Review

Cholesterol lowering in the older population: time for reassessment?

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Summary

Hypercholesterolaemia is an established major risk factor for coronary heart disease (CHD) in the general population. In the vast majority of studies that focused on this particular age group and carefully eliminated other confounding factors such as co-morbid conditions, hypercholesterolaemia was a risk factor for CHD in the older population. Because the prevalence of CHD increases with advancing age, studies that consider not only the relative risk attributed to cholesterol but also the absolute numbers of people affected, show hypercholesterolaemia to be an even stronger risk factor in the elderly. Large primary and secondary prevention studies of HMG-CoA reductase inhibitors (statins) in the elderly have shown a reduction in major coronary events similar to that observed in the younger age group. The role of hypercholesterolaemia as a risk factor for stroke is less clear, and a major limitation is the heterogeneous nature of the disease. Nevertheless, most studies that evaluated non-haemorrhagic strokes separately showed a positive association with cholesterol levels, and statin therapy is effective in preventing stroke. These data provide a rationale for treating older hypercholesterolaemic people with statins, not only to prevent CHD, but also to prevent stroke.

Introduction

Cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, is the leading cause of morbidity and mortality in elderly men and women.¹ Hypercholesterolaemia is an established major risk factor for CVD in the general population, and the need to treat according to specific guidelines has produced a consensus.² However, the role of hypercholesterolaemia as a risk factor for CVD in older people, and whether to treat it with lipid-lowering medications, remain controversial issues.³ The relationship between serum cholesterol and stroke incidence is debatable, both in general and in older populations,⁴ although recent lipid-lowering trials have clearly shown a beneficial effect of HMG-CoA reductase inhibitors (statins) in reducing strokes in all age groups.⁵⁻⁷ We review current data regarding the role of cholesterol as risk factor for CVD and the results of major clinical trials with statins, in the older population, based on a search of the Medline and Cochrane Library (1989 to present).

Cholesterol as a risk factor for CHD in the older population

Hypercholesterolaemia is a major risk factor for CHD in the general population, according to...
many epidemiological and intervention studies.3,5–8 However in older people, the association between high serum cholesterol levels and CHD is still disputed, because of the results of some of the earlier studies.3,9 For example, the Framingham Heart Study showed a reduction of the CHD risk ratio between the highest and lowest quartiles for total cholesterol, for men 50 years and older, compared to younger men.3 The first report from the EPESE study, which included results for one of the three centres participating, failed to show that cholesterol was a risk factor for CHD in men and women aged > 70 years.9

CHD is the major cause of morbidity and mortality in older people, and the age group > 65 years represents an increasing percentage of the population treated for CHD by the health-care systems.1 The importance of identifying CHD risk factors in this specific population has led in recent years to a re-examination of the role of cholesterol, in large-scale studies focusing on older subjects. In Table 1, we summarize the data from seven large-scale prospective studies, including 22,656 older men and women. Five of the seven studies demonstrated that a high level of serum total cholesterol was a risk factor for CHD in elderly men.10–15 Three out of five studies found that total cholesterol was a significant predictor in women.10,12,14 Two important lessons emerge from these studies. The first, demonstrated by the third report from the EPESE study,10 is the significant effect of adjusting for indicators of health status (serum albumin and iron) and exclusion of first-year events. Only after these adjustments were made did the association between total cholesterol levels and death from CHD become significant. As co-morbid conditions are common in the geriatric population, these results may explain why previous reports from the EPESE study,9,14 and some of the other studies that did not perform these adjustments, showed conflicting results. The second lesson, from the Kaiser Permanente CHD in the Elderly Study, is that the effect of high cholesterol levels with advancing age, may be better estimated by evaluation of the increase in absolute mortality from CHD than by relative risk measures.13 In this study both relative risk and excess risk were used, and while the first statistical analysis remained fairly constant with increasing age, the second showed a marked increase, reaching an excess rate of 11.3 deaths per 1000 person-years in men 75–79-years-old. Manolio et al. analysed data of 25 different populations and found that although relative risks were generally lower in older subjects, the absolute risks were greater.16

