Dual Antiplatelet Therapy and the Severity Risk of Lower Intestinal Bleeding

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Abstract

Background: Dual antiplatelet (Plt) therapy with aspirin and clopidogrel is recommended for up to 1 year following acute coronary syndrome. Many of these cardiac patients are also on antithrombotic therapy like warfarin. Lower gastrointestinal bleeding (LGIB) is the main adverse event of this treatment. Aims: The main purpose of this study was to analyze the relationship of dual anti-Plt therapy and the risk of LGIB. Methods: Patients' electronic charts were reviewed to include a total of 19 variables, which included age, sex, ethnicity, daily use of aspirin of any dose, daily use of clopidogrel, use of nonsteroidal anti-inflammatory drugs (NSAIDs) at least twice in the last week prior to admission and the daily use of anticoagulants (warfarin, heparin), and were obtained from history and physical examination reports, lab transcripts and procedural reports. Settings/Design: A retrospective cohort study of the records of 3436 patients admitted to our hospital from January 1, 2009, to December 31, 2011, was evaluated. All the patients included were admitted through the emergency department with complaints of or relating to LGIB. The primary outcome studied was severe LGIB as defined by the requirement of at least two units of packed red blood cells and/or a decrease in the hematocrit of 20% or more or recurrent bleeding after 24 h of clinical stability with additional transfusions required. Other outcomes included surgical intervention. Statistical Methods/Analysis: Univariate analysis using t-test on continuous variables and Chi-square test on categorical variables were done before carrying out logistic regression analysis. Logistic regression analyses were conducted to measures of association between the variables and LGIB. Logistic regression analysis was not carried for surgical intervention and death because none of the variables was significant from univariate tests. Results: A total of 511 patients were found to have true LGIB. Among these subjects, 61 were shown to be on dual or multiple antithrombotic therapies. Further exploration revealed that while the use of multiple blood thinning agents may, in fact, pose a significant risk to overall LGIB, it did not significantly increase the risk for severe bleeding as outlined above. Conclusion: The use of multiple blood thinning agents does not significantly increase the risk for severe LGIB.

Keywords: Antiplatelet, antithrombotic, lower gastrointestinal bleeding

Introduction

Lower gastrointestinal bleeding (LGIB) is a common complaint and is defined as bleeding of a gastrointestinal (GI) source distal to the ligament of Treitz. LGIB accounts for about 20% of major GI bleeding, and is generally less severe than upper GI bleeding. LGIB is a fairly common cause of hospitalization and accounts for 20–27 hospitalizations per 100,000 adults in the United States of America. Fortunately, nearly 80% of LGIB stops spontaneously. The overall mortality rate of LGIB is 2%–4% but may be as high as 23% if LGIB occurs in inpatient settings.[1,2] The causes of LGIB are various and numerous. In a large nationwide study that evaluated 227,022 hospitalized patients, diverticular bleeding was the most common cause of LGIB (33.1%), followed by hemorrhoidal bleeding (20%), colorectal polyps (13.1%), colorectal cancer (8.2%), intestinal ischemia (6.6%), and angiodysplasia (6.0%).[3]

Early recognition of high-risk patients presenting with LGIB might assist healthcare providers to accurately triage these patients and to economize the use of the available resources.

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High quality of care is most desired when balanced with cost-effectiveness. Although early identification of the bleeding source of LGIB is desired by many health-care providers, outcomes may not be altered by early endoscopic interventions as shown by two randomized trials.14,5

Unlike upper GI bleed, very few studies were done to help triage the patients presenting to the hospital with chief complaint of LGIB. The challenges stem from the variety of the causes of LGIB with different morbidity and mortality rates. The initial clinical presentation may not correlate with the severity of LGIB as shown in previous studies aimed to determine the predictors of poor outcomes. Although the incidence of LGIB is increased with the use of anti-thrombotic (AT) medications (including antiplatelet [Plt] and anticoagulant medications), the severity of LGIB and the need of surgical interventions in patients taking AT medications is not well defined.6,8 The use of AT medication in combination have been on the rise. To further evaluate the risks of these medications, we collected clinical data retrospectively from a cohort of patients using the above-mentioned medications admitted to our institution for LGIB with a goal of evaluating the risk of severe bleeding.

