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Timely Cessation of Proton Pump Inhibitors in Critically Ill Patients Impacts Morbidity and Mortality: A Propensity Score-Matched Cohort Study*

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OBJECTIVE: Proton pump inhibitors (PPIs) are among the drugs most commonly used in critically ill patients. Although mainly applied temporarily for stress ulcer prophylaxis, their application is frequently not terminated. Potential adverse effects of PPI treatment could impact the outcome in case of unnecessary and, therefore, avoidable long-term continuation. We tested the hypotheses that nonindicated PPI therapy continued beyond hospital discharge is associated with increased morbidity, rehospitalization rate, and mortality.

DESIGN: Nationwide retrospective cohort study considering critically ill patients treated on German ICUs between January, 2017, and December, 2018 with a 2-year follow-up.

SETTING: A total of 591,207 patient datasets of a German healthcare insurer were screened.

PATIENTS: We identified 11,576 ICU patients who received PPI therapy for the first time during their index ICU stay without having an indication for its continuation.

INTERVENTIONS: The cohort was stratified into two groups: 1) patients without further PPI therapy and 2) patients with continuation of PPI therapy beyond 8 weeks after hospital discharge.

MEASUREMENTS AND MAIN RESULTS: Frequency of predescribed adverse events associated with PPI therapy, 1-year rehospitalization rate, and 2-year mortality were determined. The proportion of patients with continued PPI therapy without an objectifiable indication was 41.7% (4,825 of 11,576 patients). These patients had a 27% greater risk of pneumonia (odds ratio [OR] 1.27; 95% CI, 1.15–1.39; $p < 0.001$) and a 17% greater risk of cardiovascular events (OR 1.17; 95% CI, 1.08–1.26; $p < 0.001$). Continued PPI therapy was associated with a 34% greater risk of rehospitalization (OR 1.34; 95% CI, 1.23–1.47) and a nearly 20% greater 2-year mortality risk (hazard ratio 1.17; 95% CI, 1.08–1.27; $p = 0.006$).

CONCLUSIONS: These data demonstrate that an unnecessary continuation of PPI therapy after hospital discharge may significantly impact morbidity and mortality. To avoid potentially harmful overuse of a PPIs, intensivists should ensure timely cessation of a temporarily indicated PPI therapy.

KEYWORDS: adverse effects; cessation; overuse, overtreatment; proton pump inhibitors

Proton pump inhibitors (PPIs) are among the most commonly prescribed medications, usually with a short-term indication and a recommended duration of less than 8 weeks (1–3). A major short-term indication is stress ulcer prophylaxis (SUP) (4), especially in ICUs, where certain critically

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KEY POINTS

Question: Does unnecessary long-term continuation of newly initiated stress ulcer prophylaxis in the ICU impact on morbidity and mortality after hospital discharge?

Findings: This retrospective cohort study shows that a continued proton pump inhibitor therapy without indication after hospital discharge in former critically ill patients is frequent and associated with increased morbidity, higher 1-year rehospitalization rate and lower 2-year survival.

Meaning: To avoid potentially harmful overtreatment with proton pump inhibitors in previously critically ill patients, intensivists should ensure timely cessation of an only temporarily indicated pump inhibitor therapy.

ill patients are at increased risk of gastrointestinal bleeding (5–7). Although there is controversy about which patients in the ICU benefit from SUP, the latter is currently initiated in up to 90% of all critically ill patients (8–12). However, regardless of the debate on which ICU patients should receive PPI therapy, its timely cessation once the indication has expired is of utmost importance since PPI therapies not only result in an economic burden but may also evoke serious side effects (3, 13, 14). Greater risk of clostridium difficile infection (15–18), gastritis (17), pneumonia (15), cardiovascular events (19, 20), chronic renal failure (21, 22), greater frequency of various neoplasms (23–27), possibly malabsorption disorders evoking vitamin B12 deficiency (28, 29), hypocalcemia (30), and hypomagnesemia (30) are specific predescribed side effects of a long-term PPI therapy. Even an increased risk of mortality has been observed in retrospective studies (31–34).

Nevertheless, temporary PPI treatment started in an ICU is often continued over the further hospital course and, in some cases, even beyond hospital discharge (35, 36). This may inadvertently turn into an unnecessary permanent PPI medication as the initial indication, for example, SUP, no longer prevails (4, 37). Studies showed that approximately one-third of former ICU patients are discharged from the hospital with a continuing PPI therapy, but without an appropriate ongoing indication (38). Because ICU patients are often characterized by various transfers and handovers between different departments until hospital discharge, they may particularly carry a high risk of missing the timely cessation of their PPI medication. However, to the best of our knowledge, there is no data that examines an intensive care cohort with new-onset SUP and unnecessary continuation beyond hospital discharge. It is unclear to what extent this pharmacologic overtreatment affects the long-term outcome of former critically ill patients. Accordingly, we tested former ICU patients to ascertain whether the hypotheses that continuation of a PPI therapy without an objectifiable indication beyond 8 weeks after hospital discharge is associated with: 1) an increased frequency of adverse effects, 2) a higher rehospitalization rate, or 3) increased mortality.

MATERIALS AND METHODS

Data Source and Study Design

We used health claims data from a large German health insurer in this retrospective cohort study. These data have been rigorously reviewed internally and externally (e.g., by the German medical service of public health insurances).

The study was reviewed and approved by the ethics committee of the Medical Faculty of the University of Bochum (ethics vote: number 21-7392-BR). The requirement for informed consent was waived due to the deidentified nature of the data.

Patient Collective

A dataset covering 591,207 adult patients hospitalized between January 1, 2017, and December 31, 2018, was screened. We initially selected critically ill patients in need of a complex multimodal intensive care treatment (German OPS-Code 8-980 and 8-98f) and the initiation of PPI therapy during the ICU stay. Subsequently, we aimed to form a cohort of previously critically ill patients with the following characteristics:

1) Not receiving PPI for a period of more than one month in the year prior to the index hospital admission.
2) Newly initiated PPI treatment during their ICU stay.
3) No coded indication for PPI therapy beyond eight weeks after hospital discharge.

The documented diagnoses and preexisting conditions were reviewed to identify the patients with a potentially inappropriate PPI therapy. All cases were identified using the *International Classification of Diseases*, 10th revision, German modification. We assessed our cohort regarding the indications listed in **eTable 1** (http://links.lww.com/CCM/H451) and deemed a PPI therapy as appropriate when at least one of these criteria applied to a patient. If the assessment revealed an appropriate objectifiable indication for a continued PPI therapy, these patients were excluded from our study so as to focus on temporary SUP (14). A total of 11,576 patients without missing values met the selection criteria mentioned above and were included in propensity score matching (**Fig. 1**).

Subsequently, all patients included (n = 11,576) were screened for the presence of PPI therapy after hospital discharge using the documentation available. Patients were then allocated to two groups. Members of group 1 have not received any further PPI therapy beyond 8 weeks after hospital discharge, deemed as appropriate cessation of a short-term PPI treatment. Members of group 2 have received PPI therapy after hospital discharge without an objectifiable indication for at least 8 weeks after discharge, deemed as inappropriate continuation.

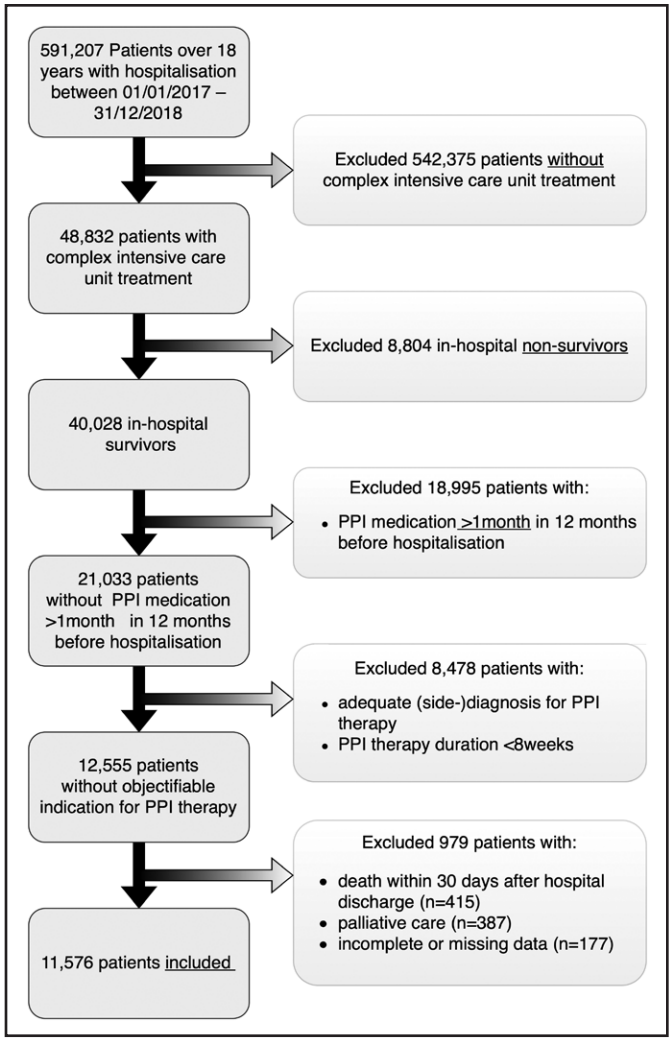

Figure 1. Data from 591,207 adult patients hospitalized between January 1, 2017, and December 31, 2018, were screened. A total of 48,832 patients who received intensive care treatment and survived the hospitalization were considered. Existing proton pump inhibitor (PPI) therapy before admission and an indication for PPI therapy after discharge led to exclusion. Palliative discharges, death within the first 30 days after discharge and incoherent or missing health claims data also led to exclusion. A total of 11,576 patients were included and allocated into two groups according to the presence of PPI therapy.

Patient Matching

We performed a propensity score matching to compare outcomes between patients without PPI therapy and those who unnecessarily continued the therapy. Using the literature available, we created a directed acyclic graph model to determine which variables potentially impact the outcome and probability of receiving PPI. Using regression analyses, we identified relevant factors that we implemented in our propensity score model. These include age, gender, year of admission, Charlson index (39) before hospital admission, number of comorbidities before hospital admission and diagnoses acquired during the index stay, number of medications prescribed at hospital discharge, prescription of anticoagulation for at least 3 months after hospitalization, prescription of antiplatelet drugs for at least 3 months after hospitalization, prescription of nonsteroidal anti-inflammatory drugs for at least 3 months after hospitalization, prescription of corticosteroids for at least 3 months after hospitalization, and the reason for their admission to the ICU. We included the case mix index of the hospital stay as an element for comparability of the disease severity, as it is a metric of the diversity, complexity and severity of the patients treated at a healthcare facility. We achieved the best balance by using the logit of a logistic regression propensity score. Nearest neighbor matching using the propensity score difference as a distance measure to determine which control case is closest to each patient treated with PPI using a caliper width set at 20% of the SD

of the propensity scores. A 1:1 matching without replacement in a random order was used. The criteria by which a matching specification was judged were balance and remaining sample size after matching. The balance of the propensity score matching was assessed using the standardized mean difference, and standardized differences of no more than 10% were considered negligible imbalances between both groups. See **eTable 2** and **eFigure 1** (http://links.lww.com/CCM/H451) for a more detailed description of the matching procedure and the distribution of the propensity scores before and after matching.

Outcome

We first analyzed the prevalence of the potential adverse effects of a continued PPI therapy within the first year after hospital discharge of the index admission mentioned above in both groups by assessment-confirmed medical diagnoses in a claim database as an outcome measure. Second, we determined the rehospitalization rate during the first year after discharge. Third, we assessed mortality rates within the first 2 years after hospital discharge.

