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Gastrointestinal bleeding in high risk survivors of myocardial infarction: the VALIANT Trial

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Aims The risk of gastrointestinal (GI) bleeding limits the use of antiplatelet and anticoagulant drugs. Risk factors for GI bleeding in post- myocardial infarction (MI) patients have not been well defined. We sought to identify risk factors for GI bleeding in patients following MI.

Methods and results The VALsartan In Acute myocardial iNfarcTion trial (VALIANT) enrolled 14 703 post-MI patients with left ventricular dysfunction and/or heart failure and followed them for a median of 24.7 months. In the present secondary analysis, times from baseline to first GI bleeding were identified from the VALIANT serious adverse event database. Potential risk factors were explored from medical history, demographics, clinical profile, and medications, both at baseline and during follow-up. We also explored the relationship between the occurrence of GI bleeding and subsequent mortality. During follow-up, 98 (0.7%) patients had a serious GI bleeding event. These patients were older, had more comorbidities, were more likely to be taking additional antiplatelet drugs, and had worse left ventricular systolic and renal function. The Kaplan–Meier estimated rate of GI bleeding at 6 months was 0.37% (95% CI 0.27–0.47). In a multivariable Cox model, dual antiplatelet therapy was the most powerful predictor of GI bleeding, with an adjusted hazard ratio of 3.18 (95% CI 1.91–5.29). Other predictors were non-white race, history of alcohol abuse, increasing age, worse New York Heart Association class, anticoagulant therapy, diabetes, lower estimated glomerular filtration rate, and male sex. Gastrointestinal bleeding was associated with increased risk of death [adjusted hazard ratio 2.54 (95% CI 1.66–3.89)].

Conclusion Following MI, clinical characteristics can identify patients with increased risk of GI bleeding. The use of dual antiplatelet agents appears to be the most profound risk factor. Whether these patients would benefit from GI prophylaxis therapy remains unknown.

Keywords Myocardial infarction • Risk factors • Gastrointestinal haemorrhage

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Introduction

Gastrointestinal (GI) bleeding is an important cause of morbidity and mortality in the general population as well as in patients with heart disease.[1,2] A recent analysis of patients undergoing primary percutaneous coronary intervention (PCI) for acute myocardial infarction (MI) found that GI bleeding was independently associated with an increased length of hospitalization and higher mortality.[3] Because the management of acute coronary syndromes (ACS) often necessitates the combined use of potent anti-platelet and anti-thrombotic medications, the potential risk of GI bleeding may be substantially increased in the ACS and post-MI populations.[4] Nevertheless, the risk factors for GI bleeding in this patient population have not been well defined. Although the GI tract is a potential target for therapeutic and preventive interventions,[5,6] whether these therapies are warranted or cost effective in

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ACS or post-MI patients remains unknown. The recently published Expert Consensus Document[7] on reducing the GI risks of antiplatelet therapy and non-steroidal anti-inflammatory drugs (NSAIDs) use suggests a risk factor-guided approach to the utilization of gastroprotective agents.

The VALsartan In Acute myocardial iNfarcTion (VALIANT) trial randomized 14 703 patients with heart failure, left ventricular dysfunction, or both post-MI, to receive the angiotensin receptor blocker valsartan, either alone or in combination with captopril, or captopril alone, with a median follow-up of 24.7 months.[8] In the present study, a secondary analysis of the VALIANT population was undertaken using the adverse event database, to identify predictors of GI bleeding in a high-risk post-MI population.

Methods

Study population

Patients were enrolled within 10 days after an acute MI complicated by heart failure (defined by the presence of clinical or radiologic signs), left ventricular dysfunction (evidenced by an ejection fraction of $\leq$0.35 on echocardiography or contrast left ventriculography, and $\leq$0.40 by radionuclide ventriculography), or both to receive treatment with captopril, valsartan, or the combination of the two drugs. The main exclusion criteria were clinically significant valvular disease, severely limited life expectancy due to another disease, intolerance to angiotensin converting enzyme inhibitor or angiotensin receptor blocker, systolic blood pressure less than 100 mmHg and serum creatinine concentration higher than 2.5 mg/dL at randomization and the absence of an informed consent. The primary endpoint was death from any cause and the median follow-up duration was 24.7 months. The rationale, methods,[9] and primary results[8] of the VALIANT trial have been previously published.