Methods

Study design

A retrospective cohort study of the records of the patients admitted to St. Joseph Regional Medical Center from January 1, 2009, to December 31, 2011, was evaluated. All the patients included were admitted through the emergency department with complaints of or relating to LGIB. The study was approved by the institutional review board of the hospital.

Subject selection

A total of 3436 subjects were selected for review using International Classification of Diseases, Ninth Revision codes representing various etiologies of LGIB. Once a master participant list was compiled, all personal patient information was removed and subjects were assigned independent identification numbers that correlated electronic medical record files. A solitary copy of this master list was held by the lead investigator solely for reference, as needed, to ensure patient confidentiality and observer objectivity. The electronic records of these patients were reviewed, and patients were excluded from the study if any evidence of upper GI bleed was found on the admission report, emergency room record, upper gastroedodenoendoscopy report, nasogastric aspirate, nuclear or angiographic studies. Additional exclusion criteria included: low grade bleeding (scant blood on toilet tissue only or positive tests of occult blood stool cards), patients transferred from other acute care facilities, hospitalized patients for a different complaint, or populations younger than 18 years of age. Ultimately, 511 met the inclusion criteria and were incorporated into our study.

Studied variables

Once included, patients’ electronic charts were reviewed to include a total of 19 variables obtained from history and physical examination reports, laboratory transcripts and procedural reports. Variables were: age, sex, ethnicity, daily use aspirin of any dose, daily use of clopidogrel, use of nonsteroidal anti-inflammatory drugs (NSAIDs) at least twice in the last week prior to admission, the daily use of anticoagulants (warfarin, heparin), stool color, the presence of presyncope or syncope, encephalopathy, the presence of abdominal pain, heart rate (HR) and systolic blood pressure (SBP), abdominal tenderness, gross blood on rectal examination, Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II severity index, Plt count, and international normalized ratio (INR). Our data were documented on subject specific, individual data collection forms identifiable only by the assigned independent identification numbers, to be entered into our database.

Outcomes

The primary outcome studied was severe LGIB as defined by the requirement of at least two units of packed red blood cells and/or a decrease in the hematocrit (Hct) of 20% or more or recurrent bleeding after 24 h of clinical stability with additional transfusions required. Other outcomes included surgical intervention. The initial recorded Hct was considered baseline as compared to the lowest Hct level in the following 24 h. Same rule was applied to the recurrent bleeding when measuring Hct before the recurrence of LGIB (baseline Hct) and compare it to the lowest Hct level in the next 24 h.

Statistical methods

Univariate analysis using t-test on continuous variables and Chi-square test on categorical variables were done before carrying out logistic regression analysis. Logistic regression analyses were conducted to measures of association between the variables and LGIB. Logistic regression analysis was not carried for surgical intervention and death because none of the variables was significant from univariate tests.

Results

There were statistically significant association of age <65 years, sex, white and hispanic ethnicities, aspirin use (−), NSAID, warfarin, hep/lovenox (+), acetylsalicylic acid (ASA) + plavix, ASA + warfarin, ASA alone with LGIB. Furthermore, anticoagulation or anti-Plt (no anticoagulation/Plt, (+) anticoagulation/Plt, ASA alone), stool color (red/bloody and dark/melena), history of abdominal pain, AM/PM, weekend, onset to ED (≤1 day, 2 days, and 2–7 days), HR (HR <90), SBP, abdominal tenderness, bright red blood, Plts (Plt >50), and INR were associated with LGIB [Table 1].

