Efficacy of coadministration of Drug X with Statin on cholesterol reduction

Table of Contents

Abstract 1
Data 1
Preliminary analysis 2
Pooled comparison: Is the combination therapy better than statin monotherapy ? 5
Effect of Treatment, Statin Dose and Dose by Treatment interaction 6
Effect of Statin Dose on incremental increase in percentage LDL reduction 7
Regression analysis: Effect of statin dose on percent LDL C reduction 9
Secondary Analysis: Consistency of effect across subgroups, age and gender 10

Abstract

Statins are the most common class of drugs used for treating hyperlipdemia. However, studies have shown that even at their maximum dosage of 80 mg, many patients do not reach LDL cholesterol goals recommended by the National Cholesterol Education Program Adult Treatment Panel. Combination therapy, in which a second cholesterol-reducing agent that acts via a complementary pathway is coadmininstered with statin, is one alternative of achieving higher efficacy at lower statin dosage.

In this example, we test the primary hypothesis that coadminstering drug X with statin is more effective at reducing cholesterol levels than statin monotherapy.

NOTE The dataset used in this example is purely fictitious.

The analysis presented in this example is adapted from the following publication.

Reference Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, Sun S, LeBeaut AP, Sager PT, Veltri EP; *Ezetimibe Study Group. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial.* Circulation. 2003 May 20;107(19):2409-15.

Data

650 patients were randomly assigned to one of the following 10 treatment groups (65 subjects per group)

- Placebo
- Drug X (10 mg)
- Statin (10, 20, 40 or 80 mg)
- Drug X (10 mg) + Statin (10, 20, 40 or 80 mg)

Lipid profile (LDL cholesterol, HDL CHolesterol and Triglycerides) was measured at baseline (BL) and at 12 weeks (after the start of treatment). In addition to the lipid profile, patients age, gender and Cardiac

Heart Disease (CHD) risk category was also logged at baseline.

The data from the study is stored in a Microsoft Excel (R) file. Note that the data could also be imported from other sources such as text files, any JDBC/ODBC compliant database, SAS transport files, etc.

The columns in the data are as follows:

- ID - Patient ID
- Group - Treatment group
- Dose_A - Dosage of Statin (mg)
- Dose_X - Dosage of Drug X (mg)
- Age - Patient Age
- Gender - Patient Gender
- Risk - Patient CHD risk category (1 is high risk, and 3 is low risk)
- LDL_BL - HDL_BL & TC_BL - Lipid levels at baseline
- LDL_12wks , HDL_12wks & TC_12wks - Lipid levels after treatment

We will import the data into a dataset array that affords better data managemment and organization.

```
% Import data from an Excel file
  ds = dataset('xlsfile', 'Data.xls') ;
```

Preliminary analysis

Our primary efficacy endpoint is the level of LDL cholesterol. Let us compare the LDL C levels at baseline to LDL C levels after treatment

```
% Use custom scatter plot
  LDLplot(ds.LDL_BL, ds.LDL_12wk, 50, 'g')
```

The mean LDL C level at baseline is around 4.2 and mean level after treatment is 2.5. So, at least for the data pooled across all the treatment groups, it seems that the treatment causes lowering of the LDL cholesterol levels

```
% Use a grouped scatter plot
  figure
  gscatter(ds.LDL_BL, ds.LDL_12wk, ds.Group)
```

The grouped plot shows that LDL C levels before the start of treatment have similar means. However, the LDL C levels after treatment show difference across treatment groups. The Placebo group show no improvement. Statin monotherapy seems to outperform the Drug X monotherapy. There is overlap between the Statin and Statin + X groups; however, it the combination treatment does seem to perform better that the statin monotherapy. Remember that the "Statin" and "Statin + X" groups are further split based on Statin dose.

In this example, we will use percentage change of LDL C from the baseline level as the primary metric of efficacy.

```
% Calculate the percentage improvement over baseline level

  ds.Change_LDL = ( ds.LDL_BL - ds.LDL_12wk ) ./ ds.LDL_BL * 100 ;
```

In the following graph, we can see that

1. In the "Statin" and "Statin + X" group, there appears to be a positive linear correlation between percentage improvement and statin dose
2. Even at the smallest dose of 10 mg, monotherapy with statin seems to be better than the Drug X monotherapy group

```
% Visualize effect of treatment and statin dose on perecentage LDL reduction
  figure
  gscatter(ds.ID, ds.Change_LDL, {ds.Group, ds.Dose_S})
  legend('Location', 'Best')
```

Pooled comparison: Is the combination therapy better than statin monotherapy ?

First, we will extract percent change in LDL C level for the Statin and the Statin + X groups only. We will test the null hypothesis that the percent change in LDL C level for the "Statin + X" groups is greater than that in the "Statin + X" using pooled data. We use a 2 sample t-test to test this hypothesis.

```
% Convert Group into a categorical variable
ds.Group = nominal(ds.Group) ;

grp1 = ds.Change_LDL(ds.Group == 'Statin')          ;
grp2 = ds.Change_LDL(ds.Group == 'Statin + X')      ;

[h, p] = ttest2(grp1, grp2, .01, 'left')
```

```
h =

     1


p =

  7.6969e-050
```

We performed a tailed hypothesis to see if Statin + X group (grp2) is better than the Statin group (grp1).

We test against the alternative that that mean LDL change of grp1 (Statin only) is less than mean LDL change of grp2 (Statin + X)

The null hypothesis is rejected ($p < 0.01$), implying that grp1 mean is less that grp2 mean, i.e. the Statin group is less effective at lowering LDL C levels than the Statin + X group.

The pooled analysis shows that coadministering drug X with statin is more effective than statin monotherapy.

Effect of Treatment, Statin Dose and Dose by Treatment interaction

Our analysis so far was done on pooled data. We analysed the effect of treatment (statin alone (X = 0) vs. statin + 10 mg X) on the LDL C levels. We ignored levels of statin dose within each treatment group

Next, we will perform a 2-way ANOVA (analysis of variance) to simultaneously understand the effect of both factors - statin dose (4 levels - 10 20, 40, 80 mg) and Treatment (2 level - statin only or Statin + 10 mg X) - on the percentage change of LDL C levels.

```
% First, we filter the data to include only the Statin and Statin + X groups
ds1       = ds(ds.Group == 'Statin' | ds.Group == 'Statin + X', :)    ;

anovan(ds1.Change_LDL , {ds1.Dose_S, ds1.Group }         , ...
        'varnames'    , {'Statin Dose', 'Treatment'}    ) ;
```

Source	Sum Sq.	d.f.	Mean Sq.	F	Prob>F
Statin Dose	15352.3	3	5117.4	111.09	1.7789e-055
# Treatment	20578.6	1	20578.6	446.72	7.35818e-072
Error	23724	515	46.1		
Total	59654.9	519			

Effect of Statin Dose on incremental increase in percentage LDL reduction

The ANOVA results indicate that statin dose is a significant factor, but it doesn't compare means across individual dose-treatment level combination. Let's look at the individual cell means.

```
ds2 = grpstats(ds1 , {'Dose_X', 'Dose_S'}, '', 'DataVars', 'Change_LDL')
```

```
ds2 =

              Dose_X    Dose_S    GroupCount    mean_Change_LDL
    0_10       0        10        65            34.467
    0_20       0        20        65            40.085
    0_40       0        40        65            47.453
    0_80       0        80        65            52.329
    10_10     10        10        65            50.656
    10_20     10        20        65            54.444
    10_40     10        40        65            58.075
    10_80     10        80        65            61.485
```

Convert to wide format

```
ds2 = unstack(ds2, 'mean_Change_LDL' , 'Dose_X', ...
                   'NewDataVarNames' , {'Change_LDL_St', 'Change_LDL_St_X'} )
```

ds2 =

	Dose_S	GroupCount	Change_LDL_St	Change_LDL_St_X
0_10	10	65	34.467	50.656
0_20	20	65	40.085	54.444
0_40	40	65	47.453	58.075
0_80	80	65	52.329	61.485

From the above table, we can clearly see that the average efficacy of the combination therapy is better than statin monotherapy at all statin dosages.

In the plot of the individual means, notice that the percentage reduction in LDL C levels achieved in the low dose combination therapy group (~50.5 %) is comparable to that achieved in the higher dose Statin monotherapy group (~ 49.4 %). Thus combination therapy with Drug X could help patients that cannot tolerate high statin doses.

```
figure
bar([ds2.Change_LDL_St, ds2.Change_LDL_St_X])
set(gca, 'XTickLabel', [10, 20 40, 80])
colormap summer
xlabel('Statin Dose Groups(mg)')
ylabel('Percentage reduction of LDL C from Baseline (mmol/L)')
legend('Statin', 'Statin + X')
```

Regression analysis: Effect of statin dose on percent LDL C reduction

In the above graph, there appears to be linear improvement in the effectiveness metric for both treatment groups. In general it seems that for every doubling of the statin dose, there is a 5-6 point improvement in the percentage LDL C reduction. Let's fit a linear regression line to the entire dataset, instead of to the mean level.

```
x = ds1.Dose_S    (  ds1.Group == 'Statin' ) ;
y = ds1.Change_LDL(  ds1.Group == 'Statin' ) ;

x1 = ds1.Dose_S    (ds1.Group == 'Statin + X')  ;
y1 = ds1.Change_LDL(ds1.Group == 'Statin + X')  ;


cftool
```

The regression line for the Statin and the Statin + X group run almost parallel. This probably indicates mechanism of actions of drug X and statins are independent.

```
% Fit
[m1, m2] = createFit(x,y,x1, y1)



m1 =

     Linear model Poly1:
     m1(x) = p1*x + p2
     Coefficients (with 95% confidence bounds):
       p1 =      0.2412  (0.2064, 0.2759)
       p2 =       34.54  (32.94, 36.14)

m2 =

     Linear model Poly1:
     m2(x) = p1*x + p2
     Coefficients (with 95% confidence bounds):
       p1 =      0.1435  (0.116, 0.1709)
       p2 =       50.79  (49.52, 52.05)
```

Secondary Analysis: Consistency of effect across subgroups, age and gender

Finally, we will make a visual check to ensure that the efficacy of the Statin + X treatment at various statin doses is consistent across gender and age subgroups. We will perform this check for only the Statin + X treatment group.

```
idx = ds.Group == 'Statin + X' ;
boxplot(ds.Change_LDL(idx), { ds.Dose_S(idx), ds.Gender(idx)} )
```

We will convert the continuous age variable into a catergorical variable, with 2 categories: Age < 65 and Age >= 65

```
% Convert age into a ordinal array
ds.AgeGroup = ordinal(ds.Age ,{'< 65', '>= 65'} , [] ,[0 65 100] )  ;

% Plot
boxplot(ds.Change_LDL(idx), { ds.Dose_S(idx), ds.AgeGroup(idx)} )
```

Copyright 2010 The MathWorks, Inc.
Published with MATLAB® 7.11