Continuation of Statin Treatment and All-Cause Mortality

A Population-Based Cohort Study

Varda Shalev, MD; Gabriel Chodick, PhD; Haim Silber, MD; Ehud Kokia, MD; Joseph Jan, MHA; Anthony D. Heymann, MD

Background: The beneficial effects of statins on cardiovascular mortality in secondary prevention have been established in several long-term, placebo-controlled trials. However, the value of statin therapy in reduction of overall mortality in patients without coronary heart disease (CHD) is questionable. This study evaluated the effect of statin therapy in subjects with no indication of cardiovascular disease (primary prevention) and patients with known CHD (secondary prevention).

Methods: This retrospective cohort study included 229,918 adult enrollees in a health maintenance organization in Israel who initiated statin treatment from 1998 through 2006 (mean age, 57.6 years; 50.8% female). Proportion of days covered (PDC) with statins was measured by the number of dispensed statin prescriptions during the interval between the date of the first statin prescription and the end of follow-up.

Results: During a mean of 4.0 and 5.0 years of follow-up, there were 4259 and 8906 deaths among the primary prevention and secondary prevention cohorts, respectively. In both cohorts, continuity of treatment with statins (PDC, ≥90%) conferred at least a 45% reduction in risk of death compared with patients with a PDC of less than 10%. A stronger risk reduction was calculated among patients with high baseline low-density lipoprotein cholesterol level and patients initially treated with high-efficacy statins.

Conclusions: Better continuity of statin treatment provided an ongoing reduction in mortality among patients with and without a known history of CHD. The observed benefits from statins were greater than expected from randomized clinical trials.

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The beneficial effects on cardiovascular mortality of treatment with statins to decrease levels of low-density lipoprotein cholesterol (LDL-C) have been established in several long-term, placebo-controlled trials. Following these clinical findings, the National Cholesterol Education Program Adult Treatment Panel III has recommended setting LDL-C targets that depend on a patient’s individual risk.

Primary prevention refers to efforts to modify risk factors or prevent their development with the aim of delaying or preventing the onset of coronary heart disease (CHD). A secondary prevention strategy is aimed at both control of risk factors and direct therapeutic protection of coronary arteries from recurrent CHD events leading to decreased coronary mortality in patients with established CHD. The value of primary prevention with statin therapy in the reduction of overall mortality has recently been questioned.

Because clinical trials do not usually include individuals with multiple comorbid conditions or those receiving an extensive list of medications, there are considerable concerns regarding the applicability of findings from randomized clinical trials to the general population of patients seen in routine clinical practice. A pooled analysis of 8 randomized trials in primary prevention populations showed that statins did not reduce overall mortality, indicating that lipid-lowering therapy with statins should not be prescribed for true primary prevention in women of any age or in men older than 69 years.

In light of the controversy surrounding lipid-lowering treatment for reduction of mortality among primary prevention populations, we undertook the present study to evaluate the effect of statin therapy in a large and diverse cohort of patients treated for dyslipidemia in a single health maintenance organization.
METHODS

SOURCES OF DATA

The present retrospective cohort study was carried out at Maccabi Healthcare Services (MHS), a 1.7 million–enrollee health maintenance organization operating in Israel. All MHS enrollees may fill prescriptions at pharmacies throughout the country and pay a minimal copayment with each prescription (usually $3 per 30-day supply of medication). All data were obtained from MHS automated databases that have previously been described and were used to elicit information on all dispensed community prescriptions, hospital discharge data, and biochemistry results, using a unique 9-digit national identification number for each patient. The study was approved by the MHS institutional review board.

COHORT DEFINITION

The cohort included members who were continuously enrolled in the plan since at least 1995. New users of statins were identified among all MHS enrollees aged 18 years or older who, from January 1, 1998, to December 31, 2006, had at least 1 dispensed prescription of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (eg, lovastatin, pravastatin sodium, or simvastatin). The date of the first purchased statin was defined as the index date. We selected included patients who were enrolled in MHS and did not have a statin prescription for at least 3 years before the index date. Using a drug database search for any statin agent dispensed during the study period, we were able to assemble a cohort of 229,918 eligible patients.