Multivariate analysis

Eight variables were significant at $P=0.05$ from logistic regression analysis. The logistic regression coefficients are presented in Tables 2, 3, and Figure 1. Odd ratios (ORs) were calculated using only variables that were significant, and are presented in Table 4. We can see that the ORs of stool color,
| Variable                        | Primary outcome | No outcome | P      |
|--------------------------------|----------------|------------|--------|
| **Primary variable**           |                |            |        |
| Age <65 (223)                  | 74             | 149        | 0.001053295 |
| Age ≥65 (288)                  | 119            | 169        | 0.154173614 |
| Sex Male (245)                 | 98             | 147        | 2.35E-05  |
| Sex Female (266)               | 95             | 171        | 2.02E-14  |
| Ethnicity Black (142)          | 64             | 78         | 0.2753   |
| Ethnicity Hispanic (99)        | 29             | 70         | 5.82E-05  |
| Ethnicity Other (24)           | 9              | 15         | 0.3074   |
| ASA (as individual variable)  |                |            |        |
| ASA+ (112)                     | 54             | 58         | 0.7768   |
| ASA− (396)                     | 138            | 258        | 2.23E-09  |
| Plavix (as individual variable)|                |            |        |
| Plavix+ (61)                   | 33             | 28         | 0.6085   |
| Plavix− (447)                  | 159            | 288        | 0.7051   |
| NSAI D                         |                |            |        |
| NSAI D+ (37)                   | 12             | 25         | 0.03026  |
| NSAI D− (471)                  | 180            | 291        | 2.33E-10  |
| Warfarin                       |                |            |        |
| Warfarin+ (60)                 | 16             | 44         | 0.0004909|
| Warfarin− (445)                | 176            | 269        | 1.29E-05  |
| Hep/lovenox                    |                |            |        |
| Hep/lovenox+ (3)               | 1              | 2          | NA      |
| Hep/lovenox− (445)             | 176            | 269        | 1.29E-05  |
| ASA                            |                |            |        |
| ASA + plavix                   | 25             | 16         | 0.2301   |
| ASA + plavix + warfarin        | 3              | 2          | NA      |
| ASA + plavix + nsaid           | 2              | 0          | NA      |
| ASA + plavix + lovenox         | 1              | 1          | NA      |
| ASA + NSAI D                   | 6              | 3          | NA      |
| NSAI D + plavix                | 4              | 1          | NA      |
| NSAI D + warfarin              | 1              | 1          | NA      |
| ASA + warfarin                 | 16             | 13         | 0.005905 |
| ASA + lovenox                  | 1              | 0          | NA      |
| Plavix + lovenox               | 1              | 1          | NA      |
| Plavix + warfarin              | 2              | 2          | NA      |
| ASA alone                      | 61             | 22         | 0.0004351|
| Anti-coagulation or anti-platelet| 298          | 94         | 2.72E-10  |
| Platelet                       |                |            |        |
| <50 (8)                        | 3              | 5          | 0.7237   |
| >50 (500)                      | 190            | 310        | 1.57E-10  |
| INR                            |                |            |        |
| >2 (53)                        | 35             | 18         | 0.02797  |
| <2 (399)                       | 147            | 252        | 1.92E-07  |
| **Stool color**                |                |            |        |
| Red/bloody                     | 155            | 248        | 1.65E-05  |
| Dark/melena                    | 29             | 52         | 0.02627  |
| Black/other                    | 9              | 18         | 0.1237   |
| History of abdominal pain      |                |            |        |
| History of pain+               | 75             | 156        | 1.41E-07  |
| History of pain−               | 117            | 162        | 0.008433 |

**Table 1: Contd...**

| Variable                        | Primary outcome | No outcome | P      |
|--------------------------------|----------------|------------|--------|
| LOC/light headed                |                |            |        |
| LOC+                           | 57             | 38         | 0.05478  |
| LOC−                           | 136            | 279        | 3.16E-12 |
| AM/PM                          |                |            |        |
| AM                             | 124            | 204        | 1.29E-05 |
| PM                             | 68             | 109        | 0.002642 |
| Onset to ED                    |                |            |        |
| ≤1 day                         | 90             | 145        | 0.0004274|
| 2 days                         | 27             | 65         | 0.0001145|
| 2-7 days                       | 32             | 67         | 0.0006329|
| 7+ days                        | 26             | 24         | 0.5     |
| Abdominal tenderness           |                |            |        |
| Abdominal tender+              | 54             | 135        | 5.92E-09 |
| Abdominal tender−              | 139            | 183        | 0.01656  |
| HR                             |                |            |        |
| >90 (192)                      | 86             | 106        | 0.1703   |
| <90 (311)                      | 104            | 207        | 5.22E-08 |
| SBP                            |                |            |        |
| >100 (443)                     | 177            | 266        | 2.90E-05 |
| <100 (62)                      | 15             | 47         | 8.25E-05 |
| Significance variables at $P \leq 0.05$ are bolded, and variables with N/A had very small samples. NSAI D: Nonsteroidal anti-inflammatory drugs, NA: Not available, ASA: American society of anesthesiologists, HR: Heart rate, SBP: Systolic blood pressure, INR: International normalized ratio, ED: Emergency department, LOC: Loss of consciousness, BRB: Bright red blood per retum

