International Journal of Cardiology 184 (2015) 128–134

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Predictors and prognostic consequence of gastrointestinal bleeding in patients with ST-segment elevation myocardial infarction

Wouter J. Kikkert [1], Mariëlla E.C.J. Hassell [1], Ronak Delewi [1], Mariet H. van der Laan [1], Jan Baan Jr. [1], Marije M. Vis [1], Karel T. Koch [1], Robbert J. de Winter [1], Jan J. Piek [1], Jan G.P. Tijssen [1], José P.S. Henriques *,[1]

Department of Cardiology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 12 August 2014
Received in revised form 7 January 2015
Accepted 25 January 2015
Available online 27 January 2015

Keywords:
Gastrointestinal bleeding
ST-segment elevation myocardial infarction
Primary percutaneous coronary intervention
Major bleeding
Acute myocardial infarction

ABSTRACT

Background: Limited data are available on the predictors and implications of gastrointestinal (GI) bleeding in ST-segment elevation myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention (PPCI) and dual antiplatelet therapy.

Methods and results: Predictors of and clinical outcome after GI bleeding were assessed in 2002 STEMI patients undergoing PPCI between 1-1-2003 and 31-07-2008. 139 patients suffered GI bleeding during a median follow-up of 4.9 years. Predictors of GI bleeding were age, history of bleeding, anemia, baseline thrombocytopenia, previous coronary artery bypass grafting, cardiogenic shock, anterior infarction and the use of GP IIb/IIIa inhibitor. By multivariable analysis, a first occurrence of GI bleeding was associated with a twofold increase in risk of subsequent GI bleeding (hazard ratio (HR) 2.19; 95% confidence interval (CI) 1.15–4.17). GI bleeding was not significantly associated with subsequent major adverse cardiac events (HR 1.33; 95% CI 0.98–1.79), cardiac (HR 1.40; 95% CI 0.97–2.02) and all-cause mortality (HR 1.34; 95% CI 0.96–1.85), recurrent MI (HR 0.97; 95% CI 0.58–1.63), stroke (HR 1.26; 95% CI 0.57–2.79) or stent thrombosis (HR 0.71; 95% CI 0.33–1.69).

Conclusion: Among STEMI patients undergoing PPCI, the risk of GI bleeding is related to a number of risk factors, including advanced age, previous (GI) bleeding, GP IIB/IIIA inhibitors, anterior infarction and anemia. GI bleeding does not substantially increase the risk of subsequent recurrent ischemic events in STEMI patients undergoing PPCI, whereas the risk of GI bleeding after a first occurrence is more than doubled.

1. Introduction

Primary percutaneous coronary intervention (PPCI) in conjunction with potent anti-thrombotic therapy has led to significant reductions in recurrent ischemic events and mortality in patients with ST-segment elevation myocardial infarction (STEMI) [1–3]. Unfortunately, these reductions were paralleled by an increase in iatrogenic hemorrhagic complications [3]. Recent analyses have shown that particularly bleeding complications not related to arterial access site required for PCI are associated with adverse outcome [4,5]. Of these non-access site bleeding complications, gastrointestinal (GI) bleedings represent the most frequent source [4,5]. Therefore, identifying baseline predictors of GI-bleeding might be useful, as hemorrhage in the intestinal tract provides an attractive target for preventive measures, such as gastroprotective agents (proton pump inhibitors), lifestyle intervention, and avoidance of agents that cause ulceration of the GI tract (high dose aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs)) [6]. Previous studies have focused on predictors of GI bleeding occurring during the initial hospitalization. However, it is of particular interest to identify patients at high risk of GI bleeding after the initial hospital discharge, as these patients might derive most benefit of preventive treatment. Moreover, it is currently unknown whether patients who develop a GI bleeding after PPCI are at increased risk of subsequent GI bleeding complications. This is an important issue, given the need for prolonged antithrombotic therapy after drug eluting stent implantation or for secondary prevention after STEMI and the distinctive bleeding profiles of the different antithrombotic agents. GI bleeding has been previously associated with an increased risk of subsequent mortality [7–9], but the influence of GI bleeding on recurrent ischemic events remains to be elucidated. Therefore, the aims of the current analysis are fourfold: 1) to investigate the incidence and predictors of GI-bleeding, both in-hospital and after hospital discharge, in STEMI patients treated with dual antiplatelet therapy undergoing PPCI, 2) to investigate if the instantaneous risk of a subsequent GI bleeding was increased after a first GI bleeding, 3) to investigate the relationship between GI bleeding and subsequent recurrent ischemic and hemorrhagic events and 4) to investigate the management of in-hospital GI bleeding, including its effect on the rates of discontinuation of antithrombotic therapy.

* Corresponding author at: Department of Cardiology, B2-115, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
E-mail address: j.p.henriques@amc.uva.nl (J.P.S. Henriques).

[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2015.01.041
0167-5273/

2. Methods

2.1. Source population and procedures

The data analyzed in this study were obtained from consecutive STEMI patients who were accepted for PPCI at the Academic Medical Center-University of Amsterdam between January 1, 2003, and July 31, 2008. The study complied with the Declaration of Helsinki, and the local ethics committee approved the study protocol. In general, patients qualified for PPCI if they had typical ischaemic chest pain and at least 1 mm ST-segment elevation in 2 or more contiguous leads, a new left bundle-branch block, or a true posterior myocardial infarction. Patients received a standard 300–600 mg loading dose clopidogrel. If a coronary stent was implanted, clopidogrel was prescribed for at least one month to patients with a bare metal stent and for six to 12 months to patients with a drug-eluting stent. Patients were routinely pretreated with 300 mg aspirin and 5000 IU unfractionated heparin (UFH). An additional heparin bolus was administered at the catheterization laboratory if necessary to achieve a targeted activated clotting time (ACT) of 300 s followed by an infusion of 12 U/kg/h with titration to achieve a target activated partial thromboplastin time (aPTT) of 1.5–2.0 times the control. Glycoprotein IIb/IIIa inhibitors (GPIs) were used at the discretion of the operator.