PRIMARY PREVENTION AND SECONDARY PREVENTION COHORTS

The study assessed risk of mortality in 2 separate cohorts: (1) a primary prevention cohort of subjects with no indication of CHD or other cardiovascular disease, as evidenced by the absence of clinical diagnosis of cardiovascular disease at baseline, and (2) a secondary prevention cohort of patients with coronary artery disease who were identified from the MHS registry of cardiovascular diseases. This registry includes all patients with diagnosed cardiovascular diseases (eg, ischemic heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular diseases, atrial fibrillation) that are classified according to the International Classification of Diseases, Ninth Revision codes, or patients with previous coronary artery bypass grafting or percutaneous coronary intervention classified with the use of relevant Current Procedural Terminology codes. Registry patients were routinely identified by a computerized search of personal medical record files, hospitalizations, medical procedures, laboratory tests, medications, signals, images, and reports from investigations.

PROPORTION OF DAYS COVERED

In accordance with previous studies, we calculated the mean proportion of days covered (PDC) by dividing the quantity of statins dispensed by the total interval from index date to death, leaving MHS, or December 31, 2006, whichever occurred earlier.

STUDY OUTCOME

In Israel, mortality data are retrieved from the Israel National Population Registry, which maintains a registry of all citizens and permanent residents. Death records are routinely routed from the Israel National Population Registry to MHS via the National Insurance Institute (NII), usually within a month from the date of death, by means of a unique identification number, facilitating record linkage. Because the MHS public budget is determined by the NII on the basis of a capitation formula that takes into account the number of members, the data regarding deaths are closely supervised. However, we were unable to retrieve the underlying cause of death from death notifications.

DETERMINANTS OF ALL-CAUSE MORTALITY

Demographic variables at index date included baseline values of age, sex, marital status, place of residency, and nationality that were based on place of residency and self-reports to personal marketing questionnaires. The socioeconomic status (SES) was categorized into quintiles according to the poverty index of the member’s enumeration area as defined by the 1995 national census. The poverty index is based on several factors, including household income, educational qualifications, crowding, material conditions, and car ownership. Enrollees who were regularly paid an income support benefit by the NII, which is aimed at assisting individuals and families who are not capable of earning a basic minimum income for subsistence, were categorized into the lowest SES quintile. During the last 2 decades, Israel has absorbed approximately 1 million new immigrants, of whom 85% arrived from the former Soviet Union. To adjust for immigration status, we defined years of living in Israel as the period from the year of immigration to the index date. Native patients were categorized as having lived in Israel 20 years or longer. Disability was determined according to the NII reports on members who are paid a monthly disability pension. Enrollees’ electronic medical records were studied for a diagnosis of chronic conditions such as chronic obstructive pulmonary disease, chronic psychotic disease, morbid obesity, Alzheimer disease, and asthma. Patients with diabetes mellitus were identified by using the MHS computerized diabetes mellitus patient registry. Information on cancer history was provided by the Israel National Cancer Registry, which has been continuously collecting information on diagnosed cancer cases from all medical institutions in Israel since 1960.

Information on health services utilization, such as the number of hospitalizations in general hospitals, visits to outpatient clinics, and filled prescriptions for antihypertensive drugs and diuretics, was based on data collected for the year before the index date. Laboratory test results included liver function tests and the median of all LDL-C tests during the year before the index date.

LIPID-LOWERING PHARMACOTHERAPY

On the basis of previous clinical trials and classification of statin therapy, initial statin therapy was categorized into 3 relative efficacy levels that were determined according to expected amounts of LDL-C reduction from baseline: (1) low efficacy (≤30% LDL-C reduction): daily dose of fluvastatin sodium, 40 mg or less; pravastatin sodium, 40 mg or less; simvastatin, 10 mg or less; cerivastatin sodium, 0.2 mg; or lovastatin, 40 mg or less or 10 mg twice a day; (2) moderate efficacy (31%-40% LDL-C reduction): daily dose of fluvastatin sodium, 80 mg; cerivastatin sodium, 0.3 or 0.4 mg; rosuvastatin calcium, 10 mg or less; simvastatin, 20 mg or 40 mg; or atorvastatin calcium, 10 mg; or (3) high efficacy (≥41% LDL-C reduction): simvastatin, 80 mg; atorvastatin calcium, 20 mg or more; rosuvastatin calcium, 10 mg or more; pravastatin sodium, 80 mg; or lovastatin, 80 mg.

