Risk of Upper Gastrointestinal Bleeding With Low-Dose Acetylsalicylic Acid Alone and in Combination With Clopidogrel and Other Medications

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Background—This study evaluated the risk of upper gastrointestinal bleeding (UGIB) associated with use of low-dose acetylsalicylic acid (ASA) alone and in combination with other gastrotoxic medications.

Methods and Results—The Health Improvement Network UK primary care database was used to identify individuals 40 to 84 years of age with a UGIB diagnosis in 2000 to 2007 (n=20 004). An age-, sex-, and calendar year-matched control group (n=20 000) was identified from the same source population. The relative risk (RR) of UGIB associated with use of low-dose ASA (75 to 300 mg/d), clopidogrel, and other commonly coadministered medications was estimated by multivariate logistic regression. The risk of UGIB was increased in current users of low-dose ASA (RR, 1.80; 95% confidence interval [CI], 1.59 to 2.03) or clopidogrel (RR, 1.67; 95% CI, 1.24 to 2.24) compared with nonusers. Compared with low-dose ASA monotherapy, the risk of UGIB was significantly increased when low-dose ASA was coadministered with clopidogrel (RR, 2.08; 95% CI, 1.34 to 3.21), oral anticoagulants (RR, 2.00; 95% CI, 1.15 to 3.45), low-/medium-dose nonsteroidal antiinflammatory drugs (RR, 2.63; 95% CI, 1.93 to 3.60), high-dose nonsteroidal antiinflammatory drugs (RR, 2.66; 95% CI, 1.88 to 3.76), or high-dose oral corticosteroids (RR, 4.43; 95% CI, 2.10 to 9.34); this was not apparent with coadministration of statins (RR, 0.99; 95% CI, 0.81 to 1.21) or low-dose oral corticosteroids (RR, 1.01; 95% CI, 0.58 to 1.77).

Conclusions—Use of low-dose ASA is associated with an almost 2-fold increase in the risk of UGIB compared with nonuse. This risk is increased further in individuals taking low-dose ASA along with clopidogrel, oral anticoagulants, nonsteroidal antiinflammatory drugs, or high-dose oral corticosteroids. (Circulation. 2011;123:1108-1115.)

Key Words: aspirin ■ clopidogrel ■ drug therapy, combination ■ hemorrhage ■ safety

Antiplatelet therapy with low-dose acetylsalicylic acid (ASA) (75 to 325 mg/d) and clopidogrel, alone or in combination, is now standard for the secondary prevention of cardiovascular events.1 These drugs have been shown to reduce the risk of cardiovascular events when used as monotherapy2 and in combination.3 Guidelines recommend the use of combination antiplatelet therapy for up to 1 year after myocardial infarction or acute coronary syndromes.4 However, clinical trials have shown that both low-dose ASA and clopidogrel are associated with an increased risk of upper gastrointestinal bleeding (UGIB), and there is evidence to suggest that this risk is increased further with the combination of the 2 therapies.2,3

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Other medications commonly coadministered with antiplatelet therapy such as nonsteroidal antiinflammatory drugs (NSAIDs), oral anticoagulants, and corticosteroids are also known to increase the risk of UGIB.5-9 Although concomitant use of these medications and antiplatelet therapy might increase the risk of UGIB further and thus change the risk-to-benefit ratio, very few studies have actually quantified the risk of UGIB associated with specific combination therapies in the general population.

The aims of this study were to examine the risk of UGIB among users of low-dose ASA and clopidogrel (either alone or in combination) and to assess the effects of concomitant administration of other gastrotoxic medications on this risk of UGIB in the general population.

Methods

Source Population and Case Ascertainment

A cohort study with nested case-control analysis was performed with data extracted from The Health Improvement Network (THIN) UK...
primary care database. Anonymized data on >3 million patients are systematically recorded by participating primary care practitioners (PCPs) as part of their routine patient care and sent to THIN for use in research projects.

THIN contains patient information such as demographic factors, consultation rates, referrals, hospitalizations, laboratory test results, and prescriptions ordered by PCPs, including the doses and duration of treatment. Diagnoses and test procedures are recorded with Read Codes.10 Prescriptions written by PCPs are generated and recorded systematically recorded by participating primary care practitioners (Multilex).11 Previous studies have provided evidence to support the validity of THIN in pharmacoepidemiological research, particularly when UGIB is the outcome of interest.12,13

The present study is an extension of an earlier study that demonstrated the validity of the procedure used for ascertaining UGIB events.7 A positive predictive value of >95% was estimated for the UGIB definition compared with PCPs’ records in a random sample.7,12 Therefore, no further validation was performed as part of the present study.