Low levels of high-density lipoprotein cholesterol (HDL-C) are another risk factor for CHD in the general population. As shown in Table 1, three of the six studies that reported data on HDL-C levels found that low HDL-C was associated with increased risk for CHD in older men and women.10,12,14 The Dubbo Study found it to be a predictor of CHD in men only.11 The FINE Study, which included only men from three countries, found low HDL-C to be related to CHD mortality in Finnish men, as well as in lean Italian men who drank < 40 g alcohol daily.15

Statin therapy for prevention of CHD in the older population

The advent of statins has revolutionized the treatment of hypercholesterolaemia, as these drugs are highly effective in reducing low-density lipoprotein cholesterol (LDL-C) levels and are generally well tolerated. Most of the data on the effect of statins on preventing CHD in the elderly are derived from secondary-prevention trials. Three of the large secondary-prevention trials, The Scandinavian Simvastatin Survival Study (4S),5,17 Cholesterol and Recurrent Events (CARE)6 and Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID),7 included men and women aged > 65 years. The results of these studies are shown in Table 2. A marked reduction in coronary events in the older age group was found, similar to the reduction observed in patients aged < 65 years.5–7,17 Based on these data, statin therapy may be regarded as part of the standard care of elderly hypercholesterolaemic patients with CHD, along with aspirin, beta-blockers and other accepted therapies. The major limitation of these studies is that they included ‘young’ elderly patients, up to age 75. However, as the results of statin therapy do not show a tendency to decrease with advancing age, it is reasonable to extrapolate these results to the ‘older’ elderly, as long as the patient is in relatively good health.

Only one primary-prevention trial with statins included a large number of older people: the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).18 The 6605 participants in the trial included 1416 men and women aged ≥ 65 years. The results (Table 2) showed a marked reduction of 37% in major coronary events in the whole group, and similar results were observed in the older age group. No significant adverse events were reported related to drug therapy in this study. The study suggests that primary prevention with statin therapy is beneficial in the elderly, at least in the ‘young’ elderly, without significant adverse effects. Based upon these data, a recent statement
<table>
<thead>
<tr>
<th>Study, year, reference</th>
<th>Subjects (n) (male/female)</th>
<th>Age (years) (mean)</th>
<th>Follow-up (years)</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPESE, 1994&lt;sup&gt;9&lt;/sup&gt;</td>
<td>997 (387/610)</td>
<td>&gt; 70 (79)</td>
<td>4</td>
<td>CHD mortality</td>
<td>OR 0.6 (0.2–2.0)</td>
<td>OR 1.2 (0.4–3.2)</td>
</tr>
<tr>
<td>EPESE, 1995&lt;sup&gt;14&lt;/sup&gt;</td>
<td>3904 (1377/2527)</td>
<td>≥ 71 (79)</td>
<td>4</td>
<td>CHD mortality</td>
<td>RR: men 1.0 (0.5–2.0); women 1.8 (1.03–3.0)</td>
<td>RR 2.5 (1.6–4.0)</td>
</tr>
<tr>
<td>EPESE, 1997&lt;sup&gt;10&lt;/sup&gt;</td>
<td>4066 (men and women)</td>
<td>≥ 65 (79)</td>
<td>5</td>
<td>CHD mortality</td>
<td>RR 1.6 (1.1–2.3)</td>
<td>RR −2.2 (1.4–3.4)*</td>
</tr>
<tr>
<td>Kaiser Permanente CHD in the Elderly Study, 1990&lt;sup&gt;13&lt;/sup&gt;</td>
<td>2746 (men only)</td>
<td>60–79</td>
<td>10</td>
<td>CHD mortality</td>
<td>RR 1.5 (1.2–2.0)</td>
<td>ER 4.3 (1.3–7.2)</td>
</tr>
<tr>
<td>Dubbo Study, 1995&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2805 (1236/1569)</td>
<td>≥ 60 (69)</td>
<td>5</td>
<td>CHD event</td>
<td>RR: men 1.2 (1.1–1.5); women 0.96 (0.8–1.1)</td>
<td>RR: men 1.2 (1.02–1.5); women 1.1 (0.9–1.3)</td>
</tr>
<tr>
<td>Rotterdam Study, 1999&lt;sup&gt;12&lt;/sup&gt;</td>
<td>6006 (2453/3553), 2580</td>
<td>≥ 55 (69)</td>
<td>4</td>
<td>MI</td>
<td>RR: men 1.9 (1.1–3.3); women 3.2 (1.5–6.4)</td>
<td>RR: men 2.1 (1.1–4.0); women 2.3 (1.1–4.5)</td>
</tr>
<tr>
<td>FINE Study, (Finland, Italy, Netherlands), 2000&lt;sup&gt;15&lt;/sup&gt;</td>
<td>2132 (men only)</td>
<td>65–84</td>
<td>10</td>
<td>CHD mortality</td>
<td>RR 1.17 (1.06–1.29)**</td>
<td>HDL-C was only related in Finland: RR 1.07 (1.01–1.13)**</td>
</tr>
</tbody>
</table>

EPESE, Established Populations for Epidemiological Studies of the Elderly; MI, myocardial infarction; CHD, coronary heart disease; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; RR, relative risk; ER, excess risk. *Approximation of 95% CI; **per each 1 mmol/l change in lipoprotein.
article was published by the Committee of the National Cholesterol Education Program, suggesting consideration of drug therapy for primary prevention in elderly patients with significant hypercholesterolaemia, according to: (i) the general health status and functional capacity of the elderly individual; and (ii) CHD risk stratification. According to these guidelines, drug therapy should be considered in elderly patients without debilitating diseases with a very high LDL-C, >190 mg/dl (corresponding roughly to a total cholesterol of 270 mg/dl), or in patients with an LDL-C in the range of 160–189 mg/dl (corresponding roughly to a total cholesterol 240–269 mg/dl) with two or more CHD risk factors. Total cholesterol may serve as a screening measure; however, we recommend that in cases in which total cholesterol is >240 mg/dl, HDL-C and LDL-C should be determined before deciding upon appropriate therapy.

### Cholesterol as a risk factor for stroke in the older population

The prevalence of stroke, the third leading cause of death and the most prevalent disabling disorder, increases with age and doubles every decade after age 55. The relationship between serum cholesterol and stroke incidence is controversial. One of the major limitations in analysing the possible relationship is the heterogeneous nature of the disease, which includes haemorrhagic and non-haemorrhagic stroke. About 80% of first strokes are non-haemorrhagic, and can be further divided into atherothrombotic, cardioembolic, lacunar, etc. The results from the Kaiser Permanente Medical Care program showed that in men aged 65 or older, low serum cholesterol levels compared with high levels, were associated with a relative risk of 2.7 (95% CI 1.4–5) of intracerebral haemorrhage. Therefore meta-analysis studies such as the Prospective Studies Collaboration, which included studies with no reference to stroke subtype, are difficult to interpret. The heterogeneous nature of non-haemorrhagic stroke may also obscure the possible association with cholesterol, as strokes caused by atherothrombotic process involving extracranial vessels may be more likely to be associated with high cholesterol levels than cardioembolic or lacunar strokes. Determining precisely the aetiology of stroke is technically difficult and not carried out routinely, and therefore data from most existing studies are incomplete.

In Table 3a, we summarize three case-control studies that include data on older patients with ischaemic strokes, and all of them showed significant correlation between cholesterol and stroke. In cases in which total cholesterol is >240 mg/dl, HDL-C and LDL-C should be determined before deciding upon appropriate therapy.