Statistics

Continuous variables are presented as means ± SD in the case of normal distribution and as median and interquartile range (25th–75th percentile) in the case of non-normally distributed variables. Categorical variables were characterized by numbers (and percentages) and compared using the Chi-square test. Continuous variables were compared using Student *t* test for parametric variables, and the Mann-Whitney *U* test for nonparametric variables, as appropriate. An alpha error *p* value of less than 0.05 was considered statistically significant. Survival probabilities were graphically assessed by Kaplan-Meier curves and compared using a two-sided log-rank test. We used an univariate Cox regression to determine a crude hazard ratio (HR_{crude}) between the propensity score-matched groups. Potential persistent confounders were determined in accordance with our baseline covariates, with a standardized difference of more than 10% indicating an insufficient covariate balance. Thereafter, we used a multivariate Cox regression analysis to determine an adjusted HR_{adj} with chronic kidney disease, diabetes mellitus, hypertension, and ischemic heart disease as covariates to compare the survival between both propensity score-matched groups.

RESULTS

Patients Without Objectifiable PPI Indication

The proportion of patients on PPI therapy for at least 8 weeks after hospital discharge without objectifiable indication was 41.7% (4,825 of 11,576 patients). See **eTable 3** (http://links.lww.com/CCM/H451) for characteristics of the matched cohort. Characteristics of the unmatched cohort are available in **eTables 4** and **5** (http://links.lww.com/CCM/H451). The distribution of the 4,825 patients included long-term (> 8 wk–1 yr) PPI therapy in 2,154 (45%) and permanent therapy (> 1 yr) in 2,671 (55%) patients. Their baseline characteristics and outcomes are shown in **eTables 6** and **7** (http://links.lww.com/CCM/H451). We did not observe an association between medical, surgical, or cardiac surgery patients, nor between academic and nonacademic hospitals and a continuation of an SUP (eTable 3, http://links.lww.com/CCM/H451).

Associations With Possible Adverse Effects of PPI Therapy

Focusing on cardiopulmonary diseases, patients with continued PPI therapy had a 27% greater risk of pneumonia (OR 1.27; 95% CI, 1.15–1.39; $p < 0.001$) and a 17% greater risk of cardiovascular events (OR 1.17; 95% CI, 1.08–1.26; $p < 0.001$).

Regarding renal disease, there was a 26% greater risk of developing chronic renal failure (OR 1.26; 95% CI, 1.12–1.41; $p < 0.001$). There was no significant difference regarding acute intestinal nephritis (OR 1.21; 95% CI, 0.70–2.08; $p = 0.69$).

Considering malignancies, a 2.7-fold increased risk of esophageal (OR 2.74; 95% CI, 1.37–5.47; $p = 0.004$) and a 2.4-fold increased risk of pancreatic cancer (OR 2.44; 95% CI, 1.63–3.64; $p < 0.001$) was associated with PPI therapy. The risk of colorectal cancer was increased by 19% (OR 1.19; 95% CI, 1.03–1.37; $p = 0.006$), whereas there was no difference regarding gastric neoplasms (OR 0.87; 95% CI, 0.56–1.33; $p = 0.51$).

When malabsorption was examined, a 1.3-fold increased risk of vitamin B12 deficiency (OR 1.30; 95% CI, 1.13–1.49; $p < 0.001$), a 2.1-fold increased risk of hypomagnesemia (OR 2.11; 95% CI 1.24–3.60;

p = 0.006) and a 1.6-fold increased risk of hypocalcemia (OR 1.55; 95% CI, 1.22–1.96; p < 0.001) were observed (**Fig. 2**).

One-Year Rehospitalization Rate

A total of 3,544 of 4,825 patients with continued PPI therapy without objectifiable indication were readmitted to hospital within the first year, that is, a rehospitalization rate of 73.4%. This rate was 67.3% in the group without PPI therapy. This implies an absolute risk difference of 6.1% and an increased odd of rehospitalization of 35% (OR 1.35; 95% CI, 1.23–1.47; p < 0.001) in the first year in association with continued unobjectifiable PPI therapy (Fig. 2).

Two-Year Mortality Rate

After 2 years, 72.5% of all patients (3,497 of 4,825) in the continued PPI therapy group were alive. By contrast, 74.7% patients (3,604 of 4,825) without PPI therapy survived. Accordingly, the continuation of PPI therapy was associated with a nearly 20% increased 2-year mortality risk (HR_{adj} 1.17; 95% CI, 1.08–1.27; p < 0.001) (**Fig. 3**).

DISCUSSION

The main findings of this study are: 1) there is a large number of former critically ill patients who have received PPI therapy beyond 8 weeks of hospital discharge without objectifiable indication and 2) the continuation of PPI therapy without clear indication is associated with serious morbidity, an increased 1-year rehospitalization rate and increased 2-year mortality rate.

Focusing on a large and important cohort of former critically ill patients, our study revealed that a continued PPI therapy may significantly impact outcome and sequelae. We clearly illustrate that timely cessation of a temporarily indicated PPI treatment, for example, in terms of SUP, is of utmost importance but often neglected in clinical routine. In this context, our study

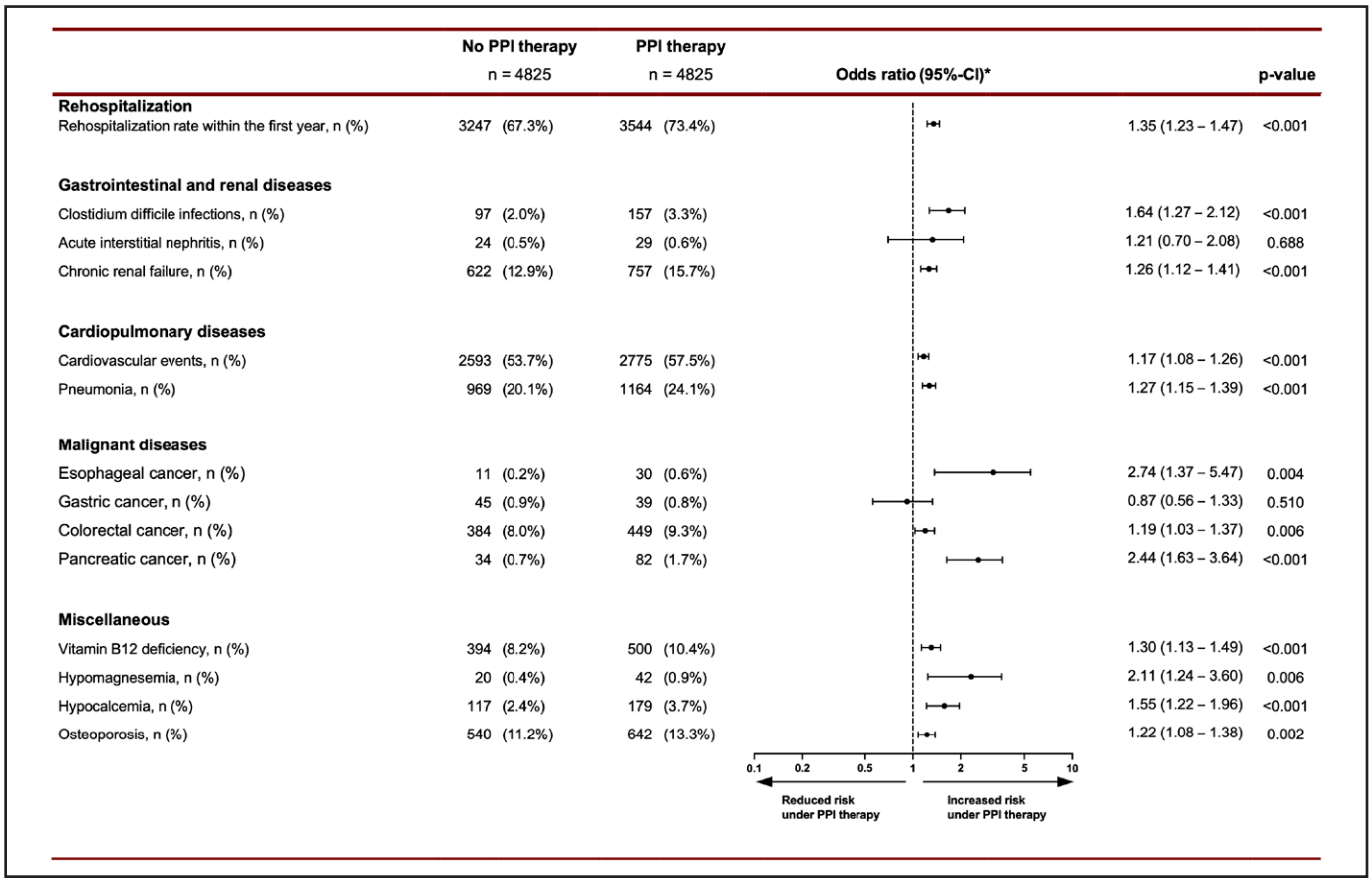

Figure 2. Frequency of rehospitalization and a selection of possible sequelae of proton pump inhibitor (PPI) with the resulting odds ratios and 95% CIs.The "no PPI therapy" group did not receive any further PPI therapy after hospital discharge. The "PPI therapy" group included patients in whom PPI therapy was started during hospital stay and continued for at least 8 weeks after discharge.

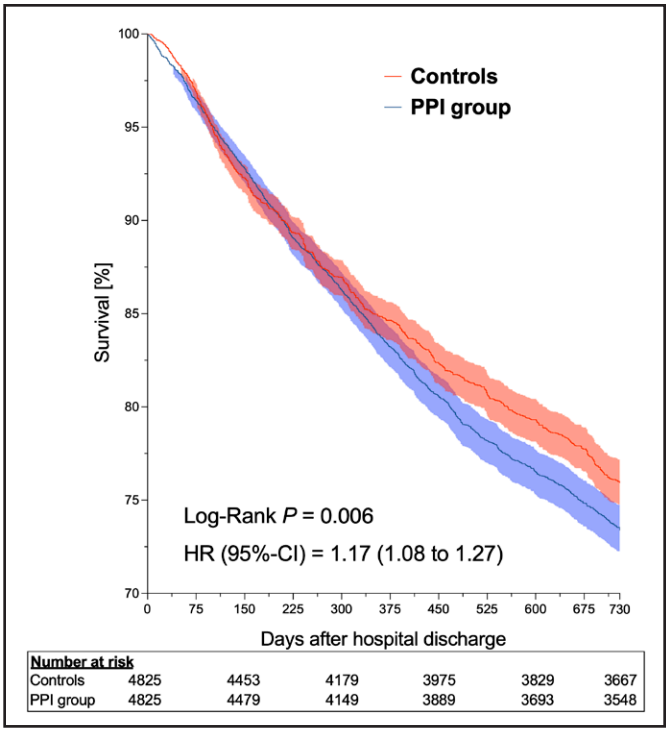

Figure 3. Kaplan-Meier estimator for a 2-year mortality rate with depiction of patients without proton pump inhibitor (PPI) therapy (*red color*) as well as those with unobjectifiable PPI therapy indication (*blue color*), where PPI therapy started within the hospital and was continued for at least 8 weeks after discharge. At 2 years after discharge from the index hospitalization, continued PPI therapy without an objectifiable indication was associated with a 17% increased 2-year mortality risk. HR = hazard ratio.

is the first that focuses exclusively on potentially inappropriate prescribing patterns in critically ill patients after the ICU and hospital discharge. It is alarming that a routine intervention such as the cessation of PPI treatments can become a major burden, which is even more unacceptable for the vulnerable group of former ICU patients.

Our results particularly include an association with an increased risk of the occurrence of cardiorespiratory diseases, such as a nearly 30% greater risk of pneumonia. While this magnitude of risk is lower than those of recent meta-analyses, which report an up to two-fold greater risk of developing community-acquired pneumonia (40), the smaller effect in our study may be partially explained by the a priori high frequency of community-acquired pneumonia of about 20% in former ICU patients even without PPI therapy in the first year after discharge. Additionally, we used a complex matching procedure allowing the implication of as many pertinent confounders as possible to avoid a biased overinterpretation of our data to achieve sufficient comparability between both groups. Consequently, our statistical approach appears more conservative compared with the studies included in the referenced meta-analysis (40). Nevertheless, PPI therapy for no objectifiable reason increases our observed baseline of a 20% pneumonia rate in the first year after hospital discharge to almost a quarter of all cases, which implies an important harmful impact for our population of former critically ill patients.

Analogous to pneumonia, our cohort without PPI already shows a high vulnerability with a risk of more than 50% for cardiovascular events in the first year after discharge. This is increased by nearly another 20% in association with an PPI treatment. In this context, a high-risk group for new or recurrent cardiovascular events had already been excluded from our study due to receiving dual antiplatelet therapy as part of their acute and postacute treatment and, therefore, having a potential indication for PPI therapy (41).

Our results are consistent with a recent meta-analysis reporting a 22% increased risk of cardiovascular events associated with PPI therapy in different populations and settings across the heterogeneous field of literature (42). Based on these findings, the concernedly increased risk of 35% for hospital readmission in the first year after hospital discharge found in our study seems a logical consequence, with pneumonia and cardiovascular events being the leading causes of hospital readmissions after ICU care (43).

However, the evidence and plausibility of some of the adverse effects of a PPI treatment mentioned above are being controversially debated based on the mostly observational or retrospective design of the studies currently available. In particular, associations of neoplasia with PPI therapy are situated in a heterogeneous data setting. Here, our balanced and conservative statistical approach detected no significant associations with gastric carcinomas and a continued PPI therapy, although it is frequently reported in other studies (44). However, our findings are in accordance with the results of a recent meta-analysis by Piovani et al (45). They also could not demonstrate a significant association between gastric cancer and PPIs when considering age, sex and at least two additional potential confounders lying on the causal pathway of gastric

cancer development. In doing so, they followed an approach similar to ours, in which we considered 12 variables for propensity score matching and achieved a fair level of comparability without significant differences between both groups (eTable 3, http://links.lww.com/CCM/H451). Regarding mortality, although a recent prospective study failed to demonstrate an impact of PPI therapy on mortality in ICU patients when evaluating 90-day survival (11), the observation period of 2 years after hospital discharge is a further strength of our study. Within the first 90 days up to the first year after hospital discharge, these results are congruent with our data, as we did not find an impact on mortality during this period. Consideration of the second year after discharge appears to be of importance, as the mortality differences were particularly presented here. This finding lines up with observational studies showing an increasing risk of mortality with an increasing duration of a PPI therapy (32).

Regardless of the controversy surrounding the evidence and study quality, our study reinforces the potentially harmful impact of PPI therapy. This becomes more important as our study focuses exclusively on patients who did not require further PPI treatment after hospital discharge.

With 41.7% (4,825 of 11,576) of former ICU patients discharged from the hospital with ongoing unnecessary PPI therapy for longer than 8 weeks, the question arises as to why this problem occurs so frequently. Unfortunately, due to the nature of the claims data analyzed of a large German healthcare insurer operating nationwide, we cannot pinpoint the causality between the source of the problem and physicians' behavior. Nevertheless, we tried to exclude the most significant confounders that may bias the proper interpretation of our data, for example, limiting our observation period so as to minimize any impact of different or changing coding and prescribing patterns over time.