STATISTICAL ANALYSIS

The χ² test for categorical variables and Kruskal-Wallis test for continuous variables were performed to determine significant
differences in baseline characteristics and PDC between primary and secondary prevention cohorts. Cox proportional hazards regression with years of follow-up as the time scale was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs)\(^2\) and to identify variables significantly associated with increased risk of death. Each participant was followed up from the first purchase of a statin until death, leaving MHS, discontinuation of the hypolipidemic treatment, or July 1, 2007, whichever occurred earlier. The maximum follow-up was therefore approximately 9.5 years. Analyses were carried out separately for primary and secondary prevention cohorts. The full multivariate model included the following baseline values: age at baseline (in 1-year categories), sex, marital status, nationality, SES, presence of chronic comorbidities, utilization of health services, LDL-C level, and efficacy of the initial statin therapy. Tests for trend of ordinal variables were based on the category’s median values. Analyses were stratified by age categories, sex, baseline LDL-C levels, and efficacy of initial statin therapy. A \(\chi^2\) test was performed to assess heterogeneity.

**RESULTS**

The median number of health plan enrollees during the study period was more than 1.61 million, with those per-
Table 1. Characteristics of Adults Initiating a New Treatment With a Statin Agent, Maccabi Healthcare Services, Israel, 1998-2006 (continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary Prevention (n=136 052)</th>
<th>Secondary Prevention (n=93 866)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health care services used in year before index date</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of hospitalizations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12 3548 (90.8)</td>
<td>75 704 (80.7)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9400 (6.9)</td>
<td>11 470 (12.2)</td>
<td>.001</td>
</tr>
<tr>
<td>≥2</td>
<td>3104 (2.3)</td>
<td>6692 (7.1)</td>
<td></td>
</tr>
<tr>
<td>No. of outpatient visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7</td>
<td>32 771 (24.1)</td>
<td>16 642 (17.7)</td>
<td>.001</td>
</tr>
<tr>
<td>8-12</td>
<td>28 009 (20.6)</td>
<td>15 674 (16.7)</td>
<td></td>
</tr>
<tr>
<td>13-19</td>
<td>29 913 (22.0)</td>
<td>19 805 (21.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>20-29</td>
<td>23 914 (17.6)</td>
<td>19 358 (20.6)</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>21 445 (15.8)</td>
<td>22 387 (23.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Initial statin therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin at index prescription</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>113 061 (83.1)</td>
<td>68 460 (72.9)</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin sodium</td>
<td>1609 (1.2)</td>
<td>2212 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin calcium</td>
<td>9610 (7.1)</td>
<td>9638 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Pravastatin sodium</td>
<td>9011 (6.6)</td>
<td>8206 (8.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cerivastatin sodium</td>
<td>1388 (1.0)</td>
<td>2315 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>1147 (0.8)</td>
<td>2899 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin calcium</td>
<td>224 (0.2)</td>
<td>134 (0.1)</td>
<td></td>
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<tr>
<td>Statin agent efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>41 933 (30.8)</td>
<td>38 517 (41.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Moderate</td>
<td>86 811 (63.8)</td>
<td>48 657 (51.9)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>7301 (5.4)</td>
<td>6662 (7.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Year of index date</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>12 188 (9.0)</td>
<td>18 066 (19.2)</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>8082 (6.0)</td>
<td>8428 (9.0)</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>9730 (7.2)</td>
<td>8754 (9.3)</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>11 553 (8.5)</td>
<td>8881 (9.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2002</td>
<td>11 172 (8.2)</td>
<td>8013 (8.5)</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>15 854 (11.7)</td>
<td>9965 (10.6)</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>20 918 (15.4)</td>
<td>11 469 (12.2)</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>23 757 (17.5)</td>
<td>10 883 (11.6)</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>22 798 (16.8)</td>
<td>9407 (10.0)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: LDL-C, low-density lipoprotein cholesterol.
SI conversion factor: To convert LDL-C to millimoles per liter, multiply by 0.0259.
* Because of rounding, percentages may not sum to 100.
+ These patients did not undergo tests to determine LDL-C level in the year before the index date but had a known risk of death.
* Or born in Israel.
* Explained in the “Determinants of All-Cause Mortality” subsection of the “Methods” section.
* Explained in the “Lipid-Lowering Pharmacotherapy” subsection of the “Methods” section.

sons 18 years or older accounting for 66% of the population. After the inclusion and exclusion criteria were applied, a total of 93 866 individuals for the secondary prevention group and 136 052 individuals for the primary prevention group were identified as being newly treated with statin agents during the study period. The total study population constituted 21.6% of the MHS adult population. During the study period, 13 165 individuals (5.7%) died and 3745 (1.6%) left MHS.

Baseline characteristics of both cohorts in the year before the index date are given in Table 1. The mean age of these patients was 57.6 years and 50.8% were female. Patients in the secondary prevention group were more likely to be older (61.5 vs 54.8 years), male (55.7% vs 44.3%), have lived in Israel longer, and belong to the highest quintile of SES (22.7% vs 13.1%). In addition, they were more likely to use high-efficacy statin agents as initial therapy, to be hospitalized twice or more (7.1% vs 2.3%), to have a higher number of physician visits, and to have lower median LDL-C levels (154.8 vs 162.5 mg/dL) (to convert to millimoles per liter, multiply by 0.0259). Common comorbid conditions were hypertension, diabetes mellitus, and morbid obesity. In both cohorts, simvastatin was the most frequently used statin agent.

During the mean follow-up of 4.0 and 5.0 years, there were 4259 (7.8 per 1000 person-years) and 8906 (19.0 per 1000 person-years) deaths among subjects in the primary prevention and secondary prevention groups, respectively. Baseline medical characteristics that were associated with increased risk of mortality included diabetes mellitus, cancer, one or more chronic morbidities (among the primary prevention group), use of antihypertensive drugs or diuretics, hospitalizations during the
year before the index date, and LDL-C levels of 190 mg/dL or higher (among the primary prevention group). Frequent visits to physicians during the year before the index date and higher statin efficacy were significantly (P < .001) associated with a mortality risk reduction. The HR associated with 10% PDC was 0.94 (95% CI, 0.93-0.95) and 0.93 (0.93-0.94) in the primary and secondary prevention cohorts, respectively (Table 2). In stratified analyses, the association between continuation of statin therapy (per 10% PDC) and risk reduction among the primary prevention cohort was stronger for patients aged 55 to 64 years (HR, 0.91; 95% CI, 0.89-0.93). Among the secondary prevention group, there was a significant trend (P < .01) toward greater reduction in mortality associated with younger age at baseline, reaching an HR of 0.86 (95% CI, 0.80-0.93) per 10% PDC for patients younger than 45 years (Figure 1). In both cohorts, a stronger risk reduction was calculated among patients with baseline LDL-C levels of 190 mg/dL or higher and patients initially treated with high-efficacy statins.

After adjustment for age and sex, a PDC of 10% to less than 20% was associated with increased risk of mortality compared with patients with a PDC of less than 10% among both primary and secondary prevention cohorts. In higher levels of PDC, a significant negative association was calculated between PDC level and risk of mortality (Table 3). Similar trends were observed after adjustment for baseline values of SES, marital status, nationality, socioeconomic status, years living in Israel, and residence area. These patients did not undergo tests to determine LDL-C level in the year before the index date but had a known HR.
primary prevention and secondary prevention groups, respectively (Table 3).

Medication may be discontinued when a patient becomes acutely ill and at a higher acute risk of death, which could bias results toward observed lower mortality with use of the medication. To further investigate the possibility of such potential bias, we also performed sensitivity analyses by excluding patients with less than 1 year of follow-up since the index date. When these exclusion criteria were applied, a PDC of 10% to less than 20% was no longer associated with an increased risk of mortality and fit with the overall trend. Compared with a PDC of less than 10%, a PDC of 90% or higher was associated with a fully adjusted HR of 0.42 (95% CI, 0.37-0.47) and 0.39 (0.36-0.42) among the primary prevention and secondary prevention cohorts, respectively. Similar results were calculated after exclusion of patients with less than 5 years of follow-up from the time of the initial dispensed statin (Figure 2).