**Figure 1:** Logistic regression coefficients of the variables that were significant
Table 2: Logistic regression analysis results of variables

| Variable                          | Estimate | SE  | P    |
|----------------------------------|----------|-----|------|
| Intercept                        | -3.6033933 | 1.6916244 | 0.03316 |
| Age                              | -0.0077009 | 0.0076323 | 0.312977 |
| Sex                              | 0.0357515 | 0.2265662 | 0.874616 |
| Ethnicity                        | -0.1631181 | 0.1151785 | 0.156711 |
| Aspirin                          | 0.2435659 | 0.262507 | 0.535488 |
| Clopidogrel                      | 0.4435809 | 0.3340099 | 0.182389 |
| NSAID use in last 7 days         | -0.3206295 | 0.4067022 | 0.430484 |
| Anticoagulant                    | 0.2477155 | 0.4189258 | 0.554312 |
| Stool color                      | 0.5367763 | 0.171654 | 0.001765 |
| Light headedness/syncope         | 0.9980933 | 0.2746707 | 0.000279 |
| AMS                              | -0.12174 | 0.4757831 | 0.79049 |
| History of abdominal pain crampin| 0.2480852 | 0.2774748 | 0.371278 |
| Onset to ED                      | 0.0109197 | 0.009107 | 0.230511 |
| Weekday                          | -0.926969 | 1.3391912 | 0.488821 |
| Weekend                          | -0.4683195 | 1.3395788 | 0.726637 |
| AM                               | 0.1891395 | 1.0555441 | 0.857791 |
| PM                               | 0.0148162 | 1.0631323 | 0.988881 |
| HR                               | 0.0133699 | 0.0058034 | 0.021233 |
| Abdominal tenderness on exam     | -0.5759474 | 0.2862023 | 0.04418 |
| Gross blood on rectal            | 0.4186887 | 0.2271953 | 0.05535 |
| APACHE II                        | 0.1354154 | 0.0256883 | 1.35E-07 |
| Platelet count                   | 0.0020525 | 0.0009509 | 0.308382 |
| PT                               | 0.0256217 | 0.0235043 | 0.275676 |
| INR                              | 0.0402919 | 0.2220008 | 0.855979 |

Significant variables at $P \leq 0.05$ are bolded. NSAID: Nonsteroidal anti-inflammatory drugs, HR: Heart rate, APACHE: Acute physiology and chronic health evaluation, INR: International normalized ratio, SE: Standard error, ED: Emergency department, PT: Prothrombin time, AMS: Altered mental status

Table 3: Logistic regression analysis results of the select variables

| Variable                          | Estimate | SE  | P    |
|----------------------------------|----------|-----|------|
| Intercept                        | -4.9211848 | 0.6732018 | 2.67E-13 |
| Stool color                      | 0.4913423 | 0.1661593 | 0.003106 |
| Lightheadedness/syncope          | 0.9634891 | 0.2584342 | 0.000193 |
| HR                               | 0.014295 | 0.0050569 | 0.009436 |
| Abdominal tenderness on exam     | -0.3998366 | 0.223365 | 0.503444 |
| Gross blood on rectal            | 0.3790709 | 0.2177564 | 0.051718 |
| APACHE II                        | 0.1252504 | 0.0222669 | 1.86E-08 |
| Platelet count                   | 0.0023825 | 0.0008988 | 0.008033 |
| PT                               | 0.0342372 | 0.0117161 | 0.003475 |

All variables are significant variables at $P \leq 0.05$. HR: Heart rate, APACHE: Acute physiology and chronic health evaluation, SE: Standard error, PT: Prothrombin time

Discussion

The use of dual anti-Plt therapy after percutaneous coronary intervention with drug-eluting stents has been used in 1.2 million patients yearly in the United States of America.[9,15] The use of NSAIDs, aspirin and/or clopidogrel are commonly prescribed and have been associated with increased overall GI bleeding risk; some studies suggested that the risk of GI bleed even higher when the above medications are used in combination.[9,10] Heparin and vitamin K antagonist, namely, warfarin, both increase the risk and incidence of bleed, especially the GI bleed, shown to be the most common major and fatal cause of bleeding in blood in a previous studies.[11] The incidence of GI bleeding is not uncommon, up to 2.7% reported in a previous study with most of bleeding events occur early in the first 30 days of therapy. Especially those at high risk for bleeding such as patients with previous history of GI bleed, peptic ulcer bleed, untreated *Helicobacter pylori* infection, intestinal polyps, or cancer.[12-15] In addition, the incidence of lower intestinal bleeding (LIB), especially diverticular bleed, was also found to be increased in patients taking antithrombotic medication.[16-18]

