Impact of Eye Laser Treatment on Delaying Vision Loss Caused by Diabetic Retinopathy

Introduction

Diabetic retinopathy is a diabetes complication that affects eyes, which is caused by damage to the blood vessels of the light-sensitive tissue at the retina or back of the eye. It can lead to blindness if not treated in time. Ophthalmologists at Michigan Medicine conducted a medical study to explore the impact of two eye laser treatments (xenon and argon) on delaying vision loss caused by diabetic retinopathy. This report aims to analyze the data of 197 participants of this medical study, who presented high-risk diabetic retinopathy, to determine the efficacy of treatment type on visual acuity, quantify the improvement between eyes by treatment type, and better understand the impacts of age at diagnosis and clinical risk of diabetic retinopathy on visual acuity. We performed survival analysis and modeled the probability of vision loss for the censored data, and we concluded that laser treatment can help delay vision loss caused by diabetic retinopathy and risk of diabetic retinopathy has an impact on visual acuity.

Method

For the result analysis of this medical study, there are two main concerns: the censored data and the associations between observations. Firstly, during the medical study, participants either lost vision or were lost to follow-up because of death, dropout, or end of the study. There is no further information on the vision loss for those participants who were lost to follow-up. Given the censored data, survival analysis was performed to measure the fraction of patients who don't lose vision, and model the probability of vision loss, after some certain time. The analysis was structured into two parts: Kaplan-Meier (KM) Curve with Log-Rank Test and Cox Proportional-Hazards (Cox PH) model. Secondly, since every participant's left eye and right eye are regarded as two samples in our data and obviously, there might be some association between the left eye and right eye from the same participant. So, we constructed a frailty model by adding frailty term to Cox PH model to depict the potential association.

KM Curve was used to estimate the probability of an eye not losing vision after some certain time. We fit the curve with different characteristics and factors including treatment type (xenon or argon), age at diagnosis, age type (adult or juvenile), and clinical risk score of diabetic retinopathy. The KM curve stratified by a specific characteristic can reflect the trend of proportion of eyes not losing vision over time for different values of this characteristic, thus help us understand how different characteristics or factors would affect the vision loss. For example, the curve stratified by treatment type can present the trend of proportion of eyes not losing vision over time for three groups (xenon, argon, and control), and finally help us determine the efficacy of treatment on visual acuity. Furthermore, the log-rank test was applied to all survival curves to calculate the significance of difference among values or levels for a certain characteristicor factor.

Next, Cox Proportional-Hazards with a frailty term to investigate the association between the survival time (the time passed before an eye lost vision) of eyes and multiple characteristics and factors mentioned above and access simultaneously the effects of these characteristics and factors instead of considering one characteristic or factor at a time in KM curves. The survival object formed by futime (lag-corrected time to loss of vision or last follow-up in months) and status (lost to follow-up or loss of vision in eye) worked as the outcome/response in the model. Participant's id as the frailty term and other characteristics and factors that were significant at the level of 0.1 in log-rank test, including treatment type, age, treatment eye (left or right) and clinical risk score, worked as predictors. And different treatment type (argon or xenon) may have different impacts between left and right eyes. To address this issue, we also considered the interaction between treatment eye and treatment type in our model and verified the significance of this interaction using likelihood ratio test. Finally, we analyzed the fitted coefficient and corresponding significance (P-value) of treatment type, treatment eye and their interaction term to quantify the improvement between eyes by treatment type, and the fitted coefficient and corresponding significance (P-value) of age and clinical risk score to understand their potential impacts on visual acuity.

Results

The dataset contains 394 rows and 9 columns. Every two rows correspond to one participant (197 participants in total), one for each eye and 9 columns record 9 variables for each participant's each eye: id is the subject id; laser is the type of treatment that was used, either xenon or argon; eye indicates left or right eye which received treatment for each participant; age is age in years at time of diabetes diagnosis; type represents whether a participant is adult or juvenile at time of diabetes; trt represents the eye is treated eye (1) or control eye (0); futime is the lag-corrected time to loss of vision or last follow-up in months; status represents the eye is lost to follow-up (0) or lose vision (1); risk is the clinical risk of loss of acuity and must be at least 6 in one eye to participate in study. Table 1 shows the distribution metrics for these 9 variables of 197 participants.

Variable	**Mean**	**Standard Deviation**	**Median**	**IQR**
age (in years old)	20.78	14.81	16.00	20.00
futime (in months) for vision loss	18.70	15.31	13.83	20.17
futime (in months) for lost to follow-up	46.53	17.19	48.53	19.76
risk (score 6 - 12) for lost to follow-up	9.70	1.48	10.00	2.00
id	197 unique values for 197 participants			
laser	97 for argon; 100 for xenon			
eye	1 left and 1 right for each participant			
type	83 for adult; 114 for juvenile			
trt	1 treatment and 1 control for each participant			
status	155 for vision loss; 239 for lost to follow-up (394 eyes in total)			

Table 1: Distribution Metrics.

The average age of people participating in the study is about 21 years old, where most of participants are juvenile at the time of diagnosis and then adults. The average risk score for all participants is 9.70. 97 out of 197 participants received argon treatment for one eye and the other 100 participants received xenon treatment for one eye. Among 394 eyes for 197 participants, there are 155 eyes losing vision and the other 239 lost to follow-up. For those eyes losing vision, the average time for loss of vision is about 19 months and the average risk score for eyes losing vision is 9.92.

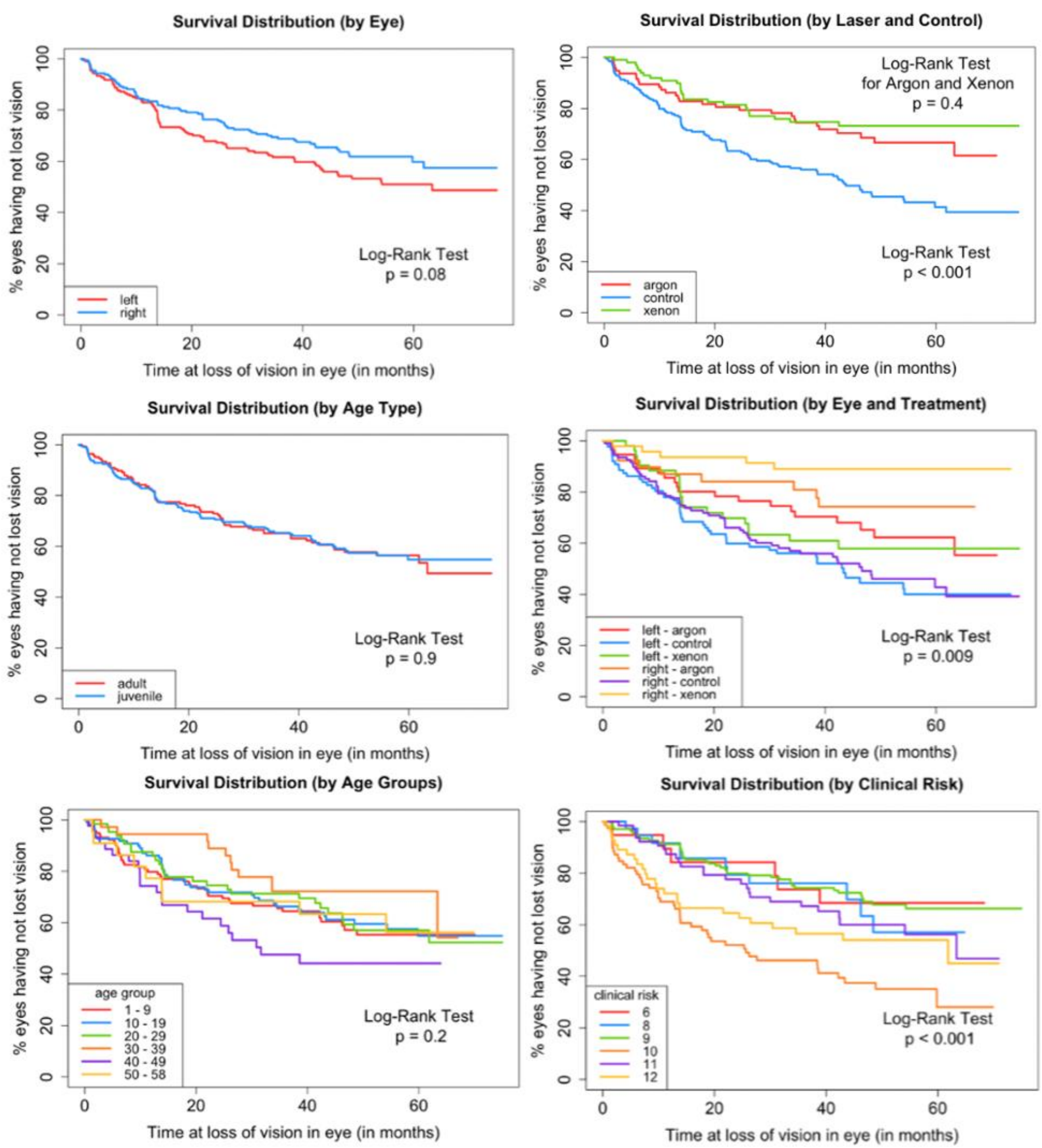


Figure 1: KM Survival Curves (by Eye, Treatment Type, Laser and Control, Eye and Laser, Age, Clinical Risk)

