Statins and All-Cause Mortality in High-Risk Primary Prevention: A Meta-analysis of 11 Randomized Controlled Trials Involving 65,229 Participants

Archives of Internal Medicine
June 29, 2010, Vol. 170, No. 12, pp. 1024-1031

Kausik K. Ray, MD; Sreenivasa Rao Kondapally Seshasai, MD; Sebhat Erqou, MD, PhD; Peter Sever, PhD; J. Wouter Jukema, MD, PhD; Ian Ford, PhD; Naveed Sattar:
The authors are from University of Cambridge
FROM ABSTRACT:

Background: Statins have been shown to reduce the risk of all-cause mortality among individuals with clinical history of coronary heart disease. However, it remains uncertain whether statins have similar mortality benefit in a high-risk primary prevention setting.

Notably, all systematic reviews to date included trials that in part incorporated participants with prior cardiovascular disease (CVD) at baseline. Our objective was to reliably determine if statin therapy reduces all-cause mortality among intermediate to high-risk individuals without a history of CVD.

Data Sources: Trials were identified through computerized literature searches of MEDLINE and Cochrane databases (January 1970-May 2009) using terms related to statins, clinical trials, and cardiovascular end points and through bibliographies of retrieved studies.

Study Selection: Prospective, randomized controlled trials of statin therapy performed in individuals free from CVD at baseline and that reported details, or could supply data, on all-cause mortality.

Data Extraction: Relevant data including the number of patients randomized, mean duration of follow-up, and the number of incident deaths were obtained from the principal publication or by correspondence with the investigators.

Data Synthesis: Data were combined from 11 studies and effect estimates were pooled using a random-effects model meta-analysis, with heterogeneity assessed with the I2 statistic. Data were available on 65,229 participants followed for approximately 244,000 person-years, during which 2,793 deaths occurred.

The use of statins in this high-risk primary prevention setting was not associated with a statistically significant reduction in the risk of all-cause mortality.

Conclusion: This literature-based meta-analysis did not find evidence for the benefit of statin therapy on all-cause mortality in a high-risk primary prevention set-up.

THESE AUTHORS ALSO NOTE:

"There is little debate that, compared with placebo, statin therapy among individuals with established coronary heart disease (CHD) not only prevents complications related to atherosclerosis but also reduces all-cause mortality."

However, some researchers have questioned the benefits of statins among individuals without cardiovascular disease, noting there is little evidence for reductions of all-cause mortality, and the potential to cause "serious unrecognized harm."

Therefore, these authors assessed the effect of statin therapy (compared with placebo) on all-cause mortality in individuals who did **not** have cardiovascular disease. They used 65,229 subjects and a follow-up period of 3.7 years:

Placebo Group	**Statin Group**
# of participants: 32,606	# of participants: 32,623
# of deaths: 1,447	# of deaths: 1,346
Cholesterol level: 134 mg/dL	Cholesterol level with statins: 94 mg/dL

Taking statin drugs lowered LDL-C by 40 mg/dL compared to the placebo group.

"This literature-based meta-analysis of 11 clinical trials involving 65,229 participants with approximately 244,000 person-years of follow-up and 2,793 deaths provides more reliable evidence than previously available on the impact of statin therapy on all-cause mortality among high-risk individuals without prior CVD. These data indicate that over an average treatment period of 3.7 years, the use of statin therapy did not result in reduction in all-cause mortality."

"There were on average an estimated 7 fewer deaths for every 10,000 person-years of treatment" with statin drugs.

"Our meta-analysis was based on data from only those individuals without clinically manifest CVD, including previously unpublished data, thus providing the most reliable effect estimates about the effect of statins in this population."

"The present data suggest that the all-cause mortality reduction of 20% reported in JUPITER is likely to be an extreme and exaggerated finding as often occurs when trials are stopped early, hence, indicating that more liberal use of potent statin regimens, particularly in the setting of lower risk primary prevention subjects, is unlikely, at least in the short term, to have a major impact on all-cause mortality reduction."

This study "failed to observe any statistically significant correlation between on-treatment difference in LDL-C levels and the relative reduction in all-cause mortality" by taking statin drugs.

Fibrates are drugs that primarily lower triglyceride levels. A 2007 meta-analysis of randomized controlled trials published in the *American Heart Journal* "showed that despite a significant reduction in nonfatal myocardial infarction, all-cause mortality was approximately 7% higher among individuals randomized to a fibrate."

"In conclusion, based on aggregate data on 65,229 men and women from 11 studies, yielding approximately 244,000 person-years of follow-up and 2,793 deaths, we observed that statin therapy for an average period of 3.7 years had no benefit on all-cause mortality in a high-risk primary prevention population."

COMMENTS FROM REUTERS HEALTH, June 28, 2010, By Kate Kelland

"There is no evidence that prescribing cholesterol-lowering drugs known as statins to patients at risk of heart disease reduces their chances of premature death in the short term, scientists said on Monday."

"The results of a study by British researchers call into question the expanded use of statins such as Pfizer's Lipitor and AstraZeneca's Crestor in patients who do not have heart disease but may develop it."

"'There is little evidence that statins reduce the risk of dying from any cause in individuals without heart disease,' they wrote in the study in Archives of Internal Medicine journal."

"'"This, along with harms caused by statins in some subgroups, have called into question the benefit of statins in primary prevention (prevention of the development of heart disease)."'"

A study published last month found that people taking statin drugs may have higher risks of liver dysfunction, kidney failure, muscle weakness and cataracts.

"While low-density lipoprotein (LDL), or 'bad' cholesterol levels, were higher among those taking placebo than those taking statins (134 milligrams per deciliter versus 94 milligrams per deciliter), this had no effect on the risk of premature death."

