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Revising the link between proton pump inhibitors and risk for acute myocardial infarction – a case-crossover analysis.

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Abstract

Purpose: To investigate if the prescription of proton pump inhibitors (PPIs) was associated with a sudden risk of acute myocardial infarction (AMI) while controlling for time-invariant confounding by using a case-crossover design. An association might indicate that physicians take prodromal symptoms of myocardial ischemia for dyspepsia.

Methods: We applied a case-crossover design to investigate all AMI patients admitted to hospital in the Skåne region, Sweden, between Oct 14th 2005 and Dec 31st 2006 and their PPIs prescriptions and dispensations three months prior to the AMI onset. We retrieved the information about prescribed medication from the Swedish Drug Register containing individual information on all dispensed drugs prescribed in the outpatient care and dispensed in any of the Swedish pharmacies. Additionally, we stratified the analyses by history of AMI.

Results: We identified 3490 AMI cases aged 40 to 90, 61% were men. The odds ratio for AMI onset in those with a prescription of PPIs during a hazard period of 3-days compared to control periods was 1.36 (95%CI: 0.82-2.25) in the whole study cohort and 1.66 (95%CI: 1.00-2.76) in those without history of AMI. The corresponding OR based on the dispensation date (suggesting use of the drug) was 1.26 (95%CI: 0.92-1.72) and 1.29 (95%CI: 0.92-1.83), respectively.

Conclusions: In our opinion, the previously reported increase in risk of adverse cardiac events in patients using PPIs may reflect the fact that an AMI may be misinterpreted as dyspepsia.

Keywords: case-crossover, acute myocardial infarction, proton pump inhibitors, epidemiology

Introduction

The association between the use of proton pump inhibitors (PPIs) and adverse cardiovascular events has been studied extensively in recent years due to a possible interaction with antiplatelet therapy [1-5]. The use of PPIs itself has been reported to increase the risk for major adverse cardiovascular events and a biological mechanism linking PPIs and those events in the general population has been proposed [6,7]. In observational studies drug use in general has been reported to increase in the period before acute hospitalization due to a cardiac event suggesting no causal relationship between drug use and the adverse event but rather an effect of unmeasured confounding [8,9]. On the other hand, because of their potential similarity, prodromal symptoms of acute myocardial infarction (AMI) are sometimes interpreted as dyspepsia [10-12]; a mistake that represents a common cause of malpractice allegations in primary healthcare [13-15]. Further, patients with antecedents of acute coronary syndrome and atherosclerosis habitually take antiplatelet agents like aspirin or clopidogrel to prevent thrombotic complications and, in turn, are co-prescribed PPI to prevent dyspepsia which is a common side effect of antiplatelet therapy[16-18].

In the present study we investigated the association of prescription and dispensation of PPIs and onset of AMI by using the same individual as its own control in a case-crossover design. We speculated that an association between the PPIs prescription and AMI might indicate that physicians take prodromal symptoms of myocardial ischemia for dyspepsia.

Materials and methods

Data sources and case definition

Linking the Swedish Population Register administrated by Statistics Sweden to the Skåne Healthcare Register by the unique personal identification number assigned to all residents in Sweden, we identified patients with a hospital discharge diagnostic code I21 (AMI) according the 10th edition of the International Classification of Diseases (ICD-10). Among individuals residing in the Skåne region, Sweden by Dec 31st 2005 we included all with an AMI event occurring between Oct 14st 2005 and Dec 31 2006 and aged 40 to 90 at the time of the AMI. We defined previous AMI as any hospitalization with a discharge diagnosis with ICD-10 code I21 occurring up to 5 years prior the study event.

We linked every AMI case to the Swedish Drug Register maintained at the Swedish National Board of Health and Welfare to track individual information on pharmacological agents prescribed at outpatient healthcare, and dispensed at any of the Swedish pharmacies. We used the Anatomical Therapeutical Chemical (ATC)

classification maintained by the WHO International Working Group for Drug Statistics Methodology (http://www.whocc.no/atcddd/) to define prescription of proton pump inhibitors (ATC code: A02BC) during the hazard/control period in the case-crossover design (se statistical methods section for details) from July 1st 2005, when the register started, until the day of the AMI onset. In Sweden, a prescription for most drugs may be valid during the following two year period, and a person can get the drug dispensed several times every three/four months based on the same prescription. Thus, the prescription date and the dispensation date are not necessarily the same. The prescription reflects the opinion of the physician while the dispensation suggests the (potential) beginning of pharmacological exposure.

Statistical methods

We applied a case-crossover design in order to assess if prescription or dispensation of PPIs was more frequent during the 3 day period directly preceding the day of the AMI hospitalization (i.e., the *hazard period*) than in the average of 30 three day periods preceding the hazard period (i.e., the *control periods*) (Figure 1) [19-21].

We performed two case-crossover analyses. In the first, to determine PPI prescription during hazard and control periods we used the prescription date of the drug (the date when the prescription was ordinated at the doctors' office). In the second, to determine the PPI dispensation we used the date when the drug was dispensed from the pharmacy. In both cases, we required that the drug was dispensed latest on the day of the AMI to avoid reverse causality as only dispensed drugs are registered in the Swedish Drug Register. We repeated above analyses in a subgroup of individuals with no previous AMI. We used conditional logistic regression to estimate odds ratio (OR) and its 95 % confidence intervals (CI).

The present study is a part of a project approved by the Regional Ethical Committee in South Sweden and the database has been assembled with the allowance and assistance of Statistics Sweden, The National Board of Health and Welfare (Centre for epidemiology), and the County Council of the Region of Skåne.

Results

In the population of Skåne region, Sweden (1.2 million inhabitants on Dec 31st 2005) we identified 3 490 persons aged 40 to 90 with an incident AMI between Oct 14th 2005 to Dec 31st 2006. The mean (SD) age was 73.4 (11.7), 61% were men and 356 (10%) had a previous AMI. In the hazard period 16 persons had a PPI prescription and 46 persons had their drug dispensed, compared to 304 and 567 in the control periods, respectively. (Table 1)

Table 1. Characteristics of patients with acute myocardial infarction (N= 3 490) by prescription and dispensation of proton pump inhibitors (PPIs) in the hazard period.

	Prescription of PPIs in hazard period		Dispensation of PPIs in hazard period	
	No (N=3 474)	Yes (N=16)	No (N=3 444)	Yes (N=46)
Age in years, mean (SD)	73.4 (11.7)	70.5 (12.5)	73.3 (11.7)	76.3 (10.9)
Men, n (%)	2112 (61)	7 (44)	2099 (61)	20 (44)
Previous AMI[a], n (%)	337 (10)	0 (0)	328 (10)	9 (20)
Prescription/dispensation of PPIs during the control periods, n (%)	302 (9)	2 (13)	539 (16)	28 (61)
Mortality within 10 days, n (%)	226 (7)	0 (0)	219 (6)	7 (16)

[a] Hospitalization with discharge code I21 (International Classification of Diseases) in previous 5 yeares

Two persons had a prescription of PPI both during the hazard period and in at least one of 30 control periods, while 28 persons had PPI dispensed during both the hazard and at least one of control periods.

The results from the case crossover analysis showed that the prescription of PPIs during the hazard period was not conclusively higher than in the control periods with odds ratio (OR) of 1.36 (95% confidence intervals [CI]: 0.82, 2.25). In persons without a history of AMI the risk of PPI prescription was conclusively elevated (OR 1.66 [95%CI: 1.00-2.76]). (Table 2)

Table 2. Prescription and dispensation of proton pump inhibitors in the hazard period versus the control periods preceding an acute myocardial infarction (AMI). Odds ratios and 95% confidence intervals (in parentheses).

	Prescription of PPIs	Dispensation of PPIs
All	1.36 (0.82-2.25)	1.26 (0.92-1.72)
No previous AMI	1.66 (1.00-2.76)	1.29 (0.92-1.83)

In other words, the prescription of PPIs during the hazard period appeared to increase the risk of subsequent AMI by 70% in persons without previous AMI within 5 years. When the dispensation of drug was used, the OR of having PPI dispensed during the hazard period compared to control period was 1.25 (95%CI: 0.92-1.72) for all AMI cases and 1.29 (0.92-1.83) for those without previous AMI.

Discussion

Using a case-crossover design that allows for controlling of time-invariant confounding we found 70% increased risk of AMI when being prescribed PPIs during the hazard period in Skåne residents aged 40 to 90 without a previous AMI. A naïve interpretation of our findings suggests that use of PPIs conveys unwanted side effects and triggers AMI. However, when the dispensation date was used to determine PPIs usage this increase attenuated.

Given that several symptoms of myocardial ischemia like nausea and heartburn, are also typical of dyspeptic disorders, a more probable interpretation of our findings is that the physician may take prodromal symptoms of myocardial infarction for dyspepsia and therefore prescribe PPIs [10,14]. This conclusion is supported by the fact that this increase in risk was diluted when dispensing date, the date when the patient receives the medication and thus could start the treatment, was used instead of prescription date. If there was a biological effect of PPI on AMI we would expect the contrary. However, as an alternative explanation of our findings it could be speculated that the association between PPI and AMI is confounded by gastric trouble itself.

This possible mistake in identifying early AMI symptoms might be less frequent in patients with antecedents of cardiac disorders as this knowledge possibly forewarns the physician on the possibility of a recurrence. Furthermore, in our data none of persons using PPI in the hazard period died within 10 days from the AMI. One

could speculate that the confusions regarding diagnosis may be expected in patients presenting with mild or unusual symptoms.[22] However due to a low number of PPI prescription in the hazard period those results should be interpreted with caution.

Since the number of cases was relatively small we could not investigate a possible interaction between simultaneous use of clopidrogel and PPI in relation to AMI risk. However, the validity of this suspected interaction has been questioned by other investigations [23,1,4,5,3]. Our analysis may suggest that the observed higher risk of AMI in patients using PPIs may reflect that patients with AMI are treated for dyspepsia. However, as ticagrelor use instead of clopidogrel becomes more frequent, the clinical significance of this possible interaction will decrease.[24] Contrary to findings reported from a self-matched case series design we haven't found similar results for prescription of benzodiazepines (data not shown) [8]. Our findings are in line with data indicating that AMI is currently the most prevalent condition involved in "failure to diagnose" claims against general practitioners and that, concerning AMI, the most common incorrect diagnose made by the physicians is gastrointestinal problems [15,13,14].

The results of a case-crossover analysis are known to depend on the length of the hazard period [19]. Our results from a sensitivity analysis with different lengths of the hazard/control period didn't show an increase in risk of AMI if using PPI in a hazard period of 1 or 2 days, while the estimates for the length of period 4 and 5 days were similar to those from our primary analysis (data not shown). That could be expected as we included only patients that get dispensed their drugs before the AMI onset – thus, those who had more severe symptoms and were admitted to the hospital shortly after the PPI prescription would hardly be able to visit the pharmacy and get the drug dispensed.

Our study is based on a large database including the whole population in the region, and the identification of AMI cases as well as information on individual use of pharmacological agents were based on standardised procedures that seem to be reliable and valid sources of information [25-27]. However, a considerable proportion of patients didn't use PPI neither in the hazard or control period, which reduced the frequency of discordant pairs and the statistical power in the case-crossover analysis. The choice of study period depended on the ethical permission for data use and thus we were not able to include register data from more years which could have increased the power of the study and thus yielded narrower confidence intervals for the association of PPI prescription with AMI.

The case-crossover design eliminates time-invariant confounding (both measured and unmeasured). However, this study design does not completely prevent confounding by factors within individuals that change over time and we did not measure the actual exposure to drugs. Nevertheless, for our hypothesis the pharmacological effect of PPI on AMI is less relevant, since in this study the prescription of PPI was considered as a proxy for ´failure to diagnose'. We were not able to identify the prescription of drugs that were not dispensed at the pharmacy or those available over the counter. However, this would result in a bias towards the null if the dispensation was prevented by an AMI onset.

In summary, our findings provide a piece of evidence in the discussion of the association of PPI and adverse cardiac events. We could not find evidence of a causal link between those two and our results may suggest that the results of observational studies reporting an association may be a result of increased use of PPI preceding an AMI caused by 'failure to diagnose'.

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Conflict of interest

The authors declare no conflict of interests.

Contributions of Authors statement

Conception and design: JM, AT, HO

Acquisition of data: JM

Analysis of data: AT, RPV, HO, JM

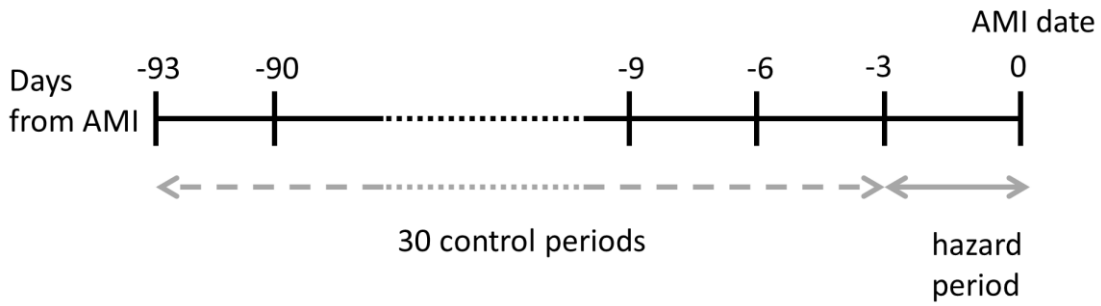
Interpretation of data: AT, RPV, JM, HO, PT

Drafting the article: AT, JM

Critical revision of the article for important intellectual content and approval of the final version: all authors

Figure legend

Figure 1. Case-crossover design. AMI – acute myocardial infarction.



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