### Table 2  CHD prevention trials in older people

<table>
<thead>
<tr>
<th>Trial, year, reference</th>
<th>Patients ((n))</th>
<th>Age (years)</th>
<th>Drug</th>
<th>Follow-up (years)</th>
<th>Clinical end point</th>
<th>Relative risk reduction (%)(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S, 1997(^{17})</td>
<td>1848</td>
<td>&gt;65</td>
<td>Simvastatin</td>
<td>5.4</td>
<td>Major coronary event</td>
<td>34 (16–48)</td>
</tr>
<tr>
<td>CARE, 1998(^{6})</td>
<td>1283</td>
<td>65–75</td>
<td>Pravastatin</td>
<td>5</td>
<td>Major coronary event</td>
<td>32 (15–46)</td>
</tr>
<tr>
<td>LIPID, 1998(^{7})</td>
<td>2168</td>
<td>65–69</td>
<td>Pravastatin</td>
<td>6.1</td>
<td>Major coronary event</td>
<td>26 (11–41)</td>
</tr>
<tr>
<td>AFCAPS/TEXCAPS, 1998(^{18})</td>
<td>1416</td>
<td>&gt;65</td>
<td>Lovastatin</td>
<td>5.2</td>
<td>First acute major coronary event</td>
<td>37 (21–50)</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease; AFCAPS/TEXCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study. *Not significant.

The majority of the patients in these studies underwent computed tomography, and in the study of Hachinski et al., even cases with cardiac source for emboli were excluded. These data may indicate that future studies using sophisticated diagnostic modalities may demonstrate more compelling evidence for the association between stroke and cholesterol. The inclusion of cases with ischaemic strokes, and all of them showed significant correlation between cholesterol and stroke. In Table 3b, we summarize two prospective observational studies that included elderly people. The Honolulu Heart Project, an epidemiological study of men of Japanese ancestry, evaluated the association between cholesterol and CHD and thromboembolic stroke in a large cohort aged 51–74 years, including 2872 men aged 60–74 years. In the older age group, there was a significant correlation between total cholesterol and stroke.

In Table 3b, we summarize two prospective observational studies that included elderly people. The Honolulu Heart Project, an epidemiological study of men of Japanese ancestry, evaluated the association between cholesterol and CHD and thromboembolic stroke in a large cohort aged 51–74 years, including 2872 men aged 60–74 years. In the older age group, there was a significant correlation between total cholesterol and stroke.

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In Table 3a, we summarize three case-control studies that include data on older patients with ischaemic strokes, and all of them showed significant correlation between cholesterol and stroke. The majority of the patients in these studies underwent computed tomography, and in the study of Hachinski et al., even cases with cardiac source for emboli were excluded. These data may indicate that future studies using sophisticated diagnostic modalities may demonstrate more compelling evidence for the association between stroke and cholesterol. One limitation of case-control studies can be a drop in cholesterol levels during hospitalization; however this would tend to underestimate the association between cholesterol and stroke. Another limitation in some studies is the exclusion of fatal cases.

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### Table 3a  Stroke and cholesterol levels in older people: case-control studies

<table>
<thead>
<tr>
<th>Study or source, year, reference</th>
<th>No. of patients (male/female)</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxfordshire Community Stroke Project, 1991&lt;sup&gt;24&lt;/sup&gt;</td>
<td>105 (68/37)</td>
<td>68 (mean)</td>
<td>TIA, minor ischaemic stroke</td>
<td>OR 1.7 (0.9–3.3)</td>
<td>CT done in all patients with strokes and 74% with TIA</td>
</tr>
<tr>
<td>Di Mascio et al., 1995&lt;sup&gt;25&lt;/sup&gt;</td>
<td>230 (154/76)</td>
<td>64 (mean)</td>
<td>Ischaemic stroke</td>
<td>OR 2.6 (1.4–4.8)</td>
<td>CT done in all patients</td>
</tr>
<tr>
<td>Hachinski et al., 1996&lt;sup&gt;26&lt;/sup&gt;</td>
<td>90 (61/29)</td>
<td>65 (mean)</td>
<td>Ischaemic stroke</td>
<td>OR 1.7 (1.2–2.5)</td>
<td>Strokes or TIA attributable to non-atherosclerotic process excluded</td>
</tr>
</tbody>
</table>

*Per 1 mmol/l increase in lipid parameter. RR, relative risk; AF, aetiological fraction (proportion of all cases of stroke in the target population attributable to high TC or low HDL-C); OR, odds ratio; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TIA, transient ischaemic attack; CT, computed tomography.