While many studies examine the risk for generalized intestinal bleeding and the overall incidence related to anti-Plt therapy, very few explore the growing population of patients on dual anti-Plt treatment, and to elucidate the incidence of severe LIB and the risks associated.[7-15] Having been identified as a risk factor for generalized bleeding, it is important to stratify and consider seriousness of bleeding episodes associated with dual anti-Plt therapy. In our study, a total of 511 patients were found to have true lower intestinal bleeding. Among these subjects 61 were shown to be on dual or multiple AT therapies. Further exploration revealed that while use of multiple blood thinning agents may in fact pose a significant risk to overall LIB, it did not significantly increase the risk for severe bleeding as outlined above. The need for surgical intervention was documented in 28 patients (5.47%), and death was encountered in six patients (1.17%). This information is not only useful with regards to triage and early intervention, but as a cost-effective measure to delineate which patients will benefit from early endoscopy and those that will not.

Although the incidence of GI bleed is increased in patients taking the anti-Plt medications or the anticoagulants, the predictors of severe LGIB in patients taking the above-mentioned medications have rarely been studied.[17] The early recognition of patients at high risk of severe LGIB is of most importance due to increased risk of complication and surgical intervention. Although still debatable, colonoscopy within 24 h of admission does not necessarily change the outcomes.[4,5,13] The exception is in selected cases, mainly in diverticular bleed, where early colonoscopy with endoscopic interventions (epinephrine injection, clipping, and/or endoscopic band ligation) may be an option to control the LGIB and locate the bleeding site to help minimize surgical resection if needed during the hospital course.[14]

This study represents a greater understanding and perspective on a common GI disease complication that is greatly affected lightheadedness/syncope, gross blood on rectal, APACHE II, and PT are >1. This means that these variables are associated with higher odds of LGIB. The odds ratio of abdominal tenderness on examination is <1, and this would suggest that abdominal tenderness on examination is associated with lower odds of LGIB. The results also revealed that HR and Plt count have no association with risk of LGIB because their ORs are equal to 1.
by increased patient exposure to AT agents. There is limited data in the academic literature regarding outcomes of patients on novel AT agents, especially in the growing incidence of polypharmacy. This investigation provides significant evidence within a substantial cohort of subjects on dual anti-Plt therapies. These findings, while meaningful may need to be replicated and enhanced by a larger patient sample size. The study is also limited by its retrospective nature, inability to control confounding variables, and inadequacy of medication exposure data (duration of exposure, dosing, and compliance) as is the concern in any analysis of medication exposure. As the pool of data expands and additional agents are employed for effective AT treatment, there will certainly be a need for future analysis of multiple drug-drug interactions and their association with adverse events, desired outcomes, and risk stratification. In the future, further data, ideally from randomized trials are needed to better identify and manage the effects of dual anti-Plt therapy, with and without warfarin or the newer antithrombotic agents currently in use, and the optimal duration of anti-Plt therapy among different risk subgroups.

**CONCLUSION**

Our study found that the use of multiple blood thinners does not significantly increase the risk for severe LGIB. Even though risk factors such as old age, intensity of anti-Plt use and or anticoagulation, race, sex, presence of abdominal pain, etc., may, in fact, pose a significant risk to overall LGIB, they did not significantly increase the risk of severity of the LGIB. To decrease the risk of LGIB while maintaining the effect of anticoagulation, we recommend close follow-ups, frequent monitoring of INR values and a strategy of low to moderate intensity of anticoagulation and or anti-Plt use could be considered in patients with many risk factors of LGIB.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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**Table 4: Odd ratios and 95% confidence intervals**

| Variable                        | OR  | 95% CI          |
|---------------------------------|-----|-----------------|
| Stool color                     | 1.6345087 | 1.1801907-2.63718 |
| Light headedness/syncope        | 2.6208249 | 1.5792774-4.349282 |
| HR                              | 1.0043976 | 1.0035078-1.025406 |
| Abdominal tenderness on exam    | 0.6704296 | 0.4327375-1.038680 |
| Gross blood on rectal           | 1.4609266 | 0.9533971-2.38634 |
| APACHE II                       | 1.1334322 | 1.0850305-1.183993 |
| Platelet count                  | 1.0023853 | 1.0006210-1.004153 |
| PT                              | 1.2348300 | 1.0113379-1.258868 |