The present study demonstrates a strong and independent association between statin therapy and the improved survival of patients with and without known CHD. Our findings confirm that the benefits of statins extend to unselected patients in community settings. Higher con-

Figure 1. Proportional effects of continuation of statins on reduction in all-cause mortality per 10% proportion of days covered with statins in primary prevention (A) and secondary prevention (B) cohorts. Squares indicate weighted hazard ratios; horizontal lines, 95% confidence intervals. LDL-C indicates low-density lipoprotein cholesterol (to convert to millimoles per liter, multiply by 0.0259). Of the primary-prevention patients (A), 36 who had missing or uncertain data on vital status were omitted from the analysis shown. Seven patients who had missing data on statin efficacy (one of whom died) were also omitted. When combined with the 36 patients who had missing data regarding death, a total of 43 primary-prevention patients were missing information regarding statin efficacy. Of the secondary-prevention patients (B), 30 were missing data regarding statin efficacy and were omitted; 2 of these patients died.
Continuity of treatment and increased drug efficacy are associated with better survival among both primary prevention and secondary prevention cohorts.

While previous analyses of data from randomized clinical trials provided evidence that statin therapy produces only a modest (12%) reduction in all-cause mortality or no reduction at all, the present and other observational studies indicate a 40% to 50% reduction in mortality after consistent statin therapy and an even more dramatic reduction among older and hospitalized patients. The discrepancy between observational studies and clinical trials is even more intriguing given the lack of adequate drug dose titration and poor continuity of statin therapy in the elderly. The difference could have occurred if patients with a better prognosis had been more likely to be treated more intensively. Nonetheless, if residual confounding explained our results, then we could have expected the HRs to tend toward unity after multivariate adjustments, which was not the case in general. Furthermore, survivor treatment selection bias and competing medical issues, 2 potential problems with observational studies of treatment efficacy, are also unlikely to affect our results because the protective effect of statins was apparent even when analyses were limited to patients with more than 5 years of follow-up.

Other study strengths include a prospective study design, the use of administrative databases to avoid the problem of differential recall bias, and the systematic and comprehensive collection of personal sociodemographic data, medical history, and utilization of health services before the index date, which reduces the possibility of bias due to study outcomes. As of 1973, only approximately 3% of deaths were not medically certified, with most of them out-of-hospital sudden deaths, suggesting high validity of the study outcome.

Nevertheless, some limitations of the study should be considered. Our analysis was retrospective, and allocation of statin therapy was not randomized. Despite adjustment for baseline differences and an abundance of poor prognostic factors, a higher PDC with statins could still be a surrogate for other unmeasured variables that reflect a higher quality of care and more aggressive treatment strategies. The evaluation of statin continuation in the present study was based on dispensing information, which is the most feasible method of estimating medication use in large populations. However, it does not ensure that the drug is actually consumed, which may potentially contribute to lower overall morbidity and improved survival.

The present historical prospective study is one of the largest undertaken to date on statin therapy in community settings with respect to follow-up period and size of study population. Previous investigations that compared statin users and nonusers may have introduced a “confounding by indication” due to differences in pretreatment characteristics between those who do and do not receive treatment because the risk of death or severe outcome is intrinsically higher in patients selected for treatment and because most treatments reduce, but do not remove, risks. The current study sought to minimize this potentially serious confounding by using internal comparisons among patients who had at least 1 dispensed prescription of statins. Confounding by indication could have occurred if patients with a better prognosis had been more likely to be treated more intensively. Nonetheless, if residual confounding explained our results, then we could have expected the HRs to tend toward unity after multivariate adjustments, which was not the case in general. Furthermore, survivor treatment selection bias and competing medical issues, 2 potential problems with observational studies of treatment efficacy, are also unlikely to affect our results because the protective effect of statins was apparent even when analyses were limited to patients with more than 5 years of follow-up.

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Previous clinical trials have indicated that in patients with chronic disease, good adherence to medication, and

### Table 3. Proportion of Days Covered With Statins and All-Cause Mortality, Maccabi Healthcare Services, Israel, 1998-2006

<table>
<thead>
<tr>
<th>PDC, %</th>
<th>Primary Prevention</th>
<th>Secondary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1a</td>
<td>Model 2b</td>
</tr>
<tr>
<td>10-19</td>
<td>1.16 (1.04-1.28)</td>
<td>1.34 (1.21-1.49)</td>
</tr>
<tr>
<td>20-29</td>
<td>0.97 (0.86-1.09)</td>
<td>1.06 (0.94-1.20)</td>
</tr>
<tr>
<td>30-39</td>
<td>0.77 (0.67-0.87)</td>
<td>0.87 (0.77-1.00)</td>
</tr>
<tr>
<td>40-49</td>
<td>0.75 (0.66-0.86)</td>
<td>0.86 (0.75-0.98)</td>
</tr>
<tr>
<td>50-59</td>
<td>0.70 (0.62-0.81)</td>
<td>0.76 (0.67-0.87)</td>
</tr>
<tr>
<td>60-69</td>
<td>0.55 (0.48-0.64)</td>
<td>0.63 (0.54-0.72)</td>
</tr>
<tr>
<td>70-79</td>
<td>0.53 (0.47-0.61)</td>
<td>0.59 (0.52-0.68)</td>
</tr>
<tr>
<td>80-89</td>
<td>0.56 (0.49-0.64)</td>
<td>0.60 (0.53-0.69)</td>
</tr>
<tr>
<td>≥90</td>
<td>0.53 (0.47-0.58)</td>
<td>0.54 (0.49-0.60)</td>
</tr>
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Abbreviations: CI, confidence interval; HR, hazard ratio; PDC, proportion of days covered.

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even to placebo, is strongly associated with a lower risk of mortality irrespective of assigned treatment, suggesting that adherent behavior is itself associated with outcome. To investigate the potential effect of such adherence effect in the MHS, we performed similar analyses among 65,259 new users (mean age, 49 years; 22% men) of levothyroxine sodium, a synthetic hormone used in thyroid replacement therapy, where treatment discontinuation would not be expected to directly increase mortality. During the retrospective follow-up period (432,340 person-years) there were 5081 deaths. In a multivariate model (adjusted for age, sex, chronic diseases, and SES), the HR for

Figure 2. Hazard ratios and 95% confidence intervals of all-cause mortality according to proportion of days covered with statins in primary prevention (A) and secondary prevention (B) cohorts, Maccabi Healthcare Services, Israel, 1998-2006.
all-cause mortality associated with 10% PDC with levothyr-oxine was 1.06 (95% CI, 1.05-1.07), suggesting no adhe-
rence effect among levothyroxine users in the MHS. To
assess whether discontinuation of statin therapy may re-
late to serious side effects, we obtained data on ab-
normal liver function test results or elevated serum cre-
tine phosphokinase levels that indicate serious myopathy-
related events. During the study follow-up period, there 
was little difference in the proportion of patients with cre-
tine phosphokinase levels of more than 10 times the 
upper normal limit among patients with a statin PDC of 
less than 10% (0.3%) compared with patients with a statin 
PDC of more than 90% (0.4%). Similarly, only small dif-
ferences were observed in the proportion of patients with 
at least 1 measurement of serum alanine aminotransfer-
ase level more than 2.5 times the upper normal limit 
among patients with a statin PDC of less than 10% (6.8%) 
compared with patients with a statin PDC of more than 
90% (5.6%).

In conclusion, this study showed that continuation of 
statin treatment provided an ongoing reduction in all-
cause mortality for up to 9.5 years among patients with 
and without a history of CHD. The observed benefits from

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care Services, 27 HArMered St, Tel Aviv 68125, Israel (hodik 
g@mac.org.il).

**Author Contributions:** Dr Chodick had full access to all 
the data in the study and takes responsibility for the in-
tegrity of the data and the accuracy of the data analysis. 
Dr Shalev and Chodick contributed equally to the manu-
script. **Study concept and design:** Shalev, Chodick, and 
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**Analysis and interpretation of data:** Shalev, Chodick, and 
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lectual content:** Shalev, Silber, Kokia, Jan, and Heymann. 
**Statistical analysis:** Chodick. **Administrative, technical, 
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**Study supervision:** Shalev, Kokia, and Heymann.

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