After the manual review of computerized records, the final number of confirmed cases of UGIB was 2049. A control group of 20,000 individuals, frequency matched by age, sex, and calendar year to the cases, was randomly sampled from the same source population.

### Analysis

Computerized prescription records were used to assess the use of low-dose ASA (75 to 300 mg/d), clopidogrel, oral anticoagulants, NSAIDs (selective inhibitors of cyclooxygenase-2 [coxibs] and traditional NSAIDs), oral corticosteroids, selective serotonin reuptake inhibitors and statins before the index date (for cases, this was the date of the UGIB diagnosis; for controls, it was a random date during follow-up).

### Table 1. Risk Factors for Upper Gastrointestinal Bleeding

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>UGIB Cases (n=2049), n (%)</th>
<th>Controls (n=20 000), n (%)</th>
<th>RR (95% CI)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP visits, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>349 (17.0)</td>
<td>6157 (30.8)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>4–7</td>
<td>440 (21.5)</td>
<td>4895 (24.5)</td>
<td>1.80 (1.55–2.09)</td>
<td>1.44 (1.24–1.69)</td>
</tr>
<tr>
<td>8–13</td>
<td>537 (26.2)</td>
<td>4752 (23.8)</td>
<td>2.46 (2.13–2.85)</td>
<td>1.60 (1.37–1.88)</td>
</tr>
<tr>
<td>≥13</td>
<td>723 (35.3)</td>
<td>4196 (21.0)</td>
<td>4.04 (3.50–4.66)</td>
<td>2.02 (1.71–2.40)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1686 (82.3)</td>
<td>18 172 (90.9)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>286 (14.0)</td>
<td>1594 (8.0)</td>
<td>2.00 (1.74–2.29)</td>
<td>1.36 (1.18–1.58)</td>
</tr>
<tr>
<td>≥2</td>
<td>77 (3.8)</td>
<td>234 (1.2)</td>
<td>3.73 (2.86–4.86)</td>
<td>2.03 (1.52–2.72)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>884 (43.1)</td>
<td>9892 (49.5)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current</td>
<td>412 (20.1)</td>
<td>2981 (14.9)</td>
<td>1.58 (1.39–1.79)</td>
<td>1.45 (1.27–1.66)</td>
</tr>
<tr>
<td>Former</td>
<td>631 (30.8)</td>
<td>5554 (27.8)</td>
<td>1.41 (1.26–1.58)</td>
<td>1.09 (0.97–1.23)</td>
</tr>
<tr>
<td>Alcohol use, units per week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>968 (47.2)</td>
<td>8991 (45.0)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≥2–24</td>
<td>691 (33.7)</td>
<td>7115 (35.6)</td>
<td>0.90 (0.81–1.00)</td>
<td>0.94 (0.84–1.04)</td>
</tr>
<tr>
<td>≥25</td>
<td>106 (5.2)</td>
<td>642 (3.2)</td>
<td>1.53 (1.22–1.91)</td>
<td>1.52 (1.20–1.93)</td>
</tr>
<tr>
<td>History of upper gastrointestinal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No peptic ulcer disease/dyspepsia</td>
<td>1133 (55.3)</td>
<td>15 092 (75.5)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Dyspepsia/gastritis</td>
<td>557 (27.2)</td>
<td>3803 (19.0)</td>
<td>2.00 (1.79–2.23)</td>
<td>1.55 (1.37–1.74)</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>213 (10.4)</td>
<td>714 (3.6)</td>
<td>3.97 (3.36–4.69)</td>
<td>3.33 (2.78–3.99)</td>
</tr>
<tr>
<td>Complicated peptic ulcer disease</td>
<td>146 (7.1)</td>
<td>391 (2.0)</td>
<td>4.94 (4.04–6.05)</td>
<td>4.43 (3.57–5.50)</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1566 (76.4)</td>
<td>17 018 (85.1)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>192 (9.4)</td>
<td>1071 (5.4)</td>
<td>1.94 (1.64–2.29)</td>
<td>1.03 (0.83–1.27)</td>
</tr>
<tr>
<td>Other</td>
<td>291 (14.2)</td>
<td>1911 (9.6)</td>
<td>1.64 (1.43–1.88)</td>
<td>0.93 (0.78–1.11)</td>
</tr>
</tbody>
</table>

UGIB indicates upper gastrointestinal bleeding; RR, relative risk; CI, confidence interval; PCP, primary care practitioner.
Drug exposure was classified into 2 categories based on the expected pharmacological effects: current use, defined as use lasting until the index date or ending in the 30 days before the index date, and past use, defined as use ending 31 to 365 days before the index date. However, in a previous study, we found that the risk of UGIB among NSAID users starts to decrease quite markedly around 7 days after treatment cessation, reflecting the reversible nature of the inhibition of cyclooxygenase by NSAIDs. Therefore, for NSAID use, current use was defined as lasting until the index date or ending in the 7 days before the index date, recent use was defined as ending 8 to 90 days before the index date, and past use was defined as ending 91 to 365 days before the index date. For all studied medications, the reference group (nonuse) was defined as no exposure to the drug in the year before the index date. It should be noted, however, that a minority of the individuals in the nonuse group may have been taking over-the-counter low-dose ASA or NSAIDs. To eliminate any continued effects from the previous medication after recent switching from low-dose ASA to clopidogrel or vice versa, monotherapy with ASA or clopidogrel was defined as current use of the drug in question with no use of the other antiplatelet drug in the previous year. The risk of UGIB in new users was evaluated in subanalyses to assess any potential selection bias when considering long-term users. NSAIDs and oral corticosteroids were stratified by daily dose (see the online-only Data Supplement for more information).

Table 2. Risk of Upper Gastrointestinal Bleeding Associated With Antiplatelet Therapy

<table>
<thead>
<tr>
<th></th>
<th>UGIB Cases (n=2049), n (%)</th>
<th>Controls (n=20 000), n (%)</th>
<th>RR (95% CI)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose ASA (with or without clopidogrel)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nonuse</td>
<td>1285 (62.7)</td>
<td>15 401 (77.0)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current use (all doses)</td>
<td>587 (28.6)</td>
<td>3610 (18.1)</td>
<td>2.11 (1.89–2.37)</td>
<td>1.79 (1.57–2.03)</td>
</tr>
<tr>
<td>Daily dose ≤75 mg</td>
<td>495 (24.2)</td>
<td>3022 (15.1)</td>
<td>2.19 (1.94–2.46)</td>
<td>1.81 (1.58–2.06)</td>
</tr>
<tr>
<td>Daily dose &gt;75 mg</td>
<td>77 (3.8)</td>
<td>472 (2.4)</td>
<td>1.89 (1.47–2.44)</td>
<td>1.62 (1.24–2.12)</td>
</tr>
<tr>
<td>Treatment duration 0–365 d</td>
<td>173 (8.4)</td>
<td>869 (4.3)</td>
<td>2.44 (2.05–2.92)</td>
<td>1.85 (1.53–2.24)</td>
</tr>
<tr>
<td>Treatment duration &gt;365 d</td>
<td>414 (20.2)</td>
<td>2741 (13.7)</td>
<td>2.00 (1.76–2.27)</td>
<td>1.74 (1.52–2.00)</td>
</tr>
<tr>
<td>Clopidogrel as antiplatelet monotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuse of clopidogrel or ASA</td>
<td>1285 (62.7)</td>
<td>15 401 (77.0)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current use (all doses)</td>
<td>30 (1.5)</td>
<td>170 (0.9)</td>
<td>2.55 (1.72–3.80)</td>
<td>1.48 (0.96–2.27)</td>
</tr>
<tr>
<td>Treatment duration 0–365 d</td>
<td>8 (0.4)</td>
<td>45 (0.2)</td>
<td>2.45 (1.15–5.24)</td>
<td>1.46 (0.65–3.26)</td>
</tr>
<tr>
<td>Treatment duration &gt;365 d</td>
<td>22 (1.1)</td>
<td>125 (0.6)</td>
<td>2.58 (1.62–4.09)</td>
<td>1.46 (0.89–2.39)</td>
</tr>
<tr>
<td>Dual antiplatelet therapy with clopidogrel and low-dose ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuse of clopidogrel or ASA</td>
<td>1285 (62.7)</td>
<td>15 401 (77.0)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current use (all doses)</td>
<td>32 (1.6)</td>
<td>101 (0.5)</td>
<td>4.65 (3.10–6.99)</td>
<td>3.71 (2.38–5.76)</td>
</tr>
<tr>
<td>Treatment duration for ASA and clopidogrel 0–365 d</td>
<td>10 (0.5)</td>
<td>32 (0.2)</td>
<td>4.43 (2.16–9.08)</td>
<td>3.06 (1.40–6.69)</td>
</tr>
<tr>
<td>Treatment duration for ASA and clopidogrel &gt;365 d</td>
<td>8 (0.4)</td>
<td>32 (0.2)</td>
<td>3.76 (1.72–8.23)</td>
<td>3.28 (1.45–7.43)</td>
</tr>
</tbody>
</table>

UGIB indicates upper gastrointestinal bleeding; RR, relative risk; CI, confidence interval; ASA, acetylsalicylic acid.

Results

Risk Factors for UGIB

Risk factors for UGIB are shown in Table 1. The risk of UGIB was significantly higher in individuals with a history of upper gastrointestinal disease than in those without. There was no significant association between a history of cardiovascular disease and the risk of UGIB in the fully adjusted
analysis. The associations between these factors and the risk of UGIB were similar when the analysis was restricted to users of antithrombotic therapy (data not shown).

Antiplatelet Therapy and UGIB

Of the 2049 confirmed UGIB cases, 631 (30.8%) were taking low-dose ASA at the time of the event, 68 (3.3%) were taking clopidogrel, and 32 (1.6%) were taking low-dose ASA and clopidogrel (Table 2). Compared with nonuse of either ASA or clopidogrel, low-dose ASA monotherapy was associated with an increased risk of UGIB (RR, 1.79; 95% CI, 1.57 to 2.03; Figure 1 and Table 2). This increased risk of UGIB was similar in patients who had received ASA monotherapy for >365 days and for ≤365 days (Table 2). The risk of UGIB was also similar across all of the daily doses of ASA studied.

The RR of UGIB among users of clopidogrel monotherapy, compared with those not taking either ASA or clopidogrel, was 1.48 (95% CI, 0.96 to 2.27; Figure 1 and Table 2). This increase in risk was similar regardless of the duration of therapy. More than 95% of patients taking clopidogrel were receiving 75 mg/d; therefore, an analysis of any dose-response relationship with UGIB was not possible.

The RR of UGIB in patients receiving low-dose ASA and clopidogrel combination therapy was 3.71 (95% CI, 2.38 to 5.76) compared with those receiving neither antithrombotic therapy (Figure 1 and Table 2) and 2.08 (95% CI, 1.34 to 3.21) compared with those receiving low-dose ASA alone (Figure 2).

Other Medications and UGIB

Among the 2049 patients with confirmed UGIB, 113 (5.5%) were receiving oral anticoagulants at the time of the event, 370 (18.1%) were receiving NSAIDs, 87 (4.2%) were taking oral corticosteroids, 519 (25.3%) were taking statins, and 123 (6.0%) were taking selective serotonin reuptake inhibitors (Table 3).

The risk of UGIB was increased in current users of oral anticoagulants, NSAIDs, or oral corticosteroids compared with those not taking these medications (Table 3). The increase in the risk of UGIB associated with corticosteroids was significant only in those using high-dose oral corticosteroids, not in those taking low-/medium-dose oral corticosteroids. However, the increased risk of UGIB associated with NSAID use was observed with both high and low doses of NSAIDs. There was a small increase in the risk of UGIB associated with current selective serotonin reuptake inhibitor use, but it did not reach significance. There was also no significant association between statin use and the risk of UGIB.

Concomitant Medication Increases the Risk of UGIB

Compared with nonuse of either low-dose ASA or oral anticoagulants, the RR of UGIB was 3.62 (95% CI, 2.09 to 6.29) for individuals receiving low-dose ASA and oral anticoagulants (Table 4 and Figure 1). Compared with low-dose ASA monotherapy, concomitant use of low-dose ASA and oral anticoagulants was associated with an increased risk of UGIB (RR, 2.08; 95% CI, 1.34 to 3.21; Figure 2).
and oral anticoagulants was associated with a significant increase in the risk of UGIB (Figure 2).

Similarly, compared with nonuse of either low-dose ASA or NSAIDs, the RR of UGIB was 4.80 (95% CI, 3.53 to 6.55) for concomitant users of a low-/medium-dose NSAID and low-dose ASA and 4.86 (95% CI, 3.44 to 6.84) for concomitant users of a high-dose NSAID and low-dose ASA (Table 4 and Figure 1). Compared with the use of low-dose ASA alone, the risk of UGIB was significantly higher in individuals taking low-dose ASA and a low-/medium-dose NSAID and in those taking low-dose ASA and a high-dose NSAID (Figure 2).

When users of NSAIDs were separated into those using traditional NSAIDs and those using coxibs, the risk of UGIB was significantly increased in patients taking traditional NSAIDs but not low-dose ASA and in those taking coxibs but not low-dose ASA compared with individuals taking neither the respective medication nor low-dose ASA (Table 4 and Figure 1). The risk of UGIB was increased further in individuals taking traditional NSAIDs and low-dose ASA and in those taking coxibs and low-dose ASA.

Compared with patients not receiving either oral corticosteroids or low-dose ASA, the RR of UGIB was 7.87 (95% CI, 3.73 to 16.63) for concomitant users of high-dose oral corticosteroids and low-dose ASA and 1.80 (95% CI, 1.03 to 3.15) for concomitant users of low-/medium-dose corticosteroids and low-dose ASA (Table 4; Figure 1). Compared with the use of low-dose ASA alone, the RR of UGIB was significantly higher in patients receiving a combination of high-dose corticosteroids and low-dose ASA but not in individuals taking low-/medium-dose corticosteroids and low-dose ASA (Figure 2).

Concomitant treatment with low-dose ASA and statins was not significantly associated with the risk of UGIB compared with low-dose ASA monotherapy (RR, 0.99; 95% CI, 0.81 to 1.21). Likewise, concurrent use of selective serotonin reuptake inhibitors and low-dose ASA did not significantly increase the risk of UGIB compared with low-dose ASA monotherapy (RR, 0.80; 95% CI, 0.54 to 1.20).

Discussion

In this large-scale study in UK primary care, treatment with low-dose ASA monotherapy or clopidogrel monotherapy was associated with an increase in the risk of UGIB compared with nonuse of either therapy. Low-dose ASA monotherapy and clopidogrel monotherapy increased the risk of UGIB by a similar extent, which suggests that neither therapy is superior to the other in terms of their UGIB risk profile. The
risk of UGIB associated with ASA or clopidogrel as monotherapies appeared to be independent of the duration of therapy; dose effects could not be fully evaluated in this study. Combination therapy with low-dose ASA and clopidogrel was associated with a greater increase in the risk of UGIB than either monotherapy; the risk was estimated to be 2.4- to 5.8-fold greater than that associated with nonuse of either therapy.

Clinical trials have shown that combination therapy with clopidogrel and low-dose ASA is associated with an increased risk of UGIB compared with low-dose ASA alone. However, there are limited data on the safety of the combination of these 2 antiplatelet therapies in the general population. One population-based case-control study in Denmark reported that, compared with nonuse of any antiplatelet therapy, combination therapy with clopidogrel and ASA was associated with a significant increase in the risk of UGIB (odds ratio, 7.4; 95% CI, 3.5 to 15.0). The corresponding odds ratio for ASA monotherapy was 1.8 (95% CI, 1.5 to 2.1), whereas the odds ratio for clopidogrel monotherapy was 1.1 (95% CI, 0.6 to 2.1). A more recent study of nationwide registries in Denmark found that, in patients with acute myocardial infarction, ASA and clopidogrel combination therapy was associated with a higher risk of any bleeding event than ASA monotherapy (hazard ratio [HR], 1.47; 95% CI, 1.28 to 1.69). In contrast to the results of the present study, the recent Danish study also found clopidogrel monotherapy to be associated with a higher risk of any bleeding event than ASA monotherapy (hazard ratio, 1.33; 95% CI, 1.11 to 1.59). It is important to note that this study examined all types of bleeding, whereas we focused on UGIB. In addition, their findings may be explained by clopidogrel being prescribed to patients with a higher baseline risk of UGIB. To reduce this

<table>
<thead>
<tr>
<th>Interaction with oral anticoagulants</th>
<th>UGIB Cases (n=2049), n (%)</th>
<th>Controls (n=20 000), n (%)</th>
<th>RR (95% CI)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonuse of both oral anticoagulants and low-dose ASA</td>
<td>1220 (59.5)</td>
<td>14 979 (74.9)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Oral anticoagulants alone</td>
<td>83 (4.1)</td>
<td>527 (2.6)</td>
<td>2.17 (1.70–2.77)</td>
<td>1.77 (1.36–2.30)</td>
</tr>
<tr>
<td>Low-dose ASA alone</td>
<td>607 (29.6)</td>
<td>3695 (18.5)</td>
<td>2.24 (2.00–2.51)</td>
<td>1.82 (1.60–2.06)</td>
</tr>
<tr>
<td>Oral anticoagulants + low-dose ASA</td>
<td>20 (1.0)</td>
<td>55 (0.3)</td>
<td>4.79 (2.84–8.08)</td>
<td>3.62 (2.09–6.29)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Interaction with NSAIDs</th>
<th>UGIB Cases (n=2049), n (%)</th>
<th>Controls (n=20 000), n (%)</th>
<th>RR (95% CI)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonuse of both NSAIDs and low-dose ASA</td>
<td>874 (42.7)</td>
<td>12 519 (62.6)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Low-/medium-dose NSAIDs alone</td>
<td>94 (4.6)</td>
<td>557 (2.8)</td>
<td>2.39 (1.90–3.01)</td>
<td>2.03 (1.59–2.58)</td>
</tr>
<tr>
<td>High-dose NSAIDs alone</td>
<td>126 (6.1)</td>
<td>408 (2.0)</td>
<td>4.32 (3.49–5.33)</td>
<td>3.90 (3.12–4.88)</td>
</tr>
<tr>
<td>Low-dose ASA alone</td>
<td>407 (19.9)</td>
<td>2886 (14.4)</td>
<td>2.17 (1.91–2.48)</td>
<td>1.83 (1.58–2.12)</td>
</tr>
<tr>
<td>Low-/medium-dose NSAIDs + low-dose ASA</td>
<td>71 (3.5)</td>
<td>176 (0.9)</td>
<td>6.15 (4.61–8.21)</td>
<td>4.80 (3.53–6.55)</td>
</tr>
<tr>
<td>High-dose NSAIDs + low-dose ASA</td>
<td>54 (2.6)</td>
<td>142 (0.7)</td>
<td>5.73 (4.14–7.94)</td>
<td>4.86 (3.44–6.84)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interaction with coxibs</th>
<th>UGIB Cases (n=2049), n (%)</th>
<th>Controls (n=20 000), n (%)</th>
<th>RR (95% CI)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonuse of both coxibs and low-dose ASA</td>
<td>1253 (61.2)</td>
<td>15 109 (75.5)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Coxibs alone</td>
<td>38 (1.9)</td>
<td>158 (0.8)</td>
<td>2.76 (1.92–3.96)</td>
<td>2.38 (1.63–3.47)</td>
</tr>
<tr>
<td>Low-dose ASA alone</td>
<td>592 (29.9)</td>
<td>3640 (18.2)</td>
<td>2.12 (1.90–2.37)</td>
<td>1.76 (1.55–2.00)</td>
</tr>
<tr>
<td>Coxibs and low-dose ASA</td>
<td>23 (1.1)</td>
<td>34 (0.2)</td>
<td>7.73 (4.51–13.24)</td>
<td>5.83 (3.26–10.41)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interaction with corticosteroids</th>
<th>UGIB Cases (n=2049), n (%)</th>
<th>Controls (n=20 000), n (%)</th>
<th>RR (95% CI)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonuse of both corticosteroids and low-dose ASA</td>
<td>1225 (59.8)</td>
<td>14 873 (74.4)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Low-/medium-dose corticosteroids alone</td>
<td>35 (1.7)</td>
<td>235 (1.2)</td>
<td>1.91 (1.33–2.74)</td>
<td>1.27 (0.87–1.85)</td>
</tr>
<tr>
<td>High-dose corticosteroids alone</td>
<td>15 (0.7)</td>
<td>73 (0.4)</td>
<td>2.56 (1.46–4.50)</td>
<td>1.89 (1.05–3.38)</td>
</tr>
<tr>
<td>Low-dose ASA alone</td>
<td>578 (28.2)</td>
<td>3542 (17.7)</td>
<td>2.16 (1.93–2.41)</td>
<td>1.78 (1.57–2.02)</td>
</tr>
<tr>
<td>Low-/medium-dose corticosteroids + low-dose ASA</td>
<td>17 (0.8)</td>
<td>88 (0.4)</td>
<td>2.52 (1.48–4.27)</td>
<td>1.86 (1.03–3.15)</td>
</tr>
<tr>
<td>High-dose steroids + low-dose ASA</td>
<td>15 (0.7)</td>
<td>18 (0.1)</td>
<td>11.09 (5.51–22.32)</td>
<td>7.87 (3.73–16.63)</td>
</tr>
</tbody>
</table>

UGIB indicates upper gastrointestinal bleeding; RR, relative risk; CI, confidence interval; ASA, acetylsalicylic acid; NSAIDs, nonsteroidal antiinflammatory drugs; tNSAIDs, traditional NSAIDs; coxibs, selective inhibitors of cyclooxygenase-2.
potential bias in the present study, our estimates were adjusted for UGIB risk factors. Moreover, we defined mono-
therapy with clopidogrel as current use of clopidogrel with no
record of low-dose ASA use in the previous year to account
for the fact that some patients may have switched from
low-dose ASA to clopidogrel because of gastrointestinal
intolerance. Because these factors were not considered in
the Danish study, it is not surprising that they reported a higher
risk of bleeding associated with clopidogrel monotherapy
compared with low-dose ASA monotherapy than shown in
our study. Indeed, when we adjusted only for matching
factors, the RR of UGIB was 2.6 for current use of clopi-
dogrel and 2.1 for current use of low-dose ASA.

As the most commonly prescribed medicine for primary or
secondary prevention of cardiovascular events, low-dose
ASA is frequently coprescribed with other gastrotoxic agents.
This study shows that patients receiving low-dose ASA along
with other gastrotoxic medications have a significantly
greater increase in the risk of UGIB than patients receiving
low-dose ASA alone. There was an almost 8-fold increased
risk of UGIB associated with concomitant use of low-dose
ASA and high-dose corticosteroids compared with nonuse of
either drug, which suggests that caution is warranted before
prescribing such a combination of treatments. Such an inter-
action was not observed with concomitant administration of
low-dose ASA and low-/medium-dose oral corticosteroids.

There was no significant association (in either direction)
between statin use and the risk of UGIB. This was the case in
the total study population and in those taking low-dose ASA.

This study provides support for the results of several
previous observational studies on this topic, which also found
no association between statin use and gastrointestinal bleed-
ing.17,18 A retrospective, posthoc analysis of a clinical trial of
orbofiban found statin users in the active treatment group to
be at a lower risk of some categories of gastrointestinal
risks when it is used in secondary prevention24 but not necessarily when it is used in primary prevention,
particularly not if individuals are already taking statins.24,25

These modeling studies often take into account only the age
of patients when assessing the risks and benefits of ASA.
However, our results suggest that they should also take into
account the other gastrotoxic agents that may be coadminis-
tered to these patients.

Strengths and Limitations

A major strength of this study is its large sample size. In
addition, patients recorded within THIN are representative of
the entire UK general population.20 Furthermore, the outcome
of this study has been validated: >95% of UGIB cases from
a random sample were confirmed on consultation with the
PCPs in a previous study.7,12

A limitation of THIN is that it captures only recorded
prescription medications. It is likely that some patients were
using over-the-counter ASA or NSAIDs and may have been
misclassified as nonusers in this study. However, over-the-
counter use of low-dose ASA in elderly populations is low in
the United Kingdom,21 and significant underrecording of the
use of low-dose ASA is unlikely given that prescriptions are
free for patients >60 years of age. Furthermore, in a previous
study, the influence of underrecording of ASA use on odds
ratios was investigated and found to be minimal.22

Conclusions and Clinical Implications

The present study confirms the increase in the risk of UGIB
associated with ASA and clopidogrel monotherapies in the
general population. Use of low-dose ASA or clopidogrel is
associated with an almost 2-fold increase in the risk of UGIB
compared with nonuse. Concomitant use of low-dose ASA
with clopidogrel or other gastrotoxic medications is associ-
ated with an even greater increase in the risk of UGIB than
that conferred by the monotherapies. The incidence of UGIB
has been estimated to be between 0.5 and 1 per 1000
person-years in the general population.23 The RR of 3.7
associated with current use of dual antiplatelet therapy in
the present study would therefore translate to an excess risk of
UGIB on the order of 1.4 to 2.7 cases among 1000 exposed
individuals annually.

Several studies have assessed the risks and benefits of ASA
in various settings and have tended to conclude that the
cardiovascular benefits of ASA definitely outweigh its gas-
atrointestinal risks when it is used in secondary prevention24
but not necessarily when it is used in primary prevention,
particularly not if individuals are already taking statins.24,25

These modeling studies often take into account only the age
of patients when assessing the risks and benefits of ASA.
However, our results suggest that they should also take into
account the other gastrotoxic agents that may be coadminis-
tered to these patients.

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Disclosures

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no disclosures.

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compared with clopidogrel alone after recent ischaemic stroke or transient
ischaemic attack in high-risk patients (MATCH): randomised, double-
Clinical trials have shown that low-dose acetylsalicylic acid (ASA) and clopidogrel are associated with an increased risk of upper gastrointestinal bleeding (UGIB). Other medications that are commonly coadministered with low-dose ASA and clopidogrel can also increase the risk of UGIB. However, few studies have quantified the risk of UGIB associated with specific combinations of these therapies in the general population. We used The Health Improvement Network (a UK primary care database) to identify 2049 patients with a UGIB diagnosis in 2000 to 2007 and 20,000 controls with no UGIB diagnosis. We evaluated drug use in these patients and estimated the relative risk (RR) of UGIB associated with various medications. We found that the RR of UGIB was 1.80 (95% confidence interval [CI], 1.59 to 2.03) in users of low-dose ASA and 1.67 (95% CI, 1.24 to 2.24) in users of clopidogrel. Compared with low-dose ASA monotherapy, the risk of UGIB was significantly increased when low-dose ASA was coadministered with clopidogrel (RR, 2.08; 95% CI, 1.34 to 3.21), oral anticoagulants (RR, 2.00; 95% CI, 1.15 to 3.45), low-/medium-dose nonsteroidal antiinflammatory drugs (RR, 2.63; 95% CI, 1.93 to 3.60), high-dose nonsteroidal antiinflammatory drugs (RR, 2.66; 95% CI, 1.88 to 3.76), or high-dose oral corticosteroids (RR, 4.43; 95% CI, 2.10 to 9.34). Our findings confirm that low-dose ASA and clopidogrel are associated with an increased risk of UGIB in the general population and show that the risk of UGIB is increased further in patients using combination therapies. These factors should be taken into account when assessing the risk-to-benefit ratio of low-dose ASA.
Risk of Upper Gastrointestinal Bleeding With Low-Dose Acetylsalicylic Acid Alone and in Combination With Clopidogrel and Other Medications
Luis A. García Rodríguez, Kueiyu Joshua Lin, Sonia Hernández-Díaz and Saga Johansson

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SUPPLEMENTAL MATERIAL

Supplemental methods

Dose definitions

High-dose NSAIDs were defined as a daily dose greater than the following: 200 mg for aceclofenac, 120 mg for acemetacin, 600 mg for azapropazone, 200 mg for celecoxib, 100 mg for diclofenac, 1500 mg for diflunisal, 400 mg for etodolac, 90 mg for etoricoxib, 900 mg for fenbufen, 1200 mg for fenprofen, 150 mg for flurbiprofen, 1200 mg for ibuprofen, 75 mg for indomethacin, 150 mg for ketoprofen, 30 mg for ketorolac, 1000 mg for mefenamic acid, 7.5 mg for meloxicam, 1000 mg for nabumetone, 750 mg for naproxen, 10 mg for piroxicam, 25 mg for rofecoxib, 200 mg for sulindac, 10 mg for tenoxicam, 600 mg for tiaprofenac, and 20 mg for valdecoxib. Doses less than or equal to these cut-off values were grouped under low/medium doses. High-dose corticosteroids were defined as > 10 mg/day prednisolone or the equivalent dose for other corticosteroids.