Curr Atheroscler Rep (2013) 15:316
DOI 10.1007/s11883-013-0316-x

Aggressive Statin Therapy and the Risk of Malignancy

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Published online: 23 February 2013

Abstract The advent of pharmacologic agents which partially inhibit the rate limiting enzyme in cholesterol synthesis (3-hydroxy-3-methylglutaryl Co-A reductase) provided a major advance in preventive medicine. Clinical trials in both primary and secondary prevention have demonstrated reduction in cardiovascular events by statin therapy. However, early epidemiologic studies proposed an inverse relationship between cholesterol levels and mortality. While the epidemiologic studies were controversial and did not establish a cause and effect relationship, concern was raised that aggressive lipid lowering by pharmacological means may be associated with increased risk for noncardiac mortality, including malignancy. The theoretical concern was intensified by meta-analysis of statin trials, which confirmed the reduction in cardiovascular mortality but also demonstrated a potential increase in cancer risk. This review evaluates the epidemiologic and prospective trial data which address the potential relationship between aggressive statin therapy and the risk of malignancy

Keywords Statins · Cancer · Epidemiology · Clinical trials · Aggressive therapy · Lipids · Cholesterol

This article is part of the Topical Collection on *Coronary Heart Disease*

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Introduction

Atherosclerosis and its complications remain the major cause of death in the United States despite an encouraging recent decline in age adjusted cardiovascular mortality. Atherosclerosis is best regarded as a syndrome with multiple modifiable and non-modifiable risk factors which interact with genetic tendencies and environmental exposures. The major modifiable risk factors are hypertension, diabetes mellitus, sedentary lifestyle, increased body mass index, consumption of tobacco products and dyslipidemia. While the process of atherosclerosis is multifactorial, dyslipidemia is central to the pathogenesis of vascular disease. Experimental studies have demonstrated difficulty in the generation of an atherosclerotic plaque in the absence of a lipid abnormality (increased low-density lipoprotein, very low-density lipoprotein, intermediate density lipoprotein, remnant particles, lipoprotein (a) or reduced high-density lipoprotein). The advent of pharmacologic agents which partially inhibit the rate limiting enzyme in cholesterol synthesis (3-hydroxy-3-methylglutaryl Coenzyme A or HMG-CoA reductase inhibitors) revolutionized the ability to optimize the lipid profile in subjects at risk for the development of atherosclerosis. Multiple prospective controlled clinical studies utilizing HMG-CoA reductase inhibitors or statins have demonstrated benefits in the reduction of cardiovascular risk in both primary and secondary clinical trials. However, the administration of pharmacologic agents is not without risk and statin therapy has been extensively scrutinized for safety and efficacy in a variety of pre- and post-marketing studies. The major concern relative to statin side effects has focused on the potential for the induction of muscular or hepatic toxicity. Additionally, possibilities of induced cognitive decline, ocular toxicity,

diabetes mellitus, dementia, neuropathy and malignancy have also been proposed as possible side effects of statin therapy. This review focuses on the role of aggressive statin therapy as a risk factor for the development of cancer

Dyslipidemia and Mortality

The lipid hypothesis was proposed to explain the central role of dyslipidemia in atherosclerosis. Epidemiologic studies have demonstrated a curvilinear relationship between cardiovascular mortality and levels of cholesterol in multiple epidemiologic studies [1]. In addition to the epidemiologic studies, the validity of the lipid hypothesis is supported by an overwhelming body of genetic, experimental and clinical trial data. However, the relationship of cholesterol to non-cardiovascular morbidity and mortality is controversial, and studies have suggested that low cholesterol levels are associated with increased total mortality. Additionally, early epidemiologic evidence suggested that a U-shaped relationship existed between cholesterol and cancer risk [2]. The epidemiologic studies generated concern that low levels of cholesterol or other lipid subfractions may be associated with adverse physiologic effects which may increase the risk for development of cancer. The Honolulu Heart Study and other observational trials correlated a greater risk for the development of malignancy (especially colon cancer) and low total serum cholesterol levels [3, 4]. Additionally, the Whitehall Study was conducted in 17,718 male civil servants in London and correlated low cholesterol levels with increased cancer risk [5]. The study demonstrated that over a 7.5 year follow-up period, total mortality demonstrated a J-shaped relationship with the entry level of plasma cholesterol. Cancer mortality was 66 % higher in the group with the lowest plasma cholesterol relative to the group with the highest plasma cholesterol. Combined analysis of multiple studies suggested that the risk ratio for cancer death was greater than 1.0 in 15 of the 18 analyzed studies, and the relative risk was calculated to be 1.18 in the pooled studies [6]. The data correlating other lipid subfractions to increased risk for cancer are less robust and lack the large body of epidemiologic studies which analyzed the relationship between total cholesterol and malignancy. However, the Swedish Apolipoprotein Mortality Risk (AMORIS) trial evaluated 540,309 participants, of which 84,774 had determinations of baseline LDL, HDL, Apolipoprotein B and Apolipoprotein and A-1 levels [7•]. The presence of low HDL cholesterol and elevated triglycerides were associated with a significant increase in the risk for the development of esophageal cancer. Additionally, the European Prospective Investigation into Cancer and Nutrition (EPIC) conducted a study of 520,000 individuals in 10 Western European countries. The EPIC study documented that a total of 1238 cases of incident colorectal cancer were diagnosed following enrollment in the trial. Individuals who were diagnosed with cancer were compared to a matched control population. After the adjustments for height, weight, smoking habits, physical activity, education and diet, the EPIC study established an inverse correlation between the concentration of HDL and Apo A-1 which suggested that low HDL levels increase the risk for cancer.

