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Original article

Clinical utility of new bleeding criteria: A prospective study of evaluation for the Bleeding Academic Research Consortium definition of bleeding in patients undergoing percutaneous coronary intervention

Jae-Hyuk Choi (MD)[a], Jeong-Min Seo (MD)[a], Dong Hyun Lee (MD)[a], Kyungil Park (MD)[a,b,*], Young-Dae Kim (MD)[a,b]

[a] Regional Cardiocerebrovascular Center, Dong-A University Hospital, Dong-A University College of Medicine, Busan, South Korea
[b] Division of Cardiology, Department of Internal Medicine, Dong-A University College of Medicine, Busan, South Korea

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ABSTRACT

Objectives: The aim of this study was to evaluate the clinical utility of the new bleeding criteria, proposed by the Bleeding Academic Research Consortium (BARC), compared with the old criteria for determining the action of physicians in contact with bleeding events, after percutaneous coronary intervention (PCI).
Background: The BARC criteria were independently associated with an increased risk of 1-year mortality after PCI, and provided a predictive value, in regard to 1-year mortality. The standardized bleeding definitions will be expected to help the physician to correctly analyze the bleeding events, to select an optimal treatment, and to objectively compare the results of multiple trials and registries.
Methods: All the patients undergoing PCI from June to September 2012 were prospectively enrolled. Patients who experienced a bleeding event were further classified, based on three different bleeding severity criteria: BARC, Thrombolysis In Myocardial Infarction (TIMI), and Global Use of Strategies To Open coronary arteries (GUSTO). The primary outcome was the occurrence of bleeding events requiring interruption of antiplatelet therapy (IAT) by physicians.
Results: A total of 376 consecutive patients were included in this study. Total bleeding events occurred in 46 patients (12.2%). BARC type $\geq$2 bleeding occurred in 30 patients (8.0%); however, TIMI major or minor bleeding, and GUSTO moderate or severe bleeding occurred in 6 (1.6%) and 11 patients (2.9%), respectively. Of the 46 patients, 28 (60.9% of patients) required IAT. On receiver-operating characteristic curve analysis, bleeding defined BARC type $\geq$2 effectively predicted IAT, with a sensitivity of 89.3%, and a specificity of 98.5% ($p < 0.001$), compared with TIMI (sensitivity, 21.4%; specificity, 100%; $p < 0.001$), and GUSTO (sensitivity, 39.3%; specificity, 100%; $p < 0.001$).
Conclusions: Compared with TIMI and GUSTO, the BARC definition may be a more useful tool for the detection of bleeding with clinical relevance, for patients undergoing PCI.

Introduction

The developments of antithrombotic and antiplatelet therapy have reduced the risk of recurrent ischemic complications and death, in patients undergoing percutaneous coronary intervention (PCI) [1–3]. However, bleeding complications have increased, with the concurrent use of those drugs [4–6]. Previous studies have shown that bleeding complications have been associated with adverse clinical outcomes, in patients with acute coronary syndrome (ACS), and those undergoing PCI [7–10]. As a result, bleeding avoidance strategies (BAS), such as radial artery approach, vascular closure device, and novel antithrombotic agents, have been developed for patients undergoing PCI, and have contributed to reducing the risk of bleeding events [11–14]. While the reduction of bleeding events has the potential to improve clinical outcomes, the variable criteria of bleeding definitions make it difficult to interpret the safety of BAS or

* Corresponding author at: Regional Cardiovascular Center, Dong-A University Hospital, Division of Cardiology, Department of Internal Medicine, Dong-A University College of Medicine, 1-3 Ga, Dongdaesin-Dong, Seo-Gu, Busan 602-714, South Korea. Tel.: +82 51 240 2733; fax: +82 51 242 5852.
E-mail address: cardiopark@gmail.com (K. Park).

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antithrombotic drugs, and to compare inter-study outcomes [15]. Recently, a consensus effort by academics, research organizations, industry, and regulator representatives resulted in the Bleeding Academic Research Consortium (BARC) suggesting a new objective: a hierarchically graded, consensus classification for bleeding complications [16]. The BARC criteria are a consensus-based report, rather than clinically based or laboratory-based assessments. According to previous large clinical trials to evaluate the validation of the BARC definition, bleeding complications as defined by BARC criteria were independently associated with an increased risk of 1-year mortality after PCI, and provided a predictive value in regard to 1-year mortality [17–19].

The purpose of this present study was to prospectively compare the clinical utility of new bleeding criteria and old bleeding definitions associated with decision making, for bleeding events in real-world clinical practice.

Materials and methods

Study population

We prospectively enrolled consecutive patients undergoing PCI with second-generation drug-eluting stents between June and September 2012. Patients were excluded, if they had thrombocytopenia, or previous history of any bleeding events within the prior 30 days; or if patients had hemodynamic instability, malignancy, recent trauma or major surgery, including coronary artery bypass graft (CABG) in the last month; or if patients have been taking proton pump inhibitors, steroid or non-steroidal anti-inflammatory drugs. They underwent clinical examination, including hemoglobin level, platelet count, serum creatinine, cardiac enzyme, lipid level, chest X-ray, electrocardiogram, and echocardiography.

Clinical endpoint measurements were conducted in-hospital, at 4 weeks, and at 6 months. Hemoglobin or hematocrit levels after each bleeding event, and hemodynamic status during each bleeding event were recorded. In the case of multiple bleeding events, the most severe bleeding episode was considered. The medical history and data from physical examinations were recorded by a single examiner. The bleeding severity was assessed by a trained independent physician. Bleeding data were collected over telephone interview, for 6 months after being discharged.

Study approval was given by the institutional review board at Dong-A University Hospital, and consecutive, eligible patients provided written, informed consent.

Procedures and arterial puncture site management

All the procedures were performed according to the latest standard guidelines [20]. Sheath sizes of 5–7 French were used for the percutaneous procedure during the study period. Enrolled patients were pretreated with 300 mg of clopidogrel. At the beginning of the procedure, 5000 units of heparin were administered intra-arterially, as a routine. Patients were treated with dual antiplatelet therapy for 6 months and advised to maintain aspirin ($\geq$80 mg/day) lifelong. Conventional manual compression was performed on all study populations, as arterial puncture site management. If bleeding events occurred during the study period, the choice of treatment was determined by the patient's physician.

Study endpoint and definitions

The primary outcome was the occurrence of bleeding complications requiring the interruption of antiplatelet therapy (IAT). In the present study, IAT was defined as either a temporary interruption of aspirin and/or a thienopyridine (interruption of >1 day), or a permanent discontinuation by physician [21].

Patients who experienced a bleeding event were further classified, based on three different bleeding severity criteria: Thrombolysis In Myocardial Infarction (TIMI) [22], Global Use of Strategies To Open coronary arteries (GUSTO) [23], and the BARC criteria [16]. A detailed description of these bleeding classifications is given in online Table 1. Concurrently, we repeatedly evaluated bleeding complications for the need for IAT, in all the study population.

Supplementary Table 1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jjcc.2014.06.011.

The secondary outcome of this study was 6-month cardiac mortality. Deaths were categorized as cardiac, or non-cardiac. All deaths were considered cardiac, unless an unequivocal non-cardiac cause could be established.

Statistical analysis

Data are presented as mean $\pm$ SD for continuous variables, or as numbers (%) for categorical variables, as appropriate. Differences between continuous variables in patients who did, and did not, experience bleeding events, were compared, using the Student *t* test or Mann–Whitney test, depending on the results of normality testing by the Shapiro–Wilk test. Chi-square test was used to compare the categorical variables. Odds ratios (ORs) and confidence intervals (CIs) were derived by use of the linear logistic regression mode, to estimate which predictors identified in the univariate analysis were significantly related to the primary outcome. Sensitivity, specificity, and accuracy with respect to bleeding requiring IAT were calculated for BARC, TIMI, and GUSTO criteria, with the use of standard formulae, and compared with the McNemar test. To assess cut-off values of three bleeding criteria in need for IAT, receiver-operating characteristic (ROC) curve analysis was used. The cut-off values were selected as those with the maximal sum of sensitivity and specificity. Chi-square test and Fisher's exact test were used to evaluate the association between the three bleeding definitions, and bleeding requiring IAT. All data were analyzed by IBM SPSS statistics software, version 20 (SPSS Inc., Chicago, IL, USA). A probability value of $p < 0.05$ was taken as a cut-off value for statistical significance.

Results

Baseline characteristics

A total of 376 patients were recruited in this study. All the patients were clinically followed up. Table 1 shows baseline characteristics of the study populations. The proportion of women and ACS patients was 147 patients (39.1%) and 214 patients (56.9%), respectively. Twenty-three patients (6.1%) were diagnosed to have ST-elevation myocardial infarction. The vascular access site was usually radial (86.2%). The overall population was classified into bleeding and non-bleeding groups, according to the bleeding events.

Bleeding events

Total bleeding events occurred in 46 patients (12.2%) at 6-month follow-up. The most common bleeding events were hematoma or oozing in puncture site (65%) in the 46 bleeding patients (Table 2). Other bleeding complications were gastrointestinal bleeding (13%), gross hematuria (10%), upper airway bleeding (4%), pericardial effusion (4%), and aortic dissection (2.5%). Nine patients (19%) underwent blood transfusion, due to large blood loss, or lowering of hemoglobin level ($\geq$3 g/dL). Differences between the "bleeding group" and "non-bleeding