### Table 3b  Stroke and cholesterol levels in older people: prospective observational studies

<table>
<thead>
<tr>
<th>Study or source, year, reference</th>
<th>No. of patients (male/female)</th>
<th>Age (years)</th>
<th>Outcome and years of follow-up</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copenhagen City Heart Study, 1994&lt;sup&gt;29&lt;/sup&gt;</td>
<td>11 358 (men and women)</td>
<td>20–80</td>
<td>Stroke and TIA, 6 years</td>
<td>RR 1.12* (1.01–1.16)</td>
<td>TC was significantly associated with stroke only at levels &gt;300 mg/dl and the correlation decreased with age. CT or autopsy were not consistently done</td>
</tr>
<tr>
<td>Honolulu Heart Program, 1994&lt;sup&gt;28&lt;/sup&gt;</td>
<td>2872 (men only)</td>
<td>60–74</td>
<td>Thrombo-embolic stroke, 15 years</td>
<td>RR 1.6 (1.2–2.3)</td>
<td></td>
</tr>
</tbody>
</table>

*Per 1 mmol/l increase in lipid parameter. RR, relative risk; OR, odds ratio; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TIA, transient ischaemic attack; CT, computed tomography.
large prospective observational study that included men and women aged 20–80, did not show a linear correlation between total cholesterol and stroke.\(^{29}\) The only correlation found was between cholesterol levels > 300 mg/dl and non-haemorrhagic stroke. This association decreased with advancing age. However, a limitation of this study is that the diagnosis of non-haemorrhagic and haemorrhagic stroke was based on the results of computed tomography or autopsy in fewer than half of the cases. In conclusion, although the role of hypercholesterolaemia in stroke is still inconclusive, most studies that carefully evaluated non-haemorrhagic strokes have shown a positive association with cholesterol levels.

**Trials on stroke prevention with statins in older patients with CHD**

Trials in the pre-statin era did not show beneficial effect of treatment on stroke risk in middle-aged men, and studies using clofibrate even showed an increased risk of fatal strokes.\(^{30}\) The large statin trials have conclusively demonstrated for the first time a marked stroke reduction: a meta-analysis of 12 primary and secondary intervention trials with statins showed an overall reduction of 27% (\(p = 0.001\)).\(^{31}\) The strongest evidence comes from the secondary prevention trials including patients with CHD.\(^{5,7}\) In the Scandinavian Simvastatin Survival Study, which included 4444 men and women aged 35–70, a 30% relative risk reduction for stroke was found in patients receiving simvastatin compared to the placebo group.\(^{5}\) The LIPID trial included 9014 men and women with a mean age of 61 years, and showed a 19% relative risk reduction for stroke in patients receiving pravastatin.\(^{7}\) In the CARE study, a separate analysis of 2129 men and women aged >60 years showed a 35% relative risk reduction for stroke and TIAs. Notably, patients in the older age group benefited more than patients <60 years of age.\(^{6}\) The data from these three large trials show a risk reduction of stroke by statins that is comparable to that achieved by conventionally accepted treatments such as anti-platelet or anti-hypertensive medications.

The marked decrease in stroke rate in these studies caused by statins, which is not fully explained by cholesterol reduction alone, and the discrepancy between the therapeutic efficacy achieved with statins and the lack of beneficial effect with the other lipid-lowering treatments, has led to consideration of other possible mechanisms beyond cholesterol reduction.\(^{32}\) The other possible beneficial effects include: plaque stabilization, suppression of inflammation, improving endothelial dysfunction and effects on platelet function and coagulation. As statins may reduce stroke by mechanisms that go beyond cholesterol reduction, further studies are needed in determining their role in normocholesterolaemic patients who are at high risk for developing stroke.

**References**