OR: Odds ratio, CI: Confidence intervals, HR: Heart rate, APACHE: Acute physiology and chronic health evaluation, PT: Prothrombin time

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**REFERENCES**

1. Barnett J, Messmann H. Diagnosis and management of lower gastrointestinal bleeding. Nat Rev Gastroenterol Hepatol 2009;6:637-46.
2. Longstreth GF. Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: A population-based study. Am J Gastroenterol 1997;92:419-24.
3. Strate LL, Ayanian JZ, Kotler G, Syngal S. Risk factors for mortality in lower intestinal bleeding. Clin Gastroenterol Hepatol 2008;6:1004-10.
4. Green BT, Rockey DC, Portwood G, Tarnasky PR, Guarisco S, Branch MS, et al. Urgent colonoscopy for evaluation and management of acute lower gastrointestinal hemorrhage: A randomized controlled trial. Am J Gastroenterol 2005;100:2395-402.
5. Laine L, Shah A. Randomized trial of urgent vs. elective colonoscopy in patients hospitalized with lower GI bleeding. Am J Gastroenterol 2010;105:2636-41.
6. Strate LL, Orav EJ, Syngal S. Early predictors of severity in acute lower intestinal tract bleeding. Arch Intern Med 2003;163:838-43.
7. Strate LL, Saltzman JR, Mosko R, Mutanga ML, Syngal S. Validation of a clinical prediction rule for severe acute lower intestinal bleeding. Am J Gastroenterol 2005;100:1821-7.
8. Velayos FS, Williamson A, Sousa KH, Lung E, Bostrom A, Weber EJ, et al. Early predictors of severe lower gastrointestinal hemorrhage and adverse outcomes: A prospective study. Clin Gastroenterol Hepatol 2004;2:485-90.
9. Casado Arroyo R, Polo-Tomas M, Roncales MP, Scheiman J, Lanas A. Bleeding risk associated with 1 year of dual antiplatelet therapy after percutaneous coronary intervention: Insights from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Heart 2012;98:718-23.
10. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706-17.
11. Nieto JA, Solano R, Traperro Iglesias N, Ruiz-Giménez N, Fernández-Capitán C, Valero B, et al. Validation of a score for predicting fatal bleeding in patients receiving anticoagulation for venous thromboembolism. Thromb Res 2013;132:175-9.
12. Ng FH, Wong SY, Lam KE, Chang CM, Lau YK, Chu WM, et al. Gastrointestinal bleeding in patients receiving a combination of aspirin, clopidogrel, and warfarin in acute coronary syndrome. Am J Gastroenterol 2008;103:865-71.
13. Parasa S, Balasubramanian G, Chowdhury A, Olden K. 584 Timing of Colonoscopy and Outcomes Among Hospitalized Patients With Lower Gastrointestinal Bleeding-a Population Based Study. Gastrointest Endosc 2013;77:AB161-2.
14. Ishii N, Setoyama T, Deshpande GA, Omata F, Matsuda M, Suzuki S, et al. Endoscopic band ligation for colonic diverticular hemorrhage. Gastrointest Endosc 2012;75:382-7.
15. Alli O, Smith C, Hoffman M, Amanullah S, Katz P, Amanullah AM. Incidence, predictors, and outcomes of gastrointestinal bleeding in patients on dual antiplatelet therapy with aspirin and clopidogrel. J Clin Gastroenterol 2011;45:410-4.
16. Lamberts M, Gislason GH, Lip GY, Lassen JF, Olesen JB, Mikkelsen AP, et al. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: A nationwide cohort study. Circulation 2014;129:1577-85.
17. Abraham NS, Hartman C, Richardson P, Castillo D, Street RL Jr, Naik AD. Risk of lower and upper gastrointestinal bleeding, transfusions, and hospitalizations with complex antithrombotic therapy in elderly patients. Circulation 2013;128:1869-77.
18. Nagata N, Niikura R, Aoki T, Shimbo T, Kishida Y, Sekine K, et al. Colonic diverticular hemorrhage associated with the use of nonsteroidal anti-inflammatory drugs, low-dose aspirin, antiplatelet drugs, and dual therapy. J Gastroenterol Hepatol 2014;29:1786-93.