Proton-Pump Inhibitors Are Associated With Increased Cardiovascular Risk Independent of Clopidogrel Use
A Nationwide Cohort Study

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Background: Controversy remains on whether the dual use of clopidogrel and proton-pump inhibitors (PPIs) affects clinical efficacy of clopidogrel.

Objective: To examine the risk for adverse cardiovascular outcomes related to concomitant use of PPIs and clopidogrel compared with that of PPIs alone in adults hospitalized for myocardial infarction.

Design: A nationwide cohort study based on linked administrative registry data.

Setting: All hospitals in Denmark.

Patients: All patients discharged after first-time myocardial infarction from 2000 to 2006.

Measurements: The primary outcome was a composite of rehospitalization for myocardial infarction or stroke or cardiovascular death. Patients were examined at several assembly time points, including 7, 14, 21, and 30 days after myocardial infarction. Follow-up was 1 year.

Results: Of 56,406 included patients, 9,137 (16.2%) were rehospitalized for cardiovascular death. Patients were examined at several assembly time points, including 7, 14, 21, and 30 days after myocardial infarction. The hazard ratio for cardiovascular death or rehospitalization for myocardial infarction or stroke for concomitant use of a PPI and clopidogrel compared with that of PPIs alone was 1.29 (95% CI, 1.17 to 1.42). No statistically significant interaction occurred between a PPI and clopidogrel (P = 0.72).

Limitations: Unmeasured and residual confounding, time-varying measurement errors of exposure, and biases from survival effects were possible.

Conclusion: Proton-pump inhibitors seem to be associated with increased risk for adverse cardiovascular outcomes after discharge, regardless of clopidogrel use for myocardial infarction. Dual PPI and clopidogrel use was not associated with any additional risk for adverse cardiovascular events over that observed for patients prescribed a PPI alone.

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Clopidogrel is a platelet inhibitor that reduces the risk for new ischemic cardiovascular events, in combination with aspirin, in patients treated either medically or with percutaneous coronary intervention (PCI) after myocardial infarction (1–3). Proton-pump inhibitors (PPIs) are often given in combination with clopidogrel and aspirin to reduce the risk for upper gastrointestinal bleeding. Clopidogrel is a prodrug that is metabolized to an active metabolite primarily by the hepatic P-450 enzyme 2C19 (4). Because PPIs are metabolized by the same hepatic isoenzyme (5), concern has been raised that PPIs might inhibit the conversion of clopidogrel to its active metabolite and thereby diminish its clinical benefit.

Recent studies show that PPIs reduce the ex vivo inhibition of platelet aggregation achieved during treatment with clopidogrel (6–8). Clinical studies involving selected populations (9–13) show conflicting results regarding risk for adverse cardiovascular events associated with the dual use of clopidogrel and PPIs. The U.S. Food and Drug Administration (14, 15) and the European Medicines Agency (16) have recently discouraged the combined use of these agents unless strongly indicated, while emphasizing the need for further studies. We sought to examine the risk for adverse cardiovascular outcomes related to concomitant use of PPIs and clopidogrel compared with that of PPIs alone in a large, unselected cohort of patients hospitalized with first-time myocardial infarction.

Methods

Design Overview

In Denmark, every resident is provided with a permanent and unique civil registration number that enables individual-level linkage between different registries. Our
nationwide cohort study linked Danish national registry data relevant to hospitalizations, pharmacy prescription claims, and deaths for 4.65 million people.

For all hospital admissions in Denmark, the Danish National Patient Registry registers a primary diagnosis and, if appropriate, 1 or more secondary diagnoses, as defined by the International Classification of Diseases. The Danish Registry of Medicinal Product Statistics (a national prescription registry) records every prescription dispensed from pharmacies in Denmark, and each drug is classified according to the International Anatomical Therapeutical Chemical system. Information on vital status and causes of death were obtained, respectively, from the Danish Civil Registry and the National Causes of Death Registry.

The Danish Data Protection Agency approved the study, and the data made available to us were such that individuals could not be identified. Retrospective registry studies do not require ethical approval in Denmark. The authors had full access to the data and take full responsibility for its integrity.

Patient Population

From the National Patient Registry, we identified all consecutive patients older than 30 years who were hospitalized with acute myocardial infarction between 2000 and 2006 in Denmark. To ensure the homogeneity of our population, patients with previous myocardial infarction and patients with partially missing data were excluded. We depended on patients filling prescriptions to identify users. Our primary analysis included patients who survived at least 30 days because we reasoned that a 30-day period would facilitate correct classification of drug use; most patients who filled their prescriptions did so within 30 days (Appendix Figure 1, available at www.annals.org). We also examined the sensitivity of the results to the 30-day cutoff by examining alternative cohorts that included patients who survived 7, 14, and 21 days after myocardial infarction. Patients who emigrated were censored at the time of emigration.

Drug Use

Using the national prescription registry, we identified all prescriptions of drugs claimed up to 90 days after discharge (Table 1), as well as all prescriptions for PPIs and H2-antagonists claimed within 1 year after discharge. Information on medication exposure for each day of follow-up was also obtained, including dispensing date, type, quantity, dose of drug, and days of drug supply. No data on patient-reported adherence were available. We defined current use as the period from the prescription filling date to the calculated end of the period drug supply. Of note, the national prescription registry has demonstrated accuracy (17), and the use of clopidogrel is reasonably stable over time in this cohort, with a 1-year persistency of 89% after 2004 (18).

