Treatment of dyslipidemia in the older adult

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INTRODUCTION — Clinical trials of cholesterol lowering therapies have demonstrated consistent near-term benefits for patients with established coronary heart disease (CHD) and long-term benefits for those with severe hypercholesterolemia who are currently free of clinical CHD (see "Clinical trials of cholesterol lowering in patients with cardiovascular disease or diabetes"). Unfortunately, these trials have typically excluded older patients.

The bias against older individuals stems from illusory concerns regarding life expectancy, comorbidity, safety of lipid lowering agents, and cost-benefit analysis of preventive care in older adults. In fact, the absolute risk for CHD increases dramatically with age in both men and women (figure 1). Thus, the absolute number of persons benefiting from cholesterol lowering should be greater in older adults [1,2].

CARDIOVASCULAR DISEASE IN OLDER ADULTS — A large proportion of older individuals will suffer from CHD. In men over the age of 65, for example, nearly one-half of all deaths are attributed to CHD, compared to less than 25 percent for all cancers and less than 2 percent for all infections. An even higher proportion of deaths are due to CHD in older women (56 percent) with less than 20 percent being due to cancer.

Age-related changes in lipoprotein metabolism — Longitudinal studies have shown that total cholesterol levels increase in males after the onset of puberty until age 50. This is followed by a plateau until age 70, with the serum cholesterol concentration then falling slightly. Although it has been suspected that the latter change may be an artifact resulting from CHD deaths in hypercholesterolemic men [3], the most important factor influencing cholesterol may be weight change [4]. The reduction in total and LDL cholesterol and the increase in HDL-cholesterol in older men, primarily occur in those who lost weight, while age is not a factor.

In women, the serum cholesterol concentration is slightly higher than in men prior to age 20 to 25. Between the ages of 25 to 55, the serum cholesterol rises although at a slower incremental rate than in men. Cholesterol levels in women are equal to those of men between the ages of 55 to 60 and exceed those in men in older age groups.

The age-related changes in the serum cholesterol concentration primarily result from an increase in LDL-cholesterol (figure 2) [3]. In comparison, HDL-cholesterol levels do not vary much with age, being about 10 mg/dL (0.26 mmol/L) higher in women than men.

The mechanisms responsible for the progressive age-related elevation in LDL-cholesterol have not been fully explained; however, the data support a primary role for a decrease in the fractional catabolic rate of LDL-cholesterol. This reduction in LDL catabolism is thought to result from diminished activity of hepatic LDL receptors [5].

Cholesterol as a predictor of cardiovascular risk — The association between hypercholesterolemia and CHD in elderly men and women has been demonstrated in a number of large series [6-11]. In the Framingham Heart Study, for example, the relative risk of developing symptomatic CHD was 1.5 in men and 2.3 in women with a total cholesterol level at the 90th percentile when compared to those with a plasma cholesterol concentration below 200 mg/dL (5.2 mmol/L) [6]. These findings have been confirmed in almost all other major epidemiologic studies of older men [7-9]. The relative risk for CHD varied between 1.5 and 1.65 for subjects with a total cholesterol level in the upper quartile or upper 10 percent.

Low HDL cholesterol is also a risk factor. This was illustrated in a prospective cohort study of 2,527 women and

1,377 men which examined the effect of total cholesterol and HDL cholesterol on the CHD death rate in persons over age 70 [12]. At a follow-up of 4.4 years, an elevated total cholesterol concentration (>240 mg/dL or 6.2 mmol/L) was significantly correlated with CHD mortality in women (relative risk = 1.8) but not in men (relative risk = 1.1). The relative risk of coronary mortality for those with low HDL levels (<35 mg/dL or 0.9 mmol/L) was 4.9 in men and 2.0 in women. The Framingham Heart Study and the Systolic Hypertension in the Elderly Program (SHEP) also found that both high LDL and low HDL-cholesterol levels were significant CHD risk factors in elderly subjects [6,10].

Some reports have observed a U- or J-shaped curve in the elderly in which lower cholesterol levels are paradoxically associated with an increase in cardiovascular risk. In a longitudinal study of 4066 elderly men and women, for example, death from coronary heart disease increased at serum cholesterol levels below 160 mg/dL (4.1 mmol/L) [13]. If, however, adjustments were made for CHD risk factors and for serum iron and albumin (to account for comorbid disease and frailty), the increase in risk at lower cholesterol values disappeared.

Relative risk versus attributable risk — In assessing the importance of the relation between cholesterol and CHD in the elderly and the potential value of hypolipidemic therapy, it is critical to distinguish between relative risk and attributable or absolute risk. The relative risk or risk ratio is the ratio of disease prevalence in one population without the risk factor to the risk in another population possessing the risk factor. The attributable risk is the absolute difference in disease prevalence between the two groups. Suppose, for example, that the incidence of CHD at five years is 20 percent in hypercholesterolemic subjects and 12 percent in subjects with normal cholesterol levels. The relative risk for CHD in hypercholesterolemia in this setting is 1.67 (20 ÷ 12) while the attributable risk is 8 percent, meaning that eight out of every 100 hypercholesterolemic patients will have a coronary event not seen in those with a normal plasma cholesterol concentration.

The relative risk or risk ratio is a good measure of the strength of an association in assessing causality. Use of the risk ratio was valuable in early analyses because a significantly elevated risk ratio implied causality and strengthened the argument that elevated serum cholesterol levels are causally linked to CHD [14].

However, the attributable risk is a more useful clinical measurement, since it estimates how much elevated cholesterol levels contribute to coronary heart disease. It also estimates how much the risk might be reduced if the hypercholesterolemia were corrected [15]. Because CHD morbidity and mortality rates increase with age, the attributable risk of high total cholesterol is greater in the elderly even though the relative risk decreases with age (ie, a smaller percentage of a larger number of events results in a larger increase in absolute risk) (figure 3). The increase in absolute risk in the elderly suggests that the benefit from cholesterol-lowering therapy should be greater than in younger individuals. This point, although not widely appreciated, has important implications for treating hypercholesterolemia in the elderly.

BENEFITS OF LIPID LOWERING IN THE ELDERLY

Clinical trials — The secondary prevention trials of LDL-cholesterol lowering therapies have shown a reduction in cardiac events and all cause mortality (see "Clinical trials of cholesterol lowering in patients with cardiovascular disease or diabetes"). However, these studies had only limited data in older subjects. Nevertheless, subgroup analysis of trials that included elderly individuals suggests that they have a similar benefit from lipid lowering therapy as younger subjects [2,16-21].

- The Scandinavian Simvastatin Survival Study (4S trial) included 1021 patients greater than 65 years of age with angina or a previous myocardial infarction and hypercholesterolemia (baseline plasma total cholesterol levels between 212 and 309 mg/dL [5.5 and 8.0 mmol/L]) [16]. Similar reductions in serum lipids were observed among elderly and younger individuals. In the older patients, treatment with simvastatin reduced all cause mortality (34 percent lower), mortality from coronary heart disease (43 percent), major coronary events (34 percent), and the number of revascularization procedures (41 percent).

- The Cholesterol and Recurrent Events (CARE) trial included 1283 patients between the ages of 65 and 75 who had average levels of total, LDL and HDL cholesterol of 209 mg/dL, 139 mg/dL, and 39 mg/dL (5.4, 3.6, and 1.0 mmol/L) [18]. Reductions in coronary events were similar to the 4S trial (figure 4). It was estimated that for

every 1000 older patients treated, 225 cardiovascular hospitalizations and 207 cardiovascular events would be prevented compared with 121 hospitalizations and 150 cardiovascular events in 1000 younger patients [18,19].

- The LIPID trial included 3514 patients between the ages of 65 and 75 years who had a prior infarction or unstable angina in addition to a baseline serum cholesterol of 155 to 271 mg/dL (4 to 7 mmol/L) [20]. Although the risk of all cardiovascular events and all-cause mortality were reduced by pravastatin therapy to a similar degree in older and younger patients, the absolute benefit was greater in the elderly because of a greater risk for these events; fewer elderly patients needed to be treated to prevent one death from any cause (22 versus 46 for younger patients), one death from CHD (35 versus 71), one cardiovascular death (28 versus 61), one fatal or nonfatal MI (30 versus 36), or one stroke (79 versus 170).

