8.5.A Randomized trial of evolocumab (Repatha®) plus statin therapy (with thanks to *Christopher Groh and Nalini Colaco)*

High LDL cholesterol (bad cholesterol) is a well-known risk factor for cardiovascular disease. For many years, the cornerstone of LDL treatment has been statin-based therapy. Statins are one of the few lipid lowering therapies with well-established evidence for decreasing cardiovascular events. However, statins have side-effects including risk of diabetes, myalgias (muscle pain), or rarely, rhabdomyolysis (muscle damage). Recent discoveries have shown that PCSK9 plays an integral role in LDL metabolism. This has spawned a variety of new lipid-lowering therapies called *PCSK9 Inhibitors* that are more potent in LDL reduction than statins. The clinical outcome performance of this class of drugs has been minimally studied. Evolocumab is one such agent that has been studied in cardiovascular outcomes.

We briefly mentioned the 2017 Amgen-supported FOURIER trial[1] in Chapter 8. It was a randomized trial of evolocumab injections (either 140 mg every 2 weeks or 420 mg every month depending on patient preference) plus a statin vs. placebo plus a statin in high-risk patients who had a previous cardiovascular event. The following outcomes were obtained after an average follow up of roughly 24 months (excerpted from Table 2):

Outcome	Evolocumab	Placebo	Hazard Ratio	95% CI	P
Primary endpoint: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	1344 (9.8%)	1563 (11.3%)	0.85	(0.79, 0.92)	<0.001
Key secondary endpoint: cardiovascular death, myocardial infarction of stroke	816 (5.9%)	1013 (7.4%)	0.8	(0.73, 0.88)	<0.001
Cardiovascular death	251 (1.8%)	240 (1.7%)	1.05	(0.88, 1.25)	0.62

Note: myocardial infarction is a heart attack, unstable angina is almost a heart attack, coronary revascularization would imply a coronary stent placement or bypass surgery.

a. What is the difference in the definition of the "Primary end point" and the "Key secondary end point"? Which end point do you prefer? Why? [2]

The difference is that the key secondary endpoint does not include hospitalization for unstable angina and coronary revascularization.

We prefer the key secondary end point because it seems more relevant to patients and more objective. But the study was blinded, so it would not be wrong to prefer the more inclusive and subjective endpoint. This is a rare example where the ARR is preserved even for the more serious secondary end point (though, as discussed in the next part, not for cardiovascular mortality.

b. In the evolucomab group there were 816 key secondary endpoints and 251 cardiovascular deaths. In the placebo group there were 1013 key secondary endpoints and 240 cardiovascular deaths. How could the placebo group have fewer cardiovascular deaths but more key secondary endpoints? Is the difference in the composition of the key secondary endpoints a chance finding? Explain. [2]

The small excess in mortality in the treatment group over the control group is easily explicable by chance. On the other hand, cardiovascular death made up about 31% of the "Key secondary endpoints" in the treatment group and only about 24% of them in the control group. This difference is greater than expected by chance; P = 0.0007. The only other outcomes in the key secondary endpoint are non-fatal MI and non-fatal stroke. This suggests that the treatment reduced these two non-fatal secondary endpoints without affecting mortality. As noted in Chapter 8, this fits a consistent pattern that cardiovascular mortality is much harder to reduce than nonfatal cardiovascular events.

c. If one considers estimates within the 95% confidence interval to be consistent with the study results, what is the *lowest* number needed to treat for 2 years to prevent one death from any cause consistent with the study's results? [2]
(Note that we have provided the Stata output; Cases are deaths from any cause and "Exposed" got evolucumab.)

```
. csi 444 426 13340 13354

                 |   Exposed   Unexposed  |      Total
-----------------+------------------------+------------
           Cases |       444         426  |        870
        Noncases |     13340       13354  |      26694
-----------------+------------------------+------------
           Total |     13784       13780  |      27564
                 |                        |
            Risk |  .0322113    .0309144  |   .0315629
                 |                        |
                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
 Risk difference |         .0012969       |    -.002831    .0054248
      Risk ratio |         1.041951       |    .9141891    1.187568
 Attr. frac. ex. |          .040262       |   -.0938655    .1579432
 Attr. frac. pop |         .0205475       |
                 +-------------------------------------------------
                              chi2(1) =     0.38  Pr>chi2 = 0.5380
```

Confidence intervals that include both benefit and harm can be confusing. We recommend first answering the question, "Which group did better?" then looking at the sign of the risk difference.

In this case the unexposed had lower mortality, so the positive point estimate for the risk difference must favor the unexposed. Therefore, in order to have lower mortality, the risk difference would have to be negative. So the most negative part of the confidence interval is for the most favorable effect consistent with what was observed; in this case a risk difference of -0.002831, so the lowest NNT for two years to prevent one death consistent with this study is 353.

Note that as the risk difference moves towards zero, the NNT increases to infinity and then turns into an NNH. The point estimate from this study is an NNH of 771, and the NNH could be as low as 184.

d. Calculate the absolute risk reduction for evolocumab therapy in comparison to placebo for the "Key secondary end point".[2]

ARR = 7.4%-5.9% = 1.5%
Or using raw numbers: 1013/13780 − 816/13784 = 1.43%

e. Calculate the number needed to treat for 24 months to prevent one "Key secondary end point"[2]

NNT = 1/ARR = 1/0.015 = 66.7 patients need to be treated for 24 months to prevent the "Key secondary end point"
Or 1/1.43% = 70

f. Your clinic patient who recently had a myocardial infarction and is already on a statin called pravastatin (40 mg/day) wants to take evolocumab. His insurance is unwilling to cover this new medication and he will have to pay out of pocket. Interestingly, your patient happens also to be an economist and is curious as to the financial burden of such a novel medication. Evolocumab is an injectable monoclonal antibody that is estimated to costs about $1244 per 420mg injection[1], or $14,928 for an annual set of injections. What is the cost of preventing a "Key secondary end point" at 24 months (CBOP)? [2]

The cost of the therapy is $14,928/year × 2 years and we need to treat 70 patients to prevent one key secondary endpoint.

So CBOP = NNT × Cost = $14,928 × 2 × 70 = $2,089,920.

REFERENCES

1. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713-22.

[1] Cost with a coupon from GoodRx.com, accessed 12/5/18