Previous attempts to explain why a temporarily intended PPI therapy has not been ceased after an ICU stay include a lack of documentation of the PPI indication, knowledge gaps of the responsible physician regarding recommended guidelines and insufficient physician time to review the patients' complete medical history (46, 47). A potential strategy to avoid an unnecessary long-term PPI therapy may be to stop temporary medication orders prior to transfer from the ICU to the ward if appropriate. If this is not applicable due to an ongoing indication for PPI, discharge letters should explicitly include the indication and the suggested duration of such a prescription. In this way, the ward physicians who continue the patient's treatment can find out immediately how long the therapy is suggested by the initiating intensive care physician.

Regular staff training, visits by clinical pharmacists and the establishment of standard operating procedures have already shown to significantly decrease unnecessary PPI prescriptions (48–50). These studies consistently demonstrate that inappropriate continuation of PPI therapy can be decreased by simple but targeted interventions, and the sufficient vigilance of attending physicians is decisive. Thus, our data call for an immediate improvement to avoid potential harm related to an unnecessary PPI overtreatment.

LIMITATION

Despite the inclusion of all possible indications for PPI therapy, the retrospective design of our study may not completely rule out that PPI continuation was still reasonable in individual cases. In addition, despite great statistical efforts made to control all pertinent confounders, we cannot entirely exclude a residual bias, even after our conservative statistical approach to adjust for intergroup imbalances. Health claim data do not include information on several important clinical factors, such as laboratory values or more detailed disease severity (e.g., Sequential Organ Failure Assessment Score). Therefore, the data may be susceptible to biased patient selection and limited patient stratification. Furthermore, it must be considered that our retrospective study design only supports associations and does not necessarily describe causality. Thus, we cannot exclude uncertainty about some PPI-associated posthospital diagnoses (e.g., cancer). To overcome these uncertainties, additional analyses in diverse populations will be important to confirm these findings. Such studies would ideally be prospective and allow the collection of detailed data on additional potential confounders, such as comorbidities and conditions acquired during the hospital stay. However, randomizing patients to prolonged unnecessary PPI therapy in an upcoming randomized controlled trial might not be ethically feasible. Causal inference models may be particularly helpful here for analysis if randomized controlled trials are not

feasible. In addition, it must be mentioned that only PPI drugs were considered in our study. Histamine-2-receptor antagonists are also commonly used for SUP, and these should be assessed in further studies. It would also be of great interest to elucidate any risk factors that influence whether a SUP is stopped in a timely manner or not. Finally, although our data showed significant associations with adverse effects, they do not provide specific insights into why PPI therapy is so often administered without an objectifiable indication. Further work, for example, in the form of surveys, is needed to investigate the causes of the overprescribing practice observed.

CONCLUSIONS

Our results demonstrate an excessive overtreatment with PPI in prior critically ill ICU patients following 8 weeks after hospital discharge, with a lack of indication for PPI treatment in a large proportion of patients. This may be due to an unreflective continuation of PPI therapy started in the ICU, which results in remarkable harm with multiple adverse effects, increased readmission to hospital and an increased 2-year mortality. These data force the vigilance of the ICU physician toward communication and interventions ensuring timely cessation of an only temporarily indicated PPI therapy.

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Drs. Palmowski and Rahmel, von Busch, Schmitz were involved in conceptualization. Drs. Palmowski, Rahmel, and Peters were involved in writing the original draft. Drs. Palmowski, Rahmel, Peters, Unterberg, Bergmann, Adamzik, and Schmitz were involved in revision of original draft. Drs. Schmitz, Schlüter, Rahmel, and von Busch were involved in data generation and patient recruitment. Drs. Palmowski, Rahmel, Schmitz, and von Busch were involved in data analysis. Drs. Bergmann, Unterberg, Adamzik, and Schlüter were involved in supervision.

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The dataset analyzed during the current study is available from the corresponding author on reasonable request.

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