BACKGROUND FROM DAN MURPHY:

LDL-C means low density lipoprotein cholesterol. This is the "bad" cholesterol because it can plaque on the arterial wall. Ideally, it should measure less then 100 mg/dL. High is over 130 mg/dL.

In 2007, the *New England Journal of Medicine* published the JUPITER study. This study claimed that individuals with low cholesterol but high levels of inflammation [high sensitivity C-Reactive protein {hs-CRP}] could "significantly reduce all-cause mortality by 20%" by taking statin drugs. However, other studies have "questioned these findings as a chance or exaggerated observation."
[Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207].

Therefore, these authors analyzed 11 randomized controlled trials involving a total of 65,229 participants to provide the most robust information to assess whether statins reduce all-cause mortality. All of the participants had high cholesterol, but **none** of them had cardiovascular disease. The study represented about 244,000 person-years of follow-up.

Statin drugs are commonly prescribed for two groups of patients:

Group I	**Group II**
Those that have established cardiovascular disease	**Those that do not have cardiovascular disease, but do have high cholesterol levels**
It is thought that statins for this group will prevent atherosclerosis and subsequent heart attack	**It is thought that statins for this group will prevent cardiovascular disease and heart attack**

KEY POINTS FROM DAN MURPHY

1) Some researchers have questioned the benefits of statins among individuals without cardiovascular disease, noting there is little evidence for reductions of all-cause mortality, and the potential to cause "serious unrecognized harm."

2) These authors assessed the effect of statin therapy (compared with placebo) on all-cause mortality in individuals who did **not** have cardiovascular disease. They used 65,229 subjects and a follow-up period of 3.7 years:

Placebo Group	**Statin Group**
# of participants: 32,606	# of participants: 32,623
# of deaths: 1,447	# of deaths: 1,346
LDL Cholesterol level: 134 mg/dL	LDL Cholesterol level with statins: 94 mg/dL
Death rate: 4.44%	Death rate: 4.13%

3) Taking statin drugs lowered LDL-C by 40 mg/dL compared to the placebo group. This lowered the death rate by .31% (4.44% - 4.13%). The authors considered such a small reduction in death to be nonsignificant.

4) "This literature-based meta-analysis of 11 clinical trials involving 65,229 participants with approximately 244,000 person-years of follow-up and 2,793 deaths provides more reliable evidence than previously available on the impact of statin therapy on all-cause mortality among high-risk individuals without prior CVD. These data indicate that over an average treatment period of 3.7 years, the use of statin therapy did not result in reduction in all-cause mortality."

5) "There were on average an estimated 7 fewer deaths for every 10,000 person-years of treatment" with statin drugs.

6) "Our meta-analysis was based on data from only those individuals without clinically manifest CVD, including previously unpublished data, thus providing the most reliable effect estimates about the effect of statins in this population."

7) "The present data suggest that the all-cause mortality reduction of 20% reported in JUPITER is likely to be an extreme and exaggerated finding as often occurs when trials are stopped early, hence, indicating that more liberal use of potent statin regimens, particularly in the setting of lower risk primary prevention subjects, is unlikely, at least in the short term, to have a major impact on all-cause mortality reduction."

8) Fibrates are drugs that primarily lower triglyceride levels. A 2007 meta-analysis of randomized controlled trials published in the *American Heart Journal* "showed that despite a significant reduction in nonfatal myocardial infarction, all-cause mortality was approximately 7% higher among individuals randomized to a fibrate."

9) "In conclusion, based on aggregate data on 65,229 men and women from 11 studies, yielding approximately 244,000 person-years of follow-up and 2,793 deaths, we observed that statin therapy for an average period of 3.7 years had no benefit on all-cause mortality in a high-risk primary prevention population."

10) "There is no evidence that prescribing cholesterol-lowering drugs known as statins to patients at risk of heart disease reduces their chances of premature death in the short term."

11) "There is little evidence that statins reduce the risk of dying from any cause in individuals without heart disease."

12) People taking statin drugs may have higher risks of liver dysfunction, kidney failure, muscle weakness and cataracts.

13) "While low-density lipoprotein (LDL), or 'bad' cholesterol levels, were higher among those taking placebo than those taking statins (134 milligrams per deciliter versus 94 milligrams per deciliter), this had no effect on the risk of premature death."

COMMENTS FROM DAN MURPHY

The number needed to treat (NNT) is an epidemiological measure used to assess the effectiveness of a health-care intervention. The NNT is the number of patients who need to be treated in order to prevent one additional bad outcome. The ideal NNT is 1, where everyone improves with treatment and no one improves with placebo or in the control group. The higher the NNT, the less effective is the treatment.

NNT values are time-specific. A study's NNT would be multiplied by the number of years of the study. For example, if a study ran for 3.7 years and it was found that the NNT was 321 during this 3.7-year period, in one year the NNT would have to be multiplied by 3.7 to correctly assume the right NNT for only the one-year period (in the example the one year NNT would be 1,188).

Even though NNT is an important measure in a clinical trial, it is infrequently included in medical journal articles reporting the results of clinical trials.

In this study, the Number Needed to Treat (NNT) was 321 over a period of 3.7 years. The one-year NNT was 1,188:

1) This means for a period of 3.7 years for every 321 people taking a statin drug only one is benefited, and 320 are not benefited, although they are spending about $1000/year on the drugs, and often experiencing numerous side effects.

2) This means for a period of 1 year for every 1,188 people taking a statin drug only one is benefited, and 1,187 are not benefited.

One can calculate the NNT using a calculator, or there are web pages that will do it for you by plugging in the numbers, such as www.graphpad.com, or just Googling "Number Needed to Treat" or "NNT."

In the end, the consumer is paying for all of this, either through taxes (the government pays), or health insurance premiums, or cash.