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Impact of Statin Adherence on Cardiovascular Morbidity and All-Cause Mortality in the Primary Prevention of Cardiovascular Disease: A Population-Based Cohort Study in Finland

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ABSTRACT

Objectives: To assess the extent to which adherence to statins is associated with the incidence of cardiovascular (CV) events and all-cause mortality in the primary prevention of CV diseases and whether different analytical approaches influence the observed associations. **Methods:** This population-based cohort study used data from Finnish registers. The cohort included 97,575 new statin users aged 45 to 75 years in 2001 to 2004 with no CV diseases at baseline. *Exposure* was defined as adherence to statins (proportion of days covered [PDC]). The primary outcome was any CV event or death during a 3-year follow-up. Different analytical approaches, including multivariable-adjusted Cox regression, inverse probability weighting with time-varying adherence, and propensity score calibration, were used. **Results:** During the first year of follow-up, 53% displayed good (PDC ≥80%), 26% had intermediate (PDC 40%–79%), and 21% exhibited poor (PDC <40%) adherence. After adjustment for sociodemographic and clinical covariates, a 25% relative risk reduction (hazard ratio [HR] 0.75; 95% confidence interval [CI] 0.71–0.79) was observed in the rate of any CV event or death among good versus poor adherers. Good adherers also had a lower incidence than poor adherers of acute coronary syndrome (HR 0.56; 95% CI 0.49–0.65) and acute cerebrovascular disease events (HR 0.67; 95% CI 0.60–0.76). The different analytical approaches achieved comparable results for all the outcomes. **Conclusions:** The incidence of CV events and mortality was higher in poor versus good adherers. Different analytical methods that took into account changes in adherence and confounding at baseline did not appreciably affect the results.

Keywords: cardiovascular disease, healthy adherer effect, medication adherence, statins.

Introduction

Several large randomized controlled trials (RCTs) and meta-analyses have provided convincing evidence for the benefits of statins in the primary and secondary prevention of cardiovascular (CV) events [1,2]. A recent meta-analysis including 18 RCTs and almost 57,000 high-risk primary prevention patients have demonstrated that statins can reduce the risk of cardiac events by 27% and all-cause mortality by 14% during a median 5 years of follow-up [3].

In RCTs, the adherence to study medication has generally been good. In real life, however, many patients adhere poorly to preventive medications, such as statins, and the benefits observed in highly adherent RCT populations may not be substantiated. A meta-analysis of 44 epidemiological studies estimated that the prevalence of *poor adherence* to statins (defined as consuming <80% of the prescribed medication) is as high as 46%, which would translate to 47 excess CV deaths per 100,000 Americans offered statin therapy per year [4]. Only one of the studies, however, included in that meta-analysis investigated the risk of CV events in relation to statin adherence in primary prevention [5]. This observational study found that good adherers had a 20% lower risk of CV events than poor adherers. In fact, some observational studies of primary prevention populations have reported much larger reductions in the risk of CV events (up to ~40%) and all-cause mortality (up to 45%) for high versus low levels of statin adherence [5–12].

In light of the RCT evidence, the findings of observational studies may exaggerate the risk of CV events and death associated with poor statin adherence. Most of these studies have failed to consider how differences in patients' overall adherence

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behavior (healthy adherer effect) may affect the results [13]. We therefore assessed the extent to which adherence to statins would be associated with the incidence of CV events and all-cause mortality in the primary prevention of CV disease in the general population and whether different analytical approaches for controlling confounding, including the healthy adherer effect, would affect these associations.

Methods

We used data extracted from prescription, special reimbursement, and hospital discharge registers and registers of Statistics Finland (SF). The linkage between the databases was conducted using patient identification numbers. Data were de-identified by the SF after the linkage, and researchers used only de-identified data.

The prescription register is a national electronic pharmacy-claims database maintained by the Social Insurance Institution Finland [14]. The register contains records of all medications reimbursed to community-dwelling residents of Finland, including data on each dispensed medication (e.g., Anatomical Therapeutic Chemical [ATC] classification code [15], date of prescription, dispensing date, quantity, and costs) and on the patient (e.g., date of birth and death, sex, and place of residence).

The special reimbursement register is also maintained by the Social Insurance Institution. The register includes the records of patients who are entitled to a higher rate of refund because of certain severe or chronic diseases, such as diabetes, hypertension, and coronary heart disease (CHD).

The hospital discharge register maintained by the National Institute for Health and Welfare covers all Finnish hospitals and includes data on discharge diagnoses (the *International Classification of Diseases, 10th Revision* [*ICD-10*] codes since 1996), procedure codes, and admission and discharge dates [16].

The SF compiles data from many administrative sources such as information on marital status and family type from the Population Information System of the Population Register Center [17]. The SF also maintains several registers such as the Register of Completed Education and Degrees.

Study Population

All noninstitutionalized residents of Finland aged 45 to 75 years purchasing statins (ATC codes C10AA01–C10AA07) for the first time between January 1, 2001, and December 31, 2004, were identified. The prescription register contains information since 1994, and a *new statin user* was defined as a patient who had not purchased any statin since then. Patients whose first statin purchase was cerivastatin (C10AA06, withdrawn from the market in 2001) were excluded from the cohort. In addition, patients who were institutionalized permanently before their first statin purchase were excluded because they are not eligible for drug reimbursement; their drug therapy is provided by the institution and for the most part, it is not recorded in the prescription register. In addition, we used data from a large cohort study for external adjustment for variables not available in the main study (for details, see Appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.06.002).

A flowchart of the cohort definition is shown in Figure 1. We wanted to focus on primary prevention patients because the use of statins in individuals with no history of CV diseases has been debated [2,3,18]. Therefore, we excluded all secondary prevention patients, that is, patients who had been hospitalized because of CHD (*ICD-10* codes I20–I25), cerebrovascular diseases (*ICD-10* codes I60–I66, I68, I69, G45, and G46), atherosclerosis (*ICD-10* code I70), aneurysm (*ICD-10* code I71), heart failure (*ICD-10* code I50) or cardiac arrhythmia (*ICD-10* codes I46–I49), or any medical

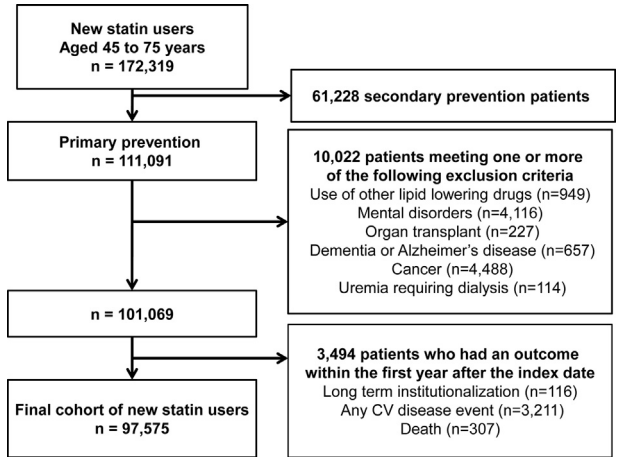

Fig. 1 – Flowchart of the cohort definition. CV, cardiovascular.

procedure related to CHD, cerebrovascular diseases, or peripheral artery disease within the previous three years before cohort entry (index date). In addition, those subjects who had purchased digoxin, antiarrhythmic agents, nitrates, or other cardiac drugs (ATC code C01) within three years before the index date were excluded as potential secondary prevention patients, as were patients who were entitled to special reimbursements for medicines used in the treatment of CHD, cardiac insufficiency, or chronic arrhythmias at the index date or within the first year after it. The one-year time span was included to allow for administrative delays in processing the entitlements. Patients who had purchased lipid-modifying drugs other than statins within three years before the cohort entry were also excluded from the study.

We also excluded patients with mental disorders, organ transplantation, dementia or Alzheimer disease, cancer, or uremia requiring dialysis. These patients were excluded because they often require repeated institutional care and their exposure to statin therapy is therefore potentially misclassified because of incomplete registration of medications used (the prescription register does not include medication use in hospitals or public nursing homes) or because they are not always able to look after and manage their own medications. The exclusion criteria were operationalized by excluding patients who were discharged from hospital with a diagnosis of severe mental disorders, Alzheimer disease, or cancer within three years before the index date, or were entitled to special reimbursement for medicines used in the treatment of severe mental disorders, organ transplantations, Alzheimer disease, cancer, or uremia requiring dialysis at the index date or within the first year after the index date, or patients who purchased antidementia drugs, antipsychotics, or antineoplastic agents within three years before the index date. Patients who had an outcome (CV event or death) or were institutionalized permanently within one year after the index date were also excluded.

Details of all variables used in the cohort definition are reported in Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.06.002.

No ethics committee approval was required because no patients were contacted during this register-based study. Permissions from the Social Insurance Institution, the National Institute for Health and Welfare, and the SF were obtained to use their register data.

Study Design and Follow-Up

We conducted a retrospective register-based cohort study as outlined in Figure 2. The index date (t_0) is the date of the cohort