- The Heart Protection Study included over 20,000 patients with varying lipid profiles (33 percent had baseline LDL cholesterol <116 mg/dL [<3 mmol/L], 25 percent had a level of 116 to 135 mg/dL [3 to 3.5 mmol/L], and 42 percent had levels >135 mg/dL [>3.5 mmol/L]) who were randomly assigned to simvastatin or placebo [21]. Entry criteria were age 40 to 80 years, a history of cardiovascular disease (coronary cerebrovascular, or peripheral vascular disease), diabetes mellitus, or treated hypertension. Thus, most patients were treated for secondary prevention. Treatment with simvastatin was associated with a reduction in cardiovascular events that was similar in patients above and below age 65. (See "Clinical trials of cholesterol lowering in patients with cardiovascular disease or diabetes", section on 'Heart Protection Study'.)

- Similarly, in the CARDS study in patients with type 2 diabetes without known CHD, atorvastatin 10 mg daily reduced first major cardiovascular events by 37 percent in patients younger than 65 and by 38 percent in patients 65 and older [22].

- In the TNT (Treating to New Targets) study, atorvastatin 80 mg versus 10 mg in 10,001 patients with stable CHD significantly decreased the risk for major cardiovascular events in those both ages 65 and older (n = 3809) and in younger patients [23,24]. (See "Clinical trials of cholesterol lowering in patients with cardiovascular disease or diabetes", section on 'TNT trial'.)

Similar findings were noted in an analysis of pooled data from three randomized trials of pravastatin involving 19,768 patients (CARE, LIPID, and WOSCOPS) [25]; two of these are discussed individually above. The relative reduction in the risk of cardiac events was comparable for patients ages <55 years, 55 to 64 years, and 65 to 75 years (32, 21, and 26, respectively).

Subgroup analyses from primary prevention trials of statins, including AFCAPS/TexCAPS, and ASCOT-LLA found similar relative effects of therapy on clinical endpoints in younger and older individuals [26-28]. In JUPITER, a large trial of rosuvastatin in patients with low-to-average LDL-C levels and elevated c-reactive protein levels, although the relative risk reductions were similar in older and younger patients, the absolute reduction in the primary composite cardiovascular endpoint was 0.77 events per 100 patient-years in the 5695 patients ages 70 and older, which was greater than the reduction of 0.52 events per 100 patient-years seen in the 12,107 patients ages 50 to 69 [28].

Other studies that specifically included older adult patients add further evidence that treatment of hypercholesterolemia in older adults provides similar benefits to that of treatment in younger people [29,30]:

- The PROSPER trial randomly assigned 5804 men and women ages 70 to 82 years with a history of or risk factors for vascular disease to pravastatin (40 mg per day) or placebo [30]. During a mean follow-up of only three years, pravastatin treatment was associated with both significantly lower LDL concentrations and a significantly reduced risk of the primary end point (coronary death, nonfatal myocardial infarction, and fatal or nonfatal stroke, hazard ratio [HR] 0.81, 95% CI 0.74-0.97). Stroke risk alone was unaffected by therapy, but pravastatin was associated with significantly lower risk of coronary death and nonfatal myocardial infarction. There was, however, no significant reduction in all-cause mortality (HR 0.97, CI 0.83-1.14), and there was a significant increase in new diagnoses of cancer (HR 1.25, CI 1.04-1.51). The authors performed a meta-analysis of statin trials including PROSPER and found no overall evidence of an increased risk of cancer with statins (HR 1.02, CI 0.96-1.09). (See "Statins: Actions, side effects, and administration", section on 'Side

effects'.)

- The SAGE trial compared intensive and moderate statin therapy in patients with known CHD ages 65 to 85 who had at least one episode of ischemia on baseline screening with 48-hour ambulatory monitoring [31]. Patients were randomly assigned to treatment with atorvastatin 80 mg daily or pravastatin 40 mg daily. There was no difference between the two groups in the primary endpoint of duration of ischemia on ambulatory monitoring at month 12. However, there was a trend toward a reduction in a composite endpoint of major cardiovascular events with intensive therapy (HR 0.71, CI 0.46-1.09), and a post-hoc analysis found a reduction in mortality (HR 0.33, CI 0.13-0.83). In contrast, no similar reduction in mortality was seen with intensive statin therapy in patients ages 65 and older (n = 3809) in the TNT trial (HR 1.08, CI 0.87-1.33) [24,32]. (See "Clinical trials of cholesterol lowering in patients with cardiovascular disease or diabetes", section on 'TNT trial' and "Intensity of lipid lowering therapy in secondary prevention of cardiovascular disease".)

A meta-analysis of eight randomized trials of primary prevention with statins that included patients ages 65 and older (n = 24,627; including all the primary prevention trials discussed above except for SAGE), found that statin therapy reduced the risk of stroke (relative risk [RR] 0.76, 95% CI 0.63-0.93) and myocardial infarction (RR 0.61, CI 0.43-0.85), but found no statistically significant reduction in mortality (RR 0.94, CI 0.86-1.04) or cardiovascular mortality (RR 0.91, CI 0.69-1.20) [33]. The confidence intervals around these point estimates all include the levels of risk reduction seen with statin therapy in primary prevention in other age groups.

Despite the apparent benefits of statin therapy, adherence declines substantially with time in older adult patients [34,35]. This occurs even when cost is not an issue. The adherence rate is similar to that observed for treatment of hypertension, another asymptomatic condition.

Time course for CHD benefit — The prevention of CHD in elderly subjects has been hindered by the perception that LDL lowering therapy requires many years before the course of atherosclerosis can be altered. This concept has been challenged by the observation that clinical benefits are seen as early as **six months to two years** (figure 5), in many cases before atherosclerosis regression has occurred [36-38]. In addition, statin therapy can improve endothelial dysfunction within three days of initiating therapy [39]. (See "Mechanisms of benefit of lipid-lowering drugs in patients with coronary heart disease".)

Side effects — The safety of lipid lowering agents in older subjects was evaluated in two double-blind, placebo-controlled trials that included 573 patients over the age of 64 [40,41]. Treatment with lovastatin or pravastatin was associated with a fall in cholesterol levels similar to that seen in younger subjects. There was no statistically significant difference in side effects between the treatment and placebo groups. Neither trial provided information regarding the effect of therapy on morbidity and mortality.

An analysis from the CARDS study of atorvastatin 10 mg daily in patients with type 2 diabetes without known CHD found similar rates of adverse events in patients younger than age 65 and in those ages 65 and older [22]. For both younger and older patients, the rates of adverse events were no different with atorvastatin or placebo.

Summary

The decision whether to treat high or high-normal serum cholesterol in an elderly individual needs to be individualized, being based upon both chronological and physiologic age [42]. As an example, a patient with a limited life span from a concomitant illness is probably not a candidate for drug therapy. On the other hand, an otherwise healthy elderly individual should not be denied drug therapy simply on the basis of age alone [2].

The studies described above support the use of lipid lowering therapy for **secondary prevention** in older patients with established CHD who do not have life-limiting comorbid disease [16-18,20,21]. These patients should be treated similar to younger patients according to the guidelines established by the National Cholesterol Education Program (see "Treatment of lipids (including hypercholesterolemia) in secondary prevention") [1,2]. There are limited data on the value of treating elderly patients with low HDL-cholesterol (<40 mg/dL [1.03 mmol/L]), but again,

presumably the same principles would apply as in younger patients. (See "HDL-cholesterol: Clinical aspects of abnormal values".)

In comparison, there are more limited data concerning the use of lipid lowering for **primary prevention** of CHD in elderly hypercholesterolemic patients. Because of the progressive elevation in total and LDL cholesterol levels with aging (figure 2), it has been estimated 40 percent or more of those above age 65 meet the National Cholesterol Education Program guidelines for treating hypercholesterolemia (see "Treatment of lipids (including hypercholesterolemia) in primary prevention") This would entail a large annual cost.

On the other hand, over 50 percent of older individuals will eventually die from cardiovascular disease and data from the Cardiovascular Health Study suggest significant benefit from primary prevention in patients ages 65 and older [43].

Despite their proven benefit, lipid-lowering drugs are markedly underutilized in elderly patients. This was illustrated in a prospective study of 500 patients with a mean age of 81 years and a Q wave myocardial infarction [44]. Although 67 percent had a serum LDL-cholesterol concentration above 125 mg/dL (3.2 mmol/L); only 5 percent were treated with a lipid-lowering drug. A retrospective cohort study of 396,077 high-risk elderly patients found that prescription of statins decreased with increasing age and also with increasing cardiovascular risk and risk of death; thus, the elderly patients likely to get the greatest absolute benefit from statins appear least likely to receive them [45].

ADDITIONAL ISSUES IN OLDER ADULTS

Secondary causes — Older adult patients commonly have medical conditions that may contribute to dyslipidemia. Etiologies to consider include hypothyroidism, diabetes mellitus, and nephrotic syndrome. Therapies may also contribute to dyslipidemias. As examples, thiazide diuretics can affect lipid metabolism, and antipsychotics used for agitation in dementia can produce weight gain. (See "Secondary causes of dyslipidemia".)

Dietary modifications — While therapeutic lifestyle changes involving exercise and diet are generally the first line of treatment for dyslipidemias, providers should avoid dietary restrictions in older patients who are at high risk of malnutrition. These include patients with dementia or physical disabilities that limit their access to adequate nutrition. (See "Treatment of dementia", section on 'Nutrition'.)

Drug interactions and side effects — Elderly patients are frequently treated with multiple medications and so are at increased risk for complications of drug interactions. As an example, macrolide antibiotics can raise statin levels and thus the risk of muscle toxicity (see "Statins: Actions, side effects, and administration"). Providers should be particularly cautious of such interactions in older patients.

Additionally, older adult patients may have greater susceptibility to medication side effects, such as bloating and constipation with bile acid sequestrants, and hyperglycemia and gout with niacin. (See "Lipid lowering with drugs other than statins and fibrates", section on 'Bile acid sequestrants' and "Lipid lowering with drugs other than statins and fibrates", section on 'Nicotinic acid (Niacin)'.)

SUMMARY AND RECOMMENDATIONS

- Coronary heart disease (CHD) is the most common cause of death in older patients, and, as in younger patients, dyslipidemia is associated with an increased risk of CHD. (See 'Cardiovascular disease in older adults' above.)
- Although the relative risk of hypercholesterolemia is somewhat lower in older patients, the absolute risk is higher than in younger patients. (See 'Relative risk versus attributable risk' above.)
- The relative benefit of lipid lowering therapy in older patients is similar to that in younger patients, and the absolute benefit is typically greater than in younger patients. Particularly in secondary prevention, the absolute benefits are large enough that many older patients with CHD would benefit from lipid-lowering therapy, and older patients with a reasonable life expectancy may also benefit in primary prevention. Side

effects of lipid lowering therapy may also be similar in older and younger patients. (See 'Benefits of lipid lowering in the elderly' above.)

- Reductions in events with statin therapy can occur quickly (within weeks to months), and so even in older patients such therapy can be expected to reduce events during a patient's expected lifespan. (See 'Time course for CHD benefit' above.)
- Secondary causes of dyslipidemia such as hypothyroidism, diabetes, nephrotic syndrome, and drug effects should be considered, particularly in older patients. (See "Secondary causes of dyslipidemia".)

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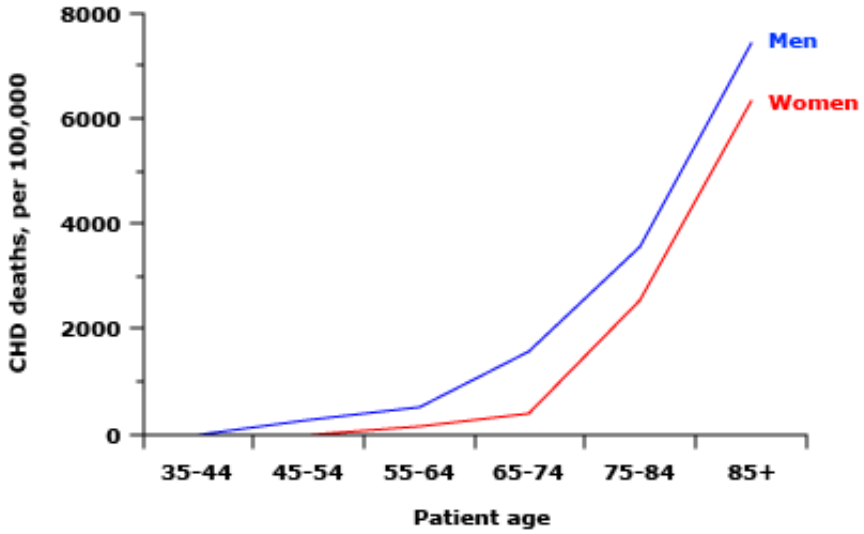
Topic 4569 Version 10.0

GRAPHICS

Increase in coronary deaths with age

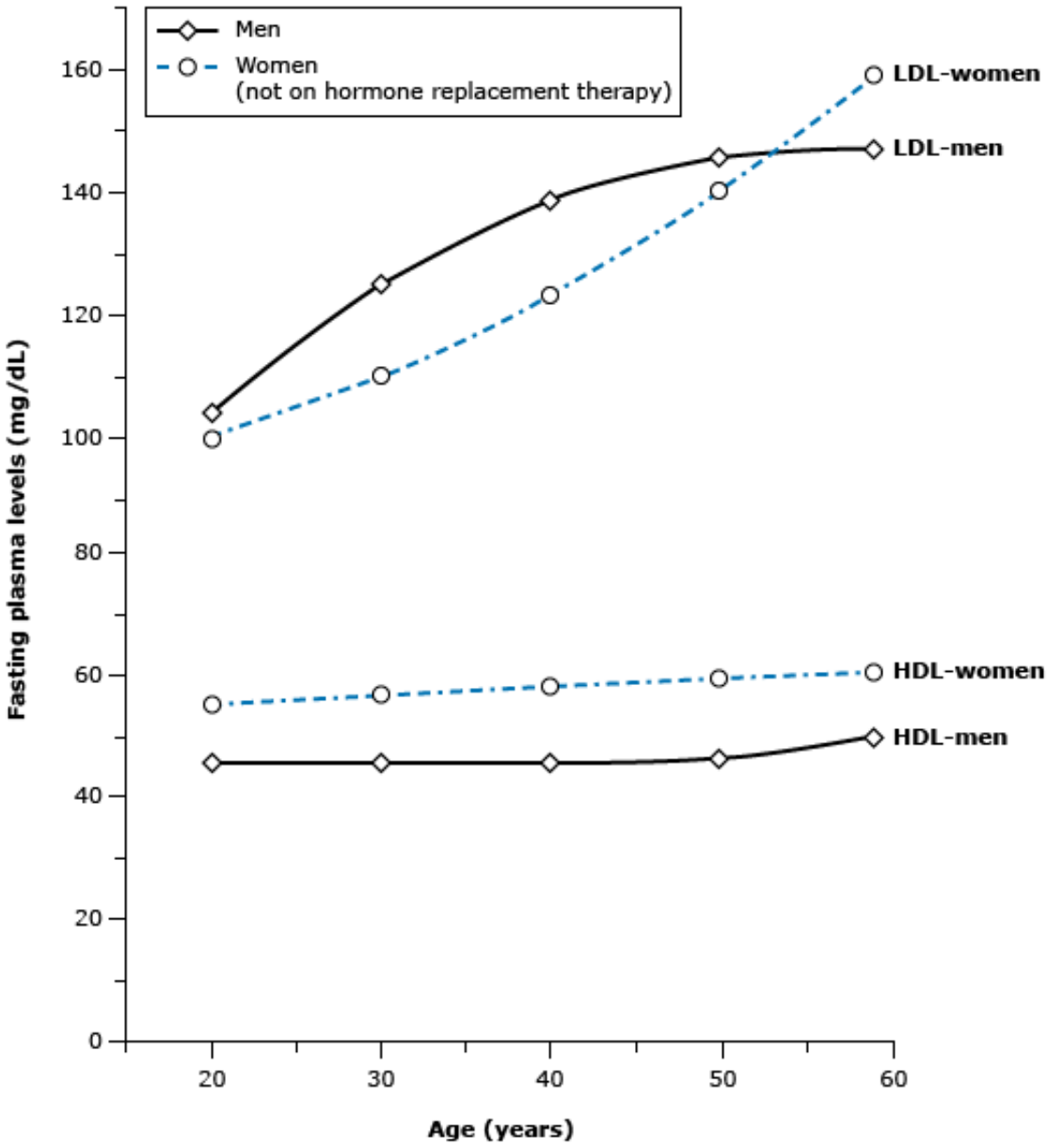


Death rates from coronary heart disease (CHD) in men and women with increasing age. The mortality rate rises dramatically in the elderly.

Data from Sullivan, JT, Prospect Biol Med 1983; 26:658.

Graphic 77317 Version 1.0

Change in lipid levels with age

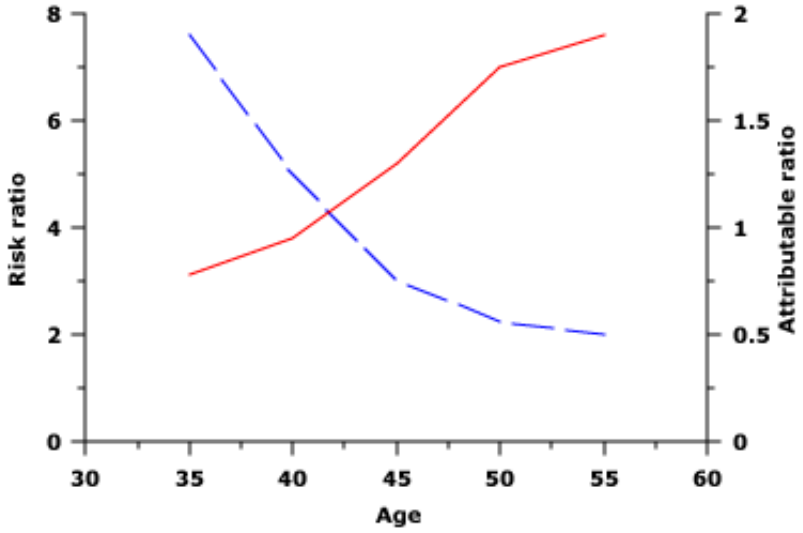


Changes in plasma LDL- and HDL-cholesterol concentrations with age in men and women. LDL-cholesterol levels rise with age; this effect is initially more prominent in men but, by age 70, LDL-cholesterol levels are higher in women.

Data from: Heiss G, Tamir I, Davis CE, et al, Circulation, 1980; 61:302.

Graphic 61522 Version 3.0

Age-related changes in risk for CHD

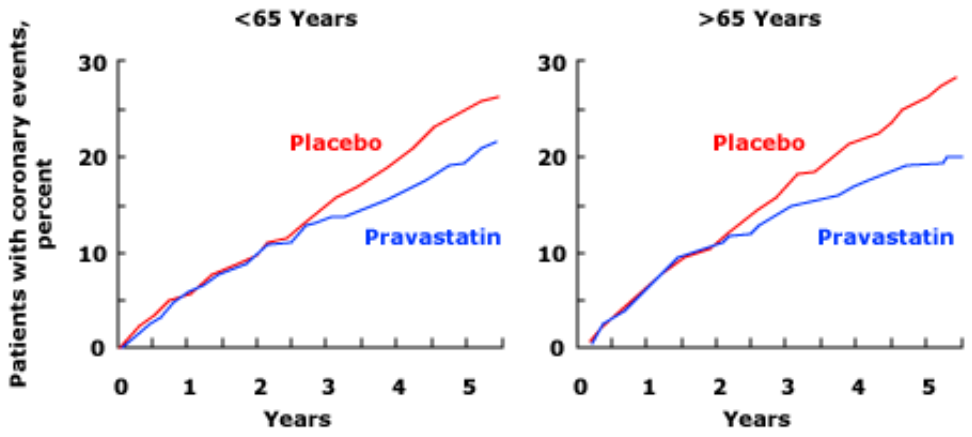


Changes in risk ratio (dashed line) and attributable risk for coronary heart disease (CHD) with age (solid line). Although the risk ratio (relative risk) declines with age, the increasing prevalence of CHD in older patients results in an increase in attributable (absolute) risk.

Data from Malenka, DJ, Baron, JA, Arch Intern Med 1988; 148:2247.

Graphic 63524 Version 1.0

Benefit of lipid lowering with pravastatin is greater in the elderly

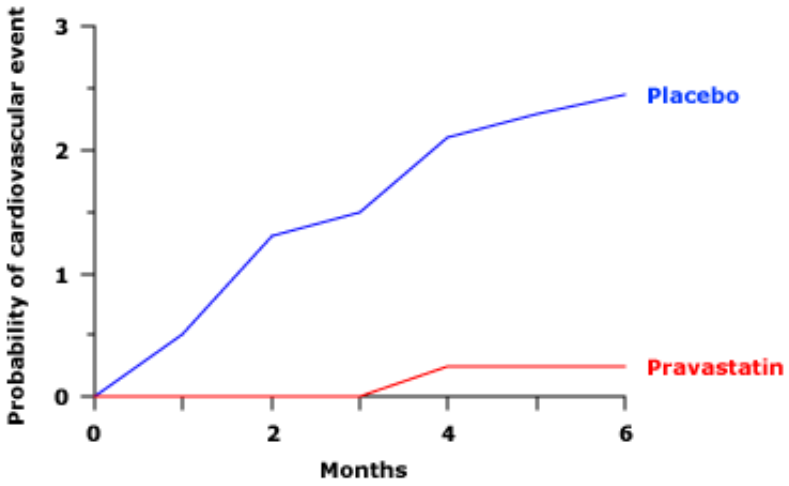


Kaplan-Meier estimates from the CARE trial of patients with a recent history of myocardial infarction who had "average" lipid levels. Pravastatin lowered the incidence of coronary events (cardiac mortality, nonfatal myocardial infarction, coronary artery bypass grafting, and angioplasty) in all age groups but the percentage relative risk reduction attributable to pravastatin was more prominent in the elderly (32 versus 19 percent in younger patients).

Data from Lewis, SJ, Moye, LA, Sacks, FM, et al, for the CARE Investigators. Ann Intern Med 1998; 129:681.

Graphic 81441 Version 1.0

Pravastatin improves outcome in hypercholesterolemia



Probability (in percent) of a cardiovascular event in patients with a plasma cholesterol concentration between 200 and 300 mg/dL (5.2 to 6.2 mmol/L) and two additional coronary risk factors who were treated with placebo or pravastatin. Pravastatin diminished the incidence of cardiovascular events, a benefit that was demonstrated within six months.

Data from The Pravastatin Multinational Study Group for Cardiac Risk Patients, Am J Cardiol 1993; 72:1031.

Graphic 62070 Version 1.0

Disclosures

Disclosures: **Robert S Rosenson, MD** Grant/Research/Clinical Trial Support: Amgen [Lipids (Evolocumab)]; Sanofi [Lipids (Alirocumab)]; As (Relovir)]; Astra Zeneca [Lipids (Evolocumab)]; Genzyme [Lipids (Epanova)]; Sanofi [Lipids (Mipomersen)]; GlaxoSmithKline [Lipids (Alirocuma (alirocumab)]; Sanofi [LDL cholesterol treatment (alirocumab)]. **Kenneth E Schmader, MD** Grant/Research/Clinical Trial Support: Merck [Herp (Spouse): Bonfire Development Advisors [CBT (iCBT)].

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