Gastrointestinal bleeding as a serious adverse event

In the VALIANT trial, a serious adverse event was defined as any untoward medical occurrence that '(i) results in death, (ii) is life-threatening, (iii) requires inpatient hospitalization or prolongs existing hospitalization, or (iv) results in persistent or significant disability/incapacity.' Gastrointestinal bleeding events that were reported by site investigators as serious adverse events, and their occurrence times, were identified from the VALIANT serious adverse event database.

Variables recorded

We identified risk factors from medical history, demographics, baseline clinical profile, and medications. To assess the influence of drugs on the occurrence of GI bleeding, medication intake, including antiplatelets, anticoagulants, various cardiovascular drugs, NSAIDs, and selective serotonin reuptake inhibitors was recorded from each study visit. The first (baseline) VALIANT study visit occurred within 10 days following the index MI. Subsequent study visits occurred at 2 weeks after randomization, at the first month of follow-up and then every 3 months for the first year and every 4 months in subsequent years. Blood pressure and heart rate were also measured at every study visit. Serum creatinine levels were measured during early study visits in the course of titrating the dose of study medication. The four component modification of diet in renal disease equation[10] was used to calculate the estimated glomerular filtration rate (eGFR) at each study visit. When serum creatinine levels were not available during later visits, the last known value was recorded.

Statistical analyses

Values are reported as absolute numbers with percentages for categorical variables and as means with standard deviations for continuous variables. We used the χ^2 test to compare categorical variables between patients who did and those who did not develop GI bleeding. Continuous variables (age, eGFR, and ejection fraction) were compared using the non-parametric Wilcoxon's rank sum test, as they were not normally distributed. The cumulative rate of GI bleeding in the entire population was estimated using Kaplan–Meier analysis. Univariate Cox proportional hazards models were used to evaluate associations between the hazard of GI bleeding and variables available in the VALIANT trial, including demographic variables (age, gender, and race), past medical history (history of MI, heart failure, diabetes, hypertension, hypercholesterolaemia), clinical characteristics at the time of the index MI (vital signs, presence or absence of heart failure symptoms and signs, type and location of the MI, and presence of cardiogenic shock), treatment used at the time of the index MI (thrombolysis, mechanical reperfusion, adjunct antiplatelet and anti-thrombotic therapy, ACE inhibitors, and beta-blockers), as well as clinical profile (eGFR, vital signs, New York Heart Association (NYHA) class), and medication use during the follow-up period (as described above). Predictors with significant ($P < 0.05$) univariate associations were entered into a backward stepwise selection, with an entry *P*-value threshold of 0.01 and a removal threshold of 0.05, to build a multivariable Cox proportional hazards model. Longitudinally measured clinical markers and medication use entered the Cox models as time-varying covariates whose values at each time point were obtained from the most recent study visit. Trends in medication use during follow-up were described by averaging the time-varying covariate across all available patients at each follow-up time point. Using the fitted univariate Cox model for the effect of dual antiplatelet therapy on the hazard of GI bleeding, we calculated the projected rates of GI bleeding under continuous, long-term dual antiplatelet therapy. All analyses were performed using Intercooled Stata statistical software version 8.2 for Windows.

Results

Incidence and time course of gastrointestinal bleeding events

During the follow-up period of the VALIANT trial, 98 (0.7%) patients experienced a GI bleeding event, and 7 patients had a recurrent event. In this analysis, only first bleeding events were included. The bleeding originated from the upper GI tract in 21 (21.4%), from the lower GI tract in 16 (16.3%), and was not specified in the remainder on whom endoscopy was not performed (62.3%). *Table 1* summarizes the baseline characteristics of patients with and without GI bleeding. Of note, patients who developed GI bleeding were older, more likely to be of non-white race and have a history of diabetes, dyslipidaemia, congestive heart failure, and alcohol abuse. In addition, they had a lower eGFR (62.8 ± 20.9 vs. 70.2 ± 21.3 mL/min/1.73 m^2) and a lower echocardiographically measured left ventricular ejection fraction (32.6 ± 11.0 vs. 35.7 ± 10.3%) at baseline, and were more likely to have received other antiplatelet drugs in addition to aspirin at the time of MI. However, they were less likely to have received thrombolytic

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Table 1 Baseline characteristics of the VALIANT study patients according to gastrointestinal bleeding event

	Without GI bleeding (n = 14 605)	With GI bleeding (n = 98)	P-value
Age (years); mean (SD); median (Q1, Q3)	64.8 (11.8); 65.8 (56.2, 73.8)	71.3 (10.6); 73.2 (65.7, 78.3)	<0.001
Male	10 060 (68.9)	73 (74.5)	0.23
Non-white race	936 (6.4)	19 (19.4)	<0.001
History of MI	4071 (27.9)	33 (33.7)	0.20
History of CHF pre-qualifying MI	2152 (14.7)	22 (22.5)	0.032
History of diabetes	3363 (23.0)	37 (37.8)	0.001
History of dyslipidaemia	4297 (29.9)	38 (39.2)	0.046
History of unstable angina	3115 (21.5)	14 (14.3)	0.083
History of PCI	1056 (7.2)	11 (11.2)	0.13
History of CABG	1015 (7.0)	11 (11.2)	0.098
History of AF	951 (6.6)	9 (9.2)	0.30
History of hypertension	8043 (55.1)	57 (58.2)	0.54
History of PVD	1227 (8.5)	10 (10.2)	0.54
History of stroke	888 (6.1)	7 (7.1)	0.68
History of TIA	411 (2.8)	2 (2.0)	0.64
History of renal insufficiency	263 (1.8)	3 (3.1)	0.36
eGFR post-MI (mL/min/1.73 m^2); mean (SD); median (Q1, Q3)	70.2 (21.3); 68.8 (55.4, 83.2)	62.8 (20.9); 61.9 (49.0, 74.1)	0.0002
History of COPD	1242 (8.6)	16 (16.3)	0.006
History of cancer	314 (2.2)	5 (5.1)	0.048
History of smoking	4639 (31.8)	25 (25.8)	0.25
Current smoker	4642 (31.8)	38 (39.2)	
History of alcohol abuse	243 (1.7)	6 (6.1)	0.001
Baseline LVEF[a] (%); mean (SD); median (Q1, Q3)	35.7 (10.3); 34.0 (30.0, 40.0)	32.6 (11.0); 31.0 (25.0, 37.0)	0.008
Thrombolytic use with qualifying MI	5148 (35.3)	22 (22.5)	0.008
Underwent primary PCI	2157 (14.8)	21 (21.4)	0.06
ECG MI site			
Anterior	8339 (59.5)	53 (57.6)	0.72
ECG MI type			
Q-wave	9401 (66.7)	42 (46)	<0.001
Use of antiplatelets/anticoagulants at randomization			
Aspirin	13 333 (91.3)	85 (86.73)	0.1
Other oral antiplatelets (thienopyridines)	3611 (24.7)	36 (36.7)	0.006
Glycoprotein IIb/IIIa inhibitor	961 (6.6)	11 (11.2)	0.065
Heparin	7545 (51.7)	50 (51.0)	0.90
Oral anticoagulant	1374 (9.4)	12 (12.2)	0.34
Use of NSAIDs	648 (4.4)	5 (5.1)	0.75

AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; Q, quartile; SD, standard deviation; TIA, transient ischaemic attack. Categorical variables are shown as number (%).
[a]Baseline echocardiographic determination of ejection fraction was available for only 9154 of the patients enrolled in the VALIANT trial.

therapy at the time of MI and had a lower incidence of Q-wave MI. *Figure 1* illustrates the cumulative incidence of GI bleeding over 3 years of follow-up. The Kaplan–Meier estimated rate of GI bleeding at 6 months was 0.37% (95% CI 0.27–0.47). The estimated rates at 1, 2, and 3 years of follow-up were 0.47% (95% CI 0.35–0.58), 0.66% (95% CI 0.52–0.79), and 0.84% (95% CI 0.63–1.05), respectively. The incidence rate was substantially higher during the early months following the index MI. Kaplan–Meier estimates of the monthly incidence of serious GI bleeding were 0.13% during the first 60 days and 0.018% between 60 days and 2 years (*Figure 1*).

Use of antiplatelet and anticoagulant medications

The majority (85–90%) of the VALIANT patients were treated with aspirin during the follow-up period, consistent with their recent MI. Heparin was used in 53% of the patients in the early

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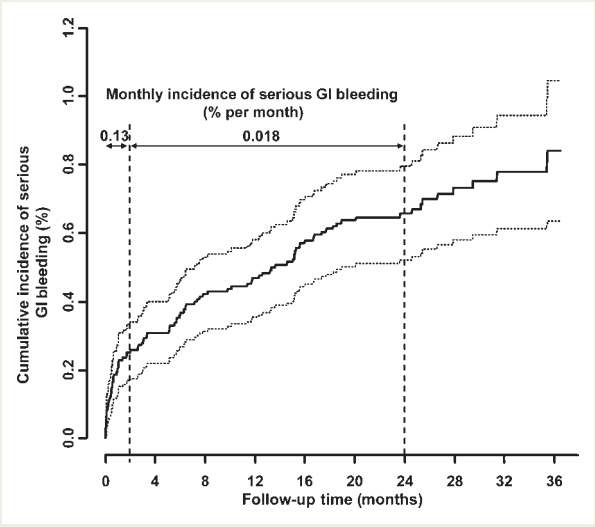

Figure 1 Cumulative incidence of gastrointestinal (GI) bleeding during the VALIANT follow-up. The dotted lines represent the 95% confidence intervals of the estimated rate. The monthly incidence rates of GI bleeding in the first 2 months and between 2 months and 2 years are noted.

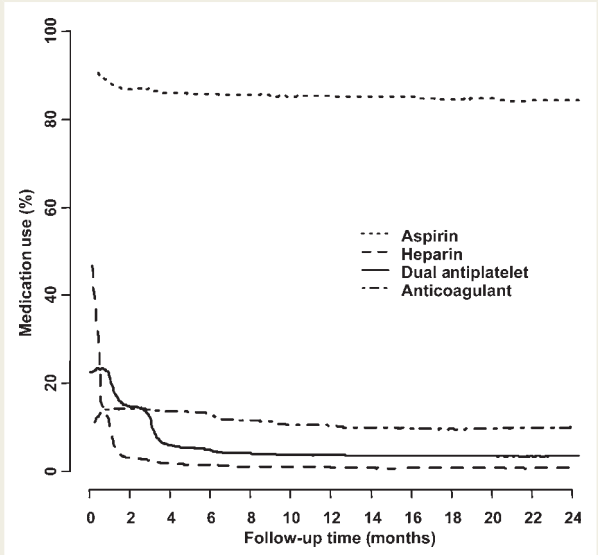

Figure 2 Rates of use of various antiplatelet and anticoagulant drugs during follow-up.

days following the index MI. The use of oral anticoagulants varied during the trial period between 14% (at 1 month) and 10% (beyond the first year). Dual antiplatelet therapy was prescribed to 23% of the patients in the first month following their MI. This rate declined to 5% after the third month. This was consistent with the prevailing practice guidelines at the time of the VALIANT trial, which did not advocate for longer term dual antiplatelet therapy following coronary interventions. The VALIANT trial concluded enrolment of patients in June 2001. At that time, drug eluting stents were not available for clinical use. The rate of utilization of antiplatelets and anticoagulants throughout the follow-up period is shown in *Figure 2*.

Risk factors for gastrointestinal bleeding

Significant univariate predictors of GI bleeding included gender; age; race; NYHA class, diastolic blood pressure, and eGFR throughout the duration of follow up; non-Q-wave MI at randomization; use of thrombolytic with qualifying MI; symptomatic hypotension; use of beta-blocker within 24 h before randomization; atrial fibrillation, ventricular tachycardia, and pacemaker placement between index MI and randomization; history of PCI/coronary artery bypass grafting, alcohol abuse, diabetes, antihypertensive treatment, congestive heart failure, dyslipidaemia, cancer, and chronic obstructive lung disease before index MI; use of dual antiplatelet therapy, oral anticoagulation, digoxin, insulin, amiodarone, calcium channel blocker, selective serotonin re-uptake inhibitor, statin, oral hypoglycaemic agent, and other diuretic throughout the duration of follow-up. All of these factors were entered into the multivariable stepwise regression analysis. Baseline echocardiographic determination of ejection fraction was available for only 9154 of the patients enrolled in the VALIANT trial and was not entered in the analysis. NSAIDs were used in 4.4% of the VALIANT population at baseline and in 3.1% during the first 2 years. However, they did not prove to be significant predictors in the univariate analysis and therefore were not included in the multivariable analysis.

Table 2 Independent predictors of increased risk of gastrointestinal bleeding

	Hazard ratio	95% Confidence interval	Z-score	*P*-value
Dual antiplatelet therapy	3.18	1.91–5.29	4.44	<0.001
Non-white race	3.26	1.89–5.61	4.26	<0.001
History of alcohol abuse	4.71	2.02–11.01	3.58	<0.001
Age (10 year increment)	1.51	1.21–1.90	3.57	<0.001
NYHA class 3 or 4	2.27	1.41–3.64	3.39	0.001
Anticoagulant therapy	2.13	1.28–3.52	2.93	0.003
Diabetes	1.76	1.13–2.74	2.48	0.013
eGFR (10 mL/min/1.73 m^2 decrement)	1.18	1.03–1.34	2.44	0.015
Male sex	1.82	1.10–3.01	2.32	0.021

eGFR, estimated glomerular filtration rate; GI, gastrointestinal; NYHA, New York Heart Association.

Table 2 shows the predictors of GI bleeding identified through the multivariable stepwise regression analysis. Dual antiplatelet therapy was the most powerful predictor, and was associated with a more than three-fold increased hazard of GI bleeding. For every decade increase in age, there was a 51% increase in the hazard of GI bleeding. A 10 mL/min/1.73 m^2 decrement in eGFR

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was associated with 18% increase in the hazard of GI bleeding. Other independent predictors include non-white race, history of alcohol abuse, NYHA class 3 or 4, use of anticoagulant drugs, diabetes, and male sex.

Relationship between gastrointestinal bleeding and survival

Out of the 98 patients who experience a GI bleeding event, 35 (35.7%) patients died (21 from a cardiovascular cause) during the VALIANT follow-up period. Of these 35 patients, four died secondary to their bleeding. The median time to death of the remaining 31 patients was 83 days. All death events were adjudicated by a central committee. Gastrointestinal bleeding was associated with increased risk of all-cause death, with a hazard ratio of 3.57 (95% CI 2.56–5.00; $P < 0.001$). It remained a significant predictor of death after adjusting for sex, age, history of diabetes, MI, chronic obstructive pulmonary disease, heart failure, and angina, baseline PCI, atrial fibrillation, and ejection fraction, as well as NYHA class, eGFR and use of aspirin, anticoagulants, and dual antiplatelet therapy during follow-up (HR 1.79; 95% CI 1.17–2.74; $P = 0.008$).

Discussion

Incidence and risk factors for gastrointestinal bleeding

In this *post hoc* analysis of high-risk post-MI patients, the cumulative incidence of GI bleeding events was relatively low, at about 0.5% at 1 year post-MI, with the majority of these events occurring during the first 6 months (*Figure 1*). The incidence rate was higher in the first few months following the MI and declined rapidly thereafter. Exploring a large number of potential risk factors, we identified several clinical characteristics that are associated with increased risk of GI bleeding, with dual antiplatelet therapy being the most powerful predictor, conferring a three-fold increased risk.

Dual antiplatelet therapy with aspirin and a thienopyridine derivative reduces ischaemic events in patients with ACS[11,12] and after PCI.[13,14] The current American College of Cardiology–American Heart Association guidelines advocate extended (up to 1 year) treatment with dual antiplatelet therapy for ACS patients treated medically with or without bare metal stenting, and for at least 1 year when a drug eluting stent is used.[15] Bleeding complications, in particular those originating from the GI tract, can limit the use of antiplatelet drugs in these patients.

That dual antiplatelet therapy significantly increased the risk of GI bleeding in VALIANT is consistent with other studies. In the CURE study,[11] which randomized patients with ACS to treatment with aspirin and clopidogrel vs. aspirin alone for a mean duration of follow-up of 9 months, the incidence of GI bleeding was 1.33% in the dual antiplatelet group compared with 0.75% in the aspirin group. Likewise, the secondary stroke prevention MATCH trial,[16] which followed patients with a recent stroke or transient ischaemic attack for 18 months, found a higher incidence of GI bleeding in the dual antiplatelet arm (2.47%) than in the aspirin arm (0.85%). The higher incidence of GI bleeding with antiplatelet therapy in these two trials compared with the overall rate in our study is consistent with the declining use of dual antiplatelet therapy in VALIANT after the first 3 months of treatment. Using the fitted Cox model under a hypothetical scenario in which VALIANT patients are assumed to receive continuous dual antiplatelet therapy, the incidence of GI bleeding was projected to be 0.92% (95% CI 0.56–1.29%) at 6 months and 1.25% (95% CI 0.74–1.74%) at 1 year; this is more than twice the observed rate in VALIANT and comparable to the observed rates in the dual antiplatelet arms of the CURE and MATCH trials.

Patients with GI bleeding were less likely to have presented with a Q-wave MI than patients who did not develop bleeding (*Table 1*). This may be related to differences in the type of heparin (unfractionated vs. low molecular weight) used in patients with different MI types. This information was, unfortunately, unavailable in this trial; therefore, it is not possible to draw conclusions in that regard. In addition, there was a trend towards more use of Glycoprotein IIb/IIIa inhibitor in the group with bleeding. The use of Glycoprotein IIb/IIIa inhibitor in the VALIANT trial was more frequent in patients with non-Q-wave MI (7.3%) than in those with Q-Wave MI (6.3%; $P = 0.023$).

We confirm the results of other studies[3,17] demonstrating that increasing age is a predictor of GI bleeding in a cardiovascular population. We also found that the presence of advanced heart failure symptoms, which are markers of haemodynamic instability, to be associated with increased risk of GI bleeding. Reduced cardiac output can cause mucosal ischaemia, increasing the likelihood of developing ulcerations and subsequent bleeding.[18] Renal dysfunction, which has been related to impairment of platelet aggregation and alteration of their interaction with the vessel wall, was also a risk factor, as shown previously in patients with or without cardiovascular disease.[19–21]

The VALIANT post-MI patients exhibited the previously established association[22] between male gender and increased risk of GI bleeding in the general population. While hormonal factors may play a role in ulcer development and healing,[23] smoking and other risk factors such as high alcohol intake may be relevant as well.[24] Gastrointestinal bleeding has also been associated with diabetes in prior studies,[17,25,26] and may be related, in part, to microvascular ischaemia increasing the vulnerability to drug-induced injury and concomitant impaired healing of mucosal damage.

Non-white race and alcohol abuse were among the most potent predictors of GI bleeding in VALIANT. While the association of race and GI bleeding risk is not well understood, the relationship between alcohol consumption and GI bleeding appears to be dose related, is generally felt to be a consequence of significant liver disease with portal hypertension,[27] and can be aggravated in patients with congestive heart failure. Also, alcohol has been shown to have a synergistic effect on aspirin-induced prolongation of the bleeding time,[28] a property that is particularly important in our patient population. In one study,[29] heavy alcohol consumption was associated with almost a three-fold increase in the incidence of GI bleed compared with light consumption.

Clinical implications

This analysis can be useful in identifying patients with increased GI bleeding risk potentially leading to increased vigilance with regard to GI outcomes. A recently published trial[30] found that the use of a proton pump inhibitor reduces the risk of GI bleeding associated

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with aspirin therapy. While observational studies support the value of proton pump inhibitors in reducing the risk of aspirin and clopidogrel monotherapy,[31] these have not been rigorously tested in the context of dual antiplatelet therapy in ACS or following PCI, although a recent observational study suggests the risk of bleeding in this setting was reduced.[32] Whether the use of gastroprotective agents in this patient population is warranted and cost-effective, remains to be proven.

The finding that the occurrence of GI bleeding portended an increased risk of death extends the previously reported association.[17,32] The majority of deaths in our study were not caused by the bleeding event, but were secondary to a cardiovascular cause. It is likely that the cohort experiencing GI bleeding events represented a group of patients with additional comorbidities not accounted for by our multivariable model.

Study strengths and limitations

Rather than testing *a priori* hypotheses about GI bleeding in a post-MI population, the present study evaluated a large number of potential risk factors. The *P*-values in the final selected model should therefore be interpreted in light of prior knowledge and clinical plausibility. This *post hoc* study is strengthened by the fact that it analyses prospectively collected data in a large number of patients with long-term follow-up that most often extended beyond the initial hospitalization for MI, and offers the opportunity to examine the trends of occurrence of GI bleeding over time. Our analysis included a diverse population of post-MI patients, not restricted to those undergoing PCI, thus providing a broader perspective of the issue in this clinical context and allowing better identification of patients who might be appropriate targets for potential therapeutic and preventive measures. Nevertheless, some limitations should be mentioned. The GI bleeding events were reported by site investigators and were not confirmed by a central adjudication committee. Underreporting by site investigators may have lead to an underestimation of the true incidence of events. In addition, since this is a randomized trial population, it is possible that our results do not fully represent the incidence rates that are encountered in routine clinical practice, given that patients who do not participate in clinical trials are usually older and have more comorbidities. The origin of GI bleeds (upper vs. lower) was not recorded for all patients and we did not have results of endoscopy in these patients. We also did not have information on the history of GI bleeding events prior to the index MI, which is an important risk factor for GI bleeding,[33,34] or baseline and follow-up haemoglobin values. We could not assess the effect of varying doses of aspirin on the incidence of GI bleeding as individual aspirin dosing was not available. Also, the type of heparin used (unfractionated vs. low molecular weight) was not recorded. Finally, we lacked information regarding the use of H2-blockers and proton pump inhibitors during the trial period and therefore we could not assess for their potential effect on the occurrence of GI bleeding events. It might be logical to presume that the use of gastroprotective therapy is reasonable in high-risk patients during the first 2–3 months post-MI or as long as they are maintained on dual antiplatelet therapy. However, definite proof of benefit of such treatment strategy should come from randomized clinical trials.

Conclusions

In patients with MI complicated by heart failure, systolic dysfunction, or both, the risk of GI bleeding is related to a number of demographic and historical risk factors, including age, non-white race, and history of alcohol abuse. Moreover, in this population, the use of dual antiplatelet therapy, increasingly common in the post-MI and ACS population, represents a very important long-term risk factor. These data argue for the need for increased vigilance in cardiovascular patients with multiple risk factors for GI bleeding. Whether therapy aimed at attenuating that risk would be of benefit or cost-effective in this population remains unknown.

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