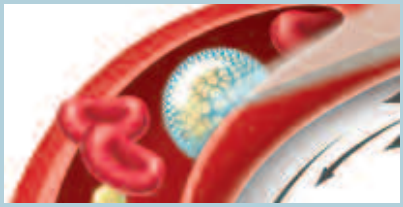
abstract



Coronary and cerebrovascular disease is the leading cause of death and disability in the older population. Control of vascular risk factors such as blood pressure, lipids, and glucose is important in higher risk patients to reduce the impact of stroke and myocardial infarction, whatever their age. Although total and LDL cholesterol levels are less predictive of coronary heart disease in the older patient, clinical trials demonstrate an important benefit from statin therapy in high-risk individuals over a wide age range with either established cardiovascular disease or diabetes. Older patients with multiple risk factors for vascular disease, yet without coronary, cerebrovascular, or peripheral vascular disease, should also be considered for statin treatment.

Key words: *cholesterol, lipid management, statin, cardiovascular disease*

Lipid Management—Who to Screen? Who to Treat?

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Introduction

Over the next 20 years the proportion of the population more than 65 years of age is expected to increase from approximately 15% to more than 20%. Coronary heart disease (CHD) and cerebrovascular disease are the leading causes of death and disability in this older population. Consequently, as the population ages, measures to prevent heart attack and stroke in the older patient achieve increasing importance. Vascular disease has an impact on life expectancy but most importantly results in considerable morbidity. Stroke and heart failure, usually the consequence of atherosclerotic vascular disease, have a major impact on the quality of life, independence, and the need for institutional care in the older adult. Lipid management, as an important component of vascular risk factor control, plays a pivotal role in cardiovascular risk factor management in all age groups.

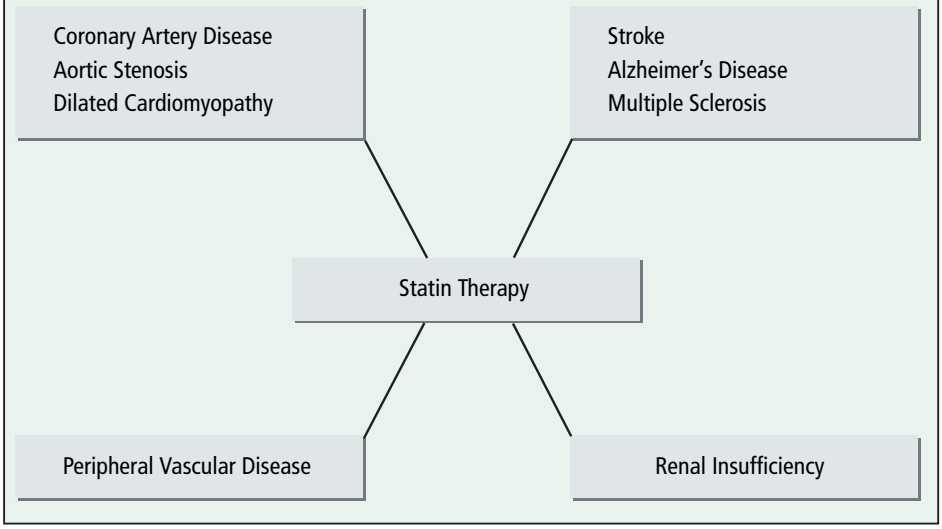
Lipid reduction with statin therapy reduces mortality and recurrent coronary events in a wide range of patients independent of age, known presence of coronary artery disease, or LDL cholesterol level. Furthermore, there are additional potential benefits of statin therapy for older patients that are under investigation (Figure 1).[1–4] A number of questions remain unanswered in the lipid management of the older adult. Although studies have included patients well into their eighth decade of life, it remains controversial whether older patients without clinically apparent vascular disease derive benefit from cholesterol lowering. Although many older patients may not have symptomatic vascular disease, the burden of coronary and cerebrovascular disease in the older individual is substantial. In the population over 75 years old, the distinction between primary and secondary prevention of vascular events becomes blurred as a high proportion have atherosclerotic disease. The present report aims to analyze the benefit and use of statins in older patients with and without apparent vascular disease and recommend a practical approach to treatment.

Dyslipidemia as a Risk Factor

The prevalence of abnormal lipid profiles declines with increasing age, partially due to selective survival (Figure 2). In addition, epidemiological studies have suggested that the relationship between cholesterol levels and coronary heart disease decreases with aging. Consequently, it was assumed there would be a lesser benefit from treating dyslipidemia in the older patient. Yet later studies have indicated that an abnormal lipid profile is an important risk factor for vascular disease in the older adult.[6,7] In the Framingham heart study, although total cholesterol did not predict coronary heart disease in men over 70 years of age, it predicted CHD in women into the ninth decade.[5] Furthermore, approximately one-third of older men and half of older women have cholesterol levels >6.3 mmol/L (>240 mg/dL).[8] Thus, treatable hyperlipidemia remains important at an advanced age and should guide treatment to prevent cardiovascular disease.

Lipid abnormalities in the older patient tend to cluster with other risk factors such as hypertension, diabetes, and obesity. In the Cardiovascular Health Study[9] (CHS) of 5,888 subjects >65 years

Figure 1: Potential Impact of Statin Therapy in the Older Patient



of age, triglycerides, HDL levels, and, to a lesser extent, LDL levels were associated with modifiable risk factors such as obesity, glucose intolerance, impairment of renal function, and use of medication. Although there was no difference in total cholesterol and LDL in those with and without CHD or stroke, triglycerides were higher and HDL lower in subjects with vascular disease.

Despite the relative risk attributable to high total or low HDL decreasing with age, the overall risk of abnormal lipids is potentially greater in the older subject because of the higher prevalence of coronary events and the greater absolute and attributable risk. Consequently, the totality of the evidence shows that abnormal lipid levels are associated with increased vascular risk in the older population. Although both total cholesterol and the total cholesterol/HDL ratio predict coronary disease in older patients, the total C/HDL ratio is most predictive of CHD in the older patient.

Benefits of Statin Therapy Are Not Contingent on Age

Observational studies and randomized controlled trials have shown the benefits attributable to statin therapy in the older population. The Cardiovascular Health Study showed that statin therapy in patients >65 years of age (mean age 72 years) was associated with a 56% reduction of cardiovascular events and a 44% reduction of all-cause mortality. In other observational studies, similar benefits from statin treatment were observed even in those >80 years of age.

A meta-analysis of randomized controlled trials[10] shows similar benefits from statin therapy in patients younger or older than 65 years. Furthermore, older cohorts of patients in controlled trials had an enhanced absolute benefit from statin therapy compared to younger subjects. In the 4S study, patients[11] 65–70 years old had a 34% relative risk reduction (RRR) of all-cause mortality, a 43% RRR of coronary heart disease mortality, and a 44% RRR of major coronary events. As mortality rates increased substantially with age, the absolute risk reduction was twice as large in the subjects >65 years old compared to the younger patients.

The Prospective Pravastatin Pooling Project[12] examined outcomes in specified subpopulations of the CARE,[13] WOSCOPS,[14] and LIPID[15] trials. For patients older than 65 years, there was a 26% reduction of the primary endpoint of CHD death or nonfatal MI. To prevent one primary event, it would be necessary to treat 25 patients. In the CARE[16] trial, pravastatin also reduced the incidence of stroke by 40%.

The Heart Protection Study[17] enrolled patients 40–80 years old who were at high risk of cardiovascular events. These patients had a history of coronary heart disease, cerebrovascular disease, or diabetes. Simvastatin 40 mg daily reduced major vascular events by 24%, with similar treatment benefits observed in the 65–69, 70–74, and >75-year-old age groups (Figure 3). In patients 75–80 years old, treatment of 25 patients prevented one major event.

The Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial[18] specifically investigated the benefits of pravastatin therapy for the prevention of coronary and cerebrovascular events in high risk older patients 70–82 years of age who had either had a vascular event (myocardial infarction, stroke, or peripheral vascular disease) or were at high risk of developing one because they had diabetes, hypertension, or were smokers. Pravastatin 40 mg daily for 3.2 years resulted in a 15% reduction ($P = 0.014$) of the primary endpoint of CHD death, nonfatal myocardial infarction, or stroke. Coronary heart disease mortality was reduced by 24% ($P = 0.043$). Although there was no significant reduction of stroke, it is likely that a longer period of treatment is necessary to reduce stroke risk (Figure 4).

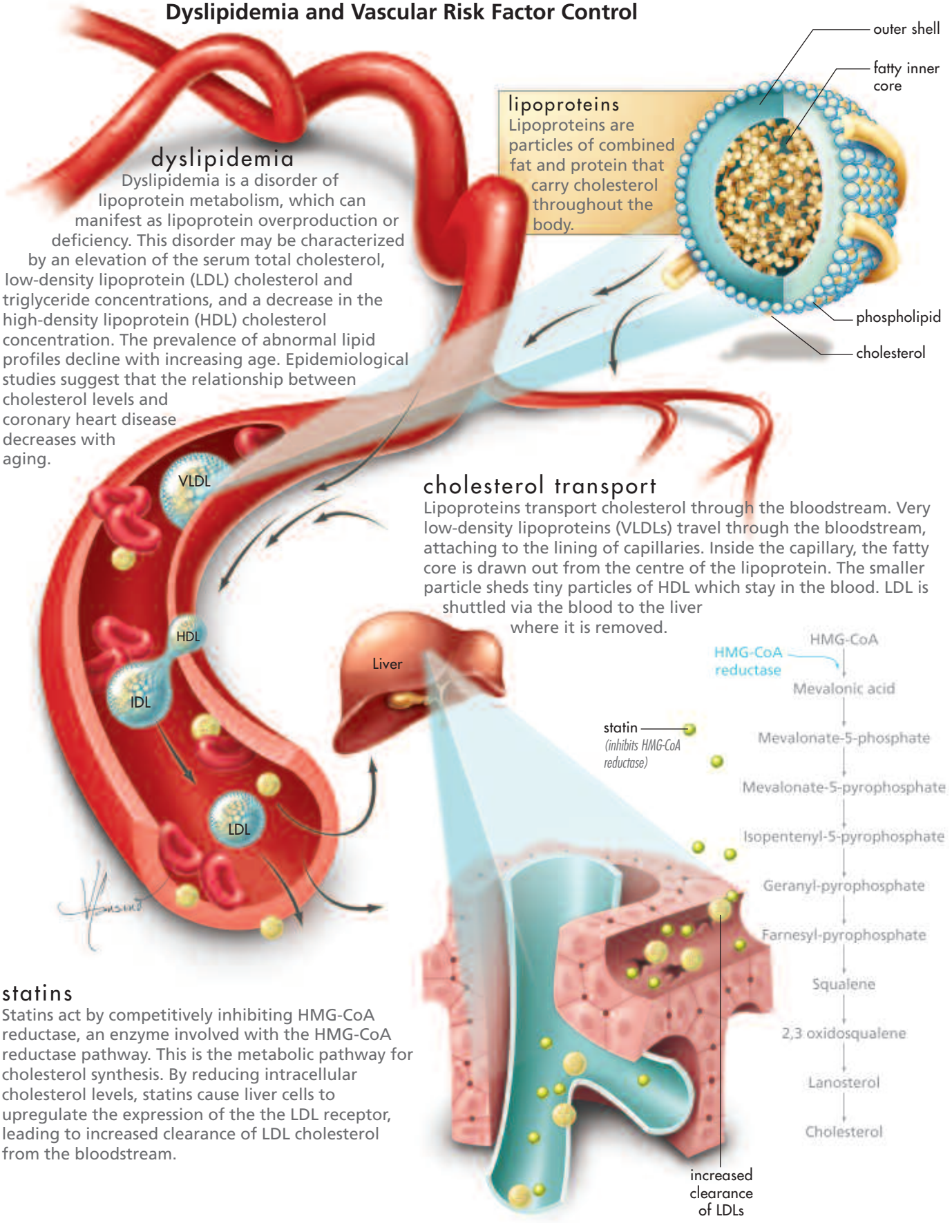
The PROSPER trial confirmed the epidemiological observations discussed above that there was no correlation between the LDL-C levels and the risk of a coronary event or the efficacy of pravastatin in preventing an event. The highest risk for a cardiovascular event was in subjects with the lowest HDL, and these patients had the greatest benefit from pravastatin therapy.

Benefit of Statins in Patients with Diabetes

Diabetes is an important risk factor for cardiovascular events at all ages. Statin therapy provides important protection from cardiovascular events in patients with diabetes whether or not they have evidence of vascular disease. Both the Heart Protection Study[17] and the Collaborative Atorvastatin Diabetes Study (CARDS)[19] showed that the benefit of statins in patients with diabetes and no

Figure 2:

Dyslipidemia and Vascular Risk Factor Control



lipoproteins

Lipoproteins are particles of combined fat and protein that carry cholesterol throughout the body.

dyslipidemia

Dyslipidemia is a disorder of lipoprotein metabolism, which can manifest as lipoprotein overproduction or deficiency. This disorder may be characterized by an elevation of the serum total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride concentrations, and a decrease in the high-density lipoprotein (HDL) cholesterol concentration. The prevalence of abnormal lipid profiles decline with increasing age. Epidemiological studies suggest that the relationship between cholesterol levels and coronary heart disease decreases with aging.

cholesterol transport

Lipoproteins transport cholesterol through the bloodstream. Very low-density lipoproteins (VLDLs) travel through the bloodstream, attaching to the lining of capillaries. Inside the capillary, the fatty core is drawn out from the centre of the lipoprotein. The smaller particle sheds tiny particles of HDL which stay in the blood. LDL is shuttled via the blood to the liver where it is removed.

statins

Statins act by competitively inhibiting HMG-CoA reductase, an enzyme involved with the HMG-CoA reductase pathway. This is the metabolic pathway for cholesterol synthesis. By reducing intracellular cholesterol levels, statins cause liver cells to upregulate the expression of the the LDL receptor, leading to increased clearance of LDL cholesterol from the bloodstream.

apparent vascular disease was independent of the age of the patient. All patients with diabetes, with or without coronary heart disease, should be considered for statin therapy.

Stroke Prevention with Statins

A recent meta-analysis of lipid lowering therapy[20] shows stroke is reduced in both primary and secondary prevention trials. Statins reduced the risk of stroke by 26% (P<0.001). Benefit was seen when total cholesterol was reduced to below 6 mmol/l. The reduction of stroke in the older patient at risk is a compelling reason to prescribe a statin for patients at risk. Stroke is the third leading cause of death in older adults. Among survivors, one-third is permanently disabled and a high proportion requires long-term institutional care.

Benefit of Statins Is Dependent on the Risk of Cardiovascular Event

Although increasing age is associated with an increased risk of both coronary heart and cerebrovascular disease,[21] certain older patients, especially those with known vascular disease or diabetes, are at especially high risk of cardiovascular events. The PROSPER study showed that a prior history of cardiovascular disease and male sex were associated with a significantly higher incidence of events, yet a history of hypertension and smoking did not appear to increase risk over the three-year period of the trial. However, men and women with or without these risk factors benefited from treatment. Furthermore, the benefit from statin treatment was independent of the pretreatment LDL cholesterol level.

Is Lower LDL Better in the Older Patient?

Recent clinical trials have indicated that there are enhanced benefits from treatment that lowers LDL below currently recommended treatment target of 2.5 mmol/L in high-risk individuals. The treating to new targets (TNT) trial included high-risk patients 35–75 years of age who were randomly assigned to either atorvastatin 10 mg or 80 mg daily. The more aggressive treatment reduced LDL to below 2 mmol/L and resulted in a 22% relative risk reduction of major cardiovascular events compared to patients given the lower dose of atorvastatin. Similar benefits from the higher dose of atorvastatin were observed in younger and older subjects.

Adverse Effects of Statin Therapy

Adverse effects of statin therapy are generally uncommon. However, older patients are at higher risk for these effects, especially for the development of myositis and rhabdomyolysis. Risk factors for the development of rhabdomyolysis, including untreated hypothyroidism, female sex, small muscle mass, renal insufficiency, and drug interactions that increase blood levels of statins, are more frequent in the older patient. Serious adverse effects of atorvastatin were uncommon in the TNT trial, with five cases of rhabdomyolysis in 10,000 patients unrelated to the atorvastatin dose. However, there was a four-fold increase in the incidence of liver function abnormalities as the dose of atorvastatin was increased from 10–80 mg. Consequently, if new lower treatment targets of LDL C <2.0 mmol/L are sought in the older patient, careful selection and increased vigilance will be necessary to minimize serious adverse events. In the older patient, especially one with any degree of renal dysfunction, it is recommended that CK and liver function tests be checked four to six weeks after initiating treatment and then at six-month intervals.

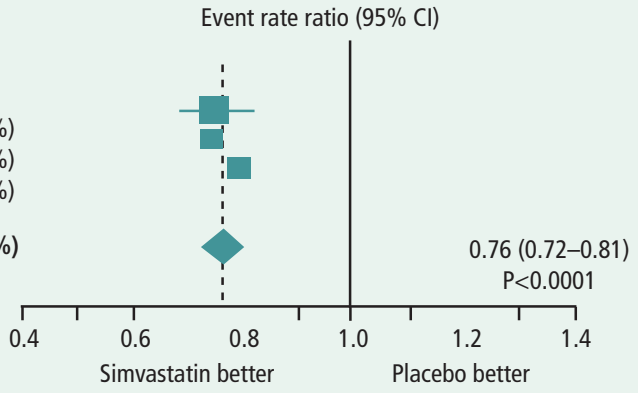
In the PROSPER trial, treatment with pravastatin was associated with a small increase in the risk of developing cancer. Yet a meta-analysis of other trials showed no excess of cancer in the statin treated patients. As the age of patients in the meta-analysis was considerably younger than in the PROSPER trial, it remains possible that statins do have a small impact on the risk of cancer in the older patient.

Care Gap in Lipid Management

Despite strong evidence for the benefits of statin therapy in the older patient population, many high-risk patients do not receive treatment. In fact, a recent study

Figure 3: Benefit from Statin Therapy Not Dependent on Age

Presenting feature	Simvastatin-allocated	Placebo-allocated
Age (years)		
<65	831/4,903 (16.9%)	1,091/4,936 (22.1%)
65–70	512/2,447 (20.9%)	665/2,444 (27.2%)
≥70	690/2,919 (23.6%)	829/2,887 (28.7%)
ALL PATIENTS	**2,033/10,269 (19.8%)**	**2,585/10,267 (25.2%)**



Benefit from statin therapy was seen in patients in the Heart Protection Study across all age groups. Source: Adapted from Heart Protection Collaboration Group, 2002.[17]

indicated that there was a treatment-risk paradox with the prescription of statins diminishing progressively as baseline cardiovascular risk increased.[22] In an Ontario cohort of patients >65 years old with a history of cardiovascular disease or diabetes, only 19% of patients were receiving a statin. Independent of age, statins were less frequently prescribed in patients at the highest risk. The reasons for this treatment paradox include concerns about a possible harmful effect of treatment and poor patient adherence. Two recent studies[23,24] have confirmed that treatment adherence was lowest in the oldest patients and in the poorest patient groups. In a group of patients more than 65 years of age with coronary artery disease, adherence was only 36% after two years of follow-up.[23] Such low rates of adherence are consistent with those reported for patients receiving long-term medication for hypertension.

Lipid Management

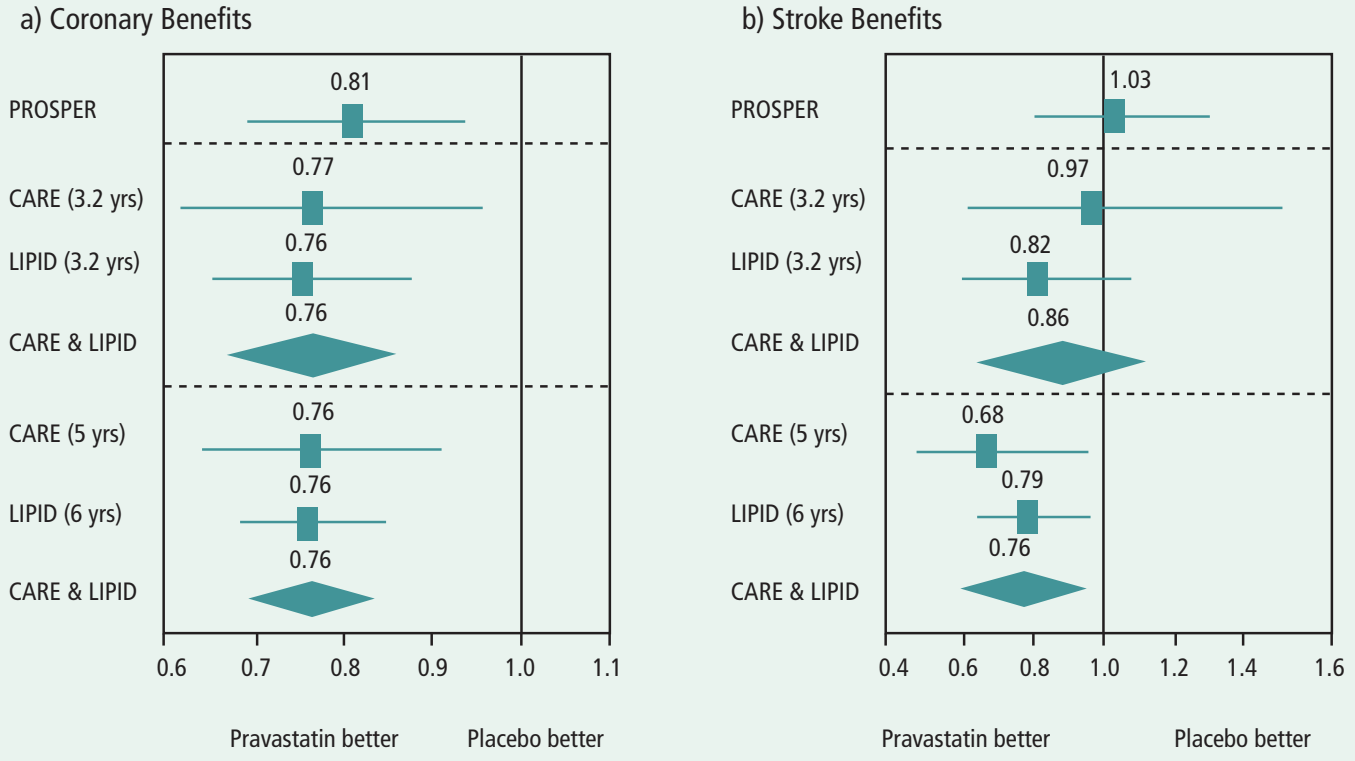
The principles for the use of statin therapy in the older patient are shown in Table 1. Lifestyle modification that includes smoking cessation, weight loss, and increased physical activity should be encouraged in all patients. Older patients at the highest risk of heart attack and stroke are those who already have vascular disease or diabetes. Treatment with a statin should be considered in a wide range of older patients with established cardiovascular disease (e.g., prior MI, angina, stroke, or evidence for peripheral vascular disease) and diabetes. Although increased age in itself should not be a reason to avoid using a statin, it is recognized that competing risks (such as comorbidity that limits quality of life and life expectancy, and impaired renal function that increases the risk for adverse effects of treatment) are more frequent with increasing age.

Moderate-risk patients with no evidence of vascular disease include those with low HDL levels, LDL levels that are substantially elevated, and multiple risk factors for vascular disease (e.g., hypertension, smoking, and abdominal obesity). As moderate-risk patients have a lower frequency of cardiovascular events, it is even more important in the older patient to consider competing risks carefully before starting treatment with any long-term therapy.

Treatment Goals

The Canadian guidelines[25] for lipid management recommend an on-treatment target LDL cholesterol of 2.5 mmol/L, and/or a 40% reduction of baseline LDL. Clinical trials demonstrate that the benefit of statins is based upon the achieved LDL. If treatment with statins is initiated in an older patient, treatment targets as recommended for all patients should be

Figure 4: Coronary and Stroke Benefit of Pravastatin



Comparison of a) coronary and b) stroke benefit of pravastatin (40 mg/day) over 3.2 years in the PROSPER study with outcomes at a similar time point in CARE and LIPID. Note that in PROSPER[18], CARE[13], and LIPID[15] trials, a coronary heart benefit was observed at three years yet no stroke benefit was seen. At five to six years, a clear CHD and stroke benefit was observed in both the CARE and LIPID trials.
Source: Shepherd J, 2004.[26]

Table 1: Principles of Risk Factor Modification and Statin Therapy in the Older Patient

1. Consider lifestyle modifications at all ages Examples: weight loss, exercise, smoking cessation, and heart-healthy diet
2. Consider statin therapy for all high-risk patients irrespective of age Examples: atorvastatin 10–80 mg, cerivastatin 5–10 mg, simvastatin 10–40 mg, pravastatin 10–40 mg
3. Consider statins for some moderate-risk patients, such as those with a. evidence of vascular disease (carotid bruit, abnormal ABI, or silent MI), b. low HDL or high LDL, or c. multiple risk factors
4. Consider competing risks when making decision to treat a. overall quality of life b. life-limiting medical conditions, c. impaired renal and hepatic function, or d. concomitant medications

sought by titrating the statin dose until the LDL cholesterol target is achieved.

Conclusions

Although hypercholesterolemia is less predictive of adverse outcomes with increasing age, older patients at high risk of myocardial infarction or stroke with exiting vascular disease or diabetes benefit from statin therapy independent of the baseline cholesterol level. Statin therapy not only reduces the risk for coronary heart disease but also reduces the risk of stroke.

Treatment targets of LDL cholesterol <2.5 mmol/L should be sought in high-risk patients of all ages.

Older patients with multiple risk factors for cardiovascular disease yet no clinical vascular disease should be considered for statin therapy, especially when LDL cholesterol is >3.5 mmol/L. ◆

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