The KM survival curves stratified by eye, treatment type, age type, eye and treatment, age, and clinical risk, are visualized in Figure 1. It can be concluded that, at the level of 0.1, (1) the proportion of eyes having not lost vision remains higher for right eyes than for left eyes; (2) the proportion of eyes having not lost vision remains higher for treated eyes than control eyes, which suggests that the treatment helps to delay the diabetic retinopathy vision loss; however, the proportion remains the same for two treatments (xenon and argon), which indicates two treatments perform similarly in delaying vision loss; (3) the proportion remains the same for adult and juvenile, which indicates age type does not affect the visual acuity; (4) the proportion of eyes having not lost vision remains higher for treated right eyes (both xenon and argon) than treated left eyes; xenon performs better than argon for right eyes but argon performs better for left eyes; (5) there is no enough evidence to support that the proportion of eyes having not lost vision remains different for different age groups, which means age would not affect the visual acuity; (6) the proportion of eyes having not lost vision remains different for different clinical risk scores which indicates that risk score would affect the visual acuity; and generally, higher risk score implies lower proportion of eyes having not lost vision.

Variable	**Rate (95% CI)**	**P-value**
frailty (participant's id)	1.00 (1.00, 1.00)	0.007*
risk (score from 6 to 12)	1.20 (1.04, 1.39)	0.011*
argon treatment vs. control	0.42 (0.22, 0.81)	0.009*
xenon treatment vs. control	0.72 (0.38, 1.39)	0.330
right eye vs. left eye	0.93 (0.55, 1.56)	0.780
argon treatment + right eye vs. control + left eye	0.80 (0.26, 2.46)	0.700
xenon treatment + right eye vs. control + left eye	0.16 (0.05, 0.57)	0.005*

Table 2: Coefficient Estimates for All Predictors in Cox Proportional-Hazards Model.

The Cox PH model with frailty term including the interaction term between laser (argon, xenon, control) and eye (right, left) gave a log-likelihood of -747.70 which is much larger than the log-likelihood of simple Cox PH model with and without interaction. The likelihood ratio test gave a P-value much smaller than 0.01, which indicates that the model with frailty term including the interaction term performs best. And the estimated exponential rate of coefficient for each predictor predictors in this Cox Proportional-Hazard model with frailty and interaction term are shown in Table 2. From Table 2, only risk, argon treatment and xenon treatment for right eye are significant at the level of 0.05. 1 score increase in risk would increase the instantaneous probability (hazard) of vision loss by a factor of 1.20; argon laser treatment would reduce the instantaneous probability (hazard) of vision loss by a factor of 0.42; and xenon treatment would reduce the instantaneous probability (hazard rate) of vision loss for right eye by a factor of 0.16.

Conclusion

This report analyzed the research data from a medical study conducted by ophthalmologists at Michigan Medicine to determine the efficacy of treatment type on visual acuity, quantify the improvement between eyes by treatment type, and better understand the impacts of age at diagnosis and clinical risk of diabetic retinopathy on visual acuity. Since some participants were lost to follow-up either because of death, drop-out or end of the study, we performed survival analysis to fit the censored data. We modeled the proportion of eyes having not lost vision over time using KM curves for treatment type (xenon or argon), age at diagnosis, age type (adult or juvenile), and clinical risk score of diabetic retinopathy. And we also constructed Cox Proportional-Hazard model using significant predictors given by log-rank test. It can be concluded that the treatment is indeed able to delay the diabetic retinopathy vision loss; argon and xenon have statistically the same impact. Quantitatively, argon laser treatment would reduce the instantaneous probability (hazard) of vision loss by a factor of 0.42; and xenon treatment would reduce the instantaneous probability (hazard) of vision loss for right eye by a factor of 0.16. Additionally, the risk score does impact the visual acuity, and in general, higher risk score implies lower proportion of eyes having not lost vision; 1 score increase in risk would increase the instantaneous probability (hazard) of vision loss by a factor of 1.20. However, there is no evidence to support that age have an impact on visual acuity.

There are still limitations in this work. The study was limited to 7 predictors, but there might be some other factors or characteristics having an impact on visual acuity, like gender and whether the participant has other diseases. More factors and characteristics can be taken into consideration in the future study.

STATS 504 Assignment 2: Diabetic Retinopathy

In [1]:

```
# Load libraries
library(survival)
library(tidyverse)
library(ggplot2)
library(coxme)
```

```
── Attaching packages ─────────────────────────────────────────────────────────
──────────────────────────────────────────────────────── tidyverse 1.3.1 ──

✔ ggplot2 3.3.6     ✔ purrr   0.3.4
✔ tibble  3.1.7     ✔ dplyr   1.0.9
✔ tidyr   1.2.0     ✔ stringr 1.4.0
✔ readr   2.1.2     ✔ forcats 0.5.1

── Conflicts ──────────────────────────────────────────────────────────────────
────────────────────────────────────────────────── tidyverse_conflicts() ──
✖ dplyr::filter() masks stats::filter()
✖ dplyr::lag()    masks stats::lag()

Loading required package: bdsmatrix


Attaching package: ‘bdsmatrix’


The following object is masked from ‘package:base’:

    backsolve
```

In [2]:

```
# Load Data
diabetic = read.csv("diabeticVision.csv", stringsAsFactors = TRUE, row.names =
```

In [3]:

```
head(diabetic)
```

A data.frame: 6 × 9

	id	laser	eye	age	type	trt	futime	status	risk
	<int>	<fct>	<fct>	<int>	<fct>	<int>	<dbl>	<int>	<int>
1	5	argon	left	28	adult	1	46.23	0	9
2	5	argon	left	28	adult	0	46.23	0	9
3	14	argon	right	12	juvenile	1	42.50	0	8
4	14	argon	right	12	juvenile	0	31.30	1	6
5	16	xenon	right	9	juvenile	1	42.27	0	11
6	16	xenon	right	9	juvenile	0	42.27	0	11

Exploratory Data Analysis

In [4]:
```
str(diabetic)
```

```
'data.frame':	394 obs. of  9 variables:
 $ id    : int  5 5 14 14 16 16 25 25 29 29 ...
 $ laser : Factor w/ 2 levels "argon","xenon": 1 1 1 1 2 2 1 1 2 2 ...
 $ eye   : Factor w/ 2 levels "left","right": 1 1 2 2 2 2 1 1 1 1 ...
 $ age   : int  28 28 12 12 9 9 9 9 13 13 ...
 $ type  : Factor w/ 2 levels "adult","juvenile": 1 1 2 2 2 2 2 2 2 2 ...
 $ trt   : int  1 0 1 0 1 0 1 0 1 0 ...
 $ futime: num  46.2 46.2 42.5 31.3 42.3 ...
 $ status: int  0 0 0 1 0 0 0 0 0 1 ...
 $ risk  : int  9 9 8 6 11 11 11 11 9 10 ...
```

In [5]:
```
diabetic$trt = factor(diabetic$trt, levels = c(1, 0), labels = c('treatment', '
diabetic$eye[diabetic$trt=='control'] = ifelse(diabetic$eye[diabetic$trt=='cont
```

In [6]:
```
# Variable for laser
diabetic$laser = as.character(diabetic$laser)
diabetic$laser[diabetic$trt=='control'] = 'control'

# Variable for eye (by treatment eye)
diabetic$eye.trt = paste(diabetic$eye, '-', diabetic$laser)
```

