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Attributable Cost and Length of Stay for Patients with Enoxaparin-Associated Bleeding

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ABSTRACT

Objectives: Patients receiving enoxaparin are at risk of bleeding. The study of the economic impact of enoxaparin-associated bleeding in Asian population, however, is limited. This study aimed to estimate the attributable costs and length of stay (LOS) of patients experiencing enoxaparin-associated bleeding compared with nonbleeding patients in the setting of acute coronary syndrome. **Methods:** We conducted a retrospective cohort study of hospitalized patients with acute coronary syndrome who received enoxaparin in a large university-affiliated hospital. Cost and LOS were compared among three groups of patients according to the status of bleeding event. The attributable cost and LOS were estimated by using multiple linear regressions with log-transformed model and adjusted by confounders. The adjusted means of cost and LOS estimates were retransformed to their natural values by using Duan's smearing estimator. The differences of costs and LOS were presented as mean with 95% confidence intervals (CIs). **Results:** Out of 346 patients, 134 experienced enoxaparin-

associated bleeding (28 and 106 patients experienced major and minor bleeding, respectively). The average age and gender in both groups were similar. Compared to the nonbleeding group, the attributable cost and LOS were 108,226 Thai baht (95% CI: 87,068–129,386) and 8 days (95% CI: 7.1–9.0) for major bleeding and 72,997 Thai baht (95% CI: 57,822–88,172) and 3.1 days (95% CI: 2.5–3.7) for minor bleeding, respectively. **Conclusions:** Bleeding is significantly associated with increased cost and LOS among enoxaparin users. These findings suggest that strategies aiming to reduce bleeding events may potentially help reduce the cost of care among patients with acute coronary syndrome receiving enoxaparin therapy.

Keywords: acute coronary syndrome, bleeding, cost, enoxaparin, length of stay.

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Introduction

Enoxaparin is a low-molecular-weight heparin (LMWH) derived from unfractionated heparin through chemical or enzymatic depolymerization. Compared with unfractionated heparin in the treatment of venous thromboembolism and acute coronary syndrome (ACS), LMWHs provide greater effectiveness without an increased risk of complications [1,2].

ACS is a cardiac condition that can lead to myocardial infarction and death [3]. LMWHs are currently recommended as an important component in the management of ACS and have superseded unfractionated heparin in this regard [4]. Enoxaparin has become the LMWH of choice in this setting due to a large body of supportive evidence [4–8].

Despite this proven efficacy, bleeding complications are still of particular concern in patients who receive enoxaparin therapy [9]. Major bleeding is clinically more important because it has been shown to be an independent predictor of short- and long-term

mortality in patients with ACS and was associated with increased cost and a longer duration of hospital stay [10–12].

Although there are numerous studies [13,14] evaluating the impact of bleeding in terms of clinical consequences, extended stays in hospital, and increasing costs of care, there is currently a lack of such data from Asian countries where the management of ACS can be quite different from that in the Western world. This study therefore aimed to estimate the attributable costs and length of stay (LOS) of Thai patients experiencing enoxaparin-associated bleeding compared with nonbleeding patients.

Methods

Setting, patient sample, and data collection

All cases of patients with ACS who were admitted at a large university-affiliated hospital in Bangkok, Thailand, during January

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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2006 to February 2009 with records-coded ACS were retrospectively reviewed. In case of patients experiencing more than one admission, the most recent admission was considered. The inclusion criteria were 1) age 18 years or older, 2) having a diagnosis of ACS, and 3) receiving at least one dose of enoxaparin. We excluded patients from our analysis if they met the following criteria: 1) enoxaparin dose, dosing interval, date of birth, serum creatinine, or weight values were missing; 2) pregnancy; 3) burn; 4) hemophilia A or B, von Willebrand's disease, hereditary hemorrhagic telangiectasis, idiopathic thrombocytopenic purpura, thrombocytopenia, dengue, hemorrhagic fever, antithrombin III deficiency; and 5) thrombocytopenia (platelet count 50,000 cells/mL or lower). All medical records meeting the above criteria were reviewed by using a standardized data collection form.

We defined enoxaparin-associated bleeding as the bleeding that occurred during enoxaparin therapy or within 24 hours following the discontinuation of enoxaparin therapy. For patients who experienced more than one bleeding episode, only the most severe bleeding episode was considered.

This study protocol was approved by the Committee on Human Rights Related to Researches Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital.

Statistical analyses

Patients were categorized into three groups according to the status of an in-hospital bleeding event as 1) nonbleeding, 2) major bleeding, and 3) minor bleeding based on Thai Acute Coronary Syndrome Registry (TACSR) major bleeding classification [15]. Major bleeding, defined by TACSR, is an overt clinical bleeding (or documented intracranial or retroperitoneal hemorrhage) requiring blood transfusion or associated with a drop in hemoglobin of greater than 5 g/dL or in hematocrit of greater than 15%. Baseline characteristics were compared by using the chi-square test for categorical variables and the analysis of variance test or the Kruskal-Wallis rank test for continuous variables as appropriate. A *P* value of <0.05 was considered statistically significant.

Cost and LOS were compared among the three groups by using multivariable linear regression analysis and included baseline patient characteristics and presenting sign and symptom as covariates. The criteria for retention variables in the model was based on clinical predictors and a *P* value of <0.25. The cost variable was log-transformed prior to analysis to correct for skewness [16,17]. After analysis using multivariable linear regression, it was re-transformed to their natural values by using Duan's smearing estimator [16,18].

Sensitivity analysis

To evaluate the robustness of our analysis, we performed sensitivity analysis of cost and LOS stratified by patient groups on the basis of two standard bleeding severity classification systems. The first was a clinically based scale, Global Use of Strategies to Open Occluded Coronary Arteries criteria [19], and the second was a laboratory-based scale, Thrombolysis in Myocardial Infarction criteria [20].

Results

Of 346 patients enrolled in this study, the majority were admitted because of non-ST-segment elevation myocardial infarction (NSTEMI) (*n* = 196; 57%) followed by ST-segment elevation myocardial infarction (STEMI) (*n* = 87; 25%) and unstable angina (UA) (*n* = 63; 18%) (Fig. 1). There were 212 (61%) patients who did not experience any bleeding events while 28 (8%) and 106 (31%) patients experienced major and minor bleeding, based on TACSR classification, respectively. Demographic data of the patients in

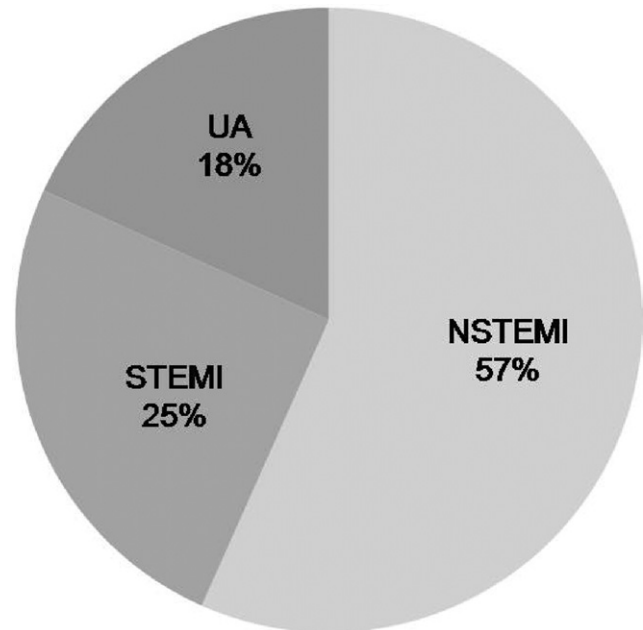


Fig. 1 – Proportion of acute coronary syndrome patients included in the study. STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; UA, unstable angina.

each group were comparable with regard to age and sex. However, some variables were different such as the presence of diabetes mellitus and the degree of renal function (Table 1).

After adjustment for potential confounders, ACS patients with major bleeding had a significant increase in total cost of care (108,226 Thai bhat [THB]; 95% confidence interval [CI] 87,068–129,386; *P* < 0.001) and LOS (8 days; 95% CI 7.1–9.0; *P* < 0.001) compared with those without a bleeding event (Table 2). For ACS patients with a minor bleeding event, the attributable cost and LOS was 72,997 THB (95% CI 57,822–88,172; *P* = 0.031) and 3.1 days (95% CI 2.5–3.7; *P* < 0.001), respectively (Table 2). It should be noted, however, that the mortality rate was 42.8% (12 of 28), 12.3% (13 of 106), and 2.4% (5 of 212) in major, minor, and nonbleeding groups, respectively.

Sensitivity analysis (Table 3) was performed to investigate the robustness of the results. Despite changing the bleeding definition by using Global Use of Strategies to Open Occluded Coronary Arteries and Thrombolysis in Myocardial Infarction criteria, the estimated cost and LOS showed similar trends, indicating that the higher the severity of bleeding, the higher the cost and LOS observed. There is an exception for severe bleeding group in Global Use of Strategies to Open Occluded Coronary Arteries criteria and major bleeding group in Thrombolysis in Myocardial Infarction criteria; the estimated cost and LOS were lower than other groups. This finding is most likely a result of small number of patients in these groups and premature death experienced by these patients.

Discussion

ACS has now become a worldwide problem [3,7,8,15]. The economical impact of ACS management would likely post a huge burden on health care spending on these countries [21,22]. This was illustrated not only in this study but also in a recent study that found that the average cost of care for a patient with ACS is approximately 120,000 THB per admission, with around 71 million THB for all Thai patients with ACS during the first year of therapy [22].

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