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Statin therapy for elderly patients should be assessed for each individual

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ABSTRACT A critical appraisal and clinical application of Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360(9346):1623-30. doi:[10.1016/S0140-6736\(02\)11600-X](https://doi.org/10.1016/S0140-6736(02)11600-X)

Keywords: statin, elderly, cardiovascular risk, myalgias

Clinical Context

An 83-year old African-American male presented with weakness and fatigue for the past several months. He had a BMI of 28 and a past medical history of COPD, osteoarthritis, GERD, chronic kidney disease, hypertension, and coronary artery disease. He had a 20 pack-year history of smoking and quit 15 years prior. In addition to the chief complaint, the patient reported chronic pain of his knees and lower back along with occasional muscle aches.

The patient was admitted and treated for anemia and occult gastrointestinal bleeding. His list of home medications included atorvastatin. As this was reviewed with the patient, he inquired about the purpose of his medications and any potential side effects. He expressed concern over the large number of medications he was on and asked if it was necessary to remain on a statin.

Clinical Question

Do the benefits outweigh the harms when placing patients greater than 65 years of age on statin therapy for cardiovascular risk reduction?

Research Article

Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360(9346):1623-30. doi:[10.1016/S0140-6736\(02\)11600-X](https://doi.org/10.1016/S0140-6736(02)11600-X)

Literature Review

A search for original research studies was done using the keywords "statin", "elderly", and ">65" in PubMed and Google Scholar. For each relevant article that was found, the references were reviewed looking for more original research studies that addressed the clinical question. The 2013 atherosclerotic cardiovascular disease (ASCVD) risk reduction guidelines from the American College of Cardiology/American Heart Association (ACC/AHA)¹ were also reviewed for recommendations on statin therapy in adults greater than 65 years of age and the evidence on which they were based.

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Nine publications describing original research were found that discussed the use of statins in the elderly.²⁻¹⁰ All were randomized controlled trials. However, the majority of these studies were not exclusively centered on the elderly and based their conclusions on sub-group analyses and an extension of the main trial results to encompass the elderly population.⁴⁻¹⁰ Two studies were designed specifically around adults greater than 65 years of age: "Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial" and "Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE)".^{2,3} The PROSPER study was chosen for critical appraisal because it more closely addressed the clinical question by comparing statin therapy versus placebo, as opposed to the SAGE study, which compared moderate intensity versus high intensity statin therapy without a placebo control group. In addition, the PROSPER study is cited as evidence in recommending the use of statins in adults with ASCVD greater than 75 years of age in the 2013 ASCVD risk reduction guidelines from the ACC/AHA.

Critical Appraisal

The PROSPER study is a double-blinded randomized control trial with the goal of assessing the benefits of pravastatin treatment in an elderly cohort of men and women at risk of developing cardiovascular disease. Initial screening required individuals aged 70-82 years of age to have plasma total cholesterol levels between 4.0-9.0 mmol/L (155-348 mg/dL) and triglyceride concentrations less than 6.0 mmol/L (531 mg/dL). The study ultimately assigned 2804 men and 3000 women aged 70-82 years of age (mean 75) with a history of, or risk factors for, cardiovascular disease to either pravastatin 40mg per day ($n = 2913$) or placebo ($n = 2891$). With a target treatment period of 3 years, all 5804 participants were followed-up at a mean of 3.2 years. Assuming a 16% placebo event rate, the study had 92% power to detect a 20% reduction in the primary outcome, which was the combined endpoint of coronary heart disease death or non-fatal myocardial infarction or fatal or non-fatal stroke. The study also reported 95% power in detecting reductions in the secondary outcomes, which were coronary and cerebrovascular events, considered separately. All analyses were by intention-to-treat.

Given the PROSPER study's characteristics, it can be designated as a level 1 study according to Strength of Recommendation Taxonomy (SORT) criteria.¹¹ The major strengths of the study are embodied within this classification. One such strength is that the study's measured outcomes are patient-oriented, addressing the impact of treatment on patient morbidity and mortality from cardiovascular disease. Furthermore, the study's large sample size with adequate statistical power, concealed allocation, double-blinding, and complete follow-up are all strong points that help describe the study as a high-quality randomized controlled trial.

However, the study's design is not without flaws. A weakness of the study is its lack of consideration for race or ethnicity as a variate. Without racial or ethnic demographic data, it is difficult to say whether the study population recruited in Scotland, Ireland, and the Netherlands is representative of the populations in other countries such as the U.S. Distinguishing race or ethnicity as a characteristic is significant because non-white populations often carry higher risks for cardiovascular disease.¹²

The study reports that 277 (10%) individuals in the placebo group and 131 (5%) individuals in the treatment group initiated non-study statin therapy during the trial. The inclusion of these individuals in analysis, established as intention-to-treat, is another limitation of the study. The substantial contamination with non-study statins that occurred in both groups after randomization could have interfered with the accuracy in assessing pravastatin's efficacy. The presence of statin-treated individuals in the placebo group may erroneously lower ASCVD risk in that arm. In the treatment arm, including individuals that initiated a non-study statin may increase or decrease the perceived level of reduction in ASCVD risk, depending on the relative efficacy of the non-study statin. Performing a per-protocol analysis that includes only patients who receive treatment as originally allocated may have been more ideal.

Adverse events were also monitored through participant reports, which were submitted by 1604 (55%) participants allocated to placebo and by 1608 (56%) participants allocated to pravastatin. According to this data, attributable risk was 1% and NNH = 100. The study mentions that there were no cases of rhabdomyolysis and that there were 32 (1.1%) and 36 (1.2%) instances of myalgia in the placebo and pravastatin groups, respectively. Though adverse events were reported by the majority of participants in both groups, the study fails to provide further details, such as an itemization of these adverse events besides rhabdomyolysis and myalgia. In addition, the study's low number of myalgia reports should be recognized with caution. Rosenbaum et. al. found that muscular symptoms occurred in up to 10% of statin-treated patients, with pain being the most commonly described symptom (87%).¹³ Other common symptoms reported in this study included muscle cramps (67%), stiffness (62%), and weakness on exertion (55%),



symptoms not communicated by the PROSPER study. Parker et. al. had similar findings, reporting that 9% of statin-treated individuals developed myalgia, a statistically significant difference compared to placebo (5%).¹⁴

The PROSPER study also attempts to address the concern of increased cancer risk associated with the lowering of cholesterol with statins, but does so in an inappropriate manner. After finding 25% more new cancer diagnoses in the treatment group, the authors of this study conducted a large meta-analysis ($n = 58834$) of cancer rates selecting seven other studies in addition to their own. While it did not find an association between statin therapy and increased cancer rates, this meta-analysis was not part of the original study, and therefore should not be included in the article. Like any other significant difference found in the study, the increased risk of cancer should be interpreted as such, and should not be dismissed so easily by the authors.

Finally, the study's results were produced at the 3-year mark. It is reported that treatment with pravastatin led to a 2.1% absolute reduction in the risk (NNT = 48) of the primary outcome, with risk reduction being more pronounced in secondary prevention, men, and in the lowest tertile of HDL-cholesterol. When separated into the secondary outcomes of coronary and cerebrovascular events, a 19% relative risk reduction was noted in coronary events but no discernible effect was found on cerebrovascular events. Furthermore, there was no evidence of selective benefit in smokers and individuals with hypertension and no observed difference in cognitive decline or all-cause mortality. While there may have been a reduction in the primary outcome, it is crucial to emphasize the lack of effect on all-cause mortality found in this study. Beyond isolated cardiovascular risk, the overall care of the elderly warrants consideration of other issues that determine long-term health, such as polypharmacy, falls (for example, due to muscular symptoms), and the management of multiple comorbid conditions simultaneously. With its current design, the study fails to acknowledge the potential interplay between statins and these issues and, as such, does not take into account the reality of caring for the elderly and demonstrates how little statins may be of benefit for these individuals.

Conclusions about the study should also be made with caution given the financial interests that Bristol-Meyers Squibb, the manufacturer of pravastatin, had in funding this study. With this conflict of interest disclosed, readers should be aware of the potential for the introduction of measurement bias.

Clinical Application

As the PROSPER study indicates, elderly patients may benefit from statin therapy if they meet specific characteristics, such as male sex, history of previous vascular disease, and low HDL-cholesterol. The patient described above meets some of these criteria and, as demonstrated in the study, he may lower his ASCVD risk by remaining on a statin. However, given the multiple comorbidities that this patient has and the lack of effect on all-cause mortality found in the study, we ultimately decided that statin therapy would not be beneficial for him. The patient described in the clinical scenario was advised to discontinue statin therapy based on his history of muscle aches. While agreeable to this idea, he expressed lingering concerns about his heart health, demonstrating ambivalence. Exploring his beliefs and values as part of shared decision making is appropriate in this case. Physicians should quantify possible outcomes to assist patients during these conversations.

Furthermore, risks of statin therapy in the elderly include metabolic derangements (accelerated risk of developing diabetes mellitus), musculoskeletal disorders (myalgia, myositis, rare rhabdomyolysis), and potential injury to major organs such as the liver and kidneys.¹⁵ In respect to the patient described above, it is possible that the myalgia he experienced was a side effect of his statin therapy. It is also important to recognize that elderly patients are prone to polypharmacy, as illustrated by the described patient, and are more susceptible to adverse drug-drug interactions.¹⁵

In truth, the PROSPER study may not be entirely applicable to patients like the one behind the clinical question. Our patient, an African-American living in Detroit, may not be accurately represented by the study's Northwestern European participants. Additionally, the study centers on pravastatin and not atorvastatin, which this patient was prescribed. Research has shown that the various statins on the market differ in terms of efficacy and safety.¹⁶⁻¹⁸ Due to these limitations, recommendations for statin therapy in the elderly are not clear-cut and individualized evaluations for each patient are required.



Take Home Points:

- 1.) Statin therapy provides some benefit in reducing risk for coronary disease in the elderly, particularly for secondary prevention in males with low HDL-cholesterol. However, there is no observed difference in all-cause mortality.
- 2.) Risks of statin therapy in the elderly include metabolic derangements, musculoskeletal disorders, potential injury to major organs such as the liver and kidneys, and drug-drug interactions. It is important to keep these risks in mind when evaluating statin therapy for each individual patient.
- 3.) More research is needed to strengthen recommendations for statin therapy in the elderly. For now, physicians should make decisions about starting statin therapy in the elderly on a case-by-case basis.

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