In [7]:
```
# Age group
diabetic$age.group = case_when(
    between(diabetic$age, 1, 10) ~ "1 - 9",
    between(diabetic$age, 11, 19) ~ "10 - 19",
    between(diabetic$age, 20, 29) ~ "20 - 29",
    between(diabetic$age, 30, 39) ~ "30 - 39",
    between(diabetic$age, 40, 49) ~ "40 - 49",
    between(diabetic$age, 50, 58) ~ "50 - 58"
)
```

In [8]:
```
# make variables as factor
diabetic$laser = as.factor(diabetic$laser)
diabetic$eye.trt = as.factor(diabetic$eye.trt)
diabetic$age.group = as.factor(diabetic$age.group)
```

In [9]:
```
summary(diabetic)
```

```
       id               laser          eye            age                type    
 Min.   :   5.0   argon  : 97   left :197   Min.   : 1.00   adult   :166  
 1st Qu.: 480.0   control:197   right:197   1st Qu.:10.00   juvenile:228  
 Median : 834.0   xenon  :100               Median :16.00                 
 Mean   : 873.2                             Mean   :20.78                 
 3rd Qu.:1296.0                             3rd Qu.:30.00                 
 Max.   :1749.0                             Max.   :58.00                 
        trt            futime          status            risk       
 treatment:197   Min.   : 0.30   Min.   :0.0000   Min.   : 6.000  
 control  :197   1st Qu.:13.98   1st Qu.:0.0000   1st Qu.: 9.000  
                 Median :38.80   Median :0.0000   Median :10.000  
                 Mean   :35.58   Mean   :0.3934   Mean   : 9.698  
                 3rd Qu.:54.25   3rd Qu.:1.0000   3rd Qu.:11.000  
                 Max.   :74.97   Max.   :1.0000   Max.   :12.000  
            eye.trt       age.group  
 left - argon   : 56   1 - 9  :116  
 left - control : 89   10 - 19:112  
 left - xenon   : 52   20 - 29: 64  
 right - argon  : 41   30 - 39: 36  
 right - control:108   40 - 49: 44  
 right - xenon  : 48   50 - 58: 22  
```

In [10]:
```
sqrt(diag(var(diabetic[, c('age', 'futime', 'risk')])))
```

age: 14.8120737171584 **futime:** 21.3558959090673 **risk:** 1.47503256153693

In [11]:
```
table(diabetic$status)
```

```
  0   1 
239 155 
```

In [12]:
```
summary(diabetic$futime[diabetic$status==1])
```

```
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max. 
   0.30    6.25   13.83   18.70   26.42   63.33 
```

In [13]:
```
sqrt(var(diabetic$futime[diabetic$status==1]))
```

15.3070976297491

In [14]:
```
summary(diabetic$futime[diabetic$status==0])
```

```
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max. 
   1.47   38.77   48.53   46.53   58.53   74.97 
```

In [15]:
```
sqrt(var(diabetic$futime[diabetic$status==0]))
```

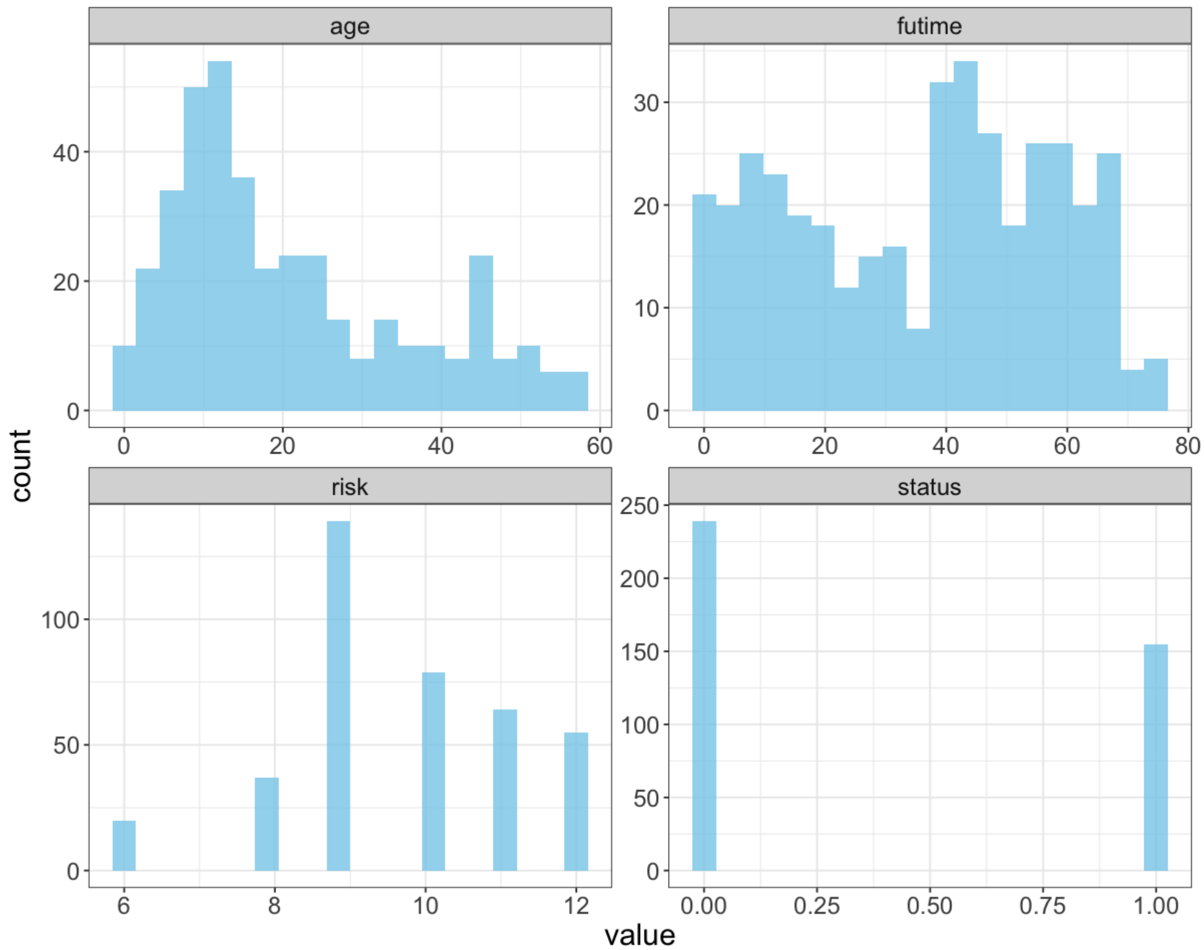
17.1883180916374

In [16]:
```
num.hist = diabetic[,sapply(diabetic, is.numeric)] # filter all numerical varia
cat.bar = diabetic[,sapply(diabetic, is.factor)] # filter all factor variables
# melt the dataframe to plot
num.hist = num.hist %>% gather(key = "variable", value = "value")
cat.bar = cat.bar %>% gather(key = "variable", value = "value")
```

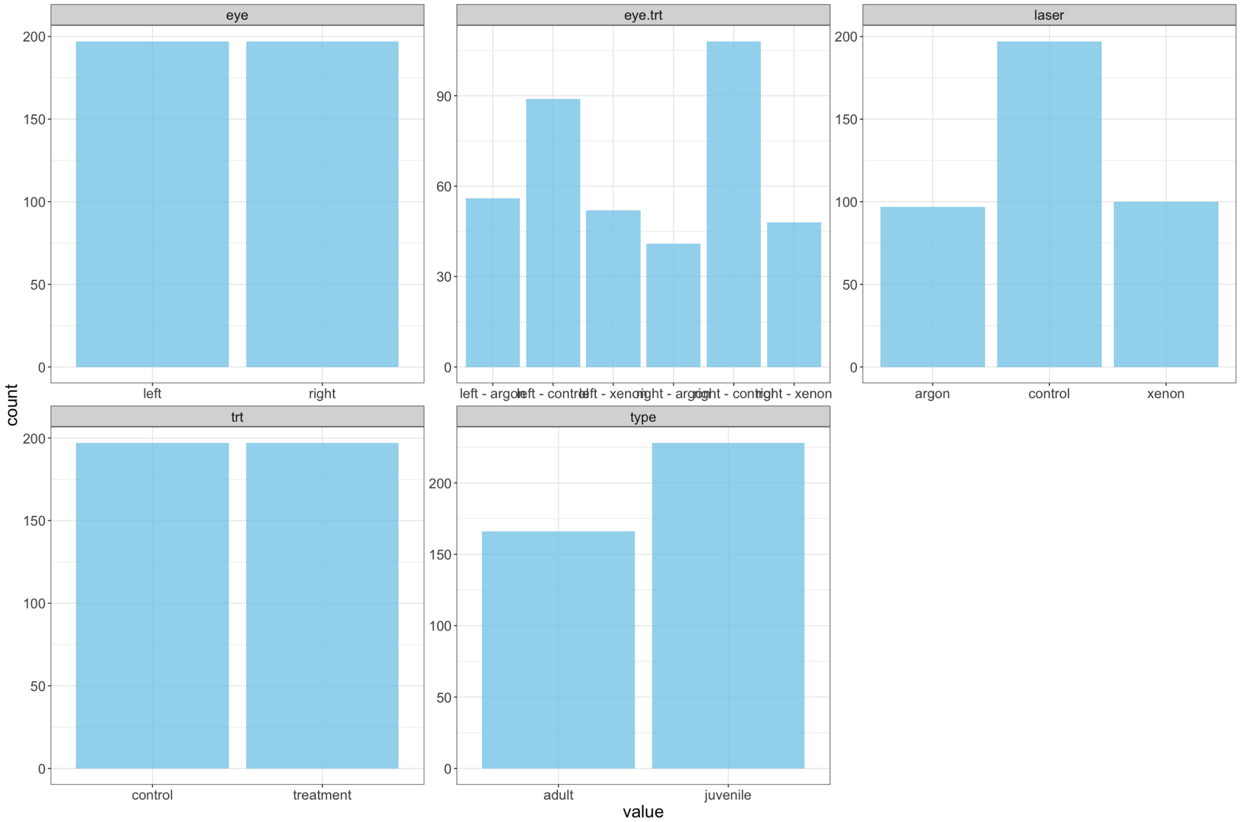
```
Warning message:
“attributes are not identical across measure variables;
they will be dropped”
```

In [17]:
```
options(repr.plot.width = 10, repr.plot.height = 8)
```

```
# histogram for numerical variables
num.hist %>% filter(variable != 'id') %>% ggplot() +
    geom_histogram(aes(x = value), bins = 20, fill="skyblue", alpha=0.8) +
    facet_wrap(~variable, scales = 'free') + theme_bw() +
    theme(text = element_text(size = 18))
```

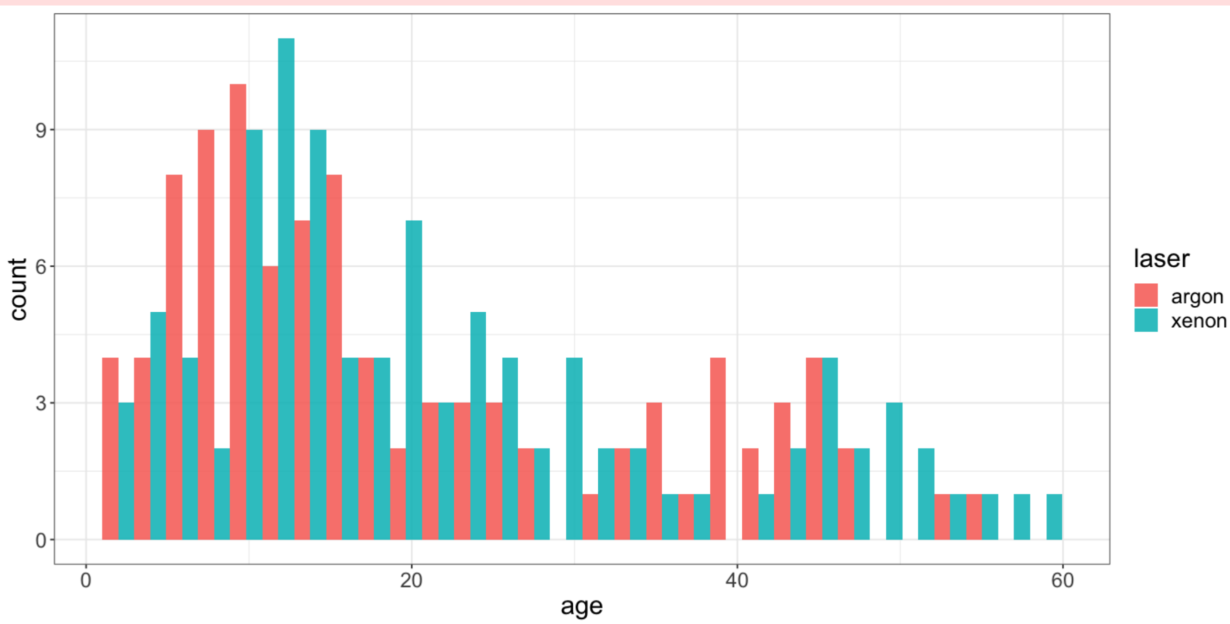


In [18]:
```
options(repr.plot.width = 18, repr.plot.height = 12)
# barplot for categorical variables
cat.bar %>% filter(variable != 'age.group') %>% ggplot() +
    geom_bar(aes(x = value), fill="skyblue", alpha=0.8) +
    facet_wrap(~variable, scales = 'free') + theme_bw() +
    theme(text = element_text(size = 18))
```

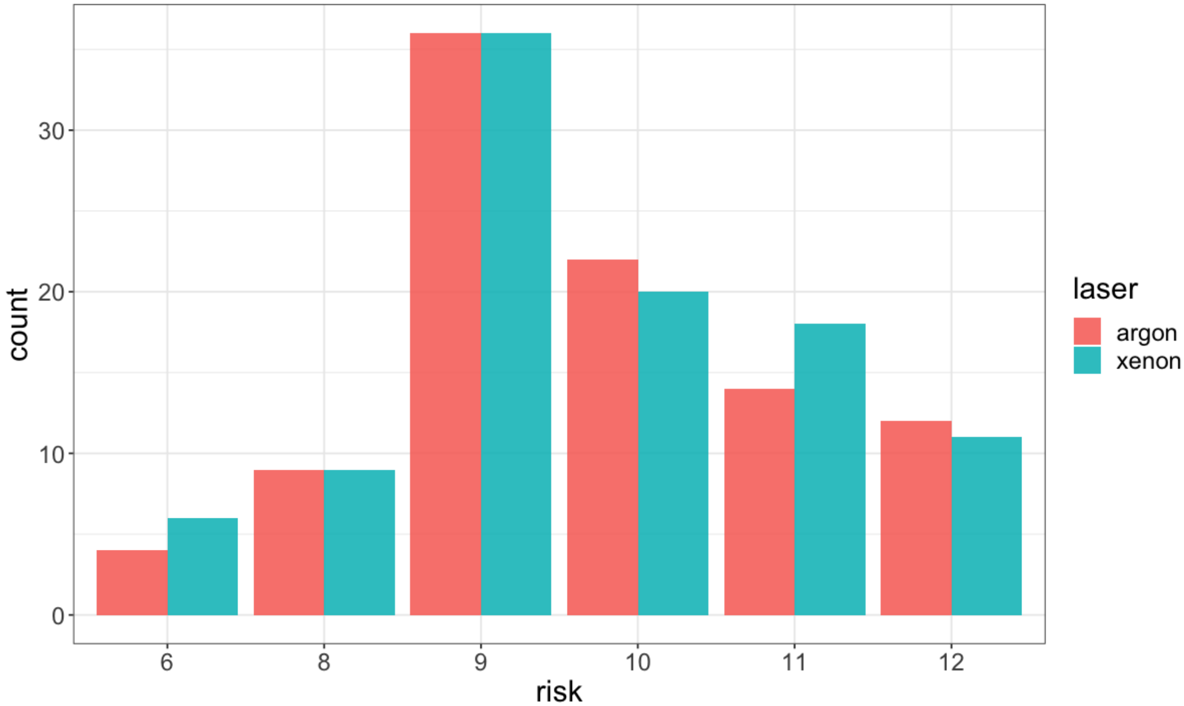


In [19]:
```
# age and laser
options(repr.plot.width = 12, repr.plot.height = 6)
diabetic %>% filter(trt == 'treatment') %>% ggplot(aes(x = age, fill = laser))
    geom_histogram(alpha = 0.9, position = 'dodge') + theme_bw() +
    theme(text = element_text(size = 18))
```

```
`stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
```



In [20]:
```
# risk and laser
options(repr.plot.width = 10, repr.plot.height = 6)
diabetic %>% filter(trt == 'treatment') %>% ggplot(aes(x = as.factor(risk), fil
    geom_bar(alpha = 0.9, position = 'dodge') + theme_bw() +
    theme(text = element_text(size = 18)) +  xlab('risk')
```

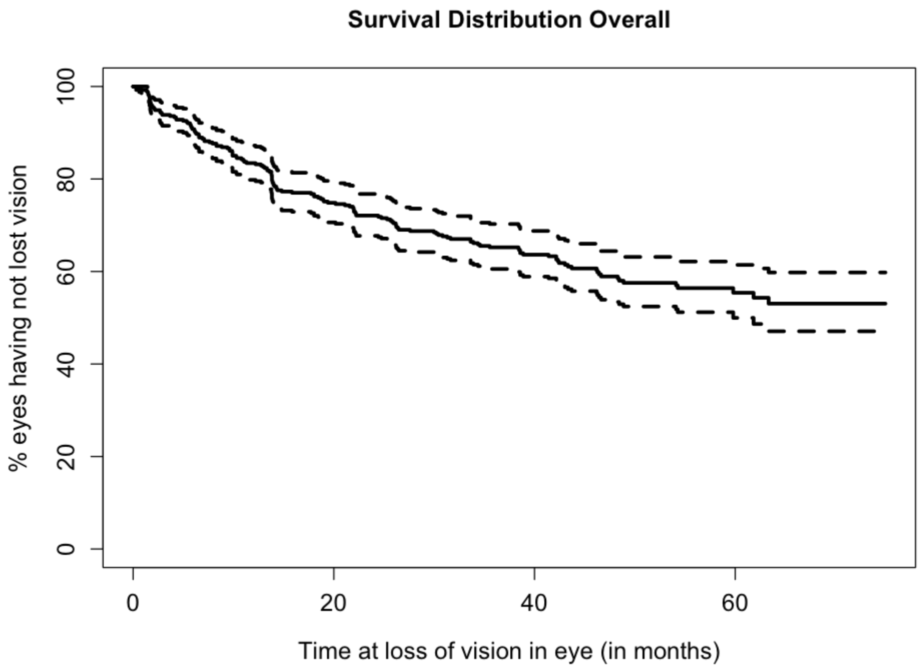


Data Analysis

In [21]:
```
# Create survival object
survobj = with(diabetic, Surv(futime, status))
```

The Kaplan-Meier Survival Curve

In [22]:
```
options(repr.plot.width = 8, repr.plot.height = 6)
plot(survfit(survobj ~ 1, data=diabetic),
     xlab="Time at loss of vision in eye (in months)",
     ylab="% eyes having not lost vision", yscale=100,
     main ="Survival Distribution Overall", lwd = 3,
    cex.lab=1.2, cex.axis=1.2, cex.main=1.2, cex.sub=1.2)
```



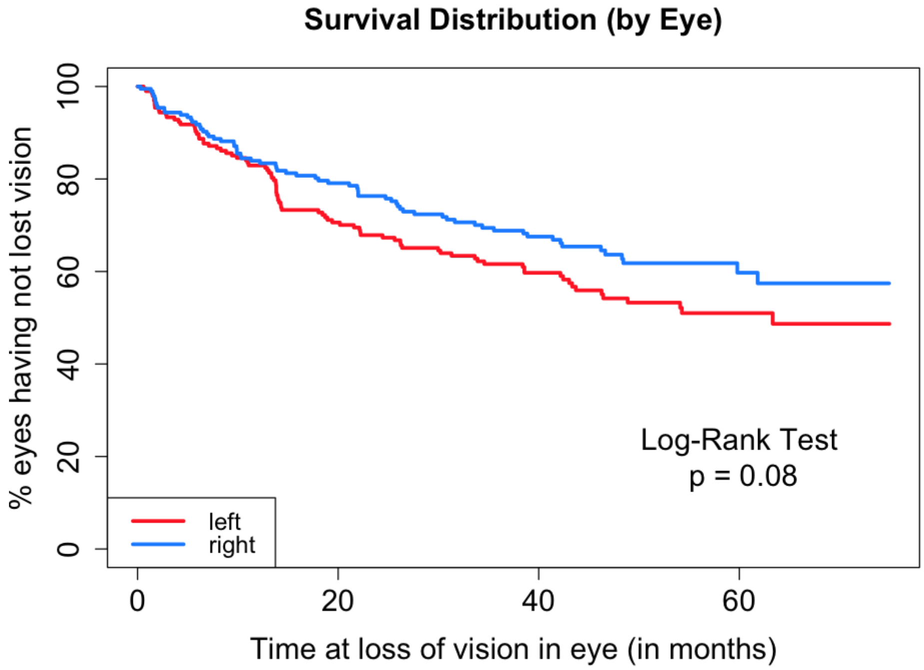
In [23]:
```
# Differences between left and right eye
survdiff(survobj ~ eye, data=diabetic)
```

```
Call:
survdiff(formula = survobj ~ eye, data = diabetic)

            N Observed Expected (O-E)^2/E (O-E)^2/V
eye=left  197       86     75.2      1.56      3.03
eye=right 197       69     79.8      1.47      3.03

 Chisq= 3  on 1 degrees of freedom, p= 0.08
```

In [24]:
```
# left/right eye
plot(
    survfit(survobj ~ eye, data=diabetic),
    xlab="Time at loss of vision in eye (in months)",
    ylab="% eyes having not lost vision", yscale=100,
    main ="Survival Distribution (by Eye)",
    col = c('firebrick1', 'dodgerblue'),
    lwd = 3, cex.lab=1.5, cex.axis=1.5, cex.main=1.5, cex.sub=1.5
    )
legend('bottomleft', legend=levels(diabetic$eye),
       col = c('firebrick1', 'dodgerblue'),
       lty=1, lwd = 3, cex = 1.2)
text(60, 0.2, labels = 'Log-Rank Test\n p = 0.08', cex = 1.5)
```



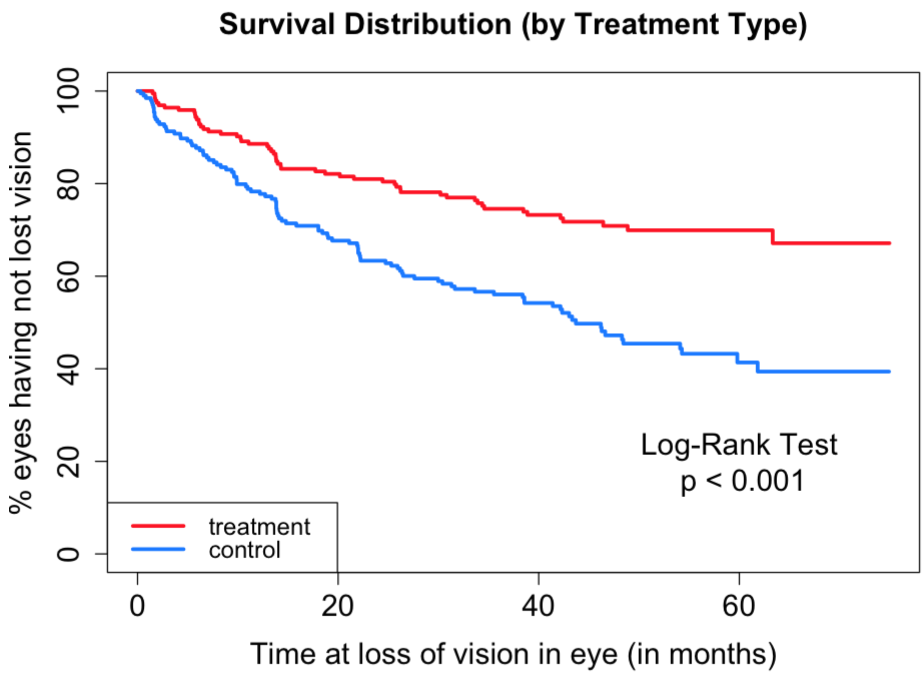
In [25]:
```
# Differences between treatment and control
survdiff(survobj ~ trt, data=diabetic)
```

```
Call:
survdiff(formula = survobj ~ trt, data = diabetic)

                 N Observed Expected (O-E)^2/E (O-E)^2/V
trt=treatment 197       54     83.2      10.3      22.2
trt=control   197      101     71.8      11.9      22.2

 Chisq= 22.2  on 1 degrees of freedom, p= 2e-06
```

In [26]:
```
# treatment/control
plot(
    survfit(survobj ~ trt, data=diabetic),
    xlab="Time at loss of vision in eye (in months)",
    ylab="% eyes having not lost vision", yscale=100,
    main ="Survival Distribution (by Treatment Type)",
    col = c('firebrick1', 'dodgerblue'),
    lwd = 3, cex.lab=1.5, cex.axis=1.5, cex.main=1.5, cex.sub=1.5
    )
legend('bottomleft', legend=levels(diabetic$trt),
       col = c('firebrick1', 'dodgerblue'),
       lty=1, lwd = 3, cex = 1.2)
text(60, 0.2, labels = 'Log-Rank Test\n p < 0.001', cex = 1.5)
```



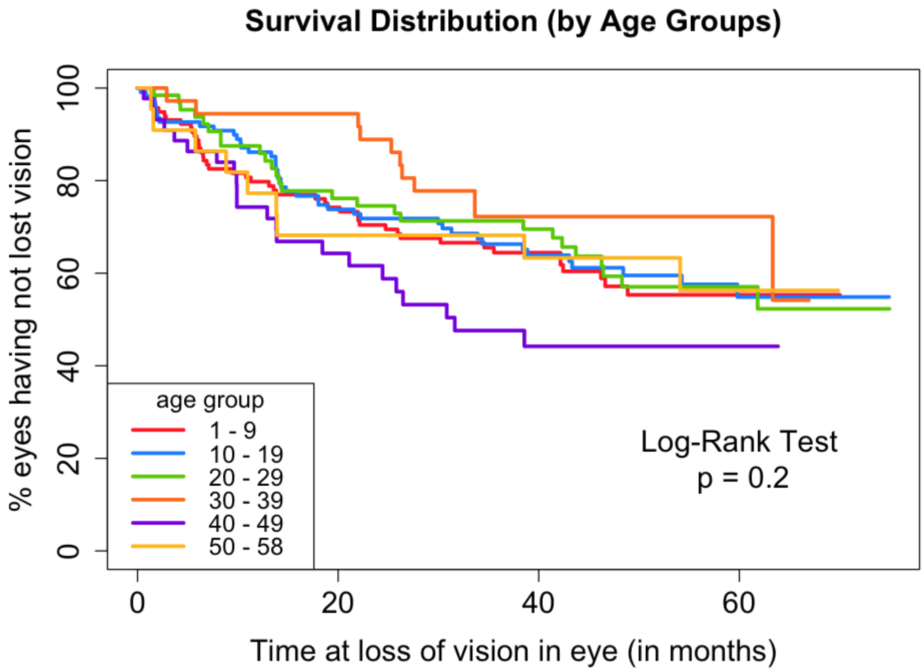
In [27]:
```
# Differences between age groups
survdiff(survobj ~ age.group, data=diabetic)
```

```
Call:
survdiff(formula = survobj ~ age.group, data = diabetic)

                    N Observed Expected (O-E)^2/E (O-E)^2/V
age.group=1 - 9   116       45    43.70   0.03882   0.05416
age.group=10 - 19 112       42    44.12   0.10159   0.14241
age.group=20 - 29  64       26    27.41   0.07213   0.08782
age.group=30 - 39  36       11    16.95   2.09050   2.35286
age.group=40 - 49  44       22    14.10   4.42272   4.88735
age.group=50 - 58  22        9     8.72   0.00875   0.00928

 Chisq= 6.8  on 5 degrees of freedom, p= 0.2
```

In [28]:
```
# age group
plot(
    survfit(survobj ~ age.group, data=diabetic),
    xlab="Time at loss of vision in eye (in months)",
    ylab="% eyes having not lost vision", yscale=100,
    main ="Survival Distribution (by Age Groups)",
    col = c('firebrick1', 'dodgerblue', 'chartreuse3', 'chocolate1', 'blueviole
    lwd = 3, cex.lab=1.5, cex.axis=1.5, cex.main=1.5, cex.sub=1.5
    )
legend('bottomleft', legend=levels(diabetic$age.group),
       col = c('firebrick1', 'dodgerblue', 'chartreuse3', 'chocolate1', 'bluevi
       lty=1, lwd = 3, cex = 1.2, title = 'age group')
text(60, 0.2, labels = 'Log-Rank Test\n p = 0.2', cex = 1.5)
```



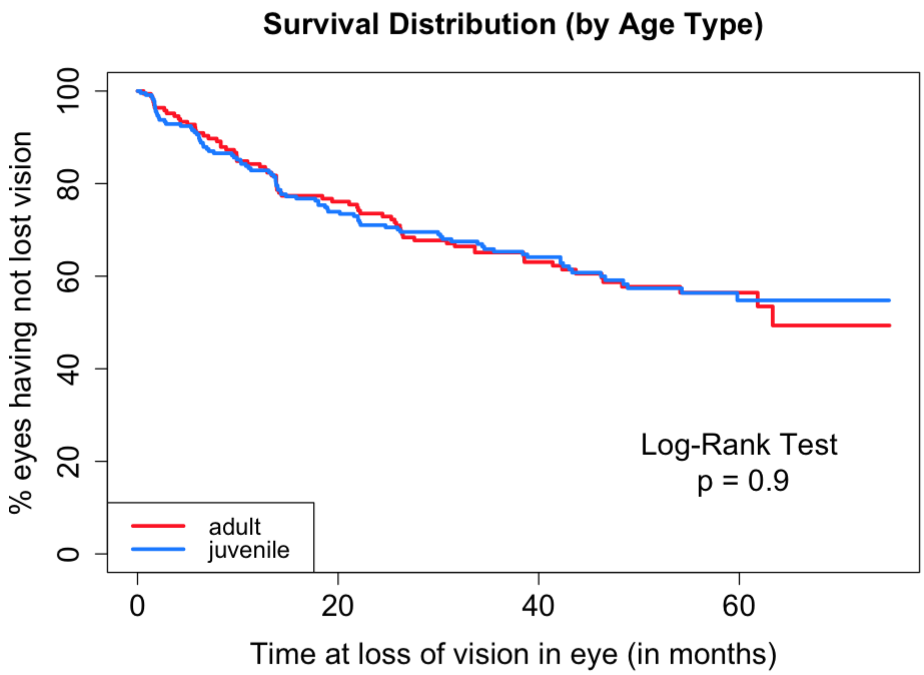
In [29]:
```
# Differences between adult and juvenile
survdiff(survobj ~ type, data=diabetic)
```

```
Call:
survdiff(formula = survobj ~ type, data = diabetic)

                N Observed Expected (O-E)^2/E (O-E)^2/V
type=adult    166       68     67.2   0.00988    0.0175
type=juvenile 228       87     87.8   0.00756    0.0175

 Chisq= 0  on 1 degrees of freedom, p= 0.9
```

In [30]:
```
# type
plot(
    survfit(survobj ~ type, data=diabetic),
    xlab="Time at loss of vision in eye (in months)",
    ylab="% eyes having not lost vision", yscale=100,
    main ="Survival Distribution (by Age Type)",
    col = c('firebrick1', 'dodgerblue'),
    lwd = 3, cex.lab=1.5, cex.axis=1.5, cex.main=1.5, cex.sub=1.5
    )
legend('bottomleft', legend=levels(diabetic$type),
       col = c('firebrick1', 'dodgerblue'),
       lty=1, lwd = 3, cex = 1.2)
text(60, 0.2, labels = 'Log-Rank Test\n p = 0.9', cex = 1.5)
```



In [31]:
```
# Differences among treatment types and control
survdiff(survobj ~ laser, data=diabetic)
```

```
Call:
survdiff(formula = survobj ~ laser, data = diabetic)

                N Observed Expected (O-E)^2/E (O-E)^2/V
laser=argon    97       29     40.1      3.09      4.17
laser=control 197      101     71.8     11.90     22.25
laser=xenon   100       25     43.1      7.60     10.55

 Chisq= 22.7  on 2 degrees of freedom, p= 1e-05
```

In [32]:
```
# Differences between treatment types
diabetic.sub = diabetic[diabetic$trt== 'treatment', ]
survdiff(Surv(futime, status) ~ laser, data=diabetic.sub)
```

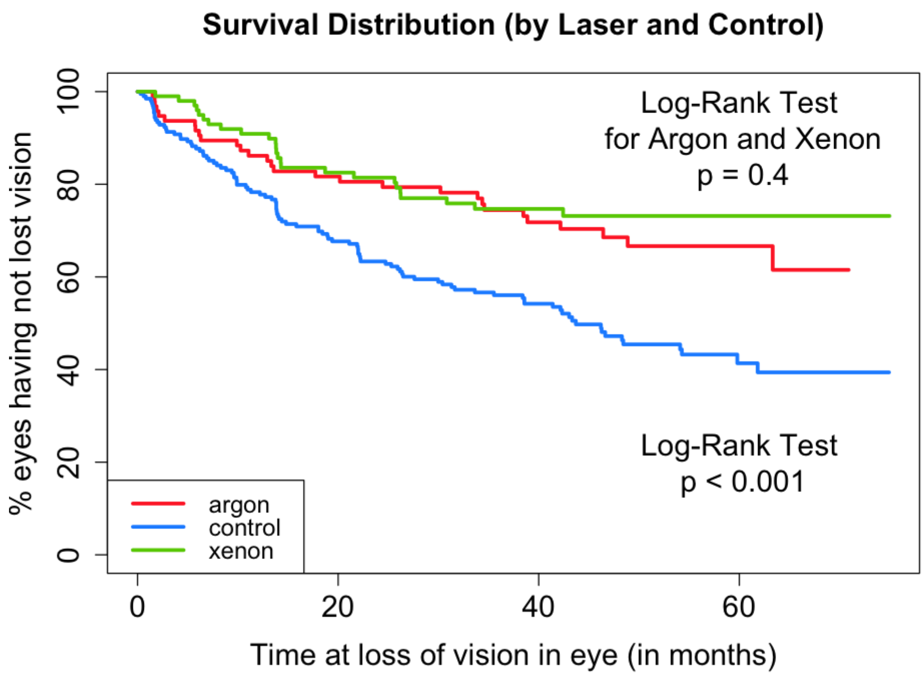
```
Call:
survdiff(formula = Surv(futime, status) ~ laser, data = diabetic.sub)

              N Observed Expected (O-E)^2/E (O-E)^2/V
laser=argon  97       29       26     0.348     0.672
laser=xenon 100       25       28     0.323     0.672

 Chisq= 0.7  on 1 degrees of freedom, p= 0.4
```

In [33]:
```
# laser
plot(
    survfit(survobj ~ laser, data=diabetic),
    xlab="Time at loss of vision in eye (in months)",
    ylab="% eyes having not lost vision", yscale=100,
    main ="Survival Distribution (by Laser and Control)",
    col = c('firebrick1', 'dodgerblue', 'chartreuse3'),
    lwd = 3, cex.lab=1.5, cex.axis=1.5, cex.main=1.5, cex.sub=1.5
    )
legend('bottomleft', legend=levels(diabetic$laser),
       col = c('firebrick1', 'dodgerblue', 'chartreuse3'),
```

```
       lty=1, lwd = 3, cex = 1.2)
text(60, 0.2, labels = 'Log-Rank Test\n p < 0.001', cex = 1.5)
text(60, 0.9, labels = 'Log-Rank Test\n for Argon and Xenon\n p = 0.4', cex = 1
```



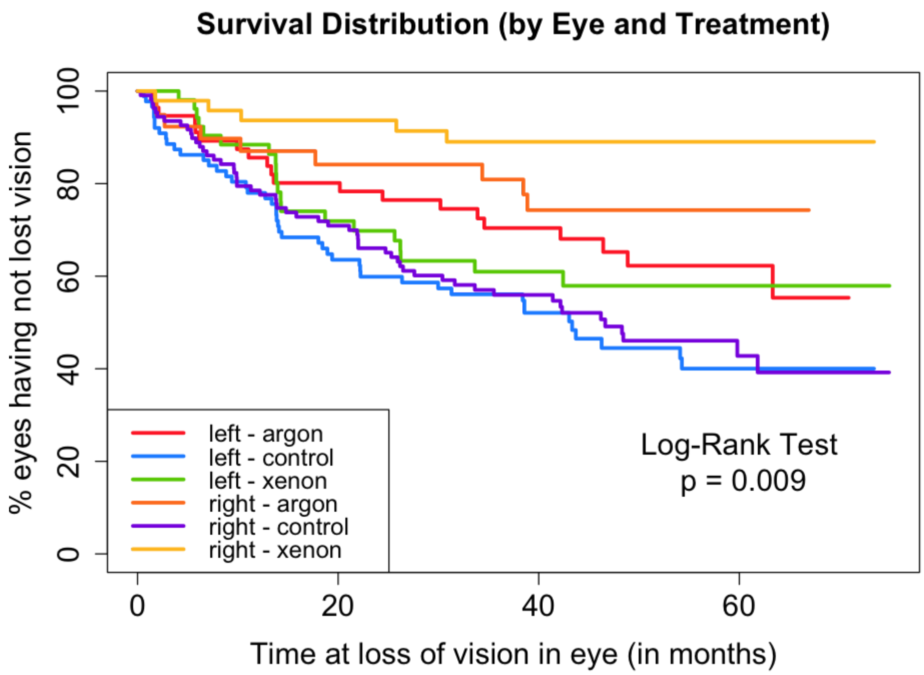
In [34]:
```
# Differences between eyes by treatment
survdiff(Surv(futime, status) ~ eye.trt, data=diabetic)
```

```
Call:
survdiff(formula = Surv(futime, status) ~ eye.trt, data = diabetic)

                          N Observed Expected (O-E)^2/E (O-E)^2/V
eye.trt=left - argon     56       20     23.9  6.39e-01  7.57e-01
eye.trt=left - control   89       46     31.1  7.09e+00  8.89e+00
eye.trt=left - xenon     52       20     20.1  7.35e-04  8.46e-04
eye.trt=right - argon    41        9     16.2  3.21e+00  3.59e+00
eye.trt=right - control 108       55     40.6  5.08e+00  6.90e+00
eye.trt=right - xenon    48        5     23.0  1.41e+01  1.66e+01

 Chisq= 30.2  on 5 degrees of freedom, p= 1e-05
```

In [35]:
```
# eye and laser
plot(
    survfit(survobj ~ eye.trt, data=diabetic),
    xlab="Time at loss of vision in eye (in months)",
    ylab="% eyes having not lost vision", yscale=100,
    main ="Survival Distribution (by Eye and Treatment)",
    col = c('firebrick1', 'dodgerblue', 'chartreuse3', 'chocolate1', 'blueviole
    lwd = 3, cex.lab=1.5, cex.axis=1.5, cex.main=1.5, cex.sub=1.5
    )
legend('bottomleft', legend=levels(diabetic$eye.trt),
       col = c('firebrick1', 'dodgerblue', 'chartreuse3', 'chocolate1', 'bluevi
       lty=1, lwd = 3, cex = 1.2)
text(60, 0.2, labels = 'Log-Rank Test\n p = 0.009', cex = 1.5)
```



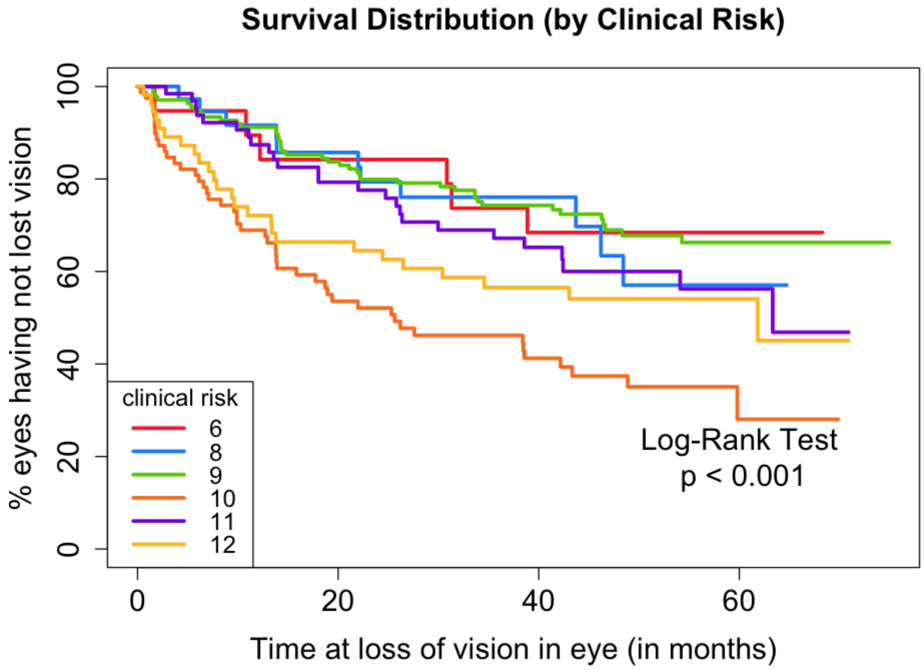
In [36]:
```
# Differences among risks
survdiff(survobj ~ risk, data=diabetic)
```

```
Call:
survdiff(formula = survobj ~ risk, data = diabetic)

          N Observed Expected (O-E)^2/E (O-E)^2/V
risk=6   20        6     8.68    0.8285    0.8791
risk=8   37       11    14.73    0.9467    1.0480
risk=9  139       41    61.67    6.9299   11.5767
risk=10  79       47    23.81   22.5717   26.8303
risk=11  64       25    26.33    0.0668    0.0806
risk=12  55       25    19.77    1.3842    1.5887

 Chisq= 33  on 5 degrees of freedom, p= 4e-06
```

In [37]:
```
# risk
plot(
    survfit(survobj ~ risk, data=diabetic),
    xlab="Time at loss of vision in eye (in months)",
    ylab="% eyes having not lost vision", yscale=100,
    main ="Survival Distribution (by Clinical Risk)",
    col = c('firebrick1', 'dodgerblue', 'chartreuse3', 'chocolate1', 'blueviole
    lwd = 3, cex.lab=1.5, cex.axis=1.5, cex.main=1.5, cex.sub=1.5
    )
legend('bottomleft', legend=levels(as.factor(diabetic$risk)),
       col = c('firebrick1', 'dodgerblue', 'chartreuse3', 'chocolate1', 'bluevi
       lty=1, lwd = 3, cex = 1.2, title = 'clinical risk')
text(60, 0.2, labels = 'Log-Rank Test\n p < 0.001', cex = 1.5)
```



Modeling

In [44]:
```
# Coxph model
diabetic$laser = relevel(diabetic$laser, ref = "control")
cox.model1 <- coxph(Surv(futime, status) ~ laser + eye + age + risk, data=diabe
summary(cox.model1)
```

```
Call:
coxph(formula = Surv(futime, status) ~ laser + eye + age + risk,
    data = diabetic)

  n= 394, number of events= 155

                coef exp(coef)  se(coef)      z Pr(>|z|)
laserargon -0.739968  0.477129  0.213257 -3.470 0.000521 ***
laserxenon -0.905359  0.404397  0.223649 -4.048 5.16e-05 ***
eyeright   -0.329018  0.719630  0.163862 -2.008 0.044655 *
age         0.004204  1.004213  0.005451  0.771 0.440590
risk        0.143537  1.154349  0.055637  2.580 0.009884 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

           exp(coef) exp(-coef) lower .95 upper .95
laserargon    0.4771     2.0959    0.3141    0.7247
laserxenon    0.4044     2.4728    0.2609    0.6269
eyeright      0.7196     1.3896    0.5220    0.9922
age           1.0042     0.9958    0.9935    1.0150
risk          1.1543     0.8663    1.0351    1.2873

Concordance= 0.634  (se = 0.023 )
Likelihood ratio test= 34.82  on 5 df,   p=2e-06
Wald test            = 33.03  on 5 df,   p=4e-06
Score (logrank) test = 34.17  on 5 df,   p=2e-06
```

In [45]:
```
# Coxph model with interaction term
```

```
cox.model2 <- coxph(Surv(futime, status) ~ id + laser + eye + laser:eye + age +
summary(cox.model2)
```

```
Call:
coxph(formula = Surv(futime, status) ~ id + laser + eye + laser:eye +
    age + risk, data = diabetic)

  n= 394, number of events= 155

                          coef  exp(coef)   se(coef)      z Pr(>|z|)
id                  -0.0003775  0.9996225  0.0001659 -2.275   0.0229 *
laserargon          -0.6562401  0.5187983  0.2693283 -2.437   0.0148 *
laserxenon          -0.3806508  0.6834165  0.2686345 -1.417   0.1565
eyeright            -0.0707893  0.9316582  0.2012895 -0.352   0.7251
age                  0.0071525  1.0071781  0.0055311  1.293   0.1960
risk                 0.1454324  1.1565396  0.0565689  2.571   0.0101 *
laserargon:eyeright -0.2323409  0.7926758  0.4524489 -0.514   0.6076
laserxenon:eyeright -1.4522273  0.2340484  0.5422542 -2.678   0.0074 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

                    exp(coef) exp(-coef) lower .95 upper .95
id                     0.9996     1.0004   0.99930    0.9999
laserargon             0.5188     1.9275   0.30602    0.8795
laserxenon             0.6834     1.4632   0.40367    1.1570
eyeright               0.9317     1.0734   0.62794    1.3823
age                    1.0072     0.9929   0.99632    1.0182
risk                   1.1565     0.8646   1.03516    1.2921
laserargon:eyeright    0.7927     1.2615   0.32657    1.9241
laserxenon:eyeright    0.2340     4.2726   0.08086    0.6774

Concordance= 0.65  (se = 0.023 )
Likelihood ratio test= 48.9  on 8 df,   p=7e-08
Wald test            = 38  on 8 df,   p=8e-06
Score (logrank) test = 42.77  on 8 df,   p=1e-06
```

In [46]:
```
print(anova(cox.model1, cox.model2))
```

```
Analysis of Deviance Table
 Cox model: response is  Surv(futime, status)
 Model 1: ~ laser + eye + age + risk
 Model 2: ~ id + laser + eye + laser:eye + age + risk
   loglik  Chisq Df P(>|Chi|)
1 -850.58
2 -843.53 14.086  3  0.002791 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

In [48]:
```
# frailty model
frail = coxph(Surv(futime, status) ~ id + laser + eye + laser:eye + age + risk
summary(frail)
```

```
Call:
coxph(formula = Surv(futime, status) ~ id + laser + eye + laser:eye +
    age + risk + frailty(id), data = diabetic)

  n= 394, number of events= 155

                    coef       se(coef)  se2       Chisq  DF    p
id                  -0.0005096 0.0002343 0.0001735   4.73  1.00 0.0300
laserargon          -0.8636798 0.3309242 0.2802858   6.81  1.00 0.0091
laserxenon          -0.3255214 0.3323481 0.2807310   0.96  1.00 0.3300
eyeright            -0.0730513 0.2647719 0.2092455   0.08  1.00 0.7800
age                  0.0078638 0.0078177 0.0058067   1.01  1.00 0.3100
risk                 0.1847500 0.0728981 0.0618071   6.42  1.00 0.0110
frailty(id)                                        122.10 86.51 0.0071
laserargon:eyeright -0.2203070 0.5719450 0.4680341   0.15  1.00 0.7000
laserxenon:eyeright -1.8216229 0.6435822 0.5551445   8.01  1.00 0.0046

                    exp(coef) exp(-coef) lower .95 upper .95
id                     0.9995     1.0005   0.99903    0.9999
laserargon             0.4216     2.3719   0.22041    0.8065
laserxenon             0.7222     1.3848   0.37647    1.3852
eyeright               0.9296     1.0758   0.55322    1.5619
age                    1.0079     0.9922   0.99257    1.0235
risk                   1.2029     0.8313   1.04276    1.3877
laserargon:eyeright    0.8023     1.2465   0.26151    2.4613
laserxenon:eyeright    0.1618     6.1819   0.04582    0.5711

Iterations: 6 outer, 31 Newton-Raphson
     Variance of random effect= 0.93553   I-likelihood = -836.6
Degrees of freedom for terms=  0.5  1.5  0.6  0.6  0.7 86.5  1.5
Concordance= 0.86  (se = 0.017 )
Likelihood ratio test= 240.6  on 91.97 df,   p=3e-15
```

In [50]:

```
print(anova(cox.model2, frail))
```

```
Analysis of Deviance Table
 Cox model: response is  Surv(futime, status)
 Model 1: ~ id + laser + eye + laser:eye + age + risk
 Model 2: ~ id + laser + eye + laser:eye + age + risk + frailty(id)
   loglik  Chisq     Df P(>|Chi|)
1 -843.53
2 -747.70 191.66 83.974 2.144e-10 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

In [ ]: