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Risk of mortality and recurrent cardiovascular events in patients with acute coronary syndromes on high intensity statin treatment

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ABSTRACT

Several randomized controlled trials have shown a benefit of high-dose intensive statin treatment in reducing risk of death and second cardiovascular disease (CVD) events in patients previously diagnosed with an acute coronary syndrome (ACS). Non-randomized studies in clinical settings support these findings, but large, long-term, observational studies addressing CVD and non-CVD endpoints are lacking. In this retrospective longitudinal study, we followed ACS patients in Sweden during 2001–2012 using national health registry and medical record data. A total of 49,857 patients were identified, of whom 10,092 (20.2%) received high dose statins and 21,174 (42.7%) received no statins. Royston-Parmar parametric time-to-event models were implemented to model hazard for second CVD events and death, stratified by gender and diabetes diagnosis. We found that risk of a second CVD event developed similarly in both treatment groups, but was much higher in the no statin group. Risk of CVD-related death remained relatively constant for the high-statin group, while it increased over time for the no-statin group. Interestingly, males had higher mortality rates in the no-statin group, but not in the high-statin group. All-cause mortality and non-CVD-related death followed similar trends to those observed for CVD-related death. This work provides additional real-world evidence for effect of statins in CVD-related mortality. The hazard functions presented here can provide a basis for future survival modeling and health economic evaluation.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, responsible for 17.3 million, about 30% of all, deaths each year (Mozaffarian et al., 2015), (World Health Organization, 2011), a figure expected to grow to >23.6 million deaths per year by 2030 according to the World Health Organization. CVD encompasses many different diagnoses and conditions, including acute coronary syndrome (ACS), which alone was responsible for 1,141,000 unique hospitalizations in the USA in 2010 (Mozaffarian et al., 2015).

ACS is a group of conditions including unstable angina and myocardial infarctions (MI) with or without an observed ST elevation (Grech and Ramsdale, 2003; Kumar and Cannon, 2009). Risk factors for ACS are common to other CVD and include behavioural and non-behavioural factors such as smoking, physical inactivity, obesity, high blood pressure, high blood cholesterol, diabetes mellitus, metabolic syndrome and chronic kidney disease (Mozaffarian et al., 2015). In the acute phase ACS is treated with anti-thrombotic and anti-ischemic medication, and revascularization procedures (percutaneous coronary intervention (PCI) or coronary artery bypass grafting) (Hamm et al., 2011; Van de Werf et al., 2008). Secondary prevention according to current guidelines typically includes lifestyle changes, medical treatment to control risk factors, and continued anti-thrombotic therapy (Hamm et al., 2011; Van de Werf et al., 2008).

Statins, widely used to lower cholesterol levels in primary and secondary prevention of CVD (Zhou and Liao, 2010), have an anti-thrombotic effect and are also often a part of secondary prevention of ACS. While their short-term benefits are unclear (Vale et al., 2014), several randomized controlled trials (RCTs), clinical observational studies, and meta-analyses have shown that statin treatment, in particular high-dose intensive treatment, improves long-term (months to years) outcomes in post-ACS patients reducing risk for death and/or cardiovascular events compared to lower-intensity treatments (Bavry et al., 2007; Cannon et al., 2006; Cholesterol Treatment Trialists et al., 2010; Farnier, 2008; Hulten et al., 2006; Josan et al., 2008), (Kasai et al., 2007a; Kasai et al., 2007b; Tentzeris et al., 2014). However, large, long-term, observational studies addressing their effect on risk of cardiovascular and non-cardiovascular morbidity and mortality in a clinical setting over time are warranted.

Abbreviations: ACS, Acute Coronary Syndrome; CVD, Cardiovascular Disease; EMR, Electronic Medical Records; HF, Heart Failure; ICD, International Classification of Diseases; IS, Ischemic Stroke; LDL, Low Density Lipoprotein; MI, Myocardial Infarction; PCI, Percutaneous Coronary Intervention; RCT, Randomized Controlled Trial; STEMI, ST Elevation Myocardial Infarction.

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For the purposes of risk estimation and health economic evaluation we derived and compared time-dependent hazard functions for post-ACS mortality and recurrence of CVD events. Risk estimates were based on up to 12 years of continuous follow-up health data for a large cohort of Swedish patients receiving no statins or on sustained intensive statin treatment after experiencing their first ACS event.

2. Materials and methods

2.1. Data sources

Retrospective longitudinal observational data from 1992 to 2012 was collected from electronic medical records (EMRs) of selected primary care centres in Sweden and supplemented with data from mandatory national health registers containing information reported by Swedish health care providers, some going back to 1967.

Individual patient data from EMRs was extracted using the Pygargus Customized eXtraction Program, CXP (Pygargus, Stockholm, Sweden). This data extraction method allows extraction of anonymized structured and non-structured data, and has been validated (Martinell et al., 2012) and used in a number of earlier studies (Bodegard et al., 2013; Janson et al., 2013; Kjeldsen et al., 2010; Lindgren et al., 2005; Pettersson et al., 2010; Ringborg et al., 2008). Data extracted from the EMRs included patient's age, gender, prescriptions (coded according to the Anatomical Therapeutic Chemical (ATC) Classification System), diagnoses, physical measures, lab tests, health care visits, referrals, and lifestyle factors. During the extraction process, a key code was automatically generated to allow linkage of patient-level data across different datasets.

Patient-level data from the National Patient Register (NPR), Cause of Death Register (CDR), and Prescription Drug Register (PDR) was linked to extracted EMR data by the Swedish National Board of Health and Welfare using the key code generated at the EMR extraction step. These registries are compulsory and have been found to have a high degree of completeness (Ludvigsson et al., 2016; Ludvigsson et al., 2011). Data extracted from the NPR included patient age, gender, records of hospital procedures, visits, hospital admissions and discharges, as well as underlying diagnoses. Data extracted from CDR included patient age, date of death and cause of death. Data extracted from the PDR included patient age, gender, and prescriptions (ATC code, dose, length).

All diagnoses in EMRs, NPR, and CDR were coded according to ICD-9 until 1997 and ICD-10 from 1997 and onwards. Data from the EMRs and NPR was extracted from January 1992 (earliest EMR availability) to December 2012. Data from the CDR was extracted from January 2000 to December 2012. Data from the NPR was extracted from 2005 to 2012.

The study was approved and data access granted by the regional ethical review board in Stockholm.

2.2. Study population and outcome variables

The source population for the study was patients treated at any of the 43 participating Swedish primary care centres at any time during the inclusion period (January 2001 to extraction date). The chosen primary care centres, covering 14% of the Swedish population, were selected to reflect the full spectrum of Swedish primary care and varied in size (small, medium, or large centre), location (urban and rural), and type of practice (public and private). Patients from the source population who had a record of at least one ACS diagnosis during the inclusion period were included in the study, with ACS diagnosis date taken as the index date. Patients under 30 years of age at index or on a low-dose/intermittent statin regimen (see below), as well as patients with a diagnosis of malignancy other than skin, or a CVD diagnosis (CVD event [see below], chronic ischemic heart disease [ICD-10 I25.x] peripheral vascular disease [ICD-10 I70.x, I73.9, G45.0]) within the two years prior to index were excluded.

Included patients were followed until loss to follow-up (death, emigration) or 31st December 2012. During the study period, the time from first ACS event to next CVD event or death was monitored. Diagnosis codes were used to identify ACS events (unstable angina [ICD-10 I20.0] or myocardial infarction [ICD-10 I21.x]) and CVD events (ACS event, ischemic stroke [ICD-10 G45.9], heart failure [ICD-10 I50.x]). CVD death was defined as death where the recorded cause of death was an ACS or CVD event.

2.3. Statin therapy

Statin treatment regimens for all patients were analysed based on prescription data from EMRs and CDR and classified as no statin, low-dose/intermittent treatment, or high-dose continuous treatment. No statins regimen was defined as an average of <0.1 statin prescriptions/year of follow-up (i.e., <1 prescription during 10 years of follow-up). High-dose continuous treatment regimen was defined as any treatment regimen equivalent to an average of >1.3 prescription/year of follow-up with each prescription being for at a daily intake of any of the following: 40 mg of atorvastatin, simvastatin or pravastatin; 40 mg of lovastatin; 20 mg of rosuvastatin and 80 mg of fluvastatin. Statin regimens not fulfilling either of the criteria above were classified as low-dose/intermittent.

The demographic characteristics of the two study groups, divided according to presence or absence of information on low density lipoprotein (LDL) cholesterol levels, is presented in Table 1. LDL was calculated according to the formula of Friedewald (Friedewald et al., 1972).

2.4. Missing data

No imputation of missing data was performed. The number of subjects included in different analyses therefore varied according to availability of some data elements.

2.5. Statistical analyses

Data management and descriptive statistics were performed using SAS v 9.3 (Leavitt et al., 1990).

In order to analyse the hazard functions for a second CVD-event after the initial ACS-event over time, a Royston-Parmar (RP) model was used. Unlike the Cox proportional hazard model, which does not contain any assumptions on the hazard function, the RP model is a parametric model for analysing time-to-event data, relying on splines to model the baseline function (Royston and Parmar, 2002). The RP model, first published in 2002, offers a more flexible analysis than the classical parametric models (Reibnegger, 2012). The main drawback of parametric hazard models is the risk for arbitrary decisions regarding the baseline hazard rate (Box-Steffensmeier, 2004). At the time of analysis the RP models were not implemented in SAS, so input files were generated in SAS and the RP analyses performed using R version 3.0.2 (R Core Team, 2013) and the flexsurv package (Jackson, 2014).

The hazard functions for events of interest were estimated by modeling the Log cumulative Hazard (scale = hazard) as a spline function of log time, using two knots ($k = 2$). For each group/strata and outcome one crude analysis (presented as “crude rate” in results tables) and one adjusted analysis were run. In the adjusted analysis gender and diabetes were treated as categorical covariates (female/male, and absence/presence of diabetes, respectively) and age and LDL as continuous covariates (presented in results tables). In each analysis (every group/strata and outcome) age and LDL were centered around the same values. For age, 65 years was used, and for LDL the values were centered around 100 mg/dl, meaning that the difference between each data point for age and LDL and their global mean values were modeled in each case.