High prevalence of ulcer bleeding risk factors in dual antiplatelet-treated patients after percutaneous coronary intervention

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ABSTRACT

INTRODUCTION: Dual antiplatelet therapy is standard treatment following percutaneous coronary intervention (PCI) and stenting. However, such therapy increases the risk of upper gastrointestinal bleeding (UGIB). The risk factors of UGIB are well-documented and proton pump inhibitor (PPI) treatment reduces the risk. The aim was to describe the prevalence of risk factors of UGIB in dual antiplatelet-treated patients.

METHODS: A questionnaire was used to assess the prevalence of risk factors of upper gastrointestinal bleeding among dual antiplatelet-treated first-time PCI patients in Western Denmark. The following characteristics were considered risk factors: increasing age (age 60-69 years and ≥ 70 years); dyspepsia; previous peptic ulcer; use of non-steroidal anti-inflammatory drugs (NSAIDs) (weekly or daily), corticosteroids, selective serotonin reuptake inhibitors (SSRIs) and anticoagulants.

RESULTS: A total of 1,358 patients with a mean age of 64.1 years (range: 33-92 years) were included. The distribution of risk factors was as follows: dyspepsia: 681 patients (50.1%); previous ulcer: 110 (8.1%; 2.3% with bleeding); use of NSAIDs: 214 (15.8%); corticosteroids (2.9%), SSRIs (5.8%) and anticoagulants (6.3%). Defined high-risk patients: 886 (65.2%). PPI treatment prior to PCI was found in 248 (18.3%), of whom 86% were at high risk of UGIB.

CONCLUSION: This study demonstrates a high prevalence of risk factors among PCI patients treated with dual antiplatelet therapy, many of whom were not in PPI treatment.

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Dual antiplatelet treatment (DAPT) with an adenosine diphosphate (ADP)-receptor inhibitor and low-dose acetylsalicylic acid (ASA) reduces the risk of ischaemic complications after acute coronary syndrome [1] and is standard treatment following percutaneous coronary intervention (PCI) and stenting [2].

Antiplatelet treatment, however, increases the risk of bleeding, including gastrointestinal bleeding [3], Several studies have found that this risk is further increased by combining low-dose ASA and clopidogrel [3]. The CURE study [4] found an incidence rate of gastrointestinal bleeding of 1.3% during a mean period of nine months of combination treatment with low-dose ASA and clopidogrel. However, a three to four times higher incidence rate of bleeding has been found in relation to combination treatment when this was implemented in real-life, unselected patient groups [5]. In up to 40% of all patients admitted with a bleeding ulcer, the bleeding episode is related to antithrombotic treatment [6].

The risk factors of upper gastrointestinal bleeding (UGIB) include a history of peptic ulcer [7], age [7], non-steroidal anti-inflammatory drugs (NSAIDs) [8], selective serotonin reuptake inhibitors (SSRIs) [9], warfarin [10] and corticosteroids [11]; and these risk factors are well-documented in ASA-treated patients [12].

Approximately two thirds of patients who are treated with a low-dose ASA/clopidogrel combination are considered to have a high risk of UGIB [7]. Others have demonstrated that 40-50% of dual antiplatelet-treated patients were at high risk of developing UGIB [13]. No prospective data on the risk of UGIB in patients treated with DAPT in Northern Europe are available, and no study has included gastrointestinal symptoms as a risk factor.

This population-based study aimed to characterise the prevalence of risk factors of UGIB (i.e. age, dyspepsia, previous peptic ulcer, treatment with NSAIDs, SSRIs, corticosteroids and anticoagulant treatment) among DAPT-treated patients at the time of their first time PCI.

METHODS

We conducted a population-based descriptive study of risk factors of UGIB during the period from April 2011 through August 2012 in the western part of Denmark (population: 3.3 million).

We included first-time PCI patients from the departments of cardiology at Odense University Hospital, Aarhus University Hospital, Skejby, and Aalborg University Hospital. These hospitals perform all PCIs in the western part of Denmark. All patients were prescribed one-year DAPT with low-dose ASA and an ADP-receptor inhibitor.

Patients were excluded if they had previously had a PCI, were in treatment with an ADP-receptor inhibitor

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FIGURE 1

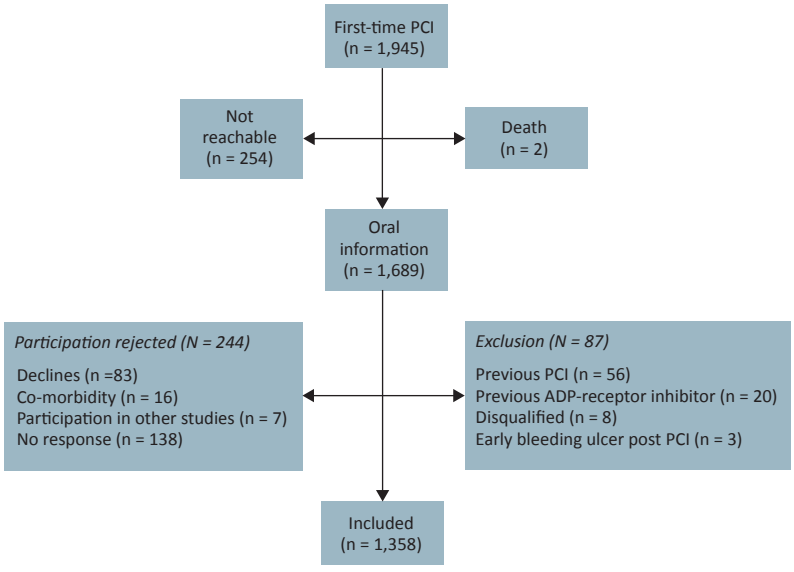
Risk factor definition.

Risk factors	
Increasing age	
Dyspepsia[a]	
Previous peptic ulcer[b]	
Use of NSAID[c]	
Use of corticosteroid	
Use of SSRI	
Use of oral anticoagulant	
Low risk	**High risk**
No risk factors	Age < 60 yrs and ≥ 1 risk factor other than dyspepsia
Age < 60 yrs and dyspepsia as the only risk factor	Age 60-69 yrs and ≥ 1 risk factor
Age 60-69 yrs and no other risk factor	Age ≥ 70 yrs ± other risk factors

NSAID = non-steroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor.
a) Dyspepsia: pain in the upper part of the stomach, acid reflux, heartburn or nausea/vomiting.
b) Confirmed.
c) Weekly or daily use.

FIGURE 2

Study flow.



ADP = adenosine diphosphate; PCI = percutaneous coronary intervention.

prior to PCI (since most PCI patients initiate DAPT treatment prior to their PCI; a treatment duration of less than one month was accepted) or lack of informed consent. This approach was chosen in order not to include patients based on their former tolerability to ADP-receptor inhibitor, i.e., to achieve an unselected group of patients.

Following PCI, the patients completed a questionnaire to assess the risk factors of UGIB. In order to increase the participation rate, non-responders were sent a reminder by letter or telephone after one week. Likewise, the patients were contacted in case of unclear or lacking answers. The questionnaire included questions of: 1) previous or present dyspepsia (defined as upper abdominal pain, acid reflux, heartburn or nausea/vomiting); 2) previous peptic ulcer and how it was diagnosed (general practitioner, endoscopy, X-ray or operation): 3) previous peptic ulcer bleeding; 4) use of low-dose ASA prior to PCI; 5) use of NSAIDs within the past three months prior to PCI, and, if yes: product name and frequency of administration (rarely, weekly or daily); 6) treatment with corticosteroids, SSRIs and anticoagulants; 7) in addition, patients were asked if they had been treated with proton pump inhibitor (PPI) prior to their PCI.

Based on the questionnaire, the patients were classified into two risk groups (**Figure 1**). This approach was described previously [13].

Low-dose ASA was defined as 100 mg or 75 mg. ASA in an analgesic dose was defined as ≥ 500 mg. Peptic ulcer disease was confirmed cases (endoscopy, X-ray or operation).

The Regional Scientific Ethical Committees for Southern Denmark approved the study on 4 October 2010. Furthermore, permission to establish a private research register as well as permission to use register data were accepted by the Danish Data Protection Agency. The prospective study from which the data were collected was registered at Clinical Trials with the registration number: NCT01447498. All participants provided written consent.

Statistical analyses

The results were recorded as absolute numbers and percentages. Stratified analyses were performed to elucidate relations between risk factors and to analyse risk factors in the subgroup of patients treated with PPI prior to PCI. As the baseline risk of UGIB considerably increases with increasing age [14], the patients were stratified into three age groups: < 60 years, 60-69 years and ≥ 70 years. To compare the mean age between users and non-users of PPI, we used a two-sample t-test. One-way ANOVA was used to compare continuous variables between the age groups. Otherwise, we used Pearson's chi-squared test for categorical variables to compare the presence of risk factors between groups (age groups, PPI users/non-users and history/no history of peptic ulcer). A p-value < 0.05 was regarded as statistically significant.

Microsoft Office Access 2010 was used for registration of data. For processing of data, STATA version 12 was used.

Trial registration: ClinicalTrials.gov: CT01447498.

RESULTS

During 16 months, at total of 1,358 patients were included in the study, representing a 70% participation rate (**Figure 2**). Baseline characteristics are presented in **Table 1**. The mean age was 64.1 years (standard deviation = 10.3 years; range: 33-92 years) and 1,022 (75.3%) were men. Nearly half of the patients were treated with low-dose ASA prior to PCI. Two thirds of the patients had a high risk of UGIB (Table 1). One third of the population used NSAID of whom nearly 50% used NSAID daily or weekly. The most frequently used NSAIDs were ibuprofen (60.7%), diclofenac (9.3%) or ASA used in analgesic doses (22.0%).

Stratification by age: The proportion of high-risk patients increases with age, as age itself is a risk factor (34-100%). The number of risk factors (besides age) was similar in the three age groups (p = 0.391) (Table 1).

Stratification by low-dose ASA: Low-dose ASA use prior to PCI did not influence the number or type of risk factors. The proportion of patients in low-dose ASA treatment increased with age (p < 0.001).

Stratification by previous ulcer: Patients with previous peptic ulcer more frequently reported dyspepsia than patients without a history of ulcer (p < 0.001); no other risk factors were more prevalent in this group. PPI use prior to PCI was significantly more common in this group than in patients without previous ulcer (p < 0.001).

Stratification by PPI: PPI was used by 248 (18%) of the included patients prior to their PCI. Patients in PPI treatment were characterised by a higher number of risk factors than patients not in PPI treatment (**Table 2**) In total, 49% (671/1,358) of the included patients were at high risk of ulcer bleeding and without PPI treatment.

DISCUSSION

This study is the first to register risk factors of UGIB with a prospective collection of data from first-time PCI patients. The results demonstrate that 65% of the included patients were judged to be at a high risk of UGIB.

The present study included a very large number of patients in a wide age range. Also, the participation rate was fairly high at 70%, and the patients originated from a population (Western Denmark) representing more than half of the PCIs performed in Denmark. In addition, information on individual risk factors was registered prospectively by a questionnaire completed by the patients within a few days after their PCI. This method facilitated the collection of important information on gastrointestinal symptoms and use of over-the-counter (OTC) drugs.

In the general population, up to 40% have dyspepsia [15], which is lower than in this study. A possible explanation could be the large proportion of patients treated with low-dose ASA prior to PCI, but it could also be due to selection bias as not all invited patients chose to participate. This leaves a possibility of a higher participation rate among patients with previous gastroentestinal problems. However, as baseline characteristics in

TABLE 1

Baseline of total population and stratified by age groups. The values are n (%).

	All (N = 1,358)	< 60 yrs (N = 436)	60-69 yrs (N = 482)	≥ 70 yrs (N = 440)	p-value[a]
Symptoms					
Dyspepsia	681 (50.1)	247 (56.7)	233 (48.3)	201 (45.7)	ns
Peptic ulcer history					
Uncomplicated	79 (5.8)	23 (5.3)	27 (5.6)	29 (6.6)	
Bleeding	31 (2.3)	7 (1.6)	8 (1.7)	16 (3.6)	
Total	110 (8.1)	30 (6.9)	35 (7.3)	45 (10.2)	ns
PPI[b]	248 (18.3)	69 (15.8)	77 (16.0)	102 (23.2)	ns
Low-dose ASA	622 (45.8)	133 (30.5)	239 (49.6)	250 (56.8)	ns
NSAID use					
Weekly	125 (9.2)	58 (13.3)	42 (8.7)	25 (5.7)	
Daily	89 (6.6)	33 (7.6)	32 (6.6)	24 (5.5)	
Total	214 (15.8)	91 (20.9)	74 (15.4)	49 (11.1)	< 0.001
Corticosteroid use	39 (2.9)	11 (2.5)	11 (2.3)	17 (3.9)	ns
SSRI use	79 (5.8)	28 (6.4)	25 (5.2)	26 (5.9)	ns
Oral anticoagulant use	86 (6.3)	16 (3.7)	33 (6.8)	37 (8.4)	0.013
eGFR; mean (95% CI)	82 (80-85)	90 (88-92)	82 (78-87)	75 (71-79)	< 0.001
High-risk patients[c]	886 (65.2)	149 (34.2)	297 (61.6)	440 (100.0)	–

ASA = acetylsalicylic acid; CI = confidence interval; eGFR = estimated glomerular filtration rate; ns = non-significant; NSAID = non-steroidal anti-inflammatory drug; PPI = proton pump inhibitor; SSRI = selective serotonin reuptake inhibitor.
a) Comparison between age groups.
b) Regular use prior to percutaneous coronary intervention, 3 missing values.
c) According to risk factors (Figure 1).

TABLE 2

Risk factors for upper gastrointestinal bleeding according to proton pump inhibitor.

	PPI prior to PCI (N_{tot} = 1,356)[a]		
	use (N = 248 (18%))	none use (N = 1,108 (82%))	p-value
Age, yrs, mean (95% CI)	65.5 (64.2-66.8)	63.8 (63.2-64.4)	0.018
Dyspepsia, n (%)	222 (89.5)	458 (41.3)	< 0.001
Previous ulcer, n (%)	52 (21.0)	57 (5.1)	< 0.001
NSAID[b], n (%)	50 (20.2)	163 (14.7)	0.033
Glucocorticoid use, n (%)	10 (4.0)	29 (2.6)	ns
SSRI use, n (%)	25 (10.1)	53 (2.6)	0.001
Oral anticoagulant use, n (%)	22 (8.9)	63 (5.7)	ns
High-risk patients[c], n (%)	213 (86)	671 (61)	< 0.001

CI = confidence interval; ns = non-significant; NSAID = non-steroidal anti-inflammatory drug; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; SSRI = selective serotonin reuptake inhibitor.
a) Due to the questionnaire, answers for 2 patients were missing.
b) Weekly or daily use of NSAID.
c) According to risk factors.

this study were similar to those of national [16] and international cohorts [13, 17], the present cohort was considered representative for PCI-treated patients in general. *Helicobacter pylori* is also a well-known risk factor of UGIB, but this aetiology was not included as a risk factor in this study as a proven *H. pylori* infection almost always will lead to *H. pylori* eradication, thus eliminating this risk factor [18].

The higher use of PPI and low-dose ASA prior to PCI among older patients may explain the lower and more cautious use of NSAIDs in this age group. The higher consumption of NSAIDs among the younger patients, in particular the intermittent use of these drugs, could probably be explained by the liberal access to these drugs as ibuprofen and ASA used in analgesic doses ≥ 500 mg are available as OTC drugs in Denmark. For ibuprofen alone, 31% of the daily defined dose is sold as OTC [19]. Overall, there was no difference in the number of risk factors (besides age) in the three age groups. This can probably be explained by the use of anticoagulant treatment which increases with age and equals the use of NSAIDs as a risk factor in this population. Significantly more risk factors were seen among PPI users and these may have prompted the PPI treatment.

A significant difference in the estimated glomerular filtration rate was seen between the age groups. As expected, the renal function was decreasing with increasing age. Use of clopidogrel was previously found to be associated with an increased risk of bleeding [20] among patients in haemodialysis, but renal impairment was not considered a risk factor in this study.

Cassado-Arroyo et al [13] performed a retrospective cross-sectional study in Spain and the United States, evaluating risk factors of UGIB in 429 patients treated with DAPT after PCI. Risk stratification was performed for those not taking PPI prior to PCI (70% and 68% in Spain and United States, respectively). The assessment of risk stratification resembles the risk stratification used in this study. However, exceptions are that the frequency of NSAID use was not defined and gastrointestinal symptoms and the use of SSRI was not included as risk factors. Cassado-Arroyo et al demonstrated that 41.2-50.4% were at high risk of UGIB at baseline (both users and non-users of PPI). Overall, more patients in our study were categorised as having a high risk of UGIB. This may reflect that in the present study, risk stratification also included gastrointestinal symptoms and SSRI.

In this study, 49% of the included patients were at a high risk without PPI treatment. In order to reduce UGIB in DAPT-treated patients, the patients could be examined for risk factors before discharge after PCI, and prophylactic PPI in patients at high-risk should be considered. However, there is currently no risk stratification model for this purpose. In Denmark, the recommendations from The Danish Association of Cardiology on prophylactic PPI treatment suggest that patients with a history of gastrointestinal bleeding and patients at high risk of developing gastrointestinal bleeding (high age, previous or actual *H. pylori* infection, significant renal impairment, concomitant anticoagulant treatment, treatment with steroids and NSAIDs) should be treated with prophylactic PPI, but it is not further specified [2].

CONCLUSION

Our data demonstrate a high prevalence of risk factors of UGIB among PCI patients treated with DAPT, many of whom are not in prophylactic PPI treatment. We suggest that the effect of a routine screening for risk factors in patients on DAPT be evaluated in a large randomised trial.

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