While not all epidemiologic studies demonstrate a correlation between low levels of circulating cholesterol and the risk for the development of malignancy, considerable concern has been generated. The early pharmacologic agents employed in the treatment of dyslipidemia such as nicotinic acid, fibric acid derivatives and bile acid sequestrants, exhibited a relatively modest effect in lowering serum cholesterol and were not associated with cancer risk. However, the advent of potent agents such as statins have generated concern that overzealous lowering of cholesterol by pharmacologic therapy would predispose to malignancy. While the early observational studies did demonstrate a statistical association between low cholesterol levels and malignancy, evidence was lacking for a definite cause and effect relationship. Epidemiologic studies are best looked upon as hypothesis generating, and further research is required to analyze the presence of possible confounding factors such as social economic status, lifestyle alterations, smoking status, alcohol consumption and other multiple other factors. Criteria have been established to assess the validity of potential harmful associations and epidemiologic studies.

1. Temporal relationship: Exposure of a potential risk factor must predate the diagnosis of disease by an appropriate time period.
2. Plausibility: The risk factor would ideally have a biological mechanism which would explain the potential adverse effects upon physiological processes which would result in a negative outcome
3. Magnitude of relationship: Increasing the intensity of exposure of a risk factor should result in a more significant adverse effect with increasing incidence of morbidity or mortality
4. Consistency of data: The potentially adverse risk factors or intervention should demonstrate an association which is demonstrable in multiple observations and demonstrates consistency and a variety of populations, ethnic groups and gender.
5. Experimental support: The gold standard for potential beneficial and negative effects of therapeutic interventions is an adequately powered randomized prospective clinical trial with an adequate matched control group

The epidemiologic studies linking low cholesterol and cancer deserve further investigation, although multiple

potential issues were raised relative to the validity of the data interpretation. The presence of undiagnosed but incipient cancers is difficult to establish in an epidemiologic observation and brings the temporal relationship into question. The possibility exists that a low level of cholesterol is a manifestation of a pre-existing but undiagnosed disease process with catabolic or inflammatory characteristics and raises the possibility of reverse causality. The clinical evidence supporting alteration of the cholesterol level in preclinical disease states is sparse. However, the potential association between low cholesterol levels and the development of malignancy has been evaluated for possible biologic mechanisms. Cholesterol is essential in multiple aspects of cell structure and function. Cholesterol is a major determinant of membrane permeability, signal transduction, transmembrane exchange and cellular membrane activity. The hypothesis was put forth that perturbations of normal cholesterol physiology may predispose to malignancy. Rare genetic disorders such as homozygous abetalipoproteinemia provide possible insight into the relationship of very low levels of cholesterol and malignancy. Homozygous abetalipoproteinemia is a rare autosomal recessive disorder which is secondary to a mutation in microsomal triglyceride transfer protein and results in deficiencies of apolipoprotein B-48 and B-100 [8]. Apolipoprotein B-48 and B-100 are required for the absorption of fats, cholesterol, and fat-soluble vitamins from the diet and are also necessary for the transport and receptor mediated clearance of these compounds in the bloodstream. The mutation in microsomal triglyceride transfer protein results in severe abnormalities in circulating lipid levels with extremely low levels of low-density lipoprotein. Abetalipoproteinemia is associated with multiple abnormalities including red blood cell hemolysis, fat-soluble vitamin deficiencies, gastrointestinal malabsorption, cardiomyopathy, plus both central and peripheral nervous system degeneration. However, it is not clear that this genetic disorder is associated with an increased risk for the development of malignancies, although isolated case reports have been published [9].

Statin Trials and Malignancy

If the epidemiological studies which link low cholesterol to an increased risk of malignancy are valid, the corollary would follow that aggressive pharmacologic therapy with agents such as statins may be associated with an increased incidence of cancer. The administration of statin therapy significantly reduces the level of circulating lipoproteins which carry Apo B or Apo E by a complex mechanism. The administration of statins results in a partial inhibition of the rate limiting enzyme in cholesterol synthesis which is coupled with an increase in the number or function of the Apo B /E receptor. The net result is an increased clearance of Apo B/E containing particles from the circulation coupled with partial inhibition of hepatic cholesterol production. Additionally, statin therapy has demonstrated a positive, albeit less striking, increase in circulating levels of high-density lipoprotein. Statin therapy also exhibits a variety of non-lipid or pleotropic effects including modulation of endothelial function, oxidative stress, inflammation, platelet function, coagulation and other factors [10]. Clinical trials which compared aggressive statin therapy against more conservative regimens demonstrated a significant reduction in cardiovascular endpoints correlated with lower achieved LDL levels [11]. The totality of evidence favored aggressive lipid goals and prompted the National Cholesterol Education Program (NCEP) to revise treatment targets. The Adult Treatment Panel (ATP-III) of the NCEP recommended aggressive treatment goals based on an individual's ten-year risk for the development of coronary artery disease, which was determined by the global risk factor profile. The ATP-III recommendations emphasized initial intervention by modification of lifestyle utilizing implementation of the therapeutic lifestyle program which focused on diet and exercise. However, in individuals who did not achieve the lipid goals, statins were recommended as the initial pharmacologic option to achieve the target for LDL cholesterol. The ATP-III guidelines recommended the achievement of LDL cholesterol of 100 mg/dl in individuals with documented coronary artery disease. Additionally, a goal of 70 mg/dL was recommended in high-risk individuals with risk factor clustering. The clinical evidence supporting aggressive lipid goals in the management of subjects at risk for the development of coronary artery disease with established atherosclerosis is overwhelming. However, the previous concerns relative to low cholesterol and malignancy were resurrected in light of the ability of statin therapy to dramatically lower LDL cholesterol levels. Additionally, concerns about direct adverse effects of statins also have been of concern. The controversy which arose with the early epidemiologic studies was expanded to statin therapy. A meta-analysis was performed which analyzed the effects of aggressive lipid-lowering achieved by statin therapy and the subsequent risk for the development for hepatotoxicity, rhabdomyolysis and malignancy [12]. The meta-analysis collected clinical data obtained from 23 statin treatment arms and analyzed 75,317 statin allocated patients. The meta-analysis accounted for 309,506 patient years of follow-up. The purpose of the study was to examine the possibility that statin associated side effects such as hepatic and muscle toxicity were related to the degree of lipid-lowering. Additionally, the study was subsequently expanded to evaluate the potential role of statin therapy as a risk factor for the development of malignancy. The results of the pooled studies were analyzed and determined that there was no significant relationship between the percent of low-density lipoprotein cholesterol lowering and the incidence of elevated hepatic enzymes. However, there was a positive graded relationship between the incidence of

elevated liver enzymes and statin dose. The statistical relationship held when the levels of absolute LDL reduction and achieved LDL reduction was examined. In contrast, there was no significant relationship between the percentage of LDL cholesterol lowering achieved by statin therapy and the risk for the development of rhabdomyolysis. The absolute reduction of LDL cholesterol and the percent of LDL cholesterol lowering did not correlate with the risk of rhabdomyolysis. However, analysis of the data for newly diagnosed cancers in the trial demonstrated a significant inverse relationship between the levels of achieved low-density lipoprotein and cancer risk. The absolute reduction and percent of LDL cholesterol lowering and cancer risk were not significantly related. The number of newly diagnosed cancer cases was evaluated in 13 treatment arms, since all of the clinical trials in the original cohort did not report incident cancer rates. The statistical relationship was greatest when the high-dose statin group was compared to subjects receiving lower doses. The study was initiated to analyze potential mechanisms in predisposing factors which may be associated with adverse statin effects. The analyzed trials utilized primary end points which were prespecified and composed of cardiovascular events which were adjudicated. In contrast, retrospective analysis of secondary endpoints and other non-adjudicated beneficial or adverse effects is potentially problematic. The meta-analysis did not contradict the clear and significant reduction in cardiovascular endpoints associated with statin therapy. Individual analysis of the clinical trials did not demonstrate an increased risk in cancer, with the sole exception of the PROSPER trial with pravastatin therapy [13]. The authors of the PROSPER study were concerned about the increased risk of malignancy, so they analyzed pravastatin trials in the context of the available data utilizing this agent. A meta-analysis of all pravastatin trials, including PROSPER, was performed and demonstrated no significant effect of pravastatin on cancer rates. Due to the concern that cholesterol lowering with statin therapy may reduce the risk of cardiovascular events at the expense of an increased risk of cancer, the authors expanded upon the original meta-analysis and attempted to address potential confounding variables in the study [14]. The authors considered the effects of statin therapy and the achieved LDL cholesterol levels and cancer risk. The analysis demonstrated an inverse association between on treatment LDL cholesterol levels and incident cancer in statin treated patients which persisted after accounting for gender, age, smoking, diabetes, hypertension and body mass index. Additionally, a relationship between on treatment LDL cholesterol levels and incident cancer was also observed in the control population that was not treated with statins. Importantly, comparison of the association between achieved LDL cholesterol level and risk of cancer in the statin treated versus control patients demonstrated that the statin line was significantly shifted horizontally to the left. The statin treated patients achieved lower levels of LDL cholesterol while maintaining a similar risk of cancer. The conclusion was that the lower levels of on treatment LDL cholesterol and incident cancer is not driven by statins, and that statin therapy, despite producing marked reductions in LDL cholesterol, is not associated with an increased risk of cancer, although further long-term evaluation was recommended.

While not included in this meta-analysis, the recently published SEAS (Effects of Simvastatin and Ezetimibe on Clinical Outcomes) trial evaluated 1873 subjects with aortic stenosis to determine if aggressive lipid-lowering by combination therapy would alter the course of progressive valvular obstruction [15]. Low-density lipoprotein was decreased by 61 % to a mean of 52 mg/dL in the treatment arm. The primary endpoint was echocardiographic modification in valvular aortic stenosis which was not achieved by the combination of the ezetimibe and simvastatin, although ischemic events not related to aortic stenosis were significantly decreased. However, a statistically significant increase in cancer did occur in the group randomized combination therapy. The concern was that the addition of ezetimibe to simvastatin or significant LDL reductions may be associated with an increased risk for malignancy. The safety issue resulted in an evaluation of two prior studies which utilized ezetimibe in addition to a large ongoing unpublished study [16]. The safety analysis evaluated 22,490 subjects and did not demonstrate an increase in cancer related to the addition of ezetimibe as a means to lower LDL, although methodologic concerns have been raised relative to the analysis [17]. The largest prospective statin study, the Heart Protection Study, analyzed simvastatin therapy versus a placebo in a controlled prospective clinical trial which randomized over 20,000 patients [18]. The Heart Protection Study was designed to analyze the effect of statin therapy in high risk subjects who were underrepresented in previous clinical trials (women, diabetics, elderly, etc.). The analysis of the Heart Protection Study database did not demonstrate an increased risk of malignancy when the placebo and simvastatin groups were compared. The controversy relative to aggressive LDL lowering and malignancy also resulted in a ten-year safety follow-up evaluation of the Scandinavian Simvastatin Survival Study (4S). The 4S study analyzed high-risk individuals following an acute myocardial infarction and was the first major prospective trial to clearly demonstrate reductions in both cardiovascular and total mortality with aggressive statin therapy. The ten-year follow-up safety data demonstrated a continued reduction and mortality without an increase in risk for the development of cancer [19].

Multiple observational studies have been performed which address the potential role of statin therapy in malignancy. Cardiac transplantation represents a major advance in the treatment of individuals with end-stage cardiovascular disease. Immune mediated rejection had been a major obstacle to survival in cardiac transplant recipients until the development of more sophisticated immunosuppressive regimens coupled with the development of cyclosporin

revolutionized the management of transplant recipients and markedly improved survival rates. However, long-term survival in cardiovascular transplantation is frequently limited by the development of malignancy, which may be partially related to the patient's immunosuppressive regimen. Newer immunosuppressive agents have been associated with decreased risk for the development of malignancy. Statin therapy has been implicated as an intervention that may exhibit beneficial effects beyond lipid-lowering activities. European studies analyzed heart transplant recipients who survived for at least 12 months following transplantation [20•]. The primary outcome measure was the recurrence of malignancy and overall survival was also analyzed in the follow-up period. Malignancy was diagnosed in 42 % of the subjects. However, the use of statin therapy was associated with a significantly increased cancer free interval and improved overall survival. The utilization of statin therapy decreased the hazard of recurrence of any malignancy by 67 % when adjusted for age, gender, specific cardiomyopathy and immunosuppressive therapy. A meta-analysis was also performed on the role of statin therapy and prostate cancer [21]. Utilizing data obtained in individuals from 2005-2010, statin therapy was associated with a statistically significant reduction in prostate cancer. The association of altered liver enzymes induced by statin therapy has raised the possibility that an increase in hepatocellular carcinoma may occur in statin recipients. A meta-analysis was performed evaluating the association between statin exposure and risk for hepatocellular carcinoma [22]. The meta-analysis evaluated five observational studies based on 2,574 individuals with hepatocellular carcinoma. The administration of statin therapy was inversely related to the risk of development of hepatocellular carcinoma. The analysis is compatible with a potential beneficial effect of statin therapy, although methodologic issues have been raised. The observation that statin therapy may play a role in the prevention of malignancy due to the pleotropic effects, including inhibition of tumor growth, resulted in an analysis of a computer database in Israel [23]. The study evaluated 202,648 individuals who received statin therapy. During the observation period, a total of 8,662 cancers were initially diagnosed. The highest cancer risk was determined to be in nonpersistent statin users. A strong negative association between continuation of statin therapy and cancer was established for hematopoietic malignancy. The study demonstrated that there was a statistical association with continuous statin use and a lower risk of cancer which was significantly marked in hepatic hematopoietic malignancies. Additionally, the entire Danish population who received a diagnosis of cancer between the years 1995 and 2007 was analyzed for statin usage. A total of 18,721 individuals had received statin therapy during the observation period compared to 277,204 who had never been prescribed statin therapy. The administration of statin therapy was associated with a reduction and mortality related to cancer [24•]. The cited meta-analysis and observational studies, again, should be viewed as hypothesis generating but do provide a degree of reassurance that the use of statin therapy does not predispose to increased risk of malignancy.

Conclusion

Epidemiologic studies associated low cholesterol levels with increased mortality and raised questions as to the benefits of aggressive lipid lowering. While the clinical benefits of aggressive cholesterol lowering in the reduction of cardiovascular disease is supported by multiple prospective trials, the question of an increase in non-cardiovascular mortality has always been controversial. The Whitehall study was one of the original investigations to raise the possibility that low cholesterol may be associated with increased total mortality. However, subsequent interpretation of the study addressed the effects of improving survival and cardiovascular disease upon the pattern of mortality [25]. The control of the modifiable risk factors reduces morbidity and increases longevity. However, the increased longevity is associated with more years of exposure to other potential conditions. Additionally, competing mortality from other conditions such as malignancy may be increased. The epidemiologic studies which demonstrated a J-shaped relationship was felt to represent a short-term phenomenon reflecting the nutritional and metabolic effects of early cancer. The concept that an unsuspected illness phenomenon implying the lowering of cholesterol level is secondary to the presence of subclinical but undiagnosed disease has gained credence. Early studies have demonstrated that malignancy may be associated with the induction of low levels of cholesterol for many years prior to diagnosis [26]. In contrast, populations characterized by low national levels of cholesterol do not have excess mortality from malignancy and the preponderance of evidence does not indicate a cause and effect relationship between low cholesterol and subsequent malignancy.

The question has been raised relative to the possibility of statin therapy inducing an increased risk from cancer, especially with the new more aggressive guidelines proposed by the ATP-III. Importantly, the prospective clinical trials conducted with statin therapy, even with aggressive goals, did not demonstrate a clear increase in risk for malignancy. The controversy surrounding statin therapy has recently been addressed in a state of the art paper [27••]. The side effects that are clearly related to statin therapy, such as the induction of myopathy or elevated liver enzymes, are generally reversible with discontinuation of the drug. The potential carcinogenicity of statin therapy was evaluated by the compilation of multiple reviews and analysis of prospective clinical trials. The systematic reviews have demonstrated no increased risk

for cancer with statin therapy, including the most recent meta-analysis which evaluated 33 randomized clinical trials, which included data on first incident cancers recorded after randomization [28]. The incidence of cancer in the individuals who are randomized to receive statin therapy was not significantly different from the control population. The conclusion following analysis of multiple prospective clinical trials, meta-analyses and epidemiologic studies would support the premise that the administration of statin therapy and aggressive lowering of LDL cholesterol by these agents does not predispose to cancer.

Disclosure No potential conflicts of interest relevant to this article were reported.

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- • Of importance
- •• Of major importance

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