Context

Observational studies show mixed signals about risk for cardiovascular events with the dual use of proton-pump inhibitors (PPIs) and clopidogrel compared with clopidogrel alone.

Contribution

This observational study, based on administrative data from all hospitals in Denmark, found that patients who received clopidogrel and PPIs at discharge after a first-time myocardial infarction had similar risks for cardiovascular death, myocardial infarction, or stroke as did those of patients who received PPIs alone.

Caution

Possible confounding and no information on adherence or over-the-counter drug use limit interpretation.

Implication

Concurrent PPI and clopidogrel use after myocardial infarction may not be associated with additional risk over that observed with PPIs alone.

Outcomes

The primary outcome was a composite of rehospitalization for myocardial infarction or stroke or cardiovascular death. Secondary outcomes included all-cause death, cardiovascular death, and rehospitalization for myocardial infarction, stroke, or gastrointestinal bleeding. Follow-up was up to 1 year after discharge. The diagnoses of acute myocardial infarction and stroke have been validated in the Danish National Patient Registry (19, 20).

Comorbidity

Comorbid conditions were established on the basis of diagnoses noted at the time of discharge from the index myocardial infarction, as specified in the Ontario acute myocardial infarction mortality prediction rule (21). The comorbidity index was further enhanced by adding diagnoses from the year before the event, as was done by Rasmussen and colleagues (22).

Concomitant use of loop diuretics or diabetes medication was a proxy for heart failure or diabetes, respectively, to define high-risk subgroups of patients, as was done by Gislason and colleagues (23).

Statistical Analysis

We used 2 statistical methods to estimate the risk associated with PPI treatment with or without concomitant treatment with clopidogrel.

First, we used Cox proportional hazards models to derive hazard ratios (HRs) and 95% CIs. These models were adjusted for the variables shown in Table 1, including age, sex, PCI, income, concomitant medical treatment, and comorbid conditions. Exposure to PPIs was included as a time-dependent covariate.
Second, we performed a propensity score–matched analysis, in which we quantified a propensity score for the likelihood of receiving a PPI in the first year after discharge by using multivariate logistic regression analysis, conditional on the baseline covariates specified in Table 1. Using the Greedy matching macro (http://mayoresearch.mayo.edu/mayo/research/biostat/upload/gmatch.sas; accessed on 27 July 2010), we matched each case patient to a control participant on the basis of propensity score. Use of PPIs was included as a time-dependent covariate, and propensity score-matched Kaplan–Meier estimates were generated to show event rates and time-to-event curves.

To assess the robustness of our results, we performed a series of additional analyses, including an analysis that evaluated how large the effect of an unmeasured confounder would need to be to explain the results, subgroup analyses of different types of PPIs, and a dose-dependent analysis (24). We also assessed the variation of both PPI use and outcome between hospitals and performed a stratified analysis according to PCI and aspirin use. All statistical calculations were performed with SAS, version 9.2 (SAS Institute, Cary, North Carolina).

Role of the Funding Source
Our study was funded by the Danish Medical Research Council and the Danish Heart Foundation. The study sponsors had no influence on the study design, data collection, analysis, data interpretation, or decision to submit the manuscript for publication.

RESULTS

Patients
A total of 71,987 patients were admitted with myocardial infarction from 2000 to 2006 (Figure 1). Of these, we excluded 1,889 patients with previous myocardial infarction, 13,324 patients who died during hospitalization or within 30 days of discharge, and 368 patients with partially missing data. Of the 56,406 patients included in the study, 24,704 (43.8%) claimed at least 1 prescription for PPIs within 30 days of discharge, and 368 patients with partially missing data. Of the 56,406 patients included in the study, 24,704 (43.8%) claimed at least 1 prescription for PPIs within 30 days of discharge, and 368 patients with partially missing data. Of the 56,406 patients included in the study, 24,704 (43.8%) claimed at least 1 prescription for PPIs within 1 year of discharge. The use of PPIs was equal in the 2 cohorts and independent of clopidogrel use (Appendix Table 1, available at www.annals.org).

Table 1 shows baseline characteristics of the study sample at the time of inclusion. Patients who received clopidogrel were younger, were more often male, received less concomitant medical treatment, had fewer comorbid conditions, and more often had PCI than patients who did not receive it.
receive clopidogrel. Patients who received PPIs were older, were more often female, received more concomitant medical treatment, and had more comorbid conditions than those who did not receive PPIs.

### Outcome

In the first year after inclusion, 9137 (16.2%) cardiovascular deaths and rehospitalizations for myocardial infarction or strokes were registered (Appendix Table 2, available at www.annals.org). Clopidogrel was associated with lower event rates, and PPIs were associated with higher event rates. The event rates were highest among patients who received a PPI but not clopidogrel (26.3%).

