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Concomitant use of statins and macrolide antibiotics and risk of serious renal events: A nationwide cohort study

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ABSTRACT

Background: Concomitant use of statins metabolized by the cytochrome P450 isoenzyme 3A4 (CYP3A4) and CYP3A4-inhibiting macrolide antibiotics may confer an increased risk of renal failure. We investigated the risk of serious renal events associated with concomitant use of such statins and such macrolides.
Methods: In a nationwide register-based cohort study (Denmark, 1999–2017), we identified 906,423 new users (40–79 years old), of CYP3A4-metabolized statins. In propensity score-matched analyses, we compared the risk of serious renal events during episodes of concomitant use of statins and CYP3A4-inhibiting macrolides (n = 71,521) with episodes of use of statins alone (n = 285,488) and, as the primary analysis, with episodes of concomitant use of statins and an active comparator (penicillin V, n = 139,446). Using proportional hazards regression, we estimated hazard ratios (HRs) for serious renal events within 30 days of start of follow-up.
Results: We observed 25 serious renal events during concomitant use of statins and macrolides (incidence rate [IR], 4.9 per 1000 person-years). Compared with use of statins alone (50 events; IR, 2.3), concomitant use of statins and macrolides was associated with a significantly increased risk of serious renal events (HR 2.16, 95% confidence interval [CI] 1.33, 3.49). Compared with concomitant use of statins and penicillin V (52 events; IR, 5.3), however, we observed no increased risk (HR 0.93, 95% CI 0.58, 1.49).
Conclusions: In this nationwide cohort study concomitant use of statins and macrolides was not associated with a significantly increased risk of serious renal events.

1. Introduction

3-Hydroxy-3-metylglutaryl coenzyme A inhibitors, also called statins, are widely used drugs in both primary and secondary prevention of cardiovascular disease [1]. Rhabdomyolysis with or without acute renal failure is a known, albeit rare, dose dependent side effect of statin treatment [2, 3]. Clinical trials of rosuvastatin [4, 5] have raised renal safety concerns that have subsequently prompted observational studies of acute renal failure among statin users. These studies point towards the possibility of a dose dependent increased risk of acute renal failure among users of different statins for which, however, the mechanism remains to be elucidated [6, 7].

The cytochrome P450 enzymes are a key pathway for drug metabolism. Among statins, metabolization by the cytochrome P450 3A4 isoenzyme (CYP3A4) occurs for e.g. simvastatin, atorvastatin and lovastatin. If CYP3A4 is inhibited, metabolization of these statins is therefore impaired [8], and patients treated with statins metabolized by CYP3A4 have been reported to develop rhabdomyolysis and/or renal failure after concurrent treatment with macrolide antibiotics such as erythromycin or clarithromycin [9–13]. In March 2012, the United States Food and Drug Administration (FDA) published a warning regarding potential drug-drug interactions between statins metabolized by CYP3A4 and concurrent use of medications used to treat HIV and hepatitis. The latter medications are potent inhibitors of CYP3A4. Also, the FDA warned that concentrations of lovastatin and simvastatin in the blood could be increased with use of macrolides with CYP3A4-inhibitory properties, e.g. erythromycin and clarithromycin [14]. A subsequent Canadian study utilizing population based data from an elderly population aged 65 years or older, reported an approximately two-fold increased risk of both rhabdomyolysis and acute kidney failure after co-prescription of a statin metabolized by CYP3A4 with clarithromycin or

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erythromycin compared with azithromycin [15]. Azithromycin is a macrolide for which metabolization by CYP3A4 is not important.

To further understand the potential impact of this drug-drug interaction in a general population, we conducted a nationwide register-based cohort study of all new users of statins metabolized by CYP3A4. We investigated the occurrence of serious renal events with concomitant use of macrolide antibiotics inhibiting CYP3A4 as compared with no antibiotic use and as compared with an active comparator, penicillin V.