Procedural and angiographic data were prospectively collected in a dedicated database. Chart review for consecutive STEMI patients with available aPTT measurements was performed in the context of a study designed to investigate the relationship between periprocedural aPTT and clinical outcome in STEMI patients treated with PPCI. A detailed description of the study protocol has been previously published [10]. We obtained clinical history and detailed information on peri-procedural treatment from in-patients records in the PPCI center and referring hospitals. We obtained follow-up of clinical outcome, including reinfarction, stroke, stent thrombosis and bleeding, by reviewing in- and outpatients charts in the PPCI center and referring hospitals between 2011 and 2012. For every patient, we systematically checked in-patients charts of every hospital admission for the occurrence of clinical events, including hemorrhagic events and their location. Follow-up of clinical events was censored at the actual date of chart review. Patients whose whereabouts could not be traced were considered lost to follow-up from the date of last known medical contact. Follow-up information regarding vital status was obtained from computerized, long-term mortality records from the National Death Index. If a patient could not be identified in these records (e.g. foreign patients), censoring was at the date of last contact.

2.2. Study design

The study cohort consisted of all STEMI patients included in our study database, who were alive at the end of the procedure. This cohort has been previously described [5,11]. A GI bleeding was defined as an episode of hematemesis, blood in the nasogastric tube aspirate, melena, or red blood loss per anum. GI bleeding events were classified according to the Bleeding Academic Research Consortium (BARC), Thrombolysis In Myocardial Infarction (TIMI), and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) classifications [12–14]. For each gastrointestinal bleeding the following items were recorded in the database: the date of the bleeding, the hemoglobin decrease associated with the GI bleeding event (adjusted for the amount of transfusions), the number of blood transfusions, discontinuation of antithrombotic therapy associated with bleeding (including the date of discontinuation and the date of re-initiation), whether endoscopy was performed (including the date of the procedure), complications during endoscopic procedures, surgery to control GI bleeding, the use of vasoactive agents for GI bleeding, and the source of gastrointestinal bleeding (confirmed by endoscopy and imaging techniques).

Cardiac mortality, recurrent MI, stent thrombosis (definite) and target lesion revascularization (TLR) were defined according to the Academic Research Consortium (ARC) criteria [15]. Stroke was defined as an irreversible neurological deficit, as classified by the treating neurologist, on the basis of supporting information, including brain images and neurologic evaluation. Chronic kidney disease (CKD) was defined as an estimated creatinine clearance <60 mL/min/1.73 m^2 [16].

2.3. Statistical analysis

Kaplan Meier analyses were used to estimate the cumulative GI bleeding rates at different time points and to plot time to GI bleeding curves. Predictors of in hospital GI bleeding were identified by performing a stepwise backward elimination logistic regression model. Predictors of GI bleeding occurring after discharge and predictors of all GI bleedings were identified using stepwise backward elimination Cox regression analyses. Candidate covariables considered for inclusion in these models were all the variables in Table 1 with a significant relationship by univariate analysis ($p < 0.10$). In the model investigating predictors of GI bleeding after discharge we also included in-hospital GI bleeding and antithrombotic treatment at discharge (aspirin, thienopyridine and vitamin-K antagonist) as candidate covariables.

To investigate the relationship between the occurrence of a GI bleeding and the risk of subsequent clinical outcome (major adverse cardiac events (MACE, a composite of cardiac mortality, recurrent MI, stroke and TLR), cardiac and non-cardiac mortality, recurrent MI, stent thrombosis, stroke and TLR), we developed 2 sets of Cox proportional hazards models for each outcome measure: unadjusted models and models adjusted for relevant predictors of these clinical outcomes. In these models, GI bleeding was treated as a time-updated covariate. Relevant predictors were identified by performing stepwise backward elimination Cox regression analyses. Entry criterion was set at $p < 0.05$ and exit criterion was set at $p = 0.10$.

To analyze if a first GI bleeding would increase the instantaneous risk of a subsequent GI bleeding, we developed 2 additional regression models according to the method formulated by Andersen and Gill: [17] unadjusted and adjusted for the previously identified predictors of a first GI bleeding. In this model GI bleeding was treated both as outcome as well as a time updated covariate.

Data were complete for all outcomes and for 18 out of 33 variables. Missing patient-level covariates were assumed to be missing at random and were imputed with the use of multiple imputations. The imputation procedure and subsequent Cox proportional hazards regression estimation (including the regression according to Andersen and Gill) were performed according to Rubin's protocol [18]. All tests were 2-sided and a p value below 0.05 was considered statistically significant. Analyses were performed with Statistical Package for Social Sciences software

Table 1
Classification of gastrointestinal bleeding.

Bleeding classification	%	n/N
BARC		
BARC type 1	5.0	7/139
BARC type 2	32.3	45/139
BARC type 3a	46.0	64/139
BARC type 3b	16.5	23/139
TIMI		
TIMI minimal	59.0	82/139
TIMI minor	28.1	39/139
TIMI major	12.9	18/139
GUSTO		
GUSTO mild	51.4	71/139
GUSTO moderate	33.8	47/139
GUSTO severe	15.1	21/139

BARC indicates Bleeding Academic Research Consortium; TIMI: Thrombolysis In Myocardial Infarction; and GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries.