

## Literature Review for OHIE Expected Treatment Effect on Cholesterol (HDL and Total)

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- **STUDY:** Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus (Bolen, Shari et al)
  - o <http://annals.org/article.aspx?articleid=736504>
  - o **Summary:** Meta-analysis that summarizes the effects of oral agents on health measures of adults with Type II diabetes (obviously a specialized group, so treatment effects may not be generalizable to a general population).
    - Study duration ranged from 12 weeks to 10 years, but most studies lasted 24 weeks or less. Participants were mainly middle-aged, overweight or obese adults who had had diabetes for more than 2 years and no major comorbid conditions
  - o **Relevant Data:** Some oral agents (Thiazolidinediones) had a beneficial effect on **HDL cholesterol** levels (mean increase of 3-5 mg/dL)
    - **HDL cholesterol increased by 3-5 mg/dL**
  
- **STUDY:** TSH-Controlled L-Thyroxine Therapy Reduces Cholesterol Levels and Clinical Symptoms in Subclinical Hypothyroidism (Meyer, Christian et al)
  - o <http://jcem.endojournals.org/content/86/10/4860.full.pdf+html>
  - o **Summary:** Study on 63 **women** with subclinical hypothyroidism. Looks at total cholesterol levels (among many other measures) in examining the effect of L-Thyroxine treatment vs. a placebo. The small scale of this experiment seems like an issue when thinking of generalizing results (in addition to the non-representative population studied). The treatment lasted 48 weeks (just less than one year).
  - o **Relevant Data:** In the experimental group (31 subjects), **total cholesterol** was decreased by 12.8 mg/dL. More specifically, those experimental subjects with baseline cholesterol levels above a threshold of 240 mg/dL<sup>1</sup> (the same threshold used in the Oregon Health Insurance Experiment (OHIE) to determine high vs. normal cholesterol) showed a significant decrease in total cholesterol, while those with initially normal cholesterol levels were no different than the control group. This suggests that any expected treatment effect on cholesterol in the OHIE would be miniscule, given that only 14% of the OHIE subjects had initially high cholesterol.
    - **Total cholesterol decreased by 12.8 mg/dL**
  
- **STUDY:** Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations (Sever, Peter et al)
  - o <http://www.thelancet.com/journals/lancet/article/PIIS0140673603129480/fulltext/>
  - o **Summary:** Study was conducted on 10,305 hypertensive patients with baseline total cholesterol of 251.6 mg/dL or less (similar to the OHIE threshold of 240 mg/dL for high cholesterol). The experimental group was treated with atorvastatin and the control group was given a placebo. Treatment took place over the course of roughly three years.
  - o **Relevant Data:** The treatment effect (relative to placebo) was a **50 mg/dL reduction in total cholesterol levels after one year, and a 43 mg/dL reduction after three years.** (However, that the subjects were hypertensive may play a large role in these figures.)
  
- **STUDY:** Effect of Statins on Risk of Coronary Disease: A Meta-analysis of Randomized Controlled Trials (LaRosa, John et al)

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<sup>1</sup> Data in most of the studies in this review were in mmol/L and were converted to mg/dL (1 mmol/L = 38.7 mg/dL)

- <http://jama.jamanetwork.com/article.aspx?articleid=192226#JMA90005T1>
- **Summary:** Meta-analysis of statin drug treatment with 30,817 total participants. Studies included randomly assigned participants to either statin or placebo groups. This seems like a relatively generalizable study. Three of the studies used participants with initially high cholesterol levels, and two used participants with normal baseline cholesterol levels. All studies treated for less than four years and followed up in 5-6 years.
- **Relevant Data:** The three studies with high baseline cholesterol are denoted 4S, WOSCOPS, and LIPID below, as in the study. The two normal groups are denoted CARE and AFCAPS. (see Table 1 of study for more)

Relevant Results from the Statin Meta-Analysis					
Group	High Baseline Cholesterol			Normal Baseline Cholesterol	
	4S	WOSCOPS	LIPID	CARE	AFCAPS
Baseline Total Cholesterol (mg/dL)	261.2	272.1	218.3	209.0	221.0
% Change in Total Cholesterol	-26	-20	-18	-20	-19
Treatment Effect Size (mg/dL)	-68.1	-54.6	-39.5	-41.8	-41.8
Baseline HDL Cholesterol (mg/dL)	46.1	44.1	36.0	39.1	36.8
% Change in HDL Cholesterol	7	5	5	5	5
Treatment Effect Size (mg/dL)	3.1	2.3	1.9	1.9	1.9

As shown, the treatment effects on total cholesterol ranged from **39.5 to 68.1 mg/dL**. For those with normal baseline cholesterol, the treatment effect was **-41.8 mg/dL**. The treatment effects on HDL cholesterol ranged from 1.9 to 3.1 mg/dL. These values are close to those found in the study listed immediately above this one.

- **STUDY:** Lowering cholesterol concentrations and mortality: A Quantitative Review of Primary Prevention Trials (Muldoon, Matthew et al)
  - <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1663605/pdf/bmj00192-0015.pdf>
  - **Summary:** Another meta-analysis using six studies with a mean treatment duration of 4.8 years. These studies used either dietary changes, drugs, or both as interventions to decrease cholesterol. Each of these groups varied in some way from the others, and four of the six groups only included men.
  - **Relevant Data:** The treatment effects on total cholesterol levels were similar across all the studies, despite the large ranges in baseline cholesterol, treatment time and the varying methods used. Only the “diet only” groups had baseline cholesterol levels that the OHIE researchers would not consider high (<240 mg/dL). **The treatment effects ranged from -22.4 to -29.8 mg/dL.**
    - See table below

Relevant Results from the Meta-Analysis						
Group	Diet Only		Drug Only		Combination	
	LA Vet	MN Coronary	WHO	CU	Lipid RC	Helsinki
Years of Follow-Up	8	1.1	5.3	1.9	7.4	5
Baseline Total Cholesterol (mg/dL)	233.4	207.0	248.1	308.1	280.2	289.1
% Change in Total Cholesterol	-12.7	-13.6	-9.0	-9.6	-8.5	-9.6
Treatment Effect Size (mg/dL)	-29.8	-28.3	-22.4	-29.4	-24.0	-27.9

- **STUDY:** Multiple Risk Factor Interventions for Primary Prevention of Coronary Heart Disease (Ebrahim et al) – from the Cochrane Library

- <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001561.pub3/abstract>
  - **Summary:** Review of 55 total trials with interventions ranging from health promotion and health education to pharmacological treatments. Sixteen of these studies were of patients with hypertension, and five were on diabetic patients. Mean age over all trials was 50 years, and median follow-up time was one year. 44 of these trials reported blood cholesterol as an outcome.
  - **Relevant Data:** Total cholesterol levels showed a treatment effect of -2.71 mg/dL. This small effect was highly significant using a random effects model. Interestingly, even when analysis was confined to the trials that used cholesterol-lowering drugs, the effect was about the same size. The treatment effect grew to -6.97 mg/dL when both antihypertensive and lipid-lowering drugs were used.
    - More importantly, the mean weighted treatment effect in this analysis, which is most useful for our purposes, was **-9.3 mg/dL**.
- **STUDY:** Statins for the Primary Prevention of Cardiovascular Disease (Taylor et al) – from the Cochrane Library
- <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004816.pub5/abstract>
  - **Summary:** Review of 18 trials (dates ranging from 1994-2008, conducted worldwide), 14 of which recruited specific subsets of patients (i.e. diabetics, raised lipids, etc.). All tested the effectiveness of statins relative to a placebo, and five also added diet counseling or other forms of non-pharmacological aid. Total of 56,934 subjects across all trials, with a mean age of 57 years. 14 of these trials gave data on total cholesterol.
  - **Relevant Data:** All trials showed significant reductions in total cholesterol, with the net treatment effect across them being **-40.64 mg/dL**. This is a larger effect than in the other Cochrane study, possibly because a majority of these subjects had high baseline cholesterol while most of the subjects in the previous study were not specifically targeted for a health problem.
    - As a result, I would expect the OHIE treatment effect to be much closer to the -9.3 mg/dL figure in the previous Cochrane study, since the majority of OHIE subjects were also normal with respect to lipid and cholesterol levels.
- **Conclusions based on Lit Review**
- For total cholesterol, the expected treatment size for those in the OHIE should have been a reduction of roughly 20-40 mg/dL if **everyone** who gained access to Medicaid was treated with a cholesterol-lowering drug or diet. However, since only 14% of the OHIE subjects had high baseline cholesterol, it is highly unlikely that this is a valid assumption. As such, the expected treatment size should be **less** than the 20-40 mg/dL figure, perhaps less than a 10 mg/dL reduction. This is a preliminary expectation, as it is largely based off of only a couple of studies.
    - This prediction may fall inside the 95% confidence interval of the OHIE's effect on total cholesterol (-3.44 to 7.84 mg/dL).
    - Moreover, the second study summarized in this review provides evidence that for those with normal cholesterol, some treatments may not have an effect at all, which would also imply a small expected treatment size.
    - With these numbers, the most optimistic expected reduction in total cholesterol for the OHIE would be roughly  $-40 \text{ mg/dL} \times 0.14 = -5.6 \text{ mg/dL}$ .
  - The expected treatment effect of HDL cholesterol is roughly 1-5 mg/dL, which largely falls within the 95% confidence interval of the effect obtained by the OHIE.