# Proton pump inhibitors and the risk of CKD progression

## The Stockholm CREAtinine Measurements (SCREAM) project

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## INTRODUCTION

Proton pump inhibitors (PPI) are widely used, but they are often started inappropriately and are continued without clear medial indication. They have been linked to acute kidney injury (AKI) and, recently in the United States, to the incidence of chronic kidney disease (CKD). We here aimed to confirm and expand this finding in Swedish healthcare.

## METHODS

We used SCREAM, a healthcare extraction with diagnoses, dispensation claims and laboratory measures for all citizens in the region of Stockholm during 2007–2010, to build a cohort of new users of PPI (n= 105305) and new users of $H_2$ blockers ($H_2$B; n= 9578), followed over median 2.7 (IQR 1.5-3.8) years to ascertain renal endpoints. The primary outcome was CKD progression, defined as doubling of creatinine or >30% eGFR decline. Secondary outcomes were end-stage renal disease (ESRD) and acute kidney injury (AKI). Complete collection of repeated PPI and $H_2$B dispensations at Swedish pharmacies allowed calculation of cumulative drug usage (DU) by taking the defined daily dosages (DDD) into account. The association found between cumulative PPI or $H_2$B use and risk of CKD progression was modelled with the cumulative DU for each drug treated as a time-dependent exposure in the Cox model.

## RESULTS

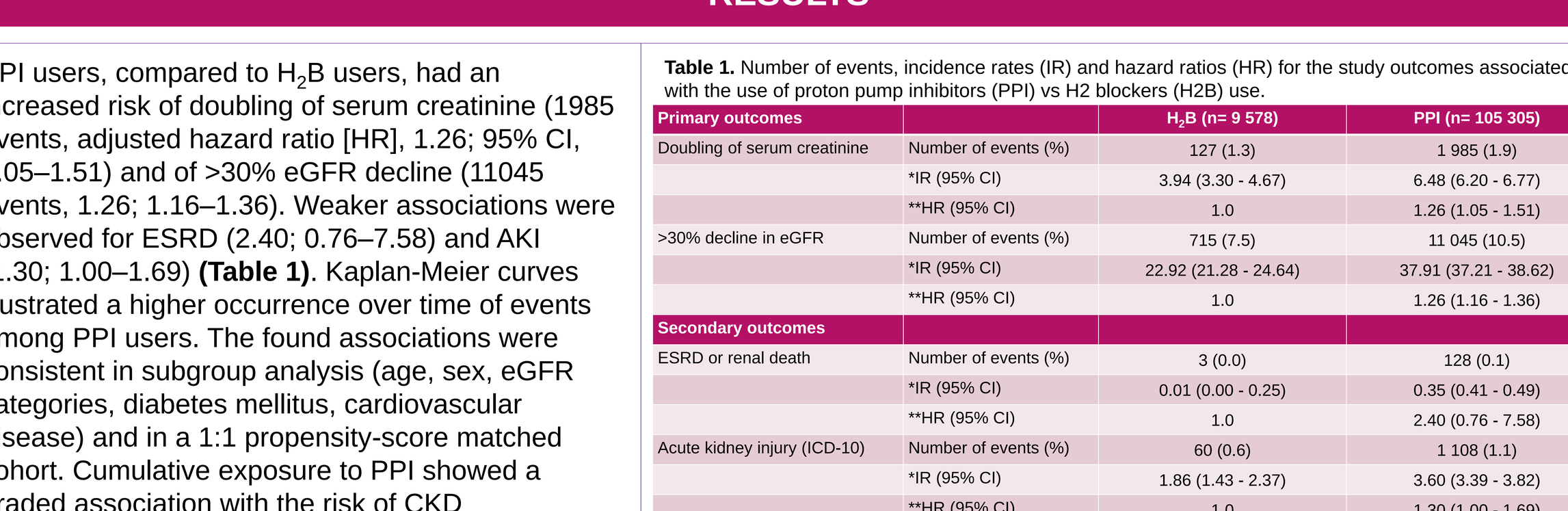
PPI users, compared to $H_2$B users, had an increased risk of doubling of serum creatinine (1985 events, adjusted hazard ratio [HR], 1.26; 95% CI, 1.05–1.51) and of >30% eGFR decline (11045 events, 1.26; 1.16–1.36). Weaker associations were observed for ESRD (2.40; 0.76–7.58) and AKI (1.30; 1.00–1.69) **(Table 1)**. Kaplan-Meier curves illustrated a higher occurrence over time of events among PPI users. The found associations were consistent in subgroup analysis (age, sex, eGFR categories, diabetes mellitus, cardiovascular disease) and in a 1:1 propensity-score matched cohort. Cumulative exposure to PPI showed a graded association with the risk of CKD progression. This was not the case for cumulative $H_2$B use **(Figure 1)**.

**Table 1.** Number of events, incidence rates (IR) and hazard ratios (HR) for the study outcomes associated with the use of proton pump inhibitors (PPI) vs H2 blockers (H2B) use.

| Primary outcomes | | $H_2$B (n= 9 578) | PPI (n= 105 305) |
|---|---|---|---|
| Doubling of serum creatinine | Number of events (%) | 127 (1.3) | 1 985 (1.9) |
| | *IR (95% CI) | 3.94 (3.30 - 4.67) | 6.48 (6.20 - 6.77) |
| | **HR (95% CI) | 1.0 | 1.26 (1.05 - 1.51) |
| >30% decline in eGFR | Number of events (%) | 715 (7.5) | 11 045 (10.5) |
| | *IR (95% CI) | 22.92 (21.28 - 24.64) | 37.91 (37.21 - 38.62) |
| | **HR (95% CI) | 1.0 | 1.26 (1.16 - 1.36) |
| **Secondary outcomes** | | | |
| ESRD or renal death | Number of events (%) | 3 (0.0) | 128 (0.1) |
| | *IR (95% CI) | 0.01 (0.00 - 0.25) | 0.35 (0.41 - 0.49) |
| | **HR (95% CI) | 1.0 | 2.40 (0.76 - 7.58) |
| Acute kidney injury (ICD-10) | Number of events (%) | 60 (0.6) | 1 108 (1.1) |
| | *IR (95% CI) | 1.86 (1.43 - 2.37) | 3.60 (3.39 - 3.82) |
| | **HR (95% CI) | 1.0 | 1.30 (1.00 - 1.69) |

*IRs reported per 1 000 persons-years.
**HRs were obtained from Cox models adjusted for age, sex, eGFR at baseline, indications for acid-suppression therapy (gastroesophageal reflux disease, Barret oesophagus, ulcer disease, H. pylori infection, upper gastrointestinal tract bleeding), diabetes mellitus, hypertension, peripheral vascular disease, acute myocardial infarction, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, NSAIDs, RAAS-inhibitors, beta blockers, calcium channel blockers, antithrombotics, statins, and diuretics.

**Figure 1.** Hazard ratios (and 95% confidence intervals) for the risk of doubling of serum creatinine (Panel A) or >30% eGFR decline (Panel B) associated with the cumulative use of proton pump inhibitors (PPI). Histograms depict the proportion of participants across cumulative exposure strata**.**




Cumulative exposure to PPI was calculated as the time-updated sum of drug use (DU) since therapy initiation, which was modelled as a time-dependent variable in restricted cubic spline regressions. Five knots were set at 5th, 27.5th, 50th, 72.5th, and 95th percentiles of DDDs distribution. Hazards were adjusted for age, sex, eGFR at baseline, indications for acid-suppression therapy (gastroesophageal reflux disease, Barret oesophagus, ulcer disease, H. pylori infection and upper gastrointestinal tract bleeding), diabetes mellitus, hypertension, peripheral vascular disease, acute myocardial infarction, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease and concomitant medications (NSAIDs, RAAS-inhibitors, beta blockers, calcium channel blockers, anti-thrombotics, statins, and diuretics). The lowest cumulative DU (0.50 mg) was used as the reference.

## CONCLUSIONS

Initiation of PPI therapy and cumulative PPI exposure associated with increased risk of CKD progression in a large North European healthcare system.

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