### Cox Proportional Hazards Regression Analysis

The time-dependent Cox proportional hazards regression analysis (Table 2), based on patients who filled prescriptions for clopidogrel within 30 days of discharge, demonstrated an increased risk for the primary end point (cardiovascular death or rehospitalization for myocardial infarction or stroke) among patients who received both clopidogrel and a PPI (HR, 1.29 [95% CI, 1.17 to 1.42]; \( P < 0.001 \)) compared with those who did not receive a PPI. Among patients who did not receive clopidogrel, PPI therapy was associated with a similar increase in risk (HR, 1.29 [CI, 1.21 to 1.37]; \( P < 0.001 \)). Results were consistent for the risk for all secondary outcomes (Table 2). The hazard rate ratio of the effect of the interaction between PPI and clopidogrel for the primary outcome analysis was 0.98 (CI, 0.88 to 1.10; \( P = 0.72 \)).

### Time-Dependent, Propensity Score–Matched Cox Proportional Hazards Regression Analysis

Using the propensity score generated from logistic regression models conditional on baseline covariates, we matched 6556 patients who received both clopidogrel and a PPI with the same number of patients who received clopidogrel but not a PPI. We also matched 8437 patients who did not receive clopidogrel but did receive a PPI with the same number of patients who received neither clopidogrel nor a PPI. Use of PPIs was included as a time-dependent covariate. The c-statistics were 0.65 and 0.65 for the clopidogrel and nonclopidogrel groups, respectively, which indicates an acceptable discriminative power for the models. Table 1 shows the baseline characteristics of the propensity score–matched populations and \( P \) values for the between-group differences (Appendix Tables 3 and 4 and Appendix Figure 2, available at www.annals.org, provide further details). For use of a PPI in combination with clopidogrel, with no PPI therapy as the reference, the HR for cardiovascular death or rehospitalization for myocardial infarction or stroke was 1.35 (CI, 1.22 to 1.50; \( P < 0.001 \)), whereas the HR for use of a PPI without clopidogrel was 1.43 (CI, 1.34 to 1.53; \( P < 0.001 \)). Analysis of the risk for the secondary outcomes generated similar results (Table 2). The propensity score–matched Kaplan–Meier analysis (Figure 2) depicts the elevated risk for cardiovascular death or rehospitalization for myocardial infarction or stroke for patients who received PPIs with or without clopidogrel.

### Subgroup Analyses of Different Types of PPIs

Of the 15 642 patients who claimed at least 1 prescription for PPIs, 4698 (30.0%) claimed prescriptions for pantoprazole, 2798 (17.9%) for lansoprazole, 2717 (17.4%) for omeprazole, 5316 (34.0%) for esomeprazole, and 113 (0.1%) for rabeprazole. Results from the time-dependent, Cox proportional hazards regression analysis and the Kaplan–Meier cumulative hazard estimates demonstrated no difference in risk associated with the type of PPI independent of clopidogrel treatment (Appendix Figures 3 and 4, available at www.annals.org). We did not include rabeprazole data in this analysis because the cohort was too small to generate reliable results.

### Additional Analyses

In the propensity score matching based on baseline covariates that predicted treatment with a PPI, the risk reduction for gastrointestinal bleeding in patients who received clopidogrel and a PPI was 0.82 (CI, 0.63 to 1.07; \( P = 0.140 \)) compared with patients who did not receive a PPI. Therapy with a PPI had no effect in the group that did not receive clopidogrel (risk reduction, 0.99 [CI, 0.80 to 1.22]; \( P = 0.89 \)).

We estimated that an unmeasured confounder would have to elevate risk by 2.5 to 3 to fully explain the insubstantial HRs with absolute risk differences of only 1% to 2% for cardiovascular death or rehospitalization for myocardial infarction or stroke.
Included (n = 60,393)

Excluded (n = 11,594)
Previous MI: 1889
Missing data: 368
Died before discharge: 9,337

Included (n = 60,393)

Died within 7 d of discharge (n = 1,811)

>7-d cohort (n = 58,582)

No clopidogrel (n = 36,955)

Clopidogrel (n = 21,627)

>14-d cohort (n = 57,683)

No clopidogrel (n = 35,130)

Clopidogrel (n = 22,553)

>21-d cohort (n = 57,044)

No clopidogrel (n = 33,380)

Clopidogrel (n = 23,664)

>30-d cohort (n = 56,406)

No clopidogrel (n = 31,704)

Clopidogrel (n = 24,702)

No PPI (n = 27,031)
PPI (n = 9,924)

No PPI (n = 15,655)
PPI (n = 5,972)

No PPI (n = 16,327)
PPI (n = 6,226)

No PPI (n = 17,169)
PPI (n = 6,495)

No PPI (n = 17,949)
PPI (n = 6,753)

MI = myocardial infarction; PPI = proton-pump inhibitor.
increased risk for cardiovascular events observed with either PPI or clopidogrel and PPI (Appendix Figure 5, available at www.annals.org). To ensure the validity of using day 30 after discharge as the inclusion day, we examined differences in baseline characteristics at discharge and at day 30. We found that most patients (83.5%) who died in the first 30 days were from the cohort that had not filled prescriptions for clopidogrel or a PPI (Appendix Table 5, available at www.annals.org). Examinations of the study cohort at various assembly time points, including 7 and 21 days after myocardial infarction, revealed no differences in the hazard rate ratios of the effect of the interaction between PPIs and clopidogrel (Table 3).

An analysis subdivided by patients seen before and after 2004 provided no evidence of any differences in the effect of PPIs on outcome ($P = 0.14$). Interaction analyses between relevant subgroups of patients, PPI therapy, and outcome showed interactions ($P = 0.035$) for concomitant treatment with a PPI and clopidogrel and PCI, with a statistically significant higher risk for cardiovascular death or rehospitalization for myocardial infarction or stroke in a stratified analysis (HR, 1.40 [CI, 1.19 to 1.64]) than in the patient groups who did not have PCI (HR, 1.21 [CI, 1.07 to 1.38]) (Appendix Figure 6, available at www.annals.org). Stratifying patients by concomitant aspirin treatment showed no effect. Additional sensitivity analyses demonstrated no evidence of any clustering between hospitals and no evidence of any difference between high and low PPI doses (Appendix Figure 7 and Appendix Table 6, available at www.annals.org).

**Table 2. Association Between PPI Therapy and Risk for Adverse Cardiovascular Outcomes During 1-Year Follow-up**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time-Dependent Cox Proportional Hazards Model</th>
<th>Time-Dependent, Propensity Score–Matched Cox Proportional Hazards Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients Receiving a PPI but Not Clopidogrel</td>
<td>Patients Receiving a PPI and Clopidogrel</td>
</tr>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>Cardiovascular death, MI, or stroke</td>
<td>1.29 (1.21–1.37)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>All-cause death</td>
<td>1.58 (1.48–1.68)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1.49 (1.38–1.60)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>MI</td>
<td>1.13 (1.02–1.26)</td>
<td>0.020</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.32 (1.17–1.49)</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; PPI = proton-pump inhibitor.

* Reference was no PPI therapy. Exposure to PPIs was included as a time-dependent covariate.

An intense debate is now occurring about whether the diminished ex vivo antiplatelet effect of clopidogrel when combined with a PPI. Other studies (8, 14, 20, 21) have confirmed this finding.

A discussion is now occurring about whether the diminished ex vivo antiplatelet effect is of clinically significant importance. Several large observational studies (9–11, 25) found concomitant use of clopidogrel and a PPI to be associated with increased risk for death or rehospitalization for myocardial infarction. However, these studies were not based on populations that represent the average patient

**Figure 2. Propensity score–matched Kaplan–Meier analysis of risk for cardiovascular death, myocardial infarction, or stroke.**

PPI = proton-pump inhibitor.
who has had a myocardial infarction. For example, the studies from Juurlink and colleagues (9) and Rassen and associates (25) were based on retired patients older than 65 years, and Ho and colleagues (10) presented data from U.S. veterans (98% of whom were men). In contrast, a post hoc analysis of the randomized TRITON-TIMI 38 (Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel Thrombolysis In Myocardial Infarction 38) (12) found no increased risk for cardiovascular events with the combined use of PPIs and clopidogrel and no difference in risk between the various types of PPIs. A post hoc analysis of the randomized CREDO (Clopidogrel for the Reduction of Events During Observation) trial (11) also found baseline PPI use to be associated with increased cardiovascular events, regardless of whether clopidogrel was used. These studies were based on selected patients eligible for randomized trials, who were usually younger and less likely to have significant comorbid conditions than many patients who are prescribed both clopidogrel and a PPI. The prospective, randomized COGENT (Clopidogrel and the Optimization of Gastrointestinal Events) study (26), which was stopped before inclusion of patients was complete, evaluated the cardiovascular safety of concomitant treatment with omeprazole and clopidogrel and found no evidence of increased cardiovascular risk. Similar results were recently reported by Ray and colleagues (13). Of note, preliminary results from the COGENT study demonstrated an increased risk for gastrointestinal bleeding in patients who received dual antiplatelet treatment without PPI therapy. This increased bleeding risk was confirmed by Yasuda and colleagues (27), which emphasizes the importance of establishing the cardiovascular safety of concomitant PPI treatment. Ray and colleagues’ study (13) also illustrated the efficacy of PPI therapy in combination with dual antiplatelet treatment by showing a remarkable reduction in risk for gastrointestinal bleeding in patients who received combination therapy.

Our study furthers the research in this area by investigating the risk for cardiovascular events in a nationwide, unselected population that represents the average patient who has had a myocardial infarction. We demonstrated that PPI therapy did not modify the effect of clopidogrel on cardiovascular outcomes and that PPI use was associated with increased cardiovascular risk independent of concomitant use of clopidogrel.

We suspect that the increased cardiovascular risk in all patients who received a PPI can be explained by differences in baseline comorbid conditions that were unmeasured or measured imperfectly. Such unmeasured confounders would have to elevate the risk 2.5- to 3-fold to explain the observed increased risk for cardiovascular events. This is a large but potentially plausible amount of risk elevation for a confounder or a mix of confounders, particularly because these registry data lacked detailed information on risk factors, such as smoking, lipid levels, body mass index, and left ventricle ejection fraction.

We also demonstrated a reduction in risk for gastrointestinal bleeding related to PPI therapy for patients who received clopidogrel, although it did not reach statistical significance. In Denmark, PPIs are prescribed mainly for patients with a clear indication, such as peptic ulcer. Thus, we expected the cohort of patients treated with PPIs to be heavily confounded by the indication for PPIs and to have a higher bleeding risk than patients in countries where guidelines recommend routine use of PPIs in combination with dual antiplatelet therapy. This may explain why our study did not find a statistically significant protective effect of PPIs on risk for gastrointestinal bleeding.

Previous studies (9, 10) have reported that the risk for adverse cardiovascular outcomes was particularly increased by concomitant treatment with omeprazole and clopidogrel, on the basis of proposed differences in drug-specific metabolism and diminished antiplatelet effects ex vivo (6, 7, 23). Our data set provided no evidence of differences in risk between the subtypes of PPIs, with or without clopidogrel. Sensitivity analyses also provided no evidence of differences in risk related to heart failure, diabetes, age, hospitals, or PPI dosages. However, we did find a statistically significant interaction between PCI and PPIs in the group that received clopidogrel.

Several considerations and limitations may affect the interpretation of our results. We had no self-reported patient data regarding adherence. We were also dependent on patients filling prescriptions after discharge, and we chose

### Table 3. Association Between PPI Therapy and Risk for Adverse Cardiovascular Outcomes During 1-Year Follow-up*

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Patients Receiving a PPI but Not Clopidogrel†</th>
<th>Patients Receiving a PPI and Clopidogrel†</th>
<th>Hazard Rate Ratio (95% CI) P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>&gt;7 d</td>
<td>1.18 (1.10–1.24)</td>
<td>&lt;0.001</td>
<td>1.21 (1.09–1.34)</td>
</tr>
<tr>
<td>&gt;14 d</td>
<td>1.23 (1.16–1.30)</td>
<td>&lt;0.001</td>
<td>1.22 (1.10–1.36)</td>
</tr>
<tr>
<td>&gt;21 d</td>
<td>1.26 (1.19–1.34)</td>
<td>&lt;0.001</td>
<td>1.24 (1.12–1.37)</td>
</tr>
<tr>
<td>&gt;30 d</td>
<td>1.29 (1.21–1.37)</td>
<td>&lt;0.001</td>
<td>1.29 (1.17–1.42)</td>
</tr>
</tbody>
</table>

PPI = proton-pump inhibitor.
* Time-dependent Cox proportional hazards model. Reference was no PPI therapy. Times are in relation to inclusion day after discharge. Assessed outcomes were cardiovascular death, myocardial infarction, or stroke.
† Patients who filled or did not fill a prescription for clopidogrel.
day 30 as the inclusion day for primary analyses to avoid a potential immortal time bias. The comparison of baseline characteristics between day 30 and discharge (Table 1 and Appendix Table 5) illustrates this potential bias, because 83.5% of the patients who died in the first 30 days were in the cohort who did not fill a prescription for either clopidogrel or a PPI. The high 30-day mortality rate in this cohort can be explained by the inclusion of high-risk patients who may not have received clopidogrel or a PPI by the choice of their physicians, whereas other high-risk patients who were actually given prescriptions at discharge could have been too sick to fill their prescriptions or could have been readmitted to the hospital before they filled them. Of note, we examined the cohort at various assembly time points, including 7 and 21 days after myocardial infarction, and found no differences in the hazard rate ratios of the effect of the interaction between PPIs and clopidogrel in relation to assembly time point.

Our study’s strengths include the large size of our cohort based on a nationwide, unselected population that represents average patients in a contemporary clinical setting who have had a myocardial infarction. The Danish National Patient Registry includes all hospital admissions in Denmark and is therefore not affected by selection bias stemming from selective inclusion of specific hospitals, health insurance systems, or age groups. The concordance between drug dispensing and drug consumption is probably high, because reimbursement of drug expenses is only partial, and most drugs, including PPIs, were not available over the counter in Denmark during the study period (exceptions include aspirin and H₂-antagonists). Because of the partial reimbursement of drug expenses by Danish authorities, we reasonably assumed that a patient who claimed a prescription from the pharmacy intended to take the drug.

Our study has additional limitations. Clopidogrel resistance has been linked to genotype polymorphisms. Although we have no knowledge of the precise distribution of these polymorphisms in our largely white study population, several studies (28, 29) based in the countries that surround Denmark found variations in relevant genes that matched those reported earlier for white populations. However, generalizing these data to other racial and ethnic groups should be done with caution. Finally, we had no information on the indications for PPI therapy.

In conclusion, PPIs seem to be associated with an increased risk for adverse cardiovascular outcomes regardless of clopidogrel use, but concomitant PPI and clopidogrel use was not associated with any additional increase in risk over that observed for patients who received a PPI alone. We believe that the increased cardiovascular risk associated with PPI use independent of clopidogrel is caused by unmeasured confounders. These results seem to refute concerns about increased risk for ischemic events during concomitant PPI and clopidogrel therapy.

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Appendix Figure 1. Cumulative claimed prescriptions for clopidogrel after discharge for first myocardial infarction.
### Appendix Table 1. Descriptive Statistics for Clopidogrel and PPI Therapy During Follow-up

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patients Not Receiving Clopidogrel</th>
<th>Patients Receiving Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of PPI therapy (SD), d</td>
<td>147 (120)</td>
<td>152 (120)</td>
</tr>
<tr>
<td>Median duration of PPI therapy (IQR), d</td>
<td>104 (35–269)</td>
<td>113 (38–275)</td>
</tr>
<tr>
<td>Mean duration of PPI and clopidogrel combination therapy (SD), d</td>
<td>33 (80)</td>
<td>-</td>
</tr>
<tr>
<td>Mean breaks in PPI therapy (SD), n</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Initially receiving a PPI before starting clopidogrel therapy, n</td>
<td>2335</td>
<td>-</td>
</tr>
<tr>
<td>Started PPI therapy after starting clopidogrel therapy, n</td>
<td>-</td>
<td>5653</td>
</tr>
<tr>
<td>Stopped PPI therapy before stopping clopidogrel therapy, n</td>
<td>4566</td>
<td>-</td>
</tr>
<tr>
<td>Receiving a PPI at end of study, n</td>
<td>4834</td>
<td>3465</td>
</tr>
<tr>
<td>Receiving clopidogrel at end of study, n</td>
<td>-</td>
<td>156</td>
</tr>
<tr>
<td>Receiving a PPI and clopidogrel at end of study, n</td>
<td>2335</td>
<td>-</td>
</tr>
<tr>
<td>Mean duration of clopidogrel therapy (SD), d</td>
<td>-</td>
<td>235 (129)</td>
</tr>
<tr>
<td>Median duration of clopidogrel therapy (IQR), d</td>
<td>-</td>
<td>298 (90–354)</td>
</tr>
</tbody>
</table>

IQR = interquartile range; PPI = proton-pump inhibitor.

### Appendix Table 2. Adverse Outcomes at 1 Year After Inclusion

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients Not Receiving Clopidogrel (n = 31 704)</th>
<th>Patients Receiving Clopidogrel (n = 24 702)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, MI, or stroke</td>
<td>Person-Years</td>
<td>Events, n (%)*</td>
</tr>
<tr>
<td>Patients Not Receiving a PPI (n = 22 815)</td>
<td>19 453</td>
<td>4232 (18.6)</td>
</tr>
<tr>
<td>Patients Receiving a PPI (n = 8889)</td>
<td>20 437</td>
<td>3269 (14.3)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>19 453</td>
<td>4232 (18.6)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>20 437</td>
<td>3269 (14.3)</td>
</tr>
<tr>
<td>MI</td>
<td>19 453</td>
<td>1791 (7.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>22 815</td>
<td>1509 (6.6)</td>
</tr>
<tr>
<td>Patients Not Receiving a PPI (n = 17 949)</td>
<td>16 216</td>
<td>603 (3.4)</td>
</tr>
<tr>
<td>Patients Receiving a PPI (n = 6753)</td>
<td>15 583</td>
<td>1506 (8.4)</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; PPI = proton-pump inhibitor.
* Calculated by using the Kaplan–Meier method.
### Appendix Table 3. Propensity Score–Matched Model Results of Probability of PPI Therapy During 1-Year Follow-up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients Not Receiving Clopidogrel (n = 31,704)</th>
<th>Patients Receiving Clopidogrel (n = 24,702)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>0.06</td>
<td>1.06 (1.03–1.09)</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.15</td>
<td>0.85 (0.81–0.91)</td>
</tr>
<tr>
<td>Income group</td>
<td>−0.06</td>
<td>0.94 (0.92–0.96)</td>
</tr>
<tr>
<td>Shock</td>
<td>0.36</td>
<td>1.43 (1.17–1.75)</td>
</tr>
<tr>
<td>Diabetes with complications</td>
<td>−0.01</td>
<td>0.99 (0.87–1.12)</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>2.05</td>
<td>7.76 (6.47–9.31)</td>
</tr>
<tr>
<td>PCI</td>
<td>0.07</td>
<td>1.07 (0.97–1.17)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>−0.11</td>
<td>0.89 (0.73–1.10)</td>
</tr>
<tr>
<td>Cerebral vascular disease</td>
<td>0.16</td>
<td>1.17 (1.06–1.29)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.30</td>
<td>1.36 (0.94–1.95)</td>
</tr>
<tr>
<td>Cardiac dysrhythmias</td>
<td>−0.17</td>
<td>0.84 (0.78–0.91)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0.47</td>
<td>1.62 (1.31–2.00)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>0.75</td>
<td>2.11 (1.76–2.52)</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>0.38</td>
<td>1.60 (1.29–1.98)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>0.12</td>
<td>1.13 (1.04–1.22)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>−0.26</td>
<td>0.77 (0.73–0.82)</td>
</tr>
<tr>
<td>Statin</td>
<td>−0.08</td>
<td>0.93 (0.87–0.98)</td>
</tr>
<tr>
<td>ß-Blocker</td>
<td>0.06</td>
<td>1.07 (1.01–1.13)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>−0.08</td>
<td>0.92 (0.87–0.97)</td>
</tr>
<tr>
<td>Diabetes medication</td>
<td>0.06</td>
<td>1.06 (0.98–1.16)</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; PCI = percutaneous coronary intervention; PPI = proton-pump inhibitor.

* Reference was no PPI therapy.

### Appendix Table 4. Summary Data for Propensity Score–Matched Case Patients and Control Participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients Not Receiving Clopidogrel (n = 8,437)</th>
<th>Patients Receiving Clopidogrel (n = 6,556)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients Not Receiving a PPI</td>
<td>Patients Receiving a PPI</td>
</tr>
<tr>
<td>Mean</td>
<td>30.703</td>
<td>30.707</td>
</tr>
<tr>
<td>Minimum</td>
<td>10.518</td>
<td>10.320</td>
</tr>
<tr>
<td>10th percentile</td>
<td>18.101</td>
<td>18.101</td>
</tr>
<tr>
<td>25th percentile</td>
<td>22.754</td>
<td>22.753</td>
</tr>
<tr>
<td>75th percentile</td>
<td>36.380</td>
<td>36.378</td>
</tr>
<tr>
<td>90th percentile</td>
<td>43.768</td>
<td>43.771</td>
</tr>
<tr>
<td>Maximum</td>
<td>95.385</td>
<td>96.674</td>
</tr>
<tr>
<td>Total propensity score for all patients in group</td>
<td>259,042.1</td>
<td>259,078.3</td>
</tr>
</tbody>
</table>

PPI = proton-pump inhibitor.
Appendix Figure 2. Distribution of probabilities of treatment with PPIs in propensity score–matched analysis.