2. Methods

2.1. Study design

We conducted a historical prospective study using data from Danish registers, 1999 to 2017. In a cohort of new users of statins with major metabolism by the CYP3A4 enzymes (of statins prescribed in Denmark: lovastatin, atorvastatin, simvastatin), we assessed the risk of serious renal events associated with concomitant use of statins and macrolides in two different setups. In one setup, we compared episodes of concomitant use of statins and macrolide antibiotics with CYP3A4-inhibitory properties (of macrolides prescribed in Denmark: clarithromycin, erythromycin or roxithromycin) with control episodes of use of statins alone (i.e. use of statins with no concomitant use of antibiotics). However, since comparisons with no use may be susceptible to confounding by indication, in a second setup (primary analysis) we compared episodes of concomitant use of statins and macrolides with CYP3A4-inhibitory properties with control episodes of concomitant use of statins and an active comparator, penicillin V, which does not inhibit CYP3A4 and which has indications similar to the macrolides studied. The indications between penicillin V and roxithromycin, clarithromycin and erythromycin overlap with respect to upper and lower respiratory tract infections and skin- and soft tissue-infections. All three macrolides are also indicated for mycoplasma-, chlamydia-, chlamydophila- and legionella-species infections whereas clarithromycin is also indicated as part of helicobacter pylori eradication [16]. As the primary outcome, we studied serious renal events at 30 days follow-up. The primary outcome definition (as defined in Table S1) included hospital admission with a broad range of renal disease, including anuria/oliguria, renal failure (alone or in combination with hypertensive disease) and diabetes with renal complications. A sudden loss of renal function is a central symptom characterizing acute kidney injury [22] and the broad outcome definition in our study was intended to reflect kidney injury and worsening renal function among a cohort with no previous hospital contact for any renal disease. As additional outcome, we studied 30-day all-cause mortality. Table S1 lists the specific definitions of the study population, outcome, exposure and control episodes according to the International Classification of Diseases version 10 [ICD10] or the Anatomic Therapeutic Classification (ATC)-system.

We took several additional measures to minimize the potential for confounding (Table S1). First, to reduce confounding by indication, we used an active comparator study design comparing concomitant use of statins and macrolide antibiotics with CYP3A4-inhibitory properties with concomitant use of statins and penicillin V. Second, to reduce the risk of confounding from unmeasured factors related to age (e.g. polypharmacy or age-related changes in pharmacokinetics and pharmacodynamics) [17,18], we restricted the age of the study participants to 40 to 79 years. Third, since the risk of the outcome may vary with statin treatment duration, we excluded participants with prevalent or previous statin use at baseline, using a look back period of one year. Fourth, we excluded all episodes in participants with use of antibiotics or hospitalization in the previous 30 days as well as episodes with receipt of multiple antibiotics on the index date. Fifth, to further increase the likelihood of isolating an association attributable to the studied drug-drug interaction, we excluded participants with endstage illness who may be at high risk of renal failure from other causes. Sixth, to increase the likelihood of capturing first time occurrence of a serious renal event we excluded participants with a previous hospital contact for a broad range of renal disease or rhabdomyolysis. Finally, to account for baseline differences in the risk of serious renal events, we matched users of macrolides and penicillin V on a propensity score incorporating a large number of potential confounders.

The study was approved by the Danish Data Protection Agency. Approval by a biomedical ethics committee is not needed for register-based research in Denmark.

2.2. Data sources

By use of a unique personal identification number assigned to all Danish citizens, we linked individual level information on drug use and hospital contacts with outcome and potential confounders. For demographic data, we used the Danish Civil Registration System which contains continuously updated demographic information with nationwide coverage [19]. For disease-related information, we used the Danish National Patient Registry [20] which contains nationwide data on hospital diagnoses (inpatient, outpatient, and emergency room contacts) throughout the study period. For information on drug use, we used the Register of Medicinal Product Statistics [21] which contains information on filled prescriptions at Danish pharmacies. Neither statins nor antibiotics are available over-the-counter in Denmark.

2.3. Study cohort

We defined the source population on the basis of the Danish Civil Registration System including all individuals aged 40 to 79 years during the study period. We based the cohort on first time treatment with statins for each participant. Statin treatment was defined to last for as long as new overlapping prescriptions were filled. We defined the duration of each prescription by the number of pills dispensed: each pill counted as one day of use. To avoid gaps in continuous statin treatment, we allowed for a 30-day gap between the last day of the previous prescription and the date of the new prescription.

Each filling of a prescription for a macrolide or penicillin V during ongoing use of statins was considered a separate treatment episode. The index date (study entry) for each treatment episode was defined as the date of filling the prescription. All time periods during ongoing use of statins alone (no previous prescription for any antibiotic in the previous 30 days) were split into 30 day long episodes. Using frequency matching, each episode of use of macrolides was randomly assigned up to 20 control episodes of use of statins alone, based on sex, age (in 5-year age bands), calendar year, and time since start of new use of statins (<30 days, 30–89 days, 90–364 days, 1–2 years, ≥3 years), that formed a pool of control episodes of use of statins alone. Each participant could contribute multiple treatment and control episodes to the study.

2.4. Statistical analyses

We conducted the statistical analyses using proportional hazards regression. Follow-up started on the index date and ended on date of the first of the following: loss to follow-up, becoming 80 years of age, hospitalization with occurrence of outcome, switch to any other antibiotic, 30 days after index date, end of statin treatment, or end of study (December 31, 2017). P-values for homogeneity were estimated using Wald tests. We matched episodes of concomitant use of macrolides and penicillin V and episodes of concomitant use of macrolides and use of statins alone, in a ratio of 1:2 and 1:4, respectively, on the propensity score using greedy nearest neighbor matching (SAS 9.4, PROC PSMATCH). Using all potential confounders listed in Table S2 as predictors, we estimated the propensity score for macrolide treatment using a logistic regression model. We assessed baseline covariate balance between treatment and control episodes before and after propensity score matching using standardized differences. For any given covariate, we considered the treatment groups well-balanced if the standardized difference was <10%. We calculated the absolute risk difference per 100,000 treatment episodes as $(HR - 1) * IR_0$ where HR was the hazard ratio for concomitant use of statins and macrolides and IR_0 was the incidence rate per 100,000 treatment episodes (1 treatment episode = 30 days) with concomitant use of penicillin V. We conducted subgroup analyses with stratification according to sex, current age and macrolide subtype. To investigate any differential effect on prescription practice after the FDA warning in 2012 [14], we also conducted a sensitivity analysis according to calendar period.

3. Results

3.1. Cohort and baseline characteristics

We identified 906,423 new users of statins. After application of exclusion criteria, 71,521 episodes of concomitant use of statins and macrolides, 256,202 episodes of concomitant use of statins and penicillin V and 2,076,516 episodes of use of statins alone were eligible for propensity score matching. For details on the selection of the study cohort, see Fig. 1. Table S3 shows characteristics at baseline according to treatment groups for the unmatched cohort.

3.2. Concomitant use of statins and macrolides vs. use of statins alone

After propensity-score matching, the cohort included 71,521 episodes of concomitant use of statins and macrolides and 285,488 episodes of use of statins alone. Table 1 shows characteristics at baseline according to treatment groups for the matched cohort. After propensity score matching, episodes of concomitant use of statins and macrolides were well-balanced with episodes of use of statins alone on all covariates.

During follow-up, 25 serious renal events occurred during concomitant use of statins and macrolides (incidence rate [IR] 4.9 per 1000 person years), compared with 50 events during episodes of use of statins alone (IR, 2.3 per 1000 person years). Concomitant use of statins and macrolides was associated with a significantly increased risk of serious renal events (HR 2.16, 95% confidence interval [CI] 1.33 to 3.49) compared with use of statins alone (Table 2).

In analysis of the additional outcome all-cause mortality, concomitant use of statins and macrolides was associated with a significantly

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