

ORIGINAL INVESTIGATIONS

# Poor Adherence to Statin and Antihypertensive Therapies as Risk Factors for Fatal Stroke



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## ABSTRACT

**BACKGROUND** Poor adherence to medication regimens is common, potentially contributing to the occurrence of related disease.

**OBJECTIVES** The authors sought to assess the risk of fatal stroke associated with nonadherence to statin and/or antihypertensive therapy.

**METHODS** We conducted a population-based study using electronic medical and prescription records from Finnish national registers in 1995 to 2007. Of the 58,266 hypercholesterolemia patients age 30+ years without pre-existing stroke or cardiovascular disease, 532 patients died of stroke (cases), and 57,734 remained free of incident stroke (controls) during the mean follow-up of 5.5 years. We captured year-by-year adherence to statin and antihypertensive therapy in both study groups and estimated the excess risk of stroke death associated with nonadherence.

**RESULTS** In all hypercholesterolemia patients, the adjusted odds ratio for stroke death for nonadherent compared with adherent statin users was 1.35 (95% confidence interval [CI] 1.04 to 1.74) 4 years before and 2.04 (95% CI: 1.72 to 2.43) at the year of stroke death or the end of the follow-up. In hypercholesterolemia patients with hypertension, relative to those who adhered to statins and antihypertensive therapy, the odds ratio at the year of stroke death was 7.43 (95% CI: 5.22 to 10.59) for those nonadherent both to statin and antihypertensive therapy, 1.82 (95% CI: 1.43 to 2.33) for those non-adherent to statin but adherent to antihypertensive therapy, and 1.30 (95% CI: 0.53 to 3.20) for those adherent to statin, but nonadherent to antihypertensive, therapy.

**CONCLUSIONS** Individuals with hypercholesterolemia and hypertension who fail to take their prescribed statin and antihypertensive medication experience a substantially increased risk of fatal stroke. The risk is lower if the patient is adherent to either one of these therapies. (J Am Coll Cardiol 2016;67:1507-15)

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## ABBREVIATIONS AND ACRONYMS

CI = confidence interval

ICD-10 = International  
Classification of Diseases-10th  
Revision

LDL = low-density lipoprotein

OR = odds ratio

Responsible for 12% of all deaths worldwide, stroke is the second leading cause of mortality after ischemic heart disease (1). Despite a decline of 20% in age-standardized stroke mortality rates from 1990 to 2013, the number of stroke deaths has increased by 40% (2). Moreover, stroke accounted for a total of 66.4 million disability-adjusted life years in people aged 60 years or older in 2010, and this burden of disease is predicted to increase by 44% from 2004 to 2030 (3,4).

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High blood pressure and high cholesterol concentration are key risk factors for stroke for which effective pharmacological therapies are available. Evidence from trials suggest that statin treatment reduces stroke risk by between 15% and 25%, irrespective of the patient's baseline cardiovascular disease risk (5,6). For stroke prevention, the benefits of antihypertensive medication are of similar magnitude to those seen for statins, such that a 15% to 25% decrease in 5-year stroke risk is apparent, irrespective of baseline stroke risk (7). Stroke rates also appear to decline in proportion to the reduction in cholesterol and blood pressure (6,8).

In clinical settings, a major obstacle for the full benefits of lipid-lowering and antihypertensive treatments is the nonadherence of patients to drug therapy (9-11); that is, a failure to take their medications as prescribed by their physician. At least 3 studies have shown a significantly increased risk of stroke in hypertensive patients who do not adhere to their antihypertensive treatment regimens relative to those who are more compliant (9-11). Few studies have examined the effects of nonadherence to statin use on stroke risk, however, and we are aware of no studies that have quantified the extent to which nonadherence to statin therapy is associated with stroke risk among hypercholesterolemia patients with hypertension.

In the present study, we used records from nationwide drug prescription, hospitalization, and death registers to determine the risk of fatal stroke associated with nonadherence to statin therapy among hypercholesterolemia patients. In addition, we examined the risk of fatal stroke associated with nonadherence to statin therapy, antihypertension therapy, or both among hypercholesterolemia patients with a hypertension diagnosis.

## METHODS

**STUDY DESIGN.** We conducted a record-linkage study using the Statistics Finland Labor Market

data, which cover all permanent residents in Finland, and cause-specific death records from the National Death Register during the period January 1, 1995, to December 31, 2007. Labor Market data are collected on an annual basis from different administrative sources to provide labor force statistics. We used the individually unique personal identification codes of Finnish residents to link these data to medication records from the National Drug Reimbursement Register and the Drug Prescription Register curated by the Social Insurance Institution of Finland, along with information on principal causes of hospitalizations between January 1, 1987, and December 31, 2007, provided by the National Institute for Health and Welfare. Ethical permissions for this project were provided by the ethics committee of Statistics Finland (linkage permission TK 53-1519-09).

In accordance with the data protection regulations of living individuals in Finland, Statistics Finland provided a representative 11% sample of the national population and an oversample of individuals who died in the period between January 1, 1995, and December 31, 2007. Our data covered a total 80% of all deaths in Finland during that period. We used sampling weights, constructed from the sampling probabilities, to take account of the sampling design. Thus, the results derived from the analyses of this study are nationally representative. We restricted the sample to persons >30 years of age because stroke events are rare in younger people (Figure 1).

**ADHERENCE TO STATIN THERAPY.** Information on purchase of statins drugs was drawn from the Drug Prescription Register. Since 1994, all prescription reimbursed by the sickness insurance scheme have been recorded in this register. Hypercholesterolemic individuals requiring continuous statin therapy were identified from this register from January 1, 1995, through December 31, 2007, coded as C10AA according to the World Health Organization Anatomical Therapeutic Chemical Classification (12). The Social Insurance Institution obtains these data from all pharmacies in Finland as part of the national drug reimbursement scheme. These records cover the entire study population but exclude institutionalized patients.

In our study, year-by-year adherence to statin therapy was measured for the days covered by filled prescriptions (i.e., purchases) of statins. The rates of filled prescriptions are considered an accurate measure of medical adherence in a closed pharmacy system, such as in Finland, especially when the refills

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