PPI = proton-pump inhibitor.
Appendix Figure 3. Propensity score–matched Kaplan–Meier estimates of cardiovascular death, myocardial infarction, or stroke for subtypes of PPIs.

Appendix Figure 4. Risk for cardiovascular death, myocardial infarction, or stroke for subtypes of PPIs.

Pantoprazole
- Clopidogrel
+ Clopidogrel

Omeprazole
- Clopidogrel
+ Clopidogrel

Lansoprazole
- Clopidogrel
+ Clopidogrel

Esomeprazole
- Clopidogrel
+ Clopidogrel

H2-antagonist
- Clopidogrel
+ Clopidogrel

Any PPI
- Clopidogrel
+ Clopidogrel

No PPI*

Risk in Patients Receiving Clopidogrel, %

Time, d

Risk in Patients Not Receiving Clopidogrel, %

Time, d

Hazard Ratio (95% CI)

Time-dependent, propensity score–matched Cox proportional hazards analysis. PPI = proton-pump inhibitor.

* Used as reference.

Appendix Figure 5. Required size for an unmeasured confounder.

Size needed to account for the elevation of risk from 1 to 1.29. OR_{Ec} = association between drug use category and confounder; RR_{CD} = association between confounder and disease outcome.
### Appendix Table 5. Baseline and Propensity Score–Matched Baseline Characteristics at Discharge After Myocardial Infarction*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients Not Receiving a Clopidogrel</th>
<th>Propensity Score–Matched Patients Not Receiving a Clopidogrel</th>
<th>Patients Receiving Clopidogrel</th>
<th>Propensity Score–Matched Patients Receiving Clopidogrel</th>
<th>P Value</th>
<th>P Value</th>
<th>P Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (n = 26 010)</td>
<td>Patients (n = 8797)</td>
<td>Patients (n = 18 440)</td>
<td>Patients (n = 6845)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>71.0 (13.3)</td>
<td>73.5 (12.6)</td>
<td>64.1 (12.4)</td>
<td>63.7 (12.3)</td>
<td>&lt;0.001</td>
<td>67.4 (12.6)</td>
<td>67.4 (12.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>Men</td>
<td>15 498 (58.6)</td>
<td>4838 (53.2)</td>
<td>13 143 (71.3)</td>
<td>4232 (61.8)</td>
<td>0.001</td>
<td>4109 (61.7)</td>
<td>4127 (62.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>Income group</td>
<td>4160 (16.0)</td>
<td>1521 (16.7)</td>
<td>13 143 (71.3)</td>
<td>4232 (61.8)</td>
<td>0.001</td>
<td>161 (1.8)</td>
<td>70 (1.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>0</td>
<td>4198 (58.6)</td>
<td>4838 (53.2)</td>
<td>13 143 (71.3)</td>
<td>4232 (61.8)</td>
<td>0.001</td>
<td>4109 (61.7)</td>
<td>4127 (62.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>1</td>
<td>5808 (22.3)</td>
<td>2389 (26.3)</td>
<td>1161 (17.5)</td>
<td>1119 (16.8)</td>
<td>0.001</td>
<td>1146 (17.2)</td>
<td>1146 (17.2)</td>
<td>0.89</td>
</tr>
<tr>
<td>2</td>
<td>5507 (21.2)</td>
<td>2157 (23.7)</td>
<td>1161 (17.5)</td>
<td>1146 (17.2)</td>
<td>0.001</td>
<td>1146 (17.2)</td>
<td>1146 (17.2)</td>
<td>0.89</td>
</tr>
<tr>
<td>3</td>
<td>5331 (20.5)</td>
<td>1754 (19.3)</td>
<td>1161 (17.5)</td>
<td>1146 (17.2)</td>
<td>0.001</td>
<td>1146 (17.2)</td>
<td>1146 (17.2)</td>
<td>0.89</td>
</tr>
<tr>
<td>4</td>
<td>5204 (10.0)</td>
<td>1277 (14.0)</td>
<td>1161 (17.5)</td>
<td>1146 (17.2)</td>
<td>0.001</td>
<td>1146 (17.2)</td>
<td>1146 (17.2)</td>
<td>0.89</td>
</tr>
<tr>
<td>Shock</td>
<td>446 (1.7)</td>
<td>197 (2.2)</td>
<td>4109 (61.7)</td>
<td>4127 (62.0)</td>
<td>0.001</td>
<td>4109 (61.7)</td>
<td>4127 (62.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>Diabetes with complications</td>
<td>1501 (5.8)</td>
<td>622 (6.8)</td>
<td>525 (6.0)</td>
<td>400 (5.8)</td>
<td>0.001</td>
<td>351 (5.3)</td>
<td>370 (5.6)</td>
<td>0.47</td>
</tr>
<tr>
<td>Cardiac dysrhythmias</td>
<td>3658 (14.1)</td>
<td>1337 (14.7)</td>
<td>1226 (13.9)</td>
<td>1287 (14.6)</td>
<td>0.195</td>
<td>1226 (13.9)</td>
<td>1287 (14.6)</td>
<td>0.195</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>342 (1.3)</td>
<td>217 (2.4)</td>
<td>101 (1.1)</td>
<td>140 (1.6)</td>
<td>0.01</td>
<td>101 (0.6)</td>
<td>65 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>385 (1.5)</td>
<td>327 (3.6)</td>
<td>72 (0.8)</td>
<td>72 (0.8)</td>
<td>0.31</td>
<td>518 (2.8)</td>
<td>315 (4.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>11 377 (43.7)</td>
<td>5296 (58.2)</td>
<td>5118 (58.2)</td>
<td>5618 (58.2)</td>
<td>0.44</td>
<td>4477 (24.3)</td>
<td>2723 (40.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>2800 (10.8)</td>
<td>1351 (14.9)</td>
<td>1351 (14.9)</td>
<td>1351 (14.9)</td>
<td>0.62</td>
<td>1228 (6.7)</td>
<td>760 (11.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>11 587 (44.6)</td>
<td>4015 (44.1)</td>
<td>11 587 (44.6)</td>
<td>4015 (44.1)</td>
<td>0.49</td>
<td>13 431 (72.8)</td>
<td>4462 (65.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>11 711 (45.0)</td>
<td>4008 (44.1)</td>
<td>11 711 (45.0)</td>
<td>4008 (44.1)</td>
<td>0.019</td>
<td>18 440 (88.7)</td>
<td>5747 (84.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>16 509 (63.5)</td>
<td>5990 (65.8)</td>
<td>16 509 (63.5)</td>
<td>5990 (65.8)</td>
<td>0.001</td>
<td>16 126 (87.5)</td>
<td>6845 (83.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>10 074 (38.7)</td>
<td>3807 (41.8)</td>
<td>10 074 (38.7)</td>
<td>3807 (41.8)</td>
<td>0.001</td>
<td>3755 (56.4)</td>
<td>3649 (54.8)</td>
<td>0.064</td>
</tr>
<tr>
<td>Diabetes medication</td>
<td>3352 (12.9)</td>
<td>1337 (14.7)</td>
<td>1201 (13.7)</td>
<td>1287 (14.6)</td>
<td>0.063</td>
<td>1989 (10.8)</td>
<td>938 (13.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*ACE = angiotensin-converting enzyme; PCI = percutaneous coronary intervention; PPI = proton-pump inhibitor.

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ACE = angiotensin-converting enzyme; PCI = percutaneous coronary intervention; PPI = proton-pump inhibitor.
### Appendix Figure 6. Hazard ratio for cardiovascular death, myocardial infarction, or stroke in subgroups treated with PPIs.

#### Patients Not Receiving Clopidogrel
- Aged >70 y
- Aged ≤70 y
- Male
- Female
- Diabetes
  - Yes
  - No
- Heart failure
  - Yes
  - No
- PCI
  - Yes
  - No
- Any PPI
- No PPI

#### Patients Receiving Clopidogrel
- Aged >70 y
- Aged ≤70 y
- Male
- Female
- Diabetes
  - Yes
  - No
- Heart failure
  - Yes
  - No
- PCI
  - Yes
  - No
- Any PPI
- No PPI

Hazard Ratio (95% CI)

Time-dependent, propensity score–matched Cox proportional hazards analysis. Diabetes was defined as requiring glucose-lowering medication. PCI = percutaneous coronary intervention; PPI = proton-pump inhibitor.

* Used as reference.

### Appendix Figure 7. Clopidogrel and PPI therapy, by individual participating hospital.

Proportion of patients, by individual hospital, who received clopidogrel (top) or a PPI (bottom) within 1 year of discharge after a myocardial infarction. Outliers are small hospitals with few patients. PPI = proton-pump inhibitor.

### Appendix Table 6. Risk for Cardiovascular Death, Myocardial Infarction, or Stroke in Relation to PPI Dose

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Receiving PPI but Not Clopidogrel</th>
<th>Patients Receiving PPI and Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>High PPI dose*</td>
<td>Risk (95% CI) 1.25 (1.16–1.34)</td>
<td>1.26 (1.12–1.41)</td>
</tr>
<tr>
<td>Low PPI dose</td>
<td>Risk (95% CI) 1.39 (1.24–1.55)</td>
<td>1.36 (1.16–1.60)</td>
</tr>
<tr>
<td>P value for difference</td>
<td>0.051</td>
<td>0.39</td>
</tr>
</tbody>
</table>

PPI = proton-pump inhibitor.
* >20 mg for pantoprazole, omeprazole, and esomeprazole; >15 mg for lansoprazole; and >10 mg for rabeprazole.
**Correction**

In a recent article (1), the labels in Figure 2 for “PPI only” and “No clopidogrel or PPI” were switched. The corrected figure appears below. This has been corrected in the online version.

*Figure 2.* Propensity score–matched Kaplan–Meier analysis of risk for cardiovascular death, myocardial infarction, or stroke.

PPI = proton-pump inhibitor.

**Reference**