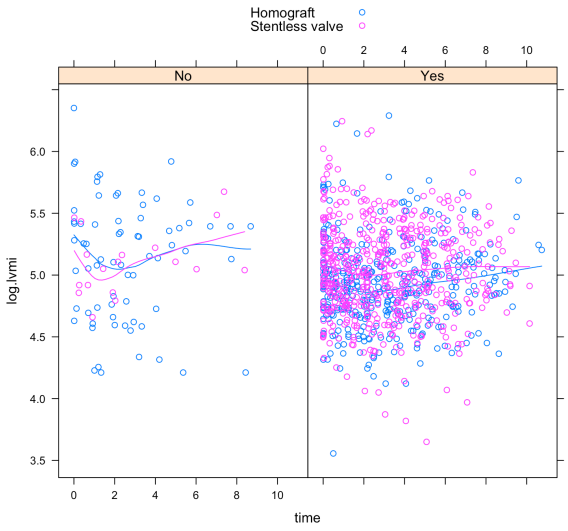
Figure 1: scatterplots of log lvmi over time



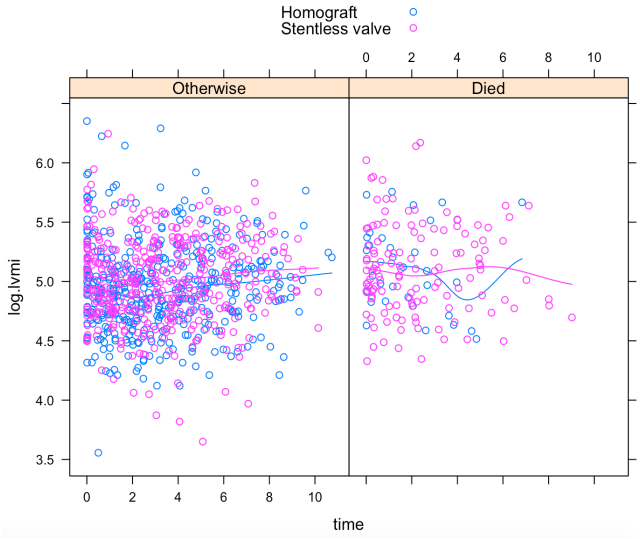
(a)



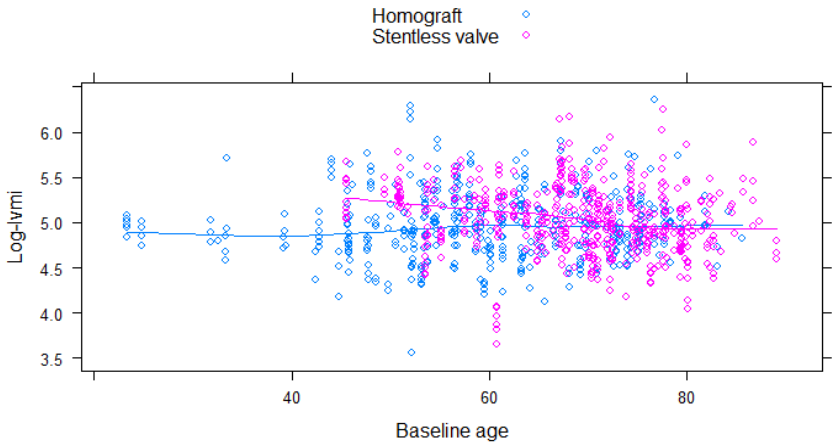
(b)



(c)



(d)



(e)

Table 3: Regression coefficient of valve replacement type and log lvmi

	Without interaction			With interaction		
	Coefficient	95%CI	P-value	Coefficient	95%CI	P-value
Stentless valve vs. Homograft	0.070	(-0.022, 0.162)	0.138	0.083	(-0.027-0.193)	0.139
Time	-0.074	(-0.113, -0.036)	<0.001**	-0.072	(-0.113-0.031)	0.001**
AgeSpline2	0.094	(0.048, 0.140)	<0.001**	0.094	(0.047-0.140)	<0.001**
Stentless valve*Time	-	-	-	-0.004	(-0.028-0.020)	0.729

Note:

* p<0.05, ** p<0.01.

Figure 2: Fitted values of the regression model

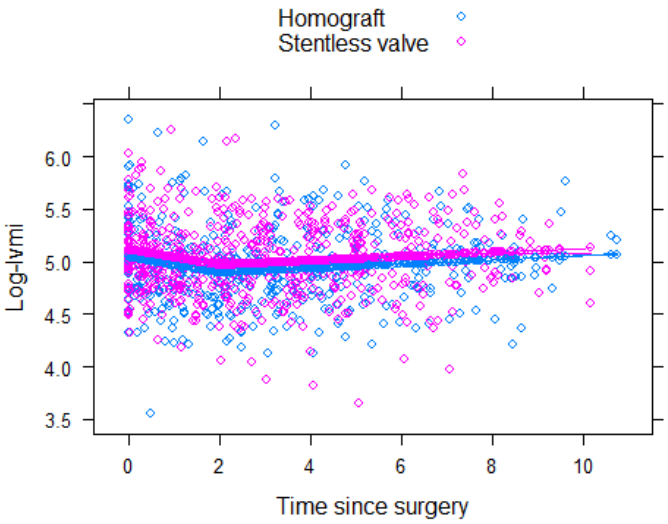


Table 4: Regression coefficient with interaction between time and valve type and preoperative left ventricular hypertrophy

	Coefficient	95%CI	P-value
Baseline age	-0.0001	(-0.004, 0.003)	0.646
Sex	-0.162	(-0.271, -0.053)	0.004**
Lvh	-0.148	(-0.333, 0.037)	0.117
Time	-0.064	(-0.120, -0.001)	0.024*
Stentless valve vs. Homograft	0.125	(0.024, 0.226)	0.016*

AgeSpline2	0.093	(0.047, 0.139)	<0.001**
Lvh * time	-0.007	(-0.050, 0.036)	0.754
Stentless valve * time	-0.009	(-0.033, 0.014)	0.439

Note:

* p<0.05, ** p<0.01.

Table 5. Joint test of interactions

x^2 statistic	P-value
0.713	0.7

Appendix

R Code

```
library(dplyr)

library(reshape)

library(lattice)

library(ggplot2)

library(table1)

library(geepack)

library(doBy)


data<-read.csv("/Users/ziyuxiao/Desktop/UW/Spring2020/BIOST540/Dataset/heart.csv")[,-1]

# label them

data$status <- factor(heart$status, levels=c(0,1),labels=c("Otherwise", "Died"))

data$sex <- factor(heart$sex, levels=c(0,1),labels=c("Male", "Female"))

data$lvh <- factor(heart$lvh, levels=c(0,1),labels=c("No", "Yes"))

## q1

# figure1a

xyplot(log.lvmi~time,data = data,group =as.factor(hs),auto.key = TRUE,type=c("p","smooth"))

# figure1b

xyplot(log.lvmi~time|sex,data = data,group =as.factor(hs),auto.key = TRUE,type=c("p","smooth"))

# figure1c

xyplot(log.lvmi~time|lvh,data = data,group =as.factor(hs),auto.key = TRUE,type=c("p","smooth"))

# figure1d
```

```
xyplot(log.lvmi~time|status,data = data, group =as.factor(hs),auto.key = TRUE,type=c("p","smooth"))

# figure1e

xyplot(log.lvmi~age,data = data,group =as.factor(hs),auto.key = TRUE,type=c("p","smooth"))


## q2a.

data <- arrange(data, num, time)

data$ageSpline2 <- (data$time - 2)*(data$time > 2)

mod0 <- geeglm(formula = log.lvmi ~ hs+time+ageSpline2,

            data = data, id = data$num, corstr = "independence")

data$r0<-as.numeric(mod0$residuals)

data$fitted0 <- as.numeric(mod0$fitted.values)

plot(data$r0~data$fitted0)

xyplot(log.lvmi ~ time, group=as.factor(hs),data=data, type=c('p','smooth'), ylab="Log-lvmi", xlab="Time
since surgery",auto.key=T) +

  as.layer(xyplot(fitted0 ~ time,group=as.factor(hs), data=data, type=c('p','smooth')))

summary(mod0)

confint.default(mod0)

## q2b. GEE

mod2<-geeglm(formula = log.lvmi ~ age+sex+lvh*time+hs*time+ageSpline2, data = data, id = num,

          corstr = "independence")

summary(mod2)

confint.default(mod2)

## jointly testing interactions
```

```
lambda1<-c(0,0,0,0,0,0,0,1,0)

lambda2<-c(0,0,0,0,0,0,0,0,1)

esticon(mod2,L=rbind(lambda1,lambda2),beta0=c(0,0),joint.test=TRUE)
```